CSA046918

Organización y
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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

1/1

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 09-81886

54. **TÍTULO** DERIVADO DE AMINOPIRROLIDINA SUSTITUIDO FUSIONADO

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** DAIICHI SANKYO COMPANY, LIMITED

DOMICILIO TOKYO, JAPON

74. **APODERADO** LUZ CLEMENCIA DE PAEZ

C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-081886- -00000-0000
Fecha: 2009-08-05 17:19:13 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1117

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **DAIICHI SANKYO COMPANY, LIMITED**
Sociedad constituida y existente bajo las leyes de Japón.

Dirección: 3-5-1, Nihonbashi Honcho,
Chuo-ku,
Tokyo 103-8426,
Japón

Domicilio: Tokyo,
Japón

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 35.456.344 T.P 23.555

4 INVENTOR (ES) (72)

1. **Hisashi TAKAHASHI**
c/o DAICCHI SANKYO COMPANY LIMITED
1-16-13 Kitakasai,
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2. **Satoshi KOMORIYA**
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3. **Takahiro KITAMURA**
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Japón

11. Masatoshi NAGAMOCHI
c/o DAICCHI SANKYO COMPANY LIMITED
1-16-13 Kitakasai,
Edogawa-ku,
Tokyo 134-8630
Japón

(5) **PCT (86)**
Solicitud Internacional No. PCT/JP2007/075434 Fecha: 28 de diciembre de 2007
Publicación Internacional No. WO 2008/082009 A3 Fecha: 10 de julio de 2008

(6) **Título (54)**
DERIVADO DE AMINOPIRROLIDINA SUSTITUIDO FUSIONADO

(7) **Clasificación Internacional (51)** C07D 401/004

(8) **Prioridad** SI ☒ NO ☐

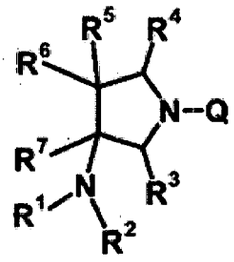
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	05 de enero de 2007	2007-000667
JP	22 de marzo de 2007	2007-074991

(9)
Comprobante de pago No.: 09-53,098 **Fecha:** 21 de julio de 2009
Comprobante de pago No.: 09-53,099 **Fecha:** 21 de julio de 2009
Comprobante de pago No.: 09-53,130 **Fecha:** 21 de julio de 2009
Comprobante de pago No.: 09-53,277 **Fecha:** 22 de julio de 2009

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- ☒ Comprobante de pago por 31 reivindicaciones adicionales después de la decimoquinta reivindicación por $775.000.oo.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11 **FIGURA CARACTERÍSTICA**



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Paez

C.C. 35.456.344 de Usaquén T.P. 23.555

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/082009 A3

   Descripción:

   Páginas 571 en el idioma original

   Páginas 467 en español

   Reivindicaciones: Número (s) 46

   Figuras: Número (s) 2

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

COLO -15869-841-015-2

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

15869
G113

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

DAIICHI SANKYO COMPANY, LIMITED

domiciliado (s) en/of 3-5-1, Nihonbashi Honcho,

Chuo-ku, Tokyo 103-8426, Japan

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el sólo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio,

hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of

ESTA COPIA ES TOMADA DEL CIRCULO DE BOGOTÁ D.C. HAY QUE CONSTAR QUE LA FOTOCOPIA BOGOTÁ D.C. CORRESPONDE CON LA VISTA
18 JUN 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this May 11, 2007

en/in Tokyo, Japan

por/by DAIICHI SANKYO COMPANY, LIMITED

By:

Firma Tsutomu Une
Member of the Board and
Senior Executive Officer

Signature

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA ... COLOMBIA
18 JUN 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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7.

CERTIFICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de _____

es auténtica; que el signatario desempeña actualmente el cargo de _____

de la compañía **DAIICHI SANKYO COMPANY, LIMITED**

_____,

sociedad que actualmente existe y está organizada de acuerdo a las leyes de Japón _____

_____,

que la dirección de dicha compañía es 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokio 103-8426, Japón _____

_____,

y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe.

Dado y firmado en _____

El _____

NOTARIAL CERTIFICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature of Tsutomu Une

is authentic, that the signatory currently acts in the position of Member of the Board and Senior Executive Officer

of the company **DAIICHI SANKYO COMPANY, LIMITED**

_____,

a company currently existing and organized under the laws of Japan _____

_____,

that the address is 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan _____

_____,

and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon examination of the corresponding documents.

Given and signed in _____

On _____

_____

El Notario Público - The Notary Public
(Firma-sello) (Signature-seal)

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HACE CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HA TENIDO A LA VISTA
18 JUN 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

Certified

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

....

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8

NOTARIAL CERTIFICATE Registration No 897

This is to certify that the signature on the foregoing document is genuine and authentic signature of

Tsutomu Une, Member of the Board and Senior Executive Officer of

DAIICHI SANKYO COMPANY, LIMITED,

a corporation existing and organized under the laws of Japan,

who has produced sufficient proof of his power to execute the said instrument on behalf of the above-mentioned corporation.

MAY 14 2007

TOKYO LEGAL AFFAIRS BUREAU
NOTARY
1-1, 2CHOME UCHISAIWAICHO
CHIYODA-KU
TOKYO JAPAN

Tadahiko Mitsuda

TADAHIKO MITSUDA
NOTARY

COMO NOTARIA SEXTA(E) DEL CIRCULO DE BOGO
D.C., HAGO CONSTAR QUE LA FOTOCOPIA
COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA REPUBLICA DE COLOMBIA
18 JUN 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

平成１９年登簿第　897　号

9

認　　証

嘱託人第一三共株式会社取締役采孟の代理人城野喬は、本公証人に対し、嘱託人が別添文書に署名したことを自認している旨陳述した。

よって、これを認証する。

平成１９年　5　月　14　日、本公証人役場において

東京都千代田区内幸町２丁目１番１号

東　京　法　務　局　所　属

公　証　人

Notary　満田忠彦

TADAHIKO MITSUDA

証　　明

上記署名は、東京法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成１９年　5　月　14　日

東　京　法　務　局　長　戸田信久

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, HACE CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 JUN 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

1. Country: JAPAN
   This public document
2. has been signed by TADAHIKO MITSUDA
3. acting in the capacity of Notary of the Tokyo Legal Affairs Bureau
4. bears the seal/stamp of TADAHIKO MITSUDA
   Certified
5. at Tokyo
6. MAY 14 2007
7. by the Ministry of Foreign Affairs
8. 07- Nº 001649
9. Seal/stamp:
10. Signature

MINISTRY OF FOREIGN AFFAIRS JAPAN

K. Oyabe

Kazutoyo OYABE

For the Minister for Foreign Affairs

40.

TRADUCCIÓN OFICIAL 186/2007 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **DAIICHI SANKYO COMPANY LIMITED.**, EMPRESA DOMICILIADA EN 3-5-1, NIHONBASHI HONCHO, CHUO-KU, TOKIO 103-8426, JAPÓN OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A DANIEL PEÑA, TPA 65620.

EXPEDIDO Y FIRMADO HOY 11 DE MAYO DE 2007 EN TOKIO, JAPÓN POR DAIICHI SANKYO COMPANY, LIMITED.

FIRMADO: TSUTOME UNE, MIEMBRO DE LA JUNTA Y EJECUTIVO PRINCIPAL

CERTIFICACIÓN NOTARIAL EN INGLÉS Y EN ESPAÑOL, PARA CERTIFICAR LA COMPARECENCIA DE TSUTOMU UNE, COMO MIEMBRO DE LA JUNTA Y EJECUTIVO PRINCIPAL DE LA EMPRESA DAIICHI SANKYO COMPANY LIMITED, UNA EMPRESA ACTUALMENTE EXISTENTE Y CONSTITUIDA DE ACUERDO CON LAS LEYES DE JAPÓN, CON DOMICILIO EN 3-5-1.NIHONBASI HONCHO, CHUO-KU, TOKIO, 103-8426, JAPÓN.

CERTIFICACIÓN NOTARIAL

REGISTRO 897

Por la presente certifico que la firma en el documento precedente es la firma genuina y auténtica de TSUTOMU UNE, miembro de la junta y ejecutivo principal de DAIICHI SANKYO COMPANY, LIMITED, una sociedad constituida y organizada de acuerdo con las leyes de Japón, que ha presentado prueba suficien[illegible] firmar dicho documento a nombre de dicha soc[illegible]

Firmado: Tadahiko Mitsuda, notario

SELLO: OFICINA DE ASUNTOS JURÍDICOS DE TOKIO NOTARIO 1-1 2CHOME UCHISAIWAICHO CHIYODA-KU TOKIO, JAPÓN.

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
18 JUN 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: JAPÓN

Este documento público

2. ha sido firmado por TADAHIKO MITSUDA

Libro de registro 2007 No.897

CERTIFICADO

Takashi Siroco, delegado del solicitante,el Gerente de Saiichi Sankyo Co.Ltd Tsutomu Une, manifesto ante el suscrito que dicho señor reconoce la firma que aparece en el documento adjunto.

Por lo tanto certifico que esta firma es autentica.

Mayo 14, 2007, en el despacho notarial
2-1-1, Uchisaiwai-Cho, Chiyoda-Ku, Tokio.
Notario adscrito al Departamento de Asuntos Juridicos de Tokio
Tadahiko Mitsuda (firma y sello oficial)

MINISTERIO DE RELACIONES EXTERIORES
2007 AGO 21 A 10:47
JEFE DE LEGALIZACIONES BOGOTA D.C.

CERTIFICACION

Certifico que la firma que aparece arriba es del notario adscrito al Departamento de Asuntos Juridicos de Tokio, y su sello estampado en el documento también es legítimo.

Mayo 14, 2007
Director del Departamento de Asuntos Juridicos de Tokio
Nobuhisa Toda -sello oficial-

LA FIRMA Y SELLO CORRESPONDEN A FUNCIONARIOS INDICADOS
NO SE ASUME RESPONSABILIDAD DEL TEXTO

COMO NOTARIA SESENTA (60) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
18 JUN 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

La presente traduccion oficial se ha efectuado bajo amparo de APOSTILLE No. 001649 del Ministerio de Asuntos Extranjeros del Japon con fecha May 8 14, 2007, y esta firmado por Kazutoyo Oyabe.

Traductor Oficial
Japonés - Español
Tsutomu Muramatsu
Resolución No. 909 Mayo 6 1987

3. quien actúa en su calidad de notario de la Oficina de asuntos jurídicos de Tokio

4. y lleva el sello/estampilla de TADAHIKO MITSUDA

CERTIFICADO

5. en Tokio, 6. el 14 de mayo de 2007

7. por el Ministerio de Asuntos Exteriores

8. 07-no.001649

9. Sello: MINISTERIO DE ASUNTOS EXTERIORES, JAPÓN

10. Firma: KAZUTOYO OYABE a nombre del Ministro de Asuntos Exteriores.

COLO- 15869-845-001-8

WPCL002G ID 9090

Bogotá, 13 de agosto de 2007.

Eduardo Calado
Eduardo Calado Nomero
"TRADUCTOR OFICIAL"
INGLES - ESPAÑOL INGLES
Res. 591 Febrero de 1978

MINISTERIO DE RELACIONES EXTERIORES
2007 AGO 21 A 10:47
JEFE DE LEGALIZACIONES
BOGOTA D.C.

COMO NOTARIA SEXTA (E) DEL CÍRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
18 JUN 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

645605
Eduar Calado
LA FIRMA PARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a No 72-35
BOGOTA, B-COLOMBIA

Dec CO 13

CESION

Yo, (nosotros), abajo firmado(s)

domiciliado(s) en

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of
(1)-(11) c/o DAIICHI SANKYO COMPANY, LIMITED, 1-16-13, Kitakasai, Edogawa-ku, Tokyo 134-8630 Japan

state(s) under oath to be sole and true inventor(s) of the invention:
"FUSED SUBSTITUTED AMINOPYRROLIDINE DERIVATIVE"
state as well, that assign, without reservations or limitations in favour of
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domiciled in 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426 Japan

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JUN 11 2009

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CHIYODA-KU
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TADAHIKO MITSUDA
NOTARY

平成２１年登簿第 1042 号

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証　　明

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5. at Tokyo
6. JUN 11 2009
7. by the Ministry of Foreign Affairs
8. 09- Nº 001716
9. Seal/stamp:
10. Signature

MINISTRY OF FOREIGN AFFAIRS 外務省 JAPAN

K. Oyabe

Kazutoyo OYABE

For the Minister for Foreign Affairs

TRADUCCIÓN OFICIAL 225/2009 DE UN DOCUMENTO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL, APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA.

CESIÓN

Nosotros, los abajo firmantes (1) TAKAHASHI, HISASHI, (2) KOMORIYA, SATOSHI, (3) KITAMURA, TAKAHIRO, (4) ODAGIRI, TAKASHI, (5) INAGAKI, HIROAKI, (6) TSUDA, TOSHIFUMI, (7) NAKAYAMA, KIYOSHI, (8) TAKEMURA, MAKOTO, (9) TOSHIDA, KENICHI, (10) MIYAUCHI, RIE, (11) NAGAMOCHI, MASATOSHI

TODOS DOMICILIADOS EN C/O DAIICHI SANKYO COMPANY LIMITED, 1-16-13, KITAKASAI, EDOGAWA-KU, TOKIO 134-8630, JAPÓN, declaramos bajo juramento ser los únicos y verdaderos inventores de la invención: DERIVADOS FUSIONADOS Y SUSTITUIDOS DE AMINOPIRROLIDINA. Igualmente declaramos que lo cedemos sin reservas ni limitaciones en favor de DAIICHI SANKYO COMPANY, LIMITED, una sociedad constituida y existente de conformidad con las leyes del JAPÓN, domiciliada en 3-5-1, NIHONBASHI HONCHO, CHUO-KU, TOKIO 103-8426, JAPÓN, todos los derechos inherentes a dicho invento y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Dado y firmado hoy en Tokio, Japón

(A continuación aparecen todas las firmas de los once inventores arriba mencionados)

CERTIFICACIÓN NOTARIAL

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

REGISTRO NO. 1042

Por la presente se certifica que las firmas en el documento precedente son las firmas genuinas y autenticas de (aquí aparecen los nombres de todos los once inventores arriba mencionados).

11 de junio de 2009.

Firmado: TADAHIKO MITSUDA, notario

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5. en Tokio 6. 11 de junio de 2009

7. por el Ministerio de Relaciones Exteriores

8. 09-No. 001716

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10. Firma: KAZUTOYO OYABE, a nombre del Ministerio de Relaciones Exteriores.

ECN\ECN\ID-155007\WPCL002G

COLO-15869-841-015-2
Bogotá, 30 de julio de 2009.

Eduardo Calado N.
Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2008 (10.07.2008)

PCT

(10) International Publication Number
WO 2008/082009 A3

(51) International Patent Classification:
C07D 401/04 (2006.01) *C07D 498/04* (2006.01)
C07D 401/14 (2006.01) *A61K 31/47* (2006.01)
C07D 491/052 (2006.01) *A61P 31/04* (2006.01)

(21) International Application Number:
PCT/JP2007/075434

(22) International Filing Date:
28 December 2007 (28.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2007-000667 5 January 2007 (05.01.2007) JP
2007-074991 22 March 2007 (22.03.2007) JP

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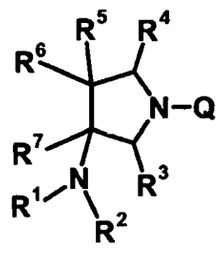
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: FUSED SUBSTITUTED AMINOPYRROLIDINE DERIVATIVE



(I)

(57) Abstract: A quinolone synthetic antibacterial agent having excellent properties as a medicine is provided, which has strong antibacterial activity not only to Gram-negative bacteria but also to Gram-positive cocci that have low sensitivity to quinolone antibacterial agents, and which exhibits high safety and excellent pharmacokinetics. A compound represented by the formula (I) or a salt thereof, or a hydrate thereof. Specifically, a quinolone derivative of the formula (I) wherein substituents R6 and R7 taken together with the carbon atoms to which they are bonded form a cyclic structure which may contain an oxygen atom as a ring constituent atom, the cyclic structure forming a 5-4, 5-5, or 5-6 fused bicyclic pyrrolidinyl substituent, the substituent being bonded to a quinolone mother skeleton Q containing a pyridobenzoxazine structure.

WO 2008/082009 A3

WO 2008/082009 A3



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
11 December 2008

Gram-positive cocci including Staphylococcus aureus (methicillin-resistant Staphylococcus aureus: MRSA) and pneumococcus (penicillin-resistant Streptococcus pneumonia: PRSP) having low sensitivity to β-lactam antibiotics; and enterococci having low sensitivity to aminoglycoside antibacterial agents (vancomycin-resistant enterococcus: VRE) and having also low sensitivity to quinolone synthetic antibacterial agents has increased. Bacterial infections caused by such resistant Gram-positive bacteria are known to be generally severe (fatal) and intractable. Accordingly, drugs more effective to Gram-positive cocci are particularly desired in the clinical field (see Drugs, Vol.66, No.6, p.751 (2005)).

On the other hand, quinolone synthetic antibacterial compounds created in recent years have antibacterial activities that are much higher than those of previous ones (see Japanese Patent Laid-Open No. 2-231475 or Japanese Patent Laid-Open No. 3-95176). However, many of such quinolone compounds having high antibacterial activity cause side effects based on their physiological and pharmacological effects not observed for previous quinolone synthetic antibacterial agents.

Examples of the side effects of quinolone synthetic antibacterial agents include conventionally reported side effects such as induction of convulsion by use in

combination with non-steroidal anti-inflammatory drugs (NSAIDs), central actions (mild central nervous system disorders such as sway, headache, and insomnia, and serious side effects such as the onset of fatal convulsion), and phototoxicity (photosensitivity); as well as recently disclosed side effects such as hepatotoxicity (serious allergic hepatitis), cardiotoxicity (electrocardiographic abnormality inducing fatal arrhythmia, observed as QT or QTc prolongation), delayed drug eruption (skin rash), and blood glucose level abnormality (see Hiroyuki Kobayashi (ed.), Clinical Application of New Quinolone Agents, Iyaku (Medicine and Drug) Journal Co., Ltd.; Drugs, Vol.62, No.1, p.13 (2002); Toxicology Letters, Vol. 127, p.269 (2002); Clinical Infectious Diseases, Vol.41, p.1269 (2005)); and International Journal of Antimicrobial Agents, Vol.23, No.5, p.421 (2004)).

The clinical onset of cardiotoxicity among such side effects is a particular problem in recent years. Distinct QT or QTc prolongation is reported and some serious conditions (electrocardiographic abnormality inducing fatal arrhythmia) are also reported for some commercially available quinolone synthetic antibacterial agents (such as grepafloxacin, sparfloxacin, moxifloxacin, gatifloxacin, and gemifloxacin). Serious side effects such as the onset of serious allergic hepatitis accompanying liver

transplantation (trovafloxacin: see Clinical Infectious Diseases, Vol.41, p.1269 (2005)) and blood glucose level abnormality including fatal hypoglycemia (gatifloxacin: see International Journal of Antimicrobial Agents, Vol.23, No.5, p.421 (2004)) are also clinical problems. Further, delayed drug eruption (skin rash) caused by repeated administration of a quinolone agent in a clinical test (gatifloxacin: see Clinical Infectious Diseases, Vol.41, p.1269 (2005)) is reported. In such circumstances, the administration of some quinolone synthetic antibacterial agents has been limited, and the development and use as human medicines of some quinolone synthetic antibacterial agents has been abandoned. That is, some quinolone synthetic antibacterial agents have been observed which have strong antibacterial activity but which in terms of side effects are not sufficiently suitable as medicines.

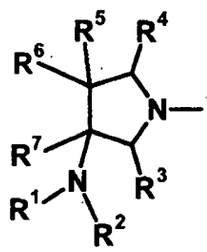
Accordingly, there is a need for safer quinolone synthetic antibacterial agents for use as human medicines, having only low side effects such as induction of convulsion by use in combination with non-steroidal anti-inflammatory drugs, central actions, and phototoxicity (photosensitivity) which are conventionally known as side effects; as well as cardiotoxicity, hepatotoxicity, delayed drug eruption (skin rash), and blood glucose level abnormality which are clinical problems in recent years.

Therefore, there is a need for the development of compounds conceptually different from conventional compounds that have high antibacterial activity but cause side effects and thus cannot be used as medicines. That is, there is a need for quinolone compounds having both strong antibacterial activity and high safety (see The Japanese Journal for History of Pharmacy, Vol.38, No.2, p.161 (2003)).

Antibacterial activity, pharmacokinetics, and safety of a quinolone synthetic antibacterial agent are known to be influenced by the structure of the substituents at each position of the quinolone skeleton, in particular, the structure of the substituent at the 7-position (corresponding to the 10-position of the pyridobenzoxazine skeleton) (see Clinical Microbiology and Infection, Vol.11, No.4, p.256 (2005), for example).

The characteristic feature of the compounds of the present invention is that they have, at the 7-position of the quinolone mother skeleton, a substituent represented by the following formula 1:

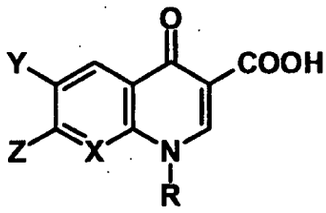
[Formula 1]



wherein R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in claim 1. That is, the 7-position substituent in the compounds of the present invention has a fused bicyclic amine structure that is formed by fusion of the pyrrolidine ring with a cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded, and further the fused bicyclic amine structure has an amino group at the bridgehead position. In relation to quinolone derivatives substituted with a 7-position substituent having such a structure, the following compounds are known.

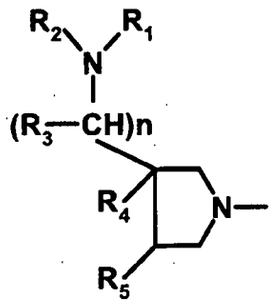
For example, Japanese Patent Laid-Open No. 64-56673 describes a pyridonecarboxylic acid derivative represented by the general formula 2:

[Formula 2]



wherein R represents a lower alkyl group, a halogeno lower alkyl group, a lower alkenyl group, a cycloalkyl group, or a phenyl group which may have a substituent; X represents a nitrogen atom or C-A, wherein A represents a hydrogen atom or a halogen atom; Y represents a hydrogen atom or a halogen atom; and Z represents a group represented by the following formula 3:

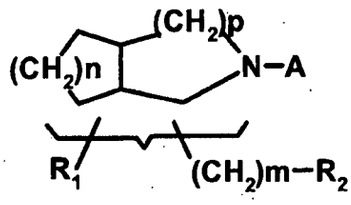
[Formula 3]



wherein R_1 represents a hydrogen atom, a lower alkyloxycarbonyl group, or an acyl group which may be substituted with a halogen atom; two of R_2, R_3, R_4, and R_5 are bonded directly or through a lower alkyl chain to form a ring and the remaining two of R_2, R_3, R_4, and R_5 each represents a hydrogen atom; and n represents 0 or 1, provided that R_2 and R_3 are a bond when these are bonded to each other. The definitions of substituents and the like in the compound represented by the formula 2 do not apply to the compounds of the present invention although the same symbols are used. However, Japanese Patent Laid-Open No. 64-56673 does not specifically disclose a quinolone compound in accordance with the present invention wherein R_4 and R_5 in the formula 3 are taken together to form a four- to seven-membered ring and n = 0.

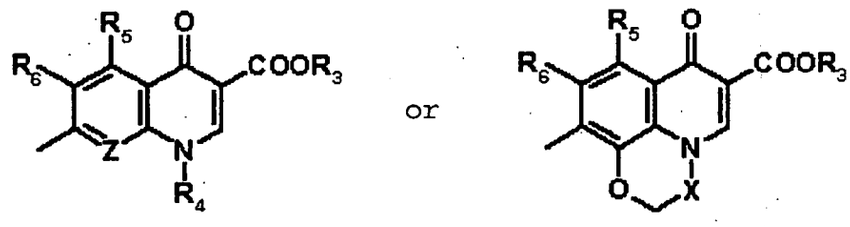
EP-A-343524 discloses a pyridonecarboxylic acid antibacterial agent represented by the general formula 4:

[Formula 4]



wherein R_1 is hydrogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, oxo, halogen, or amino which may optionally be substituted with C_1-C_4 alkyl and/or C_1-C_4 alkanoyl; R_2 is azide, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkanoyl, or amino which may optionally be substituted with C_1-C_4 alkyl and/or C_1-C_4 alkanoyl; A is a quinolone structure represented by the following formula 5:

[Formula 5]

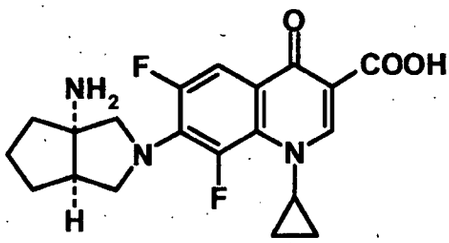


;

R_3 is hydrogen or a carboxy protecting group; R_4 is C_1-C_4 alkyl, C_2-C_5 alkenyl, C_3-C_5 cycloalkyl, mono- or di-fluorophenyl, or a five- or six-membered heterocycle which may optionally be substituted with halogen and/or C_1-C_4 alkyl; R_5 is hydrogen, amino, hydroxy, or C_1-C_4 alkoxy; R_6 is halogen; X is CH-(C_1-C_4 alkyl), $C=CH_2$, N-H, or N-(C_1-C_4 alkyl); Z is CQ or N; Q is hydrogen, C_1-C_4 alkoxy, halogen, C_1-C_4 alkyl, or cyano; m is an integer of 0 or 1; and n and

p are each an integer of 1 to 3. However, as a specific compound related to the compounds of the present invention, EP-A-343524 discloses only a quinolonecarboxylic acid derivative represented by the following formula 6, that is, a derivative in which m is 0, p is 1, and the substituent R_2 is an amino group at the bridgehead position of the bicyclic amine:

[Formula 6]

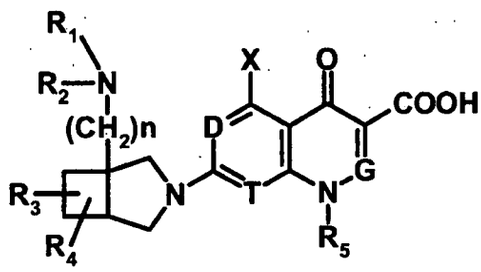


Moreover, EP-A-343524 does not disclose a compound having a halogenocyclopropyl group at the 1-position which is a typical example of the compounds of the present invention. The structure of the 7-position substituent is a (1R*,5S*)-configuration in the compound represented as the formula 6 as disclosed in EP-A-343524. This compound is a so-called cis-racemate, and EP-A-343524 does not describe the antibacterial activity of an optical isomer. Further, EP-A-343524 does not describe the safety of the disclosed compound. A stereochemically single compound is preferable as a human medicine in terms of effectiveness and safety. In addition, the compound represented by the formula 6 has a fluorine atom at the 8-position of the quinolone skeleton

and is thus presumed to cause phototoxicity (photosensitivity) with high probability (see Journal of Antimicrobial Chemotherapy, Vol.33, p.683 (1994), for example). That is, the compound represented by the formula 6 is not thought to be necessarily sufficient as a medicine for effective use in humans with safety. European Journal of Medicinal Chemistry, Vol.26, p.889 (1991) only describes the content in accordance with EP-A-343524.

WO 95/21163 discloses a pyridonecarboxylic acid antibacterial agent substituted with a bicyclic amino group, which is represented by the following general formula 7:

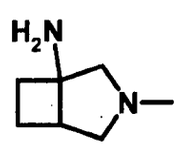
[Formula 7]



wherein R_1 and R_2 are the same or different and each represents a hydrogen atom, a lower alkyl group, or an amino-protecting group; R_3 and R_4 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a hydroxy group, an oxo group, a lower alkoxy group, or a lower alkyl group; n represents an integer of 0 or 1; R_5 represents a lower alkyl group, a lower alkenyl group, a lower cycloalkyl group, a phenyl group, or a

heterocyclic group (these may be further substituted); G represents C-E, wherein E represents a hydrogen atom or together with R_5 forms a crosslinkage represented by -S-SE(CH_3)-; T represents C-Z or a nitrogen atom, wherein Z represents a hydrogen atom, a halogen atom, a cyano group, a lower alkoxy group, a halogeno lower alkoxy group, a lower alkyl group, or a halogeno lower alkyl group or together with R_5 forms a crosslinkage represented by -O-CH_2-CH(CH_3)-; X represents a hydrogen atom, a halogen atom, a hydroxy group, a lower alkyl group, or an amino group which may be protected; and D represents C-Y, wherein Y represents a hydrogen atom or a halogen atom. However, in relation to the compounds of the present invention, as a bicyclic amino group in the 7-position substituent of the quinolone derivative, only the substituent represented by the following formula 8, that is where R_3 and R_4 are each a hydrogen atom in the formula 7 and n is 0, is specifically disclosed:

[Formula 8]

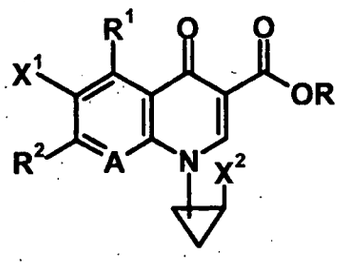


Further, WO 95/21163 does not specifically disclose a fused substituted aminopyrrolidine derivative (bicyclic amine) which is a feature of the present invention, that is

where in the compound represented by the formula 7 one or both of the substituents R_3 and R_4 on the bicyclic amine has a substituent other than a hydrogen atom.

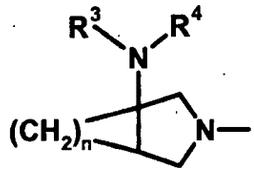
WO 96/23782 discloses a N_1-(halogenocyclopropyl) substituted pyridonecarboxylic acid derivative represented by the general formula 9:

[Formula 9]



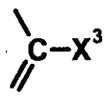
wherein X^1 represents a halogen atom or a hydrogen atom; X^2 represents a halogen atom; R^1 represents a hydrogen atom, a hydroxy group, a thiol group, a halogenomethyl group, an amino group, an alkyl group, or an alkoxy group; R^2 represents a substituent of formula 10:

[Formula 10]



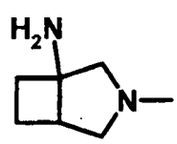
wherein R^3 and R^4 each represents a hydrogen atom or an alkyl group and n represents an integer of 1 or 2; A represents a group of formula 11:

[Formula 11]



wherein X^3 represents a hydrogen atom, a halogen atom, a cyano group, an amino group, an alkyl group, a halogenomethyl group, an alkoxy group, or a halogenomethoxy group; and R represents a hydrogen atom, a phenyl group, an acetoxymethyl group, a pivaloyloxymethyl group, an ethoxycarbonyl group, a choline group, a dimethylaminoethyl group, a 5-indanyl group, a phthalidinyl group, a 5-alkyl-2-oxo-1,3-dioxol-4-ylmethyl group, a 3-acetoxy-2-oxobutyl group, an alkyl group, an alkoxymethyl group, or a phenyl group. The definitions of substituents and the like in the compound represented by the formula 9 do not apply to the compounds of the present invention although the same symbols are used. However, in relation to the compounds of the present invention, as a bicyclic amino group in the 7-position substituent of the quinolone derivative, only the substituent represented by the following formula 12, that is where n is 2 in the formula 10, is specifically disclosed:

[Formula 12]



Further, WO 96/23782 does not disclose a 1-amino-3-azabicyclo[3.2.0]heptane derivative having a substituent other than a hydrogen atom on the bicyclic ring, which is a feature of the compounds of the present invention.

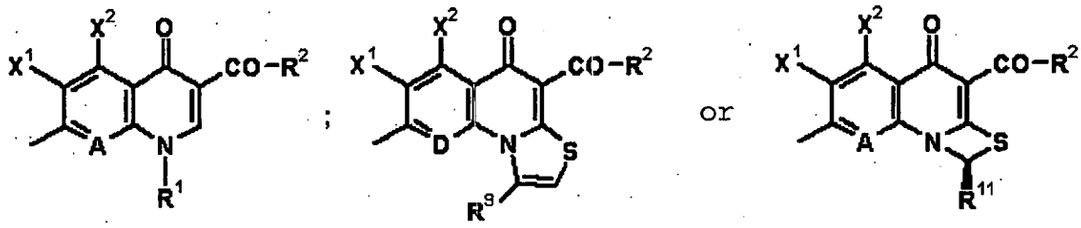
Japanese Patent Laid-Open No. 8-225567 discloses a quinolone- or naphthylidone-carboxylic acid derivative represented by the general formula 13:

[Formula 13]

T–Q

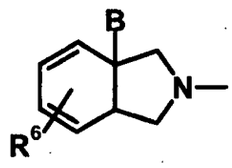
wherein Q represents a quinolone structure of formula 14:

[Formula 14]



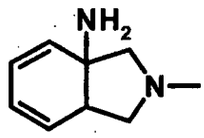
wherein X^1 represents halogen or nitro; X^2 represents hydrogen, halogen, amino, hydroxy, methoxy, or the like; A and D each represent N or C-R^7 (wherein R^7 = H, F, OCH_3, or the like); R^1 represents C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or the like; R^2 represents hydroxy, methoxy, benzyloxy, or the like; R^9 represents hydrogen or C_1-C_3 alkyl; and R^{11} represents hydrogen, methyl, or CH_2F; and T represents the following formula 15:

[Formula 15]



wherein B represents amino, hydroxy, or the like; and R^6 represents hydrogen or methyl. The definitions of substituents and the like in the compound represented by the formula 13 do not apply to the compounds of the present invention although the same symbols are used. However, Japanese Patent Laid-Open No. 8-225567 only discloses a compound represented by the following formula 16 as such a derivative where B is an amino group.

[Formula 16]



Further, Japanese Patent Laid-Open No. 8-225567 does not describe a specific compound related to the present invention.

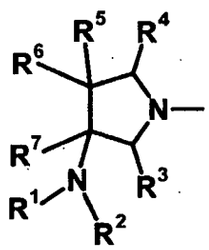
SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is to provide a quinolone synthetic antibacterial agent and a therapeutic agent for infections which has wide and strong antibacterial activity to Gram-positive bacteria, including

those having low sensitivity to quinolone, and to Gram-negative bacteria, and which also has high safety.

The present inventors have conducted research on compounds having a 3-aminopyrrolidinyl group at the 7-position of quinolone compounds or its corresponding position (for example, the 10-position of pyridobenzoxazine compounds). The inventors have found that quinolone derivatives having a fused substituted aminopyrrolidinyl substituent represented by the following formula 17:

[Formula 17]



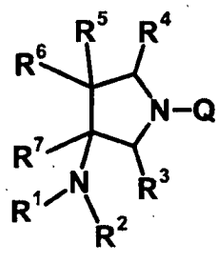
wherein substituents at 3- and 4-positions in the 3-aminopyrrolidinyl group taken together with the carbon atoms to which they are bonded form a four- to seven-membered cyclic structure which may contain a double bond and may contain an oxygen atom or a sulfur atom, the cyclic structure together with the pyrrolidine ring forming a fused cyclic (bicyclic) structure, have wide and strong antibacterial activity to Gram-positive bacteria, notably to resistant Gram-positive cocci such as pneumococcus resistant to multiple drugs including quinolone, and to

Gram-negative bacteria. Various preclinical evaluations have revealed that the quinolone compounds not only have such high antibacterial activity but also cause only with low probability conventionally known side effects of quinolone antibacterial agents such as convulsion induction and phototoxicity (photosensitivity) and recently clinically reported side effects such as cardiotoxicity (QT prolongation), blood glucose level abnormality, and delayed drug eruption. It has also become clear that the quinolone compounds show excellent oral absorbability and permeability to organs. These results are quite unexpected from the contents disclosed in the aforementioned patent documents.

Finally, the inventors have found that quinolone compounds represented by the later-described formula (I) and their corresponding salts and hydrates are quinolone synthetic antibacterial agents having excellent properties as medicines, which have high antibacterial activity and safety and which also exhibit excellent pharmacokinetics. These findings have led to the completion of the present invention.

Specifically, the present invention provides a compound represented by the following formula (I), a salt, or a hydrate thereof:

[Formula 18]



I

wherein R^1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, or a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide, said alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a cyano group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and said cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom;

R^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 6 carbon atoms, said alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and said cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl

group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom;

R^3 and R^4 each independently represents a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, and said alkyl group may have one or more substituents selected from the group consisting a halogen atom and an alkoxy group having 1 to 6 carbon atoms;

R^5 represents a hydrogen atom, a halogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, an alkynyl group having 2 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, or a heteroaryl group which may have a substituent, said alkyl group, alkenyl group, and alkynyl group may be linear or branched, the alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and the alkenyl group may have one or more substituents selected from the group consisting of a halogen atom and an alkoxy group having 1 to 6 carbon atoms;

R^6 and R^7 taken together with the carbon atoms to which they are bonded form a four- to seven-membered cyclic

structure, the cyclic structure representing a partial structure that together with the pyrrolidine ring forms a fused cyclic (bicyclic) structure, the four- to seven-membered cyclic structure may contain a double bond and may contain an oxygen atom or a sulfur atom as a ring constituent atom,

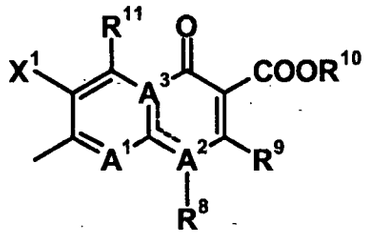
R^5 may be a methylene group taken together with R^6 to form a three-membered fused cyclic structure moiety, and

the ring formed as described above may be located in other part of the fused cyclic (bicyclic) structure, and said four- to seven-membered cyclic structure may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms which may have a substituent, an alkoxy group having 1 to 6 carbon atoms which may have a substituent, an alkenyl group having 2 to 6 carbon atoms which may have a substituent, an alkynyl group having 2 to 6 carbon atoms which may have a substituent, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an exomethylene group which may have a substituent, a spiroalkyl group which may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, a heteroaryl group which may have a substituent, an alkoxyimino group having 1 to 6 carbon atoms which may have a substituent, a halogen atom, a hydroxy group, a cyano group, and a hydroxyimino group;

or a polymethylene chain of 2 to 5 carbon atoms may bind so as to form a spirocyclic ring system; and

Q represents a partial structure represented by the following formula (II):

[Formula 19]



II

wherein R^8 represents an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, a halogen-substituted alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, a halogen-substituted phenyl group which may have a substituent, a halogen-substituted heteroaryl group which may have a substituent, an alkoxy group having 1 to 6 carbon atoms, or an alkylamino group having 1 to 6 carbon atoms;

R^9 represents a hydrogen atom or an alkylthio group having 1 to 6 carbon atoms, or R^9 and R^8 taken together with the atoms to which they are bonded form a cyclic structure, said cyclic structure may contain a sulfur atom as a ring constituent atom and may have an alkyl group having 1 to 6 carbon atoms or a halogen-substituted alkyl group having 1 to 6 carbon atoms as a substituent;

R^{10} represents a hydrogen atom, a phenyl group, an acetoxymethyl group, a pivaloyloxymethyl group, an ethoxycarbonyl group, a choline group, a dimethylaminoethyl group, a 5-indanyl group, a phthalidinyl group, a 5-alkyl-2-oxobutyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxymethyl group having 2 to 7 carbon atoms, or a phenylalkyl group formed by an alkylene group having 1 to 6 carbon atoms and a phenyl group;

R^{11} represents a hydrogen atom, an amino group, a hydroxy group, a thiol group, a halogenomethyl group, or an alkyl group having 1 to 6 carbon atoms, and the amino group may have one or two substituents selected from the group consisting of a formyl group, an alkyl group having 1 to 6 carbon atoms, and an acyl group having 2 to 5 carbon atoms;

X^1 represents a halogen atom or a hydrogen atom;

A^1 represents a nitrogen atom or a partial structure represented by the formula (III):

[Formula 20]



III

wherein X^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, a cyano group, a halogen atom, a halogen-substituted methyl group, or a halogenomethoxy group, or X^2 and R^8 taken together with their connecting part of the mother skeleton

form a cyclic structure, said cyclic structure may contain an oxygen atom, a nitrogen atom, or a sulfur atom as a ring constituent atom, and may be substituted with an alkyl group having 1 to 6 carbon atoms which may have a substituent; and

A^2 and A^3 each represents a nitrogen atom or a carbon atom, and A^1, A^2, A^3, R^8 and the carbon atom to which A^2 and A^3 are bonded together represent a partial structure:

>C=C(-A^1=)-N(-R^8)-

or a partial structure:

>N-C(-A^1=)=C(-R^8)-.

The present invention also provides a medicine comprising a compound represented by the formula (I), a salt, or a hydrate thereof as an active ingredient.

The present invention further provides a method for treating diseases comprising administering a compound represented by the formula (I), a salt, or a hydrate thereof. The present invention still further provides use of a compound represented by the formula (I), a salt or a hydrate thereof for production of a medicine.

The present invention can provide a quinolone synthetic antibacterial agent having excellent properties as a medicine, which has strong antibacterial activity not only to Gram-negative bacteria but also to Gram-positive cocci

that have low sensitivity to quinolone antibacterial agents, and exhibits high safety and excellent pharmacokinetics.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the ORTEP diagram obtained by the X-ray crystallography for (3S)-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester obtained in Reference Example 24.

FIG. 2 shows the absolute configuration of (3S)-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl] pyrrolidine-3-carboxylic acid tert-butyl ester obtained in Reference Example 24.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

R^1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, or a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide. The alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a cyano group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and the cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl

group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom.

R^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 6 carbon atoms. The alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms. The cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom.

When R^1 or R^2 is an alkyl group, the alkyl group may be linear or branched, and is preferably a methyl group, an ethyl group, a propyl group, or an isopropyl group, more preferably a methyl group or an ethyl group, and still more preferably a methyl group.

When R^1 or R^2 is an alkyl group having a hydroxy group, an amino group, or a cyano group as a substituent, the alkyl group may be a linear or branched alkyl group having 1 to 6 carbon atoms and is preferably substituted with the substituent on the terminal carbon atom of the alkyl group. The alkyl group having a hydroxy group is suitably an alkyl group having up to 3 carbon atoms and is preferably a 2-hydroxyethyl group, a 2-hydroxypropyl group, or a 3-

hydroxypropyl group. The alkyl group having an amino group is suitably an alkyl group having up to 3 carbon atoms and is preferably a 2-aminoethyl group, a 2-aminopropyl group, or a 3-aminopropyl group. The alkyl group having a cyano group is suitably an alkyl group having 2 to 4 carbon atoms and is preferably a 2-cyanoethyl group or a 2-cyano-2,2-dimethylethyl group.

When R^1 or R^2 is an alkyl group having a halogen atom as a substituent, the alkyl group may be a linear or branched alkyl group having 1 to 6 carbon atoms and the halogen atom is preferably a fluorine atom. The alkyl group may be monofluoro-substituted to perfluoro-substituted. Suitable examples of the halogen-substituted alkyl group include a monofluoromethyl group, a difluoromethyl group, a trifluoromethyl group, and a 2,2,2-trifluoroethyl group.

When R^1 or R^2 is an alkyl group having an alkylthio group or an alkoxy group as a substituent, the alkyl group may be linear or branched and the alkyl moiety in the alkylthio group or alkoxy group may also be linear or branched. The alkyl group having an alkylthio group is preferably an alkylthiomethyl group, an alkylthioethyl group, or an alkylthiopropyl group, and the alkylthio group preferably has 1 to 3 carbon atoms. More preferred examples of the alkyl group having an alkylthio group include a methylthiomethyl group, an ethylthiomethyl group, and a

methylthioethyl group. The alkyl group having an alkoxy group is preferably an alkoxymethyl group, an alkoxyethyl group, or an alkoxypropyl group, and the alkoxy group preferably has 1 to 3 carbon atoms. More preferred examples of the alkyl group having an alkoxy group include a methoxymethyl group, an ethoxymethyl group, and a methoxyethyl group.

When R^1 or R^2 is a cycloalkyl group, the cycloalkyl group is preferably a cyclopropyl group or a cyclobutyl group, and more preferably a cyclopropyl group. The cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom. Specifically, the substituent is preferably a methyl group, an ethyl group, an amino group, a hydroxy group, a fluorine atom, or a chlorine atom.

A preferred combination of R^1 and R^2 is that wherein R^1 is selected from a hydrogen atom, an alkyl group, a cycloalkyl group and a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide, and R^2 is a hydrogen. A more preferred combination of R^1 and R^2 is that wherein R^1 is selected from a hydrogen atom, an alkyl group and a cycloalkyl group and R^2 is a hydrogen. The alkyl group is preferably a methyl group or an ethyl group, and particularly preferably a methyl group. The cycloalkyl

group is preferably a cyclopropyl group or a cyclobutyl group, and particularly preferably a cyclopropyl group. A still more preferred combination that wherein both of R^1 and R^2 are hydrogen atoms or that wherein one of R^1 and R^2 is a hydrogen atom and the other is a methyl group, an ethyl group, a fluoroethyl group, or a cyclopropyl group.

A quinolone derivative, wherein R^1 is a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide and R^2 is a hydrogen atom, is useful as a prodrug. Amino acids, dipeptides, or tripeptides used for providing such a prodrug are those forming a peptide bond between a carboxyl group and the amino group to which R^1 and R^2 bonded and forming a free amine compound after being cleaved in vivo. Examples of substituted carbonyl groups for providing such a prodrug include substituted carbonyl groups derived from amino acids such as glycine, alanine, and aspartic acid; dipeptides formed by glycine, alanine, or asparagine such as glycine-glycine, glycine-alanine, and alanine-alanine; and tripeptides formed by glycine, alanine, or asparagine such as glycine-glycine-alanine and glycine-alanine-alanine.

R^3 and R^4 independently represent a hydrogen atom or an alkyl group having 1 to 6 carbon atoms. The alkyl group may have one or more substituents selected from the group

consisting a halogen atom and an alkoxy group having 1 to 6 carbon atoms.

When R^3 and R^4 are independently an alkyl group, the alkyl group may be linear or branched, and is preferably a methyl group, an ethyl group, a propyl group, or an isopropyl group, more preferably a methyl group or an ethyl group, and still more preferably a methyl group.

When R^3 and R^4 are independently an alkyl group, the substituent may be a group selected from the group consisting of a halogen atom and an alkoxy group having 1 to 6 carbon atoms. The halogen atom is preferably a fluorine atom. The alkyl group may be monofluoro-substituted to perfluoro-substituted. Suitable examples of the halogen-substituted alkyl group include a monofluoromethyl group, a difluoromethyl group, and a trifluoromethyl group. Preferred examples of the alkoxy group having 1 to 6 carbon atoms include a methoxymethyl group, an ethoxymethyl group, and a methoxyethyl group. When R^3 and R^4 are independently a substituted alkyl group, the group is particularly preferably a fluoromethyl group.

A preferred combination of R^3 and R^4 is that wherein one of R^3 and R^4 is a hydrogen atom and the other is a methyl group or a fluoromethyl group. A more preferred combination of R^3 and R^4 is that wherein both of R^3 and R^4 are hydrogen atoms.

R^5 represents a hydrogen atom, a halogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, an alkynyl group having 2 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, or a heteroaryl group which may have a substituent.

When R^5 is an alkyl group, an alkenyl group, or an alkynyl group, the group may be linear or branched. The alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms. The alkenyl group may have one or more substituents selected from the group consisting of a halogen atom and an alkoxy group having 1 to 6 carbon atoms.

When R^5 is a halogen atom, the halogen atom is preferably a fluorine atom or a chlorine atom, and particularly preferably a fluorine atom.

When R^5 is an alkyl group having 1 to 6 carbon atoms, the alkyl group is preferably a methyl group, an ethyl group, a propyl group, or an isopropyl group. The alkyl group is more preferably a methyl group or an ethyl group, and particularly preferably a methyl group.

The alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms.

When a hydroxy group or an amino group is a substituent on the alkyl group, the substituent is preferably on the terminal carbon atom of the alkyl group. The alkyl group having a hydroxy group is preferably a hydroxymethyl group, a 2-hydroxyethyl group, a 2-hydroxypropyl group, or a 3-hydroxypropyl group. The alkyl group having an amino group is preferably an aminomethyl group, a 2-aminoethyl group, a 2-aminopropyl group, or a 3-aminopropyl group. The alkyl group having a hydroxy group or an amino group is preferably a methyl group or an ethyl group, and more preferably a hydroxymethyl group or an aminomethyl group having a hydroxy group or an amino group on the methyl group.

When the alkyl group has a halogen atom as a substituent, the alkyl group may be a linear or branched alkyl group having 1 to 6 carbon atoms, and is more preferably a methyl group or an ethyl group, and particularly preferably a methyl group. The halogen atom is preferably a fluorine atom. The alkyl group may be monofluoro-substituted to perfluoro-substituted. Examples

of the halogen-substituted alkyl group include a monofluoromethyl group, a difluoromethyl group, a trifluoromethyl group, and a 2,2,2-trifluoroethyl group. A monofluoromethyl group, a difluoromethyl group, or a trifluoromethyl group are particularly preferred.

When the alkyl group has an alkylthio group or an alkoxy group as a substituent, the alkyl group may be linear or branched and the alkyl moiety in the alkylthio group or alkoxy group may also be linear or branched. The alkyl group having an alkylthio group is preferably an alkylthiomethyl group or an alkylthioethyl group, and the alkylthio group preferably has 1 or 2 carbon atoms. More preferred examples of the alkyl group having an alkylthio group include a methylthiomethyl group, an ethylthiomethyl group, and a methylthioethyl group. The alkyl group having an alkoxy group is preferably an alkoxymethyl group or an alkoxyethyl group, and the alkoxy group preferably has 1 or 2 carbon atoms. More preferred examples of the alkyl group having an alkoxy group include a methoxymethyl group, an ethoxymethyl group, and a methoxyethyl group. Among these, a methylthio group and a methoxymethyl group are still more preferred.

When R^5 is an alkoxy group having 1 to 6 carbon atoms, the alkoxy group is preferably an alkoxy group having 1 to

3 carbon atoms, specifically, a methoxy group or an ethoxy group.

When R^5 is an alkenyl group having 2 to 6 carbon atoms, the alkenyl group preferably contains one double bond and there are no specific limitations to the position of the double bond. The alkenyl group is preferably a vinyl group, a propenyl group, or a butenyl group, and particularly preferably a vinyl group, for example.

The alkenyl group may have one or more substituents selected from the group consisting of a halogen atom and an alkoxy group having 1 to 6 carbon atoms.

The halogen atom is preferably a fluorine atom. When the alkenyl group has a halogen atom as a substituent, the alkenyl group is preferably an alkenyl group having 2 or 3 carbon atoms, more preferably a vinyl group having a fluorine atom, and particularly preferably a fluorovinyl group.

When the alkenyl group has an alkoxy group as a substituent, the alkenyl group preferably has 2 or 3 carbon atoms. Examples of the alkenyl group having an alkoxy group include an alkoxyvinyl group and an alkoxypropenyl group, specifically, a methoxyvinyl group and an ethoxyvinyl group. A methoxyvinyl group is particularly preferred.

When R^5 is an alkynyl group having 2 to 6 carbon atoms, the alkynyl group preferably contains one triple bond and

the triple bond may be at any position. The alkynyl group is preferably an ethynyl group, a propynyl group, or a butynyl group, and particularly preferably an ethynyl group.

When R^5 is a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, the cycloalkyl group is preferably a cyclopropyl group or a cyclobutyl group, and more preferably a cyclopropyl group.

The cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, a phenyl group, a halogen atom, an amino group, and a hydroxy group. Specifically, the substituent is preferably a methyl group, an ethyl group, a phenyl group, a fluorine atom, or a chlorine atom, and more preferably a methyl group or a fluorine atom.

When R^5 is an aryl group having 6 to 10 carbon atoms which may have a substituent or is a heteroaryl group which may have a substituent, the heteroaryl group is a five-membered ring or a six-membered ring and may contain 1 to 4 heteroatoms arbitrarily selected from a nitrogen atom, an oxygen atom, and a sulfur atom, and the aryl group or heteroaryl group may have one or more substituents selected from the group consisting of a halogen atom, an amino group, a hydroxy group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms,

an alkoxycarbonyl group having 2 to 6 carbon atoms, and an acyl group having 2 to 5 carbon atoms. The alkyl group, alkoxy group, alkoxycarbonyl group, or acyl group may have one or more substituents selected from the group consisting of a halogen atom, a hydroxy group, and an alkoxy group having 1 to 6 carbon atoms.

The substituent on the aryl group or heteroaryl group is preferably a halogen atom, an amino group, a hydroxy group, a cyano group, a carboxyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, or an alkoxycarbonyl group having 2 to 6 carbon atoms.

The halogen atom as a preferred substituent is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom.

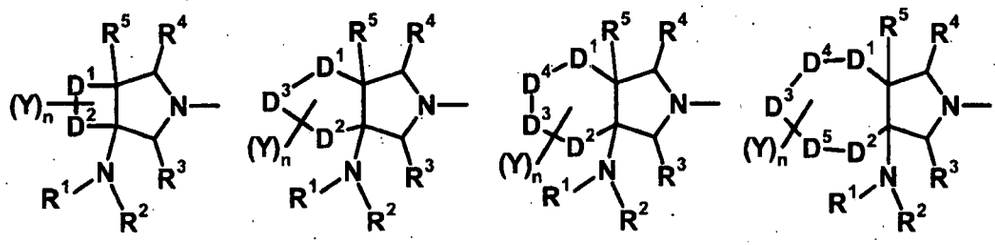
The alkyl group as a preferred substituent may be a linear or branched alkyl group having 1 to 6 carbon atoms and is for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, or a tert-butyl group, and preferably a methyl group or an ethyl group. The substituent on the alkyl group is preferably a halogen atom, and more preferably a fluorine atom. Examples of the halogen-substituted alkyl group include a fluoromethyl group and a trifluoromethyl group.

The alkoxy group as a preferred substituent is preferably an alkoxy group having 1 to 3 carbon atoms, specifically, a methoxy group or an ethoxy group, and particularly preferably a methoxy group. The substituent on the alkoxy group is preferably a halogen atom, and more preferably a fluorine atom. Examples of the halogen-substituted alkoxy group include a trifluoromethoxy group.

The alkoxycarbonyl group as a preferred substituent is preferably an alkoxycarbonyl group having up to 3 carbon atoms. Preferred examples of the alkoxycarbonyl group include a methoxycarbonyl group and an ethoxycarbonyl group. The substituent on the alkoxycarbonyl group is preferably a halogen atom, and more preferably a fluorine atom. Examples of the halogen-substituted alkoxycarbonyl group include a trifluoromethoxycarbonyl group.

R^6 and R^7 taken together with the carbon atoms to which they are bonded form a four- to seven-membered cyclic structure, the cyclic structure representing a partial structure that together with the pyrrolidine ring forms a fused cyclic (bicyclic) structure. The four- to seven-membered cyclic structure moiety formed in this manner may contain an oxygen atom or a sulfur atom as a ring constituent atom. Such fused cyclic amines are represented by the following formulas:

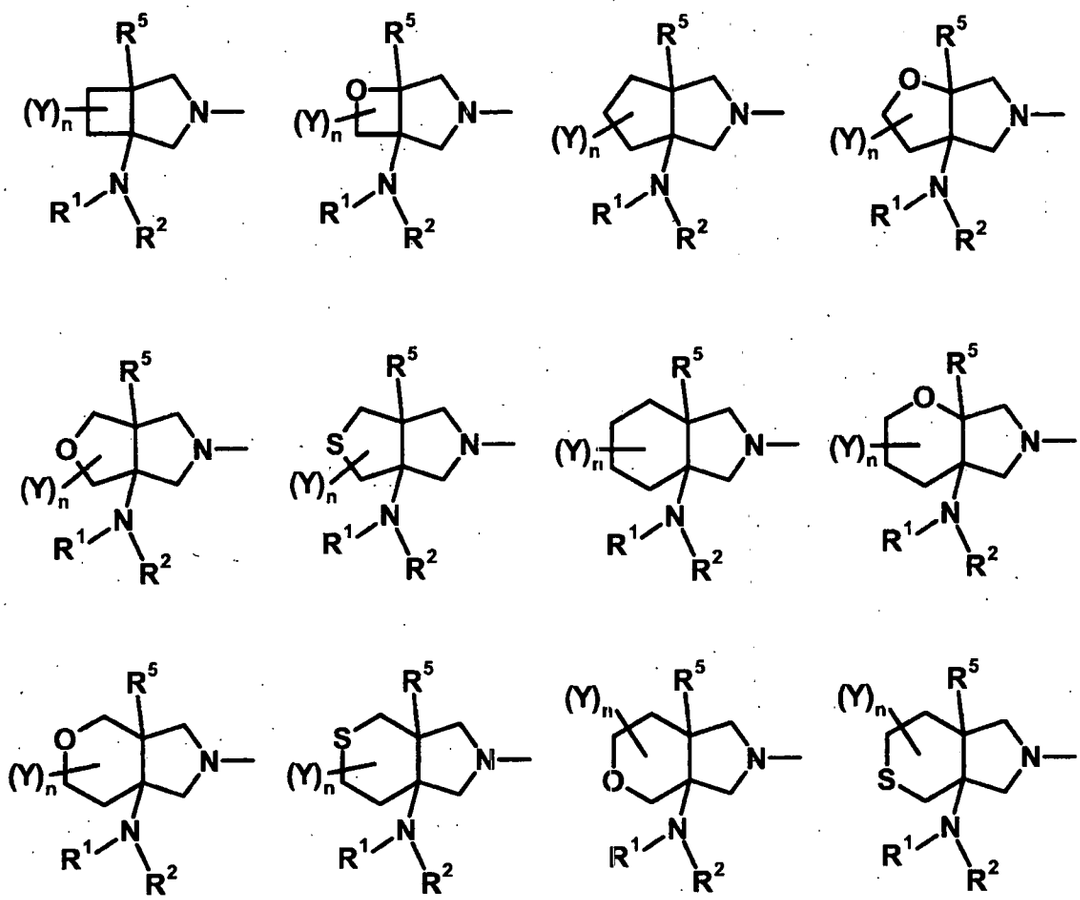
[Formula 21]



wherein R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1; D^1, D^2, D^3, D^4, and D^5 each represents a carbon atom which may have a substituent, an oxygen atom, or a sulfur atom, provided that when two or more of D^1, D^2, D^3, D^4 and D^5 are each an oxygen atom or a sulfur atom, no adjacent two of them are simultaneously oxygen atoms or sulfur atoms, and the sulfur atom may be an oxidized sulfur atom such as S=O or $S(=O)_2$; Y represents a substituent on the ring (described later); and n represents an integer of 0 to 3.

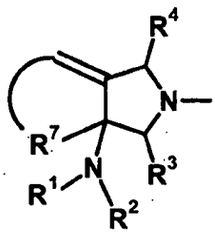
R^6 and R^7 form a four- to seven-membered cyclic structure when taken together with the carbon atoms to which they are bonded. Preferred examples of the fused cyclic amine are listed as follows:

[Formula 22]



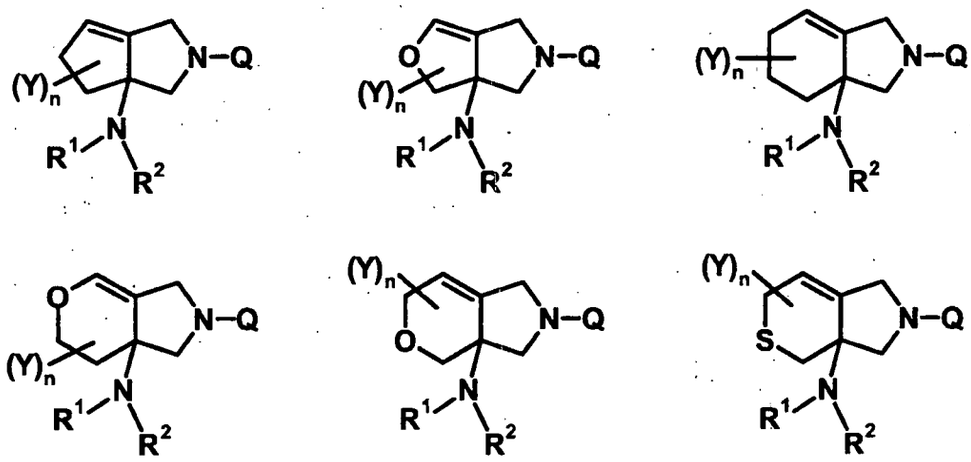
The four- to seven-membered cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded may contain a ring double bond formed as a constituent structure. When the cyclic structure contains the double bond as a constituent structure, part of R^6 (the carbon atom substituted on the pyrrolidine ring) and R^5 may be taken together to form a double bond partial structure that together with R^7 forms a five- to seven-membered cyclic structure represented by the following formula:

[Formula 23]



However, the double bond partial structure and R^7 preferably form a five- or six-membered cyclic structure. Preferred examples of the bicyclic amine are listed as follows:

[Formula 24]



The four- to seven-membered cyclic structure may have a substituent selected from the group consisting of an alkyl group having 1 to 6 carbon atoms which may have a substituent, an alkoxy group having 1 to 6 carbon atoms which may have a substituent, an alkenyl group having 2 to 6 carbon atoms which may have a substituent, an alkynyl group having 2 to 6 carbon atoms which may have a substituent, a cycloalkyl group having 3 to 6 carbon atoms

which may have a substituent, a heterocycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an exomethylene group which may have a substituent, a spiroalkyl group which may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, a heteroaryl group which may have a substituent, a halogen atom, a hydroxy group, a cyano group, a hydroxyimino group, and an alkoxyimino group having 1 to 6 carbon atoms which may have a substituent.

The alkyl group having 1 to 6 carbon atoms which may have a substituent may be linear or branched. Specific examples of the alkyl group include a methyl group, an ethyl group, a propyl group, an isopropyl group, a tert-butyl group, a fluoromethyl group, a trifluoromethyl group, a 2-fluoroethyl group, a 2,2,2-trifluoroethyl group, a fluorine-substituted tert-butyl group, a hydroxymethyl group, a 2-hydroxyethyl group, a 2-cyanoethyl group, a methoxymethyl group, and a 2-methoxyethyl group. The alkyl group is preferably a methyl group, an ethyl group, an isopropyl group, a fluoromethyl group, a 2-cyanoethyl group, or a methoxymethyl group.

The alkoxy group having 1 to 6 carbon atoms which may have a substituent may be an alkoxy group derived from the aforementioned alkyl group, and is preferably an alkoxy

group having 1 to 3 carbon atoms, specifically, a methoxy group or an ethoxy group.

The alkenyl group having 2 to 6 carbon atoms which may have a substituent preferably contains one double bond and the position of the double bond is not limited. The alkenyl group is preferably a vinyl group, a propenyl group, or a butenyl group. The substituent on the alkenyl group is preferably a halogen atom or an alkoxy group, and the halogen atom is preferably a fluorine atom. Examples of the substituted alkenyl group include a fluorovinyl group and a methoxyvinyl group.

The alkynyl group having 2 to 6 carbon atoms which may have a substituent preferably contains one triple bond and the triple bond may be at any position. The alkynyl group is preferably an ethynyl group, a propynyl group, or a butynyl group. Preferably, the alkynyl group does not have a substituent other than a hydrogen atom.

The cycloalkyl group having 3 to 6 carbon atoms which may have a substituent is preferably a cyclopropyl group or a cyclobutyl group. The cycloalkyl group may be substituted with one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, a halogen atom, an amino group, and a hydroxy group. Specifically, the substituent is preferably a methyl group, an ethyl group, a fluorine atom, or a chlorine atom.

The heterocycloalkyl group having 3 to 6 carbon atoms which may have a substituent is preferably an oxetan-3-yl group, a thioxetan-3-yl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, or a 2,2-dimethyl-1,3-dioxan-4-yl group.

The exomethylene group which may have a substituent is preferably one that does not have a substituent other than a hydrogen atom. The substituent other than a hydrogen atom is preferably an amino group, a fluorine atom, a chlorine atom, a methylthio group, or a methoxy group.

The spiroalkyl group which may have a substituent is preferably a spirocyclopropyl group or a spirocyclobutyl group. The spiroalkyl group is composed of an alicyclic component and forms a spiro cyclic ring system. The spirocycloalkyl group may be substituted with one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, a halogen atom, an amino group, and a hydroxy group. Specifically, the substituent is preferably a methyl group, an ethyl group, a fluorine atom, or a chlorine atom.

When the substituent on the four- to seven-membered cyclic structure is an aryl group having 6 to 10 carbon atoms which may have a substituent or is a heteroaryl group which may have a substituent, the heteroaryl group is a five- or six-membered ring and may contain 1 to 4

heteroatoms arbitrarily selected from a nitrogen atom, an oxygen atom, and a sulfur atom. The aryl group or heteroaryl group may have one or more substituents selected from the group consisting of a halogen atom, an amino group, a hydroxy group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, an alkoxycarbonyl group having 2 to 6 carbon atoms, and an acyl group having 2 to 5 carbon atoms (i.e. alkyl carbonyl group of 2 to 5 carbon atoms). The alkyl group, alkoxy group, alkoxycarbonyl group, or acyl group may have one or more substituents selected from the group consisting of a halogen atom, a hydroxy group, and an alkoxy group having 1 to 6 carbon atoms. The substituent on the aryl group or heteroaryl group is preferably a halogen atom, an amino group, a hydroxy group, a cyano group, a carboxyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, or an alkoxycarbonyl group having 2 to 6 carbon atoms. Particularly preferred substituents on the aryl group or heteroaryl group include a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a methoxy group, an ethoxy group, a methoxycarbonyl group, and an ethoxycarbonyl group.

When the substituent is a halogen atom, the halogen atom is preferably a fluorine atom or a chlorine atom, and particularly preferably a fluorine atom.

Preferred examples of the alkoxyimino group having 1 to 6 carbon atoms which may have a substituent include a methoxyimino group and an ethoxyimino group.

Preferred examples of the aforementioned substituent include a methyl group, an ethyl group, a fluoromethyl group, a 2-fluoroethyl group, a methoxymethyl group, a cyanoethyl group, a methoxy group, a cyclopropyl group, a spirocyclopropyl group, a phenyl group, an oxazole group, a fluorine atom, a hydroxy group, a hydroxyimino group, and a methoxyimino group. Among these, a methyl group, a fluoromethyl group, a methoxymethyl group, a methoxy group, a fluorine atom, a cyanoethyl group, and a methoxyimino group are particularly preferred.

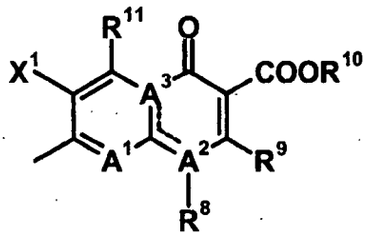
The polymethylene chain which binds to form a spirocyclic ring system is preferably one of 2 or 3 carbon atoms, and still preferably one having 2 carbon atoms.

R^5 may be a methylene group taken together with R^6 to form a three-membered fused cyclic structure, and this cyclic structure makes the fused bicyclic structure formed by combining R^6 and R^7 into a tri-cyclic ring system. Moreover, the third ring system derived from R^5 and R^6 may locate in another part of the fused bicyclic ring system

derived from R^6 and R^7. In other words, the fused bicyclic substituent at 7-position may become a tri-cyclic ring system by incorporating a cyclopropan ring on any part of the bicyclic ring structure.

Q represents a partial structure represented by the following formula:

[Formula 25]



wherein A^2 and A^3 each represents a nitrogen atom or a carbon atom, and A^1, A^2, A^3, R^8 and the carbon atom to which A^2 and A^3 are bonded together form a partial structure:

>C=C(-A^1=)-N(-R^8)-

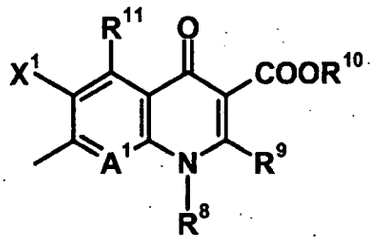
or a partial structure:

>N-C(-A^1=)=C(-R^8)-

wherein ">" means that there are two bonds to a nitrogen atom or a carbon atom (hereinafter the same).

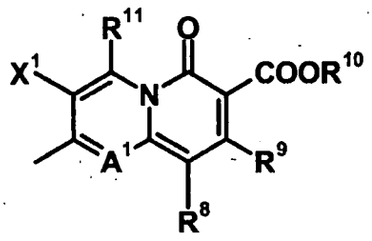
Q preferably represents a fused heterocyclic system partial structure represented by the formula:

[Formula 26]



or the formula:

[Formula 27]



wherein R^8 represents an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, a halogen-substituted alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, a halogen-substituted phenyl group which may have a substituent, a halogen-substituted heteroaryl group which may have a substituent, an alkoxy group having 1 to 6 carbon atoms, or an alkylamino group having 1 to 6 carbon atoms.

When R^8 is an alkyl group having 1 to 6 carbon atoms, the alkyl group may be linear or branched. Specific examples of the alkyl group include a methyl group, an ethyl group, an isopropyl group, a sec-butyl group, and a tert-butyl group. Among these, an ethyl group and a tert-butyl group are preferred.

When R^8 is an alkenyl group having 2 to 6 carbon atoms, the alkenyl group may be linear or branched. Preferred specific examples of the alkenyl group include a vinyl group and an isopropenyl group.

When R^8 is a halogen-substituted alkyl group having 1 to 6 carbon atoms, the alkyl moiety may be linear or branched. Specific examples of the alkyl moiety include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, and a tert-butyl group. Among these, an ethyl group and a tert-butyl group are preferred. The halogen atom substituent on the alkyl group is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom. Examples of the halogen-substituted alkyl group include a fluoromethyl group, a trifluoromethyl group, a 1-fluoroethyl group, a 2-fluoroethyl group, a 2,2,2-trifluoroethyl group, a 1,1-dimethyl-2-fluoroethyl group, a 1-methyl-1-(fluoromethyl)-2-fluoroethyl group, and a 1,1-(difluoromethyl)-2-fluoroethyl group. Among these, a 2-fluoroethyl group and a 1,1-dimethyl-2-fluoroethyl group are preferred.

When R^8 is a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, examples of the cycloalkyl group include a cyclopropyl group, a cyclobutyl group, and a cyclopentyl group. Among these, a cyclopropyl

group is preferred. The substituent on the cycloalkyl group is preferably a halogen atom, a methyl group, or a phenyl group, and more preferably a halogen atom. The halogen atom is preferably a fluorine atom or a chlorine atom, and particularly preferably a fluorine atom. The number of substituents may be 1 or 2 but is preferably 1. Specifically, the cycloalkyl group which may have a substituent is preferably a monofluorocyclopropyl group, more preferably a 1,2-cis-2-fluorocyclopropyl group, and particularly preferably a (1R,2S)-2-fluorocyclopropyl group.

When R^8 is a halogen-substituted phenyl group which may have a substituent, the halogen atom is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom. The number of halogen atom substituents is preferably 1 or 2. The substituent on the halogen-substituted phenyl group is preferably an amino group, a hydroxy group, or a methyl group. Examples of the halogen-substituted phenyl group which may have a substituent include a 2-fluorophenyl group, a 4-fluorophenyl group, a 2,4-fluorophenyl group, and a 5-amino-2,4-difluorophenyl group. Among these, a 2,4-difluorophenyl group and a 5-amino-2,4-difluorophenyl group are preferred.

When R^8 is a halogen-substituted heteroaryl group which may have a substituent, the heteroaryl group may be a five- or six-membered aromatic heterocyclic group containing one

or more heteroatoms selected from a nitrogen atom, a sulfur atom, and an oxygen atom. Such a heteroaryl group is preferably a five- or six-membered nitrogen-containing aromatic heterocyclic group containing 1 or 2 nitrogen atoms. Specific examples of the heteroaryl group include a pyridyl group, a pyrimidyl group, a pyridazinyl group, an imidazolyl group, a thiazolyl group, and an oxazolyl group. Among these, a pyridyl group is preferred. The halogen atom is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom. The number of halogen atoms is preferably 1 or 2. Preferred examples of the substituent on the halogen-substituted heteroaryl group include an amino group, a hydroxy group, and a methyl group. Such a halogen-substituted heteroaryl group which may have a substituent is preferably a 6-amino-3,5-difluoropyridin-2-yl group.

When R^8 is an alkoxy group having 1 to 6 carbon atoms, the alkoxy group is preferably a methoxy group.

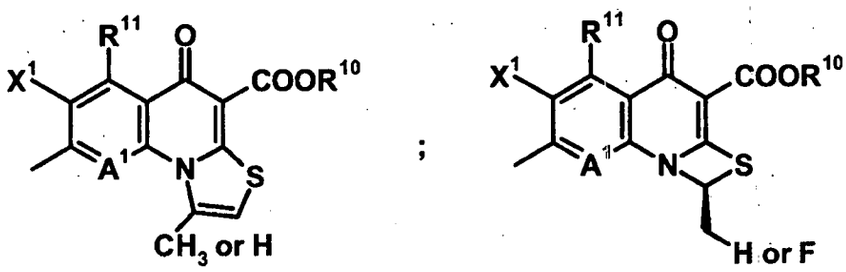
When R^8 is an alkylamino group having 1 to 6 carbon atoms, the alkylamino group is preferably a methylamino group.

The aforementioned R^8 is preferably a cyclopropyl group or a 1,2-cis-2-fluorocyclopropyl group, and more preferably a (1R,2S)-2-fluorocyclopropyl group.

R^9 represents a hydrogen atom or an alkylthio group having 1 to 6 carbon atoms. R^9 and the aforementioned R^8

may be taken together with part of the mother skeleton (including the carbon atom to which R^9 is bonded and A^2; hereinafter the same) to form a cyclic structure. The ring formed in this manner may contain a sulfur atom as a ring constituent atom, and may have an alkyl group having 1 to 6 carbon atoms or a halogen-substituted alkyl group having 1 to 6 carbon atoms as a substituent. The ring formed here may be a four- to six-membered ring and may be saturated, partially saturated, or unsaturated. The fused ring structure formed in this manner may be represented by the following formulas:

[Formula 28]



R^{10} represents a hydrogen atom, a phenyl group, an acetoxymethyl group, a pivaloyloxymethyl group, an ethoxycarbonyl group, a choline group, a dimethylaminoethyl group, a 5-indanyl group, a phthalidinyl group, a 5-alkyl-2-oxobutyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxymethyl group having 2 to 7 carbon atoms, or a phenylalkyl group formed by an alkylene group having 1 to 6 carbon atoms and a phenyl group.

R^{10} is preferably a hydrogen atom.

R^{11} represents a hydrogen atom, an amino group, a hydroxy group, a thiol group, a halogenomethyl group, or an alkyl group having 1 to 6 carbon atoms. The amino group may have one or two substituents selected from the group consisting of a formyl group, an alkyl group having 1 to 6 carbon atoms, and an acyl group having 2 to 5 carbon atoms.

When R^{11} is an alkyl group having 1 to 6 carbon atoms, the alkyl group may be linear or branched and is preferably a methyl group, an ethyl group, a propyl group, or an isopropyl group, and particularly preferably a methyl group.

When R^{11} is a halogenomethyl group, the halogen atom is preferably a fluorine atom and the number of halogen atoms may be 1 to 3.

When R^{11} is an amino group, a hydroxy group, or a thiol group, the group may be protected by a protecting group ordinarily used.

Examples of such a protecting group include (substituted) alkoxycarbonyl groups such as a tert-butoxycarbonyl group and a 2,2,2-trichloroethoxycarbonyl group; (substituted) aralkyloxycarbonyl groups such as a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, and a p-nitrobenzyloxycarbonyl group; (substituted) acyl groups such as an acetyl group, a methoxyacetyl group, a trifluoroacetyl group, a chloroacetyl group, a pivaloyl

group, a formyl group, and a benzoyl group; (substituted) alkyl groups or (substituted) aralkyl groups such as a tert-butyl group, a benzyl group, a p-nitrobenzyl group, a p-methoxybenzyl group, and a triphenylmethyl group; (substituted) ethers such as a methoxymethyl group, a tert-butoxymethyl group, a tetrahydropyranyl group, and a 2,2,2-trichloroethoxymethyl group; and (alkyl- and/or aralkyl-)substituted silyl groups such as a trimethylsilyl group, an isopropyldimethylsilyl group, and a tert-butyldiphenylsilyl group. A compound having a substituent protected by such a protecting group is particularly preferable as a production intermediate.

Among the aforementioned examples, R^{11} is preferably a hydrogen atom, an amino group, a hydroxy group, or a methyl group, and particularly preferably a hydrogen atom or an amino group.

X^1 represents a halogen atom or a hydrogen atom. The halogen atom is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom. X^1 is preferably a fluorine atom or a hydrogen atom.

A^1 represents a nitrogen atom or a partial structure represented by the formula (III):

[Formula 29]



III

wherein X^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, a cyano group, a halogen atom, a halogeno-substituted methyl group, or a halogenomethoxy group, the X^2 and the R^8 may be taken together with their connecting part of the mother skeleton (including the carbon atom to which X^2 is bonded and A^2) to form a cyclic structure, the ring formed in this manner may contain an oxygen atom, a nitrogen atom, or a sulfur atom as a ring constituent atom, and the ring may be substituted with an alkyl group having 1 to 6 carbon atoms which may have a substituent.

When A^1 is a partial structure represented by the formula (III) and X^2 is an alkyl group having 1 to 6 carbon atoms, the alkyl group may be linear or branched, and is preferably a methyl group, an ethyl group, a propyl group, or an isopropyl group, more preferably a methyl group or an ethyl group, and still more preferably a methyl group.

When X^2 is an alkoxy group having 1 to 6 carbon atoms, the alkoxy group may be an alkoxy group derived from the aforementioned alkyl group. The alkoxy group is preferably an alkoxy group having 1 to 3 carbon atoms, and particularly preferably a methoxy group.

When X^2 is a halogen atom, the halogen atom is preferably a fluorine atom or a chlorine atom. When the aforementioned R^{11} is a hydrogen atom, X^2 is preferably a

chlorine atom; when the R^{11} is an amino group, a hydroxy group, or a methyl group, X^2 is preferably a fluorine atom.

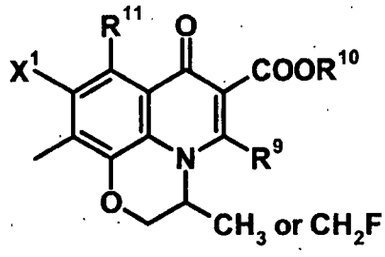
When X^2 is a halogeno-substituted methyl group, the halogen atom is preferably a fluorine atom. Preferred examples of the halogeno-substituted methyl group include a fluoromethyl group, a difluoromethyl group, and a trifluoromethyl group.

When X^2 is a halogenomethoxy group, the halogen atom is preferably a fluorine atom as in the aforementioned case. Specific examples of the halogenomethoxy group include a fluoromethoxy group, a difluoromethoxy group, and a trifluoromethoxy group. Among these, a difluoromethoxy group is more preferred.

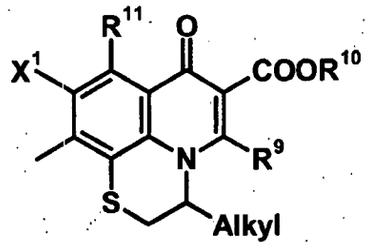
When A^1 is a partial structure represented by the formula (III), X^2 and R^8 may form a cyclic structure including part of the quinolone skeleton [the carbon atom to which X^2 is bonded, A^2 to which R^8 is bonded (where A^2 is a nitrogen atom or a carbon atom), and the skeleton ring carbon atom to which the carbon atom and the A^2 are bonded]. The ring formed here is preferably a five- to seven-membered ring and may be saturated or unsaturated. The cyclic structure may contain an oxygen atom, a nitrogen atom, or a sulfur atom and may be substituted with an alkyl group having 1 to 6 carbon atoms or a halogenomethyl group

described for X^2. The fused ring structure formed in this manner may be represented by the following formulas:

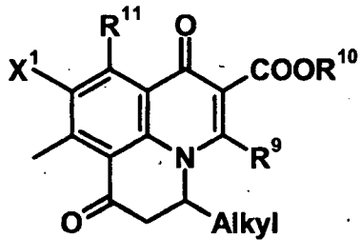
[Formula 30]



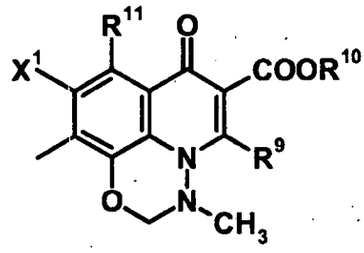
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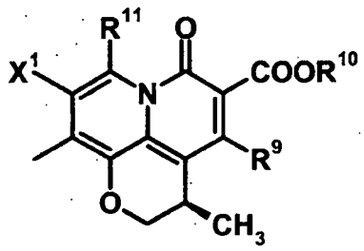
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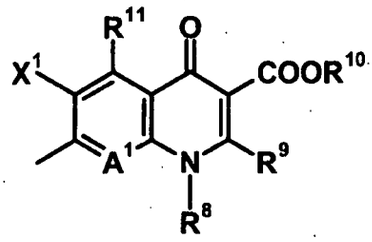


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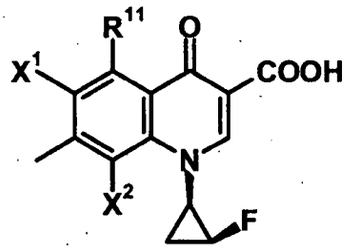
When A^1 is a partial structure represented by the formula (III) and the substituent X^2 does not form a cyclic structure, X^2 is preferably a methyl group, an ethyl group, a methoxy group, a difluoromethoxy group, a cyano group, or a chlorine atom, and particularly preferably a methyl group, a methoxy group, a difluoromethoxy group, or a cyano group. Such a substituent is particularly preferred when A is a partial structure represented by the following formula:

[Formula 31]



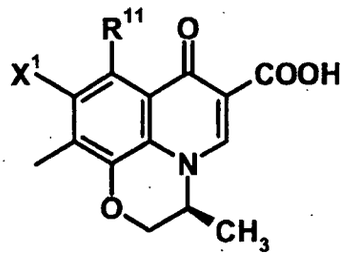
Moreover, such a substituent is more particularly preferred when Q is a partial structure 1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid skeleton represented by the following formula:

[Formula 32]



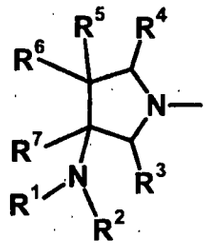
When A^1 is a partial structure represented by the formula (III) and the substituent X^2 forms a cyclic structure, a 2,3-dihydro-3-methyl (or fluoromethyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid skeleton is preferably formed. A 3-(S)-methylpyridobenzoxazine skeleton represented by the following formula (the compound of Y^0 is methyl) is particularly preferred:

[Formula 33]



The compound of the present invention is characterized by having a substituent of a structure represented by the following formula at the 7-position of the quinolone skeleton (or its corresponding position):

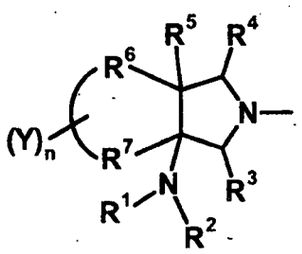
[Formula 34]



Specifically, the substituent of the compound of the present invention has an amino group at a position corresponding to the 3-position of the pyrrolidinyl group, and the substituent R^7 on the carbon atom substituted with the amino group and the substituent R^6 at a position corresponding to the 4-position of the pyrrolidinyl group are taken together with the carbon atoms to which they are bonded to form a four- to seven-membered cyclic structure. That is, the substituent of the compound of the present invention is a fused substituted aminopyrrolidine structure, in which the cyclic structure together with the pyrrolidine

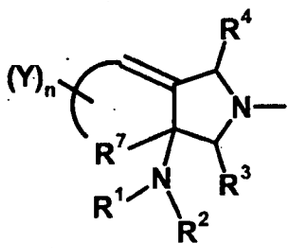
ring forms a fused cyclic (bicyclic) structure represented by the following formula, in which the fused cyclic structure is substituted with an amino group at the bridgehead position as follows:

[Formula 35]



Further, the substituent of the compound of the present invention has a cyclic structure represented by the following formula, in which the cyclic structure formed by taking the substituents R^6 and R^7 together with the carbon atoms to which they are bonded is a five- or six-membered ring, and R^5 and R^6 are taken together to form a double bond partial structure as follows:

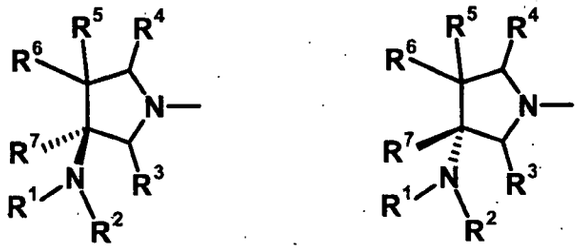
[Formula 36]



The bicyclic amino group contains an asymmetric carbon atom and stereoisomerism (optical isomerism) occurs. This stereoisomerism will now be described. Further, there are

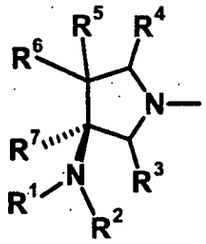
the following two kinds with regard to the bridgehead position substituted with an amino group:

[Formula 37]



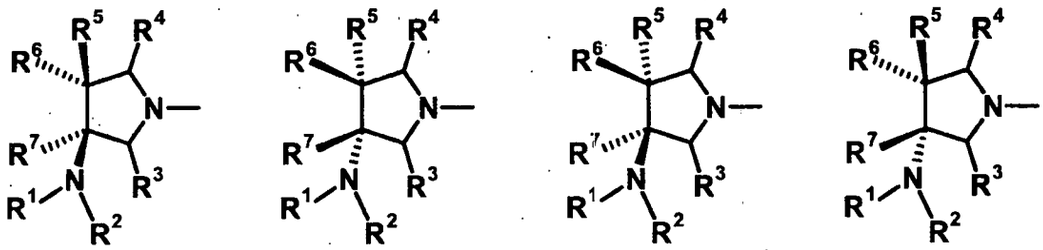
Here, the following structure where the amino group is in the β-configuration is preferred:

[Formula 38]



Further, when the substituents R^5 and R^6 are not taken together to form a double bond, there are the following four kinds with regard to the asymmetric carbon atom substituted with R^5:

[Formula 39]



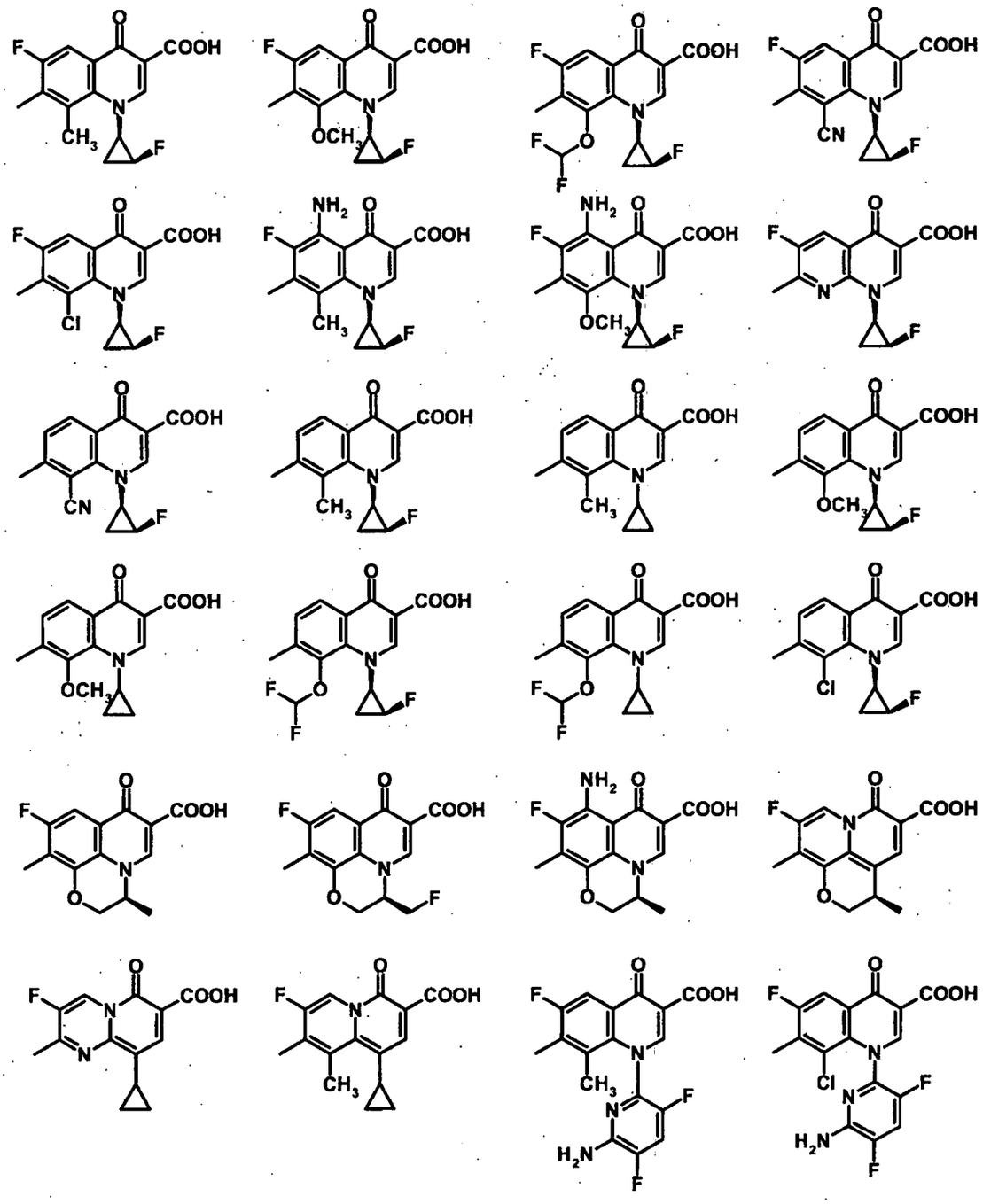
1 2 3 4

Typically, the structure 1 is more preferred than the

structure 2 and the structure 3 is more preferred than the structure 4; however, which structure is preferred depends on the structure of the substituent R^5. Typically, the structure 1 is more preferred than the structure 3 when the substituents R^6 and R^7 form a four-membered ring, and the structure 3 is more preferred than the structure 1 when the substituents R^6 and R^7 form a six-membered ring; however, which structure is preferred depends on the size of the ring formed by the substituents R^6 and R^7. The present invention includes all of the aforementioned types.

Preferred mother skeletons are listed below taking, as an example, a quinolonecarboxylic acid (or pyridobenzoxazinecarboxylic acid) basic skeleton having the aforementioned substituent at the 7-position (or its corresponding position):

[Formula 40]



Preferred examples of the substituent at the 7-position (or its corresponding position) are listed below:

a (1R,5S)-1-amino-5-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S,6R)-1-amino-6-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S,6S)-1-amino-6-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S)-1-amino-6,6-difluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6R)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6R)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6S)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a spiro[(1S,5S)-1-amino-3-azabicyclo[3.2.0]heptane-6,1'-cyclopropan]-3-yl group;

a (1S,5R)-1-amino-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[3.3.0]octan-3-yl group;

a (1R,5S)-1-amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1R,5R)-1-amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,6S)-1-amino-6-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R)-1-amino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,7S)-1-amino-7-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,7R)-1-amino-7-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl group;

a (1S,5R)-1-amino-7-methyl-3-azabicyclo[3.3.0]oct-7-en-3-yl group;

a (1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl group;

a (1S)-1-amino-6-methyl-3-azabicyclo[3.3.0]oct-5-en-3-yl group;

a (1R,5R)-1-amino-3-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5S)-1-amino-3-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5R)-1-amino-4-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5S)-1-amino-4-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a 6-amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonan-8-yl group;

a (1S,5R)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]non-7-en-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]non-8-en-3-yl group;

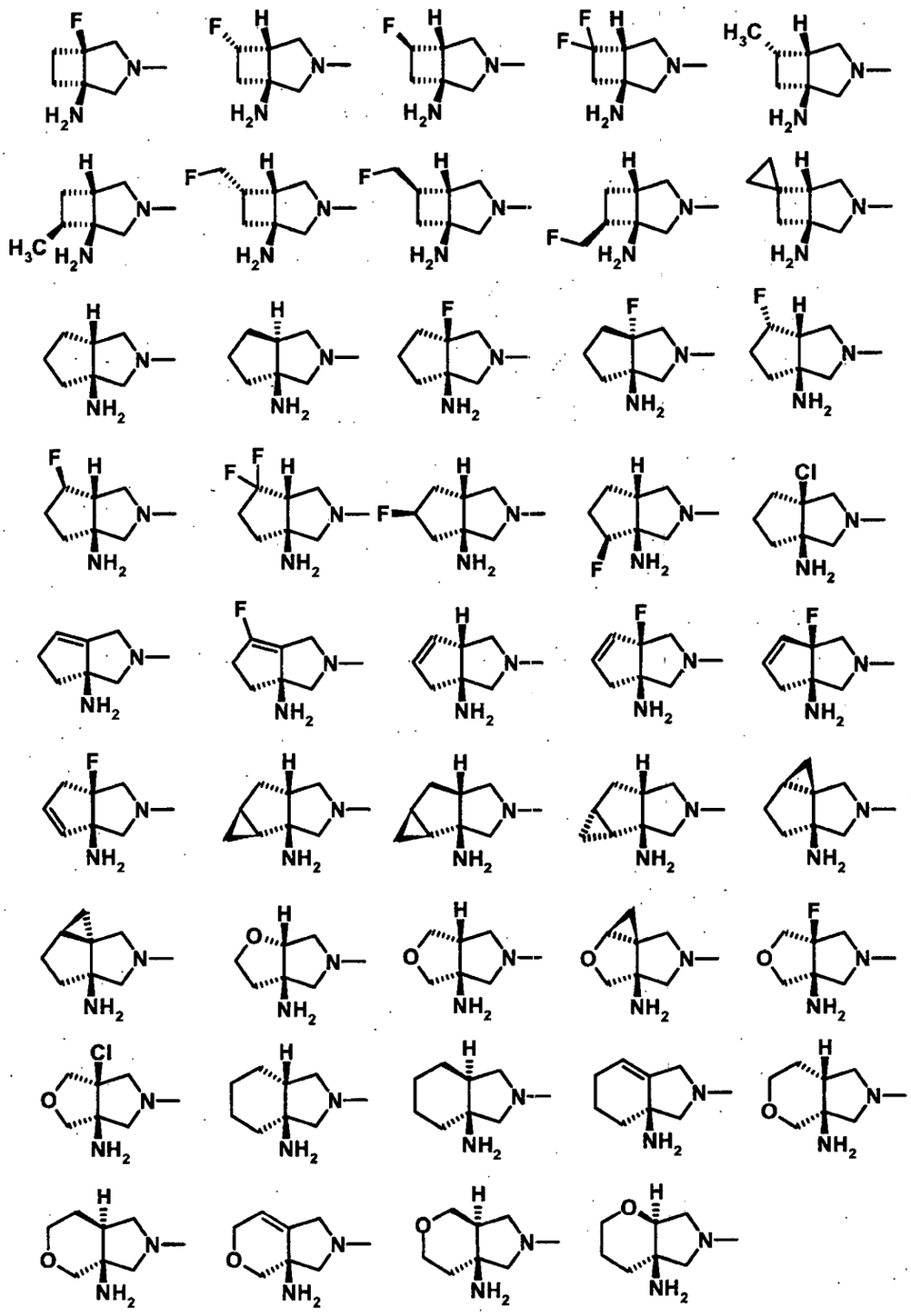
a (1S)-1-amino-3-azabicyclo[4.3.0]non-5-en-3-yl group;

a (1R,6S)-1-amino-5-oxa-8-azabicyclo[4.3.0]nonan-8-yl group;

a (1S,6S)-1-amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl group; and

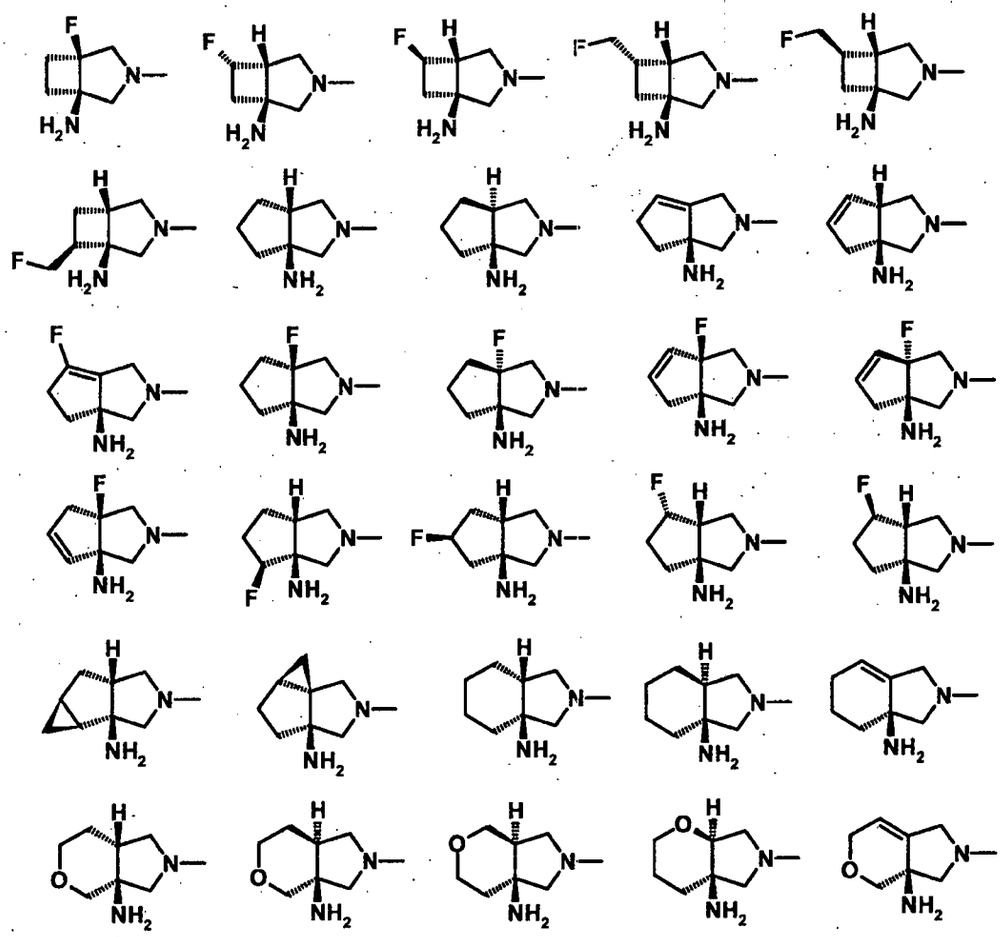
a (1S,6S)-1-amino-3-oxa-8-azabicyclo[4.3.0]nonan-8-yl group.

[Formula 41]



And still more preferred examples of the substituent at the 7-position (or its corresponding position) are listed below:

[Formula 42]



Accordingly, preferred compounds of the present invention are compounds each having the above-exemplified quinolonecarboxylic skeleton substituted with the above-exemplified 7-position substituent (a combination of the exemplified mother skeleton with the exemplified substituent). In the above formulas, the configuration of

the 3-position (or its corresponding position) substituted with an amino group on the pyrrolidine ring is preferably the β-configuration. The absolute configuration of the 3-position (or its corresponding position) may be 3S or 3R according to the type of the 4-position substituent. The compounds of the present invention are preferably stereochemically single.

Preferred examples of the compounds of the present invention, which may be in a form of salts or hydrates are as follows:

7-[(1S,5R,6R)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5R,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

10-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-chlorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-chlorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-5-methyl-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

10-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

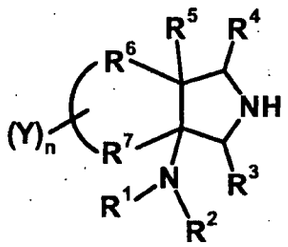
7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,6S)-1-amino-8-aza-3-oxa-bicyclo[4.3.0]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid.

Next, the substituent at the 7-position of the quinolone skeleton (or its corresponding position) in relation to the compound of the present invention will be described. Specifically, the substituent has an amino group at a position corresponding to the 3-position of the pyrrolidinyl group, and the substituent R^7 on the carbon atom substituted with the amino group and the substituent R^6

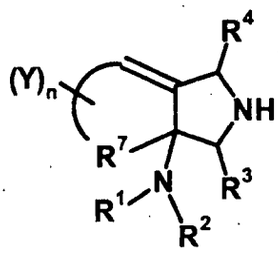
at a position corresponding to the 4-position of the pyrrolidinyl group are taken together with the carbon atoms to which they are bonded to form a four- to seven-membered cyclic structure. More specifically, the substituent is a fused substituted aminopyrrolidine derivative, in which the cyclic structure together with the pyrrolidine ring forms a fused cyclic (bicyclic) structure represented by the following formula, in which the fused cyclic structure is substituted with an amino group at the bridgehead position:

[Formula 43]



Further, the substituent is a fused substituted aminopyrrolidinyl substituent having a cyclic structure represented by the following formula, in which the cyclic structure formed by taking the substituents R^6 and R^7 together with the carbon atoms to which they are bonded is a five- or six-membered ring, and R^5 and R^6 are taken together to form a double bond partial structure:

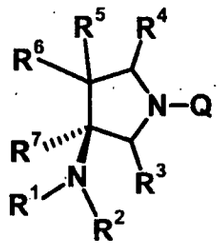
[Formula 44]



Preferred compounds of the present invention, which may be in the form of a salt or a hydrate are exemplified as follows:

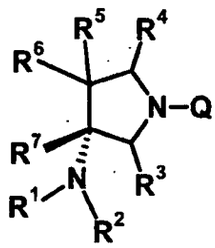
[1] The compound represented by the formula (I) wherein it is a compound represented by the following formula:

[Formula 45]



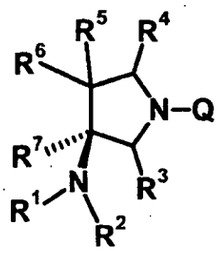
or the following formula:

[Formula 46]



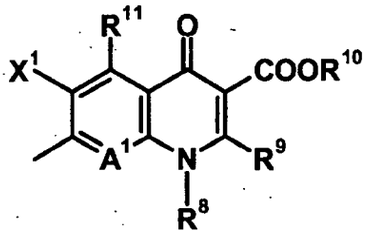
[2] The compound represented by the formula (I) wherein it is a compound represented by the following formula:

[Formula 47]



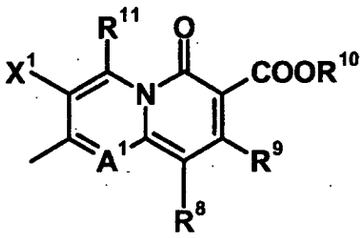
[3] The compound, wherein Q represented by the formula (II) in the compound represented by the formula (I) has a structure represented by the following formula:

[Formula 48]



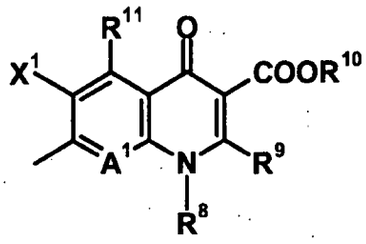
or the following formula:

[Formula 49]



[4] The compound, wherein Q represented by the formula (II) in the compound represented by the formula (I) has a structure represented by the following formula:

[Formula 50]



[5] The compound, wherein R^1 and R^2 in the formula (I) are each a hydrogen atom.

[6] The compound, wherein one of R^1 and R^2 in the formula (I) is a hydrogen atom and the other is a substituent selected from a methyl group, an ethyl group, an isopropyl group, a fluoroethyl group, a cyanoethyl group, a cyclopropyl group, and a cyclobutyl group.

[7] The compound, wherein R^3 and R^4 in the formula (I) are each a hydrogen atom.

[8] The compound, wherein R^5 in the formula (I) is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, an isopropyl group, a cyclopropyl group, a fluoromethyl group, a fluoroethyl group, a trifluoromethyl group, a methoxymethyl group, a vinyl group, an ethynyl group, a methoxy group, a phenyl group, or an oxazol-2-yl group.

[9] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a four-membered ring which may be substituted by one or more substituents.

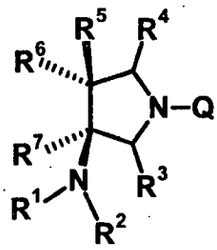
[10] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring which may be substituted by one or more substituents.

[11] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring containing a double bond as a constituent structure which may be substituted by one or more substituents.

[12] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring containing an oxygen atom as a constituent atom which may be substituted by one or more substituents.

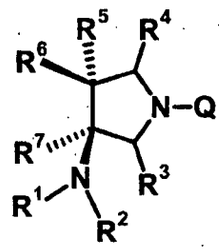
[13] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring and is fused with the pyrrolidine ring to form a cis-fused bicyclic structure represented by the following formula:

[Formula 51]



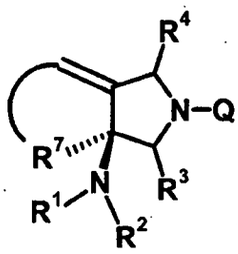
[14] The compound, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring and is fused with the pyrrolidine ring to form a trans-fused bicyclic structure represented by the following formula:

[Formula 52]



[15] The compound, wherein in the formula (I), the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded is a five- or six-membered ring, R^5 and R^6 are taken together to form a double bond partial structure, and the resulting cyclic structure is represented by the following formula:

[Formula 53]



[16] The compound, wherein X^1 is a hydrogen atom or a fluorine atom in the partial structure Q in the formula (I) represented by the formula (II).

[17] The compound, wherein X^1 is a fluorine atom in the partial structure Q in the formula (I) represented by the formula (II).

[18] The compound, wherein A^1 is a nitrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

[19] The compound, wherein A^1 is a partial structure represented by the formula (III) in the partial structure Q in the formula (I) represented by the formula (II).

[20] The compound, wherein X^2 in the formula (III) is a methyl group, an ethyl group, a methoxy group, a difluoromethoxy group, a cyano group, or a chlorine atom.

[21] The compound, wherein X^2 in the formula (III) is a methyl group or a methoxy group.

[22] The compound, wherein R^8 is a 1,2-cis-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

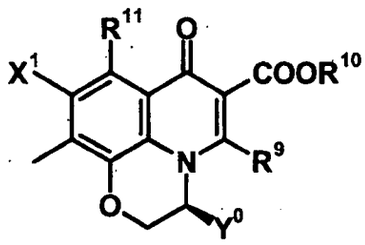
[23] The compound, wherein R^8 is a stereochemically single 1,2-cis-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

[24] The compound, wherein the 1,2-cis-2-halogenocyclopropyl group of R^8 is a (1R,2S)-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

[25] The compound, wherein the (1R,2S)-2-halogenocyclopropyl group of R^8 is a (1R,2S)-2-fluorocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

[26] The compound, wherein Q in the compound represented by the formula (I) is a compound represented by the following formula:

[Formula 54]

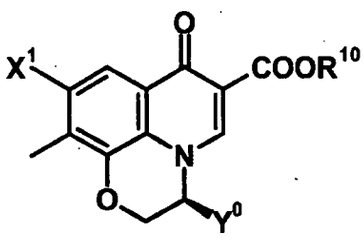


wherein Y^0 is a methyl group or a fluoromethyl group.

[27] The compound, wherein R^9 is a hydrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

[28] The compound, wherein Q in the compound represented by the formula (I) is a compound represented by the following formula (IV):

[Formula 55]



IV

wherein Y^0 is a methyl group or a fluoromethyl group.

[29] The compound, wherein Y^0 in the formula (IV) is a methyl group.

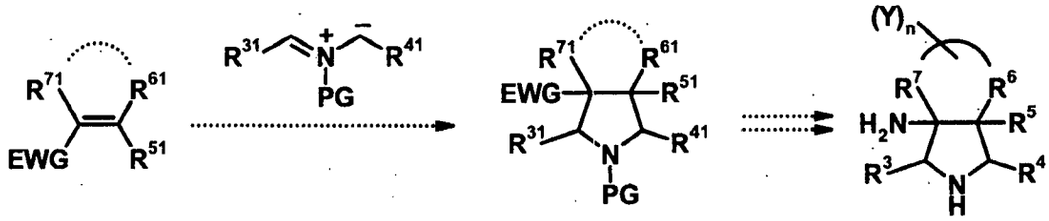
[30] The compound, wherein R^{10} is a hydrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

[31] The compound, wherein the compound represented by the formula (I) is a stereochemically single compound.

Synthesis of a pyrrolidine compound necessary for introducing the substituent into the quinolone mother skeleton will be described below. There are several possible methods for synthesizing the fused substituted aminopyrrolidine derivative. Several examples of representative synthesis methods carried out by the present inventors will be summarized below (the details are described in reference examples in the section "Examples"). However, the method for synthesizing the fused substituted aminopyrrolidine derivative of the present invention is not limited thereto.

The present inventors have synthesized an important synthetic intermediate using the 1,3-dipolar cycloaddition reaction represented by the following scheme, with a β-electron-withdrawing group-substituted α,β-unsaturated cyclic or non-cyclic compound and an azomethine ylide as reactive elements, and synthesized fused substituted aminopyrrolidine derivatives through appropriate reaction steps:

[Formula 56]



In this scheme, EWG is an electron-withdrawing group;

PG is an amino-protecting group; R^{31}, R^{41}, R^{51}, R^{61}, and R^{71} are each a hydrogen atom or a substituent appropriate for the intermediate; and R^3, R^4, R^5, R^6, R^7, Y, and n are as defined above.

The β-electron-withdrawing group-substituted α,β-unsaturated compound used in this reaction may be cyclic or non-cyclic. The bicyclic pyrrolidine derivatives can be synthesized from cyclic compounds in one step. Non-cyclic compounds can be converted to the bicyclic pyrrolidine derivatives by subjecting an appropriate synthetic intermediate to an appropriate cyclization or ring-closing reaction such as carbon-carbon bond formation reaction or carbon-oxygen (or sulfur) bond formation reaction by nucleophilic reaction of a carbanion; ether (or thioether) ring formation reaction by intramolecular Mitsunobu reaction; cyclic esterification or cyclic amidation which is called lactone or lactam formation reaction; intramolecular condensation ring-closing reaction such as aldol condensation, Dieckmann condensation, acyloin condensation, Wittig condensation, or Reformatsky reaction; ring-closing metathesis reaction (RCM); Diels-Alder reaction; deoxygenation coupling cyclization reaction such as McMurry reaction; radical cyclization reaction; coupling ring-closing reaction using a metal complex; or photocyclization reaction.

Further, the electron-withdrawing group (EWG) in the β-electron-withdrawing group-substituted α,β-unsaturated compound used in the above reaction may be converted into an amino group or an amino group protected by an appropriate protecting group in one or several steps. Examples of such a group include an ester group, a cyano group, an acyl group, a carbamoyl group, a carboxyl group, and a nitro group. The ester group or cyano group can be converted into an amine derivative by Curtius rearrangement reaction after conversion to a carboxylic group (carboxylic acid) by hydrolysis. The cyano group or carboxylic group can be converted into an amine derivative by Hofmann rearrangement reaction after conversion to a carbamoyl group. The acyl group can be converted into an amine derivative by Beckmann rearrangement reaction or the like after conversion to a hydroxyimino group. The nitro group can be converted to an amine derivative by reduction.

On the other hand, the azomethine ylide used as a reactive element in this reaction can be produced by adding a catalytic amount of trifluoroacetic acid or a catalytic amount of silver fluoride to N-benzyl-N-(methoxymethyl)trimethylsilylmethylamine as a reagent, for example [see Journal of Organic Chemistry, Vol.52, No.2, p.235 (1987)]. PG in the azomethine ylide in the above reaction formula represents an appropriate amino-protecting

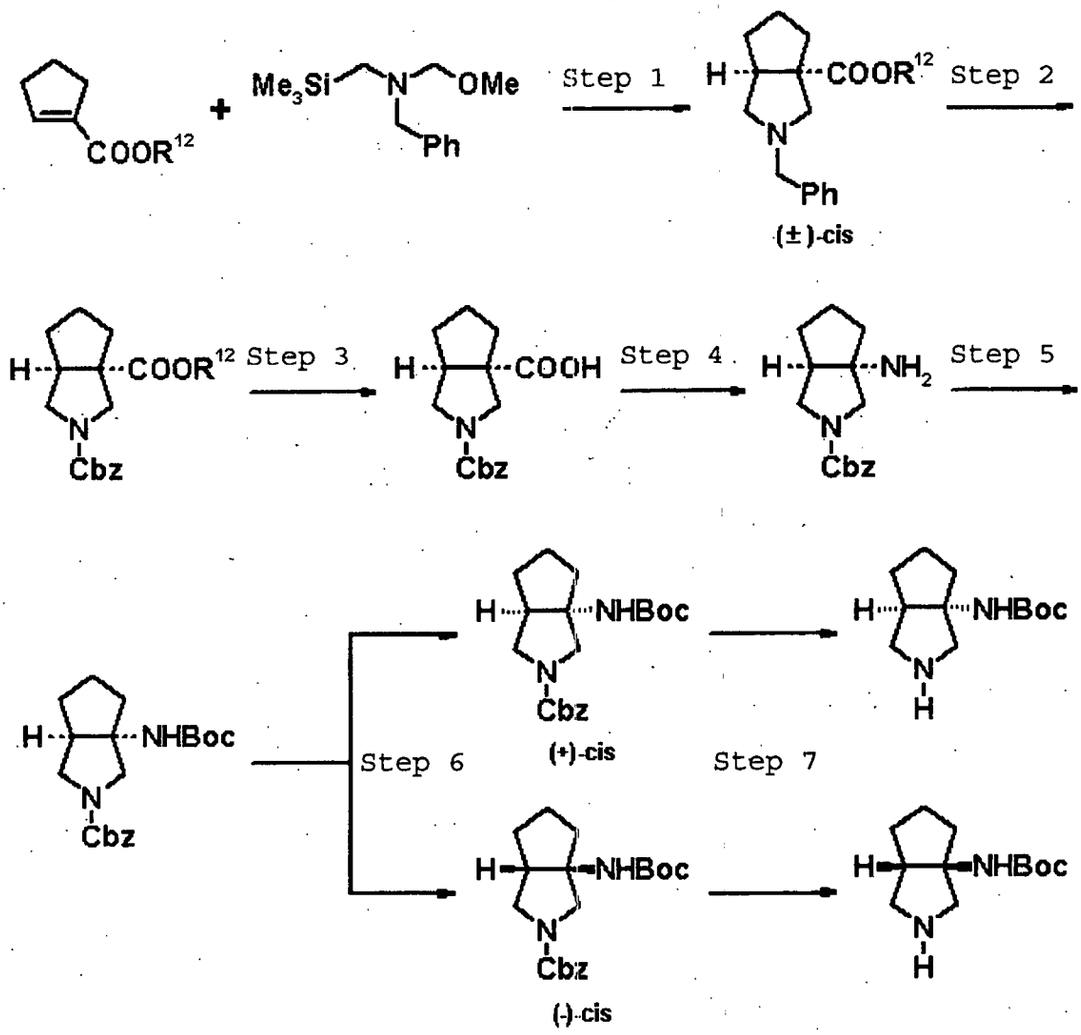
group. The protecting group is a benzyl group in the aforementioned reagent for producing the azomethine ylide, but may be an optically active 1-phenylethyl group as a preferred example. The amino-protecting group (PG) and an amino-protecting group produced by converting the electron-withdrawing group in a later step may be the same or different; the protecting groups may be appropriately selected from generally used protecting groups for an amino group so long as they do not affect the reaction, for example, do not inhibit each reaction step, and can easily be later deprotected.

Next, synthesis of an optically active substance will be described. An optically active substance can be synthesized by optical resolution of an appropriate intermediate, for example. Specific examples of the optical resolution include HPLC resolution using a chiral column and diastereomer salt preferential crystallization for an appropriate intermediate; and a method of bonding a chiral element to an appropriate intermediate to convert the intermediate to diastereomers, then separating the diastereomers using an appropriate separation technique such as silica gel chromatography, and removing the chiral element to convert the diastereomer to an optically active substance. An optically active substance may also be synthesized from a chiral building block as a starting

material. Specifically, an optically active cycloadduct can be obtained by enantioselective 1,3-dipolar cycloaddition reaction using a dipolarophile having an asymmetric element (for example, an asymmetric functional group such as a 1-menthyl group, a (2'S)-bornane-10,2-sultam group, or a (S)-4-benzyl-2-oxazolidinone group); enantioselective 1,3-dipolar cycloaddition reaction using an azomethine ylide having an asymmetric element (for example, a (1R)-1-phenylethyl group) in the molecule; or diastereoselective 1,3-dipolar cycloaddition reaction using both an asymmetric dipolarophile and an asymmetric azomethine ylide [see Journal of the Chemical Society Perkin Transactions 1, p.1076 (2002)]. Further, an optically active cycloadduct can be obtained by asymmetric 1,3-dipolar cycloaddition reaction using an asymmetric metal complex or salt as a catalyst [see Angewandte Chemie International Edition, Vol.44, p.6272 (2005)].

The synthesis of fused substituted aminopyrrolidine derivatives carried out by the present inventors using, as a key reaction, 1,3-dipolar cycloaddition reaction with a β-electron-withdrawing group-substituted α,β-unsaturated compound and an azomethine ylide as reactive elements will be more specifically described taking the synthesis of a 1-amino-3-azabicyclo[3.3.0]octane derivative as an example:

[Formula 57]



In the above scheme, Boc represents a tert-butoxycarbonyl group and Cbz represents a benzyloxycarbonyl group, provided that these substituents may be the same or different generally used protecting groups for an amino group; and R^{12} represents an alkyl group having 1 to 6 carbon atoms.

Step 1 is a step of synthesizing a 1-alkoxycarbonyl-3-azabicyclo[3.3.0]octane derivative which is a fused substituted pyrrolidine derivative using 1,3-dipolar

cycloaddition reaction with a 1-cyclopentene-1-ester and an azomethine ylide as reactive elements. The azomethine ylide reactive element is produced by adding a catalytic amount of trifluoroacetic acid or a catalytic amount of silver fluoride to N-benzyl-N-(methoxymethyl)trimethylsilylmethylamine as a reagent, for example, as described above. The reaction solvent may be any solvent that does not inhibit production of the azomethine ylide and 1,3-dipolar cycloaddition reaction, but is preferably dichloromethane or 1,2-dichloroethane. The reaction may be carried out at -20°C to the solvent reflux temperature, but preferably at room temperature to the solvent reflux temperature.

Step 2 is a step of converting the benzyl group at the 3-position of the 3-azabicyclo[3.3.0]octane ring to a protecting group. This step is carried out in order to easily extract, isolate, and purify the carboxylic acid derivative produced after hydrolysis of the 1-position ester (without conversion of the benzyl group, an amino acid derivative is formed and isolation and purification may be difficult). The 3-position protecting group is preferably a protecting group that can generally be distinguished in the deprotection step from the protecting group for the 1-position amino group produced after conversion of the 1-position carboxylic acid, but may be

the same as the protecting group for the 1-position amino group. The 3-position protecting group is preferably a benzyloxycarbonyl group or a tert-butoxycarbonyl group, and particularly preferably a benzyloxycarbonyl group. The benzyloxycarbonylation reaction is usually carried out by direct conversion by von Braun reaction using benzyl chloroformate in a solvent such as dichloromethane; or by reacting benzyl chloroformate in an appropriate solvent in the presence of a base after catalytic hydrogenolysis using a catalyst such as palladium-carbon.

Step 3 is a step of hydrolyzing the ester at the 1-position of the 3-azabicyclo[3.3.0]octane ring. The ester is an alkyl ester having 1 to 6 carbon atoms, and preferably a methyl ester, ethyl ester, or tert-butyl ester. The hydrolysis reaction may be carried out by a common method using a base or an acid that does not affect the 3-position protecting group. In the hydrolysis of a methyl ester or ethyl ester, the ester is reacted with an alkaline solution such as a sodium hydroxide solution, potassium hydroxide solution, or barium hydroxide solution in ethanol or water, then made acidic with an appropriate acid that does not affect the 3-position protecting group, and isolated and purified. The tert-butyl ester is hydrolyzed in an appropriate solvent in which the ester can be dissolved under acidic conditions or in the presence of an

acid catalyst. Preferred acids include hydrochloric acid, formic acid, acetic acid, trifluoroacetic acid, and p-toluenesulfonic acid.

Step 4 is a step of converting the carboxylic acid at the 1-position of the 3-azabicyclo[3.3.0]octane ring to an amine. This step is usually carried out by rearrangement reaction from carboxylic acid to an amine. For example, when the rearrangement reaction is Curtius rearrangement reaction, the carboxylic acid is converted to an acid azide in an appropriate solvent such as toluene using a reagent such as sodium azide, trimethylsilyl azide, or diphenylphosphoryl azide (DPPA), the reaction solution is then heated to form an isocyanate, and the isocyanate is converted to an amine by hydrolysis using hydrochloric acid or the like.

Step 5 is a step of protecting the amino group at the 1-position of the 1-amino-3-azabicyclo[3.3.0]octane ring; however, the subsequent steps may be carried out without this protection. The protecting group for the 1-position amino group may be a commonly used amino-protecting group, but is preferably a protecting group that can be distinguished from the 3-position protecting group in the deprotection step. Specific examples of the protecting group include a tert-butoxycarbonyl group, an acetyl group,

and a trifluoroacetyl group. The present inventors have selected a tert-butoxycarbonyl group.

Steps 4 and 5 can be carried out in one step by rearrangement reaction using an appropriate solvent. For example, a 1-(tert-butoxycarbonyl)amino-3-azabicyclo[3.3.0]octane derivative can be prepared by Curtius rearrangement reaction using diphenylphosphoryl azide (DPPA) in tert-butyl alcohol.

Step 6 is a step of optical resolution of the 1-amino-3-azabicyclo[3.3.0]octane derivative. This step can be carried out by HPLC resolution using an appropriate chiral column. As a result of this optical resolution, it has been found that a quinolonecarboxylic acid derivative derived from the resulting enantiomer of the 1-amino-3-azabicyclo[3.3.0]octane derivative having a positive optical rotation is superior in antibacterial activity to a quinolonecarboxylic acid derivative derived from the resulting enantiomer having a negative optical rotation (see the section "Examples"). The present inventors have selected a tert-butoxycarbonyl group as the protecting group for the 1-position amino group; however, it is possible to carry out optical resolution even when the 1-position amino group is not protected or is protected by a protecting group other than a tert-butoxycarbonyl group. For example, when the 1-position amino group is not

protected or is protected by a protecting group such as a benzyl group or a tert-butyl group (the protected amino group is basic in this case), it is also possible to carry out a method of converting an appropriate optically active acid to a diastereomer salt and preferentially crystallizing the diastereomer salt, in addition to HPLC optical resolution using an appropriate chiral column. In this case, an optically active 1-amino-3-azabicyclo[3.3.0]octane derivative can be obtained by converting the preferentially crystallized diastereomer salt to a free base. Further, when the 1-position amino group is not protected, it is possible to use a method of bonding a chiral element to convert the derivative to diastereomers, then separating the diastereomers using an appropriate separation technique such as silica gel chromatography, and removing the chiral element to convert the diastereomer to an optically active substance.

The present inventors have described a specific optical resolution method in this step; however, when an appropriate synthetic intermediate can be optically resolved, the intermediate may be appropriately selected and optically resolved as described above.

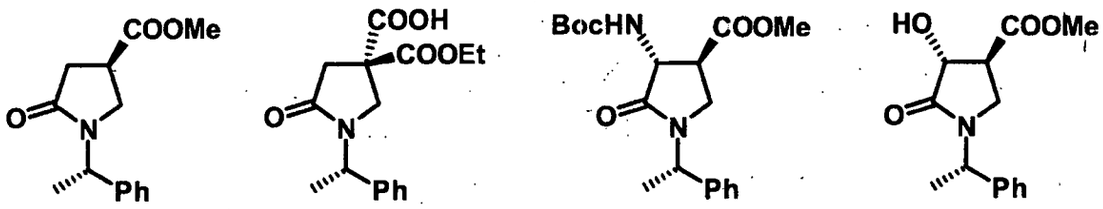
Step 7 is a step of deprotecting the 3-position of the 1-amino-3-azabicyclo[3.3.0]octane derivative. The deprotection reaction may be carried out under any

conditions that do not change other functional groups and the configuration. Accordingly, since the 1-position protecting group in relation to the compound of the present invention is a benzyloxycarbonyl group, the deprotection reaction is carried out under commonly used deprotection conditions, for example, under conditions using a catalyst such as palladium-carbon, or by catalytic hydrogenolysis reaction using ammonium formate in a protic polar solvent. When the 3-azabicyclo[3.3.0]octane derivative has a carbon-carbon unsaturated bond in the molecule, the deprotection must be carried out with the carbon-carbon unsaturated bond maintained. Accordingly, since the 3-position protecting group in relation to the compound of the present invention is a benzyloxycarbonyl group, the deprotection may be carried out with the carbon-carbon unsaturated bond maintained on the 3-azabicyclo[3.3.0]octane ring under strong acid conditions (for example, hydrobromic acid-acetic acid, trifluoroacetic acid, or trifluoromethanesulfonic acid-trifluoroacetic acid), by use of sodium-liquid ammonia (Birch reduction conditions), or by use of barium hydroxide, for example.

Further, the fused substituted aminopyrrolidine derivative which is the compound of the present invention can be synthesized from a chiral pyrrolidine derivative as a starting material. The following synthetic intermediates

are used in synthesis using a so-called chiral building block, for example. The chiral pyrrolidine derivatives that can be used as intermediates are not limited to the following compounds.

[Formula 58]



[Journal of Medicinal Chemistry, Vol.30, No.10, p.1171 (1987); WO 94/14794; Tetrahedron, Vol.61, No.23, p.5465 (2005); Tetrahedron Asymmetry, Vol.15, No.20, p.3249 (2004)]

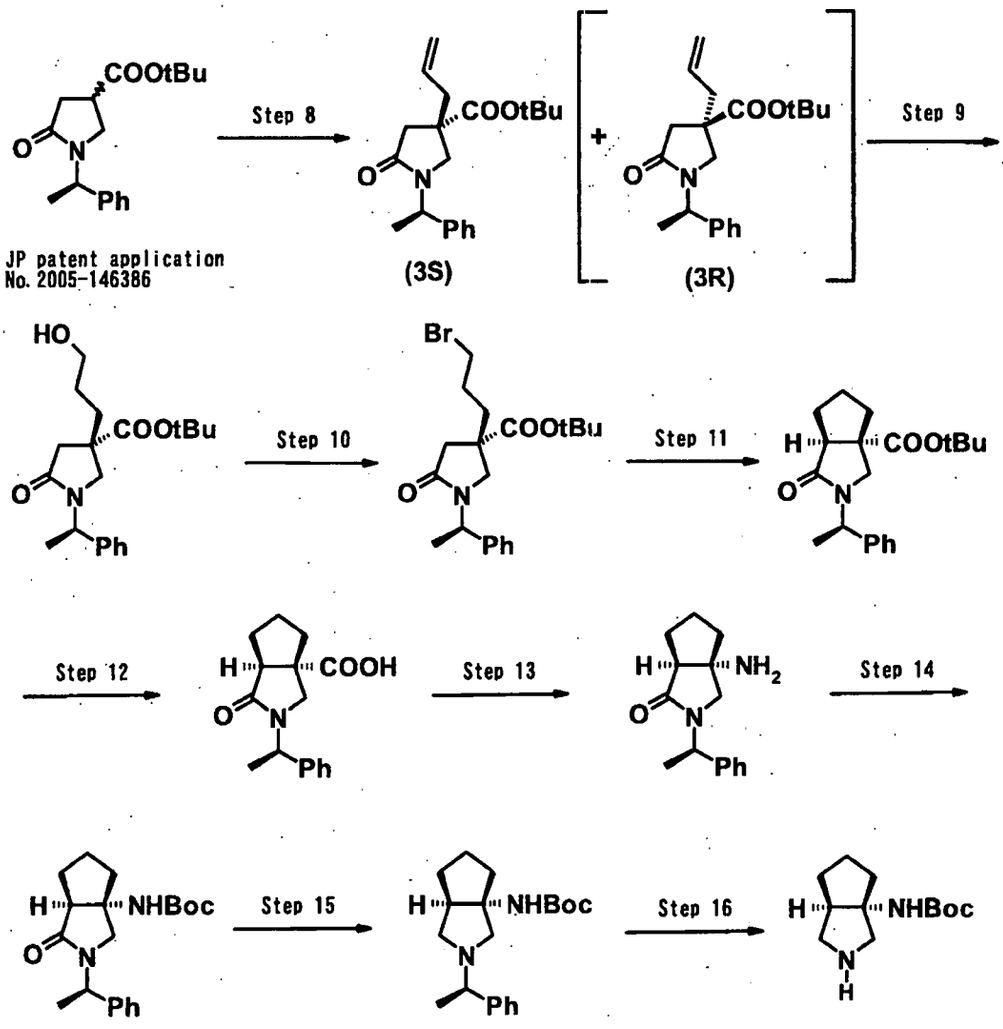
Such chiral pyrrolidine derivatives can be converted to the bicyclic pyrrolidine derivatives which are the compounds of the present invention in an appropriate number of steps. For example, the chiral pyrrolidine derivatives can be converted to the fused substituted aminopyrrolidine derivatives by introducing appropriate substituents into the 3- and 4-positions on the pyrrolidine ring, then carrying out appropriate homologation reaction or functional group conversion, and carrying out cyclization (ring-closing) reaction. Examples of cyclization (ring-closing) reactions for an appropriate synthetic intermediate which is an important step for this conversion

include carbon-carbon bond formation reaction or carbon-oxygen (or sulfur) bond formation reaction by nucleophilic reaction of a carbanion; ether (or thioether) ring formation reaction by intramolecular Mitsunobu reaction; cyclic esterification or cyclic amidation which is called lactone or lactam formation reaction; intramolecular condensation ring-closing reaction such as aldol condensation, Dieckmann condensation, acyloin condensation, Wittig condensation, or Reformatsky reaction; deoxygenation coupling cyclization reaction such as McMurry reaction; ring-closing metathesis reaction (RCM); Diels-Alder reaction; radical cyclization reaction; coupling ring-closing reaction using a metal complex; and photocyclization reaction.

The synthesis of fused substituted aminopyrrolidine derivatives carried out by the present inventors using a chiral pyrrolidine derivative as an important intermediate will more specifically be described taking the synthesis of a (1S,5R)-1-amino-3-azabicyclo[3.3.0]octane derivative as an example. The present inventors have selected a tert-butoxycarbonyl group as the protecting group for the 1-position amine moiety; however, the protecting group for the 1-position amino group may be a protecting group other than a tert-butoxycarbonyl group which does not affect, for example, does not inhibit each reaction step and can easily

be deprotected, and the protecting group may be the same as the 3-position protecting group. In the following case, the 1-position protecting group is a (1R)-1-phenylethyl group:

[Formula 59]



In the above scheme, Boc represents a tert-butoxycarbonyl group.

Step 8 is a step of allylating the 3-position of the pyrrolidine ring (the α-position of the ester). Step 8 is

usually carried out using an allyl halide such as allyl bromide as an allylating agent in the presence of a base. Examples of the base include potassium carbonate, cesium carbonate, sodium hydride, metallic sodium, sodium ethoxide, potassium tert-butoxide, lithium diisopropylamide (LDA), and lithium bis(trimethylsilyl)amide. Examples of the reaction solvent include tetrahydrofuran, acetone, N,N-dimethylformamide, toluene, and mixed solvents thereof. After completion of the reaction, diastereomers of the allylated compound can be separated and purified by silica gel chromatography or the like. The present inventors have used a tert-butyl ester as the ester at the 3-position of the pyrrolidine ring; however, other ester derivatives can also be used. The above diastereomer separation operation is easily carried out when a bulky tert-butyl ester is used.

Step 9 is a step of converting the allyl group moiety to a primary alcohol, specifically, a 1-hydroxypropyl group by hydroboration-oxidation reaction of the terminal olefin of the allyl group moiety. The hydroboration reaction is usually carried out in anhydrous tetrahydrofuran using, as reagents, various borane complexes (such as a borane-tetrahydrofuran complex and a borane-dimethyl sulfide complex), monoalkylboranes (such as hexylborane), dialkylboranes (such as 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane, and disiamylborane), a chloroborane-

dimethyl sulfide complex, a dichloroborane-dimethyl sulfide complex, catecholborane, and the like. Oxidation of the organoborane compound produced by the hydroboration reaction is usually carried out using aqueous hydrogen peroxide under alkaline conditions of a sodium hydroxide solution or the like in water or ethanol-containing water.

The present inventors have synthesized a compound in which a 1-hydroxypropyl group is introduced into the 3-position of the pyrrolidine ring in two steps shown as Steps 8 and 9; however, this product can be synthesized by another synthesis method. For example, the product can be synthesized by protecting a hydroxy group moiety of commercially available 3-iodopropanol using an appropriate protecting group (such as a tert-butyldimethylsilyl group), then 3-substitution oxypropylating in the presence of an appropriate base (such as a base described for Step 8), and subsequently deprotecting under appropriate conditions. Further, the 3-substitution oxypropylation reaction can be carried out after protecting one hydroxy group of 1,3-propanediol using an appropriate protecting group and then converting the other hydroxy group to a halogen atom or a commonly known leaving group. Examples of the leaving group in this case include a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a benzenesulfonyloxy group, and a p-toluenesulfonyloxy group.

Step 10 is a step of brominating the hydroxy group. It is inappropriate to carry out the bromination reaction under typical strong acidic conditions of hydrobromic acid-concentrated sulfuric acid, sodium bromide-sulfuric acid, or the like, because there is a tert-butyl ester in the molecule. The bromination reaction is appropriately reaction using triphenylphosphine-tetrabromomethane in dichloromethane or tetrahydrofuran, reaction using triphenylphosphine dibromide in N,N-dimethylformamide, or the like [see Journal of American Chemical Society, Vol.125, No.43, p.13625 (2003)]. Further, tetrabutylammonium bromide or a Vilsmeier reagent [(chloromethylene)dimethyliminium chloride] can be used as a reagent in N,N-dimethylformamide in this bromination reaction. The bromination reaction can be carried out using a brominating agent such as sodium bromide, lithium bromide, or calcium bromide in N,N-dimethylformamide or dimethyl sulfoxide after converting the hydroxy group moiety to an appropriate leaving group. Examples of the leaving group in this case include a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a benzenesulfonyloxy group, and a p-toluenesulfonyloxy group.

The present inventors have synthesized a compound in which a 1-bromopropyl group is introduced into the 3-position of the pyrrolidine ring as a compound used in the

next step. Examples of compounds that can be used in the next step other than this product include a 1-iodo compound and a compound into which a leaving group such as a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a benzenesulfonyloxy group, or a p-toluenesulfonyloxy group is introduced.

Step 11 is a step of generating a carbanion at the 4-position of the pyrrolidine ring of the bromo compound synthesized in Step 10 (amide: α-position of pyrrolidone) using an appropriate base to cause a reaction of forming a carbon-carbon double bond by intramolecular nucleophilic substitution (intramolecular ring-closing reaction). Typical examples of the base include potassium carbonate, cesium carbonate, sodium hydride, metallic sodium, sodium ethoxide, potassium tert-butoxide, lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, and sodium bis(trimethylsilyl)amide. Examples of the reaction solvent include tetrahydrofuran, acetone, N,N-dimethylformamide, toluene, and mixed solvents thereof. The cyclopentane ring formed by the intramolecular ring-closing reaction usually forms a cis-fused ring (cis-3-azabicyclo[3.3.0]octane ring) together with the pyrrolidine ring moiety. This synthesis method can be applied to synthesis of a fused substituted aminopyrrolidine derivative such as a 3-

azabicyclo[4.3.0]nonane derivative, but may produce a mixture of cis- and trans-isomers of the fused substituted aminopyrrolidine derivative. In this case, a necessary isomer may be separated by an appropriate separation and purification operation such as silica gel chromatography.

Step 12 is a step of converting the tert-butyl ester to carboxylic acid by hydrolysis or deprotection. The present inventors have selected tert-butyl ester as an ester; however, the ester is suitably an alkyl ester having 1 to 6 carbon atoms, and preferably a methyl ester, ethyl ester, or tert-butyl ester. The tert-butyl ester is hydrolyzed or deprotected in an appropriate solvent in which the ester can be dissolved under acidic conditions or in the presence of an acid catalyst. Preferred acids include hydrochloric acid, formic acid, acetic acid, trifluoroacetic acid, and p-toluenesulfonic acid. In the hydrolysis of a methyl ester or ethyl ester, the ester is reacted with an alkaline solution such as a sodium hydroxide solution, potassium hydroxide solution, or barium hydroxide solution in ethanol or water, then made acidic with an appropriate acid that does not affect the 3-position protecting group, and isolated and purified.

Step 13 is a step of converting the carboxylic acid at the 1-position of the 3-azabicyclo[3.3.0]octane ring to an amine. This step is usually carried out by rearrangement

reaction from carboxylic acid to an amine. For example, when the rearrangement reaction is Curtius rearrangement reaction, the carboxylic acid is converted to an acid azide in an appropriate solvent such as toluene using a reagent such as sodium azide, trimethylsilyl azide, or diphenylphosphoryl azide (DPPA), the reaction solution is then heated to form an isocyanate, and the isocyanate is converted to an amine by hydrolysis using hydrochloric acid or the like.

Step 14 is a step of protecting the amino group at the 1-position of the 1-amino-3-azabicyclo[3.3.0]octane ring; however, the subsequent steps may be carried out without this protection. The protecting group for the 1-position amino group may be a commonly used amino-protecting group, but is preferably a protecting group that can be distinguished from the 3-position protecting group in the deprotection step. Specific examples of the protecting group include a tert-butoxycarbonyl group, an acetyl group, and a trifluoroacetyl group. The present inventors have selected a tert-butoxycarbonyl group.

Steps 13 and 14 can be carried out in one step by rearrangement reaction using an azide reagent in an appropriate solvent. For example, a 1-(tert-butoxycarbonyl)amino-3-azabicyclo[3.3.0]octane derivative

can be prepared by Curtius rearrangement reaction using diphenylphosphoryl azide (DPPA) in tert-butyl alcohol.

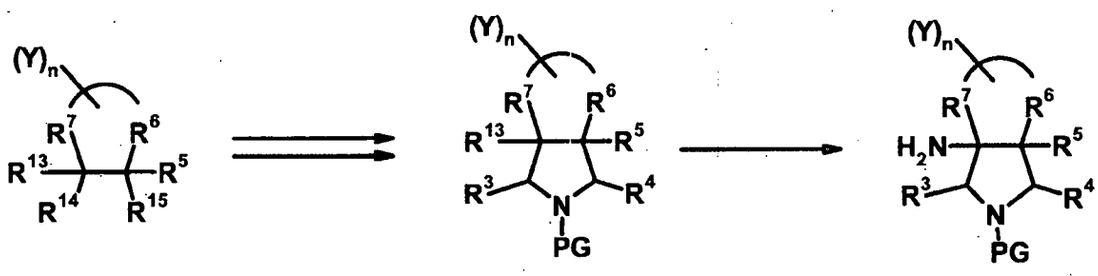
Step 15 is a step of reducing the carbonyl group of the pyrrolidone (called amide). Step 15 is carried out using a metal hydride such as lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, or a borohydride compound such as diborane or a borane-tetrahydrofuran complex, as a reduction reagent. An ether solvent represented by toluene or tetrahydrofuran is usually used as a solvent. The reaction is carried out usually at a temperature of -78°C to 100°C.

Step 16 is a step of deprotecting the 1-position of the pyrrolidine ring. The deprotection reaction may be carried out under any conditions that do not change other functional groups and the configuration. Accordingly, since the 1-position protecting group in relation to the compound of the present invention is a (1R)-1-phenylethyl group, the deprotection reaction is carried out under commonly used deprotection conditions, for example, under conditions using a catalyst such as palladium-carbon, or by catalytic hydrogenolysis reaction using ammonium formate in a protic polar solvent. When there is a carbon-carbon unsaturated bond as a substituent in the molecule, the deprotection must be carried out with the carbon-carbon unsaturated bond maintained. Accordingly, since the 1-position protecting

group in relation to the compound of the present invention is a (1R)-1-phenylethyl group, the deprotection may be carried out with the carbon-carbon unsaturated bond maintained in the molecule by use of sodium-liquid ammonia (Birch reduction conditions), for example. After the 1-position (1R)-1-phenylethyl group is converted to a benzyloxycarbonyl group by von Braun reaction using benzyl chloroformate typically in a solvent such as dichloromethane, the group can be deprotected by the method described above.

Further, the pyrrolidine ring of the fused substituted aminopyrrolidine derivatives which are the compounds of the present invention can be formed by a common synthesis method or the like after previously synthesizing a corresponding heterocyclic compound (important synthetic intermediate) appropriately, as shown in the following scheme:

[Formula 60]



wherein R^{13} is an ester group having 2 to 7 carbon atoms, a carbamoyl group, a nitro group, or a cyano group, which may

be converted to an amino group, or an amino group which may have a substituent; PG is an amino-protecting group; R^{14} and R^{15} are generally known appropriate substituents that can be taken together and then optionally subjected to an appropriate reaction to form a pyrrolidine ring; and R^3, R^4, R^5, R^6, R^7, Y, and n are as defined above.

The substituent R^{13} is preferably an ester group having 2 to 7 carbon atoms or an amino group which may have a substituent, and particularly preferably such a group stable in each reaction step listed below in the pyrrolidine ring formation reaction.

Here, there will be described the substituents R^{14} and R^{15} and the pyrrolidine ring formation method in which R^{14} and R^{15} are taken together and then optionally subjected to an appropriate reaction.

When the substituents R^{14} and R^{15} are each a hydroxymethyl group ($-CH_2OH$), the pyrrolidine ring can be formed by alkylating the primary amine directly or after converting the hydroxy group moiety to a halogen atom or an appropriate leaving group. Preferred examples of the halogen atom include chlorine, bromine, and iodine. Examples of the leaving group include a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group, a benzenesulfonyloxy group, and a p-toluenesulfonyloxy group.

When the substituents R^{14} and R^{15} are each a carboxyl group, an ester group, or an acid halide, the synthetic intermediate can be converted to the pyrrolidine derivative by synthesizing an imide derivative directly or through an acid anhydride synthesized by an appropriate condensation reaction and then subjecting the imide to a reduction. The ester group preferably has 2 to 7 carbon atoms. The imide is reduced using a metal hydride such as lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, or a borohydride compound such as diborane or a borane-tetrahydrofuran complex, as an imide reduction reagent. An ether solvent represented by tetrahydrofuran is usually used as a solvent. The reaction is carried out usually at a temperature of -78°C to 100°C.

When one of the substituents R^{14} and R^{15} is an aminomethyl group ($-CH_2NH_2$) and the other is a carboxylic group or an ester group, the synthetic intermediate can be converted to the pyrrolidine derivative by synthesizing an amide derivative (lactam derivative) using an appropriate condensation reaction and then subjecting the amide to a reduction. The ester group preferably has 2 to 7 carbon atoms. The amide derivative (lactam derivative) is generally synthesized by heating in an alcohol solvent in the presence or absence of an appropriate base. The amide is reduced using a metal hydride such as lithium aluminum

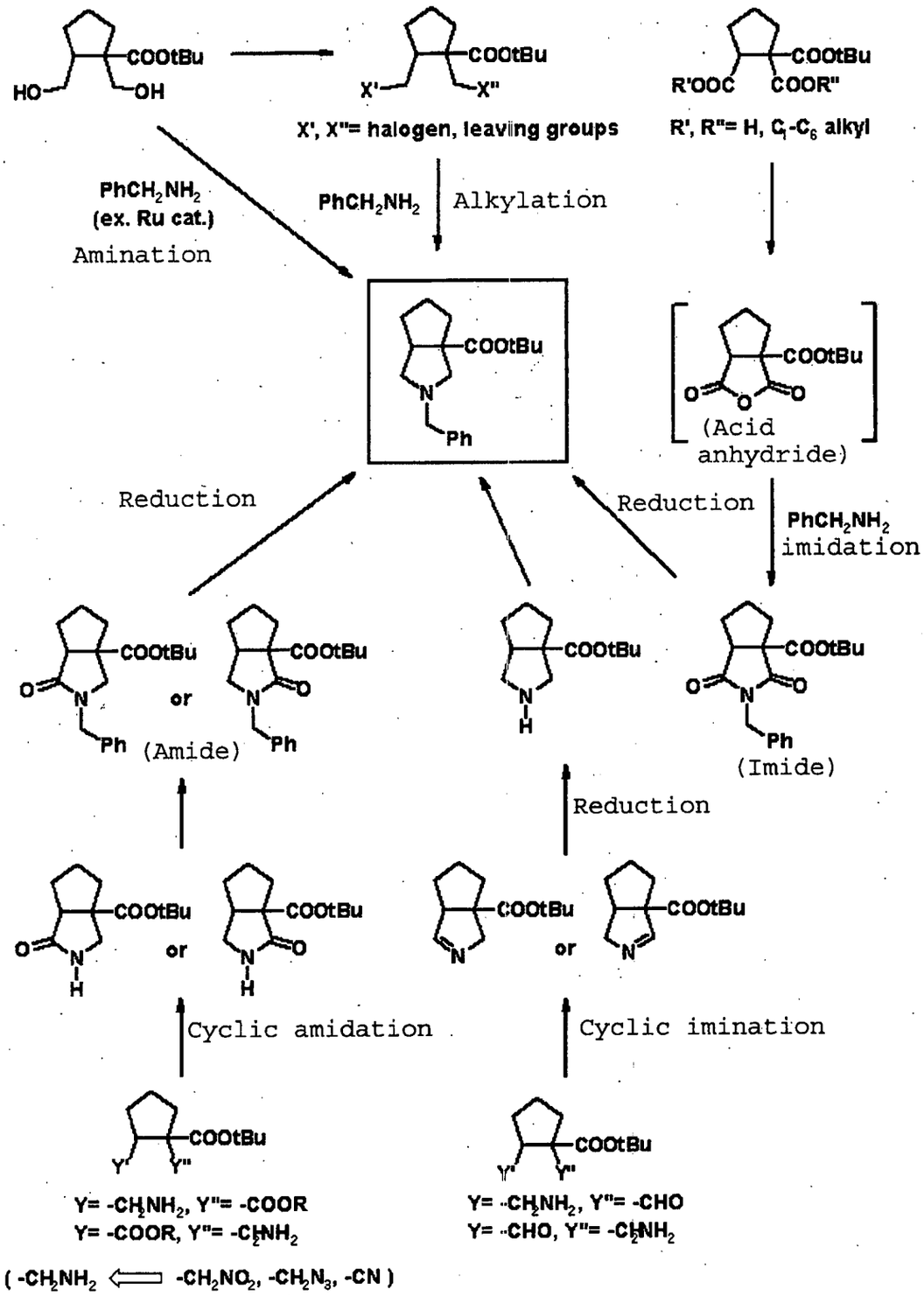
hydride or sodium bis(2-methoxyethoxy)aluminum hydride, or a borohydride compound such as diborane or a borane-tetrahydrofuran complex as an imide reduction reagent. An ether solvent represented by tetrahydrofuran is usually used as a solvent. The reaction is carried out usually at a temperature of -78°C to 100°C. One of substituents R^{14} and R^{15} of a precursor useful for synthesizing the intermediate amide derivative (lactam derivative) may be a nitromethyl group ($-CH_2NO_2$), an azidomethyl group ($-CH_2N_3$), or a cyano group (-CN) (in this case, the other substituent is a carboxyl group or an ester group). The precursor can be converted to the amide derivative (lactam derivative) by converting the substituent into an aminomethyl group ($-CH_2NH_2$) in a reduction step and then performing a condensation reaction. The reduction step is carried out using catalytic hydrogen reduction; a metal hydride such as lithium borohydride, lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride; or a borohydride compound such as diborane or a borane-tetrahydrofuran complex. Further, when one of the substituents R^{14} and R^{15} is a hydroxymethyl group ($-CH_2OH$) or a halogenomethyl group and the other is a carboxylic group or an ester group, a lactone derivative synthesized by an appropriate condensation reaction can be converted to the lactam derivative.

When one of the substituents R^{14} and R^{15} is an aminomethyl group ($-CH_2NH_2$) and the other is a formyl group, the synthetic intermediate can be converted to the pyrrolidine derivative by synthesizing a cyclic imine derivative using an appropriate condensation reaction and then subjecting the imine to a reduction, specifically, a reductive amination reaction. The synthetic intermediate can be converted to the pyrrolidine derivative by subjecting the imine to catalytic hydrogen reduction and an appropriate condensation reaction to synthesize an amide derivative (lactam derivative) and then subjecting the amide to a reduction.

When one of the substituents R^{14} and R^{15} is a methyl group and the other is a N-halogenoaminomethyl group (such as $-CH_2NCl-$), the pyrrolidine ring can be formed by radical reaction (Hofmann-Loeffler-Freitag pyrrolidine synthesis reaction).

Several representative pyrrolidine ring formation methods are represented by the following scheme taking, as an example, the synthesis of a 3-benzyl-1-(tert-butoxycarbonyl)-3-azabicyclo[3.3.0]octane derivative which is a synthetic intermediate for a 1-amino-3-azabicyclo[3.3.0]octane derivative which is a representative compound of the present invention:

[Formula 61]

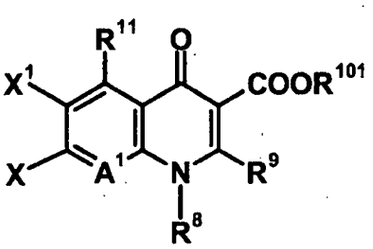


Reactions in the above-exemplified steps for synthesizing the fused substituted aminopyrrolidine

derivatives can be appropriately modified by those skilled in the art based on the above description to find a new synthesis method, and the above description should not be construed as limiting.

In order to produce a compound included in the present invention by introduction of a 1-(tert-butoxycarbonyl)amino-3-azabicyclo[3.3.0]octane derivative which is a fused substituted aminopyrrolidine derivative obtained as described above as the 7-position (10-position) substituent of a quinolonecarboxylic acid mother skeleton (pyridobenzoxazinecarboxylic acid mother skeleton), a quinolonecarboxylic acid mother skeleton compound represented by the following formula:

[Formula 62]



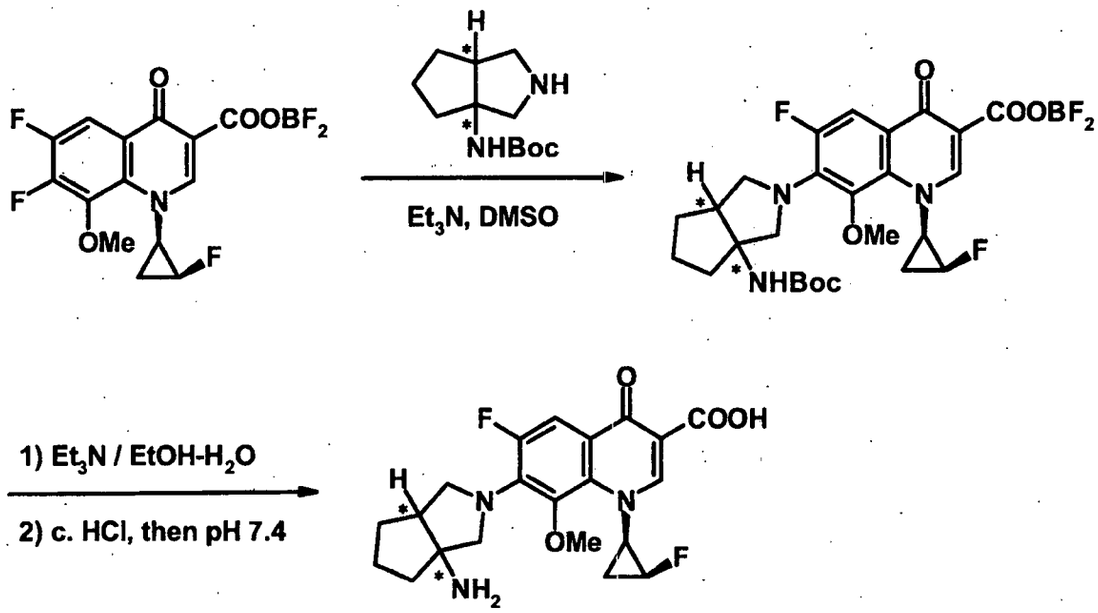
wherein R^8, R^9, R^{11}, X^1, and A^1 are as defined above; R^{101} represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, or a boron substituent that can form a boron chelate; and X represents a leaving group, can be reacted with 1-(tert-butoxycarbonyl)amino-3-azabicyclo[3.3.0]octane.

Preferred examples of the alkyl group having 1 to 6 carbon atoms include a methyl group, an ethyl group, an

isopropyl group, and a tert-butyl group. The boron substituent may be dihalogenoboron or diacyloxyboron. The dihalogenoboron is preferably difluoroboron ($-BF_2$). The diacyloxyboron is preferably diacetyloxyboron [$-B(OAc)_2$]. Such boron substituents can be obtained according to known methods.

Production of such a compound included in the present invention will be described taking a compound of the later-described Example 11 as an example.

[Formula 63]



The target compound can be obtained by dissolving a quinolonecarboxylic acid mother skeleton compound in an appropriate solvent and reacting the compound with (-)-1-(tert-butoxycarbonyl)amino-3-azabicyclo[3.3.0]octane which is a compound for introduction as the 7-position

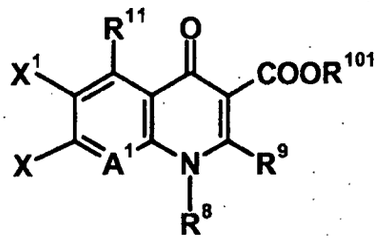
substituent in the presence of a base. The amino group in the compound for introduction as the 7-position substituent may be protected by a protecting group. Examples of the protecting group include, in addition to a tert-butoxycarbonyl group (Boc group), a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, an acetyl group, a methoxyacetyl group, a trifluoroacetyl group, a pivaloyl group, a formyl group, a benzoyl group, a tert-butyl group, a benzyl group, a trimethylsilyl group, and an isopropyldimethylsilyl group. Examples of bases that can be used include carbonates, bicarbonates, or hydroxide salts of alkali metals or alkali earth metals; trialkylamines such as triethylamine and N,N-diisopropylethylamine; and nitrogen-containing heterocyclic compounds such as pyridine, 1,8-diazabicycloundecene, and N-methylpiperidine. Trialkylamines, N-methylpiperidine, and triethylamine are preferred. There are no specific limitations to the solvent used so long as it does not inhibit the reaction. The solvent is preferably N,N-dimethylformamide, dimethyl sulfoxide, sulfolane, acetonitrile, dimethylacetamide, tetrahydrofuran, or N-methylpyrrolidone, and particularly preferably dimethyl sulfoxide, sulfolane, acetonitrile, or dimethylacetamide.

When the quinolonecarboxylic acid mother skeleton compound is a boron chelate compound, the target compound

can be obtained by cleaving the boron substituent moiety by hydrolysis and then deprotecting the protecting group for the amino group. The boron substituent may be hydrolyzed under commonly used conditions. For example, the boron substituent can be hydrolyzed by reacting a base in the presence of an aqueous alcohol solvent such as methanol or ethanol. The base is preferably triethylamine. The reaction is preferably carried out in a temperature range between ice-cold and 90°C. The deprotection can be carried out under conditions suitable for the protecting group used by treating the hydrolysate with concentrated hydrochloric acid, for example. After completion of the reaction, the reaction solution is made basic with a sodium hydroxide solution, for example, and then neutralized with an appropriate acid such as hydrochloric acid; the precipitated crystals are subsequently collected by filtration or extracted with chloroform; and the resulting compound is appropriately purified by a recrystallization operation using an appropriate solvent, for example, to obtain the target compound.

The quinolone compounds of the present invention, especially those having a methyl group at the 8-position, are prepared by the reaction of fused substituted aminopyrrolidine derivatives and the quinolone skeleton compounds of the following formula:

[Formula 64]



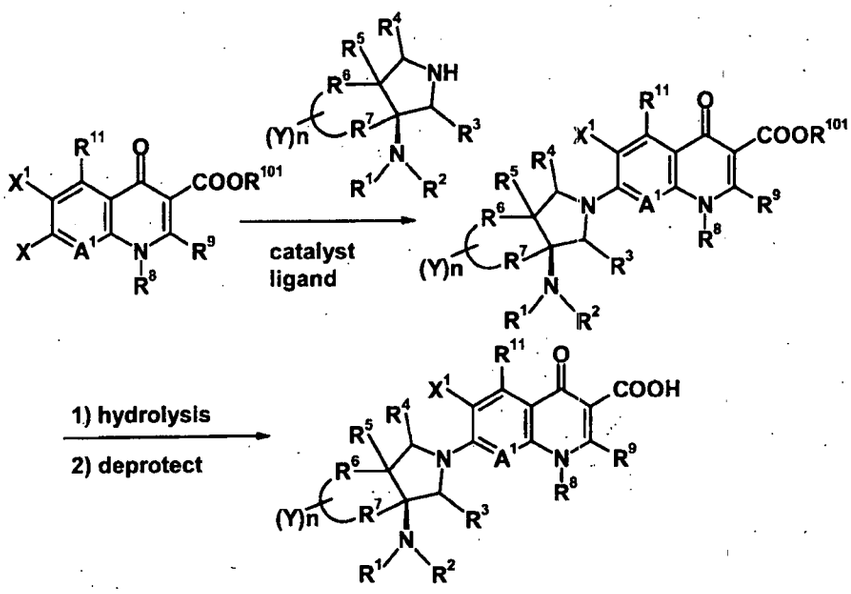
in the presence of an appropriate solvent and a catalyst, optionally with the coexistence of a ligand, and in the presence of a base. This reaction may be carried out without ligand.

The substituent R^{101} of the quinolone skeleton compound is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms. Examples of the preferred alkyl groups are a methyl group, an ethyl group, an isopropyl group, and a tert-butyl group. In relation to the leaving group X^1, those ordinarily used in this field are also preferably applicable to this reaction. The preferred example of such leaving group is a halogen atom such as a bromine atom, or an iodine atom; a substituted sulfonyloxy group such as a trifluoromethansulfonyloxy group. As for the catalyst, those ordinally used in this field are preferably applicable to this reaction. A Pd catalyst, Cu catalyst, or Ni catalyst is preferably used, and more preferably a Pd catalyst or a Cu catalyst. The catalyst may be applied to the reaction mixture in the from of tris(dibenzylideneacetone)dipalladium(0), palladium(II)

acetate, tetrakis(triphenylphosphine)nickel(0), nickel(II) acetylacetonato, copper(I) iodide, or copper (I) bromide and the like. As for the ligand for the present reaction, monodentate ligands or bidentate ligands ordinarily used in this field are preferably applicable to this reaction. Examples of such ligand are 1,1-bis(diphenylphosphino)ferrocene, 4,5-bis(diphenylphospino)-9,9-dimethylxanthene, or BINAP. As for the base, those ordinarily used in this field are preferably applicable to this reaction. The carbonates of alkaline earth metal or alkali metal such as cesium carbonate, potassium carbonate, or sodium carbonate, and alkoxide of alkali metal such as sodium methoxide, sodium ethoxide, or potassium tert-butoxide are preferably used.

This reaction is explained in the following reaction scheme:

[Formula 65]



The quinolone compounds of the present invention are obtained by the reaction of the quinolone carboxylic acid skeleton compounds with fused substituted aminopyrrolidine compounds in an appropriate solvent, in the presence of a catalyst, optionally with the coexistence of a ligand, and in the presence of a base. The amino group of the fused substituted pyyrolidine compound used for the introduction of 7-positioned substituent may have a protective group. Examples of such protective groups are an alkyloxycarbonyl group such as a tert-butoxycarbonyl group; an aralkyloxycarbonyl group such as a benzyloxycarbonyl group, or a p-methoxy benzyloxycarbonyl group; an acyl or an alkyl carbonyl group such as an acetyl group, a methoxy acetyl group, a trifluoroacetyl group, a pivaloyl group, or a formyl group; an arylkylcarbonyl group such as a benzoyl group, or a p-nitrobenzoyl group; an alkyl group such as a

tert-butyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, or a p-nitro benzyl group; a substituted silyl group such as a trimethylsilyl group, or an isopropyldimethylsilyl group. The example of the base for this reaction is a carbonate, a bicarbonate, a phosphate, a hydrate, or an alkoxide of an alkali metal atom or an alkaline earth metal atom; a trialkylamine such as a triethylamine, or an N,N-diisopropylethylamine; a nitrogen containing heterocyclic compound such as a pyridine, a 1,8-diazabicycloundecene, or an N-methylpiperidine. As for the solvent, any solvent that does not inhibit the reaction is preferably applied for this reaction. Examples of the solvent are an amide such as an N,N-dimethylformamide, an N,N-dimethylacetamide, or an N-methyl-2-pyrrolidone; an aryl hydrocarbon such as a toluene, or a xylene; an ether such as a tetrahydrofuran, a 1,4-dioxane, or a 1,2-dimethoxyethane; and an acetonitrile. More preferred solvents are an N,N-dimethylformamide, a xylene, a 1,4-dioxane, or a 1,2-dimethoxyethane.

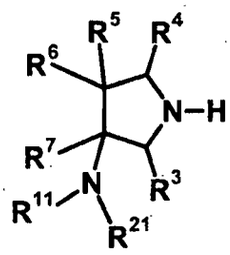
The reaction may be conducted in the forms of both homogeneous and heterogeneous reactions. The reaction is also preferably carried out in a catalytic phase reaction. The reaction is completed in from 10 minutes to 7 days. The reaction can be conducted at a temperature between 0°C to 300°C, preferably between 30°C to the temperature of the

boiling point of the solvent used. The catalyst compound and ligand compound may be mixed to form the catalyst complex prior to the addition of the other reacting compounds, or all of the reaction components may be mixed at once. The amount of the catalyst is in the range of a catalytic amount to the equimolar amount, and a catalytic amount is preferred.

In case that the quinolone skeleton compounds have an ester moiety, the carboxy compounds are obtained by cleavage of the ester group according to already known methods in this field. The quinolone compounds are obtained by cleavage of the protective group of the amino moiety on the fused substituted aminopyrrolidine moiety according to an already known method of the corresponding protective group. The quinolone compounds are isolated after cleavage of the protective group by an already known method in this field, such as recrystallization from appropriate solvents or the like.

Compounds represented by the following two formulas are useful as production intermediates for the compound (I) of the present invention, respectively:

[Formula 66]



In the above formula, R^{11} represents R^1 as already defined (a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, or a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide; the alkyl group may have a substituent selected from the group consisting of a hydroxy group, an amino group, a cyano group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and the cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom) or an amino-protecting group;

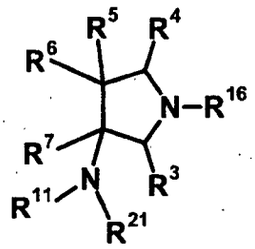
R^{21} represents R^2 as already defined (a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 6 carbon atoms; the alkyl group may have a substituent selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and the cycloalkyl group may have one or more substituents selected from the group

consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom) or an amino-protecting group; and

R^3, R^4, R^5, R^6, and R^7 are as already defined.

Here, the amino-protecting group represented by R^{11} or R^{21} will be described. The protecting group is not limited so long as it is generally used in the art. Examples of the protecting group include alkoxycarbonyl groups such as a tert-butoxycarbonyl group and a 2,2,2-trichloroethoxycarbonyl group; aralkyloxycarbonyl groups such as a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, and a p-nitrobenzyloxycarbonyl group; acyl groups such as an acetyl group, a methoxyacetyl group, a trifluoroacetyl group, a chloroacetyl group, a pivaloyl group, a formyl group, and a benzoyl group; alkyl groups or aralkyl groups such as a tert-butyl group, a benzyl group, a p-nitrobenzyl group, a p-methoxybenzyl group, and a triphenylmethyl group; ethers such as a methoxymethyl group, a tert-butoxymethyl group, a tetrahydropyranyl group, and a 2,2,2-trichloroethoxymethyl group; (alkyl- and/or aralkyl-)substituted silyl groups such as a trimethylsilyl group, an isopropyldimethylsilyl group, a tert-butyldimethylsilyl group, a tribenzylsilyl group, and a tert-butyldiphenylsilyl group; and an allyl group.

[Formula 67]



In the above formula, R^{16} represents an amino-protecting group; and R^{11}, R^{21}, R^3, R^4, R^5, R^6, and R^7 are as already defined.

The protecting group represented by R^{16} is not limited so long as it is generally used in the art. Examples of the protecting group include alkoxycarbonyl groups such as a tert-butoxycarbonyl group and a 2,2,2-trichloroethoxycarbonyl group; aralkyloxycarbonyl groups such as a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, and a p-nitrobenzyloxycarbonyl group; acyl groups such as an acetyl group, a methoxyacetyl group, a trifluoroacetyl group, a chloroacetyl group, a pivaloyl group, a formyl group, and a benzoyl group; alkyl groups or aralkyl groups such as a tert-butyl group, a benzyl group, a p-nitrobenzyl group, a p-methoxybenzyl group, and a triphenylmethyl group; ethers such as a methoxymethyl group, a tert-butoxymethyl group, a tetrahydropyranyl group, and a 2,2,2-trichloroethoxymethyl group; (alkyl- and/or aralkyl-)substituted silyl groups such as a trimethylsilyl group, an isopropyldimethylsilyl

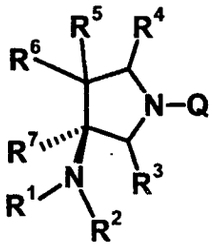
group, a tert-butyldimethylsilyl group, a tribenzylsilyl group, and a tert-butyldiphenylsilyl group; and an allyl group.

When two or more of R^{11}, R^{21}, and R^{16} are protecting groups, any protecting groups can be selected based on the common knowledge in the art so that the protecting groups can be selectively removed.

It has been found from the later-described test example that compounds obtained as described above having the 7-position of the quinolonecarboxylic acid mother skeleton (or its corresponding position) substituted with the fused bicyclic aminopyrrolidine derivative of the present invention, which are represented by a compound of Example X, have antibacterial activity, in particular, antibacterial activity to Staphylococcus aureus and Gram-positive bacteria such as pneumococcus stronger than that of levofloxacin or ciprofloxacin generally used in the art. It has been confirmed in this case that the site substituted with an amino group in the 7-position substituent is an asymmetric carbon, and that quinolonecarboxylic acid substituted with a 7-position substituent derived from one enantiomer has higher activity and exhibits more excellent properties, pharmacokinetics, and safety. As a result of X-ray crystallography of the highly active 7-position substituent or synthesis of each enantiomer by the chiral

pool method and measurement of antibacterial activity, it has been confirmed that the 7-position amino group has a configuration represented by the following formula:

[Formula 68]



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Q are as already defined.

The compound of the present invention may be of a free form. Alternatively, an acid addition salt or a salt with a carboxylic group may be formed. Examples of the acid addition salt include inorganic acid salts such as hydrochloride, sulfate, nitride, hydrobromide, hydriodate, and phosphate; and organic acid salts such as sulfonate (e.g., methanesulfonate, benzenesulfonate, p-toluenesulfonate), and carboxylate (e.g., acetate, citrate, maleate, fumarate, lactate). Examples of the salt with a carboxyl group include alkali metal salts such as lithium salt, sodium salt, and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt, triethylamine salt, N-methylglucamine salt, and tris-(hydroxymethyl)aminomethane salt. The compound of the present invention in free form and an acid addition salt or

a salt with a carboxyl group of the compound may be present as a hydrate.

The compound (I) of the present invention has strong antibacterial activity and therefore can be used as a medicine for humans, animals, and fish, an agricultural chemical, or a food preservative. The dose of the compound of the present invention used as a human medicine is 50 mg to 1 g, and more preferably 100 to 500 mg, per day for an adult. The dose for an animal varies depending on the purpose of administration, the size of the animal to be treated, the type of the pathogen with which the animal is infected, and the degree of the disease; the daily dose is generally 1 to 200 mg, and more preferably 5 to 100 mg, per kg body weight of the animal. The daily dose is administered once or in two to four divided doses. The daily dose may exceed the aforementioned dose if necessary.

The compound (I) of the present invention is active to a wide range of microorganisms causing various infections and can treat, prevent, or relieve diseases caused by these pathogens. Examples of bacteria or bacteria-like microorganisms for which the compound of the present invention is effective include *Staphylococcus*, *Streptococcus pyogenes*, hemolytic streptococcus, enterococcus, pneumococcus, *Peptostreptococcus*, gonococcus, *Escherichia coli*, *Citrobacter*, *Shigella*, *Klebsiella*

pneumoniae, *Enterobacter*, *Serratia*, *Proteus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Acinetobacter*, *Campylobacter*, and *Chlamydia trachomatis*.

Examples of diseases caused by these pathogens include folliculitis, furuncle, carbuncle, erysipelas, cellulitis, lymphangitis, whitlow, subcutaneous abscess, hidradenitis, acne conglobata, infectious atheroma, perirectal abscess, mastitis, superficial secondary infection such as traumatic infection, burn infection, or surgical wound infection, laryngopharyngitis, acute bronchitis, tonsillitis, chronic bronchitis, bronchiectasis, diffuse panbronchiolitis, infection secondary to a chronic breathing disease, pneumonia, pyelonephritis, cystitis, prostatitis, epididymitis, gonococcal urethritis, nongonococcal urethritis, cholecystitis, cholangitis, shigellosis, enteritis, adnexitis, intrauterine infection, bartholinitis, blepharitis, hordeolum, dacryocystitis, meibomianitis, corneal ulcer, otitis media, sinusitis, periodontitis, pericoronitis, jaw inflammation, peritonitis, endocarditis, sepsis, meningitis, and skin infection.

Examples of Mycobacterium spp. for which the compound (I) of the present invention is effective include tubercle bacilli (*Mycobacterium tuberculosis*, *M. bobis*, and *M. africanum*) and atypical mycobacteria (*M. cansasii*, *M. marinum*, *M. scrofulaceum*, *M. avium*, *M. intracellulare*, *M.*

xenopi, *M. fortuitum*, and *M. chelonae*). Mycobacterial infections caused by these pathogens are broadly classified into tuberculosis, atypical mycobacterial infections, and leprosy. Mycobacterium tuberculosis infections are observed in the thoracic cavity, trachea and bronchus, lymph node, systemic dissemination, bone joints, meninges and brain, digestive organs (intestine and liver), skin, mammary gland, eyes, middle ear and pharynx, urinary tract, male genital organs, and female genital organs, in addition to lung. Atypical mycobacterial infections (nontuberculous mycobacterial infections) mainly affect the lung, and may also appear as local lymphadenitis, soft skin tissue infection, osteoarthritis, or systemic dissemination-type infection.

The compound of the present invention is also effective for various microorganisms causing animal infections such as *Escherichia*, *Salmonella*, *Pasteurella*, *Haemophilus*, *Bordetella*, *Staphylococcus*, and *Mycoplasma*. Specific examples of animal diseases include bird diseases such as Escherichia coli disease, pullorum disease, fowl paratyphoid, fowl cholera, infectious coryza, staphylococcal disease, and mycoplasma infection; pig diseases such as Escherichia coli disease, salmonellosis, pasteurellosis, hemophilus infection, atrophic rhinitis, exudative epidermitis, and mycoplasma infection; bovine

diseases such as Escherichia coli disease, salmonellosis, hemorrhagic septicemia, mycoplasma infection, contagious bovine pleuropneumonia, and mastitis; dog diseases such as Escherichia coli sepsis, salmonella infection, hemorrhagic septicemia, pyometra, and cystitis; and cat diseases such as exudative pleuritis, cystitis, chronic rhinitis, hemophilus infection, kitten diarrhea, and mycoplasma infection.

An antibacterial agent containing the compound (I) of the present invention can be appropriately selected according to the administration method and prepared by a method for preparing various preparations commonly used. Examples of the antibacterial agent dosage form containing the compound of the present invention as a main agent include tablets, powders, granules, capsules, solutions, syrups, elixirs, and oily or aqueous suspensions. An injection preparation may contain an additive such as a stabilizer, a preservative, or a solution adjuvant, and may be prepared before use from a solid preparation formed by storing a solution that may contain such an additive in a container and then lyophilizing the solution, for example. One dose may be stored in a container, or multiple doses may be stored in a single container. Examples of external preparations include solutions, suspensions, emulsions, ointments, gels, creams, lotions, and sprays. A solid

preparation may contain a pharmaceutically acceptable additive together with the active compound. Examples of the additive include fillers, binders, disintegrants, solution promoters, wetting agents, and lubricants. A liquid preparation may be a solution, a suspension, an emulsion, or the like, and may contain an additive such as a suspending agent or an emulsifier.

Next, preparation examples will be described.

Preparation Example 1 [Capsules]:

Compound of Example 11	100.0 mg
Corn starch	23.0 mg
Calcium carboxymethylcellulose	22.5 mg
Hydroxymethylcellulose	3.0 mg
Magnesium stearate	1.5 mg
Total	150.0 mg

Preparation Example 2 [Solution preparation]:

Compound of Example 11	1 to 10 g
Acetic acid or sodium hydroxide	0.5 to 2 g
Ethyl p-oxybenzoate	0.1 g
Purified water	87.9 to 98.4 g
Total	100 g

Preparation Example 3 [Powder to be mixed with forage]

Compound of Example 17	1 to 10 g
Corn starch	89.5 to 98.5 g
Light anhydrous silicic acid	0.5 g

Total 100 g

Examples

The present invention will be specifically described below with reference to examples; however, the present invention is not limited to the examples, and the examples should not be construed as limitative in any sense.

[Reference Example 1]

(S)-3-(tert-Butyldimethylsilyloxy)-2-methylpropionic acid methyl ester

[Formula 69]



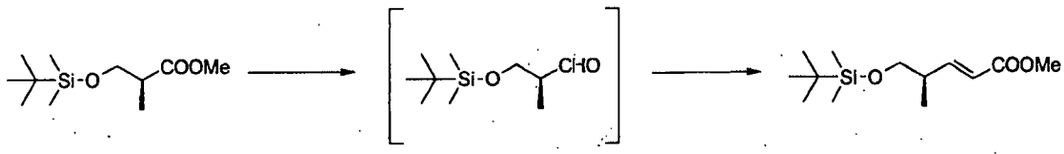
Imidazole (13.3 g, 196 mmol) and tert-butyldimethylsilyl chloride (14.2 g, 94.1 mmol) were added to a solution of (S)-3-hydroxy-2-methylpropionic acid methyl ester (11.0 g, 93.1 mmol) in dimethylformamide (100 mL), and the mixture was stirred at room temperature for four hours. Water was added to the reaction mixture, followed by extraction with hexane twice. The extract was then dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 24 g (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.76-3.72 (1H, m), 3.64 (3H, s), 3.63-3.59 (1H, m), 2.65-2.57 (1H, m), 1.10 (3H, d, J=6.84 Hz), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s).

[Reference Example 2]

(E)-(R)-5-(tert-Butyldimethylsilyloxy)-4-methylpent-2-ene acid methyl ester

[Formula 70]



Diisobutylaluminum hydride (1 M solution in hexane, 86 mL) was added to a solution of (S)-3-(tert-butyldimethylsilyloxy)-2-methylpropionic acid methyl ester (20 g, 86.1 mmol) in dichloromethane (400 mL) at -78°C, and the mixture was stirred at the same temperature for two hours. A saturated potassium sodium tartrate solution was added to the reaction mixture which was then stirred while heating to room temperature. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, and filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (200 mL). Triphenylphosphonylideneacetic acid methyl ester (32 g, 94.7 mmol) was added under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction solution was filtered, and then the solvent was evaporated under reduced pressure. Hexane was added to the resulting

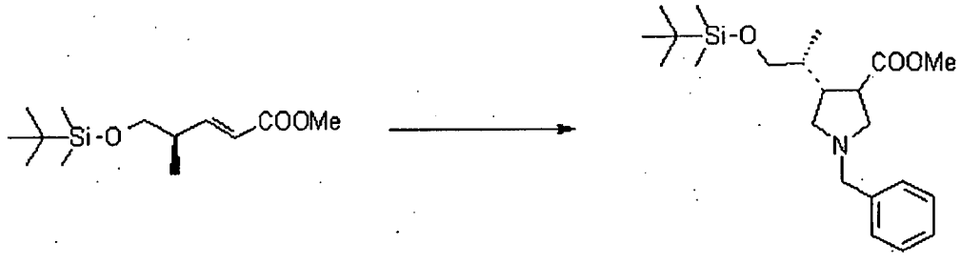
residue, and the insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 25 g (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.94 (1H, dd, J=7.10, 15.90 Hz), 5.84 (1H, dd, J=1.20, 15.90 Hz), 3.73 (3H, s), 3.57-3.49 (2H, m), 2.53-2.46 (1H, m), 1.05 (3H, d, J=6.80 Hz), 0.89 (9H, s), 0.04 (6H, s).

[Reference Example 3]

1-Benzyl-4-[(R)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-3-carboxylic acid methyl ester

[Formula 71]



3,4-dl-trans

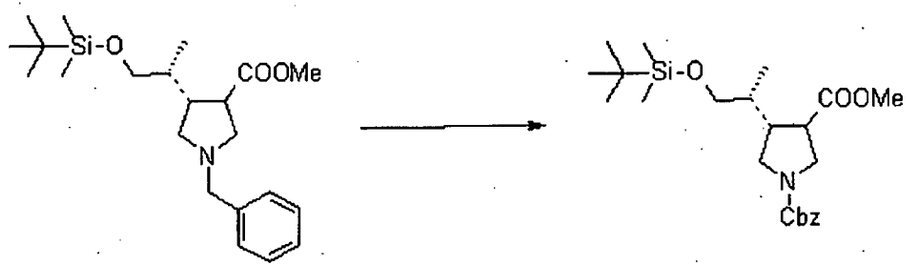
N-Benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine (16.6 mL, 65.0 mmol) was added to a solution of (E)-(R)-5-(tert-butyldimethylsilyloxy)-4-methylpent-2-ene acid methyl ester (14 g, 54.2 mmol) in methylene chloride (100 mL), and then a trace amount of trifluoroacetic acid was added. The mixture was stirred for 30 minutes and then saturated

sodium bicarbonate water was added. The organic layer was separated and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 14.6 g (69%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 4]

4-[(R)-2-(tert-Butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 72]



3,4-dl-trans 3,4-dl-trans

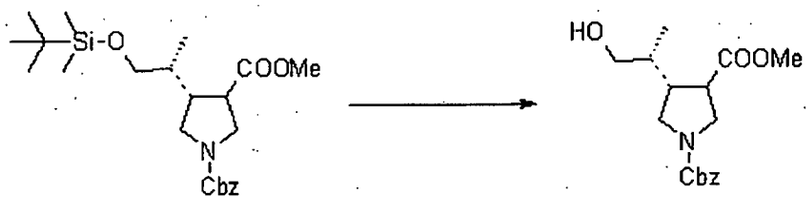
Benzyloxycarbonyl chloride (10.2 mL, 71.5 mmol) was added to a solution of 1-benzyl-4-[(R)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-3-carboxylic acid methyl ester (14.0 g, 35.8 mmol) in dichloromethane (200 mL), and the mixture was stirred for one hour. Saturated sodium bicarbonate water was added to the reaction mixture. The organic layer was separated,

dried over magnesium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 13.9 g (89%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 5]

4-[(R)-2-Hydroxy-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 73]



3,4-dl-trans 3,4-dl-trans

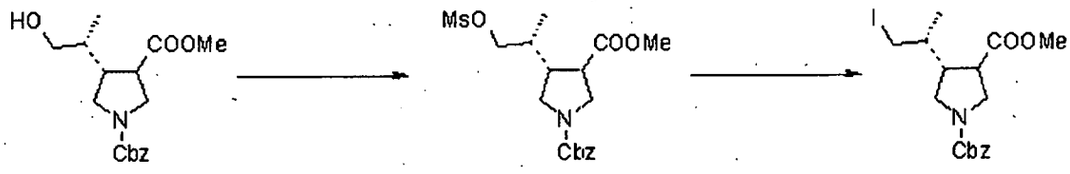
Hydrogen fluoride-pyridine (4 mL) was added to a solution of 4-[(R)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (6.0 g, 7.1 mmol) in pyridine (20 mL) under ice-cooling, and the mixture was stirred at room temperature for 13 hours. The reaction mixture was poured into ice water, followed by extraction with ethyl acetate and washing with 1N hydrochloric acid and brine. After drying over magnesium sulfate and filtration, the solvent was evaporated under reduced pressure to give 4.1 g (93%)

of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 6]

4-[(R)-2-Iodo-1-(methyl)ethyl]-pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 74]



3,4-dl-trans 3,4-dl-trans 3,4-dl-trans

Triethylamine (2.7 mL, 19.1 mmol) and mesyl chloride (1.2 mL, 15.3 mmol) were added to a solution of 4-[(R)-2-hydroxy-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (4.1 g, 12.8 mmol) in dichloromethane (100 mL) under ice-cooling, and then the mixture was stirred at room temperature for 30 minutes. After adding methanol to the reaction mixture, the mixture was blended with a mixture of ethyl acetate and a 10% citric acid solution. The organic layer was washed with brine and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in acetone (100 mL). Sodium iodide (4.1 g, 27.4 mmol) was added, and the mixture was heated to reflux for 20 hours. The reaction mixture was

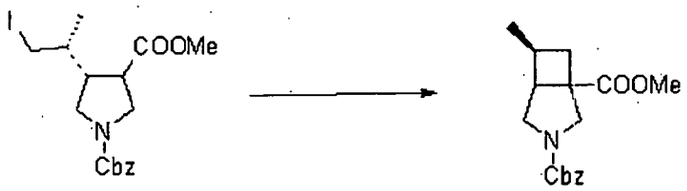
cooled and then the solvent was evaporated under reduced pressure. The resulting residue was blended with a mixture of ethyl acetate and water. The organic layer was washed with a saturated sodium thiosulfate solution and brine, dried over magnesium sulfate, and then filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 7:3) to give 5.0 g (84%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.33 (5H, m), 5.13 (2H, s), 3.83-3.71 (4H, m), 3.58-3.51 (1H, m), 3.27-3.23 (1H, m), 3.18-3.09 (2H, m), 2.92-2.83 (1H, m), 2.64-2.55 (1H, m), 1.81-1.75 (1H, m), 1.53-1.48 (1H, m), 1.06-1.01 (3H, m).

[Reference Example 7]

(S)-6-Methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester 1-methyl ester

[Formula 75]



3,4-dl-trans

A 0.5 M solution of potassium hexamethyldisilazide in toluene (28 mL, 14.0 mmol) was added dropwise to a solution

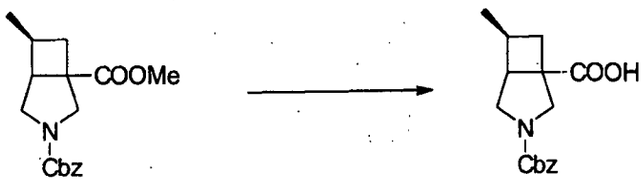
of 4-[(R)-2-iodo-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (5.0 g, 11.5 mmol) in anhydrous tetrahydrofuran (100 mL) in an argon atmosphere at -78°C. After completion of dropwise addition, the mixture was stirred at the same temperature for 30 minutes. An ammonium chloride solution was added, and the mixture was heated to room temperature. After extraction with ethyl acetate, drying over magnesium sulfate, and filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 7:3) to give 3.2 g (91%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.32 (5H, m), 5.17-5.14 (2H, m), 3.94 (0.5H, dd, J=10.86, 18.92 Hz), 3.76-3.69 (5H, m), 3.46 (0.5H, d, J=11.72 Hz), 3.36 (0.5H, dd, J=6.10, 11.47 Hz), 3.25 (0.5H, dd, J=8.06, 11.96 Hz), 3.06 (0.5H, t, J=8.30 Hz), 2.73-2.65 (1.5H, m), 2.13-2.09 (1.5H, m), 1.11 (1.5H, d, J=6.10 Hz), 0.94 (1.5H, brs).

[Reference Example 8]

(S)-6-Methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester

[Formula 76]

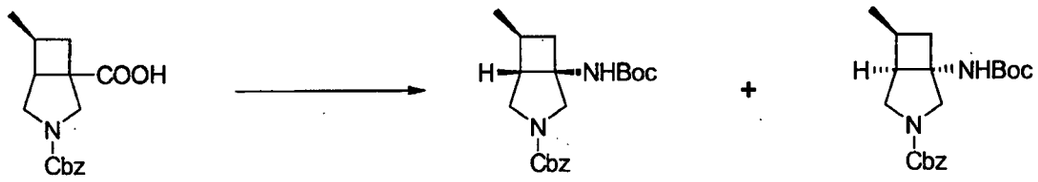


A 1N sodium hydroxide solution (21 ml) was added dropwise to a mixed solution of (S)-6-methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester 1-methyl ester (3.2 g, 10.4 mmol) in tetrahydrofuran (60 ml) and methanol (20 ml) under ice-cooling, and the mixture was stirred for 30 minutes. The reaction solution was neutralized with 1N hydrochloric acid, followed by extraction with ethyl acetate. The extract was dried over magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give 3.0 g (quantitative) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 9]

(S)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (optical isomer A, optical isomer B)

[Formula 77]



Triethylamine (2.9 mL, 20.7 mmol) and diphenyl

phosphoazide (3.4 mL, 15.6 mmol) were added to a solution of (S)-6-methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester (3.0 g, 10.4 mmol) in toluene (60 mL) at room temperature, and then tert-butyl alcohol (60 mL) was added. The mixture was heated with stirring at 100°C for 15 hours. The reaction mixture was cooled, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 8:2) to give the diastereomer mixture title compound (3.1 g) as a colorless oil. The diastereomers were separated by Chiralpak AD (2 cm, hexane:isopropyl alcohol = 92.5:7.5, flow: 30 mL/min) to give 1.48 g (40%) of a first fraction colorless oil (optical isomer A) and 1.38 g (37%) of a second fraction colorless oil (optical isomer B).

Optical isomer A:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.14 (2H, s), 4.81-4.76 (1H, m), 3.84 (1H, d, J=10.70 Hz), 3.61-3.53 (3H, brm), 2.43-2.31 (2H, m), 1.92-1.86 (1H, m), 1.75-1.68 (1H, m), 1.43 (9H, s), 1.14 (3H, d, J=6.80 Hz).

Optical isomer B:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.30 (5H, m), 5.16 (2H, s), 4.87-4.73 (1H, brm), 3.88-3.79 (1H, m), 3.72 (1H, d, J=11.00 Hz), 3.43-3.28 (2H, brm), 2.89-2.77 (1H, brm),

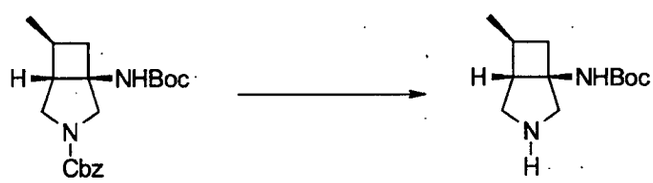
2.67-2.58 (1H, m), 2.32 (1H, t, J=11.70 Hz), 1.76-1.68 (1H, m), 1.44 (9H, s), 0.95-0.92 (3H, m).

Based on NMR comparison between the more polar isomer and the less polar isomer, the optical isomer A was identified as (1R,5S,6S)-1-tert-butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester, and the optical isomer B was identified as (1S,5R,6S)-1-tert-butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester.

[Reference Example 10]

(1R,5S,6S)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane

[Formula 78]



(1R,5S,6S)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (1.4 g, 3.9 mmol) was dissolved in a mixed solvent of methanol (20 mL) and tetrahydrofuran (10 mL). A small amount of 10% palladium-carbon (50% wet) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give

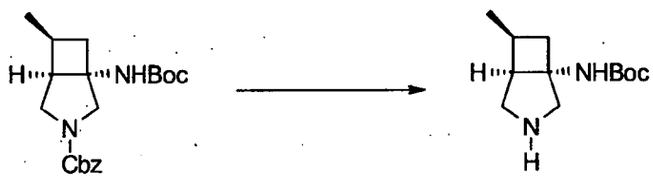
0.89 g (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.80 (1H, brs), 3.09 (1H, d, J=11.20 Hz), 3.02 (2H, dd, J=5.40, 11.20 Hz), 2.82 (2H, d, J=11.20 Hz), 2.27-2.22 (2H, m), 1.77-1.69 (2H, m), 1.44 (9H, s), 1.17 (3H, d, J=6.60 Hz).

[Reference Example 11]

(1S,5R,6S)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane

[Formula 79]



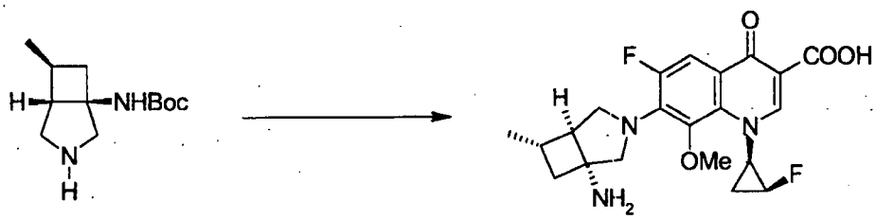
(1S,5R,6S)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (1.4 g, 3.8 mmol) was dissolved in a mixed solvent of methanol (20 mL) and tetrahydrofuran (10 mL). A small amount of 10% palladium-carbon (50% wet) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give 0.85 g (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.88 (1H, brs), 3.06 (1H, d, J=12.00 Hz), 2.96-2.89 (2H, m), 2.71-2.61 (3H, m), 2.39-2.33 (1H, m), 1.58 (1H, dd, J=7.40, 12.80 Hz), 1.45 (9H, s), 0.94 (3H, d, J=6.80 Hz).

[Example 1]

7-{(1R,5S,6S)-1-Amino-6-methyl-3-azabicyclo[3.2.0]hept-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 80]



(1R,5S,6S)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane (870 mg, 3.84 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (1.25 g, 3.46 mmol) were dissolved in dimethyl sulfoxide (15 mL). Triethylamine (0.64 mL) was added, and the mixture was stirred at 40°C for 12 hours. After cooling the reaction solution with ice, water was added, and the precipitate was collected by filtration, washed with water, and dried. The precipitate was dissolved in ethanol (140 mL). Water (30 mL) and triethylamine (0.64 mL) were added, and the mixture was heated to reflux for five hours. The reaction mixture

was diluted with ethyl acetate and washed with a 10% citric acid solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. Concentrated hydrochloric acid (25 mL) was added to the residue, and the mixture was stirred at room temperature for one hour. Then, the reaction solution was washed with chloroform. The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform-methanol (9:1) eight times. The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol, and the insoluble material was removed by filtration. The solvent was evaporated under reduced pressure, and the resulting powder was dried under reduced pressure to give 562 mg (35%) of the title compound as a pale yellow solid. ^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.49 (1H, brs), 7.70 (1H, d, J=13.70 Hz), 5.03-4.85 (1H, m), 4.09-4.03 (1H, m), 3.90 (1H, d, J=10.50 Hz), 3.67 (3H, s), 3.48 (1H, d, J=10.50 Hz), 3.03 (1H, d, J=10.50 Hz), 2.44 (1H, dd, J=12.00, 8.80 Hz), 2.15 (1H, t, J=5.10 Hz), 1.92-1.84 (1H, m), 1.69-1.62 (1H, m), 1.61-1.49 (1H, m), 1.14 (3H, d, J=7.10 Hz).

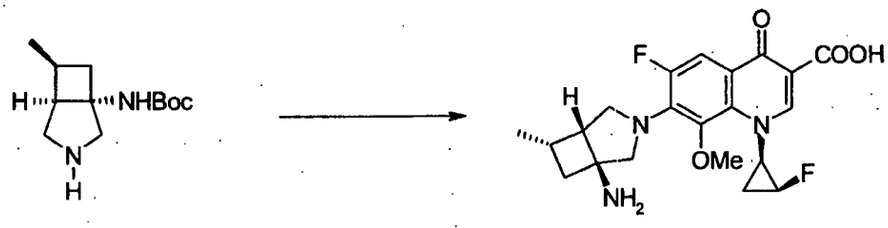
Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.7H_2O \cdot 0.2EtOH$: C, 58.25; H, 5.85; F, 8.61; N, 9.52. Found: C, 58.22; H, 5.84; F, 8.47; N, 9.37.

MS (ESI) m/z: 420 $(M+H)^+$.

[Example 2]

7-{(1S,5R,6S)-1-Amino-6-methyl-3-azabicyclo[3.2.0]hept-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 81]



(1S,5R,6S)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane (820 mg, 3.62 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (1.18 g, 3.26 mmol) were dissolved in dimethyl sulfoxide (15 mL). Triethylamine (0.61 mL) was added, and the mixture was stirred at 40°C for 12 hours. After cooling the reaction solution with ice, water was added, and the precipitate was collected by filtration, washed with water, and dried. The precipitate was dissolved in ethanol (120 mL). Water (30 mL) and triethylamine (0.61 mL) were added, and the mixture was heated to reflux for five hours. The reaction mixture

was diluted with ethyl acetate and washed with a 10% citric acid solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. Concentrated hydrochloric acid (25 mL) was added to the residue, and the mixture was stirred at room temperature for one hour. Then, the reaction solution was washed with chloroform. The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform-methanol (9:1) six times. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol, and the insoluble material was removed by filtration. The solvent was evaporated under reduced pressure, and the resulting powder was dried under reduced pressure to give 1.1 g (72%) of the title compound as a pale yellow solid.

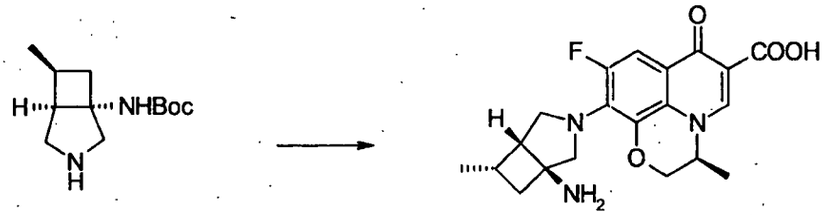
^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.46 (1H, d, J=2.20 Hz), 7.72 (1H, d, J=13.70 Hz), 5.10-4.90 (1H, m), 4.07-4.02 (1H, m), 3.75 (1H, d, J=11.20 Hz), 3.64 (3H, s), 3.64-3.59 (1H, m), 3.49-3.47 (1H, m), 3.09 (1H, d, J=10.00 Hz), 2.68-2.60 (1H, m), 2.51 (1H, t, J=7.30 Hz), 2.20 (1H, t, 10.5 Hz), 1.85 (1H, dd, J=8.50, 12.70 Hz), 1.63-1.42 (2H, m), 0.96 (3H, d, J=7.30 Hz).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.7H_2O$: C, 58.38; H, 5.69; F, 8.79; N, 9.73. Found: C, 58.24; H, 5.69; F, 8.59; N, 9.52. MS (ESI) m/z: 420 $(M+H)^+$.

[Example 3]

10-{(1S,5R,6S)-1-Amino-6-methyl-3-azabicyclo[3.2.0]hept-3-yl}-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid

[Formula 82]



(1S,5R,6S)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane (546.3 mg, 2.41 mmol) was dissolved in dimethyl sulfoxide (12 mL). 9,10-Difluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF_2 chelate (794.1 mg, 2.41 mmol) and triethylamine (1221 mg, 12.07 mmol) were added, and the mixture was stirred for five days. Then, 90% aqueous ethanol (135 mL) and triethylamine (15 mL) were added to the reaction mixture, which was stirred at 80°C for 4.5 hours. The solvent was evaporated under reduced pressure and a 10% citric acid solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium

sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with dichloromethane. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting solid was washed with ethanol and dried under reduced pressure to give the title compound (695 mg) as a pale yellow solid.

mp: 122-124°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.31 (1H, s), 7.46 (1H, d, J=13.67 Hz), 4.55 (1H, d, J=6.84 Hz), 4.46 (1H, d, J=11.47 Hz), 4.30 (1H, d, J=11.47 Hz), 3.71 (1H, d, J=10.74 Hz), 3.45 (1H, d, J=9.77 Hz), 3.27 (1H, t, J=8.79 Hz), 3.09 (1H, d, J=9.77 Hz), 2.58-2.56 (1H, m), 2.37 (1H, t, J=7.81 Hz), 2.12 (1H, t, J=11.47 Hz), 1.78 (1H, dd, J=12.33, 8.42 Hz), 1.48 (3H, d, J=6.59 Hz), 0.94 (3H, d, J=7.08 Hz).

Anal; Calcd for $C_{20}H_{22}FN_3O_4 \cdot H_2O$: C, 59.25; H, 5.97; N, 10.36; F, 4.69. Found: C, 59.41; H, 5.65; N, 10.36; F, 4.97.

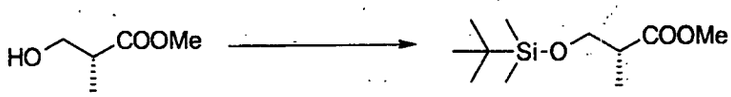
MS (EI) m/z: 388 $(M+H)^+$.

IR (ATR) ν: 2956, 2929, 2866, 1716, 1612, 1579, 1523, 1450, 1385, 1335, 1298, 1255 cm^{-1}.

[Reference Example 12]

(R)-3-(tert-Butyldimethylsilyloxy)-2-methylpropionic acid methyl ester

[Formula 83]



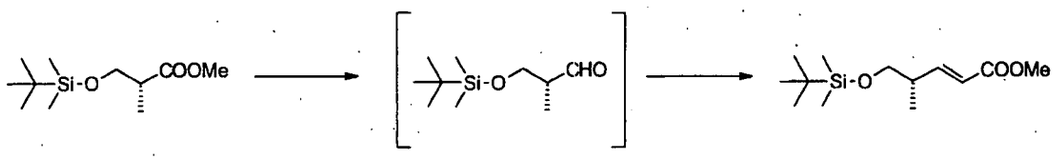
Imidazole (6.44 g, 42.8 mmol) and tert-butyldimethylsilyl chloride (6.05 g, 88.8 mmol) were added to a solution of (R)-3-hydroxy-2-methylpropionic acid methyl ester (5.0 g, 42.33 mmol) in dimethylformamide (50 mL), and the mixture was stirred at room temperature for 1.5 hours. Water was added to the reaction mixture, followed by extraction with hexane twice. The extract was then dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to give 9.3 g (95%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.76-3.72 (1H, m), 3.64 (3H, s), 3.63-3.59 (1H, m), 2.65-2.57 (1H, m), 1.10 (3H, d, J=6.84 Hz), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s).

[Reference Example 13]

(E)-(S)-5-(tert-Butyldimethylsilyloxy)-4-methylpent-2-ene acid methyl ester

[Formula 84]



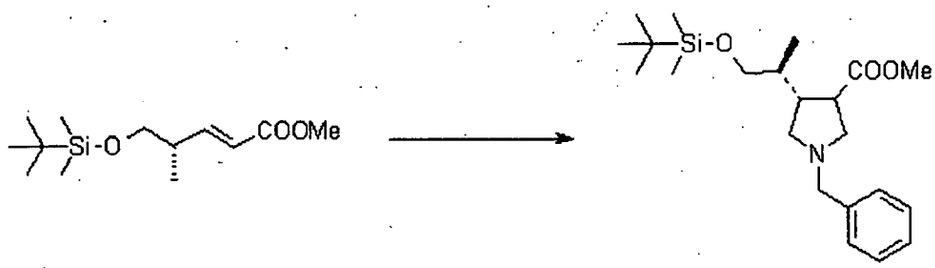
Diisobutylaluminum hydride (1 M solution in hexane, 17.2 mL) was added to a solution of (R)-3-(tert-butyldimethylsilyloxy)-2-methylpropionic acid methyl ester (4.0 g, 17.2 mmol) in dichloromethane (100 mL) at -78°C, and the mixture was stirred at the same temperature for four hours. A saturated potassium sodium tartrate solution was added to the reaction mixture which was then stirred while heating to room temperature. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure to give aldehyde (3.5 g) as a colorless oil. The aldehyde was dissolved in dichloromethane (50 mL). Triphenylphosphonylideneacetic acid methyl ester (7.08 g, 20.75 mmol) was added under ice-cooling, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 3.8 g (85%) of the title compound as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.94 (1H, dd, J=7.10, 15.90 Hz), 5.84 (1H, dd, J=1.20, 15.90 Hz), 3.73 (3H, s), 3.57-3.49

(2H, m), 2.53-2.46 (1H, m), 1.05 (3H, d, J=6.80 Hz), 0.89 (9H, s), 0.04 (6H, s).

[Reference Example 14]

1-Benzyl-4-[(S)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-3-carboxylic acid methyl ester

[Formula 85]



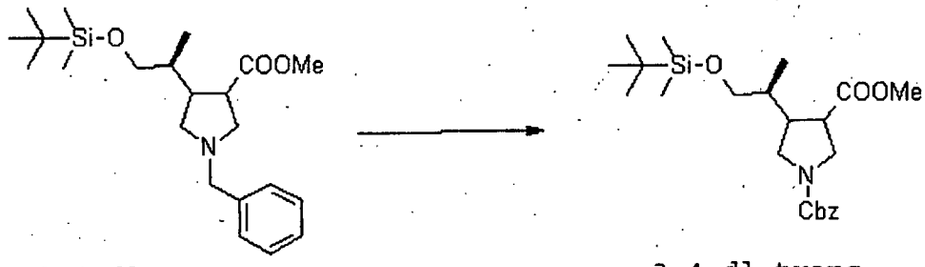
3,4-dl-trans

N-Benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine (2.97 mL, 11.6 mmol) was added to a solution of (E)-(S)-5-(tert-butyldimethylsilyloxy)-4-methylpent-2-ene acid methyl ester (2.5 g, 9.67 mmol) in dichloromethane (20 mL), and then a trace amount of trifluoroacetic acid was added. The mixture was stirred for 30 minutes and then saturated sodium bicarbonate water was added. The organic layer was separated and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 3.0 g (78%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 15]

4-[(S)-2-(tert-Butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 86]



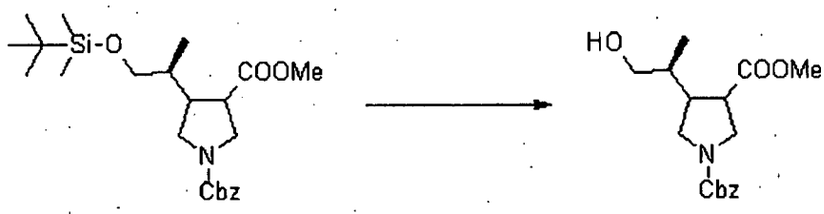
3,4-dl-trans 3,4-dl-trans

Benzyloxycarbonyl chloride (3.25 mL, 22.8 mmol) was added to a solution of 1-benzyl-4-[(S)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-3-carboxylic acid methyl ester (2.97 g, 7.58 mmol) in dichloromethane (20 mL), and the mixture was stirred for one hour. Saturated sodium bicarbonate water was added to the reaction mixture. The organic layer was separated, dried over magnesium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give 3.1 g (96%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

[Reference Example 16]

4-[(S)-2-Hydroxy-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 87]



3,4-dl-trans 3,4-dl-trans

Hydrogen fluoride-pyridine (2 mL) was added to a solution of 4-[(S)-2-(tert-butyldimethylsilyloxy)-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (6.0 g, 7.1 mmol) in pyridine (20 mL) under ice-cooling, and the mixture was stirred at room temperature for 13 hours. Further 2 mL of hydrogen fluoride-pyridine was added, and the mixture was stirred for 23 hours. The reaction mixture was poured into ice water, followed by extraction with ethyl acetate and washing with 1N hydrochloric acid and brine. After drying over magnesium sulfate and filtration, the solvent was evaporated under reduced pressure to give 4.5 g (quantitative) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

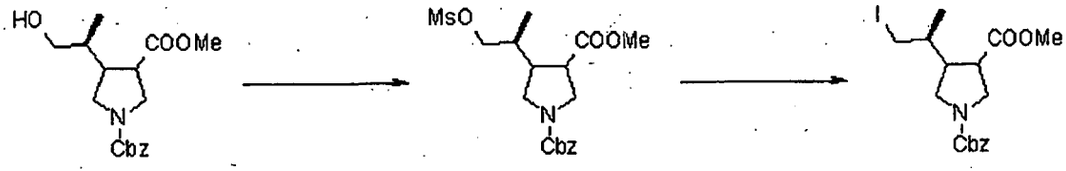
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m), 5.13 (2H, brs), 3.87-3.75 (2H, brm), 3.72 (3H, s), 3.52-3.47 (3H, m), 3.27-

3.11 (1H, m), 2.98-2.90 (1H, m), 2.69-2.58 (1H, m), 1.82-1.66 (2H, m), 0.95 (3H, d, J=19.80 Hz).

[Reference Example 17]

4-[(S)-2-Iodo-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester

[Formula 88]



3,4-dl-trans 3,4-dl-trans 3,4-dl-trans

Triethylamine (3.4 mL, 24 mmol) and mesyl chloride (1.5 mL, 19.2 mmol) were added to a solution of 4-[(S)-2-hydroxy-1-(methyl)ethyl]pyrrolidine-1,3-dicarboxylic acid 1-benzyl ester 3-methyl ester (5.1 g, 16 mmol) in dichloromethane (50 mL) under ice-cooling, and then the mixture was stirred at room temperature for 30 minutes. After adding methanol to the reaction mixture, the mixture was blended with a mixture of ethyl acetate and a 10% citric acid solution. The organic layer was washed with brine and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure, and then the residue was dissolved in acetone (100 mL). Sodium iodide (4.8 g, 32 mmol) was added, and the mixture was heated to reflux for 20 hours. The reaction mixture was cooled and then the solvent was evaporated under reduced

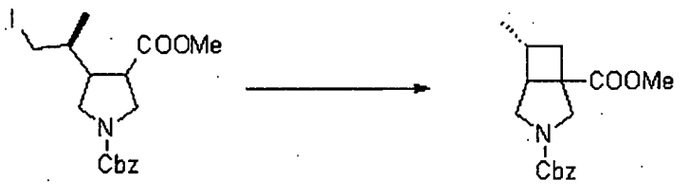
pressure. The resulting residue was blended with a mixture of ethyl acetate and water. The organic layer was washed with a saturated sodium thiosulfate solution and brine, dried over magnesium sulfate, and then filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 7:3) to give 6.5 g (94%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.35 (5H, m), 5.13 (2H, s), 3.83-3.71 (4H, m), 3.58-3.51 (1H, m), 3.27-3.23 (1H, m), 3.18-3.09 (2H, m), 2.92-2.83 (1H, m), 2.64-2.55 (1H, m), 1.59-1.48 (2H, m), 1.02 (3H, d, J=6.60 Hz).

[Reference Example 18]

(R)-6-Methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester 1-methyl ester

[Formula 89]



3,4-dl-trans

A 0.5 M solution of potassium hexamethyldisilazide in toluene (33 mL, 16.5 mmol) was added dropwise to a solution of 4-[(S)-2-iodo-1-(methyl)ethyl]pyrrolidine-1,3-

dicarboxylic acid 1-benzyl ester 3-methyl ester (6.4 g, 14.8 mmol) in anhydrous tetrahydrofuran (100 mL) in an argon atmosphere at -78°C. After completion of dropwise addition, the mixture was stirred at the same temperature for 30 minutes. An ammonium chloride solution was added, and the mixture was heated to room temperature. After extraction with ethyl acetate, drying over magnesium sulfate, and filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 7:3) to give 3.5 g (78%) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.29 (5H, m), 5.18 (2H, brs), 3.97-3.89 (1H, m), 3.77-3.69 (4H, m), 3.46 (1H, d, J=11.70 Hz), 3.25 (1H, dd, J=12.10, 7.90 Hz), 3.08-3.03 (1H, m), 2.60-2.75 (2H, m), 1.51-1.57 (1H, m), 0.94 (3H, brs).

[Reference Example 19]

(R)-6-Methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester

[Formula 90]



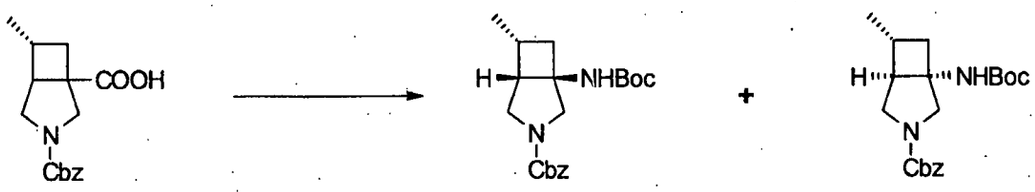
A 1N sodium hydroxide solution (23 mL) was added dropwise to a mixed solution of (R)-6-methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester 1-methyl ester (3.5 g, 11.5 mmol) in tetrahydrofuran (60 mL) and methanol (20 mL) under ice-cooling, and the mixture was stirred for 30 minutes. The reaction solution was neutralized with 1N hydrochloric acid, followed by extraction with ethyl acetate. The extract was dried over magnesium sulfate and filtered. The solvent was evaporated under reduced pressure to give 3.4 g (quantitative) of the diastereomer mixture title compound as a colorless oil. The diastereomers were used for the next step without separation.

^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.38-7.30 (5H, m), 5.19 (2H, brs), 4.00-3.91 (1H, m), 3.81-3.70 (1H, m), 3.50 (1H, d, J=11.70 Hz), 3.27 (1H, dd, J=11.70, 7.80 Hz), 3.11 (1H, t, J=7.70 Hz), 2.80-2.66 (2H, m), 0.95 (3H, s).

[Reference Example 20]

(R)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (optical isomer C, optical isomer D)

[Formula 91]



Triethylamine (3.2 mL, 22.8 mmol) and diphenyl phosphoazide (3.7 mL, 17.1 mmol) were added to a solution of (R)-6-methyl-3-azabicyclo[3.2.0]heptane-1,3-dicarboxylic acid 3-benzyl ester (3.3 g, 11.4 mmol) in toluene (70 mL) at room temperature, and then tert-butyl alcohol (70 mL) was added. The mixture was heated with stirring at 100°C for 15 hours. The reaction mixture was cooled, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 -> 8:2) to give 3.5 g of the diastereomer mixture title compound as a colorless oil. The diastereomers were separated by Chiralpak AD (2 cm, hexane:isopropyl alcohol = 92.5:7.5, flow: 30 mL/min) to give 1.72 g (42%) of a first fraction colorless oil (optical isomer C) and 1.68 g (41%) of a second fraction colorless oil (optical isomer D).

Optical isomer C:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.30 (5H, m), 5.16 (2H, s), 4.87-4.73 (1H, brm), 3.88-3.79 (1H, m), 3.72 (1H, d, J=11.00 Hz), 3.43-3.28 (2H, brm), 2.89-2.77 (1H, brm),

2.67-2.58 (1H, m), 2.32 (1H, t, J=11.70 Hz), 1.76-1.68 (1H, m), 1.44 (9H, s), 0.95-0.92 (3H, m).

Optical isomer D:

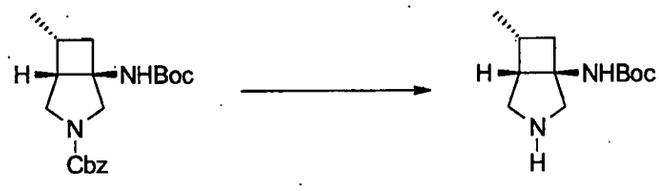
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.14 (2H, s), 4.81-4.76 (1H, m), 3.84 (1H, d, J=10.70 Hz), 3.61-3.53 (3H, brm), 2.43-2.31 (2H, m), 1.92-1.86 (1H, m), 1.75-1.68 (1H, m), 1.43 (9H, s), 1.14 (3H, d, J=6.80 Hz).

Based on the results of NOE test, the optical isomer C was identified as (1R,5S,6R)-1-tert-butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester, and the optical isomer D was identified as (1S,5R,6R)-1-tert-butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester.

[Reference Example 21]

(1R,5S,6R)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane

[Formula 92]



(1R,5S,6R)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (180 mg, 0.59 mmol) was dissolved in a methanol (5 mL). A small amount of 10% palladium-carbon (50% wet) was added,

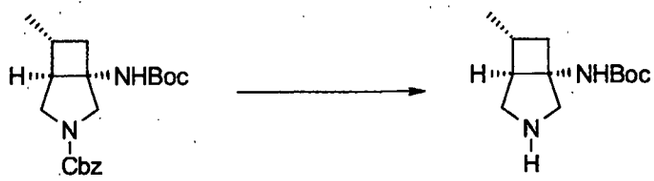
and the mixture was stirred in a hydrogen atmosphere for one hour. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give 114 mg (85%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.88 (1H, brs), 3.06 (1H, d, J=12.00 Hz), 2.96-2.89 (2H, m), 2.71-2.61 (3H, m), 2.39-2.33 (1H, m), 1.58 (1H, dd, J=12.80, 7.40 Hz), 1.45 (9H, s), 0.94 (3H, d, J=6.80 Hz).

[Reference Example 22]

(1S,5R,6R)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane

[Formula 93]



(1S,5R,6R)-1-tert-Butoxycarbonylamino-6-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylic acid benzyl ester (1.1 g, 3.1 mmol) was dissolved in a mixed solvent of methanol (20 mL) and tetrahydrofuran (10 mL). A small amount of 10% palladium-carbon (50% wet) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give

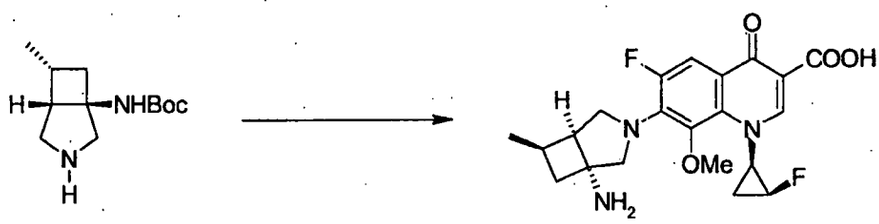
0.70 g (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.80 (1H, brs), 3.09 (1H, d, J=11.20 Hz), 3.02 (2H, dd, J=11.20, 5.40 Hz), 2.82 (2H, d, J=11.20 Hz), 2.27-2.22 (2H, m), 1.77-1.69 (2H, m), 1.44 (9H, s), 1.17 (3H, d, J=6.60 Hz).

[Example 4]

7-{(1R,5S,6R)-1-Amino-6-methyl-3-azabicyclo[3.2.0]hept-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 94]



(1R,5S,6R)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane (114 mg, 0.50 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (155 mg, 0.43 mmol) were dissolved in dimethyl sulfoxide (2 mL). Triethylamine (0.084 mL) was added, and the mixture was stirred at 40°C for 12 hours. After cooling the reaction solution with ice, water was added, and the precipitate was collected by filtration, washed with water, and dried. The precipitate was dissolved in ethanol (20 mL). Water (5 mL)

and triethylamine (0.084 mL) were added, and the mixture was heated to reflux for three hours. The reaction mixture was dissolved in ethyl acetate and washed with a 10% citric acid solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. Concentrated hydrochloric acid (5 mL) was added to the residue, and the mixture was stirred at room temperature for one hour. Then, the reaction solution was washed with chloroform. The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform-methanol (9:1) eight times. The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol, and the insoluble material was removed by filtration. The solvent was evaporated under reduced pressure, and the resulting powder was dried under reduced pressure to give 70 mg (39%) of the title compound as a pale yellow solid. ^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.50 (1H, s), 7.70 (1H, d, J=13.67 Hz), 5.02-4.84 (1H, m), 4.07-4.03 (1H, m), 3.74 (1H, d, J=10.25 Hz), 3.62 (3H, s), 3.60-3.56 (2H, m), 2.94 (1H, d, J=10.25 Hz), 2.63-2.55 (1H, m), 2.51-2.47 (1H, m), 2.24-

2.18 (1H, m), 1.85 (1H, dd, J=12.57, 7.93 Hz), 1.69-1.48 (2H, m), 0.87 (3H, d, J=6.84 Hz).

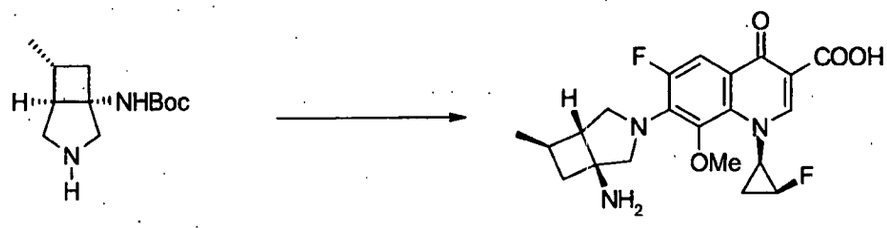
Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.4H_2O \cdot 0.3EtOH$: C, 58.90; H, 5.86; F, 8.63; N, 9.54. Found: C, 58.84; H, 5.78; F, 8.66; N, 9.51.

MS (ESI) m/z: 420 $(M+H)^+$.

[Example 5]

7-{(1S,5R,6R)-1-Amino-6-methyl-3-azabicyclo[3.2.0]hept-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 95]



(1S,5R,6R)-1-(tert-Butoxycarbonylamino)-6-methyl-3-azabicyclo[3.2.0]heptane (705 mg, 3.12 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (1.07 g, 2.96 mmol) were dissolved in dimethyl sulfoxide (12 mL). Triethylamine (0.52 mL) was added, and the mixture was stirred at 40°C for 12 hours. After cooling the reaction solution with ice, water was added, and the precipitate was collected by filtration, washed with water, and dried. The precipitate was dissolved in ethanol (120 mL). Water (30

mL) and triethylamine (0.52 mL) were added, and the mixture was heated to reflux for three hours. The reaction mixture was dissolved in ethyl acetate and washed with a 10% citric acid solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. Concentrated hydrochloric acid (25 mL) was added to the residue, and the mixture was stirred at room temperature for one hour. Then, the reaction solution was washed with chloroform. The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform-methanol (9:1) eight times. The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol, and the insoluble material was removed by filtration. The solvent was evaporated under reduced pressure, and the resulting powder was dried under reduced pressure to give 740 mg (57%) of the title compound as a pale yellow solid. ^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, d, J=1.71 Hz), 7.70 (1H, d, J=13.67 Hz), 5.07-4.88 (1H, m), 4.08-4.03 (1H, m), 3.73-3.63 (2H, m), 3.67 (3H, s), 3.55-3.51 (1H, m), 3.18 (1H, d, J=10.50 Hz), 2.40 (1H, dd, J=12.21, 8.79 Hz), 2.13

(1H, t, J=5.13 Hz), 1.95-1.89 (1H, m), 1.16 (3H, d, J=7.08 Hz), 1.66-1.57 (2H, m), 1.56-1.44 (1H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot HCl \cdot 1.3H_2O \cdot 0.6EtOH$: C, 52.60; H, 6.00; Cl, 6.99; F, 7.50; N, 8.29. Found: C, 52.35; H, 5.74; Cl, 6.84; F, 7.54; N, 8.01.

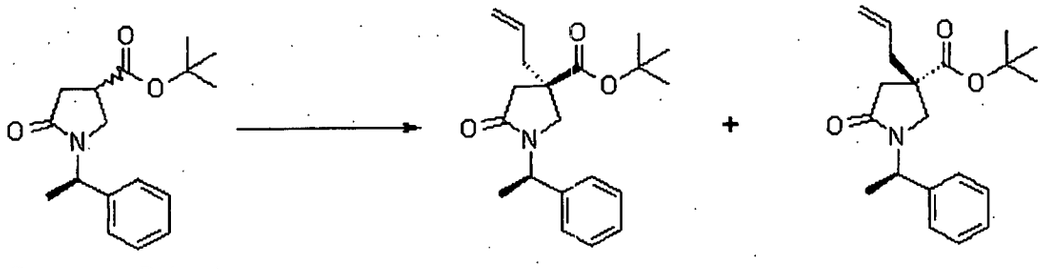
MS (ESI); m/z: 420 $(M+H)^+$.

[Reference Example 23]

(3R)-3-Allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (less polar isomer)

(3S)-3-Allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (more polar isomer)

[Formula 96]



5-Oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (30 g, 104 mmol) and allyl bromide (62.71 g, 518 mmoL) were dissolved in dimethylformamide (300 mL), and the atmosphere was replaced with argon. Sodium hydride (55% oil dispersion, 11.3 g, 259 mmol) was added under ice-cooling, and the mixture was stirred at room temperature for five hours. A 10% tartaric acid

solution was added, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. Then, the residue was separated and purified by silica gel chromatography (hexane:ethyl acetate = 100:0 -> 80:20 -> 65:35) to give 15.8 g (46%) of a colorless oil as a first fraction (less polar isomer) and 15.1 g (44%) of a colorless oil as a second fraction (more polar isomer). The resulting more polar isomer was left to stand at room temperature and crystallized.

The absolute configuration at the 3-position of each isomer was determined based on X-ray crystallography of the product described in Reference Example 24 after converting the more polar isomer to the product.

Less polar isomer:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.52-5.42 (2H, m), 4.95 (1H, dd, J=10.30, 1.00 Hz), 4.78 (1H, dd, J=17.10, 1.20 Hz), 3.60 (1H, d, J=10.30 Hz), 2.86 (1H, d, J=17.10 Hz), 2.80 (1H, d, J=10.30 Hz), 2.35 (1H, d, J=17.10 Hz), 2.27 (1H, dd, J=13.70, 6.80 Hz), 2.16 (1H, dd, J=13.70, 7.80 Hz), 1.52 (3H, d, J=7.30 Hz), 1.44 (9H, s).

More polar isomer:

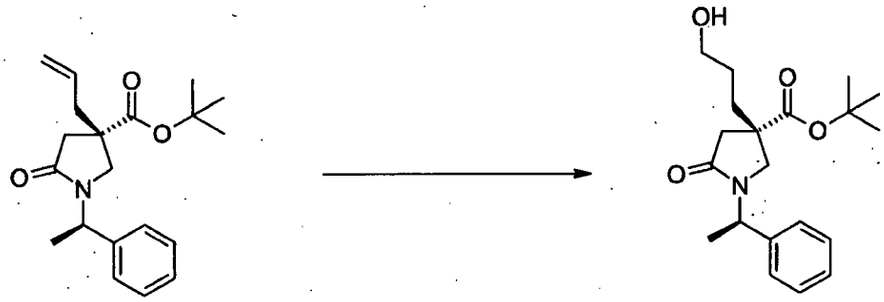
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.72-5.62 (1H, m), 5.49 (1H, q, J=7.20 Hz), 5.15 (1H, s), 5.13-5.10 (1H,

m), 3.28 (1H, d, J=10.30 Hz), 3.16 (1H, d, J=10.30 Hz), 2.88 (1H, d, J=17.10 Hz), 2.48-2.35 (3H, m), 1.51 (3H, d, J=7.10 Hz), 1.35 (9H, s).

[Reference Example 24]

(3S)-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (derived from more polar isomer)

[Formula 97]



more polar

(3S)-3-Allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (more polar isomer) (51.5 g, 0.156 mol) was dissolved in tetrahydrofuran (780 mL). Then, a 0.5 M solution of 9-BBN in tetrahydrofuran (345 mL, 0.173 mol) was added dropwise from a dropping funnel in a nitrogen stream under cooling and stirring in an ice salt bath at an internal temperature of 0°C. After completion of the dropwise addition, the mixture was stirred at the same temperature for 30 minutes and subsequently at room temperature for 1.5 hours. The mixture was cooled again in an ice salt bath, and a 0.5 M solution of 9-BBN in

tetrahydrofuran (156 mL, 78 mmol) was added dropwise from a dropping funnel at an internal temperature of 2°C. After completion of the dropwise addition, the mixture was stirred at the same temperature for 30 minutes and then at room temperature for 1.5 hours. The mixture was cooled again in an ice salt bath, and a 0.5 M solution of 9-BBN in tetrahydrofuran (120 mL, 60 mmol) was added dropwise from a dropping funnel at an internal temperature of 2°C. After completion of the dropwise addition, the mixture was stirred at the same temperature for 30 minutes and then at room temperature for one hour. The mixture was cooled again in an ice salt bath, and 780 mL of a 1N sodium hydroxide solution was added dropwise at an internal temperature of 0°C over 15 minutes (internal temperature: 2°C or less). The mixture was stirred for 10 minutes, and then 78 mL of a 30% hydrogen peroxide solution was added dropwise at an internal temperature of 4°C or less over 30 minutes. After vigorously stirring at the same temperature for 30 minutes, 1.6 L of diethyl ether was added. After addition of 1.6 L of a saturated sodium bicarbonate solution, the layers are separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, a 10% citric acid solution, a 10% sodium thiosulfate solution, and then brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated,

and the resulting residue was subjected to flash silica gel column chromatography and eluted with a mixed solvent of methanol-chloroform (1:50, v/v). The fractions containing the target substance were combined and concentrated and dried under reduced pressure to give 40.61 g (74.9%) of the title compound as a colorless oil. Further, part of the title compound was purified by recrystallization from diethyl ether to provide needle-like crystals which were used for X-ray crystallography. As a result, the absolute configuration at the 3-position of this product was determined as a (3S)-configuration.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.48 (1H, q, J=7.3 Hz), 3.62 (2H, t, J=6.2 Hz), 3.34 (1H, d, J=10.3 Hz), 3.14 (1H, d, J=10.3 Hz), 2.95 (1H, d, J=17.1 Hz), 2.33 (1H, d, J=16.8 Hz), 1.88-1.67 (3H, m), 1.51 (3H, d, J=7.1 Hz), 1.54-1.47 (1H, m), 1.33 (9H, s).

[Table 1]

X-ray crystallography conditions:

Crystal size 0.36 mm × 0.18 mm × 0.08 mm

Radiation CuKα (1.54178 Å)

Tube current 50 kV

Tube Voltage 80 mA

Diffractometer AFC7R

Temperature 25°C

Formula $C_{20}H_{29}NO_4$

Formula weight 347.45

Crystal system orthorhombic

Space group $P2_12_12$

Z value 4

Cell parameters a = 13.2806(14) Å b = 26.6894(16) Å

c = 5.8585(11) Å

α = 90.0000° β = 90.0000° γ = 90.0000°

d_{calc} 1.11g/cm^3

No. of reflection measured 1828 (unique)

μ 6.19cm^{-1}

Phase determination Direct method (software; *SIR92*)

Phase refinement Full matrix least-square

R1 5.3% = $\Sigma||Fo|-|Fc||/\Sigma|Fo|$ for $I>2.0\sigma$ data

R 7.0% = $\Sigma(Fo^2-Fc^2)/\Sigma Fo^2$

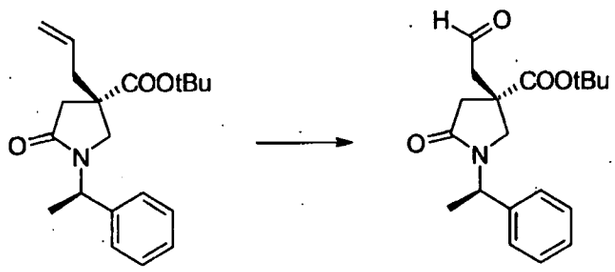
Rw 14.0% = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma w(Fo^2)^2]^{1/2}$

Data were collected under the measurement conditions shown in the above table, and then the initial phase was determined by the direct method, and the phase was refined by full matrix least-squares method. For refinement, an anisotropic temperature factor was applied to a non-hydrogen atom and the position of a hydrogen atom was determined by calculation to fix the coordinates. As a result of the analysis, the relative configuration of this compound is as shown in the ORTEP diagram of FIG. 1. The absolute configuration of the asymmetric carbon b was determined from the asymmetric carbon a having a known absolute configuration. The results are shown in FIG. 2.

[Reference Example 25]

(3S)-5-Oxo-3-(2-oxoethyl)-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 98]



A solution of (3S)-3-allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (3.29 g, 10.0 mmol) in methanol (100 mL) was bubbled with

ozone at -74°C. When the reaction solution turned blue, ozone bubbling was stopped and then the solution was bubbled with nitrogen at the same temperature. Sodium borohydride (568 mg) was added at the same temperature, and the mixture was stirred for 1.5 hours while heating to -40°C. The reaction solution was poured into a 10% citric acid solution (50 mL), and then the mixture was stirred sufficiently. The methanol component was evaporated, and then the aqueous layer was extracted with ethyl acetate (200 mL, 100 mL). The organic layer was washed with brine (50 mL × 2), and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure into a slurry. Hexane was added to the resulting residue, and the slurry was stirred. The solid was collected by filtration and dried to give 1.70 g of the title compound as a white solid. The filtrate was concentrated, hexane was added to the resulting residue, and the slurry was stirred. The solid was collected by filtration to give 0.66 g of the title compound as a white solid. The same operation was repeated to give 0.35 g of the title compound as a white solid (total yield: 2.71 g, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.71 (1H, s), 7.35-7.24 (5H, m), 5.50 (1H, q, J=7.3 Hz), 3.41 (1H, d, J=10.5 Hz), 3.20 (1H, d, J=10.5 Hz), 2.98 (1H, d, J=17.1 Hz), 2.92 (1H, d, J=17.8

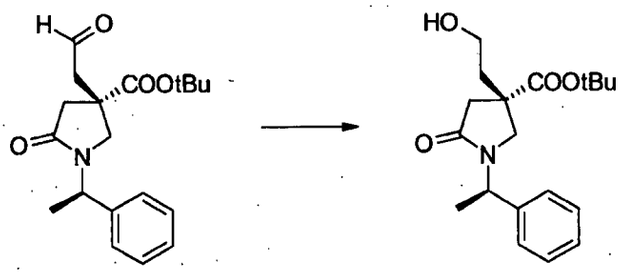
Hz), 2.87 (1H, d, J=17.8 Hz), 2.37 (1H, d, J=17.1 Hz), 1.51 (3H, d, J=7.3 Hz), 1.31 (9H, s).

MS (ESI) m/z: 332 $(M+H)^+$.

[Reference Example 26]

(3S)-3-(2-Hydroxyethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 99]



Sodium borohydride (465 mg) was added to a solution of (3S)-5-oxo-3-(2-oxoethyl)-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.71 g, 8.19 mmol) in methanol at -40°C. After heating to room temperature, a 10% citric acid solution was added to the reaction solution, and the mixture was stirred. The reaction solution was poured into a mixture of ethyl acetate (50 mL) and a 10% citric acid solution (10 mL), followed by extraction with ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (100 mL), and then the organic layers were combined and washed with brine (50 mL × 2). The resulting organic layer was dried over anhydrous sodium sulfate and filtered, and then the

filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1 -> 0:1 -> ethyl acetate-methanol = 10:1) to give 2.20 g (81%) of the title compound as a white solid.

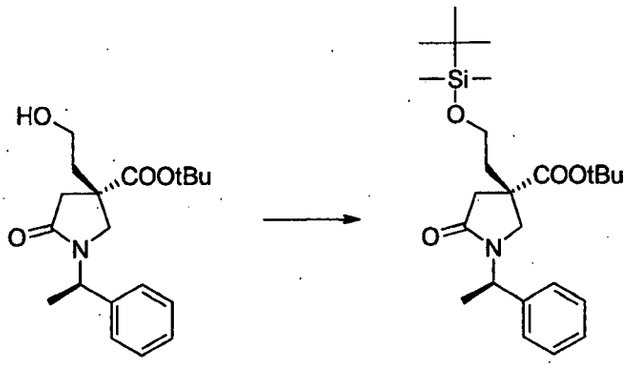
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.24 (5H, m), 5.48 (1H, q, J=7.1 Hz), 3.73-3.64 (2H, m), 3.38 (1H, d, J=10.2 Hz), 3.23 (1H, d, J=10.2 Hz), 2.97 (1H, d, J=17.0 Hz), 2.41 (1H, d, J=17.0 Hz), 2.05 (1H, dt, J=14.0, 6.8 Hz), 1.91 (1H, dt, J=14.0, 6.6 Hz), 1.51 (3H, d, J=7.1 Hz), 1.32 (9H, s).

MS (ESI) m/z: 334 $(M+H)^+$.

[Reference Example 27]

(3S)-3-[2-(tert-Butyldimethylsilyloxy)ethyl]-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 100]



Triethylamine (3.0 mL, 21.8 mmol) was added to a solution of (3S)-3-(2-hydroxyethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

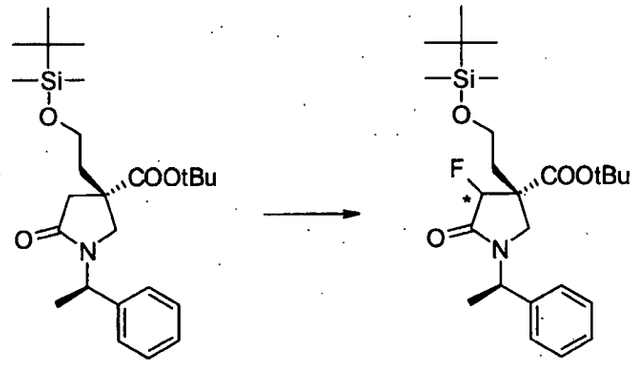
(2.42 g, 7.25 mmol) in dichloromethane (70 mL), and the mixture was cooled to 0°C. tert-Butyldimethylsilyl trifluoromethanesulfonate (2.50 mL, 10.9 mmol) was added dropwise, and the mixture was stirred at the same temperature for 1.5 hours. After addition of an ice piece and stirring, the reaction solution was poured into a mixture of ethyl acetate (50 mL) and saturated sodium bicarbonate (50 mL), followed by extraction with ethyl acetate (200 mL, 100 mL). The organic layers were combined and washed with brine (50 mL). After drying over anhydrous sodium sulfate and filtration, the solvent was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane:ethyl acetate = 4:1 -> 2:1) to give 2.84 g (88%) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 5.45 (1H, q, J=7.1 Hz), 3.62-3.57 (2H, m), 3.38 (1H, d, J=10.3 Hz), 3.26 (1H, d, J=10.3 Hz), 2.93 (1H, d, J=17.0 Hz), 2.42 (1H, d, J=17.0 Hz), 1.98 (1H, dt, J=13.7, 6.8 Hz), 1.88 (1H, dt, J=13.7, 6.7 Hz), 1.50 (3H, d, J=7.1 Hz), 1.31 (9H, s)

[Reference Example 28]

(3S)-3-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 101]



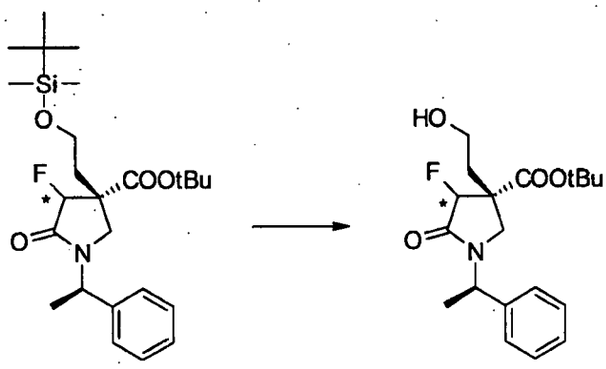
A 1.8 M solution of lithium diisopropylamide in tetrahydrofuran (4.10 mL) was added dropwise to a solution of (3S)-3-[2-(tert-butyldimethylsilyloxy)ethyl]-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester in tetrahydrofuran in a nitrogen atmosphere at -73°C over 10 minutes. After stirring at the same temperature for 15 minutes, a solution of N-fluorobenzenesulfonimide (2.63 g, 8.33 mmol) in tetrahydrofuran (18 mL) was added dropwise over 15 minutes. After stirring at the same temperature for 30 minutes, a saturated ammonium chloride solution (20 mL) was added, and the mixture was heated to 0°C. The reaction solution was poured into a mixture of ethyl acetate (100 mL) and 1 mol/mL hydrochloric acid (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was sequentially washed with a saturated sodium bicarbonate solution (50 mL) and brine (50 mL × 2) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Dichloromethane

was added to the resulting residue to prepare a slurry, and the solid was removed by filtration. The filtrate was concentrated, and the resulting solid was removed by filtration. The filtrate was further concentrated to give 3.44 g of the crude title compound as a pale yellow oil. The resulting crude was used for the next reaction without further purification.

[Reference Example 29]

(3S)-4-Fluoro-3-(2-hydroxyethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 102]



Acetic acid (0.66 mL, 11.54 mmol) and a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (8.3 mL, 8.3 mmol) were sequentially added to a solution of the crude (3S)-3-[2-(tert-butyldimethylsilyloxy)ethyl]-4-fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (3.44 g) in tetrahydrofuran in a nitrogen atmosphere at 0°C. After stirring at room temperature for 20 hours, the reaction solution was poured into a mixture

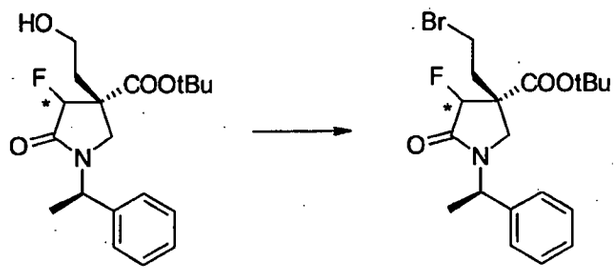
of ethyl acetate (100 mL) and a saturated sodium bicarbonate solution (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL × 2), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1) to give 2.06 g (91%, two steps) of the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.48 (1H, q, J=7.1 Hz), 5.21 (1H, d, J=51.7 Hz), 3.78-3.69 (2H, m), 3.38 (1H, dd, J=1.1, 10.5 Hz), 3.30 (1H, d, J=10.5 Hz), 2.10 (1H, m), 2.01 (1H, m), 1.56 (3H, d, J=7.1 Hz), 1.32 (9H, s).

[Reference Example 30]

(3S)-3-(2-Bromoethyl)-4-fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 103]



Carbon tetrabromide (1.88 g, 5.68 mmol) and triphenylphosphine (1.49 g, 5.68 mmol) were sequentially added to a solution of (3S)-4-fluoro-3-(2-hydroxyethyl)-5-

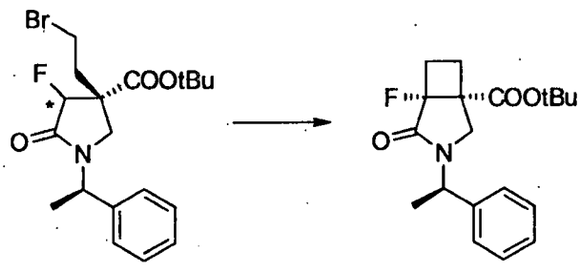
oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (1.66 g, 4.74 mmol) in dichloromethane (20 mL) in a nitrogen atmosphere at 0°C. After heating to room temperature, the reaction solution was stirred for one hour and concentrated to about 5 mL. The residue was purified by silica gel column chromatography (dichloromethane -> hexane:ethyl acetate = 2:1) to give 2.17 g (91%) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.48 (1H, q, J=7.1 Hz), 5.22 (1H, d, J=51.5 Hz), 3.39 (1H, ddd, J=5.5, 10.7, 11.0 Hz), 3.30-3.23 (3H, m), 2.42 (1H, dddd, J=1.2, 5.5, 11.0, 14.2 Hz), 2.32 (1H, dddd, J=2.4, 5.5, 10.7, 14.2 Hz), 1.57 (3H, d, J=7.1 Hz), 1.33 (9H, s).

[Reference Example 31]

(1S,5R)-5-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester

[Formula 104]



A 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran (5.02 mL) was added dropwise to a solution of (3S)-3-(2-bromoethyl)-4-fluoro-5-oxo-1-[(1R)-1-

phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.04 g, 4.92 mmol) in tetrahydrofuran (40 mL) in a nitrogen atmosphere at -72°C over 10 minutes. The mixture was stirred at the same temperature for 15 minutes and then at 0°C for 30 minutes. The reaction was quenched with a 10% citric acid solution (2 mL) and then poured into a mixture of ethyl acetate (100 mL) and a 10% citric acid solution (20 mL). After extraction with ethyl acetate (150 mL), the organic layer was washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give 1.41 g (86%) of the title compound as a white solid.

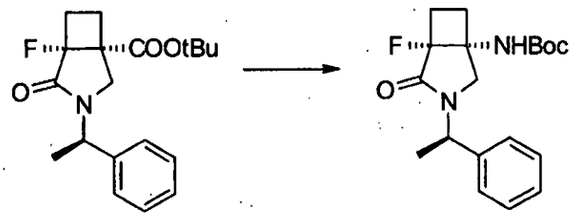
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.57 (1H, q, J=7.3 Hz), 3.53 (1H, d, J=10.7 Hz), 3.09 (1H, dd, J=4.9, 10.7 Hz), 2.76-2.51 (3H, m), 1.57 (3H, d, J=7.3 Hz), 1.45 (9H, s), 1.42 (1H, m).

MS (ESI) m/z: 334 $(M+H)^+$.

[Reference Example 32]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 105]



Trifluoroacetic acid (10 mL) was added to a solution of (1S,5R)-1-5-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (1.06 g, 3.18 mmol) in dichloromethane (10 mL). The mixture was stirred for four hours, and then the solvent was concentrated under reduced pressure. Toluene (40 mL) was added to the residue, and trifluoroacetic acid was removed by evaporation. The residue was dried under reduced pressure to give crude carboxylic acid as a pale yellow solid.

Triethylamine (0.89 mL) and diphenylphosphoryl azide (0.75 mL) were sequentially added to a solution of the crude carboxylic acid obtained above in toluene (10 mL) and tert-butyl alcohol (10 mL). The mixture was stirred at room temperature for 20 minutes, at 40°C for one hour, and further at 90°C for one hour. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1 -> 3:2) to give 811 mg (73%) of the title compound as a white amorphous.

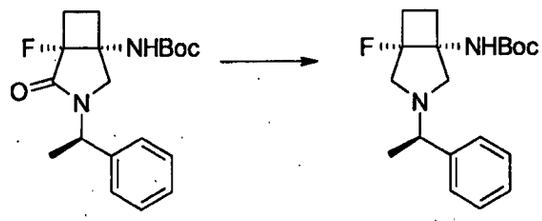
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.59 (1H, q, J=7.3 Hz), 5.36 (1H, br), 3.68 (1H, br), 2.96 (1H, brd, J=10.0 Hz), 2.66-2.45 (2H, m), 2.39 (1H, br), 1.72 (1H, dt, J=12.9, 9.0 Hz), 1.56 (3H, d, J=7.3 Hz), 1.40 (9H, s).

MS (ESI) m/z: 349 $(M+H)^+$.

[Reference Example 33]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 106]



A 1.16 M solution of a borane-tetrahydrofuran complex in tetrahydrofuran (6.0 mL) was added dropwise to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (811 mg, 2.33 mmol) in tetrahydrofuran (6.0 mL) at 0°C over five minutes. The mixture was heated to room temperature, stirred for five hours, and then cooled to -10°C. A mixture of ethanol (9.0 mL)-water (1.0 mL) was carefully added dropwise. After addition of triethylamine (3.0 mL) dropwise, the mixture was heated to reflux for one hour. The reaction solution was concentrated, and the precipitated white solid was removed by filtration through Celite. The filtrate was

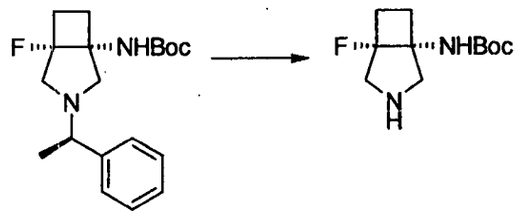
concentrated, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 4:1) to give 530 mg (68%) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.18 (5H, m), 5.19 (1H, br), 3.37 (1H, q, J=6.8 Hz), 3.27 (1H, dd, J=1.7, 9.0 Hz), 3.13 (1H, brd, J=8.3 Hz), 2.49-2.38 (2H, m), 2.23 (1H, m), 2.13-2.08 (2H, m), 2.00 (1H, m), 1.39 (9H, brs), 1.36 (3H, d, J=6.8 Hz).

[Reference Example 34]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.2.0]heptane

[Formula 107]



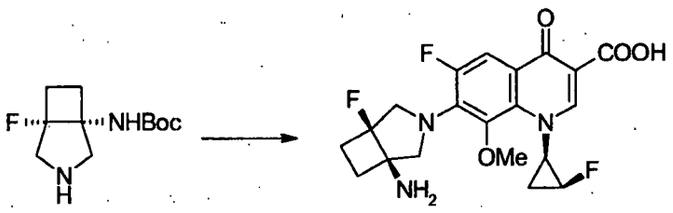
A 10% palladium-carbon catalyst (50% wet, 50 mg) was added to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (530 mg, 1.58 mmol) in ethanol, and the mixture was stirred in a hydrogen atmosphere at 50°C for five hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give 321 mg of crude amine as a white solid.

^{1}H-NMR (400 MHz, CD_3OD) δ: 3.07-3.00 (2H, m), 2.87-2.80 (2H, m), 2.35 (1H, m), 2.03-1.95 (2H, m), 1.67 (1H, dt, J=12.0, 9.0 Hz), 1.34 (9H, s), 1.00 (1H, dd, J=2.1, 6.2 Hz).

[Example 6]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.2.0]hept-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 108]



6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (577 mg, 1.60 mmol) and triethylamine (0.699 mL, 5.02 mmol) were sequentially added to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.2.0]heptane (crude; 321 mg) in dimethyl sulfoxide (5.0 mL). The mixture was heated with stirring at 40°C for 24 hours. Triethylamine (0.35 mL) was added, and the mixture was further stirred at the same temperature for 17 hours. Then, 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (58 mg) and triethylamine (0.125 mL) were added. Further, 6,7-difluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (480 mg, 240 mg) and triethylamine (0.389 mL, 0.195 mL) were added after 6 hours and 24 hours, respectively. After the final reagent addition, the mixture was stirred for 5.5 hours. Then, a mixture of ethanol:water = 4:1 (30 mL) and triethylamine (4.5 mL) were added to the reaction solution, and the mixture was heated to reflux for two hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and sequentially washed with a 10% citric acid solution (30 mL), water (30 mL × 2), and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue (890 mg) was dissolved in concentrated hydrochloric acid (4.0 mL), and the solution was stirred at room temperature for 10 minutes. The reaction solution was diluted with 6 M hydrochloric acid and washed with chloroform (5 mL × 15). The aqueous layer was adjusted to pH 13.2 with a saturated sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 mL × 3). The organic layer was dried over anhydrous sodium sulfate, and the drying agent was removed by filtration. Then, the filtrate was concentrated under reduced pressure. The

residue was sufficiently dried under vacuum and then dissolved in a mixed solvent of chloroform:methanol = 10:1 and filtered through a membrane filter. The filtrate was concentrated under reduced pressure to give a yellow brown solid. The resulting solid was purified by recrystallization from ethanol-aqueous ammonia to give 193 mg (33%) of the title compound as pale yellow needle-like crystals.

mp: 235°C (dec.).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, d, J=1.2 Hz), 7.73 (1H, d, J=13.4 Hz), 4.96 (1H, m), 4.13 (1H, m), 4.07 (1H, m), 3.72 (3H, s), 3.60 (1H, brd, J=10.4 Hz), 3.52 (1H, m), 3.42 (1H, brd, J=10.4 Hz), 2.51 (1H, m), 2.32 (1H, m), 1.99-1.92 (2H, m), 1.70-1.52 (2H, m).

Anal; Calcd for $C_{20}H_{20}F_3N_3O_4$: C, 56.74; H, 4.76; F, 13.46; N, 9.92. Found: C, 56.68; H, 4.71; F, 13.15; N, 9.86.

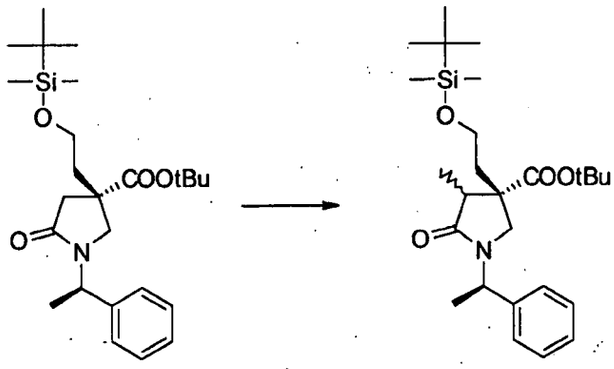
HRMS (FAB); m/z Calcd for $C_{20}H_{21}F_3N_3O_4$ $(M+H)^+$: 424.1484. Found: 424.1475.

IR (ATR) ν: 2938, 2842, 1720, 1616, 1544, 1511, 1450, 1436, 1365, 1324, 1276, 1222, 1180, 1159, 1135, 1052, 1010, 931 cm^{-1}.

[Reference Example 35]

(3S)-3-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 109]



A 1.8 M solution of lithium diisopropylamide in tetrahydrofuran (3.10 mL) was added dropwise to a solution of (3S)-3-[2-(tert-butyldimethylsilyloxy)ethyl]-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.24 g, 5.00 mmol) in tetrahydrofuran (20 mL) in a nitrogen atmosphere at -72°C over five minutes. After stirring at the same temperature for 10 minutes, methyl iodide (0.34 mL, 5.50 mmol) was added. The mixture was stirred at the same temperature for 15 minutes and then heated to -10°C over 10 minutes. Thereafter, a 10% citric acid aqueous solution (5 mL) was added. The reaction solution was poured into a mixture of ethyl acetate (100 mL) and 10% citric acid solution (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The resulting dark

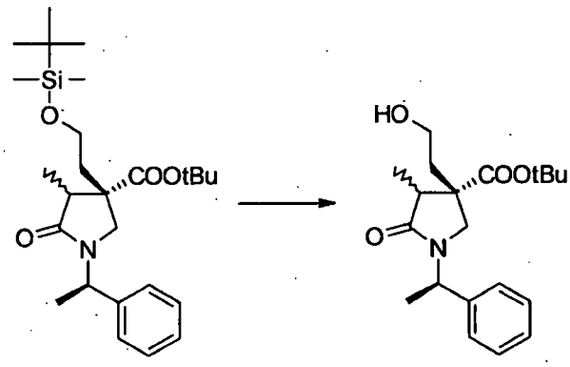
brown residue was used for the next reaction without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.46 (0.5H, q, J=7.1 Hz), 5.45 (0.5H, q, J=7.1 Hz), 3.73-3.54 (2H, m), 3.37 (0.5H, d, J=10.5 Hz), 3.36-3.31 (1H, m), 3.28 (0.5H, d, J=10.2 Hz), 2.75 (0.5H, q, J=7.3 Hz), 2.40 (0.5H, q, J=7.3 Hz), 2.03 (0.5H, m), 1.92 (0.5H, ddd, J=5.4, 7.2, 13.8 Hz), 1.83 (0.5H, m), 1.71 (0.5H, m), 1.51 (1.5H, d, J=7.1 Hz), 1.50 (1.5H, d, J=7.1 Hz), 1.35 (4.5H, s), 1.34 (4.5H, s), 1.21 (1.5H, d, J=7.3 Hz), 1.12 (1.5H, d, J=7.3 Hz), 0.88 (2×4.5H, s), 0.03 (2×1.5H, s), 0.02 (1.5H, s), 0.01 (1.5H, s).

[Reference Example 36]

(3S)-3-(2-Hydroxyethyl)-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 110]



The aforementioned crude (3S)-3-[2-(tert-butyldimethylsilyloxy)ethyl]-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

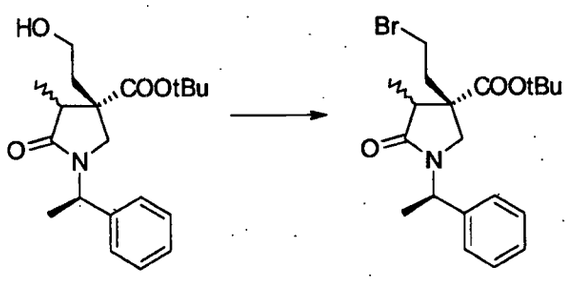
was dissolved in tetrahydrofuran (10 mL). Then, acetic acid (0.572 mL, 10.0 mmol) and a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (10.0 mL, 10.0 mmol) were sequentially added in a nitrogen atmosphere. After stirring at room temperature for 12 hours, the reaction solution was poured into a mixture of ethyl acetate (100 mL) and brine (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 -> 1:2) to give 1.56 g (90%, two steps) of the diastereomer mixture title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.25 (5H, m), 5.46 (0.5H, q, J=7.1 Hz), 5.45 (0.5H, q, J=7.1 Hz), 3.73-3.62 (2H, m), 3.35 (0.5H, d, J=10.5 Hz), 3.33 (0.5H, d, J=10.5 Hz), 3.26 (0.5H, d, J=10.5 Hz), 3.25 (0.5H, d, J=10.5 Hz), 2.78 (0.5H, q, J=7.3 Hz), 2.42 (0.5H, q, J=7.3 Hz), 2.13 (0.5H, dt, J=14.2, 6.6 Hz), 2.00 (0.5H, dt, J=14.2, 6.8 Hz), 1.84 (0.5H, dt, J=14.2, 6.4 Hz), 1.71 (0.5H, dt, J=14.2, 6.4 Hz), 1.52 (1.5H, d, J=7.1 Hz), 1.50 (1.5H, d, J=7.1 Hz), 1.37 (4.5H, s), 1.35 (4.5H, s), 1.22 (1.5H, d, J=7.3 Hz), 1.14 (1.5H, d, J=7.3 Hz).

[Reference Example 37]

(3S)-3-(2-Bromoethyl)-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 111]



Carbon tetrabromide (1.64 g, 4.95 mmol) and triphenylphosphine (1.30 g, 4.95 mmol) were sequentially added to a solution of (3S)-3-(2-hydroxyethyl)-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (1.56 g, 4.50 mmol) in dichloromethane (20 mL) in a nitrogen atmosphere at 0°C. After heating to room temperature, the reaction solution was stirred for 10 minutes and concentrated to about 5 mL. The residue was purified by silica gel column chromatography (dichloromethane -> hexane:ethyl acetate = 4:1 -> 2:1 -> 1.5:1) to give 1.30 g (70%) of the diastereomer mixture title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.47 (0.5H, q, J=7.1 Hz), 5.46 (0.5H, q, J=7.1 Hz), 3.35-3.19 (3H, m), 3.14 (0.5H, d, J=10.5 Hz), 3.13 (0.5H, d, J=10.5 Hz), 2.80 (0.5H, q, J=7.4 Hz), 2.48-2.39 (1H, m), 2.30 (0.5H, ddd, J=6.2, 10.4, 13.9 Hz), 2.19-2.02 (1H, m), 1.54 (1.5H, d,

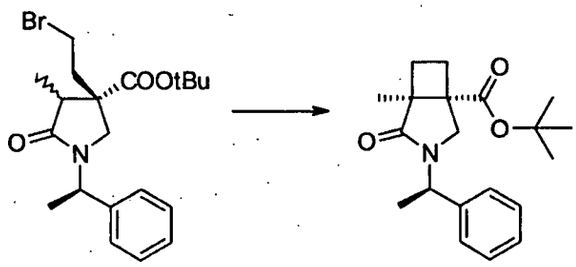
J=7.1 Hz), 1.52 (1.5H, d, J=7.1 Hz), 1.37 (4.5H, s), 1.36 (4.5H, s), 1.22 (1.5H, d, J=7.4 Hz), 1.14 (1.5H, d, J=7.4 Hz).

MS (ESI) m/z: 410 $(M+H)^+$.

[Reference Example 38]

(1S,5S)-5-Methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester

[Formula 112]



A 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran (3.8 mL, 3.80 mmol) was added dropwise to a solution of (3S)-3-(2-bromoethyl)-4-methyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (1.30 g, 3.17 mmol) in tetrahydrofuran (20 mL) in a nitrogen atmosphere at -72°C over seven minutes. The mixture was stirred at the same temperature for 30 minutes. After heating to -10°C and stirring for 1.5 hours, a 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran (4.0 mL, 4.0 mmol) was added over two minutes, and the mixture was stirred at 0°C for 20 hours. A 10% citric acid solution (20 mL) was added at the same temperature. The

reaction solution was poured into a mixture of ethyl acetate (100 mL) and a 10% citric acid solution (10 mL). After extraction with ethyl acetate (150 mL), the organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1) to give 0.845 g (81%) of the title compound as a white solid.

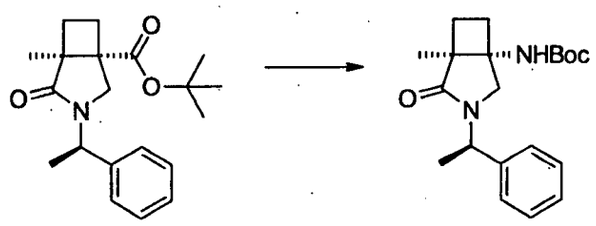
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.56 (1H, q, J=7.1 Hz), 3.42 (1H, d, J=10.2 Hz), 3.13 (1H, d, J=10.2 Hz), 2.65 (1H, ddd, J=4.7, 10.3, 11.9 Hz), 2.25 (1H, ddd, J=4.7, 9.5, 11.9 Hz), 2.09 (1H, m), 1.86 (1H, dt, J=11.9, 9.5 Hz), 1.57 (3H, d, J=7.1 Hz), 0.71 (9H, s), 1.25 (3H, s).

MS (ESI) m/z: 330 $(M+H)^+$.

[Reference Example 39]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 113]



Trifluoroacetic acid (5 mL) was added to a solution of (1S,5S)-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-

azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (0.845 g, 2.56 mmol) in dichloromethane (10 mL). The mixture was stirred for 15 hours, and then the reaction solution was concentrated under reduced pressure. Toluene (3 × 40 mL) was added to the residue, and trifluoroacetic acid was removed by evaporation. The residue was dried under reduced pressure to give crude carboxylic acid as a white solid.

Triethylamine (0.786 mL) and diphenylphosphoryl azide (0.608 mL) were sequentially added to a solution of the crude carboxylic acid obtained above in toluene (10 mL) and tert-butyl alcohol (10 mL). The mixture was stirred at room temperature for one hour and at 80°C for 10 hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7:3 -> 3:2) to give 548 mg (62%, two steps) of the title compound as a colorless viscous oil.

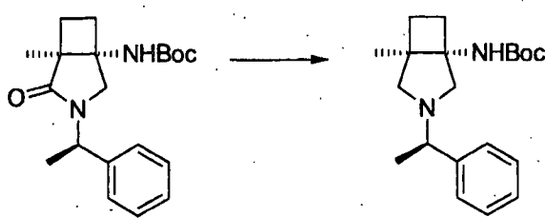
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.55 (1H, q, J=7.1 Hz), 4.81 (1H, br), 3.60 (1H, br), 3.02 (1H, d, J=11.3 Hz), 2.30-2.10 (3H, m), 2.02 (1H, m), 1.56 (3H, d, J=7.1 Hz), 1.38 (9H, s), 1.27 (3H, s).

MS (ESI) m/z: 345 $(M+H)^+$.

[Reference Example 40]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 114]



A 1.09 M solution of a borane/tetrahydrofuran complex in tetrahydrofuran (3.6 mL, 3.98 mmol) was added dropwise to a solution of (1S,5S)-1-(tert-butoxycarbonylamino)-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (548 mg, 1.59 mmol) in tetrahydrofuran (10 mL) at 0°C over five minutes. After heating to room temperature and stirring for three hours, a 1.09 M solution of a borane/tetrahydrofuran complex in tetrahydrofuran (3.6 mL, 3.98 mmol) was added at the same temperature. The mixture was stirred at room temperature for 15 hours and then cooled to 0°C. A mixture of ethanol (9.0 mL)-water (1.0 mL) was carefully added dropwise. After addition of triethylamine (3.0 mL) dropwise, the mixture was heated to reflux for one hour. The reaction solution was concentrated, and the precipitated white solid was removed by filtration through Celite. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate =

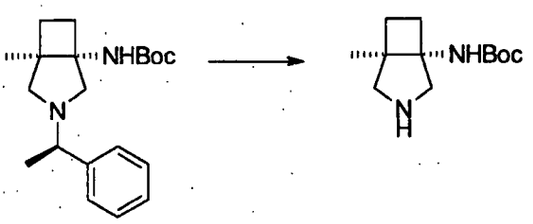
10:1 -> 5:1) to give 184 mg (35%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.17 (5H, m), 4.58 (1H, br), 3.28 (1H, q, J=6.6 Hz), 2.95 (1H, d, J=8.5 Hz), 2.91 (1H, brd, J=9.0 Hz), 2.14-2.05 (4H, m), 1.68 (1H, m), 1.38 (9H, brs), 1.34 (3H, d, J=6.6 Hz), 1.14 (3H, s).

[Reference Example 41]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-3-azabicyclo[3.2.0]heptane

[Formula 115]



A 10% palladium-carbon catalyst (50% wet, 200 mg) was added to a solution of (1S,5S)-1-(tert-butoxycarbonylamino)-5-methyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (184 mg, 0.057 mmol) in ethanol, and the mixture was stirred in a hydrogen atmosphere at 40°C for five hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give crude amine as a white solid.

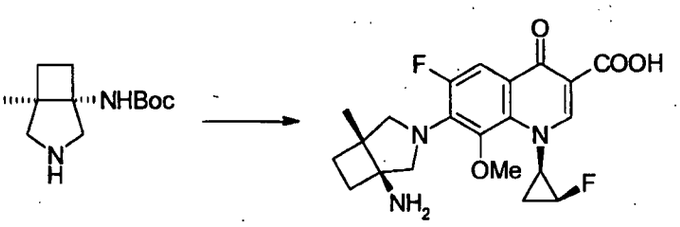
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.69 (1H, br), 3.27 (1H, d, J=11.5 Hz), 2.92 (1H, br), 2.82 (1H, d, J=11.2 Hz), 2.62 (1H, brd, J=11.2 Hz), 2.13 (1H, brm), 1.98 (1H, ddd, J=5.6,

9.8, 12.7 Hz), 1.71 (1H, m), 1.59 (1H, m), 1.44 (9H, s), 1.16 (3H, s).

[Example 7]

7-[(1R,5S)-1-Amino-5-methyl-3-azabicyclo[3.2.0]hept-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 116]



6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (231 mg, 0.668 mmol) and triethylamine (0.279 mL, 2.01 mmol) were sequentially added to a solution of the aforementioned crude (1S,5S)-1-(tert-butoxycarbonylamino)-5-methyl-3-azabicyclo[3.2.0]heptane in dimethyl sulfoxide (2.0 mL). The mixture was heated with stirring at 40°C for five hours. Then, a mixture of ethanol:water = 4:1 (7.5 mL) and triethylamine (1.0 mL) was added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and sequentially washed with a 10% citric acid solution (20 mL), water (20 mL × 2), and brine (20 mL). The organic

layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by reverse phase preparative HPLC (0.1% formic acid solution-acetonitrile system) to give a pale yellow solid. The resulting pale yellow solid was dissolved in concentrated hydrochloric acid (1.0 mL), and then the solution was stirred at room temperature for 10 minutes. The reaction solution was diluted with 6 M hydrochloric acid (8 mL) and washed with chloroform (5 mL). The aqueous layer was adjusted to pH 12.4 with a saturated sodium hydroxide solution under ice-cooling and then adjusted to pH 7.3 with hydrochloric acid, and then diluted with water (10 mL), followed by extraction with chloroform (50 mL × 3). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was sufficiently dried under vacuum and then dissolved in a mixed solvent of chloroform:methanol = 10:1 and filtered through a membrane filter. The filtrate was concentrated under reduced pressure to give 60 mg (26%) of the title compound as a pale yellow solid.

mp: 123-125°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.46 (1H, d, J=1.7 Hz), 7.70 (1H, d, J=13.7 Hz), 4.97 (1H, m), 4.05 (1H, m), 3.74 (1H, d,

J=11.5 Hz), 3.68 (3H, s), 3.65 (1H, m), 3.20 (1H, brd, J=9.8 Hz), 3.11 (1H, brd, J=10.3 Hz), 2.11 (1H, m), 1.95 (1H, m), 1.83 (1H, m), 1.72-1.46 (3H, m), 1.14 (3H, s).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot H_2O \cdot 0.25EtOH$: C, 57.52; H, 5.95; F, 8.46; N, 9.36. Found: C, 57.80; H, 5.77; F, 8.41; N, 9.40.

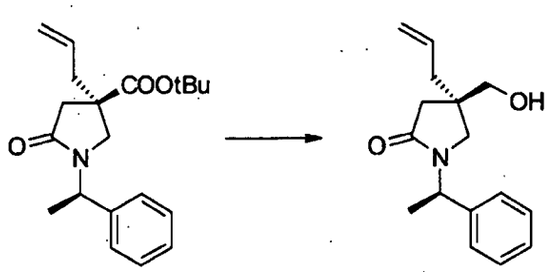
HRMS (FAB); m/z Calcd for $C_{21}H_{24}F_2N_3O_4$ $(M+H)^+$: 420.1735. Found: 420.1739.

IR (ATR) ν: 2931, 2842, 1727, 1616, 1540, 1508, 1436, 1346, 1315, 1270, 1226, 1187, 1133, 1097, 1051 cm^{-1}.

[Reference Example 42]

(4R)-4-Allyl-4-hydroxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 117]



Lithium borohydride (4.96 g, 0.228 mol) was suspended in tetrahydrofuran (500 mL). A solution of (3R)-3-allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (50.0 g, 0.152 mol) in tetrahydrofuran (100 mL)-ethanol (17.7 mL) was added to the suspension using a dropping funnel over 10 minutes. The mixture was heated to 40°C, stirred for 12 hours, and then heated to

reflux for 20 hours. After cooling to 0°C, a saturated ammonium chloride solution (100 mL) was carefully added. After the tetrahydrofuran component was evaporated under reduced pressure, the reaction solution was poured into a mixture of ethyl acetate (100 mL) and a saturated ammonium chloride solution (100 mL), followed by extraction with ethyl acetate (1000 mL, 750 mL). The organic layers were combined and washed with brine (200 mL). After drying over anhydrous sodium sulfate and filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:4) to give 29.9 g (76%) of the title compound as a colorless viscous oil.

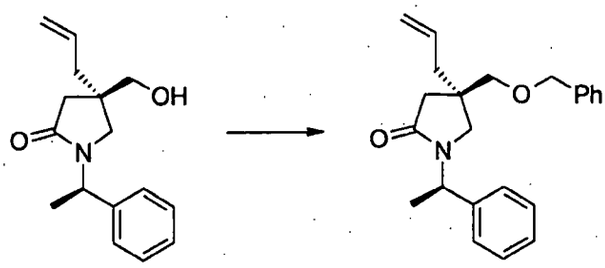
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.59-5.47 (2H, m), 4.97 (1H, m), 4.90 (1H, m), 3.50 (2H, d, J=5.1 Hz), 3.23 (1H, d, J=10.1 Hz), 2.71 (1H, d, J=10.1 Hz), 2.37 (1H, d, J=16.8 Hz), 2.26 (1H, d, J=16.8 Hz), 2.08 (2H, d, J=7.3 Hz), 1.84 (1H, m), 1.51 (3H, d, J=7.1 Hz).

MS (ESI) m/z: 260 $(M+H)^+$.

[Reference Example 43]

(4R)-4-Allyl-4-benzyloxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 118]



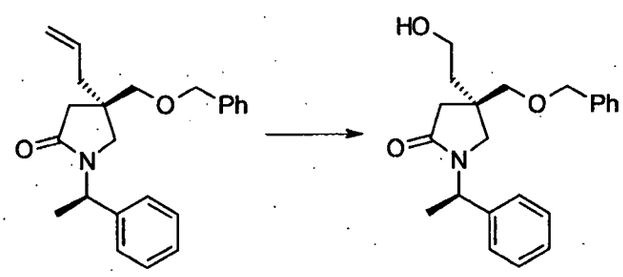
Benzyl bromide (17.1 mL, 0.144 mol) and sodium hydride (55% in liquid paraffin, 6.27 g, 0.144 mol) were sequentially added to a solution of (4R)-4-allyl-4-hydroxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (31.1 g, 0.120 mol) in tetrahydrofuran (300 mL)-dimethylformamide (75 mL) in a nitrogen atmosphere at 0°C. The mixture was stirred at the same temperature for 30 minutes. Methanol (5 mL) was carefully added and stirred until gas was not generated. Then, the reaction was quenched with a saturated ammonium chloride solution (50 mL). The reaction solution was poured into a mixture of ethyl acetate (1000 mL) and water (150 mL), followed by extraction with ethyl acetate (1500 mL). The organic layer was sequentially washed with water (200 mL) and brine (200 mL × 2), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 -> 2:1 -> 1:1) to give 41.3 g (99%) of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.23 (10H, m), 5.52-5.42 (2H, m), 4.93 (1H, m), 4.84 (1H, m), 4.51 (1H, d, J=12.2 Hz), 4.47 (1H, d, J=12.2 Hz), 3.27 (2H, s), 3.21 (1H, d, J=10.0 Hz), 2.69 (1H, d, J=10.0 Hz), 2.37 (1H, d, J=16.9 Hz), 2.26 (1H, d, J=16.9 Hz), 2.11 (1H, m), 2.05 (1H, m), 1.46 (3H, d, J=7.3 Hz).

[Reference Example 44]

(4R)-4-Benzyloxymethyl-4-(2-hydroxyethyl)-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 119]



A solution of (4R)-4-allyl-4-benzyloxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (4.00 g, 11.45 mmol) in dichloromethane (100 mL) was bubbled with ozone gas at -70°C and stirred at the same temperature for 15 minutes. Ozone bubbling was stopped when the reaction solution was turned dark blue, and then the reaction solution was bubbled with nitrogen gas until the solution turned colorless. Sodium borohydride (434 mg, 11.45 mmol) and methanol (40 mL) were added at the same temperature, and the mixture was heated to room temperature over three hours. Sodium borohydride

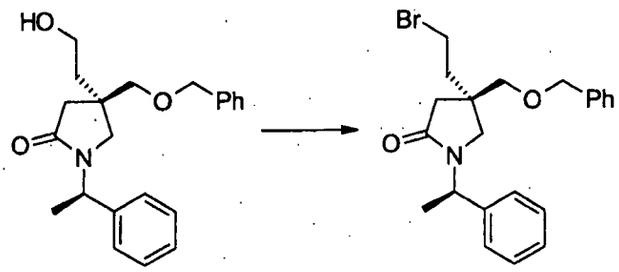
(325 mg, 8.58 mmol) was added, and the mixture was stirred at room temperature for further 24 hours. A saturated ammonium chloride solution was added, and the mixture was stirred for 10 minutes. Then, the reaction solution was poured into a mixture of ethyl acetate (200 mL) and water (200 mL), followed by extraction with ethyl acetate (500 mL). The organic layer was washed with brine (200 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:2 -> 1:9 -> 0:1) to give 3.22 g (79%) of the title compound as a colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.23 (10H, m), 5.46 (1H, q, J=7.1 Hz), 4.55 (1H, d, J=11.8 Hz), 4.48 (1H, d, J=11.8 Hz), 3.54-3.45 (2H, brm), 3.36 (2H, s), 3.24 (1H, d, J=10.2 Hz), 2.72 (1H, d, J=10.2 Hz), 2.38 (1H, d, J=17.0 Hz), 2.28 (1H, d, J=17.0 Hz), 2.15 (1H, br), 1.69-1.58 (2H, m), 1.44 (3H, d, J=7.1 Hz).

[Reference Example 45]

(4S)-4-Benzyloxymethyl-4-(2-bromoethyl)-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 120]



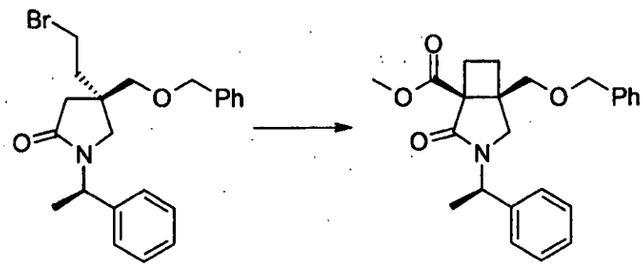
Carbon tetrabromide (3.17 g, 9.56 mmol) and triphenylphosphine (2.51 g, 9.56 mmol) were sequentially added to a solution of (4R)-4-benzyloxymethyl-4-(2-hydroxyethyl)-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (3.22 g, 9.10 mmol) in dichloromethane (20 mL) in a nitrogen atmosphere, and the mixture was stirred for 15 minutes. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1 -> 1:2) to give 3.18 g (84%) of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.25 (10H, m), 5.46 (1H, q, J=7.1 Hz), 4.52 (1H, d, J=12.2 Hz), 4.46 (1H, d, J=12.2 Hz), 3.28 (2H, s), 3.25 (1H, d, J=10.1 Hz), 3.17-3.04 (2H, m), 2.67 (1H, d, J=10.1 Hz), 2.37 (1H, d, J=17.1 Hz), 2.26 (1H, d, J=17.1 Hz), 2.05 (1H, ddd, J=5.9, 10.4, 14.0 Hz), 1.96 (1H, ddd, J=6.1, 10.6, 14.0 Hz), 1.44 (3H, d, J=7.1 Hz).

[Reference Example 46]

(1S,5R)-5-Benzyloxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester

[Formula 121]



A 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran (14.5 mL, 14.5 mmol) was added to a solution of (4S)-4-benzyloxymethyl-4-(2-bromoethyl)-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (2.75 g, 6.60 mmol) and methyl chloroformate (0.54 mL, 6.93 mmol) in tetrahydrofuran (20 mL) in a nitrogen atmosphere at 0°C. The mixture was stirred for 12 hours while gradually heating to room temperature. The reaction solution was cooled to 0°C. A saturated ammonium chloride solution (5 mL) was added, and the mixture was stirred for 10 minutes. Then, the reaction solution was poured into a mixture of ethyl acetate (100 mL) and water (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 -> 2:1 -> 1:1)

to give 2.12 g (82%) of the title compound as a pale yellow oil.

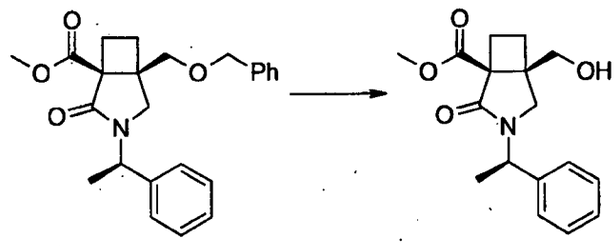
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.24 (10H, m), 5.59 (1H, q, J=7.1 Hz), 4.47 (1H, d, J=12.0 Hz), 4.43 (1H, d, J=12.0 Hz), 3.63 (3H, s), 3.53 (1H, d, J=9.3 Hz), 3.49 (1H, d, J=9.3 Hz), 3.37 (1H, d, J=10.0 Hz), 2.78 (1H, ddd, J=9.3, 9.5, 12.2 Hz), 2.73 (1H, d, J=10.0 Hz), 2.22 (1H, ddd, J=3.4, 9.3, 12.2 Hz), 1.91 (1H, ddd, J=3.4, 10.5, 12.2 Hz), 1.63 (1H, ddd, J=9.5, 10.5, 12.2 Hz), 1.58 (3H, d, J=7.1 Hz).

MS (ESI) m/z: 394 $(M+H)^+$.

[Reference Example 47]

(1S,5R)-5-Hydroxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester

[Formula 122]



A 10% palladium-carbon catalyst (50% wet, 200 mg) was added to a solution of (1S,5R)-5-benzyloxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester (1.82 g, 4.62 mmol) in ethanol (20 mL)-tetrahydrofuran (20 mL), and the mixture was stirred in a hydrogen atmosphere at 40°C for 2.5 hours. After removing the catalyst by filtration, the filtrate was

concentrated to give the title compound as colorless crystals.

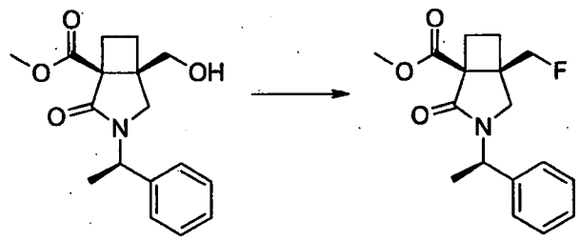
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.60 (1H, q, J=7.1 Hz), 3.79 (1H, dd, J=4.2, 11.8 Hz), 3.78 (3H, s), 3.58 (1H, dd, J=7.1, 11.8 Hz), 3.56 (1H, d, J=10.0 Hz), 2.73-2.65 (2H, m), 2.57 (1H, dd, J=4.2, 7.1 Hz), 2.30 (1H, m), 1.83 (1H, m), 1.62 (1H, m), 1.59 (3H, d, J=7.1 Hz).

MS (ESI) m/z: 304 $(M+H)^+$.

[Reference Example 48]

(1S,5R)-5-Fluoromethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester

[Formula 123]



Bis(2-methoxyethyl)aminosulfur trifluoride (1.98 mL, 10.7 mmol) was added to a solution of (1S,5R)-5-hydroxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester (1.30 g, 4.30 mmol) in dichloromethane in a nitrogen atmosphere at room temperature. The mixture was heated to 50°C and stirred for 12 hours. Then, a saturated sodium bicarbonate solution (10 mL) was added, and the mixture was stirred for 10 minutes. The reaction solution was poured

into a mixture of ethyl acetate (50 mL) and water (30 mL), followed by extraction with ethyl acetate (200 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 -> 2:1 -> 1.5:1) to give 1.26 g (96%) of the title compound as a pale yellow oil.

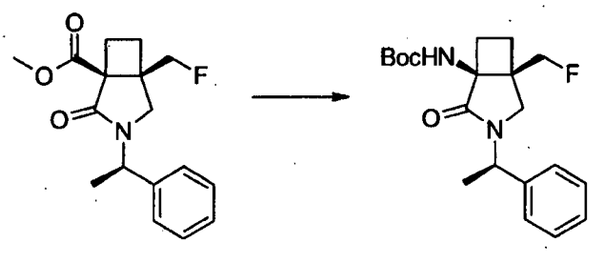
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.63 (1H, q, J=7.2 Hz), 4.51 (1H, dd, J=9.8, 47.1 Hz), 4.47 (1H, dd, J=9.8, 47.0 Hz), 3.76 (3H, s), 3.41 (1H, d, J=10.0 Hz), 2.78 (1H, m), 2.76 (1H, d, J=10.0 Hz), 2.27 (1H, ddd, J=3.6, 9.3, 12.5 Hz), 1.93 (1H, ddd, J=3.6, 10.5, 12.4 Hz), 1.68 (1H, m), 1.62 (3H, d, J=7.2 Hz).

MS (ESI) m/z: 306 $(M+H)^+$.

[Reference Example 49]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-fluoromethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 124]



A 1 M sodium hydroxide solution was added to a solution of (1S,5R)-5-fluoromethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester

(1.26 g, 4.13 mmol) in tetrahydrofuran (10 mL)-methanol (5.0 mL). The mixture was stirred for 12 hours. The reaction solution was adjusted to pH 2 or less with 6 M hydrochloric acid, and the tetrahydrofuran and methanol components were removed by filtration under reduced pressure. The residue was poured into a mixture of ethyl acetate and 1 M hydrochloric acid, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After removing the drying agent by filtration, the filtrate was concentrated under reduced pressure to give 1.17 g (97%) of crude carboxylic acid as a white solid.

The crude carboxylic acid (1.02 g, 3.51 mmol) was dissolved in a mixture of toluene (20 mL), tert-butyl alcohol (20 mL), and triethylamine (0.98 mL, 7.03 mmol), and diphenylphosphoryl azide (0.833 mL, 3.87 mmol) was added in a nitrogen atmosphere. The mixture was stirred at 40°C for one hour and then at 80°C for 12 hours. The reaction solution was poured into a mixture of ethyl acetate (50 mL) and a saturated sodium bicarbonate solution (30 mL), followed by extraction with ethyl acetate (150 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The resulting

residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 -> 2:1 -> 1:1) to give 746 mg (59%) of the title compound as colorless crystals.

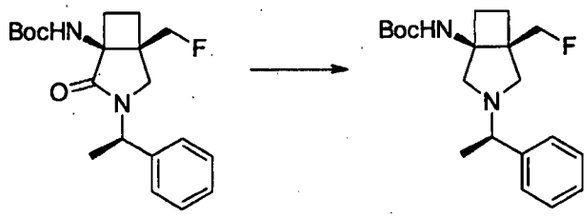
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.29 (5H, m), 5.60 (1H, q, J=7.1 Hz), 4.95 (1H, br), 4.61 (1H, dd, J=9.6, 47.3 Hz), 4.47 (1H, dd, J=9.6, 47.3 Hz), 2.15 (1H, d, J=9.5 Hz), 2.70 (1H, d, J=9.5 Hz), 2.36 (1H, m), 2.17-2.08 (2H, m), 1.60 (3H, d, J=7.1 Hz), 1.42 (9H, s).

MS (ESI) m/z: 363 $(M+H)^+$.

[Reference Example 50]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-fluoromethyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 125]



A 65% solution of Red-Al™ in toluene (1.76 mL, 5.85 mmol) was added dropwise to a solution of (1S,5S)-1-(tert-butoxycarbonylamino)-5-fluoromethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (707 mg, 1.95 mmol) in toluene in a nitrogen atmosphere at -15°C over 10 minutes. The mixture was heated to room temperature, stirred for 1.5 hours, and cooled to 0°C. A 25% potassium sodium tartrate tetrahydrate solution (10 mL) was carefully added while

maintaining the internal temperature of the reaction solution at 10°C or less. The reaction solution was poured into a mixture of ethyl acetate (10 mL) and brine (10 mL), followed by extraction with ethyl acetate (150 mL). The organic layer was washed with brine (30 mL) and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 5:1 -> 2:1) to give 567 mg (83%) of the title compound as a pale yellow oil.

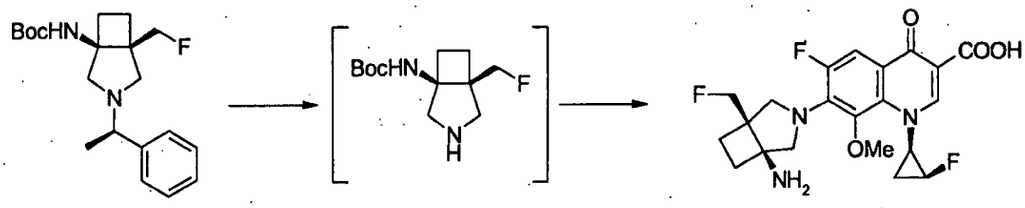
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.18 (5H, m), 4.89 (1H, br), 4.63 (1H, dd, J=9.8, 47.9 Hz), 4.53 (1H, J=9.8, 47.6 Hz), 3.33 (1H, q, J=6.4 Hz), 2.95 (2H, d, J=8.8 Hz), 2.40 (1H, d, J=8.8 Hz), 2.18-2.14 (3H, m), 1.93-1.87 (2H, m), 1.37 (9H, s), 1.36 (3H, d, J=6.4 Hz).

MS (ESI) m/z: 349 $(M+H)^+$.

[Example 8]

7-[(1S,5S)-1-Amino-5-fluoromethyl-3-bicyclo[3.2.0]hept-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 126]



A 10% palladium-carbon catalyst (M, about 50% wet, 50 mg) was added to a solution of (1S,5S)-1-(tert-butoxycarbonylamino)-5-fluoromethyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (567 mg, 1.63 mmol) in ethanol (10 mL), and the mixture was stirred in a hydrogen atmosphere at 50°C for 2.5 hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give crude amine (364 mg) as colorless crystals.

The crude amine was dissolved in dimethyl sulfoxide (4.0 mL), and triethylamine (0.62 mL, 4.45 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (642 mg, 1.78 mmol) were sequentially added. The mixture was heated with stirring at 40°C for 24 hours. Then, a mixture of ethanol:water = 3:1 (20.0 mL) and triethylamine (3.0 mL) were added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The reaction solution was poured into a mixture of ethyl acetate (20 mL) and a 10% citric acid solution (10 mL), followed by extraction with ethyl acetate (50 mL × 3). The organic layers were combined

and washed with brine (50 mL). Thereafter, the organic layers were dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by reverse phase preparative HPLC (0.1% formic acid solution-acetonitrile system) to give a pale yellow solid. The resulting pale yellow solid was dissolved in concentrated hydrochloric acid (1.5 mL), and the solution was stirred at room temperature for 10 minutes. The reaction solution was diluted with 6 M hydrochloric acid (20 mL) and washed with chloroform (7 mL). The aqueous layer was adjusted to pH 12.4 with a saturated sodium hydroxide solution under ice-cooling and then adjusted to pH 7.3 with hydrochloric acid, followed by extraction with chloroform (50 mL × 2). The aqueous layer was readjusted to pH 7.4, followed by extraction with chloroform (50 mL × 2). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the filtrate was concentrated under reduced pressure. The residue was sufficiently dried under vacuum and then dissolved in chloroform. The solution was filtered through a membrane filter, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in ethanol and then reprecipitated with hexane. The resulting solid was collected by filtration and

dried to give 219 mg (31%) of the title compound as a pale yellow solid.

mp: 186-188°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 4.34 (1H, d, J=7.9 Hz), 4.96 (1H, m), 4.70 (1H, dd, J=10.0, 47.4 Hz), 4.64 (1H, dd, J=10.0, 47.1 Hz), 4.02 (1H, m), 3.67-3.61 (5H, m), 3.33 (1H, brd, J=10.5 Hz), 3.22 (1H, brd, J=9.8 Hz), 2.11 (1H, m), 2.00-1.88 (2H, m), 1.73 (1H, m), 1.60 (1H, m), 1.47 (1H, m).

Anal; Calcd for $C_{21}H_{22}F_3N_3O_4 \cdot 0.25H_2O \cdot 0.25EtOH$: C, 56.95; H, 5.33; F, 12.57; N, 9.27. Found: C, 56.94; H, 5.11; F, 12.74; N, 9.23.

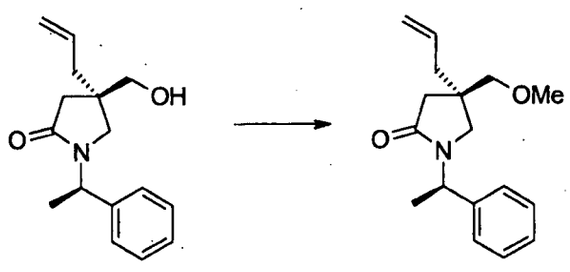
HRMS (FAB); m/z Calcd for $C_{21}H_{23}F_3N_3O_4$ $(M+H)^+$: 438.16406. Found: 438.16743.

IR (ATR) ν: 3386, 2935, 1716, 1616, 1540, 1508, 1442, 1436, 1351, 1319, 1274, 1228, 1184, 1122, 1051 cm^{-1}.

[Reference Example 51]

(4R)-4-Allyl-4-methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 127]



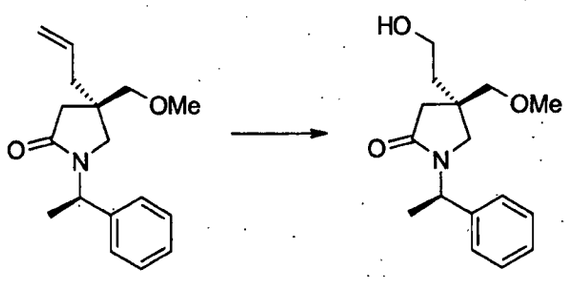
Methyl iodide (1.87 mL, 30.1 mmol) and sodium hydride (55% in liquid paraffin, 1.31 g, 30.1 mol) were sequentially added to a solution of (4R)-4-allyl-4-hydroxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (7.09 g, 27.3 mmol) in tetrahydrofuran (80 mL)-dimethylformamide (20 mL) in a nitrogen atmosphere at 0°C. The mixture was heated to room temperature and stirred for one hour. Methanol (2 mL) was carefully added and stirred until gas was not generated. Then, the reaction was quenched with a saturated ammonium chloride solution (10 mL). The reaction solution was poured into a mixture of ethyl acetate (100 mL) and water (100 mL), followed by extraction with ethyl acetate (800 mL). The organic layer was sequentially washed with water (200 mL) and brine (200 mL × 2), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1 -> 2:1 -> 1:1) to give 7.42 g (99%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.54-5.43 (2H, m), 4.94 (1H, m), 4.84 (1H, m), 3.33 (3H, s), 3.20 (2H, s), 3.19 (1H, d, J=10.0 Hz), 2.69 (1H, d, J=10.0 Hz), 2.36 (1H, d, J=17.1 Hz), 2.24 (1H, d, J=17.1 Hz), 2.05-2.03 (2H, m), 1.50 (3H, d, J=7.3 Hz).

[Reference Example 52]

(4R)-4-(2-Hydroxyethyl)-4-methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 128]



A solution of (4R)-4-allyl-4-methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (3.28 g, 12.0 mmol) in methanol (20 mL)-dichloromethane (20 mL) was bubbled with ozone gas at -70°C and stirred at the same temperature for 30 minutes. Ozone bubbling was stopped when the reaction solution was turned dark blue, and then the reaction solution was bubbled with nitrogen gas until the solution turned colorless. Sodium borohydride (454 mg, 12.0 mmol) was added at the same temperature, and the mixture was heated to room temperature over two hours. After heating, sodium borohydride (227 mg, 6.0 mmol) was added and the mixture was stirred for 24 hours. Then, sodium borohydride (113 mg, 3.0 mmol) was further added and the mixture was stirred for 0.5 hour. A saturated ammonium chloride solution (10 mL) was added, and the mixture was stirred for 10 minutes. Then, the reaction solution was poured into a mixture of ethyl acetate (50 mL) and water (50 mL),

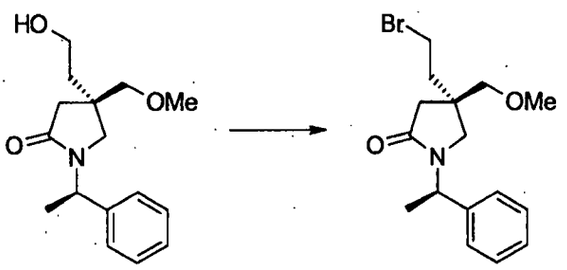
followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol = 10:0 -> 10:1) to give 2.85 g (86%) of the title compound as a colorless viscous oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.49 (1H, q, J=7.1 Hz), 3.55-3.44 (2H, m), 3.37 (3H, s), 3.30 (1H, d, J=9.5 Hz), 3.28 (1H, d, J=9.5 Hz), 3.22 (1H, d, J=10.0 Hz), 2.72 (1H, d, J=10.0 Hz), 2.38 (1H, d, J=16.8 Hz), 2.26 (1H, d, J=16.8 Hz), 1.64 (2H, t, J=6.0 Hz), 1.50 (3H, d, J=7.1 Hz).

[Reference Example 53]

(4S)-4-(2-Bromoethyl)-4-methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one

[Formula 129]



Carbon tetrabromide (3.58 g, 10.8 mmol) and triphenylphosphine (2.83 g, 10.8 mmol) were sequentially added to a solution of (4R)-4-(2-hydroxyethyl)-4-

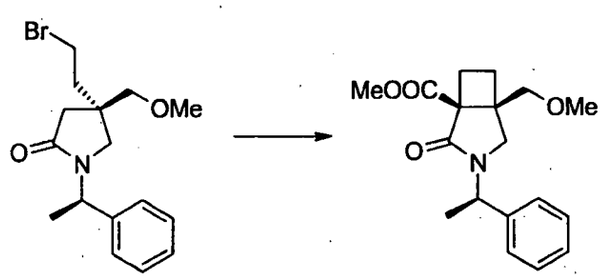
methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (2.85 g, 10.3 mmol) in dichloromethane (30 mL) in a nitrogen atmosphere at 0°C, and the mixture was stirred for 10 minutes. The mixture was heated to room temperature and stirred for 24 hours, and then the reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane -> hexane:ethyl acetate = 2:1 -> 1:1 -> 1:2) to give 2.07 g (59%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.49 (1H, q, J=7.3 Hz), 3.32 (3H, s), 3.24 (1H, d, J=10.3 Hz), 3.23 (2H, s), 3.20-3.07 (2H, m), 2.67 (1H, d, J=10.3 Hz), 2.38 (1H, d, J=16.8 Hz), 2.25 (1H, d, J=16.8 Hz), 2.03-1.90 (2H, m), 1.50 (3H, d, J=7.3 Hz).

[Reference Example 54]

(1S,5R)-5-Methoxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester

[Formula 130]



A 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran (13.4 mL, 13.4 mmol) was added to a solution of (4S)-4-(2-bromoethyl)-4-methoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidin-2-one (2.07 g, 6.08 mmol) and methyl chloroformate (0.493 mL, 6.38 mmol) in tetrahydrofuran (20 mL) in a nitrogen atmosphere at -70°C. The mixture was stirred for 14 hours while gradually heating to room temperature. The reaction solution was cooled to 0°C. A 10% citric acid solution (20 mL) was added, and the mixture was stirred for 10 minutes. Then, the reaction solution was poured into a mixture of ethyl acetate (100 mL) and water (50 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1 -> 2:1) to give 1.53 g (79%) of the title compound as a pale brown oil.

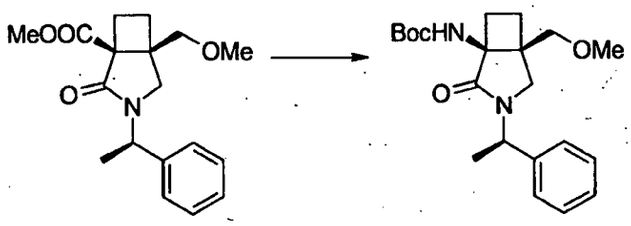
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.60 (1H, q, J=7.1), 3.72 (3H, s), 3.43 (1H, d, J=9.5 Hz), 3.40 (1H, d, J=9.5 Hz), 3.36 (1H, d, J=9.8 Hz), 3.28 (3H, s), 2.75 (1H, dt, J=12.2, 10.5 Hz), 2.72 (1H, d, J=9.5 Hz), 2.21 (1H, ddd, J=3.4, 9.3, 12.2 Hz), 1.86 (1H, ddd, J=3.4, 10.5, 12.2 Hz), 1.62 (1H, dt, J=12.2, 9.3 Hz), 1.58 (3H, d, J=7.1 Hz).

MS (ESI) m/z: 318 $(M+H)^+$.

[Reference Example 55]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methoxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 131]



A 1 M sodium hydroxide solution (5.0 mL) was added to a solution of (1S,5R)-5-methoxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane-1-carboxylic acid methyl ester (1.53 g, 4.82 mmol) in tetrahydrofuran (10 mL)-methanol (5.0 mL). The mixture was stirred for nine hours. The reaction solution was adjusted to pH 2 or less with 6 M hydrochloric acid, and the tetrahydrofuran and methanol components were removed by filtration under reduced pressure. The residue was poured into a mixture of ethyl acetate (30 mL) and 1 M hydrochloric acid (30 mL), followed by extraction with ethyl acetate (150 mL). The organic layer was washed with a saturated sodium chloride solution (30 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure to give crude carboxylic acid as a pale yellow oil.

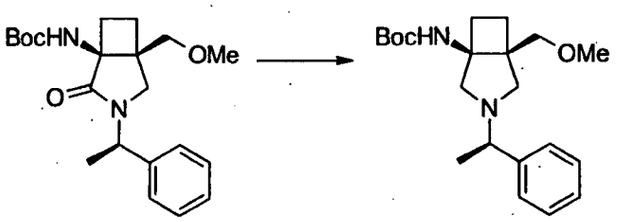
The crude carboxylic acid was dissolved in a mixture of tert-butyl alcohol (30 mL) and triethylamine (1.34 mL, 9.64 mmol), and diphenylphosphoryl azide (1.14 mL, 5.30 mmol) was added in a nitrogen atmosphere. The mixture was stirred at 40°C for two hours and then at 80°C for 20 hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1) to give 595 mg (33%, two steps) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 2.25 (1H, q, J=7.1H), 4.87 (1H, brs), 3.55 (1H, d, J=9.2 Hz), 3.42 (1H, brd, J=9.2 Hz), 3.35 (1H, d, J=9.6 Hz), 3.33 (3H, s), 2.71 (1H, d, J=9.6 Hz), 2.33 (1H, m), 2.12-2.00 (2H, m), 1.60 (3H, d, J=7.1 Hz), 1.43 (9H, s).

[Reference Example 56]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methoxymethyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane

[Formula 132]



A 65% solution of Red-Al™ in toluene (1.43 mL, 4.75 mmol) was added dropwise to a solution of (1S,5S)-1-(tert-

butoxycarbonylamino)-5-methoxymethyl-2-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (593 mg, 1.58 mmol) in toluene in a nitrogen atmosphere at 0°C over two minutes. The mixture was heated to room temperature, stirred for two hours, and cooled to 0°C. A 20% potassium sodium tartrate tetrahydrate solution (10 mL) was carefully added while maintaining the internal temperature of the reaction solution at 10°C or less. The reaction solution was poured into a mixture of ethyl acetate (10 mL) and brine (10 mL), followed by extraction with ethyl acetate (100 mL). The organic layer was washed with brine (20 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 19:1 -> 9:1) to give 244 mg (43%) of the title compound as colorless crystals.

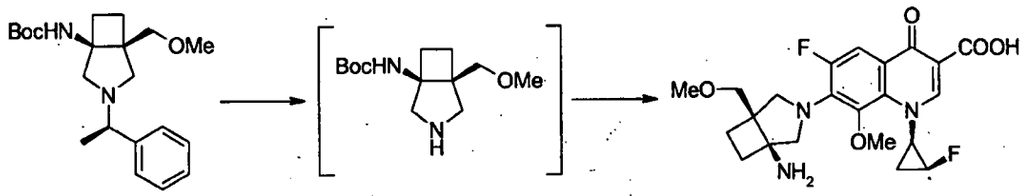
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.17 (5H, m), 5.56 (1H, brs), 3.58 (1H, d, J=10.0 Hz), 3.43 (1H, d, J=10.0 Hz), 3.37 (3H, s), 3.28 (1H, q, J=6.5 Hz), 3.10 (1H, br), 2.86 (1H, d, J=8.7 Hz), 2.34 (1H, d, J=8.7 Hz), 2.23-2.01 (3H, brm), 1.84 (2H, brt, J=8.1 Hz), 1.35 (9H, brs), 1.34 (3H, d, J=6.5 Hz).

MS (ESI) m/z: 361 $(M+H)^+$.

[Example 9]

7-[(1S,5S)-1-Amino-5-methoxymethyl-3-azabicyclo[3.2.0]hept-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 133]



A 10% palladium-carbon catalyst (50% wet, 50 mg) was added to a solution of (1S,5S)-1-(tert-butoxycarbonylamino)-5-methoxymethyl-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.2.0]heptane (242 mg, 0.67 mmol) in ethanol (20 mL), and the mixture was stirred in a hydrogen atmosphere at 50°C for seven hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give crude amine (164 mg) as a colorless viscous oil.

The crude amine (164 mg) was dissolved in dimethyl sulfoxide (2.0 mL), and triethylamine (0.178 mL, 1.28 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid-BF_2 chelate (254 mg, 0.704 mmol) were sequentially added. The mixture was heated with stirring at 40°C for 23 hours. Then, a mixture of ethanol:water = 5:1 (6.0 mL) and triethylamine (1.0 mL) were added to the reaction solution, and the

mixture was heated to reflux for two hours. After the ethanol and triethylamine components in the reaction solution were evaporated under reduced pressure, the residue was poured into a mixture of ethyl acetate (20 mL) and a 10% citric acid solution (10 mL), followed by extraction with ethyl acetate (80 mL). The organic layer was washed with brine (20 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by reverse phase preparative HPLC (0.1% formic acid solution-acetonitrile system) to give a pale yellow amorphous. The resulting pale yellow amorphous was dissolved in concentrated hydrochloric acid (2.0 mL), and the solution was stirred at room temperature for 10 minutes. The reaction solution was diluted with 6 M hydrochloric acid (15 mL) and washed with chloroform (10 mL). The aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (50 mL × 2, 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the filtrate was concentrated under reduced pressure. The residue was sufficiently dried under vacuum and then dissolved in chloroform. The solution was filtered through a membrane filter, and the filtrate was

concentrated under reduced pressure. The resulting residue was crystallized from hexane, and the crystals were collected by filtration and dried to give 184 mg (61%) of the title compound as a pale yellow solid.

mp: 86-88°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, d, J=1.5 Hz), 7.69 (1H, d, J=13.4 Hz), 4.95 (1H, m), 4.02 (1H, m), 3.70-3.58 (7H, m), 3.39 (3H, s), 3.23 (1H, d, J=10.5 Hz), 3.19 (1H, d, J=10.3 Hz), 2.09 (1H, m), 1.99-1.87 (2H, m), 1.74 (1H, m), 1.61 (1H, m), 1.48 (1H, m).

Anal; Calcd for $C_{22}H_{25}F_2N_3O_5 \cdot 0.25H_2O \cdot 0.25EtOH$: C, 58.06; H, 5.85; F, 8.16; N, 9.03. Found: C, 57.92; H, 5.86; F, 8.16; N, 9.09.

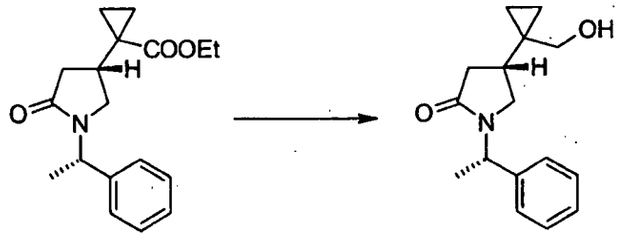
HRMS (FAB); m/z Calcd for $C_{22}H_{26}F_2N_3O_5$ $(M+H)^+$: 450.18405. Found: 450.18358.

IR (ATR) ν: 2931, 2827, 1724, 1616, 1546, 1504, 1434, 1392, 1348, 1313, 1274, 1228, 1184, 1101, 1051 cm^{-1}.

[Reference Example 57]

(3R)-3-[1-(Hydroxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidine

[Formula 134]



Lithium borohydride (1.174 g, 53.90 mmol) was added to a solution of 1-[(3R)-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-3-yl]cyclopropanecarboxylic acid ethyl ester [see Journal of Medicinal Chemistry, Vol.46, No.6, p.1005 (2003)] (2.03 g, 6.74 mmol) in tetrahydrofuran (20 mL). The mixture was heated with stirring on an oil bath at 70°C for 30 hours. After cooling to room temperature, the reaction solution was poured into an ice-cooled 10% citric acid solution (80 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with water (80 mL) and brine (80 mL), dried over anhydrous sodium sulfate, and then filtered, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:2 -> 1:1 -> 2:1 -> 1:0 -> chloroform:methanol = 9:1) to give 1.30 g (74%) of the title compound as a colorless transparent gummy solid.

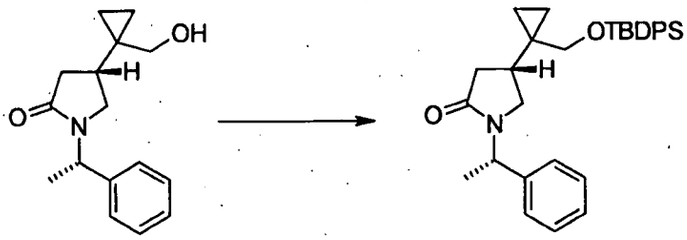
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.35 (5H, m), 5.48 (1H, q, J=6.9 Hz), 3.45 (2H, s), 3.04-3.12 (1H, m), 2.37-2.50 (2H, m), 2.19 (1H, dd, J=16.0, 8.9 Hz), 1.51 (2H, d, J=7.1 Hz), 0.43 (4H, s).

MS (ESI) m/z: 260 $(M+H)^+$.

[Reference Example 58]

(3R)-3-[1-(tert-Butyldiphenylsiloxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidine

[Formula 135]



tert-Butyldiphenylsilyl chloride (2.83 ml, 10.88 mmol) was added to a solution of (3R)-3-[1-(hydroxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidine (2.35 g, 9.06 mmol) and imidazole (925 mg, 13.59 mmol) in N,N-dimethylformamide (30 mL), and the mixture was stirred at room temperature for 20 hours. The reaction solution was diluted with ethyl acetate (150 mL), washed with water (50 mL × 2) and brine (50 mL × 2), dried over anhydrous sodium sulfate, and then filtered. The solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:19 -> 1:9 -> 1:4 -> 1:1) to give 3.88 g (86%) of the title compound as a colorless transparent gummy solid.

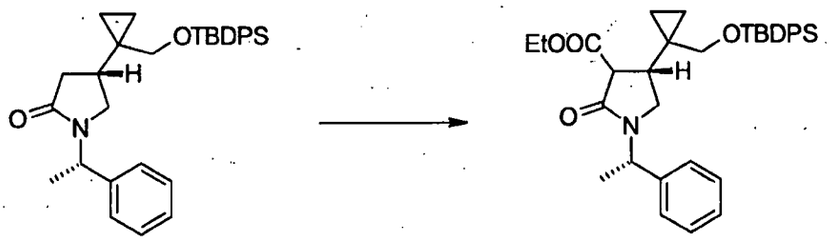
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.56-7.59 (4H, m), 7.26-7.46 (11H, m), 5.48 (1H, q, J=7.0 Hz), 3.46 (1H, d, J=10.7 Hz), 3.39 (1H, d, J=10.7 Hz), 3.10 (2H, td, J=18.4, 9.6 Hz), 2.51 (1H, m), 2.32 (1H, dd, J=16.5, 8.9 Hz), 2.14 (1H, dd, J=16.5, 10.4 Hz), 1.46 (3H, d, J=7.1 Hz), 1.01 (9H, s), 0.33-0.39 (4H, m).

MS (ESI) m/z: 498 $(M+H)^+$.

[Reference Example 59]

(3R)-3-[1-(tert-Butyldiphenylsiloxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester

[Formula 136]



Ethyl chloroformate (0.059 mL, 0.617 mmol) and a solution of lithium hexamethyldisilazide in tetrahydrofuran (1.0 M, 0.57 mL, 0.570 mmol) were sequentially added dropwise to a solution of (3R)-3-[1-(tert-butyldiphenylsiloxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidine (258 mg, 0.518 mmol) in tetrahydrofuran (2 mL) at 0°C over two minutes. The mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes, and a solution of lithium hexamethyldisilazide in tetrahydrofuran (1.0 M, 0.57 mL, 0.570 mmol) was further added. The mixture was stirred at room temperature for 2.5 hours and then ice-cooled. The reaction was quenched with a 10% citric acid solution (20 mL). The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with water (20 mL)

and brine (20 mL) and then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9 -> 1:4 -> 1:2) to give 227 mg (77%) of the title compound as a colorless transparent gummy solid.

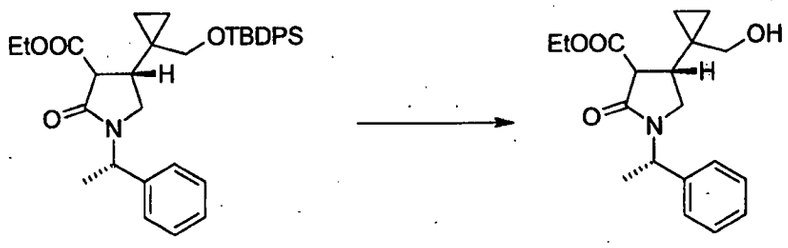
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.54-7.64 (4H, m), 7.26-7.45 (11H, m), 5.46 (1H, q, J=6.9 Hz), 4.23 (1H, ddd, J=14.3, 7.1, 1.8 Hz), 3.29-3.52 (4H, m), 3.12 (1H, t, J=9.0 Hz), 2.65 (1H, dd, J=18.6, 8.5 Hz), 1.48 (2H, d, J=7.1 Hz), 1.29 (3H, t, J=7.1 Hz), 1.02 (9H, s), 0.33 (4H, m).

MS (ESI) m/z: 570 $(M+H)^+$.

[Reference Example 60]

(3R)-3-[1-(Hydroxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester

[Formula 137]



A hydrogen fluoride-pyridine complex (10 mL) was added dropwise to a solution of (3R)-3-[1-(tert-butyldiphenylsiloxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester (2.81 g, 4.93 mmol) in pyridine (20 mL) at 0°C over five

minutes. The mixture was stirred at room temperature for 2.5 hours and then poured into ice water (150 mL), followed by extraction with ethyl acetate (300 mL). The resulting organic layer was washed with a 10% citric acid solution (100 mL), water (100 mL), and brine (100 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and then the resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:2 -> 1:1 -> 2:1) to give 1.378 g (84%) of the title compound as a pale yellow gummy solid.

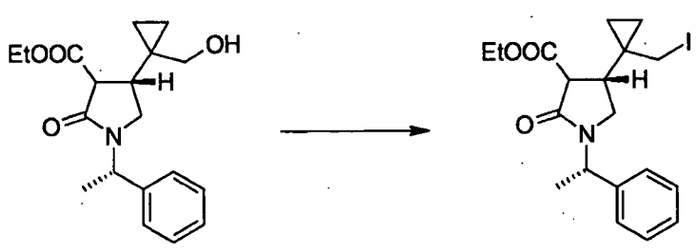
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.36 (5H, m), 5.46 (1H, q, J=7.1 Hz), 4.25 (2H, q, J=7.2 Hz), 3.49 (2H, dd, J=23.2, 10.5 Hz), 3.36 (1H, d, J=11.7 Hz), 3.09 (2H, dt, J=20.8, 8.9 Hz), 2.67 (1H, q, J=8.5 Hz), 1.54 (3H, d, J=7.1 Hz), 1.31 (3H, t, J=7.1 Hz), 0.35-0.50 (4H, m).

MS (ESI) m/z: 332 $(M+H)^+$.

[Reference Example 61]

(3R)-3-[1-(Iodomethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester

[Formula 138]



Imidazole (708 mg, 10.40 mmol), triphenylphosphine (2.727 g, 10.40 mmol), and iodine (2.111 g, 8.32 mmol) were sequentially added to a solution of (3R)-3-[1-(hydroxymethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester (1.378 g, 4.16 mmol) in dichloromethane (50 mL) at room temperature. The mixture was stirred at room temperature for 15 hours. The solvent was evaporated under reduced pressure. Then, the residue was dissolved in ethyl acetate (200 mL) and washed with water (50 mL × 2) and brine (50 mL). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9 -> 1:4 -> 1:2) to give 1.606 g (88%) of the title compound as a pale yellow gummy solid.

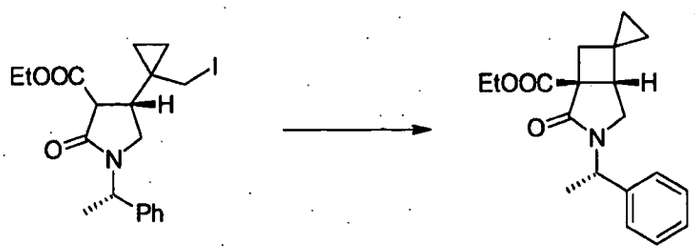
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.39 (5H, m), 5.47 (1H, q, J=7.2 Hz), 4.28 (2H, q, J=7.2 Hz), 3.19-3.23 (2H, m), 3.03-3.12 (3H, m), 2.94 (1H, m), 1.54 (3H, d, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz), 0.80-0.87 (2H, m), 0.63 (2H, m).

MS (ESI) m/z: 442 $(M+H)^+$.

[Reference Example 62]

(1S,5S)-2-Oxo-3-[(1S)-1-phenylethyl]-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester

[Formula 139]



A solution of potassium hexamethyldisilazide in toluene (0.5 M, 8.94 mL, 4.47 mmol) was added dropwise to a solution of (3R)-3-[1-(iodomethyl)cyclopropan-1-yl]-5-oxo-1-[(1S)-1-phenylethyl]pyrrolidin-4-ylcarboxylic acid ethyl ester (1.517 g, 3.44 mmol) in toluene (30 mL) under salt-ice cooling over five minutes. The mixture was stirred at the same temperature for one hour and 20 minutes and then at room temperature for 5.5 hours. The reaction solution was ice-cooled and the reaction was quenched with a 10% citric acid solution (20 mL), followed by extraction with ethyl acetate (200 mL). The organic layer was washed with water (50 mL × 2) and brine (50 mL). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9 -> 1:4 -> 1:2) to give 717 mg (67%) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27-7.38 (5H, m), 5.61 (1H, q, J=7.1 Hz), 4.14-4.28 (2H, m), 3.02-3.07 (3H, m), 2.91 (1H, dt, J=9.8, 3.8 Hz), 2.29 (1H, d, J=12.2 Hz), 1.61 (3H, d,

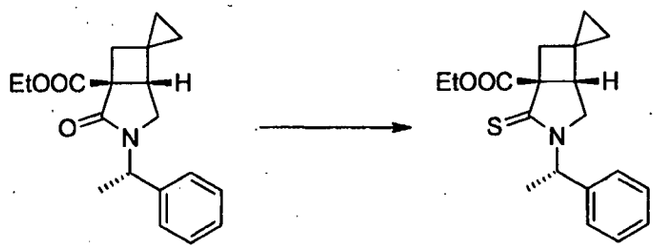
J=7.1 Hz), 1.28 (3H, t, J=7.2 Hz), 0.62 (2H, m), 0.44 (2H, m).

MS (ESI) m/z: 314 $(M+H)^+$.

[Reference Example 63]

(1R,5S)-3-[(1S)-1-Phenylethyl]-6-spirocyclopropane-2-thioxo-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester

[Formula 140]



Lawesson's reagent (1.146 g, 2.83 mmol) was added to a solution of (1S,5S)-2-oxo-3-[(1S)-1-phenylethyl]-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester (592 mg, 1.89 mmol) in toluene (20 mL). The mixture was heated with stirring in a nitrogen atmosphere on an oil bath at 90°C for 6.5 hours. The solvent was evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:19 -> 1:9 -> 1:4) to give 0.57 g (92%) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.36 (5H, m), 6.40 (1H, q, J=7.1 Hz), 4.11-4.32 (2H, m), 3.33 (1H, dd, J=12.0, 6.8 Hz),

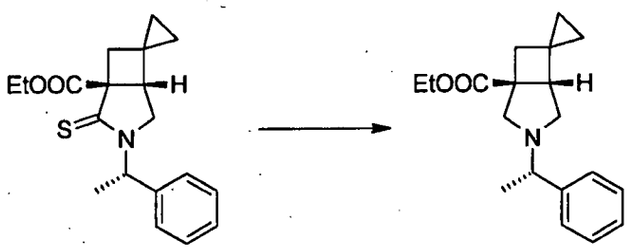
3.22 (2H, t, J=11.7 Hz), 3.09 (1H, d, J=6.3 Hz), 2.37 (1H, d, J=12.2 Hz), 1.68 (3H, d, J=7.1 Hz), 1.28 (3H, t, J=7.2 Hz), 0.58 (1H, m), 0.42 (2H, m).

MS (ESI) m/z: 330 $(M+H)^+$.

[Reference Example 64]

(1S,5S)-3-[(1S)-1-Phenylethyl]-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester

[Formula 141]



Raney nickel (4 mL) was added to a solution of (1R,5S)-3-[(1S)-1-phenylethyl]-6-spirocyclopropane-2-thioxo-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester (0.57 g, 1.73 mmol) in ethanol (40 mL). The mixture was stirred in a nitrogen atmosphere at room temperature for 30 minutes. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and then filtered through a short silica gel column. The filtrate was evaporated under reduced pressure to give 503 mg (97%) of the title compound as a colorless oil.

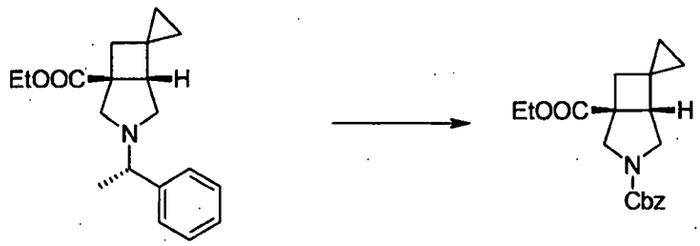
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.22-7.44 (5H, m), 4.20 (2H, q, J=7.0 Hz), 3.30 (1H, m), 3.24 (1H, d, J=8.8 Hz), 2.72 (1H, d, J=5.1 Hz), 2.59 (1H, d, J=11.5 Hz), 2.52 (1H, d, J=9.8 Hz), 2.45 (1H, d, J=8.8 Hz), 2.26 (1H, d, J=11.5 Hz), 1.95 (1H, dd, J=9.3, 5.6 Hz), 1.39 (3H, d, J=6.3 Hz), 1.29 (3H, t, J=7.1 Hz), 0.51 (1H, m), 0.31-0.40 (3H, m).

MS (ESI); m/z: 300 $(M+H)^+$.

[Reference Example 65]

(1S,5S)-3-Benzyloxycarbonyl-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester

[Formula 142]



Benzyl chloroformate (0.72 mL, 5.04 mmol) was added to a solution of (1S,5S)-3-[(1S)-1-phenylethyl]-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester (503 mg, 1.68 mmol) in dichloromethane (10 mL). The mixture was stirred in a nitrogen atmosphere at room temperature for 16 hours. The solvent was evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (ethyl acetate:hexane =

1:9 -> 1:4 -> 1:2) to give 505 mg (91%) of the title compound as a colorless oil.

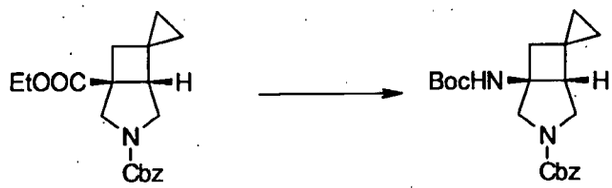
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27-7.40 (5H, m), 5.18 (2H, m), 4.21 (2H, q, J=7.2 Hz), 3.92 (1H, dd, J=36.6, 12.0 Hz), 3.64 (2H, dd, J=23.3, 11.6 Hz), 3.27 (1H, m), 3.02 (1H, d, J=6.1 Hz), 2.73 (1H, m), 2.02 (1H, t, J=10.4 Hz), 1.29 (3H, t, J=7.1 Hz), 0.47-0.58 (3H, m), 0.32 (1H, m).

MS (ESI); m/z: 330 $(M+H)^+$.

[Reference Example 66]

(1S,5R)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-spirocyclopropane-3-azabicyclo[3.2.0]heptane

[Formula 143]



A 1N sodium hydroxide solution (4.60 mL, 4.60 mmol) was added to a solution of (1S,5S)-3-benzyloxycarbonyl-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid ethyl ester (500 mg, 1.52 mmol) in ethanol/tetrahydrofuran (4.6 mL/2.3 mL) at room temperature. The mixture was stirred at the same temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was made acidic with 1N hydrochloric acid, followed by extraction with ethyl acetate (100 mL). The

organic layer was dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated under reduced pressure to give crude (1S,5S)-3-benzyloxycarbonyl-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid (501 mg) as a colorless transparent gummy solid.

Diphenylphosphoryl azide (0.393 mL, 1.82 mmol) was added to a solution of the resulting crude (1S,5S)-3-benzyloxycarbonyl-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-1-ylcarboxylic acid (501 mg) and triethylamine (0.381 mL, 2.73 mmol) in toluene (7.5 mL) at room temperature. The mixture was stirred in a nitrogen atmosphere at room temperature for five minutes and subsequently on an oil bath at 90°C for 40 minutes. Next, tert-butyl alcohol (15 mL) was added to the reaction solution, and the mixture was heated with stirring on an oil bath at 120°C for six hours. The reaction solvent was evaporated under reduced pressure, and then the resulting residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:9 -> 1:4 -> 1:2) to give 347 mg (two steps, 61%) of the title compound as a colorless transparent gummy solid.

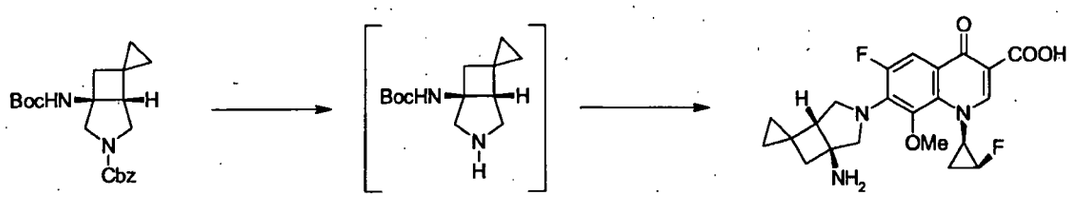
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28-7.39 (5H, m), 5.16 (2H, m), 4.90 (1H, m), 3.95 (1H, t, J=11.6 Hz), 3.41-3.58 (3H, m), 2.80 (1H, m), 2.34 (1H, t, J=10.3 Hz), 2.20 (1H, d, J=12.0 Hz), 1.45 (9H, s), 0.46-0.56 (3H, m), 0.28 (1H, m).

MS (ESI) m/z: 317 $(M-tBu+H)^+$.

[Example 10]

7-[(1S,5R)-1-Amino-6-spirocyclopropane-3-azabicyclo[3.2.0]heptan-3-yl]-1-[(1R,2S)-2-fluorocyclopropyl]-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 144]



A 10% palladium-carbon catalyst (about 50% wet, 103 mg) was added to a solution of (1S,5R)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-spirocyclopropane-3-azabicyclo[3.2.0]heptane (342 mg, 0.918 mmol) in methanol (30 mL), and the mixture was stirred in a hydrogen atmosphere at room temperature for 1.5 hours. The catalyst was removed by filtration, and then the solvent was evaporated under reduced pressure to give crude (1S,5R)-1-(tert-butoxycarbonylamino)-6-spirocyclopropane-3-azabicyclo[3.2.0]heptane (230 mg) as a colorless transparent gummy solid.

A mixture of the resulting crude (1S,5R)-1-(tert-butoxycarbonylamino)-6-spirocyclopropane-3-azabicyclo[3.2.0]heptane (230 mg), 6,7-difluoro-1-[(1R,2S)-

2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (331 mg, 0.918 mmol), triethylamine (0.384 mL, 2.76 mmol), and dimethyl sulfoxide (3 mL) was stirred in a nitrogen atmosphere at room temperature for 17 hours. Next, ethanol (20 mL), water (5 mL), and triethylamine (2.5 mL) were added to the reaction solution, and the mixture was heated to reflux on an oil bath at 110°C for three hours. The solvent was evaporated under reduced pressure, and then a 10% citric acid solution (50 mL) was added to the residue, followed by extraction with ethyl acetate (200 mL). The organic layer was washed with water (50 mL × 2) and brine (50 mL) and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in concentrated hydrochloric acid (20 mL). The resulting acidic solution was transferred to a separatory funnel and then washed with chloroform (20 mL × 8). The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with a mixed solvent of chloroform:methanol = 9:1 (200 mL × 2). The organic layers were combined and dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by recrystallization from

ethanol and dried under reduced pressure to give 125 mg (32%) of the title compound as a light pink powder.

mp: 182-203°C (dec.).

$[\alpha]_D^{23.5}$=-14.4° (c=0.104, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, d, J=1.2 Hz), 7.71 (1H, d, J=13.9 Hz), 4.98 (1H, dm, J=47.4 Hz), 4.03-4.08 (1H, m), 3.70-3.73 (1H, m), 3.70 (3H, s), 3.61 (1H, d, J=10.7 Hz), 3.37 (1H, m), 3.23 (1H, d, J=10.0 Hz), 2.42 (1H, d, J=5.9 Hz), 2.29 (1H, d, J=12.2 Hz), 2.16 (1H, d, J=12.5 Hz), 1.44-1.66 (2H, m), 0.48-0.57 (3H, m), 0.29-0.33 (1H, m).

Anal; Calcd for $C_{22}H_{23}F_2N_3O_4 \cdot 0.75H_2O \cdot 0.25HCl$: C, 58.19; H, 5.49; N, 9.25; F, 8.37; Cl, 1.95. Found: C, 57.93; H, 5.41; N, 9.15; F, 8.43; Cl, 2.44.

MS (FAB) m/z: 432 $(M+H)^+$.

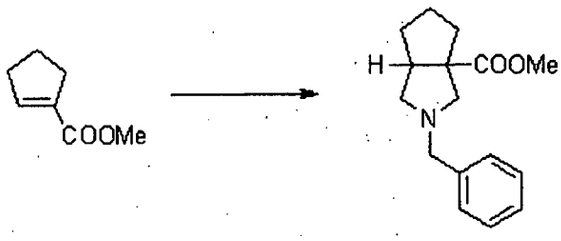
HRMS (FAB) Calcd for $C_{22}H_{23}F_2N_3O_4$+H: 432.1735. Found: 432.1714.

IR (ATR) ν: 2871, 2763, 2721, 2575, 2517, 1720, 1612, 1568, 1535, 1493, 1456, 1365, 1350, 1321, 1267, 1205, 1157 cm^{-1}.

[Reference Example 67]

(1R*,5R*)-3-Benzyl-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester

[Formula 145]



(±)-cis

A catalytic amount of trifluoroacetic acid was added to a solution of 1-cyclopentene-1-carboxylic acid methyl ester (2.52 g, 20.0 mmol) and N-benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine (5.00 g, 21.1 mmol) in dichloromethane (40 mL) at room temperature, and the mixture was heated with stirring at room temperature for 15.5 hours. The reaction solution was diluted with dichloromethane (100 mL) and washed with a saturated sodium bicarbonate solution (80 mL). The washed aqueous layer was further extracted with dichloromethane (50 mL). The organic layers were combined and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 95:5 -> 90:10 -> 80:20) to give 4.28 g (83%) of the title compound as a colorless transparent oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.21 (5H, m), 3.67 (3H, s), 3.58 (1H, d, J=13.2 Hz), 3.52 (1H, d, J=13.2 Hz), 2.92 (1H, d, J=9.3 Hz), 2.88 (1H, m), 2.67 (1H, t, J=8.2 Hz), 2.44

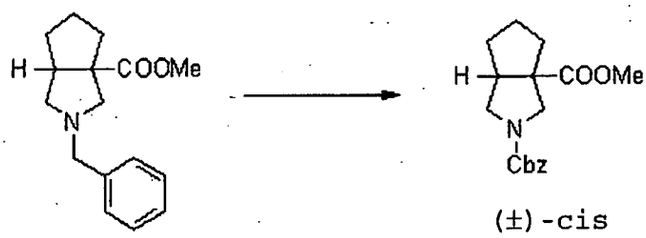
(1H, d, J=9.3 Hz), 2.31 (1H, dd, J=8.8, 4.4 Hz), 2.06-1.60 (5H, m), 1.54-1.47 (1H, m).

MS (ESI); m/z: 260 $(M+H)^+$.

[Reference Example 68]

(1R*,5R*)-3-Benzyloxycarbonyl-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester

[Formula 146]



(±)-cis (±)-cis

Benzyl chloroformate (3.53 mL, 24.6 mmol) was added to a solution of (1R*,5R*)-3-benzyl-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester (4.27 g, 16.46 mmol) in dichloromethane (50 mL) at room temperature, and the mixture was stirred on an oil bath at 40°C for 23 hours. The solvent was evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 -> 80:20 -> 67:33) to give 2.24 g (45%) of the title compound as a colorless transparent oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.28 (5H, m), 5.12 (2H, s), 3.97 (1H, d, J=11.7 Hz), 3.71-3.64 (4H, m), 3.45-3.28 (2H,

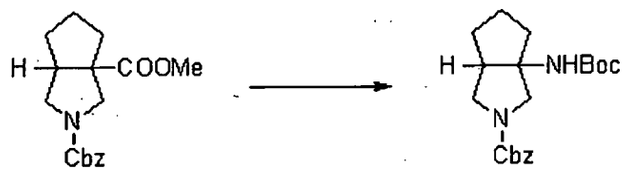
m), 2.94-2.87 (1H, m), 2.23-2.15 (1H, m), 2.03-1.94 (1H, m), 1.85-1.71 (3H, m), 1.52 (1H, m).

MS (ESI) m/z: 304 $(M+H)^+$.

[Reference Example 69]

(1R*,5R*)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane

[Formula 147]



(±)-cis (±)-cis

A 1N sodium hydroxide solution (22.0 mL, 22.0 mmol) was added to a solution of (1R*,5R*)-3-benzyloxycarbonyl-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester (2.21 g, 7.29 mmol) in methanol (22 mL)-tetrahydrofuran (44 mL) at room temperature, and the mixture was stirred at room temperature for two hours. The solvent was concentrated under reduced pressure, and then the residue was made acidic with 3N hydrochloric acid, followed by extraction with ethyl acetate (200 mL). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the solvent was evaporated under reduced pressure to give crude carboxylic acid. The resulting crude carboxylic acid was used for the next reaction without further purification.

Diphenylphosphoryl azide (2.03 mL, 9.42 mmol) was added to a solution of the crude carboxylic acid obtained above and triethylamine (2.02 mL, 14.5 mmol) in toluene (40 mL) under ice-cooling. The mixture was heated with stirring at room temperature for 30 minutes and then on an oil bath at 90°C for 3.5 hours. The reaction solution was diluted with ethyl acetate (200 mL) and sequentially washed with a saturated sodium bicarbonate solution (80 mL), water (80 mL), and brine (80 mL). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the solvent was evaporated under reduced pressure to give crude isocyanate. The resulting crude isocyanate was dissolved in 1,4-dioxane (20 mL), and 6N hydrochloric acid (20 mL) was added. Then, the mixture was heated with stirring on an oil bath at 50°C for 0.5 hour. The reaction solution was diluted with water and ethanol, concentrated under reduced pressure, and then azeotropically distilled with ethanol (twice). The residue was dissolved in dichloromethane (40 mL), and triethylamine (5.05 mL, 36.3 mmol) and di-tert-butyl dicarbonate (3.17 g, 14.5 mmol) were sequentially added at room temperature. The reaction solution was stirred at room temperature for five hours, and then diluted with ethyl acetate (200 mL) and washed with water (80 mL) and brine (80 mL). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the

solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 -> 80:20 -> 67:33) to give 1.32 g (3.66 mmol, 51%) of the title compound as a colorless transparent gummy solid.

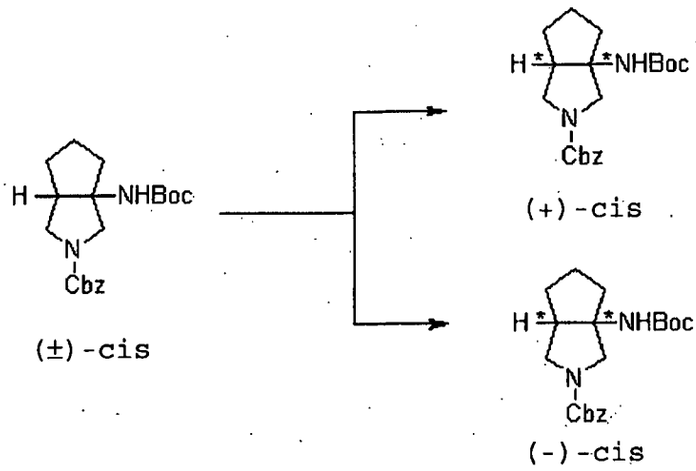
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.27 (5H, m), 5.12 (2H, s), 4.75 (1H, brs), 3.74-3.59 (3H, m), 3.31-3.23 (1H, m), 2.74-2.48 (1H, m), 2.04-1.88 (3H, m), 1.80-1.71 (2H, m), 1.43 (10H, m).

MS (ESI) m/z: 305 $(M-tBu+H)^+$.

[Reference Example 70]

(+)-(1R*,5S*)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane and (-)-(1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane

[Formula 148]



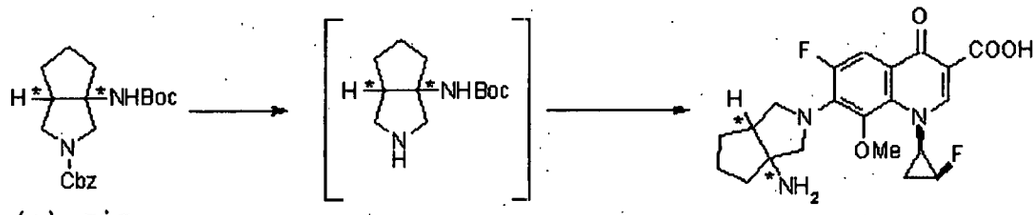
The racemate (1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (1.32 g, 3.66 mmol) obtained as described above was optically resolved by an optically active column (CHIRALCEL OJ, 20 mm diameter × 250 mm, hexane:isopropyl alcohol = 90:10, flow rate = 20 mL/min, resolving 50 mg each time) to give (+)-(1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (586 mg, 1.626 mmol, retention time = 5.5 min, $[\alpha]_D^{25.1}$ = +19.3° (c = 0.145, chloroform)) and (-)-(1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (590 mg, 1.637 mmol, retention time = 6.9 min, $[\alpha]_D^{25.1}$ = -20.0° (c = 0.155, chloroform).

[Example 11]

7-{(1R*,5S*)-1-Amino-3-azabicyclo[3.3.0]octan-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-1,4-

dihydro-4-oxoquinoline-3-carboxylic acid [7-position substituent derived from (+)-optical isomer]

[Formula 149]



(+)-cis

A 10% palladium-carbon catalyst (about 50% wet, 115 mg) was added to a solution of (+)-(1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (575 mg, 1.595 mmol) in methanol (20 mL), and the mixture was stirred in a hydrogen atmosphere at room temperature for two hours. The catalyst was removed by filtration, and then the solvent was evaporated under reduced pressure to give crude 1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (388 mg) as a colorless transparent gummy solid.

The crude 1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane obtained above (388 mg), 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (576 mg, 1.595 mmol), and triethylamine (0.667 mL, 4.79 mmol) were dissolved in dimethyl sulfoxide (4 mL), and the solution was heated with stirring on an oil bath at 35 to 40°C for 16 hours. A mixed solution of ethanol:water = 4:1 (50 mL) and

triethylamine (5 mL) was added to the reaction solution, and the mixture was heated to reflux on an oil bath at 90°C for three hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with a 10% citric acid solution (80 mL), water (50 mL × 2), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in concentrated hydrochloric acid (10 mL) under ice-cooling. After stirring at room temperature for 20 minutes, the reaction solution was washed with chloroform (30 mL × 3). The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid. Thereafter, the solvent was evaporated under reduced pressure. The residue was suspended in methanol and filtered. Then, the filtrate was concentrated under reduced pressure (twice), suspended in a mixed solvent of chloroform:methanol = 9:1 subsequently, and filtered. The mother liquor was concentrated under reduced pressure to remove sodium chloride. The resulting residue was purified by PTLC (preparative TLC; lower layer solvent of chloroform:methanol:water = 7:3:1) and subsequently purified by recrystallization from ethanol-aqueous ammonia

to give 111 mg (17%) of the title compound as a pale yellow powder.

mp: 169-172°C.

$[\alpha]_D^{25.1}$=+103.5° (c=0.228, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 7.68 (1H, d, J=13.9 Hz), 5.05-4.80 (1H, m), 4.04 (1H, m), 3.77 (1H, t, J=9.0 Hz), 3.63 (3H, s), 3.52 (2H, s), 3.35 (1H, dd, J=9.8, 4.9 Hz), 2.30 (1H, m), 2.04 (1H, m), 1.89-1.47 (7H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.25EtOH \cdot 0.75H_2O$: C, 58.10; H, 5.90; F, 8.55; N, 9.45. Found: C, 57.87; H, 5.51; F, 8.60; N, 9.11.

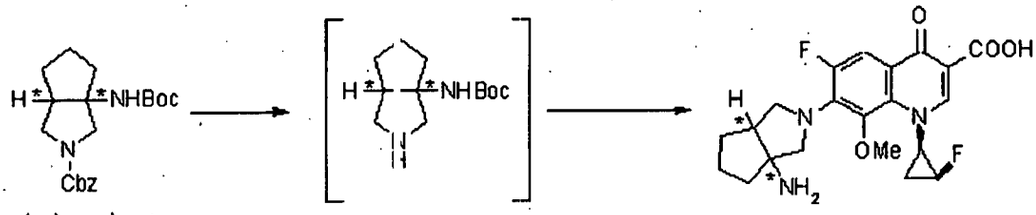
MS (EI); m/z: 419 (M^+).

IR (ATR) ν: 2952, 2873, 2831, 2177, 1712, 1614, 1577, 1535, 1498, 1460, 1389, 1360, 1323, 1271, 1205 cm^{-1}.

[Example 12]

7-[(1R*,5S*)-1-Amino-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid [7-position substituent derived from (-)-optical isomer]

[Formula 150]



(-)-cis

A 10% palladium-carbon catalyst (about 50% wet, 114 mg) was added to a solution of (-)-(1R*,5S*)-3-benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (569 mg, 1.579 mmol) in methanol (30 mL), and the mixture was stirred in a hydrogen atmosphere at room temperature for two hours. The catalyst was removed by filtration, and then the solvent was evaporated under reduced pressure to give crude 1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane (373 mg) as a colorless transparent gummy solid.

The crude 1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane obtained above (373 mg), 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (570 mg, 1.579 mmol), and triethylamine (0.660 mL, 4.74 mmol) were dissolved in dimethyl sulfoxide (4 mL), and the solution was heated with stirring on an oil bath at 35 to 40°C for 16 hours. A mixed solution of ethanol:water = 4:1 (50 mL) and triethylamine (5 mL) was added to the reaction solution, and the mixture was heated to reflux on an oil bath at 90°C for three hours. The reaction solution was concentrated

under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with a 10% citric acid solution (80 mL), water (50 mL × 2), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in concentrated hydrochloric acid (10 mL) under ice-cooling. After stirring at room temperature for 20 minutes, the reaction solution was washed with chloroform (30 mL × 3). The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid. Thereafter, the solvent was evaporated under reduced pressure. The residue was suspended in methanol:aqueous ammonia = 20:1 and filtered. Then, the filtrate was concentrated under reduced pressure (twice), and subsequently suspended in a mixed solvent of chloroform:methanol = 9:1 and filtered. The mother liquor was concentrated under reduced pressure to remove sodium chloride. The resulting residue was purified by PTLC (lower layer solvent of chloroform:methanol:water = 7:3:1) and crystallized in ethanol-diethyl ether to give 32 mg (5%) of the title compound as a yellow brown powder.

mp: 171-174°C.

$[\alpha]_D^{25.1}$=+52.1° (c=0.073, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 7.65 (1H, d, J=13.9 Hz), 5.02-4.82 (1H, m), 4.00 (1H, m), 3.86-3.80 (1H, m), 3.62-3.55 (4H, m), 3.36-3.31 (1H, m), 3.15-3.10 (1H, m), 2.24 (1H, m), 2.05-1.30 (8H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.5EtOH \cdot 1.25H_2O$: C, 56.83; H, 6.18; F, 8.17; N, 9.04. Found: C, 56.41; H, 5.68; F, 8.76; N, 8.64.

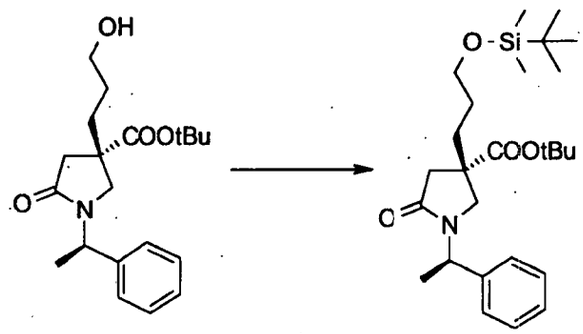
MS (EI); m/z: 419 (M^+).

IR (ATR) ν: 2948, 2871, 2576, 2162, 1712, 1616, 1566, 1495, 1456, 1390, 1363, 1319, 1269 cm^{-1}.

[Reference Example 71]

(3S)-3-[3-(tert-Butyldimethylsilyloxy)-1-propyl]-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 151]



(3S)-3-(3-Hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (46 g) and imidazole (11.9 g) were dissolved in dimethylformamide (600 mL). After addition of tert-

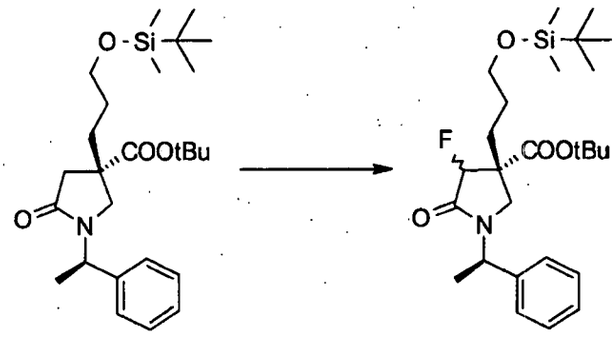
butyldimethylsilyl chloride (23.2 g) under ice-cooling, the mixture was stirred at room temperature for 59.5 hours. The reaction solution was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was sequentially washed with saturated sodium bicarbonate water and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 8:2 -> 2:1) to give 29.7 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.22 (5H, m), 5.48 (1H, q, J=7.11 Hz), 3.58 (2H, t, J=6.13 Hz), 3.34 (1H, d, J=10.05 Hz), 3.12 (1H, d, J=10.05 Hz), 2.94 (1H, d, J=16.91 Hz), 2.31 (1H, d, J=17.16 Hz), 1.86-1.74 (1H, m), 1.72-1.62 (1H, m), 1.51 (3H, d, J=7.11 Hz), 1.49-1.24 (2H, m), 1.33 (9H, s), 0.88 (9H, s), 0.03 (6H, s).

[Reference Example 72]

(3S)-3-[3-(tert-Butyldimethylsilyloxy)-1-propyl]-4-fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 152]



(3S)-3-[3-(tert-Butyldimethylsilyloxy)-1-propyl]-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (30 g) was dissolved in tetrahydrofuran (280 mL), and the atmosphere was replaced with argon. Then, lithium hexamethyldisilazide (1.0 M solution in tetrahydrofuran) (78.0 mL) was added dropwise at -15°C, and the mixture was stirred at -5°C for 30 minutes. After cooling to -15°C again, a solution of N-fluorobenzenesulfonimide (26.6 g) in tetrahydrofuran (220 mL) was added dropwise, and the mixture was stirred at room temperature for 17 hours. The reaction solution was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 8:2) to give 8.15 g of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.23 (5H, m), 5.53-5.44 (1H, m), 5.18 (1H, d, J=51.72 Hz), 3.64-3.52 (2H, m), 3.32-3.19 (2H, m), 1.92-1.65 (2H, m), 1.55 (3H, d, J=4.66 Hz), 1.33 (9H, s), 0.88 (9H, s), 0.03 (6H, s).

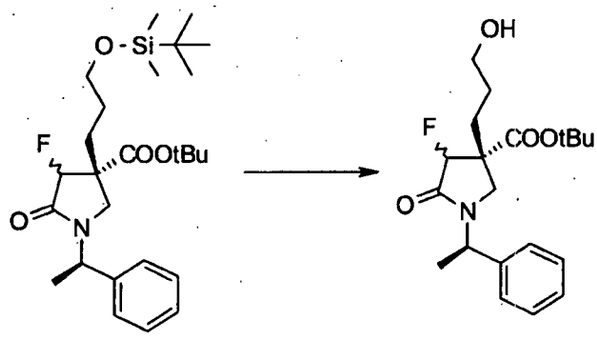
MS (FAB) m/z: 480 $(M+H)^+$.

IR (ATR) ν: 3421, 2977, 2935, 2877, 1698, 1454, 1369, 1309, 1249, 1153, 1058, 1035, 1006, 842 cm^{-1}.

[Reference Example 73]

(3S)-4-Fluoro-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 153]



(3S)-3-[3-(tert-Butyldimethylsilyloxy)-1-propyl]-4-fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (8.15 g) was dissolved in tetrahydrofuran (25.0 mL). Acetic acid (22.0 mL) and tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) (25.0 mL) were added under ice-cooling, and the mixture was stirred at room temperature for 21.5 hours. The reaction solution was extracted with a 10%

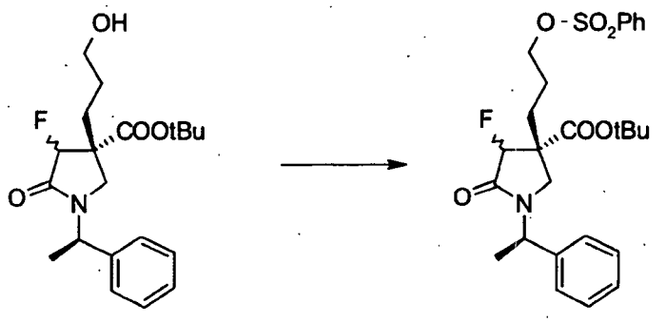
citric acid solution and ethyl acetate. Then, the organic layer was sequentially washed with saturated sodium bicarbonate water and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 8:2 -> 1:1) to give 5.77 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.22 (5H, m), 5.48 (1H, q, J=7.03 Hz), 5.20 (1H, d, J=51.48 Hz), 3.69-3.59 (2H, m), 3.31-3.21 (2H, m), 1.95-1.72 (2H, m), 1.68-1.43 (2H, m), 1.56 (3H, d, J=7.11 Hz), 1.33 (9H, s).

[Reference Example 74]

(3S)-3-(3-benzenesulfonyloxy-1-propyl)-4-Fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 154]



(3S)-4-Fluoro-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (12.20 g) was dissolved in dichloromethane (400 mL).

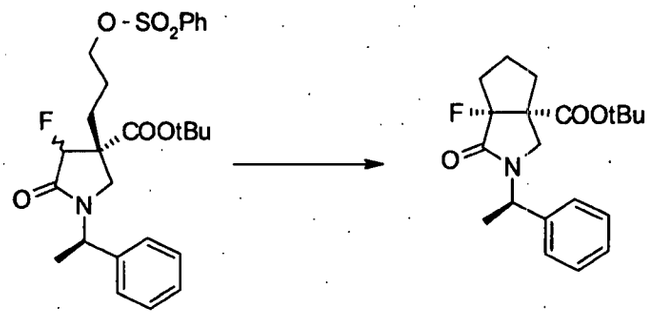
Benzenesulfonyl chloride (9.06 mL), triethylamine (10.7 mL), and 4-dimethylaminopyridine (2.04 g) were added under ice-cooling, and the mixture was stirred at room temperature for 12.5 hours. Saturated sodium bicarbonate water was added to the reaction solution, and the mixture was stirred for 30 minutes, followed by extraction with dichloromethane. The organic layer was sequentially washed with a 10% citric acid solution and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 8:2 -> 1:1) to give 11.7 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94-7.87 (2H, m), 7.71-7.63 (1H, m), 7.60-7.53 (2H, m), 7.37-7.23 (5H, m), 5.46 (1H, q, J=7.11 Hz), 5.15 (1H, d, J=51.48 Hz), 4.10-3.98 (2H, m), 3.26-3.15 (2H, m), 1.88-1.50 (4H, m), 1.55 (3H, s), 1.30 (9H, s).

[Reference Example 75]

(1S,5R)-5-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester

[Formula 155]



(3S)-3-(3-benzenesulfonyloxy-1-propyl)-4-Fluoro-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (10.9 g) was dissolved in tetrahydrofuran (350 mL), and the atmosphere was replaced with argon. Then, potassium hexamethyldisilazide (0.5 M solution in toluene) (86.5 mL) was added dropwise at -15°C, and the mixture was stirred at 0°C for 1.5 hours. After cooling to -10°C, saturated aqueous ammonium chloride (100 mL) was added dropwise, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 7:1) to give 4.36 g of the title compound as a pale yellow solid.

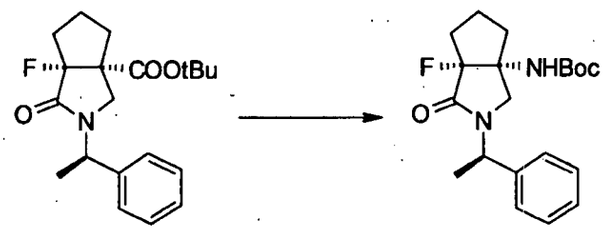
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.58-5.49 (1H, m), 3.63 (1H, d, J=10.3 Hz), 2.91 (1H, dd, J=10.3, 3.2 Hz),

2.67-2.56 (1H, m), 2.50-2.38 (1H, m), 2.26-2.09 (1H, m), 2.06-1.94 (1H, m), 1.74-1.66 (1H, m), 1.54 (3H, d, J=7.1 Hz), 1.50-1.40 (1H, m), 1.34 (9H, s).

[Reference Example 76]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 156]



(1S,5R)-5-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester (4.36 g, 12.5 mmol) was dissolved in dichloromethane (70 mL). Trifluoroacetic acid (70 mL) was added dropwise, and the mixture was stirred at room temperature for six hours. The solvent was evaporated under reduced pressure, and then the residue was azeotropically distilled with toluene to give carboxylic acid (3.70 g).

The resulting carboxylic acid was dissolved in toluene. Triethylamine (3.51 mL, 25.2 mmol) and diphenylphosphoryl azide (2.98 ml, 13.8 mmol) were added, and the mixture was heated to reflux for five hours. The solvent was evaporated under reduced pressure. Then, 1,4-dioxane (110 ml) and 6N hydrochloric acid (110 mL) were added to the residue, and

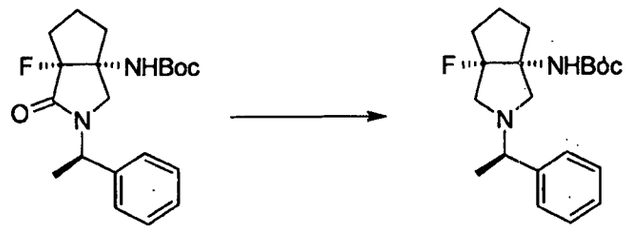
the mixture was stirred at 60°C for 2.5 hours. After extraction with water and ethyl acetate, the aqueous layer was made alkaline with a saturated sodium hydroxide solution and extracted with chloroform twice. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered, and then the solvent was evaporated under reduced pressure. Di-tert-butyl dicarbonate (11.05 g) was added to the residue, and the mixture was stirred at 75°C for six hours. The reaction solution was concentrated under reduced pressure, and then the residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 9:1 -> 1:1) to give 3.69 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.23 (5H, m), 5.50 (1H, q, J=7.1 Hz), 5.22 (1H, brs), 3.34 (2H, s), 2.49-2.37 (1H, m), 2.32-2.03 (3H, m), 2.02-1.90 (1H, m), 1.51 (3H, d, J=7.1 Hz), 1.55-1.48 (1H, m), 1.35 (9H, s).

[Reference Example 77]

(1R,5S)-1-(tert-Butoxycarbonylamino)-5-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 157]



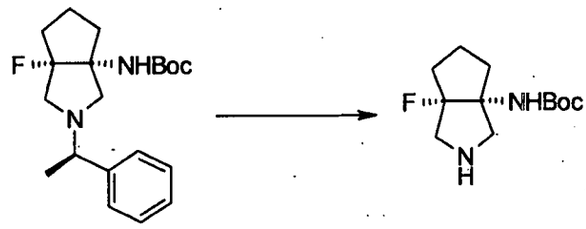
(1R,5R)-1-(tert-Butoxycarbonylamino)-5-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (3.69 g, 10.2 mmol) was dissolved in tetrahydrofuran (200 mL). A 1.20 M solution of a borane-tetrahydrofuran complex in tetrahydrofuran (42.4 mL, 50.9 mmol) was added dropwise under ice-cooling, and the mixture was stirred for two hours while gradually heating to room temperature. The solvent was evaporated under reduced pressure. Under ice-cooling, 90% aqueous ethanol (100 mL) and triethylamine (100 mL) were added to the residue, and the mixture was heated to reflux for two hours. The solvent was evaporated under reduced pressure, and then the residue was extracted with saturated sodium bicarbonate water and dichloromethane. Thereafter, the target substance was extracted from the aqueous layer with dichloromethane. The organic layers were combined, washed with brine, and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 95:5 -> 90:10) to give 3.33 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.18 (5H, m), 5.38 (1H, brs), 3.22 (1H, q, J=6.37 Hz), 2.92-2.57 (4H, m), 2.12-1.86 (4H, m), 1.80-1.67 (1H, m), 1.63-1.52 (3H, m), 1.42 (9H, s), 1.32 (3H, d, J=6.37 Hz).

[Reference Example 78]

(1R,5S)-1-(tert-Butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane

[Formula 158]



(1R,5S)-1-(tert-Butoxycarbonylamino)-5-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (700 mg, 2.0 mmol) was dissolved in ethanol (30 mL). 10% palladium-carbon (50% wet) (1.01 g) was added, and the mixture was stirred in a hydrogen atmosphere at 50°C for 15 hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (dichloromethane:methanol = 98:2 -> 95:5) to give 446 mg of the title compound as a pale yellow solid.

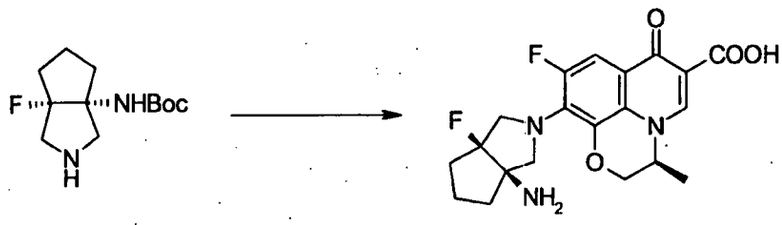
$[\alpha]_D^{23}$-15° (c=0.100, MeOH).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.29 (1H, brs), 3.47-3.18 (2H, m), 2.93-2.79 (2H, m), 2.15-1.71 (6H, m), 1.45 (9H, s).

[Example 13]

10-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid

[Formula 159]



Triethylamine (0.222 mL, 1.59 mmol) and 9,10-difluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF_2 chelate (209 mg, 0.64 mmol) were added to a solution of (1R,5S)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane (129 mg, 0.53 mmol) in dimethyl sulfoxide (4.0 mL). The mixture was stirred at 40°C for 18.5 hours. Triethylamine (0.111 mL, 0.80 mmol) was further added to the reaction solution, and the mixture was stirred at 40°C for 6.5 hours. Ethanol (6.0 mL), water (2.0 mL), and triethylamine (2.0 mL) were added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The solvent was evaporated under reduced pressure, and then the residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water twice and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (dichloromethane:methanol = 99:1 -> 98:2) to give an oil (261 mg). The resulting oil (261 mg) was

dissolved in concentrated hydrochloric acid (2.4 ml) under ice-cooling, and the solution was stirred at room temperature for three hours. The reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. 10% methanol-chloroform was added to the residue. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from ethanol-aqueous ammonia to give 145 mg of the title compound as a pale yellow solid.

mp: 285-293°C (dec.).

$[\alpha]_D^{24}$-40.3° (c=0.100, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, d, J=1.23 Hz), 7.70 (1H, d, J=13.7 Hz), 5.07-4.85 (1H, m), 4.10-4.02 (1H, m), 3.93-3.78 (2H, m), 3.70-3.53 (2H, m), 3.66 (3H, s), 2.21-2.04 (2H, m), 2.01-1.83 (2H, m), 1.83-1.46 (4H, m).

MS (FAB) m/z: 406 $(M+H)^+$.

Anal.Calcd $C_{20}H_{21}F_2N_3O_4$: C, 59.25; H, 5.22; F, 9.37; N, 10.37.

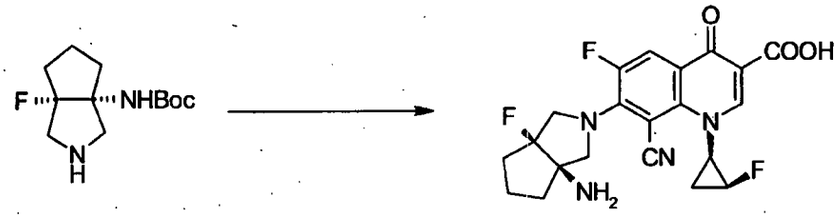
Found: C, 59.22; H, 5.16; F, 9.16; N, 10.27.

IR (ATR) ν: 3365, 2931, 2861, 1706, 1619, 1521, 1461, 1442, 1415, 1396, 1278, 1230, 1141, 1130, 1093, 1047, 983, 964, 900, 879, 863, 800 cm^{-1}.

[Example 14]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 160]



Triethylamine (0.272 mL, 1.95 mmol) and 8-cyano-6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (240 mg, 0.71 mmol) were added to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane (148 mg, 0.61 mmol) in acetonitrile (10 ml), and the mixture was stirred at room temperature for three days. The solvent was evaporated under reduced pressure, and then the residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column

chromatography (hexane:ethyl acetate = 1:1 -> 3:7) to give ethyl ester substituted with a 7-position substituent (231 mg). The resulting ethyl ester (231 mg) was dissolved in tetrahydrofuran (3.0 mL) and ethanol (6.0 mL). A 1N sodium hydroxide solution (0.82 mL) was added, and the mixture was stirred at room temperature for 3.5 hours. The solvent was evaporated under reduced pressure, and then the residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. Concentrated hydrochloric acid (2.0 ml) was added to the residue, and the mixture was stirred at room temperature for one hour. Thereafter, the reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. 10% methanol-chloroform was added to the residue, and the insoluble material was removed by filtration. Then, the filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from ethanol-

aqueous ammonia to give 128 mg of the title compound as a pale yellow solid.

mp: 268-280°C (dec.).

$[\alpha]_D^{24}$-1.8° (c=0.100, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.40 (1H, d, J=1.96 Hz), 7.96 (1H, d, J=14.46 Hz), 5.29-5.05 (1H, m), 4.28-4.00 (3H, m), 3.94-3.80 (2H, m), 2.23-2.10 (2H, m), 2.04-1.56 (6H, m).

MS (FAB); m/z: 433 $(M+H)^+$.

Anal.Calcd $C_{21}H_{19}F_3N_4O_3$: C, 58.33; H, 4.43; F, 13.18; N, 12.96.

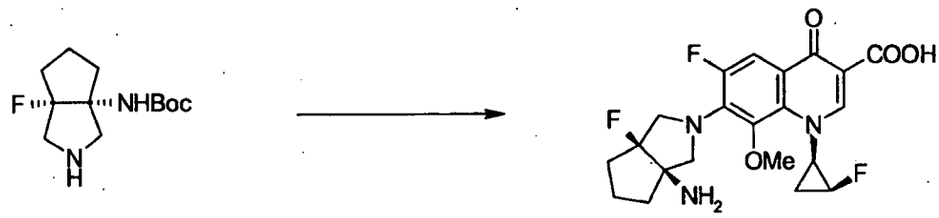
Found: C, 58.24; H, 4.36; F, 13.10; N, 12.84.

IR (ATR) ν: 3359, 3039, 2213, 1720, 1623, 1552, 1477, 1452, 1405, 1375, 1311, 1259, 1226, 1172, 1137, 1112, 1074, 1054, 991, 931, 887, 806 cm^{-1}.

[Example 15]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 161]



Triethylamine (3.30 mL, 23.7 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (2.93 g, 8.12

mmol) were added to a solution of (1R,5S)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane (1.32 g, 5.40 mmol) in dimethyl sulfoxide (30 mL). The mixture was stirred at 40°C for 19 hours. Triethylamine (1.70 mL, 12.3 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (1.00 g, 2.77 mmol) were further added to the reaction solution, and the mixture was stirred at 40°C for 16 hours. Ethanol (45 mL), water (15 mL), and triethylamine (15 mL) were added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The solvent was evaporated under reduced pressure, and then the resulting residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water three times and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (dichloromethane:methanol = 99:1). The resulting oil (3.30 g) was dissolved in concentrated hydrochloric acid (20 mL) under ice-cooling, and the solution was stirred at room temperature for one hour. The reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with

hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. Chloroform was added to the residue. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to give 769 mg of the title compound as a pale yellow solid.

mp: 191-195°C (dec.).

$[\alpha]_D^{24}$+97° (c=0.100, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, d, J=1.23 Hz), 7.70 (1H, d, J=13.73 Hz), 5.07-4.85 (1H, m), 4.10-4.02 (1H, m), 3.93-3.78 (2H, m), 3.70-3.53 (2H, m), 3.66 (3H, s), 2.21-2.04 (2H, m), 2.01-1.83 (2H, m), 1.83-1.46 (4H, m).

MS (FAB); m/z: 438 $(M+H)^+$.

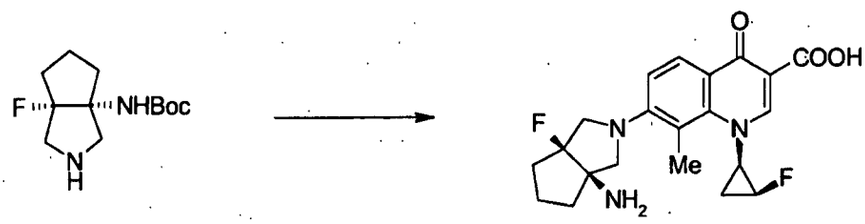
Anal.Calcd $C_{21}H_{22}F_3N_3O_4 \cdot 0.75H_2O$: C, 55.94; H, 5.25; F, 12.64; N, 9.32. Found: C, 56.03; H, 5.51; F, 12.79; N, 9.66.

IR (ATR) ν: 2958, 2871, 1724, 1621, 1513, 1452, 1319, 1056, 929, 804 cm^{-1}.

[Example 16]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 162]



Triethylamine (0.447 mL, 3.21 mmol) and 7-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (450 mg, 1.61 mmol) were added to a solution of (1R,5S)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane (260 mg, 1.07 mmol) in dimethyl sulfoxide (6.0 mL), and the mixture was stirred at 70 to 80°C for 18.5 hours. Triethylamine (0.224 mL, 1.61 mmol) was added again to the reaction solution, and the mixture was stirred at 70 to 80°C for six days. Triethylamine (0.447 mL, 3.21 mmol) was further added, the mixture was stirred at 70 to 80°C for 10 days. The reaction solution was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water twice and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (dichloromethane:methanol = 98:2) to give an oil (369 mg). The resulting oil (369 mg) was dissolved in concentrated hydrochloric acid (3.0 mL) under ice-cooling, and the solution was stirred at room temperature for one hour. The

reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by PTLC (developed with the lower layer of chloroform:methanol:water = 7:3:1). Then, the resulting fraction was concentrated under reduced pressure to give a residue, which was solidified with isopropanol to give 21 mg of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.50 (1H, d, J=2.94 Hz), 8.06 (1H, d, J=8.58 Hz), 7.13 (1H, d, J=8.82 Hz), 5.13-4.90 (1H, m), 4.18-4.10 (1H, m), 3.89-3.77 (1H, m), 3.45-3.25 (3H, m), 2.58 (3H, s), 2.20-1.98 (3H, m), 1.93-1.82 (1H, m), 1.81-1.57 (3H, m), 1.37-1.22 (1H, m).

MS (FAB); m/z: 404 $(M+H)^+$.

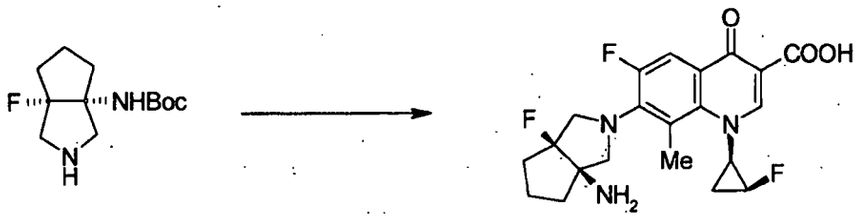
Anal.Calcd $C_{21}H_{23}F_2N_3O_3 \cdot 0.5H_2O \cdot 0.25IPA$: C, 61.11; H, 6.13; N, 9.83. Found: C, 61.11; H, 5.72; N, 9.74.

IR (ATR) ν: 2956, 2873, 2823, 1708, 1610, 1508, 1432, 1355, 1313, 1255, 1133, 929 cm^{-1}.

[Example 17]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 163]



Triethylamine (0.215 mL, 1.54 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (530 mg, 1.53 mmol) were added to a solution of (1R,5S)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane (250 mg, 1.02 mmol) in dimethyl sulfoxide (5.0 mL). The mixture was stirred at room temperature for seven days. Triethylamine (0.215 mL, 1.54 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (530 mg, 1.53 mmol) were further added to the reaction solution, and the mixture was stirred at room temperature for seven days. Triethylamine (0.215 mL, 1.54 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (530 mg, 1.53 mmol) were further added to the reaction solution, and the mixture was stirred at room temperature for ten days.

Ethanol (6.0 mL), water (2.0 mL), and triethylamine (2.0 mL) were added to the reaction solution, and the mixture was stirred at 80°C for one hour. The solvent was evaporated under reduced pressure, and then the residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water twice and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (dichloromethane:methanol = 98:2), and the resulting fraction was concentrated under reduced pressure. Then, the residue was dissolved in concentrated hydrochloric acid (3.5 mL) under ice-cooling, and the solution was stirred at room temperature for one hour. The reaction solution was washed with chloroform five times, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by PTLC (developed with the lower layer of chloroform:methanol:water = 7:3:1). The resulting residue was solidified with isopropanol to give 7.1 mg of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.50 (1H, s), 7.77 (1H, d, J=13.73 Hz), 5.80-4.80 (1H, m), 4.22-4.10 (1H, m), 3.99-3.85 (1H, m), 3.68-3.47 (2H, m), 3.43-3.34 (1H, m), 2.68 (3H, s), 2.21-1.98 (3H, m), 1.97-1.56 (4H, m), 1.42-1.23 (1H, m).

MS (FAB); m/z: 422 $(M+H)^+$.

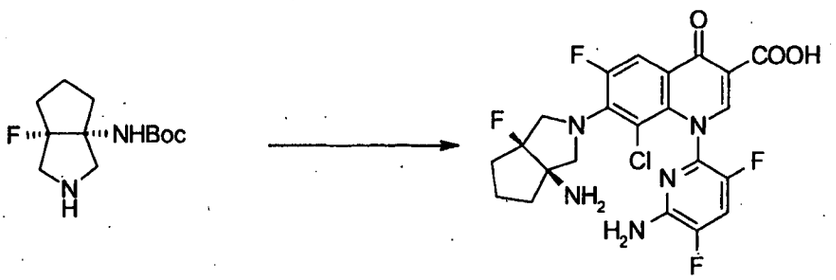
Anal.Calcd $C_{21}H_{22}F_3N_3O_3 \cdot 0.5H_2O \cdot 0.25IPA$: C, 58.65; H, 5.66; F, 12.80; N, 9.43. Found: C, 58.63; H, 5.35; F, 12.35; N, 9.22.

IR (ATR) ν: 2971, 2856, 1722, 1614, 1450, 1432, 1322, 1132, 1097, 987, 954, 929, 887, 856, 804 cm^{-1}.

[Example 18]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-1-(6-amino-3,5-difluoropyridin-2-yl)-1,4-dihydro-8-chloro-6-fluoro-4-oxoquinoline-3-carboxylic acid

[Formula 164]



N-methylpyrrolidine (0.246 mL, 2.37 mmol) and 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (306 mg, 0.79 mmol) were added to a solution of (1R,5S)-1-(tert-butoxycarbonylamino)-5-fluoro-3-azabicyclo[3.3.0]octane

(193 mg, 0.79 mmol) in acetonitrile (10.0 mL), and the mixture was heated to reflux for 10 hours. 1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (92 mg, 0.24 mmol) was added again to the reaction solution, and the mixture was further heated to reflux for 4.5 hours. The solvent was evaporated under reduced pressure, and then the residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water twice and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (dichloromethane:methanol = 99:1). The resulting oil (409 mg) was dissolved in concentrated hydrochloric acid (3.0 mL) under ice-cooling, and the solution was stirred at room temperature for 2.5 hours. The reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. Chloroform was added to the residue, and the insoluble material was removed by filtration. Then, the filtrate was evaporated

under reduced pressure, and the resulting residue was purified by recrystallization from ethanol to give 47 mg of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.79 (1H, s), 8.07-7.90 (2H, m), 6.75 (2H, d, J=8.58 Hz), 3.87-3.65 (2H, m), 3.50-3.25 (2H, m), 2.09-1.96 (2H, m), 1.88-1.53 (4H, m).

MS (FAB); m/z: 512 $(M+H)^+$.

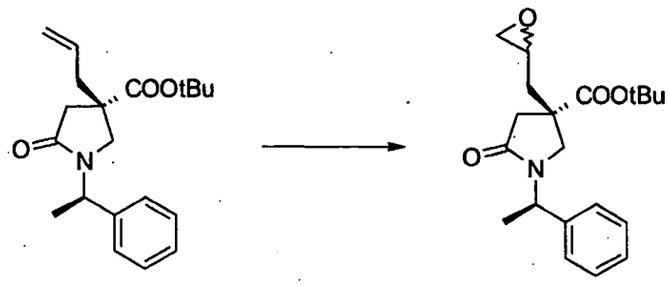
Anal.Calcd $C_{22}H_{18}ClF_4N_5O_3 \cdot 0.5H_2O$: C, 50.73; H, 3.68; Cl, 6.81; F, 14.59; N, 13.45. Found: C, 50.75; H, 3.58; Cl, 6.52; F, 14.31; N, 13.09.

IR (ATR) ν: 3480, 3345, 3070, 2954, 2865, 1724, 1606, 1484, 1438, 1386, 1307, 1112 cm^{-1}.

[Reference Example 79]

3-(Oxiran-2-ylmethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 165]



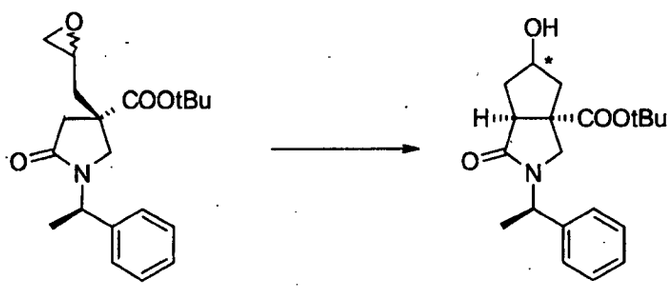
(3S)-3-Allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.9 g, 14.9 mmol) was dissolved in methylene chloride, and mCPBA (10.3 g, 59.5 mmol) was added. The mixture was stirred at room

temperature for 15 hours and then heated to reflux for three hours. The solvent was evaporated under reduced pressure, and then the residue was blended with a mixture of ethyl acetate and a saturated sodium thiosulfate solution. The organic layer was washed with saturated sodium bicarbonate water, dried over magnesium sulfate, and filtered, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 4:1 -> 1:1) to give 4.33 g (84%) of the colorless oil title compound as a diastereomer mixture. The diastereomers were used for the next step without separation and purification.

[Reference Example 80]

(1S,5S)-7-Hydroxy-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester

[Formula 166]



3-(Oxiran-2-ylmethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.2 g, 12.16 mmol) was dissolved in tetrahydrofuran (50 mL). A 1 M solution of lithium hexamethyldisilazide in

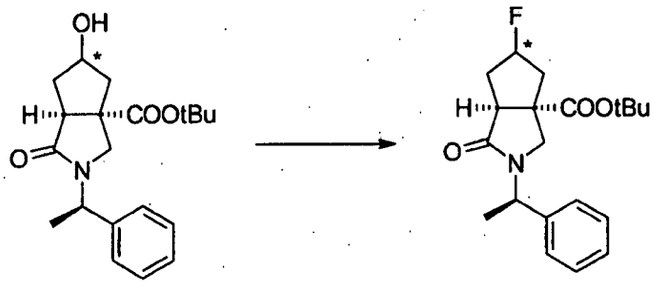
tetrahydrofuran (18 mL, 1.5 equivalents) was added in an argon atmosphere at -78°C, and the mixture was gradually heated. When the reaction temperature reached about room temperature, the reaction was quenched with an ammonium chloride solution, followed by extraction with ethyl acetate. The extract was dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane:ethyl acetate = 4:1 -> 2:1 -> 1:1 -> 1:2) to give 1.07 g (26%) of the title compound having a single isomer as a colorless oil. 1.0 g (24%) of the raw material was collected. 1.20 g (29%) of a four-membered ring-closed compound as a by-product was obtained as a diastereomer mixture.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.48 (1H, q, J=7.08 Hz), 4.36-4.30 (1H, m), 3.35-3.30 (2H, m), 3.12 (1H, d, J=10.25 Hz), 2.44-2.38 (2H, m), 2.29 (1H, dt, J=13.83, 4.94 Hz), 2.16-2.09 (1H, m), 1.84 (1H, dd, J=13.79, 5.25 Hz), 1.50 (3H, d, J=7.08 Hz), 1.37 (9H, s).

[Reference Example 81]

(1R,5R)-7-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester

[Formula 167]



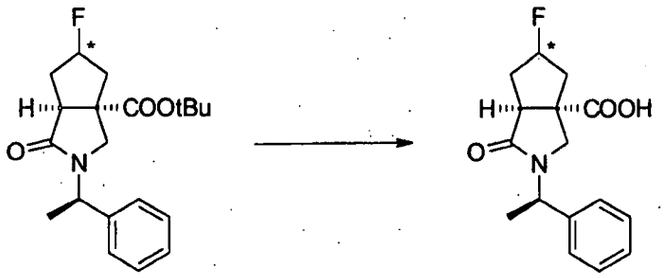
(1S,5S)-7-Hydroxy-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester (1.0 g, 2.89 mmol) was dissolved in methylene chloride (15 mL). Bis(2-methoxyethyl)aminosulfur trifluoride (BAST) (0.59 mL) was added under ice-cooling, and the mixture was stirred at the same temperature for one hour. The reaction solution was washed with saturated sodium bicarbonate water, dried over magnesium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate = 10:1 -> 4:1 -> 1:1) to give 711 mg (71%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.50 (1H, q, J=7.1 Hz), 5.24 (1H, dt, J=52.2, 3.2 Hz), 3.48 (1H, d, J=10.0 Hz), 3.26-3.21 (2H, m), 2.61-2.37 (2H, m), 2.21-2.04 (2H, m), 1.48 (3H, d, J=7.1 Hz), 1.36 (9H, s).

[Reference Example 82]

(1R,5R)-7-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid

[Formula 168]



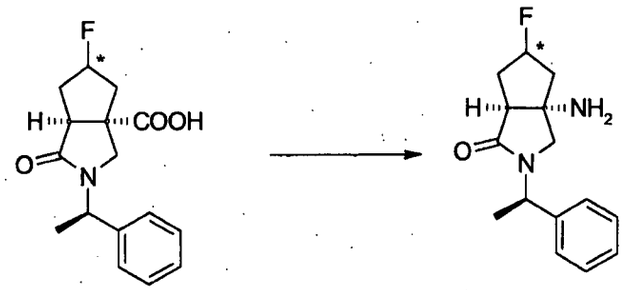
(1R,5R)-7-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester (705 mg, 2.03 mmol) was dissolved in methylene chloride (4 mL). Trifluoroacetic acid (4 mL) was added under ice-cooling, and then the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure. Toluene was added to the residue, and the mixture was concentrated under reduced pressure again to give 595 mg (quantitative) of the title compound as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.14 (5H, m), 5.48 (1H, q, J=7.08 Hz), 5.32-5.19 (1H, m), 3.61 (1H, d, J=10.74 Hz), 3.43 (1H, d, J=10.01 Hz), 3.33 (1H, d, J=10.50 Hz), 2.64-2.05 (4H, m), 1.49 (3H, d, J=7.08 Hz).

[Reference Example 83]

(1R,5S)-1-Amino-7-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 169]



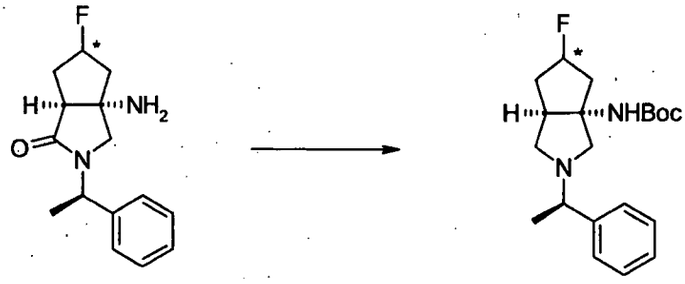
Toluene (10 mL) and triethylamine (565 μL, 4.05 mmol) were added to (1R,5R)-7-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid (590 mg, 2.03 mmol). Then, diphenylphosphoryl azide (567 μL) was added, and the mixture was stirred at room temperature for 30 minutes. Thereafter, the reaction solution was heated to reflux for one hour and blended with a mixture of ethyl acetate-saturated sodium bicarbonate water. The organic layer was dried over magnesium sulfate and filtered. Then, the solvent was evaporated under reduced pressure. The residue was dissolved in dioxane (10 mL). 6N hydrochloric acid (10 mL) was added, and the mixture was heated with stirring at 70°C for two hours. After washing with ether, the aqueous layer was made basic with a 10 M sodium hydroxide solution, followed by extraction with toluene five times. The extract was dried over magnesium sulfate and filtered, and then the solvent was evaporated under reduced pressure to give 476 mg (90%) of the title compound as a colorless oil. The product was used for the next step without purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.16 (5H, m), 5.53 (1H, q, J=7.00 Hz), 5.20 (1H, dt, J=52.70, 4.40 Hz), 3.49 (1H, d, J=10.30 Hz), 2.86 (1H, d, J=10.30 Hz), 2.66 (1H, d, J=10.00 Hz), 2.52-2.19 (3H, m), 1.93 (1H, ddd, J=39.50, 15.00, 4.10 Hz), 1.52 (2H, brs), 1.47 (3H, d, J=7.10 Hz).

[Reference Example 84]

(1R,5S)-1-(tert-Butoxycarbonylamino)-7-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 170]



(1R,5S)-1-Amino-7-fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (537 mg, 2.05 mmol) was dissolved in toluene (20 mL). Red-Al™ (65% solution in toluene) (2.53 mL, 8.12 mmol) was added in an argon atmosphere, the mixture was stirred at 80°C for one hour. A 5 M sodium hydroxide solution was added to the reaction solution, followed by extraction with toluene. The extract was dried over magnesium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The residue was dissolved in toluene (20 mL). Di-tert-butyl dicarbonate (475 mg, 2.18 mmol) was added, and the mixture was stirred

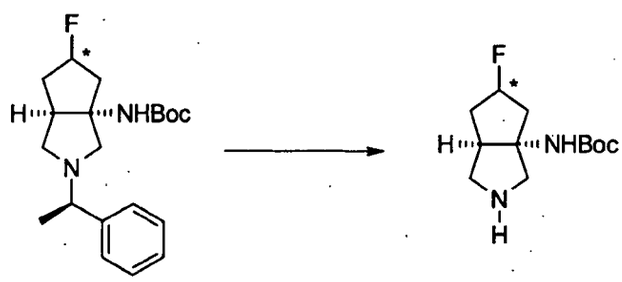
at 50°C for one hour. The solvent was evaporated under reduced pressure, and then the residue was purified by silica gel chromatography (hexane:ethyl acetate = 9:1 -> 8:2 -> 7:3) to give 450 mg (71%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.20 (5H, m), 5.20 (1H, d, J=54.00 Hz), 4.90 (1H, brs), 3.22 (1H, q, J=6.50 Hz), 2.92 (1H, d, J=7.60 Hz), 2.58 (1H, d, J=9.80 Hz), 2.48-2.20 (4H, m), 1.79 (1H, t, J=16.80 Hz), 1.43 (9H, s), 1.33 (3H, d, J=6.60 Hz).

[Reference Example 85]

(1R,5S)-1-(tert-Butoxycarbonylamino)-7-fluoro-3-bicyclo[3.3.0]octane

[Formula 171]



(1R,5S)-1-(tert-Butoxycarbonylamino)-7-fluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (450 mg, 1.29 mmol) was dissolved in methanol (15 mL). A catalytic amount of a 10% palladium-carbon catalyst (50% wet) was added, and the mixture was stirred in a hydrogen atmosphere at 40°C for 12 hours. After removing the catalyst by filtration, the

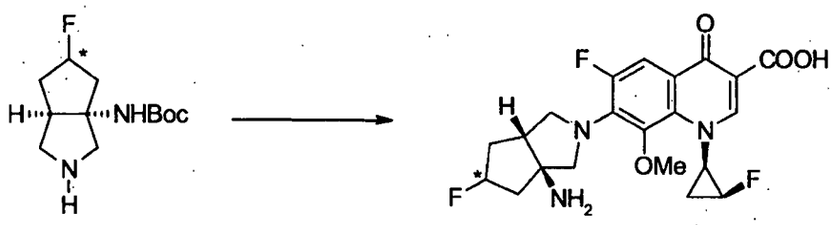
filtrate was concentrated under reduced pressure to give 316 mg (quantitative) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.24 (1H, d, J=53.71 Hz), 5.07 (1H, s), 3.48-3.42 (1H, m), 3.23 (2H, dd, J=14.77, 12.33 Hz), 2.93-2.87 (1H, m), 2.76 (1H, brs), 2.44-2.16 (3H, m), 1.95-1.86 (1H, m), 1.44 (9H, s).

[Example 19]

7-{(1R,5S)-1-Amino-7-fluoro-3-azabicyclo[3.3.0]octan-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 172]



(1R,5S)-1-(tert-Butoxycarbonylamino)-7-fluoro-3-azabicyclo[3.3.0]octane (296 mg, 1.21 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (437 mg, 1.21 mmol) were dissolved in dimethyl sulfoxide (6 mL). Triethylamine (203 μL, 1.45 mmol) was added, and the mixture was stirred at 40°C for one day. Water was added to the reaction solution, and the precipitated crystals were collected by filtration, washed with water, and dried to

give a yellow powder. This was dissolved in ethanol (35 mL)-water (9 mL). Triethylamine (202 μL) were added, and the mixture was heated to reflux for four hours. The solvent was evaporated under reduced pressure, and the residue was blended with a mixture of ethyl acetate and a 10% citric acid solution. The organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. Then, concentrated hydrochloric acid (9 mL) was added to the residue, and the mixture was stirred at room temperature for two hours. The reaction solution was diluted with concentrated hydrochloric acid, then transferred to a separatory funnel, and washed with chloroform three times. Thereafter, the hydrochloric acid layer was adjusted to pH 12 with a 12 M sodium hydroxide solution under ice-cooling. The layer was further adjusted to pH 7.4 with 1 M hydrochloric acid and 0.01 M hydrochloric acid, followed by extraction with chloroform-methanol (9:1). Then, the aqueous layer was adjusted to pH 7.4 again and an extraction operation was performed. After repeating this operation five times, the organic layer was dried over magnesium sulfate and filtered, and the filtrate was evaporated under reduced pressure. Ethanol was added to the residue, and the solvent was evaporated under reduced pressure. The residue was dried under reduced pressure to

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give 220 mg (42%) of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 7.66 (1H, d, J=13.70 Hz), 5.45-5.31 (1H, brm), 5.04-4.86 (1H, brm), 4.06-4.01 (1H, m), 3.87 (1H, t, J=8.90 Hz), 3.73-3.51 (6H, m), 2.52-2.25 (3H, m), 2.15-1.89 (2H, m), 1.64-1.47 (2H, m).

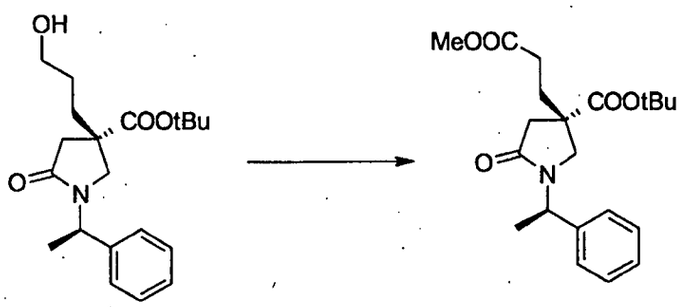
Anal; Calcd for $C_{21}H_{22}F_3N_3O_4 \cdot 1.0H_2O \cdot 0.4EtOH$: C, 55.26; H, 5.62; F, 12.03; N, 8.87. Found: C, 55.05; H, 5.35; F, 12.32; N, 8.76.

MS (ESI) m/z: 438 $(M+H)^+$.

[Reference Example 86]

(3S)-3-(2-Methoxycarbonyl-1-ethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 173]



Carbon tetrachloride (550 mL), acetonitrile (550 mL), and water (550 mL) were dissolved in (3S)-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (38.2 g, 0.110 mol), and ruthenium (III) chloride hydrate (456 mg, 2.20 mmol) and sodium periodide (94.1 g, 0.440 mol) were sequentially

added. The mixture was stirred in a water bath with a thermostatic circulator at 15°C for 2.5 hours while maintaining the internal temperature at 20 to 25°C. The reaction solution was cooled in an ice bath and a 1N hydrochloric acid solution (2.2 L) was added at an internal temperature of 10°C or less, followed by extraction with 2 L of chloroform. The aqueous layer was extracted with chloroform (1 L × 3). Then, the organic layers were combined, washed with brine (2 L × 2), and dried over anhydrous sodium sulfate. After filtration, the solvent was concentrated under reduced pressure. The resulting crude was dissolved in N,N-dimethylformamide (370 mL). Sodium bicarbonate (37.9 g, 0.451 mol) and methyl iodide (70.7 g, 0.498 mol) were added with stirring at room temperature, and the mixture was stirred for three days. The reaction solution was poured into ice water (1.8 L), followed by extraction with ethyl acetate (1.8 L, 0.5 L). The organic layers were combined, washed with brine, and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, the residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 1:1), and the fraction containing the target substance was concentrated under reduced pressure. The resulting solid was dissolved in ethyl acetate, washed with a 10% sodium thiosulfate solution, and

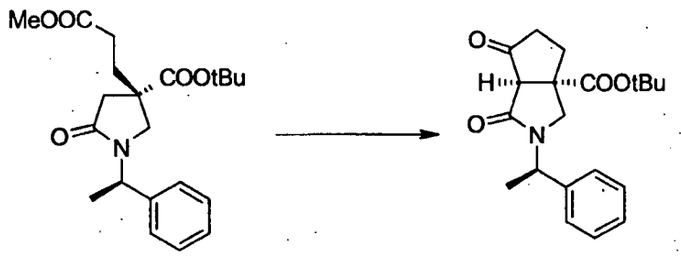
dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the resulting solid was dried to give 35.0 g of the title compound as a pale yellow brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.48 (1H, q, J=7.1 Hz), 3.68 (3H, s), 3.33 (1H, d, J=10.3 Hz), 3.13 (1H, d, J=10.3 Hz), 2.93 (1H, d, J=16.8 Hz), 2.34-2.20 (3H, m), 2.13-1.94 (2H, m), 1.51 (3H, d, J=7.1 Hz), 1.32 (9H, s).

[Reference Example 87]

{(1S,5R)-4,6-Dioxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 174]



(3S)-3-(2-Methoxycarbonyl-1-ethyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (35.0 g, 93.2 mmol) was dissolved in tetrahydrofuran (1 L). A 2 M lithium diisopropylamide/heptane/tetrahydrofuran/ethylbenzene solution (100 mL, 200 mmol) was added dropwise in a nitrogen atmosphere at an internal temperature of -69°C over

30 minutes. After stirring at the same temperature for one hour, the reaction solution was poured into a 1N hydrochloric acid solution (2 L) in an ice bath, followed by extraction with ethyl acetate (2 L, 1 L). The organic layers were combined, washed with brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the precipitated solid was collected by filtration to give 22.2 g of the title compound as pale red crystals. The filtrate was further concentrated to give 2.88 g of the title compound as pale red crystals. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 1:1) to give 2.09 g of the title compound as colorless crystals.

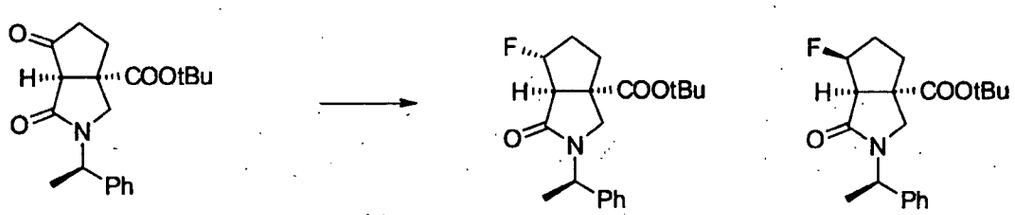
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.50 (1H, q, J=7.1 Hz), 3.38 (1H, d, J=10.5 Hz), 3.23 (1H, d, J=10.5 Hz), 2.55-2.35 (3H, m), 2.05-1.94 (1H, m), 1.53 (3H, d, J=7.1 Hz), 1.38 (9H, s).

[Reference Example 88]

{(1S,5R,6R)-6-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester;

{(1S,5R,6S)-6-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 175]



{(1S,5R)-4,6-Dioxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (1.30 g, 3.88 mmol) was dissolved in tetrahydrofuran (40 mL). Sodium borohydride (185 mg, 4.92 mmol) was added at 0°C, and the mixture was stirred for one hour. A saturated ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in dichloromethane (20 mL). [Bis(2-methoxymethyl)amino]sulfur trifluoride (1.73 g, 7.82 mmol) was added in a nitrogen atmosphere, and the mixture was stirred for two hours. The reaction solution was poured into saturated sodium bicarbonate water in an ice bath, followed by extraction with ethyl acetate. The organic layer was washed with a

saturated sodium thiosulfate solution and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (30% ethyl acetate/hexane) to give 797 mg of the title (6R)-fluoro isomer as a colorless oil and 170 mg of the title (6S)-fluoro isomer as a colorless oil.

(6R)-fluoro isomer:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.46 (1H, q, J=7.08 Hz), 5.28 (1H, d, J=51.76 Hz), 3.48 (1H, d, J=22.71 Hz), 3.41 (1H, d, J=10.50 Hz), 3.08 (1H, d, J=10.50 Hz), 2.57-2.49 (1H, m), 2.21-2.12 (1H, m), 1.83-1.58 (2H, m), 1.50 (3H, d, J=7.08 Hz), 1.35 (9H, s).

MS (EI); m/z: 348 $(M+H)^+$.

(6S)-fluoro isomer:

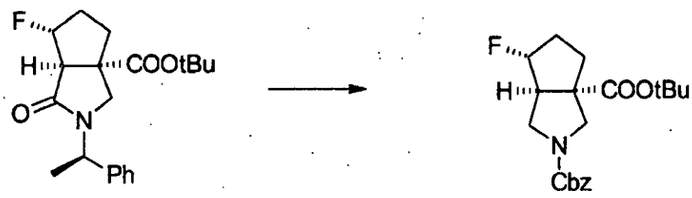
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.26 (5H, m), 5.49-5.40 (2H, m), 3.51 (1H, d, J=10.24 Hz), 3.41 (1H, d, J=29.76 Hz), 3.21 (1H, d, J=10.00 Hz), 2.46-2.44 (1H, m), 2.23-2.20 (1H, m), 2.03-1.93 (1H, m), 1.88-1.82 (1H, m), 1.52 (3H, d, J=6.83 Hz), 1.32 (9H, s).

MS (EI); m/z: 348 $(M+H)^+$.

[Reference Example 89]

{(1S,5S,6R)-3-Benzyloxycarbonyl-6-fluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 176]



{(1S,5R,6R)-6-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (420 mg, 1.21 mmol) was dissolved in tetrahydrofuran (20 mL), and a 1 M borane-tetrahydrofuran complex (3.63 mL, 3.63 mmol) was added dropwise in a nitrogen atmosphere. After five hours, a 1 M borane-tetrahydrofuran complex (3.63 mL, 3.63 mmol) was added; after 15 hours, a 1 M borane-tetrahydrofuran complex (3.63 mL, 3.63 mmol) was further added. After stirring for three hours, ethanol (18 mL), water (2 mL), and triethylamine (2 mL) were added, and the mixture was stirred at 80°C for two hours. The reaction solution was evaporated under reduced pressure, and a saturated ammonium chloride solution was added to the resulting residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in dichloromethane (3 mL). Benzyloxycarbonyl chloride (1.03 g, 6.04 mmol) was added, and the mixture was stirred for 16

hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (30% ethyl acetate/hexane) to give 367 mg of the title compound as a colorless oil.

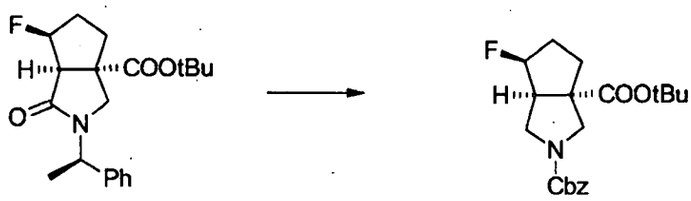
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.26 (5H, m), 5.12 (2H, s), 4.85 (1H, d, J=52.44 Hz), 3.86 (1H, d, J=11.71 Hz), 3.77-3.73 (1H, m), 3.40-3.35 (2H, m), 3.16-3.10 (1H, m), 2.46-2.42 (1H, m), 2.03-1.82 (3H, m), 1.45 (9H, s).

MS (EI) m/z: 386 $(M+Na)^+$.

[Reference Example 90]

{(1S,5S,6S)-3-Benzyloxycarbonyl-6-fluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 177]



{(1S,5R,6S)-6-Fluoro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (402 mg, 1.16 mmol) was dissolved in tetrahydrofuran (20 mL), and a 1 M borane-tetrahydrofuran complex (5.79 mL, 5.79 mmol) was added dropwise in a nitrogen atmosphere. After two hours, a 1 M borane-tetrahydrofuran complex (3.47 mL, 3.47 mmol) was added; after 14 hours, a 1 M borane-

tetrahydrofuran complex (3.47 mL, 3.47 mmol) was further added. After stirring for 2.5 hours, ethanol (18 mL), water (2 mL), and triethylamine (2 mL) were added, and the mixture was stirred at 80°C for two hours. The reaction solution was evaporated under reduced pressure, and a saturated ammonium chloride solution was added to the resulting residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in dichloromethane (2.8 mL). Benzyloxycarbonyl chloride (1.03 g, 6.04 mmol) was added, and the mixture was stirred at 40°C for 14 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give 359 mg of the title compound as a colorless oil.

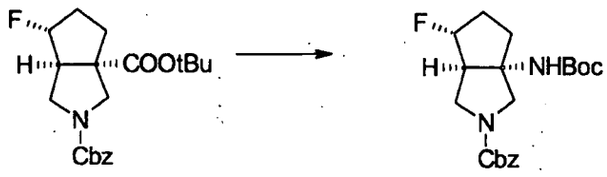
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.29 (5H, m), 5.13 (2H, s), 5.06 (1H, d, J=49.84 Hz), 3.99 (1H, dd, J=20.12, 11.59 Hz), 3.79 (1H, d, J=11.95 Hz), 3.58-3.55 (1H, m), 3.38 (1H, dd, J=46.71, 11.34 Hz), 3.00 (1H, brd, J=25.37 Hz), 2.26-1.94 (4H, m), 1.43 (9.0H, s).

MS (EI) m/z: 386 $(M+Na)^+$.

[Reference Example 91]

{(1S,5R,6R)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl}carboxylic acid benzyl ester

[Formula 178]



{(1S,5S,6R)-3-Benzyloxycarbonyl-6-fluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (362 mg, 1.00 mmol) was dissolved in dichloromethane (10 mL). Trifluoroacetic acid (2.5 mL) was added, and the mixture was stirred for 15 hours. The solvent was evaporated under reduced pressure. A 1N sodium hydroxide solution was added to the resulting residue, and the mixture was washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in toluene (10 mL). Triethylamine (202 mg, 1.99 mmol) and diphenylphosphoryl azide (339 mg, 1.20 mmol) were added in a nitrogen atmosphere, and the mixture was stirred at 100°C for two hours. The reaction solution was concentrated under reduced pressure. Then, dioxane (20 mL) and 6N hydrochloric acid (20 mL) were added, and the mixture was stirred at 40°C for three hours. After

concentration under reduced pressure and azeotropic distillation with ethanol, a 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure. Di-tert-butyl dicarbonate (1087 mg, 4.98 mmol) was added to the resulting residue, and the mixture was stirred at 50°C for two hours. The reaction solution was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give 125 mg of the title compound as a colorless oil.

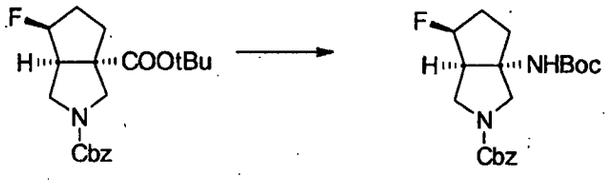
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.11 (2H, s), 4.95-4.80 (2H, m), 3.88-3.63 (3H, m), 3.28-3.24 (1H, m), 2.83-2.75 (1H, m), 2.12-1.98 (4H, m), 1.44 (9H, s).

MS (EI) m/z: 401 $(M+Na)^+$.

[Reference Example 92]

{(1S,5R,6S)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl}carboxylic acid benzyl ester

[Formula 179]



{(1S,5S,6S)-3-Benzyloxycarbonyl-6-fluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (354 mg, 0.97 mmol) was dissolved in dichloromethane (10 mL). Trifluoroacetic acid (3 mL) was added, and the

mixture was stirred for 21 hours. The solvent was evaporated under reduced pressure. A 1N sodium hydroxide solution was added to the resulting residue, and the mixture was washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in toluene (8 mL). Triethylamine (197 mg, 1.95 mmol) and diphenylphosphoryl azide (359 mg, 1.27 mmol) were added in a nitrogen atmosphere, and the mixture was stirred for one hour. Thereafter, tert-butanol (8 mL) was added, and the mixture was stirred at 100°C for 19 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give 136 mg of the title compound as a colorless oil.

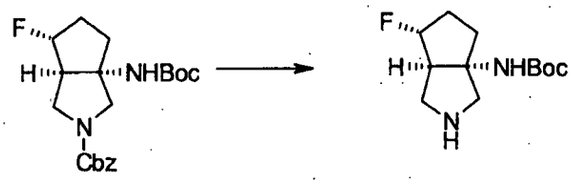
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.13 (2H, s), 5.05 (1H, d, J=58.77 Hz), 4.68 (1H, brs), 3.77 (1H, d, J=10.46 Hz), 3.71-3.60 (2H, m), 3.57-3.44 (1H, m), 3.11-2.86 (1H, m), 2.29-2.02 (4H, m), 1.43 (9H, s).

MS (EI); m/z: 401 $(M+Na)^+$.

[Reference Example 93]

(1S,5R,6R)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octane

[Formula 180]



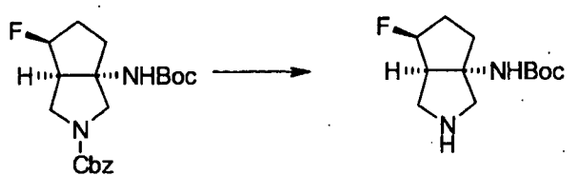
{(1S,5R,6R)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl}carboxylic acid benzyl ester (120 mg, 0.32 mmol) was dissolved in methanol (10 mL). 10% palladium-carbon (M, wet) (50 mg) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the filtrate was concentrated under reduced pressure to give 77.5 mg of the title compound as a colorless oil.

MS(EI); m/z: 245$(M+H)^+$.

[Reference Example 94]

(1S,5R,6S)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octane

[Formula 181]



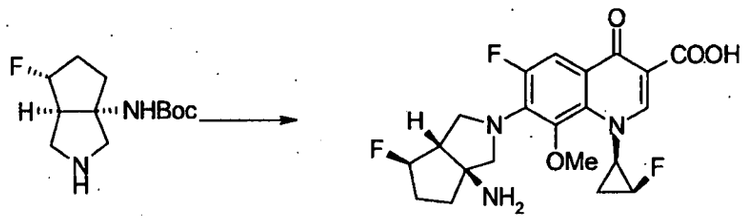
{(1S,5R,6S)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl}carboxylic acid benzyl ester (132 mg, 0.35 mmol) was dissolved in methanol (10 mL). 10% palladium-carbon (M, wet) (50 mg) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the filtrate was concentrated under reduced pressure to give 85 mg of the title compound as a colorless oil.

MS (EI); m/z: 245 $(M+H)^+$.

[Example 20]

7-{(1S,5R,6R)-1-Amino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 182]



(1S,5R,6R)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octane (77.5 mg, 0.32 mmol) was dissolved in dimethyl sulfoxide (2 mL). 6,7-Difluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (120.2 mg, 0.33 mmol) and triethylamine (96.3 mg, 0.95 mmol) were added, and the mixture was stirred at 40°C for 18 hours. Then, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for three hours. The solvent was evaporated under reduced pressure, and a 10% citric acid solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (5% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.5 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting solid was washed with diethyl ether and dried under reduced pressure to give 96 mg of the title compound as a colorless solid.

mp: 179-181°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, s), 7.71 (1H, d, J=13.67 Hz), 5.10-5.07 (1H, m), 5.09 (1H, d, J=52.00 Hz), 4.07-4.04 (1H, m), 3.88 (1H, t, J=9.64 Hz), 3.68-3.63 (4H, m), 3.57 (1H, dd, J=16.97, 10.62 Hz), 3.45 (1H, d, J=11.72 Hz), 2.63-2.56 (1H, m), 2.10-2.01 (4H, m), 1.61-1.51 (2H, m).

Anal; Calcd for $C_{21}H_{22}F_3N_3O_4 \cdot 0.5H_2O$: C, 56.50; H, 5.19; N, 9.41; F, 12.77. Found: C, 56.28; H, 5.17; N, 9.03; F, 12.47.

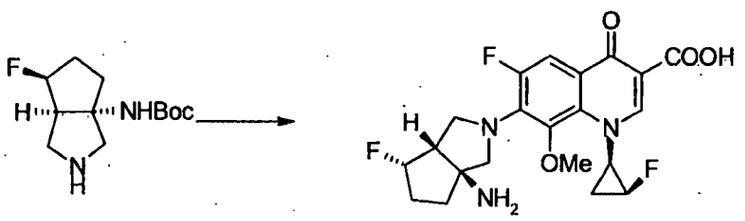
MS (EI); m/z: 438 $(M+H)^+$.

IR (ATR) ν: 3390, 2943, 2872, 1720, 1618, 1512, 1452, 1360, 1321, 1277, 1213 cm^{-1}.

[Example 21]

7-[(1S,5R,6S)-1-Amino-6-fluoro-3-azabicyclo[3,3,0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 183]



(1S,5R,6S)-1-tert-Butoxycarbonylamino-6-fluoro-3-azabicyclo[3,3,0]octane (85.2 mg, 0.35 mmol) was dissolved in dimethyl sulfoxide (2 mL). 6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (132.2 mg, 0.37 mmol) and

triethylamine (105.9 mg, 1.05 mmol) were added, and the mixture was stirred at 40°C for 15 hours. Then, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for three hours. The solvent was evaporated under reduced pressure, and a 10% citric acid solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (5% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.5 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting solid was washed with diethyl ether and dried under reduced pressure to give 101 mg of the title compound as a colorless solid.

mp: 117-119°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.45 (1H, s), 7.70 (1H, d, J=14.15 Hz), 5.28 (1H, d, J=53.41 Hz), 5.07-4.73 (1H, m), 4.05-4.02 (1H, m), 3.84-3.64 (6H, m), 3.47 (1H, d, J=10.73

Hz), 2.59-2.53 (1H, m), 2.26-2.06 (3H, m), 1.79-1.78 (1H, m), 1.58-1.46 (2H, m).

Anal; Calcd for $C_{21}H_{22}F_3N_3O_4 \cdot H_2O$: C, 55.38; H, 5.31; N, 9.23; F, 12.51. Found: C, 55.43; H, 5.46; N, 9.00; F, 12.21.

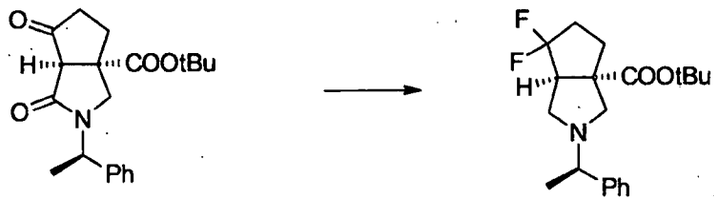
MS (EI) m/z: 438 $(M+H)^+$.

IR (ATR) ν: 2966, 2839, 1720, 1614, 1576, 1537, 1508, 1446, 1362, 1319, 1271, 1207 cm^{-1}.

[Reference Example 95]

{(1S,5S)-6,6-Difluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 184]



{(1S,5R)-4,6-Dioxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (500 mg, 1.46 mmol) was dissolved in dichloromethane (20 mL). [Bis(2-methoxymethyl)amino]sulfur trifluoride (966.3 mg, 4.37 mmol) was added in a nitrogen atmosphere at 0°C, and the mixture was stirred at 20°C for 17 hours. The reaction solution was poured into saturated sodium bicarbonate water in an ice bath, followed by extraction with ethyl acetate. The organic layer was washed with a

saturated sodium thiosulfate solution and brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (25% ethyl acetate/hexane). The resulting crude was dissolved in tetrahydrofuran (15 mL). A 1 M borane-tetrahydrofuran complex (4.37 mL, 4.37 mmol) was added in a nitrogen atmosphere, and the mixture was stirred for 16 hours. A 1 M borane-tetrahydrofuran complex (4.37 mL, 4.37 mmol) was added, and the mixture was stirred for nine hours. A 1 M borane-tetrahydrofuran complex (4.37 mL, 4.37 mmol) was further added, and the mixture was stirred for 16 hours. Ethanol (45 mL), water (5 mL), and triethylamine (5 mL) were added to the reaction solution, and the mixture was stirred at 80°C for four hours. Then, the solvent was evaporated under reduced pressure, and a saturated ammonium chloride solution was added to the residue. The organic layer was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (15% ethyl acetate/hexane) to give 375.8 mg of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 3.28 (1H, d, J=9.77 Hz), 3.13 (1H, q, J=6.51 Hz), 3.01 (1H, dd, J=19.04,

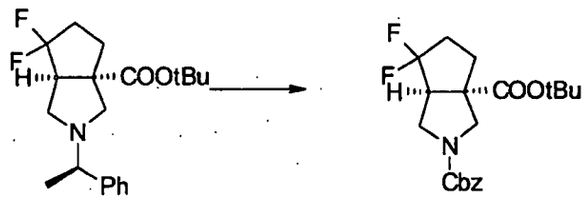
7.08 Hz), 2.60 (1H, d, J=9.28 Hz), 2.39-2.30 (3H, m), 2.15-2.09 (2H, m), 1.80-1.75 (1H, m), 1.41 (9H, s), 1.33 (3H, d, J=6.59 Hz).

MS (EI) m/z: 352 $(M+H)^+$.

[Reference Example 96]

{(1S,5S)-3-Benzyloxycarbonyl-6,6-difluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester

[Formula 185]



{(1S,5S)-6,6-Difluoro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (370.0 mg, 1.05 mmol) was dissolved in dichloromethane (3 mL). Benzyloxycarbonyl chloride (898 mg, 5.26 mmol) was added, and the mixture was stirred at 40°C for 17 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give 338 mg of the title compound as a colorless oil.

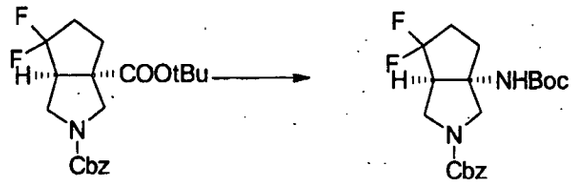
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.26 (5H, m), 5.13 (2H, s), 3.86 (2H, d, J=11.71 Hz), 3.54-3.42 (2H, m), 3.16-3.07 (1H, m), 2.37-2.11 (3H, m), 1.88-1.82 (1H, m), 1.45 (9H, s).

MS (EI) m/z: 404 $(M+Na)^+$.

[Reference Example 97]

{(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3,3,0]octan-3-yl}carboxylic acid benzyl ester

[Formula 186]



{(1S,5S)-3-Benzyloxycarbonyl-6,6-difluoro-3-azabicyclo[3,3,0]octan-1-yl}carboxylic acid tert-butyl ester (332.0 mg, 0.87 mmol) was dissolved in dichloromethane (10 mL). Trifluoroacetic acid (2 mL) was added, and the mixture was stirred for 23 hours. The reaction solution was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, and the mixture was washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in toluene (10 mL). Triethylamine (176.2 mg, 1.74 mmol) and diphenylphosphoryl azide (370.4 mg, 1.31 mmol) were added in a nitrogen atmosphere, and the mixture was stirred at 100°C for 20 hours. The reaction solution was concentrated under reduced pressure. Then, dioxane (10 mL)

and 6N hydrochloric acid (10 mL) were added, and the mixture was stirred at 40°C for 1.5 hours. After concentration under reduced pressure and azeotropic distillation with ethanol, a 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure. Di-tert-butyl dicarbonate (949.9 mg, 4.35 mmol) was added to the resulting residue, and the mixture was stirred at 50°C for 16 hours. The reaction solution was purified by silica gel column chromatography (25% ethyl acetate/hexane) to give 67.0 mg of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.17 (5H, m), 5.13 (2H, s), 4.80 (1H, s), 3.84-3.80 (1H, m), 3.71-3.65 (3H, m), 3.06-2.96 (1H, m), 2.39-2.31 (1H, m), 2.16-2.08 (3H, m), 1.44 (9H, s).

MS (EI) m/z: 397 $(M+H)^+$.

[Reference Example 98]

(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3,3,0]octane

[Formula 187]



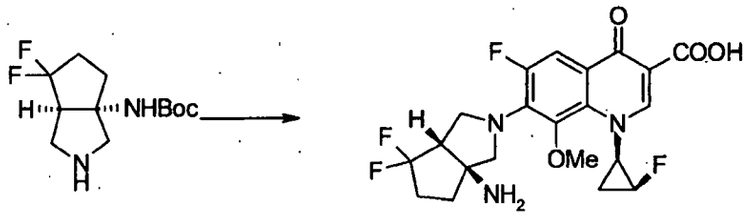
[(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3,3,0]octan-3-yl]carboxylic acid benzyl ester (65.0 mg, 0.16 mmol) was dissolved in methanol (10 mL). 10% palladium-carbon (50% wet) (20 mg) was added, and the mixture was stirred in a hydrogen atmosphere for one hour. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the filtrate was concentrated under reduced pressure to give 43 mg of the title compound as a colorless solid.

MS(EI); m/z: 263$(M+H)^+$.

[Example 22]

7-[(1S,5R)-1-Amino-6,6-difluoro-3-azabicyclo[3,3,0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 188]



(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3,3,0]octane (43.0 mg, 0.16 mmol) was dissolved in dimethyl sulfoxide (1.8 mL). 6,7-Difluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (62.2 mg, 0.17 mmol) and triethylamine (49.8 mg, 0.49 mmol) were added, and the mixture was stirred at 40°C for 16 hours. Then, 90% aqueous ethanol (20 mL) and triethylamine (2 mL) were added to the reaction solution, and the mixture was stirred at 80°C for 2.5 hours. The solvent was evaporated under reduced pressure, and a 10% citric acid solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting solid was dissolved in ethanol-aqueous ammonia, and the solution was heated and stirred. After vaporization of ammonia, the precipitated crystals were collected by filtration and

dried under reduced pressure to give 15.2 mg of the title compound as a pale yellow solid.

mp: 239-241°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 7.73 (1H, d, J=13.67 Hz), 5.07-4.91 (1H, m), 4.08-4.05 (1H, m), 3.91-3.88 (1H, m), 3.79-3.77 (1H, m), 3.72-3.70 (1H, m), 3.68 (3H, s), 3.55 (1H, d, J=10.74 Hz), 2.67-2.62 (1H, m), 2.36-2.33 (2H, m), 2.16-2.12 (1H, m), 1.96-1.89 (1H, m), 1.64-1.51 (2H, m).

Anal; Calcd for $C_{21}H_{21}F_4N_3O_4 \cdot 0.25H_2O$: C, 54.84; H, 4.71; N, 9.14; F, 16.52. Found: C, 54.97, H, 4.53; N, 9.09; F, 16.53.

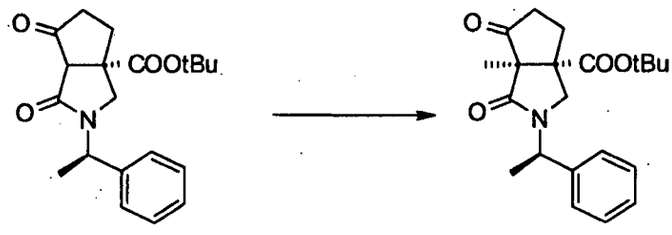
MS (EI); m/z: 456 $(M+H)^+$.

IR (ATR) ν: 3392, 3031, 2883, 1718, 1618, 1510, 1450, 1360, 1333, 1306, 1250 cm^{-1}.

[Reference Example 99]

(1S,5R)-5-Methyl-4,6-dioxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester

[Formula 189]



N,N-Dimethylformamide (2.0 mL) was added to sodium hydride (152 mg, 3.48 mmol) in an argon atmosphere. A solution of (1S,5R)-4,6-dioxo-3-[(1R)-1-phenylethyl]-3-

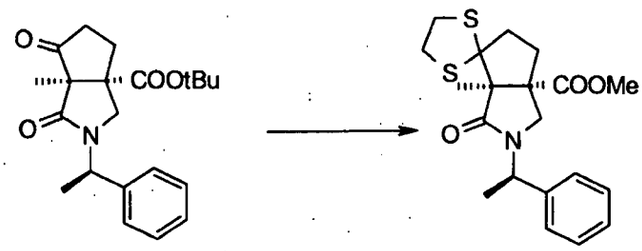
azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester (1.00 g, 2.91 mmol) in N,N-dimethylformamide (8.0 mL) was added dropwise to this suspension under ice-cooling, and the mixture was stirred at 0°C for 30 minutes. Subsequently, methyl iodide (0.217 mL, 3.49 mmol) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2.5 hours. The reaction solution was ice-cooled and then the reaction was quenched with water, followed by extraction with ethyl acetate. Then, the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 2:1 -> 1:1) to give 0.79 g of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41-7.23 (5H, m), 5.48 (1H, q, J=6.62 Hz), 3.40 (1H, d, J=10.54 Hz), 3.13 (1H, d, J=10.54 Hz), 2.63-2.40 (3H, m), 1.96-1.83 (1H, m), 1.54 (3H, d, J=7.11 Hz), 1.39 (9H, s), 1.22 (3H, s).

[Reference Example 100]

(1S,5R)-6,6-Ethanediyldimercapto-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester

[Formula 190]



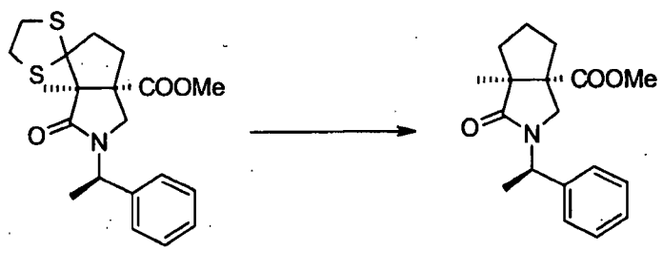
(1S,5R)-5-Methyl-4,6-dioxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid tert-butyl ester (0.28 g, 0.78 mmol) was dissolved in toluene (14 mL). Toluenesulfonic acid monohydrate (155 mg, 0.81 mmol) and ethanedithiol (0.14 mL, 1.7 mmol) were added, and the mixture was heated to reflux for nine hours. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (dichloromethane:methanol = 98:2) to give the target 1-position carboxylic acid (289 mg) as a pale yellow solid. The carboxylic acid (289 mg) was dissolved in tetrahydrofuran (10 mL) and methanol (3.0 mL). Trimethylsilyldiazomethane (1.7 mL) was added under ice-cooling, and the mixture was stirred at room temperature for two hours. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 3:2) to give 267 mg of the title compound as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.23 (5H, m), 5.52 (1H, q, J=6.86 Hz), 3.60 (3H, s), 3.55 (1H, d, J=10.05 Hz), 3.44-

3.31 (1H, m), 3.28-3.19 (1H, m), 3.16 (1H, d, J=10.05 Hz), 2.79-2.70 (1H, m), 2.54-2.44 (1H, m), 2.26-2.15 (1H, m), 1.81-1.70 (1H, m), 1.59-1.52 (2H, m), 1.56 (3H, d, J=7.11 Hz), 1.33 (3H, s).

[Reference Example 101]

(1S,5R)-5-Methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester

[Formula 191]



(1S,5R)-6,6-Ethanediyldimercapto-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester (266 mg, 0.68 mmol) was dissolved in ethanol (10 mL). Raney nickel (2.0 mL) was added dropwise, and the mixture was heated to reflux for 5.5 hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 7:3 -> 1:1) to give 133 mg of the title compound as a pale yellow solid.

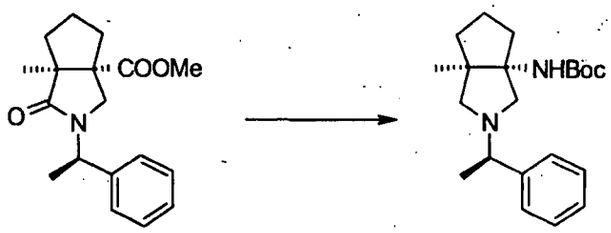
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.24 (5H, m), 5.56-5.44 (1H, m), 3.64 (3H, s), 3.51 (1H, d, J=10.05 Hz), 3.02-2.96 (1H,

m), 2.49-2.26 (2H, m), 1.91-1.44 (4H, m), 1.52 (3H, d, J=7.35 Hz), 1.12 (3H, s).

[Reference Example 102]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 192]



(1S,5R)-5-Methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid methyl ester (130 mg, 0.43 mmol) was dissolved in methanol (5.0 mL). A 1N sodium hydroxide solution (1.5 mL) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for four hours. Then, a 1N sodium hydroxide solution (1.5 mL) was added dropwise, and the mixture was stirred at room temperature for 15 hours. Sodium hydroxide (93 mg) was further added, and the mixture was stirred at room temperature for six hours. Sodium hydroxide (90 mg) was added again, and the mixture was stirred at room temperature for four hours and then at 50°C for one hour. The reaction solution was made weakly acidic with hydrochloric acid, and the solvent was evaporated under reduced pressure. The resulting residue was extracted with

dichloromethane and dilute hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in toluene (5.0 mL). Triethylamine (0.132 mL, 0.95 mmol) and diphenylphosphoryl azide (0.111 ml, 0.52 mmol) were added, and the mixture was heated to reflux for three hours. The reaction solution was extracted with ethyl acetate and saturated sodium bicarbonate water. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. 1,4-Dioxane (2.0 mL) and 6N hydrochloric acid (2.0 mL) were added to the resulting residue, and the mixture was stirred at 50°C for 15 hours. After extraction with water and ethyl acetate, the aqueous layer was made alkaline with a saturated sodium hydroxide solution and extracted with chloroform twice. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered, and then the solvent was evaporated under reduced pressure. Toluene (3.0 mL) and Red-Al™ (65% solution in toluene) (0.50 mL) were sequentially added to the resulting residue, and the mixture was stirred at 80°C for 2.5 hours. A 3N sodium hydroxide solution was added to the reaction solution under ice-cooling, and the layers were separated with toluene. The organic layer was dried over anhydrous

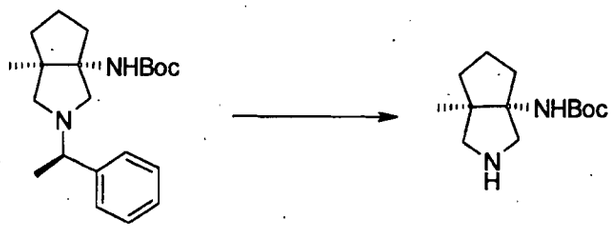
sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in dichloromethane (10 mL) and methanol (5.0 mL). Di-tert-butyl dicarbonate (560 mg, 2.57 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction solution was subjected to silica gel column chromatography (dichloromethane:methanol = 98:2) to give 77 mg of the title compound as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.16 (5H, m), 4.79 (1H, brs), 3.17-3.00 (1H, m), 2.74-2.58 (2H, m), 2.53-2.44 (1H, m), 2.27-2.13 (1H, m), 2.08-1.89 (2H, m), 1.74-1.62 (2H, m), 1.60-1.24 (2H, m), 1.41 (9H, s), 1.28 (3H, d, J=6.59 Hz), 1.07 (3H, s).

[Reference Example 103]

(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-4-oxo-3-azabicyclo[3.3.0]octane

[Formula 193]



(1S,5S)-1-(tert-Butoxycarbonylamino)-5-methyl-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (77 mg, 0.22 mmol) was dissolved in ethanol (6.0 mL). 10% palladium-carbon (50% wet) (69 mg) was added, and the mixture was

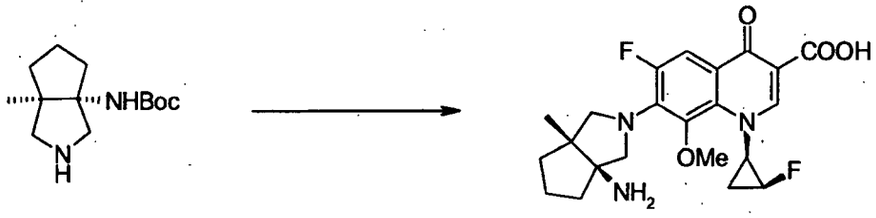
stirred in a hydrogen atmosphere at 45°C for 19.5 hours. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure to give 50 mg of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.68 (1H, brs), 3.36-3.19 (1H, m), 3.00-2.58 (4H, m), 2.40-1.89 (4H, m), 1.81-1.26 (2H, m), 1.44 (9H, s), 1.07 (3H, s).

[Example 23]

7-[(1R,5R)-1-Amino-3-aza-5-methylbicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 194]



Triethylamine (0.092 mL, 0.66 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (79.1 mg, 0.22 mmol) were added to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-methyl-3-azabicyclo[3.3.0]octane (50.1 mg, 0.21 mmol) in dimethyl sulfoxide (2.0 mL). The mixture was stirred at 45°C for 24 hours. Ethanol (3.0 mL), water (1.0 mL), and triethylamine (1.0 mL) were added to the reaction solution, and the mixture was heated to reflux

for 2.5 hours. The solvent was evaporated under reduced pressure, and the resulting residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water twice and brine, dried over anhydrous sodium sulfate, and filtered. Thereafter, the solvent was evaporated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (dichloromethane:methanol = 99:1). The resulting oil (92.5 mg) was dissolved in concentrated hydrochloric acid (1.0 mL) under ice-cooling, and the solution was stirred at room temperature for 0.5 hour. The reaction solution was washed with chloroform twice, and then the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by recrystallization from ethanol to give 47 mg of the title compound as a pale yellow solid.

mp: 109-113°C (dec.).

$[\alpha]_D^{24}$+78.2° (c=0.135, 0.1NNaOH).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.45 (1H, s), 7.66 (1H, d, J=14.5 Hz), 4.79-4.85 (1H, m), 4.00-4.10 (1H, m), 3.61 (3H,

s), 3.51-3.75 (3H, m), 3.34-3.44 (1H, m), 1.94-2.07 (1H, m), 1.43-1.93 (7H, m), 1.10 (3H, s).

MS (FAB); m/z: 434 $(M+H)^+$.

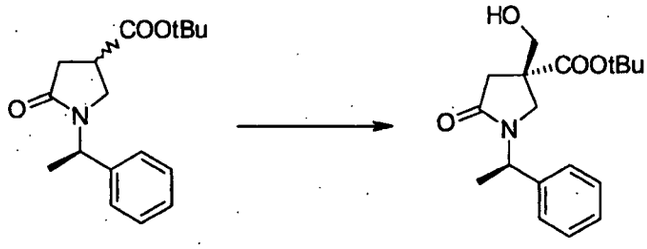
Anal.Calcd for $C_{22}H_{25}F_2N_3O_4 \cdot 2H_2O$: C, 56.28; H, 6.23; F, 8.09; N, 8.95. Found: C, 56.57; H, 6.24; F, 8.19; N, 9.01.

IR (ATR) ν: 2942, 2877, 1612, 1573, 1448, 1434, 1392, 1349, 1342, 1311, 1301, 1290, 1272, 821, 804 cm^{-1}.

[Reference Example 104]

(3S)-3-Hydroxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 195]



5-Oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4 g, 13.82 mol) was dissolved in N,N-dimethylformamide (40 mL), and paraformaldehyde (0.83 g, 27.65 mmol) was suspended in the solution. Sodium hydride (0.60 g, 13.82 mmol) was added at room temperature, and the mixture was stirred for 30 minutes. Then, the reaction solution was poured into a 10% citric acid solution (150 mL) at 0°C. The mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with water (100 mL × 2) and brine (100 mL), dried over anhydrous sodium sulfate,

and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (30% ethyl acetate/hexane -> 80% ethyl acetate/hexane) to give 1.03 g of the title compound as a colorless solid.

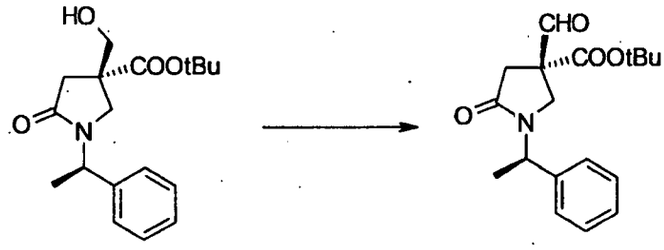
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.28 (5H, m), 5.51 (1H, q, J=7.16 Hz), 3.77 (1H, dd, J=11.23, 5.37 Hz), 3.61 (1H, dd, J=11.23, 7.81 Hz), 3.39 (1H, d, J=10.50 Hz), 3.21 (1H, d, J=10.25 Hz), 2.78 (1H, d, J=17.09 Hz), 2.51 (1H, dd, J=7.81, 5.37 Hz), 2.40 (1H, d, J=17.33 Hz), 1.53 (3H, d, J=7.33 Hz), 1.35 (9H, s).

MS (EI); m/z: 320 $(M+H)^+$.

[Reference Example 105]

(3S)-3-Formyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 196]



(3S)-3-Hydroxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.0 g, 12.52 mmol) was dissolved in dichloromethane. Triethylamine (6.34 g, 62.62 mmol), dimethyl sulfoxide

(3.91 g, 50.09 mmol), and a SO_3-pyridine complex (3.99 g, 25.05 mmol) were sequentially added at 0°C, and the mixture was stirred for 17 hours. The reaction solution was concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (60% ethyl acetate/hexane) to give 2.85 g of the title compound as a colorless solid.

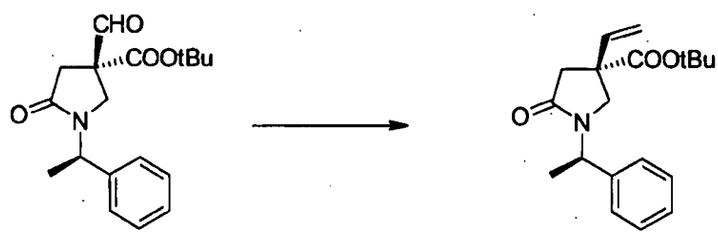
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.62 (1H, s), 7.35-7.28 (5H, m), 5.47 (1H, q, J=7.00 Hz), 3.79 (1H, t, J=9.52 Hz), 3.24 (1H, d, J=10.50 Hz), 2.93 (1H, d, J=17.33 Hz), 2.85 (1H, d, J=17.33 Hz), 1.53 (3H, d, J=7.08 Hz), 1.38 (9H, s).

MS (EI); m/z: 318 $(M+H)^+$.

[Reference Example 106]

(3R)-5-Oxo-1-[(1R)-1-phenylethyl]-3-vinylpyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 197]



Methyltriphenylphosphonium bromide (187.4 mg, 0.52 mmol) was dissolved in tetrahydrofuran. A 2.62 M solution of n-butyllithium in hexane (0.16 mL, 0.42 mmol) was added dropwise in a nitrogen atmosphere at -78°C, and the mixture was stirred for one hour. After heating to 0°C, a solution of (3S)-3-formyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (111 mg, 0.35 mmol) in tetrahydrofuran was added dropwise, and the mixture was stirred for one hour. A saturated ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (25% ethyl acetate/hexane) to give 54 mg of the title compound as a yellow oil.

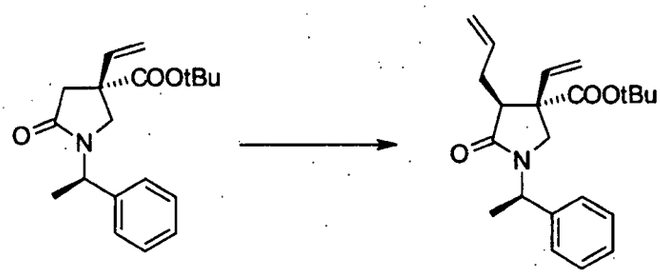
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.26 (5H, m), 5.96 (1H, dd, J=17.33, 10.74 Hz), 5.52-5.45 (1H, m), 5.21-5.17 (2H, m), 3.45 (1H, d, J=10.25 Hz), 3.26 (1H, d, J=10.01 Hz), 3.01 (1H, d, J=16.60 Hz), 2.54 (1H, d, J=16.60 Hz), 1.50 (3H, d, J=7.08 Hz), 1.33 (9H, s).

MS (EI) m/z: 318 $(M+H)^+$.

[Reference Example 107]

(3S,4S)-4-Allyl-5-oxo-1-[(1R)-1-phenylethyl]-3-vinylpyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 198]



(3R)-5-Oxo-1-[(1R)-1-phenylethyl]-3-vinylpyrrolidine-3-carboxylic acid tert-butyl ester (236.0 mg, 0.75 mmol) and allyl bromide (271.6 mg, 2.24 mmol) were dissolved in tetrahydrofuran. A 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (1.12 mL, 1.12 mmol) was added dropwise in a nitrogen atmosphere at 0°C. After stirring for 1.5 hours, a saturated ammonium chloride solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (10% ethyl acetate/hexane) to give 135 mg of the title compound as a colorless oil.

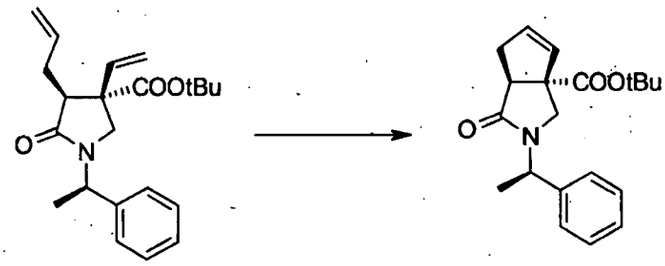
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.26 (5H, m), 5.98-5.82 (2H, m), 5.47 (1H, q, J=7.00 Hz), 5.24-4.97 (4H, m), 3.35-3.25 (2H, m), 3.03 (1H, t, J=6.82 Hz), 2.48-2.41 (1H, m), 2.39-2.32 (1H, m), 1.54 (3H, d, J=7.08 Hz), 1.33 (9H, s).

MS (EI); m/z: 356 $(M+H)^+$.

[Reference Example 108]

[(1S,5S)-4-Oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester

[Formula 199]



(3S,4S)-4-Allyl-5-oxo-1-[(1R)-1-phenylethyl]-3-vinylpyrrolidine-3-carboxylic acid tert-butyl ester (130.0 mg, 0.37 mmol) was dissolved in benzene (8 mL). The second generation Grubbs' catalyst (31.0 mg, 0.04 mmol) was added, and the mixture was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (15% ethyl acetate/hexane) to give 93.2 mg of the title compound as a yellow oil.

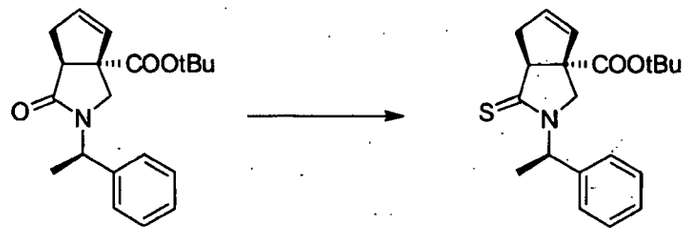
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.28 (5H, m), 5.94-5.91 (1H, m), 5.60-5.59 (1H, m), 5.51 (1H, q, J=7.16 Hz), 3.34-3.24 (3H, m), 2.81-2.79 (2H, m), 1.45 (3H, d, J=7.32 Hz), 1.38 (9H, s).

MS (EI) m/z: 328 $(M+H)^+$.

[Reference Example 109]

[(1S,5S)-3-[(1R)-1-Phenylethyl]-4-thioxo-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester

[Formula 200]



[(1S,5S)-4-Oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester (88.0 mg, 0.27 mmol) was dissolved in toluene (8 mL). Lawesson's reagent (81.5 mg, 0.20 mmol) was added, and the mixture was stirred at 80°C for four hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (10% ethyl acetate/hexane) to give 91.6 mg of the title compound as a yellow oil.

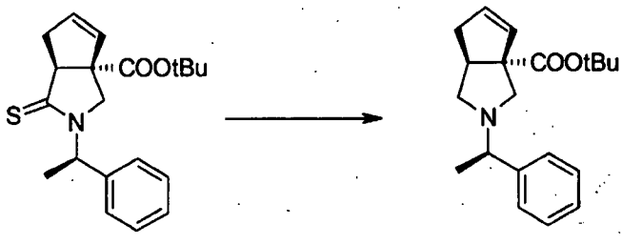
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 6.41 (1H, q, J=7.08 Hz), 5.95-5.94 (1H, m), 5.55-5.54 (1H, m), 3.74 (1H, d, J=8.30 Hz), 3.60 (1H, d, J=11.96 Hz), 3.49 (1H, d, J=12.21 Hz), 3.15 (1H, d, J=17.09 Hz), 3.02-2.98 (1H, m), 1.51 (3H, d, J=7.08 Hz), 1.36 (9H, s).

MS (EI) m/z: 344 $(M+H)^+$.

[Reference Example 110]

[(1S,5S)-3-[(1R)-1-Phenylethyl]-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester

[Formula 201]



[(1S,5S)-3-[(1R)-1-Phenylethyl]-4-thioxo-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester (88.2 mg, 0.27 mmol) was dissolved in ethanol. Raney nickel was added, and the mixture was stirred for one hour. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (10% ethyl acetate/hexane) to give 55.4 mg of the title compound as a colorless oil.

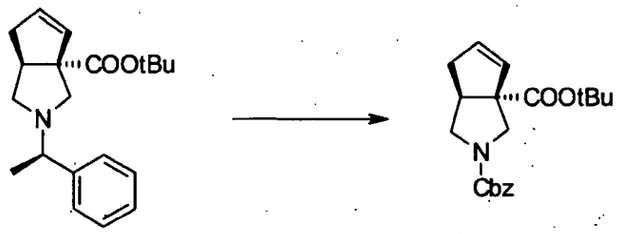
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.21 (5H, m), 5.74 (1H, brs), 5.54 (1H, brs), 3.15 (1H, q, J=6.75 Hz), 3.04 (1H, brs), 2.72-2.70 (2H, m), 2.61 (1H, t, J=7.81 Hz), 2.53-2.51 (2H, m), 2.18 (1H, d, J=16.85 Hz), 1.41 (9H, s), 1.32 (3H, d, J=6.59 Hz).

MS (EI) m/z: 314 $(M+H)^+$.

[Reference Example 111]

[(1S,5S)-3-Benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester

[Formula 202]



[(1S,5S)-3-[(1R)-1-Phenylethyl]-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester (370 mg, 1.18 mmol) was dissolved in dichloroethane (3 mL). Benzyloxycarbonyl chloride (1.01 g, 5.90 mmol) was added, and the mixture was stirred at 40°C for three hours. The reaction solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (10% ethyl acetate/hexane) to give 385 mg of the title compound as a colorless oil.

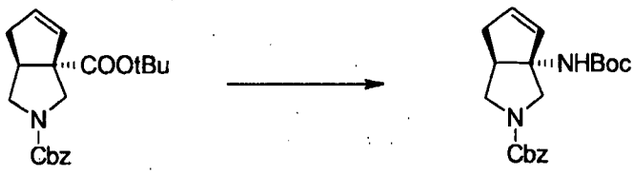
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.29 (5H, m), 5.79 (1H, brs), 5.64 (1H, brs), 5.12 (2H, s), 3.79-3.68 (3H, m), 3.21-3.12 (2H, m), 2.74 (1H, dd, J=17.44, 6.22 Hz), 2.19 (1H, t, J=18.54 Hz), 1.43 (9H, s).

MS; (EI) m/z: 366 $(M+Na)^+$.

[Reference Example 112]

[(1S,5R)-1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-7-en-3-yl]carboxylic acid benzyl ester

[Formula 203]



[(1S,5S)-3-Benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-7-en-1-yl]carboxylic acid tert-butyl ester (380 mg, 1.11 mmol) was dissolved in dichloromethane (8 mL). Trifluoroacetic acid (1.5 mL) was added, and the mixture was stirred for one day. The reaction solution was concentrated under reduced pressure, and a 1N sodium hydroxide solution (100 mL) was added, and the mixture was washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform (200 mL × 2). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in toluene (10 mL). Triethylamine (223.3 mg, 2.21 mmol) and diphenylphosphoryl azide (469.5 mg, 1.66 mmol) were added in a nitrogen atmosphere, and the mixture was stirred at 80°C for 20 hours. The reaction solution was concentrated under reduced pressure. Then, 1,4-dioxane (10 mL) and 6N hydrochloric acid (10 mL) were added, and the mixture was stirred for three days. After concentration under reduced pressure and azeotropic distillation with ethanol, a 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous

sodium sulfate and filtration, the solvent was evaporated under reduced pressure. Di-tert-butyl dicarbonate (1204 mg, 5.52 mmol) was added to the resulting residue, and the mixture was stirred at 50°C for 16 hours. The reaction solution was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give 92.1 mg of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.25 (5H, m), 5.84 (1H, s), 5.78 (1H, s), 5.10 (2H, s), 4.70 (1H, s), 3.87 (1H, dd, J=11.23, 8.79 Hz), 3.79-3.76 (2H, m), 3.24-3.21 (1H, m), 2.87-2.72 (2H, m), 2.21-2.18 (1H, m), 1.43 (9H, s).

MS (EI); m/z: 359 $(M+H)^+$.

[Reference Example 113]

(1S,5R)-1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-7-ene

[Formula 204]



[(1S,5R)-1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-7-en-3-yl]carboxylic acid benzyl ester (85.0 mg, 0.24 mmol) was dissolved in tetrahydrofuran (20 mL). After bubbling with liquid ammonia (20 mL) at -78°C, sodium (17.1 mg, 0.71 mmol) was added, and the mixture was stirred for one hour. A saturated ammonium chloride

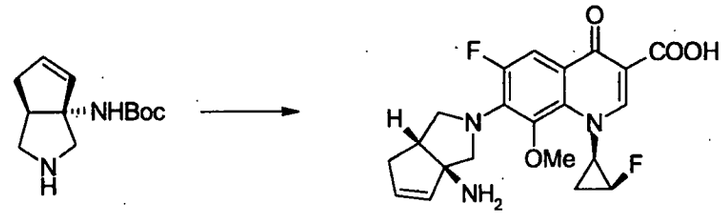
solution (6 drops) were added, and then ammonia was vaporized in an ice water bath. A 1N sodium hydroxide solution was added, followed by extraction with chloroform twice. The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the filtrate was concentrated under reduced pressure to give 52.9 mg of the title compound as a colorless solid.

MS (EI) m/z: 225$(M+H)^+$.

[Example 24]

7-[(1S,5R)-1-Amino-3-azabicyclo[3.3.0]oct-7-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 205]



(1S,5R)-1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-7-ene (52.9 mg, 0.24 mmol) was dissolved in dimethyl sulfoxide (2 mL). 6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (89.4 mg, 0.25 mmol) and triethylamine (71.6 mg, 0.71 mmol) were added, and the mixture was stirred at 40°C for 20 hours. Then, 90% aqueous ethanol (20 mL) and triethylamine (2 mL) were added

to the reaction solution, and the mixture was stirred at 80°C for two hours. The solvent was evaporated under reduced pressure and a 10% citric acid solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 8 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was washed with ethanol-diethyl ether and dried under reduced pressure to give 57.8 mg of the title compound as a pale yellow solid.

mp: 206-208°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, s), 7.69 (1H, d, J=13.67 Hz), 5.90 (1H, brs), 5.69 (1H, brs), 4.96 (1H, d, J=60.79 Hz), 4.08-4.04 (1H, m), 3.77 (1H, t, J=8.91 Hz), 3.70 (3H, d, J=10.25 Hz), 3.64 (1H, s), 3.59-3.57 (1H, m), 3.54-3.51 (1H, m), 2.91-2.87 (1H, m), 2.55-2.53 (1H, m), 2.30 (1H, d, J=17.09 Hz), 1.63-1.55 (2H, m).

Anal; Calcd for $C_{21}H_{21}F_2N_3O_4 \cdot 0.25H_2O \cdot 0.5EtOH$: C, 59.39; H, 5.55; N, 9.44; F, 8.54. Found: C, 59.32; H, 5.44; N, 9.50; F, 8.28.

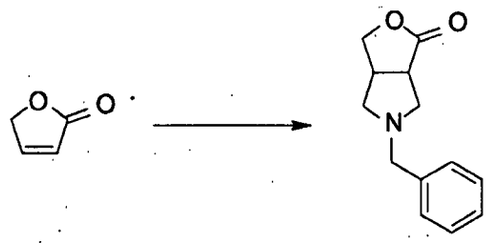
MS (EI); m/z: 418 $(M+H)^+$.

IR (ATR) ν: 2929, 2848, 2758, 1726, 1614, 1577, 1537, 1504, 1435, 1392, 1352, 1315, 1269 cm^{-1}.

[Reference Example 114]

(1R*,5S*)-7-Benzyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one

[Formula 206]



(±)-cis

Trifluoroacetic acid (0.136 mL) was added to a solution of N-benzyl-N-(methoxymethyl)-N-trimethylsilylamine (43.9 g, 185 mmol) and γ-crotonolactone (12.5 g, 176 mmol) in 1,2-dichloromethane (176 mL), and the mixture was stirred in a nitrogen atmosphere at room temperature for four hours. A saturated sodium bicarbonate solution (250 mL) was added to the reaction solution, followed by extraction with chloroform (200 mL × 2). The organic layer was washed with brine (400 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under

reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 84:16 -> 80:20 -> 75:25 -> 66:34 -> 50:50) to give 37.1 g of the title compound.

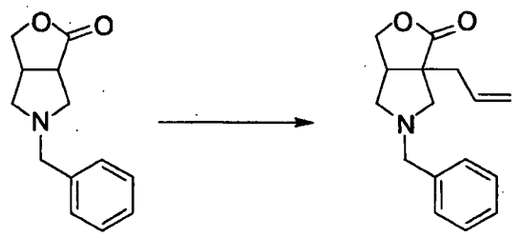
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.26 (5H, m), 4.48 (1H, t, J=8.58 Hz), 4.08 (1H, dd, J=9.19, 3.55 Hz), 3.69 (1H, d, J=13.24 Hz), 3.54 (1H, d, J=13.24 Hz), 3.26 (1H, d, J=9.31 Hz), 3.08-2.98 (2H, m), 2.80 (1H, d, J=9.56 Hz), 2.49-2.38 (2H, m).

MS (ESI) m/z: 218 $(M+H)^+$.

[Reference Example 115]

1-Allyl-7-benzyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one

[Formula 207]



(±)-cis

Allyl bromide (2.48 mL, 29.3 mmol) was added to a solution of (1R*,5S*)-7-benzyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one (4.25 g, 19.6 mmol) in tetrahydrofuran (98 mL) with stirring under salt-ice cooling. A 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (23.5 mL, 23.5 mmol) was added dropwise under cooling with ice-acetone. The mixture was stirred for

two hours while gradually heating to room temperature. A saturated ammonium chloride solution (200 mL) was added to the reaction solution, followed by extraction with ethyl acetate (100 mL x 2). The organic layer was washed with water (250 mL) and brine (250 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25 -> 66:34 -> 50:50) to give 1.51 g of the title compound.

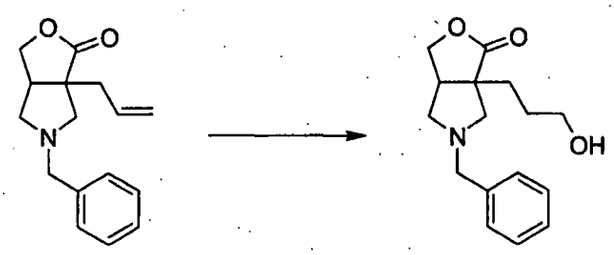
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.21 (5H, m), 5.80-5.70 (1H, m), 5.20-5.14 (2H, m), 4.35 (1H, t, J=8.95 Hz), 4.03 (1H, dd, J=9.19, 3.55 Hz), 3.63 (1H, d, J=13.24 Hz), 3.51 (1H, d, J=13.24 Hz), 3.26 (1H, d, J=9.07 Hz), 2.81 (1H, d, J=9.56 Hz), 2.73-2.71 (1H, m), 2.57 (1H, dd, J=13.73, 6.62 Hz), 2.49 (1H, dd, J=9.44, 6.74 Hz), 2.30 (1H, dd, J=13.85, 8.21 Hz), 2.23 (1H, d, J=9.07 Hz).

MS (ESI); m/z: 258 $(M+H)^+$.

[Reference Example 116]

7-Benzyl-1-(3-hydroxypropyl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one

[Formula 208]



A solution of 1-allyl-7-benzyl-3-oxa-7-azabicyclo[3.3.0]octan-2-one (11.0 g, 42.7 mmol) in tetrahydrofuran (142 mL) was cooled with ice-acetone. A 0.5 mol/L solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (264 mL, 132 mmol) was added in a nitrogen atmosphere, and the mixture was stirred at room temperature for two hours. After cooling with ice-acetone, A 1 mol/L solution of sodium hydroxide (142 mL) and a 30% hydrogen peroxide solution were added in a nitrogen atmosphere, and the mixture was stirred at room temperature for one hour. The organic layer of the reaction solution was concentrated under reduced pressure and extracted with chloroform (300 mL × 1, 250 mL × 1). The organic layer was washed with brine (600 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 66:34 -> 50:50 -> 34:66 -> 20:80) to give 12.9 g of a residue containing the title compound which was directly used for the next reaction.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 4.41 (1H, t, J=8.82 Hz), 4.05 (1H, dd, J=9.19, 3.55 Hz), 3.81 (1H, t, J=8.95 Hz), 3.68-3.63 (3H, m), 3.51 (1H, d, J=13.24 Hz), 3.29 (1H, d, J=9.31 Hz), 2.83 (1H, d, J=9.56 Hz), 2.69 (1H, s), 2.49 (1H, t, J=7.84 Hz), 2.19 (1H, t, J=8.58 Hz), 1.93-1.82 (3H, m).

MS (ESI); m/z: 276 $(M+H)^+$.

[Reference Example 117]

7-Benzyl-3-oxa-1-(3-oxopropyl)-7-azabicyclo[3.3.0]octan-2-one

[Formula 209]



A dichloromethane (113 mL) solution was cooled with dry ice-methanol in a nitrogen atmosphere. Oxalyl chloride (11.2 mL, 128 mmol) and dimethyl sulfoxide (15.2 mL, 214 mmol) were added, and the mixture was stirred under cooling for 30 minutes. A solution of the residue containing 7-benzyl-1-(3-hydroxypropyl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one (12.9 g, 42.7 mmol) in dichloromethane (100 mL) was added, and the mixture was stirred under ice-cooling for one hour. Triethylamine (35.8 mL, 256 mmol) was added under ice-cooling, and the mixture was stirred under cooling for

one hour and then at room temperature for one hour. A saturated ammonium chloride solution (200 mL) was added to the reaction solution, followed by extraction with chloroform (150 mL × 2). The organic layer was washed with brine (450 ml) and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 50:50) to give 8.91 g of a residue containing the title compound which was directly used for the next reaction.

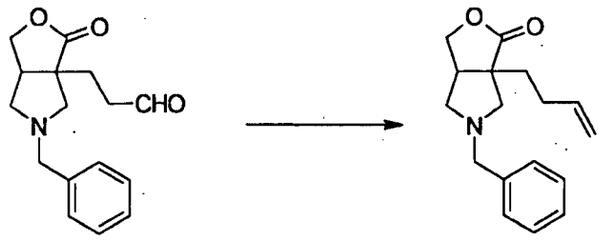
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.77 (1H, s), 7.32-7.22 (5H, m), 4.42 (1H, t, J=8.95 Hz), 4.06 (1H, dd, J=9.31, 3.68 Hz), 3.62 (1H, d, J=12.99 Hz), 3.53 (1H, d, J=13.24 Hz), 3.30 (1H, d, J=9.31 Hz), 2.84 (1.0H, d, J=9.31 Hz), 2.73-2.62 (2.0H, m), 2.55-2.51 (2.0H, m), 2.04-2.00 (2H, m).

MS (ESI); m/z: 274 $(M+H)^+$.

[Reference Example 118]

7-Benzyl-1-(3-buten-1-yl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one

[Formula 210]



Tetrahydrofuran (45.7 mL) was added to methyltriphenylphosphonium iodide (6.16 g, 15.2 mmol) in a nitrogen atmosphere. A 1.57 mol/L solution of butyllithium in hexane (14.0 mL, 22.0 mmol) was added under ice-cooling, and then the reaction solution was stirred for 15 minutes. A solution of the residue containing 7-benzyl-3-oxa-1-(3-oxopropyl)-7-azabicyclo[3.3.0]octan-2-one (5.00 g, 18.3 mmol) in tetrahydrofuran (45.7 mL) was added dropwise thereto under ice-cooling, and the mixture was stirred at room temperature for one hour. Water (150 mL) was added to the reaction solution, followed by extraction with ethyl acetate (150 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 1.09 g of the title compound.

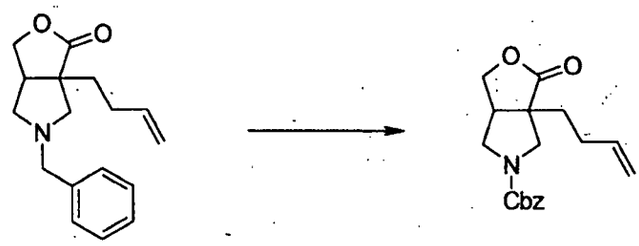
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.22 (10.8H, m), 5.83-5.73 (1H, m), 5.07-4.96 (2.1H, m), 4.40 (1H, t, J=8.95 Hz), 4.04 (1H, dd, J=9.19, 3.55 Hz), 3.63 (1H, d, J=12.99 Hz), 3.50 (1H, d, J=13.24 Hz), 3.29 (1H, d, J=9.31 Hz), 2.83 (1H, d, J=9.56 Hz), 2.71-2.69 (1H, m), 2.47 (1H, dd, J=9.56, 6.62 Hz), 2.23-2.02 (3H, m), 1.92-1.88 (1H, m), 1.69-1.65 (1H, m).

MS (ESI); m/z: 272 $(M+H)^+$.

[Reference Example 119]

7-Benzyloxycarbonyl-1-(3-buten-1-yl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one

[Formula 211]



Benzyl chloroformate (1.72 mL, 12.0 mmol) was added to a solution of 7-benzyl-1-(3-buten-1-yl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one (1.09 g, 4.02 mmol) in dichloromethane (13.4 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for five days. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 84:16 -> 80:20 -> 75:25 -> 66:34 -> 50:50) to give 1.13 g of the title compound.

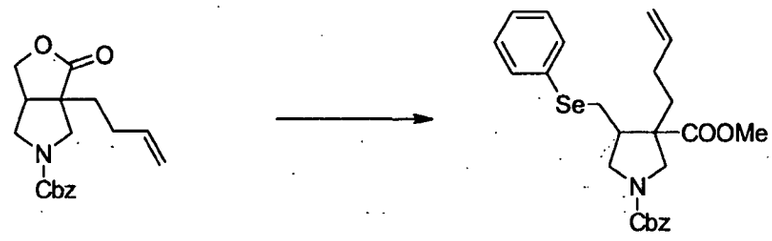
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.82-5.72 (1H, m), 5.12-5.00 (4H, m), 4.42 (1H, t, J=8.33 Hz), 4.12 (1H, brs), 4.00 (1H, d, J=11.77 Hz), 3.83 (1H, dd, J=11.77, 8.33 Hz), 3.44 (2H, d, J=37.75 Hz), 2.95-2.89 (1H, m), 2.26-2.17 (1H, m), 2.10-2.06, (1H, m), 1.90-1.76 (2H, m).

MS (ESI); m/z: 316 $(M+H)^+$.

[Reference Example 120]

1-Benzyloxycarbonyl-3-(3-buten-1-yl)-4-phenylselenylmethyl-3-carboxylic acid methyl ester

[Formula 212]



N,N-Dimethylformamide (16.3 mL) was added to diphenyl diselenide (946 mg, 3.03 mmol) in a nitrogen atmosphere. Then, the mixture was depressurized to vacuum and freeze-degassed (× 3) while cooling with liquid nitrogen. Sodium borohydride (229 mg, 6.05 mmol) was added thereto at room temperature. The mixture was stirred at room temperature until gas generation was completed, and then depressurized to vacuum and freeze-degassed (× 3) to prepare a reaction solution A.

Separately, a solution of 7-benzyl-1-(3-buten-1-yl)-3-oxa-7-azabicyclo[3.3.0]octan-2-one (955 mg, 3.03 mmol) in N,N-dimethylformamide (14.0 mL) was depressurized to vacuum and freeze-degassed (three times) while cooling with liquid nitrogen to prepare a reaction solution B.

The reaction solution B was added to the reaction solution A, and the mixture was stirred at 100°C for one hour. The reaction solution was cooled to room temperature

and then 1N hydrochloric acid (10 to 20 mL) was added, followed by extraction with ethyl acetate (100 mL × 2). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2 -> 97:3 -> 96:4) to give 2.08 g of the title compound which was directly used for the esterification step.

Trimethylsilyldiazomethane (9.09 mL) was added to a solution of 2.08 g of the residue in methanol (30.3 mL) under ice-cooling, and the mixture was stirred at room temperature for 20 minutes. The reaction solution was concentrated under reduced pressure. Then, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 485 mg of the title compound.

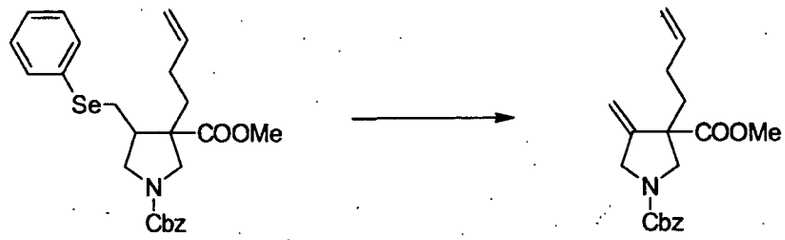
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.49-7.23 (5H, m), 5.73-5.69 (1H, m), 5.16-5.09 (2H, m), 4.98-4.95 (2H, m), 3.98 (1H, dd, J=21.33, 11.28 Hz), 3.80 (1H, ddd, J=24.08, 10.97, 7.05 Hz), 3.70 (3H, s), 3.32-3.21 (2H, m), 3.12 (1H, dd, J=12.38, 3.06 Hz), 2.49 (1H, t, J=12.01 Hz), 2.34-2.29 (1H, m), 2.10-2.05 (1H, m), 1.96-1.92 (2H, m), 1.38-1.35 (1H, m).

MS (ESI); m/z: 378 $(M+H)^+$.

[Reference Example 121]

1-Benzyloxycarbonyl-3-(3-buten-1-yl)-4-methylenepyrrolidine-3-carboxylic acid methyl ester

[Formula 213]



A 0.5N sodium periodide solution (4.99 mL, 2.50 mmol) was added to a solution of 1-benzyloxycarbonyl-3-(3-buten-1-yl)-4-phenylselenylmethyl-3-carboxylic acid methyl ester (485 mg, 0.997 mmol) in tetrahydrofuran (9.97 mL). The mixture was stirred at room temperature for five hours and then at 40°C to 50°C for 24 hours. Water (50 mL) was added to the reaction solution, followed by extraction with ethyl acetate (50 mL × 2). The organic layer was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 285 mg of the title compound.

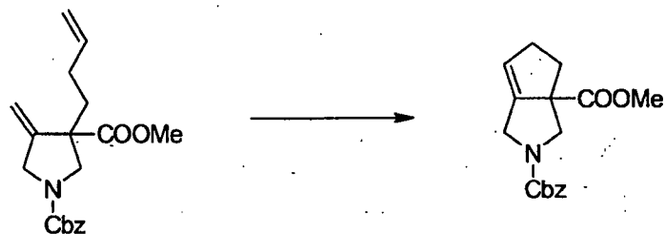
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.42-7.28 (5H, m), 5.79-5.75 (1H, m), 5.20-5.15 (4H, m), 5.03-4.98 (2H, m), 4.21-4.13 (3H, m), 3.69 (3H, s), 3.41 (1H, dd, J=19.49, 11.40 Hz), 2.17-2.10 (1H, m), 2.04-2.02 (2H, m), 1.68-1.64 (1H, m).

MS (ESI) m/z: 330 $(M+H)^+$.

[Reference Example 122]

{3-Benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-5-en-1-yl}carboxylic acid methyl ester

[Formula 214]



The Second Generation Grubbs' catalyst (29.6 mg, 0.871 mmol) was added to a solution of 1-benzyloxycarbonyl-3-(3-buten-1-yl)-4-methylenepyrrolidine-3-carboxylic acid methyl ester (286 mg, 0.871 mmol) in dichloromethane (8.71 mL) in a nitrogen atmosphere. The mixture was stirred at room temperature for 19 hours, and the dichloromethane (17.4 mL) was added. After stirring at 45°C for six hours, the reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 87:13 -> 85:15 -> 83:17 -> 80:20 -> 75:25 -> 66:34) to give 187 mg of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.72 (1H, d, J=13.73 Hz), 5.17-5.12 (2H, m), 4.20 (1H, dd, J=10.79, 2.70 Hz), 4.04-3.94 (2H, m), 3.68 (3H, d, J=1.47 Hz), 3.07 (1H, dd, J=10.79, 7.11 Hz), 2.95-2.87 (1H, m), 2.63-2.48 (2H, m), 1.88-1.83 (1H, m).

MS (ESI) m/z: 302 $(M+H)^+$.

[Reference Example 123]

{3-Benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-5-en-1-yl}carboxylic acid

[Formula 215]



A 1N sodium hydroxide solution (1.86 mL) was added to a solution of {3-benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-5-en-1-yl}carboxylic acid methyl ester (187 mg, 0.620 mmol) in methanol (6.20 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure and then washed with diethyl ether (50 mL × 2). The aqueous layer was made acidic with 1N hydrochloric acid under ice-cooling, followed by extraction with ethyl acetate (100 mL × 1, 80 mL × 1). The organic layer was washed with water (80 mL) and brine (80 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 186 mg (quantitative) of the title compound.

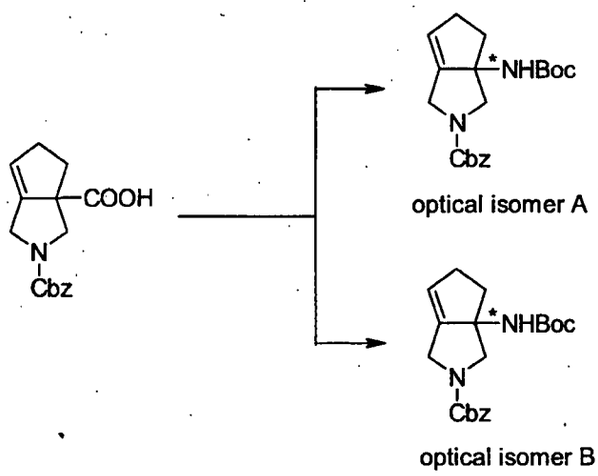
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (5H, m), 5.77 (1H, d, J=17.16 Hz), 5.21-5.10 (2H, m), 4.25 (1H, dd, J=10.91, 5.02

Hz), 4.02 (2H, t, J=17.53 Hz), 3.09 (1H, dd, J=10.91, 7.72 Hz), 2.93 (1H, brs), 2.60-2.54 (2H, m), 1.93-1.83 (1H, m). MS (ESI); m/z: 288 $(M+H)^+$.

[Reference Example 124]

3-Benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (optical isomer A, optical isomer B)

[Formula 216]



Triethylamine (0.181 mL, 1.30 mmol) and diphenylphosphoryl azide (0.181 mL, 0.840 mmol) were added to a solution of {3-benzyloxycarbonyl-3-azabicyclo[3.3.0]oct-5-en-1-yl}carboxylic acid (186 mg, 0.647 mmol) in toluene (3.23 ml) in a nitrogen atmosphere. The mixture was stirred at room temperature for 30 minutes and then at 100°C for 30 minutes. The reaction solution was concentrated under reduced pressure, and triethylamine was azeotropically distilled with toluene (× 3). 1,4-Dioxane

(1.62 mL) and 6N hydrochloric acid (1.62 mL) were added to the resulting residue, and the mixture was stirred at 50°C for one hour. The reaction solution was distilled with water (6.5 mL), and the organic layer was evaporated off by concentration under reduced pressure. The residue was washed with diethyl ether (20 mL × 2). The aqueous layer was made alkaline with a 1N sodium hydroxide solution under ice-cooling, followed by extraction with chloroform (40 mL × 1, 30 mL × 1). The organic layer was washed with water (40 mL) and brine (40 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Dichloromethane (3.23 ml) was added to the resulting residue, and di-tert-butyl dicarbonate (283 mg, 1.30 mmol) was added in a nitrogen atmosphere. After stirring at room temperature for 17 hours, the reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 120 mg of the title compound.

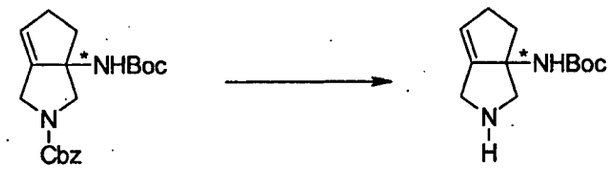
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m), 5.74 (1H, d, J=7.48 Hz), 5.17-5.11 (2H, m), 4.58 (1H, s), 4.26 (1H, dd, J=25.37, 11.40 Hz), 4.02-4.01 (2H, m), 3.14 (1H, dd, J=11.28, 8.82 Hz), 2.80 (1H, brs), 2.55-2.52 (1H, m), 2.37 (1H, brs), 1.94-1.91 (1H, m), 1.43 (9H, s).

The racemate 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (108 mg, 0.301 mmol) obtained as described above was optically resolved by an optically active column (CHIRALCEL OJ, 20 mm diameter × 250 mm, hexane:isopropyl alcohol = 90:10, flow rate = 20 mL/min, resolving 20 mg each time) to give 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (optical isomer A) (50.5 mg, 1.41 mmol, retention time = 8.0 min) and its enantiomer 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (optical isomer B) (55.6 mg, 0.155 mmol, retention time = 11.5 min).

[Reference Example 125]

1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (derived from optical isomer A)

[Formula 217]



optical isomer A

A solution of 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (optical isomer A) (50.5 mg, 0.141 mmol) in tetrahydrofuran (1.41 mL) was bubbled with ammonia gas under cooling with dry ice-acetone to add 30 to 40 mL of liquid ammonia to the

solution. Sodium (17.0 mg, 0.709 mmol) was added in a nitrogen atmosphere, and the mixture was stirred for 10 minutes. A saturated ammonium chloride solution (3 drops) was added at room temperature, and the mixture was stirred at room temperature to evaporate ammonia. A 1N sodium hydroxide solution (12.0 mL) was added, followed by extraction with chloroform (40 mL × 1, 20 mL × 1) and the lower layer of chloroform/methanol/water = 7/3/1 (40 mL × 1, 20 mL × 1). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the filtrate was concentrated under reduced pressure to give 33 mg (quantitative) of the title compound.

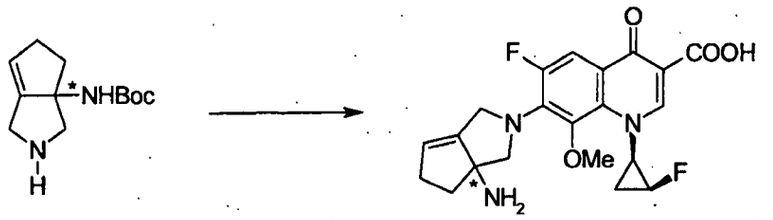
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.58 (1H, brs), 4.62 (1H, brs), 3.47 (3H, tt, J=14.34, 9.68 Hz), 2.96-2.87 (1H, m), 2.61-2.57 (2H, m), 2.28-2.25 (1H, m), 1.85 (1H, dt, J=16.42, 6.62 Hz), 1.45 (9H, s).

MS (ESI) m/z: 225 $(M+H)^+$.

[Example 25]

7-[1-Amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer A)

[Formula 218]



Triethylamine (0.0595 mL, 0.426 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (51.2 mg, 0.142 mmol) were added to a solution of 1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (derived from optical isomer A) (33.0 mg, 0.135 mmol) in dimethyl sulfoxide (0.284 mL). The mixture was stirred at room temperature for two hours and at 40°C for 14 hours. A mixed solution of ethanol:water = 4:1 (5 mL) and triethylamine (0.5 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with a 10% citric acid solution (15 mL), water (15 mL), and brine (15 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 61.4 mg of the resulting residue was dissolved in concentrated hydrochloric acid (1 mL) under ice-cooling, and the

solution was stirred at room temperature for 15 minutes. After washing with chloroform (15 mL x 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 mL), chloroform/methanol = 10/1 (80 mL), and the lower layer of chloroform/methanol/water = 7/3/1 (80 mL x 3). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in hot ethanol (5 mL) and a 28% ammonia solution (1 to 2 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated under reduced pressure while heating with stirring. Further, ammonia was azeotropically distilled with ethanol (3 to 5 mL) (x 10). Ethanol was concentrated until crystals were precipitated, followed by stirring at room temperature overnight. The precipitated crystals were collected by filtration, washed with ethanol and diethyl ether, and then dried under reduced pressure at 60°C to give 9.65 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.40 (1H, d, J=3.19 Hz), 7.69 (1H, d, J=14.46 Hz), 5.62 (1H, s), 5.12-4.96 (1H, m), 4.50 (1H, d, J=12.50 Hz), 4.04-4.01 (2H, m), 3.60 (5H, dd, J=16.67, 9.31 Hz), 2.91 (1H, s), 2.62-2.59 (1H, m), 2.15-

2.07 (1H, m), 1.99-1.92 (1H, m), 1.58-1.54 (1H, m), 1.48-1.37 (1H, m).

Anal; Calcd for $C_{21}H_{21}F_2N_3O_4 \cdot 1.5H_2O$: C, 56.75; H, 5.44; N, 99.45. Found: C, 56.53; H, 4.96; N, 9.01.

MS (ESI); m/z: 418 $(M+H)^+$.

IR (ATR) ν: 2935, 2852, 2755, 2657, 2572, 2103, 1716, 1614, 1569, 1531, 1498, 1463, 1455, 1361, 1324, 1116, 1043, 943, 919, 808 cm^{-1}.

[Reference Example 126]

1-tert-Butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (derived from optical isomer B)

[Formula 219]



optical isomer B

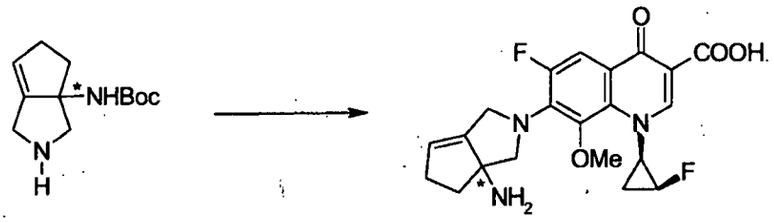
A solution of 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (optical isomer B) (54.7 mg, 0.153 mmol) in tetrahydrofuran (1.53 mL) was bubbled with ammonia gas under cooling with dry ice-acetone to add 30 to 40 mL of liquid ammonia to the solution. Sodium (18.4 mg, 0.767 mmol) was added in a nitrogen atmosphere, and the mixture was stirred for 10 minutes. A saturated ammonium chloride solution (10 drops) was added at room temperature, and the mixture was stirred

at room temperature to evaporate ammonia. A 1N sodium hydroxide solution (3 to 4 mL) was added, and the mixture was concentrated under reduced pressure. Chloroform/methanol = 10/1 (10 to 20 mL) was added. After ultrasonic treatment, the insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to give 150 mg of a residue containing the title compound, which was directly used for the next reaction. MS(ESI) m/z: 225$(M+H)^+$.

[Example 26]

7-[1-Amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer B)

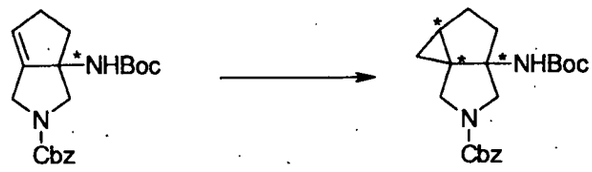
[Formula 220]



Triethylamine (0.0641 mL, 0.460 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (58.0 mg, 0.161 mmol) were added to a solution of the residue containing 1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]oct-5-ene (derived from optical isomer B) (150 mg, 0.153 mmol) in

6-tert-Butoxycarbonylamino-8-benzyloxycarbonyl-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (derived from optical isomer A)

[Formula 221]



optical isomer A

A dichloromethane (3.52 mL) solution was cooled with ice-acetone. A 1.0 M solution of diethylzinc in n-hexane (0.88 mL, 0.88 mmol) and diiodomethane (0.071 mL, 0.881 mmol) were slowly added in a nitrogen atmosphere, and the mixture was stirred for 20 minutes under cooling. A solution of 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.2.0]oct-5-ene (optical isomer A) (126 mg, 0.352 mmol) in dichloromethane (3.52 mL) was slowly added under cooling, the mixture was stirred at room temperature for 24 hours. A saturated sodium bicarbonate aqueous solution (10 mL) and a 10% sodium thiosulfate solution (10 mL) were added under cooling with ice-acetone, and the mixture was stirred until the vermillion color disappeared. The organic layer was extracted with chloroform (50 mL × 1, 40 mL × 1). The organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure.

Acetonitrile (7.04 mL) and di-tert-butyl dicarbonate (384 mg, 1.76 mmol) were sequentially added to 212 mg of the resulting residue in a nitrogen atmosphere. After stirring at room temperature for 19 hours, the reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 95.2 mg of the title compound.

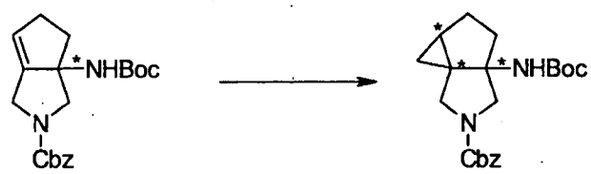
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.31 (5H, m), 5.17-5.11 (2H, m), 4.93 (1H, brs), 4.21-4.11 (1H, m), 3.75 (1H, dd, J=10.91, 6.74 Hz), 3.32-3.12 (2H, m), 2.47-2.31 (1H, m), 1.97-1.88 (1H, m), 1.81-1.78 (1H, m), 1.43 (9H, s), 1.35-1.31 (1H, m), 1.19-1.16 (1H, m), 0.82-0.76 (2H, m).

MS (ESI); m/z: 395 $(M+Na)^+$.

[Reference Example 128]

6-tert-Butoxycarbonylamino-8-benzyloxycarbonyl-8-azatricyclo[4.3.0.0^{1,3}]nonane (derived from optical isomer B)

[Formula 222]



optical isomer B

A dichloromethane (4.18 mL) solution was cooled with ice-acetone. A 1.0 M solution of diethylzinc in n-hexane

(1.05 mL, 1.05 mmol) and diiodomethane (0.0842 mL, 1.05 mmol) were slowly added in a nitrogen atmosphere, and the mixture was stirred for 20 minutes under cooling. A solution of 3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.2.0]oct-5-ene (optical isomer B) (150 mg, 0.418 mmol) in dichloromethane (4.18 mL) was slowly added under cooling, the mixture was stirred at room temperature for 22 hours. A saturated sodium bicarbonate aqueous solution (10 mL) and a 10% sodium thiosulfate solution (10 mL) were added under cooling with ice-acetone, and the mixture was stirred until the vermillion color disappeared. The organic layer was extracted with chloroform (60 mL × 1, 50 mL × 1). The organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure. Acetonitrile (8.36 mL) and di-tert-butyl dicarbonate (274 mg, 1.25 mmol) were sequentially added to 256 mg of the resulting residue in a nitrogen atmosphere. After stirring at room temperature for 13 hours, the reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 84:16 -> 80:20 -> 75:25) to give 113 mg of the title compound.

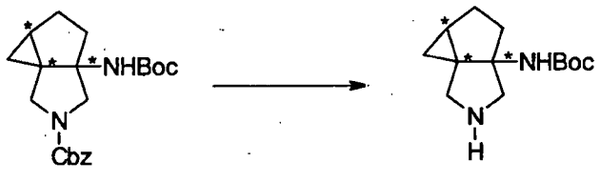
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.13 (2H, t, J=6.74 Hz), 4.93 (1H, d, J=16.18 Hz), 4.23-4.09 (1H, m),

3.75 (1H, dd, J=11.03, 6.62 Hz), 3.27-3.19 (2H, m), 2.43 (1H, brs), 1.98-1.88 (1H, m), 1.82-1.74 (2H, m), 1.43 (9H, s), 1.37-1.22 (1H, m), 1.22-1.14 (1H, m), 0.81-0.77 (2H, m). MS (ESI); m/z: 395 $(M+Na)^+$.

[Reference Example 129]

6-tert-Butoxycarbonylamino-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (derived from optical isomer A)

[Formula 223]



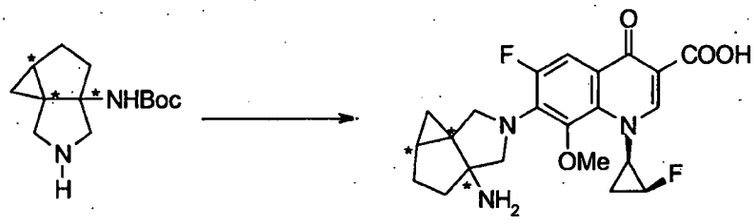
A 10% palladium-carbon catalyst (47.6 mg, 50 wt%) was added to a solution of 6-tert-butoxycarbonylamino-8-benzyloxycarbonyl-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (derived from optical isomer A) (95.2 mg, 0.255 mmol) in methanol (2.55 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred at room temperature for one hour. A 10% palladium-carbon catalyst (28.6 mg, 30 wt%) was added. After the atmosphere was replaced with hydrogen, the mixture was stirred at room temperature for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure to give 56.0 mg of the title compound as a black oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.98 (1H, brs), 3.63 (1H, s), 3.46-3.44 (1H, m), 2.92 (2H, dd, J=30.52, 11.15 Hz), 2.37 (1H, brs), 2.00-1.96 (1H, m), 1.76-1.70 (1H, m), 1.44 (9H, s), 1.35-1.25 (1H, m), 1.21-1.15 (1H, m), 0.86-0.69 (2H, m). MS (ESI); m/z: 239 $(M+H)^+$.

[Example 27]

7-[6-Amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer A)

[Formula 224]



Triethylamine (0.0984 mL, 0.705 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (89.1 mg, 0.247 mmol) were added to a solution of 6-tert-butoxycarbonylamino-8-azatricyclo[4.3.0.0^{1,3}]nonane (derived from optical isomer A) 56.0 mg (0.235 mmol) in dimethyl sulfoxide (0.470 mL). The mixture was stirred at 35°C for 19 hours. A mixed solution of ethanol:water = 4:1 (5.0 mL) and triethylamine (0.5 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour.

The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (35 mL) and washed with a 10% citric acid solution (25 mL), water (25 mL), and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1). 80.5 mg of the resulting residue was dissolved in concentrated hydrochloric acid (1 mL) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (30 mL × 4), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (60 mL × 2) and chloroform/methanol = 10/1 (60 mL × 3). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was purified by PTLC (lower layer of chloroform/methanol/water = 7/3/1). The resulting residue was dissolved in chloroform/methanol = 10/1 (10 mL). The insoluble material was removed by filtration, and then the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in hot ethanol (20 to 30 ml), and then

concentrated under reduced pressure and dried. Ethanol (0.5 mL) and diethyl ether (5 mL) were added to the resulting residue, and the mixture was ultrasonically treated and ice-cooled. Then, the precipitated crystals were collected by filtration and washed with diethyl ether. The crystals were dried under reduced pressure at 45°C to give 21.0 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.38 (1H, d, J=2.94 Hz), 7.67 (1H, d, J=14.22 Hz), 5.12-4.96 (1H, m), 4.32-4.29 (1H, m), 4.04-3.99 (1H, m), 3.80 (1H, d, J=10.30 Hz), 3.61 (3H, s), 3.44 (1H, d, J=10.54 Hz), 3.31 (1H, d, J=10.30 Hz), 2.02-1.89 (2H, m), 1.77 (1H, dd, J=12.62, 8.46 Hz), 1.58-1.24 (4H, m), 0.82 (2H, dt, J=23.78, 5.82 Hz).

Anal; Calcd for $C_{22}H_{23}F_2N_3O_4$: C, 57.64; H, 5.72; F, 8.29; N, 9.17. Found: C, 57.70; H, 5.77; F, 8.57; N, 9.09.

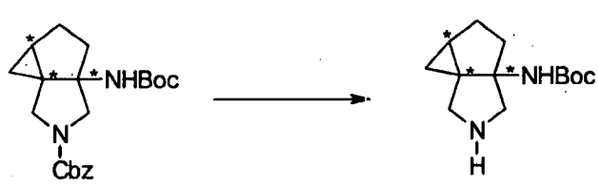
MS (ESI); m/z: 432 $(M+H)^+$.

IR (ATR) ν: 2935, 2869, 1725, 1616, 1432, 1363, 1319, 1182, 1137, 1045, 943, 923, 806 cm^{-1}.

[Reference Example 130]

6-tert-Butoxycarbonylamino-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (derived from optical isomer B)

[Formula 225]



A 10% palladium-carbon catalyst (27.7 mg, 30 wt%) was added to a solution of 6-tert-butoxycarbonylamino-8-benzyloxycarbonyl-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (derived from optical isomer B) (92.3 mg, 0.248 mmol) in methanol (2.48 mL) in a nitrogen atmosphere. The mixture was stirred in a hydrogen atmosphere at room temperature for one hour. A 10% palladium-carbon catalyst (18.5 mg, 20 wt%) was added, and the mixture was stirred in a hydrogen atmosphere at room temperature for 2.5 hours. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure to give 64.4 mg of a residue containing the title compound.

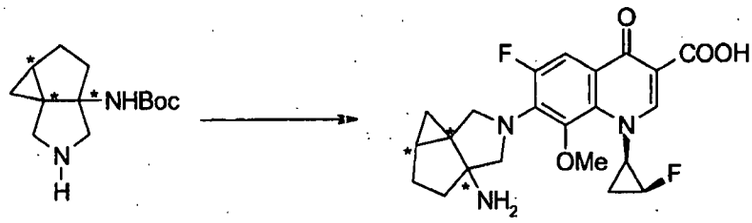
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.87 (1H, brs), 3.50 (1H, brs), 3.29 (1H, d, J=11.03 Hz), 3.14-3.12 (1H, m), 2.76 (2H, dd, J=19.12, 11.28 Hz), 2.47-1.66 (3H, m), 1.43 (9H, s), 1.32 (1H, dd, J=24.14, 10.17 Hz), 1.08-1.04 (1H, m), 0.82-0.67 (2H, m).

MS (ESI); m/z: 239 $(M+H)^+$.

[Example 28]

7-[6-Amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer B)

[Formula 224]



Triethylamine (0.104 mL, 0.745 mmol) and 1-[(1R,2S)-2-fluorocyclopropan-1-yl]-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (89.5 mg, 0.248 mmol) were added to a solution of 64.4 mg of the residue containing 6-tert-butoxycarbonylamino-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (0.248 mmol equivalent) in dimethyl sulfoxide (0.496 mL), and the mixture was stirred at 35°C for 17 hours. A mixed solution of ethanol:water = 4:1 (5.0 mL) and triethylamine (0.5 mL) were added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (35 mL) and washed with a 10% citric acid solution (25 mL), water (25 mL), and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1). 75.5 mg of the resulting residue was dissolved in concentrated hydrochloric acid (1 mL) under ice-cooling, and the solution was stirred at room temperature for 15

minutes. After washing with chloroform (30 mL × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 mL × 1, 70 mL × 1, 50 mL × 1). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot ethanol (10 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated under reduced pressure while heating with stirring. Then, the solution was concentrated until ethanol was about 0.5 mL, and then returned to room temperature. Diethyl ether (5 mL) was added and the mixture was ice-cooled. Then, the precipitated crystals were collected by filtration and then washed with diethyl ether. The crystals were dried under reduced pressure at 50°C to give 25.9 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.50 (1H, s), 7.67 (1H, d, J=14.71 Hz), 4.99-4.93 (1H, m), 4.39 (1H, dd, J=10.30, 3.43 Hz), 4.09 (1H, q, J=6.21 Hz), 3.87 (1H, dd, J=10.54, 2.94 Hz), 3.63 (3H, s), 3.37 (1H, d, J=10.54 Hz), 3.23 (1H, d, J=10.30 Hz), 2.01-1.95 (2H, m), 1.79-1.58 (3H, m), 1.34-1.17 (2H, m), 0.82 (2H, dt, J=22.22, 5.94 Hz).

Anal; Calcd for $C_{22}H_{23}F_2N_3O_4 \cdot 0.5H_2O$: C, 59.99; H, 5.49; F, 8.63; N, 9.54. Found: C, 60.28; H, 5.34; F, 8.57; N, 9.52.

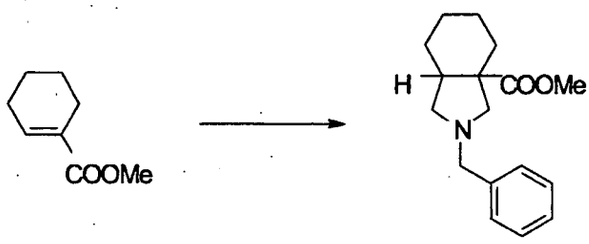
MS (ESI); m/z: 432 $(M+H)^+$.

IR (ATR) ν: 2937, 2863, 1716, 1616, 1508, 1434, 1321, 1187, 1120, 1054, 939, 889, 804 cm^{-1}.

[Reference Example 131]

[(1R*,6R*)-8-Benzyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid methyl ester

[Formula 227]



(±)-cis

A catalytic amount of trifluoroacetic acid was added to a solution of 1-cyclohexene-1-carboxylic acid methyl ester (25.0 g, 178 mmol) and N-benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine (46.6 g, 196 mmol) in 1,2-dichloroethane (178 mL) at room temperature, and the mixture was stirred at room temperature for two hours. A saturated sodium bicarbonate solution (200 mL) was added to the reaction solution, followed by extraction with chloroform (150 mL × 1, 100 mL × 1). The organic layer was washed with brine (450 ml) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated

under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 85:15 -> 75:25) to give 21.3 g of the title compound.

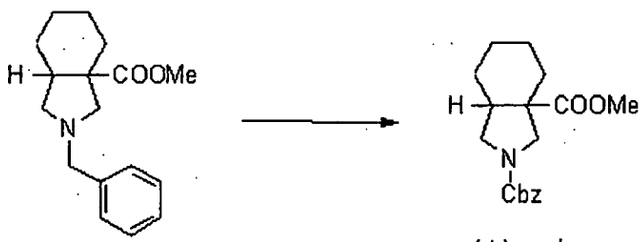
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.24 (5H, m), 3.70-3.65 (5H, m), 2.92 (1H, d, J=9.31 Hz), 2.73-2.68 (3H, m), 1.93 (1H, td, J=9.01, 4.82 Hz), 1.79-1.65 (2H, m), 1.53-1.21 (6H, m).

MS (ESI); m/z: 274 $(M+H)^+$.

[Reference Example 132]

[(1R*,6R*)-8-Benzyloxycarbonyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid methyl ester

[Formula 228]



(±)-cis (±)-cis

Benzyl chloroformate (33.4 mL, 234 mmol) was added to a solution of [(1R*,6R*)-8-benzyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid methyl ester (21.3 g, 77.9 mmol) in dichloromethane (259 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure. Then, the residue (58.0 g) was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5

-> 90:10 -> 80:20 -> 75:25) to give 17.5 g of the title compound.

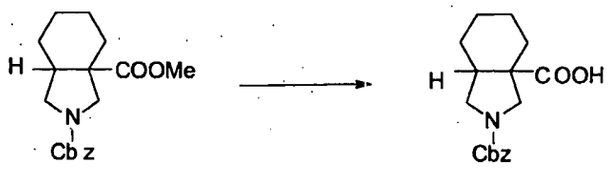
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.13 (2H, m), 3.71 (3H, d, J=3.19 Hz), 3.63 (1H, dd, J=10.91, 8.21 Hz), 3.52-3.28 (3H, m), 2.72-2.64 (1H, m), 1.93 (1H, m), 1.75 (1H, dq, J=20.41, 5.23 Hz), 1.63-1.38 (6H, m).

MS (ESI); m/z: 318 $(M+H)^+$.

[Reference Example 133]

[(1R*,6R*)-8-Benzyloxycarbonyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid

[Formula 229]



(±)-cis (±)-cis

A 1 mol/L sodium hydroxide solution (70.8 mL) and tetrahydrofuran (78.8 mL) were added to a solution of [(1R*,6R*)-8-benzyloxycarbonyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid methyl ester (7.50 g, 23.6 mmol) in methanol (78.8 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for three days. The reaction solution was concentrated under reduced pressure and then washed with diethyl ether (50 mL × 2). The aqueous layer was made acidic with 3 mol/L hydrochloric acid (28 mL) under ice-cooling, followed by extraction with ethyl

acetate (100 mL × 2). The organic layer was washed with brine (250 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 6.70 g of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5, m), 5.13 (2H, m), 3.70 (1H, dd, J=10.91, 4.78 Hz), 3.51 (2H, m), 3.40-3.30 (1H, m), 2.68 (1H, m), 2.00-1.96 (1H, m), 1.78-1.76 (1H, m), 1.65-1.60 (1H, m), 1.51-1.45 (5H, m).

MS (ESI); m/z: 304 $(M+H)^+$.

[Reference Example 134]

(1R*,6S*)-8-Benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane

[Formula 230]



(±)-cis (±)-cis

Triethylamine (6.17 mL, 44.2 mmol) and diphenylphosphoryl azide (6.19 mL, 28.7 mmol) were added to a solution of [(1R*,6R*)-8-benzyloxycarbonyl-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid (6.70 g, 22.1 mmol) in toluene (110 mL) while stirring under ice-cooling in a nitrogen atmosphere. The mixture was stirred at room temperature for 40 minutes and then at 90°C for one hour. The reaction solution was diluted with ethyl acetate (150

mL) at room temperature, washed with a saturated sodium bicarbonate solution (200 mL), water (200 mL), and brine (200 mL), and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. 1,4-Dioxane (55.0 mL) and 6 mol/L hydrochloric acid (55.0 mL) were added to the resulting residue, and the mixture was stirred at 50°C for two hours. The reaction solution was distilled with water (55.0 mL) and concentrated under reduced pressure. Then, the residue was azeotropically dried with ethanol (× 5). Dichloromethane (110 mL) was added to the precipitated white solid (7.41 g). Triethylamine (15.4 mL, 110 mmol) and di-tert-butoxycarbonyl (9.65 g, 44.2 mol) were added in a nitrogen atmosphere, and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure, and ethyl acetate (150 mL) was added. The mixture was washed with water (200 mL) and brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 83:17 -> 66:34) to give 6.65 g of the title compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.13 (2H, s), 4.55 (1H, d, J=13.97 Hz), 3.69 (1H, d, J=11.28 Hz), 3.58-

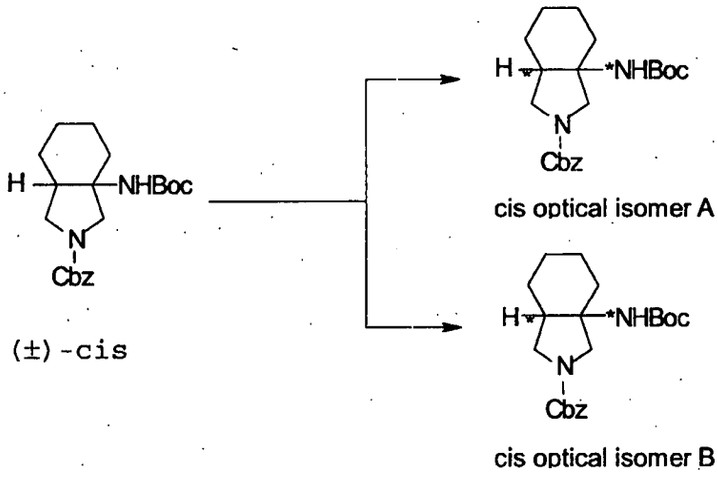
3.45 (2H, m), 3.30 (1H, ddd, J=21.33, 10.66, 6.74 Hz), 2.03-1.99 (1H, m), 1.66-1.43 (17H, m).

MS (ESI); m/z: 374 $(M+H)^+$.

[Reference Example 135]

(1R,6S)-/(1S,6R)-8-Benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (optical isomer A, optical isomer B)

[Formula 231]



The racemate (1R*,6S*)-8-benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (6.65 g, 17.8 mmol) was optically resolved by an optically active column (CHIRALPAK AD, 20 mm diameter × 250 mm, hexane:isopropyl alcohol = 95:5, flow rate = 20 ml/min) to give optically active 8-benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (optical isomer A) (427 mg, 1.14 mmol, retention time = 14.2 min) and its optically active enantiomer 8-benzyloxycarbonyl-1-tert-butoxycarbonylamino-

8-azabicyclo[4.3.0]nonane (optical isomer B) (415 mg, 1.11 mmol, retention time = 19.4 min).

[Reference Example 136]

1-tert-Butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (derived from optical isomer A)

[Formula 232]



cis optical isomer A

A 10% palladium-carbon catalyst (80.0 mg, 20 wt%) was added to a solution of 8-benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (optical isomer A) (400 mg, 1.07 mmol) in methanol (10.7 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at room temperature for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure to give the title compound quantitatively.

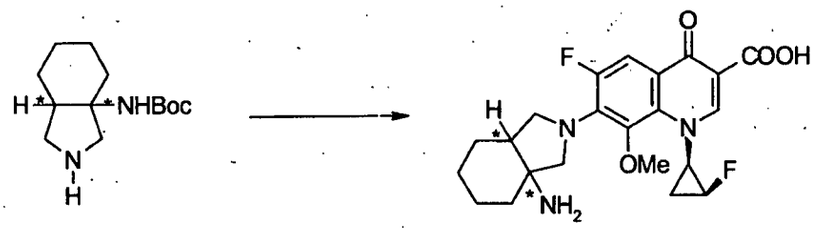
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.61 (1H, brs), 3.18-3.12 (2H, m), 3.02 (1H, d, J=11.28 Hz), 2.81 (1H, dd, J=10.66, 6.74 Hz), 2.16 (1H, brs), 2.01 (1H, brs), 1.57-1.43 (8H, m), 1.43 (9H, s).

MS (ESI); m/z: 241 $(M+H)^+$.

[Example 29]

7-[1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer A)

[Formula 233]



Triethylamine (0.407 mL, 2.92 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (351 mg, 0.972 mmol) were added to a solution of 1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (derived from optical isomer A) (277 mg, 1.07 mmol) in dimethyl sulfoxide (1.94 mL), and the mixture was stirred at 35°C for 17 hours. A mixed solution of ethanol:water = 4:1 (20 mL) and triethylamine (2 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (40 mL) and washed with a 10% citric acid solution (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the

filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 456 mg of the resulting residue was dissolved in concentrated hydrochloric acid (3.0 mL) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. The reaction solution was adjusted to pH 13.6 with a saturated sodium hydroxide solution, and the basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (100 mL), chloroform/methanol = 10/1 (150 mL × 1, 100 mL × 2), and the lower layer of chloroform/methanol/water = 7/3/1 (150 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot ethanol (67.5 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. The solution was concentrated until ethanol was 10 mL, and then stirred at room temperature overnight. The precipitated crystals were collected by filtration and then washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 50°C to give 271 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.42 (1H, d, J=1.96 Hz), 7.65 (1H, d, J=14.71 Hz), 4.97 (1H, dt, J=49.76, 17.89 Hz),

4.05-4.00 (1H, m), 3.84 (1H, t, J=7.48 Hz), 3.71 (1H, d, J=10.30 Hz), 3.60 (4H, t, J=12.01 Hz), 3.36 (1H, d, J=8.33 Hz), 2.01 (1H, m), 1.77 (2H, m), 1.60-1.41 (8H, m).

Anal; Calcd for $C_{22}H_{25}F_2N_3O_4 \cdot 0.5H_2O$: C, 59.72; H, 5.92; F, 8.59; N, 9.50. Found: C, 59.91; H, 5.97; F, 8.68; N, 9.39.

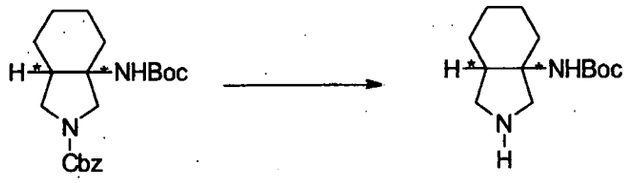
MS (ESI); m/z: 434 $(M+H)^+$.

IR (ATR) ν: 2927, 2856, 1724, 1616, 1508, 1430, 1324, 1268, 1186, 1120, 1049, 925, 877, 806 cm^{-1}.

[Reference Example 137]

1-tert-Butoxycarbonylamino-3-azabicyclo[4.3.0]nonane (derived from optical isomer B)

[Formula 234]



cis optical isomer B

A 10% palladium-carbon catalyst (83.0 mg, 20 wt%) was added to a solution of 8-benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (optical isomer B) (415 mg, 1.11 mmol) in methanol (11.1 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at room temperature for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered

through Celite and concentrated under reduced pressure to give the title compound quantitatively.

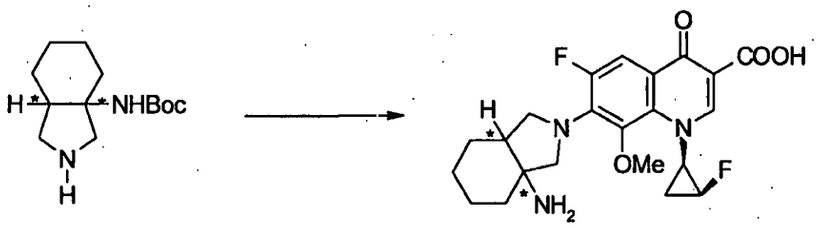
^{1}H-NMR ($CDCl_3$) δ: 4.60 (1H, brs), 3.17-3.12 (2H, m), 3.02 (1H, d, J=11.52 Hz), 2.81 (1H, brs), 2.15 (1H, brs), 2.00 (1H, s), 1.63-1.36 (8H, m), 1.43 (9H, s).

MS (ESI); m/z: 241 $(M+H)^+$.

[Example 30]

7-[1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (7-position substituent: derived from optical isomer B)

[Formula 235]



Triethylamine (0.422 mL, 3.03 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (364 mg, 1.01 mmol) were added to a solution of 1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (derived from optical isomer B) (273 mg, 1.11 mmol) in dimethyl sulfoxide (1.94 mL), and the mixture was stirred at 35°C for 17 hours. A mixed solution of ethanol:water = 4:1 (20 mL) and triethylamine (2 mL) were added to the reaction solution,

and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (40 mL) and washed with a 10% citric acid solution (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 536 mg of the resulting residue was dissolved in concentrated hydrochloric acid (3.0 mL) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (20 mL × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7 with hydrochloric acid, followed by extraction with chloroform/methanol = 10/1 (150 mL × 1, 100 mL × 2). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot ethanol (67.5 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. The solution was concentrated until ethanol was 10 mL, and then stirred at room temperature overnight. The precipitated crystals were collected by

filtration and washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 50°C to give 315 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.45 (1H, d, J=1.47 Hz), 7.64 (1H, d, J=14.95 Hz), 5.04-4.84 (1H, m), 4.06-3.99 (2H, m), 3.88 (1H, dd, J=10.54, 2.21 Hz), 3.57 (3H, s), 3.42 (1H, d, J=10.54 Hz), 3.20 (1H, d, J=8.82 Hz), 1.94 (1H, m), 1.83 (1H, m), 1.73 (1H, m), 1.67-1.46 (6H, m), 1.33 (2H, m).

Anal; Calcd for $C_{22}H_{25}F_2N_3O_4 \cdot 0.75H_2O$: C, 59.12; H, 5.98; F, 8.50; N, 9.40. Found: C, 59.05; H, 6.12; F, 8.36; N, 9.20.

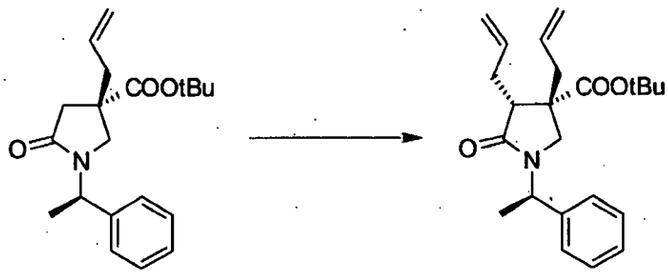
MS (ESI); m/z: 434 $(M+H)^+$.

IR (ATR) ν: 2927, 2859, 1724, 1616, 1573, 1509, 1432, 1369, 1355, 1319, 1267, 1118, 1049, 933, 879, 804 cm^{-1}.

[Reference Example 138]

(3S,4R)-3,4-Diallyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 236]



Allyl bromide (1.36 mL, 16.1 mmol) was added to a solution of (3S)-3-allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

(4.05 g, 12.3 mmol) in tetrahydrofuran (41.0 mL) with stirring under salt ice cooling. A 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (16.0 mL, 16.0 mmol) was added dropwise with stirring under salt ice cooling, and the mixture was stirred under salt ice cooling for 15 minutes. A saturated ammonium chloride solution (40 mL) and water (20 mL) were added to the reaction solution, followed by extraction with ethyl acetate (40 mL × 1, 20 mL × 1). The organic layer was washed with brine (140 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 89:11 -> 88:12 -> 87:13 -> 83:17 -> 80:20 -> 75:25) to give 2.02 g of the title compound.

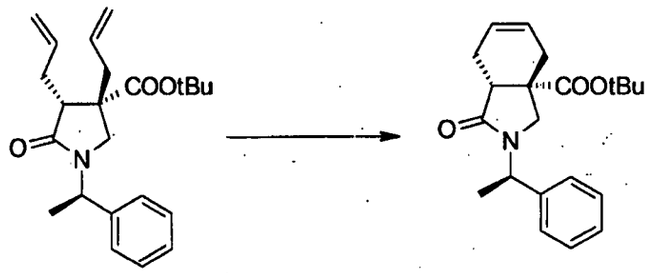
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 (5H, m), 5.77-5.62 (2H, m), 5.48 (1H, q, J=7.11 Hz), 5.13 (2H, dd, J=13.36, 11.89 Hz), 5.02 (1H, t, J=9.07 Hz), 4.91 (1H, dd, J=5.52, 2.76 Hz), 3.21 (1H, d, J=10.54 Hz), 3.09 (1H, d, J=10.79 Hz), 2.56 (1H, dd, J=14.34, 6.01 Hz), 2.40 (3H, d, J=4.41 Hz), 2.27 (1H, dd, J=13.73, 8.33 Hz), 1.50 (3H, d, J=7.11 Hz), 1.40 (9H, s).

MS (ESI); m/z: 370 $(M+H)^+$.

[Reference Example 139]

[(1S,6R)-7-Oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-en-1-yl]carboxylic acid tert-butyl ester

[Formula 237]



The Second Generation Grubbs' catalyst (91.9 mg, 0.108 mmol) was added to a solution of (3S,4R)-3,4-diallyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.00 g, 5.41 mmol) in dichloromethane (54.1 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 75:25 -> 66:34 -> 50:50) to give 1.61 g of the title compound.

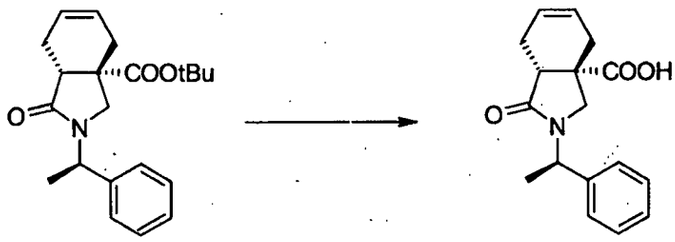
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.21 (5H, m), 5.75 (1H, m), 5.67-5.62 (1H, m), 5.49 (1H, q, J=7.19 Hz), 3.22 (2H, dd, J=13.97, 10.05 Hz), 2.74 (1H, dd, J=16.42, 5.15 Hz), 2.62-2.54 (1H, m), 2.49 (1H, d, J=5.39 Hz), 2.42 (1H, m), 2.15-2.08 (1H, m), 1.48 (3H, d, J=7.11 Hz), 1.18 (9H, s).

MS (ESI); m/z: 342 $(M+H)^+$.

[Reference Example 140]

[(1S,6R)-7-Oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-en-1-yl]carboxylic acid

[Formula 238]



Trifluoroacetic acid (18.0 mL) was added to a solution of [(1S,6R)-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-en-1-yl]carboxylic acid tert-butyl ester (2.04 g, 5.99 mmol) in dichloromethane (18.0 mL) with stirring under ice-cooling, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (× 3). A 1 mol/L sodium hydroxide solution (15.0 mL) was added to the resulting residue under ice-cooling, and the mixture was washed with diethyl ether (40 mL × 2). The aqueous layer was made acidic with 1 mol/L hydrochloric acid (20 mL) under ice-cooling. Then, the precipitated crystals were collected by filtration and washed with 0.5 mol/L hydrochloric acid, ethyl acetate, and diethyl ether. The resulting crystals were dried under reduced pressure at 50°C overnight to give 1.40 g of the title compound as white

crystals. The aqueous layer of the filtrate was extracted with ethyl acetate (50 mL). The organic layers were combined, washed with water (150 mL) and brine (150 mL), and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 250 mg of the title compound as white crystals.

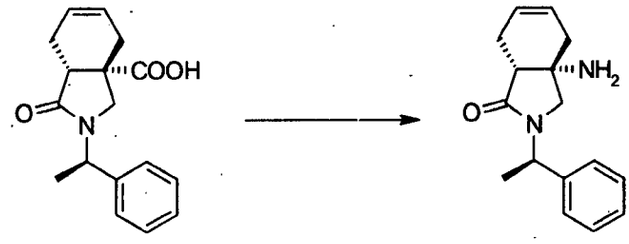
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.23 (5H, m), 5.81 (1H, m), 5.69 (1H, m), 5.51 (1H, q, J=7.11 Hz), 3.27 (1H, d, J=10.05 Hz), 3.18 (1H, d, J=10.05 Hz), 2.74 (1H, dd, J=16.67, 4.90 Hz), 2.59 (1H, m), 2.47 (1H, m), 2.22 (1H, d, J=16.67 Hz), 2.14 (1H, brs), 1.49 (3H, d, J=7.11 Hz).

MS (ESI); m/z: 286 $(M+H)^+$.

[Reference Example 141]

(1S,6R)-1-Amino-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene

[Formula 239]



Triethylamine (1.61 mL, 11.5 mmol) and diphenylphosphoryl azide (1.62 mL, 7.52 mmol) were added to a solution of [(1S,6R)-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-en-1-yl]carboxylic acid (1.65 g,

5.78 mmol) in toluene (28.9 mL) in a nitrogen atmosphere with stirring under ice-cooling, and the mixture was stirred at 100°C for 30 minutes. The reaction solution was concentrated under reduced pressure, and triethylamine was azeotropically distilled with toluene (× 3). 1,4-Dioxane (14.4 mL) and 4 mol/L hydrochloric acid (14.4 mL) were added to the resulting residue, and the mixture was stirred at 50°C for six hours. The reaction solution was diluted with water (30.0 mL) and washed with ethyl acetate (50 mL × 2). A 1 mol/L sodium hydroxide solution (55.0 mL) was added to the aqueous layer, followed by extraction with chloroform (100 mL × 1, 80 mL × 1). The organic layer was washed with brine (150 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 1.24 g of the title compound as an amorphous.

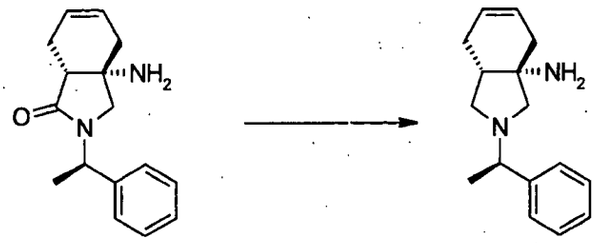
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.23 (5H, m), 5.81-5.77 (1H, m), 5.67-5.62 (1H, m), 5.53 (1H, q, J=7.11 Hz), 3.70 (2H, s), 3.23 (1H, d, J=9.80 Hz), 2.96 (1H, d, J=9.80 Hz), 2.45 (2H, m), 2.33 (1H, m), 2.27-2.16 (1H, m), 2.10 (1H, dd, J=16.79, 5.02 Hz), 1.50 (3H, d, J=7.11 Hz).

MS (ESI); m/z: 257 $(M+H)^+$.

[Reference Example 142]

(1S,6S)-1-Amino-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene

[Formula 240]



A 65% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (2.87 mL, 9.56 mmol) was added to a solution of (1S,6R)-1-amino-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene (612 mg, 2.39 mmol) in toluene (11.9 mL), and the mixture was stirred at 80°C for one hour. A 5 mol/L sodium hydroxide solution (15.0 mL) was added to the reaction solution with stirring under ice-cooling, followed by extraction with toluene (30 mL × 2). The organic layer was washed with brine (90 ml) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 450 mg of the title compound.

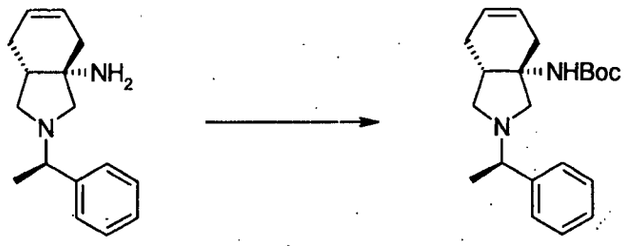
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.19 (5H, m), 5.72-5.59 (2H, m), 3.58 (1H, q, J=6.54 Hz), 2.86 (1H, d, J=9.07 Hz), 2.70 (1H, dd, J=9.56, 8.09 Hz), 2.54-2.48 (2H, m), 2.22-1.73 (5H, m), 1.33 (3H, d, J=6.62 Hz).

MS (ESI); m/z: 243 $(M+H)^+$.

[Reference Example 143]

(1S,6S)-1-tert-Butoxycarbonylamino-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene

[Formula 241]



Di-tert-butyl dicarbonate (689 mg, 3.16 mmol) was added to a solution of (1S,6S)-1-amino-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene (450 mg, 1.86 mmol) in dichloromethane (9.3 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 66:34 -> 50:50 -> 25:75 -> 16:84) to give 456 mg of the title compound.

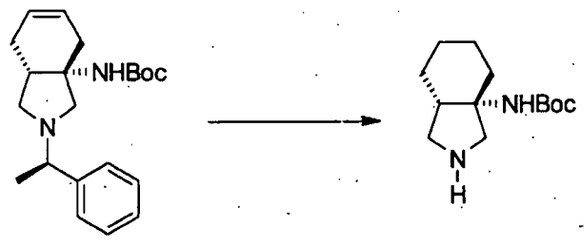
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29-7.18 (5H, m), 5.69-5.59 (2H, m), 4.43 (1H, s), 3.62 (1H, q, J=6.54 Hz), 3.53 (1H, d, J=10.54 Hz), 3.04 (1H, dd, J=8.95, 7.23 Hz), 2.89 (1H, d, J=18.38 Hz), 2.60 (1H, d, J=11.03 Hz), 2.52 (1H, dd, J=11.28, 9.31 Hz), 2.26-2.08 (2H, m), 1.99-1.83 (2H, m), 1.44 (9H, s), 1.32 (3H, d, J=6.62 Hz).

MS (ESI); m/z: 343 $(M+H)^+$.

[Reference Example 144]

(1S,6S)-1-tert-Butoxycarbonylamino-8-azabicyclo[4.3.0]nonane

[Formula 242]



A 10% palladium-carbon catalyst (406 mg, 100 wt%) was added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene (406 mg, 1.18 mmol) in ethanol (11.8 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at 40°C to 50°C for seven hours. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure to give the title compound quantitatively.

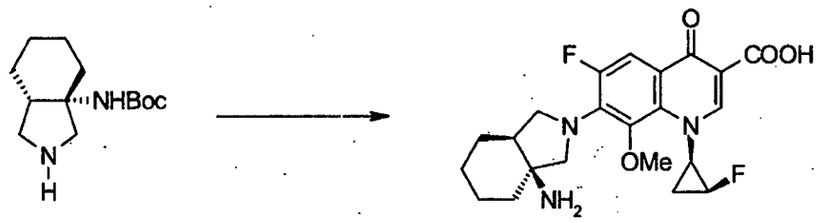
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.24 (1H, brs), 3.59 (1H, brs), 3.01 (1H, dd, J=9.80, 7.60 Hz), 2.67-2.62 (2H, m), 2.52 (1H, d, J=11.28 Hz), 1.79-1.53 (9H, m), 1.44 (9H, s).

MS (ESI); m/z: 241 $(M+H)^+$.

[Example 31]

7-[(1S,6S)-1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 243]



Triethylamine (0.449 mL, 3.22 mmol) and 1-[(1R,2S)-2-fluorocyclopropan-1-yl]-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (387 mg, 1.07 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (301 mg, 1.18 mmol) in dimethyl sulfoxide (2.14 mL), and the mixture was stirred at 35°C for 15 hours. A mixed solution of ethanol:water = 4:1 (20 mL) and triethylamine (2 mL) were added to the reaction solution, and the mixture was heated to reflux for 1.5 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with a 10% citric acid solution (40 mL), water (40 mL), and brine (40 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography

(chloroform:methanol = 100:0 -> 99:1 -> 98:2). 506 mg of the resulting residue was dissolved in concentrated hydrochloric acid (3.0 mL) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (20 mL × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (150 mL) and chloroform/methanol = 10/1 (100 mL × 2). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot ethanol (45 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. The solution was concentrated until ethanol was 10 mL, and then stirred at room temperature overnight. The precipitated crystals were collected by filtration and then washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 50°C to 60°C to give 126 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.35 (1H, d, J=3.92 Hz), 7.65 (1H, d, J=14.71 Hz), 5.15-4.96 (1H, m), 3.99 (1H, dt, J=10.21, 4.47 Hz), 3.62 (3H, m), 3.54 (3H, s), 3.44 (1H, t, J=8.46 Hz), 3.27 (1H, d, J=9.56 Hz), 1.87-1.28 (11H, m).

Anal; Calcd for $C_{22}H_{25}F_2N_3O_4 \cdot 0.25H_2O$: C, 60.33; H, 5.87; F, 8.68; N, 9.59. Found: C, 60.27; H, 5.84; F, 8.60; N, 9.58.

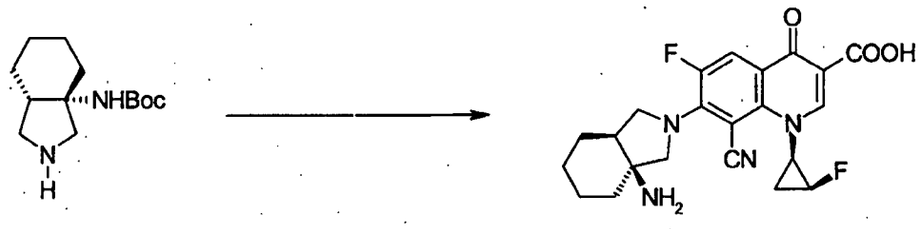
MS (ESI); m/z: 434 $(M+H)^+$.

IR (ATR) ν: 2929, 2859, 1722, 1617, 1508, 1432, 1363, 1319, 1045, 925, 804 cm^{-1}.

[Example 32]

7-[(1S,6S)-1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 244]



Triethylamine (478 μL, 3.42 mmol) and 8-cyano-6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (384 mg, 1.14 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (302 mg, 1.26 mmol) in acetonitrile (2.28 mL) in a nitrogen atmosphere. The mixture was stirred at room temperature for one hour and then at 45°C for one hour. The reaction solution was concentrated under reduced pressure. Then, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 50:50 -> 40:60 ->

30:70) to give a pale yellow amorphous. A 1 mol/L sodium hydroxide solution (4.64 mL) was added to a solution of 644 mg of the amorphous in ethanol (5.80 mL) under ice-cooling, and the mixture was stirred at room temperature for one hour. Then, tetrahydrofuran (8.70 mL) was added, and the mixture was stirred at room temperature for one hour. A 10% citric acid solution (15 mL) was added to the reaction solution, followed by extraction with ethyl acetate (50 mL × 1, 40 mL × 1). The organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 554 mg of the resulting residue was dissolved in concentrated hydrochloric acid (2 mL) under ice-cooling, and the solution was stirred at room temperature for 10 minutes. The solution was washed with chloroform (25 mL × 2). The reaction solution was adjusted to pH 12.5 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with the lower layer of chloroform/methanol/water = 7/3/1 (200 mL × 3). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. Hot ethanol (80 mL) and 28% aqueous ammonia (5

mL) were added to the residue, and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. Ammonia was azeotropically removed with ethanol several times. The solution was concentrated to about 20 mL and then stirred at room temperature. The precipitated crystals were collected by filtration and then washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 50°C overnight to give 341 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.29 (1H, d, J=3.92 Hz), 7.85 (1H, d, J=15.44 Hz), 5.18 (1H, ddd, J=66.61, 6.92, 4.47 Hz), 4.01-3.88 (3H, m), 3.70-3.65 (1H, m), 3.46 (1H, t, J=5.27 Hz), 1.95-1.32 (11H, m).

Anal; Calcd for $C_{22}H_{22}F_2N_4O_3 \cdot 1.25H_2O \cdot 0.25EtOH$: C, 58.91; H, 5.71; F, 8.28; N, 12.21. Found: C, 58.71; H, 5.66; N, 11.96.

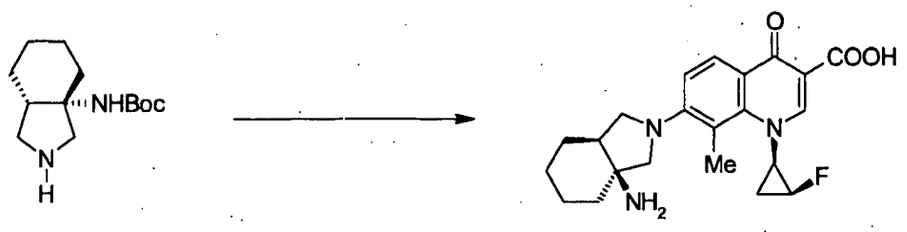
MS (ESI); m/z: 429 $(M+H)^+$.

IR (ATR) ν: 3623, 2938, 2886, 2202, 1641, 1610, 1556, 1535, 1515, 1490, 1461, 1353, 1342, 1301, 1261 cm^{-1}.

[Example 33]

7-[(1S,6S)-1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 245]



Triethylamine (0.277 mL, 1.98 mmol) and 7-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (185 mg, 0.663 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (175 mg, 0.728 mmol) in dimethyl sulfoxide (1.33 mL) in a nitrogen atmosphere, and the mixture was stirred at 75°C for 12 days. The reaction solution was diluted with ethyl acetate (45 mL) and then washed with a 10% citric acid solution (40 mL), water (40 mL), and a saturated sodium hydroxide solution (40 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 260 mg (0.578 mmol) of the resulting residue was dissolved in concentrated hydrochloric acid (2.5 mL) under ice-cooling, and the solution was stirred at room temperature for 10 minutes. After washing with chloroform (50 mL × 2), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH

7.4 with hydrochloric acid, followed by extraction with chloroform (100 mL × 2) and chloroform/methanol = 10/1 (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by PTLC (developed with the lower layer of chloroform/methanol/water = 7/3/1). After the fluorescent part was collected, the lower layer of chloroform/methanol/water = 7/3/1 (70 mL) was added. After ultrasonic treatment, the silica gel was filtered off. The filtrate was concentrated under reduced pressure and then vacuum dried. Ethanol (1 mL), diethyl ether, and 2-propanol were added to the residue. Diethyl ether was added. After repeating ultrasonic treatment and ice-cooling several times, the mixture was stirred at 40°C for 30 minutes. After stirring at room temperature for two hours, the crystals were collected by filtration and dried under reduced pressure to give 88.7 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.40 (1H, d, J=3.68 Hz), 7.98 (1H, d, J=8.82 Hz), 7.07 (1H, d, J=9.31 Hz), 5.17-4.94 (1H, m), 4.06 (1H, dd, J=13.97, 5.64 Hz), 3.55 (2H, dd, J=19.36, 10.30 Hz), 3.22 (1H, t, J=8.09 Hz), 3.13 (1H, d, J=9.56 Hz), 2.43 (3H, s), 1.92-1.19 (11H, m).

Anal; Calcd for $C_{22}H_{26}FN_3O_3 \cdot 0.25H_2O$: C, 65.41; H, 6.61; F, 4.70; N, 10.40. Found: C, 65.18; H, 6.60; N, 10.48.

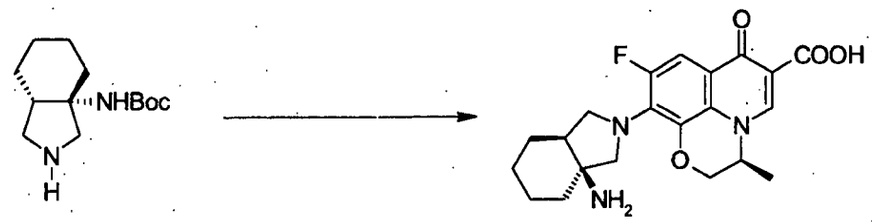
MS (ESI); m/z: 400 $(M+H)^+$.

IR (ATR) ν: 3380, 2927, 2863, 1712, 1614, 1509, 1428, 1396, 1359, 1348, 1340, 1315, 1301, 1035, 927 cm^{-1}.

[Example 34]

10-[(1S,6S)-1-Amino-8-azabicyclo[4.3.0]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid

[Formula 246]



Triethylamine (0.208 mL, 1.49 mmol) and 9,10-difluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF_2 chelate (164 mg, 0.498 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]nonane (126 mg, 0.524 mmol) in dimethyl sulfoxide (0.996 mL), and the mixture was stirred at 35°C for 15 hours. A mixed solution of ethanol:water = 4:1 (10 mL) and triethylamine (1 mL) were added to the reaction solution, and the mixture was heated to reflux for three hours. The reaction solution was concentrated under reduced pressure, and then a 10% citric

acid solution (30 mL) was added to the residue, followed by extraction with ethyl acetate (30 mL). The interface part was extracted with chloroform. The organic layer was washed with water (30 mL) and brine (30 mL), respectively, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 169 mg the resulting residue was dissolved in concentrated hydrochloric acid (1 mL) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (20 mL × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (100 mL × 2) and chloroform/methanol = 10/1 (100 mL × 3). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue (130 mg) was dissolved in ethanol/28% aqueous ammonia = 7/1 (60 mL), and the insoluble material was removed by filtration. The filtrate was heated with stirring to gradually evaporate the solvent. Ammonia was azeotropically removed with ethanol several times. The solution was concentrated to 10 mL and then returned to room temperature. The precipitated

crystals were collected by filtration, washed with ethanol and diethyl ether, and then dried under reduced pressure to give 109 mg of the title compound as pale yellow crystals.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.30 (1H, s), 7.51 (1H, d, J=14.46 Hz), 4.62-4.54 (1H, m), 4.45 (1H, dd, J=11.40, 2.08 Hz), 4.26 (1H, dd, J=11.28, 2.21 Hz), 3.74 (1H, dd, J=10.05, 3.43 Hz), 3.70-3.64 (1H, m), 3.43 (1H, t, J=8.33 Hz), 3.34 (1H, d, J=8.33 Hz), 1.87-1.63 (5H, m), 1.56-1.22 (4H, m), 1.52 (3H, d, J=6.86 Hz).

Anal; Calcd for $C_{21}H_{24}FN_3O_4 \cdot 0.25H_2O$: C, 62.13; H, 6.08; F, 4.68; N, 10.35. Found: C, 62.03; H, 6.10; N, 10.31.

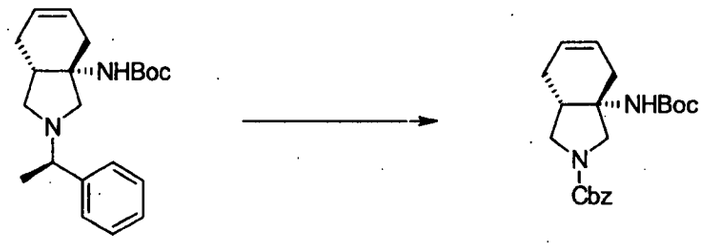
MS (ESI); m/z: 402 $(M+H)^+$.

IR (ATR) ν: 3590, 3295, 3222, 2929, 2883, 1614, 1554, 1471, 1344, 1311, 1259, 1234, 1110, 1041, 985, 815 cm^{-1}.

[Reference Example 145]

(1S,6S)-8-Benzyloxycarbonyl-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]non-3-ene

[Formula 247]



Benzyl chloroformate (0.600 mL, 4.20 mmol) was added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]non-3-ene (479 mg, 1.40

mmol) in dichloromethane (4.66 mL) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 17 hours. The reaction solution was concentrated under reduced pressure. Then, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 75:25 -> 66:34) to give 401 mg of the title compound.

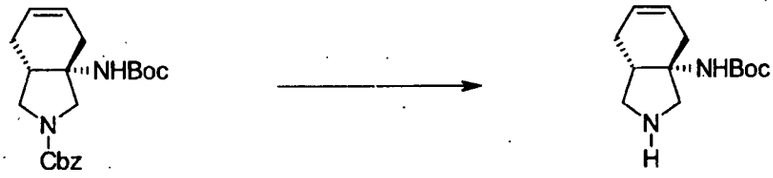
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43-7.18 (5H, m), 5.76-5.58 (2H, m), 5.19-5.09 (2H, m), 4.54-4.32 (2H, m), 3.70 (1H, dd, J=18.02, 7.97 Hz), 3.17-2.97 (3H, m), 2.39-1.47 (4H, m), 1.41 (9H, s).

MS (ESI); m/z: 395 $(M+Na)^+$.

[Reference Example 146]

(1S,6S)-1-tert-Butoxycarbonylamino-8-azabicyclo[4.3.0]non-3-ene

[Formula 248]



A solution of (1S,6S)-1-tert-butoxycarbonylamino-8-benzyloxycarbonyl-8-azabicyclo[4.3.0]non-3-ene (400 mg, 1.07 mmol) in tetrahydrofuran (5.35 mL) was bubbled with ammonia gas under cooling with dry ice-methanol for 10 minutes to add 30 to 40 mL of liquid ammonia to the solution. Sodium (128 mg, 5.34 mmol) was added, and the

mixture was stirred for 10 minutes. A saturated ammonium chloride solution (15 drops) was added at room temperature, and the mixture was stirred at room temperature to evaporate ammonia. A 1 mol/L sodium hydroxide solution (15.0 mL) was added, followed by extraction with chloroform (30 mL × 2). The aqueous layer was concentrated under reduced pressure. A 1 mol/L sodium hydroxide solution (5.0 mL) was added, followed by extraction with the lower layer of chloroform/methanol/water = 7/3/1 (35 mL × 2). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the filtrate was concentrated under reduced pressure to give 136 mg of the title compound as a white amorphous.

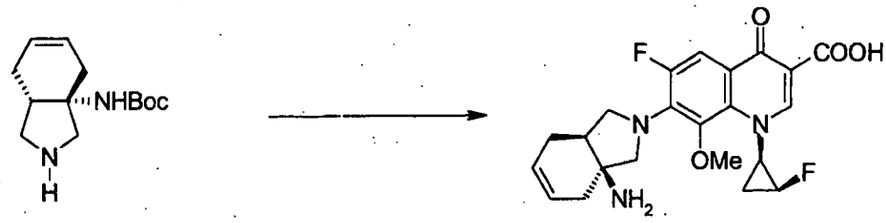
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.74-5.63 (2H, m), 4.44-4.36 (1H, m), 3.12 (1H, dd, J=9.93, 7.72 Hz), 3.02-2.88 (2H, m), 2.72 (1H, t, J=10.79 Hz), 2.60 (2H, d, J=11.52 Hz), 2.30 (1H, t, J=11.52 Hz), 2.18-1.82 (4H, m), 1.39 (9H, s).

MS (ESI); m/z: 239 $(M+H)^+$.

[Example 35]

7-[(1S,6S)-1-Amino-8-azabicyclo[4.3.0]non-3-en-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 249]



Triethylamine (0.217 mL, 1.55 mmol) and 1-[(1R,2S)-2-fluorocyclopropan-1-yl]-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (187 mg, 0.518 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-8-azabicyclo[4.3.0]non-3-ene (136 mg, 0.571 mmol) in dimethyl sulfoxide (2.04 mL), and the mixture was stirred at 35°C for 16 hours. A mixed solution of ethanol:water = 4:1 (10 mL) and triethylamine (1 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with a 10% citric acid solution (30 mL), water (30 mL), and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). 242 mg of the resulting residue was dissolved in concentrated hydrochloric acid (2.0 mL) under ice-cooling, and the solution was stirred at room temperature for 10 minutes.

After washing with chloroform (25 mL × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform/methanol = 10/1 (150 mL × 1, 75 mL × 1, 50 mL × 1). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot 2-propanol (40 ml), and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. The solution was concentrated to 10 ml and then stirred at room temperature overnight. The precipitated crystals were collected by filtration, washed with 2-propanol and diethyl ether, and then dried under reduced pressure to give 129 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.36 (1H, d, J=3.68 Hz), 7.66 (1H, d, J=14.46 Hz), 5.88-5.72 (2H, m), 5.15-4.94 (1H, m), 4.05-3.98 (1H, m), 3.80-3.61 (3H, m), 3.57 (3H, s), 3.45 (1H, d, J=9.31 Hz), 2.48-1.97 (5H, m), 1.55-1.48 (1H, m), 1.45-1.29 (1H, m).

Anal; Calcd for $C_{22}H_{23}F_2N_3O_4 \cdot 0.5H_2O \cdot iPrOH$: C, 59.99; H, 6.44; F, 7.59; N, 8.39. Found: C, 59.95; H, 6.30; F, 7.61; N, 8.25.

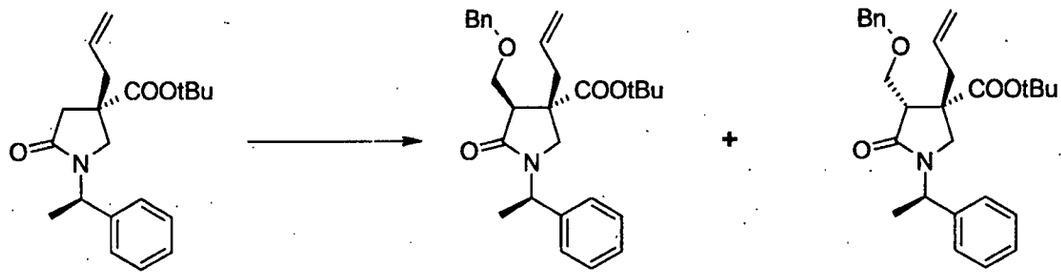
MS (ESI); m/z: 432 $(M+H)^+$.

IR (ATR) ν: 2962, 1725, 1612, 1450, 1436, 1386, 1351, 1309, 1035, 819 cm^{-1}.

[Reference Example 147]

(3S,4R)-3-Allyl-4-benzyloxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester; (3S,4S)-3-Allyl-4-benzyloxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 250]



Allyl bromide (11.0 ml, 79.1 mmol) was added to a solution of (3S)-3-allyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (20.0 g, 60.7 mmol) in tetrahydrofuran (303 mL) with stirring under salt ice cooling. A 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (78.9 mL, 78.9 mmol) was added dropwise with stirring under salt ice cooling, and the mixture was stirred under ice-cooling for 10 minutes. A saturated ammonium chloride solution (300 mL) was added to the reaction solution, followed by extraction with ethyl acetate (200 mL). The organic layer was washed with brine (600 mL) and dried over anhydrous sodium sulfate.

After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 84:16 -> 75:25 -> 66:34) to give 9.81 g of the title compound (3S,4R)-isomer and 6.76 g of the title compound (3R,4S)-isomer.

(3S,4R)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.21 (10H, m), 5.75-5.59 (1H, m), 5.51-5.41 (1H, m), 5.17-5.08 (1H, m), 5.06-4.97 (1H, m), 4.71 (1H, s), 4.50 (1H, dd, J=22.31, 11.77 Hz), 3.97-3.95 (1H, m), 3.85-3.83 (1H, m), 3.35-3.04 (2H, m), 2.64-2.61 (1H, m), 2.45-2.37 (1H, m), 1.49 (1H, dd, J=7.11, 4.66 Hz), 1.42 (3H, d, J=7.35 Hz), 1.28 (9.H, s).

MS (ESI); m/z: 450 $(M+H)^+$.

(3R,4S)-isomer:

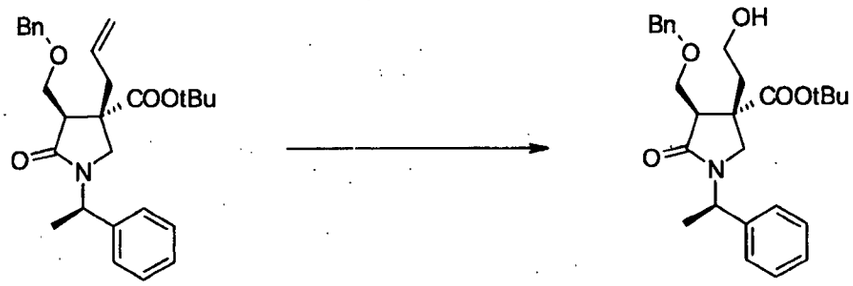
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27-6.96 (10H, m), 5.76-5.65 (1H, m), 5.52 (1H, q, J=7.03 Hz), 5.17-5.12 (2H, m), 4.42-4.35 (2H, m), 3.50 (1H, d, J=10.05 Hz), 3.04 (1H, d, J=10.05 Hz), 2.52 (1H, dd, J=13.73, 6.37 Hz), 2.45 (1H, t, J=2.82 Hz), 2.36 (1H, dd, J=13.73, 8.09 Hz), 1.51 (3H, d, J=7.11 Hz), 1.38 (9H, s).

MS (ESI); m/z: 450 $(M+H)^+$.

[Reference Example 148]

(3S,4R)-4-Benzyloxymethyl-3-hydroxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 251]



A solution of (3S,4R)-3-allyl-4-benzyloxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (8.00 g, 17.8 mmol) in methanol (177 mL) was bubbled with oxygen for 10 minutes. After bubbling with ozone for 30 minutes with stirring under cooling with dry ice-methanol, ozone was removed by bubbling with nitrogen. Sodium borohydride (1.68 g, 44.4 mmol) was added under cooling with ice-acetone, and the mixture was stirred under cooling for 1.5 hours. A saturated ammonium chloride solution (150 mL) was added to the reaction solution, and methanol was evaporated by concentration under reduced pressure. The mixture was extracted with ethyl acetate (200 mL x 1, 150 mL x 1). The organic layer was washed with brine (300 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 50:50) to give 3.79 g of the title compound as a pale yellow oil.

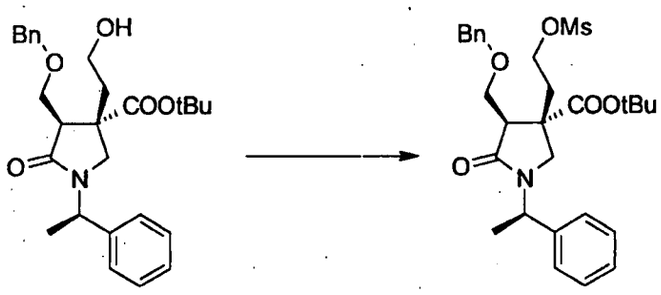
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.22 (5H, m), 5.46 (1H, q, J=7.03 Hz), 4.50 (2H, dd, J=17.28, 11.64 Hz), 3.97 (1H, dd, J=9.80, 4.41 Hz), 3.84 (1H, dd, J=9.80, 2.45 Hz), 3.60 (2H, t, J=6.37 Hz), 3.42 (1H, d, J=9.31 Hz), 3.26 (1H, d, J=9.31 Hz), 3.10 (1H, dd, J=4.41, 2.45 Hz), 2.11 (1H, dt, J=15.52, 5.58 Hz), 1.99-1.93 (1H, m), 1.41 (3H, d, J=7.35 Hz), 1.28 (9H, s).

MS (ESI); m/z: 454 $(M+H)^+$.

[Reference Example 149]

(3S,4R)-3-Benzyloxymethyl-3-methanesulfonyloxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 252]



Triethylamine (2.79 mL, 19.9 mmol) was added to a solution of (3S,4R)-4-benzyloxymethyl-3-hydroxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.57 g, 10.0 mmol) in dichloromethane (50.0 mL) in a nitrogen atmosphere. Methanesulfonyl chloride (1.17 mL, 15.1 mmol) was added under cooling with ice-acetone, and the mixture was stirred at room temperature

for 15 minutes. Water (150 mL) was added to the reaction solution, followed by extraction with chloroform (150 mL × 1, 80 mL × 1). The organic layer was washed with brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 7.09 g of a residue containing the title compound, which was directly used for the next step without further purification.

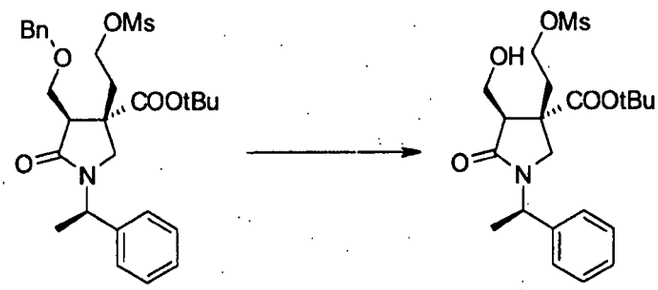
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (10H, m), 5.45 (1H, q, J=7.11 Hz), 4.50 (2H, dd, J=17.16, 11.52 Hz), 4.23-4.20 (1H, m), 4.14-4.11 (1H, m), 3.99 (1H, dd, J=9.93, 4.29 Hz), 3.81 (1H, dd, J=9.93, 2.57 Hz), 3.37 (1H, d, J=9.56 Hz), 3.25 (1H, d, J=9.56 Hz), 3.08 (1H, dd, J=4.41, 2.45 Hz), 2.90 (3H, s), 2.33-2.26 (1H, m), 2.21-2.17 (1H, m), 1.42 (3H, d, J=7.11 Hz), 1.28 (9H, s).

MS (ESI); m/z: 532 $(M+H)^+$.

[Reference Example 150]

(3S,4R)-4-Hydroxymethyl-3-methanesulfonyloxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 253]



A 20% palladium hydroxide-carbon catalyst (7.09 g, 100 wt%) was added to a solution of (3S,4R)-3-benzyloxymethyl-3-methanesulfonyloxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (7.09 g) in ethanol (100 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at room temperature for one hour and at 50°C for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite, concentrated under reduced pressure, and dried under reduced pressure to give 4.49 g of a residue containing the title compound, which was directly used for the next step without further purification.

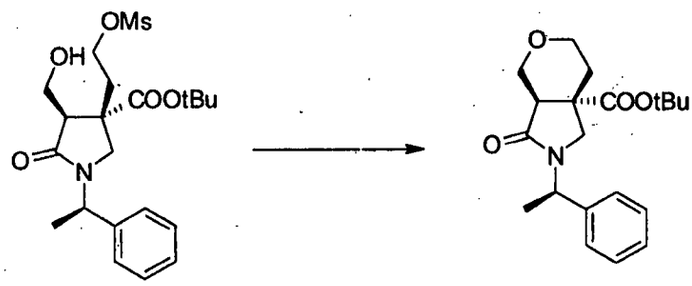
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.30-4.19 (2H, m), 4.11-3.96 (2H, m), 3.34 (2H, dd, J=26.72, 10.54 Hz), 2.99 (3H, s), 2.98-2.95 (1H, m), 2.31-2.24 (1H, m), 2.17-2.10 (1H, m), 1.56 (3H, d, J=7.11 Hz), 1.37 (9H, s).

MS (ESI); m/z: 442 $(M+H)^+$.

[Reference Example 151]

(1S,6R)-{4-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester

[Formula 254]



A solution of (3S,4R)-4-hydroxymethyl-3-methanesulfonyloxyethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.49 g) in pyridine (100 mL) was stirred in a nitrogen atmosphere at 50°C for 15 hours. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 50:50 -> 10:90) to give 1.75 g of the title compound as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.23 (5H, m), 5.58 (1H, q, J=7.11 Hz), 4.38 (1H, d, J=11.77 Hz), 3.83-3.79 (1H, m), 3.71 (1H, dd, J=12.01, 3.92 Hz), 3.42 (1H, td, J=12.01, 2.21 Hz), 3.04 (1H, d, J=10.05 Hz), 2.96 (1H, d, J=9.80 Hz), 2.62 (1H, d, J=3.43 Hz), 1.97 (1H, d, J=14.22 Hz), 1.75 (1H,

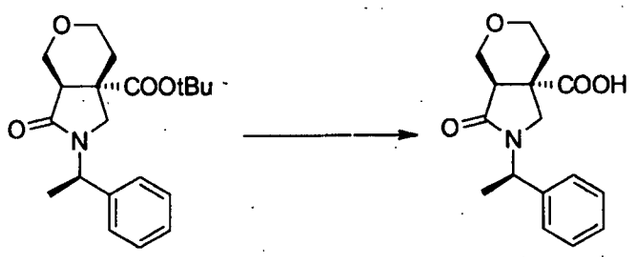
ddd, J=15.44, 10.79, 3.19 Hz), 1.54 (3H, d, J=7.11 Hz), 1.44 (9H, s).

MS (ESI); m/z: 346 $(M+H)^+$.

[Reference Example 152]

(1S,6R)-{4-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid

[Formula 255]



Trifluoroacetic acid (6.63 mL) was added to a solution of (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester (763 mg, 2.21 mmol) in dichloromethane (6.63 mL) with stirring under ice-cooling, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (three times). A 1 mol/L sodium hydroxide solution (20 mL) was added to the resulting residue under ice-cooling, and the mixture was washed with diethyl ether (50 mL × 2). The aqueous layer was made acidic with 1 mol/L hydrochloric acid (20 mL) under ice-cooling, followed by extraction with

ethyl acetate (60 mL × 1, 50 mL × 1). The organic layers were combined, washed with brine (90 mL), and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 637 mg of the title compound as white crystals.

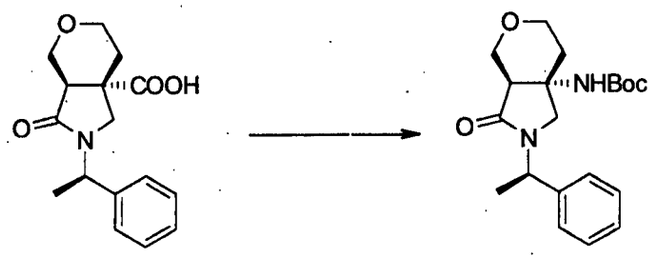
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43-7.24 (5H, m), 5.58 (1H, q, J=7.11 Hz), 4.41 (1H, d, J=12.26 Hz), 3.83 (1H, dd, J=12.13, 2.82 Hz), 3.70 (1H, dd, J=12.01, 3.68 Hz), 3.44 (1H, td, J=12.13, 1.88 Hz), 3.11 (1H, d, J=10.05 Hz), 3.02 (1H, d, J=10.05 Hz), 2.69 (1H, d, J=3.43 Hz), 2.09-2.05 (1H, m), 1.84-1.76 (1H, m), 1.55 (3H, d, J=7.11 Hz).

MS (ESI); m/z: 290 $(M+H)^+$.

[Reference Example 153]

(1S,6R)-1-tert-Butoxycarbonylamino-4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane

[Formula 256]



Triethylamine (0.720 mL, 5.16 mmol) and diphenylphosphoryl azide (0.723 mL, 3.35 mmol) were added to a solution of (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid

(747 mg, 2.58 mmol) in toluene (12.9 mL) in a nitrogen atmosphere with stirring under ice-cooling. The mixture was stirred at room temperature for 30 minutes and then at 100°C for 30 minutes. The reaction solution was concentrated under reduced pressure, and triethylamine was azeotropically distilled with toluene (× 3). 1,4-Dioxane (6.45 mL) and 6 mol/L hydrochloric acid (6.45 mL) were added to the resulting residue, and the mixture was stirred at 50°C for one hour. The reaction solution was diluted with water (15 mL) and washed with ethyl acetate (50 mL × 2). The aqueous layer was made alkaline with a 1 mol/L sodium hydroxide solution under ice-cooling, followed by extraction with chloroform (50 mL × 2). The organic layer was washed with brine (80 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Dichloromethane (14.9 mL) was added to the resulting residue, di-tert-butyl dicarbonate (813 mg, 3.73 mmol) was added in a nitrogen atmosphere, and the mixture was stirred at room temperature for four days. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 75:25 -> 60:40 -> 50:50) to give 470 mg (51%) of the title compound.

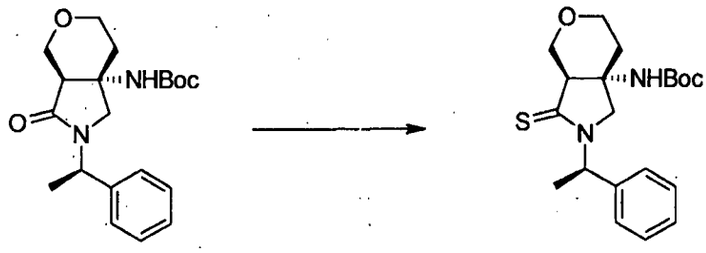
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.58 (1H, q, J=7.19 Hz), 4.81 (1H, brs), 4.31 (1H, dd, J=12.26, 1.72 Hz), 3.77 (1H, td, J=7.54, 4.09 Hz), 3.61 (1H, dd, J=12.26, 3.92 Hz), 3.48 (2H, m), 3.09 (1H, d, J=10.05 Hz), 2.39 (1H, brs), 2.16-2.05 (1H, m), 1.81 (1H, ddd, J=15.26, 10.85, 3.62 Hz), 1.53 (3H, d, J=7.11 Hz), 1.39 (9H, s).

MS (ESI); m/z: 361 $(M+H)^+$.

[Reference Example 154]

(1S,6R)-1-tert-Butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-7-thioxo-8-azabicyclo[4.3.0]nonane

[Formula 257]



Lawesson's reagent was added to a solution of (1S,6R)-1-tert-butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-7-oxo-8-azabicyclo[4.3.0]nonane (470 mg, 1.30 mmol) in tetrahydrofuran (13.0 mL), and the mixture was stirred at 60°C for 2.5 hours. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 80:20 -> 75:25 -> 66:34) to give a residue containing the title compound, which was directly used for the next step.

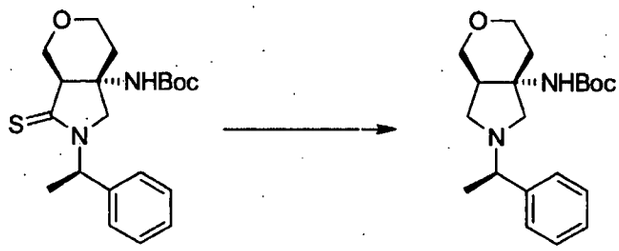
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.29 (5H, m), 6.97 (1H, dt, J=12.83, 4.60 Hz), 6.44 (1H, q, J=7.03 Hz), 4.39 (1H, d, J=9.31 Hz), 3.87-3.82 (3H, m), 3.72-3.57 (2H, m), 2.70 (1H, brs), 2.03-1.94 (1H, m), 1.90-1.79 (1H, m), 1.60 (3H, d, J=7.11 Hz), 1.36 (9H, s).

MS (ESI); m/z: 377 $(M+H)^+$.

[Reference Example 155]

(1S,6R)-1-tert-Butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane

[Formula 258]



Raney nickel (14.2 mL) was added to a solution of (1S,6R)-1-tert-Butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-7-thioxo-8-azabicyclo[4.3.0]nonane (700 mg) in ethanol (28.4 mL) in a nitrogen atmosphere. The mixture was vigorously stirred at room temperature for one hour. The reaction solution was filtered through Celite and concentrated under reduced pressure to give 423 mg of the title compound quantitatively.

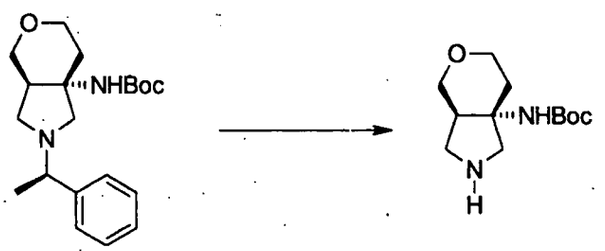
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.20 (5H, m), 4.66 (1H, brs), 3.75-3.40 (4H, m), 2.90 (2H, s), 2.78-2.69 (2H, m), 2.20-1.96 (3H, m), 1.41 (9H, s), 1.34 (3H, d, J=6.59 Hz).

MS (ESI); m/z: 347 $(M+H)^+$.

[Reference Example 156]

(1S,6S)-1-tert-Butoxycarbonylamino-4-oxabicyclo[4.3.0]nonane

[Formula 259]



A 10% palladium-carbon catalyst (205 mg) was added to a solution of (1S,6R)-1-tert-butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane (205 mg, 0.592 mmol) in ethanol (5.92 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at room temperature for 45 minutes and at 50°C for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure. A 10% palladium-carbon catalyst (205 mg) was added to a solution of the resulting residue in ethanol (5.92 mL) in a nitrogen atmosphere. After the atmosphere

was replaced with hydrogen, the mixture was stirred at 50°C for 16 hours. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure. A 20% palladium hydroxide-carbon catalyst (205 mg) was added to a solution of the resulting residue in ethanol (5.92 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at 50°C for one hour. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite, concentrated under reduced pressure, and dried under reduced pressure to give 128 mg of the title compound as a pale vermillion oil.

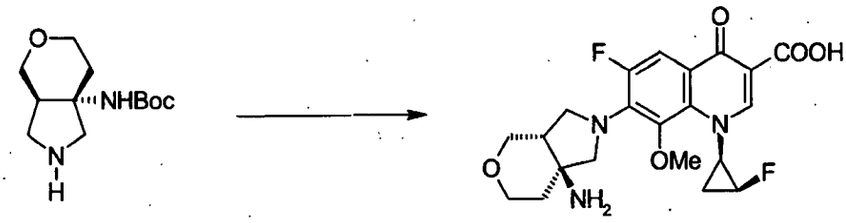
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.83 (1H, brs), 3.68-3.57 (4H, m), 3.30-3.19 (3H, m), 3.00-2.98 (1H, m), 2.14-1.96 (3H, m), 1.44 (9H, s).

MS (ESI); m/z: 243 $(M+H)^+$.

[Example 36]

7-[(1S,6R)-1-Amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 260]



Triethylamine (0.198 mL, 1.42 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (171 mg, 0.474 mmol) were added to a solution of (1S,6R)-8-aza-1-tert-butoxycarbonylamino-4-oxabicyclo[4.3.0]nonane (126 mg, 0.520 mmol) in dimethyl sulfoxide (0.948 mL), and the mixture was stirred at 35°C for 16 hours. A mixed solution of ethanol:water = 4:1 (10 mL) and triethylamine (1 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with a 10% citric acid solution (30 mL), water (30 mL), and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2).

Trifluoroacetic acid (0.694 mL, 3 v/w) was added to a solution of 125 mg of the resulting residue in dichloromethane (2.31 mL) with stirring under ice-cooling,

and the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (× 3). Hydrochloric acid at pH 1 (20.0 mL) was added to the resulting residue under ice-cooling, and the mixture was washed with diethyl ether (40 mL × 4). The aqueous layer was adjusted to pH 12 with a 1 mol/L sodium hydroxide solution under ice-cooling. The basic solution was adjusted to pH 7.4 with 1 mol/L hydrochloric acid, followed by extraction with chloroform (100 mL × 2) and chloroform/methanol = 10/1 (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in hot ethanol (10 mL), and the insoluble material was removed by filtration. The solvent was gradually evaporated while heating with stirring. The residue was concentrated until ethanol was 3 to 4 ml, and then stirred at room temperature overnight. The precipitated crystals were collected by filtration, washed with ethanol and diethyl ether, and then dried under reduced pressure at 60°C to give 20.5 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.45 (1H, s), 7.68 (1H, d, J=14.71 Hz), 5.08-4.92 (1H, m), 4.07 (1H, dd, J=13.73, 6.13 Hz), 3.92 (1H, dd, J=12.50, 3.68 Hz), 3.83 (4H, dd, J=13.85,

8.95 Hz), 3.73-3.58 (6H, m), 2.20-2.13 (1H, m), 2.06-1.99 (1H, m), 1.68-1.49 (3H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_5 \cdot 0.75H_2O$: C, 56.18; H, 5.50; N, 9.36. Found: C, 56.15; H, 5.46; N, 9.65.

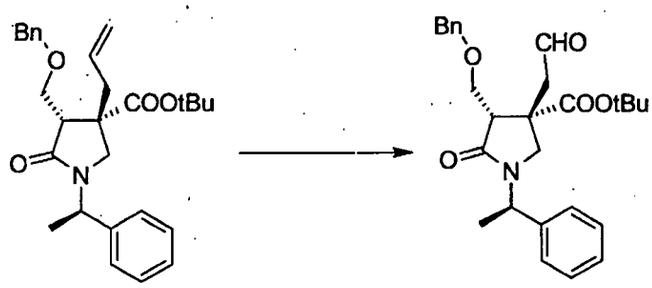
MS (ESI); m/z: 436 $(M+H)^+$.

IR (ATR) ν: 2937, 2892, 2856, 1724, 1625, 1515, 1454, 1324, 1137, 1099, 1054, 985, 927, 887, 802 cm^{-1}.

[Reference Example 157]

(3S,4S)-4-Benzyloxymethyl-5-oxo-3-(2-oxoethyl)-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 261]



A solution of (3S,4S)-3-allyl-4-benzyloxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (6.76 g, 15.0 mmol) in methanol (150 mL) was bubbled with oxygen for five minutes. After bubbling with ozone for 1.5 hours with stirring under cooling with dry ice-methanol, ozone was removed by bubbling with nitrogen. Dimethyl sulfide (5.64 mL, 76.8 mmol) was added under cooling, and the mixture was stirred for 19 hours. The reaction solution was concentrated under reduced pressure.

The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 75:25 -> 66:34 -> 50:50) to give 4.58 g of the title compound as a transparent oil.

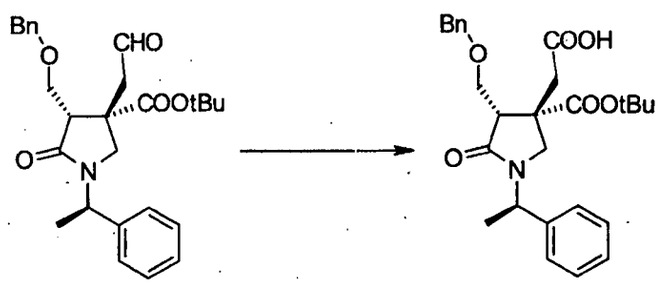
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.74 (1H, s), 7.37-7.15 (5H, m), 5.47 (1H, q, J=7.19 Hz), 4.42 (2H, s), 3.92 (1H, dd, J=9.80, 3.68 Hz), 3.81 (1H, dd, J=9.56, 6.62 Hz), 3.68 (1H, d, J=10.54 Hz), 3.21 (1H, t, J=8.58 Hz), 3.13 (1H, d, J=10.54 Hz), 2.70 (1H, dd, J=6.37, 3.68 Hz), 2.61 (1H, d, J=17.16 Hz), 1.50 (3H, d, J=7.11 Hz), 1.27 (9H, s).

MS (ESI); m/z: 452 $(M+H)^+$.

[Reference Example 158]

(3S,4S)-4-Benzyloxymethyl-3-carboxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 262]



2-Methyl-2-butene was added to a solution of (3S,4S)-4-benzyloxymethyl-5-oxo-3-(2-oxoethyl)-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.58 g, 10.1 mmol) in tert-butyl alcohol (25.2 mL) under ice-cooling, and the mixture was stirred. Sodium chlorite

(2.29 g, 25.3 mmol) was added to a solution of sodium dihydrogenphosphate dihydrate (4.10 g, 26.3 mmol) in water (20.2 mL) to separately prepare a solution. This solution was added to the above solution under ice-cooling, and the mixture was stirred at room temperature for one hour. The precipitated solid was collected by filtration, washed with water and hexane, and then dried under reduced pressure at 40°C to give 3.93 g of the title compound as white powder crystals.

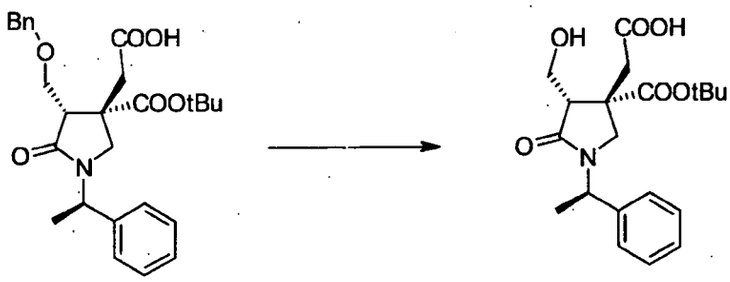
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.14 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.42 (2H, s), 3.90 (1H, dd, J=9.68, 3.55 Hz), 3.82 (1H, dd, J=9.56, 6.13 Hz), 3.69 (1H, d, J=10.54 Hz), 3.27 (1H, d, J=10.79 Hz), 3.10 (1H, d, J=16.18 Hz), 2.70 (1H, dd, J=6.13, 3.68 Hz), 2.58 (1H, d, J=16.18 Hz), 1.79 (1H, brs), 1.52 (3H, d, J=7.11 Hz), 1.29 (9H, s).

MS (ESI); m/z: 468 $(M+H)^+$.

[Reference Example 159]

(3S,4S)-3-Carboxymethyl-4-hydroxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 263]



A 10% palladium-carbon catalyst (3.93 g) was added to a solution of (3S,4S)-4-benzyloxymethyl-3-carboxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (3.93 g, 8.41 mmol) in methanol (84.0 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at room temperature for three days. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite and concentrated under reduced pressure to give 2.54 g of the title compound.

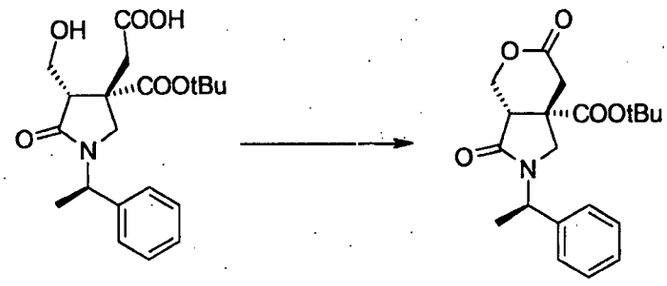
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.27 (5H, m), 5.44 (1H, q, J=7.11 Hz), 3.88 (1H, dd, J=11.28, 7.60 Hz), 3.80 (1H, dd, J=11.28, 5.39 Hz), 3.69 (1H, d, J=10.79 Hz), 3.26 (1H, d, J=10.79 Hz), 3.05 (1H, d, J=16.91 Hz), 2.68 (1H, dd, J=7.35, 5.39 Hz), 2.59 (1H, d, J=16.91 Hz), 1.53 (3H, d, J=7.11 Hz), 1.28 (9H, s).

MS (ESI); m/z: 378 $(M+H)^+$.

[Reference Example 160]

{(1S,6S)-4-Oxa-3,7-dioxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester

[Formula 264]



Triethylamine (1.32 mL, 9.46 mmol) and 2,4,6-trichlorobenzoyl chloride (1.16 mL, 7.45 mmol) were added to a solution of (3S,4S)-3-carboxymethyl-4-hydroxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.54 g, 6.73 mmol) in tetrahydrofuran (44.8 mL) in a nitrogen atmosphere. After stirring at room temperature for 30 minutes, and then toluene (179 mL) and 4-dimethylamino pyridine (1.23 g, 10.1 mmol) were added. After stirring at room temperature for 18 hours, the reaction solution was diluted with ethyl acetate (100 ml) and washed with 1 mol/L hydrochloric acid (150 mL), water (150 mL), a saturated sodium bicarbonate solution (150 mL), water (150 mL), and brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 66:34 -> 50:50 -> 34:66 -> 25:75) to give 2.06 g of the title compound.

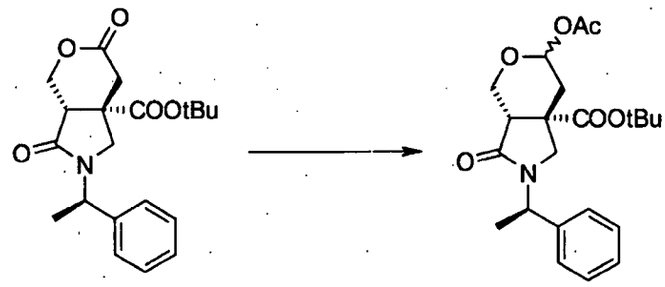
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.43 (1H, q, J=7.19 Hz), 4.76-4.72 (2H, m), 3.34-3.20 (3H, m), 2.90 (1H, dd, J=10.42, 7.97 Hz), 2.56 (1H, d, J=16.91 Hz), 1.52 (3H, d, J=7.35 Hz), 1.24 (9H, s).

MS (ESI); m/z: 360 $(M+H)^+$.

[Reference Example 161]

{(1S,6S)-3-Acetoxy-4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester

[Formula 265]



A 0.97 mol/L solution of diisobutylaluminum hydride in hexane (1.65 mL, 1.60 mmol) was added to a solution of {(1S,6S)-4-oxa-3,7-dioxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester (500 mg, 1.39 mmol) in dichloromethane (6.95 mL) with stirring under cooling with dry ice-methanol. After stirring under cooling for one hour, a 0.97 mol/L solution of diisobutylaluminum hydride in hexane (0.716 mL, 0.695 mmol) was added. After stirring under cooling for two hours, a solution of pyridine (0.338 mL, 4.18 mmol) and 4-

dimethylaminopyridine (204 mg, 1.67 mmol) in dichloromethane (3.5 mL) and a solution of acetic anhydride (0.526 mL, 5.56 mmol) in dichloromethane (1.8 mL) were added. The mixture was stirred under cooling for one hour and then ice-cooled, and a saturated tetraammonium chloride solution (20 mL) was added. After stirring under ice-cooling for 30 minutes, the reaction solution was extracted with ethyl acetate (50 mL × 1, 40 mL × 1). The organic layer was washed with 10% citric acid (60 mL), water (60 mL), a saturated sodium bicarbonate solution (60 mL), and brine (60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 60:40 -> 50:50) to give 350 mg of the title compound as a white solid.

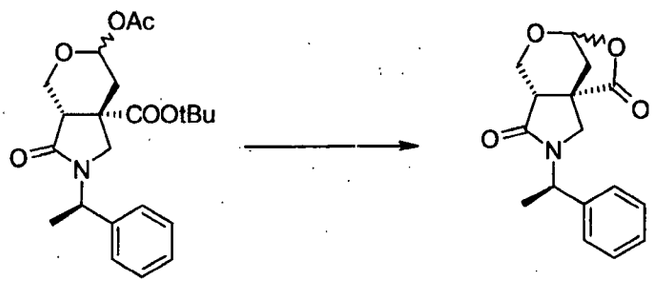
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.23 (5H, m), 5.74 (1H, dd, J=7.35, 4.17 Hz), 5.45 (1H, dd, J=20.84, 10.42 Hz), 4.29-4.14 (2H, m), 2.70-2.60 (2H, m), 2.09 (3H, s), 1.67 (1H, dd, J=12.62, 7.23 Hz), 1.48 (3H, d, J=7.11 Hz), 1.23 (9H, s).

MS (ESI); m/z: 404 $(M+H)^+$.

[Reference Example 162]

(1S,5S)-3-Aza-4,10-dioxo-3-[(1R)-1-phenylethyl]-7,9-dioxatricyclo[6.2.1.$0^{1,5}$]undecane

[Formula 266]



A solution of {(1S,6S)-3-acetoxy-7-oxa-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid tert-butyl ester (663 mg, 1.64 mmol) in acetonitrile (8.20 mL) was cooled with ice-acetone. Triethylsilane (0.787 ml, 4.93 mmol) and trimethylsilyl triflate (0.595 mL, 3.29 mmol) were added in a nitrogen atmosphere, and the mixture was stirred under cooling for 15 minutes. A saturated sodium bicarbonate solution (50 mL) was added to the reaction solution, followed by extraction with ethyl acetate (100 mL × 1, 60 mL × 1). The organic layer was washed with water (50 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 75:25 -> 66:34 -> 50:50 -> 34:66) to give 413 mg of the title compound as a transparent oil.

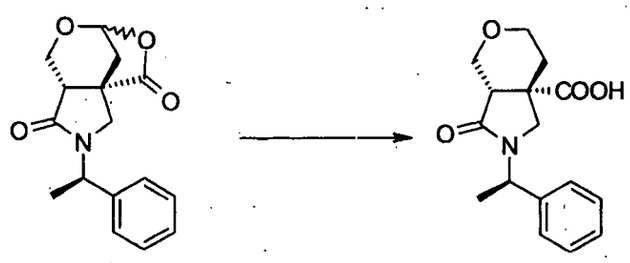
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.17 (5H, m), 5.45 (1H, q, J=7.03 Hz), 4.25 (1H, dd, J=11.28, 4.17 Hz), 4.18-4.10 (1H,

m), 3.97-3.92 (2H, m), 3.31-3.25 (2H, m), 2.61 (1H, dd, J=10.66, 4.29 Hz), 2.19 (1H, d, J=13.24 Hz), 1.80 (1H, td, J=12.62, 4.66 Hz), 1.48 (3H, d, J=7.11 Hz).

[Reference Example 163]

{(1S,6S)-4-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl}carboxylic acid

[Formula 267]



A solution of (1S,5S)-3-aza-4,10-dioxo-3-[(1R)-1-phenylethyl]-7,9-dioxatricyclo[6.2.1.$0^{1,5}$]undecane (413 mg, 1.44 mmol) in dichloromethane (7.20 mL) was cooled with dry ice-methanol. Triethylsilane (0.690 mL, 4.32 mmol) and a 1.0 mol/L solution of tetrachlorotitanium in dichloromethane (2.88 mL, 2.88 mmol) were added in a nitrogen atmosphere, and the mixture was stirred under cooling for 30 minutes. A saturated sodium bicarbonate solution (50 mL) was added to the reaction solution, and the mixture was washed with ethyl acetate (100 mL × 2). The aqueous layer was made acidic with 6 mol/L hydrochloric acid and 1 mol/L hydrochloric acid, followed by extraction with chloroform (100 mL × 1, 60 mL × 1). The organic layer

was washed with water (100 mL) and brine (150 mL), and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure and dried under reduced pressure to give 235 mg of the title compound as white crystals.

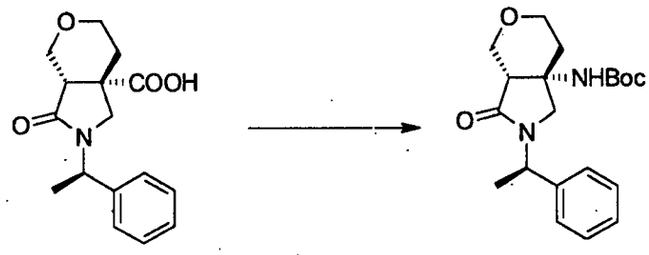
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.23 (5H, m), 5.46 (1H, d, J=7.35 Hz), 4.26 (1H, dd, J=11.03, 4.41 Hz), 3.97-3.91 (2H, m), 3.33-3.24 (3H, m), 2.60 (1H, dd, J=10.66, 4.29 Hz), 2.19 (1H, d, J=12.50 Hz), 1.85-1.67 (2H, m), 1.49 (3H, d, J=7.11 Hz).

MS (ESI); m/z: 290 $(M+H)^+$.

[Reference Example 164]

(1S,6S)-1-tert-Butoxycarbonylamino-4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane

[Formula 268]



Triethylamine (0.330 mL, 2.36 mmol) and diphenylphosphoryl azide (0.330 mL, 1.53 mmol) were added to a solution of [(1S,6S)-4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonan-1-yl]carboxylic acid (340 mg, 1.18 mmol) in toluene (5.90 mL) in a nitrogen

atmosphere with stirring under ice-cooling. The mixture was stirred at room temperature for 30 minutes and then at 100°C for one hour. The reaction solution was concentrated under reduced pressure, and triethylamine was azeotropically distilled with toluene (× 3). 1,4-Dioxane (2.95 mL) and 6 mol/L hydrochloric acid (2.95 mL) were added to the resulting residue, and the mixture was stirred at 50°C for one hour. The reaction solution was diluted with water (9.0 mL) and washed with diethyl ether (40 mL × 2). The aqueous layer was made alkaline with a 1 mol/L sodium hydroxide solution under ice-cooling, followed by extraction with chloroform (80 mL × 1, 60 mL × 1). The organic layer was washed with water (80 mL) and brine (80 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Dichloromethane (5.90 mL) was added to the resulting residue, and di-tert-butyl dicarbonate (773 mg, 3.54 mmol) was added in a nitrogen atmosphere. The mixture was stirred at room temperature for 14 hours and at 50°C for seven hours, di-tert-butyl dicarbonate (515 mg, 2.36 mmol) was added. After stirring at 50°C for 17 hours, the reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 80:20 -> 66:34 -> 60:40) to give 320 mg of the title compound.

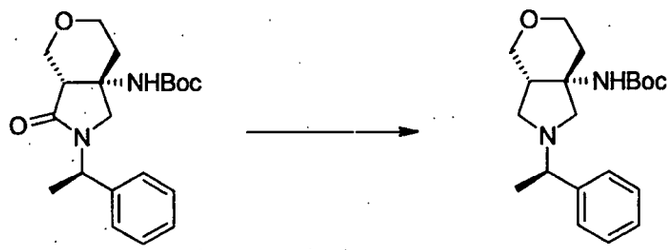
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.44 (1H, q, J=6.95 Hz), 4.53 (1H, brs), 4.16-4.11 (1H, m), 3.81 (1H, dd, J=12.13, 3.80 Hz), 3.62 (3H, tt, J=14.83, 6.37 Hz), 3.15 (1H, d, J=10.30 Hz), 2.69 (1H, dd, J=11.52, 4.41 Hz), 1.71 (1H, td, J=12.68, 4.98 Hz), 1.49 (3H, d, J=7.11 Hz), 1.26 (9H, s).

MS (ESI); m/z: 361 $(M+H)^+$.

[Reference Example 165]

(1S,6S)-1-tert-Butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane

[Formula 269]



A solution of (1S,6S)-1-tert-butoxycarbonylamino-4-oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane (331 mg, 0.918 mmol) in tetrahydrofuran (3.0 mL) was cooled with ice-acetone. A 1.2 mol/L solution of borane in tetrahydrofuran (3.83 mL, 4.59 mmol) was added in a nitrogen atmosphere, and the mixture was stirred at room temperature for 19 hours. After cooling with ice-acetone again, a 1.2 mol/L solution of borane in tetrahydrofuran (3.83 mL, 4.59 mmol) was added in a nitrogen atmosphere, and the mixture was stirred at room temperature for one

hour. The reaction solution was concentrated under reduced pressure. Then, a mixed solution of ethanol:water = 4:1 (10 mL) and triethylamine (1 mL) were added, and the mixture was heated to reflux for 1.5 hours. The reaction solution was concentrated under reduced pressure and a saturated sodium bicarbonate solution (50 mL) was added to the residue, followed by extraction with chloroform (50 mL × 1, 40 mL × 1). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> -> 90:10 -> 60:40 -> 50:50 -> 34:66 -> 25:75 -> 16:84 -> 10:90 -> 5:95 -> 2:98 -> 0:100) to give 255 mg of the title compound.

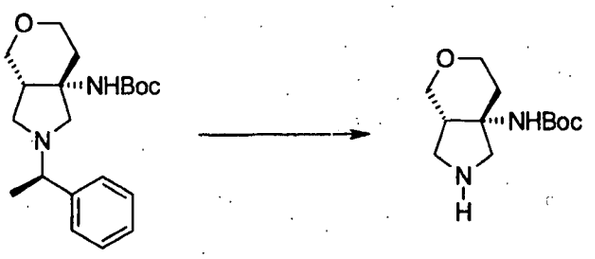
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31-7.21 (5H, m), 4.35 (1H, s), 3.81 (2H, ddd, J=22.43, 11.64, 4.04 Hz), 3.62 (2H, td, J=11.95, 2.37 Hz), 3.49 (1H, t, J=11.52 Hz), 3.37 (1H, d, J=10.05 Hz), 2.91 (1H, t, J=8.33 Hz), 2.55-2.42 (2H, m), 2.17 (1H, t, J=5.88 Hz), 1.56-1.50 (1H, m), 1.47 (9H, s), 1.32 (3H, d, J=6.37 Hz).

MS (ESI); m/z: 347 $(M+H)^+$.

[Reference Example 166]

(1S,6S)-1-tert-Butoxycarbonylamino-4-oxa-8-bicyclo[4.3.0]nonane

[Formula 270]



A 20% palladium hydroxide-carbon catalyst (262 mg) was added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-4-oxa-8-[(1R)-1-phenylethyl]-8-azabicyclo[4.3.0]nonane (262 mg, 0.756 mmol) in ethanol (7.56 mL) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred in a hydrogen atmosphere at 45°C for 2.5 hours. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite, concentrated under reduced pressure, and dried under reduced pressure to give 183 mg of the title compound.

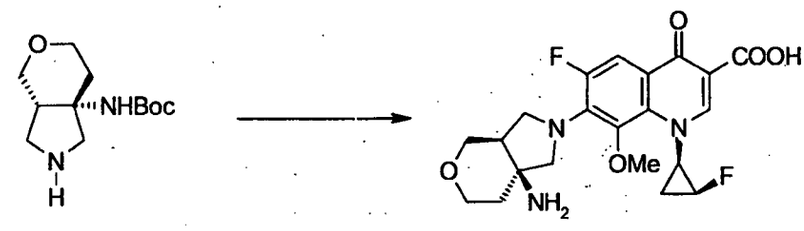
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.33 (1H, brs), 3.95 (1H, dd, J=11.64, 4.29 Hz), 3.84 (1H, dd, J=12.50, 4.66 Hz), 3.72 (1H, q, J=7.03 Hz), 3.62-3.55 (2H, m), 3.49 (1H, t, J=11.64 Hz), 3.06 (1H, dd, J=9.93, 7.97 Hz), 2.68-2.57 (3H, m), 2.13-2.04 (1H, m), 1.57 (1H, td, J=12.93, 4.74 Hz), 1.45 (9H, s).

MS (ESI); m/z: 243 $(M+H)^+$.

[Example 37]

7-[(1S,6S)-1-Amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 271]



Triethylamine (0.165 mL, 1.18 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (142 mg, 0.393 mmol) were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-4-oxa-8-bicyclo[4.3.0]nonane (142 mg, 0.421 mmol) in dimethyl sulfoxide (0.787 mL), and the mixture was stirred at room temperature for 14 hours. A mixed solution of ethanol:water = 4:1 (10 mL) and triethylamine (1 mL) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with a 10% citric acid solution (30 mL), water (30 mL), and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). Trifluoroacetic acid (0.975 mL, 3 v/w) was added to a solution of 174 mg of the resulting residue in dichloromethane (3.25 mL) with stirring under ice-cooling, and the mixture was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (× 3). 1N hydrochloric acid (25.0 mL) was added to the resulting residue under ice-cooling, and the mixture was washed with diethyl ether (50 mL × 5). The aqueous layer was adjusted to pH 12 with a 1 mol/L sodium hydroxide solution under ice-cooling. The basic solution was adjusted to pH 7.4 with 1 mol/L hydrochloric acid, followed by extraction with chloroform (100 mL × 2, 50 mL × 2). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform/methanol = 10/1, and the insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure and dissolved in hot ethanol. The solvent was gradually evaporated while heating with stirring. Then, the solution was concentrated until ethanol was about 10 ml, and stirred at room temperature for three hours. The precipitated crystals were collected by filtration and then washed with ethanol and diethyl

ether. The crystals were dried under reduced pressure at 50°C overnight to give 55.3 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.36 (1H, d, J=3.68 Hz), 7.67 (1H, d, J=14.46 Hz), 5.15-4.96 (1H, m), 4.00 (3H, ddd, J=20.71, 11.03, 4.53 Hz), 3.84-3.63 (4H, m), 3.58 (3H, s), 3.53 (1H, t, J=8.58 Hz), 3.39 (1H, d, J=9.31 Hz), 2.32-2.20 (1H, m), 1.99-1.85 (2H, m), 1.58-1.43 (1H, m), 1.43-1.27 (1H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_5 \cdot 0.25H_2O$: C, 57.33; H, 5.38; N, 9.55. Found: C, 57.55; H, 5.40; N, 9.47.

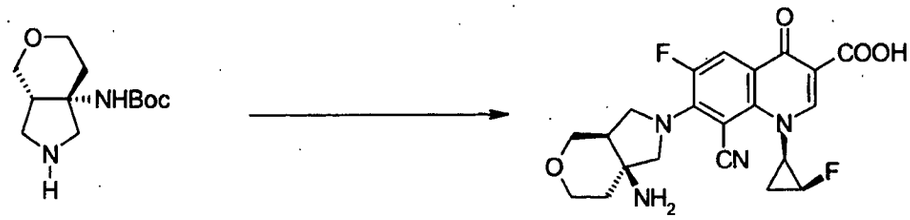
MS (ESI); m/z: 436 $(M+H)^+$.

IR (ATR) ν: 3052, 2927, 2869, 1727, 1614, 1594, 1508, 1446, 1428, 1363, 1322, 1110, 1078, 1043, 989, 948, 910, 809 cm^{-1}.

[Example 38]

7-[(1S,6S)-1-amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 272]



Triethylamine (0.263 mL, 1.88 mmol) and ethyl 8-cyano-6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylate (211 mg, 0.627 mmol)

were added to a solution of (1S,6S)-1-tert-butoxycarbonylamino-4-oxa-8-azabicyclo[4.3.0]nonane (151 mg, 0.628 mmol) in acetonitrile (1.25 mL) in a nitrogen atmosphere. The mixture was stirred at room temperature for 18 hours. The reaction solution was concentrated under reduced pressure. Then, the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 60:40 -> 50:50 -> 34:66 -> 25:75 -> 16:84). A 1 mol/L sodium hydroxide solution (1.94 mL) was added to a solution of the resulting residue in ethanol (2.42 mL) under ice-cooling, and the mixture was stirred at room temperature for one hour. A 10% citric acid solution (30 mL) was added to the reaction solution, followed by extraction with ethyl acetate (40 mL × 1, 30 mL × 1). The organic layer was washed with brine (45 mL) and then dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2).

Trifluoroacetic acid (1.38 ml, 3 v/w) was added to a solution of 243 mg of the resulting residue in dichloromethane (4.58 mL) with stirring under ice-cooling, and the mixture was stirred at room temperature for 2.5 hours. The reaction solution was concentrated under reduced pressure. Then, hydrochloric acid at pH 1 was added to the

resulting residue under ice-cooling, and the mixture was washed with chloroform (40 mL × 3). The aqueous layer was adjusted to pH 12 with a 1 mol/L sodium hydroxide solution under ice-cooling. The basic solution was adjusted to pH 7.4 with 1 mol/L hydrochloric acid, followed by extraction with chloroform (100 mL × 1, 70 mL × 1, 50 mL × 1). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The aqueous layer was concentrated under reduced pressure. The resulting residue was dissolved in chloroform/methanol = 10/1, and the insoluble material was removed by filtration (× 2). The residues obtained from the organic layer and the aqueous layer were purified by PTLC (lower layer of chloroform/methanol/water = 7/3/1), respectively. These were combined and dissolved in dichloromethane (20 mL), and dichloromethane was azeotropically removed with ethanol (three times). Ethanol (5 mL) was added to the resulting residue, and the mixture was ultrasonically treated and then cooled. The precipitated solid was collected by filtration, washed with ethanol and diethyl ether, and dried under reduced pressure at 60°C to give 122 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.30 (1H, d, J=3.92 Hz), 7.90 (1H, d, J=15.44 Hz), 5.19 (1H, dd, J=63.24, 3.43 Hz), 4.06-

3.97 (5H, m), 3.81-3.74 (3H, m), 3.58 (1H, d, J=10.30 Hz), 2.33-2.31 (1H, m), 2.03-1.73 (3H, m), 1.61-1.49 (1H, m).

Anal; Calcd for $C_{21}H_{20}F_2N_4O_4 \cdot 0.25H_2O$: C, 58.00; H, 4.75; F, 8.74; N, 12.88. Found: C, 58.07; H, 4.60; F, 8.70; N, 12.74.

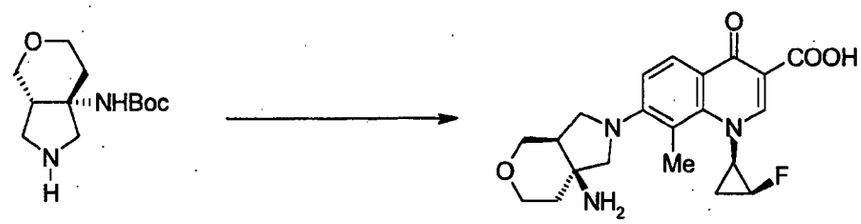
MS (ESI); m/z: 431 $(M+H)^+$.

IR (ATR) ν: 3081, 2960, 2873, 2211, 1725, 1629, 1446, 1400, 1307, 1261, 927, 912, 804 cm^{-1}.

[Example 39]

7-[(1S,6S)-1-Amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl]-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 273]



Triethylamine (0.0737 ml, 0.528 mmol) and 7-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (49.0 mg, 0.175 mmol) were added to a (1S,6S)-1-tert-butoxycarbonylamino-4-oxa-8-azabicyclo[4.3.0]nonane (42.2 mg, 0.176 mmol) in dimethyl sulfoxide (0.352 mL) in a nitrogen atmosphere, and the mixture was stirred at 75°C for two days. Dimethyl sulfoxide (0.352 mL) and triethylamine (0.147 mL, 1.06 mmol) were added to the reaction solution, and the mixture

was stirred at 75°C for four days. Dimethyl sulfoxide (0.352 mL) and triethylamine (0.147 ml, 1.06 mmol) were added to the reaction solution, and the mixture was stirred at 75°C for two days. 7-Fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (24.6 mg, 0.0881 mmol) and triethylamine (0.147 mL, 1.06 mmol) were added to the reaction solution, and the mixture was stirred for five days. The reaction solution was diluted with ethyl acetate (30 mL) and then washed with a 10% citric acid solution (25 mL), water (25 mL), and a saturated sodium hydroxide solution (25 mL). Further, the organic layer was extracted again from the washing 10% citric acid solution and the washing water with ethyl acetate (40 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). Trifluoroacetic acid (0.402 mL, 3 v/w) was added to a solution of 67.5 mg of the resulting residue in dichloromethane (1.32 mL) with stirring under ice-cooling, and the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (× 3). 6 mol/L hydrochloric acid was

added to the resulting residue under ice-cooling, and the mixture was washed with chloroform (30 mL × 5). The aqueous layer was adjusted to pH 12 with a 1 mol/L sodium hydroxide solution under ice-cooling. The basic solution was adjusted to pH 7.4 with 1 mol/L hydrochloric acid, followed by extraction with chloroform (100 mL × 2) and chloroform/methanol = 10/1 (50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue was purified by PTLC (lower layer of chloroform / methanol / water = 7/3/1) and concentrated under reduced pressure. The resulting residue was dissolved in hot ethanol, and the insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure, dissolved in hot ethanol (1 mL), ultrasonically treated, and cooled with ice water. Then, the slurry was washed with diethyl ether (10 mL). After stirring at room temperature overnight, the precipitated crystals were collected by filtration, washed with ethanol and diethyl ether, and then dried under reduced pressure at 60°C to give 12.4 mg of the title compound.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.41 (1H, d, J=3.68 Hz), 8.00 (1H, d, J=8.58 Hz), 7.09 (1H, d, J=8.82 Hz), 5.16-4.96 (1H, m), 4.10-3.95 (3H, m), 3.83-3.77 (2H, m), 3.66 (1H, d, J=9.80 Hz), 3.59 (1H, t, J=10.91 Hz), 3.26 (2H, dd, J=15.32,

8.70 Hz), 2.45 (3H, s), 2.33-2.23 (1H, m), 2.02-1.87 (3H, m), 1.68-1.57 (1H, m), 1.33-1.21 (1H, m).

Anal; Calcd for $C_{21}H_{24}FN_3O_4 \cdot 1.5H_2O$: C, 58.87; H, 6.35; N, 9.81. Found: C, 58.97; H, 5.98; N, 9.40.

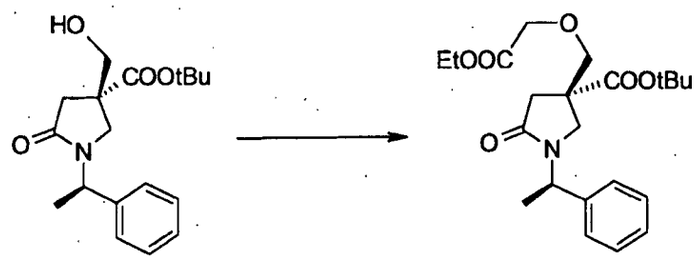
MS (ESI); m/z: 402 $(M+H)^+$.

IR (ATR) ν: 2937, 2865, 1710, 1608, 1508, 1428, 1388, 1349, 1315, 1257, 794 cm^{-1}.

[Reference Example 167]

(3S)-3-Ethoxycarbonylmethoxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 274]



(3S)-3-Hydroxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (2.0 g, 6.26 mmol) and bromoethyl acetate (2.09 g, 12.52 mmol) were dissolved in tetrahydrofuran (40 mL). Sodium hydride (0.33 g, 7.51 mmol) was added at 0°C, and the mixture was stirred at room temperature for 18 hours. A saturated ammonium chloride solution (100 mL) was added to the reaction solution at 0°C, followed by extraction with ethyl acetate (300 mL). The organic layer was washed with

water (100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (40% ethyl acetate/hexane) to give 1.74 g of the title compound as a colorless oil.

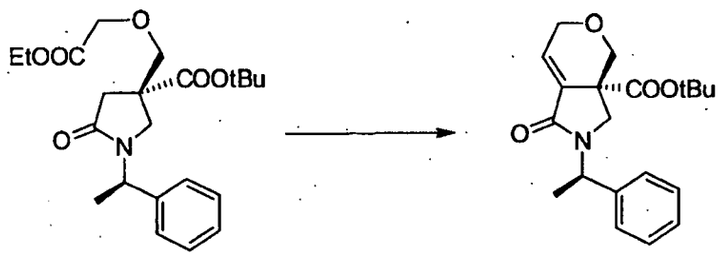
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30 (5H, m), 5.49 (1H, q, J=6.99 Hz), 4.21 (2H, q, J=7.15 Hz), 4.08 (2H, s), 3.68 (2H, brs), 3.46 (1H, d, J=10.24 Hz), 3.31 (1H, d, J=10.24 Hz), 2.80 (1H, d, J=17.07 Hz), 2.56 (1H, d, J=17.07 Hz), 1.53 (3H, d, J=7.32 Hz), 1.35 (9H, s), 1.28 (3H, t, J=7.19 Hz).

MS (EI) m/z: 406 $(M+H)^+$.

[Reference Example 168]

{(1S)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]non-5-en-1-yl}carboxylic acid tert-butyl ester

[Formula 275]



(3S)-3-Ethoxycarbonylmethoxymethyl-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (9.31 g, 25.9 mmol) was dissolved in tetrahydrofuran (200

mL). A 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (64.7 mL) was added dropwise in a nitrogen atmosphere at 0°C, and the mixture was stirred for 1.5 hours. A saturated ammonium chloride solution (300 mL) was added, followed by extraction with ethyl acetate (900 mL). The organic layer was washed with water (300 mL) and brine (100 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in tetrahydrofuran (200 mL). Sodium borohydride (1.27 g, 33.67 mmol) was added at 0°C, and the mixture was stirred for one hour. A saturated ammonium chloride solution (200 mL) was added to the reaction solution, followed by extraction with ethyl acetate (600 mL). The organic layer was washed with water (200 mL) and brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (40% ethyl acetate/hexane). The concentrate was dissolved in dichloromethane (150 mL). Triethylamine (5.69 mL, 41.02 mmol) was added, and methanesulfonyl chloride (1.90 mL, 24.61 mmol) was added dropwise at -10°C. After stirring for one hour, a saturated ammonium chloride solution (200 mL) was added to the reaction solution, followed by extraction with ethyl acetate (600 mL). The

organic layer was washed with water (200 mL) and brine (200 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in toluene (150 mL). DBU (12.24 mL, 82.03 mmol) was added, and the mixture was stirred at 40°C for 15 hours. The reaction solution was concentrated under reduced pressure and then a saturated ammonium chloride solution (150 mL) was added, followed by extraction with ethyl acetate (400 mL). The organic layer was washed with water (150 mL) and brine (150 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (75% ethyl acetate/hexane) to give 3.28 g of the title compound as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.29 (5H, m), 6.60 (1H, t, J=2.32 Hz), 5.57 (1H, q, J=7.16 Hz), 4.50-4.45 (2H, m), 4.24 (1H, dd, J=18.55, 2.44 Hz), 3.26 (1H, d, J=10.25 Hz), 3.21 (1H, d, J=10.01 Hz), 3.13 (1H, d, J=10.01 Hz), 1.51 (3H, d, J=7.08 Hz), 1.27 (9H, s).

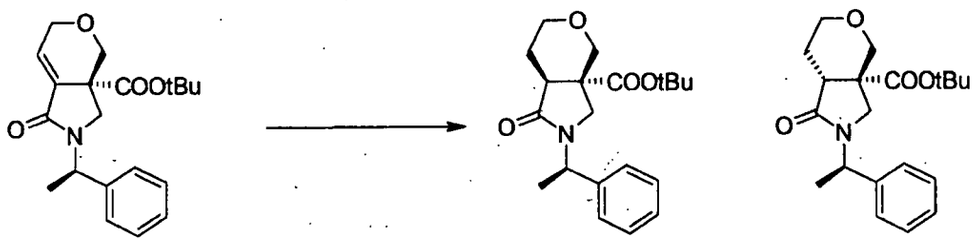
MS (EI) m/z: 344 $(M+H)^+$.

[Reference Example 169]

{(1S,6S)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester;

{(1S,6R)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester

[Formula 276]



{(1S)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]non-5-en-1-yl}carboxylic acid tert-butyl ester (231 mg, 0.67 mmol) was dissolved in tetrahydrofuran. 10% palladium-carbon (50% wet) (100 mg) was added, and the mixture was stirred in a hydrogen atmosphere for four hours. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (20% ethyl acetate/hexane -> 50%) to give 187 mg of the title compound (1S,6S)-isomer as a colorless solid and 44 mg of the title compound (1S,6R)-isomer as a colorless solid.

(1S,6S)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29-7.24 (5H, m), 5.48 (1H, q, J=7.24 Hz), 4.41 (1H, d, J=10.24 Hz), 4.10 (1H, dd, J=10.98, 4.39 Hz), 3.38-3.33 (2H, m), 3.17 (1H, d, J=9.76 Hz), 3.08 (1H, d, J=10.00 Hz), 2.28-2.19 (2H, m), 1.96-1.92 (1H, m), 1.46 (3H, d, J=7.32 Hz), 1.23 (9H, s).

MS (EI) m/z: 346 $(M+H)^+$.

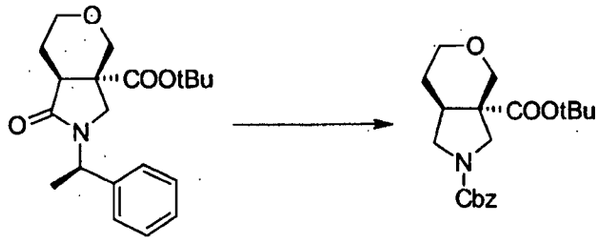
(1S,6R)-isomer:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.54 (1H, q, J=7.07 Hz), 4.12 (1H, d, J=11.71 Hz), 3.82-3.77 (1H, m), 3.39 (1H, m), 3.29 (1H, d, J=11.71 Hz), 3.02 (1H, t, J=4.63 Hz), 2.91 (2H, dd, J=18.29, 10.24 Hz), 2.03-2.01 (2H, m), 1.53 (3H, d, J=7.07 Hz), 1.41 (9H, s).

MS (EI) m/z: 346 $(M+H)^+$.

[(1S,6S)-3-Oxa-8-benzyloxycarbonyl-8-azabicyclo[4,3,0]nonan-1-yl]carboxylic acid tert-butyl ester

[Formula 277]



[(1S,6S)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]nonan-1-yl]carboxylic acid tert-butyl ester (3.36 g, 9.73 mmol) was dissolved in tetrahydrofuran (50 mL), and a 1 M solution of a borane-tetrahydrofuran complex in tetrahydrofuran (48.63 mL) was added dropwise in a nitrogen atmosphere. After stirring for three days, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for two hours. The reaction solution was concentrated

under reduced pressure and then a saturated ammonium chloride solution (100 mL) was added, followed by extraction with ethyl acetate (300 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the residue was subjected to short silica gel column chromatography (35% ethyl acetate/hexane). The resulting crude was dissolved in 1,2-dichloroethane (18 mL). Benzyloxycarbonyl chloride (3.40 g, 19.91 mmol) was added, and the mixture was stirred at 40°C for one day. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (35% ethyl acetate/hexane) to give 2.39 g of the title compound as a colorless oil.

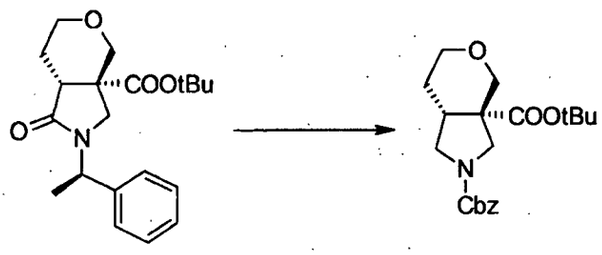
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.24 (5H, m), 5.14 (2H, s), 3.88 (1H, dd, J=20.63, 11.84 Hz), 3.77-3.54 (6H, m), 3.48 (1H, t, J=10.50 Hz), 3.41-3.33 (1H, m), 2.81-2.70 (1H, m), 1.93-1.80 (1H, m), 1.44 (9H, s).

MS (EI) m/z: 384 $(M+Na)^+$.

[Reference Example 171]

{(1S,6R)-8-Benzyloxycarbonyl-3-oxa-8-azabicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester

[Formula 278]



{(1S,6R)-3-Oxa-7-oxo-8-[(1R)-1-phenylethyl]-8-azabicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester (709 mg, 2.05 mmol) was dissolved in tetrahydrofuran (20 mL), and a 1 M solution of a borane-tetrahydrofuran complex in tetrahydrofuran (10.26 mL) was added dropwise in a nitrogen atmosphere. After stirring for three days, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for two hours. The reaction solution was concentrated under reduced pressure and then a saturated ammonium chloride solution (80 mL) was added, followed by extraction with ethyl acetate (240 mL). The organic layer was washed with water (80 mL) and brine (80 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (35% ethyl acetate/hexane). The resulting fraction was concentrated under reduced pressure, and the residue was dissolved in 1,2-dichloroethane (4 mL). Benzyloxycarbonyl chloride (788 mg, 4.62 mmol) was added, and the mixture was stirred at 40°C for four days. The

reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (40% ethyl acetate/hexane) to give 435 mg of the title compound as a colorless oil.

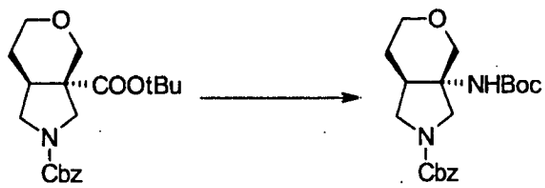
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.28 (5H, m), 5.13 (2H, d, J=3.42 Hz), 4.48 (1H, dd, J=20.75, 10.50 Hz), 4.10-4.07 (1H, m), 3.77 (1H, dd, J=24.05, 11.11 Hz), 3.62-3.52 (2H, m), 3.38 (1H, td, J=11.66, 2.77 Hz), 3.22 (1H, dd, J=10.50, 6.84 Hz), 3.07 (1H, dd, J=10.99, 3.42 Hz), 2.24-2.21 (1H, m), 1.98-1.96 (1H, m), 1.63-1.60 (1H, m), 1.44 (9H, s).

MS (EI); m/z: 384 $(M+Na)^+$.

[Reference Example 172]

[(1S,6R)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]carboxylic acid benzyl ester

[Formula 279]



{(1S,6S)-8-Benzyloxycarbonyl-3-oxa-8-azabicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester (2.30 g, 6.94 mmol) was dissolved in dichloromethane (20 mL). Trifluoroacetic acid (10 mL) was added, and the mixture was stirred for one day. The reaction solution was concentrated under reduced pressure, and a 1N sodium hydroxide solution (100 mL) was added, and the mixture was

washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform (200 mL × 2). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure, and the resulting residue was dissolved in acetonitrile (40 mL). 1,1-Carbonylbis-1H-imidazole (1.55 g, 9.53 mmol) was added in a nitrogen atmosphere at 0°C, and the mixture was stirred for one hour and then bubbled with ammonia gas at room temperature. Ethyl acetate and water were added, and the mixture was washed with brine. The organic layer was dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (ethyl acetate). The resulting crude was dissolved in tert-butanol (50 mL). Lead tetraacetate (3.98 g, 8.97 mmol) was added, and the mixture was stirred in a nitrogen atmosphere at 80°C for one hour. Sodium bicarbonate (3.52 g, 41.86 mmol) and ethyl acetate were added to the reaction solution, and the mixture was filtered through Celite. Then, the filtrate was washed with saturated sodium bicarbonate water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (30% ethyl

acetate/hexane) to give 1.70 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (5H, m), 5.13 (2H, s), 4.66 (1H, d, J=7.57 Hz), 3.86-3.57 (7H, m), 3.36 (1H, dq, J=23.01, 5.45 Hz), 2.63-2.55 (1H, m), 1.87-1.79 (1H, m), 1.54-1.50 (1H, m), 1.43 (9H, s).

MS (EI) m/z: 399 $(M+Na)^+$.

[Reference Example 173]

{(1S,6S)-1-tert-Butoxycarbonylamino-3-oxa-8-bicyclo[4,3,0]nonan-8-yl}carboxylic acid benzyl ester

[Formula 280]



{(1S,6R)-8-Benzyloxycarbonyl-3-oxa-8-bicyclo[4,3,0]nonan-1-yl}carboxylic acid tert-butyl ester (725 mg, 2.01 mmol) was dissolved in dichloromethane (20 mL). Trifluoroacetic acid (4 mL) was added, and the mixture was stirred for 15 hours. The reaction solution was concentrated under reduced pressure, and a 1N sodium hydroxide solution (50 mL) was added, and the mixture was washed with chloroform. The aqueous layer was made acidic with a hydrochloric acid solution, followed by extraction with chloroform (50 mL × 2). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated

under reduced pressure, and the resulting residue was dissolved in toluene (20 mL). Triethylamine (406 mg, 4.01 mmol) and diphenylphosphoryl azide (740 mg, 2.61 mmol) were added in a nitrogen atmosphere, and the mixture was stirred at 110°C for 1.5 hours. The reaction solution was concentrated under reduced pressure. Then, dioxane (20 mL) and 6N hydrochloric acid (20 mL) were added, and the mixture was stirred at 50°C for two hours. After concentration under reduced pressure and azeotropic distillation with ethanol, a 1N sodium hydroxide solution (50 mL) was added, followed by extraction with chloroform (100 mL × 2). After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure. Di-tert-butyl dicarbonate (2189 mg, 10.03 mmol) was added to the resulting residue, and the mixture was stirred at 50°C for 1.5 hours. The reaction solution was purified by silica gel column chromatography (60% ethyl acetate/hexane) to give 623 mg of the title compound as a colorless oil.

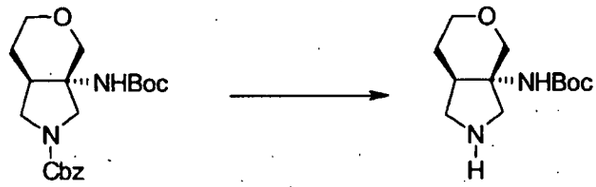
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.52-7.26 (5H, m), 5.13 (2H, s), 4.55 (1H, dd, J=19.51, 11.22 Hz), 4.45 (1H, d, J=10.73 Hz), 4.25 (1H, t, J=12.44 Hz), 4.13-4.08 (1H, m), 3.70-3.62 (1H, m), 3.36-3.34 (1H, m), 3.16-3.09 (3H, m), 2.02-1.97 (1H, m), 1.69-1.62 (2H, m), 1.43 (9H, s).

MS (EI) m/z: 399 $(M+Na)^+$.

[Reference Example 174]

(1S,6R)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonane

[Formula 281]



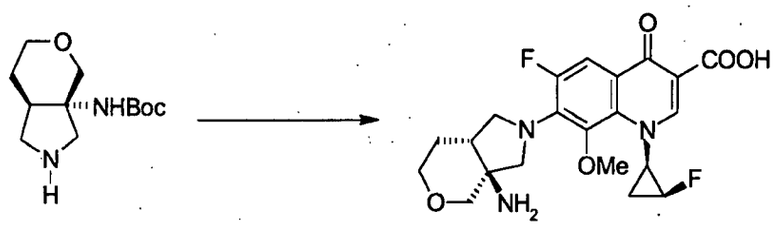
[(1S,6R)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]carboxylic acid benzyl ester (401 mg, 1.07 mmol) was dissolved in methanol (20 mL). 10% palladium-carbon (50% wet) (200 mg) was added, and the mixture was stirred in a hydrogen atmosphere for 2.5 hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure to give 256 mg of the title compound as a colorless solid.

MS(EI) m/z: 243$(M+H)^+$.

[Example 40]

7-[(1S,6R)-1-Amino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 282]



(1S,6R)-8-Aza-1-tert-butoxycarbonylamino-3-oxabicyclo[4,3,0]nonane (252 mg, 1.04 mmol) was dissolved in dimethyl sulfoxide (8 mL). 6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (450.6 mg, 1.25 mmol) and triethylamine (315.7 mg, 3.12 mmol) were added, and the mixture was stirred at 40°C for 17 hours. Then, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for five hours. The solvent was evaporated under reduced pressure, and then a 10% citric acid solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting fraction was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 8 with hydrochloric acid, followed by

extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was washed with ethanol and diethyl ether and dried under reduced pressure to give 302 mg of the title compound as pale yellow crystals.

mp: 132-134°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.41 (1H, s), 7.66 (1H, d, J=14.63 Hz), 4.99 (1H, d, J=63.90 Hz), 4.04-4.03 (2H, m), 3.91-3.88 (1H, m), 3.82 (2H, t, J=11.22 Hz), 3.68-3.62 (2H, m), 3.59 (3H, s), 3.51 (1H, d, J=11.95 Hz), 3.37 (1H, d, J=10.98 Hz), 2.23-2.20 (1H, m), 1.93-1.91 (1H, m), 1.57-1.47 (3H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_5 \cdot 0.5H_2O$ 0.4$CHCl_3$: C, 55.42; H, 5.30; N, 9.06; F, 8.19. Found: C, 55.19; H, 5.19; N, 9.09; F, 8.32.

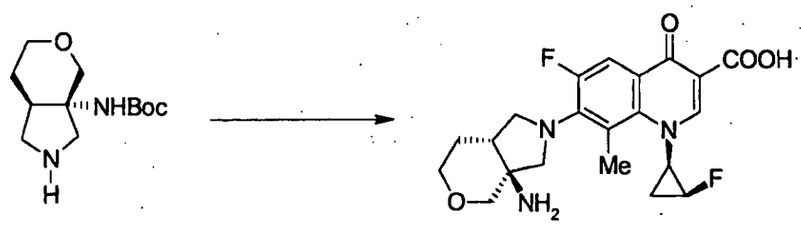
MS (EI) m/z: 436 $(M+H)^+$.

IR (ATR) ν: 2943, 2887, 2845, 1720, 1622, 1516, 1452, 1346, 1323, 1275 cm^{-1}.

[Example 41]

7-[(1S,6R)-1-Amino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 283]



(1S,6R)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonane (187 mg, 0.77 mmol) was dissolved in dimethyl sulfoxide (4 mL). 6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (316.5 mg, 0.92 mmol) and triethylamine (93.6 mg, 0.92 mmol) were added, and the mixture was stirred for 14 days. Then, 90% aqueous ethanol (18 mL) and triethylamine (2 mL) were added to the reaction solution, and the mixture was stirred at 80°C for two hours. The solvent was evaporated under reduced pressure, and a 10% citric acid solution was added to the resulting residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure. Then, the residue was purified by PTLC (5% methanol/chloroform), and the resulting fraction was dissolved in concentrated hydrochloric acid and washed with chloroform twice. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.9 with hydrochloric acid, followed by extraction with 5%

methanol/chloroform twice. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The precipitated crystals were collected by filtration and dried under reduced pressure to give 51 mg of the title compound as colorless crystals.

mp: 158-160°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.44 (1H, d, J=3.17 Hz), 7.67 (1H, d, J=14.16 Hz), 5.01 (1H, d, J=64.94 Hz), 4.16 (1H, t, J=6.71 Hz), 4.07 (1H, dt, J=9.93, 4.46 Hz), 4.01 (1H, d, J=10.01 Hz), 3.95-3.92 (1H, m), 3.85 (1H, d, J=11.96 Hz), 3.62-3.54 (1H, m), 3.47 (1H, d, J=11.72 Hz), 3.17 (1H, d, J=9.77 Hz), 3.06 (1H, d, J=10.01 Hz), 2.48 (3H, s), 2.20-2.15 (1H, m), 1.89-1.82 (1H, m), 1.65-1.60 (2H, m), 1.26-1.19 (1H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 0.75H_2O \cdot 0.25EtOH$: C, 58.10; H, 5.90; N, 9.45; F, 8.55. Found: C, 58.35; H, 5.86; N, 9.19; F, 8.53.

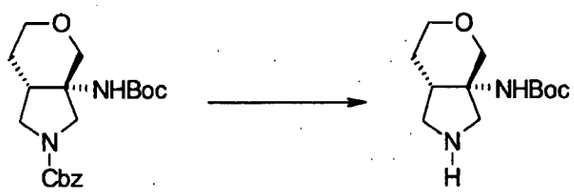
MS (EI) m/z: 420 $(M+H)^+$.

IR (ATR) ν: 3365, 2945, 2839, 1716, 1616, 1510, 1466, 1454, 1431, 1342, 1311, 1265, 1215 cm^{-1}.

[Reference Example 175]

(1S,6S)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonane

[Formula 284]



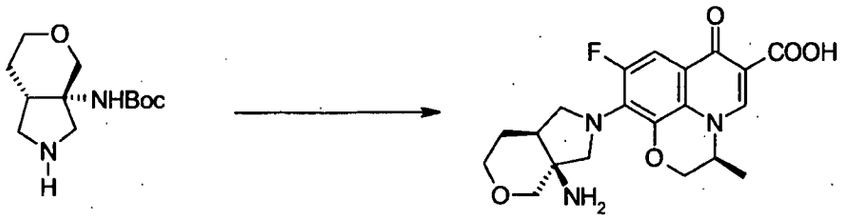
{(1S,6S)-1-tert-Butoxycarbonylamino-3-oxa-8-bicyclo[4,3,0]nonan-8-yl}carboxylic acid benzyl ester (610 mg, 1.62 mmol) was dissolved in methanol (20 mL). 10% palladium-carbon (50% wet) (200 mg) was added, and the mixture was stirred in a hydrogen atmosphere for three hours. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1N sodium hydroxide solution was added, followed by extraction with chloroform. After drying over anhydrous sodium sulfate and filtration, the solvent was evaporated under reduced pressure to give 362 mg of the title compound as a colorless solid.

MS(EI) m/z: 243$(M+H)^+$.

[Example 42]

10-[(1S,6S)-1-Amino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]-9-fluoro-2,3-dihydro-3-methyl-(S)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid

[Formula 285]



(1S,6S)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonane (147.7 mg, 0.61 mmol) was dissolved in dimethyl sulfoxide (2.5 mL). 9,10-Difluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF_2 chelate (211.3 mg, 0.64 mmol) and triethylamine (185.7 mg, 1.83 mmol)were added, and the mixture was stirred at 40°C for 18 hours. Then, 90% aqueous ethanol (33 mL) and triethylamine (3 mL) were added to the reaction mixture, which was stirred at 80°C for four hours. The solvent was evaporated under reduced pressure and a 10% citric acid solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting fraction was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol-aqueous ammonia, and the solution was heated and stirred. After vaporization

of ammonia, the precipitated crystals were collected by filtration and dried under reduced pressure to give 180 mg of the title compound as colorless crystals.

mp: >300°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.31 (1H, s), 7.51 (1H, d, J=14.63 Hz), 4.58 (1H, d, J=7.07 Hz), 4.45 (1H, dd, J=11.34, 1.83 Hz), 4.27 (1H, d, J=11.22 Hz), 4.08 (1H, dd, J=11.22, 3.66 Hz), 3.93 (1H, d, J=10.49 Hz), 3.78 (1H, dd, J=10.37, 3.05 Hz), 3.75-3.68 (1H, m), 3.55 (1H, d, J=10.98 Hz), 3.49-3.43 (2H, m), 3.29 (1H, d, J=10.00 Hz), 2.04-2.01 (1H, m), 1.81-1.72 (2H, m), 1.52 (3H, d, J=6.59 Hz).

Anal; Calcd for $C_{20}H_{22}FN_3O_5 \cdot 1.5H_2O$: C, 55.81; H, 5.85; N, 9.76; F, 4.41. Found: C, 55.80; H, 5.89; N, 9.74; F, 4.34.

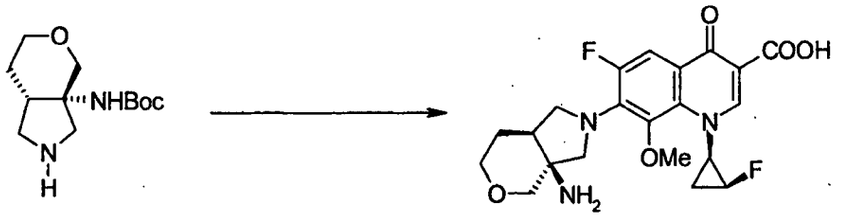
MS (EI) m/z: 404 $(M+H)^+$.

IR (ATR) ν: 3498, 3407, 3224, 3045, 2956, 2877, 1616, 1573, 1523, 1473, 1379, 1352, 1306, 1261 cm^{-1}.

[Example 43]

7-[(1S,6S)-1-Amino-8-aza-3-oxabicyclo[4,3,0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 286]



(1S,6S)-8-Aza-1-tert-butoxycarbonylamino-3-oxabicyclo[4,3,0]nonane (108.8 mg, 0.45 mmol) was dissolved in dimethyl sulfoxide (4 mL). 6,7-Difluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (210.7 mg, 0.58 mmol) and triethylamine (136.3 mg, 1.35 mmol) were added, and the mixture was stirred at 40°C for 18 hours. Then, 90% aqueous ethanol (30 mL) and triethylamine (3 mL) were added to the reaction solution, and the mixture was stirred at 80°C for five hours. The solvent was evaporated under reduced pressure, and a 10% citric acid solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting crude was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by recrystallization from ethanol and dried

under reduced pressure to give 121 mg of the title compound as pale yellow crystals.

mp: 190-192°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.36 (1H, d, J=3.66 Hz), 7.65 (1H, d, J=14.40 Hz), 5.06 (1H, dd, J=64.09, 3.54 Hz), 4.09 (1H, dd, J=11.35, 4.03 Hz), 4.02-3.95 (2H, m), 3.67-3.51 (8H, m), 3.24 (1H, d, J=10.25 Hz), 2.14-2.11 (1H, m), 1.88-1.71 (2H, m), 1.54-1.48 (1H, m), 1.36-1.32 (1H, m).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_5 \cdot 0.25H_2O$: C, 57.33; H, 5.38; N, 9.55; F, 8.64. Found: C, 57.28; H, 5.39; N, 9.27; F, 8.48.

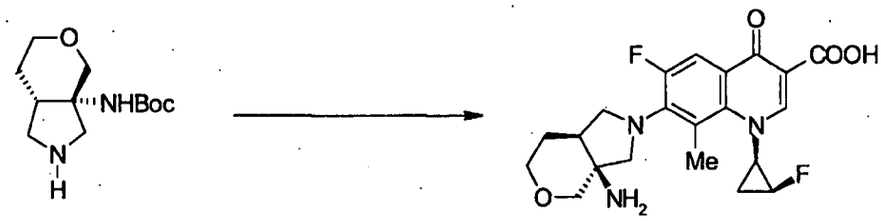
MS (EI) m/z: 436 $(M+H)^+$.

IR (ATR) ν: 3502, 3374, 3091, 2948, 2881, 2850, 1716, 1617, 1513, 1450, 1365, 1321, 1309, 1268, 1223 cm^{-1}.

[Example 44]

7-[(1S,6S)-1-Amino-3-oxa-8-azabicyclo[4,3,0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 287]



(1S,6S)-1-tert-Butoxycarbonylamino-3-oxa-8-azabicyclo[4,3,0]nonane (184.7 mg, 0.76 mmol) was dissolved in dimethyl sulfoxide (4 mL). 6,7-Difluoro-1-[(1R,2S)-2-

fluorocyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (289.4 mg, 0.84 mmol) and triethylamine (115.7 mg, 1.14 mmol) were added, and the mixture was stirred for seven days. Then, 90% aqueous ethanol (22 mL) and triethylamine (2 mL) were added to the reaction solution, and the mixture was stirred at 75°C for two hours. The solvent was evaporated under reduced pressure and a 10% citric acid solution was added, followed by extraction with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to short silica gel column chromatography (3% methanol/chloroform). The resulting fraction was dissolved in concentrated hydrochloric acid and washed with chloroform. The aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide at 0°C and then adjusted to pH 7.5 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The resulting residue was dissolved in ethanol-aqueous ammonia, and the solution was heated and stirred. After vaporization of ammonia, the precipitated crystals were collected by filtration and

dried under reduced pressure to give 94.7 mg of the title compound as colorless crystals.

mp: 159-161°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.42 (1H, s), 7.67 (1H, d, J=14.15 Hz), 5.03 (1H, d, J=60.24 Hz), 4.10-4.08 (2H, m), 3.96 (1H, d, J=10.49 Hz), 3.82 (1H, d, J=9.27 Hz), 3.68 (1H, t, J=10.49 Hz), 3.61 (1H, d, J=10.49 Hz), 3.49 (1H, t, J=11.10 Hz), 3.26 (1H, t, J=8.17 Hz), 3.08 (1H, d, J=9.51 Hz), 2.45 (3H, s), 2.21-2.18 (1H, m), 1.84-1.57 (3H, m), 1.23 (1H, d, J=26.10 Hz).

Anal; Calcd for $C_{21}H_{23}F_2N_3O_4 \cdot 1.25H_2O$: C, 57.07; H, 5.82; N, 9.51; F, 8.60. Found: C, 56.87; H, 5.99; N, 9.49; F, 8.43.

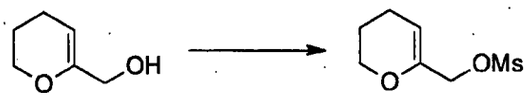
MS (EI) m/z: 420 $(M+H)^+$.

IR (ATR) ν: 3518, 3251, 3059, 2935, 2885, 1720, 1614, 1540, 1508, 1441, 1387, 1358, 1325, 1306, 1273 cm^{-1}.

[Reference Example 176]

(5,6-Dihydro-4H-pyran-2-yl)methyl methanesulfonate

[Formula 288]



Methanesulfonyl chloride (17.9 mL, 232 mmol) was added dropwise to a solution of (5,6-dihydro-4H-pyran-2-yl)methanol (25.51 g, 193 mmol) [see Synlett, Vol.5, p.533 (1997)] and triethylamine (40.4 mL, 290 mmol) in dichloromethane (600 mL) under salt ice cooling over 15

minutes. After stirring at the same temperature for two hours, triethylamine (18.8 mL, 135 mmol) and methanesulfonyl chloride (7.5 mL, 97 mmol) were added, and the mixture was further stirred for 30 minutes. Water (300 mL) was added to the reaction solution, followed by extraction with ethyl acetate (1.5 L). The resulting organic layer was washed with water (300 mL) and brine (300 mL). The organic layer was dried over anhydrous sodium sulfate and then filtered, and the solvent was evaporated under reduced pressure. The resulting crude title compound was used for the next reaction without purification.

[Reference Example 177]

2-Azidomethyl-5,6-dihydro-4H-pyran

[Formula 289]



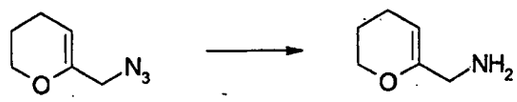
Water (35 mL) and sodium azide (15.1 g, 232 mmol) were added to a solution of the crude (5,6-dihydro-4H-pyran-2-yl)methyl methanesulfonate (about 193 mmol) in N,N-dimethylformamide (350 mL), and the mixture was stirred at room temperature for 20 hours. Water (300 mL) was added to the reaction solution, followed by extraction with ethyl acetate (1.5 L). The resulting organic layer was washed with water (3 × 200 mL) and brine (200 mL). The organic layer was dried over anhydrous sodium sulfate and then

filtered, and the solvent was evaporated under reduced pressure to about 300 mL. The resulting crude title compound solution was used for the next reaction without purification.

[Reference Example 178]

2-Aminomethyl-5,6-dihydro-4H-pyran

[Formula 290]

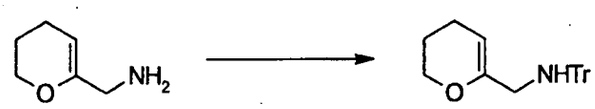


Tetrahydrofuran (500 mL), water (50 mL), and triphenylphosphine (35.4 g, 135 mmol) were sequentially added to the crude 2-azidomethyl-5,6-dihydro-4H-pyran (about 193 mmol), and the mixture was heated with stirring on an oil bath at 60°C for two hours. Ethyl acetate (1 L) was added to the reaction solution, and the aqueous layer was removed. Then, the organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure. The resulting crude title compound was used for the next reaction without further purification.

[Reference Example 179]

2-(Tritylamino)methyl-5,6-dihydro-4H-pyran

[Formula 291]



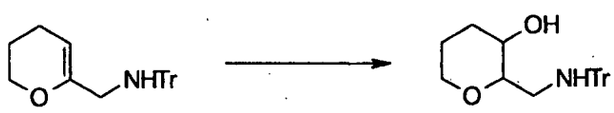
Triethylamine (37.7 mL, 270 mmol) and trityl chloride (41.4 g, 149 mmol) were sequentially added to a solution of the crude 2-aminomethyl-5,6-dihydro-4H-pyran (about 193 mmol) in dichloromethane (500 mL), and the mixture was stirred at room temperature for 11 hours. The reaction solution was diluted with dichloromethane (500 mL), washed with water (2 × 500 mL) and brine (500 mL), and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure. Then, the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 5:95 -> 10:90) to give 22.2 g (four steps, 32%) of the title compound as a colorless transparent gummy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.16-7.49 (15H, m), 4.81 (1H, brs), 3.97 (2H, t, J=5.1 Hz), 2.66 (2H, brs), 2.02-2.04 (2H, m), 1.76-1.82 (2H, m).

[Reference Example 180]

2-(Tritylamino)methyl-3,4,5,6-tetrahydro-2H-pyran-3-ol

[Formula 292]



A solution of a borane-tetrahydrofuran complex in tetrahydrofuran (1 M, 187 mL, 187 mmol) was added dropwise to a solution of 2-(tritylamino)methyl-5,6-dihydro-4H-pyran (22.2 g, 62.4 mmol) in tetrahydrofuran (180 mL) at room

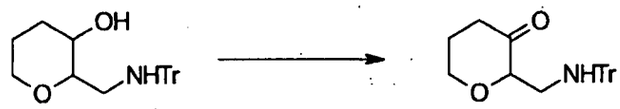
temperature over 20 minutes. After stirring at room temperature for 2.5 hours, the reaction solution was ice-cooled, and a 3N sodium hydroxide solution (208 mL, 624 mmol) was added dropwise over 10 minutes. Subsequently a 31% hydrogen peroxide solution (69 mL, 629 mmol) was added dropwise at the same temperature over 10 minutes, and then the mixture was stirred at room temperature for one hour. The reaction solution was extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with water (300 mL) and brine (300 mL), and then dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure, and then the residue was suspended in a mixed solvent of dichloromethane/hexane (1:1, 80 mL). The insoluble material was removed by filtration, and then the filtrate was evaporated under reduced pressure to give 18.54 g (80%) of the title compound as a pale yellow gummy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41-7.46 (6H, m), 7.26-7.33 (6H, m), 7.18-7.23 (3H, m), 3.81-3.84 (1H, m), 3.73-3.76 (1H, m), 3.60-3.66 (1H, m), 3.25-3.32 (1H, m), 3.05-3.10 (1H, m), 2.64 (1H, dd, J=11.6, 7.7 Hz), 2.35 (1H, dd, J=11.7, 4.9 Hz), 2.13-2.21 (1H, m), 1.83-1.86 (1H, m), 1.62-1.68 (1H, m), 1.38-1.48 (1H, m).

[Reference Example 181]

2-(Tritylamino)methyl-5,6-dihydro-2H-pyran-3(4H)-one

[Formula 293]



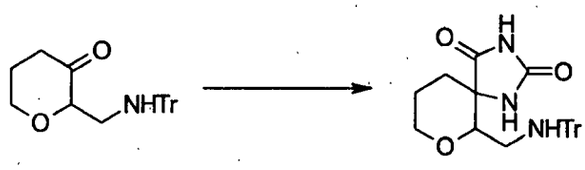
A solution of a sulfur trioxide-pyridine complex (23.7 g, 149 mmol) in dimethyl sulfoxide (150 mL) was added to a solution of 2-(tritylamino)methyl-3,4,5,6-tetrahydro-2H-pyran-3-ol (18.54 g , 49.6 mmol) and triethylamine (45 mL, 323 mmol) in dimethyl sulfoxide (150 mL) in a nitrogen atmosphere at room temperature. The mixture was stirred at the same temperature for 10 hours. The reaction solution was poured into ice water (1 L), followed by extraction with ethyl acetate (2 × 1 L). Then, the organic layers were combined and washed with water (2 × 1 L) and brine (1 L). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 5:95 -> 10:90 -> 20:80) to give 9.56 g (52%) of the title compound as a colorless transparent gummy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44-7.47 (6H, m), 7.15-7.28 (9H, m), 3.93-4.00 (2H, m), 3.65-3.72 (1H, m), 2.41-2.61 (4H, m), 1.99-2.20 (2H, m).

[Reference Example 182]

6-(Tritylamino)methyl-7-oxa-1,3-diazaspiro[4.5]decane-2,4-dione

[Formula 294]



A mixture of 2-(tritylamino)methyl-5,6-dihydro-2H-pyran-3(4H)-one (9.56 g, 25.7 mmol), sodium cyanide (2.52 g, 51.4 mmol), ammonium chloride (2.75 g, 51.4 mmol), ammonium carbonate (10.18 g, 128.7 mmol), concentrated aqueous ammonia (50 mL), and ethanol (50 mL) was stirred in a nitrogen atmosphere on an oil bath at 60°C for 4.5 hours. Ammonium carbonate (10.18 g, 128.7 mmol) was added, and the mixture was stirred at the same temperature for further 19.5 hours. The resulting reaction solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (300 mL, 100 mL). Then, the organic layers were combined and washed with water (2 × 100 mL) and brine (100 mL). The resulting organic layer was dried over anhydrous magnesium sulfate and filtered. Then, the solvent was evaporated under reduced pressure to give 11.35 g (quantitative) of the title compound as a colorless amorphous.

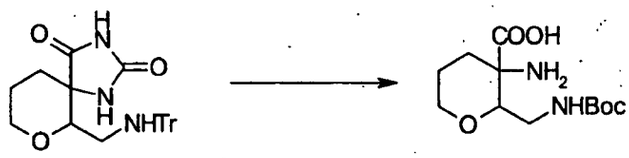
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (1H, s), 7.38-7.49 (6H, m), 7.15-7.30 (9H, m), 5.79 (1H, s), 3.97 (1H, dm, J=13.2 Hz), 3.68 (1H, dd, J=7.1, 5.1 Hz), 3.51 (1H, dt, J=11.2, 4.4 Hz),

2.34 (1H, dd, J=12.1, 5.0 Hz), 2.18-2.23 (1H, m), 2.05-2.14 (1H, m), 1.81 (1H, brd, J=13.4 Hz), 1.55-1.70 (2H, m).

[Reference Example 183]

(2R*,3R*)-3-Amino-2-(tert-butoxycarbonylamino)methyl-3,4,5,6-tetrahydro-2H-pyrane-3-carboxylic acid

[Formula 295]



6-(Tritylamino)methyl-7-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (10.69 g, 24.2 mmol) was dissolved in trifluoroacetic acid (50 mL) at room temperature, and the mixture was stirred for 15 minutes. Water (50 mL) was added to the reaction solution, and the solvent was evaporated under reduced pressure. Then, water (200 mL) was added to the residue, and the mixture was washed with diethyl ether (2 × 100 mL).

Sodium hydroxide (40 g, 1.0 mol) was added to the resulting solution (about 250 mL), and the mixture was heated to reflux on an oil bath at 130°C for 16 hours. The reaction solution was ice-cooled and then adjusted to pH 7.0 by gradually adding concentrated hydrochloric acid, and the solvent was evaporated under reduced pressure.

The resulting residue was suspended in a 1N sodium hydroxide solution (75 mL) and 1,4-dioxane (150 mL). Di-

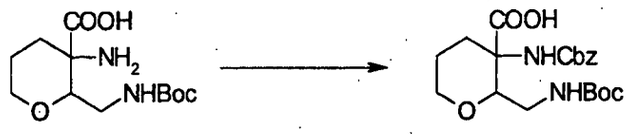
tert-butyl dicarbonate (52.8 g, 242 mmol) was added at room temperature, and the mixture was stirred at the same temperature for five days. The solvent was concentrated under reduced pressure. Then, the residue was suspended in a 1N sodium hydroxide solution (300 mL), and the mixture was washed with diisopropyl ether (3 × 300 mL). Concentrated hydrochloric acid was gradually added to the resulting aqueous layer under ice-cooling to adjust the aqueous layer to pH 7.0. The solvent was evaporated under reduced pressure. The residue was suspended in methanol (100 mL), and then most of sodium chloride was removed by filtration (twice). Thereafter, the residue was purified by an ion exchange resin HP-20 (eluted with methanol) to give 1.21 g (three steps, 18%) of the title compound as a pale brown solid.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 3.99-4.03 (1H, m), 3.69-3.73 (1H, m), 3.53 (1H, t, J=12.0 Hz), 3.00-3.12 (2H, m), 2.00-2.06 (1H, m), 1.70-1.87 (2H, m), 1.52-1.56 (1H, m), 1.43 (9H, s).

[Reference Example 184]

(2R*,3R*)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)methyl-3,4,5,6-tetrahydro-2H-pyrane-3-carboxylic acid

[Formula 296]



N-(Benzyloxycarbonyloxy)succinimide (1.49 g, 5.98 mmol) was added to a solution of (2R*,3R*)-3-amino-2-(tert-butoxycarbonylamino)methyl-3,4,5,6-tetrahydro-2H-pyrane-3-carboxylic acid (1.09 g, 3.99 mmol) and triethylamine (1.11 mL, 7.96 mmol) in tetrahydrofuran (10 mL)/water (10 mL) under ice-cooling, and the mixture was stirred at room temperature for 15 hours. The reaction solution was diluted with ethyl acetate (150 mL) and washed with 1N hydrochloric acid (50 mL). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methanol:chloroform = 2:98 -> 5:95) and then dissolved in a 1N sodium hydroxide solution (50 mL) and washed with diethyl ether (2 × 20 mL) to remove the remaining benzyl alcohol. The resulting aqueous layer was adjusted to pH 1 to 2 with concentrated hydrochloric acid, followed by extraction with dichloromethane (2 × 80 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure to obtain 1.08 g (66%) of the title compound as a white solid.

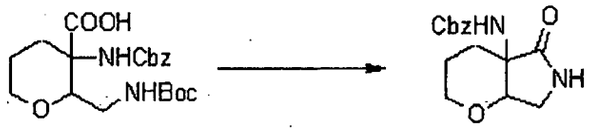
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.28 (5H, m), 5.53 (1H, brs), 5.20-5.07 (2H, m), 4.94 (1H, brs), 3.99 (1H, dd, J=11.1, 4.5 Hz), 3.65 (1H, m), 3.55-3.30 (2H, m), 3.17 (1H, m), 2.59 (1H, m), 2.06 (1H, m), 1.73 (1H, m), 1.57-1.51 (1H, m), 1.43 (9H, m).

MS (ESI); m/z: 309 $(M-Boc+2H)^+$.

[Reference Example 185]

(1R*,6R*)-6-(Benzyloxycarbonylamino)-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane

[Formula 297]



(±)-trans

(2R*,3R*)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)methyl-3,4,5,6-tetrahydro-2H-pyrane-3-carboxylic acid (1.08 g, 2.64 mmol) was dissolved in a solution of 4N hydrogen chloride in 1,4-dioxane at room temperature. The mixture was stirred at the same temperature for 20 minutes, and then the solvent was evaporated under reduced pressure. The resulting residue was azeotropically distilled with dioxane (twice) to give 921 mg (quantitative) of a residue.

691 mg (2.00 mmol) of the resulting residue and N,N-diisopropylethylamine (1.75 mL, 10.0 mmol) were dissolved in dichloromethane (25 mL). Bis(2-oxo-3-

oxazolidinyl)phosphinyl chloride (1.02 g, 4.01 mmol) was added at room temperature, and the mixture was stirred at the same temperature for 18 hours. The reaction solution was diluted with chloroform (50 mL) and sequentially washed with 1N hydrochloric acid (30 mL), water (30 mL), a saturated sodium bicarbonate solution (30 mL), and brine (30 mL). The resulting organic layer was dried over anhydrous sodium sulfate and filtered. Then, the solvent was evaporated under reduced pressure at room temperature. The residue was purified by silica gel column chromatography (methanol:chloroform = 2:98 -> 5:95) to give 834 mg (quantitative) of the title compound as a pale brown gummy solid.

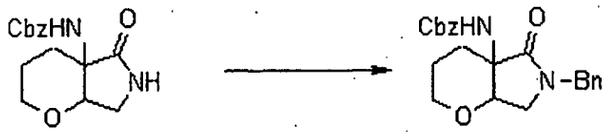
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.23 (5H, m), 5.60 (1H, brs), 5.42 (1H, brs), 5.12 (2H, s), 4.06 (1H, dd, J=11.7, 5.4 Hz), 3.67-3.55 (2H, m), 3.43-3.38 (1H, m), 3.33 (1H, t, J=4.2 Hz), 2.76-2.68 (1H, m), 1.94-1.82 (1H, m), 1.65-1.55 (2H, m).

MS (ESI); m/z: 291 $(M+H)^+$.

[Reference Example 186]

(1R*,6R*)-8-Benzyl-6-(benzyloxycarbonylamino)-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane

[Formula 298]



(±)-trans (±)-trans

Sodium hydride (55% mineral oil dispersion, 111 mg, 2.54 mmol) was added to a solution of (1R*,6R*)-6-(benzyloxycarbonylamino)-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane (818 mg, about 1.96 mmol) in N,N-dimethylformamide under ice-cooling, and the mixture was stirred at the same temperature for 20 minutes. Then, benzyl bromide (0.304 mL, 2.56 mmol) was added, and the mixture was stirred at room temperature for 20 minutes. The reaction solution was poured into a 10% citric acid solution (30 mL), followed by extraction with ethyl acetate (100 mL). The resulting organic layer was washed with water (2 × 30 mL) and brine (30 mL). This was dried over anhydrous sodium sulfate and filtered, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:chloroform = 50:50 -> methanol:chloroform = 1:99 -> 2:98) to give 224 mg (0.59 mmol, three steps, 30%) of the title compound as a colorless transparent gummy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.16 (5H, m), 5.38 (1H, brs), 5.20-5.09 (2H, m), 4.46 (2H, s), 4.02 (1H, dd, J=11.5, 5.7 Hz), 3.57-3.50 (2H, m), 3.23 (1H, t, J=9.2 Hz), 3.13 (1H,

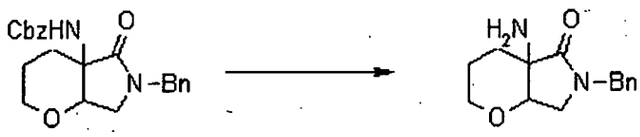
dd, J=9.2, 6.7 Hz), 2.75 (1H, m), 1.94-1.84 (1H, m), 1.68-1.61 (1H, m), 1.56-1.53 (1H, m),

MS (ESI); m/z: 381 $(M+H)^+$.

[Reference Example 187]

(1R*,6R*)-6-Amino-8-benzyl-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane

[Formula 299]



(±)-trans (±)-trans

A 10% palladium-carbon catalyst (50% wet, 80 mg) was added to a solution of (1R*,6R*)-8-benzyl-6-(benzyloxycarbonylamino)-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane (220 mg, 0.58 mmol) in methanol (10 ml), and the mixture was stirred in a hydrogen atmosphere at room temperature for 1.5 hours. The reaction solution was filtered, and the filtrate was concentrated under reduced pressure to give 143 mg (quantitative) of the title compound as a colorless transparent gummy solid.

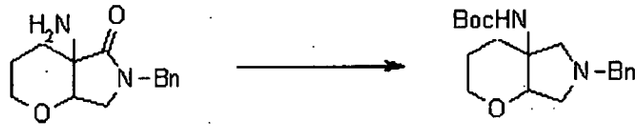
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.24 (5H, m), 4.58 (1H, d, J=15.1 Hz), 4.38 (1H, d, J=14.9 Hz), 4.09 (1H, dd, J=11.6, 5.5 Hz), 3.58-3.40 (3H, m), 3.17 (1H, dd, J=8.1, 6.1 Hz), 2.53 (2H, brs), 2.15-2.04 (2H, m), 1.79-1.72 (1H, m), 1.60-1.55 (1H, m).

MS (ESI); m/z: 247 $(M+H)^+$.

[Reference Example 188]

(1R*,6S*)-8-Benzyl-6-(tert-butoxycarbonylamino)-2-oxa-8-azabicyclo[4.3.0]nonane

[Formula 300]



(±)-trans (±)-trans

Lithium aluminum hydride (65 mg, 1.71 mmol) was added to a solution of (1R*,6R*)-6-amino-8-benzyl-2-oxa-7-oxo-8-azabicyclo[4.3.0]nonane (140 mg, 0.57 mmol) in tetrahydrofuran (6 mL) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was ice-cooled. Water (0.06 mL), a 15% sodium hydroxide solution (0.06 mL), and water (0.18 mL) were sequentially added carefully, and the mixture was stirred at room temperature for overnight. Thereafter, anhydrous magnesium sulfate was added, and the mixture was stirred for 10 minutes. The resulting mixture was filtered through Celite, and then the filtrate was concentrated under reduced pressure.

The resulting residue was dissolved in dichloromethane (3 mL). Di-tert-butyl dicarbonate (252 mg, 1.15 mmol) was added, and the mixture was stirred at room temperature for four hours. The solvent was evaporated under reduced pressure, and then the resulting residue was purified by

PTLC (methanol:chloroform = 2:98) to give 50 mg (0.152 mmol, two steps, 26%) of the title compound as a colorless transparent gummy solid.

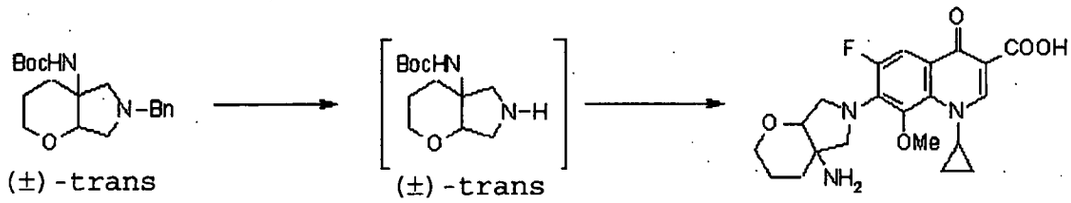
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.20 (5H, m), 4.93 (1H, brs), 4.02 (1H, dd, J=11.6, 5.2 Hz), 3.81 (2H, s), 3.61-3.48 (3H, m), 3.07 (1H, t, J=8.0 Hz), 2.71-2.67 (2H, m), 2.52 (1H, m), 1.90-1:55 (3H, m), 1.47 (9H, s).

MS (ESI); m/z: 333 $(M+H)^+$.

[Example 45]

7-[(1R*,6S*)-6-Amino-2-oxa-8-azabicyclo[4.3.0]nonan-3-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 301]



A 10% palladium-carbon catalyst (50% wet, 50 mg) was added to a solution of (1R*,6S*)-8-benzyl-6-(tert-butoxycarbonylamino)-2-oxa-8-azabicyclo[4.3.0]nonane (50 mg, 0.152 mmol) in methanol (10 mL), and the mixture was stirred in a hydrogen atmosphere at room temperature for 1.5 hours. The catalyst was removed by filtration, and then the solvent was evaporated under reduced pressure to give

45 mg of (1R*,6S*)-6-(tert-butoxycarbonylamino)-2-oxa-8-azabicyclo[4.3.0]nonane.

A mixture of the resulting (1R*,6S*)-6-(tert-butoxycarbonylamino)-2-oxa-8-azabicyclo[4.3.0]nonane (45 mg), 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (572 mg, 1.67 mmol), triethylamine (0.128 mL, 0.92 mmol) and dimethyl sulfoxide (0.5 mL) was stirred on an oil bath at 40°C for 19 hours. Next, ethanol (16 mL), water (4 mL), and triethylamine (2 mL) were added to the reaction solution, and the mixture was heated to reflux on an oil bath at 110°C for 2.5 hours. The solvent was evaporated under reduced pressure, and then a 10% citric acid solution (20 mL) was added to the resulting residue, followed by extraction with ethyl acetate (60 mL). The organic layer was washed with water (20 mL × 2) and brine (20 mL), dried over anhydrous sodium sulfate, and filtered. Then, the solvent was evaporated under reduced pressure. The resulting residue was dissolved in concentrated hydrochloric acid (10 mL) at room temperature. The resulting acidic solution was transferred to a separatory funnel and then washed with chloroform (5 × 30 mL, 3 × 50 mL). The aqueous layer was adjusted to pH 12.0 with a 10 mol/L sodium hydroxide solution under ice-cooling and then adjusted to pH 7.4 with hydrochloric acid. Thereafter, the solvent was evaporated

under reduced pressure. The residue was suspended in methanol and filtered, and the filtrate was evaporated under reduced pressure. Then, the residue was again suspended in methanol and filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was purified by PTLC (lower layer solvent of chloroform:methanol:water = 7:3:1) and further crystallized using diethyl ether and purified to give 10 mg (16%) of the title compound as a pale yellow powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, s), 7.79 (1H, d, J=12.9 Hz), 4.20-3.60 (5H, m), 3.58 (3H, s), 3.50-3.40 (3H, m), 2.02 (2H, m), 1.80-1.60 (2H, m), 1.35-1.05 (3H, m), 0.81 (1H, m).

Anal. Calcd for $C_{21}H_{24}FN_3O_5 \cdot 0.25H_2O \cdot 0.25Et_2O$: C, 59.99; H, 6.18; N, 9.54. Found: C, 59.94; H, 5.94; N, 9.12.

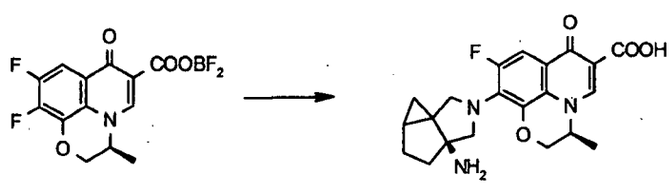
MS (EI) m/z: 417 (M^+).

HRMS (FAB) Calcdfor$C_{21}H_{24}FN_3O_5$: 417.1700. Found: 417.1695.

[Example 46]

(3S)-10-[6-Amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid

[Formula 302]



Triethylamine (0.266 ml, 1.91 mmol) and (3S)-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF_2 chelate (209 mg, 0.635 mmol) were added to a solution of 6-tert-butoxycarbonylamino-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (160 mg, 0.666 mmol) in dimethyl sulfoxide (1.27 ml), and the mixture was stirred at 35°C for 16 hours. A mixed solution of ethanol:water = 4:1 (10 ml) and triethylamine (1 ml) were added to the reaction solution, and the mixture was heated to reflux for 2.5 hours. The reaction solution was concentrated under reduced pressure, and then a 10% citric acid solution (40 ml) was added to the residue, followed by extraction with ethyl acetate (50 ml). The interface part was extracted with chloroform. The organic layer was washed with water (40 ml) and brine (40 ml), respectively, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99.5:0.5 -> 99:1 -> 98:2 -> 96:4 -> 92:8). The resulting residue (224 mg) was dissolved in concentrated hydrochloric acid (1.5 ml) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (25 ml × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted

to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 ml × 3, 60 ml × 1). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The residue (190 mg) was dissolved in hot ethanol (about 100 ml), and the insoluble material was removed by filtration through a fluted filter paper. The solvent was gradually evaporated by heating the filtrate with stirring. The solution was concentrated to about 10 to 20 ml and then stirred at room temperature overnight. The precipitated crystals were collected by filtration and washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 60°C overnight to give 120 mg of the title compound as pale yellow crystals.

^{1}H-NMR (0.1NNaOD) δ: 8.32 (1H, s), 7.53 (1H, d, J=14.46 Hz), 4.61-4.59 (1H, m), 4.48 (1H, dd, J=11.52, 1.96 Hz), 4.32-4.30 (2H, m), 3.85 (1H, dd, J=10.54, 2.70 Hz), 3.49 (1H, d, J=9.80 Hz), 3.29 (1H, d, J=10.30 Hz), 1.95-1.91 (2H, m), 1.75 (1H, dd, J=12.50, 8.58 Hz), 1.52 (3H, d, J=6.86 Hz), 1.31-1.17 (3H, m), 0.82-0.76 (2H, m).

Anal. Calcd for $C_{21}H_{22}FN_3O_4$: C, 63.15; H, 5.55; F, 4.76; N, 10.52.

Found: C, 62.94; H, 5.53; F, 4.62; N, 10.40.

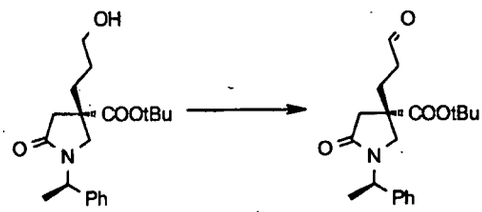
MS (ESI) m/z: 400 $(M+H)^+$.

IR (ATR): 3370, 2933, 2877, 1708, 1618, 1523, 1463, 1444, 1396, 1353, 1311, 1274, 1228, 1145, 1085, 1045, 985, 970, 956, 860, 831, 800 cm^{-1}.

[Reference Example 189]

(3S)-3-(3-Oxo-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 303]



Dichloromethane (35 ml) was cooled with dry ice-methanol in a nitrogen atmosphere. Oxalyl chloride (3.45 ml, 39.5 mmol) and dimethyl sulfoxide (4.68 ml, 66.0 mmol) were added, and the mixture was stirred under cooling for 15 minutes. A solution of (3S)-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (4.58 g, 13.2 mmol) in dichloromethane (31 mL) was added, and the mixture was stirred under cooling for one hour. Triethylamine (11.1 ml, 79.5 mmol) was added under cooling, and the mixture was stirred under cooling for one hour and then at room temperature for one hour. A saturated ammonium chloride solution (100 ml) was added to the reaction solution, followed by extraction with chloroform (100 ml × 1, 80 ml × 1). The organic layer was

washed with brine (120 ml) and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 60:40 -> 50:50 -> 40:60 -> 34:66 -> 25:75) to give 4.59 g of the title compound as white crystals.

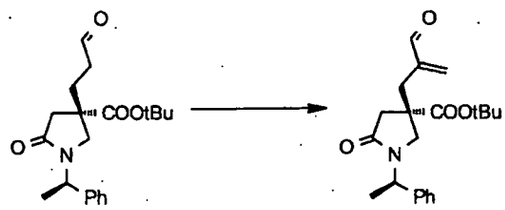
^{1}H-NMR ($CDCl_3$) δ: 9.76 (1H, s), 7.35-7.24 (5H, m), 5.49 (1H, q, J=7.19 Hz), 3.34 (1H, d, J=10.05 Hz), 3.13 (1H, d, J=10.05 Hz), 2.94 (1H, d, J=16.91 Hz), 2.44 (2H, dt, J=11.52, 4.72 Hz), 2.29 (1H, d, J=16.91 Hz), 2.12-2.05 (1H, m), 1.99-1.91 (1H, m), 1.52 (3H, d, J=7.11 Hz), 1.32 (9H, s).

MS (ESI) m/z: 346 $(M+H)^+$.

[Reference Example 190]

(3S)-3-(3-Oxo-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 304]



1,8-Diazabicyclo[5.4.0]-7-undecene (2.17 ml, 14.5 mmol) and Eschenmoser salt (3.66 g, 19.8mmol) were added to a solution of (3S)-3-(3-oxo-1-propyl)-5-oxo-1-[(1R)-1-

phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester in dichloromethane (88.0 ml) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 16 hours. Thereafter, Eschenmoser salt (1.22 g, 6.59 mmol) was added, and the mixture was stirred at room temperature for three hours. A saturated ammonium chloride solution (150 ml) was added to the reaction solution, followed by extraction with chloroform (100 ml × 1, 150 ml × 1). The organic layer was washed with brine (200 ml) and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 60:40 -> 50:50 -> 34:66) to give 3.14 g of the title compound as white crystals.

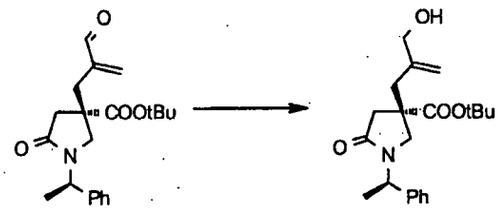
^{1}H-NMR ($CDCl_3$) δ: 9.51 (1H, s), 7.34-7.24 (5H, m), 6.31 (1H, s), 6.12 (1H, s), 5.47 (1H, q, J=7.08 Hz), 3.31 (1H, d, J=10.50 Hz), 3.22 (1H, d, J=10.25 Hz), 2.89 (1H, d, J=17.09 Hz), 2.75-2.64 (2H, m), 2.41 (1H, d, J=17.09 Hz), 1.51 (3H, d, J=7.08 Hz), 1.30 (9H, s).

MS (ESI) m/z: 358 $(M+H)^+$.

[Reference Example 191]

(3S)-3-(3-Hydroxy-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 305]



Ethanol (43.9 ml) was added to sodium borohydride (644 mg, 17.0 mmol) in a nitrogen atmosphere, and the mixture was cooled with ice-acetone. Cerium chloride heptahydrate (6.55 g, 17.6 mmol) and (3S)-3-(3-oxo-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (3.14 g, 6.55 mmol) were added under cooling. The mixture was stirred under cooling for one hour, and then cerium chloride heptahydrate (1.64 g, 4.40 mmol) and sodium borohydride (166 mg, 4.39 mmol) were added. The mixture was stirred under cooling for 30 minutes and then ice-cooled. A saturated ammonium chloride solution (150 ml) was added to the reaction solution. The mixture was concentrated under reduced pressure and ethanol was removed. The mixture was extracted with ethyl acetate (150 ml × 1, 100 ml × 1). The organic layer was washed with brine (200 ml) and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 90:10 -> 66:34 -> 50:50 -> 34:66 -> 25:75 -> 17:83 -> 5:95) to give 2.83 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ: 7.35-7.23 (5H, m), 5.49 (1H, q, J=7.11 Hz), 5.15 (1H, d, J=1.23 Hz), 4.87 (1H, d, J=1.23 Hz), 3.98 (2H, d, J=6.37 Hz), 3.33 (1H, d, J=10.30 Hz), 3.22 (1H, d, J=10.30 Hz), 2.94 (1H, d, J=17.16 Hz), 2.62 (1H, d, J=14.95 Hz), 2.46 (1H, d, J=15.44 Hz), 2.44 (1H, d, J=17.16 Hz), 1.72 (1H, t, J=6.25 Hz), 1.52 (3H, d, J=7.11 Hz), 1.32 (9H, s).

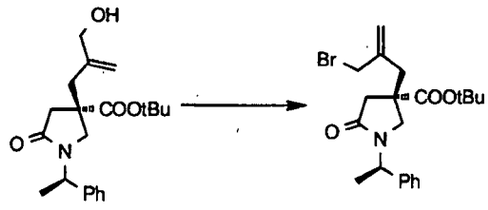
MS (ESI) m/z: 360 $(M+H)^+$.

[0751]

[Reference Example 192]

(3S)-3-(3-Bromo-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 306]



Carbon tetrabromide (3.24 g, 9.77 mmol) and triphenylphosphine (2.57 g, 9.80 mmol) were added to a solution of (3S)-3-(3-hydroxy-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester in dichloromethane (113 ml) under ice water-cooling in a nitrogen atmosphere. The mixture was stirred under ice water-cooling for 15 minutes and then concentrated under reduced pressure to remove the solvent.

The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 80:20 -> 75:25 -> 66:34) to give 3.22 g of the title compound as white crystals.

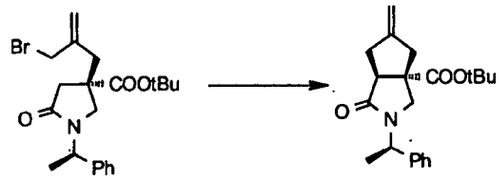
^{1}H-NMR ($CDCl_3$) δ: 7.34-7.22 (5H, m), 5.48 (1H, q, J=7.19 Hz), 5.26 (1H, s), 4.89 (1H, s), 3.88 (2H, s), 3.36 (1H, d, J=10.05 Hz), 3.21 (1H, d, J=10.30 Hz), 2.99 (1H, d, J=16.91 Hz), 2.72 (1H, d, J=15.44 Hz), 2.57 (1H, d, J=15.44 Hz), 2.44 (1H, d, J=16.91 Hz), 1.51 (3H, d, J=7.35 Hz), 1.30 (9H, s).

MS (ESI) m/z: 422 (M^+).

[Reference Example 193]

[(1S,5S)-7-Methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-aza-bicyclo[3.3.0]octan-1-yl]carboxylic acid tert-butyl ester

[Formula 307]



A 1 M solution of lithium hexamethyldisilazide in THF (9.15 ml, 9.15 mmol) was added to a solution of (3S)-3-(3-bromo-2-methylene-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (3.22 g, 7.62 mmol) in tetrahydrofuran (76.2 ml) under cooling with ice-acetone in a nitrogen atmosphere, and the

mixture was stirred for 10 minutes. A 10% citric acid solution (120 ml) was added to the reaction solution, followed by extraction with ethyl acetate (100 ml × 2). The organic layer was washed with brine (200 ml) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 83:17 -> 80:20 -> 75:25) to give 2.47 g of the title compound as white crystals.

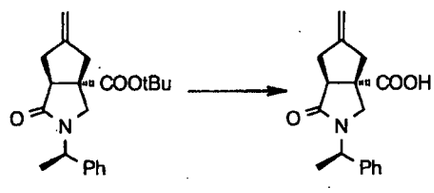
^{1}H-NMR ($CDCl_3$) δ: 7.34-7.23 (5H, m), 5.46 (1H, q, J=7.11 Hz), 4.88 (2H, d, J=1.72 Hz), 3.31 (1H, d, J=10.30 Hz), 3.13 (2H, t, J=6.37 Hz), 3.08 (2H, d, J=10.30 Hz), 2.89 (1H, d, J=15.69 Hz), 2.72 (2H, d, J=6.13 Hz), 2.30 (1H, d, J=15.93 Hz), 1.47 (3H, d, J=7.11 Hz), 1.35 (9H, s).

MS (ESI) m/z: 342 $(M+H)^+$.

[Reference Example 194]

[(1S,5S)-7-Methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-yl]carboxylic acid

[Formula 308]



Trifluoroacetic acid (26.0 ml) was added to a solution of [(1S,5S)-7-methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-aza-

bicyclo[3.3.0]octan-1-yl]carboxylic acid tert-butyl ester (2.47 g, 8.66 mmol) in dichloromethane (26.0 ml) with stirring under ice-cooling, and the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure, and trifluoroacetic acid was azeotropically distilled with toluene (× 3). A 1 mol/l sodium hydroxide solution (15.0 ml) was added to the resulting residue under ice-cooling, and the mixture was washed with diethyl ether (60 ml × 2). The aqueous layer was made acidic with 6 mol/l hydrochloric acid (4 ml) under ice-cooling, followed by extraction with ethyl acetate (100 ml × 2). The organic layers were combined, washed with water (100 mL) and brine (100 ml), and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 2.15 g of the title compound as white crystals.

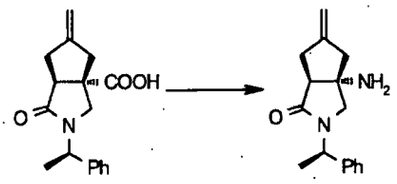
^{1}H-NMR ($CDCl_3$) δ: 7.36-7.24 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.93 (2H, s), 3.40 (1H, d, J=10.30 Hz), 3.27 (1H, dd, J=7.48, 4.78 Hz), 3.16 (1H, d, J=10.54 Hz), 3.02 (1H, d, J=15.93 Hz), 2.77 (2H, d, J=5.39 Hz), 2.38 (1H, d, J=15.93 Hz), 1.50 (3H, d, J=7.11 Hz).

MS (ESI) m/z: 342 $(M+H)^+$.

[Reference Example 195]

(1S,5S)-1-Amino-7-methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 309]



Triethylamine (0.489 ml, 3.50 mmol) and diphenylphosphoryl azide (0.491 ml, 2.28 mmol) were added to a solution of [(1S,5S)-7-methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-yl]carboxylic acid (500 mg, 1.75 mmol) in toluene (8.75 ml) in a nitrogen atmosphere with stirring under ice-cooling. The mixture was stirred at room temperature for 30 minutes and then at 100°C for 30 minutes. The reaction solution was concentrated under reduced pressure, and triethylamine was azeotropically removed with toluene (× 3). 1,4-Dioxane (4.37 ml) and 6 mol/L hydrochloric acid (4.37 ml) were added to the resulting residue, and the mixture was stirred at 50°C for one hour. The reaction solution was diluted with water (18.0 ml) and washed with diethyl ether (60 ml × 2). The aqueous layer was made alkaline with a 1 mol/l sodium hydroxide solution, followed by extraction with chloroform (80 ml × 1, 70 ml × 1). The organic layer was washed with water (80 ml) and brine (80 ml) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 238 mg of the title compound.

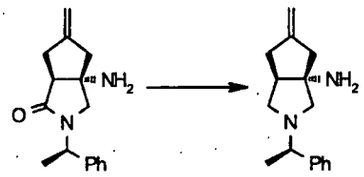
^{1}H-NMR ($CDCl_3$) δ: 7.38-7.24 (5H, m), 5.53 (1H, q, J=7.11 Hz), 4.92 (2H, brs), 3.25 (1H, d, J=10.05 Hz), 2.79-2.73 (3H, m), 2.58 (1H, dd, J=9.44, 4.04 Hz), 2.40 (2H, dd, J=35.17, 15.57 Hz), 1.48 (3H, d, J=7.11 Hz).

MS (ESI) m/z: 257 $(M+H)^+$.

[Reference Example 196]

(1S,5R)-1-Amino-7-methylene-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 310]



A 65% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (0.539 ml, 1.79 mmol) was added to a solution of (1S,5S)-1-amino-7-methylene-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (115 mg, 0.449 mmol) in toluene (2.24 ml), and the mixture was stirred at room temperature for 30 minutes and at 80°C for 30 minutes. A 5 mol/l sodium hydroxide solution (15.0 ml) was added to the reaction solution with stirring under ice-cooling, followed by extraction with toluene (30 ml × 1, 20 ml × 1). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 106 mg of the title compound.

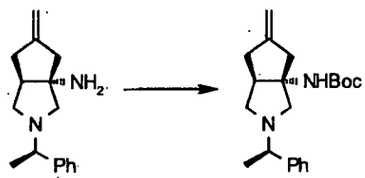
^{1}H-NMR ($CDCl_3$) δ: 7.38-7.19 (5H, m), 4.80-4.78 (2H, m), 3.14 (1H, q, J=6.45 Hz), 2.78 (1H, t, J=8.21 Hz), 2.65-2.56 (2H, m), 2.47 (1H, d, J=14.71 Hz), 2.33 (1H, d, J=9.07 Hz), 2.22 (1H, d, J=14.95 Hz), 2.13-2.06 (3H, m), 1.31 (3H, d, J=6.62 Hz).

MS (ESI) m/z: 243 $(M+H)^+$.

[Reference Example 197]

(1S,5R)-1-tert-Butoxycarbonylamino-7-methylene-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 311]



Di-tert-butyl dicarbonate (191 mg, 0.875 mmol) was added to a solution of (1S,5R)-1-amino-7-methylene-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (106 mg, 0.437 mmol) in dichloromethane (2.18 ml) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 22 hours. The reaction solution was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 88:12 -> 84:16 -> 80:20 -> 75:25) to give 203 mg of the title compound as a transparent oil.

^{1}H-NMR ($CDCl_3$) δ: 7.29-7.22 (5H, m), 4.86 (1H, brs), 4.79 (2H, d, J=7.84 Hz), 3.16 (1H, q, J=6.45 Hz), 2.92 (1H, d,

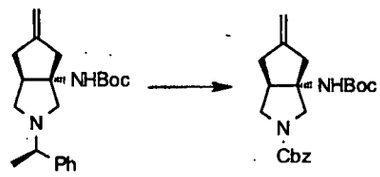
J=9.07 Hz), 2.76 (4H, t, J=8.58 Hz), 2.67-2.57 (4H, m), 2.40 (2H, d, J=9.56 Hz), 2.08-1.99 (2H, m), 1.43 (9H, s), 1.31 (3H, d, J=6.62 Hz).

MS (ESI) m/z: 343 $(M+H)^+$.

[Reference Example 198]

(1S,5R)-3-Benzyloxycarbonyl-1-tert-butoxycarbonylamino-7-methylene-3-azabicyclo[3.3.0]octane

[Formula 312]



Benzyl chloroformate (0.250 ml, 1.75 mmol) was added to a solution of the residue containing (1S,5R)-1-tert-butoxycarbonylamino-7-methylene-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (200 mg, equivalent to 0.437 mmol) in dichloromethane (1.94 ml) in a nitrogen atmosphere, and the mixture was stirred at room temperature for 15 hours and at 40°C for four hours. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 87:13 -> 86:14 -> 83:17 -> 80:20 -> 75:25) to give 95.1 mg of the title compound as a transparent oil.

^{1}H-NMR ($CDCl_3$) δ: 7.36-7.30 (7H, m), 5.12 (2H, s), 4.92 (2H, d, J=8.82 Hz), 4.67 (1H, brs), 3.74-3.72 (2H, m), 3.56 (1H,

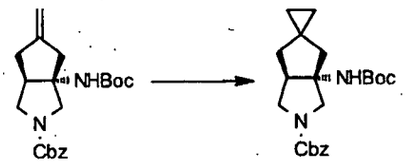
d, J=11.77 Hz), 3.27-3.24 (1H, m), 2.72-2.68 (4H, m), 2.19-2.17 (1H, m), 1.43 (9H, s).

MS (ESI) m/z: 373 $(M+H)^+$.

[Reference Example 199]

(1S,5R)-3-Benzyloxycarbonyl-1-tert-butoxycarbonylaminospiro(3-azabicyclo[3.3.0]octane-7,1'-cyclopropane)

[Formula 313]



N-Methyl-N'-nitro-N-nitrosoguanidine (50% mixture with water, 6 g) was added to a two-layer solution of a 40% potassium hydroxide solution (18 ml) and diethyl ether (60 ml) in an open system under ice water-cooling to prepare a solution of diazomethane in diethyl ether.

Palladium acetate (5.26 mg, 0.0234 mmol) was added to (1S,5R)-3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-7-methylene-3-azabicyclo[3.3.0]octane (175 mg, 0.469 mmol) in diethyl ether (4.69 ml) in an open system under ice-cooling. The previously prepared solution of diazomethane in diethyl ether (20 ml) was slowly added to this solution under ice-cooling, and the mixture was stirred at room temperature for 16 hours. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 -> 95:5 -> 90:10 -> 88:12 -> 87:13 -> 86:14 -> 85:15 -> 83:17 -> 80:20 -> 75:25) to give 138 mg of the title compound as a transparent oil.

^{1}H-NMR ($CDCl_3$) δ: 7.38-7.28 (5H, m), 5.13 (2H, s), 4.80 (1H, d, J=9.31 Hz), 3.77-3.72 (3H, m), 3.37-3.35 (1H, m), 2.66 (1H, s), 2.05-1.97 (3H, m), 1.60 (1H, s), 1.43 (10H, s), 0.47-0.46 (4H, m).

MS (ESI) m/z: 387 $(M+H)^+$.

[Reference Example 200]

(1S,5R)-1-tert-Butoxycarbonylaminospiro(3-azabicyclo[3.3.0]octane-7,1'-cyclopropane)

[Formula 314]



A 10% palladium-carbon catalyst (45.6 mg, 30 wt%) was added to a solution of (1S,5R)-3-benzyloxycarbonyl-1-tert-butoxycarbonylaminospiro(3-azabicyclo[3.3.0]octane-7,1'-cyclopropane) (152 mg, 0.393 mmol) in methanol (3.93 ml) in a nitrogen atmosphere. After the atmosphere was replaced with hydrogen, the mixture was stirred at room temperature for 30 minutes. After the atmosphere was replaced with nitrogen, the reaction solution was filtered through Celite

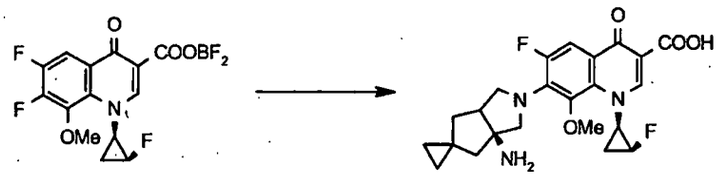
and concentrated under reduced pressure to give 97.9 mg of the title compound as a transparent oil.

MS (ESI) m/z: 253 $(M+H)^+$.

[Example 47]

7-[(1S,5R)-1-Aminospiro(3-azabicyclo[3.3.0]octane-7,1'-cyclopropane)-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

[Formula 315]



Triethylamine (0.162 ml, 0.388 mmol) and 1-[(1R,2S)-2-fluorocyclopropan-1-yl]-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (140 mg, 0.388 mmol) were added to a solution of (1S,5R)-1-tert-butoxycarbonylaminospiro(3-azabicyclo[3.3.0]octane-7,1'-cyclopropane) (97.9 mg, 0.388 mmol) in dimethyl sulfoxide (0.776 ml), and the mixture was stirred at 35°C for 14 hours. A mixed solution of ethanol:water = 4:1 (10.0 ml) and triethylamine (1.0 ml) were added to the reaction solution, and the mixture was heated to reflux for one hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 ml) and washed with a 10% citric acid solution (30 ml), water (30

ml), and brine (30 ml). The organic layer was dried over anhydrous sodium sulfate and then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 -> 99:1 -> 98:2). The resulting residue (165 mg) was dissolved in concentrated hydrochloric acid (1.0 ml) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. After washing with chloroform (25 ml × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 ml × 5) and chloroform/methanol = 10/1 (60 ml × 1). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in hot ethanol (20 ml), and the insoluble material was removed by filtration through a fluted filter paper. The solvent was gradually evaporated by heating the filtrate with stirring. The solution was concentrated to about 5 ml and then stirred at room temperature overnight. The precipitated crystals were collected by filtration and washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 50°C overnight to give 86.0 mg of the title compound as pale yellow crystals.

^{1}H-NMR (0.1NNaOD) δ: 8.46 (1H, s), 7.70 (1H, d, J=14.15 Hz), 5.06-5.04 (1H, m), 4.09-4.04 (1H, m), 3.92-3.86 (1H, m), 3.70-3.68 (4H, m), 3.58 (1H, d, J=10.73 Hz), 3.53-3.49 (1H, m), 2.54-2.46 (1H, m), 2.15-2.09 (1H, m), 1.86-1.76 (2H, m), 1.67-1.46 (3H, m), 0.57-0.45 (4H, m).

Anal. Calcd for $C_{23}H_{25}F_2N_3O_4 0.5H_2O$: C, 60.79; H, 5.77; F, 8.36; N, 9.25.

Found: C, 60.82; H, 5.73; F, 8.17; N, 9.23.

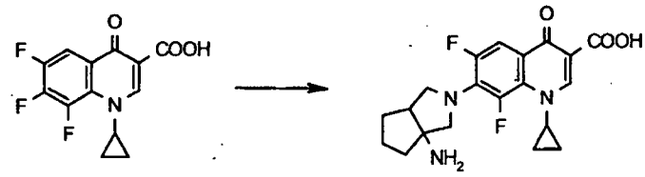
MS (ESI) m/z: 446 $(M+H)^+$.

IR (ATR): 2931, 2850, 1725, 1616, 1508, 1434, 1342, 1315, 1270, 1209, 1186, 1120, 1052, 1014, 987, 927, 881, 850, 806, 746 cm^{-1}.

[Example 48]

7-[(1S,5R)-1-Amino-3-azabicyclo[3.3.0]octan-3-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

[Formula 316]



A 10% palladium-carbon catalyst (M, about 50% wet, 72.6 mg) was added to a solution of (+)-(1S,5R)-3-benzyloxycarbonyl-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]octane (363 mg, 1.01 mmol) in methanol (10.1 ml), and the mixture was stirred in a hydrogen

atmosphere in a rubber balloon at room temperature for 45 minutes. The catalyst was removed by filtration, and then the solvent was evaporated under reduced pressure to give 229 mg of a residue containing (1S,5R)-1-(tert-butoxycarbonylamino)-3-azabicyclo[3.3.0]octane as a colorless transparent gummy solid.

Triethylamine (0.423 ml, 3.03 mmol) and 1-cyclopropyl-6,7,8-trifluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (272 mg, 0.960 mmol) were added to a solution of the residue containing (1S,5R)-1-tert-butoxycarbonylamino-3-azabicyclo[3.3.0]octane obtained above (229 mg) in acetonitrile (3.84 ml) in a nitrogen atmosphere, and the mixture was heated to reflux for six hours. The reaction solution was ice-cooled, and then the precipitated crystals were collected by filtration and washed with acetonitrile and diethyl ether. The crystals were dried under reduced pressure at 50°C overnight. The resulting residue (410 mg) was dissolved in concentrated hydrochloric acid (3 ml) under ice-cooling, and then the solution was stirred at room temperature for 15 minutes. After washing with chloroform (40 ml × 3), the aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform (80 ml × 2) and chloroform/methanol = 10/1 (100

ml × 6). The organic layer was dried over anhydrous sodium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. Hot ethanol (150 ml) and 28% aqueous ammonia (3 to 5 ml) were added to the residue, and the insoluble material was removed by filtration through a fluted filter paper. The solvent was gradually evaporated while heating with stirring. Ammonia was azeotropically removed with ethanol several times. The solution was concentrated to about 10 ml and then stirred at room temperature for four hours. The precipitated crystals were collected by filtration and washed with ethanol and diethyl ether. The crystals were dried under reduced pressure at 45°C overnight to give 289 mg of the title compound as pale yellow crystals.

^{1}H-NMR (0.1NNaOD) δ: 8.44 (1H, s), 7.62 (1H, d, J=13.73 Hz), 3.97-3.86 (2H, m), 3.59 (1H, d, J=10.30 Hz), 3.49 (1H, d, J=10.30 Hz), 3.32 (1H, d, J=5.64 Hz), 2.31-2.26 (1H, m), 2.02 (1H, dt, J=20.43, 7.48 Hz), 1.90-1.84 (1H, m), 1.81-1.74 (2H, m), 1.70-1.63 (1H, m), 1.51-1.48 (1H, m), 1.19 (2H, t, J=7.11 Hz), 1.07 (2H, s).

Anal. Calcd for $C_{20}H_{21}F_2N_3O_3 0.75H_2O$: C, 59.62; H, 5.63; F, 9.43; N, 10.43.

Found: C, 59.69; H, 5.58; F, 9.31; N, 10.35.

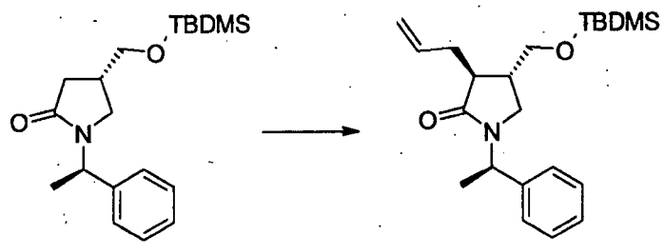
MS (ESI) m/z: 390 $(M+H)^+$.

IR (ATR): 2956, 1612, 1573, 1542, 1508, 1459, 1402, 1351, 1317, 1274, 1201, 1166, 1106, 1031, 979, 817, 732 cm^{-1}.

[Reference Example 201]

(3S,4S)-3-Allyl-4-(tert-butyldimethylsilyloxy)methyl-2-oxo-1-[(1R)-1-phenylethyl]pyrrolidine

[Formula 317]



JP09136886A (1997)

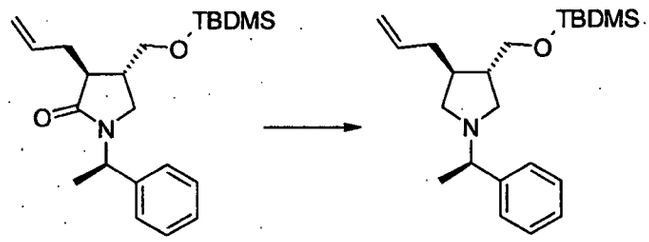
(4S)-4-(tert-Butyldimethylsilyloxy)methyl-2-oxo-1-[(1R)-1-phenylethyl]pyrrolidine (333.5 g, 1.00 mol) and allyl bromide (90.9 mL, 1.05 mol) were dissolved in tetrahydrofuran (1.10 L). Lithium hexamethyldisilazide (1.0 M solution in tetrahydrofuran) (1.10 L, 1.10 mol) was added dropwise at -15°C, and the mixture was stirred at -5°C for one hour. The reaction solution was extracted with a saturated ammonium chloride solution and ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Thereafter, the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 4:1 -> 2:1) to give 327 g of the title compound as a colorless syrup.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.42-7.32 (5H, m), 5.93-5.80 (1H, m), 5.57 (1H, q, J=7.1 Hz), 5.22-5.12 (2H, m), 3.56 (1H, dd, J=10.0, 4.9 Hz), 3.48-3.43 (1H, m), 3.34 (1H, dd, J=10.3, 8.1 Hz), 2.82 (1H, dd, J=9.8, 5.9 Hz), 2.65-2.57 (1H, m), 2.48-2.40 (2H, m), 2.32-2.24 (1H, m), 1.59 (3H, d, J=7.6 Hz), 0.86 (9H, s), 0.00 (6H, s).

[Reference Example 202]

(3S,4S)-3-Allyl-4-(tert-butyldimethylsilyloxy)methyl-1-[(1R)-1-phenylethyl]pyrrolidine

[Formula 318]



A 65% solution of Red-Al™ in toluene (788 mL, 2.63 mol) was added dropwise to a solution of (3S,4S)-3-allyl-4-(tert-butyldimethylsilyloxy)methyl-2-oxo-1-[(1R)-1-phenylethyl]pyrrolidine (327 g, 875 mmol) in toluene (1500 mL) in a nitrogen atmosphere over one hour. The reaction solution was stirred at 45°C for five hours and then cooled to 0°C, and a 20% (+)-potassium sodium tartrate tetrahydrate solution (2.00 L) was added. The reaction solution was poured into a mixture of ethyl acetate and brine, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and

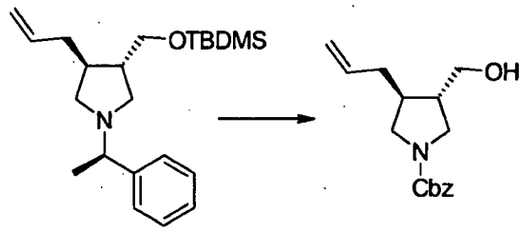
then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1 -> 4:1) to give 213 g of the title compound as a colorless syrup.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29-7.10 (5H, m), 5.73-5.63 (1H, m), 4.97-4.87 (2H, m), 3.49 (2H, d, J=6.8 Hz), 3.09 (1H, q, J=6.6 Hz), 2.57-2.49 (2H, m), 2.39 (1H, t, J=8.5 Hz), 2.20-2.13 (1H, m), 2.09-2.00 (2H, m), 1.91-1.83 (1H, m), 1.78-1.68 (1H, m), 1.28 (3H, d, J=6.6 Hz), 0.85 (9H, s), 0.27 (6H, d, J=1.0 Hz).

[Reference Example 203]

(3S,4S)-3-Allyl-1-benzyloxycarbonyl-4-hydroxymethylpyrrolidine

[Formula 319]



(3S,4S)-3-Allyl-4-(tert-butyldimethylsilyloxy)methyl-1-[(1R)-1-phenylethyl]pyrrolidine (213 g, 592 mmol) was dissolved in dichloromethane (420 mL). Benzyl chloroformate (169.2 mL, 1.19 mol) was added dropwise, and the mixture was stirred at 55°C for 10 hours and then at room temperature for 14 hours. A 1 M solution of hydrochloric acid in ethanol (250 mL, 250 mmol) was further added to the

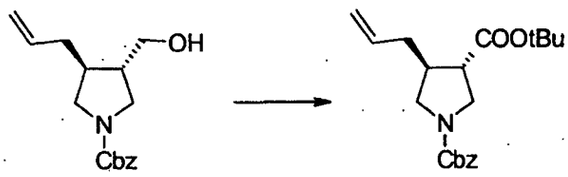
reaction solution, and the mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with a saturated sodium bicarbonate solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:1 -> 1:1) to give 140 g of the title compound as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.75 (1H, brs), 5.13-5.02 (4H, m), 3.76-3.54 (4H, m), 3.31-3.23 (1H, m), 3.15-3.07 (1H, m), 2.32-2.26 (1H, m), 2.14-2.03 (3H, m).

[Reference Example 204]

(3S,4S)-4-Allyl-1-benzyloxycarbonylpyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 320]



Oxalyl dichloride (48.0 mL, 559 mmol) was dissolved in dichloromethane (1000 mL). Dimethyl sulfoxide (39.7 mL, 559 mmol) was added dropwise at -70°C, and the mixture was stirred for 15 hours. A solution of (3S,4S)-3-allyl-1-benzyloxycarbonyl-4-hydroxymethylpyrrolidine (140 g, 508 mmol) in dichloromethane (400 mL) was added dropwise to the

reaction solution, and the mixture was stirred for 50 minutes. Triethylamine (354 mL, 2.54 mol) was added dropwise to the reaction solution, and then the mixture was stirred at -10°C for 10 minutes. The reaction solution was extracted with water and dichloromethane. Then, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.

The resulting residue was dissolved in a mixed solution of tert-butyl alcohol (250 mL) and tetrahydrofuran (750 mL). 2-Methyl-2-butene (538 mL, 5.08 mol) was added and then a suspension of sodium chlorite (60.3 g, 533 mmol) and sodium dihydrogenphosphate dihydrate (238 g, 1.52 mol) in water (250 ml) was added at 0°C, and the mixture was stirred at room temperature for 20 hours. The reaction solution was concentrated under reduced pressure, and then a 1N hydrochloric acid solution was added, followed by extraction with diethyl ether. The organic layer was washed with a 5% sodium thiosulfate solution and brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The resulting residue was dissolved in dichloromethane (1000 mL). N,N'-Diisopropyl-O-tert-butylisourea (509 g, 2.54 mol) was added dropwise, and the mixture was stirred at 50°C for four hours and then at room temperature for 15 hours. The precipitated solid was filtered off, and then

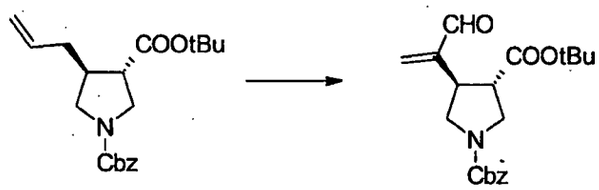
the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:1 -> 4:1) to give 126 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (5H, m), 5.81-5.65 (1H, m), 5.14-5.07 (2H, m), 5.06-5.00 (2H, m), 3.77-3.63 (2H, m), 3.58-3.49 (1H, m), 3.13-3.01 (1H, m), 2.71-2.59 (1H, m), 2.48 (1H, brs), 2.36-2.26 (1H, m), 2.16-2.04 (1H, m), 1.45 (9H, s).

[Reference Example 205]

(3S,4R)-1-Benzyloxycarbonyl-4-(1-formylvinyl)pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 321]



(3S,4S)-4-Allyl-1-benzyloxycarbonylpyrrolidine-3-carboxylic acid tert-butyl ester (70.0 g, 203 mmol) was dissolved in a mixed solution of tetrahydrofuran (350 mL) and water (350 mL). Sodium metaperiodate (86.7 g, 406 mmol) and osmium tetroxide (a catalytic amount) were sequentially added, and the mixture was stirred at room temperature for 20 hours. A 10% sodium bisulfite solution was added to the reaction solution, followed by extraction with dichloromethane. The organic layer was washed with water

and brine, and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

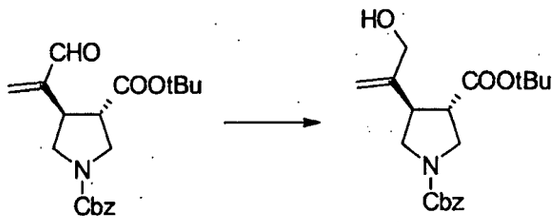
The resulting residue was dissolved in dichloromethane (700 mL). N,N-Dimethylmethyleneammonium iodide (56.3 g, 305 mmol) and 1,8-diazabicyclo[5.4.0]undecene (33.4 mL, 223 mmol) were added dropwise, and the mixture was stirred at room temperature for 59 hours. A saturated ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 24:1 -> 4:1) to give 56.7 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.55 (1H, d, J=5.1 Hz), 7.40-7.28 (5H, m), 6.38 (1H, d, J=2.0 Hz), 6.15 (1H, d, J=3.2 Hz), 5.13 (2H, d, J=4.1 Hz), 3.89-3.74 (2H, m), 3.60 (1H, t, J=9.6 Hz), 3.49-3.41 (1H, m), 3.29 (1H, dt, J=30.0, 9.7 Hz), 3.15-3.07 (1H, m), 1.41 (9H, s).

[Reference Example 206]

(3S,4R)-1-Benzyloxycarbonyl-4-[1-(hydroxymethyl)vinyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 322]



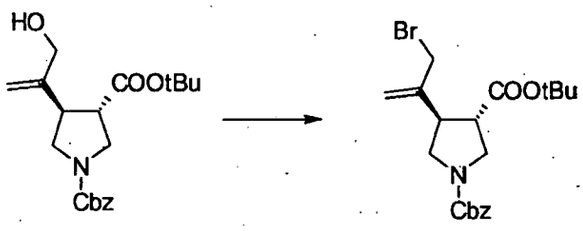
Cerium (III) chloride heptahydrate (57.0 g, 153 mmol) was dissolved in ethanol (700 mL). Sodium borohydride (5.79 g, 153 mmol) was added at 0°C, and the mixture was stirred for 10 minutes. A solution of (3S,4R)-1-benzyloxycarbonyl-4-(1-formylvinyl)pyrrolidine-3-carboxylic acid tert-butyl ester (55.0 g, 153 mmol) in ethanol (700 mL) was added dropwise to the reaction solution at 0°C, and the mixture was stirred at room temperature for three hours. The reaction solution was extracted with a 10% citric acid solution, water, and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 24:1 -> 2:1) to give 42.2 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.20 (1H, brs), 5.17-5.10 (2H, m), 5.04 (1H, d, J=5.4 Hz), 4.16-4.09 (3H, m), 3.87-3.77 (2H, m), 3.52 (1H, dd, J=17.2, 8.9 Hz), 3.29 (1H, q, J=10.9 Hz), 3.18-2.98 (2H, m), 1.43 (9H, s).

[Reference Example 207]

(3S,4R)-1-Benzyloxycarbonyl-4-[1-(bromomethyl)vinyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 323]



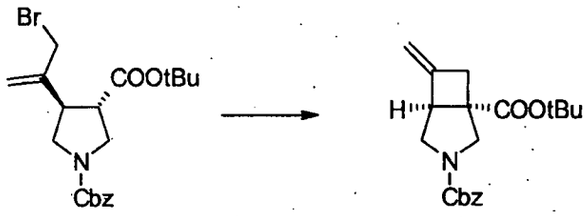
(3S,4R)-1-Benzyloxycarbonyl-4-[1-(hydroxymethyl)vinyl]pyrrolidine-3-carboxylic acid tert-butyl ester (30.0 g, 83.0 mmol) was dissolved in dichloromethane (300 mL). Triphenylphosphine (23.2 g, 87.2 mmol) and carbon tetrabromide (29.4 g, 87.2 mmol) were added, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure. Then, the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:1 -> 1:1) to give 26.9 g of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.34 (1H, s), 5.16-5.12 (3H, m), 3.99 (2H, q, J=10.6 Hz), 3.91-3.78 (2H, m), 3.59-3.53 (1H, m), 3.34-3.22 (2H, m), 3.08-2.96 (1H, m), 1.44 (9H, s).

[Reference Example 208]

(1S,5S)-3-Benzyloxycarbonyl-6-methylene-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester

[Formula 324]



(3S,4R)-1-Benzyloxycarbonyl-4-[1-(bromomethyl)vinyl]pyrrolidine-3-carboxylic acid tert-butyl ester (22.8 g, 53.7 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (19.5 mL, 161 mmol) were dissolved in a mixed solution of tetrahydrofuran (220 mL) and toluene (220 mL). Lithium hexamethyldisilazide (1.0 M solution in tetrahydrofuran) (80.6 mL, 80.6 mmol) was added dropwise at -78°C, and then the mixture was stirred at room temperature for five minutes. The reaction solution was extracted with a saturated ammonium chloride solution and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 24:1 -> 2:1) to give 8.34 g of the title compound as a colorless syrup.

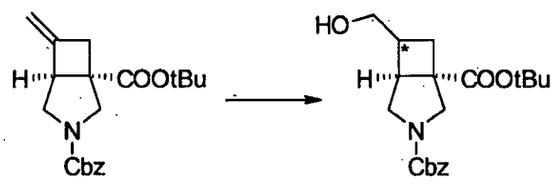
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.24 (5H, m), 5.14 (2H, d, J=2.4 Hz), 4.98-4.88 (2H, m), 3.93-3.76 (2H, m), 3.66 (1H,

d, J=11.7 Hz), 3.59-3.54 (1H, m), 3.45-3.38 (1H, m), 3.24 (1H, dt, J=16.4, 2.6 Hz), 2.67-2.57 (1H, m), 1.46 (9H, s).

[Reference Example 209]

(1S,5S,6R)-/(1S,5S,6S)-3-Benzyloxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester

[Formula 325]



(1S,5S)-3-Benzyloxycarbonyl-6-methylene-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (2.00 g, 5.82 mmol) was dissolved in tetrahydrofuran (40 mL). A 9-borabicyclo[3.3.1]nonane dimmer (0.5 M solution in tetrahydrofuran) (17.5 mL, 8.73 mmol) was added dropwise, and then the mixture was stirred for two hours. A 3 M sodium hydroxide solution (3.49 mL, 10.5 mmol) and 30% aqueous hydrogen peroxide (2.47 mL) were added dropwise to the reaction solution at 0°C, and then the mixture was stirred at room temperature for 16 hours. The reaction solution was extracted with water and ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 100:1 -> 1:2) to

give 1.58 g of an isomer A (less polar isomer) of the title compound and 50.0 mg of an isomer B (more polar isomer) of the title compound as colorless syrups.

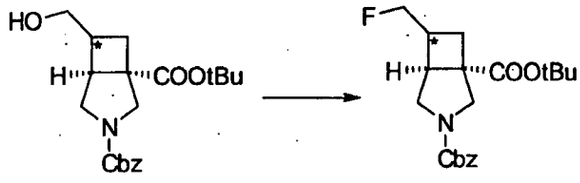
Isomer A; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.30 (5H, m), 5.17 (2H, s), 4.00 (1H, d, J=12.4 Hz), 3.75-3.54 (4H, m), 3.42 (1H, d, J=11.7 Hz), 3.29 (1H, dd, J=12.6, 7.9 Hz), 3.09 (1H, t, J=8.2 Hz), 2.74-2.64 (1H, m), 2.67-2.54 (1H, m), 1.47 (9H, s).

Isomer B; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.17 (2H, s), 3.86-3.56 (6H, m), 3.38 (1H, dd, J=11.6, 6.0 Hz), 2.85-2.78 (1H, m), 2.32-2.22 (1H, m), 2.19-2.09 (1H, m), 1.45 (9H, s).

[Reference Example 210]

(1S,5S)-3-Benzyloxycarbonyl-6-fluoromethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (derived from isomer A)

[Formula 326]



(1S,5S)-3-Benzyloxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (isomer A) (1.51 g, 4.18 mmol) was dissolved in dichloromethane (30 mL). Triethylamine (1.28 mL, 9.20 mmol) and chloromethylsulfonyl chloride (746 μL, 8.36 mmol) were

added dropwise at 0°C, and then the mixture was stirred for 15 minutes. The reaction solution was extracted with a saturated ammonium chloride solution and ethyl acetate at 0°C. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

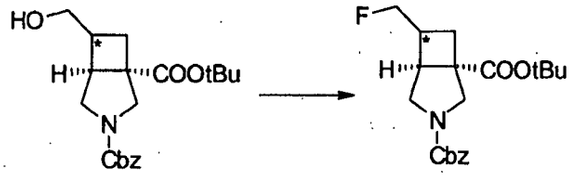
The resulting residue was dissolved in tetrahydrofuran (20 mL). Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) (16.7 mL, 16.7 mmol) was added dropwise at 0°C, and then the mixture was stirred for 16 hours. The reaction solution was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 100:1 -> 1:1) to give 1.01 g of the title compound as a colorless syrup.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m), 5.18 (2H, s), 4.48-4.26 (2H, m), 3.99 (1H, d, J=12.7 Hz), 3.72 (1H, brs), 3.43 (1H, d, J=12.6 Hz), 3.31 (1H, dd, J=13.2, 7.8 Hz), 3.11 (1H, t, J=8.0 Hz), 2.96-2.79 (1H, m), 2.62-2.53 (1H, m), 1.69-1.60 (1H, m), 1.48 (9H, s).

[Reference Example 211]

(1S,5S)-3-Benzyloxycarbonyl-6-fluoromethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (derived from isomer B)

[Formula 327]



(1S,5S)-3-Benzyloxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (isomer B) (180 mg, 498 μmol) was dissolved in dichloromethane (4 mL). Triethylamine (153 μL, 1.10 mmol) and chloromethylsulfonyl chloride (89.0 μL, 996 μmol) were added dropwise at 0°C, and then the mixture was stirred for 15 minutes. The reaction solution was extracted with a saturated ammonium chloride solution and ethyl acetate at 0°C. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The resulting residue was dissolved in tetrahydrofuran (4 mL). Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) (1.99 mL, 1.99 mmol) was added dropwise at 0°C, and then the mixture was stirred for two hours. The reaction solution was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 100:1 -> 1:1) to give 80.6 mg of the title compound as a colorless syrup.

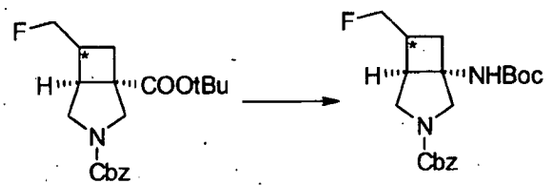
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m), 5.17 (2H, s), 4.52-4.31 (2H, m), 3.89-3.56 (3H, m), 3.38 (1H, dd, J=12.0,

6.6 Hz), 2.89 (1H, t, J=5.6 Hz), 2.40-2.25 (2H, m), 2.06-2.02 (1H, m), 1.46 (9H, s).

[Reference Example 212]

(1S,5R)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer A)

[Formula 328]



Trifluoroacetic acid (4 mL) was added dropwise to a solution of (1S,5S)-3-benzyloxycarbonyl-6-fluoromethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (derived from isomer A) (887 mg, 2.44 mmol) in dichloromethane (4 mL) under ice-cooling, and the mixture was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and then a 1 M sodium hydroxide solution was added to the residue under ice-cooling. The solution was washed with diethyl ether, and then the aqueous layer was adjusted to pH 2 to 3 with concentrated hydrochloric acid under ice-cooling, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduce pressure.

1,1'-Carbonylbis-1*H*-imidazole (594 mg, 3.66 mmol) was added to a solution of the resulting residue in acetonitrile (16 mL), and the mixture was stirred for one hour. The reaction solution was bubbled with ammonia gas for 1.5 hours. Then, water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

Lead tetraacetate (2.16 g, 4.88 mmol) was added to a solution of the resulting residue in tert-butyl alcohol (16 mL), and the mixture was heated with stirring at 80°C for 15 minutes. After allowing to cool, sodium bicarbonate (2.50 g) and diethyl ether were added to the reaction solution, and the mixture was stirred under ice-cooling for 30 minutes. The insoluble material was removed by filtration through Celite, and then the filtrate was washed with a saturated sodium bicarbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1 -> 1:1) to give 754 mg of the title compound as a colorless syrup.

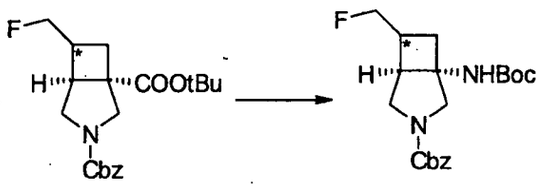
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.16 (2H, s), 4.89-4.79 (1H, m), 4.53-4.27 (2H, m), 3.91 (1H, d, J=12.5 Hz), 3.77 (1H, d, J=11.5 Hz), 3.51-3.40 (1H, m), 3.33-3.26

(1H, m), 3.00-2.86 (2H, m), 2.37-2.23 (1H, m), 1.87 (1H, dd, J=13.1, 6.7 Hz), 1.45 (9H, s).

[Reference Example 213]

(1S,5R)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer B)

[Formula 329]



Trifluoroacetic acid (3 mL) was added dropwise to a solution of (1S,5S)-3-benzyloxycarbonyl-6-fluoromethyl-3-azabicyclo[3.2.0]heptane-1-carboxylic acid tert-butyl ester (derived from isomer B) (660 mg, 1.82 mmol) in dichloromethane (3 mL) under ice-cooling, and the mixture was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, and then a 1 M sodium hydroxide solution was added to the residue under ice-cooling. The solution was washed with diethyl ether, and then the aqueous layer was adjusted to pH 2 to 3 with concentrated hydrochloric acid under ice-cooling, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

1,1'-Carbonylbis-1*H*-imidazole (443 mg, 2.73 mmol) was added to a solution of the resulting residue in acetonitrile (12 mL), and the mixture was stirred for one hour. The reaction solution was bubbled with ammonia gas for 1.5 hours. Then, water was added to the reaction solution, followed by extraction with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

Lead tetraacetate (1.61 g, 3.64 mmol) was added to a solution of the resulting residue in tert-butyl alcohol (12 mL), and the mixture was heated with stirring at 80°C for 15 minutes. After allowing to cool, sodium bicarbonate (2.00 g) and diethyl ether were added to the reaction solution, and the mixture was stirred under ice-cooling for 30 minutes. The insoluble material was filtered off through Celite, and then the filtrate was washed with a saturated sodium bicarbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 16:1 -> 1:1) to give 590 mg of the title compound as a colorless syrup.

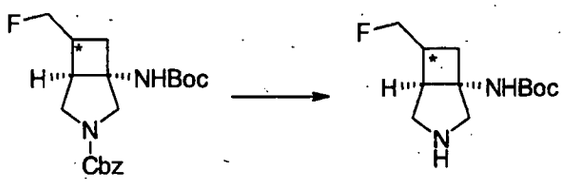
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.15 (2H, s), 4.89-4.74 (1H, m), 4.58-4.32 (2H, m), 3.91 (1H, d, J=11.7

Hz), 3.76-3.46 (3H, m), 2.83-2.66 (1H, m), 2.31 (1H, dd, J=10.7, 8.8 Hz), 2.19-2.05 (2H, m), 1.43 (9H, s).

[Reference Example 214]

(1S,5R)-1-(tert-Butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer A)

[Formula 330]



(1S,5R)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer A) (625 mg, 1.65 mmol) was dissolved in tetrahydrofuran (12 mL). 20% palladium hydroxide-carbon (50% wet) (200 mg) was added, and the mixture was stirred in a hydrogen atmosphere for one hour. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1 M sodium hydroxide solution was added to the residue under ice-cooling, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 403 mg of the title compound as a colorless syrup.

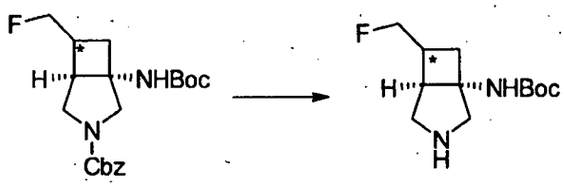
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.89-4.78 (1H, m), 4.66-4.39 (2H, m), 3.15 (1H, d, J=11.5 Hz), 3.07-2.78 (4H, m), 2.71 (1H, d,

J=10.3 Hz), 2.34-2.26 (1H, m), 1.90 (1H, dd, J=12.7, 8.3 Hz), 1.46 (9H, s).

[Reference Example 215]

(1S,5R)-1-(tert-Butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer B)

[Formula 331]



(1S,5R)-3-Benzyloxycarbonyl-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer B) (305 mg, 806 μmol) was dissolved in tetrahydrofuran (6 mL). 20% palladium hydroxide-carbon (50% wet) (100 mg) was added, and the mixture was stirred in a hydrogen atmosphere for one hour. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure. A 1 M sodium hydroxide solution was added to the residue under ice-cooling, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 196 mg of the title compound as a colorless syrup.

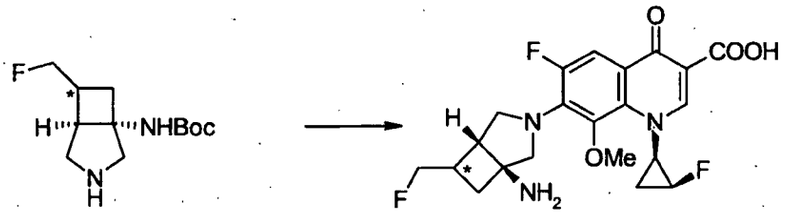
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.82 (1H, brs), 4.58-4.39 (2H, m), 3.16 (1H, d, J=11.2 Hz), 3.06 (1H, dd, J=11.1, 5.2 Hz),

2.85 (2H, dd, J=19.3, 11.7 Hz), 2.65-2.53 (1H, m), 2.27-1.86 (3H, m), 1.44 (9H, s).

[Example 49]

7-[(1S,5R)-1-Amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (derived from isomer A)

[Formula 332]



Triethylamine (143 μL, 1.03 mmol) and 6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (309 mg, 855 μmol) were added to a solution of (1S,5R)-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer A) (209 mg, 855 μmol) in sulfolane (3 mL). The mixture was stirred at 40°C for 87 hours. Ethanol (20 mL), water (2 mL), and triethylamine (0.5 mL) were added to the reaction solution, and the mixture was heated to reflux for two hours. The solvent was evaporated under reduced pressure, and then the resulting residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was

washed with water three times and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (chloroform:methanol = 99:1 -> 9:1). The resulting oil (1.02 g) was dissolved in concentrated hydrochloric acid (5 ml) under ice-cooling, and the solution was stirred at room temperature for 15 minutes. The reaction solution was washed with chloroform five times, and then the aqueous layer was adjusted to pH 11 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by PTLC (using the lower layer of chloroform:methanol:water = 7:3:1 as a developing solvent), and then the resulting fraction was concentrated under reduced pressure. The resulting residue was recrystallized from ethanol to give 120 mg of the title compound as a white solid.

mp: 122-125°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.47 (1H, brs), 7.74 (1H, d, J=13.4 Hz), 5.00 (1H, d, J=64.5 Hz), 4.70-4.49 (2H, m), 4.09-4.01 (1H, m), 3.75-3.54 (6H, m), 3.14 (1H, d, J=10.5 Hz), 3.02-2.89 (1H, m), 2.65 (1H, t, J=7.8 Hz), 2.16 (1H, t,

J=11.8 Hz), 2.00 (1H, dd, J=12.7, 7.8 Hz), 1.67-1.41 (2H, m).

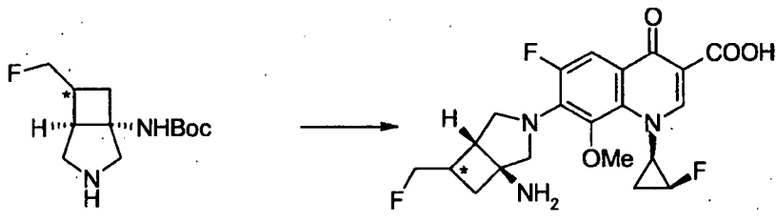
Anal. Calcd for $C_{21}H_{22}F_3N_3O_4 \cdot 2.5H_2O$: C, 52.28; H, 5.64; N, 8.71. Found: C, 52.03; H, 5.50; N, 8.47.

IR (KBr) ν: 3404, 2963, 1731, 1619, 1579, 1541, 1452, 1392, 1360, 1320, 1293, 1270, 1053 cm^{-1}.

[Example 50]

7-[(1S,5R)-1-Amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (derived from isomer B)

[Formula 333]



Triethylamine (135 μL, 967 μmol) and 6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid-BF_2 chelate (291 mg, 806 μmol) were added to a solution of (1S,5R)-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer B) (196 mg, 806 μmol) in sulfolane (2 mL). The mixture was stirred at 40°C for 111 hours. Ethanol (10 mL), water (1 mL), and triethylamine (0.5 mL) were added to the reaction solution,

and the mixture was heated to reflux for one hour. The solvent was evaporated under reduced pressure, and then the resulting residue was extracted with a 10% citric acid solution and ethyl acetate. Then, the organic layer was washed with water three times and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (chloroform:methanol = 99:1 -> 9:1). The resulting oil (515 mg) was dissolved in concentrated hydrochloric acid (5 ml) under ice-cooling, and then the solution was stirred at room temperature for 15 minutes. The reaction solution was washed with chloroform five times, and then the aqueous layer was adjusted to pH 11 with a saturated sodium hydroxide solution. The basic solution was adjusted to pH 7.4 with hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by PTLC (using the lower layer of chloroform:methanol:water = 7:3:1 as a developing solvent), and then the resulting fraction was concentrated under reduced pressure. The resulting residue was recrystallized from ethanol to give 125 mg of the title compound as a white solid.

mp: 193-195°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.48 (1H, brs), 7.73 (1H, d, J=13.7 Hz), 4.98 (1H, d, J=65.2 Hz), 4.68-4.48 (2H, m), 4.10-4.04 (1H, m), 3.76-3.67 (5H, m), 3.58-3.52 (1H, m), 3.22 (1H, d, J=10.5 Hz), 2.46-2.41 (1H, m), 2.40-2.22 (2H, m), 1.96-1.87 (1H, m), 1.69-1.44 (2H, m).

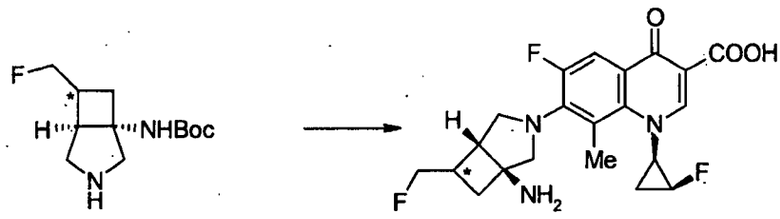
Anal. Calcd for $C_{21}H_{22}F_3N_3O_4$: C, 57.66; H, 5.07; F, 13.03; N, 9.61. Found: C, 57.42; H, 5.07; F, 12.98; N, 9.53.

IR (KBr) ν: 3393, 3086, 3063, 3034, 2954, 2930, 2897, 2872, 1720, 1621, 1514, 1452, 1395, 1365, 1344, 1318, 1288, 1273, 1186, 1123, 1108, 1060, 1038, 1020 cm^{-1}.

[Example 51]

7-[(1S,5R)-1-Amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (derived from isomer A)

[Formula 334]



A solution of (1S,5R)-1-(tert-butoxycarbonylamino)-6-fluoromethyl-3-azabicyclo[3.2.0]heptane (derived from isomer A) (157 mg, 643 μmol), 7-bromo-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (226 mg, 643

μmol), rac-2,2'-bis(diphenylphosphino)-1,1'-dinaphthyl (273 mg, 438 μmol), tris(dibenzylideneacetone)dipalladium (0) (134 mg, 146 μmol), and cesium carbonate (381 mg, 1.17 mmol) in dioxane (5.00 mL) was stirred in an argon atmosphere at room temperature for 30 minutes and at 100°C for 16 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate and chloroform. Then, the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 7:1 -> ethyl acetate).

A 1N sodium hydroxide solution (1.21 mL) was added to a solution of the resulting pale yellow foam in ethanol (5 mL) at 0°C, and the mixture was stirred at room temperature for 30 hours. A 10% citric acid solution was added to the reaction solution at 0°C, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure.

The resulting residue was dissolved in concentrated hydrochloric acid (5 mL) at 0°C. The mixture was stirred for 15 minutes and then washed with chloroform five times. The aqueous layer was adjusted to pH 12 with a saturated sodium hydroxide solution at 0°C and then adjusted to pH 7.4 with hydrochloric acid, followed by extraction with

chloroform. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by PTLC (using the lower layer of chloroform:methanol:water = 7:3:1 as a developing solvent). Then, the resulting fraction was recrystallized from ethanol to give 28.5 mg of the title compound as a white solid.

mp: 130-133°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.46 (1H, d, J=3.2 Hz), 7.73 (1H, d, J=13.8 Hz), 5.01 (1H, d, J=64.2 Hz), 4.78-4.46 (2H, m), 4.13-4.06 (1H, m), 3.91-3.84 (1H, m), 3.51 (1H, d, J=9.6 Hz), 3.34 (1H, d, J=11.0 Hz), 2.99-2.87 (2H, m), 2.71-2.64 (4H, m), 2.24-2.12 (2H, m), 1.66-1.55 (1H, m), 1.29-1.16 (1H, m).

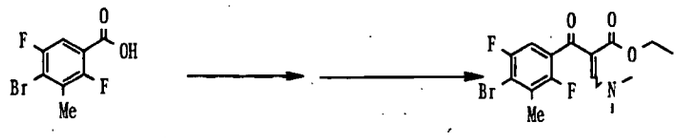
Anal. Calcd for $C_{21}H_{22}F_3N_3O_3 \cdot 2.25H_2O \cdot 0.25IPA$: C, 54.77; H, 6.02; F, 11.95; N, 8.81. Found: C, 54.82; H, 5.71; F, 11.84; N, 8.85.

IR (KBr) ν: 3414, 2970, 1723, 1616, 1580, 1546, 1508, 1458, 1434, 1394, 1363, 1320, 1103, 1023 cm^{-1}.

[Reference Example 216]

Ethyl 2-(4-bromo-2,5-difluoro-3-methylbenzoyl)-3-dimethylaminoacrylate

[Formula 335]



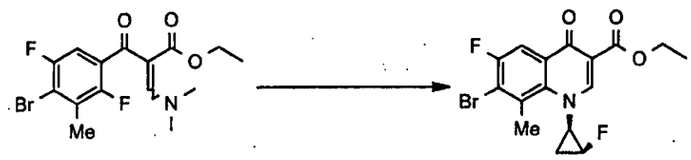
2,5-Difluoro-4-bromo-3-methylbenzoic acid (10.7 g, 42.4 mmol) was dissolved in toluene (160 mL). Thionyl chloride (5.00 mL, 63.9 mmol) and dimethylformamide (5.0 mL) were added, and the mixture was heated to reflux for two hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in tetrahydrofuran (300 mL). Ethyl 3-dimethylaminoacrylate (7.30 ml, 50.9 mmol) and triethylamine (7.60 mL, 54.5 mmol) were added, and the mixture was heated to reflux for three hours. The solvent was evaporated under reduced pressure, and dichloromethane and water were added to the residue to separate the layers. Then, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to flash column chromatography (hexane:ethyl acetate = 2:1 -> 1:1 -> 1:2) to give the title compound (11.35 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 7.81-7.74 (1H, m), 7.27-7.16 (1H, m), 4.00 (2H, q, *J*=7.1 Hz), 3.31 (3H, br s), 2.89 (3H, br s), 2.35 (3H, d, *J*=2.9 Hz), 0.97 (3H, t, *J*=7.1 Hz).

[Reference Example 217]

Ethyl 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate

[Formula 336]



Ethyl 2-(4-bromo-2,5-difluoro-3-methylbenzoyl)-3-dimethylaminoacrylate (11.4 g, 30.2 mmol) was dissolved in dichloromethane (200 mL). (1R,2S)-2-Fluorocyclopropylamine tosylate (8.24 g, 33.3 mmol) was added, and the mixture was cooled to -25°C. Triethylamine (6.60 mL, 47.4 mmol) was added dropwise to the reaction solution at -25°C, and the mixture was stirred at -15°C for one hour and at 0°C for 2.5 hours. The solvent was evaporated under reduced pressure, and ethyl acetate and water were added to the residue to separate the layers. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an aminoacrylate as a yellow oil. The resulting aminoacrylate was dissolved in N,N-dimethylformamide (350 mL). Cesium carbonate (19.8 g, 60.9 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The solvent was evaporated under reduced pressure, and ethyl acetate and water were added to the residue to separate the layers. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to flash

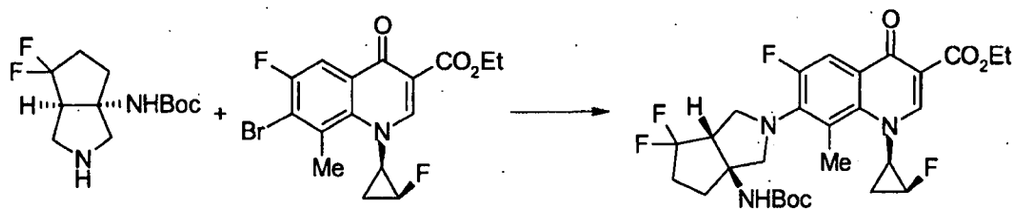
column chromatography (hexane:ethyl acetate = 9:1 -> 1:1 -> 1:2) to give the title compound (2.98 g) as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 8.56 (1H, d, *J*=3.2 Hz), 8.06 (1H, d, *J*=8.1 Hz), 4.98-4.73 (1H, m), 4.40 (2H, q, *J*=7.1 Hz), 3.91-3.82 (1H, m), 2.85 (3H, s), 1.61-1.22 (2H, m), 1.41 (3H, t, *J*=7.1 Hz).

[Reference Example 218]

Ethyl 7-[(1S,5R)-1-tert-butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate

[Formula 337]



A mixture of (1S,5R)-1-tert-butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3.3.0]octane (318 mg, 1.21 mmol), ethyl 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (426 mg, 1.10 mmol), 1,1'-bis(diphenylphosphino)ferrocene (183 mg, 0.331 mmol), tris(dibenzylideneacetone)dipalladium(0) (101 mg, 0.110 mmol) and cesium carbonate (718 mg, 2.20 mmol) in dioxane (5.51 mL) was stirred at room temperature for 30

minutes, and at 100°C for 11 hours under argon atmosphere. The mixture was diluted with water, and extracted with ethyl acetate and chloroform (3×). The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flush column chromatography (ethyl acetate/hexane = 10:90 → 50:50 → 67:33 → ethyl acetate) to afford 436 mg of the title compound as a pale yellow foam.

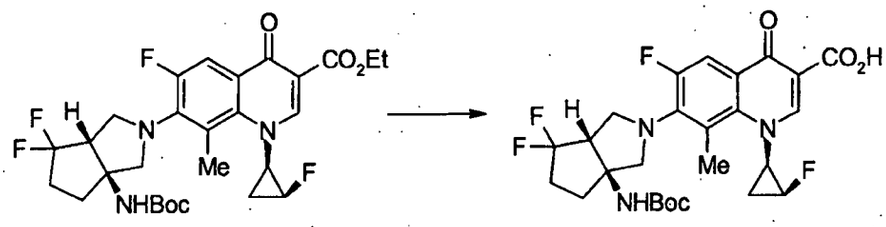
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 2.9 Hz), 7.96 (1H, d, J = 12.9 Hz), 4.99 (1H, brs), 4.94-4.72 (1H, m), 4.39 (2H, q, J = 7.1 Hz), 3.91-3.79 (2H, m), 3.62 (2H, s), 3.49-3.41 (1H, m), 2.91-2.76 (1H, m), 2.62 (3H, s), 2.42-2.12 (4H, m), 1.45 (9H, s), 1.61-1.43 (1H, m), 1.41 (3H, t, J = 7.1 Hz), 1.34-1.21 (1H, m).

MS(ESI) m/z: 568 $(M+H)^+$.

[Reference Example 219]

7-[(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 338]



To a solution of ethyl 7-[(1S,5R)-1-tert-butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (436 mg, 0.769 mmol) in ethanol (5 mL) was added 1 mol/L aqueous solution of sodium hydroxide (0.845 mL) at 0°C, and the mixture was stirred at room temperature for 13 hours. To the mixture was further added 1 mol/L aqueous solution of sodium hydroxide (0.845 mL) at 0°C, and the mixture was stirred at room temperature for 4 hours. To the mixture was added 10% aqueous solution of citric acid, and ethanol was distilled off under reduced pressure. The residue was diluted with water and extracted with dichloromethane (3x). The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flush column chromatography (ethyl acetate/hexane = 1:3 → 1:1 → 2:1 → ethyl acetate) to afford 342 mg of the title compound as a colorless foam.

^{1}H-NMR ($CDCl_3$) δ: 14.98 (1H, s), 8.78 (1H, d, J = 2.9 Hz), 7.95 (1H, d, J = 12.7 Hz), 5.03-4.77 (2H, m), 4.02-3.87 (2H,

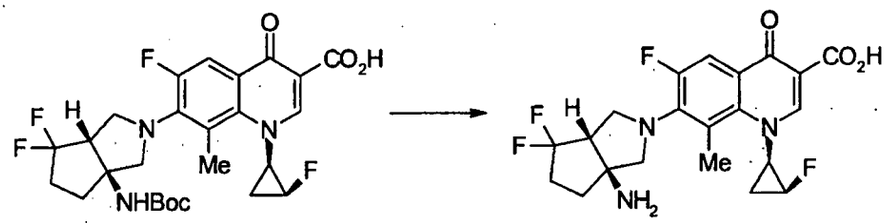
m), 3.77-3.64 (2H, m), 3.57-3.49 (1H, m), 2.98-2.83 (1H, m), 2.66 (3H, s), 2.43-2.12 (4H, m), 1.70-1.53 (1H, m), 1.46 (9H, s), 1.40-1.26 (1H, m).

MS(ESI) m/z: 540$(M+H)^+$.

[Example 52]

7-[(1S,5R)-1-Amino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-(fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 339]



7-[(1S,5R)-1-tert-Butoxycarbonylamino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (414 mg, 0.767 mmol) was dissolved in concentrated hydrochloric acid (4 mL) at 0°C, and the mixture was stirred at 0°C for an hour. The aqueous solution was washed with chloroform (3 ×). The mixture was basified to pH 12 with saturated aqueous solution of sodium hydroxide, and then neutralized to pH 7.4 at 0°C. The solution was extracted with chloroform (5 ×). The combined organic layer was dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The

residue was recrystallized from ethanol to afford 219 mg of the title compound as a white solid.

Melting point: 211-212 °C.

^{1}H-NMR (400MHz, 0.1N NaOD) δ: 8.52-8.46 (1H,m), 7.79-7.67 (1H, m), 5.12-4.88 (1H, m), 4.18-4.05 (1H, m), 3.91-3.79 (1H, m), 3.68-3.55 (1H, m), 3.52-3.40 (1H, m), 3.36-3.25 (1H, m), 2.71-2.58 (4H, m), 2.45-2.28 (2H, m), 2.24-2.12 (1H, m), 1.97-1.85 (1H, m), 1.69-1.54 (1H, m), 1.38-1.17 (1H, m).

Anal. Calcd for $C_{21}H_{21}F_4N_3O_3 \cdot 0.2H_2O$: C, 56.93; H, 4.87; N, 9.49; F, 17.15. Found: C, 56.91, H, 4.83; N, 9.47; F, 17.55.

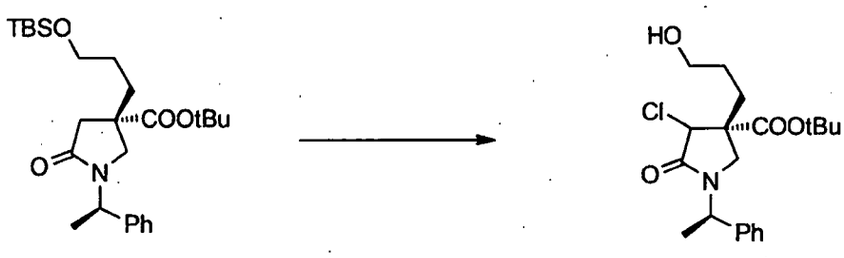
MS (ESI) m/z: 440 $(M+H)^+$.

IR (ATR) ν: 3391, 3061, 2962, 2871, 1714, 1615, 1510, 1460, 1434, 1356, 1336, 1301, 1235, 1207, 1177, 1157, 1140, 1075, 1061, 1045, 1015 cm^{-1}.

[Reference Example 220]

tert-Butyl (3S)-4-Chloro-3-(3-hydroxy-1-propyl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid

[Formula 340]



Under nitrogen atmosphere, to a solution of tert-butyl (3S)-3-[3-(tert-butyldimethylsilyloxy)propan-1-yl]-5-oxo-1-

[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid (960 mg, 2.08 mmol) in THF (15 mL) was added 1.0M lithium bis(trimethylsilyl)amide in THF solution (2.29 mL, 2.29 mmol) at -78°C, and the mixture was stirred for 30 minutes. Then, N-chlorosuccinimide (333 mg, 2.50 mmol) added and the mixture was stirred for 1 hour at -60°C, and further stirred for 10 minutes at 0°C. To the mixture were added saturated aqueous solution of ammonium chloride and ethyl acetate. The separated organic layer was washed with water and brine. The solution was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. At 0°C , to a solution of this residue in THF (20 mL) were added acetic acid (0.24 mL, 4.16 mmol) and 1.0M tetrabutylammonium fluoride in THF solution (4.16 mL, 4.16 mmol), the mixture was stirred for 16 hours at room temperature. To the mixture were added 10% aqueous solution of citric acid and ethyl acetate. The separated organic layer was washed with water and brine. The solution was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flush column chromatography (ethyl acetate/hexane = 1:1 → 1:2) to afford 506 mg of the title compound as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 7.34-7.26 (5H, m), 5.49-5.40 (1H, m), 4.75 (1H, s), 3.68-3.61 (2H, m), 3.39-3.34 (2H, m), 3.24 (0.75H,

3/4

Patente De Invención

Organizacion y Digitalizacion CSA

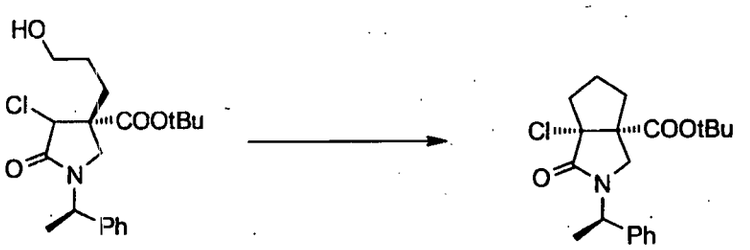
09/81886

d, J = 10.0 Hz), 3.14 (0.25H, d, J = 10.9 Hz), 1.95-1.80 (2H, m), 1.68-1.40 (2H, m), 1.52 (3H, d, J = 7.1 Hz), 1.28 (9H, s).

[Reference Example 221]

tert-Butyl (1S,5R)-5-chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid

[Formula 341]



At 0°C, to a solution of tert-butyl (3S)-4-chloro-3-(3-hydroxypropan-1-yl)-5-oxo-1-[(1R)-1-phenylethyl]pyrrolidine-3-carboxylic acid (500 mg, 1.31 mmol) in dichloromethane (10 mL) were added carbon tetrabromide (434 mg, 1.31 mmol) and triphenylphosphine (344 mg, 1.31 mmol). After stirring the mixture for 2 hours at room temperature, carbon tetrabromide (143 mg, 0.431 mmol) and triphenylphosphine (114 mg, 0.434 mmol) were added to the mixture. After stirring for 2 hours, carbon tetrabromide (72 mg, 0.216 mmol) and triphenylphosphine (57 mg, 0.217 mmol) were added and the mixture was stirred for 16 hours. The solvent was distilled off under reduced pressure. The residue was purified by short silica gel flush column chromatography (15% ethyl acetate/hexane) to

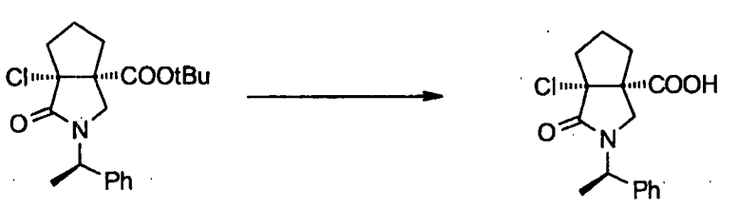
afford a colorless oil. Under nitrogen atmosphere, to a solution of this oil in THF (12 mL) was added 1.0M lithium bis(trimethylsilyl)amide in THF solution (1.46 mL, 1.46 mmol) at -78°C, and the reaction mixture was warmed to 0°C over 2 hours. To the mixture were added saturated aqueous solution of ammonium chloride and ethyl acetate. The separated organic layer was washed with water and brine. The solution was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flush column chromatography (15% ethyl acetate/hexane) to afford 337 mg of the title compound as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.37-7.26 (5H, m), 5.54 (1H, q, J = 7.1 Hz), 3.51 (1H, d, J = 10.7 Hz), 3.02 (1H, d, J = 10.7 Hz), 2.76-2.71 (1H, m), 2.52-2.45 (1H, m), 2.38-2.30 (1H, m), 2.02-1.96 (1H, m), 1.74-1.60 (2H, m), 1.53 (3H, d, J= 7.1 Hz), 1.45 (9H, s).

[Reference Example 222]

(1S,5R)-5-Chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid

[Formula 342]

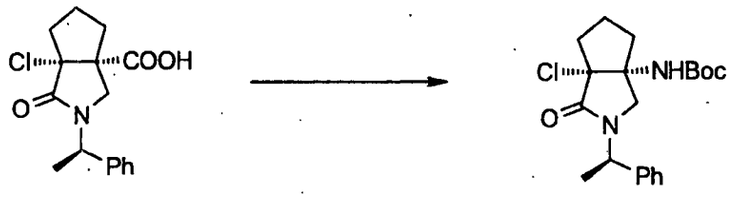


A mixture of tert-butyl (1S,5R)-5-chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid (332 mg, 0.912 mmol) and trifluoroacetic acid (2 mL) in dichloromethane (4 mL) was stirred for 14.5 hours at room temperature. The solvent was distilled off under reduced pressure. To the residue was added diethyl ether (3 mL), and then the precipitate was collected by filtration to afford 245 mg of the title compound as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.26 (5H, m), 5.50 (1H, q, J = 7.1 Hz), 3.53 (1H, d, J = 10.7 Hz), 3.07 (1H, d, J = 10.8 Hz), 2.78-2.73 (1H, m), 2.63-2.56 (1H, m), 2.41-2.33 (1H, m), 2.05-2.01 (1H, m), 1.79-1.63 (2H, m), 1.54 (3H, d, J = 7.1 Hz).

[Reference Example 223]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 343]



A solution of (1S,5R)-5-chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octan-1-ylcarboxylic acid (239 mg, 0.777 mmol), triethylamine (0.215 mL, 1.55 mmol) and diphenylphosphoryl azide (0.184 mL, 0.855 mmol) in

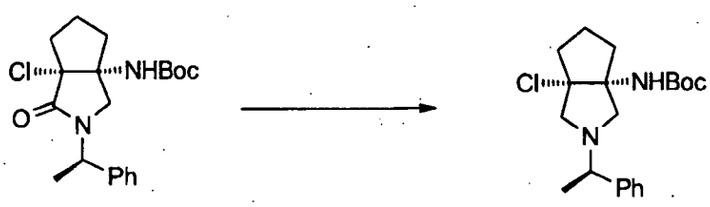
toluene (6 mL) was stirred for 30 minutes at 80°C. The solvent was distilled off under reduced pressure. To a solution of the residue in 1,4-dioxane (5 mL) was added 6N aqueous solution of hydrochloric acid (5 mL). The mixture was stirred for 5 hours at 50°C. The solvent was distilled off under reduced pressure. To the residue was added 1N aqueous solution of sodium hydroxide. The solution was extracted with $CHCl_3$ twice, and the combined organic layers were dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. A mixture of the residue and di-tert-butyl dicarbonate (847 mg, 3.89 mmol) was stirred for 3 hours at 50°C and the mixture was purified by silica gel flush column chromatography (15% ethyl acetate/hexane) to afford 222 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 7.37-7.26 (5H, m), 5.50 (1H, q, J = 6.9 Hz), 5.25 (1H, brs), 3.66 (1H, brd, J = 10.0 Hz), 2.96 (1H, d, J = 6.8 Hz), 2.76-2.69 (1H, m), 2.55-2.51 (1H, m), 2.18-2.08 (1H, m), 1.98-1.84 (2H, m), 1.51 (3H, d, J = 7.1 Hz), 1.65-1.50 (1H, m), 1.40 (9H, s).

[Reference Example 224]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-chloro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane

[Formula 344]



Under nitrogen atmosphere, to a solution of (1R,5R)-1-(tert-butoxycarbonylamino)-5-chloro-4-oxo-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (217 mg, 0.573 mmol) in THF (10 mL) was added 1.0M borane-THF complex in THF solution (1.72 mL, 1.72 mmol) at room temperature. After stirring for 14 hours, 1.0M borane-THF complex in THF solution (0.86 mL, 0.86 mmol) was added. The mixture was warmed to 50°C, and stirred for 18 hours. To the mixture was further added 1.0M borane-THF complex in THF solution (0.86 mL, 0.86 mmol) and the mixture was stirred for 24 hours at 50°C. After being cooled to 0°C, to the mixture were added water (1 mL), EtOH (9 mL) and triethylamine (1 mL). The mixture was warmed to 80°C, and stirred for 2 hours. The solvent was distilled off under reduced pressure. To the residue were added saturated aqueous solution of ammonium chloride and ethyl acetate. The separated organic layer was washed with water and brine. The solution was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flush column chromatography (10%

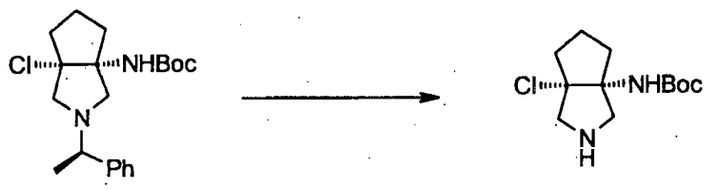
ethyl acetate/hexane) to afford 67.3 mg of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 7.29-7.19 (5H, m), 5.53 (1H, brs), 3.22 (1H, q, J = 6.8 Hz), 3.07 (1H, brd, J = 8.8 Hz), 2.93 (1H, brd, J = 8.7 Hz), 2.82-2.71 (1H, m), 2.64-2.57 (1H, m), 2.27-2.15 (2H, m), 2.09-2.06 (2H, m), 1.74-1.67 (2H, m), 1.55 (9H, s), 1.31 (3H, d, J = 6.6 Hz).

[Reference Example 225]

(1R,5R)-1-(tert-Butoxycarbonylamino)-5-chloro-3-azabicyclo[3.3.0]octane

[Formula 345]



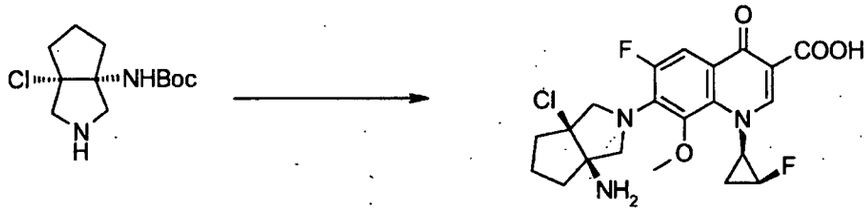
Under hydrogen atmosphere, a mixture of (1R,5R)-1-(tert-butoxycarbonylamino)-5-chloro-3-[(1R)-1-phenylethyl]-3-azabicyclo[3.3.0]octane (63.0 mg, 0.173 mmol), 10% Pd-C (50wt%, M, 32 mg) in methanol (6 mL) was stirred for 4 hours at room temperature and for 19 hours at 40°C. After removing catalyst by filtration, the filtrate was distilled off under reduced pressure.

MS (ESI) m/z : 261 $(M + H)^+$.

[Example 53]

7-[(1R,5R)-1-Amino-5-chloro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 346]



A mixture of (1R,5R)-1-(tert-butoxycarbonylamino)-5-chloro-3-azabicyclo[3.3.0]octane (45.0 mg, 0.173 mmol), 6,7-difluoro-1-[(1R,2S)-2-fluorocyclopropan]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid-difluoroboron complex (62.3 mg, 0.173 mmol) and triethylamine (0.0598 mL, 0.433 mmol) in dimethylsulfoxide (3 mL) was stirred for 45 hours at 45°C. To the mixture were added water (1 mL), EtOH (9 mL) and triethylamine (1 mL). The mixture was stirred for 1.5 hours at 80°C. After being cooled to room temperature, the solvent was distilled under reduced pressure. To the residue were added 10% aqueous solution of citric acid and ethyl acetate. The separated organic layer was washed with H_2O and brine. The solution was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by TLC (5% MeOH/$CHCl_3$) to afford 48.0 mg of the N-Boc protected compound as a yellow oil. To this oil was added

hydrochloric acid and the mixture was stirred for 30 minutes at room temperature. The mixture was basified to pH 12 with aqueous solution of sodium hydroxide, and then neutralized to pH 7.8 at 0°C. The solution was extracted with chloroform twice. The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was dried under reduced pressure to afford 33.9 mg of the title compound as a pale yellow solid.

Melting point: 161-163 °C.

^{1}H-NMR (400MHz, 0.1N NaOD) δ: 8.48 (1H,s), 7.70 (1H, d, J = 14.2 Hz), 5.07-4.85 (1H, m), 4.19-4.08 (2H, m), 3.92 (1H, d, J = 11.8 Hz), 3.76-3.63 (5H, m), 2.48-2.41 (1H, m), 2.30-2.25 (1H, m), 2.08-1.87 (4H, m), 1.70-1.51 (2H, m), 1.19 (1.8H, t, J = 7.2 Hz).

Anal. Calcd for $C_{21}H_{22}ClF_4N_3O_3 \cdot 0.6EtOH$: C, 55.38; H, 5.36; N, 8.73; F, 7.89; Cl, 7.36. Found: C, 55.24, H, 4.91; N, 8.85; F, 8.27; Cl, 6.92.

MS (ESI) m/z: 454 $(M + H)^+$.

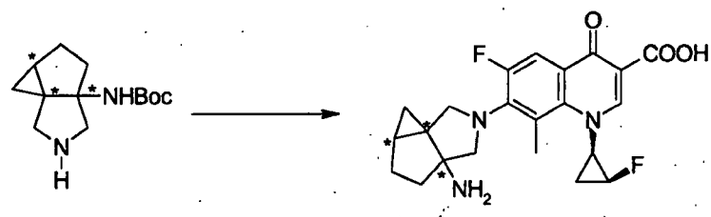
IR (ATR) ν: 3384, 3075, 2880, 1728, 1621, 1513, 1453, 1360, 1318, 1188, 1136, 1120, 1103, 1056 cm^{-1}.

[Example 54]

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methyl-4-oxo-1,4-

dihydroquinoline-3-carboxylic acid (7 position: derivative from optical isomer A)

[Formula 347]



To a solution of tris(dibenzylideneacetone)dipalladium (0) (332 mg, 0.363 mmol) and 4,5-bis(diphenyl)phosphino-9,9-dimethylxanthene (462 mg, 0.798 mmol) in 1,4-dioxane (9.06 ml) were added ethyl 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (350 mg, 0.906 mmol), 6-tert-butoxycarbonyl amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonane (216mg, 0.906 mmol) and cesium carbonate (355 mg, 1.09 mmol) and the mixture was stirred at 90°C for 22 hours under nitrogen atmosphere. The reaction mixture was diluted with water (80 ml) and extracted with ethyl acetate (90 ml). The organic layer was washed with saturated aqueous solution of sodium chloride (80 ml) and dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol; 100:0 → 99:1 → 98:2) to afford a pale yellow solid. To a solution of this solid in ethanol (3.32 ml) was added 1 mol/l aqueous solution of sodium hydroxide (1.50

ml) in an ice bath and the mixture was stirred at room temperature for 14 hours. To this reaction solution was added 1 mol/l aqueous solution of hydrochloric acid (1.50 ml) in an ice bath and the organic layer was concentrated under reduced pressure. The aqueous solution was diluted with water (30 ml) and extracted with ethyl acetate (40 ml). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol; 100:0 → 99:1 → 98:2) to afford a pale yellow solid. The solid was dissolved in concentrated hydrochloric acid (1.0 ml) in an ice bath and the aqueous solution was washed with chloroform (25 ml × 3). To the aqueous layer was added saturated solution of sodium hydroxide to adjust pH to 12.0 and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (120 ml × 1, 80 ml × 2). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to afford the title compound 68.1 mg (18%) as pale yellow solid.

mp: 145-149°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.43 (1H, d, J = 3.2 Hz), 7.70 (1H, d, J = 14.2 Hz), 5.12-4.92 (1H, m), 4.29 (1H, d, J = 9.2 Hz), 4.12-4.07 (1H, m), 3.91-3.88 (1H, m), 3.24 (1H,

d, J = 9.6 Hz), 3.08 (1H, d, J = 9.2 Hz), 2.54 (3H, s), 2.08-1.97 (1H, m), 1.92-1.87 (1H, m), 1.79-1.74 (1H, m), 1.65-1.55 (1H, m), 1.32-1.19 (3H, m), 0.84-0.76 (2H, m).

Anal.Calcd for $C_{22}H_{23}F_2N_3O_3$ $1.5H_2O$: C, 59.72; H, 5.92; F, 8.59; N, 9.50.

Found: C, 59.72; H, 5.65; F, 59.08; N, 9.47.

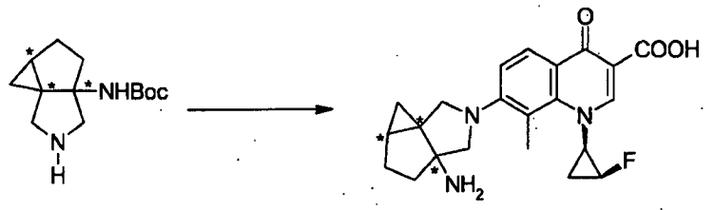
MS(ESI)m/z: 416 $(M + H)^+$.

IR(ATR):2939, 2867, 1719, 1612, 1542, 1507, 1460, 1428, 1354, 1314, 1284, 1184, 1136, 1024, 967, 921, 884, 806 cm^{-1}.

[Example 55]

7-[6-Amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7 position: derivative from optical isomer A)

[Formula 348]



To a solution of 6-tert-butoxycarbonyl amino-8-azatricyclo[4.3.0.0^{1,3}]nonane (290 mg, 1.22 mmol) in dimethyl sulfoxide (2.42 ml) were added triethylamine (0.507 ml, 3.63 mmol) and 7-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (337 mg, 1.21 mmol) and the mixture was

stirred at 70°C for 13 days under nitrogen atmosphere. The reaction solution was diluted with ethyl acetate and washed with 10% aqueous solution of citric acid (50 ml), water (60 ml), and saturated aqueous solution of sodium chloride (60 ml). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol; 100:0 → 99:1 → 98:2 → 95:5) to afford a pale yellow solid. The solid was dissolved in concentrated hydrochloric acid (1.0 ml) in an ice bath and the aqueous solution was washed with chloroform (30 ml × 5). To the aqueous layer was added saturated aqueous solution of sodium hydroxide to adjust pH to 12.0 and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (80 ml × 4) and 10% methanol - chloroform (80 ml × 1, 50 ml × 1). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to afford the title compound 138 mg (29%) as a pale yellow solid.

mp: >254°C (decomp.).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.42 (1H, d, J = 3.9 Hz), 8.00 (1H, d, J = 9.3 Hz), 7.14 (1H, d, J = 9.0 Hz), 5.13-4.94 (1H, m), 4.32 (1H, d, J = 10.0 Hz), 4.10-4.04 (1H, m), 3.73 (1H, d, J = 10.3 Hz), 3.23 (1H, d, J = 10.0 Hz), 3.00

(1H, d, J = 10.3 Hz), 2.46 (3H, s), 2.04-1.92 (2H, m), 1.79-1.73 (1H, m), 1.66-1.55 (1H, m), 1.35-1.17 (3H, m), 0.86-0.77 (2H, m).

Anal.Calcd for $C_{22}H_{24}FN_3O_3$ $0.25H_2O$: C, 65.74; H, 6.14; F, 4.73; N, 10.45.

Found: C, 65.84; H, 6.28; F, 5.00; N, 10.41.

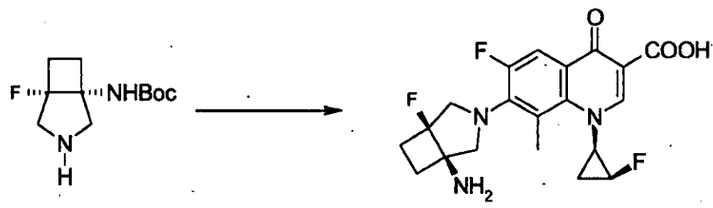
MS(ESI)m/z: 398 $(M + H)^+$.

IR(ATR):3376, 3030, 2989, 2929, 2858, 1703, 1614, 1547, 1510, 1450, 1430, 1387, 1354, 1337, 1313, 1295, 1266, 1230, 1189, 1177, 1153, 1138, 1090, 1079, 1054, 1022, 998, 990, 923 cm^{-1}.

[Example 56]

7-{(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.2.0]heptan-3-yl}-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

[Formula 349]



To a solution of tris(dibenzylideneacetone)dipalladium (0) (414 mg, 0.452 mmol) and 4,5-bis(diphenyl)phosphino-9,9-dimethylxanthene (522 mg, 0.902 mmol) in 1,4-dioxane (20.0 ml) were added ethyl 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-

carboxylate (1.28 g, 3.31 mmol), (1R,5S)-1-(tert-butoxycarbonyl amino)-5-fluoro-3-azabicyclo[3.2.0]heptane (693mg, 3.01 mmol) and cesium carbonate (1.96 g, 6.02 mmol) and the mixture was stirred at 95°C for 14 hours under nitrogen atmosphere. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (100 ml × 2). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate; 100:0 → 95:5 → 90:10 → 75:25→ 5:95 → 0:100) to afford a pale yellow solid. To a solution of this solid in ethanol (15.9 ml) was added 1 mol/l aqueous solution of sodium hydroxide (5.98 ml) in an ice bath and the mixture was stirred at room temperature for 13 hours. To this reaction solution was added 1 mol/l aqueous solution of hydrochloric acid (5.98 ml) in an ice bath and the organic layer was concentrated under reduced pressure. The aqueous solution was diluted with water (80 ml) and extracted with ethyl acetate (100 ml × 1, 80 ml × 1). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol; 100:0 → 99:1 → 98:2→ 97:3 → 96:4→ 95:5 → 94:6→ 93:7) to afford a pale yellow solid. The solid was dissolved in concentrated hydrochloric acid (3.0 ml) in an

ice bath and the aqueous solution was washed with chloroform (40 ml × 4). To the aqueous layer was added saturated solution of sodium hydroxide to adjust pH to 12.0 and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (250 ml × 4). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to afford the title compound 690 mg (56%) as pale yellow solid.

mp: >272°C (decomp.).

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.49 (1H, d, J = 2.2 Hz), 7.70 (1H, dd, J = 13.2, 4.2 Hz), 5.08-4.88 (1H, m), 4.12-4.06 (1H, m), 3.69-3.56 (2H, m), 3.42-3.39 (1H, m), 3.21-3.18 (1H, m), 2.64 (3H, d, J = 5.1 Hz), 2.54-2.39 (1H, m), 2.31-2.20 (1H, m), 2.12-1.93 (2H, m), 1.66-1.56 (1H, m), 1.32-1.19 (1H, m).

Anal.Calcd for $C_{20}H_{20}F_3N_3O_3$: C, 58.96; H, 4.95; F, 13.99; N, 10.31.

Found: C, 58.76; H, 4.88; F, 14.11; N, 10.28.

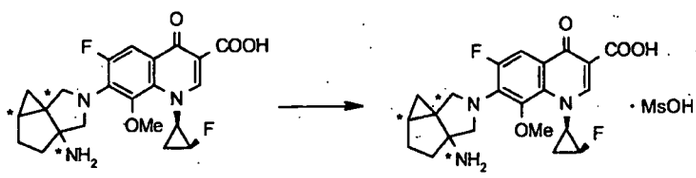
MS(ESI)m/z: 408 $(M + H)^+$.

IR(ATR):3089, 2980, 2936, 2862, 2837, 1719, 1614, 1544, 1506, 1474, 1454, 1432, 1350, 1318, 1268, 1231, 1213, 1181, 1159, 1140, 1093, 1058, 1047, 1021, 1009, 977, 962, 930, 898, 864, 837, 805 cm^{-1}.

[Example 57]

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulfonate

[Formula 350]



To a suspension of 7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropan-1-yl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2.24 g, 4.82 mmol) in ethanol (48.2 ml) was added methanesulfonic acid (0.316 ml, 4.87 mmol) and the mixture was stirred at room temperature for 15 hours. To this reaction solution was added water (5 ml) and the mixture was concentrated under reduced pressure. To this residue was added 2-propanol (20 ml) and the mixture was stirred at room temperature for 15 hours. The precipitated solids were collected by filtration. The solids were washed with an excess amount of 2-propanol to afford the title compound 2.41 g (95%) as pale yellow solid.

mp: 202-204°C.

^{1}H-NMR (400 MHz, 0.1N NaOD) δ: 8.39 (1H, d, J = 2.9 Hz), 7.64 (1H, d, J = 14.4 Hz), 5.09-4.93 (1H, m), 4.21 (1H, dd, J = 10.0, 2.7 Hz), 3.97 (1H, dt, J = 10.0, 4.6 Hz), 3.72

(1H, dd, J = 10.6, 2.7 Hz), 3.53 (3H, s), 3.39 (1H, d, J = 10.3 Hz), 3.18 (1H, d, J = 10.3 Hz), 2.83 (3H, s), 1.99-1.85 (2H, m), 1.73 (1H, dd, J = 12.2, 8.5 Hz), 1.56-1.46 (1H, m), 1.39-1.23 (2H, m), 1.17-1.13 (1H, m), 0.79-0.74 (2H, m).

Anal.Calcd for $C_{22}H_{23}F_2N_3O_4$ CH_4O_3S $0.5H_2O$: C, 51.49; H, 5.26; F, 7.08; N, 7.83; S, 5.98.

Found: C, 51.21; H, 5.20; F, 7.44; N, 7.82; S, 6.00.

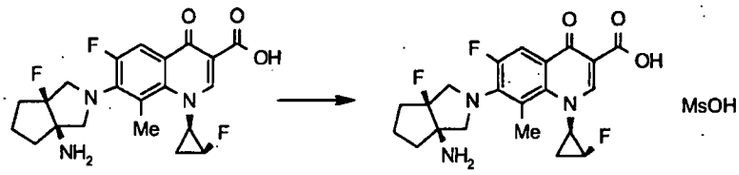
MS(ESI)m/z: 432 $(M + H)^+$.

IR(ATR):3412, 2944, 2878, 1694, 1617, 1597, 1536, 1513, 1437, 1361, 1330, 1315, 1297, 1273, 1219, 1167, 1135, 1109, 1040, 952, 925, 883, 805 cm^{-1}.

[Example_58]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid methanesulfonate

[Formula 351]



To a suspension of 7-[(1R,5S)-1-amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (4.50 g, 10.7 mmol) in ethanol (90 ml) was added methanesulfonic acid (0.695 ml, 10.7 mmol), and the

mixture was stirred at room temperature for 30 minutes. The mixture was diluted with water (20 ml), and distilled off under reduced pressure. The residue was purified by slurry in 2-propanol to afford 4.96 g of the title compound as a pale yellow powder.

^{1}H-NMR (400MHz,0.1N NaOD)δ : 8.48(1H,d,*J*=2.9Hz), 7.72(1H,d,*J*=13.7Hz), 5.11-4.86(1H,m), 4.15-4.07(1H,m), 3.93-3.81(1H,m), 3.60-3.31(3H,m), 2.82(3H,s), .62(3H,s), 2.16-1.98(3H,m), 1.92-1.55(4H,m), 1.33-1.19(1H,m).

MS(FAB);m/z:422$(M+H)^+$.

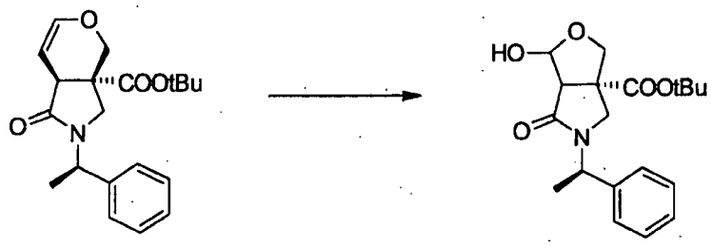
Anal.Calcd $C_{21}H_{22}F_3N_3O_3 \cdot CH_3SO_3H \cdot 1.75H_2O$:C, 48.13;H, 5.42;F, 10.38;N, 7.65;S, 5.84.Found:C, 47.81;H, 5.09;F, 10.43;N, 7.63;S, 5.75.

IR(ATR)ν: 3442, 2871, 1709, 1615, 1509, 1432, 1370, 1319, 1265, 1161, 1038, 971, 929, 892, 853, 806cm^{-1}.

[Reference Example 226]

(3aS)-1-Hydroxy-6-oxo-5-[(R)-1-phenylethyl]tetrahydrofuro[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester

[Formula 352]



A mixture of (3aS,7aS)-1-oxo-2-[(R)-1-phenylethyl]-1,2,3,7a-tetrahydropyrano[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester (4.0 g, 11.6 mmol), N-methylmorpholine-N-oxide (2.95 g, 22.0 mmol) and osmium tetroxide (cat.) was dissolved in tert-butanol (20 mL) and water (10 mL), and stirred at room temperature for 3 days. The reaction mixture was diluted with AcOEt and 10% aq. sodium thiosulfate added. The layers were separated and the aqueous layer extracted with AcOEt. The combined extracts were washed with sat. aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo, giving a dark brown oil (4.4 g). The crude product (2.6 g) was dissolved in tetrahydrofuran (60 mL) and water (30 mL), and sodium periodate (2.6 g) added. The reaction mixture was stirred at room temperature for 18 h, and diluted with AcOEt and water. The layers were separated and the aqueous layer extracted with AcOEt. The combined extracts were washed with sat. aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in ethanol and tetrahydrofuran (20 mL; 17:3) and 1N aq. NaOH (5.2 mL) added dropwise at 0°C. The mixture was stirred at room temperature for 3 h, after which time additional 1N aq. NaOH (2.2 mL) was added and the reaction mixture was stirred for another 1 h. The solvent was removed in vacuo and the resulting residue was partitioned between AcOEt and water, and the aqueous layer extracted.

The combined extracts were washed with sat. aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by silica gel chromatography eluting with 50% AcOEt in hexane to afford the title compound (1.10 g) as a white solid.

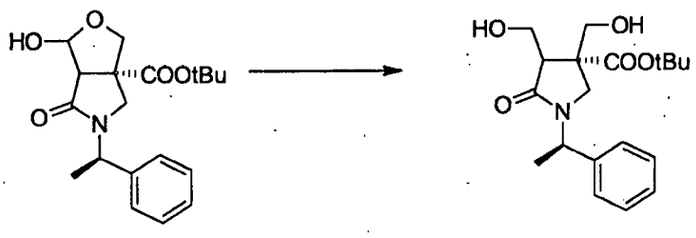
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.71 (1H, d, J = 7.3 Hz), 5.66-5.44 (1.2H, m), 4.96 (0.2H, d, J = 7.3 Hz), 4.49 (0.8H, d, J = 9.6 Hz), 4.25 (0.2H, d, J = 9.6 Hz), 4.00 (0.2H, d, J = 9.2 Hz), 3.90 (0.8H, d, J = 9.2 Hz), 3.64 (0.8H, d, J = 7.3 Hz), 3.38-3.24 (3H, m), 1.54-1.38 (12H, m).

MS(ESI)m/z:348$(M + H)^+$.

[Reference Example 227]

(3S)-3,4-Bis(hydroxymethyl)-5-oxo-1-[(R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester

[Formula 353]



To a cooled solution (-20°C) of (3aS)-1-hydroxy-6-oxo-5-[(R)-1-phenylethyl]tetrahydrofuro[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester (350 mg, 1.01 mmol) in tetrahydrofuran and ethanol (10 mL; 4:1), sodium borohydride (38.0 mg, 1.00 mmol) was added portionwise, and

the mixture was stirred at the same temperature for 5.5 h. The reaction mixture was concentrated in vacuo and taken up in AcOEt and water. The layers were separated and the aqueous layer extracted with AcOEt. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 90% AcOEt in hexane to afford the title compound (153 mg) as a colorless oil.

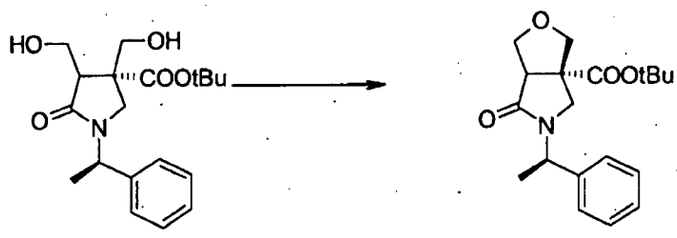
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.50 (1H, q, J = 7.0 Hz), 4.19-3.80 (4H, m), 3.40-3.05 (5H, m), 1.52 (3H, d, J = 7.0 Hz), 1.40 (9H, s).

MS(ESI)m/z:350$(M + H)^+$.

[Reference Example 228]

(3aS)-6-Oxo-5-[(R)-1-phenylethyl]tetrahydrofuro[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester

[Formula 354]



To a cooled (0°C) solution of (3S)-3,4-bis(hydroxymethyl)-5-oxo-1-[(R)-1-phenylethyl]pyrrolidine-3-carboxylic acid tert-butyl ester (710 mg, 2.03 mmol) and triphenylphosphine (450mg, 2.64 mmol) in tetrahydrofuran (10 mL) was added a solution of 40% diethyl

azodicarboxylate in toluene (1.06 mL, 2.33 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 40% AcOEt in hexane to afford the title compound (435 mg) as a white solid.

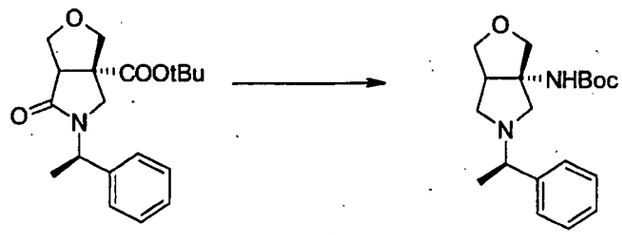
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.48 (1H, q, J = 7.2 Hz), 4.32-4.26 (1H, m), 4.01 (1H, d, J = 9.6 Hz), 3.97-3.91 (1H, m), 3.85 (1H, d, J = 9.6 Hz), 3.43 (1H, d, J = 10.1 Hz), 3.37-3.32 (1H, m), 3.26 (1H, d, J = 10.1 Hz), 1.54 (3H, d, J = 6.9 Hz), 1.38 (9H, br s).

MS(ESI)m/z:332$(M + H)^+$.

[Reference Example 229]

[(3aS)-5-[(R)-1-Phenylethyl]tetrahydrofuro[3,4-c]pyrrol-3a-yl]carbamic acid tert-butyl ester

[Formula 355]



To a solution of [(3aS)-6-oxo-5-[(R)-1-phenylethyl]tetrahydrofuro[3,4-c]pyrrol-3a-yl]carbamic acid tert-butyl ester (820 mg, 2.47 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid (8 mL), and the mixture was stirred at room temperature for 2 h. The solvent was

removed in vacuo and pumped to dryness, giving a white solid(680 mg).

1,1'-carbonybis-1H-imidazole (480 mg, 2.94 mmol) was added to a solution of the crude product (540 mg) in acetonitrile (10 ml) at 0°C, and the mixture was stirred for 1 h at the same temperature and then warmed to room temperature. Ammonia gas was bubbled through the reaction mixture for 30 min and the solvent was concentrated in vacuo. The resulting residue was taken up in dichloromethane, washed with 1N HCl, sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to give a white solid (536 mg).

To a suspension of the white solid (536 mg) in tert-butanol (20 mL) was added lead tetraacetate (1.73 g, 3.90 mmol), and the mixture was heated to 100°C for 5 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (200 mL) and sodium hydrogen carbonate (3 g) added. After stirring for 30min, the precipitate was filtered off. The filtrate was concentrated in vacuo, and the residue was taken up in dichloromethane, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was obtained as a white solid (620 mg).

Trifluoroacetic acid (6 ml) was added to a solution of the crude product (200 mg) in dichloromethane (6 mL), and

the reaction mixture was stirred for 1 h then the solvent removed in vacuo and pumped to dryness. This was taken forward to the next step.

To a solution of this material in toluene (6 mL) was slowly added sodium bis(2-methoxyethoxy)aluminum hydride (65% toluene solution, 690 μL, 2.3 mmol), and the mixture was heated to 60°C for 1 h. The reaction mixture was cooled to room temperature then 5N aq. NaOH added, and stirred for 1 h. The layers were separated and the aqueous layer extracted with toluene. The combined extracts were washed with brine, dried(Na_2SO_4), and concentrated in vacuo. The crude product (540 mg) was carried forward without purification.

Di-tert-butyl dicarbonate (589 mg) was added to a solution of the crude product in dichloromethane (6 mL), and the mixture was stirred for 18 h and the solvent removed in vacuo. The residue was purified by silica gel chromatography eluting with 30% AcOEt in hexane to afford the title compound (150 mg) as a white solid.

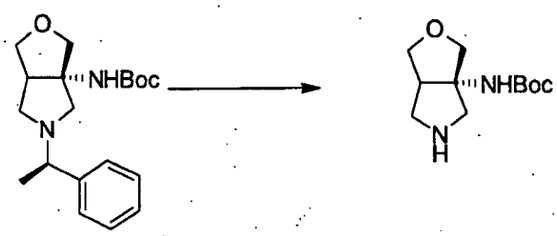
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.31-7.21 (5H, m), 5.00 (1H, s), 4.09-3.78 (3H, m), 3.53 (1H, dd, J = 8.7, 4.6 Hz), 3.27 (1H, q, J = 6.7 Hz), 2.78-2.65 (3H, m), 2.50-2.36 (2H, m), 1.42 (9H, s), 1.33 (3H, d, J = 6.4 Hz).

MS(ESI)m/z:333$(M + H)^+$

[Reference Example 230]

(3aS)-(Tetrahydrofuro[3,4-c]pyrrol-3a-yl)carbamic acid tert-butyl ester

[Formula 356]



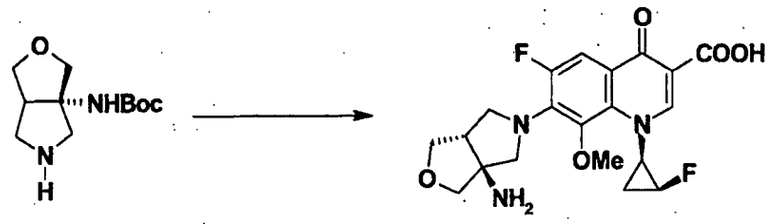
[(3aS)-5-[(R)-1-Phenylethyl]tetrahydrofuro[3,4-c]pyrrol-3a-yl]carbamic acid tert-butyl ester (355 mg, 1.06 mmol) was dissolved in dioxane (10 ml) and 20% palladium hydroxide catalyst (20 wt. % Pd on carbon, wet; cat.) was added. The mixture was vigorously stirred under a hydrogen atmosphere at 40°C for 24 h. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane, and washed with 1N aq. NaOH and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuo to give the crude title compound (243 mg) as a colorless syrup.

MS(ESI)m/z:229$(M + H)^+$.

[Example 59]

7-[(3aS)-3a-Aminotetrahydrofuro[3,4-c]pyrrol-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 357]



To a solution of 6,7-difluoro-1-[(2S,1R)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid - difluoroboron complex (426 mg, 1.18 mmol) in dimethyl sulfoxide (6 ml) were added (S)-(tetrahydro-2-oxa-5-azacyclopropa[c]pentalen-3a-yl)carbamic acid tert-butyl ester (270 mg, 1.18 mmol) and triethylamine (0.50 ml, 3.54 mmol), and the mixture was stirred at 40°C for 17 h. The reaction solution was concentrated in vacuo, and the concentrate was dissolved in a mixed solution of ethanol and water (9:1) (150 ml). After adding triethylamine (5 ml), the mixture was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure, and the concentrate was dissolved in AcOEt (100 ml x 2), and washed with 10% aq. citric acid (100 ml) and brine (100 ml). The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. After purification by silica gel column chromatography (3% MeOH in $CHCl_3$), the solid obtained was dissolved in concentrated hydrochloric acid (5 ml) in an ice bath, and the aqueous solution was washed with chloroform (50 ml x 3). To the aqueous layer was added 10 mol/l aqueous solution of sodium

hydroxide to adjust pH to 12.0, and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (100 ml × 6) and the combined extracts were dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by preparative chromatography, and further purified by recrystallization from ethanol, and subsequently, dried under reduced pressure to give the title compound (220 mg) as pale yellow crystals.

mp: 201-202℃.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 8.76 (1H, d, J = 1.4 Hz), 7.87 (1H, d, J = 12.8 Hz), 4.92-4.71 (1H, m), 4.27 (1H, dd, J = 9.2, 7.3 Hz), 3.93-3.57 (11H, m), 2.57-2.49 (1H, m), 1.68-1.47 (2H, m).

Anal;Calcd for $C_{20}H_{21}F_2N_3O_5$ H_2O:C, 54.67;H, 5.28;N, 9.56;F, 8.65.Found:C, 54.52;H, 5.18;N, 9.58;F, 8.73.

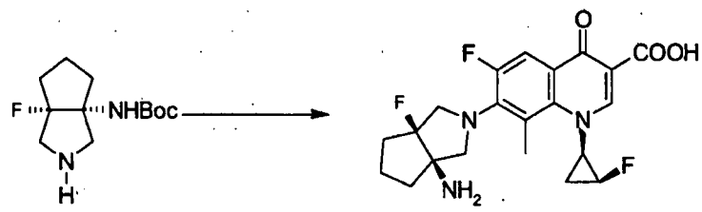
MS(ESI)m/z:422$(M + H)^+$.

IR(ATR)ν: 3301, 2974, 2847, 1722, 1614, 1580, 1516, 1447, 1403, 1378, 1365, 1355, 1340, 1316, 1289, 1265cm^{-1}.

[Example 60]

7-[(1R,5S)-1-Amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropane]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid

[Formula 358]



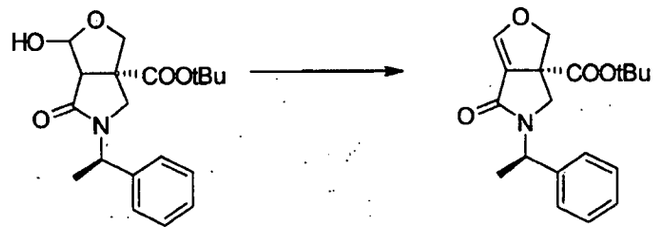
To a solution of tris(dibenzylideneacetone)dipalladium (0) (7.75 g, 8.46 mmol), 4,5-bis(diphenyl)phosphino-9,9-dimethylxanthene (14.7 g, 25.4 mmol), ethyl 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (14.2 g, 36.8 mmol) and (1R,5S)-1-(tert-butoxycarbonyl amino)-5-fluoro-3-azabicyclo[3.3.0]octan (6.90 g, 28.2 mmol)in 1,4-dioxane (345 ml) were added cesium carbonate (18.4 g, 56.5 mmol) and the mixture was stirred at 110°C for 23 hours under nitrogen atmosphere. The reaction mixture was diluted with water (400 ml) and extracted with ethyl acetate (600 ml × 1, 250 ml × 1). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol;100:0 → 99.5:0.5 → 99.25:0.75 → 99:1) to afford a solid. To a solution of this solid in ethanol (273 ml) was added 1 mol/l aqueous solution of sodium hydroxide (68.2 ml) in an ice bath and the mixture was stirred at room temperature for 1 hours. To this reaction solution was added ethanol (327 ml) and 1 mol/l aqueous solution of

sodium hydroxide (27.3 ml) and the mixture was stirred at room temperature for 13 hours. To this reaction solution was added 1 mol/l aqueous solution of hydrochloric acid (95.5 ml) in an ice bath and the organic layer was concentrated under reduced pressure. The aqueous solution was diluted with water (150 ml) and extracted with chloroform (250 ml × 1, 150 ml × 1). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate; 100:0 → 2:1 → 1:1→ 1:1.5 → 1:1.7→ 1:1.85 → 1:2→ 1:5→ 1:9→ 0:100) to afford a pale yellow solid. The solid was dissolved in concentrated hydrochloric acid (30 ml) in an ice bath and the aqueous solution was washed with chloroform (100 ml × 5). To the aqueous layer was added saturated solution of sodium hydroxide to adjust pH to 12.0. To the solution was added water (1.8 l) and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (1.5 l × 1, 800 ml × 1). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by recrystallization from 2-propanol/methanol=10/1 to afford the title compound 6.14 g (52%) as pale yellow solid. And all spectroscopic data of this compound proved to be in good agreement with those of Example 17.

[Reference Example 231]

(3aS)-6-Oxo-5-[(R)-1-phenylethyl]-5,6-dihydro-4H-furo[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester

[Formula 359]



To a solution of (3aS)-(tetrahydrofuro[3,4-c]pyrrol-3a-yl)carboxylic acid tert-butyl ester (8.80 g, 25.0 mmol) and triethylamine (7.8 mL) in dichloromethane (75 mL) was added dropwise methanesulfonyl chloride (3.13 mL, 40.0 mmol) at -10°C and the mixture was stirred for 1.5 h at the same temperature and then additional triethylamine (7.8 mL) added. The reaction mixture was heated to 40°C and stirred for 5 days. After cooling to room temperature, the solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with a mixed solution of AcOEt, hexane and triethylamine (40:60:0.5) to afford the title compound as a white solid (2.56 g).

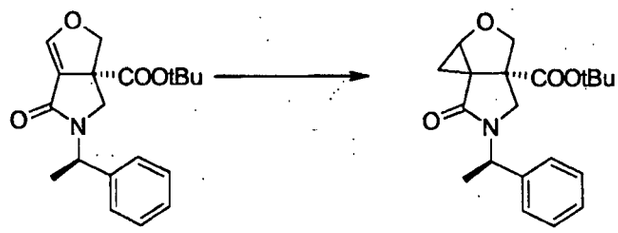
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 7.08 (1H, s), 5.48 (1H, q, J = 6.9 Hz), 5.03 (1H, d, J = 9.6 Hz), 4.25 (1H, d, J = 9.6 Hz), 3.43 (1H, d, J = 10.1 Hz), 3.26 (1H, d, J = 10.1 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.30 (9H, s).

MS(ESI)m/z:330$(M+H)^+$.

[Reference Example 232]

(S)-6-Oxo-5-[(R)-1-phenylethyl]tetrahydro-2-oxa-5-azacyclopropa[c]pentalene-3a-carboxylic acid tert-butyl ester

[Formula 360]



To a solution of diethyl zinc (1M hexane solution, 22.3 ml) in dichloromethane (75 mL) was added dropwise diiodomethane (1.79 mL, 22.3 mmol) at -10°C, and the mixture was stirred for 15min at the same temperature. A solution of (S)-6-oxo-5-[(R)-1-phenylethyl]-5,6-dihydro-4H-furo[3,4-c]pyrrole-3a-carboxylic acid tert-butyl ester in dichloromethane was added at -10°C, and the resulting mixture was stirred for 8h at room temperature. The reaction mixture was quenched with 10% aq. citric acid. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 30% AcOEt in hexane to afford the title compound (1.96 g) as a white solid.

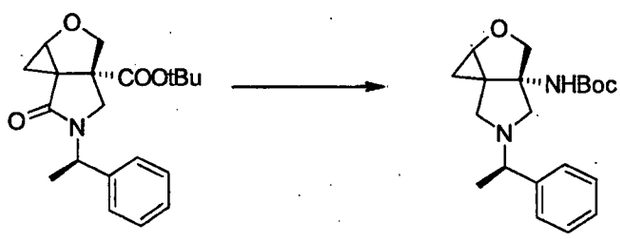
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.54 (1H, q, *J* = 7.0 Hz), 4.45 (1H, d, *J* = 9.2 Hz), 4.24 (1H, dd, *J* = 5.5, 2.8 Hz), 4.14 (1H, d, *J* = 9.2 Hz), 3.51 (1H, d, *J* = 10.1 Hz), 3.40 (1H, d, *J* = 10.1 Hz), 1.73-1.67 (1H, m), 1.58-1.53 (4H, m), 1.33 (9H, s).

MS(ESI)m/z:344$(M + H)^+$

[Reference Example 233]

[(S)-5-[(R)-1-Phenylethyl]tetrahydro-2-oxa-5-azacyclopropa[c]pentalen-3a-yl]carbamic acid tert-butyl ester

[Formula 361]



To a solution of (S)-6-oxo-5-[(R)-1-phenylethyl]tetrahydro-2-oxa-5-azacyclopropa[c]pentalene-3a-carboxylic acid tert-butyl ester (880 mg, 2.56 mmol)in dichloromethane (7 mL) was added trifluoroacetic acid (8 ml), and the mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo to give a white solid(800 mg).

1,1'-carbonybis-1H-imidazole (677 mg, 4.18 mmol) was added to a solution of the white solid (800 mg) in acetonitrile (15 ml) at -0°C, and the mixture was stirred

for 1 h at the same temperature and then allowed to warm to room temperature. Ammonia gas was bubbled through the reaction mixture for 30min and the solvent was concentrated in vacuo. The resulting residue was taken up in dichloromethane, washed with 1N HCl, sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to give a white solid (750 mg).

To a suspension of the white solid (120 mg) in tert-butanol (5 mL) was added lead tetraacetate (558 mg, 1.26 mmol), and the mixture was heated to 100°C for 5 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (50 mL) and sodium hydrogen carbonate (1g) added. After stirring for 30min, the solids were filtered off. The filtrate was removed in vacuo, and the residue was taken up in dichloromethane, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was taken on without further purification.

Trifluoroacetic acid (6 mL) was added to a solution of the crude product in dichloromethane (5 mL), and the reaction mixture was stirred for 1 h then the solvent removed in vacuo, and pumped to dryness. This was taken forward to the next step.

To a solution of this material in toluene (4 mL) was slowly added sodium bis(2-methoxyethoxy)aluminum hydride

(65% toluene solution, 600 μL, 2.0 mmol), and the mixture was heated to 60°C for 1h. The reaction mixture was cooled to room temperature and 5N aq. NaOH added, and then stirred for 1 h. The layers were separated and the aqueous layer extracted with toluene. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was carried forward without purification.

Di-tert-butyl dicarbonate (163 mg) was added to a solution of the crude product in dichloromethane (6 mL), and the mixture was stirred for 18 h and the solvent removed in vacuo. The residue was purified by silica gel chromatography eluting with 25% AcOEt in hexane to afford the title compound (140 mg) as a white solid.

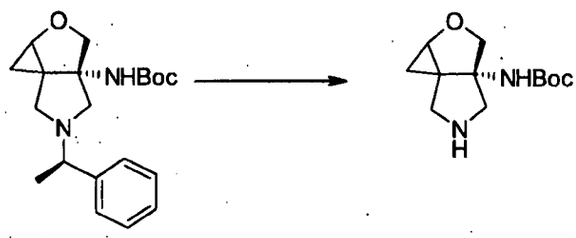
^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.36-7.19 (5H, m), 4.92 (1H, s), 4.20 (1H, d, *J* = 9.6 Hz), 3.98-3.85 (2H, m), 3.43 (1H, q, *J* = 6.6 Hz), 2.99 (1H, d, *J* = 8.7 Hz), 2.81-2.62 (3H, m), 1.40 (9H, s), 1.35 (3H, d, *J* = 6.6 Hz), 1.19 (1H, d, *J* = 6.4 Hz), 0.91 (1H, t, *J* = 5.7 Hz).

MS(ESI)m/z:345$(M + H)^+$.

[Reference Example 234]

(S)-(Tetrahydro-2-oxa-5-azacyclopropa[c]pentalen-3a-yl)carbamic acid tert-butyl ester

[Formula 362]



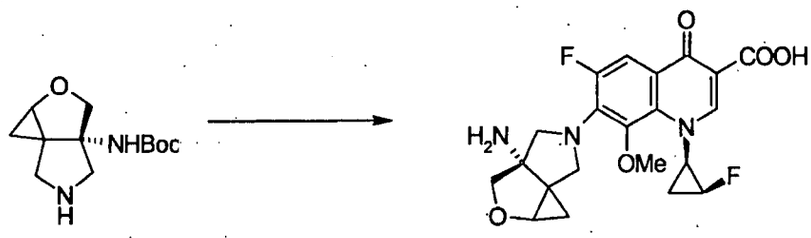
An [(S)-5-[(R)-1-Phenylethyl]tetrahydro-2-oxa-5-azacyclopropa[c]pentalen-3a-yl]carbamic acid tert-butyl ester (480 mg, 1.39 mmol) was dissolved in dioxane (10 ml) and 20% palladium hydroxide catalyst (20 wt. % Pd on carbon, wet; cat.) was added. The mixture was vigorously stirred under a hydrogen atmosphere at room temperature for 3 days. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane, and washed with 1N aq. NaOH and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuo to give the crude title compound as a white solid (280 mg).

MS(ESI)m/z:241$(M + H)^+$.

[Example 61]

7-[(3aS)-3a-Amino-5-aza-oxatetrahydrocyclopentalen-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid

[Formula 363]



To a solution of 6,7-difluoro-1-[(2S,1R)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid - difluoroboron complex (361 mg, 1.00 mmol) in dimethyl sulfoxide (5 ml) were added (S)-(tetrahydro-2-oxa-5-azacyclopropa[c]pentalen-3a-yl)carbamic acid tert-butyl ester (250 mg, 1.08 mmol) and triethylamine (0.50 ml, 3.54 mmol), and the mixture was stirred at room temperature for 2 days. The reaction solution was concentrated in vacuo, and the concentrate was dissolved in a mixed solution of ethanol and water (9:1) (150 ml). After adding triethylamine (5 ml), the mixture was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure, and the concentrate was dissolved in AcOEt (100 ml × 2), and washed with 10% aq. citric acid (100 ml)and brine (100 ml). The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. After purification by silica gel chromatography (5% MeOH in $CHCl_3$), the residue was dissolved in concentrated hydrochloric acid (5 ml) in an ice bath, and the aqueous solution was washed with chloroform (50 ml × 3). To the aqueous layer was added 10

mol/l aqueous solution of sodium hydroxide to adjust pH to 12.0, and the basic aqueous solution was adjusted with hydrochloric acid to pH 7.4. The solution was extracted with chloroform (100 ml × 6) and the combined extracts were dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by preparative chromatography, and further purified by recrystallization from ethanol, and subsequently, dried under reduced pressure to give the title compound (135 mg) as pale yellow needle crystals.

mp: 189-191 °C.

^{1}H-NMR(400MHz,0.1N NaOD)δ: 8.42 (1H, d, J = 2.8 Hz), 7.71 (1H, d, J = 13.8 Hz), 5.13-4.89 (1H, m), 4.17-4.01 (4H, m), 3.94 (1H, dd, J = 10.5, 2.3 Hz), 3.67 (3H, s), 3.64-3.47 (3H, m), 1.63-1.37 (3H, m), 1.02 (1H, dd, J = 7.8, 5.5 Hz).

Anal;Calcd for $C_{21}H_{21}F_2N_3O_5$ $1.25H_2O$:C, 55.32;H, 5.20;N, 9.22;F, 8.33.Found:C, 55.48;H, 5.12;N, 9.00;F, 8.61.

MS(ESI)m/z:434$(M + H)^+$.

IR(ATR)ν: 3358, 3076, 2941, 2879, 1721, 1620, 1513, 1437, 1367, 1323, 1274cm^{-1}.

[Test Example 1]

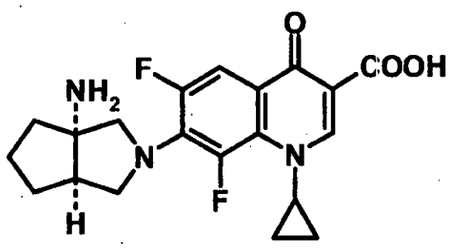
Antibacterial activity of the compounds of the present invention was measured in accordance with the standard

method specified by the Japanese Society of Chemotherapy. The results are shown as MIC (μg/mL) (Table 2).

For comparison with the MIC values of the compounds of the present invention, Table 2 also shows MIC values of 7-[3-(R)-(1-aminocyclopropyl)pyrrolidin-1-yl]-8-cyano-1-[2-(S)-fluoro-1-(R)-cyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid described in WO 02/40478 (control drug 1: the following formula), levofloxacin (LVFX), ciprofloxacin (CPFX), and moxifloxacin (MXFX).

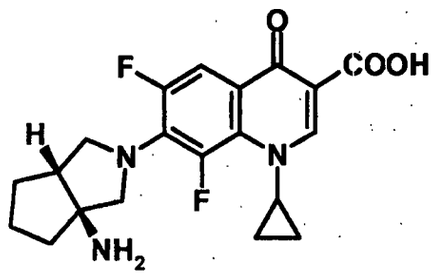
The compound specifically exemplified in EP-A-343524 described in the section "Description of the Related Art", which is represented by the following formula:

[Formula 364]



has one of two optical isomers as its 7-position substituent. The present inventors synthesized a compound represented by the following formula:

[Formula 365]



which has a (1S,5R)-1-amino-3-azabicyclo[3.3.0]octan-3-yl group that is a highly active isomer as its 7-position substituent. The compound represented by the formula 365 was confirmed to be positive for induction of micronuclei in a mouse bone marrow micronucleus test after intravenous administration. That is, the compound was suggested to be genotoxic. Further, the compound was found to be positive for phototoxicity in a mouse phototoxicity test after intravenous administration. On the other hand, the compound described in Example 11 which is a representative compound of the present invention was found to be negative in the above two tests. That is, the compound was suggested to be weakly genotoxic and not phototoxic and therefore highly safe as a human medicine.

[Table 2]

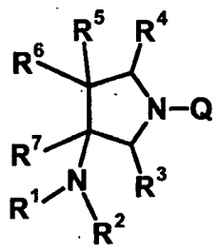
Table Antibacterial activity

Bacteria/Compound (Example No.)	2	5	10	11	15	17	24	25	27
E. coli NIHJ	0.025	0.025	0.025	0.025	0.006	≤0.003	0.025	0.012	0.012
K. pneumoniae TYPE 1	0.1	0.1	0.2	0.1	0.05	0.012	0.1	0.05	0.1
P. mirabilis 08103	0.012	0.025	0.05	0.05	0.025	0.006	0.025	0.025	0.05
E.cloacae 03400	0.025	0.025	0.025	0.012	0.025	0.006	0.025	0.012	0.025
S. marcescens 10100	0.2	0.2	0.2	0.1	0.2	0.05	0.2	0.1	0.2
P. aeruginosa PAO1	0.78	0.78	0.78	0.78	0.78	0.2	0.39	0.39	0.78
H. influenzae ATCC49247	0.006	0.012	0.012	0.006	≤0.003	≤0.003	0.006	0.006	0.006
M(B). Caterrhalis ATCC25238	0.025	0.05	0.025	0.025	0.025	0.006	0.05	0.025	0.05
S. aureus FDA 209-P	≤0.003	0.006	0.006	0.012	0.012	0.006	0.025	0.025	0.012
S. epidermidis 56500	0.012	0.025	0.025	0.05	0.05	0.025	0.1	0.1	0.05
S. pneumoniae J24	0.012	0.025	0.025	0.05	0.05	0.025	0.05	0.05	0.025
S. pyogenes JCM5674(ATCC12344)	0.025	0.05	0.025	0.025	0.05	0.025	0.1	0.05	0.05
E. faecalis 19433	0.05	0.1	0.1	0.1	0.2	0.05	0.1	0.2	0.1
S. aureus 870307	0.1	0.2	0.1	0.78	0.39	0.2	0.78	0.39	0.2
S. pneumoniae 104835	0.1	0.2	0.2	0.39	0.39	0.1	0.39	0.39	0.2

Bacteria/Compound (Example No.)	31	34	35	37	43	44	LVFX	CPFX	MXFX
E. coli NIHJ	0.006	0.006	0.006	0.006	0.006	≤0.003	0.012	≤0.003	0.012
K. pneumoniae TYPE 1	0.05	0.025	0.05	0.1	0.05	0.025	0.05	0.025	0.1
P. mirabilis 08103	0.012	0.012	0.025	0.05	0.025	0.025	0.025	0.012	0.025
E.cloacae 03400	0.012	0.006	0.012	0.025	0.012	0.006	0.012	0.006	0.012
S. marcescens 10100	0.1	0.05	0.1	0.2	0.2	0.05	0.05	0.025	0.2
P. aeruginosa PAO1	0.39	0.2	0.39	1.56	0.78	0.39	0.39	0.05	0.78
H. influenzae ATCC25238	0.012	0.006	0.012	≤0.003	0.006	≤0.003	0.012	0.006	0.012
M(B). Caterrhalis ATCC49247	0.025	0.012	0.025	0.025	0.025	0.006	0.025	0.025	0.05
S. aureus FDA 209-P	0.012	0.025	0.025	0.006	0.012	0.012	0.1	0.1	0.05
S. epidermidis 56500	0.05	0.05	0.05	0.012	0.05	0.025	0.39	0.2	0.1
S. pneumoniae J24	0.025	0.1	0.05	0.05	0.1	0.05	0.78	0.78	0.1
S. pyogenes JCM5674(ATCC12344)	0.025	0.05	0.05	0.05	0.05	0.05	0.39	0.39	0.2
E. faecalis 19433	0.1	0.1	0.2	0.1	0.2	0.1	0.78	0.78	0.2
S. aureus 870307	0.1	0.39	0.2	0.05	0.2	0.2	6.25	>6.25	0.78
S. pneumoniae 104835	0.2	0.39	0.39	0.39	0.78	0.39	>6.25	>6.25	3.13

CLAIMS

1. A compound represented by the following formula (I), a salt, or a hydrate thereof:



I

wherein R^1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, or a substituted carbonyl group derived from an amino acid, a dipeptide, or a tripeptide, said alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a cyano group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and said cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom;

R^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 6 carbon atoms, said alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an

amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and said cycloalkyl group may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, an amino group, a hydroxy group, and a halogen atom;

R^3 and R^4 independently represents a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, said alkyl group may have one or more substituents selected from the group consisting a halogen atom and an alkoxy group having 1 to 6 carbon atoms;

R^5 represents a hydrogen atom, a halogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, an alkynyl group having 2 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, or a heteroaryl group which may have a substituent, said alkyl group, alkenyl group, and alkynyl group may be linear or branched, the alkyl group may have one or more substituents selected from the group consisting of a hydroxy group, an amino group, a halogen atom, an alkylthio group having 1 to 6 carbon atoms, and an alkoxy group having 1 to 6 carbon atoms, and the alkenyl group may have one or

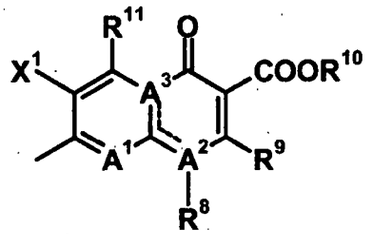
more substituents selected from the group consisting of a halogen atom and an alkoxy group having 1 to 6 carbon atoms;

R^6 and R^7 taken together with the carbon atoms to which they are bonded form a four- to seven-membered cyclic structure, the cyclic structure representing a partial structure that together with the pyrrolidine ring forms a fused cyclic (bicyclic) structure, the four- to seven-membered cyclic structure may contain a double bond and may contain an oxygen atom or a sulfur atom as a ring constituent atom,

R^5 may be a methylene group taken together with R^6 to form a three-membered fused cyclic structure moiety, and further this fused cyclic structure may be located in other part of the fused cyclic (bicyclic) structure, and the ring formed as described above may be located in other part of the fused cyclic (bicyclic) structure, and said four- to seven-membered cyclic structure may have one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms which may have a substituent, an alkoxy group having 1 to 6 carbon atoms which may have a substituent, an alkenyl group having 2 to 6 carbon atoms which may have a substituent, an alkynyl group having 2 to 6 carbon atoms which may have a substituent, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, an exomethylene group which may have a substituent, a spiroalkyl group which

may have a substituent, an aryl group having 6 to 10 carbon atoms which may have a substituent, a heteroaryl group which may have a substituent, an alkoxyimino group having 1 to 6 carbon atoms which may have a substituent, a halogen atom, a hydroxy group, a cyano group, and a hydroxyimino group; or a polymethylene chain of 2 to 5 carbon atoms may bind so as to form a spirocyclic ring system; and

Q represents a partial structure represented by the following formula (II):



II

wherein R^8 represents an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, a halogen-substituted alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which may have a substituent, a halogen-substituted phenyl group which may have a substituent, a halogen-substituted heteroaryl group which may have a substituent, an alkoxy group having 1 to 6 carbon atoms, or an alkylamino group having 1 to 6 carbon atoms;

R^9 represents a hydrogen atom or an alkylthio group having 1 to 6 carbon atoms, or R^9 and R^8 taken together with the atoms to which they are bonded form a cyclic structure,

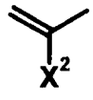
said cyclic structure may contain a sulfur atom as a ring constituent atom and may have an alkyl group having 1 to 6 carbon atoms or a halogen-substituted alkyl group having 1 to 6 carbon atoms as a substituent;

R^{10} represents a hydrogen atom, a phenyl group, an acetoxymethyl group, a pivaloyloxymethyl group, an ethoxycarbonyl group, a choline group, a dimethylaminoethyl group, a 5-indanyl group, a phthalidinyl group, a 5-alkyl-2-oxobutyl group, an alkyl group having 1 to 6 carbon atoms, an alkoxymethyl group having 2 to 7 carbon atoms, or a phenylalkyl group formed by an alkylene group having 1 to 6 carbon atoms and a phenyl group;

R^{11} represents a hydrogen atom, an amino group, a hydroxy group, a thiol group, a halogenomethyl group, or an alkyl group having 1 to 6 carbon atoms, the amino group may have one or two substituents selected from the group consisting of a formyl group, an alkyl group having 1 to 6 carbon atoms, and an acyl group having 2 to 5 carbon atoms;

X^1 represents a halogen atom or a hydrogen atom;

A^1 represents a nitrogen atom or a partial structure represented by the formula (III):



III

wherein X^2 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6

carbon atoms, a cyano group, a halogen atom, a halogen-substituted methyl group, or a halogenomethoxy group, or X^2 and R^8 taken together with their connecting part of the mother skeleton form a cyclic structure; said cyclic structure may contain an oxygen atom, a nitrogen atom, or a sulfur atom as a ring constituent atom, and may be substituted with an alkyl group having 1 to 6 carbon atoms which may have a substituent; and

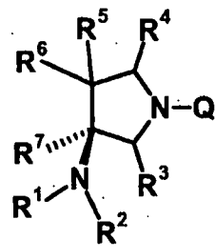
A^2 and A^3 each represents a nitrogen atom or a carbon atom, and A^1, A^2, A^3, R^8 and the carbon atom to which A^2 and A^3 are bonded together represent a partial structure:

>C=C(-A^1=)-N(-R^8)-

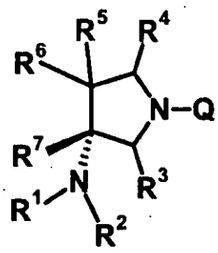
or a partial structure:

>N-C(-A^1=)=C(-R^8)-.

2. The compound according to claim 1, a salt, or a hydrate thereof, wherein the compound represented by the formula (I) is a compound represented by the following formula:

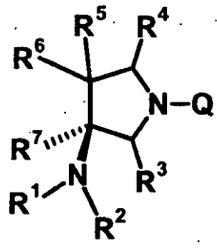


or the following formula:



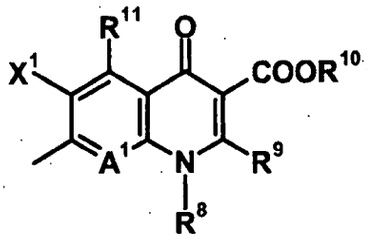
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Q are as defined in claim 1.

3. The compound according to claim 1 or a salt thereof, or a hydrate thereof, wherein the compound represented by the formula (I) is a compound represented by the following formula:

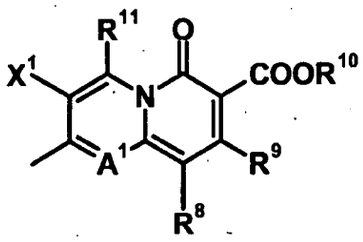


wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Q are as defined in claim 1.

4. The compound according to claim 1, a salt, or a hydrate thereof, wherein Q represented by the formula (II) in the compound represented by the formula (I) has a structure represented by the following formula:

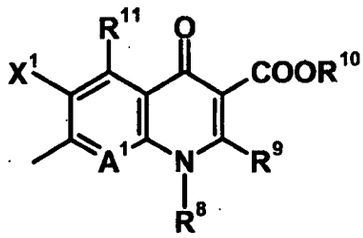


or the following formula:



wherein R^8, R^9, R^{10}, R^{11}, X^1, and A^1 are as defined in claim 1.

5. The compound according to claim 1, a salt, or a hydrate thereof, wherein Q represented by the formula (II) in the compound represented by the formula (I) has a structure represented by the following formula:



wherein R^8, R^9, R^{10}, R^{11}, X^1, and A^1 are as defined in claim 1.

6. The compound according to claim 1, 2, or 3, a salt, or a hydrate thereof, wherein R^1 and R^2 in the formula (I) are each a hydrogen atom.

7. The compound according to claim 1, 2, or 3, a salt, or a hydrate thereof, wherein one of R^1 and R^2 in the formula (I) is a hydrogen atom and the other is a substituent selected from a methyl group, an ethyl group, an isopropyl group, a fluoroethyl group, a cyanoethyl group, a cyclopropyl group, and a cyclobutyl group.

8. The compound according to any one of claims 1 to 7, a salt, or a hydrate thereof, wherein R^3 and R^4 in the formula (I) are each a hydrogen atom.

9. The compound according to any one of claims 1 to 8, a salt, or a hydrate thereof, wherein R^5 in the formula (I) is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, an isopropyl group, a cyclopropyl group, a fluoromethyl group, a fluoroethyl group, a trifluoromethyl group, a methoxymethyl group, a vinyl group, an ethynyl group, a methoxy group, a phenyl group, or an oxazol-2-yl group.

10. The compound according to any one of claims 1 to 9, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a four-membered ring which may be substituted by one or more substituents.

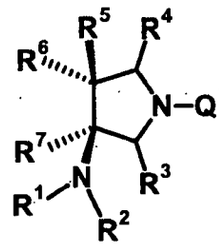
11. The compound according to any one of claims 1 to 9, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring which may be substituted by one or more substituents.

12. The compound according to any one of claims 1 to 9 and 11, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring containing a double bond as a constituent structure which may be substituted by one or more substituents.

13. The compound according to any one of claims 1 to 9 and 11 to 12, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five-

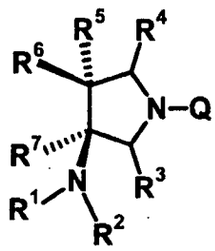
or six-membered ring containing an oxygen atom as a ring constituent atom.

14. The compound according to any one of claims 1 to 9 and 11 to 13, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring and is fused with the pyrrolidine ring to form a cis-fused bicyclic structure represented by the following formula:



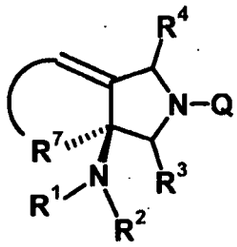
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Q are as defined in claim 1.

15. The compound according to any one of claims 1 to 9 and 11 to 13, a salt, or a hydrate thereof, wherein the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded in the formula (I) is a five- or six-membered ring and is fused with the pyrrolidine ring to form a trans-fused bicyclic structure represented by the following formula:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Q are as defined in claim 1.

16. The compound according to any one of claims 1 to 9 and 11 to 13, a salt, or a hydrate thereof, wherein in the formula (I), the cyclic structure formed by taking R^6 and R^7 together with the carbon atoms to which they are bonded is a five- or six-membered ring, R^5 and R^6 are taken together to form a double bond partial structure, and the resulting cyclic structure is represented by the following formula:



wherein R^1, R^2, R^3, R^4, R^7, and Q are as defined above.

17. The compound according to any one of claims 1 to 16, a salt, or a hydrate thereof, wherein X^1 is a hydrogen atom or a fluorine atom in the partial structure Q in the formula (I) represented by the formula (II).

18. The compound according to any one of claims 1 to 17, a salt, or a hydrate thereof, wherein X^1 is a fluorine atom in the partial structure Q in the formula (I) represented by the formula (II).

19. The compound according to any one of claims 1 to 18, a salt, or a hydrate thereof, wherein A^1 is a nitrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

20. The compound according to any one of claims 1 to 18, a salt, or a hydrate thereof, wherein A^1 is a partial structure represented by the formula (III) in the partial structure Q in the formula (I) represented by the formula (II).

21. The compound according to any one of claims 1 to 18, a salt, or a hydrate thereof, wherein X^2 in the formula (III) is a methyl group, an ethyl group, a methoxy group, a difluoromethoxy group, a cyano group, or a chlorine atom.

22. The compound according to any one of claims 1 to 18, a salt, or a hydrate thereof, wherein X^2 in the formula (III) is a methyl group or a methoxy group.

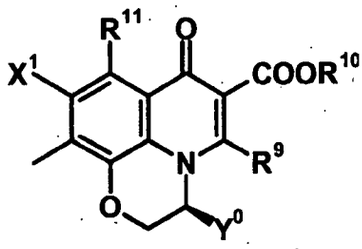
23. The compound according to any one of claims 1 to 22, a salt, or a hydrate thereof, wherein R^8 is a 1,2-cis-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

24. The compound according to any one of claims 1 to 22, a salt, or a hydrate thereof, wherein R^8 is a stereochemically single 1,2-cis-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

25. The compound according to claim 24, a salt, or a hydrate thereof, wherein the 1,2-cis-2-halogenocyclopropyl group of R^8 is a (1R,2S)-2-halogenocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

26. The compound according to claim 25, a salt, or a hydrate thereof, wherein the (1R,2S)-2-halogenocyclopropyl group of R^8 is a (1R,2S)-2-fluorocyclopropyl group in the partial structure Q in the formula (I) represented by the formula (II).

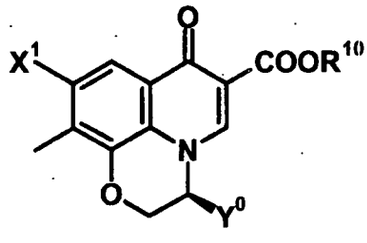
27. The compound according to claim 1, a salt, or a hydrate thereof, wherein Q in the compound represented by the formula (I) is a compound represented by the following formula:



wherein R^9, R^{10}, R^{11}, and X^1 are as defined in claim 1 and Y^0 is a methyl group or a fluoromethyl group.

28. The compound according to any one of claims 1 to 27, a salt, or a hydrate thereof, wherein R^9 is a hydrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

29. The compound according to claim 1, a salt, or a hydrate thereof, wherein Q in the compound represented by the formula (I) is a compound represented by the following formula (IV):



IV

wherein R^{10} and X^1 are as defined in claim 1 and Y^0 is a methyl group or a fluoromethyl group.

30. The compound according to claim 29 or a salt thereof, or a hydrate thereof, wherein Y^0 in the formula (IV) is a methyl group.

31. The compound according to any one of claims 1 to 30, a salt, or a hydrate thereof, wherein R^{10} is a hydrogen atom in the partial structure Q in the formula (I) represented by the formula (II).

32. The compound according to any one of claims 1 to 31, a salt, or a hydrate thereof, wherein the compound represented by the formula (I) is a stereochemically single compound.

33. The compound according to claim 1, a salt, or a hydrate thereof, wherein Q in the formula (I) has the following structure:

a 7-carboxy-9-cyclopropyl-3-fluoro-6(H)-6-oxopyrido[1,2-a]pyrimidin-4-yl group;

a 3-carboxy-1-cyclopropyl-7-fluoro-9-methyl-4(H)-4-oxoquinolizin-8-yl group;

a 5-carboxy-9-fluoro-2,3-dihydro-3-(R)-methyl-6(H)-6-oxopyrano[2,3,4-ij]quinolizin-10-yl group;

a 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-3-carboxy-6-fluoro-1,4-dihydro-4-quinolin-7-yl group;

a 1-(6-amino-3,5-difluoropyridin-2-yl)-3-carboxy-6-fluoro-1,4-dihydro-8-methyl-4-quinolin-7-yl group;

a 6-carboxy-9-fluoro-3-(R)-fluoromethyl-2,3-dihydro-methyl-7(H)-7-oxopyrido[1,2,3-de][1,4]benzoxazin-10-yl group;

a 6-carboxy-9-fluoro-2,3-dihydro-3-(S)-methyl-7(H)-7-oxopyrido[1,2,3-de][1,4]benzoxazin-10-yl group;

a 8-amino-6-carboxy-9-fluoro-2,3-dihydro-3-(S)-methyl-7(H)-7-oxopyrido[1,2,3-de][1,4]benzoxazin-10-yl group;

a 3-carboxy-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-chloro-1-cyclopropyl-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-cyano-1-cyclopropyl-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-6-fluoro-8-difluoromethoxy-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-8-difluoromethoxy-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group;

a 3-carboxy-1-cyclopropyl-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group;

a 5-amino-3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group;

a 5-amino-3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group;

a 3-carboxy-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-chloro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-8-cyano-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group;

a 3-carboxy-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group;

a 3-carboxy-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-difluoromethoxy-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-1-[(1R,2S)-2-fluorocyclopropyl]-8-difluoromethoxy-1,4-dihydro-4-oxoquinolin-7-yl group;

a 3-carboxy-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group;

a 3-carboxy-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group;

a 5-amino-3-carboxy-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinolin-7-yl group; or

a 5-amino-3-carboxy-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinolin-7-yl group.

34. The compound according to claim 1, a salt, or a hydrate thereof, wherein the partial structure substituted on Q in the formula (I) has the following structure:

a (1R,5S)-1-amino-5-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S,6R)-1-amino-6-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S,6S)-1-amino-6-fluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5S)-1-amino-6,6-difluoro-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6R)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6R)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a (1S,5R,6S)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl group;

a spiro[(1S,5S)-1-amino-3-azabicyclo[3.2.0]heptane-6,1'-cyclopropan]-3-yl group;

a (1S,5R)-1-amino-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[3.3.0]octan-3-yl group;

a (1R,5S)-1-amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1R,5R)-1-amino-5-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,6S)-1-amino-6-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R)-1-amino-6,6-difluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,7S)-1-amino-7-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R,7R)-1-amino-7-fluoro-3-azabicyclo[3.3.0]octan-3-yl group;

a (1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl group;

a (1S,5R)-1-amino-7-methyl-3-azabicyclo[3.3.0]oct-7-en-3-yl group;

a (1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl group;

a (1S)-1-amino-6-methyl-3-azabicyclo[3.3.0]oct-5-en-3-yl group;

a (1R,5R)-1-amino-3-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5S)-1-amino-3-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5R)-1-amino-4-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a (1R,5S)-1-amino-4-oxa-5-azabicyclo[3.3.0]octan-5-yl group;

a 6-amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonan-8-yl group;

a (1S,5R)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]non-7-en-3-yl group;

a (1S,5S)-1-amino-3-azabicyclo[4.3.0]non-8-en-3-yl group;

a (1S)-1-amino-3-azabicyclo[4.3.0]non-5-en-3-yl group;

a (1R,6S)-1-amino-5-oxa-8-azabicyclo[4.3.0]nonan-8-yl group;

a (1S,6S)-1-amino-4-oxa-8-azabicyclo[4.3.0]nonan-8-yl group; or

a (1S,6S)-1-amino-3-oxa-8-azabicyclo[4.3.0]nonan-8-yl group.

35. A compound of formula (I), a salt, or a hydrate thereof as follows:

7-[(1S,5R,6R)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5R,6S)-1-amino-6-methyl-3-azabicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5R,6S)-1-amino-6-fluoromethyl-3-azabicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5R,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S,6R)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S,6S)-1-amino-3-azabicyclo-6-fluorobicyclo[3.2.0]heptan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

10-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-fluorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-chlorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1R,5S)-1-amino-3-aza-5-chlorobicyclo[3.3.0]octan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5R)-1-amino-3-azabicyclo[3.3.0]oct-7-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S)-1-amino-5-methyl-3-azabicyclo[3.3.0]oct-5-en-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

10-[6-amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.$0^{1,3}$]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[6-amino-8-azatricyclo[4.3.0.0^{1,3}]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

7-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid;

10-[(1S,5S)-1-amino-3-azabicyclo[4.3.0]nonan-3-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-8-cyano-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid;

7-[(1S,6S)-1-amino-8-aza-3-oxabicyclo[4.3.0]nonan-8-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid; or

10-[(1S,6S)-1-amino-8-aza-3-oxa-bicyclo[4.3.0]nonan-8-yl]-9-fluoro-2,3-dihydro-3-(S)-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid.

36. A medicine comprising the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

37. An antibacterial agent comprising the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

38. A therapeutic agent for infections comprising the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

39. A method for treating diseases comprising administering the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

40. A method for treating infections comprising administering the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

41. A method for producing a medicine comprising adding the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

42. A method for producing an antibacterial agent comprising adding the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

43. A method for producing a therapeutic agent for infections comprising adding the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof as an active ingredient.

44. Use of the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof for production of a medicine.

45. Use of the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof for production of an antibacterial agent.

46. Use of the compound according to any one of claims 1 to 34, a salt, or a hydrate thereof for production of a therapeutic agent for infections.

FIG.1

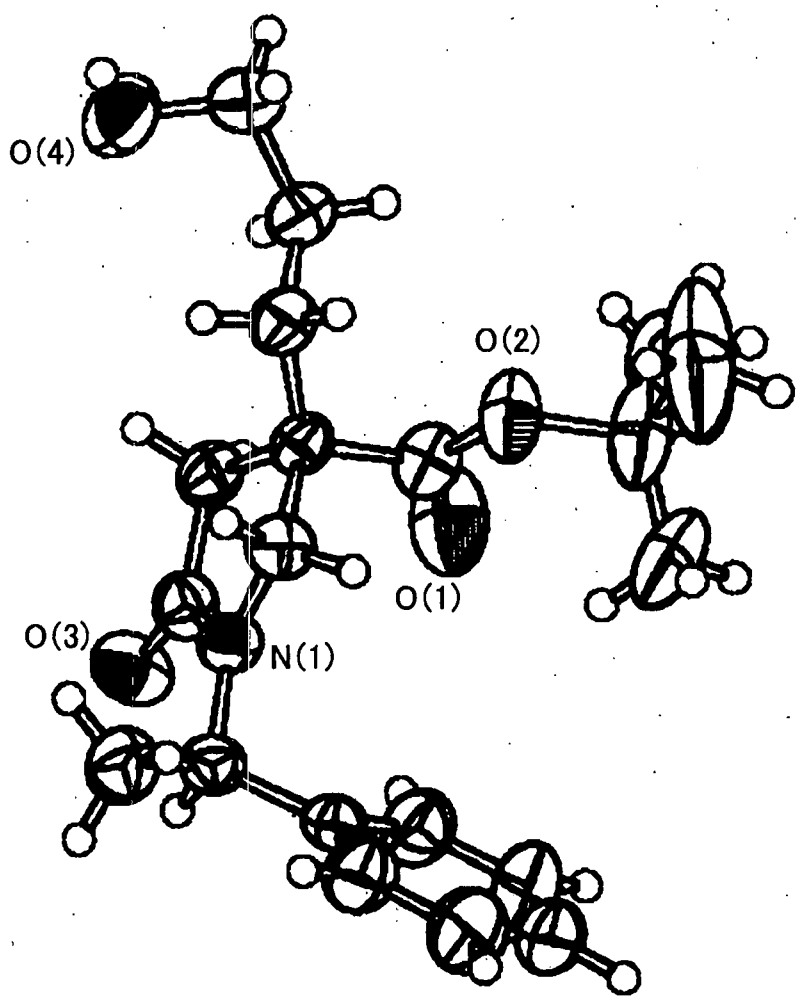
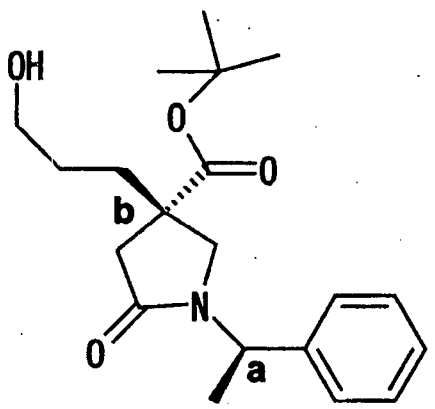


FIG.2



DERIVADO DE AMINOPIRROLIDINA SUSTITUIDO FUSIONADO

ANTECEDENTES DE LA INVENCION

CAMPO DE LA INVENCION

La presente invención se refiere a compuestos de quinolona útiles como medicinas, medicinas veterinarias, medicinas para piscifactorías o conservadores antibacterianos.

DESCRIPCION DE LA TECNICA RELACIONADA

Desde el descubrimiento de norfloxacin, los agentes antibacterianos sintéticos de quinolona (incluyendo aquellos que tienen una estructura de base de piridobenzoxazina) con actividad antibacteriana mejorada y farmacocinética se han desarrollado en agentes quimioterapéuticos efectivos para casi todas las infecciones sistémicas, y muchos de ellos no se usan clínicamente (véase patente japonesa abierta al público No. 61-282382 o patente japonesa abierta al público No. 63-45261 y Clinical Microbiology and Infection, Vol.11, No.4, p.256 (2005)).

Sin embargo, el número de tipos de bacterias que tienen sensibilidad baja a agentes antibacterianos sintéticos de quinolona ha tendido a incrementar en el campo clínico en años recientes. Por ejemplo, ha incrementado el número de tipos de bacterias resistentes a fármacos distintos a agentes antibacterianos sintéticos de quinolona, que se denominan bacterias resistentes a fármacos múltiples, tales como cocos Gram-positivos incluyendo

Staphylococcus aureus (*Staphylococcus aureus* resistente a meticilina: MRSA) y neumococos (*Streptococcus pneumonia* resistente a penicilina: PRSP) que tienen sensibilidad baja a antibióticos de β-lactama; y enterococos que tienen sensibilidad baja a agentes antibacterianos de aminoglucósido (enterococos resistentes a vancomicina: VRE) y que también tienen sensibilidad baja a agentes antibacterianos sintéticos de quinolona. Las infecciones bacterianas causadas por dichas bacterias Gram-positivas resistentes se sabe que son generalmente severas (fatales) e intratables. Por consiguiente, los fármacos más efectivos para cocos Gram-positivos son particularmente deseados en el campo clínico (véase Drugs, Vol.66, No.6, p.751 (2005)).

Por otra parte, los compuestos antibacterianos sintéticos de quinolona creados en años recientes tienen actividades antibacterianas que son mucho más altas que las de las anteriores (véase patente japonesa abierta al público No. 2-231475 o patente japonesa abierta al público No. 3-95176). Sin embargo, muchos de esos compuestos de quinolona que tienen actividad antibacteriana alta causan efectos colaterales con base en sus efectos fisiológicos y farmacológicos no observados para agentes antibacterianos sintéticos de quinolona anteriores.

Ejemplos de los efectos colaterales de agentes antibacterianos sintéticos de quinolona incluyen efectos colaterales convencionalmente reportados tales como inducción de convulsión por usarse en combinación con fármacos anti-inflamatorios no esteroideos (NSAIDs), acciones centrales (trastornos del sistema nervioso central ligeros tales como ladeo, dolor de cabeza e insomnio, y efectos colaterales severos tales como el inicio de convulsión fatal), y fototoxicidad (fotosensibilidad); así como efectos colaterales recientemente descritos tales como hepatotoxicidad (hepatitis alérgica severa),

cardiotoxicidad (anormalidad electrocardiográfica inductora de arritmia fatal, observada como prolongación de QT o QTc), erupción por fármacos retardada (salpullido de la piel), y anormalidad del nivel de glucosa en la sangre (véase Hiroyuki Kobayashi (ed.), Clinical Application of New Quinolone Agents, Iyaku (Medicine and Drug) Journal Co., Ltd.; Drugs, Vol.62, No. 1, p.13 (2002); Toxicology Letters, Vol. 127, p.269 (2002); Clinical Infectious Diseases, Vol. 41, p.1269 (2005)); e International Journal of Antimicrobial Agents, Vol.23, No.5, p.421 (2004)).

El inicio clínico de cardiotoxicidad entre esos efectos colaterales es un problema particular en años recientes. La prolongación de QT o QTc distinta se reporta y algunas condiciones severas (anormalidad electrocardiográfica que induce arritmia fatal) también se reporta para algunos agentes antibacterianos sintéticos de quinolona comercialmente disponibles (tales como grepafloxacin, esparfloxacin, moxifloxacin, gatifloxacin y gemifloxacin). Efectos colaterales severos tales como el inicio de hepatitis alérgica severa que acompaña al trasplante de hígado (trovafloxacin: véase Clinical Infectious Diseases, Vol.41, p.1269 (2005)) y anormalidad del nivel de glucosa en la sangre incluyendo hipoglicemia fatal (gatifloxacin: véase International Journal of Antimicrobial Agents, Vol.23, No.5, p.421 (2004)) tambmién son problemas clínicos. Además, se reporta la erupción por fármacos retardada (salpullido de la piel) causada por la administración repetida de un agente de quinolona en una prueba clínica (gatifloxacin: véase Clinical Infectious Diseases, Vol.41, p.1269 (2005)). En tales circunstancias, la administración de algunos agentes antibacterianos sintéticos de quinolona ha sido limitada, y el desarrollo y uso como medicinas humanas de algunos agentes antibacterianos sintéticos de quinolona ha sido abandonada. Es decir, se han observado algunos agentes antibacterianos sintéticos de

quinolona que tienen fuerte actividad antibacteriana pero que en términos de efectos colaterales no son suficientemente adecuados como medicinas.

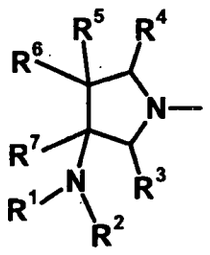
Por consiguiente, existe la necesidad de agentes antibacterianos sintéticos de quinolona más seguros para usarse como medicinas humanas, que tienen sólo efectos colaterales bajos tales como inducción de convulsión al usarse en combinación con fármacos antiinflamatorios no esteroideos, acciones centrales y fototoxicidad (fotosensibilidad) que son convencionalmente conocidos como efectos colaterales; así como cardiotoxicidad, hepatotoxicidad, la erupción por fármacos retardada (salpullido de la piel), y anormalidad del nivel de glucosa en la sangre que son problemas clínicos en años recientes. Por lo tanto, existe la necesidad del desarrollo de nuevos compuestos conceptualmente diferentes de los compuestos convencionales que tienen actividad antibacteriana alta pero causan efectos colaterales y por lo tanto no se pueden usar como medicinas. Es decir, existe la necesidad de compuestos de quinolona que tienen fuerte actividad antibacteriana y alta seguridad (véase The Japanese Journal for History of Pharmacy, Vol.38, No.2, p.161 (2003)).

La actividad antibacteriana, farmacocinética, y seguridad de un agente antibacteriano sintético de quinolona se sabe que son influenciadas por la estructura de los sustituyentes en cada posición de la estructura de base de quinolona, en particular, la estructura del sustituyente en la posición 7 (correspondiente a la posición 10 de la estructura de base de piridobenzoxazina) (véase, por ejemplo, Clinical Microbiology and Infection, Vol.11, No. 4, p.256 (2005)).

El aspecto característico de los compuestos de la presente invención es que tienen, en la posición 7 de la estructura de base madre de quinolona, un sustituyente representado por la siguiente fórmula 1:

625

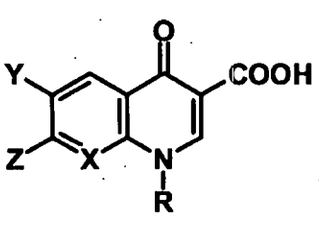
[Fórmula 1]



en donde R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son como se define en la reivindicación 1. Es decir, el sustituyente en la posición 7 en los compuestos de la presente invención tiene una estructura de amina bicíclica fusionada que se forma por fusión del anillo de pirrolidina con una estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos, y además la estructura de amina bicíclica fusionada tiene un grupo amino en la posición de cabeza de puente. En relación con los derivados de quinolona sustituidos con un sustituyente en la posición 7 que tienen dicha estructura, se conocen los siguientes compuestos.

Por ejemplo, la patente japonesa abierta al público No. 64-56673 describe un derivado de ácido piridonocarboxílico representado por la fórmula general 2:

[Fórmula 2]

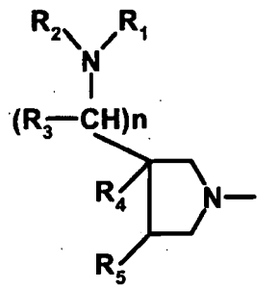


en donde R representa un grupo alquilo inferior, un grupo halogenoalquilo inferior, un grupo alquenilo inferior, un grupo cicloalquilo, o un grupo fenilo que puede tener un sustituyente; X representa un átomo de

626

nitrógeno o C-A, en donde A representa un átomo de hidrógeno o un átomo de halógeno; Y representa un átomo de hidrógeno o un átomo de halógeno; y Z representa un grupo representado por la siguiente fórmula 3:

[Fórmula 3]

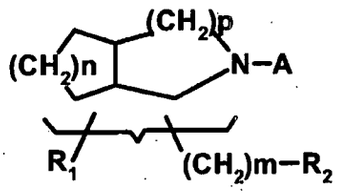


en donde R_1 representa un átomo de hidrógeno, un grupo alquiloxicarbonilo inferior, o un grupo acilo que puede ser sustituido con un átomo de halógeno; dos de R_2, R_3, R_4 y R_5 son unidos directamente o a través de una cadena de alquilo inferior para formar un anillo y los dos restantes de R_2, R_3, R_4 y R_5 cada uno representa un átomo de hidrógeno; y n representa 0 ó 1, siempre que R_2 y R_3 son un enlace cuando éstos se unen uno a otro. Las definiciones de sustituyentes y similares en el compuesto representado por la fórmula 2 no se aplica a los compuestos de la presente invención, aunque se usan los mismos símbolos. Sin embargo, la patente japonesa abierta al público No. 64-56673 no describe específicamente un compuesto de quinolona de conformidad con la presente invención en donde R_4 y R_5 en la fórmula 3 se toman juntos para formar un anillo de cuatro a siete miembros y n = 0.

El documento EP-A-343524 describe un agente antibacteriano de ácido piridonocarboxílico representado por la fórmula general 4:

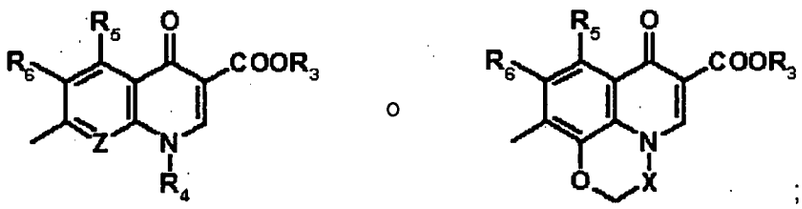
627

[Fórmula 4]



en donde R_1 es hidrógeno, hidroxi, alquilo de C_1-C_4, alcoxi de C_1-C_4, oxo, halógeno, o amino que opcionalmente puede ser sustituido con alquilo de C_1-C_4 y/o alcanoilo de C_1-C_4; R_2 es azida, hidroxi, alcoxi de C_1-C_4, alcoxicarbonilo de C_1-C_4, alcanoilo de C_1-C_4, o amino que opcionalmente puede ser sustituido con alquilo de C_1-C_4 y/o alcanoilo de C_1-C_4; A es una estructura de quinolona representada por la siguiente fórmula 5:

[Fórmula 5]

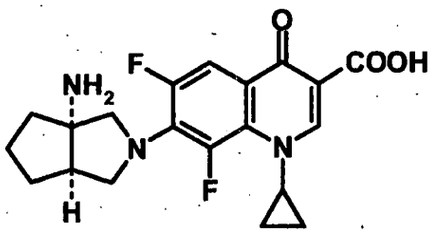


R_3 es hidrógeno o un grupo protector de carboxi; R_4 es alquilo de C_1-C_4, alquenilo de C_2-C_5, cicloalquilo de C_3-C_5, mono- o di-fluorofenilo, o un heterociclo de cinco o seis miembros que opcionalmente puede ser sustituido con halógeno y/o alquilo de C_1-C_4; R_5 es hidrógeno, amino, hidroxi, o alcoxi de C_1-C_4; R_6 es halógeno; X es CH-(alquilo de C_1-C_4), $C=CH_2$, N-H, o N-(alquilo de C_1-C_4); Z es CQ o N; Q es hidrógeno, alcoxi de C_1-C_4, halógeno, alquilo de C_1-C_4, o ciano; m es un entero de 0 ó 1; y n y p son cada uno un entero de 1 a 3. Sin embargo, como un compuesto específico relacionado con los compuestos de la presente invención, EP-A-343524 describe sólo un derivado de ácido quinolonocarboxílico representado por la siguiente fórmula 6, es decir, un

628

derivado en el cual m es 0, p es 1, y el sustituyente R_2 es un grupo amino en la posición de cabeza de puente de la amina bicíclica:

[Fórmula 6]



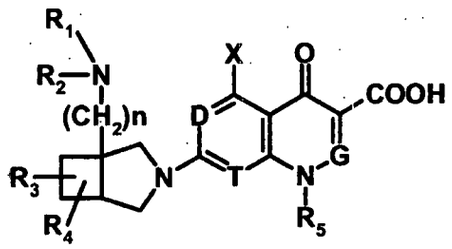
Más aún, el documento EP-A-343524 no describe un compuesto que tiene un grupo halogenociclopropilo en la posición 1 que es un ejemplo típico de los compuestos de la presente invención. La estructura del sustituyente en la posición 7 es una configuración (1R*, 5S*) en el compuesto representado como la fórmula 6 como se describe en el documento EP-A-343524. Este compuesto es también un denominado cis-racemato, y el documento EP-A-343524 no describe la actividad antibacteriana de un isómero óptico. Además, el documento EP-A-343524 no describe la seguridad del compuesto descrito. Un compuesto estereoquímicamente individual es preferible como una medicina humana en términos de efectividad y seguridad. Además, el compuesto representado por la fórmula 6 tiene un átomo de flúor en la posición 8 de la estructura de base de quinolona y por lo tanto supuestamente causa fototoxicidad (fotosensibilidad) con alta probabilidad (véase, por ejemplo, Journal of Antimicrobial Chemotherapy, Vol.33, p.683 (1994)). Es decir, se piensa que el compuesto representado por la fórmula 6 no es necesariamente suficiente como una medicina para uso efectivo en humanos con seguridad. European Journal of Medicinal Chemistry, Vol. 26, p.889 (1991) sólo describe el contenido de conformidad con el documento EP-A-343524.

El documento WO 95/21163 describe un agente antibacteriano de

629

ácido piridonocarboxílico sustituido con un grupo amino bicíclico, que está representado por la siguiente fórmula general 7:

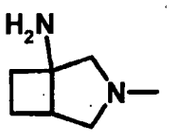
[Fórmula 7]



en donde R_1 y R_2 son los mismos o diferentes y cada uno representa un átomo de hidrógeno, un grupo alquilo inferior, o un grupo amino-protector; R_3 y R_4 son los mismos o diferentes y cada uno representa un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo hidroxi, un grupo oxo, un grupo alcoxi inferior, o un grupo alquilo inferior; n representa un entero de 0 ó 1; R_5 representa un grupo alquilo inferior, un grupo alquenilo inferior, un grupo cicloalquilo inferior, un grupo fenilo, o un grupo heterocíclico (éstos pueden ser adicionalmente sustituidos); G representa C-E, en donde E representa un átomo de hidrógeno o junto con R_5 forma un enlace cruzado representado por -S-SE(CH_3)-; T representa C-Z o un átomo de nitrógeno, en donde Z representa un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo alcoxi inferior, un grupo halogenoalcoxi inferior, un grupo alquilo inferior, o un grupo halogenoalquilo inferior o junto con R_5 forma un enlace cruzado representado por -O-CH_2- CH(CH_3)-; X representa un átomo de hidrógeno, un átomo de halógeno, un grupo hidroxi, un grupo alquilo inferior, o un grupo amino que puede ser protegido; y D representa C-Y, en donde Y representa un átomo de hidrógeno o un átomo de halógeno. Sin embargo, en relación con los compuestos de la presente invención, como un grupo amino

bicíclico en el sustituyente en la posición 7 del derivado de quinolona, sólo el sustituyente representado por la siguiente fórmula 8, es decir en donde R_3 y R_4 son cada uno un átomo de hidrógeno en la fórmula 7 y n es 0, se describe específicamente:

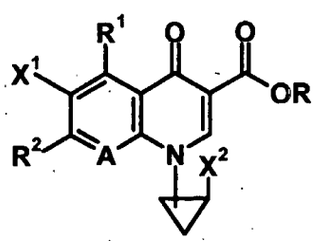
[Fórmula 8]



Además, el documento WO 95/21163 no describe específicamente un derivado de aminopirrolidina sustituido fusionado (amina bicíclica) que es una característica de la presente invención, es decir, en donde en el compuesto representado por la fórmula 7 uno o ambos de los sustituyentes R_3 y R_4 en la amina bicíclica tiene un sustituyente distinto a un átomo de hidrógeno.

El documento WO 96/23782 describe un derivado de ácido piridonocarboxílico sustituido con N_1-(halogenociclopropilo) representado por la fórmula general 9:

[Fórmula 9]

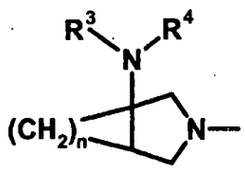


en donde X^1 representa un átomo de halógeno o un átomo de hidrógeno; X^2 representa un átomo de halógeno; R^1 representa un átomo de hidrógeno, un grupo hidroxi, un grupo tiol, un grupo halogenometilo, un grupo amino, un grupo alquilo o un grupo alcoxi; R^2 representa un sustituyente de la

631

fórmula 10:

[Fórmula 10]



en donde R^3 y R^4 cada uno representa un átomo de hidrógeno o un grupo alquilo y n representa un entero de 1 ó 2; A representa un grupo de la fórmula 11:

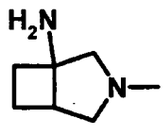
[Fórmula 11]



en donde X^3 representa un átomo de hidrógeno, un átomo de halógeno, un grupo ciano, un grupo amino, un grupo alquilo, un grupo halogenometilo, un grupo alcoxi, o un grupo halogenometoxi; y R representa un átomo de hidrógeno, un grupo fenilo, un grupo acetoximetilo, un grupo pivailoximetilo, un grupo etoxicarbonilo, un grupo colina, un grupo dimetilaminoetilo, un grupo 5-indanilo, un grupo ftalidinilo, un grupo 5-alquil-2-oxo-1,3-dioxol-4-ilmetilo, un grupo 3-acetoxi-2-oxobutilo, un grupo alquilo, un grupo alcoximetilo o un grupo fenilo. Las definiciones de sustituyentes y similares en el compuesto representado por la fórmula 9 no se aplican a los compuestos de la presente invención aunque se usan los mismos símbolos. Sin embargo, en relación con los compuestos de la presente invención, como un grupo amino bicíclico en el sustituyente en la posición 7 del derivado de quinolona, sólo el sustituyente representado por la siguiente fórmula 12, es decir en donde n es 2 en la fórmula 10, se describe específicamente:

632

[Fórmula 12]



Además, el documento WO 96/23782 no describe un derivado de 1-amino-3-azabiciclo [3.2.0] heptano que tiene un sustituyente distinto de un átomo de hidrógeno en el anillo bicíclico, que es una característica de los compuestos de la presente invención.

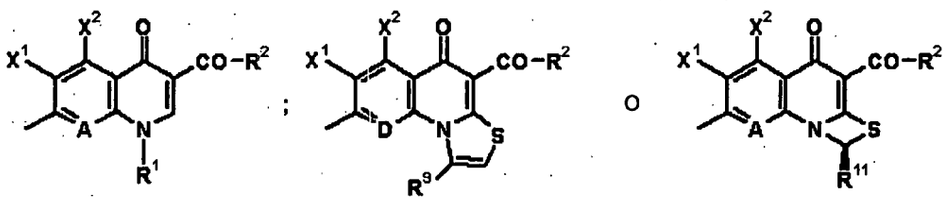
La patente japonesa abierta al público No. 8-225567 describe un derivado de ácido quinolon- o naftilidon-carboxílico representado por la fórmula general 13:

[Fórmula 13]

T–Q

en donde Q representa una estructura de quinolona de la fórmula 14 :

[Fórmula 14]

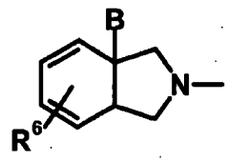


en donde X^1 representa halógeno o nitro; X^2 representa hidrógeno, halógeno, amino, hidroxi, metoxi o similar; A y D cada uno representa N o C-R^7 (en donde R^7 = H, F, OCH_3, o similar); R^1 representa alquilo de C_1-C_4, cicloalquilo de C_3-C_6, o similar; R^2 representa hidroxi, metoxi, benciloxi, o similar,- R^9 representa hidrógeno o alquilo de C_1-C_3; y R^{11} representa hidrógeno,

633

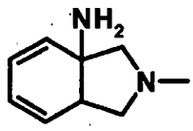
metilo o CH_2F; y T representa la siguiente fórmula 15:

[Fórmula 15]



en donde B representa amino, hidroxi o similar; y R^6 representa hidrógeno o metilo. Las definiciones de sustituyentes y similares en el compuesto representado por la fórmula 13 no se aplica a los compuestos de la presente invención aunque se usan los mismos símbolos. Sin embargo, la patente japonesa abierta al público No. 8-225567 sólo describe un compuesto representado por la siguiente fórmula 16 como tal un derivado en donde B es un grupo amino.

[Fórmula 16]



Además, la patente japonesa abierta al público No. 8-225567 no describe un compuesto específico relacionado con la presente invención.

BREVE DESCRIPCION DE LA INVENCION

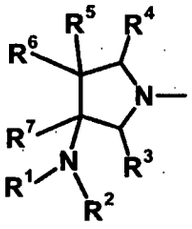
Por consiguiente, un objeto de la presente invención es proveer un agente antibacteriano sintético de quinolona y un agente terapéutico para infecciones que tiene actividad antibacteriana amplia y fuerte a bacterias Gram-positivas, incluyendo aquellos que tienen sensibilidad baja a quinolona, y a

634

bacterias Gram-negativas, y que también tiene alta seguridad.

Los inventores de la presente han conducido investigación sobre compuestos que tienen un grupo 3-aminopirrolidinilo en la posición 7 de compuestos de quinolona o su posición correspondiente (por ejemplo, la posición 10 de compuestos de piridobenzoxazina). Los inventores han encontrado que los derivados de quinolona que tienen un sustituyente de aminopirrolidinilo sustituido fusionado representado por la siguiente fórmula 17:

[Fórmula 17]



en donde los sustituyentes en las posiciones 3 y 4 en el grupo 3-aminopirrolidinilo tomado junto con los átomos de carbono a los cuales están unidos forman una estructura cíclica de cuatro a siete miembros que pueden contener un doble enlace y pueden contener un átomo de oxígeno o un átomo de azufre, la estructura cíclica junto con el anillo de pirrolidina formando una estructura cíclica fusionada (bicíclica), tiene actividad antibacteriana amplia y fuerte a bacterias Gram-positivas, notablemente a cocos Gram-positivos resistentes tales como neumococos resistentes a múltiples fármacos incluyendo quinolona, y a bacterias Gram-negativas. Varias evaluaciones preclínicas han revelado que los compuestos de quinolona no sólo tienen dicha actividad antibacteriana alta sino también causan sólo con poca probabilidad efectos colaterales convencionalmente conocidos de agentes antibacterianos de quinolona tales como inducción de convulsión y fototoxicidad (fotosensibilidad) y recientemente efectos colaterales clínicamente reportados tales como

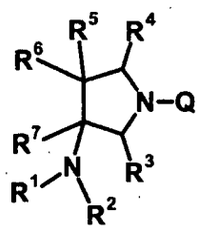
625

cardiotoxicidad (prolongación de QT), anormalidad del nivel de glucosa en la sangre, y la erupción por fármacos retardada. También se ha hecho claro que los compuestos de quinolona muestran capacidad de absorción oral excelente y permeabilidad a órganos. Estos resultados son muy inesperados del contenido descrito en los documentos de patente antes mencionados.

Finalmente, los inventores han encontrado que los compuestos de quinolona representados por la última formula (I) descrita y sus sales e hidratos correspondientes son agentes antibacterianos sintéticos de quinolona que tienen excelentes propiedades como medicinas, que tienen actividad antibacteriana y seguridad altas y que también presentan excelente farmacocinética. Estos hallazgos han conducido a la conclusión de la presente invención.

De manera específica, la presente invención provee un compuesto representado por la siguiente fórmula (I), una sal, o un hidrato del mismo:

[Fórmula 18]



I

en donde R^1 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, o un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido, o un tripéptido, dicho grupo alquilo puede tener uno o más sustituyentes seleccionado del grupo que consiste de un grupo hidroxi, un grupo amino, un grupo ciano, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y

dicho grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno;

R^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, o un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, dicho grupo alquilo puede tener uno o más sustituyentes seleccionado del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y dicho grupo cicloalquilo puede tener uno o más sustituyentes seleccionado del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi y un átomo de halógeno;

R^3 y R^4 cada uno independientemente representa un átomo de hidrógeno o un grupo alquilo que tiene 1 a 6 átomos de carbono, y dicho grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono;

R^5 representa un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquinilo que tiene 2 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, o un grupo heteroarilo que puede tener un sustituyente, dicho grupo alquilo, grupo alquenilo y grupo alquinilo puede ser lineal o ramificado, el grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un

637

grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y el grupo alquenilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono;

R^6 y R^7 tomado junto con los átomos de carbono a los cuales están unidos forman una estructura cíclica de cuatro a siete miembros, la estructura cíclica representando una estructura parcial que junto con el anillo de pirrolidina forma una estructura cíclica fusionada (bicíclica), la estructura cíclica de cuatro a siete miembros puede contener un doble enlace y puede contener un átomo de oxígeno o un átomo de azufre como un átomo constituyente de anillo,

R^5 puede ser un grupo metileno tomado junto con R^6 para formar una estructura cíclica fusionada de tres miembros, y el anillo formado como se describió antes puede ser localizado en otra parte de la estructura cíclica fusionada (bicíclica), y dicha estructura cíclica de cuatro a siete miembros puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquenilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquinilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo exometileno que puede tener un sustituyente, un grupo espiroalquilo que puede tener un sustituyente, un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, un grupo heteroarilo que puede tener un sustituyente, un grupo alcoxiimino que tiene 1 a 6 átomos de carbono que puede tener un sustituyente,

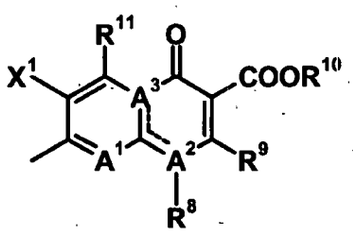
638

un átomo de halógeno, un grupo hidroxi, un grupo ciano, y un grupo hidroxiimino;

o una cadena de polimetileno de 2 a 5 átomos de carbono puede unirse para formar un sistema de anillo espirocíclico; y

Q representa una estructura parcial representada por la siguiente fórmula (II):

[Fórmula 19]



II

en donde R^8 representa un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo fenilo halógeno-sustituido que puede tener un sustituyente, un grupo heteroarilo halógeno-sustituido que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono, o un grupo alquilamino que tiene 1 a 6 átomos de carbono;

R^9 representa un átomo de hidrógeno o un grupo alquiltio que tiene 1 a 6 átomos de carbono, o R^9 y R^8 tomados junto con los átomos a los cuales están unidos forman una estructura cíclica, dicha estructura cíclica puede contener un átomo de azufre como un átomo constituyente de anillo y puede tener un grupo alquilo que tiene 1 a 6 átomos de carbono o un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono como un sustituyente;

R^{10} representa un átomo de hidrógeno, un grupo fenilo, un grupo

639

acetoximetilo, un grupo pivailoximetilo, un grupo etoxicarbonilo, un grupo colina, un grupo dimetilaminoetilo, un grupo 5-indanilo, un grupo ftalidinilo, un grupo 5-alquil-2-oxobutilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoximetilo que tiene 2 a 7 átomos de carbono, o un grupo fenilalquilo formado por un grupo alquileno que tiene 1 a 6 átomos de carbono y un grupo fenilo;

R^{11} representa un átomo de hidrógeno, un grupo amino, un grupo hidroxi, un grupo tiol, un grupo halogenometilo o un grupo alquilo que tiene 1 a 6 átomos de carbono, y el grupo amino puede tener uno o dos sustituyentes seleccionados del grupo que consiste de un grupo formilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, y un grupo acilo que tiene 2 a 5 átomos de carbono;

X^1 representa un átomo de halógeno o un átomo de hidrógeno;

A^1 representa un átomo de nitrógeno o una estructura parcial representada por la fórmula (III):

[Fórmula 20]



III

en donde X^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo ciano, un átomo de halógeno, un grupo metilo halógeno-sustituido, o un grupo halogenometoxi, o X^2 y R^8 tomados junto con su parte de conexión de la estructura de base madre forman una estructura cíclica, dicha estructura cíclica puede contener un átomo de oxígeno, un átomo de nitrógeno, o un átomo de azufre como un átomo constituyente de anillo, y puede ser sustituido con un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente; y

640.

A^2 y A^3 cada uno representa un átomo de nitrógeno o un átomo de carbono, y A^1, A^2, A^3, R^8 y el átomo de carbono al cual A^2 y A^3 están unidos juntos representan una estructura parcial:

>C=C(-A^1=) -N(-R^8) –

o una estructura parcial:

>N-C(-A^1=)=C(-R^8) -.

La presente invención también provee una medicina que comprende un compuesto representado por la fórmula (I), una sal, o un hidrato del mismo como un ingrediente activo. La presente invención además provee un método para tratar enfermedades que comprende administrar un compuesto representado por la fórmula (I), una sal, o un hidrato del mismo. La presente invención además provee el uso de un compuesto representado por la fórmula (I), una sal o un hidrato del mismo para la producción de una medicina.

La presente invención puede proveer un agente antibacteriano sintético de quinolona que tiene excelentes propiedades como una medicina, que tiene fuerte actividad antibacteriana no sólo para bacterias Gram-negativas sino también para cocos Gram-positivos que tienen sensibilidad baja a agentes antibacterianos de quinolona, y presenta alta seguridad y excelente farmacocinética.

BREVE DESCRIPCION DE LOS DIBUJOS

La figura 1 muestra el diagrama ORTEP obtenido por la cristalografía de rayos X para éster ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidino-3-carboxílico obtenido en el ejemplo de referencia 24.

642

La figura 2 muestra la configuración absoluta de éster ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidino-3-carboxílico obtenido en el ejemplo de referencia 24.

DESCRIPCION DETALLADA DE LAS MODALIDADES PREFERIDAS

R^1 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, o un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido o un tripéptido. El grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un grupo ciano, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y el grupo cicloalquilo puede tener uno o más sustituyentes seleccionado del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi y un átomo de halógeno.

R^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, o un grupo cicloalquilo que tiene 3 a 6 átomos de carbono. El grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono. El grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno.

Cuando R^1 o R^2 es un grupo alquilo, el grupo alquilo puede ser

642

lineal o ramificado, y es preferiblemente un grupo metilo, un grupo etilo, un grupo propilo, o un grupo isopropilo, muy preferiblemente un grupo metilo o un grupo etilo, y muy preferiblemente todavía un grupo metilo.

Cuando R^1 o R^2 es un grupo alquilo que tiene un grupo hidroxi, un grupo amino, o un grupo ciano como un sustituyente, el grupo alquilo puede ser un grupo alquilo lineal o ramificado que tiene 1 a 6 átomos de carbono y es preferiblemente sustituido con el sustituyente en el átomo de carbono terminal del grupo alquilo. El grupo alquilo que tiene un grupo hidroxi es adecuadamente un grupo alquilo que tiene hasta 3 átomos de carbono y es preferiblemente un grupo 2-hidroxietilo, un grupo 2-hidroxipropilo, o un grupo 3-hidroxipropilo. El grupo alquilo que tiene un grupo amino es adecuadamente un grupo alquilo que tiene hasta 3 átomos de carbono y es preferiblemente un grupo 2-aminoetilo, un grupo 2-aminopropilo o un grupo 3-aminopropilo. El grupo alquilo que tiene un grupo ciano es adecuadamente un grupo alquilo que tiene 2 a 4 átomos de carbono y es preferiblemente un grupo 2-cianoetilo o un grupo 2-ciano-2,2-dimetiletilo.

Cuando R^1 o R^2 es un grupo alquilo que tiene un átomo de halógeno como un sustituyente, el grupo alquilo puede ser un grupo alquilo lineal o ramificado que tiene 1 a 6 átomos de carbono y el átomo de halógeno es preferiblemente un átomo de flúor. El grupo alquilo puede ser monofluoro-sustituido a perfluoro-sustituido. Ejemplos adecuados del grupo alquilo halógeno-sustituido incluyen un grupo monofluorometilo, un grupo difluorometilo, un grupo trifluorometilo y un grupo 2,2,2-trifluoroetilo.

Cuando R^1 o R^2 es un grupo alquilo que tiene un grupo alquiltio o un grupo alcoxi como un sustituyente, el grupo alquilo puede ser lineal o ramificado y la porción alquilo en el grupo alquiltio o grupo alcoxi también puede

ser lineal o ramificado. El grupo alquilo que tiene un grupo alquiltio es preferiblemente un grupo alquiltiometilo, un grupo alquiltioetilo o un grupo alquiltiopropilo, y el grupo alquiltio preferiblemente tiene 1 a 3 átomos de carbono. Ejemplos más preferidos del grupo alquilo que tiene un grupo alquiltio incluyen un grupo metiltiometilo, un grupo etiltiometilo, y un grupo metiltioetilo. El grupo alquilo que tiene un grupo alcoxi es preferiblemente un grupo alcoximetilo, un grupo alcoxietilo, o un grupo alcoxipropilo, y el grupo alcoxi preferiblemente tiene 1 a 3 átomos de carbono. Ejemplos más preferidos del grupo alquilo que tiene un grupo alcoxi incluyen un grupo metoximetilo, un grupo etoximetilo y un grupo metoxietilo.

Cuando R^1 o R^2 es un grupo cicloalquilo, el grupo cicloalquilo es preferiblemente un grupo ciclopropilo o un grupo ciclobutilo, y muy preferiblemente un grupo ciclopropilo. El grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi y un átomo de halógeno. De manera específica, el sustituyente es preferiblemente un grupo metilo, un grupo etilo, un grupo amino, un grupo hidroxi, un átomo de flúor o un átomo de cloro.

Una combinación preferida de R^1 y R^2 es aquella en donde R^1 se selecciona de un átomo de hidrógeno, un grupo alquilo, un grupo cicloalquilo y un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido, o un tripéptido, y R^2 es un hidrógeno. Una combinación más preferida de R^1 y R^2 es aquella en donde R^1 se selecciona de un átomo de hidrógeno, un grupo alquilo y un grupo cicloalquilo y R^2 es un hidrógeno. El grupo alquilo es preferiblemente un grupo metilo o un grupo etilo, y en particular preferiblemente un grupo metilo. El grupo cicloalquilo es preferiblemente un grupo ciclopropilo o un grupo

644

ciclobutilo, y en particular preferiblemente un grupo ciclopropilo. Una combinación aún más preferida es aquella en donde ambos de R^1 y R^2 son átomos de hidrógeno o aquella en donde uno de R^1 y R^2 es un átomo de hidrógeno y el otro es un grupo metilo, un grupo etilo, un grupo fluoroetilo o un grupo ciclopropilo.

Un derivado de quinolona, en donde R^1 es un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido, o un tripéptido y R^2 es un átomo de hidrógeno, es útil como un profármaco. Los aminoácidos, dipéptidos, o tripéptidos usados para proveer dicho profármaco son aquellos que forman un enlace de péptido entre un grupo carboxilo y el grupo amino al cual R^1 y R^2 están unidos y forman un compuesto de amina libre después de ser digeridos *in vivo*. Ejemplos de grupos carbonilo sustituidos para proveer dicho profármaco incluyen grupos carbonilo sustituidos derivados de aminoácidos tales como glicina, alanina y ácido aspártico; dipéptidos formados por glicina, alanina o asparagina tales como glicina-glicina, glicina-alanina, y alanina-alanina; y tripéptidos formados por glicina, alanina o asparagina tales como glicina-glicina-alanina y glicina-alanina-alanina .

R^3 y R^4 independientemente representan un átomo de hidrógeno o un grupo alquilo que tiene 1 a 6 átomos de carbono. El grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono.

Cuando R^3 y R^4 son independientemente un grupo alquilo, el grupo alquilo puede ser lineal o ramificado, y es preferiblemente un grupo metilo, un grupo etilo, un grupo propilo, o un grupo isopropilo, muy preferiblemente un grupo metilo o un grupo etilo, y muy preferiblemente todavía un grupo metilo.

Cuando R^3 y R^4 son independientemente un grupo alquilo, el

sustituyente puede ser un grupo seleccionado del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono. El átomo de halógeno es preferiblemente un átomo de flúor. El grupo alquilo puede ser monofluoro-sustituido a perfluoro-sustituido. Ejemplos adecuados del grupo alquilo halógeno-sustituido incluyen un grupo monofluorometilo, un grupo difluorometilo, y un grupo trifluorometilo. Ejemplos preferidos del grupo alcoxi que tiene 1 a 6 átomos de carbono incluyen un grupo metoximetilo, un grupo etoximetilo y un grupo metoxietilo. Cuando R^3 y R^4 son independientemente un grupo alquilo sustituido, el grupo es en particular preferiblemente un grupo fluorometilo.

Una combinación preferida de R^3 y R^4 es aquella en donde uno de R^3 y R^4 es un átomo de hidrógeno y el otro es un grupo metilo o un grupo fluorometilo. Una combinación más preferida de R^3 y R^4 es aquella en donde ambos de R^3 y R^4 son átomos de hidrógeno.

R^5 representa un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquinilo que tiene 2 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, o un grupo heteroarilo que puede tener un sustituyente .

Cuando R^5 es un grupo alquilo, un grupo alquenilo o un grupo alquinilo, el grupo puede ser lineal o ramificado. El grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono. El

646

grupo alquenilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono.

Cuando R^5 es un átomo de halógeno, el átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y en particular preferiblemente un átomo de flúor.

Cuando R^5 es un grupo alquilo que tiene 1 a 6 átomos de carbono, el grupo alquilo es preferiblemente un grupo metilo, un grupo etilo, un grupo propilo, o un grupo isopropilo. El grupo alquilo es muy preferiblemente un grupo metilo o un grupo etilo, y en particular preferiblemente un grupo metilo.

El grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono y un grupo alcoxi que tiene 1 a 6 átomos de carbono.

Cuando un grupo hidroxi o un grupo amino es un sustituyente en el grupo alquilo, el sustituyente es preferiblemente en el átomo de carbono terminal del grupo alquilo. El grupo alquilo que tiene un grupo hidroxi es preferiblemente un grupo hidroximetilo, un grupo hidroxietilo, un grupo hidroxipropilo, o un grupo 3-hidroxipropilo. El grupo alquilo que tiene un grupo amino es preferiblemente un grupo aminometilo, un grupo 2-aminoetilo, un grupo 2-aminopropilo o un grupo 3-aminopropilo. El grupo alquilo que tiene un grupo hidroxi o un grupo amino es preferiblemente un grupo metilo o un grupo etilo, y muy preferiblemente un grupo hidroximetilo o un grupo aminometilo que tiene un grupo hidroxi o un grupo amino en el grupo metilo.

Cuando el grupo alquilo tiene un átomo de halógeno como un sustituyente, el grupo alquilo puede ser un grupo alquilo lineal o ramificado que

tiene 1 a 6 átomos de carbono, y es muy preferiblemente un grupo metilo o un grupo etilo, y en particular preferiblemente un grupo metilo. El átomo de halógeno es preferiblemente un átomo de flúor. El grupo alquilo puede ser monofluoro-sustituido a perfluoro-sustituido. Ejemplos del grupo alquilo halógeno-sustituido incluyen un grupo monofluorometilo, un grupo difluorometilo, un grupo trifluorometilo y un grupo 2,2,2-trifluoroetilo. Un grupo monofluorometilo, un grupo difluorometilo o un grupo trifluorometilo son particularmente preferidos.

Cuando el grupo alquilo tiene un grupo alquiltio o un grupo alcoxi como un sustituyente, el grupo alquilo puede ser lineal o ramificado y la porción alquilo en el grupo alquiltio o grupo alcoxi también puede ser lineal o ramificado. El grupo alquilo que tiene un grupo alquiltio es preferiblemente un grupo alquiltiometilo o un grupo alquiltioetilo, y el grupo alquiltio preferiblemente tiene 1 o 2 átomos de carbono. Ejemplos más preferidos del grupo alquilo que tiene un grupo alquiltio incluyen un grupo metiltiometilo, un grupo etiltiometilo y un grupo metiltioetilo. El grupo alquilo que tiene un grupo alcoxi es preferiblemente un grupo alcoximetilo o un grupo alcoxietilo, y el grupo alcoxi preferiblemente tiene 1 ó 2 átomos de carbono. Ejemplos más preferidos del grupo alquilo que tiene un grupo alcoxi incluyen un grupo metoximetilo, un grupo etoximetilo y un grupo metoxietilo. Entre éstos, un grupo metiltio y un grupo metoximetilo son aún más preferidos.

Cuando R^5 es un grupo alcoxi que tiene 1 a 6 átomos de carbono, el grupo alcoxi es preferiblemente un grupo alcoxi que tiene 1 a 3 átomos de carbono, específicamente, un grupo metoxi o un grupo etoxi.

Cuando R^5 es un grupo alquenilo que tiene 2 a 6 átomos de carbono, el grupo alquenilo preferiblemente contiene un doble enlace y no hay

648

limitaciones específicas a la posición del doble enlace. El grupo alquenilo es preferiblemente un grupo vinilo, un grupo propenilo, o un grupo butenilo, y en particular preferiblemente, por ejemplo, un grupo vinilo.

El grupo alquenilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono.

El átomo de halógeno es preferiblemente un átomo de flúor. Cuando el grupo alquenilo tiene un átomo de halógeno como un sustituyente, el grupo alquenilo es preferiblemente un grupo alquenilo que tiene 2 ó 3 átomos de carbono, muy preferiblemente un grupo vinilo que tiene un átomo de flúor, y en particular preferiblemente un grupo fluorovinilo.

Cuando el grupo alquenilo has un grupo alcoxi como un sustituyente, el grupo alquenilo preferiblemente tiene 2 ó 3 átomos de carbono. Ejemplos del grupo alquenilo que tiene un grupo alcoxi incluyen un grupo alcoxivinilo y un grupo alcoxipropenilo, específicamente, un grupo metoxivinilo y un grupo etoxivinilo. Un grupo metoxivinilo es particularmente preferido.

Cuando R^5 es un grupo alquinilo que tiene 2 a 6 átomos de carbono, el grupo alquinilo preferiblemente contiene un triple enlace y el triple enlace puede ser en cualquier posición. El grupo alquinilo es preferiblemente un grupo etinilo, un grupo propinilo o un grupo butinilo, y en particular preferiblemente un grupo etinilo.

Cuando R^5 es un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, el grupo cicloalquilo es preferiblemente un grupo ciclopropilo o un grupo ciclobutilo, y muy preferiblemente un grupo ciclopropilo.

El grupo cicloalquilo puede tener uno o más sustituyentes

seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo fenilo, un átomo de halógeno, un grupo amino y un grupo hidroxi. De manera específica, el sustituyente es preferiblemente un grupo metilo, un grupo etilo, un grupo fenilo, un átomo de flúor o un átomo de cloro, y muy preferiblemente un grupo metilo o un átomo de flúor.

Cuando R^5 es un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente o es un grupo heteroarilo que puede tener un sustituyente, el grupo heteroarilo es un anillo de cinco miembros o de seis miembros y puede contener 1 a 4 heteroátomos arbitrariamente seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y el grupo arilo o grupo heteroarilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno, un grupo amino, un grupo hidroxi, un grupo ciano, un grupo nitro, un grupo carboxilo, un grupo carbamoilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo alcoxicarbonilo que tiene 2 a 6 átomos de carbono y un grupo acilo que tiene 2 a 5 átomos de carbono. El grupo alquilo, grupo alcoxi, grupo alcoxicarbonilo o grupo acilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno, un grupo hidroxi y un grupo alcoxi que tiene 1 a 6 átomos de carbono.

El sustituyente en el grupo arilo o grupo heteroarilo es preferiblemente un átomo de halógeno, un grupo amino, un grupo hidroxi, un grupo ciano, un grupo carboxilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, o un grupo alcoxicarbonilo que tiene 2 a 6 átomos de carbono.

El átomo de halógeno como un sustituyente preferido es preferiblemente un átomo de flúor o un átomo de cloro, y muy preferiblemente

650

un átomo de flúor.

El grupo alquilo como un sustituyente preferido puede ser un grupo alquilo lineal o ramificado que tiene 1 a 6 átomos de carbono y es por ejemplo, un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, o un grupo ter-butilo, y preferiblemente un grupo metilo o un grupo etilo. El sustituyente en el grupo alquilo es preferiblemente un átomo de halógeno, y muy preferiblemente un átomo de flúor. Ejemplos del grupo alquilo halógeno-sustituido incluyen un grupo fluorometilo y un grupo trifluorometilo.

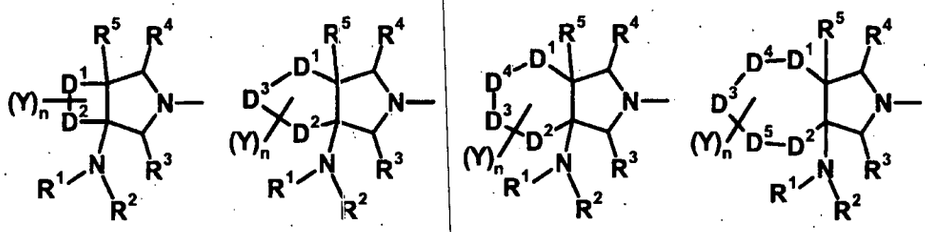
El grupo alcoxi como un sustituyente preferido es preferiblemente un grupo alcoxi que tiene 1 a 3 átomos de carbono, específicamente, un grupo metoxi o un grupo etoxi, y en particular preferiblemente un grupo metoxi. El sustituyente en el grupo alcoxi es preferiblemente un átomo de halógeno, y muy preferiblemente un átomo de flúor. Ejemplos del grupo alcoxi halógeno-sustituido incluyen un grupo trifluorometoxi.

El grupo alcoxicarbonilo como un sustituyente preferido es preferiblemente un grupo alcoxicarbonilo que tiene hasta 3 átomos de carbono. Ejemplos preferidos del grupo alcoxicarbonilo incluyen un grupo metoxicarbonilo y un grupo etoxicarbonilo. El sustituyente en el grupo alcoxicarbonilo es preferiblemente un átomo de halógeno, y muy preferiblemente un átomo de flúor. Ejemplos del grupo alcoxicarbonilo halógeno-sustituido grupo incluyen un grupo trifluorometoxicarbonilo.

R^6 y R^7 tomados junto con los átomos de carbono a los cuales están unidos forman una estructura cíclica de cuatro a siete miembros, la estructura cíclica representando una estructura parcial que junto con el anillo de pirrolidina forman una estructura cíclica fusionada (bicíclica). La porción de la estructura cíclica de cuatro a siete miembros formada de esta manera puede

contener un átomo de oxígeno o un átomo de azufre como un átomo constituyente de anillo. Dichas aminas cíclicas fusionadas están representadas por las siguientes fórmulas:

[Fórmula 21]

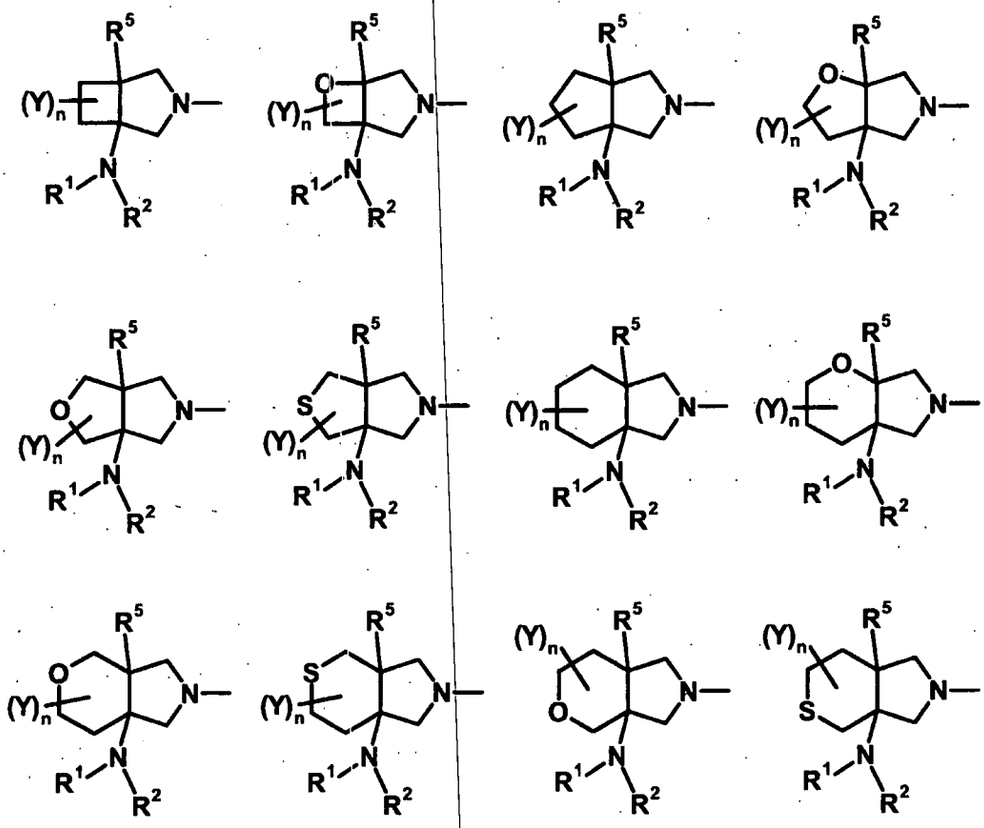


en donde R^1, R^2, R^3, R^4 y R^5 son como se define en la reivindicación 1; D^1, D^2, D^3, D^4 y D^5 cada uno representa un átomo de carbono que puede tener un sustituyente, un átomo de oxígeno o un átomo de azufre, siempre que cuando dos o más de D^1, D^2, D^3, D^4 y D^5 son cada uno un átomo de oxígeno o un átomo de azufre, no hay dos adyacentes de ellos que sean simultáneamente átomos de oxígeno o átomos de azufre, y el átomo de azufre puede ser un átomo de azufre oxidado tal como S=O o $S(=O)_2$; Y representa un sustituyente en el anillo (descrito más adelante); y n representa un entero de 0 a 3.

R^6 y R^7 forman una estructura cíclica de cuatro a siete miembros cuando tomados junto con los átomos de carbono a los cuales están unidos. Ejemplos preferidos de la amina cíclica fusionada se listan como sigue:

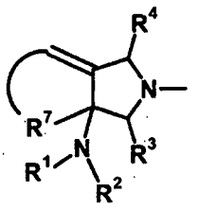
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[Fórmula 22]



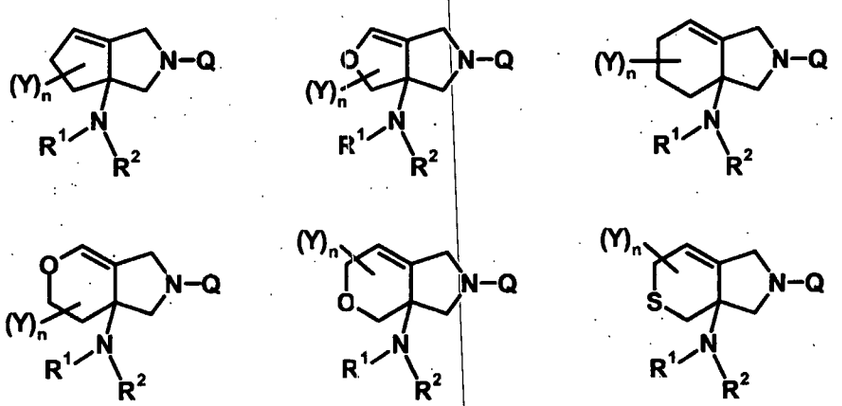
La estructura cíclica de cuatro a siete miembros formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos puede contener un doble enlace de anillo formado como una estructura constituyente. Cuando la estructura cíclica contiene el doble enlace como una estructura constituyente, parte de R^6 (el átomo de carbono sustituido en el anillo de pirrolidina) y R^5 puede pueden tomarse juntos para formar una estructura parcial de doble enlace que junto con R^7 forma estructura cíclica de cinco a siete miembros representada por la siguiente fórmula:

[Fórmula 23]



Sin embargo, la estructura parcial de doble enlace y R^7 preferiblemente forman una estructura cíclica de cinco o seis miembros. Ejemplos preferidos de la amina bicíclica se listan como sigue:

[Fórmula 24]



La estructura cíclica de cuatro a siete miembros puede tener un sustituyente seleccionado del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquenilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquinilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo heterocicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo exometileno que puede tener un sustituyente, un grupo espiroalquilo que puede tener un sustituyente,

654

un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, un grupo heteroarilo que puede tener un sustituyente, un átomo de halógeno, un grupo hidroxi, un grupo ciano, un grupo hidroxiimino, y un grupo alcoxiimino que tiene 1 a 6 átomos de carbono que puede tener un sustituyente.

El grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente puede ser lineal o ramificado. Ejemplos específicos del grupo alquilo incluyen un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo ter-butilo, un grupo fluorometilo, un grupo trifluorometilo, un grupo 2-fluoroetilo, un grupo 2,2,2-trifluoroetilo, un grupo ter-butilo fluoro-sustituido, un grupo hidroximetilo, un grupo hidroxietilo, un grupo 2-cianoetilo, un grupo metoximetilo y un grupo 2-metoxietilo. El grupo alquilo es preferiblemente un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo fluorometilo, un grupo 2-cianoetilo o un grupo metoximetilo.

El grupo alcoxi que tiene 1 a 6 átomos de carbono que puede tener un sustituyente puede ser un grupo alcoxi derivado del grupo alquilo antes mencionado, y es preferiblemente un grupo alcoxi que tiene 1 a 3 átomos de carbono, específicamente, un grupo metoxi o un grupo etoxi.

El grupo alquenilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente preferiblemente contiene un doble enlace y la posición del doble enlace no es limitada. El grupo alquenilo es preferiblemente un grupo vinilo, un grupo propenilo o un grupo butenilo. El sustituyente en el grupo alquenilo es preferiblemente un átomo de halógeno o un grupo alcoxi, y el átomo de halógeno es preferiblemente un átomo de flúor. Ejemplos del grupo alquenilo sustituido incluyen un grupo fluorovinilo y un grupo metoxivinilo.

El grupo alquinilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente preferiblemente contiene un triple enlace y el triple enlace

puede ser en cualquier posición. El grupo alquinilo es preferiblemente un grupo etinilo, un grupo propinilo o un grupo butinilo. Preferiblemente, el grupo alquinilo no tiene un sustituyente distinto de un átomo de hidrógeno.

El grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente es preferiblemente un grupo ciclopropilo o un grupo ciclobutilo. El grupo cicloalquilo puede ser sustituido con uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un átomo de halógeno, un grupo amino, y un grupo hidroxi. De manera específica, el sustituyente es preferiblemente un grupo metilo, un grupo etilo, un átomo de flúor o un átomo de cloro.

El grupo heterocicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente es preferiblemente un grupo oxetan-3-ilo, un grupo tioxetan-3-ilo, un grupo tetrahidrofuranilo, un grupo tetrahidropiranilo, o un grupo 2,2-dimetil-1,3-dioxan-4-ilo.

El grupo exometileno que puede tener un sustituyente es preferiblemente uno que no tiene un sustituyente distinto de un átomo de hidrógeno. El sustituyente distinto de un átomo de hidrógeno es preferiblemente un grupo amino, un átomo de flúor, un átomo de cloro, un grupo metiltio o un grupo metoxi.

El grupo espiroalquilo que puede tener un sustituyente es preferiblemente un grupo espirociclopropilo o un grupo espirociclobutilo. El grupo espiroalquilo está compuesto de un componente alicíclico y forma un sistema de anillo espirocíclico. El grupo espirocicloalquilo puede ser sustituido con uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un átomo de halógeno, un grupo amino, y un grupo hidroxi. De manera específica, el sustituyente es

656.

preferiblemente un grupo metilo, un grupo etilo, un átomo de flúor, o un átomo de cloro.

Cuando el sustituyente en la estructura cíclica de cuatro a siete miembros es un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente o es un grupo heteroarilo que puede tener un sustituyente, el grupo heteroarilo es un anillo de cinco o seis miembros y puede contener 1 a 4 heteroátomos arbitrariamente seleccionados de un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre. El grupo arilo o grupo heteroarilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno, un grupo amino, un grupo hidroxi, un grupo ciano, un grupo nitro, un grupo carboxilo, un grupo carbamoilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo alcoxicarbonilo que tiene 2 a 6 átomos de carbono, y un grupo acilo que tiene 2 a 5 átomos de carbono (es decir, grupo alquilcarbonilo de 2 a 5 átomos de carbono) . El grupo alquilo, grupo alcoxi, grupo alcoxicarbonilo o grupo acilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno, un grupo hidroxi y un grupo alcoxi que tiene 1 a 6 átomos de carbono. El sustituyente en el grupo arilo o grupo heteroarilo es preferiblemente un átomo de halógeno, un grupo amino, un grupo hidroxi, un grupo ciano, un grupo carboxilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, o un grupo alcoxicarbonilo que tiene 2 a 6 átomos de carbono. Sustituyentes particularmente preferidos en el grupo arilo o grupo heteroarilo incluyen un átomo de flúor, un átomo de cloro, un grupo metilo, un grupo fluorometilo, un grupo metoxi, un grupo etoxi, un grupo metoxicarbonilo y un grupo etoxicarbonilo.

Cuando el sustituyente es un átomo de halógeno, el átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y en particular preferiblemente un átomo de flúor.

Ejemplos preferidos del grupo alcoxiimino que tiene 1 a 6 átomos de carbono que puede tener un sustituyente incluyen un grupo metoxiimino y un grupo etoxiimino.

Ejemplos preferidos del sustituyente antes mencionado incluyen un grupo metilo, un grupo etilo, un grupo fluorometilo, un grupo 2-fluoroetilo, un grupo metoximetilo, un grupo cianoetilo, un grupo metoxi, un grupo ciclopropilo, un grupo espirociclopropilo, un grupo fenilo, un grupo oxazol, un átomo de flúor, un grupo hidroxi, un grupo hidroxiimino y un grupo metoxiimino. Entre éstos, un grupo metilo, un grupo fluorometilo, un grupo metoximetilo, un grupo metoxi, un átomo de flúor, un grupo cianoetilo y un grupo metoxiimino son particularmente preferidos.

La cadena de polimetileno que se une para formar un sistema de anillo espirocíclico es preferiblemente uno de 2 ó 3 átomos de carbono, y muy preferiblemente uno que tiene 2 átomos de carbono.

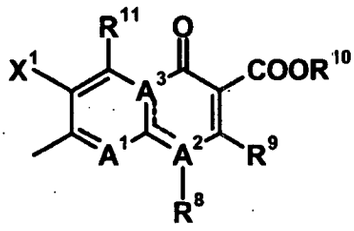
R^5 puede ser un grupo metileno tomado junto con R^6 para formar una estructura cíclica fusionada de tres miembros, y esta estructura cíclica hace luna estructura bicíclica fusionada formada al combinar R^6 y R^7 en un sistema de anillo tri-cíclico. Más aún, el sistema de tres anillos derivado de R^5 y R^6 puede localizarse en otra parte del sistema bicíclico de anillo fusionado derivado de R^6 y R^7. En otras palabras, el sustituyente bicíclico fusionado en la posición 7 puede volverse un sisterna de anillo tri-cíclico al incorporar un anillo de ciclopropano o cualquier parte de la estructura de anillo bicíclico.

Q representa una estructura parcial representada por la siguiente

658.

fórmula:

[Fórmula 25]



en donde A^2 y A^3 cada uno representa un átomo de nitrógeno o un átomo de carbono, y A^1, A^2 , A^3 , R^8 y el átomo de carbono al cual A^2 y A^3 están unidos juntos forma una estructura parcial:

>C=C(-A^1=) -N(-R^8) –

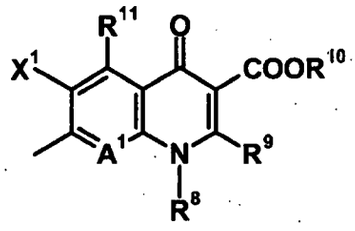
o una estructura parcial:

>N-C(-A^1=)=C(-R^8) –

en donde ">" significa que hay dos enlaces a un átomo de nitrógeno o un átomo de carbono (de aquí en adelante los mismos) .

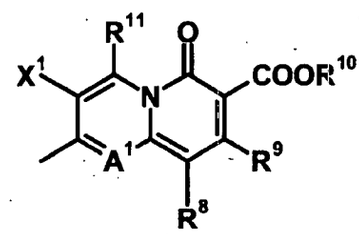
Q preferiblemente representa una estructura parcial del sistema heterocíclico fusionado representada por la fórmula:

[Fórmula 26]



o la fórmula:

[Fórmula 27]



659

en donde R^8 representa un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo fenilo halógeno-sustituido que puede tener un sustituyente, un grupo heteroarilo halógeno-sustituido que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono , o un grupo alquilamino que tiene 1 a 6 átomos de carbono.

Cuando R^8 es un grupo alquilo que tiene 1 a 6 átomos de carbono, el grupo alquilo puede ser lineal o ramificado. Ejemplos específicos del grupo alquilo incluyen un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo sec-butilo y un grupo ter-butilo. Entre éstos, un grupo etilo y un grupo ter- butilo son preferidos.

Cuando R^8 es un grupo alquenilo que tiene 2 a 6 átomos de carbono, el grupo alquenilo puede ser lineal o ramificado. Ejemplos específicos preferidos del grupo alquenilo incluyen un grupo vinilo y un grupo isopropenilo.

Cuando R^8 es un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono, la porción alquilo puede ser lineal o ramificado. Ejemplos específicos de la porción alquilo incluyen un grupo metilo, un grupo etilo, un grupo propilo, un grupo isopropilo, un grupo butilo, un grupo isobutilo, un grupo sec-butilo y un grupo ter-butilo. Entre éstos, un grupo etilo y un grupo ter-butilo son preferidos. El átomo de halógeno sustituyente en el grupo alquilo es preferiblemente un átomo de flúor o un átomo de cloro, y muy preferiblemente un átomo de flúor. Ejemplos del grupo alquilo halógeno-sustituido incluyen un grupo fluorometilo, un grupo trifluorometilo, un grupo 1-fluoroetilo, un grupo 2-fluoroetilo, un grupo 2,2,2-trifluoroetilo, un grupo 1,1-dimetil-2-fluoroetilo, un

160.

grupo 1-metil-1-(fluorometil)-2-fluoroetilo y un grupo 1,1-(difluorometil)-2-fluoroetilo. Entre éstos, un grupo 2-fluoroetilo y un grupo 1,1-dimetil-2-fluoroetilo son preferidos.

Cuando R^8 es un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, ejemplos del grupo cicloalquilo incluyen un grupo ciclopropilo, un grupo ciclobutilo y un grupo ciclopentilo. Entre éstos, un grupo ciclopropilo es preferido. El sustituyente en el grupo cicloalquilo es preferiblemente un átomo de halógeno, un grupo metilo o un grupo fenilo, y muy preferiblemente un átomo de halógeno. El átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y en particular preferiblemente un átomo de flúor. El número de sustituyentes puede ser 1 ó 2 pero es preferiblemente 1. De manera específica, el grupo cicloalquilo que puede tener un sustituyente es preferiblemente un grupo monofluorociclopropilo, muy preferiblemente un grupo 1,2-cis-2-fluorociclopropilo, y en particular preferiblemente un grupo (1R,2S)-2-fluorociclopropilo.

Cuando R^8 es un grupo fenilo halógeno-sustituido que puede tener un sustituyente, el átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y muy preferiblemente un átomo de flúor. El número de sustituyentes de átomo de halógeno es preferiblemente 1 ó 2. El sustituyente en el grupo fenilo halógeno-sustituido es preferiblemente un grupo amino, un grupo hidroxi o un grupo metilo. Ejemplos del grupo fenilo halógeno-sustituido que puede tener un sustituyente incluyen un grupo 2-fluorofenilo, un grupo 4-fluorofenilo, un grupo 2,4-fluorofenilo y un grupo 5-amino-2,4-difluorofenilo. Entre éstos, un grupo 2,4-difluorofenilo y un grupo 5-amino-2,4-difluorofenilo son preferidos.

Cuando R^8 es un grupo heteroarilo halógeno-sustituido que puede

tener un sustituyente, el grupo heteroarilo puede ser un grupo heterocíclico aromático de cinco o seis miembros que contiene uno o más heteroátomos seleccionados de un átomo de nitrógeno, un átomo de azufre y un átomo de oxígeno. Dicho grupo heteroarilo es preferiblemente un grupo heterocíclico aromático que contiene nitrógeno de cinco o seis miembros que contiene 1 ó 2 átomos de nitrógeno. Ejemplos específicos del grupo heteroarilo incluyen un grupo piridilo, un grupo pirimidilo, un grupo piridazinilo, un grupo imidazolilo, un grupo tiazolilo y un grupo oxazolilo. Entre éstos, un grupo piridilo es preferido. El átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y muy preferiblemente un átomo de flúor. El número de halógeno átomos es preferiblemente 1 ó 2. Ejemplos preferidos del sustituyente en el grupo heteroarilo halógeno-sustituido incluyen un grupo amino, un grupo hidroxi y un grupo metilo. Dicho grupo heteroarilo halógeno-sustituido que puede tener un sustituyente es preferiblemente un grupo 6-amino-3,5-difluoropiridin-2-ilo.

Cuando R^8 es un grupo alcoxi que tiene 1 a 6 átomos de carbono, el grupo alcoxi es preferiblemente un grupo metoxi.

Cuando R^8 es un grupo alquilamino que tiene 1 a 6 átomos de carbono, el grupo alquilamino es preferiblemente un grupo metilamino.

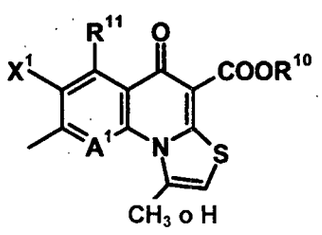
El R^8 antes mencionado es preferiblemente un grupo ciclopropilo o un grupo 1,2-cis-2-fluorociclopropilo, y muy preferiblemente un grupo (1R,2S)-2-fluorociclopropilo.

R^9 representa un átomo de hidrógeno o un grupo alquiltio que tiene 1 a 6 átomos de carbono. R^9 y el R^8 antes mencionado pueden ser tomados junto con parte de la estructura de base madre (incluyendo el átomo de carbono al cual R^9 está unido y A^2; de aquí en adelante el mismo) para formar una estructura cíclica. El anillo formado de esta manera puede contener un átomo de

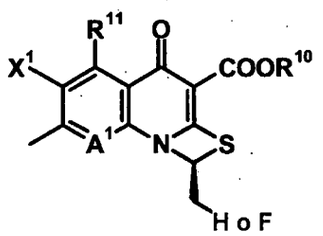
662

azufre como un átomo constituyente de anillo, y puede tener un grupo alquilo que tiene 1 a 6 átomos de carbono o un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono como un sustituyente. El anillo formado aquí puede ser un anillo de cuatro a seis miembros y puede ser saturado, parcialmente saturado o insaturado. La estructura de anillo fusionado formada de esta manera puede ser representada por las siguientes fórmulas:

[Fórmula 28]



;



R^{10} representa un átomo de hidrógeno, un grupo fenilo, un grupo acetoximetilo, un grupo pivailoximetilo, un grupo etoxicarbonilo, un grupo colina, un grupo dimetilaminoetilo, un grupo 5-indanilo, un grupo ftalidinilo, un grupo 5-alquil-2-oxobutilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoximetilo que tiene 2 a 7 átomos de carbono o un grupo fenilalquilo formado por un grupo alquileno que tiene 1 a 6 átomos de carbono y un grupo fenilo.

R^{10} es preferiblemente un átomo de hidrógeno.

R^{11} representa un átomo de hidrógeno, un grupo amino, un grupo hidroxi, un grupo tiol, un grupo halogenometilo o un grupo alquilo que tiene 1 a 6 átomos de carbono. El grupo amino puede tener uno o dos sustituyentes seleccionados del grupo que consiste de un grupo formilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, y un grupo acilo que tiene 2 a 5 átomos de carbono.

Cuando R^{11} es un grupo alquilo que tiene 1 a 6 átomos de carbono,

663

el grupo alquilo puede ser lineal o ramificado y es preferiblemente un grupo metilo, un grupo etilo, un grupo propilo o un grupo isopropilo, y en particular preferiblemente un grupo metilo.

Cuando R^{11} es un grupo halogenometilo, el átomo de halógeno es preferiblemente un átomo de flúor y el número de átomos de halógeno puede ser 1 a 3.

Cuando R^{11} es un grupo amino, un grupo hidroxi, o un grupo tiol, el grupo puede ser protegido por un grupo protector ordinariamente usado.

Ejemplos de dicho grupo protector incluyen grupos alcoxicarbonilo (sustituido) tales como un grupo ter-butoxicarbonilo y un grupo 2,2,2-tricloroetoxicarbonilo; grupos aralquiloxicarbonilo (sustituido) tales como un grupo benciloxicarbonilo, un grupo p-metoxibenciloxicarbonilo, y un grupo p-nitrobenciloxicarbonilo; grupos acilo (sustituido) tales como un grupo acetilo, un grupo metoxiacetilo, un grupo trifluoroacetilo, un grupo cloroacetilo, un grupo pivaloilo, un grupo formilo y un grupo benzoilo; grupos alquilo (sustituido) o grupos aralquilo (sustituido) tales como un grupo ter-butilo, un grupo bencilo, un grupo p-nitrobencilo, un grupo p-metoxibencilo y un grupo trifenilmetilo, éteres (sustituidos) tales como un grupo metoximetilo, un grupo ter-butoximetilo, un grupo tetrahidropiranilo, y un grupo 2,2,2-tricloroetoximetilo; y grupos siliso (alquilo- y/o aralquilo-)sustituidos tales como un grupo trimetilsililo, un grupo isopropildimetilsililo, y un grupo ter-butildifenilsililo. Un compuesto que tiene un sustituyente protegido por dicho grupo protector, es particularmente preferido como un intermediario de producción.

Entre los ejemplos antes mencionados, R^{11} es preferiblemente un átomo de hidrógeno, un grupo amino, un grupo hidroxi o un grupo metilo, y en particular preferiblemente un átomo de hidrógeno o un grupo amino.

664

X^1 representa un átomo de halógeno o un átomo de hidrógeno. El átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro, y muy preferiblemente un átomo de flúor. X^1 es preferiblemente un átomo de flúor o un átomo de hidrógeno.

A^1 representa un átomo de nitrógeno o una estructura parcial representada por la fórmula (III):

[Fórmula 29]



III

en donde X^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo ciano, un átomo de halógeno, un grupo metilo halógeno-sustituido, o un grupo halogenometoxi, el X^2 y el R^8 pueden ser tomados junto con su parte de conexión de la estructura de base madre (incluyendo el átomo de carbono al cual X^2 está unido y A^2) para formar una estructura cíclica, el anillo formado de esta manera puede contener un átomo de oxígeno, un átomo de nitrógeno o un átomo de azufre como un átomo constituyente de anillo, y el anillo puede ser sustituido con un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente.

Cuando A^1 es una estructura parcial representada por la fórmula (III) y X^2 es un grupo alquilo que tiene 1 a 6 átomos de carbono, el grupo alquilo puede ser lineal o ramificado, y es preferiblemente un grupo metilo, un grupo etilo, un grupo propilo, o un grupo isopropilo, muy preferiblemente un grupo metilo o un grupo etilo, y muy preferiblemente todavía un grupo metilo.

Cuando X^2 es un grupo alcoxi que tiene 1 a 6 átomos de carbono, el grupo alcoxi puede ser un grupo alcoxi derivado del grupo alquilo antes

mencionado. El grupo alcoxi es preferiblemente un grupo alcoxi que tiene 1 a 3 átomos de carbono, y en particular preferiblemente un grupo metoxi.

Cuando X^2 es un átomo de halógeno, el átomo de halógeno es preferiblemente un átomo de flúor o un átomo de cloro. Cuando el R^{11} antes mencionado es un átomo de hidrógeno, X^2 es preferiblemente un átomo de cloro; cuando el R^{11} es un grupo amino, un grupo hidroxi o un grupo metilo, X^2 es preferiblemente un átomo de flúor.

Cuando X^2 es un grupo metilo halógeno-sustituido, el átomo de halógeno es preferiblemente un átomo de flúor. Ejemplos preferidos del grupo metilo halógeno-sustituido incluyen un grupo fluorometilo, un grupo difluorometilo y un grupo trifluorometilo.

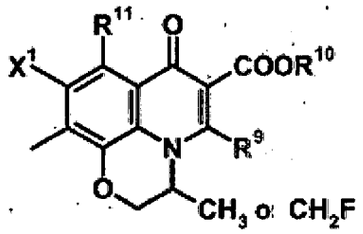
Cuando X^2 es un grupo halogenometoxi, el átomo de halógeno es preferiblemente un átomo de flúor como en el caso antes mencionado. Ejemplos específicos del grupo halogenometoxi incluyen un grupo fluorometoxi, un grupo difluorometoxi, y un grupo trifluorometoxi. Entre éstos, un grupo difluorometoxi es más preferido.

Cuando A^1 es una estructura parcial representada por la fórmula (III), X^2 y R^8 pueden formar una estructura cíclica incluyendo parte de la estructura de base de quinolona [el átomo de carbono al cual X^2 está unido, A^2 al cual R^8 está unido (en donde A^2 es un átomo de nitrógeno o un átomo de carbono), y el átomo de carbono del anillo de la estructura de base al cual el átomo de carbono y el A^2 están unidos]. El anillo formado aquí es preferiblemente un anillo de cinco a siete miembros y puede ser saturado o insaturado. La estructura cíclica puede contener un átomo de oxígeno, un átomo de nitrógeno, o un átomo de azufre y puede ser sustituido con un grupo alquilo que tiene 1 a 6 átomos de carbono o un grupo halogenometilo descrito para X^2.

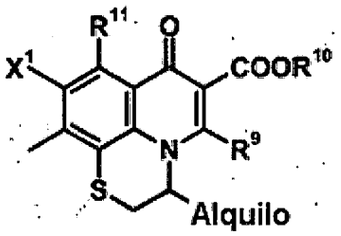
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La estructura de anillo fusionado formada de esta manera puede ser representada por las siguientes fórmulas:

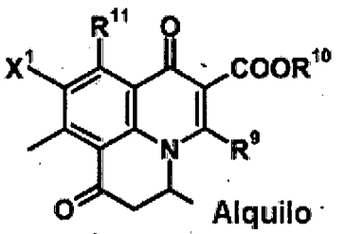
[Fórmula 30]



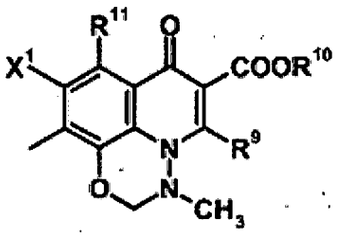
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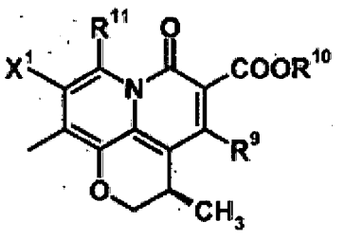
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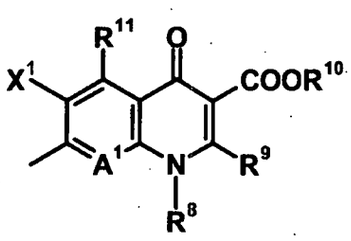


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Cuando A^1 es una estructura parcial representada por la fórmula (III) y el sustituyente X^2 no forma una estructura cíclica, X^2 es preferiblemente un grupo metilo, un grupo etilo, un grupo metoxi, un grupo difluorometoxi, un grupo ciano o un átomo de cloro, y en particular preferiblemente un grupo metilo, un grupo metoxi, un grupo difluorometoxi o un grupo ciano. Dicho sustituyente es particularmente preferido cuando A es una estructura parcial representada por la siguiente fórmula:

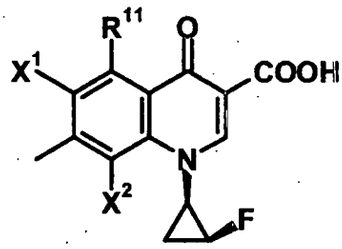
[Fórmula 31]



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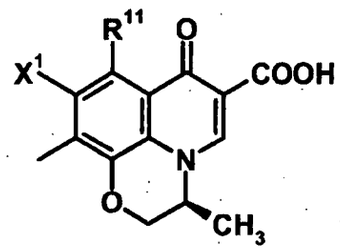
Más aún, dicho sustituyente es muy particularmente preferido cuando Q es una estructura parcial de la estructura de base del ácido 1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-4-oxoquinolino-3-carboxílico representada por la siguiente fórmula:

[Fórmula 32]



Cuando A^1 es una estructura parcial representada por la fórmula (III) y el sustituyente X^2 forma una estructura cíclica, una estructura de base del ácido 2,3-dihidro-3-metil (o fluorometil)-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico es preferiblemente formada. Una estructura de base de 3-(S)-metilpiridobenzoxazina representada por la siguiente fórmula (el compuesto de Y^0 es metilo) es particularmente preferida:

[Fórmula 33]

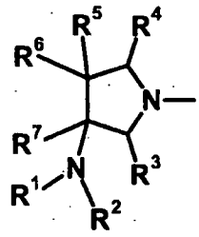


El compuesto de la presente invención se caracteriza porque tiene un sustituyente de una estructura representada por la siguiente fórmula en la

668.

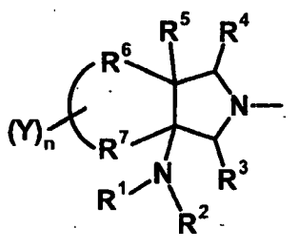
posición 7 de la estructura de base de quinolona (o su posición correspondiente):

[Fórmula 34]



De manera específica, el sustituyente del compuesto de la presente invención tiene un grupo amino en una posición correspondiente a la posición 3 del grupo pirrolidinilo, y el sustituyente R^7 en el átomo de carbono sustituido con el grupo amino y el sustituyente R^6 en una posición correspondiente a la posición 4 del grupo pirrolidinilo son tomados junto con los átomos de carbono a los cuales están unidos para formar una estructura cíclica de cuatro a siete miembros. Es decir, el sustituyente del compuesto de la presente invención es una estructura de aminopirrolidina sustituida fusionada, en la cual la estructura cíclica junto con el anillo de pirrolidina forma una estructura cíclica fusionada (bicíclica) representada por la siguiente fórmula, en la cual la estructura cíclica fusionada es sustituida con un grupo amino en la posición de cabeza de puente como sigue:

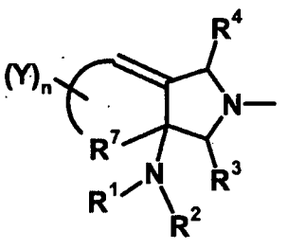
[Fórmula 35]



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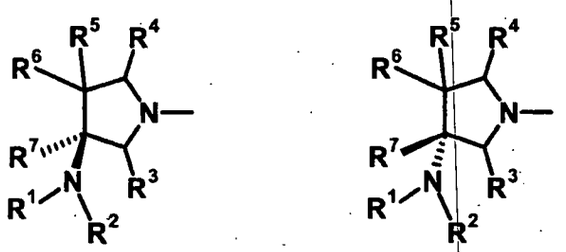
Además, el sustituyente del compuesto de la presente invención tiene una estructura cíclica representada por la siguiente fórmula, en la cual la estructura cíclica formada al tomar los sustituyentes R^6 y R^7 junto con los átomos de carbono a los cuales están unidos es un anillo de cinco o seis miembros, y R^5 y R^6 se toman juntos para formar una estructura parcial de doble enlace como sigue:

[Fórmula 36]



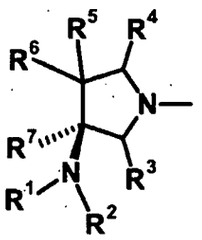
El grupo amino bicíclico contiene un átomo de carbono asimétrico y ocurre estereoisomerismo (isomerismo óptico). Este estereoisomerismo se describirá ahora. Además, existen los siguientes dos tipos con respecto a la posición de cabeza de puente sustituida con un grupo amino:

[Fórmula 37]



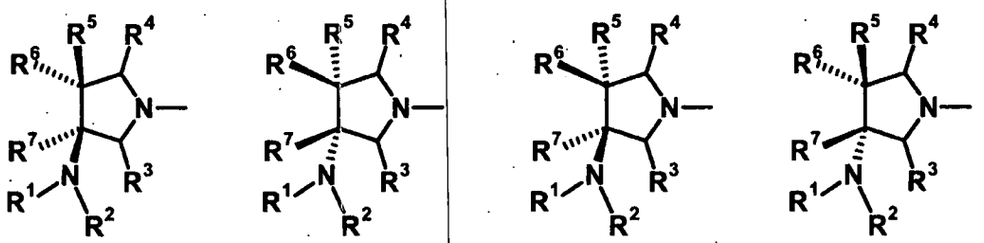
Aquí, la siguiente estructura en donde el grupo amino está en la configuración β es preferido:

[Fórmula 38]



Además, cuando los sustituyentes R^5 y R^6 no se toman juntos para formar un doble enlace, hay los cuatro tipos con respecto al átomo de carbono asimétrico sustituido con R^5:

[Fórmula 39]



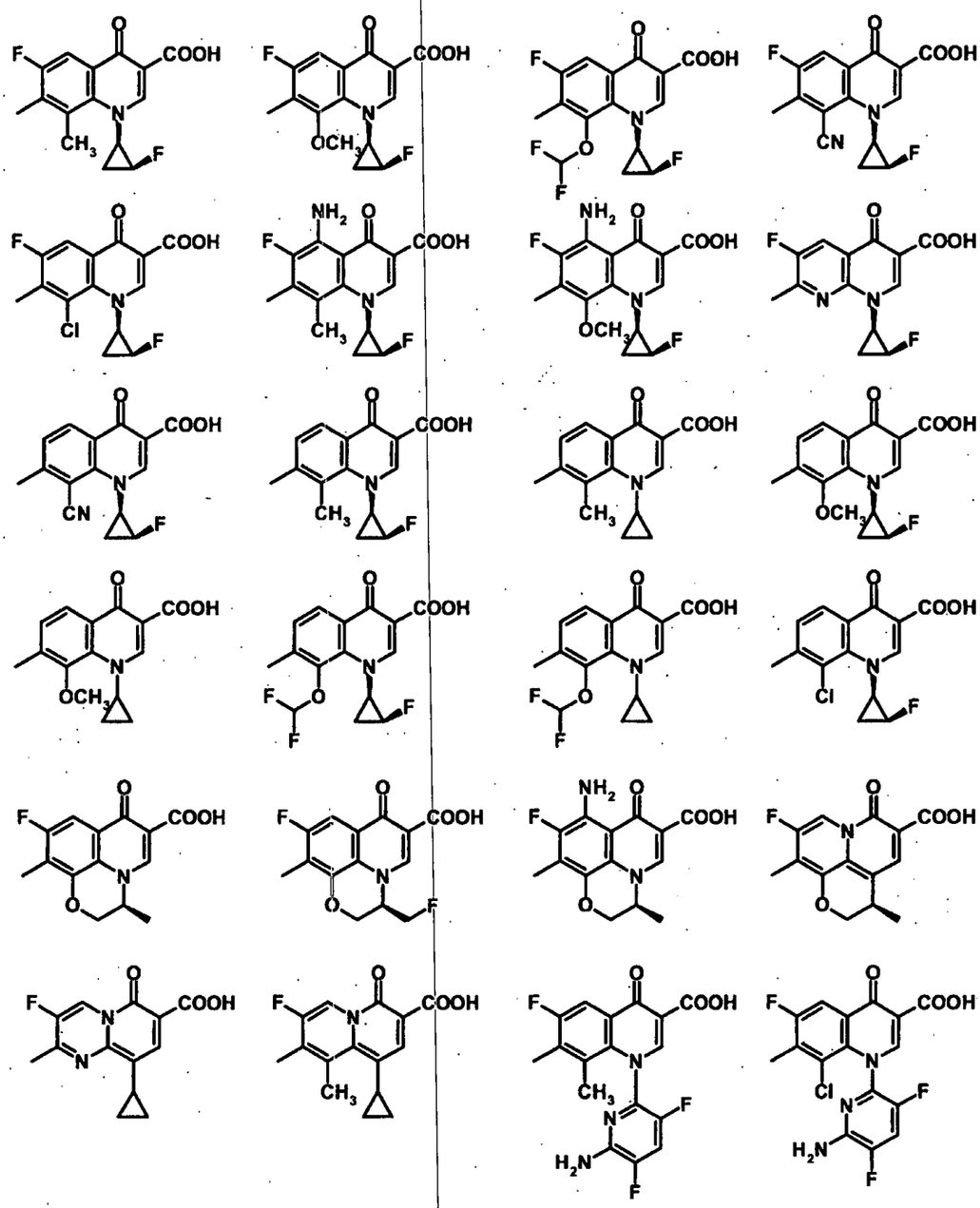
1 2 3 4

Típicamente, la estructura 1 es más preferida que la estructura 2 y la estructura 3 es más preferida que la estructura 4; sin embargo, qué estructura es preferida depende de la estructura del sustituyente R^5. Típicamente, la estructura 1 es más preferida que la estructura 3 cuando los sustituyentes R^6 y R^7 forman un anillo de cuatro miembros, y la estructura 3 es más preferida que la estructura 1 cuando los sustituyentes R^6 y R^7 forman un anillo de seis miembros; sin embargo, qué estructura es preferida depende del tamaño del anillo formado por los sustituyentes R^6 y R^7. La presente invención incluye todos los tipos antes mencionados.

Las estructuras de base madre preferidas se listan más adelante tomando, como un ejemplo, una estructura básica de ácido quinolonocarboxílico

(o ácido piridobenzoxazinocarboxílico) que tiene el sustituyente antes mencionado en la posición 7 (o su posición correspondiente):

[Fórmula 40]



Ejemplos preferidos del sustituyente en la posición 7 (o su posición correspondiente) se listan a continuación:

un grupo (1R,5S)-1-amino-6-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo;

672

un grupo (1S,5S,6R)-1-amino-6-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo (1S,5S,6S)-1-amino-6-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo (1S,5S)-1-amino-6,6-difluoro-3-azabiciclo [3.2.0]heptan-3-ilo;

un grupo (1S,5R, 6R)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo (1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo (1S,5R,6R)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo (1S,5R,6S)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-ilo;

un grupo espiro[(1S,5S)-1-amino-3-azabiciclo[3.2.0]heptano-6,1'-ciclopropan]-3-ilo;

un grupo (1S,5R)-1-amino-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1S,5S)-1-amino-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1R, 5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1R,5R)-1-amino-5-fluoro-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1S,5R,6S)-1-amino-6-fluoro-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1S,5R)-1-amino-6,6-difluoro-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1S,5R,7S)-1-amino-7-fluoro-3-azabiciclo[3.3.0]octan-3-ilo;

673

un grupo (1S,5R,7R)-1-amino-7-fluoro-3-azabiciclo[3.3.0]octan-3-ilo;

un grupo (1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-ilo;

un grupo (1S,5R)-1-amino-7-metil-3-azabiciclo[3.3.0]oct-7-en-3-ilo;

un grupo (1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-ilo,-

un grupo (1S)-1-amino-6-metil-3-azabiciclo[3.3.0]oct-5-en-3-ilo;

un grupo (1R,5R)-1-amino-S-oxa-S-azabiciclo[3.3.0]octan-5-ilo;

un grupo (1R,5S)-1-amino-3-oxa-5-azabiciclo[3.3.0]octan-5-ilo;

un grupo (1R,5R)-1-amino-4-oxa-5-azabiciclo[3.3.0]octan-5-ilo;

un grupo (1R,5S)-1-amino-4-oxa-5-azabiciclo[3.3.0]octan-5-ilo;

un grupo 6-amino-8-azatriciclo[4.3.0.$0^{1,3}$]nonan-8-ilo;

un grupo (1S,5R)-1-amino-3-azabiciclo[4.3.0]nonan-3-ilo;

un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-ilo;

un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]non-7-en-3-ilo;

un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]non-8-en-3-ilo;

un grupo (1S)-1-amino-3-azabiciclo[4.3.0]non-5-en-3-ilo;

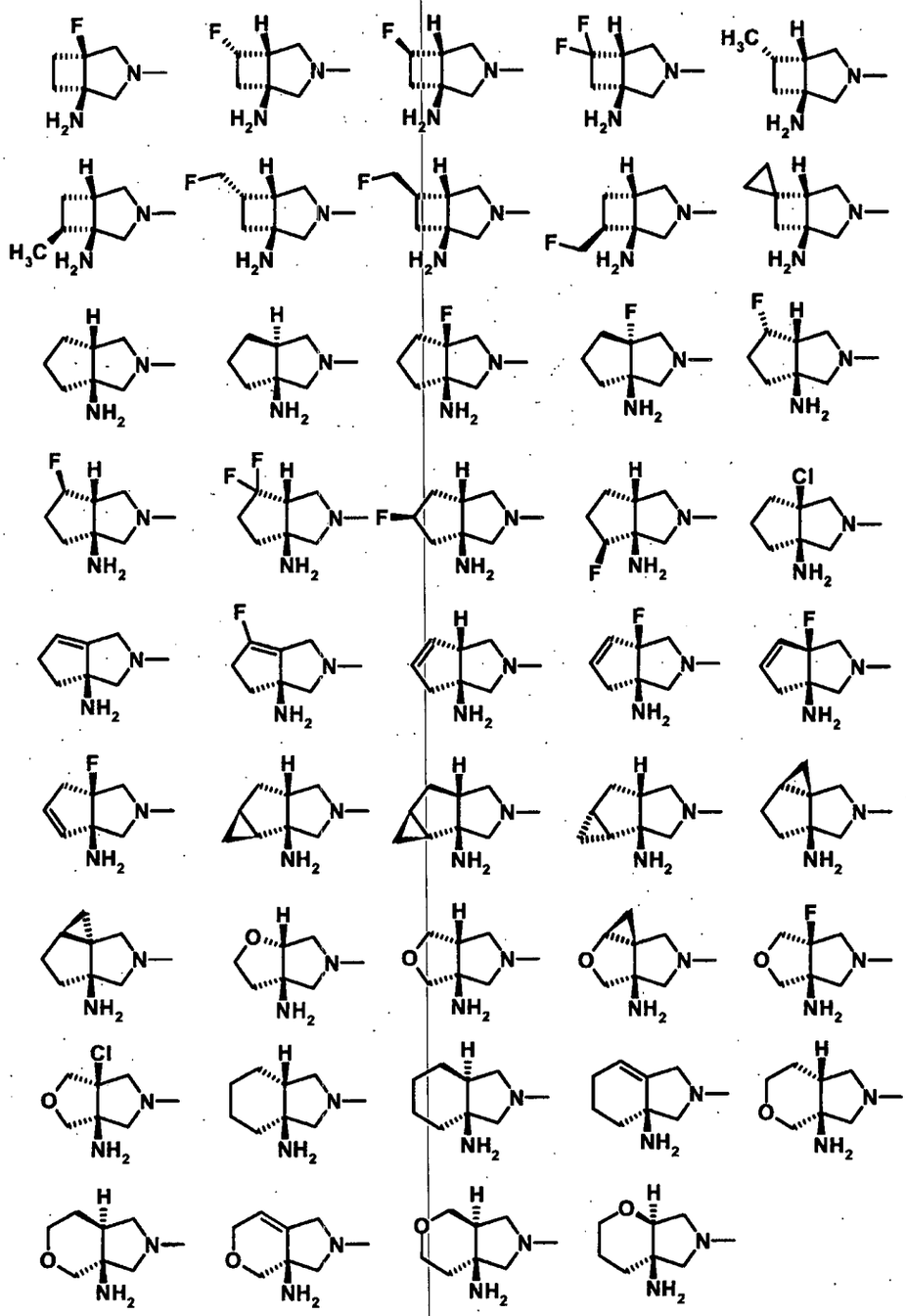
un grupo (1R,6S)-1-amino-5-oxa-8-azabiciclo[4.3.0]nonan-8-ilo;

un grupo (1S,6S)-1-amino-4-oxa-8-azabiciclo[4.3.0]nonan-8-ilo; y

un grupo (1S,6S)-1-amino-3-oxa-8-azabiciclo[4.3.0]nonan-8-ilo.

674

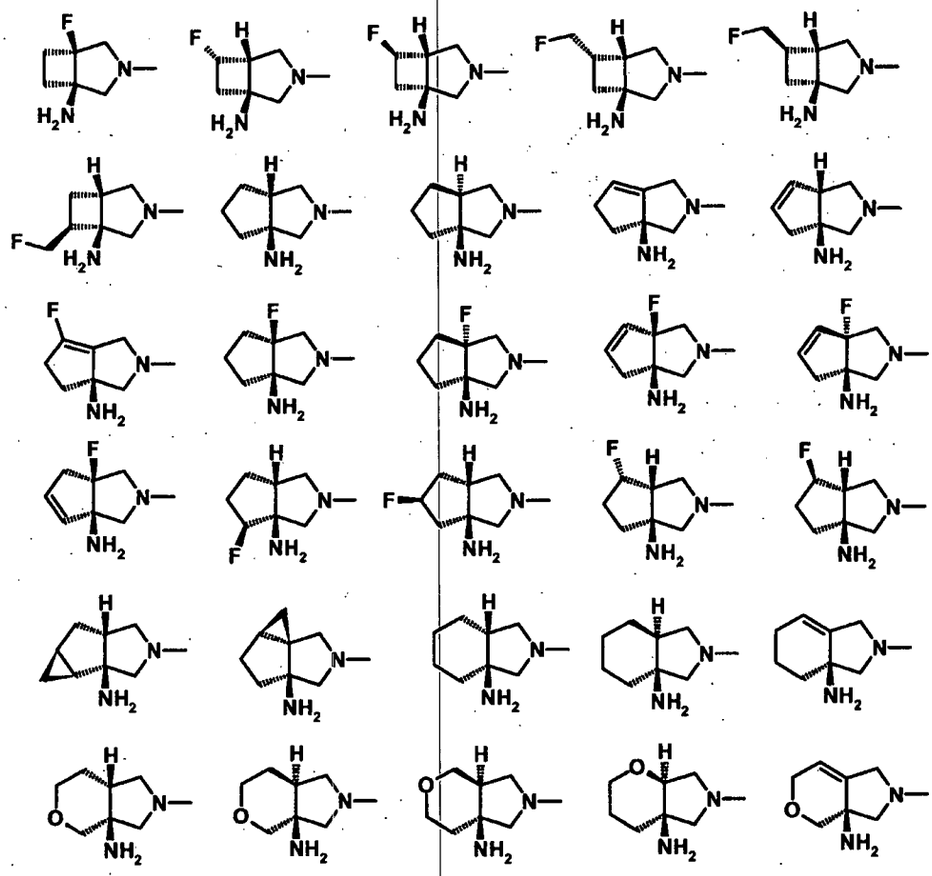
[Fórmula 41]



Y ejemplos más preferidos del sustituyente en la posición 7 (o su posición correspondiente) se listan a continuación:

675

[Fórmula 42]



Por consiguiente, compuestos preferidos de la presente invención son compuestos cada uno de los cuales tiene la estructura de base de quinoloncarboxílico anteriormente ilustrada sustituida con el sustituyente anteriormente ilustrado en la posición 7 (una combinación de la estructura de base madre ilustrada con el sustituyente ilustrado). En las fórmulas anteriores, la configuración de la posición 3 (o su posición correspondiente) sustituida con un grupo amino en el anillo de pirrolidina es preferiblemente la configuración β. La configuración absoluta de la posición 3 (o su posición correspondiente) puede ser 3S o 3R de acuerdo con el tipo de la posición 4 sustituyente. Los compuestos de la presente invención preferiblemente son estereoquímicamente individuales.

676.

Ejemplos preferidos de los compuestos de la presente invención, que puede estar en forma de sales o hidratos son como sigue:

Acido 7-[(1S,5R,6R)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5R,6S)-1-amino-6-metilo-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 10-[(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico;

Acido 7-[(1S,5R,6S)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5R,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]-heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3- carboxílico;

Acido 10-[(1S,5R,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4] benzoxazino-6-carboxílico;

Acido 7-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

677

Acido 7-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 10-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4] benzoxazino-6-carboxílico;

Acido 7-[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3- carboxílico;

Acido 7-[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 10-[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4]benzoxazino-6-carboxílico;

Acido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 10-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico;

Acido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-8-cloro-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

Acido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-8-ciano-6-fluoro-1-[(1R,2S)-2 -fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

678.

Acido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1R,5S)-1-amino-3-aza-5-clorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-тnetoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1R,5S)-1-amino-3-aza-5-clorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro- 1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S)-1-amino-5-metil-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 10-[6-amino-8-azatriciclo[4.3.0.$0^{1,3}$]nonan-8-il]-9-fluoro-2, 3-dihidro-3-(S)-metilo-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico;

Acido 7-[6-amino-8-azatriciclo [4.3.0.o^{1,3}]nonan-8-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

Acido 7-[6-amino-8-azatriciclo[4.3.0.o^{1,3}]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 10-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-9- fluoro-2, 3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4]benzoxazino-6-carboxílico;

Acido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-8-cloro-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico;

Acido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-6-

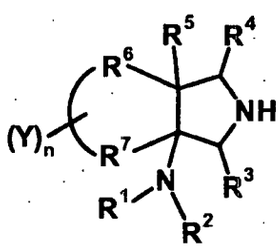
680

fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico;

Acido 10-[(1S,6S)-1-amino-8-aza-3-oxa-biciclo[4.3.0]nonan-8-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico.

Enseguida, se describirá el sustituyente en la posición 7 de la estructura de base de quinolona (o su posición correspondiente) en relación con el compuesto de la presente invención. De manera específica, el sustituyente tiene un grupo amino en una posición correspondiente a la-posición 3 del grupo pirrolidinilo, y el sustituyente R^7 en el átomo de carbono sustituido con el grupo amino y el sustituyente R^6 en una posición correspondiente a la posición 4 del grupo pirrolidinilo se toman junto con los átomos de carbono a los cuales están unidos para formar una estructura cíclica de cuatro a siete miembros. De manera más específica, el sustituyente es un derivado de aminopirrolidina sustituido fusionado, en el cual la estructura cíclica junto con el anillo de pirrolidina forma una estructura cíclica fusionada (bicíclica) representada por la siguiente fórmula, en la cual la estructura cíclica fusionada es sustituida con un grupo amino en la posición de cabeza de puente:

[Fórmula 43]

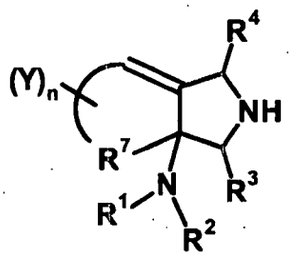


Además, el sustituyente es un sustituyente de aminopirrolidinilo

681

sustituido fusionado que tiene una estructura cíclica representada por la siguiente fórmula, en la cual la estructura cíclica formada al tomar los sustituyentes R^6 y R^7 junto con los átomos de carbono a los cuales están unidos es un anillo de cinco o seis miembros, y R^5 y R^6 se toman juntos para formar una estructura parcial de doble enlace:

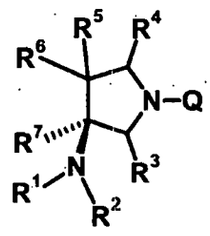
[Fórmula 44]



Los compuestos preferidos de la presente invención, que pueden estar en forma de una sal o un hidrato se ilustran como sigue:

[1] El compuesto representado por la fórmula (I) en donde es un compuesto representado por la siguiente fórmula:

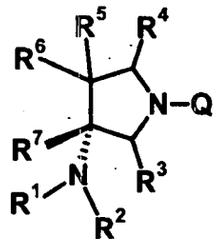
[Fórmula 45]



o la siguiente fórmula :

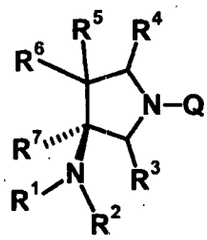
682

[Fórmula 46]



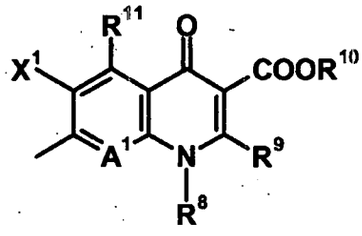
[2] El compuesto representado por la fórmula (I) en donde es un compuesto representado por la siguiente fórmula:

[Fórmula 47]



[3] El compuesto, en donde Q representado por la fórmula (II) en el compuesto representado por la fórmula (I) tiene una estructura representada por la siguiente fórmula:

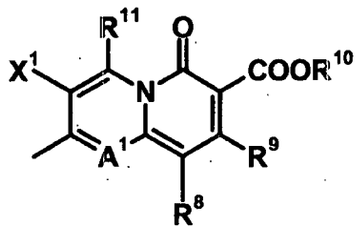
[Fórmula 48]



o la siguiente fórmula:

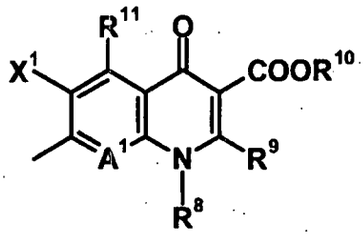
683

[Fórmula 49]



[4] El compuesto, en donde Q representado por la fórmula (II) en el compuesto representado por la fórmula (I) tiene una estructura representada por la siguiente fórmula:

[Fórmula 50]



[5] El compuesto, en donde R^1 y R^2 en la fórmula (I) son cada uno un átomo de hidrógeno.

[6] El compuesto, en donde uno de R^1 y R^2 en la fórmula (I) es un átomo de hidrógeno y el otro es un sustituyente seleccionado de un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo fluoroetilo, un cianoetilo, un grupo ciclopropilo y un grupo ciclobutilo.

[7] El compuesto, en donde R^3 y R^4 en la fórmula (I) son cada uno un átomo de hidrógeno.

[8] El compuesto, en donde R^5 en la fórmula (I) es un átomo de hidrógeno, un átomo de flúor, un átomo de cloro, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo ciclopropilo, un grupo fluorometilo, un grupo fluoroetilo, un grupo trifluorometilo, un grupo metoximetilo, un grupo vinilo, un grupo etinilo, un grupo metoxi, un grupo fenilo o un oxazol-2-ilo.

684

[9] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cuatro miembros que puede ser sustituido por uno o más sustituyentes.

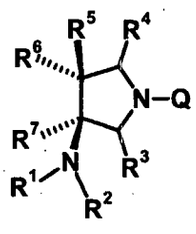
[10] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que pueden ser sustituidos por uno o más sustituyentes.

[11] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que contiene un doble enlace como una estructura constituyente que puede ser sustituida por uno o más sustituyentes .

[12] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que contiene un átomo de oxígeno como un átomo constituyente que puede ser sustituido por uno o más sustituyentes.

[13] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros y se fusiona con el anillo de pirrolidina para formar una estructura bicíclica cis-fusionada representada por la siguiente fórmula:

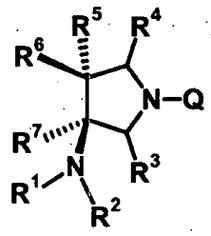
[Fórmula 51]



685

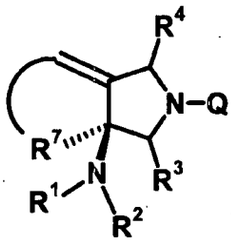
[14] El compuesto, en donde la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros y se fusiona con el anillo de pirrolidina para formar una estructura bicíclica trans-fusionada representada por la siguiente fórmula:

[Fórmula 52]



[15] El compuesto, en donde en la fórmula (I), la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos es un anillo de cinco o seis miembros, R^5 y R^6 se toman juntos para formar una estructura parcial de doble enlace, y la estructura cíclica resultante está representada por la siguiente fórmula:

[Fórmula 53]



[16] El compuesto, en donde X^1 es un átomo de hidrógeno o un átomo de flúor en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[17] El compuesto, en donde X^1 es un átomo de flúor en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

686.

[18] El compuesto, en donde A^1 es un átomo de nitrógeno en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[19] El compuesto, en donde A^1 es una estructura parcial representada por la fórmula (III) en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[20] El compuesto, en donde X^2 en la fórmula (III) es un grupo metilo, un grupo etilo, un grupo metoxi, un grupo difluorometoxi, un grupo ciano o un átomo de cloro.

[21] El compuesto, en donde X^2 en la fórmula (III) es un grupo metilo o un grupo metoxi.

[22] El compuesto, en donde R^8 es un grupo 1,2-cis-2-halogenociclopropilo en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

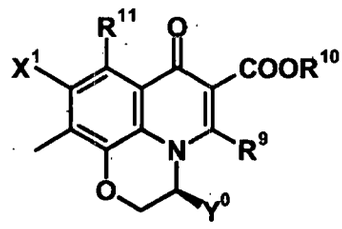
[23] El compuesto, en donde R^8 es un grupo 1,2-cis-2-halogenociclopropilo estereoquímicamente individual en la estructura parcial Q en la fórmula (I) representado por la fórmula (II).

[24] El compuesto, en donde el grupo 1,2-cis-2-halogenociclopropilo de R^8 es un grupo (1R,2S)-2-halogenociclopropilo en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[25] El compuesto, en donde el grupo (1R,2S)-2-halogenociclopropilo de R^8 es un grupo (1R,2S)-2-fluorociclopropilo en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[26] El compuesto, en donde Q en el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula:

[Fórmula 54]

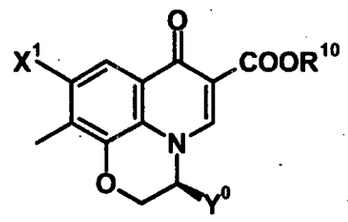


en donde Y^0 es un grupo metilo o un grupo fluorometilo.

[27] El compuesto, en donde R^9 es un átomo de hidrógeno en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

[28] El compuesto, en donde Q en el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula (IV):

[Fórmula 55]



IV

en donde Y^0 es un grupo metilo o un grupo fluorometilo.

[29] El compuesto, en donde Y^0 en la fórmula (IV) es un grupo metilo.

[30] El compuesto, en donde R^{10} es un átomo de hidrógeno en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

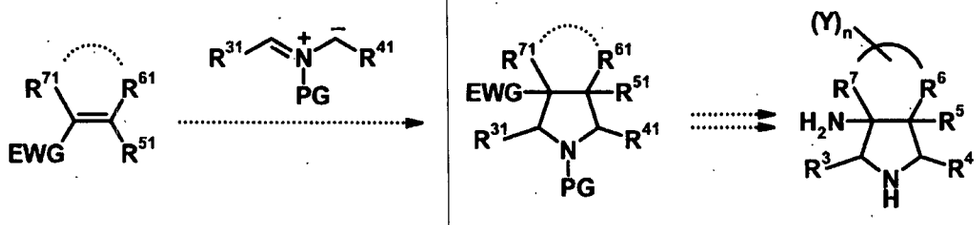
[31] El compuesto, en donde el compuesto representado por la fórmula (I) es un compuesto estereoquímicamente individual.

La síntesis de un compuesto de pirrolidina necesario para introducir el sustituyente en la estructura de base madre de quinolona se describirá más adelante. Hay varios métodos posibles para sintetizar el derivado de aminopirrolidina sustituido fusionado. Varios ejemplos de métodos de síntesis

representativos llevados a cabo por los inventores de la presente se resumirán más adelante (los detalles se describen en ejemplos de referencia en la sección "Ejemplos"). Sin embargo, el método para sintetizar el derivado de aminopirrolidina sustituido fusionado de la presente invención no se limita al mismo.

Los inventores de la presente han sintetizado un importante intermediario sintético usando la reacción de cicloadición 1,3-dipolar representada por el siguiente esquema, con un compuesto cíclico o no cíclico α,β-insaturado, β-sustituido del grupo aceptor de electrones cíclico o no cíclico, y derivados de aminopirrolidina sustituidos fusionados sintetizados a través de los pasos de reacción apropiados:

[Fórmula 56]



En este esquema, EWG es un grupo aceptor de electrones; PG es un grupo amino-protector; R^{31}, R^{41}, R^{51}, R^{61} y R^{71} son cada uno un átomo de hidrógeno o un sustituyente apropiado para el intermediario; y R^3, R^4, R^5, R^6, R^7, Y, y n son como se definió antes.

El compuesto α,β-insaturado sustituido con grupo aceptor de electrones β usado en esta reacción puede ser cíclico o no cíclico. Los derivados de pirrolidina bicíclicos pueden ser sintetizados a partir de los compuestos cíclicos en un paso. Los compuestos no cíclicos pueden ser convertidos a derivados de pirrolidina bicíclicos al someter un intermediario sintético apropiado a una ciclización apropiada o reacción de cierre de anillo

tales como reacción de formación de enlace carbono-carbono o reacción de formación de enlace carbono-oxígeno (o azufre) por reacción nucleofílica de un carbanion; reacción de formación de anillo de éter (o tioéter) por reacción de Mitsunobu intramolecular; esterificación cíclica o amidación cíclica que se denomina reacción de formación de lactona o lactama; reacción de cierre de anillo de condensación intramolecular tal como condensación de aldol, condensación de Dieckmann, condensación de aciloína, condensación de Wittig o reacción de Reformatsky; reacción de metatesis de cierre de anillo (RCM); reacción de Diels-Alder; reacción de ciclización por acoplamiento de desoxigenación tal como reacción de McMurry; reacción de ciclización por radicales; reacción de cierre de anillo por acoplamiento usando un complejo de metal; o reacción de fotociclización.

Además, el grupo aceptor de electrones (EWG) en el compuesto α,β-insaturado sustituido con grupo aceptor de electrones β usado en la reacción anterior puede ser convertido a un grupo amino o un grupo amino protegido por un grupo protector apropiado en uno o varios pasos. Ejemplos de dicho un grupo incluyen un grupo éster, un grupo ciano, un grupo acilo, un grupo carbamoilo, un grupo carboxilo, y un grupo nitro. El grupo éster o grupo ciano puede ser convertido a un derivado de amina por reacción de reordenamiento de Curtius después de conversión a un grupo carboxílico (ácido carboxílico) por hidrólisis. El grupo ciano o grupo carboxílico puede ser convertido a un derivado de amina por reacción de reordenamiento de Hofmann después de conversión a un grupo carbamoilo. El grupo acilo puede ser convertido a un derivado de amina por reacción de reordenamiento de Beckmann o similar después de la conversión a un grupo hidroxiimino. El grupo nitro puede ser convertido a un derivado de amina por reducción.

Por otra parte, el iluro de azometina usado como un elemento reactivo en esta reacción se puede producir añadiendo una cantidad catalítica de ácido trifluoroacético o una cantidad catalítica de fluoruro de plata a N-bencil-N-(metoximetil)trimetilsililmetilamina como un reactivo, por ejemplo [véase Journal of Organic Chemistry, Vol.52, No.2, p.235 (1987)]. PG en el iluro de azometina en la fórmula de reacción anterior representa un grupo protector de amino apropiado. El grupo protector es un grupo bencilo en el reactivo antes mencionado para producir el iluro de azometina, pero puede ser un 1-feniletilo ópticamente activo como un ejemplo preferido. El grupo amino-protector (PG) y un grupo amino-protector producido al convertir el grupo aceptor de electrones en un último paso puede ser el mismo o diferente; los grupos protectores pueden ser apropiadamente seleccionados generalmente de grupos protectores usados para un grupo amino siempre que no afecten la reacción, por ejemplo, no inhiben cada paso de reacción, y posteriormente pueden ser desprotegidos.

Enseguida, se describirá la síntesis de una sustancia ópticamente activa. Una sustancia ópticamente activa puede ser sintetizada, por ejemplo, por resolución óptica de un intermediario apropiado. Ejemplos específicos de la resolución óptica incluyen resolución por CLAR usando una columna quiral y cristalización preferencial de sal de diastereómero para un intermediario apropiado; y un método para unir un elemento quiral a un intermediario apropiado para convertir el intermediario a diastereómeros, después separando los diastereómeros usando una técnica de separación apropiada tal como cromatografía sobre gel de sílice, y removiendo el elemento quiral para convertir el diastereómero a una sustancia ópticamente activa. Una sustancia ópticamente activa también puede ser sintetizada a partir de un bloque de construcción quiral como un material de partida. De manera específica, un

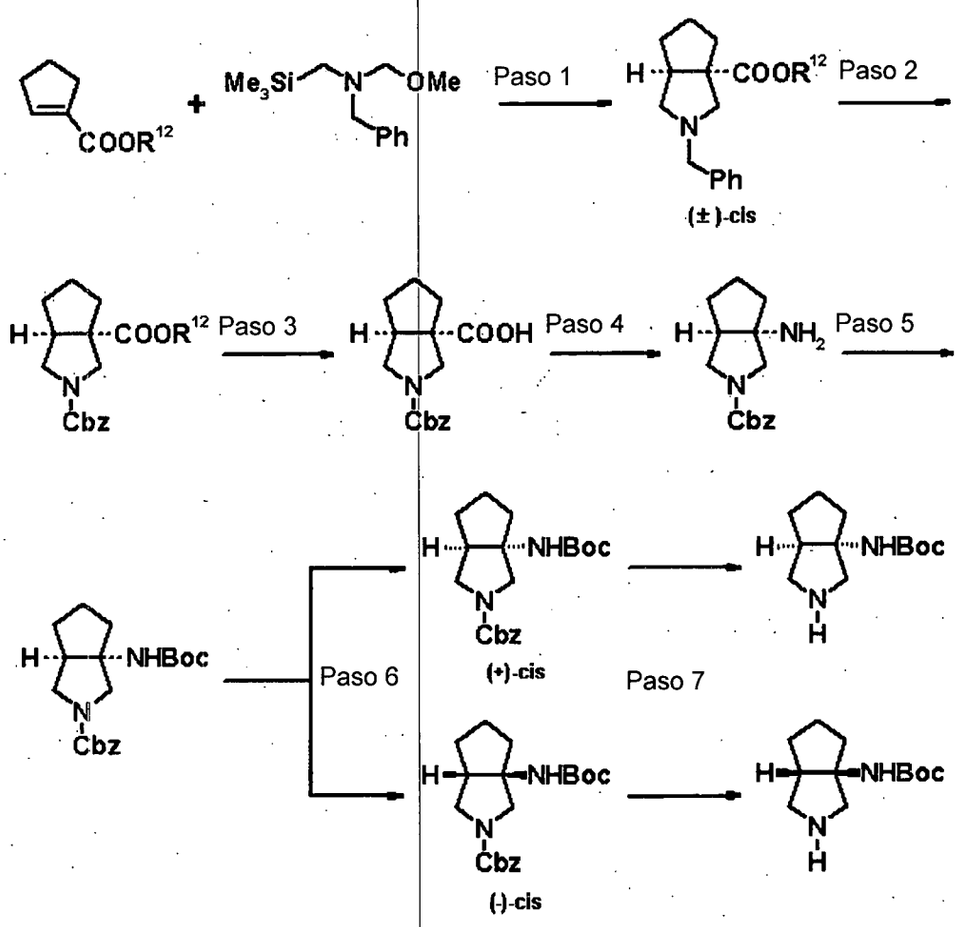
691

cicloaducto ópticamente activo se puede obtener por reacción de coadición 1,3-dipolar enantioselactiva usando un dipolarofilo que tiene un elemento asimétrico (por ejemplo, un grupo funcional asimétrico tal como un grupo 1-mentilo, un grupo (2'S)-bornano-10,2-sultam, o un grupo (S)-4-bencil-2-oxazolidinona); reacción de cicloadición 1,3-dipolar usando un iluro de azometina que tiene un elemento asimétrico (por ejemplo, un grupo (1R)-1-feniletilo) en la molécula; o reacción de cicloadición 1,3-dipolar diastereoselectiva usando tanto un dipolarofilo asimétrico como un iluro de azometina asimétrico [véase Journal of the Chemical Society Perkin Transactions 1, p.1076 (2002)]. Además, un cicloaducto ópticamente activo se puede obtener mediante reacción de cicloadición 1,3-dipolar asimétrica usando un complejo de metal asimétrico o sal como un catalizador [véase Angewandte Chemie International Edition, Vol.44, p.6272 (2005)].

La síntesis de derivados de aminopirrolidina sustituidos fusionados llevada a cabo por los inventores de la presente usando, como una reacción clave, reacción de cicloadición 1,3-dipolar con un compuesto α,β-insaturado sustituido con un grupo aceptor de electrones β y un iluro de azometina como elementos reactivos se describirán de manera más específica tomando la síntesis de un derivado de 1-amino-3-azabiciclo[3.3.0]octano como un ejemplo:

692

[Fórmula 57]



En el esquema anterior, Boc representa un ter-butoxicarbonilo y Cbz representa un benciloxicarbonilo, siempre que estos sustituyentes puedan ser los mismos o diferentes grupos protectores generalmente usados para un grupo amino; y R^{12} representa un grupo alquilo que tiene 1 a 6 átomos de carbono.

El paso 1 es un paso de síntesis de derivado de 1-alcoxicarbonil-3-azabiciclo[3.3.0]octano que es un derivado de pirrolidina sustituido fusionado usando reacción de coadición 1,3-dipolar con un 1-ciclopenteno-1-éster y un iluro de azometina como elementos de reactivo. El elemento reactivo de iluro de azometina se produce añadiendo una cantidad catalítica de ácido trifluoroacético o una cantidad catalítica de fluoruro de plata a N-bencil-N-

(metoximetil)trimetilsililmetilamina como un reactivo, por ejemplo, como se describió antes. El solvente de reacción puede ser cualquier solvente que no inhiba la producción del iluro de azometina y reacción de cicloadición 1,3-dipolar, pero es preferiblemente diclorometano o 1,2-dicloroetano. La reacción se puede llevar a cabo a -20°C a la temperatura de reflujo del solvente, pero preferiblemente a temperatura ambiente hasta la temperatura de reflujo del solvente.

El paso 2 es un paso de convertir el bencilo en la posición 3 del anillo de 3-azabiciclo[3.3.0]octano a un grupo protector. Este paso se lleva a cabo a fin de extraer fácilmente, aislar y purificar el derivado de ácido carboxílico producido después de hidrólisis del éster de posición 1 (sin conversión del bencilo, un derivado de aminoácido se forma y el aislamiento y purificación pueden ser difíciles). El grupo protector en la posición 3 es preferiblemente un grupo protector que generalmente se puede distinguir en el paso de desprotección del grupo protector para el grupo amino en la posición 1 producido después de la conversión del ácido carboxílico en la posición, pero puede ser el mismo que el grupo protector para el grupo amino en la posición 1. El grupo protector en la posición 3 es preferiblemente un benciloxicarbonilo o un ter-butoxicarbonilo, y en particular preferiblemente un benciloxicarbonilo. La reacción de benciloxicarbonilación usualmente se lleva a cabo por conversión directa por reacción de von Braun usando cloroformiato de bencilo en un solvente tal como diclorometano; o por reacción de cloroformiato de bencilo en un solvente apropiado en presencia de una base después de hidrogenólisis catalítica usando un catalizador tal como paladio-carbono.

El paso 3 es un paso de hidrólisis del éster en la reposición del anillo de 3-azabiciclo[3.3.0]octano. El éster es un éster alquílico que tiene 1 a 6

694

átomos de carbono, y preferiblemente un éster metílico, éster etílico o éster ter-butílico. La reacción de hidrólisis se puede llevar a cabo por un método común usando una base o un ácido que no afecta al grupo protector en la posición 3. En la hidrólisis de un éster metílico o éster etílico, el éster se hace reaccionar con una solución alcalina tal como una solución de hidróxido de sodio, solución de hidróxido de potasio o solución de hidróxido de bario en etanol o agua, que se hizo ácido con un ácido apropiado que no afecta al grupo protector en la posición 3, y se aísla y se purifica. El éster ter-butílico es hidrolizado en un solvente apropiado en el cual el éster se puede disolver bajo condiciones ácidas o en presencia de un catalizador ácido. Los ácidos preferidos incluyen ácido clorhídrico, ácido fórmico, ácido acético, ácido trifluoroacético, y ácido p-toluensulfónico.

El paso 4 es un paso de conversión del ácido carboxílico en la posición 1 del anillo de 3-azabiciclo[3.3.0]octano a una amina. Este paso usualmente se lleva a cabo por reacción de reordenamiento de ácido carboxílico a una amina. Por ejemplo, cuando la reacción de reordenamiento es reacción de reordenamiento de Curtius, el ácido carboxílico es convertido a una azida ácida en un solvente apropiado tal como tolueno usando un reactivo tal como azida de sodio, azida de trimetilsililo o azida de difenilfosforilo (DPPA), la solución de reacción después se calienta para formar un isocianato, y el isocianato es convertido a una amina por hidrólisis usando ácido clorhídrico o similar.

El paso 5 es un paso de protección del grupo amino en la posición 1 del anillo de 1-amino-3-azabiciclo[3.3.0]octano; sin embargo, los pasos subsiguientes se pueden llevar a cabo sin esta protección. El grupo protector para el grupo amino en la posición 1 puede ser un grupo protector de amino comúnmente usado, pero es preferiblemente un grupo protector que se puede

distinguir del grupo protector en la posición 3 en el paso de desprotección. Ejemplos específicos del grupo protector incluyen un grupo ter-butoxicarbonilo, un grupo acetilo y un grupo trifluoroacetilo. Los inventores de la presente han seleccionado un grupo ter-butoxicarbonilo.

Los pasos 4 y 5 se pueden llevar a cabo en un paso mediante reacción de reordenamiento usando un solvente apropiado. Por ejemplo, un derivado de 1-(ter-butoxicarbonilo)amino-3-azabiciclo[3.3.0]octano se puede preparar mediante reacción de reordenamiento de Curtius usando difenilfosforilo azida (DPPA) en alcohol ter-butílico.

El paso 6 es un paso de resolución óptica del derivado de 1-amino-3-azabiciclo[3.3.0]octano. Este paso se puede llevar a cabo por resolución de CLAR usando una columna quiral apropiada. Como resultado de esta resolución óptica, se ha encontrado que un derivado de ácido quinolonocarboxílico del enantiómero resultante del derivado de 1-amino-3-azabiciclo[3.3.0]octano que tiene una rotación óptica positiva es superior en actividad antibacteriana a un derivado de ácido quinolonocarboxílico del enantiómero resultante que tiene una rotación óptica negativa (véase la sección "Ejemplos"). Los inventores de la presente han seleccionado un grupo ter-butoxicarbonilo como el grupo protector para el grupo amino en la posición 1; sin embargo, es posible llevar a cabo resolución óptica aun cuando el grupo amino en la posición 1 no es protegido o es protegido por un grupo protector distinto de un grupo ter-butoxicarbonilo. Por ejemplo, cuando el grupo amino en la posición 1 no es protegido o es protegido por un grupo protector tal como un grupo bencilo o un grupo ter-butilo (el grupo amino protegido es básico en este caso), también es posible llevar a cabo un método de convertir un ácido ópticamente activo apropiado a una sal de diastereómero y preferentemente cristalizando la sal de diastereómero, además

de resolución óptica de CLAR usando una columna quiral apropiada. En este caso, un derivado de 1-amino-3-azabiciclo[3.3.0]octano ópticamente activo se puede obtener convirtiendo la sal de diastereómero preferentemente cristalizada a una base libre. Además, cuando el grupo amino en la posición 1 no es protegido, es posible usar un método para unir un elemento quiral para convertir el derivado a diastereómeros, después separar los diastereómeros usando una técnica de separación apropiada tal como cromatografía sobre gel de sílice, y remover el elemento quiral para convertir el diastereómero a una sustancia ópticamente activa.

Los inventores de la presente han descrito un método de resolución óptica específico en este paso; sin embargo, cuando un intermediario sintético apropiado se puede resolver ópticamente, el intermediario puede ser apropiadamente seleccionado y épticamente resuelto como se describió antes.

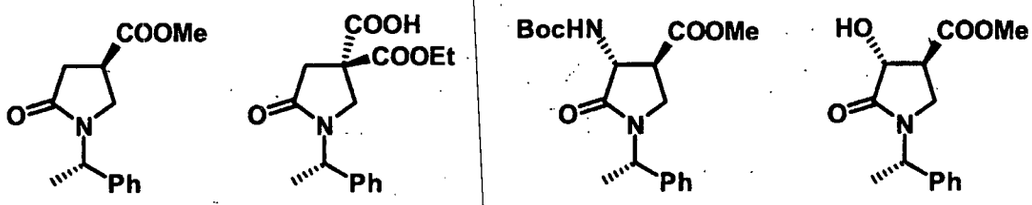
El paso 7 es un paso de desprotección en la posición 3 del derivado de 1-amino-3-azabiciclo[3.3.0]octano. La reacción de desprotección se puede llevar a cabo bajo cualesquiera condiciones que no cambien otros grupos funcionales y la configuración. Por consiguiente, puesto que el grupo protector en la posición 1 en relación con el compuesto de la presente invención es un benciloxicarbonilo, la reacción de desprotección se lleva a cabo bajo condiciones de desprotección comúnmente usada, por ejemplo, bajo condiciones que usan un catalizador tal como paladio-carbón, o por reacción de hidrogenólisis catalítica usando formiato de amonio en un solvente polar prótico. Cuando el derivado de 3-azabiciclo[3.3.0]octano tiene un enlace insaturado carbono-carbono en la molécula, la desprotección se debe llevar a cabo con el enlace insaturado carbono-carbono mantenido. Por consiguiente, puesto que el grupo protector en la posición 3 en relación con el compuesto de la presente

697

invención es un benciloxicarbonilo, la desprotección puede llevarse a cabo sin el enlace insaturado carbono-carbono mantenido en el anillo de 3-azabiciclo[3.3.0]octano bajo condiciones de ácido fuerte (por ejemplo, ácido bromhídrico-ácido acético, ácido trifluoroacético, o ácido trifluorometansulfónico-ácido trifluoroacético), mediante el uso de sodio-amoniaco líquido (condiciones de reducción de Birch), o mediante el uso, por ejemplo, de hidróxido de bario.

Además, el derivado de aminopirrolidina sustituido fusionado que es el compuesto de la presente invención se puede sintetizar a partir de un derivado de pirrolidina quiral como un material de partida. Los siguientes intermediarios sintéticos se usan en la síntesis usando, por ejemplo, un denominado bloque de construcción quiral. Los derivados de pirrolidina quirales que se pueden usar como intermediarios no se limitan a los siguientes compuestos.

[Fórmula 58]



[Journal of Medicinal Chemistry, Vol. 30, No.10, p.1171 (1987); WO 94/14794; Tetrahedron, Vol. 61, No.23, p.5465 (2005); Tetrahedron Asymmetry, Vol. 15, No.20, p.3249 (2004)].

Dichos derivados de pirrolidina quirales pueden ser convertidos a los derivados de pirrolidina bicíclicos que son los compuestos de la presente invención en un número de pasos apropiado. Por ejemplo, los derivados de pirrolidina quirales pueden ser convertidos al derivado de aminopirrolidina sustituido fusionado al introducir sustituyentes apropiados en las posiciones 3 y

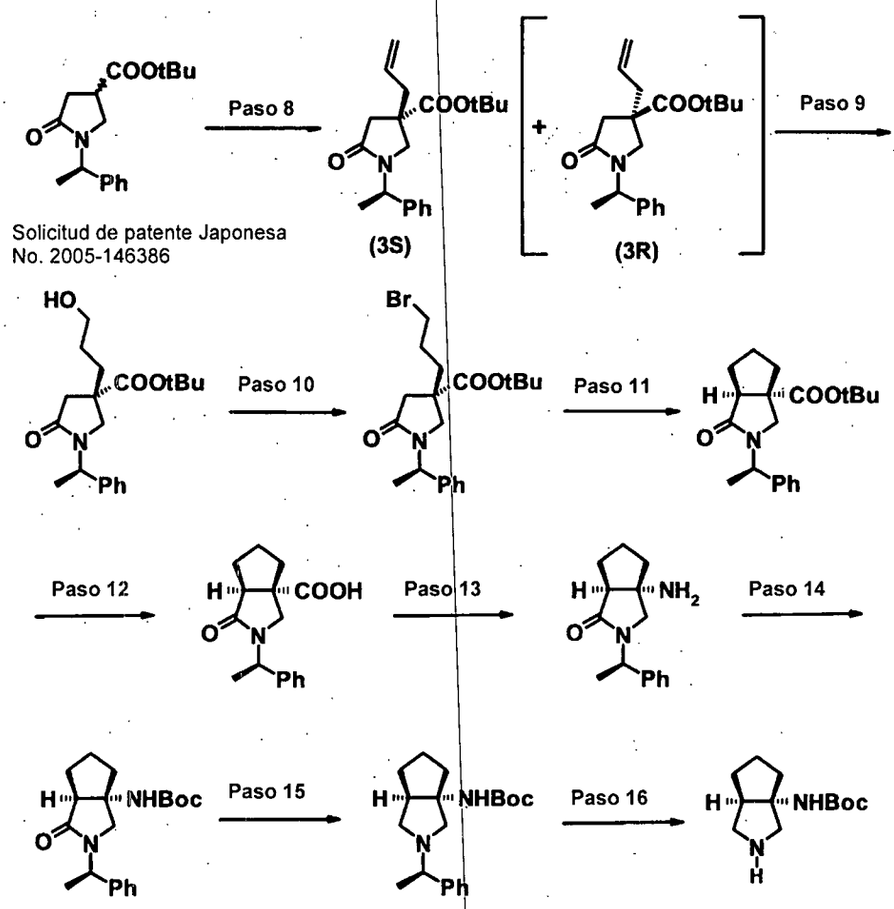
4 en el anillo de pirrolidina, después al llevar a cabo la reacción de homologación apropiada o conversión de grupo funcional, y al llevar a cabo una reacción de ciclización (cierre de anillo). Ejemplos de reacciones de ciclización (cierre de anillo) para un intermediario sintético apropiado que es un paso importante para esta conversión incluyen reacción de formación de enlace carbono-carbono o reacción de formación de enlace carbono-oxígeno (o azufre) por reacción nucleofílica de un carbanión; ya sea reacción de formación de anillo (o tioéter) por reacción de Mitsunobu intramolecular; esterificación cíclica o amidación cíclica que se denomina reacción de formación de lactona o lactama; reacción de cierre de anillo por condensación intramolecular tal como condensación de aldol, condensación de Dieckmann, condensación de aciloína, condensación de Wittig o reacción de Reformatsky; reacción deciclización - acoplamiento por desoxigenación tal como reacción de McMurry; reacción de metatesis de cierre de anillo (RCM); reacción de Diels-Alder; reacción de ciclización por radicales; reacción de cierre de anillo-acoplamiento usando un complejo de metal; y reacción de fotociclización.

La síntesis de derivados de aminopirrolidina sustituidos fusionados llevada a cabo por los inventores de la presente usando un derivado de pirrolidina quiral como un intermediario importante se describirá de manera más específica tomando la síntesis de un derivado de (1S,5R)-1-amino-3-azabiciclo[3.3.0]octano como un ejemplo. Los inventores de la presente han seleccionado un ter-butoxicarbonilo como el grupo protector para la porción de amina de reposición; sin embargo, el grupo protector para el grupo amino en la posición 1 puede ser un grupo protector distinto de un ter-butoxicarbonilo que no afecta, por ejemplo, no inhibe cada paso de reacción y puede ser fácilmente desprotegido, y el grupo protector puede ser el mismo que el grupo protector en

699

la posición 3. En el siguiente caso, el grupo protector en la posición 1 es un grupo (1R)-1-feniletilo:

[Fórmula 59]



En el esquema anterior, Boc representa un grupo ter-butoxicarbonilo.

El paso 8 es un paso de alilación la posición 3 del anillo de pirrolidina (la posición α del éster). El paso 8 usualmente se lleva a cabo usando un halogenuro de alilo tal como bromuro de alilo como un agente de alilación en presencia de una base. Ejemplos de la base incluyen carbonato de potasio, carbonato de cesio, hidruro de sodio, sodio metálico, etóxido de sodio, ter-butóxido de potasio, diisopropilamida de litio (LDA), y bis (trimetilsilil)amida de litio. Ejemplos del solvente de reacción incluyen tetrahidrofurano, acetona, N,N-

dimetilformamida, tolueno, y solventes mixtos de los mismos. Después de completarse la reacción, los diastereómeros del compuesto alilado pueden ser separados y purificados por cromatografía sobre gel de sílice o similar. Los inventores de la presente han usado un éster ter-butílico como el éster en la posición 3 del anillo de pirrolidina; sin embargo, también se pueden usar otros derivados de éster. La operación de separación de diastereómeros anterior se lleva a cabo fácilmente cuando se usa un éter ter-butílico volumétrico.

El paso 9 es un paso de convertir la porción de alilo a un alcohol primario, específicamente, un 1-hidroxipropilo por reacción de hidroboración-oxidación de la olefina terminal de la porción alilo. La reacción de hidroboración usualmente se lleva a cabo en tetrahidrofurano anhidro usando, como reactivos, varios complejos de borano (tales como un complejo de borano-tetrahidrofurano y un complejo de borano-sulfuro de dimetilo), monoalquilboranos (tales como hexilborano), dialquilboranos (tales como 9-borabiciclo[3.3.1]nonano (9-BBN), diciclohexilborano y disiamilborano), un complejo de cloroborano-sulfuro de dimetilo, un dicloroborano-sulfuro de dimetilo, catecolborano, y similares. La oxidación del compuesto de organoborano producido por la reacción de hidroboración usualmente se lleva a cabo usando peróxido de hidrógeno acuoso bajo condiciones alcalinas de una solución de hidróxido de sodio o similar en agua o agua que contiene etanol.

Los inventores de la presente han sintetizado un compuesto en el cual un 1-hidroxipropilo es introducido en la posición 3 del anillo de pirrolidina en dos pasos mostrado como los pasos 8 y 9; sin embargo, este producto puede ser sintetizado por otro método de síntesis. Por ejemplo, el producto puede ser sintetizado protegiendo una porción de grupo hidroxi de 3-yodopropanol comercialmente disponible usando un grupo protector apropiado (tal como un

ter-butildimetilsililo), después oxipropilación de sustitución 3 en presencia de una base apropiada (tales como una base descrita para el paso 8), y subsiguientemente desprotegiendo bajo condiciones apropiadas. Además, la reacción de oxipropilación de sustitución 3 se puede llevar a cabo después de proteger un grupo hidroxi de 1,3-propanodiol usando un grupo protector apropiado y después convirtiendo el otro grupo hidroxi un átomo de halógeno o un grupo residual comúnmente conocido. Ejemplos del grupo residual en este caso incluyen un grupo metansulfoniloxi, un grupo trifluorometansulfoniloxi, un grupo bencenesulfoniloxi, y un grupo p-toluensulfoniloxi.

El paso 10 es un paso de bromación del grupo hidroxi. Es inapropiado llevar a cabo la reacción de bromación bajo condiciones de ácido fuerte típicas de ácido bromhídrico-ácido sulfúrico concentrado, bromuro de sodio-ácido sulfúrico, o similar, porque hay un éster ter-butilo en la molécula. La reacción de bromación es apropiadamente una reacción que usa trifenilfosfina-tetrabromometano en diclorometano o tetrahidrofurano, reacción que usa dibromuro de trifenilfosfina en N,N-dimetilformamida, o similar [véase Journal of American Chemical Society, Vol.125, No.43, p.13625 (2003)]. Además, el bromuro de tetrabutilamonio o un reactivo de Vilsmeier [cloruro de (clorometileno)dimetilominio] se puede usar como un reactivo en N,N-dimetilformamida en esta reacción de bromación. La reacción de bromación se puede llevar a cabo usando un agente de bromación tal como bromuro de sodio, bromuro de litio o bromuro de calcio en N,N-dimetilformamida o sulfóxido de dimetilo después de convertir la porción del grupo hidroxi a un grupo residual apropiado. Ejemplos del grupo residual en este caso incluyen un grupo metansulfoniloxi, un grupo trifluorometansulfoniloxi, un grupo bencensulfoniloxi y un grupo p-toluensulfoniloxi.

Los inventores de la presente han sintetizado un compuesto en el cual un 1-bromopropilo es introducido en la posición 3 del anillo de pirrolidina como un compuesto usado en el siguiente paso. Ejemplos de compuestos que se pueden usar en el siguiente paso distintos de este producto incluyen un compuesto de 1-yodo y un compuesto en el cual se introduce un grupo residual tal como un grupo metansulfoniloxi, un grupo trifluorometansulfoniloxi, un grupo bencensulfoniloxi, o un grupo p-toluensulfoniloxi.

El paso 11 es un paso de generación de un carbanión en la posición 4 del anillo de pirrolidina del compuesto de bromo sintetizado en el paso 10 (amida: posición α de pirrolidona) usando una base apropiada para causar una reacción de formación de un doble enlace carbono-carbono por sustitución nucleofílica intramolecular (reacción de cierre de dosis intramolecular). Ejemplos típicos de la base incluyen carbonato de potasio, carbonato de cesio, hidruro de sodio, sodio metálico, etóxido de sodio, ter-butóxido de potasio, diisopropilamida de litio (LDA), bis(trimetilsilil)amida de litio, bis(trimetilsilil)amida de potasio y bis(trimetilsilil)amida de sodio. Ejemplos del solvente de reacción incluyen tetrahidrofurano, acetona, N,N-dimetilformamida, tolueno y solventes mixtos de los mismos. El anillo de ciclopentano formado por la reacción de cierre de dosis intramolecular usualmente forma un anillo cis-fusionado (anillo de cis-3-azabiciclo[3.3.0]octano) junto con la porción de anillo de pirrolidina. Este método de síntesis se puede aplicar a la síntesis de un derivado de aminopirrolidina sustituido fusionado tal como un derivado de 3-azabiciclo [4.3.0]nonano, pero puede producir una mezcla de isómeros cis y trans del derivado de aminopirrolidina sustituido fusionado. En este caso, un isómero necesario puede ser separado por una operación de separación y purificación apropiada tal como cromatografía sobre gel de sílice.

El paso 12 es un paso de convertir el éter ter-butílico a ácido carboxílico por hidrólisis o desprotección. Los inventores de la presente han seleccionado éster de ter-butilo como un éster; sin embargo, el éster es adecuadamente un éster de alquilo que tiene 1 a 6 átomos de carbono, y preferiblemente un éster metílico, éster etílico o éster ter-butílico. El éster ter-butílico es hidrolizado o desprotegido en un solvente apropiado en el cual el éster puede ser disuelto bajo condiciones ácidas o en presencia de un catalizador ácido. Los ácidos preferidos incluyen ácido clorhídrico, ácido fórmico, ácido acético, ácido trifluoroacético y ácido p-toluensulfónico. En la hidrólisis de un éster metílico o éster etílico, el éster se hace reaccionar con una solución alcalina tal como una solución de hidróxido de sodio, solución de hidróxido de potasio, o solución de hidróxido de bario en etanol o agua, entonces se hace ácida con un ácido apropiado que no afecta al grupo protector en la posición 3, y es aislado y purificado.

El paso 13 es un paso de convertir el ácido carboxílico en la posición 1 del grupo 3-azabiciclo[3.3.0]octano a una amina. Este paso usualmente se lleva a cabo por reacción de reordenamiento de ácido carboxílico a una amina. Por ejemplo, cuando la reacción de reordenamiento es reacción de reordenamiento de Curtius, el ácido carboxílico es convertido a una azida ácida en un solvente apropiado tal como tolueno usando un reactivo tal como azida de sodio, azida de trimetilsililo o azida de difenilfosforilo (DPPA), la solución de reacción después se calienta para formar un isocianato, y el isocianato es convertido a una amina por hidrólisis usando ácido clorhídrico o similar.

El paso 14 es un paso de protección del grupo amino en la posición 1 del anillo de 1-amino-3-azabiciclo[3.3.0]octano; sin embargo, los pasos subsiguientes se pueden llevar a cabo sin esta protección. El grupo

protector para el grupo amino en la posición 1 puede ser un grupo amino-protector comercialmente disponible, pero es preferiblemente un grupo protector que se puede distinguir del grupo protector en la posición 3 en el paso de desprotección. Ejemplos específicos del grupo protector incluyen un grupo ter-butoxicarbonilo, un grupo acetilo y un grupo trifluoroacetilo. Los inventores de la presente han seleccionado un grupo ter-butoxicarbonilo.

Los pasos 13 y 14 se pueden llevar a cabo en un paso por reacción de reordenamiento usando un reactivo de azida en un solvente apropiado. Por ejemplo, un derivado de 1-(ter-butoxicarbonil)amino-3-azabiciclo[3.3.0]octano se puede preparar mediante reacción de reordenamiento de Curtius usando azida de difenilfosforilo (DPPA) en alcohol ter-butílico.

El paso 15 es un paso de reducción del carbonilo de la pirrolidona (llamada amida). El paso 15 se lleva a cabo usando un hidruro de metal tal como hidruro de litio-aluminio o hidruro de sodio-bis(2-metoxietoxi)aluminio, o un compuesto de borohidruro tal como diborano o un complejo de borano-tetrahidrofurano, como un reactivo de reducción. Un solvente de éter por tolueno o tetrahidrofurano usualmente se usa como un solvente. La reacción se lleva a cabo usualmente a una temperatura de -78°C a 100°C.

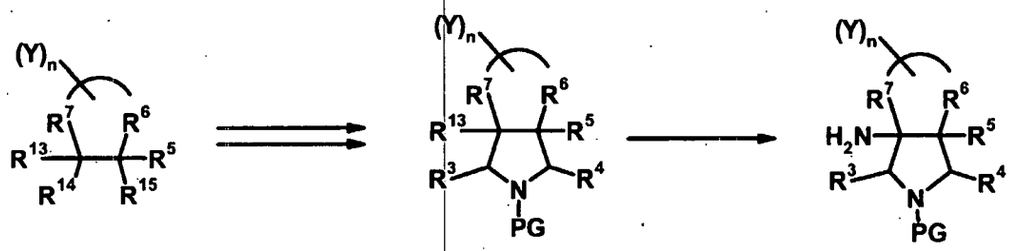
El paso 16 es un paso de desprotección de la posición 1 del anillo de pirrolidina. La reacción de desprotección se puede llevar a cabo bajo cualesquiera condiciones que no cambian otros grupos funcionales y la configuración. Por consiguiente, puesto que el grupo protector en la posición 1 en relación con el compuesto de la presente invención es un grupo (1R)-1-feniletilo, la reacción de desprotección se lleva a cabo bajo condiciones de desprotección comúnmente usadas, por ejemplo, bajo condiciones que usan un catalizador tal como paladio-carbón, o por reacción de hidrogenólisis catalítica

705.

usando formiato de amonio en un solvente polar prótico. Cuando hay un enlace insaturado carbono-carbono como un sustituyente en la molécula, la desprotección se debe llevar a cabo con el enlace insaturado carbono-carbono mantenido. Por consiguiente, puesto que el grupo protector en la posición 1 en relación con el compuesto de la presente invención es un grupo (1R)-1-feniletilo, la desprotección se puede llevar a cabo con el enlace insaturado carbono-carbono mantenido en la molécula mediante el uso de, por ejemplo, sodio-amoniaco líquido (condiciones de reducción de Birch). Después de que el (1R)-1-feniletilo en la posición 1 es convertido a un benciloxicarbonilo por reacción de von Braun usando cloroformiato de bencilo típicamente en un solvente tal como diclorometano, el grupo puede ser desprotegido por el método descrito anteriormente.

Además, el anillo de pirrolidina de los derivados de aminopirrolidina sustituidos fusionados que son los compuestos de la presente invención se pueden formar por un método de síntesis común o similar después de sintetizar previamente un compuesto heterocíclico correspondiente (intermediario sintético importante) apropiadamente, como se muestra en el siguiente esquema:

[Fórmula 60]



en donde R^{13} es un grupo éster que tiene 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo nitro, o un grupo ciano, que puede ser convertido a un grupo amino, o un grupo amino que puede tener un sustituyente; PG es un grupo amino-protector; R^{14} y R^{15} son sustituyentes apropiados generalmente

conocidos que se pueden tomar juntos y después opcionalmente sometidos a una reacción apropiada para formar un anillo de pirrolidina; y R^3, R^4, R^5, R^6, R^7, Y, y n son como se definió antes.

El sustituyente R^{13} es preferiblemente un grupo éster que tiene 2 a 7 átomos de carbono o un grupo amino que puede tener un sustituyente, y en particular preferiblemente dicho grupo estable en cada paso de reacción listado más adelante en la reacción de formación del anillo de pirrolidina.

Aquí, se describirán los sustituyentes R^{14} y R^{15} y el método de formación del anillo de pirrolidina en el cual R^{14} y R^{15} se toman juntos y después son opcionalmente sometidos a una reacción apropiada.

Cuando los sustituyentes R^{14} y R^{15} son cada uno un grupo hidroximetilo ($-CH_2OH$), el anillo de pirrolidina se puede formar mediante alquilación de la amina primaria directamente o después de convertir la porción de grupo hidroxi a un átomo de halógeno o un grupo residual apropiado. Ejemplos preferidos del átomo de halógeno incluyen cloro, bromo y yodo. Ejemplos del grupo residual incluyen un grupo metansulfoniloxi, un grupo trifluorometansulfoniloxi, un grupo bencensulfoniloxi, y un grupo p-toluensulfoniloxi.

Cuando los sustituyentes R^{14} y R^{15} son cada uno un grupo carboxilo, un grupo éster, o un halogenuro ácido, el intermediario sintético puede ser convertido al derivado de pirrolidina sintetizando un derivado de imida directamente o a través de un anhídrido ácido sintetizado por una reacción de condensación apropiada y después sometiendo la imida a una reducción. El grupo éster preferiblemente tiene 2 a 7 átomos de carbono. La imida es reducida usando un hidruro de metal tal como hidruro de litio-aluminio o hidruro de sodio-bis(2-metoxietoxi)aluminio, o un compuesto de borohidruro tal como diborano o

un complejo de borano-tetrahidrofurano, como un reactivo de reducción de imida. Un solvente de éter representado por tetrahidrofurano es usualmente usado como solvente. La reacción se lleva a cabo usualmente a una temperatura de -78°C a 100°C.

Cuando uno de los sustituyentes R^{14} y R^{15} es un grupo aminometilo ($-CH_2NH_2$) y el otro es un grupo carboxílico o un grupo éster, el intermediario sintético puede ser convertido al derivado de pirrolidina sintetizando un derivado de amida (derivado de lactama) usando una reacción de condensación apropiada y después sometiendo la amida a una reducción. El grupo éster preferiblemente tiene 2 a 7 átomos de carbono. El derivado de amida (derivado de lactama) es generalmente sintetizado al calentar en un solvente de alcohol en presencia o ausencia de una base apropiada. La amida es reducida usando un hidruro de metal tales como hidruro de litio-aluminio o hidruro de sodio-bis(2-metoxietoxi)aluminio, o un compuesto de Borohidruro tal como diborano o un complejo de borano-tetrahidrofurano como un reactivo de reducción de imida. Un solvente de éter representado por tetrahidrofurano es usualmente usado como un solvente. La reacción se lleva a cabo usualmente a una temperatura de -78°C a 100°C. Uno de los sustituyentes R^{14} y R^{15} de un precursor útil para sintetizar el intermediario derivado de amida (derivado de lactama) puede ser un nitrometilo ($-CH_2NO_2$), un azidometilo ($-CH_2N_3$), o un grupo ciano (-CN) (en este caso, el otro sustituyente es un grupo carboxilo o un grupo éster). El precursor puede ser convertido al derivado de amida (derivado de lactama) al convertir el sustituyente a un grupo aminometilo ($-CH_2NH_2$) en un paso de reducción y después realizar una reacción de condensación. El paso de reducción se lleva a cabo usando reducción catalítica de hidrógeno; un hidruro de metal tal como Borohidruro de litio, hidruro de litio-aluminio o hidruro de

sodio-bis(2-metoxietoxi)aluminio; o un compuesto de Borohidruro tal como diborano o un complejo de borano-tetrahidrofurano. Además, cuando uno de los sustituyentes R^{14} y R^{15} es un grupo hidroximetilo ($-CH_2OH$) o un grupo halogenometilo y el otro es un grupo carboxílico o un grupo éster, un derivado de lactona sintetizado por una reacción de condensación apropiada puede ser convertida al derivado de lactama.

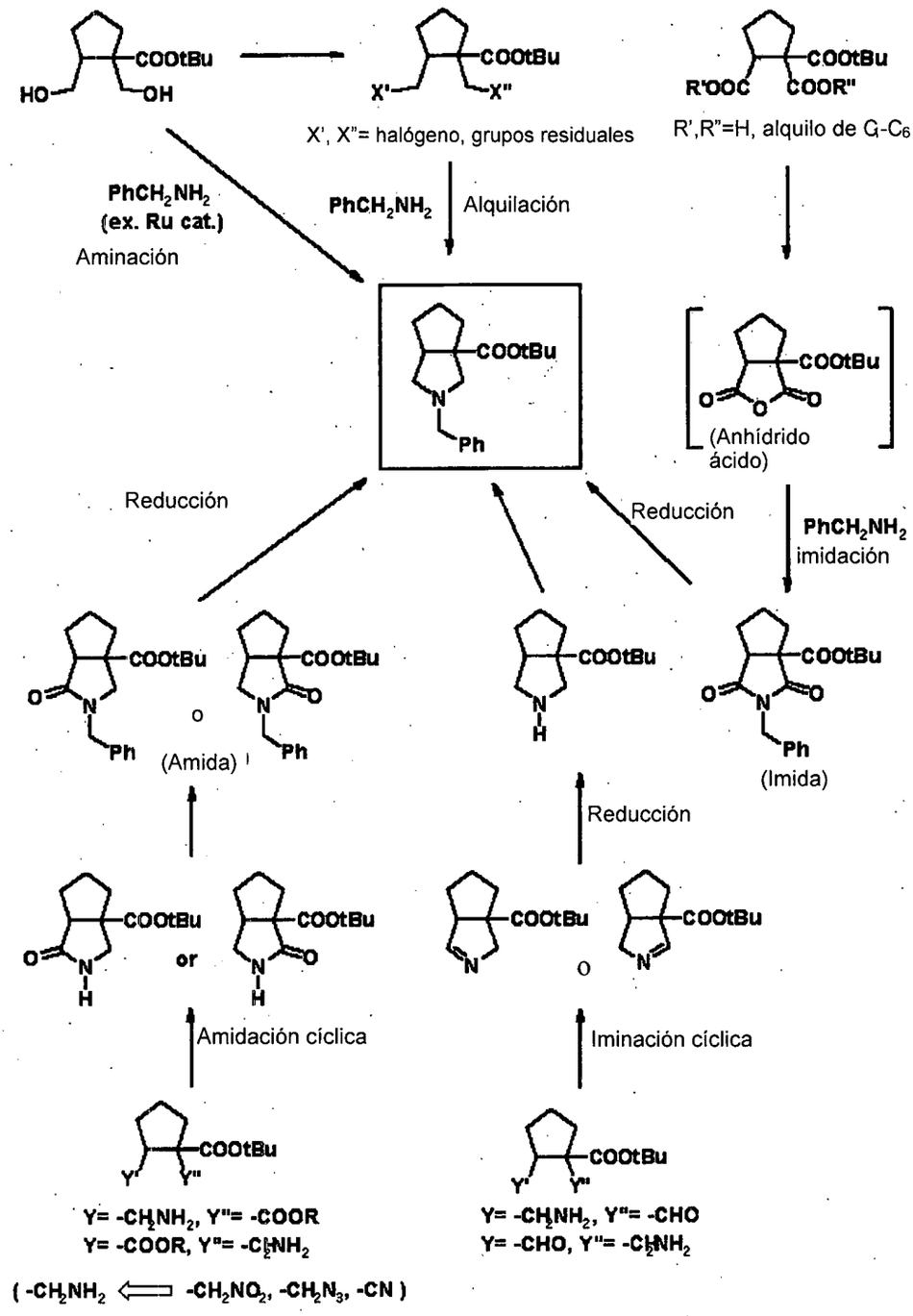
Cuando uno de los sustituyentes R^{14} y R^{15} es un grupo aminometilo ($-CH_2NH_2$) y el otro es un grupo formilo, el intermediario sintético puede ser convertido al derivado de pirrolidina sintetizando un derivado de imina cíclico usando una reacción de condensación apropiada y después sometiendo la imina a una reducción, específicamente, una reacción de afinación reductiva. El intermediario sintético puede ser convertido al derivado de pirrolidina al someter la imina a reducción catalítica de hidrógeno y una reacción de condensación apropiada para sintetizar un derivado de amida (derivado de lactama) y después sometiendo la amida a una reducción.

Cuando uno de los sustituyentes R^{14} y R^{15} es un grupo metilo y el otro es un N-halogenoaminometilo (tal como $-CH_2NCl-$), el anillo de pirrolidina se puede formar por reacción de radicales (reacción de síntesis de pirrolidina de Hofmann-Loeffler-Freitag).

Varios métodos de formación de anillo de pirrolidina representativos están representados por el siguiente esquema tomando, como un ejemplo, la síntesis de un derivado de 3-bencil-1-(ter-butoxicarbonilo)-3-azabiciclo[3.3.0]octano que es un intermediario sintético para un derivado de 1-amino-3-azabiciclo[3.3.0]octano que es un compuesto representativo de la presente invención:

709

[Fórmula 61]



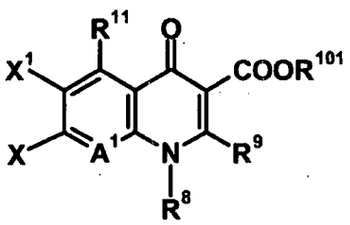
Las reacciones en los pasos antes ilustrados para sintetizar los derivados de aminopirrolidina sustituidos fusionados pueden ser apropiadamente modificados por los expertos en la técnica con base en la

710.

descripción anterior para encontrar un nuevo método de síntesis, y la descripción anterior no deben considerarse como limitantes.

Para producir un compuesto incluido en la presente invención mediante la introducción de un derivado de 1-(ter-butoxicarbonilo)amino-3-azabiciclo[3.3.0]octano que es un derivado de aminopirrolidina sustituido fusionado obtenido como se describió antes como el sustituyente en la posición 7 (posición 10) de una estructura de base madre de ácido quinoloncarboxílico (estructura de base madre de ácido piridobenzoxazincarboxílico), un compuesto de estructura de base madre de ácido quinoloncarboxílico representado por la siguiente fórmula:

[Fórmula 62]



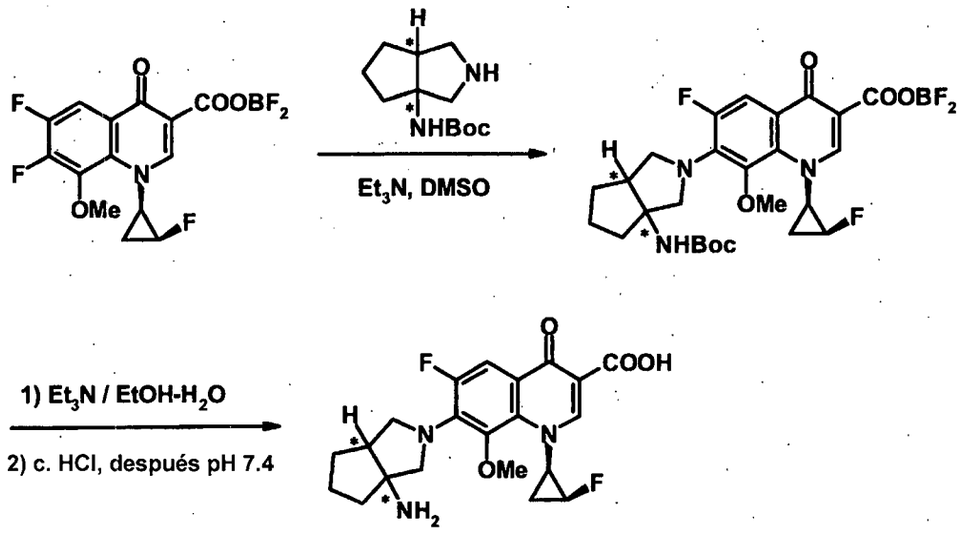
en donde R^8, R^9, R^{11}, X^1, y A^1 son como se definió antes; R^{101} representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, o un sustituyente de boro que puede formar un quelato de boro; y X representa un grupo residual, se puede hacer reaccionar con 1-(ter-butoxicarbonilo) amino-3-azabiciclo[3.3.0]octano.

Ejemplos preferidos del grupo alquilo que tiene 1 a 6 átomos de carbono incluyen un grupo metilo, un grupo etilo, un grupo isopropilo, y un grupo ter-butilo. El sustituyente de boro puede ser dihalogenoboro o diaciloxiboro. El dihalogenoboro es preferiblemente difluoroboro ($-BF_2$). El diaciloxiboro es preferiblemente diacetiloxiboro [$-B(OAc)_2$]. Dichos sustituyentes se pueden obtener de conformidad con métodos conocidos.

711

La producción de dicho compuesto incluido en la presente invención se describirá tomando un compuesto del ejemplo 11 descrito al último como un ejemplo.

[Fórmula 63]



El compuesto objetivo se puede obtener disolviendo un compuesto de estructura de base madre de ácido quinoloncarboxílico en un solvente apropiado y haciendo reaccionar el compuesto con (-)-1-(ter-butoxicarbonilo)amino-3-azabiciclo[3.3.0]octano que es un compuesto para introducción como el sustituyente en la posición 7 en presencia de a base. El grupo amino en el compuesto para la introducción como el sustituyente en la posición 7 puede ser protegido por un grupo protector. Ejemplos del grupo protector incluyen, además de un ter-butoxicarbonilo (grupo Boc), un benciloxicarbonilo, un p-metoxibenciloxicarbonilo, un acetilo, un metoxiacetilo, un trifluoroacetilo, un pivaloilo, un grupo formilo, un benzoilo, un grupo ter-butilo, un grupo bencilo, un trimetilsililo y un isopropildimetilsililo. Ejemplos de bases que se pueden usar incluyen carbonatos, bicarbonatos o sales de hidróxido de metales alcanos o metales alcalinotérreo; trialquilaminas tales como trietilamina

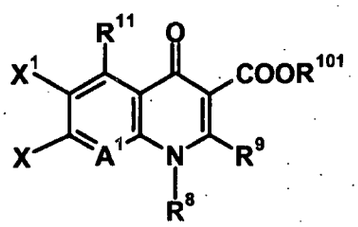
y N,N-diisopropiletilamina; y compuestos heterocíclicos que contienen nitrógeno tales como piridina, 1,8-diazabicicloundeceno, y N-metilpiperidina. Las trialquilaminas, N-metilpiperidina y trietilamina son preferidas. No hay limitaciones específicas al solvente usado siempre que no inhiba la reacción. El solvente es preferiblemente N,N-dimetilformamida, sulfóxido de dimetilo, sulfolano, acetonitrilo, dimetilacetamida, tetrahidrofurano o N-metilpirrolidona, y en particular preferiblemente sulfóxido de dimetilo, sulfolano, acetonitrilo o dimetilacetamida.

Cuando el compuesto de estructura de base madre de ácido quinoloncarboxílico es un compuesto quelato de boro, el compuesto objetivo se puede obtener digiriendo la porción del sustituyente de boro por hidrólisis y después desprotegiendo el grupo protector para el grupo amino. El sustituyente de boro puede ser hidrolizado bajo condiciones comúnmente usados. Por ejemplo, el sustituyente de boro puede ser hidrolizado haciendo reaccionar una base en presencia de un solvente de alcohol acuoso tal como metanol o etanol. La base es preferiblemente trietilamina. La reacción preferiblemente se lleva a cabo en un intervalo de temperatura entre enfriamiento con hielo y 90°C. La desprotección se puede llevar a cabo bajo condiciones adecuadas para el grupo protector usado tratando el hidrolizado, por ejemplo, con ácido clorhídrico concentrado. Después de completarse la reacción, la solución de reacción se hace básica con una solución de, por ejemplo, hidróxido de sodio y después se puede neutralizar con un ácido apropiado tal como ácido clorhídrico; los cristales precipitados son subsiguientemente recogidos por filtración o extraídos con cloroformo; y el compuesto resultante es apropiadamente purificado por una operación de recristalización usando un solvente apropiado, por ejemplo, para obtener el compuesto objetivo.

713.

Los compuestos de quinolona de la presente invención, especialmente aquellos que tienen un grupo metilo en la posición 8, se preparan mediante la reacción de derivados de aminopirrolidina sustituidos fusionados y los compuestos de estructura de base de quinolona de la siguiente fórmula:

[Fórmula 64]



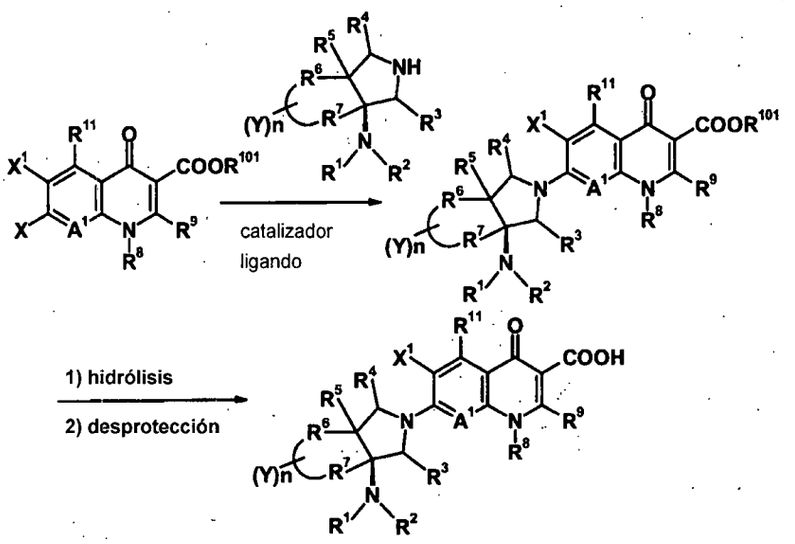
en presencia de un solvente apropiado y un catalizador, opcionalmente con la coexistencia de un ligando, y en presencia de una base. Esta reacción se puede llevar a cabo sin ligando.

El sustituyente R^{101} de la estructura de base de compuesto de quinolona es un átomo de hidrógeno o un grupo alquilo que tiene 1 a 6 átomos de carbono. Ejemplos de los alquilos preferidos son un grupo metilo, un grupo etilo, un grupo isopropilo y un grupo ter-butilo. En relación con el grupo residual X^1, aquellos ordinariamente usados en este campo también son preferiblemente aplicables a esta reacción. El ejemplo preferido de dicho grupo residual es un átomo de halógeno tal como un átomo de bromo, o un átomo de yodo; un grupo sulfoniloxi sustituido tal como un grupo trifluorometansulfoniloxi. En cuanto al catalizador, aquellos ordinariamente usados en este campo son preferiblemente aplicables a esta reacción. Un catalizador de Pd, catalizador de Cu o catalizador de Ni es preferiblemente usado, y muy preferiblemente un catalizador de Pd o un catalizador de Cu. el catalizador se puede aplicar a la mezcla de reacción en forma de tris (dibencilidenacetona)dipaladio(O), acetato de paladio (II), tetrakis (trifenilfosfina) níquel (0), acetilacetonato de níquel (II), yoduro de cobre (I), o

714

bromuro de cobre (I) y similares. En cuanto al ligando para la presente reacción, ligandos monodentados o ligandos bidentados ordinariamente usados en este campo son preferiblemente aplicables a esta reacción. Ejemplos de dicho ligando son 1,1-bis(difenilfosfino)ferroceno, 4,5-bis (difenilfosfino)-9,9-dimetilxanteno, o BINAP. En cuanto a la base, aquellos ordinariamente usados en este campo son preferiblemente aplicables a esta reacción. Los carbonatos de metal alcalinotérreo o metal alcalino tales como carbonato de cesio, carbonato de potasio o carbonato de sodio, y alcóxido de metal alcalino tales como metóxido de sodio, etóxido de sodio o ter-butóxido de potasio son preferiblemente usados. Esta reacción se explica en el siguiente esquema de reacción:

[Fórmula 65]



Los compuestos de quinolona de la presente invención se obtienen mediante la reacción de los compuestos de estructura de base quinoloncarboxílico con compuestos de aminopirrolidina sustituidos fusionados en un solvente apropiado, en presencia de un catalizador, opcionalmente con la coexistencia de un ligando, y en presencia de una base. El grupo amino del

715.

compuesto de pirrolidina sustituido fusionado usado para la introducción del sustituyente en la posición 7 puede tener un grupo protector. Ejemplos de dichos grupos protectores son un alquiloxicarbonilo tal como un ter-butoxicarbonilo; un aralquiloxicarbonilo tal como un benciloxicarbonilo, o un p-metoxibenciloxicarbonilo; un acil o un alquil carbonilo tal como un acetilo, un metoxiacetilo, un trifluoroacetilo, un pivaloilo, o un grupo formilo; un arilquilcarbonilo tal como un benzoilo, o un p-nitrobenzoilo; un grupo alquilo tal como un ter-butilo; a aralquilo tal como un grupo bencilo, un grupo p-metoxibencilo, o un p-nitrobencilo; un sililo sustituido tal como un trimetilsililo, o un isopropildimetilsililo. El ejemplo de la base para esta reacción es un carbonato, un bicarbonato, un fosfato, un hidrato, o un alcóxido de un átomo de metal alcalino o un átomo de metal alcalinotérreo; una trialquilamina tal como una trietilamina, o una N,N-diisopropiletilamina; un compuesto heterocíclico que contiene nitrógeno tal como una piridina, un 1,8-diazabicicloundeceno, o un N-metilpiperidina. En cuanto al solvente, cualquier solvente que no inhibe la reacción preferiblemente se aplica para esta reacción. Ejemplos del solvente son una amida tal como una N,N-dimetilformamida, una N,N-dimetilacetamida, o una N-metil-2-pirrolidona; un hidrocarburo de arilo tal como un tolueno, o un xileno; un éter tal como un tetrahidrofurano, un 1,4-dioxano, o un 1,2-dimetoxietano; y un acetonitrilo. Los solventes más preferidos son una N,N-dimetilformamida, un xileno, un 1,4-dioxano, o un 1,2-dimetoxietano.

La reacción puede ser conducida en las formas de ambas reacciones homogéneas y heterogéneas. La reacción también preferiblemente se lleva a cabo en una reacción de fase catalítica. La reacción se completa en un tiempo de 10 minutos a 7 días. La reacción se puede conducir a una temperatura entre 0°C a 300°C, preferiblemente entre 30°C a la temperatura del

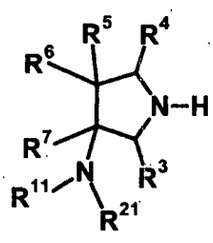
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punto de ebullición del solvente usado. El compuesto catalizador y compuesto de ligando puede ser mezclado para formar el complejo de catalizador antes de la adición de los otros compuestos de reacción, o todos los componentes de reacción se pueden mezclar al mismo tiempo. La cantidad del catalizador está en el intervalo de una cantidad catalítica a la cantidad equimolar, y una cantidad catalítica es preferida.

En el caso de que los compuestos de estructura de base de quinolona tengan una porción éster, los compuestos de carboxi se obtienen por digestión del grupo éster de conformidad con los métodos ya conocidos en este campo. Los compuestos de quinolona se obtienen por digestión del grupo protector de la porción amino sobre la porción de aminopirrolidina sustituida fusionada a un método ya conocido del grupo protector correspondiente. Los compuestos de quinolona son aislados después de la digestión del grupo protector por un método ya conocido en este campo, tales como recristalización de solventes apropiados o similares.

Los compuestos representados por las dos fórmulas siguientes son útiles como intermediarios de producción para el compuesto (I) de la presente invención, respectivamente:

[Fórmula 66]



En la formula anterior, R^{11} representa R^1 como ya se definió (un

átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, o un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido, o un tripéptido; el grupo alquilo puede tener un sustituyente seleccionado del grupo que consiste de un grupo hidroxi, un grupo amino, un grupo ciano, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y el grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno) o un grupo amino-protector;

R^{21} representa R^2 como ya se definió (un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, o un grupo cicloalquilo que tiene 3 a 6 átomos de carbono; el grupo alquilo puede tener un sustituyente seleccionado del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y el grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno) o un grupo amino-protector; y

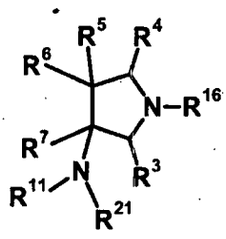
R^3, R^4, R^5, R^6, y R^7 son como ya se definió.

Aquí, se describirá el grupo amino-protector representado por R^{11} o R^{21}. El grupo protector no está limitado siempre que sea generalmente usado en la técnica. Ejemplos del grupo protector incluyen grupos alcoxicarbonilos tales como un grupo ter-butoxicarbonilo y un grupo 2,2,2-tricloroetoxicarbonilo; grupos aralquiloxicarbonilos tales como un grupo benciloxicarbonilo, un grupo p-metoxibenciloxicarbonilo, y un grupo p-nitrobenciloxicarbonilo; grupos acilo tales

718

como un grupo acetilo, un grupo metoxiacetilo, un grupo trifluoroacetilo, un grupo cloroacetilo, un grupo pivaloilo, un grupo formilo y un grupo benzoilo; grupos alquilo o aralquilo tales como un grupo ter-butilo, un grupo bencilo, un grupo p-nitrobencilo, un grupo p-metoxibencilo y un grupo trifenilmetilo; éteres tales como un grupo metoximetilo, un grupo ter-butoximetilo, un grupo tetrahidropiranilo y un grupo 2,2,2-tricloroetoximetilo; grupos sililo (alquilo- y/o aralquilo-)sustituidos tales como un grupo trimetilsililo, un grupo isopropildimetilsililo, un grupo ter-butildimetilsililo, un grupo tribencilsililo, y un grupo ter-butildifenilsililo; y un grupo alilo.

[Fórmula 67]



En la fórmula anterior, R^{16} representa un grupo amino-protector; y R^{11}, R^{21}, R^3, R^4, R^5, R^6, y R^7 son como ya se definió.

El grupo protector representado por R^{16} no está limitado siempre que sea generalmente usado en la técnica. Ejemplos del grupo protector incluyen grupos alcoxicarbonilo tales como un grupo ter-butoxicarbonilo y un grupo 2,2,2-tricloroetoxicarbonilo; grupos aralquiloxicarbonilo tales como un grupo benciloxicarbonilo, un grupo p-metoxibenciloxicarbonilo y un grupo p-nitrobenciloxicarbonilo; grupos acilo tales como un grupo acetilo, un grupo metoxiacetilo, un grupo trifluoroacetilo, un grupo cloroacetilo, un grupo pivaloilo, un grupo formilo y un grupo benzoilo; grupos alquilo o aralquilo tales como un grupo ter-butilo, un grupo bencilo, un grupo p-nitrobencilo, un grupo p-

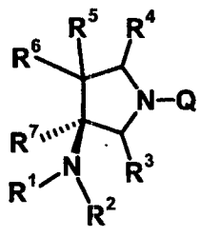
metoxibencilo y un grupo trifenilmetilo; éteres tales como un grupo metoximetilo, un grupo ter-butoximetilo, un grupo tetrahidropiranilo y un grupo 2,2,2-tricloroetoximetilo; grupos sililo (alquilo- y/o aralquilo-)sustituidos tales como un grupo trimetilsililo, un grupo isopropildimetilsililo, un grupo ter-butildimetilsililo, un grupo tribencilsililo y un grupo ter-butildifenilsililo; y un grupo alilo.

Cuando dos o más de R^{11}, R^{21}, y R^{16} son grupos protectores, cualesquiera grupos protectores se pueden seleccionar con base en el conocimiento común en la técnica por lo que los grupos protectores pueden ser selectivamente removidos.

Se ha encontrado, a partir del ejemplo de prueba descrito al último, que los compuestos obtenidos como se describió antes que tienen la posición 7 de la estructura de base madre de ácido quinolonocarboxílico (o su posición correspondiente) sustituida con el derivado de aminopirrolidina bicíclico fusionado de la presente invención, que son representados por un compuesto del ejemplo X, tienen actividad antibacteriana, en particular, actividad antibacteriana a *Staphylococcus aureus* y bacterias Gram-positivas tales como neumococos más fuertes que la de levofloxacin o ciprofloxacin generalmente usado en la técnica. En este caso, se ha confirmado que el sitio sustituido con un grupo amino en el sustituyente en la posición 7 es un carbono asimétrico, y que el ácido quinoloncarboxílico sustituido con un sustituyente en la posición 7 derivado de un enantiómero tiene actividad mayor y presenta más propiedades excelentes, farmacocinética y seguridad. Como resultado de cristalografía de rayos X del sustituyente altamente activo en la posición 7 o síntesis de cada enantiómero por el método de acervo quiral y medición de actividad antibacteriana, se ha confirmado que el grupo amino en la posición 7 tiene una configuración representada por la siguiente fórmula:

720

[Fórmula 68]



en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, y Q son como ya se definió.

El compuesto de la presente invención puede ser de una forma libre. Alternativamente, una sal ácida de adición o una sal con un grupo carboxílico se puede formar. Ejemplos de la sal ácida de adición incluyen sales de ácido inorgánico tales como clorhidrato, sulfato, nitruro, bromhidrato, yodhidrato y fosfato; y sales de ácido orgánico tales como sulfonato (v.gr., metansulfonato, bencensulfonato, p-toluensulfonato), y carboxilato (v.gr., acetato, citrato, maleato, fumarato, lactato). Ejemplos de la sal con un grupo carboxilo incluyen sales de metal alcalino tales como sal de litio, sal de sodio, y sal de potasio; sales de metal alcalinotérreo tales como sal de magnesio y sal de calcio; sal de amonio, sal de trietilamina, sal de N-metilglucamina, y sal de tris-(hidroximetil)aminometano. El compuesto de la presente invención en forma libre y una sal ácida de adición o una sal con un grupo carboxilo del compuesto puede estar presente como un hidrato.

El compuesto (I) de la presente invención tiene fuerte actividad antibacteriana y por lo tanto se puede usar como una medicina para humanos, animales y peces, una sustancia química de uso agrícola, o un conservador de alimentos. La dosis del compuesto de la presente invención usada como una medicina humana es 50 mg a 1 g, y muy preferiblemente 100 a 500 mg, por día para un adulto. La dosis para un animal varía dependiendo del propósito de administración, el tamaño del animal que se ha de tratar, el tipo de patógeno con

el cual el animal está infectado, y el grado de la enfermedad; la dosis diaria es generalmente de 1 a 200 mg, y muy preferiblemente de 5 a 100 mg, por kg de peso corporal del animal. La dosis diaria se administra una vez o en dos a cuatro dosis divididas. La dosis diaria puede exceder la dosis antes mencionada si es necesario.

El compuesto (I) de la presente invención es activo para una amplia gama de microorganismos causando varias infecciones y puede tratar, prevenir o aliviar enfermedades causadas por estos patógenos. Ejemplos de bacterias o microorganismos similares a bacterias para los cuales el compuesto de la presente invención es efectivo incluyen *Staphylococcus, Streptococcus pyogenes*, estreptococos hemolíticos, enterococos, neumococos, *Peptostreptococcus*, gonococos, *Escherichia coli, Citrobacter, Shigella, Klebsiella pneumoniae, Enterobacter, Serratia, Proteus, Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter, Campylobacter* y *Chlamydia trachomatis*.

Ejemplos de enfermedades causadas por estos patógenos incluyen foliculitis, furúnculo, carbunco, erisipelas, celulitis, linfangitis, panadizo, absceso subcutáneo, hidradenitis, acné conglobado, ateroma infeccioso, absceso perirrectal, mastitis, infección secundaria superficial tal como infección traumática, infección por quemadura, o infección por heridas quirúrgicas, laringofaringitis, bronquitis aguda, tonsilitis, bronquitis crónica, bronquiectasis, panbronquiiolitis difusa, infección secundaria a una enfermedad respiratoria crónica, neumonía, pielonefritis, cistitis, prostatitis, epididimitis, uretritis gonocócica, uretritis no gonocócica, colecistitis, colangitis, shigelosis, enteritis, adnexitis, infección intrauterina, bartolinitis, blefaritis, hordeolo, dacriocistitis, meibomianitis, úlcera corneal, otitis media, sinusitis, periodontitis, pericoronitis,

722

inflamación de la mandíbula, peritonitis, endocarditis, sepsis, meningitis e infección de la piel.

Ejemplos de *Mycobacterium* spp., para los cuales el compuesto (I) de la presente invención es efectivo incluyen bacilo de la tuberculosis (*Mycobacterium tuberculosis*, *M. bobis* y *M. africanum*) y micobacteria atípica (*M. cansasii, M. marinum, M. scrofulaceum, M. avium, M. intracellulare*, *M. xenopi, M. fortuitum, y M. chelonae*). Las infecciones micobacterianas causadas por estos patógenos se clasifican ampliamente en tuberculosis, infecciones micobacterianas atípicas y lepra. Las infecciones por *Mycobacterium tuberculosis* se observan en la cavidad torácica, tráquea y bronquios, nodo linfático, diseminación sistémica, articulaciones de los huesos, meninges y cerebro, órganos digestivos (intestino e hígado), piel, glándulas mamarias, ojos, oído medio y faringe, tracto urinario, órganos genitales masculinos y órganos genitales femeninos, además de los pulmones. Las infecciones micobacterianas atípicas (infecciones micobacterianas no tuberculosas) principalmente afecta a los pulmones, y también pueden aparecer como linfadenitis local, infección de tejido de la piel suave, osteoartritis o infección de tipo diseminación sistémica.

El compuesto de la presente invención también es efectivo para varios microorganismos causando infecciones en animales tales como *Escherichia, Salmonella, Pasteurella, Haemophilus, Bordetella, Staphylococcus* y *Mycoplasma*. Ejemplos específicos de enfermedades de animales incluyen enfermedades de aves tales como enfermedades por *Escherichia coli*, diarrea blanca bacilar de los pollos, paratifoidea de aves, cólera de aves, coriza infecciosa, enfermedad estafilocócica e infección por micoplasmas; enfermedades de los cerdos tales como enfermedad por *Escherichia coli*, salmonelosis, pasteurelosis, infección por *Hemophilus*, rinitis atrófica, epidermitis

exudativa, e infección por micoplasma; enfermedades de bovinos tales como enfermedad por *Escherichia coli*, salmonelosis, septicemia hemorrágica, infección por micoplasma, pleuroneumonía de bovinos contagiosa, y mastitis; enfermedades de perros tales como sepsis por *Escherichia coli*, infección por *Salmonella*, septicemia hemorrágica, piometra, y cistitis; y enfermedades de gatos tales como pleuritis exudativa, cistitis, rinitis crónica, infección por *Hemophilus*, diarrea de crías de gato e infección por micoplasma.

Un agente antibacteriano que contiene el compuesto (I) de la presente invención se puede seleccionar apropiadamente de conformidad con el método de administración y preparar por un método para preparar varias preparaciones comúnmente usadas. Ejemplos de forma de dosis de agente antibacteriano que contiene el compuesto de la presente invención como un agente principal incluyen tabletas, polvos, gránulos, cápsulas, soluciones, jarabes, elíxires, y suspensiones oleosas o acuosas. Una preparación de inyección puede contener un aditivo tal como un estabilizador, un conservador, o un adyuvante de solución, y se puede preparar antes de usarse a partir de una preparación sólida formada almacenando una solución que puede contener dicho aditivo en un contenedor y después liofilizando, por ejemplo, la solución. Una dosis puede ser almacenada en un contenedor, o múltiples dosis pueden ser almacenadas en un solo contenedor. Ejemplos de preparaciones externas incluyen soluciones, suspensiones, emulsiones, pomadas, geles, cremas, lociones y aspersiones. Una preparación sólida puede contener un aditivo farmacéuticamente aceptable junto con el compuesto activo. Ejemplos del aditivo incluyen llenadores, aglutinantes, desintegrantes, promotores de solución, agentes humectantes y lubricantes. Una preparación líquida puede ser una solución, una suspensión, una emulsión, o similar, y puede contener un

724

aditivo tal como un agente de suspensión o un emulsionante.

Enseguida, se describirán los ejemplos de preparación.

EJEMPLO DE PREPARACION 1

Cápsulas

Compuesto del ejemplo 11	100.0 mg
Almidón de maíz	23.0 mg
Carboximetilcelulosa de calcio	22.5 mg
Hidroximetilcelulosa	3.0 mg
Estearato de magnesio	1.5 mg
Total	150.0 mg

EJEMPLO DE PREPARACION 2

Preparación de solución

Compuesto del ejemplo 11	1 a10 g
Acido acético o hidróxido de sodio	0.5 a 2 g
p-Oxibenzoato de etilo	0.1 g
Agua purificada	87.9 a 98.4 g
Total	100 g

EJEMPLO DE PREPARACION 3

Polvo para mezclarse con forraje

Compuesto del ejemplo 17	1 a 10 g

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Almidón de maíz	89.5 a 98.5 g
Acido silícico anhidro ligero	0.5 g
Total	100 g

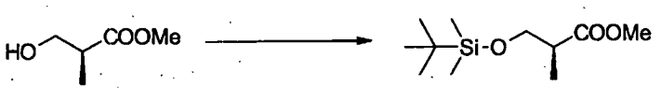
EJEMPLOS

La presente invención se describirá específicamente a continuación con referencia a los ejemplos; sin embargo, la presente invención no está limitada a los ejemplos, y los ejemplos no deben ser construidos como limitantes en ningún sentido.

EJEMPLO DE REFERENCIA 1

Ester metílico de ácido (S)-3-(ter-butildimetilsililoxi)-2-metilpropiónico

[Fórmula 69]



Imidazol (13.3 g, 196 mmoles) y cloruro de ter-butildimetilsililo (14.2 g, 94.1 mmoles) se añadieron a una solución de éster metílico de ácido (S)-3-hidroxi-2-metilpropiónico (11.0 g, 93.1 mmoles) en dimetilformamida (100 ml), y la mezcla se agitó a temperatura ambiente durante cuatro horas. Se añadió agua a la mezcla de reacción, seguido por extracción con hexano dos veces. El extracto después se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida para dar 24 g (cuantitativo) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 3.76-3.72 (1H, m), 3.64 (3H, s), 3.63-

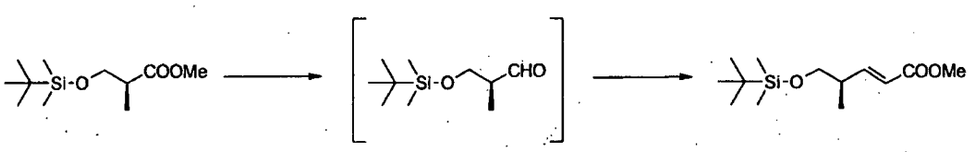
-126

3.59 (1H, m), 2.65-2.57 (1H, m), 1.10 (3H, d, J=6.84 Hz), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s).

EJEMPLO DE REFERENCIA 2

Ester metílico de ácido (E)-(R)-5-(ter-butildimetilsililoxi)-4-metilpent-2-eno

[Fórmula 70]



Hidruro de diisobutilaluminio (solución 1 M en hexano, 86 ml) se añadió a una solución de éster metílico de ácido (S)-3-(ter-butildimetilsililoxi)-2-metilpropiónico (20 g, 86.1 mmoles) en diclorometano (400 ml) a -78°C, y la mezcla se agitó a la misma temperatura durante dos horas. Se añadió una solución saturada de tartrato de potasio-sodio a la mezcla de reacción la cual se agitó después mientras se calentaba a temperatura ambiente. La capa orgánica se separó, y después la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio, y se filtraron y el solvente se evaporó bajo presión reducida. El residuo se disolvió en diclorometano (200 ml). Ester metílico de ácido trifenilfosfonilidenacético (32 g, 94.7 mmoles) se añadió bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante la noche. La solución de reacción se filtró y después el solvente se evaporó bajo presión reducida. Se añadió hexano al residuo resultante, y el material insoluble se removió por filtración. El filtrado se concentró bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 4:1) para dar 25 g (cuantitativo) del compuesto del título como un aceite incoloro.

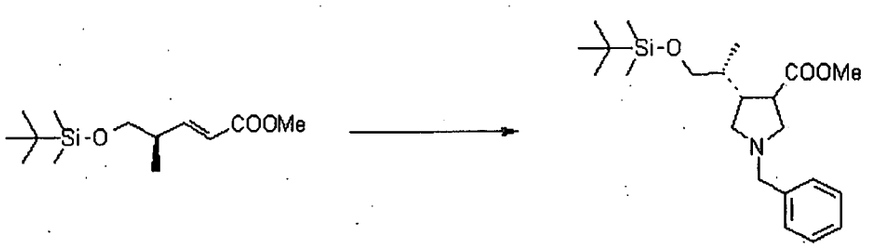
727

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 6.94 (1H, dd, J=7.10, 15.90 Hz), 5.84 (1H, dd, J=1.20, 15.90 Hz), 3.73 (3H, s), 3.57-3.49 (2H, m), 2.53-2.46 (1H, m), 1.05 (3H, d, J=6.80 Hz), 0.89 (9H, s), 0.04 (6H, s).

EJEMPLO DE REFERENCIA 3

Ester metílico de ácido 1-bencil-4-[(R)-2-(ter-butildimetilsililoxi)-1-(metil)etil] pirrolidin-3-carboxílico

[Fórmula 71]



3,4-dl-trans

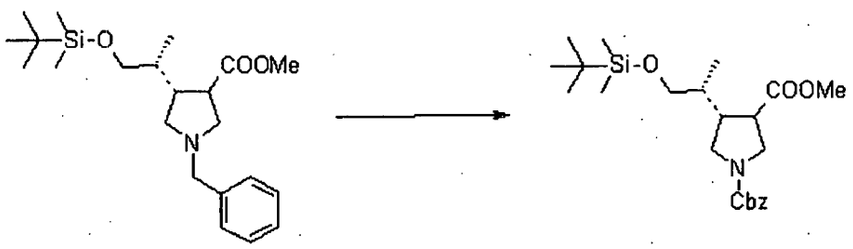
N-Bencil-N-(metoximetil)-N-trimetilsililmetilamina (16.6 ml, 65.0 mmoles) se añadió a una solución de éster metílico de ácido (E)-(R)-5-(ter-butildimetilsililoxi)-4-metilpent-2-eno (14 g, 54.2 mmoles) en cloruro de metileno (100 ml), y después se añadió una cantidad traza de ácido trifluoroacético. La mezcla se agitó durante 30 minutos y después se añadió bicarbonato de sodio saturado acuoso. La capa orgánica se separó y se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 4:1) para dar 14.6 g (69%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

128

EJEMPLO DE REFERENCIA 4

Ester 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-(ter-butildimetilsililoxi)-1-(metil)etil] pirrolidin-1,3-dicarboxílico

[Fórmula 72]



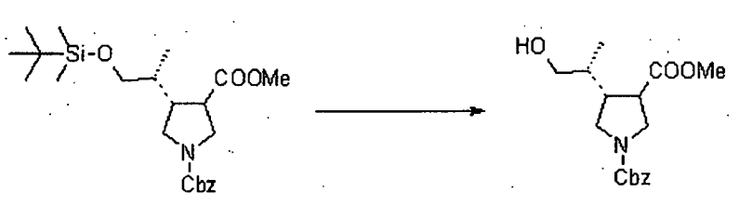
3,4-dl-trans 3,4-dl-trans

Cloruro de benciloxicarbonilo (10.2 ml, 71.5 mmoles) se añadió a una solución de éster metílico de ácido 1-bencil-4-[(R)-2-(ter-butildimetilsililoxi)-1-(metil)etil] pirrolidin-3-carboxílico (14.0 g, 35.8 mmoles) en diclorometano (200 ml), y la mezcla se agitó durante una hora. Bicarbonato de sodio saturado acuoso se añadió a la mezcla de reacción. La capa orgánica se separó, se secó sobre sulfato de magnesio, y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 4:1) para dar 13.9 g (89%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

EJEMPLO DE REFERENCIA 5

Ester 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-hidroxi-1-(metil) etil] pirrolidin-1,3-dicarboxílico

[Fórmula 73]



3,4-dl-trans 3,4-dl-trans

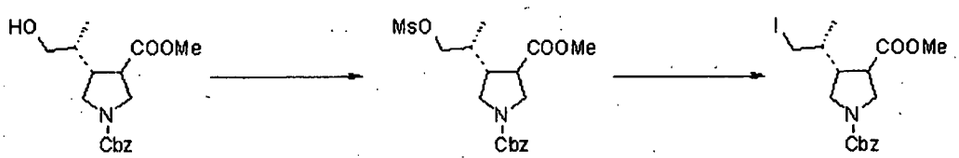
429

Fluoruro de hidrógeno-piridina (4 ml) se añadió a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-(ter-butildimetilsililoxi)-1-(metil) etil]-pirrolidin-1,3-dicarboxílico (6.0 g, 7.1 mmoles) en piridina (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 13 horas. La mezcla de reacción se vació en agua con hielo, seguido por extracción con acetato de etilo y se lavó con ácido clorhídrico 1N y salmuera. Después de secado sobre sulfato de magnesio y filtración, el solvente se evaporó bajo presión reducida para dar 4.1 g (93%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

EJEMPLO DE REFERENCIA 6

Ester 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-yodo-1-(metil)etil]-pirrolidin-1,3-dicarboxílico

[Fórmula 74]



3,4-dl-trans 3,4-dl-trans 3,4-dl-trans

Trietilamina (2.7 ml, 19.1 mmoles) y cloruro de mesilo (1.2 ml, 15.3 mmoles) se añadieron a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-hidroxi-1-(metil) etil] pirrolidin-1, 3-dicarboxílico (4.1 g, 12.8 mmoles) en diclorometano (100 ml) bajo enfriamiento con hielo, y después la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de añadir metanol a la mezcla de reacción, la mezcla se mezcló con una mezcla de acetato de etilo y una solución de ácido cítrico al 10%. La capa orgánica se lavó

730.

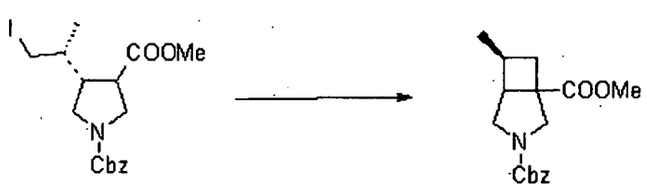
con salmuera y se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en acetona (100 ml). Yoduro de sodio (4.1 g, 27.4 mmoles) se añadió, y la mezcla se calentó a reflujo durante 20 horas. La mezcla de reacción se enfrió y después el solvente se evaporó bajo presión reducida. El residuo resultante se mezcló con una mezcla de acetato de etilo y agua. La capa orgánica se lavó con una solución saturada de tiosulfato de sodio y salmuera, se secó sobre sulfato de magnesio, y después se filtró, y el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 10:0 -> 7:3) para dar 5.0 g (84%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.33 (5H, m), 5.13 (2H, s), 3.83-3.71 (4H, m), 3.58-3.51 (1H, m), 3.27-3.23 (1H, m), 3.18-3.09 (2H, m), 2.92-2.83 (1H, m), 2.64-2.55 (1H, m), 1.81-1.75 (1H, m), 1.53-1.48 (1H, m), 1.06-1.01 (3H, m).

EJEMPLO DE REFERENCIA 7

Ester 1-metílico de éster 3-bencílico de ácido (S)-6-metil-3-azabiciclo [3.2.0] heptano-1,3-dicarboxílico

[Fórmula 75]



3,4-dl-trans

131

Una solución 0.5 M de hexametildisilazida de potasio en tolueno (28 ml, 14.0 mmoles) se añadió gota a gota a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(R)-2-yodo-1-(metil)etil]pirrolidin-1,3-dicarboxílico (5.0 g, 11.5 mmoles) en tetrahidrofurano anhidro (100 ml) en una atmósfera de argón a -78°C. Después de completarse la adición gota a gota, la mezcla se agitó a la misma temperatura durante 30 minutos. Una solución de cloruro de amonio se añadió, y la mezcla se calentó a temperatura ambiente. Después de extracción con acetato de etilo, secado sobre sulfato de magnesio y filtración, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 10:0 -> 7:3) para dar 3.2 g (91%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.32 (5H, m), 5.17-5.14 (2H, m), 3.94 (0.5H, dd, J=10.86, 18.92 Hz), 3.76-3.69 (5H, m), 3.46 (0.5H, d, J=11.72 Hz), 3.36 (0.5H, dd, J=6.10, 11.47 Hz), 3.25 (0.5H, dd, J=8.06, 11.96 Hz), 3.06 (0.5H, t, J=8.30 Hz), 2.73-2.65 (1.5H, m), 2.13-2.09 (1.5H, m), 1.11 (1.5H, d, J=6.10 Hz), 0.94 (1.5H, brs).

EJEMPLO DE REFERENCIA 8

Ester 3-bencílico de ácido (S)-6-metil-3-azabiciclo[3.2.0]heptano-1,3-dicarboxílico

[Fórmula 76]



732

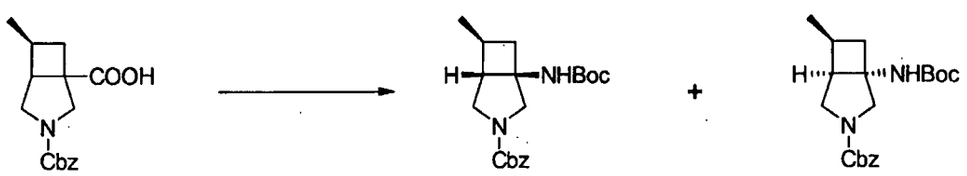
Una solución de hidróxido de sodio 1N (21 ml) se añadió gota a gota a una solución mixta de éster 1-metílico de éster 3-bencílico de ácido (S)-6-metil-3-azabiciclo [3.2.0] heptano-1,3-dicarboxílico (3.2 g, 10.4 mmoles) en tetrahidrofurano (60 ml) y metanol (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 minutos. La solución de reacción se neutralizó con ácido clorhídrico 1N, seguido por extracción con acetato de etilo. El extracto se secó sobre sulfato de magnesio y se filtró. El solvente se evaporó bajo presión reducida para dar 3.0 g (cuantitativo) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

EJEMPLO DE REFERENCIA 9

Ester bencílico de ácido (S)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico

(isómero óptico A, isómero óptico B)

[Fórmula 77]



Trietilamina (2.9 ml, 20.7 mmoles) y difenil fosfoazida (3.4 ml, 15.6 mmoles) se añadieron a una solución de éster 3-bencílico de ácido (S)-6-metil-3-azabiciclo[3.2.0] heptano-1,3-dicarboxílico (3.0 g, 10.4 mmoles) en tolueno (60 ml) a temperatura ambiente, y después se añadió alcohol ter-butílico (60 ml). La mezcla se calentó con agitación a 100°C durante 15 horas. La mezcla de

reacción se enfrió, y después el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 10:0 → 8:2) para dar el compuesto del título de mezcla diaestereomérica (3.1 g) como un aceite incoloro. Los diaestereómeros se separaron por Chiralpak AD (2 cm, hexano : alcohol isopropílico = 92.5:7.5, flujo: 30 ml/min) para dar 1.48 g (40%) de un aceite incoloro de primera fracción (isómero óptico A) y 1.38 g (37%) de de un aceite incoloro de segunda fracción (isómero óptico B).

Isómero óptico A:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.14 (2H, s), 4.81-4.76 (1H, m), 3.84 (1H, d, J=10.70 Hz), 3.61-3.53 (3H, brm), 2.43-2.31 (2H, m), 1.92-1.86 (1H, m), 1.75-1.68 (1H, m), 1.43 (9H, s), 1.14 (3H, d, J=6.80 Hz).

Isómero óptico B:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.30 (5H, m), 5.16 (2H, s), 4.87-4.73 (1H, brm), 3.88-3.79 (1H, m), 3.72 (1H, d, J=11.00 Hz), 3.43-3.28 (2H, brm), 2.89-2.77 (1H, brm), 2.67-2.58 (1H, m), 2.32 (1H, t, J=11.70 Hz), 1.76-1.68 (1H, m), 1.44 (9H, s), 0.95-0.92 (3H, m).

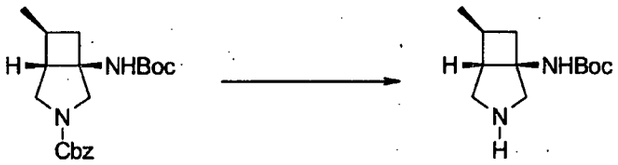
Con base en comparación de RMN entre el isómero más polar y el isómero menos polar, el isómero óptico A se identificó como éster bencílico de ácido (1R, 5S, 6S)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico, y el isómero óptico B se identificó como éster bencílico de ácido (1S, 5R, 6S)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico.

EJEMPLO DE REFERENCIA 10

(1R, 5S, 6S)-1-(ter-Butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0] heptano

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[Fórmula 78]



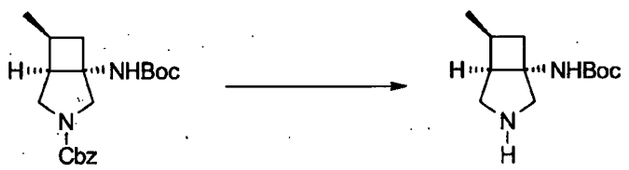
Ester bencílico de ácido (1R,5S,6S)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico (1.4 g, 3.9 mmoles) se disolvió en un solvente mixto de metanol (20 ml) y tetrahidrofurano (10 ml). Se añadió una pequeña cantidad de 10% de paladio-carbón (50% húmedo), y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 0.89 g (cuantitativo) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.80 (1H, brs), 3.09 (1H, d, J=11.20 Hz), 3.02 (2H, dd, J=5.40, 11.20 Hz), 2.82 (2H, d, J=11.20 Hz), 2.27-2.22 (2H, m), 1.77-1.69 (2H, m), 1.44 (9H, s), 1.17 (3H, d, J=6.60 Hz).

EJEMPLO DE REFERENCIA 11

(1S,5R,6S)-1-(ter-Butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0] heptano

[Fórmula 79]



Ester bencílico de ácido (1S, 5R, 6S)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico (1.4 g, 3.8 mmoles) se disolvió en un solvente mixto de metanol (20 ml) y tetrahidrofurano (10 ml). Se añadió

735

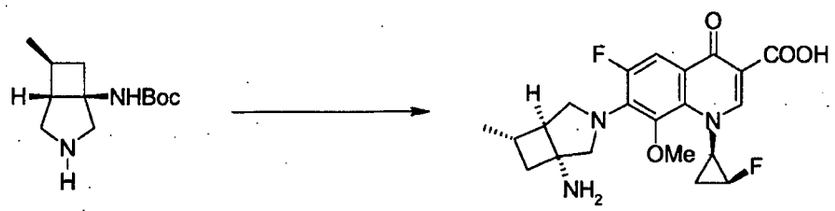
una pequeña cantidad de 10% de paladio-carbón (50% húmedo), y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 0.85 g (cuantitativo) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.88 (1H, brs), 3.06 (1H, d, J=12.00 Hz), 2.96-2.89 (2H, m), 2.71-2.61 (3H, m), 2.39-2.33 (1H, m), 1.58 (1H, dd, J=7.40, 12.80 Hz), 1.45 (9H, s), 0.94 (3H, d, J=6.80 Hz).

EJEMPLO 1

Acido 7-{(1R, 5S, 6S)-1-amino-6-metil-3-azabiciclo [3.2.0]hept-3-il}-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 80]



(1R,5S,6S)-1-(ter-butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0]heptano (870 mg, 3.84 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (1.25 g, 3.46 mmoles) se disolvieron en sulfóxido de dimetilo (15 ml). Se añadió trietilamina (0.64 ml) y la mezcla se agitó a 40°C durante 12 horas. Después de enfriar la solución de reacción con hielo, se añadió agua, y el precipitado se recogió por filtración, se lavó con agua, y se secó. El precipitado se disolvió en etanol (140 ml). Se añadieron agua (30 ml) y trietilamina (0.64 ml) y la mezcla se calentó a reflujo durante cinco horas. La mezcla de reacción se diluyó con

736.

acetato de etilo y se lavó con una solución de ácido cítrico al 10%, agua, y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Se añadió ácido clorhídrico concentrado (25 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante una hora. Después, la solución de reacción se lavó con cloroformo. La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo-metanol (9:1) ocho veces. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró, y el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol, y el material insoluble se removió por filtración. El solvente se evaporó bajo presión reducida, y el polvo resultante se secó bajo presión reducida para dar 562 mg (35%) del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.49 (1H, brs), 7.70 (1H, d, J=13.70 Hz), 5.03-4.85 (1H, m), 4.09-4.03 (1H, m), 3.90 (1H, d, J=10.50 Hz), 3.67 (3H, s), 3.48 (1H, d, J=10.50 Hz), 3.03 (1H, d, J=10.50 Hz), 2.44 (1H, dd, J=12.00, 8.80 Hz), 2.15 (1H, t, J=5.10 Hz), 1.92-1.84 (1H, m), 1.69-1.62 (1H, m), 1.61-1.49 (1H, m), 1.14 (3H, d, J=7.10 Hz).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.7H_2O$-0.2EtOH:

C, 58.25; H, 5.85; F, 8.61; N, 9.52.

Encontrado: C, 58.22; H, 5.84; F, 8.47; N, 9.37.

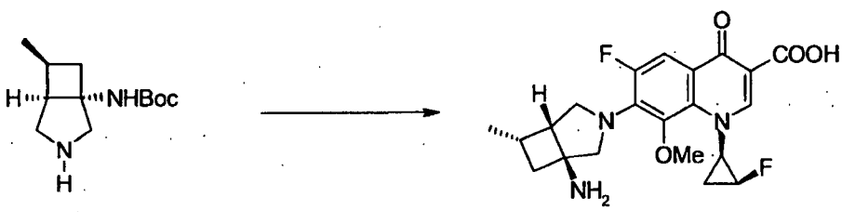
EM (ESI) m/z: 420 $(M+H)^+$.

737

EJEMPLO 2

Acido 7-{(1S, 5R, 6S)-1-amino-6-metil-3-azabiciclo [3.2.0] hept-3-il}-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 81]



(1S,5R,6S)-1-(ter-butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0] heptano (820 mg, 3.62 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (1.18 g, 3.26 mmoles) se disolvieron en sulfóxido de dimetilo (15 ml). Se añadió trietilamina (0.61 ml), y la mezcla se agitó a 40°C durante 12 horas. Después de enfriar la solución de reacción con hielo, se añadió agua y el precipitado se recogió por filtración, se lavó con agua, y se secó. El precipitado se disolvió en etanol (120 ml). Agua (30 ml) y trietilamina (0.61 ml) se añadieron, y la mezcla se calentó a reflujo durante cinco horas. La mezcla de reacción se diluyó con acetato de etilo y se lavó con una solución de ácido cítrico al 10%, agua, y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Se añadió ácido clorhídrico concentrado (25 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante una hora. Después, la solución de reacción se lavó con cloroformo. La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo-metanol (9:1) seis

738

veces. La capa orgánica se secó sobre sulfato de sodio anhidro, y el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol, y el material insoluble se removió por filtración. El solvente se evaporó bajo presión reducida, y el polvo resultante se secó bajo presión reducida para dar 1.1 g (72%) del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.46 (1H, d, J=2.20 Hz), 7.72 (1H, d, J=13.70 Hz), 5.10-4.90 (1H, m), 4.07-4.02 (1H, m), 3.75 (1H, d, J=11.20 Hz), 3.64 (3H, s), 3.64-3.59 (1H, m), 3.49-3.47 (1H, m), 3.09 (1H, d, J=10.00 Hz), 2.68-2.60 (1H, m), 2.51 (1H, t, J=7.30 Hz), 2.20 (1H, t, 10.5 Hz), 1.85 (1H, dd, J=8.50, 12.70 Hz), 1.63-1.42 (2H, m), 0.96 (3H, d, J=7.30 Hz).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.7H_2O$: C, 58.38; H, 5.69; F, 8.79; N, 9.73.

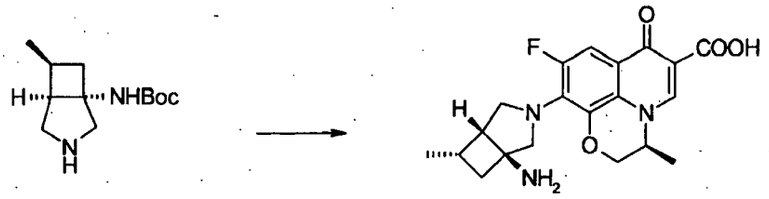
Encontrado: C, 58.24; H, 5.69; F, 8.59; N, 9.52.

EM (ESI) m/z: 420 $(M+H)^+$.

EJEMPLO 3

Acido 10-{(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]hept-3-il}-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de] [1,4] benzoxazin-6-carboxílico

[Fórmula 82]



(1S,5R,6S)-1-(ter-Butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0]heptano (546.3 mg, 2.41 mmoles) se disolvió en sulfóxido de dimetilo (12

739

ml). Se añadieron ácido 9,10-difluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de] [1, 4]benzoxazin-6-carboxílico-quelato de BF_2 (794.1 mg, 2.41 mmoles) y trietilamina (1221 mg, 12.07 mmoles) y la mezcla se agitó durante cinco días. Después, etanol acuoso al 90% (135 ml) y trietilamina (15 ml) se añadieron a la mezcla de reacción, la cual se agitó a 80°C durante 4.5 horas. El solvente se evaporó bajo presión reducida y una solución de ácido cítrico al 10% se añadió, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con diclorometano. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El sólido resultante se lavó con etanol y se secó bajo presión reducida para dar el compuesto del título (695 mg) como un sólido amarillo pálido, p.f.: 122-124°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.31 (1H, s), 7.46 (1H, d, J=13.67 Hz), 4.55 (1H, d, J=6.84 Hz), 4.46 (1H, d, J=11.47 Hz), 4.30 (1H, d, J=11.47 Hz), 3.71 (1H, d, J=10.74 Hz), 3.45 (1H, d, J=9.77 Hz), 3.27 (1H, t, J=8.79 Hz), 3.09 (1H, d, J=9.77 Hz), 2.58-2.56 (1H, m), 2.37 (1H, t, J=7.81 Hz), 2.12 (1H, t, J=11.47 Hz), 1.78 (1H, dd, J=12.33, 8.42 Hz), 1.48 (3H, d, J=6.59 Hz), 0.94 (3H, d, J=7.08 Hz).

Análisis calculado para $C_{20}H_{22}FN_3O_4$-H_2O: C, 59.25; H, 5.97; N, 10.36; F, 4.69.

140

Encontrado: C, 59.41; H, 5.65; N, 10.36; F, 4.97.

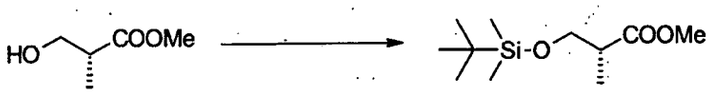
EM (EI) m/z: 388 $(M+H)^+$.

IR (ATR) ν: 2956, 2929, 2866, 1716, 1612, 1579, 1523, 1450, 1385, 1335, 1298, 1255 cm^{-1}.

EJEMPLO DE REFERENCIA 12

Ester metílico de ácido (R)-3-(ter-butildimetilsililoxi)-2-metilpropiónico

[Fórmula 83]



Imidazol (6.44 g, 42.8 mmoles) y cloruro de ter-butildimetilsililo (6.05 g, 88.8 mmoles) se añadieron a una solución de éster metílico de ácido (R)-3-hidroxi-2-metilpropiónico (5.0 g, 42.33 mmoles) en dimetilformamida (50 ml) y la mezcla se agitó a temperatura ambiente durante 1.5 horas. Se añadió agua a la mezcla de reacción, seguido por extracción con hexano dos veces. El extracto después se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida para dar 9.3 g (95%) del compuesto del título como un aceite incoloro.

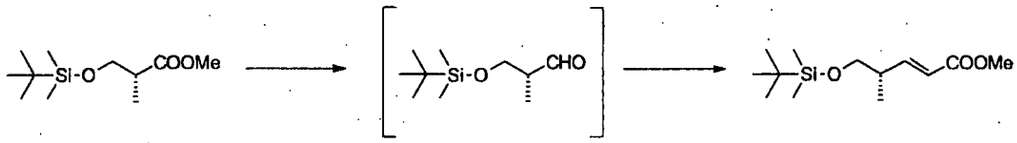
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 3.76-3.72 (1H, m), 3.64 (3H, s), 3.63-3.59 (1H, m), 2.65-2.57 (1H, m), 1.10 (3H, d, J=6.84 Hz), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s).

741

EJEMPLO DE REFERENCIA 13

Ester metílico de ácido (E)-(S)-5-(ter-butildimetilsililoxi)-4-metilpent-2-eno

[Fórmula 84]



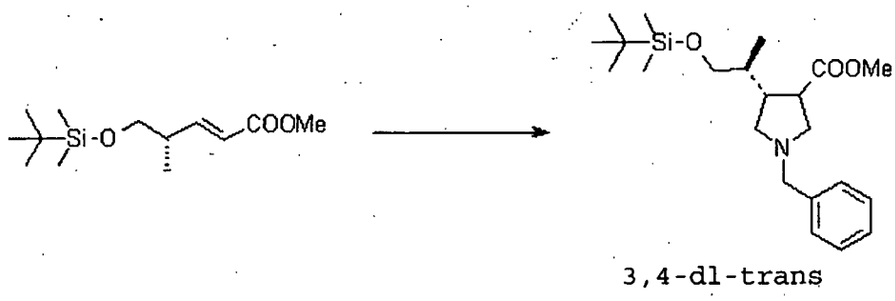
Hidruro de diisobutilaluminio (solución 1 M en hexano, 17.2 ml) se añadió a una solución de éster metílico de ácido (R)-3-(ter-butildimetilsililoxi)-2-metilpropiónico (4.0 g, 17.2 mmoles) en diclorometano (100 ml) a -78°C y la mezcla se agitó a la misma temperatura durante cuatro horas. Una solución saturada de tartrato de potasio-sodio se añadió a la mezcla de reacción, la cual se agitó después mientras se calentaba a temperatura ambiente. La capa orgánica se separó y después la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio y se filtraron. Después, el solvente se evaporó bajo presión reducida para dar aldehído (3.5 g) como un aceite incoloro. El aldehído se disolvió en diclorometano (50 ml). Se añadió éster metílico de ácido trifenilfosfonilidenacético (7.08 g, 20.75 mmoles) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 4:1) para dar 3.8 g (85%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 6.94 (1H, dd, J=7.10, 15.90 Hz), 5.84 (1H, dd, J=1.20, 15.90 Hz), 3.73 (3H, s), 3.57-3.49 (2H, m), 2.53-2.46 (1H, m), 1.05 (3H, d, J=6.80 Hz), 0.89 (9H, s), 0.04 (6H, s).

EJEMPLO DE REFERENCIA 14

Ester metílico de ácido 1-bencil-4-[(S)-2-(ter-butildimetilsililoxi)-1-(metil)etil] pirrolidin-3-carboxílico

[Fórmula 85]



3,4-dl-trans

N-Bencil-N-(metoximetil)-N-trimetilsililmetilamina (2.97 ml, 11.6 mmoles) se añadió a una solución de éster metílico de ácido (E)-(S)-5-(ter-butildimetilsililoxi)-4-metilpent-2-eno (2.5 g, 9.67 mmoles) en diclorometano (20 ml) y después se añadió una cantidad traza de ácido trifluoroacético. La mezcla se agitó durante 30 minutos y después se añadió bicarbonato de sodio saturado acuoso. La capa orgánica se separó y se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 4:1) para dar 3.0 g (78%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

EJEMPLO DE REFERENCIA 15

Ester 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-(ter-butildimetilsililoxi)-1-(metil)etil]pirrolidin-1,3-dicarboxílico

743

[Fórmula 86]

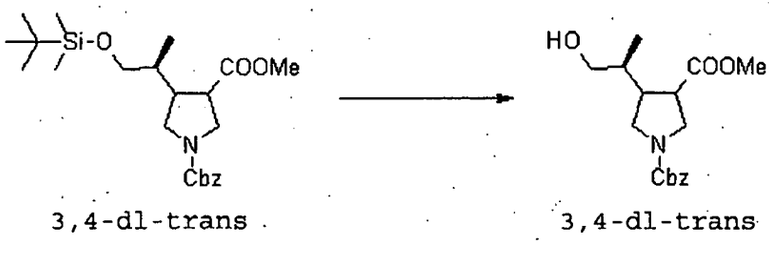


Cloruro de benciloxicarbonilo (3.25 ml, 22.8 mmoles) se añadió a una solución de éster metílico de ácido 1-bencil-4-[(S)-2-(ter-butildimetilsililoxi)-1-(metil) etil] pirrolidin-3-carboxílico (2.97 g, 7.58 mmoles) en diclorometano (20 ml) y la mezcla se agitó durante una hora. Se añadió bicarbonato de sodio saturado acuoso a la mezcla de reacción. La capa orgánica se separó, se secó sobre sulfato de magnesio, y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 4:1) para dar 3.1 g (96%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

EJEMPLO DE REFERENCIA 16

Ester 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-hidroxi-1-(metil) etil] pirrolidin-1, 3-dicarboxílico

[Fórmula 87]



144

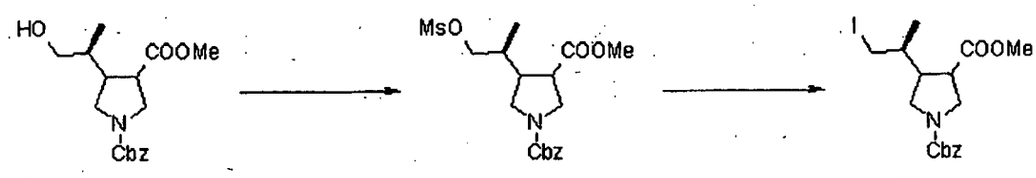
Fluoruro de hidrógeno-piridina (2 ml) se añadió a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-(ter-butildimetilsililoxi)-1-(metil)etil]pirrolidin-1,3-dicarboxílico (6.0 g, 7.1 mmoles) en piridina (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 13 horas. Se añadieron 2 ml de fluoruro de hidrógeno-piridina adicionales y la mezcla se agitó durante 23 horas. La mezcla de reacción se vació en agua con hielo, seguido por extracción con acetato de etilo y se lavó con ácido clorhídrico 1N y salmuera. Después de secado sobre sulfato de magnesio y filtración, el solvente se evaporó bajo presión reducida para dar 4.5 g (cuantitativo) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m), 5.13 (2H, brs), 3.87-3.75 (2H, brm), 3.72 (3H, s), 3.52-3.47 (3H, m), 3.27-3.11 (1H, m), 2.98-2.90 (1H, m), 2.69-2.58 (1H, m), 1.82-1.66 (2H, m), 0.95 (3H, d, J=19.80 Hz).

EJEMPLO DE REFERENCIA 17

Ester 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-yodo-1-(metil) etil] pirrolidin-1,3-dicarboxílico

[Fórmula 88]



Trietilamina (3.4 ml, 24 mmoles) y cloruro de mesilo (1.5 ml, 19.2 mmoles) se añadieron a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-hidroxi-1-(metil) etil]pirrolidin-1,3-dicarboxílico (5.1 g, 16 mmoles)

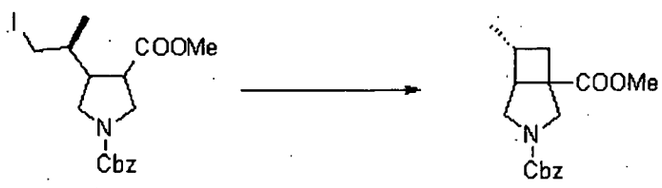
en diclorometano (50 ml) bajo enfriamiento con hielo, y después la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de añadir metanol a la mezcla de reacción, la mezcla se mezcló con una mezcla de acetato de etilo y una solución de ácido cítrico al 10%. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida, y después el residuo se disolvió en acetona (100 ml). Se añadió yoduro de sodio (4.8 g, 32 mmoles) y la mezcla se calentó a reflujo durante 20 horas. La mezcla de reacción se enfrió y después el solvente se evaporó bajo presión reducida. El residuo resultante se mezcló con una mezcla de acetato de etilo y agua. La capa orgánica se lavó con una solución saturada de tiosulfato de sodio y salmuera, se secó sobre sulfato de magnesio, y después se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 10:0 → 7:3) para dar 6.5 g (94%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.35 (5H, m), 5.13 (2H, s), 3.83-3.71 (4H, m), 3.58-3.51 (1H, m), 3.27-3.23 (1H, m), 3.18-3.09 (2H, m), 2.92-2.83 (1H, m), 2.64-2.55 (1H, m), 1.59-1.48 (2H, m), 1.02 (3H, d, J=6.60 Hz).

EJEMPLO DE REFERENCIA 18

Ester 1-metílico de éster 3-bencílico de ácido (R)-6-metil-3-azabiciclo [3.2.0] heptano-1, 3-dicarboxílico

[Fórmula 89]



3,4-dl-trans

746.

Una solución 0.5 M de hexametildisilazida de potasio en tolueno (33 ml, 16.5 mmoles) se añadió gota a gota a una solución de éster 3-metílico de éster 1-bencílico de ácido 4-[(S)-2-yodo-1-(metil) etil] pirrolidin-1,3-dicarboxílico (6.4 g, 14.8 mmoles) en tetrahidrofurano anhidro (100 ml) en una atmósfera de argón a -78°C. Después de completarse la adición gota a gota, la mezcla se agitó a la misma temperatura durante 30 minutos. Se añadió una solución de cloruro de amonio y la mezcla se calentó a temperatura ambiente. Después de extracción con acetato de etilo, secado sobre sulfato de magnesio y filtración, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 10:0 → 7:3) para dar 3.5 g (78%) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.29 (5H, m), 5.18 (2H, brs), 3.97-3.89 (1H, m), 3.77-3.69 (4H, m), 3.46 (1H, d, J=11.70 Hz), 3.25 (1H, dd, J=12.10, 7.90 Hz), 3.08-3.03 (1H, m), 2.60-2.75 (2H, m), 1.51-1.57 (1H, m), 0.94 (3H, brs).

EJEMPLO DE REFERENCIA 19

Ester 3-bencílico de ácido (R)-6-metil-3-azabiciclo [3.2.0] heptano-1,3-dicarboxílico

[Fórmula 90]



Una solución de hidróxido de sodio 1N (23 ml) se añadió gota a gota a una solución mixta de éster 1-metílico de éster 3-bencílico de ácido (R)-6-metil-3-azabiciclo [3.2.0]heptano-1,3-dicarboxílico (3.5 g, 11.5 mmoles) en tetrahidrofurano (60 ml) y metanol (20 ml) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 minutos. La solución de reacción se neutralizó con ácido clorhídrico 1N, seguido por extracción con acetato de etilo. El extracto se secó sobre sulfato de magnesio y se filtró. El solvente se evaporó bajo presión reducida para dar 3.4 g (cuantitativo) del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se usaron para el siguiente paso sin separación.

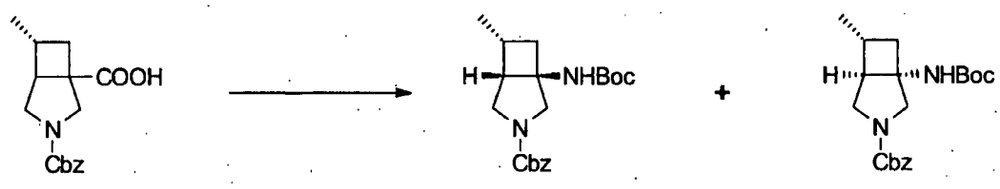
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.30 (5H, m), 5.19 (2H, brs), 4.00-3.91 (1H, m), 3.81-3.70 (1H, m), 3.50 (1H, d, J=11.70 Hz), 3.27 (1H, dd, J=11.70, 7.80 Hz), 3.11 (1H, t, J=I.10 Hz), 2.80-2.66 (2H, m), 0.95 (3H, s).

EJEMPLO DE REFERENCIA 20

Ester bencílico de ácido (R)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico

(isómero óptico C, isómero óptico D)

[Fórmula 91]



Trietilamina (3.2 ml, 22.8 mmoles) y difenil fosfoazida (3.7 ml, 17.1 mmoles) se añadieron a una solución de éster 3-bencílico de ácido (R)-6-metil-3-azabiciclo[3.2.0]heptano-1,3-dicarboxílico (3.3 g, 11.4 mmoles) en tolueno (70

748

ml) a temperatura ambiente y después se añadió alcohol ter-butílico (70 ml). La mezcla se calentó con agitación a 100°C durante 15 horas. La mezcla de reacción se enfrió, y después el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 10:0 → 8:2) para dar 3.5 g del compuesto del título de mezcla diaestereomérica como un aceite incoloro. Los diaestereómeros se separaron por Chiralpak AD (2 cm, hexano:alcohol isopropílico = 92.5:7.5, flujo: 30 ml/min) para dar 1.72 g (42%) de un aceite incoloro de primera fracción (isómero óptico C) y 1.68 g (41%) de de un aceite incoloro de segunda fracción (isómero óptico D).

Isómero óptico C:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.30 (5H, m), 5.16 (2H, s), 4.87-4.73 (1H, brm), 3.88-3.79 (1H, m), 3.72 (1H, d, J=11.00 Hz), 3.43-3.28 (2H, brm), 2.89-2.77 (1H, brm), 2.67-2.58 (1H, m), 2.32 (1H, t, J=11.70 Hz), 1.76-1.68 (1H, m), 1.44 (9H, s), 0.95-0.92 (3H, m).

Isómero óptico D:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.14 (2H, s), 4.81-4.76 (1H, m), 3.84 (1H, d, J=10.70 Hz), 3.61-3.53 (3H, brm), 2.43-2.31 (2H, m), 1.92-1.86 (1H, m), 1.75-1.68 (1H, m), 1.43 (9H, s), 1.14 (3H, d, J=6.80 Hz).

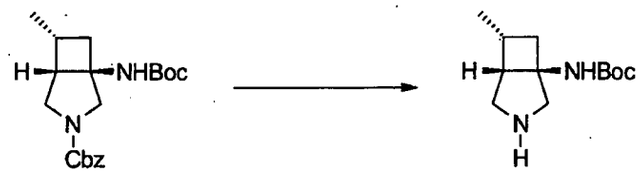
Con base en los resultados de la prueba de NOE, el isómero óptico C se identificó como éster bencílico de ácido (1R,5S,6R)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo[3.2.0]heptano-3-carboxílico y el isómero óptico D se identificó como éster bencílico de ácido (1S,5R,6R)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo[3.2.0]heptano-3-carboxílico.

749

EJEMPLO DE REFERENCIA 21

(1R,5S,6R)-1-(ter-butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0] heptano

[Fórmula 92]



Ester bencílico de ácido (1R,5S,6R)-1-ter-butoxicarbonilamino-6-metil-3-azabiciclo [3.2.0] heptano-3-carboxílico (180 mg, 0.59 mmoles) se disolvió en metanol (5 ml). Se añadió una pequeña cantidad de 10% de paladio-carbón (50% húmedo), y la mezcla se agitó en una atmósfera de hidrógeno durante una hora. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 114 mg (85%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.88 (1H, brs), 3.06 (1H, d, J=12.00 Hz), 2.96-2.89 (2H, m), 2.71-2.61 (3H, m), 2.39-2.33 (1H, m), 1.58 (1H, dd, J=12.80, 7.40 Hz), 1.45 (9H, s), 0.94 (3H, d, J=6.80 Hz).

EJEMPLO DE REFERENCIA 22

(1S,5R,6R)-1-(ter-butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0] heptano

[Fórmula 93]



Ester bencílico de ácido (1S,5R,6R)-1-ter-butoxicarbonilamino-6-

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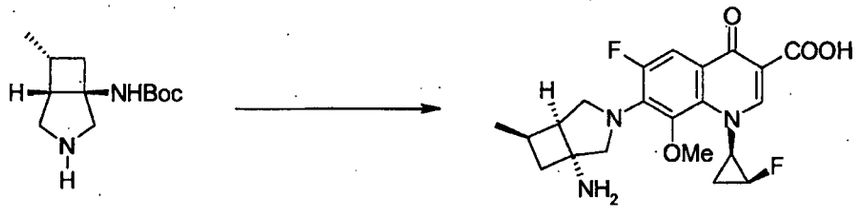
metil-3-azabiciclo [3.2.0] heptano-3-carboxílico (1.1 g, 3.1 mmoles) se disolvió en un solvente mixto de metanol (20 ml) y tetrahidrofurano (10 ml). Se añadió una pequeña cantidad de 10% de paladio-carbón (50% húmedo), y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 0.70 g (cuantitativo) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.80 (1H, brs), 3.09 (1H, d, J=11.20 Hz), 3.02 (2H, dd, J=11.20, 5.40 Hz), 2.82 (2H, d, J=11.20 Hz), 2.27-2.22 (2H, m), 1.77-1.69 (2H, m), 1.44 (9H, s), 1.17 (3H, d, J=6.60 Hz).

EJEMPLO 4

Acido 7-{(1R,5S,6R)-1-amino-6-metil-3-azabiciclo [3.2.0] hept-3-il}-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 94]



(1R,5S,6R)-1-(ter-Butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0]heptano (114 mg, 0.50 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (155 mg, 0.43 mmoles) se disolvieron en sulfóxido de dimetilo (2 ml). Se añadió trietilamina (0.084 ml) y la mezcla se agitó a 40°C durante 12 horas. Después de enfriar la solución de reacción con hielo, se añadió agua y el precipitado se recogió por filtración, se lavó con agua, y se secó. El precipitado se disolvió en

etanol (20 ml). Se añadieron agua (5 ml) y trietilamina (0.084 ml) y la mezcla se calentó a reflujo durante tres horas. La mezcla de reacción se disolvió en acetato de etilo y se lavó con una solución de ácido cítrico al 10%, agua, y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró, y el solvente se evaporó bajo presión reducida. Se añadió ácido clorhídrico concentrado (5 ml) al residuo y la mezcla se agitó a temperatura ambiente durante una hora. Después, la solución de reacción se lavó con cloroformo. La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo-metanol (9:1) ocho veces. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró y el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol y el material insoluble se removió por filtración. El solvente se evaporó bajo presión reducida y el polvo resultante se secó bajo presión reducida para dar 70 mg (39%) del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.50 (1H, s), 7.70 (1H, d, J=13.67 Hz), 5.02-4.84 (1H, m), 4.07-4.03 (1H, m), 3.74 (1H, d, J=10.25 Hz), 3.62 (3H, s), 3.60-3.56 (2H, m), 2.94 (1H, d, J=10.25 Hz), 2.63-2.55 (1H, m), 2.51-2.47 (1H, m), 2.24-2.18 (1H, m), 1.85 (1H, dd, J=12.57, 7.93 Hz), 1.69-1.48 (2H, m), 0.87 (3H, d, J=6.84 Hz).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.4H_2O \cdot 0.3EtOH$: C, 58.90; H, 5.86; F, 8.63; N, 9.54.

Encontrado: C, 58.84; H, 5.78; F, 8.66; N, 9.51.

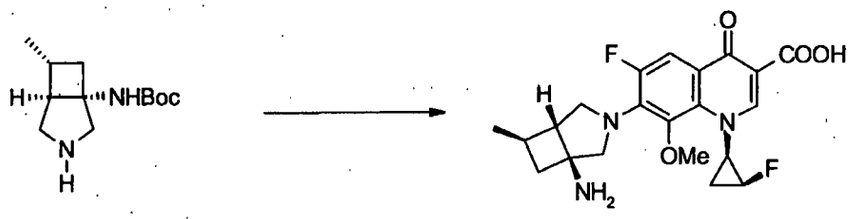
EM (ESI) m/z: 420 $(M+H)^+$.

752

EJEMPLO 5

Acido 7-{(1S,5R,6R)-1-amino-6-metil-3-azabiciclo [3.2.0]hept-3-il}-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 95]



(1S,5R,6R)-1-(ter-butoxicarbonilamino)-6-metil-3-azabiciclo [3.2.0]heptano (705 mg, 3.12 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (1.07 g, 2.96 mmoles) se disolvieron en sulfóxido de dimetilo (12 ml). Se añadió trietilamina (0.52 ml) y la mezcla se agitó a 40°C durante 12 horas. Después de enfriar la solución de reacción con hielo, se añadió agua, y el precipitado se recogió por filtración, se lavó con agua y se secó. El precipitado se disolvió en etanol (120 ml). Se añadieron agua (30 ml) y trietilamina (0.52 ml) y la mezcla se calentó a reflujo durante tres horas. La mezcla de reacción se disolvió en acetato de etilo y se lavó con una solución de ácido cítrico al 10%, agua, y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró y el solvente se evaporó bajo presión reducida. Se añadió ácido clorhídrico concentrado (25 ml) al residuo y la mezcla se agitó a temperatura ambiente durante una hora. Después, la solución de reacción se lavó con cloroformo. La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo-metanol (9:1) ocho

753

veces. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró y el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol, y el material insoluble se removió por filtración. El solvente se evaporó bajo presión reducida, y el polvo resultante se secó bajo presión reducida para dar 740 mg (57%) del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, d, J=1.71 Hz), 7.70 (1H, d, J=13.67 Hz), 5.07-4.88 (1H, m), 4.08-4.03 (1H, m), 3.73-3.63 (2H, m), 3.67 (3H, s), 3.55-3.51 (1H, m), 3.18 (1H, d, J=10.50 Hz), 2.40 (1H, dd, J=12.21, 8.79 Hz), 2.13 (1H, t, J=5.13 Hz), 1.95-1.89 (1H, m), 1.16 (3H, d, J=7.08 Hz), 1.66-1.57 (2H, m), 1.56-1.44 (1H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4$-HCl·1.3H_2O·0.6EtOH: C, 52.60; H, 6.00; Cl, 6.99; F, 7.50; N, 8.29.

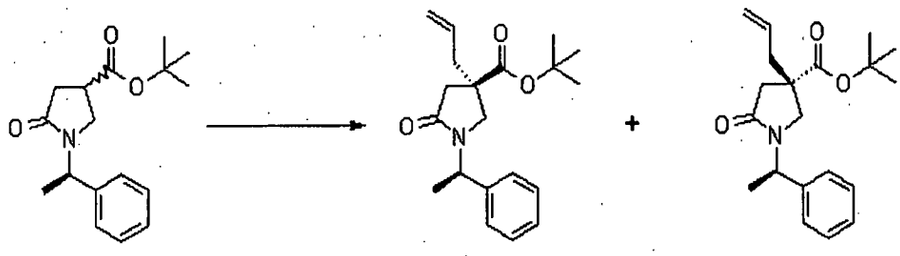
Encontrado: C, 52.35; H, 5.74; Cl, 6.84; F, 7.54; N, 8.01.

EM (ESI); m/z: 420 $(M+H)^+$.

EJEMPLO DE REFERENCIA 23

Ester ter-butílico de ácido (3R)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (isómero menos polar) éster ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (isómero más polar)

[Fórmula 96]



Solicitud de Patente Japonesa No. 2005-146386

menos polar

más polar

754

Ester ter-butílico de ácido 5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (30 g, 104 mmoles) y bromuro de alilo (62.71 g, 518 mmoles) se disolvieron en dimetilformamida (300 ml), y la atmósfera se reemplazó con argón. Hidruro de sodio (55% dispersión en aceite, 11.3 g, 259 mmoles) se añadió bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante cinco horas. Se añadió una solución de ácido tartárico al 10% seguido por extracción con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida. Después, el residuo se separó y se purificó por cromatografía sobre gel de sílice (hexano: acetato de etilo = 100:0 → 80:20 → 65:35) para dar 15.8 g (46%) de un aceite incoloro como una primera fracción (isómero menos polar) y 15.1 g (44%) de un aceite incoloro como una segunda fracción (isómero más polar). El isómero resultante más polar se dejó reposar a temperatura ambiente y se cristalizó.

La configuración absoluta en la posición 3 de cada isómero se determinó con base en cristalografía de rayos X del producto descrito en el ejemplo de referencia 24 después de convertir el isómero más polar al producto.

Isómero menos polar:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.52-5.42 (2H, m), 4.95 (1H, dd, J=10.30, 1.00 Hz), 4.78 (1H, dd, J=17.10, 1.20 Hz), 3.60 (1H, d, J=10.30 Hz), 2.86 (1H, d, J=17.10 Hz), 2.80 (1H, d, J=10.30 Hz), 2.35 (1H, d, J=17.10 Hz), 2.27 (1H, dd, J=13.70, 6.80 Hz), 2.16 (1H, dd, J=13.70, 7.80 Hz), 1.52 (3H, d, J=7.30 Hz), 1.44 (9H, s).

Isómero más polar:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.72-5.62 (1H, m), 5.49 (1H, q, J=7.20 Hz), 5.15 (1H, s), 5.13-5.10 (1H, m), 3.28 (1H, d, J=10.30

755

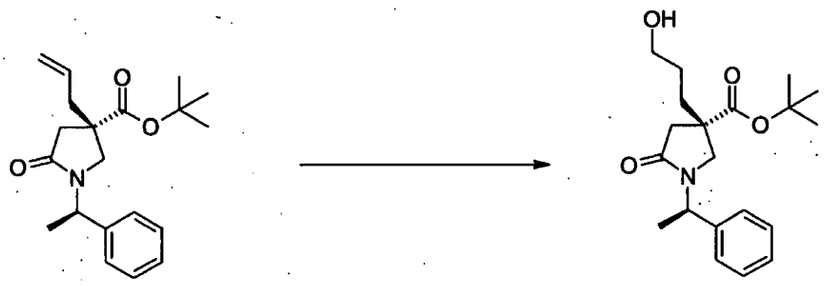
Hz), 3.16 (1H, d, J=10.30 Hz), 2.88 (1H, d, J=17.10 Hz), 2.48-2.35 (3H, m), 1.51 (3H, d, J=7.10 Hz), 1.35 (9H, s).

EJEMPLO DE REFERENCIA 24

Ester ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

(derivado del isómero más polar)

[Fórmula 97]



más polar

Ester ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (isómero más polar) (51.5 g, 0.156 moles) se disolvió en tetrahidrofurano (780 ml). Después, una solución 0.5 M de 9-BBN en tetrahidrofurano (345 ml, 0.173 moles) se añadió gota a gota desde un embudo de goteo en una corriente de nitrógeno bajo enfriamiento y agitando en un baño de hielo-sal a una temperatura interna de 0°C. Después de completarse la adición gota a gota, la mezcla se agitó a la misma temperatura durante 30 minutos y subsecuentemente a temperatura ambiente durante 1.5 horas. La mezcla se enfrió nuevamente en un baño de hielo-sal, y una solución 0.5 M de 9-BBN en tetrahidrofurano (156 ml, 78 mmoles) se añadió gota a gota desde un embudo de goteo a una temperatura interna de 2°C. Después de completarse la adición gota a gota, la mezcla se agitó a la misma temperatura durante 30

minutos y después a temperatura ambiente durante 1.5 horas. La mezcla se enfrió nuevamente en un baño de hielo-sal, y una solución 0.5 M de 9-BBN en tetrahidrofurano (120 ml, 60 mmoles) se añadió gota a gota desde un embudo de goteo a una temperatura interna de 2°C. Después de completarse la adición gota a gota, la mezcla se agitó a la misma temperatura durante 30 minutos y después a temperatura ambiente durante una hora. La mezcla se enfrió nuevamente en un baño de hielo-sal, y 780 ml de se añadió una solución de hidróxido de sodio 1N gota a gota a una temperatura interna de 0°C durante 15 minutos (temperatura interna: 2°C o menor). La mezcla se agitó durante 10 minutos, y después 78 ml de una solución de peróxido de hidrógeno al 30% se añadió gota a gota a una temperatura interna de 4°C o menor durante 30 minutos. Después de agitación vigorosa a la misma temperatura durante 30 minutos, se añadió 1.6 l de éter dietílico. Después de la adición de 1.6 l de una solución saturada de bicarbonato de sodio, las capas se separaron y la capa acuosa se extrajo con éter dietílico. Las capas orgánicas combinadas se lavaron con salmuera, una solución de ácido cítrico al 10%, una solución de tiosulfato de sodio al 10% y después salmuera, y se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice instantánea y se eluyó con un solvente mixto de metanol-cloroformo (1:50, v/v). Las fracciones que contenían la sustancia objetivo se combinaron y se concentraron y se secaron bajo presión reducida para dar 40.61 g (74.9%) del compuesto del título como un aceite incoloro. Adicionalmente, parte del compuesto del título se purificó por recristalización a partir de éter dietílico para proveer cristales como agujas que se usaron para cristalografía de rayos X. Como resultado, la configuración absoluta en la posición 3 de este producto se determinó como una configuración

(3S).

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.48 (1H, q, J=7.3 Hz), 3.62 (2H, t, J=6.2 Hz), 3.34 (1H, d, J=10.3 Hz), 3.14 (1H, d, J=10.3 Hz), 2.95 (1H, d, J=17.1 Hz), 2.33 (1H, d, J=16.8 Hz), 1.88-1.67 (3H, m), 1.51 (3H, d, J=7.1 Hz), 1.54-1.47 (1H, m), 1.33 (9H, s).

CUADRO 1

Condiciones de cristalografía de rayos X:

Tamaño del cristal	0.36 mm x 0.18 mm x 0.08 mm
Radiación	CuKα (1.54178 Å)
Corriente del tubo	80 mA
Voltaje del tubo	50 kV
Difractómetro	AFC7R
Temperatura	25°C
Fórmula	C20H29NO4
Peso de la fórmula	347.45

Sistema de cristal ortorómbico

Grupo de espacio	$P2_12_12$	
Valor de Z	4	
Parámetros de celda	a = 13.2806 (14) Å	b = 26.6894(16) Å
	c = 5.8585 (11) Å	
α = 90.0000°	β = 90.0000°	γ = 90.0000°

d_{calc} 1.11 g/cm^3

No. de reflexión medida 1828 (único)

μ 6.19 cm^{-1}

Determinación de fase Método directo (software; *SIR92*)

Fase de refinamiento Mínimos cuadrados de matriz completa

R1 5.3% $= \Sigma \; || Fo |-| Fc|| / \Sigma |Fo|$ para datos de $I > 2.0 \; \sigma$

R 7.0% $= \Sigma \; (Fo^2 - Fc^2) / \Sigma \; Fo^2$

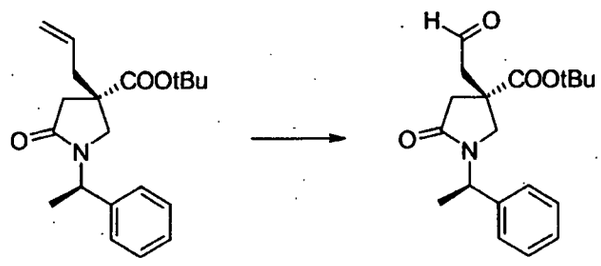
Rw 14.0% $= [\Sigma w \; (Fo^2 - Fc^2)^2 / \Sigma w (Fo^2)^2]^{1/2}$

Los datos se recopilaron bajo las condiciones de medición mostradas en el cuadro anterior, y después la fase inicial se determinó por el método directo, y la fase se refinó por el método de mínimos cuadrados de matriz completa. Para refinamiento, un factor de temperatura anisotrópica se aplicó a un átomo que no era de hidrógeno y la posición de un átomo de hidrógeno se determinó calculando para fijar las coordenadas. Como resultado del análisis, la configuración relativa de este compuesto es como se muestra en el diagrama ORTEP de la figura 1. La configuración absoluta del carbono asimétrico b se determinó a partir del carbono asimétrico que tiene una configuración absoluta conocida. Los resultados se muestran en la figura 2.

EJEMPLO DE REFERENCIA 25

Ester ter-butílico de ácido (3S)-5-oxo-3-(2-oxoetil)-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 98]



759

Una solución de éster ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (3.29 g, 10.0 mmoles) en metanol (100 ml) se hizo burbujear con ozono a -74°C. Cuando la solución de reacción se volvió azul, el burbujeo de ozono se detuvo y después la solución se hizo burbujear con nitrógeno a la misma temperatura. Borohidruro de sodio (568 mg) se añadió a la misma temperatura y la mezcla se agitó durante 1.5 horas mientras se calentaba a -40°C. La solución de reacción se vació en una solución de ácido cítrico al 10% (50 ml), y después la mezcla se agitó suficientemente. El componente de metanol se evaporó, y después la capa acuosa se extrajo con acetato de etilo (200 ml, 100 ml). La capa orgánica se lavó con salmuera (50 ml x 2), y después se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida en una suspensión. Se añadió hexano al residuo resultante, y la suspensión se agitó. El sólido se recogió por filtración y se secó para dar 1.70 g del compuesto del título como un sólido blanco. El filtrado se concentró, se añadió hexano al residuo resultante, y la suspensión se agitó. El sólido se recogió por filtración para dar 0.66 g del compuesto del título como un sólido blanco. Se repitió la misma operación para dar 0.35 g del compuesto del título como un sólido blanco (rendimiento total: 2.71 g, 82%).

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 9.71 (1H, s), 7.35-7.24 (5H, m), 5.50 (1H, q, J=7.3 Hz), 3.41 (1H, d, J=10.5 Hz), 3.20 (1H, d, J=10.5 Hz), 2.98 (1H, d, J=17.1 Hz), 2.92 (1H, d, J=17.8 Hz), 2.87 (1H, d, J=17.8 Hz), 2.37 (1H, d, J=17.1 Hz), 1.51 (3H, d, J=7.3 Hz), 1.31 (9H, s).

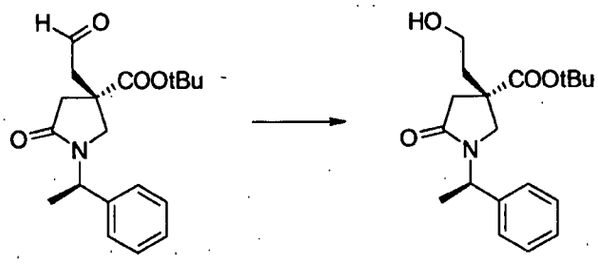
EM (ESI) m/z: 332 $(M+H)^+$.

760

EJEMPLO DE REFERENCIA 26

Ester ter-butílico de ácido (3S)-3-(2-hidroxietil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 99]



Borohidruro de sodio (465 mg) se añadió a una solución de éster ter-butílico de ácido (3S)-5-oxo-3-(2-oxoetil)-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (2.71 g, 8.19 mmoles) en metanol a -40°C. Después de calentar a temperatura ambiente, se añadió una solución de ácido cítrico al 10% a la solución de reacción, y la mezcla se agitó. La solución de reacción se vació en una mezcla de acetato de etilo (50 ml) y una solución de ácido cítrico al 10% (10 ml), seguido por extracción con acetato de etilo (100 ml). La capa acuosa se extrajo con acetato de etilo (100 ml), y después las capas orgánicas se combinaron y se lavaron con salmuera (50 ml x 2). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 2:1 → 1:1 → 0:1 → acetato de etilo-metanol = 10:1) para dar 2.20 g (81%) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.24 (5H, m), 5.48 (1H, q, J=7.1 Hz), 3.73-3.64 (2H, m), 3.38 (1H, d, J=10.2 Hz), 3.23 (1H, d, J=10.2 Hz), 2.97 (1H, d, J=17.0 Hz), 2.41 (1H, d, J=17.0 Hz), 2.05 (1H, dt, J=14.0, 6.8 Hz), 1.91

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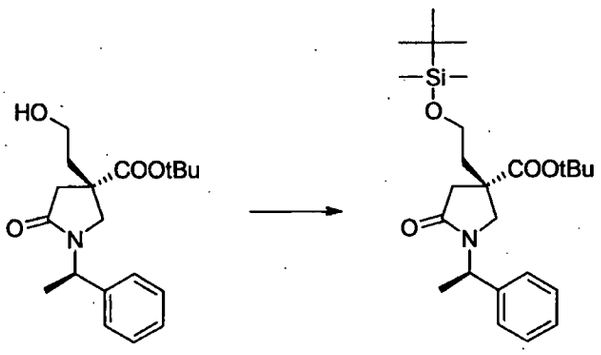
(1H, dt, J=14.0, 6.6 Hz), 1.51 (3H, d, J=7.1 Hz), 1.32 (9H, s).

EM (ESI) m/z: 334 $(M+H)^+$.

EJEMPLO DE REFERENCIA 27

Ester ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi) etil]-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 100]



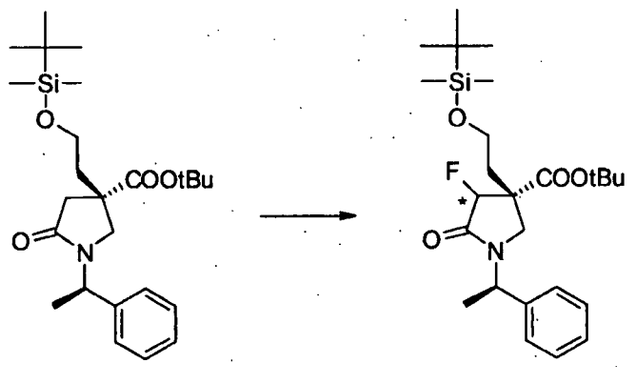
Trietilamina (3.0 ml, 21.8 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S)-3-(2-hidroxietil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (2.42 g, 7.25 mmoles) en diclorometano (70 ml), y la mezcla se enfrió a 0°C. Trifluorometansulfonato de ter-butildimetilsililo (2.50 ml, 10.9 mmoles) se añadió gota a gota, y la mezcla se agitó a la misma temperatura durante 1.5 horas. Después de la adición de una pieza de hielo y agitación, la solución de reacción se vació en una mezcla de acetato de etilo (50 ml) y bicarbonato de sodio saturado (50 ml), seguido por extracción con acetato de etilo (200 ml, 100 ml). Las capas orgánicas se combinaron y se lavaron con salmuera (50 ml). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía sobre gel de sílice (hexano:acetato de etilo = 4:1 → 2:1) para dar 2.84 g (88%) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 5.45 (1H, q, J=7.1 Hz), 3.62-3.57 (2H, m), 3.38 (1H, d, J=10.3 Hz), 3.26 (1H, d, J=10.3 Hz), 2.93 (1H, d, J=17.0 Hz), 2.42 (1H, d, J=17.0 Hz), 1.98 (1H, dt, J=13.7, 6.8 Hz), 1.88 (1H, dt, J=13.7, 6.7 Hz), 1.50 (3H, d, J=7.1 Hz), 1.31 (9H, s)

EJEMPLO DE REFERENCIA 28

Ester ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi) etil]-4-fluoro-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 101]



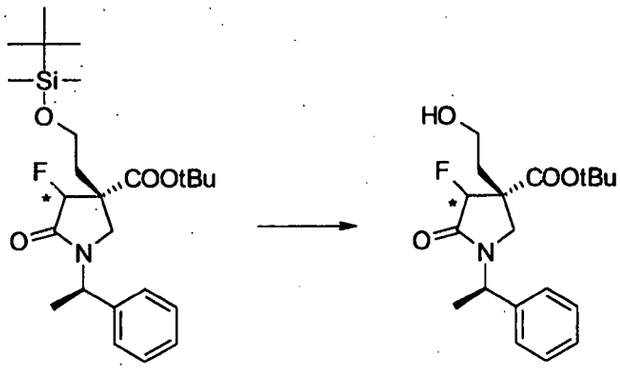
Una solución 1.8 M de diisopropilamida de litio en tetrahidrofurano (4.10 ml) se añadió gota a gota a una solución de éster ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi)etil]-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico en tetrahidrofurano en una atmósfera de nitrógeno a -73°C durante 10 minutos. Después de agitación a la misma temperatura durante 15 minutos, una solución de N-fluorobencensulfonimida (2.63 g, 8.33 mmoles) en tetrahidrofurano (18 ml) se añadió gota a gota durante 15 minutos. Después de agitación a la misma temperatura durante 30 minutos, una solución saturada de cloruro de amonio (20 ml) se añadió, y la mezcla se calentó a 0°C. La solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y 1 mol/ml de ácido clorhídrico (50 ml), seguido por extracción con acetato de etilo (200 ml). La

capa orgánica se lavó secuencialmente con una solución saturada de bicarbonato de sodio (50 ml) y salmuera (50 ml x 2) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. Diclorometano se añadió al residuo resultante para preparar una suspensión, y el sólido se removió por filtración. El filtrado se concentró, y el sólido resultante se removió por filtración. El filtrado además se concentró para dar 3.44 g del compuesto del título crudo como un aceite amarillo pálido. El crudo resultante se usó para la siguiente reacción sin purificación adicional.

EJEMPLO DE REFERENCIA 29

Ester ter-butílico de ácido (3S)-4-fluoro-3-(2-hidroxietil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 102]



Ácido acético (0.66 ml, 11.54 mmoles) y una solución 1 M de fluoruro de tetrabutilamonio en tetrahidrofurano (8.3 ml, 8.3 mmoles) se añadieron secuencialmente a una solución del éster ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi)etil]-4-fluoro-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (3.44 g) en tetrahidrofurano en una atmósfera de nitrógeno a 0°C. Después de agitación a temperatura ambiente durante 20 horas, la solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y una solución

764

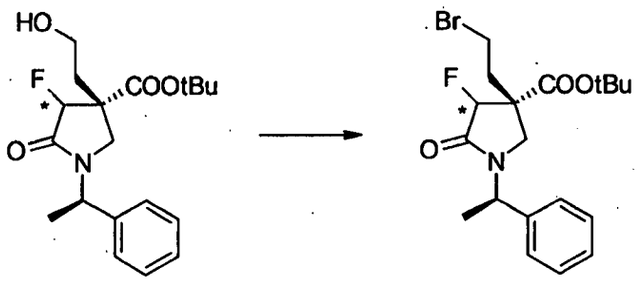
saturada de bicarbonato de sodio (50 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera (50 ml x 2), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 1:1) para dar 2.06 g (91%, dos pasos) del compuesto del título como cristales incoloros.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.48 (1H, q, J=7.1 Hz), 5.21 (1H, d, J=51.7 Hz), 3.78-3.69 (2H, m), 3.38 (1H, dd, J=1.1, 10.5 Hz), 3.30 (1H, d, J=10.5 Hz), 2.10 (1H, m), 2.01 (1H, m), 1.56 (3H, d, J=7.1 Hz), 1.32 (9H, s).

EJEMPLO DE REFERENCIA 30

Ester ter-butílico de ácido (3S)-3-(2-bromoetil)-4-fluoro-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 103]



Tetrabromuro de carbono (1.88 g, 5.68 mmoles) y trifenilfosfina (1.49 g, 5.68 mmoles) se añadieron secuencialmente a una solución de éster ter-butílico de ácido (3S)-4-fluoro-3-(2-hidroxietil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (1.66 g, 4.74 mmoles) en diclorometano (20 ml) en una atmósfera de nitrógeno a 0°C. Después de calentar a temperatura ambiente, la solución de reacción se agitó durante una hora y se concentró a

762

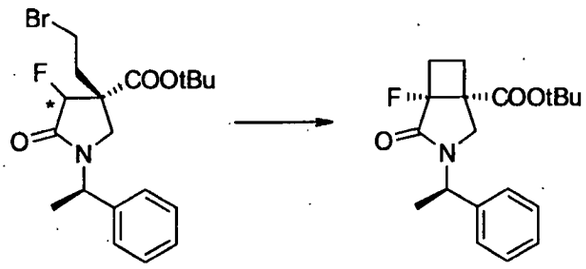
aproximadamente 5 ml. El residuo se purificó por cromatografía en columna sobre gel de sílice (diclorometano → hexano: acetato de etilo = 2:1) para dar 2.17 g (91%) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.48 (1H, q, J=7.1 Hz), 5.22 (1H, d, J=51.5 Hz), 3.39 (1H, ddd, J=5.5, 10.7, 11.0 Hz), 3.30-3.23 (3H, m), 2.42 (1H, dddd, J=1.2, 5.5, 11.0, 14.2 Hz), 2.32 (1H, dddd, J=2.4, 5.5, 10.7, 14.2 Hz), 1.57 (3H, d, J=7.1 Hz), 1.33 (9H, s).

EJEMPLO DE REFERENCIA 31

Ester ter-butílico de ácido (1S, 5R)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 104]



Una solución 1.0 M de hexametildisilazida de litio en tetrahidrofurano (5.02 ml) se añadió gota a gota a una solución de éster ter-butílico de ácido (3S)-3-(2-bromoetil)-4-fluoro-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (2.04 g, 4.92 mmoles) en tetrahidrofurano (40 ml) en una atmósfera de nitrógeno a -72°C durante 10 minutos. La mezcla se agitó a la misma temperatura durante 15 minutos y después a 0°C durante 30 minutos. La reacción se extinguió con una solución de ácido cítrico al 10% (2 ml) y después se vació en una mezcla de acetato de etilo (100 ml) y una solución de ácido cítrico al 10% (20 ml). Después de extracción con acetato de etilo (150 ml), la

f 66

capa orgánica-se lavó con salmuera (20 ml x 2), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 2:1) para dar 1.41 g (86%) del compuesto del título como un sólido blanco.

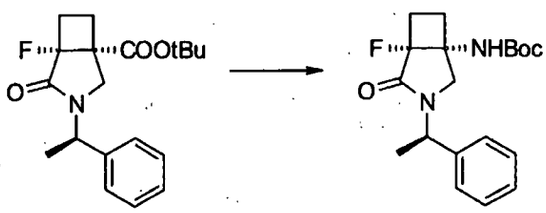
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.57 (1H, q, J=7.3 Hz), 3.53 (1H, d, J=10.7 Hz), 3.09 (1H, dd, J=4.9, 10.7 Hz), 2.76-2.51 (3H, m), 1.57 (3H, d, J=7.3 Hz), 1.45 (9H, s), 1.42 (1H, m).

EM (ESI) m/z: 334 $(M+H)^+$.

EJEMPLO DE REFERENCIA 32

(1R, 5R)-1-(ter-Butoxicarbonilamino)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 105]



Se añadió ácido trifluoroacético (10 ml) a una solución de éster ter-butílico de ácido (1S,5R)-1-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0]heptano-1-carboxílico (1.06 g, 3.18 mmoles) en diclorometano (10 ml). La mezcla se agitó durante cuatro horas, y después el solvente se concentró bajo presión reducida. Se añadió tolueno (40 ml) al residuo y el ácido trifluoroacético se removió por evaporación. El residuo se secó bajo presión reducida para dar ácido carboxílico crudo como un sólido amarillo pálido.

Trietilamina (0.89 ml) y difenilfosforil azida (0.75 ml) se añadieron

secuencialmente a una solución del ácido carboxílico crudo obtenido antes en tolueno (10 ml) y alcohol ter-butílico (10 ml). La mezcla se agitó a temperatura ambiente durante 20 minutos, a 40°C durante una hora, y adicionalmente a 90°C durante una hora. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 4:1 → 3:2) para dar 811 mg (73%) del compuesto del título como un compuesto amorfo blanco.

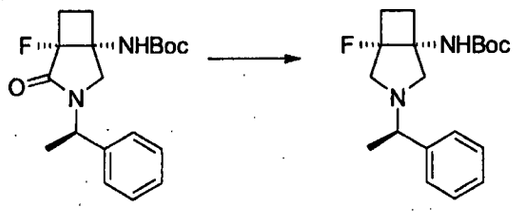
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.59 (1H, q, J=7.3 Hz), 5.36 (1H, br), 3.68 (1H, br), 2.96 (1H, brd, J=10.0 Hz), 2.66-2.45 (2H, m), 2.39 (1H, br), 1.72 (1H, dt, J=12.9, 9.0 Hz), 1.56 (3H, d, J=7.3 Hz), 1.40 (9H, s).

EM (ESI) m/z: 349 $(M+H)^+$.

EJEMPLO DE REFERENCIA 33

(1R,5R)-1-(ter-Butoxicarbonilamino)-5-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 106]



Una solución 1.16 M de un complejo de borano-tetrahidrofurano en tetrahidrofurano (6.0 ml) se añadió gota a gota a una solución de (1R,5R)-1-(ter-butoxicarbonilamino)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0]heptano (811 mg, 2.33 mmoles) en tetrahidrofurano (6.0 ml) a 0°C durante cinco minutos. La mezcla se calentó a temperatura ambiente, se agitó durante cinco horas, y después se enfrió a -10°C. Una mezcla de etanol (9.0 ml)-agua

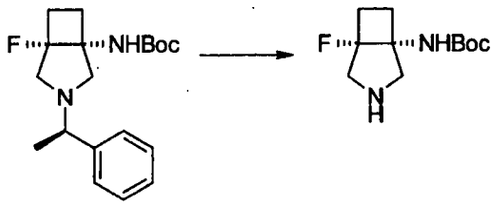
(1.0 ml) se añadió cuidadosamente gota a gota. Después de la adición de trietilamina (3.0 ml) gota a gota, la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró, y el sólido blanco precipitado se removió por filtración a través de Celite. El filtrado se concentró, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 9:1 → 4:1) para dar 530 mg (68%) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.18 (5H, m), 5.19 (1H, br), 3.37 (1H, q, J=6.8 Hz), 3.27 (1H, dd, J=1.7, 9.0 Hz), 3.13 (1H, brd, J=8.3 Hz), 2.49-2.38 (2H, m), 2.23 (1H, m), 2.13-2.08 (2H, m), 2.00 (1H, m), 1.39 (9H, brs), 1.36 (3H, d, J=6.8 Hz).

EJEMPLO DE REFERENCIA 34

(1R, 5R)-1-(ter-Butoxicarbonilamino)-5-fluoro-3-azabiciclo [3.2.0] heptano

[Fórmula 107]



Un catalizador de 10% de paladio-carbón (50% húmedo, 50 mg) se añadió a una solución de (1R, 5R)-1-(ter-butoxicarbonilamino)-5-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano (530 mg, 1.58 mmoles) en etanol, y la mezcla se agitó en una atmósfera de hidrógeno a 50°C durante cinco horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 321 mg de amina cruda como un sólido blanco.

^{1}H-RMN (400 MHz, CD_3OD) δ: 3.07-3.00 (2H, m), 2.87-2.80 (2H,

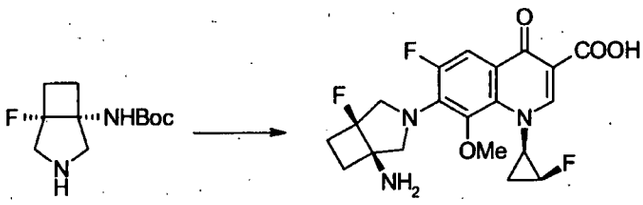
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m), 2.35 (1H, m), 2.03-1.95 (2H, m), 1.67 (1H, dt, J=12.0, 9.0 Hz), 1.34 (9H, s), 1.00 (1H, dd, J=2.1, 6.2 Hz).

EJEMPLO 6

Acido 7-[(1R, 5S)-1-amino-5-fluoro-3-azabiciclo[3.2.0]hept-3-il]-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 108]



Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (577 mg, 1.60 mmoles) y trietilamina (0.699 ml, 5.02 mmoles) se añadieron secuencialmente a una solución de (1R,5R)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.2.0] heptano (crudo; 321 mg) en sulfóxido de dimetilo (5.0 ml). La mezcla se calentó con agitación a 40°C durante 24 horas. Se añadió trietilamina (0.35 ml) y la mezcla se agitó adicionalmente a la misma temperatura durante 17 horas. Después, se añadieron ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (58 mg) y trietilamina (0.125 ml). Además, se añadieron ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (480 mg, 240 mg) y trietilamina (0.389 ml, 0.195 ml) después de 6 horas y 24 horas, respectivamente. Después de la adición del reactivo final, la mezcla se agitó durante 5.5 horas. Después, una mezcla de etanol:agua = 4:1 (30 ml) y

trietilamina (4.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante dos horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (150 ml) y secuencialmente se lavó con una solución de ácido cítrico al 10% (30 ml), agua (30 ml x 2), y salmuera (30 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante (890 mg) se disolvió en ácido clorhídrico concentrado (4.0 ml), y la solución se agitó a temperatura ambiente durante 10 minutos. La solución de reacción se diluyó con ácido clorhídrico 6 M y se lavó con cloroformo (5 ml x 15). La capa acuosa se ajustó a pH 13.2 con una solución saturada de hidróxido de sodio bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml x 3). La capa orgánica se secó sobre sulfato de sodio anhidro, y el agente de secado se removió por filtración. Después, el filtrado se concentró bajo presión reducida. El residuo se secó suficientemente bajo vacío y después se disolvió en un solvente mixto de cloroformo:metanol = 10:1 y se filtró a través de un filtro de membrana. El filtrado se concentró bajo presión reducida para dar un sólido amarillo-café. El sólido resultante se purificó por recristalización a partir de etanol-amoniaco acuoso para dar 193 mg (33%) del compuesto del título como cristales amarillo pálidos como agujas. p.f.: 235°C (dec.).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, d, J=1.2 Hz), 7.73 (1H, d, J=13.4 Hz), 4.96 (1H, m), 4.13 (1H, m), 4.07 (1H, m), 3.72 (3H, s), 3.60 (1H, brd, J=10.4 Hz), 3.52 (1H, m), 3.42 (1H, brd, J=10.4 Hz), 2.51 (1H, m), 2.32 (1H, m), 1.99-1.92 (2H, m), 1.70-1.52 (2H, m).

Análisis calculado para $C_{20}H_{20}F_3N_3O_4$: C, 56.74; H, 4.76; F, 13.46; N, 9.92.

Encontrado: C, 56.68; H, 4.71; F, 13.15; N, 9.86.

HRMS (FAB); m/z calculado para $C_{20}H_{21}F_3N_3O_4$ $(M+H)^+$: 424.1484.

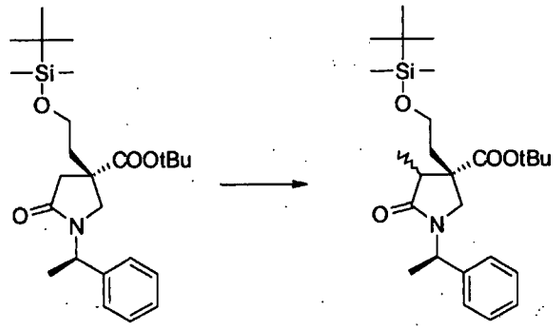
Encontrado: 424.1475.

IR (ATR) ν: 2938, 2842, 1720, 1616, 1544, 1511, 1450, 1436, 1365, 1324, 1276, 1222, 1180, 1159, 1135, 1052, 1010, 931 cm^{-1}.

EJEMPLO DE REFERENCIA 35

Ester ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi) etil]-4-metil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 109]



Una solución 1.8 M de diisopropilamida de litio en tetrahidrofurano (3.10 ml) se añadió gota a gota a una solución de éster ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi)etil]-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (2.24 g, 5.00 mmoles) en tetrahidrofurano (20 ml) en una atmósfera de nitrógeno a-72°C durante cinco minutos. Después de agitación a la misma temperatura durante 10 minutos se añadió yoduro de metilo (0.34 ml, 5.50 mmoles). La mezcla se agitó a la misma temperatura durante 15 minutos y después se calentó a -10°C durante 10 minutos. Posteriormente, se añadió solución acuosa de ácido cítrico al 10% (5 ml). La solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y solución de ácido cítrico al 10% (50

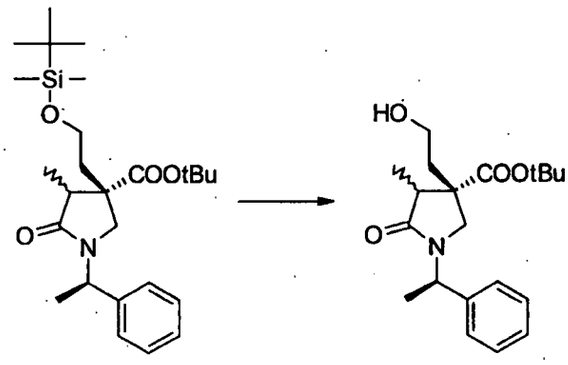
ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera (50 ml x 2), se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante café oscuro se usó para la siguiente reacción sin purificación adicional.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.46 (0.5H, q, J=7.1 Hz), 5.45 (0.5H, q, J=7.1 Hz), 3.73-3.54 (2H, m), 3.37 (0.5H, d, J=10.5 Hz), 3.36-3.31 (1H, m), 3.28 (0.5H, d, J=10.2 Hz), 2.75 (0.5H, q, J=7.3 Hz), 2.40 (0.5H, q, J=7.3 Hz), 2.03 (0.5H, m), 1.92 (0.5H, ddd, J=5.4, 7.2, 13.8 Hz), 1.83 (0.5H, m), 1.71 (0.5H, m), 1.51 (1.5H, d, J=7.1 Hz), 1.50 (1.5H, d, J=7.1 Hz), 1.35 (4.5H, s), 1.34 (4.5H, s), 1.21 (1.5H, d, J=7.3 Hz), 1.12 (1.5H, d, J=7.3 Hz), 0.88 (2x4.5H, s), 0.03 (2x1.5H, s), 0.02 (1.5H, s), 0.01 (1.5H, s).

EJEMPLO DE REFERENCIA 36

Ester ter-butílico de ácido (3S)-3-(2-hidroxietil)-4-metil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 110]



El éster ter-butílico de ácido (3S)-3-[2-(ter-butildimetilsililoxi)etil]-4-metil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico crudo antes mencionado se disolvió en tetrahidrofurano (10 ml). Después, ácido acético (0.572 ml, 10.0 mmoles) y una solución 1 M de fluoruro de tetrabutilamonio en tetrahidrofurano

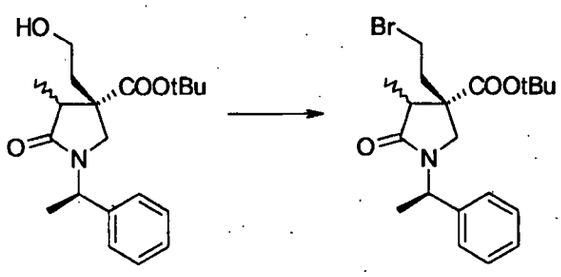
(10.0 ml, 10.0 mmoles) se añadieron secuencialmente en una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 12 horas, la solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y salmuera (50 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera (50 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 1:1 → 1:2) para dar 1.56 g (90%, dos pasos) del compuesto del título de mezcla diaestereomérica como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.25 (5H, m), 5.46 (0.5H, q, J=7.1 Hz), 5.45 (0.5H, q, J=7.1 Hz), 3.73-3.62 (2H, m), 3.35 (0.5H, d, J=10.5 Hz), 3.33 (0.5H, d, J=10.5 Hz), 3.26 (0.5H, d, J=10.5 Hz), 3.25 (0.5H, d, J=10.5 Hz), 2.78 (0.5H, q, J=7.3 Hz), 2.42 (0.5H, q, J=7.3 Hz), 2.13 (0.5H, dt, J=14.2, 6.6 Hz), 2.00 (0.5H, dt, J=14.2, 6.8 Hz), 1.84 (0.5H, dt, J=14.2, 6.4 Hz), 1.71 (0.5H, dt, J=14.2, 6.4 Hz), 1.52 (1.5H, d, J=7.1 Hz), 1.50 (1.5H, d, J=7.1 Hz), 1.37 (4.5H, s), 1.35 (4.5H, s), 1.22 (1.5H, d, J=7.3 Hz), 1.14 (1.5H, d, J=7.3 Hz).

EJEMPLO DE REFERENCIA 37

Ester ter-butílico de ácido (3S)-3-(2-bromoetil)-4-metil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 111]



Tetrabromuro de carbono (1.64 g, 4.95 mmoles) y trifenilfosfina (1.30 g, 4.95 mmoles) se añadieron secuencialmente a una solución de éster ter-butílico de ácido (3S)-3-(2-hidroxietil)-4-metil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (1.56 g, 4.50 mmoles) en diclorometano (20 ml) en una atmósfera de nitrógeno a 0°C. Después de calentar a temperatura ambiente, la solución de reacción se agitó durante 10 minutos y se concentró a aproximadamente 5 ml. El residuo se purificó por cromatografía en columna sobre gel de sílice (diclorometano → hexano : acetato de etilo = 4:1 → 2:1 → 1.5:1) para dar 1.30 g (70%) del compuesto del título de mezcla diaestereomérica como un sólido blanco.

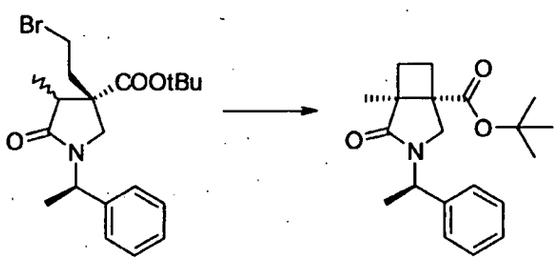
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.47 (0.5H, q, J=7.1 Hz), 5.46 (0.5H, q, J=7.1 Hz), 3.35-3.19 (3H, m), 3.14 (0.5H, d, J=10.5 Hz), 3.13 (0.5H, d, J=10.5 Hz), 2.80 (0.5H, q, J=7.4 Hz), 2.48-2.39 (1H, m), 2.30 (0.5H, ddd, J=6.2, 10.4, 13.9 Hz), 2.19-2.02 (1H, m), 1.54 (1.5H, d, J=7.1 Hz), 1.52 (1.5H, d, J=7.1 Hz), 1.37 (4.5H, s), 1.36 (4.5H, s), 1.22 (1.5H, d, J=7.4 Hz), 1.14 (1.5H, d, J=7.4 Hz).

EM (ESI) m/z: 410 $(M+H)^+$.

EJEMPLO DE REFERENCIA 38

Ester ter-butílico de ácido (1S,5S)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 112]



775

Una solución 1.0 M de hexametildisilazida de litio en tetrahidrofurano (3.8 ml, 3.80 mmoles) se añadió gota a gota a una solución de éster ter-butílico de ácido (3S)-3-(2-bromoetil)-4-metil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (1.30 g, 3.17 mmoles) en tetrahidrofurano (20 ml) en una atmósfera de nitrógeno a-72°C durante siete minutos. La mezcla se agitó a la misma temperatura durante 30 minutos. Después de calentamiento a -10°C y agitación durante 1.5 horas, una solución 1.0 M de hexametildisilazida de litio en tetrahidrofurano (4.0 ml, 4.0 mmoles) se añadió durante dos minutos, y la mezcla se agitó a 0°C durante 20 horas. Una solución de ácido cítrico al 10% (20 ml) se añadió a la misma temperatura. La solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y una solución de ácido cítrico al 10% (10 ml). Después de extracción con acetato de etilo (150 ml), la capa orgánica se lavó con salmuera (30 ml), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 2:1 → 1:1) para dar 0.845 g (81%) del compuesto del título como un sólido blanco.

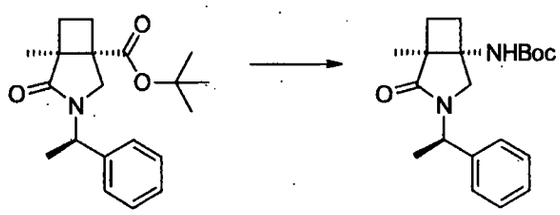
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.56 (1H, q, J=7.1 Hz), 3.42 (1H, d, J=10.2 Hz), 3.13 (1H, d, J=10.2 Hz), 2.65 (1H, ddd, J=4.7, 10.3, 11.9 Hz), 2.25 (1H, ddd, J=4.7, 9.5, 11.9 Hz), 2.09 (1H, m), 1.86 (1H, dt, J=11.9, 9.5 Hz), 1.57 (3H, d, J=7.1 Hz), 0.71 (9H, s), 1.25 (3H, s).

EM (ESI) m/z: 330 $(M+H)^+$.

EJEMPLO DE REFERENCIA 39

(1S, 5S)-1-(ter-Butoxicarbonilamino)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 113]



Se añadió ácido trifluoroacético (5 ml) a una solución de éster ter-butílico de ácido (1S,5S)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico (0.845 g, 2.56 mmoles) en diclorometano (10 ml). La mezcla se agitó durante 15 horas, y después la solución de reacción se concentró bajo presión reducida. Se añadió tolueno (3 x 40 ml) al residuo, y el ácido trifluoroacético se removió por evaporación. El residuo se secó bajo presión reducida para dar ácido carboxílico crudo como un sólido blanco.

Trietilamina (0.786 ml) y difenilfosforil azida (0.608 ml) se añadieron secuencialmente a una solución del ácido carboxílico crudo obtenido antes en tolueno (10 ml) y alcohol ter-butílico (10 ml). La mezcla se agitó a temperatura ambiente durante una hora y a 80°C durante 10 horas. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 7:3 → 3:2) para dar 548 mg (62%, dos pasos) del compuesto del título como un aceite viscoso incoloro.

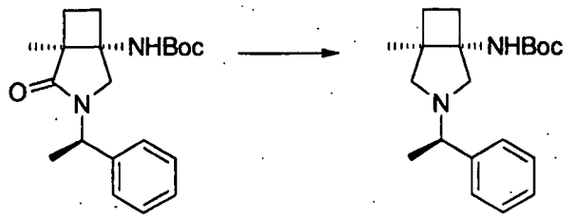
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.55 (1H, q, J=7.1 Hz), 4.81 (1H, br), 3.60 (1H, br), 3.02 (1H, d, J=11.3 Hz), 2.30-2.10 (3H, m), 2.02 (1H, m), 1.56 (3H, d, J=7.1 Hz), 1.38 (9H, s), 1.27 (3H, s).

EM (ESI) m/z: 345 $(M+H)^+$.

EJEMPLO DE REFERENCIA 40

(1S,5S)-1-(tert-Butoxicarbonilamino)-5-metil-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0]heptano

[Fórmula 114]



Una solución 1.09 M de un complejo de borano/tetrahidrofurano en tetrahidrofurano (3.6 ml, 3.98 mmoles) se añadió gota a gota a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0]heptano (548 mg, 1.59 mmoles) en tetrahidrofurano (10 ml) a 0°C durante cinco minutos. Después de calentar a temperatura ambiente y agitando durante tres horas, una solución 1.09 M de un complejo de borano/tetrahidrofurano en tetrahidrofurano (3.6 ml, 3.98 mmoles) se añadió a la misma temperatura. La mezcla se agitó a temperatura ambiente durante 15 horas y después frió a 0°C. Una mezcla de etanol (9.0 ml)-agua (1.0 ml) se añadió cuidadosamente gota a gota. Después de la adición de trietilamina (3.0 ml) gota a gota, la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró, y el sólido blanco precipitado se removió por filtración a través de Celite. El filtrado se concentró, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 10:1 → 5:1) para dar 184 mg (35%) del compuesto del título como un aceite incoloro.

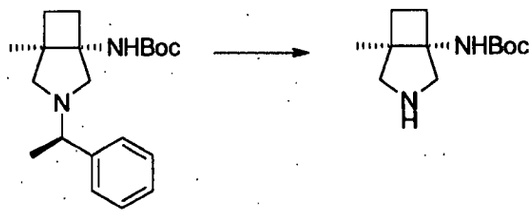
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.17 (5H, m), 4.58 (1H, br), 3.28

(1H, q, J=6.6 Hz), 2.95 (1H, d, J=8.5 Hz), 2.91 (1H, brd, J=9.0 Hz), 2.14-2.05 (4H, m), 1.68 (1H, m), 1.38 (9H, brs), 1.34 (3H, d, J=6.6 Hz), 1.14 (3H, s).

EJEMPLO DE REFERENCIA 41

(1S, 5S)-1-(ter-Butoxicarbonilamino)-5-metil-3-azabiciclo [3.2.0] heptano

[Fórmula 115]



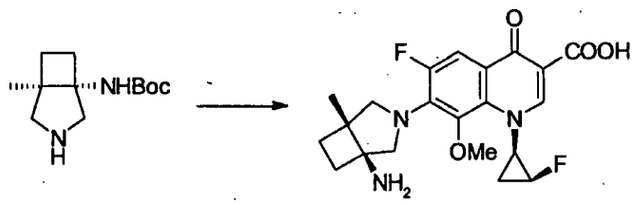
Un catalizador de 10% de paladio-carbón (50% húmedo, 200 mg) se añadió a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-metil-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0]heptano (184 mg, 0.057 mmoles) en etanol, y la mezcla se agitó en una atmósfera de hidrógeno a 40°C durante cinco horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar amina cruda como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.69 (1H, br), 3.27 (1H, d, J=11.5 Hz), 2.92 (1H, br), 2.82 (1H, d, J=11.2 Hz), 2.62 (1H, brd, J=11.2 Hz), 2.13 (1H, brm), 1.98 (1H, ddd, J=5.6, 9.8, 12.7 Hz), 1.71 (1H, m), 1.59 (1H, m), 1.44 (9H, s), 1.16 (3H, s).

EJEMPLO 7

Acido 7-[(1R,5S)-1-amino-5-metil-3-azabiciclo[3.2.0]hept-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 116]



Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (231 mg, 0.668 mmoles) y trietilamina (0.279 ml, 2.01 mmoles) se añadieron secuencialmente a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-metil-3-azabiciclo[3.2.0] heptano crudo antes mencionada en sulfóxido de dimetilo (2.0 ml). La mezcla se calentó con agitación a 40°C durante cinco horas. Después, una mezcla de etanol :agua = 4:1 (7.5 ml) y trietilamina (1.0 ml) se añadió a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (100 ml) y secuencialmente se lavó con una solución de ácido cítrico al 10% (20 ml), agua (20 ml x 2), y salmuera (20 ml). La fase orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por CLAR preparativa de fase inversa (sistema de solución de ácido fórmico al 0.1%-acetonitrilo) para dar un sólido amarillo pálido. El sólido amarillo pálido resultante se disolvió en ácido clorhídrico concentrado (1.0 ml), y después la solución se agitó a temperatura ambiente durante 10 minutos. La solución de reacción se diluyó con ácido clorhídrico 6 M (8 ml) y se lavó con cloroformo (5 ml). La capa acuosa se ajustó a pH 12.4 con una solución saturada de hidróxido de sodio bajo enfriamiento con hielo y después se ajustó a pH 7.3 con ácido clorhídrico, y después se diluyó con agua (10 ml), seguido por extracción con cloroformo (50 ml x 3). La

capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se secó suficientemente bajo vacío y después se disolvió en un solvente mixto de cloroformo:metanol = 10:1 y se filtró a través de un filtro de membrana. El filtrado se concentró bajo presión reducida para dar 60 mg (26%) del compuesto del título como un sólido amarillo pálido. p.f.: 123-125°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.46 (1H, d, J=1.7 Hz), 7.70 (1H, d, J=13.7 Hz), 4.97 (1H, m), 4.05 (1H, m), 3.74 (1H, d, J=11.5 Hz), 3.68 (3H, s), 3.65 (1H, m), 3.20 (1H, brd, J=9.8 Hz), 3.11 (1H, brd, J=10.3 Hz), 2.11 (1H, m), 1.95 (1H, m), 1.83 (1H, m), 1.72-1.46 (3H, m), 1.14 (3H, s).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4$-H_2O·0.25EtOH: C, 57.52; H, 5.95; F, 8.46; N, 9.36.

Encontrado: C, 57.80; H, 5.77; F, 8.41; N, 9.40.

HRMS (FAB); m/z calculado para $C_{21}H_{24}F_2N_3O_4$ $(M+H)^+$: 420.1735.

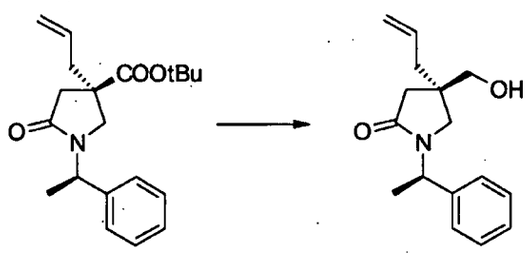
Encontrado: 420.1739.

IR (ATR) ν: 2931, 2842, 1727, 1616, 1540, 1508, 1436, 1346, 1315, 1270, 1226, 1187, 1133, 1097, 1051 cm^{-1}.

EJEMPLO DE REFERENCIA 42

(4R)-4-alil-4-hidroximetil-1-[(1R)-1-feniletil]-pirrolidin-2-ona

[Fórmula 117]



781

Borohidruro de litio (4.96 g, 0.228 moles) se suspendió en tetrahidrofurano (500 ml). Una solución de éster ter-butílico de ácido (3R)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (50.0 g, 0.152 moles) en tetrahidrofurano (100 ml)-etanol (17.7 ml) se añadió a la suspensión usando un embudo de goteo durante 10 minutos. La mezcla se calentó a 40°C, se agitó durante 12 horas, y después se calentó a reflujo durante 20 horas. Después de enfriar a 0°C, una solución saturada de cloruro de amonio (100 ml) se añadió cuidadosamente. Después de que el componente de tetrahidrofurano se evaporó bajo presión reducida, la solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y una solución saturada de cloruro de amonio (100 ml), seguido por extracción con acetato de etilo (1000 ml, 750 ml). Las capas orgánicas se combinaron y se lavaron con salmuera (200 ml). Después de secado sobre sulfato de sodio anhidro y filtración, el filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 1:4) para dar 29.9 g (76%) del compuesto del título como un aceite viscoso incoloro.

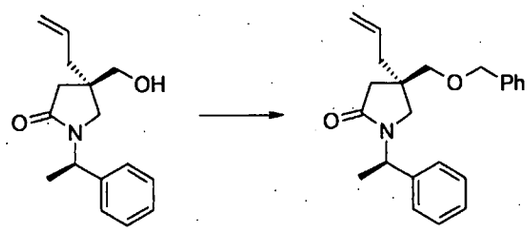
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.59-5.47 (2H, m), 4.97 (1H, m), 4.90 (1H, m), 3.50 (2H, d, J=5.1 Hz), 3.23 (1H, d, J=10.1 Hz), 2.71 (1H, d, J=10.1 Hz), 2.37 (1H, d, J=16.8 Hz), 2.26 (1H, d, J=16.8 Hz), 2.08 (2H, d, J=7.3 Hz), 1.84 (1H, m), 1.51 (3H, d,. J=7.1 Hz).

EM (ESI) m/z: 260 $(MH-H)^+$.

EJEMPLO DE REFERENCIA 43

(4R)-4-Alil-4-benciloximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 118]



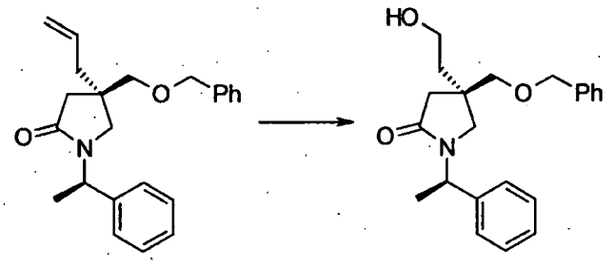
Bromuro de bencilo (17.1 ml, 0.144 moles) e hidruro de sodio (55% en parafina líquida, 6.27 g, 0.144 moles) se añadieron secuencialmente a una solución de (4R)-4-alil-4-hidroximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona (31.1 g, 0.120 moles) en tetrahidrofurano (300 ml)-dimetilformamida (75 ml) en una atmósfera de nitrógeno a 0°C. La mezcla se agitó a la misma temperatura durante 30 minutos. Metanol (5 ml) se añadió cuidadosamente y se agitó hasta que no se generó gas. Después, la reacción se extinguió con una solución saturada de cloruro de amonio (50 ml). La solución de reacción se vació en una mezcla de acetato de etilo (1000 ml) y agua (150 ml), seguido por extracción con acetato de etilo (1500 ml). La capa orgánica se lavó secuencialmente con agua (200 ml) y salmuera (200 ml x 2), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 3:1 → 2:1 → 1:1) para dar 41.3 g (99%) del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.23 (10H, m), 5.52-5.42 (2H, m), 4.93 (1H, m), 4.84 (1H, m), 4.51 (1H, d, J=12.2 Hz), 4.47 (1H, d, J=12.2 Hz), 3.27 (2H, s), 3.21 (1H, d, J=10.0 Hz), 2.69 (1H, d, J=10.0 Hz), 2.37 (1H, d, J=16.9 Hz), 2.26 (1H, d, J=16.9 Hz), 2.11 (1H, m), 2.05 (1H, m), 1.46 (3H, d, J=7.3 Hz).

EJEMPLO DE REFERENCIA 44

(4R)-4-Benciloximetil-4-(2-hidroxietil)-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 119]



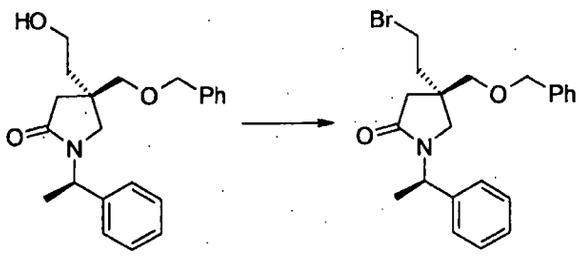
Una solución de (4R)-4-alil-4-benciloximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona (4.00 g, 11.45 mmoles) en diclorometano (100 ml) se hizo burbujear con ozono gaseoso a -70°C y se agitó a la misma temperatura durante 15 minutos. El burbujeo de ozono se detuvo cuando la solución de reacción se volvió azul oscuro y después la solución de reacción se hizo burbujear con nitrógeno gaseoso hasta que la solución se volvió incolora. Borohidruro de sodio (434 mg, 11.45 mmoles) y metanol (40 ml) se añadieron a la misma temperatura, y la mezcla se calentó a temperatura ambiente durante tres horas. Borohidruro de sodio (325 mg, 8.58 mmoles) se añadió, y la mezcla se agitó a temperatura ambiente durante 24 horas adicionales. Una solución saturada de cloruro de amonio se añadió, y la mezcla se agitó durante 10 minutos. Después, la solución de reacción se vació en una mezcla de acetato de etilo (200 ml) y agua (200 ml), seguido por extracción con acetato de etilo (500 ml). La capa orgánica se lavó con salmuera (200 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 1:2 → 1:9 → 0:1) para dar 3.22 g (79%) del compuesto del título como un aceite viscoso incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.23 (10H, m), 5.46 (1H, q, J=7.1 Hz), 4.55 (1H, d, J=11.8 Hz), 4.48 (1H, d, J=11.8 Hz), 3.54-3.45 (2H, brm), 3.36 (2H, s), 3.24 (1H, d, J=10.2 Hz), 2.72 (1H, d, J=10.2 Hz), 2.38 (1H, d, J=17.0 Hz), 2.28 (1H, d, J=17.0 Hz), 2.15 (1H, br), 1.69-1.58 (2H, m), 1.44 (3H, d, J=7.1 Hz).

EJEMPLO DE REFERENCIA 45

(4S)-4-Benciloximetil-4-(2-bromoetil)-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 120]



Tetrabromuro de carbono (3.17 g, 9.56 mmoles) y trifenilfosfina (2.51 g, 9.56 mmoles) se añadieron secuencialmente a una solución de (4R)-4-benciloximetil-4-(2-hidroxietil)-1-[(1R)-1-feniletil] pirrolidin-2-ona (3.22 g, 9.10 mmoles) en diclorometano (20 ml) en una atmósfera de nitrógeno, y la mezcla se agitó durante 15 minutos. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 2:1 → 1:1 → 1:2) para dar 3.18 g (84%) del compuesto del título como un aceite amarillo pálido.

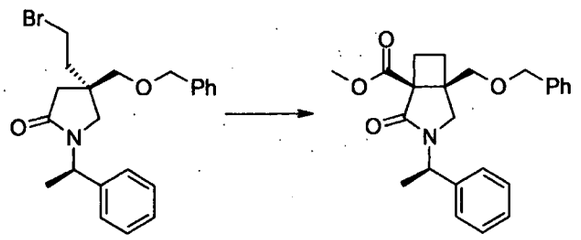
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.25 (10H, m), 5.46 (1H, q, J=7.1 Hz), 4.52 (1H, d, J=12.2 Hz), 4.46 (1H, d, J=12.2 Hz), 3.28 (2H, s), 3.25 (1H, d, J=10.1 Hz), 3.17-3.04 (2H, m), 2.67 (1H, d, J=10.1 Hz), 2.37 (1H, d, J=17.1 Hz), 2.26 (1H, d, J=17.1 Hz), 2.05 (1H, ddd, J=5.9, 10.4, 14.0 Hz), 1.96

(1H, ddd, J=6.1, 10.6, 14.0 Hz), 1.44 (3H, d, J=7.1 Hz).

EJEMPLO DE REFERENCIA 46

Ester metílico de ácido (1S,5R)-5-benciloximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 121]



Una solución 1.0 M de hexametildisilazida de litio en tetrahidrofurano (14.5 ml, 14.5 mmoles) se añadió a una solución de (4S)-4-benciloximetil-4-(2-bromoetil)-1-[(1R)-1-feniletil]pirrolidin-2-ona (2.75 g, 6.60 mmoles) y cloroformiato de metilo (0.54 ml, 6.93 mmoles) en tetrahidrofurano (20 ml) en una atmósfera de nitrógeno a 0°C. La mezcla se agitó durante 12 horas mientras se calentaba gradualmente a temperatura ambiente. La solución de reacción se enfrió a 0°C. Una solución saturada de cloruro de amonio (5 ml) se añadió, y la mezcla se agitó durante 10 minutos. Después, la solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y agua (50 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera (50 ml) y después se secó sobre sulfato de sodio anhidro. El agente de secado se removió por filtración, y después el filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 3:1 → 2:1 → 1:1) para dar 2.12 g (82%) del compuesto del título como un aceite amarillo pálido.

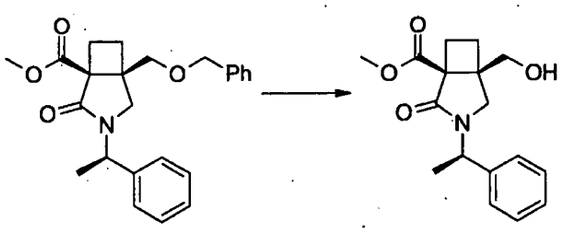
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.24 (10H, m), 5.59 (1H, q, J=7.1 Hz), 4.47 (1H, d, J=12.0 Hz), 4.43 (1H, d, J=12.0 Hz), 3.63 (3H, s), 3.53 (1H, d, J=9.3 Hz), 3.49 (1H, d, J=9.3 Hz), 3.37 (1H, d, J=10.0 Hz), 2.78 (1H, ddd, J=9.3, 9.5, 12.2 Hz), 2.73 (1H, d, J=10.0 Hz), 2.22 (1H, ddd, J=3.4, 9.3, 12.2 Hz), 1.91 (1H, ddd, J=3.4, 10.5, 12.2 Hz), 1.63 (1H, ddd, J=9.5, 10.5, 12.2 Hz), 1.58 (3H, d, J=7.1 Hz).

EM (ESI) m/z: 394 $(M+H)^+$.

EJEMPLO DE REFERENCIA 47

Ester metílico de ácido (1S,5R)-5-hidroximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 122]



Un catalizador de 10% de paladio-carbón (50% húmedo, 200 mg) se añadió a una solución de éster metílico de ácido (1S,5R)-5-benciloximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0]heptano-1-carboxílico (1.82 g, 4.62 mmoles) en etanol (20 ml)-tetrahidrofurano (20 ml), y la mezcla se agitó en una atmósfera de hidrógeno a 40°C durante 2.5 horas. Después de remover el catalizador por filtración, el filtrado se concentró para dar el compuesto del título como cristales incoloros.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.60 (1H, q, J=7.1 Hz), 3.79 (1H, dd, J=4.2, 11.8 Hz), 3.78 (3H, s), 3.58 (1H, dd, J=7.1, 11.8 Hz), 3.56 (1H, d, J=10.0 Hz), 2.73-2.65 (2H, m), 2.57 (1H, dd, J=4.2, 7.1 Hz), 2.30

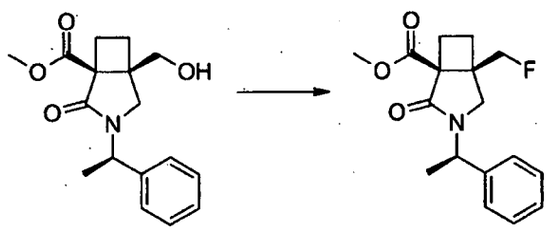
(1H, m), 1.83 (1H, m), 1.62 (1H, m), 1.59 (3H, d, J=7.1 Hz).

EM (ESI) m/z: 304 $(M+H)^+$.

EJEMPLO DE REFERENCIA 48

Eter metílico de ácido (1S, 5R)-5-fuorometil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 123]



Trifluoruro de bis (2-metoxietil)aminoazufre (1.98 ml, 10.7 mmoles) se añadió a una solución de éster metílico de ácido (1S,5R)-5-hidroximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0]heptano-1-carboxílico (1.30 g, 4.30 mmoles) en diclorometano en una atmósfera de nitrógeno a temperatura ambiente. La mezcla se calentó a 50°C y se agitó durante 12 horas. Después, una solución saturada de bicarbonato de sodio (10 ml) se añadió, y la mezcla se agitó durante 10 minutos. La solución de reacción se vació en una mezcla de acetato de etilo (50 ml) y agua (30 ml), seguido por extracción con acetato de etilo (200 ml). Después de filtración, el filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 3:1 → 2:1 → 1.5:1) para dar 1.26 g (96%) del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.63 (1H, q, J=7.2 Hz), 4.51 (1H, dd, J=9.8, 47.1 Hz), 4.47 (1H, dd, J=9.8, 47.0 Hz), 3.76 (3H, s), 3.41 (1H, d, J=10.0 Hz), 2.78 (1H, m), 2.76 (1H, d, J=10.0 Hz), 2.27 (1H, ddd,

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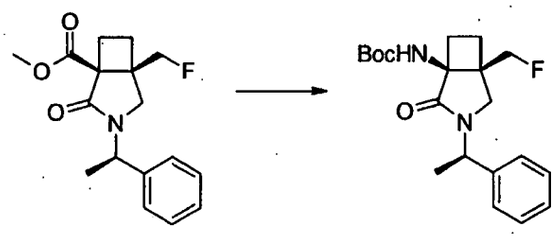
J=3.6, 9.3, 12.5 Hz), 1.93 (1H, ddd, J=3.6, 10.5, 12.4 Hz), 1.68 (1H, m), 1.62 (3H, d, J=7.2 Hz).

EM (ESI) m/z: 306 $(M+H)^+$.

EJEMPLO DE REFERENCIA 49

(1S,5S)-1-(ter-Butoxicarbonilamino)-5-fluorometil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 124]



Una solución 1 M de hidróxido de sodio se añadió a una solución de éster metílico de ácido (1S, 5R)-5-fluorometil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico (1.26 g, 4.13 mmoles) en tetrahidrofurano (10 ml)-metanol (5.0 ml). La mezcla se agitó durante 12 horas. La solución de reacción se ajustó a pH 2 o menor con ácido clorhídrico 6 M, y los componentes de tetrahidrofurano y metanol se removieron por filtración bajo presión reducida. El residuo se vació en una mezcla de acetato de etilo y ácido clorhídrico 1 M, seguido por extracción con acetato de etilo. La capa orgánica se lavó con una solución saturada de cloruro de sodio y después se secó sobre sulfato de sodio anhidro. Después de remover el agente de secado por filtración, el filtrado se concentró bajo presión reducida para dar 1.17 g (97%) de ácido carboxílico crudo como un sólido blanco.

El ácido carboxílico crudo (1.02 g, 3.51 mmoles) se disolvió en una

789

mezcla de tolueno (20 ml), alcohol ter-butílico (20 ml), y trietilamina (0.98 ml, 7.03 mmoles), y difenilfosforil azida (0.833 ml, 3.87 mmoles) se añadió en una atmósfera de nitrógeno. La mezcla se agitó a 40°C durante una hora y después a 80°C durante 12 horas. La solución de reacción se vació en una mezcla de acetato de etilo (50 ml) y una solución saturada de bicarbonato de sodio (30 ml), seguido por extracción con acetato de etilo (150 ml) La capa orgánica se lavó con salmuera (30 ml), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 3:1 → 2:1 → 1:1) para dar 746 mg (59%) del compuesto del título como cristales incoloros.

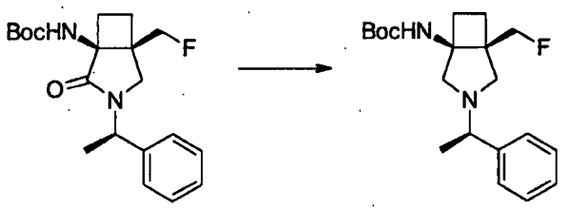
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.29 (5H, m), 5.60 (1H, q, J=7.1 Hz), 4.95 (1H, br), 4.61 (1H, dd, J=9.6, 47.3 Hz), 4.47 (1H, dd, J=9.6, 47.3 Hz), 2.15 (1H, d, J=9.5 Hz), 2.70 (1H, d, J=9.5 Hz), 2.36 (1H, m), 2.17-2.08 (2H, m), 1.60 (3H, d, J=7.1 Hz), 1.42 (9H, s).

EM (ESI) m/z: 363 $(M+H)^+$.

EJEMPLO DE REFERENCIA 50

(1S,5S)-1-(ter-Butoxicarbonilamino)-5-fluorometil-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 125]



Una solución al 65% de Red-Al™ en tolueno (1.76 ml, 5.85

190

mmoles) se añadió gota a gota a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-fluorometil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano (707 mg, 1.95 mmoles) en tolueno en una atmósfera de nitrógeno a -15°C durante 10 minutos La mezcla se calentó a temperatura ambiente, se agitó durante 1.5 horas, y se enfrió a 0°C. Una solución de tartrato de sodio-potasio tetrahidratada al 25% (10 ml) se añadió cuidadosamente mientras se mantenía la temperatura interna de la solución de reacción a 10°C o menor. La solución de reacción se vació en una mezcla de acetato de etilo (10 ml) y salmuera (10 ml), seguido por extracción con acetato de etilo (150 ml). La capa orgánica se lavó con salmuera (30 ml) y después se secó sobre sulfato de sodio anhidro. El agente de secado se removió por filtración, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 9:1 → 5:1 → 2:1) para dar 567 mg (83%) del compuesto del título como un aceite amarillo pálido.

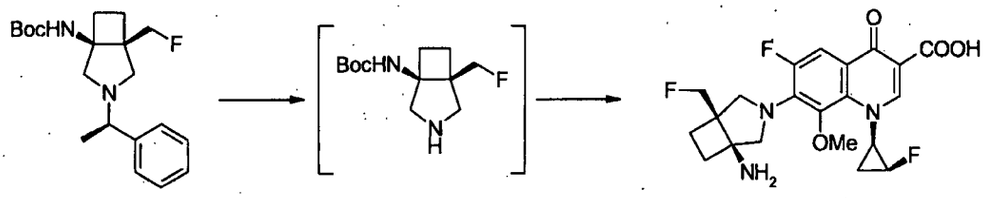
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.18 (5H, m), 4.89 (1H, br), 4.63 (1H, dd, J=9.8, 47.9 Hz), 4.53 (1H, J=9.8, 47.6 Hz), 3.33 (1H, q, J=6.4 Hz), 2.95 (2H, d, J=8.8 Hz), 2.40 (1H, d, J=8.8 Hz), 2.18-2.14 (3H, m), 1.93-1.87 (2H, m), 1.37 (9H, s), 1.36 (3H, d, J=6.4 Hz).

EM (ESI) m/z: 349 $(M+H)^+$.

EJEMPLO 8

Acido 7-[(1S,5S)-1-amino-5-fluorometil-3-biciclo[3.2.0]hept-3-il]-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 126]



Un catalizador de 10% de paladio-carbón (M, aproximadamente 50% húmedo, 50 mg) se añadió a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-fluorometil-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0] heptano (567 mg, 1.63 mmoles) en etanol (10 ml), y la mezcla se agitó en una atmósfera de hidrógeno a 50°C durante 2.5 horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar amina cruda (364 mg) como cristales incoloros.

La amina cruda se disolvió en sulfóxido de dimetilo (4.0 ml), y trietilamina (0.62 ml, 4.45 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (642 mg, 1.78 mmoles) se añadieron secuencialmente. La mezcla se calentó con agitación a 40°C durante 24 horas. Después, una mezcla de etanol : agua = 3:1 (20.0 ml) y trietilamina (3.0 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. La solución de reacción se vació en una mezcla de acetato de etilo (20 ml) y una solución de ácido cítrico al 10% (10 ml), seguido por extracción con acetato de etilo (50 ml x 3). Las capas orgánicas se combinaron y se lavaron con salmuera (50 ml). Posteriormente, las capas orgánicas se secaron sobre sulfato de sodio anhidro y se filtraron, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por CLAR preparativa de fase inversa (sistema de solución de ácido fórmico al 0.1%-acetonitrilo) para dar un sólido amarillo pálido. El sólido amarillo pálido resultante se disolvió en ácido clorhídrico concentrado (1.5 ml), y la

792

solución se agitó a temperatura ambiente durante 10 minutos. La solución de reacción se diluyó con ácido clorhídrico 6 M (20 ml) y se lavó con cloroformo (7 ml). La capa acuosa se ajustó a pH 12.4 con una solución saturada de hidróxido de sodio bajo enfriamiento con hielo y después se ajustó a pH 7.3 con ácido clorhídrico, seguido por extracción con cloroformo (50 ml x 2). La capa acuosa se reajustó a pH 7.4, seguido por extracción con cloroformo (50 ml x 2). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el filtrado se concentró bajo presión reducida. El residuo se secó suficientemente bajo vacío y después se disolvió en cloroformo. La solución se filtró a través de un filtro de membrana, y el filtrado se concentró bajo presión reducida. El residuo resultante se disolvió en etanol y después se volvió a precipitar con hexano. El sólido resultante se recogió por filtración y se secó para dar 219 mg (31%) del compuesto del título como un sólido amarillo pálido, p.f.: 186-188°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 4.34 (1H, d, J=7.9 Hz), 4.96 (1H, m), 4.70 (1H, dd, J=10.0, 47.4 Hz), 4.64 (1H, dd, J=10.0, 47.1 Hz), 4.02 (1H, m), 3.67-3.61 (5H, m), 3.33 (1H, brd, J=10.5 Hz), 3.22 (1H, brd, J=9.8 Hz), 2.11 (1H, m), 2.00-1.88 (2H, m), 1.73 (1H, m), 1.60 (1H, m), 1.47 (1H, m).

Análisis calculado para $C_{21}H_{22}F_3N_3O_4 \cdot 0.25H_2O \cdot 0.25EtOH$: C, 56.95; H, 5.33; F, 12.57; N, 9.27.

Encontrado: C, 56.94; H, 5.11; F, 12.74; N, 9.23.

HRMS (FAB) ; m/z calculado para $C_{21}H_{23}F_3N_3O_4$ $(M+H)^+$: 438.16406.

Encontrado: 438.16743.

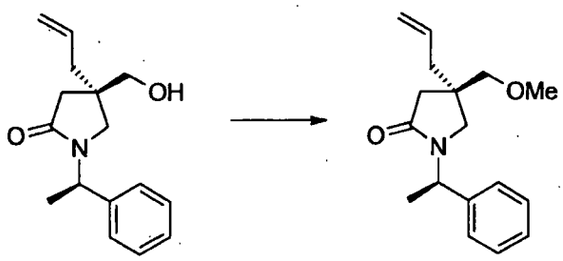
IR (ATR) ν: 3386, 2935, 1716, 1616, 1540, 1508, 1442, 1436,

1351, 1319, 1274, 1228, 1184, 1122, 1051 cm^{-1}.

EJEMPLO DE REFERENCIA 51

(4R)-4-Alil-4-metoximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 127]



Yoduro de metilo (1.87 ml, 30.1 mmoles) e hidruro de sodio (55% en parafina líquida, 1.31 g, 30.1 moles) se añadieron secuencialmente a una solución de (4R)-4-alil-4-hidroximetil-1-[(1R)-1-feniletil]pirrolidin-2-ona (7.09 g, 27.3 mmoles) en tetrahidrofurano (80 ml)-dimetilformamida (20 ml) en una atmósfera de nitrógeno a 0°C. La mezcla se calentó a temperatura ambiente y se agitó durante una hora. Metanol (2 ml) se añadió cuidadosamente y se agitó hasta que no se generó gas. Después, la reacción se extinguió con una solución saturada de cloruro de amonio (10 ml). La solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y agua (100 ml), seguido por extracción con acetato de etilo (800 ml). La capa orgánica se lavó secuencialmente con agua (200 ml) y salmuera (200 ml x 2), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 4:1 → 2:1 → 1:1) para dar 7.42 g (99%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.24 (5H, m), 5.54-5.43 (2H, m),

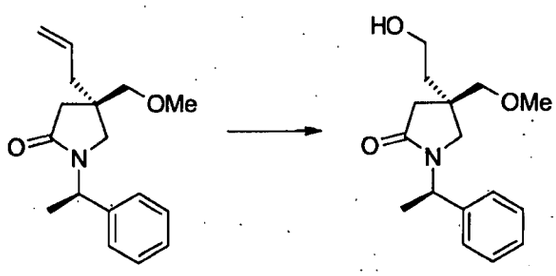
794

4.94 (1H, m), 4.84 (1H, m), 3.33 (3H, s), 3.20 (2H, s), 3.19 (1H, d, J=10.0 Hz), 2.69 (1H, d, J=10.0 Hz), 2.36 (1H, d, J=17.1 Hz), 2.24 (1H, d, J=17.1 Hz), 2.05-2.03 (2H, m), 1.50 (3H, d, J=7.3 Hz).

EJEMPLO DE REFERENCIA 52

(4R)-4-(2-Hidroxietil)-4-metoximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 128]



Una solución de (4R)-4-alil-4-metoximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona (3.28 g, 12.0 mmoles) en metanol (20 ml)-diclorometano (20 ml) se hizo burbujear con ozono gaseoso a -70°C y se agitó a la misma temperatura durante 30 minutos. El burbujeo de ozono se detuvo cuando la solución de reacción se volvió azul oscuro, y después la solución de reacción se hizo burbujear con nitrógeno gaseoso hasta que la solución se volvió incolora. Borohidruro de sodio (454 mg, 12.0 mmoles) se añadió a la misma temperatura, y la mezcla se calentó a temperatura ambiente durante dos horas. Después de calentamento, se añadió Borohidruro de sodio (227 mg, 6.0 mmoles) y la mezcla se agitó durante 24 horas. Después, Borohidruro de sodio (113 mg, 3.0 mmoles) se añadió adicionalmente y la mezcla se agitó durante 0.5 horas. Una solución saturada de cloruro de amonio (10 ml) se añadió, y la mezcla se agitó durante 10 minutos. Después, la solución de reacción se vació en una mezcla de acetato de etilo (50 ml) y agua (50 ml), seguido por extracción con acetato de etilo (200

795

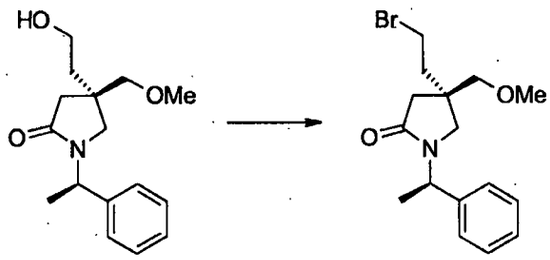
ml). La capa orgánica se lavó con salmuera (50 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo:metanol = 10:0 → 10:1) para dar 2.85 g (86%) del compuesto del título como un aceite viscoso incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.49 (1H, q, J=7.1 Hz), 3.55-3.44 (2H, m), 3.37 (3H, s), 3.30 (1H, d, J=9.5 Hz), 3.28 (1H, d, J=9.5 Hz), 3.22 (1H, d, J=10.0 Hz), 2.72 (1H, d, J=10.0 Hz), 2.38 (1H, d, J=16.8 Hz), 2.26 (1H, d, J=16.8 Hz), 1.64 (2H, t, J=6.0 Hz), 1.50 (3H, d, J=7.1 Hz).

EJEMPLO DE REFERENCIA 53

(4S)-4-(2-Bromoetil)-4-metoximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona

[Fórmula 129]



Tetrabromuro de carbono (3.58 g, 10.8 mmoles) y trifenilfosfina (2.83 g, 10.8 mmoles) se añadieron secuencialmente a una solución de (4R)-4-(2-hidroxietil)-4-metoximetil-1-[(1R)-1-feniletil] pirrolidin-2-ona (2.85 g, 10.3 mmoles) en diclorometano (30 ml) en una atmósfera de nitrógeno a 0°C, y la mezcla se agitó durante 10 minutos. La mezcla se calentó a temperatura ambiente y se agitó durante 24 horas, y después la solución de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (diclorometano → hexano: acetato de etilo = 2:1 →

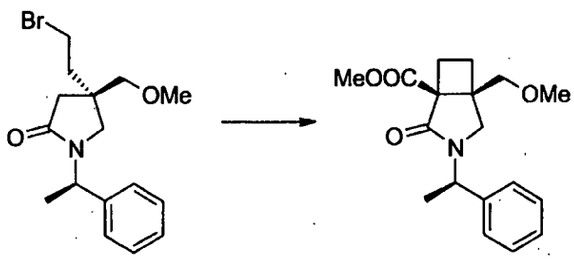
1:1 → 1:2) para dar 2.07 g (59%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.49 (1H, q, J=7.3 Hz), 3.32 (3H, s), 3.24 (1H, d, J=10.3 Hz), 3.23 (2H, s), 3.20-3.07 (2H, m), 2.67 (1H, d, J=10.3 Hz), 2.38 (1H, d, J=16.8 Hz), 2.25 (1H, d, J=16.8 Hz), 2.03-1.90 (2H, m), 1.50 (3H, d, J=7.3 Hz).

EJEMPLO DE REFERENCIA 54

Ester metílico de ácido (1S, 5R)-5-metoximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 130]



Una solución 1.0 M de hexametildisilazida de litio en tetrahidrofurano (13.4 ml, 13.4 mmoles) se añadió a una solución de (4S)-4-(2-bromoetil)-4-metoximetil-1-[(1R)-1-feniletil]pirrolidin-2-ona (2.07 g, 6.08 mmoles) y cloroformiato de metilo (0.493 ml, 6.38 mmoles) en tetrahidrofurano (20 ml) en una atmósfera de nitrógeno a -70°C. La mezcla se agitó durante 14 horas mientras se calentaba gradualmente a temperatura ambiente. La solución de reacción se enfrió a 0°C. Una solución de ácido cítrico al 10% (20 ml) se añadió, y la mezcla se agitó durante 10 minutos. Después, la solución de reacción se vació en una mezcla de acetato de etilo (100 ml) y agua (50 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera

(50 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 2:1 → 1:1 → 2:1) para dar 1.53 g (79%) del compuesto del título como un aceite café pálido.

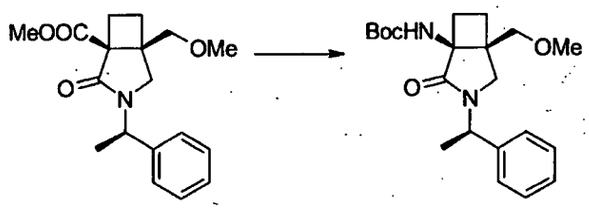
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.60 (1H, q, J=7.1), 3.72 (3H, s), 3.43 (1H, d, J=9.5 Hz), 3.40 (1H, d, J=9.5 Hz), 3.36 (1H, d, J=9.8 Hz), 3.28 (3H, s), 2.75 (1H, dt, J=12.2, 10.5 Hz), 2.72 (1H, d, J=9.5 Hz), 2.21 (1H, ddd, J=3.4, 9.3, 12.2 Hz), 1.86 (1H, ddd, J=3.4, 10.5, 12.2 Hz), 1.62 (1H, dt, J=12.2, 9.3 Hz), 1.58 (3H, d, J=7.1 Hz).

EM (ESI) m/z: 318 $(M+H)^+$.

EJEMPLO DE REFERENCIA 55

(1S,5S)-1-(ter-Butoxicarbonilamino)-5-metoximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 131]



Una solución 1 M de hidróxido de sodio (5.0 ml) se añadió a una solución de éster metílico de ácido (1S,5R)-5-metoximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0]heptano-1-carboxílico (1.53 g, 4.82 mmoles) en tetrahidrofurano (10 ml)-metanol (5.0 ml). La mezcla se agitó durante nueve horas. La solución de reacción se ajustó a pH 2 o menor con ácido clorhídrico 6 M, y los componentes de tetrahidrofurano y metanol se removieron por filtración

bajo presión reducida. El residuo se vació en una mezcla de acetato de etilo (30 ml) y ácido clorhídrico 1 M (30 ml), seguido por extracción con acetato de etilo (150 ml). La capa orgánica se lavó con una solución saturada de cloruro de sodio (30 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida para dar ácido carboxílico crudo como un aceite amarillo pálido.

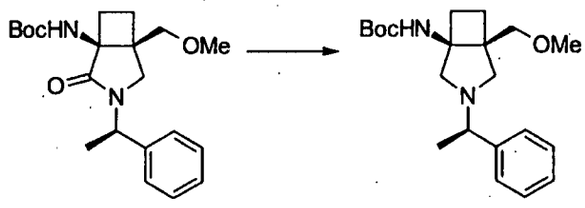
El ácido carboxílico crudo se disolvió en una mezcla de alcohol ter-butílico (30 ml) y trietilamina (1.34 ml, 9.64 mmoles), y difenilfosforil azida (1.14 ml, 5.30 mmoles) se añadió en una atmósfera de nitrógeno. La mezcla se agitó a 40°C durante dos horas y después a 80°C durante 20 horas. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 2:1 → 1:1) para dar 595 mg (33%, dos pasos) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 2.25 (1H, q, J=7.1H), 4.87 (1H, brs), 3.55 (1H, d, J=9.2 Hz), 3.42 (1H, brd, J=9.2 Hz), 3.35 (1H, d, J=9.6 Hz), 3.33 (3H, s), 2.71 (1H, d, J=9.6 Hz), 2.33 (1H, m), 2.12-2.00 (2H, m), 1.60 (3H, d, J=7.1 Hz), 1.43 (9H, s).

EJEMPLO DE REFERENCIA 56

(1S, 5S)-1-(ter-Butoxicarbonilamino)-5-metoximetil-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0] heptano

[Fórmula 132]



199

Una solución al 65% de Red-Al™ en tolueno (1.43 ml, 4.75 mmoles) se añadió gota a gota a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-metoximetil-2-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.2.0]heptano (593 mg, 1.58 mmoles) en tolueno en una atmósfera de nitrógeno a 0°C durante dos minutos. La mezcla se calentó a temperatura ambiente, se agitó durante dos horas, y se enfrió a 0°C. Una solución de tartrato de sodio-potasio tetrahidratada al 20% (10 ml) se añadió cuidadosamente mientras se mantenía la temperatura interna de la solución de reacción a 10°C o menos. La solución de reacción se vació en una mezcla de acetato de etilo (10 ml) y salmuera (10 ml), seguido por extracción con acetato de etilo (100 ml). La capa orgánica se lavó con salmuera (20 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 19:1 → 9:1) para dar 244 mg (43%) del compuesto del título como cristales incoloros.

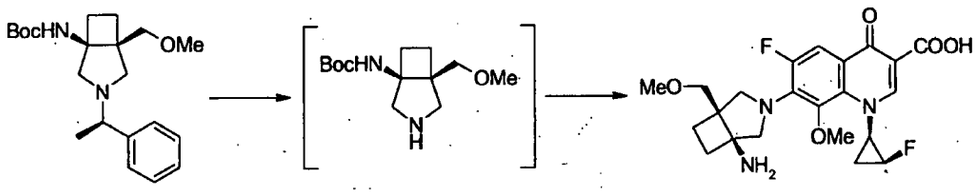
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.17 (5H, m), 5.56 (1H, brs), 3.58 (1H, d, J=10.0 Hz), 3.43 (1H, d, J=10.0 Hz), 3.37 (3H, s), 3.28 (1H, q, J=6.5 Hz), 3.10 (1H, br), 2.86 (1H, d, J=8.7 Hz), 2.34 (1H, d, J=8.7 Hz), 2.23-2.01 (3H, brm), 1.84 (2H, brt, J=8.1 Hz), 1.35 (9H, brs), 1.34 (3H, d, J=6.5 Hz).

EM (ESI) m/z: 361 $(M+H)^+$.

EJEMPLO 9

Acido 7-[(1S,5S)-1-amino-5-metoximetil-3-azabiciclo [3.2.0] hept-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 133]



Un catalizador de 10% de paladio-carbón (50% húmedo, 50 mg) se añadió a una solución de (1S,5S)-1-(ter-butoxicarbonilamino)-5-metoximetil-3-[(1R)-1-feniletil]-3-azabiciclo[3.2.0]heptano (242 mg, 0.67 mmoles) en etanol (20 ml), y la mezcla se agitó en una atmósfera de hidrógeno a 50°C durante siete horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar amina cruda (164 mg) como un aceite viscoso incoloro.

La amina cruda (164 mg) se disolvió en sulfóxido de dimetilo (2.0 ml), y trietilamina (0.178 ml, 1.28 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-4-oxo-1,4-dihidroquinolin-3-carboxílico-quelato de BF_2 (254 mg, 0.704 mmoles) se añadieron secuencialmente. La mezcla se calentó con agitación a 40°C durante 23 horas. Después, una mezcla de etanol:agua = 5:1 (6.0 ml) y trietilamina (1.0 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante dos horas. Después de que los componentes de etanol y trietilamina en la solución de reacción se evaporaron bajo presión reducida, el residuo se vació en una mezcla de acetato de etilo (20 ml) y una solución de ácido cítrico al 10% (10 ml), seguido por extracción con acetato de

801

etilo (80 ml). La capa orgánica se lavó con salmuera (20 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por CLAR preparativa de fase inversa (sistema de solución de ácido fórmico al 0.1%-acetonitrilo) para dar un compuesto amorfo amarillo pálido. El compuesto amorfo amarillo pálido resultante se disolvió en ácido clorhídrico concentrado (2.0 ml), y la solución se agitó a temperatura ambiente durante 10 minutos. La solución de reacción se diluyó con ácido clorhídrico 6 M (15 ml) y se lavó con cloroformo (10 ml). La capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (50 ml x 2, 30 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el filtrado se concentró bajo presión reducida. El residuo se secó suficientemente bajo vacío y después se disolvió en cloroformo. La solución se filtró a través de un filtro de membrana, y el filtrado se concentró bajo presión reducida. El residuo resultante se cristalizó a partir de hexano, y los cristales se recogieron por filtración y se secaron para dar 184 mg (61%) del compuesto del título como un sólido amarillo pálido. p.f.: 86-88°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, d, J=1.5 Hz), 7.69 (1H, d, J=13.4 Hz), 4.95 (1H, m), 4.02 (1H, m), 3.70-3.58 (7H, m), 3.39 (3H, s), 3.23 (1H, d, J=10.5 Hz), 3.19 (1H, d, J=10.3 Hz), 2.09 (1H, m), 1.99-1.87 (2H, m), 1.74 (1H, m), 1.61 (1H, m), 1.48 (1H, m).

Análisis calculado para $C_{22}H_{25}F_2N_3O_5 \cdot 0.25H_2O \cdot 0.25EtOH$: C, 58.06; H, 5.85; F, 8.16; N, 9.03.

Encontrado: C, 57.92; H, 5.86; F, 8.16; N, 9.09.

HRMS (FAB); m/z calculado para $C_{22}H_{26}F_2N_3O_5$ $(M+H)^+$:

802

450.18405.

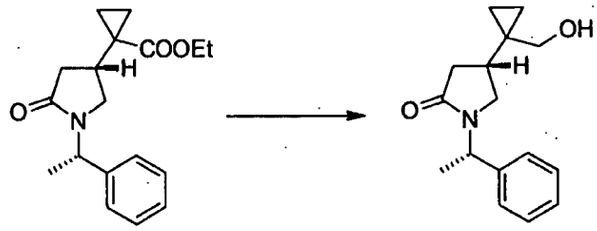
Encontrado: 450.18358.

IR (ATR) ν: 2931, 2827, 1724, 1616, 1546, 1504, 1434, 1392, 1348, 1313, 1274, 1228, 1184, 1101, 1051 cm^{-1}.

EJEMPLO DE REFERENCIA 57

(3R)-3-[1-(Hidroximetil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidina

[Fórmula 134]



Borohidruro de litio (1.174 g, 53.90 mmoles) se añadió a una solución de éster etílico de ácido de 1-[(3R)-5-oxo-1-[(1S)-1-feniletil]pirrolidin-3-il] ciclopropancarboxílico [véase Journal of Medicinal Chemistry, Vol. 46, No. 6, p.1005 (2003)] (2.03 g, 6.74 mmoles) en tetrahidrofurano (20 ml). La mezcla se calentó con agitando en un baño de aceite a 70°C durante 30 horas. Después de enfriar a temperatura ambiente, la solución de reacción se vació en solución de ácido cítrico al 10% enfriada con hielo (80 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con agua (80 ml) y salmuera (80 ml), se secó sobre sulfato de sodio anhidro, y después se filtró, y el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:2 → 1:1 → 2:1 → 1:0 → cloroformo:metanol = 9:1) para dar 1.30 g (74%) del compuesto del título como un sólido gomoso transparente incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.26-7.35 (5H, m), 5.48 (1H, q, J=6.9

863

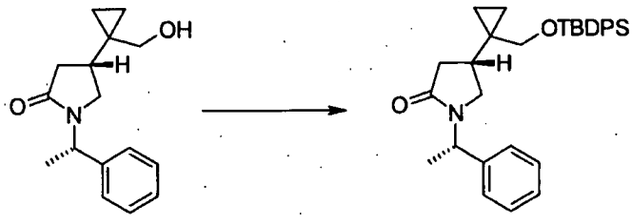
Hz), 3.45 (2H, s), 3.04-3.12 (1H, m), 2.37-2.50 (2H, m), 2.19 (1H, dd, J=16.0, 8.9 Hz), 1.51 (2H, d, J=7.1 Hz), 0.43 (4H, s).

EM (ESI) m/z: 260 $(M+H)^+$.

EJEMPLO DE REFERENCIA 58

(3R)-3-[1-(ter-Butildifenilsiloximetil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidina

[Fórmula 135]



Cloruro de ter-butildifenilsililo (2.83 ml, 10.88 mmoles) se añadió a una solución de (3R)-3-[1-(hidroximetil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidina (2.35 g, 9.06 mmoles) e imidazol (925 mg, 13.59 mmoles) en N,N-dimetilformamida (30 ml), y la mezcla se agitó a temperatura ambiente durante 20 horas. La solución de reacción se diluyó con acetato de etilo (150 ml), se lavó con agua (50 ml x 2) y salmuera (50 ml x 2), se secó sobre sulfato de sodio anhidro, y después se filtró. El solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:19 → 1:9 → 1:4 → 1:1) para dar 3.88 g (86%) del compuesto del título como un sólido gomoso transparente incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.56-7.59 (4H, m), 7.26-7.46 (11H, m), 5.48 (1H, q, J=7.0 Hz), 3.46 (1H, d, J=10.7 Hz), 3.39 (1H, d, J=10.7 Hz), 3.10 (2H, td, J=18.4, 9.6 Hz), 2.51 (1H, m), 2.32 (1H, dd, J=16.5, 8.9 Hz), 2.14 (1H, dd, J=16.5, 10.4 Hz), 1.46 (3H, d, J=7.1 Hz), 1.01 (9H, s), 0.33-0.39 (4H, m).

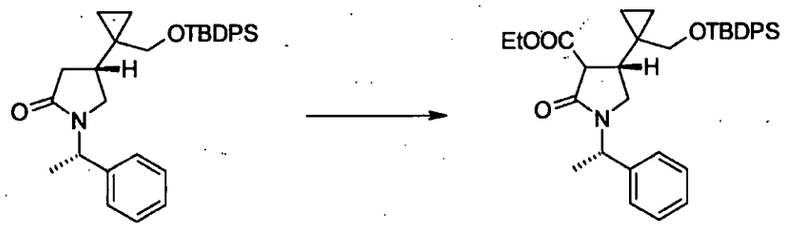
804

EM (ESI) m/z : 498 $(M+H)^+$.

EJEMPLO DE REFERENCIA 59

Ester etílico de ácido (3R)-3-[1-(ter-butildifenilsiloximetil) ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidin-4-ilcarboxílico

[Fórmula 136]



Cloroformiato de etilo (0.059 ml, 0.617 mmoles) y una solución de hexametildisilazida de litio en tetrahidrofurano (1.0 M, 0.57 ml, 0.570 mmoles) se añadieron secuencialmente gota a gota a una solución de (3R)-3-[1-(ter-butildifenilsiloximetil) ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidina (258 mg, 0.518 mmoles) en tetrahidrofurano (2 ml) a 0°C durante dos minutos. La mezcla se agitó a 0°C durante 30 minutos y a temperatura ambiente durante 30 minutos, y una solución de hexametildisilazida de litio en tetrahidrofurano (1.0 M, 0.57 ml, 0.570 mmoles) se añadió adicionalmente. La mezcla se agitó a temperatura ambiente durante 2.5 horas y después se enfrió con hielo. La reacción se extinguió con una solución de ácido cítrico al 10% (20 ml). La mezcla resultante se extrajo con acetato de etilo (50 ml). La capa orgánica se lavó con agua (20 ml) y salmuera (20 ml) y después se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida. Después, el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:9 → 1:4 → 1:2) para dar 227 mg (77%) del compuesto del título como un sólido gomoso transparente

incoloro.

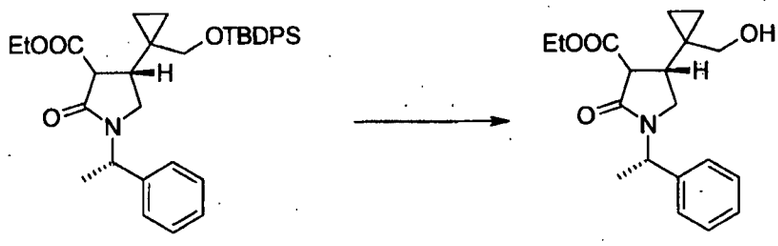
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.54-7.64 (4H, m), 7.26-7.45 (11H, m), 5.46 (1H, q, J=6.9 Hz), 4.23 (1H, ddd, J=14.3, 7.1, 1.8 Hz), 3.29-3.52 (4H, m), 3.12 (1H, t, J=9.0 Hz), 2.65 (1H, dd, J=18.6, 8.5 Hz), 1.48 (2H, d, J=7.1 Hz), 1.29 (3H, t, J=7.1 Hz), 1.02 (9H, s), 0.33 (4H, m).

EM (ESI) m/z: 570 $(M+H)^+$.

EJEMPLO DE REFERENCIA 60

Ester etílico de ácido (3R)-3-[1-(hidroximetil) ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidin-4-ilcarboxílico

[Fórmula 137]



Un complejo de fluoruro de hidrógeno-piridina (10 ml) se añadió gota a gota a una solución de éster etílico de ácido (3R)-3-[1-(ter-butildifenilsiloximetil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil]pirrolidin-4-ilcarboxílico (2.81 g, 4.93 mmoles) en piridina (20 ml) a 0°C durante cinco minutos. La mezcla se agitó a temperatura ambiente durante 2.5 horas y después se vació en agua con hielo (150 ml), seguido por extracción con acetato de etilo (300 ml). La capa orgánica resultante se lavó con una solución de ácido cítrico al 10% (100 ml), agua (100 ml), y salmuera (100 ml) y después se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida, y después el residuo resultante se purificó por cromatografía en

columna sobre gel de sílice (acetato de etilo : hexano = 1:2 → 1:1 → 2:1) para dar 1.378 g (84%) del compuesto del título como un sólido gomoso amarillo pálido.

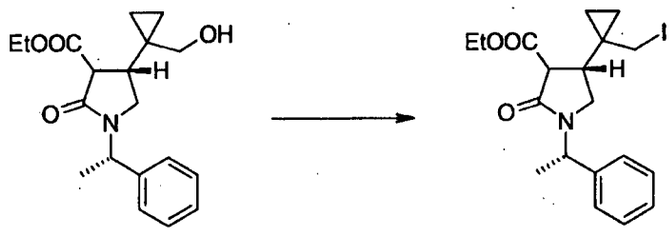
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.26-7.36 (5H, m), 5.46 (1H, q, J=7.1 Hz), 4.25 (2H, q, J=7.2 Hz), 3.49 (2H, dd, J=23.2, 10.5 Hz), 3.36 (1H, d, J=11.7 Hz), 3.09 (2H, dt, J=20.8, 8.9 Hz), 2.67 (1H, q, J=8.5 Hz), 1.54 (3H, d, J=7.1 Hz), 1.31 (3H, t, J=7.1 Hz), 0.35-0.50 (4H, m).

EM (ESI) m/z: 332 $(M+H)^+$.

EJEMPLO DE REFERENCIA 61

Ester etílico de ácido (3R)-3-[1-(yodometil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidin-4-ilcarboxílico

[Fórmula 138]



Imidazol (708 mg, 10.40 mmoles), trifenilfosfina (2.727 g, 10.40 mmoles), y yodo (2.111 g, 8.32 mmoles) se añadieron secuencialmente a una solución de éster etílico de ácido (3R)-3-[1-(hidroximetil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidin-4-ilcarboxílico (1.378 g, 4.16 mmoles) en diclorometano (50 ml) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 15 horas. El solvente se evaporó bajo presión reducida. Después, el residuo se disolvió en acetato de etilo (200 ml) y se lavó con agua (50 ml x 2) y salmuera (50 ml). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. El

residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:9 → 1:4 → 1:2) para dar 1.606 g (88%) del compuesto del título como un sólido gomoso amarillo pálido.

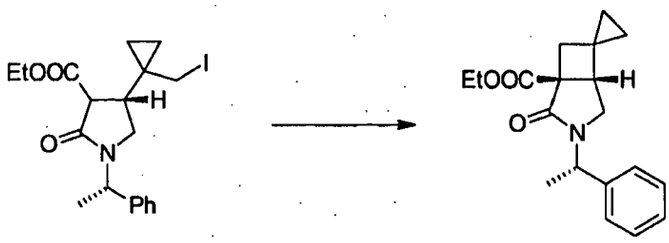
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.26-7.39 (5H, m), 5.47 (1H, q, J=7.2 Hz), 4.28 (2H, q, J=7.2 Hz), 3.19-3.23 (2H, m), 3.03-3.12 (3H, m), 2.94 (1H, m), 1.54 (3H, d, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz), 0.80-0.87 (2H, m), 0.63 (2H, m).

EM (ESI) m/z: 442 $(M+H)^+$.

EJEMPLO DE REFERENCIA 62

Ester etílico de ácido (1S, 5S)-2-oxo-3-[(1S)-1-feniletil]-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico

[Fórmula 139]



Una solución de hexametildisilazida de potasio en tolueno (0.5 M, 8.94 ml, 4.47 mmoles) se añadió gota a gota a una solución de éster etílico de ácido (3R)-3-[1-(yodometil)ciclopropan-1-il]-5-oxo-1-[(1S)-1-feniletil] pirrolidin-4-ilcarboxílico (1.517 g, 3.44 mmoles) en tolueno (30 ml) bajo enfriamiento con hielo con sal durante cinco minutos. La mezcla se agitó a la misma temperatura durante una hora y 20 minutos y después a temperatura ambiente durante 5.5 horas. La solución de reacción se enfrió con hielo y la reacción se extinguió con una solución de ácido cítrico al 10% (20 ml), seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con agua (50 ml x 2) y salmuera (50

ml). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo:hexano = 1:9 → 1:4 → 1:2) para dar 717 mg (67%) del compuesto del título como un sólido blanco.

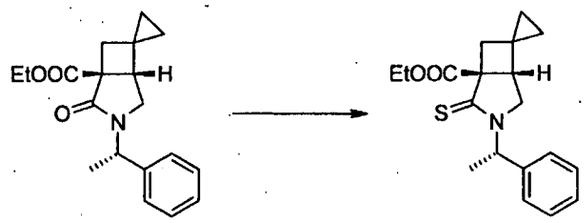
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.27-7.38 (5H, m), 5.61 (1H, q, J=7.1 Hz), 4.14-4.28 (2H, m), 3.02-3.07 (3H, m), 2.91 (1H, dt, J=9.8, 3.8 Hz), 2.29 (1H, d, J=12.2 Hz), 1.61 (3H, d, J=7.1 Hz), 1.28 (3H, t, J=7.2 Hz), 0.62 (2H, m), 0.44 (2H, m).

EM (ESI) m/z: 314 $(MH-H)^+$.

EJEMPLO DE REFERENCIA 63

Ester etílico de ácido (1R,5S)-3-[(1S)-1-feniletil]-6-espirociclopropan-2-tioxo-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico

[Fórmula 140]



Reactivo de Lawesson (1.146 g, 2.83 mmoles) se añadió a una solución de éster etílico de ácido (1S,5S)-2-oxo-3-[(1S)-1-feniletil]-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico (592 mg, 1.89 mmoles) en tolueno (20 ml). La mezcla se calentó con agitando en una atmósfera de nitrógeno sobre un baño de aceite a 90°C durante 6.5 horas. El solvente se evaporó bajo presión reducida, y después el residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo:hexano = 1:19 →

809

1:9 → 1:4) para dar 0.57 g (92%) del compuesto del título como un sólido blanco.

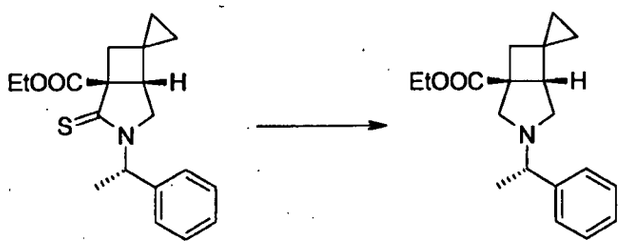
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.30-7.36 (5H, m), 6.40 (1H, q, J=7.1 Hz), 4.11-4.32 (2H, m), 3.33 (1H, dd, J=12.0, 6.8 Hz), 3.22 (2H, t, J=11.7 Hz), 3.09 (1H, d, J=6.3 Hz), 2.37 (1H, d, J=12.2 Hz), 1.68 (3H, d, J=7.1 Hz), 1.28 (3H, t, J=7.2 Hz), 0.58 (1H, m), 0.42 (2H, m).

EM (ESI) m/z: 330 $(M+H)^+$.

EJEMPLO DE REFERENCIA 64

Ester etílico de ácido (1S, 5S)-3-[(1S)-1-feniletil]-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico

[Fórmula 141]



Níquel de Raney (4 ml) se añadió a una solución de éster etílico de ácido (1R,5S)-3-[(1S)-1-feniletil]-6-espirociclopropan-2-tioxo-3-azabiciclo[3.2.0]heptan-1-ilcarboxílico (0.57 g, 1.73 mmoles) en etanol (40 ml). La mezcla se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 30 minutos. Después de filtración a través de Celite, el filtrado se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo y después se filtró a través de columna de gel de sílice corta. El filtrado se evaporó bajo presión reducida para dar 503 mg (97%) del compuesto del título como un aceite incoloro.

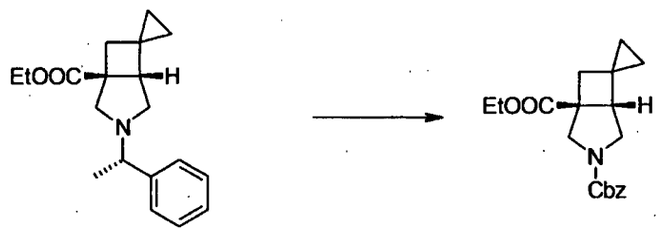
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.22-7.44 (5H, m), 4.20 (2H, q, J=7.0 Hz), 3.30 (1H, m), 3.24 (1H, d, J=8.8 Hz), 2.72 (1H, d, J=5.1 Hz), 2.59 (1H, d, J=11.5 Hz), 2.52 (1H, d, J=9.8 Hz), 2.45 (1H, d, J=8.8 Hz), 2.26 (1H, d, J=11.5 Hz), 1.95 (1H, dd, J=9.3, 5.6 Hz), 1.39 (3H, d, J=6.3 Hz), 1.29 (3H, t, J=7.1 Hz), 0.51 (1H, m), 0.31-0.40 (3H, m).

EM (ESI); m/z: 300 $(MH-H)^+$.

EJEMPLO DE REFERENCIA 65

Ester etílico de ácido (1S,5S)-3-benciloxicarbonil-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico

[Fórmula 142]



Cloroformiato de bencilo (0.72 ml, 5.04 mmoles) se añadió a una solución de éster etílico de ácido (1S,5S)-3-[(1S)-1-feniletil]-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico (503 mg, 1.68 mmoles) en diclorometano (10 ml). La mezcla se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 16 horas. El solvente se evaporó bajo presión reducida, y después el residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:9 → 1:4 → 1:2) para dar 505 mg (91%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.27-7.40 (5H, m), 5.18 (2H, m), 4.21 (2H, q, J=7.2 Hz), 3.92 (1H, dd, J=36.6, 12.0 Hz), 3.64 (2H, dd, J=23.3, 11.6 Hz), 3.27 (1H, m), 3.02 (1H, d, J=6.1 Hz), 2.73 (1H, m), 2.02 (1H, t, J=10.4 Hz), 1.29

811

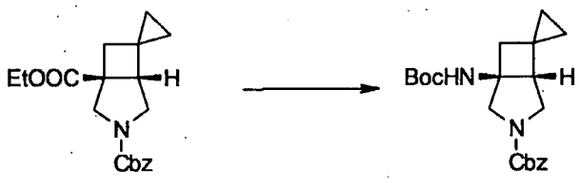
(3H, t, J=7.1 Hz), 0.47-0.58 (3H, m), 0.32 (1H, m).

EM (ESI); m/z: 330 $(M+H)^+$.

EJEMPLO DE REFERENCIA 66

(1S,5R)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-6-espirociclopropan-3-azabiciclo [3.2.0] heptano

[Fórmula 143]



Una solución de hidróxido de sodio 1N (4.60 ml, 4.60 mmoles) se añadió a una solución de éster etílico de ácido (1S,5S)-3-benciloxicarbonil-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico (500 mg, 1.52 mmoles) en etanol/tetrahidrofurano (4.6 ml/2.3 ml) a temperatura ambiente. La mezcla se agitó a la misma temperatura durante una hora. El solvente se evaporó bajo presión reducida, y el residuo se hizo ácido con ácido clorhídrico 1N, seguido por extracción con acetato de etilo (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró. El solvente se evaporó bajo presión reducida para dar ácido (1S,5S)-3-benciloxicarbonil-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico crudo (501 mg) como un sólido gomoso transparente incoloro.

Difenilfosforil azida (0.393 ml, 1.82 mmoles) se añadió a una solución del ácido (1S,5S)-3-benciloxicarbonil-6-espirociclopropan-3-azabiciclo [3.2.0] heptan-1-ilcarboxílico crudo resultante (501 mg) y trietilamina (0.381 ml, 2.73 mmoles) en tolueno (7.5 ml) a temperatura ambiente. La mezcla se agitó en

812

una atmósfera de nitrógeno a temperatura ambiente durante cinco minutos y subsecuentemente en un baño de aceite a 90°C durante 40 minutos. Enseguida, alcohol ter-butílico (15 ml) se añadió a la solución de reacción, y la mezcla se calentó con agitación en un baño de aceite a 120°C durante seis horas. El solvente de reacción se evaporó bajo presión reducida, y después el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 1:9 → 1:4 → 1:2) para dar 347 mg (dos pasos, 61%) del compuesto del título como un sólido gomoso transparente incoloro.

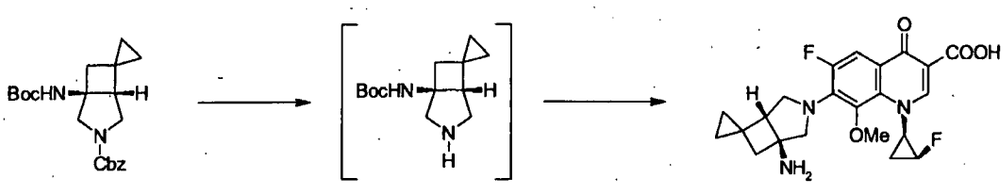
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.28-7.39 (5H, m), 5.16 (2H, m), 4.90 (1H, m), 3.95 (1H, t, J=11.6 Hz), 3.41-3.58 (3H, m), 2.80 (1H, m), 2.34 (1H, t, J=10.3 Hz), 2.20 (1H, d, J=12.0 Hz), 1.45 (9H, s), 0.46-0.56 (3H, m), 0.28 (1H, m).

EM (ESI) m/z : 317 $(M\text{-}tBu+H)^+$.

EJEMPLO 10

Acido 7-[(1S,5R)-1-amino-6-espirociclopropan-3-azabiciclo[3.2.0]heptan-3-il]-1-[(1R,2S)-2-fluorociclopropil]-6-fluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 144]



Un catalizador de 10% de paladio-carbón (aproximadamente 50% húmedo, 103 mg) se añadió a una solución de (1S,5R)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-6-espirociclopropan-3-azabiciclo [3.2.0]heptano (342 mg, 0.918 mmoles) en metanol (30 ml), y la mezcla se agitó en una atmósfera

de hidrógeno a temperatura ambiente durante 1.5 horas. El catalizador se removió por filtración, y después el solvente se evaporó bajo presión reducida para dar (1S,5R)-(ter-butoxicarbonilamino)-6-espirociclopropan-3-azabiciclo[3.2.0]heptano crudo (230 mg) como un sólido gomoso transparente incoloro.

Una mezcla del ácido (1S,5R)-1-(ter-butoxicarbonilamino)-6-espirociclopropan-3-azabiciclo [3.2.0] heptano crudo resultante (230 mg), ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (331 mg, 0.918 mmoles), trietilamina (0.384 ml, 2.76 mmoles), y sulfóxido de dimetilo (3 ml) se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 17 horas. Enseguida, etanol (20 ml), agua (5 ml), y trietilamina (2.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo en un baño de aceite a 110°C durante tres horas. El solvente se evaporó bajo presión reducida, y después una solución de ácido cítrico al 10% (50 ml) se añadió al residuo, seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con agua (50 ml x 2) y salmuera (50 ml) y se secó sobre sulfato de sodio anhidro, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en ácido clorhídrico concentrado (20 ml). La solución ácida resultante se transfirió a un embudo de separación y después se lavó con cloroformo (20 ml x 8). La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con un solvente mixto de cloroformo:metanol = 9:1 (200 ml x 2). Las capas orgánicas se combinaron y se secaron sobre sulfato de sodio anhidro y se filtraron, y después el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por recristalización a partir de etanol y se secó bajo presión reducida para dar

814

125 mg (32%) del compuesto del título como un polvo rosa claro, p.f.: 182-203°C (dec.).

$[\alpha]_D^{23.5}$=-14.4° (c= 0.104, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, d, J=1.2 Hz), 7.71 (1H, d, J=13.9 Hz), 4.98 (1H, dm, J=47.4 Hz), 4.03-4.08 (1H, m), 3.70-3.73 (1H, m), 3.70 (3H, s), 3.61 (1H, d, J=10.7 Hz), 3.37 (1H, m), 3.23 (1H, d, J=10.0 Hz), 2.42 (1H, d, J=5.9 Hz), 2.29 (1H, d, J=12.2 Hz), 2.16 (1H, d, J=12.5 Hz), 1.44-1.66 (2H, m), 0.48-0.57 (3H, m), 0.29-0.33 (1H, m).

Análisis calculado para $C_{22}H_{23}F_2N_3O_4 \cdot 0.75H_2O \cdot 0.25HCl$: C, 58.19; H, 5.49; N, 9.25; F, 8.37; Cl, 1.95.

Encontrado: C, 57.93; H, 5.41; N, 9.15; F, 8.43; Cl, 2.44.

EM (FAB) m/z: 432 $(M+H)^+$.

HRMS (FAB) calculado para $C_{22}H_{23}F_2N_3O_4$+H: 432.1735.

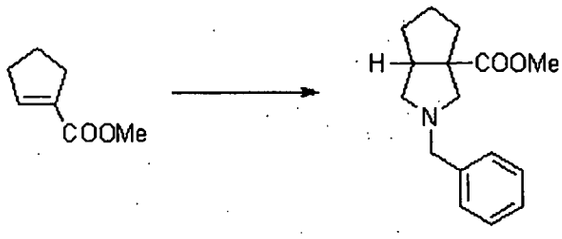
Encontrado: 432.1714.

IR (ATR) ν: 2871, 2763, 2721, 2575, 2517, 1720, 1612, 1568, 1535, 1493, 1456, 1365, 1350, 1321, 1267, 1205, 1157 cm^{-1}.

EJEMPLO DE REFERENCIA 67

Ester metílico de ácido (1R*, 5R*)-3-Bencil-3-azabiciclo[3.3.0] octan-1-ilcarboxílico

[Fórmula 145]



(±)-cis

815.

Una cantidad catalítica de ácido trifluoroacético se añadió a una solución de éster metílico de ácido 1-ciclopenten-1-carboxílico (2.52 g, 20.0 mmoles) y N-bencil-N-(metoximetil)-N-trimetilsililmetilamina (5.00 g, 21.1 mmoles) en diclorometano (40 ml) a temperatura ambiente, y la mezcla se calentó con agitación a temperatura ambiente durante 15.5 horas. La solución de reacción se diluyó con diclorometano (100 ml) y se lavó con una solución saturada de bicarbonato de sodio (80 ml). La capa acuosa lavada se extrajo adicionalmente con diclorometano (50 ml). Las capas orgánicas se combinaron y se secaron sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó gbajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 95:5 → 90:10 → 80:20) para dar 4.28 g (83%) del compuesto del título como un aceite transparente incoloro.

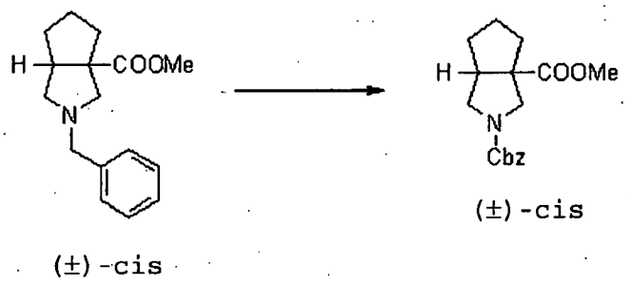
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.21 (5H, m), 3.67 (3H, s), 3.58 (1H, d, J=13.2 Hz), 3.52 (1H, d, J=13.2 Hz), 2.92 (1H, d, J=9.3 Hz), 2.88 (1H, m), 2.67 (1H, t, J=8.2 Hz), 2.44 (1H, d, J=9.3 Hz), 2.31 (1H, dd, J=8.8, 4.4 Hz), 2.06-1.60 (5H, m), 1.54-1.47 (1H, m).

EM (ESI); m/z: 260 $(M+H)^+$.

EJEMPLO DE REFERENCIA 68

Ester metílico de ácido (1R*, 5R*)-3-benciloxicarbonil-3-azabiciclo[3.3.0] octan-1-ilcarboxílico

[Fórmula 146]



Cloroformiato de bencilo (3.53 ml, 24.6 mmoles) se añadió a una solución de éster metílico de ácido (1R*,5R*)-3-bencil-3-azabiciclo[3.3.0] octan-1-ilcarboxílico (4.27 g, 16.46 mmoles) en diclorometano (50 ml) a temperatura ambiente, y la mezcla se agitó en un baño de aceite a 40°C durante 23 horas. El solvente se evaporó bajo presión reducida, y después el residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 90:10 → 80:20 → 67:33) para dar 2.24 g (45%) del compuesto del título como un aceite transparente incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.28 (5H, m), 5.12 (2H, s), 3.97 (1H, d, J=11.7 Hz), 3.71-3.64 (4H, m), 3.45-3.28 (2H, m), 2.94-2.87 (1H, m), 2.23-2.15 (1H, m), 2.03-1.94 (1H, m), 1.85-1.71 (3H, m), 1.52 (1H, m).

EM (ESI) m/z: 304 $(M+H)^+$.

EJEMPLO DE REFERENCIA 69

(1R*, 5R*)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano

[Fórmula 147]



(±)-cis (±)-cis

Una solución de hidróxido de sodio 1N (22.0 ml, 22.0 mmoles) se añadió a una solución de éster metílico de ácido (1R*,5R*)-3-benciloxicarbonil-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (2.21 g, 7.29 mmoles) en metanol (22 ml)-tetrahidrofurano (44 ml) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante dos horas. El solvente se concentró bajo presión

reducida, y después el residuo se hizo ácido con ácido clorhídrico 3N, seguido por extracción con acetato de etilo (200 ml). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida para dar ácido carboxílico crudo. El ácido carboxílico crudo resultante se usó para la siguiente reacción sin purificación adicional.

Difenilfosforil azida (2.03 ml, 9.42 mmoles) se añadió a una solución del ácido carboxílico crudo obtenido antes y trietilamina (2.02 ml, 14.5 mmoles) en tolueno (40 ml) bajo enfriamiento con hielo. La mezcla se calentó con agitación a temperatura ambiente durante 30 minutos y después en un baño de aceite a 90°C durante 3.5 horas. La solución de reacción se diluyó con acetato de etilo (200 ml) y secuencialmente se lavó con una solución saturada de bicarbonato de sodio (80 ml), agua (80 ml), y salmuera (80 ml). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida para dar isocianato crudo. El isocianato crudo resultante se disolvió en 1,4-dioxano (20 ml), y se añadió ácido clorhídrico 6N (20 ml). Después, la mezcla se calentó con agitación en un baño de aceite a 50°C durante 0.5 horas. La solución de reacción se diluyó con agua y etanol, se concentró bajo presión reducida, y después se destiló azeotrópicamente con etanol (dos veces). El residuo se disolvió en diclorometano (40 ml), y trietilamina (5.05 ml, 36.3 mmoles) y dicarbonato de di-ter-butilo (3.17 g, 14.5 mmoles) se añadieron secuencialmente a temperatura ambiente. La solución de reacción se agitó a temperatura ambiente durante cinco horas, y después se diluyó con acetato de etilo (200 ml) y se lavó con agua (80 ml) y salmuera (80 ml). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre

gel de sílice (hexano :acetato de etilo = 90:10 → 80:20 → 67:33) para dar 1.32 g (3.66 mmoles, 51%) del compuesto del título como un sólido gomoso transparente incoloro.

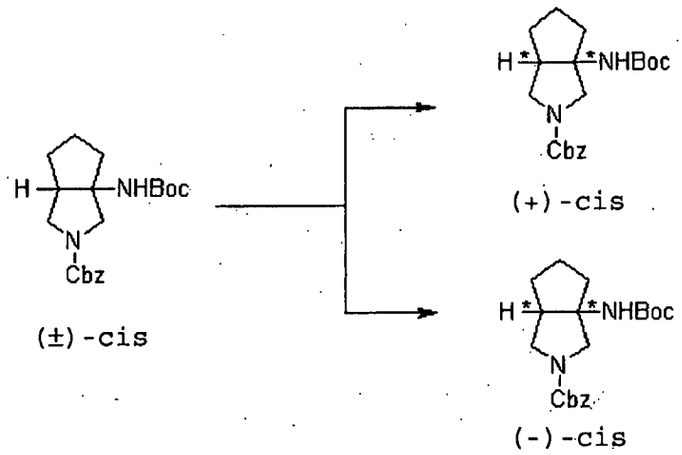
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.27 (5H, m), 5.12 (2H, s), 4.75 (1H, brs), 3.74-3.59 (3H, m), 3.31-3.23 (1H, m), 2.74-2.48 (1H, m), 2.04-1.88 (3H, m), 1.80-1.71 (2H, m), 1.43 (10H, m).

EM (ESI) m/z: 305 $(M\text{-}tBu+H)^+$.

EJEMPLO DE REFERENCIA 70

(+)-(1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano y (-)-(1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano

[Fórmula 148]



El racemato (1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonil-amino)-3-azabiciclo[3.3.0] octano (1.32 g, 3.66 mmoles) obtenido como se describió antes se resolvió ópticamente mediante una columna ópticamente activa (CHIRALCEL OJ, 20 mm de diámetro x 250 mm, hexano : alcohol isopropílico = 90:10, velocidad de flujo = 20 ml/min, resolviendo 50 mg cada vez) para dar (+)-(1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-

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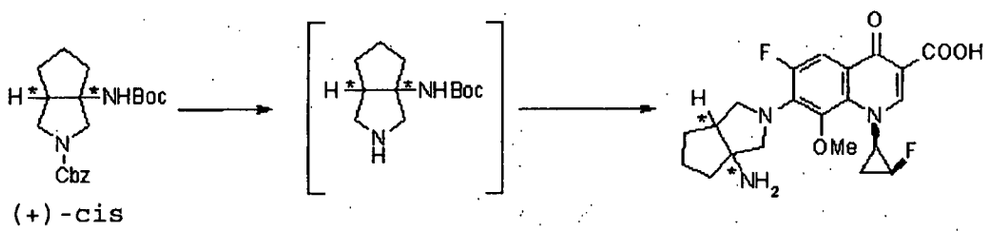
azabiciclo [3.3.0] octano (586 mg, 1.626 mmoles, tiempo de retención = 5.5 min, $[\alpha]_D^{25.1}$ = +19.3° (c = 0.145, cloroformo)) y (-)-(1R*,S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano (590 mg, 1.637 mmoles, tiempo de retención = 6.9 min, $[\alpha]_D^{25.1}$ = -20.0° (c = 0.155, cloroformo).

EJEMPLO 11

Acido 7-{(1R*,5S*)-1-amino-3-azabiciclo[3.3.0]octan-3-il}-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico

[sustituyente en la posición 7 derivado del (+)-isómero óptico]

[Fórmula 149]



Un catalizador de 10% de paladio-carbón (aproximadamente 50% húmedo, 115 mg) se añadió a una solución de (+)-(1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo[3.3.0]octano (575 mg, 1.595 mmoles) en metanol (20 ml), y la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante dos horas. El catalizador se removió por filtración, y después el solvente se evaporó bajo presión reducida para dar 1-(ter-butoxicarbonilamino)-3-azabiciclo[3.3.0]octano crudo (388 mg) como un sólido gomoso transparente incoloro.

El 1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano crudo obtenido antes (388 mg), ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (576 mg, 1.595

mmoles), y trietilamina (0.667 ml, 4.79 mmoles) se disolvieron en sulfóxido de dimetilo (4 ml), y la solución se calentó con agitación en un baño de aceite a 35 a 40°C durante 16 horas. Una solución mixta de etanol : agua = 4:1 (50 ml) y trietilamina (5 ml) se añadió a la solución de reacción, y la mezcla se calentó a reflujo en un baño de aceite a 90°C durante tres horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (200 ml) y se lavó con una solución de ácido cítrico al 10% (80 ml), agua (50 ml x 2), y salmuera (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en ácido clorhídrico concentrado (10 ml) bajo enfriamiento con hielo. Después de agitar a temperatura ambiente durante 20 minutos, la solución de reacción se lavó con cloroformo (30 ml x 3). La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se suspendió en metanol y se filtró. Después, el filtrado se concentró bajo presión reducida (dos veces), se suspendió en un solvente mixto de cloroformo:metanol = 9:1 subsecuentemente, y se filtró. La solución madre se concentró bajo presión reducida para remover cloruro de sodio. El residuo resultante se purificó por CCDP (CCD preparativa; solvente de capa inferior de cloroformo:metanol:agua = 7:3:1) y subsecuentemente se purificó por recristalización a partir de etanol-amoniaco acuoso para dar 111 mg (17%) del compuesto del título como un polvo amarillo pálido. p.f.: 169-172°C.

$[\alpha]_D^{25.1}$= +103.5° (c=0.228, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 7.68 (1H, d, J=13.9 Hz), 5.05-4.80 (1H, m), 4.04 (1H, m), 3.77 (1H, t, J=9.0 Hz), 3.63 (3H, s),

822

3.52 (2H, s), 3.35 (1H, dd, J=9.8, 4.9 Hz), 2.30 (1H, m), 2.04 (1H, m), 1.89-1.47 (7H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.25EtOH \cdot 0.75H_2O$: C, 58.10; H, 5.90; F, 8.55; N, 9.45.

Encontrado: C, 57.87; H, 5.51; F, 8.60; N, 9.11.

EM (EI) ; m/z: 419 (M^+).

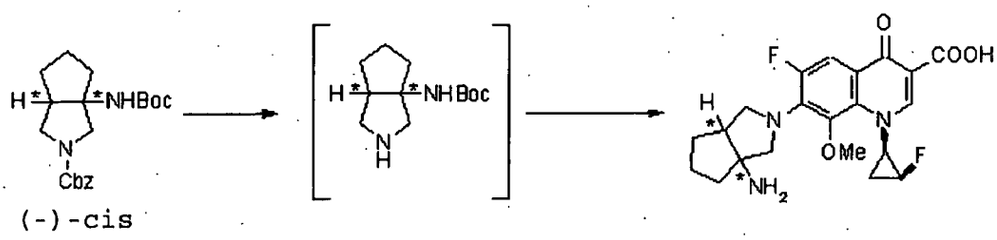
IR (ATR) ν: 2952, 2873, 2831, 2177, 1712, 1614, 1577, 1535, 1498, 1460, 1389, 1360, 1323, 1271, 1205 cm^{-1}.

EJEMPLO 12

Acido 7-[(1R*,5S*)-1-amino-3-azabiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico

[sustituyente en la posición 7 derivado del (-)-isómero óptico]

[Fórmula 150]



Un catalizador de 10% de paladio-carbón (aproximadamente 50% húmedo, 114 mg) se añadió a una solución de (-)-(1R*,5S*)-3-benciloxicarbonil-1-(ter-butoxicarbonilamino)-3-azabiciclo[3.3.0]octano (569 mg, 1.579 mmoles) en metanol (30 ml), y la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante dos horas. El catalizador se removió por filtración, y después el solvente se evaporó bajo presión reducida para dar 1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0] octano crudo (373 mg) como un sólido gomoso transparente incoloro.

823

El 1-(ter-butoxicarbonilamino)-3-azabiciclo[3.3.0]octano crudo obtenido antes (373 mg), ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (570 mg, 1.579 mmoles), y trietilamina (0.660 ml, 4.74 mmoles) se disolvieron en sulfóxido de dimetilo (4 ml), y la solución se calentó con agitación en un baño de aceite a 35 a 40°C durante 16 horas. Una solución mixta de etanol :agua = 4:1 (50 ml) y trietilamina (5 ml) se añadió a la solución de reacción, y la mezcla se calentó a reflujo en un baño de aceite a 90°C durante tres horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (200 ml) y se lavó con una solución de ácido cítrico al 10% (80 ml), agua (50 ml x 2), y salmuera (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en ácido clorhídrico concentrado (10 ml) bajo enfriamiento con hielo. Después de agitar a temperatura ambiente durante 20 minutos, la solución de reacción se lavó con cloroformo (30 ml x 3). La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se suspendió en metanol : amoniaco acuoso = 20:1 y se filtró. Después, el filtrado se concentró bajo presión reducida (dos veces), y subsecuentemente se suspendió en un solvente mixto de cloroformo:metanol = 9:1 y se filtró. La solución madre se concentró bajo presión reducida para remover cloruro de sodio. El residuo resultante se purificó por PTLC (solvente de capa inferior de cloroformo:metanol:agua = 7:3:1) y se cristalizó en etanol-éter dietílico para dar 32 mg (5%) del compuesto del título como un polvo café-amarillo, p.f.: 171-174°C.

$[\alpha]_D^{25.1}$= +52.1° (c=0.073, NaOH 0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 7.65 (1H, d, J=13.9 Hz), 5.02-4.82 (1H, m), 4.00 (1H, m), 3.86-3.80 (1H, m), 3.62-3.55 (4H, m), 3.36-3.31 (1H, m), 3.15-3.10 (1H, m), 2.24 (1H, m), 2.05-1.30 (8H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.5EtOH \cdot 1.25H_2O$: C, 56.83; H, 6.18; F, 8.17; N, 9.04.

Encontrado: C, 56.41; H, 5.68; F, 8.76; N, 8.64.

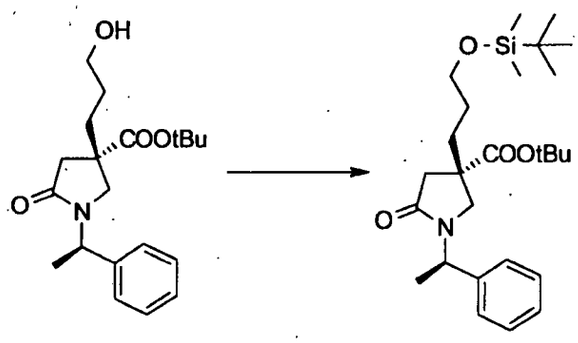
EM (EI) ; m/z: 419 (M^+).

IR (ATR) ν: 2948, 2871, 2576, 2162, 1712, 1616, 1566, 1495, 1456, 1390, 1363, 1319, 1269 cm^{-1}.

EJEMPLO DE REFERENCIA 71

Ester ter-butílico de ácido (3S)-3-[3-(ter-butildimetilsililoxi)-1-propil]-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 151]



Ester ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (46 g) e imidazol (11.9 g) se disolvieron en dimetilformamida (600 ml). Después de la adición de cloruro de ter-butildimetilsililo (23.2 g) bajo enfriamiento con hielo, la mezcla se agitó a temperatura ambiente durante 59.5 horas. La solución de reacción se extrajo

825

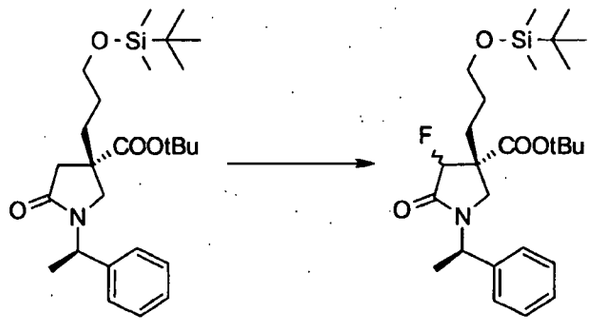
con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó secuencialmente con bicarbonato de sodio saturado acuoso y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 9:1 → 8:2 → 2:1) para dar 29.7 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.22 (5H, m), 5.48 (1H, q, J=7.11 Hz), 3.58 (2H, t, J=6.13 Hz), 3.34 (1H, d, J=10.05 Hz), 3.12 (1H, d, J=10.05 Hz), 2.94 (1H, d, J=16.91 Hz), 2.31 (1H, d, J=17.16 Hz), 1.86-1.74 (1H, m), 1.72-1.62 (1H, m), 1.51 (3H, d, J=7.11 Hz), 1.49-1.24 (2H, m), 1.33 (9H, s), 0.88 (9H, s), 0.03 (6H, s).

EJEMPLO DE REFERENCIA 72

Ester ter-butílico de ácido (3S)-3-[3-(ter-butildimetilsililoxi)-1-propil]-4-fluoro-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 152]



Ester ter-butílico de ácido (3S)-3-[3-(ter-butildimetilsililoxi)-1-propil]-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (30 g) se disolvió en tetrahidrofurano (280 ml), y la atmósfera se reemplazó con argón. Después,

826

hexametildisilazida de litio (solución 1.0 M en tetrahidrofurano) (78.0 ml) se añadió gota a gota a -15°C, y la mezcla se agitó a -5°C durante 30 minutos. Después de enfriar a -15°C nuevamente, una solución de N-fluorobencensulfonimida (26.6 g) en tetrahidrofurano (220 ml) se añadió gota a gota, y la mezcla se agitó a temperatura ambiente durante 17 horas. La solución de reacción se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 9:1 → 8:2) para dar 8.15 g del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.23 (5H, m), 5.53-5.44 (1H, m), 5.18 (1H, d, J=51.72 Hz), 3.64-3.52 (2H, m), 3.32-3.19 (2H, m), 1.92-1.65 (2H, m), 1.55 (3H, d, J=4.66 Hz), 1.33 (9H, s), 0.88 (9H, s), 0.03 (6H, s).

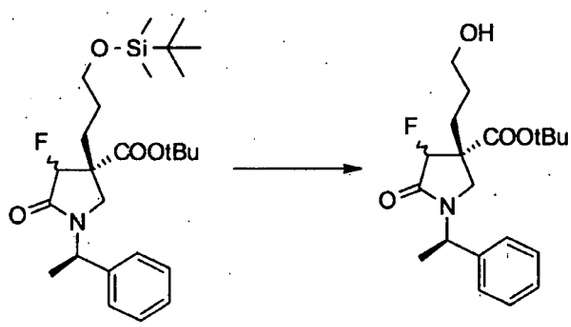
EM (FAB) m/z: 480 $(M+H)^+$.

IR (ATR) ν: 3421, 2977, 2935, 2877, 1698, 1454, 1369, 1309, 1249, 1153, 1058, 1035, 1006, 842 cm^{-1}.

EJEMPLO DE REFERENCIA 73

Ester ter-butílico de ácido (3S)-4-fluoro-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 153]



827

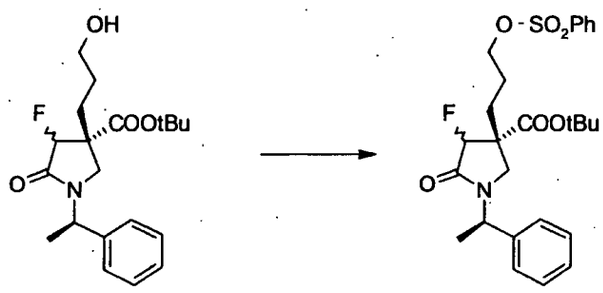
Ester ter-butílico de ácido (3S)-3-[3-(ter-butildimetilsililoxi)-1-propil]-4-fluoro-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (8.15 g) se disolvió en tetrahidrofurano (25.0 ml). Se añadieron ácido acético (22.0 ml) y fluoruro de tetrabutilamonio (solución 1.0 M en tetrahidrofurano) (25.0 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 21.5 horas. La solución de reacción se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó secuencialmente con bicarbonato de sodio saturado acuoso y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 9:1 → 8:2 → 1:1) para dar 5.77 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.22 (5H, m), 5.48 (1H, q, J=7.03 Hz), 5.20 (1H, d, J=51.48 Hz), 3.69-3.59 (2H, m), 3.31-3.21 (2H, m), 1.95-1.72 (2H, m), 1.68-1.43 (2H, m), 1.56 (3H, d, J=7.11 Hz), 1.33 (9H, s).

EJEMPLO DE REFERENCIA 74

Ester ter-butílico de ácido (3S)-3-(3-bencensulfoniloxi-1-propil)-4-fluoro-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 154]



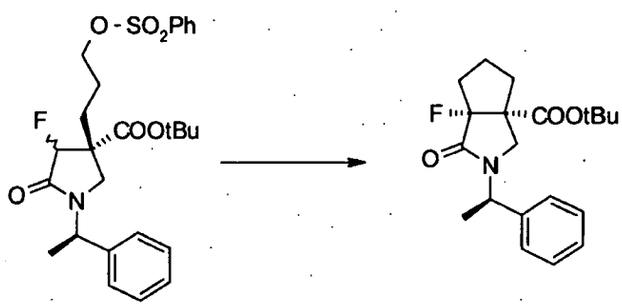
Ester ter-butílico de ácido (3S)-4-fluoro-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (12.20 g) se disolvió en diclorometano (400 ml). Cloruro de bencensulfonilo (9.06 ml), trietilamina (10.7 ml), y 4-dimetilaminopiridina (2.04 g) se añadieron bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 12.5 horas. Bicarbonato de sodio saturado acuoso se añadió a la solución de reacción, y la mezcla se agitó durante 30 minutos, seguido por extracción con diclorometano. La capa orgánica se lavó secuencialmente con una solución de ácido cítrico al 10% y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 8:2 → 1:1) para dar 11.7 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.94-7.87 (2H, m), 7.71-7.63 (1H, m), 7.60-7.53 (2H, m), 7.37-7.23 (5H, m), 5.46 (1H, q, J=7.11 Hz), 5.15 (1H, d, J=51.48 Hz), 4.10-3.98 (2H, m), 3.26-3.15 (2H, m), 1.88-1.50 (4H, m), 1.55 (3H, s), 1.30 (9H, s).

EJEMPLO DE REFERENCIA 75

Ester ter-butílico de ácido (1S,5R)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 155]



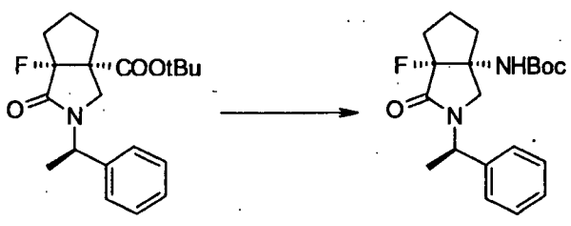
Ester ter-butílico de ácido (3S)-3-(3-bencenosulfoniloxi-1-propil)-4-fluoro-5-oxo-1-[(1R)-1-feniletillpirrolidin-3-carboxílico (10.9 g) se disolvió en tetrahidrofurano (350 ml), y la atmósfera se reemplazó con argón. Después, hexametildisilazida de potasio (solución 0.5 M en tolueno) (86.5 ml) se añadió gota a gota a -15°C, y la mezcla se agitó a 0°C durante 1.5 horas. Después de enfriar a –10°C, cloruro de amonio acuoso saturado (100 ml) se añadió gota a gota, y la mezcla se agitó a temperatura ambiente durante 30 minutos. La solución de reacción se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 9:1 → 7:1) para dar 4.36 g del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.58-5.49 (1H, m), 3.63 (1H, d, J=10.3 Hz), 2.91 (1H, dd, J=10.3, 3.2 Hz), 2.67-2.56 (1H, m), 2.50-2.38 (1H, m), 2.26-2.09 (1H, m), 2.06-1.94 (1H, m), 1.74-1.66 (1H, m), 1.54 (3H, d, J=7.1 Hz), 1.50-1.40 (1H, m), 1.34 (9H, s).

EJEMPLO DE REFERENCIA 76

(1R, 5R)-1-(ter-butoxicarbonilamino)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 156]



830.

Ester ter-butílico de ácido (1S,5R)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0]octan-1-ilcarboxílico (4.36 g, 12.5 mmoles) se disolvió en diclorometano (70 ml). Acido trifluoroacético (70 ml) se añadió gota a gota, y la mezcla se agitó a temperatura ambiente durante seis horas. El solvente se evaporó bajo presión reducida, y después el residuo se destiló azeotrópicamente con tolueno para dar ácido carboxílico (3.70 g).

El ácido carboxílico resultante se disolvió en tolueno. Trietilamina (3.51 ml, 25.2 mmoles) y difenilfosforil azida (2.98 ml, 13.8 mmoles) se añadieron, y la mezcla se calentó a reflujo durante cinco horas. El solvente se evaporó bajo presión reducida. Después, 1,4-dioxano (110 ml) y ácido clorhídrico 6N (110 ml) se añadieron al residuo, y la mezcla se agitó a 60°C durante 2.5 horas. Después de extracción con agua y acetato de etilo, la capa acuosa se hizo alcalina con una solución saturada de hidróxido de sodio y se extrajo con cloroformo dos veces. Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron, y después el solvente se evaporó bajo presión reducida. Dicarbonato de di-ter-butilo (11.05 g) se añadió al residuo, y la mezcla se agitó a 75°C durante seis horas. La solución de reacción se concentró bajo presión reducida, y después el residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 9:1 → 1:1) para dar 3.69 g del compuesto del título como un aceite amarillo pálido.

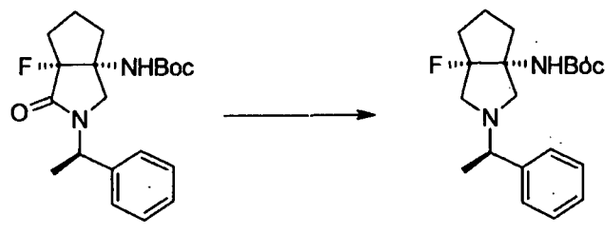
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.23 (5H, m), 5.50 (1H, q, J=7.1 Hz), 5.22 (1H, brs), 3.34 (2H, s), 2.49-2.37 (1H, m), 2.32-2.03 (3H, m), 2.02-1.90 (1H, m), 1.51 (3H, d, J=7.1 Hz), 1.55-1.48 (1H, m), 1.35 (9H, s).

831

EJEMPLO DE REFERENCIA 77

(1R, 5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 157]



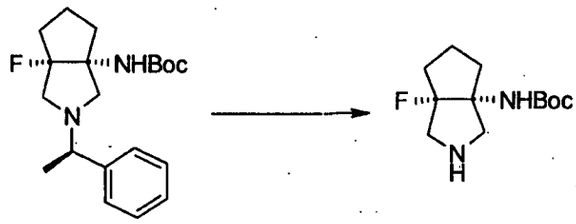
(1R,5R)-1-(ter-Butoxicarbonilamino)-5-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0]octano (3.69 g, 10.2 mmoles) se disolvió en tetrahidrofurano (200 ml). Una solución 1.20 M de un complejo de borano-tetrahidrofurano en tetrahidrofurano (42.4 ml, 50.9 mmoles) se añadió gota a gota bajo enfriamiento con hielo, y la mezcla se agitó durante dos horas mientras se calentaba gradualmente a temperatura ambiente. El solvente se evaporó bajo presión reducida. Bajo enfriamiento con hielo, etanol acuoso al 90% (100 ml) y trietilamina (100 ml) se añadieron al residuo, y la mezcla se calentó a reflujo durante dos horas. El solvente se evaporó bajo presión reducida, y después el residuo se extrajo con bicarbonato de sodio saturado acuoso y diclorometano. Posteriormente, la sustancia objetivo se extrajo a partir de la capa acuosa con diclorometano. Las capas orgánicas se combinaron, se lavaron con salmuera, y se secaron sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 95:5 → 90:10) para dar 3.33 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.18 (5H, m), 5.38 (1H, brs), 3.22 (1H, q, J=6.37 Hz), 2.92-2.57 (4H, m), 2.12-1.86 (4H, m), 1.80-1.67 (1H, m), 1.63-1.52 (3H, m), 1.42 (9H, s), 1.32 (3H, d, J=6.37 Hz).

EJEMPLO DE REFERENCIA 78

(1R, 5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo [3.3.0] octano

[Fórmula 158]



(1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octanp (700 mg, 2.0 mmoles) se disolvió en etanol (30 ml). Se añadió 10% de paladio-carbón (50% húmedo) (1.01 g) y la mezcla se agitó en una atmósfera de hidrógeno a 50°C durante 15 horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. El residuo resultante se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 98:2 → 95:5) para dar 446 mg del compuesto del título como un sólido amarillo pálido.

$[\alpha]_D^{23}$ -15° (c=0.100, MeOH).

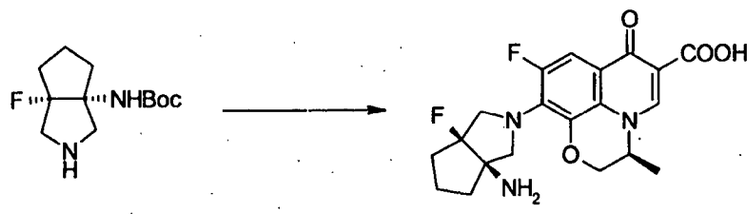
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 5.29 (1H, brs), 3.47-3.18 (2H, m), 2.93-2.79 (2H, m), 2.15-1.71 (6H, m), 1.45 (9H, s).

853

EJEMPLO 13

Acido 10-[(1R,5S)-1-amino-5-fluoro-3-azabiciclo [3.3.0] octan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2, 3-de] [1, 4] benzoxazin-6-carboxílico

[Fórmula 159]



Trietilamina (0.222 ml, 1.59 mmoles) y ácido 9,10-difluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazin-6-carboxílico-quelato de BF_2 (209 mg, 0.64 mmoles) se añadieron a una solución de (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.3.0]octano (129 mg, 0.53 mmoles) en sulfóxido de dimetilo (4.0 ml). La mezcla se agitó a 40°C durante 18.5 horas. Trietilamina (0.111 ml, 0.80 mmoles) se añadió adicionalmente a la solución de reacción, y la mezcla se agitó a 40°C durante 6.5 horas. Etanol (6.0 ml), agua (2.0 ml), y trietilamina (2.0 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. El solvente se evaporó bajo presión reducida, y después el residuo se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua dos veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 99:1 → 98:2) para dar un aceite (261 mg). El aceite resultante (261 mg) se disolvió en ácido clorhídrico concentrado (2.4 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante tres horas. La solución de

reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Se añadió 10% de metanol-cloroformo al residuo. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol-amoniaco acuoso para dar 145 mg del compuesto del título como un sólido amarillo pálido. p.f.: 285-293°C (dec).

$[\alpha]_D^{24}$ -40.3° (c=0.100, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, d, J=1.23 Hz), 7.70 (1H, d, J=13.7 Hz), 5.07-4.85 (1H, m), 4.10-4.02 (1H, m), 3.93-3.78 (2H, m), 3.70-3.53 (2H, m), 3.66 (3H, s), 2.21-2.04 (2H, m), 2.01-1.83 (2H, m), 1.83-1.46 (4H, m).

EM (FAB) m/z: 406 $(M+H)^+$.

Análisis calculado para $C_{20}H_{21}F_2N_3O_4$: C, 59.25; H, 5.22; F, 9.37; N, 10.37.

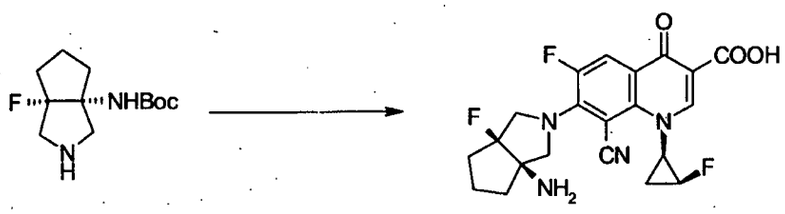
Encontrado: C, 59.22; H, 5.16; F, 9.16; N, 10.27.

IR (ATR) ν: 3365, 2931, 2861, 1706, 1619, 1521, 1461, 1442, 1415, 1396, 1278, 1230, 1141, 1130, 1093, 1047, 983, 964, 900, 879, 863, 800 cm^{-1}.

EJEMPLO 14

Acido 7-[(1R, 5S)-1-amino-5-fluoro-3-azabiciclo [3.3.0] octan-3-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-4-oxoquinolin-3-carboxílico

[Fórmula 160]



Trietilamina (0.272 ml, 1.95 mmoles) y éster etílico de ácido 8-ciano-6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-6,7-difluoro-1,4-dihidro-4-oxoquinolin-3-carboxílico (240 mg, 0.71 mmoles) se añadieron a una solución de (1R,5R)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.3.0] octano (148 mg, 0.61 mmoles) en acetonitrilo (10 ml), y la mezcla se agitó a temperatura ambiente durante tres días. El solvente se evaporó bajo presión reducida, y después el residuo se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 1:1 → 3:7) para dar éster etílico sustituido con un sustituyente en la posición 7 (231 mg). El éster etílico resultante (231 mg) se disolvió en tetrahidrofurano (3.0 ml) y etanol (6.0 ml). Una solución de hidróxido de sodio 1N (0.82 ml) se añadió, y la mezcla se agitó a temperatura ambiente durante 3.5 horas. El solvente se evaporó bajo presión reducida, y después el residuo se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio

836

anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. Se añadió ácido clorhídrico concentrado (2.0 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante una hora. Posteriormente, la solución de reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Se añadió 10% de metanol-cloroformo al residuo, y el material insoluble se removió por filtración. Después, el filtrado se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol-amoniaco acuoso para dar 128 mg del compuesto del título como un sólido amarillo pálido, p.f.: 268-280°C (dec.).

$[\alpha]_D^{24}$ -1.8° (c=0.100, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.40 (1H, d, J=1.96 Hz), 7.96 (1H, d, J=14.46 Hz), 5.29-5.05 (1H, m), 4.28-4.00 (3H, m), 3.94-3.80 (2H, m), 2.23-2.10 (2H, m), 2.04-1.56 (6H, m).

EM (FAB); m/z: 433 $(M+H)^+$.

Análisis calculado para $C_{21}H_{19}F_3N_4O_3$: C, 58.33; H, 4.43; F, 13.18; N, 12.96

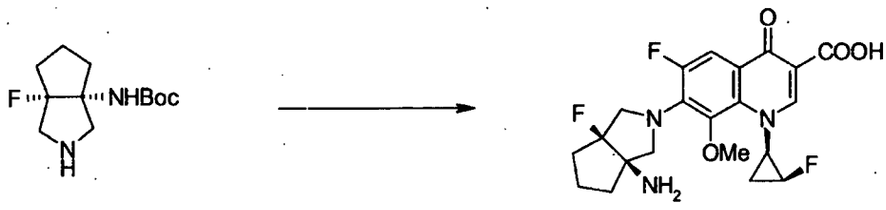
Encontrado: C, 58.24; H, 4.36; F, 13.10; N, 12.84.

IR (ATR) ν: 3359, 3039, 2213, 1720, 1623, 1552, 1477, 1452, 1405, 1375, 1311, 1259, 1226, 1172, 1137, 1112, 1074, 1054, 991, 931, 887, 806 cm^{-1}.

EJEMPLO 15

Acido 7-[(1R, 5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 161]



Trietilamina (3.30 ml, 23.7 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (2.93 g, 8.12 mmoles) se añadieron a una solución de (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.3.0]octano (1.32 g, 5.40 mmoles) en sulfóxido de dimetilo (30 ml). La mezcla se agitó a 40°C durante 19 horas. Trietilamina (1.70 ml, 12.3 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (1.00 g, 2.77 mmoles) se añadieron adicionalmente a la solución de reacción, y la mezcla se agitó a 40°C durante 16 horas. Etanol (45 ml), agua (15 ml), y trietilamina (15 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. El solvente se evaporó bajo presión reducida, y después el residuo resultante se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua tres veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 99:1). El aceite resultante (3.30 g) se disolvió en ácido clorhídrico concentrado

(20 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante una hora. La solución de reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Cloroformo se añadió al residuo. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol para dar 769 mg del compuesto del título como un sólido amarillo pálido, p.f.: 191-195°C (dec.).

$[\alpha]_D^{24}$ +97° (c=0.100, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, d, J=1.23 Hz), 7.70 (1H, d, J=13.73 Hz), 5.07-4.85 (1H, m), 4.10-4.02 (1H, m), 3.93-3.78 (2H, m), 3.70-3.53 (2H, m), 3.66 (3H, s), 2.21-2.04 (2H, m), 2.01-1.83 (2H, m), 1.83-1.46 (4H, m).

EM (FAB); m/z: 438 $(M+H)^+$.

Análisis calculado para $C_{21}H_{22}F_3N_3O_4 \cdot 0.75H_2O$: C, 55.94; H, 5.25; F, 12.64; N, 9.32.

Encontrado: C, 56.03; H, 5.51; F, 12.79; N, 9.66.

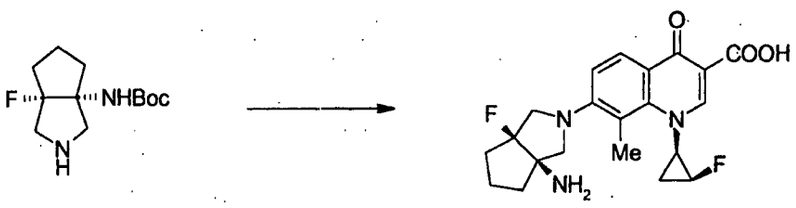
IR (ATR) ν: 2958, 2871, 1724, 1621, 1513, 1452, 1319, 1056, 929, 804 cm^{-1}.

839

EJEMPLO 16

Acido 7-[(1R,5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0] octan-3-il]-1-[(1R,2S)-2-f luorociclopropan]-1, 4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 162]



Trietilamina (0.447 ml, 3.21 mmoles) y ácido 7-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (450 mg, 1.61 mmoles) se añadieron a una solución de (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.3.0]octano (260 mg, 1.07 mmoles) en sulfóxido de dimetilo (6.0 ml), y la mezcla se agitó a 70 a 80°C durante 18.5 horas. Trietilamina (0.224 ml, 1.61 mmoles) se añadió nuevamente a la solución de reacción, y la mezcla se agitó a 70 a 80°C durante seis días. Trietilamina (0.447 ml, 3.21 mmoles) se añadió adicionalmente, la mezcla se agitó a 70 a 80°C durante 10 días. La solución de reacción se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua dos veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 98:2) para dar un aceite (369 mg). El aceite resultante (369 mg) se disolvió en ácido clorhídrico concentrado (3.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante una hora. La solución de reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH

840

7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por CCDP (revelada con la capa inferior de cloroformo:metanol:agua = 7:3:1). Después, la fracción resultante se concentró bajo presión reducida para dar un residuo, que se solidificó con isopropanol para dar 21 mg del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.50 (1H, d, J=2.94 Hz), 8.06 (1H, d, J=8.58 Hz), 7.13 (1H, d, J=8.82 Hz), 5.13-4.90 (1H, m), 4.18-4.10 (1H, m), 3.89-3.77 (1H, m), 3.45-3.25 (3H, m), 2.58 (3H, s), 2.20-1.98 (3H, m), 1.93-1.82 (1H, m), 1.81-1.57 (3H, m), 1.37-1.22 (1H, m).

EM (FAB); m/z: 404 $(M+H)^+$.

Análisis calculado para $C_{21}H_{23}F_2N_3O_3 \cdot 0.5H_2O \cdot 0.25$IPA: C, 61.11; H, 6.13; N, 9.83.

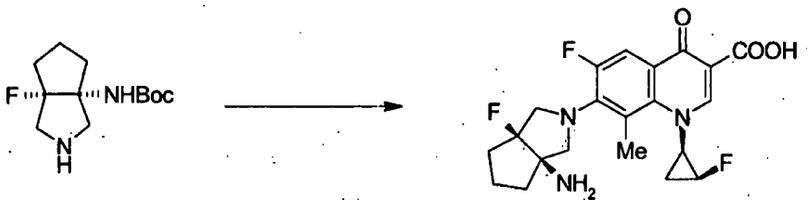
Encontrado: C, 61.11; H, 5.72; N, 9.74.

IR (ATR) ν: 2956, 2873, 2823, 1708, 1610, 1508, 1432, 1355, 1313, 1255, 1133, 929 cm^{-1}.

EJEMPLO 17

Acido 7-[(1R,5S)-1-amino-5-fluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 163]



841

Trietilamina (0.215 ml, 1.54 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico-quelato de BF_2 (530 mg, 1.53 mmoles) se añadieron a una solución de (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo[3.3.0]octano (250 mg, 1.02 mmoles) en sulfóxido de dimetilo (5.0 ml). La mezcla se agitó a temperatura ambiente durante siete días. Trietilamina (0.215 ml, 1.54 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico-quelato de BF_2 (530 mg, 1.53 mmoles) se añadieron adicionalmente a la solución de reacción, y la mezcla se agitó a temperatura ambiente durante siete días. Trietilamina (0.215 ml, 1.54 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico-quelato de BF_2 (530 mg, 1.53 mmoles) se añadieron adicionalmente a la solución de reacción, y la mezcla se agitó a temperatura ambiente durante diez días. Etanol (6.0 ml), agua (2.0 ml), y trietilamina (2.0 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante una hora. El solvente se evaporó bajo presión reducida, y después el residuo se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua dos veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 98:2), y la fracción resultante se concentró bajo presión reducida. Después, el residuo se disolvió en ácido clorhídrico concentrado (3.5 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante una hora. La solución de reacción se lavó con cloroformo cinco veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La

842

solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por CCDP (revelada con la capa inferior de cloroformo:metanol: agua = 7:3:1). El residuo resultante se solidificó con isopropanol para dar 7.1 mg del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.50 (1H, s), 7.77 (1H, d, J=13.73 Hz), 5.80-4.80 (1H, m), 4.22-4.10 (1H, m), 3.99-3.85 (1H, m), 3.68-3.47 (2H, m), 3.43-3.34 (1H, m), 2.68 (3H, s), 2.21-1.98 (3H, m), 1.97-1.56 (4H, m), 1.42-1.23 (1H, m).

EM (FAB) ; m/z: 422 $(M+H)^+$.

Análisis calculado para $C_{21}H_{22}F_3N_3O_3 \cdot 0.5H_2O \cdot 0.25$IPA: C, 58.65; H, 5.66; F, 12.80; N, 9.43.

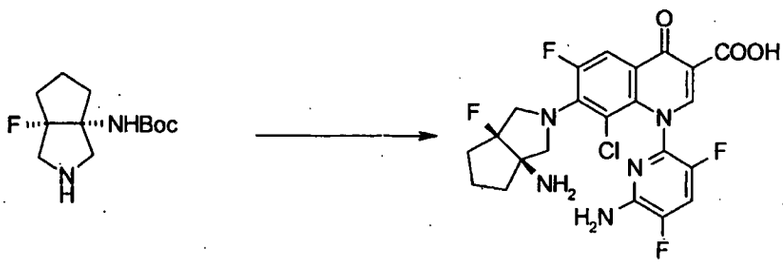
Encontrado: C, 58.63; H, 5.35; F, 12.35; N, 9.22.

IR (ATR) ν: 2971, 2856, 1722, 1614, 1450, 1432, 1322, 1132, 1097, 987, 954, 929, 887, 856, 804 cm^{-1}.

EJEMPLO 18

Acido 7-[(1R, 5S)-1-amino-5-fluoro-3-azabiciclo [3.3.0]octan-3-il]-1-(6-amino-3,5-difluoropiridin-2-il)-1, 4-dihidro-8-cloro-6-fluoro-4-oxoquinolin-3-carboxílico

[Fórmula 164]



N-metilpirrolidina (0.246 ml, 2.37 mmoles) y ácido 1-(6-amino-3,5-difluoropiridin-2-il)-8-cloro-6,7-difluoro-1,4-dihidro-4-oxoquinolin-3-carboxílico (306 mg, 0.79 mmoles) se añadieron a una solución de (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo [3.3.0] octano (193 mg, 0.79 mmoles) en acetonitrilo (10.0 ml), y la mezcla se calentó a reflujo durante 10 horas. Acido 1-(6-amino-3,5-difluoropiridin-2-il)-8-cloro-6,7-difluoro-1,4-dihidro-4-oxoquinolin-3-carboxílico (92 mg, 0.24 mmoles) se añadió nuevamente a la solución de reacción, y la mezcla se calentó adicionalmente a reflujo durante 4.5 horas. Posteriormente, el solvente se evaporó bajo presión reducida, y después el residuo se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua dos veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo resultante se sometió a cromatografía en columna sobre gel de sílice (diclorometano :metanol = 99:1). El aceite resultante (409 mg) se disolvió en ácido clorhídrico concentrado (3.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 2.5 horas. La solución de reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Se añadió cloroformo al residuo, y el material insoluble se removió por filtración. Después, el filtrado se evaporó bajo presión reducida, y el residuo resultante se purificó por recristalización a partir de etanol para dar 47 mg del compuesto del título como un sólido amarillo

844

pálido.

^{1}H-RMN (400 MHz, DMSO-d_6) δ: 8.79 (1H, s), 8.07-7.90 (2H, m), 6.75 (2H, d, J=8.58 Hz), 3.87-3.65 (2H, m), 3.50-3.25 (2H, m), 2.09-1.96 (2H, m), 1.88-1.53 (4H, m).

EM (FAB); m/z: 512 $(M+H)^+$.

Análisis calculado para $C_{22}H_{18}ClF_4N_5O_3 \cdot 0.5H_2O$: C, 50.73; H, 3.68; Cl, 6.81; F, 14.59; N, 13.45.

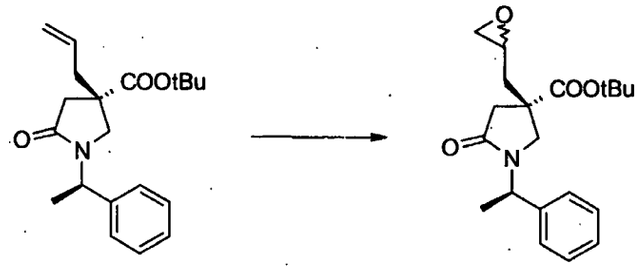
Encontrado: C, 50.75; H, 3.58; Cl, 6.52; F, 14.31; N, 13.09.

IR (ATR) ν: 3480, 3345, 3070, 2954, 2865, 1724, 1606, 1484, 1438, 1386, 1307, 1112 cm^{-1}.

EJEMPLO DE REFERENCIA 79

Ester ter-butílico de ácido 3-(oxiran-2-ilmetil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 165]



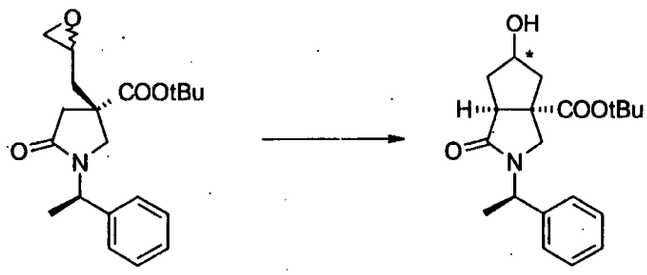
Ester ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.9 g, 14.9 mmoles) se disolvió en cloruro de metileno, y se añadió mCPBA (10.3 g, 59.5 mmoles). La mezcla se agitó a temperatura ambiente durante 15 horas y después se calentó a reflujo durante tres horas. El solvente se evaporó bajo presión reducida, y después el residuo se mezcló con una mezcla de acetato de etilo y una solución saturada de tiosulfato de sodio. La

capa orgánica se lavó con bicarbonato de sodio saturado acuoso, se secó sobre sulfato de magnesio, y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (hexano/acetato de etilo = 4:1 → 1:1) para dar 4.33 g (84%) del compuesto del título de aceite incoloro como una mezcla diaestereomérica. Los diaestereómeros se usaron para el siguiente paso sin separación y purificación.

EJEMPLO DE REFERENCIA 80

Ester ter-butílico de ácido (1S, 5S)-7-hidroxi-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 166]



Ester ter-butílico de ácido 3-(oxiran-2-ilmetil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (4.2 g, 12.16 mmoles) se disolvió en tetrahidrofurano (50 ml). Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (18 ml, 1.5 equivalentes) se añadió en una atmósfera de argón a -78°C, y la mezcla se calentó gradualmente. Cuando la temperatura de reacción alcanzó aproximadamente la temperatura ambiente, la reacción se extinguió con una solución de cloruro de amonio, seguido por extracción con acetato de etilo. El extracto se secó sobre sulfato de magnesio. Después de filtración, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía sobre gel de sílice (hexano : acetato de etilo = 4:1 →

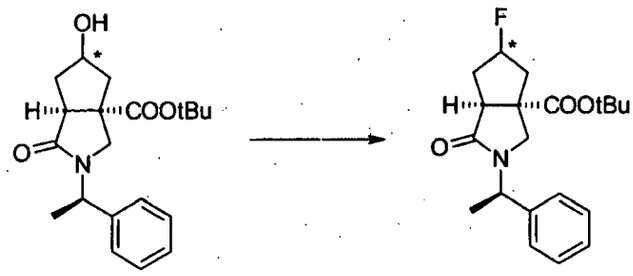
2:1 → 1:1 → 1:2) para dar 1.07 g (26%) del compuesto del título que tenía un solo isómero como un aceite incoloro. Se recogió 1.0 g (24%) del material de partida. 1.20 g (29%) de un compuesto de anillo cerrado de cuatro miembros como un subproducto se obtuvo como una mezcla diaestereomérica.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.48 (1H, q, J=7.08 Hz), 4.36-4.30 (1H, m), 3.35-3.30 (2H, m), 3.12 (1H, d, J=10.25 Hz), 2.44-2.38 (2H, m), 2.29 (1H, dt, J=13.83, 4.94 Hz), 2.16-2.09 (1H, m), 1.84 (1H, dd, J=13.79, 5.25 Hz), 1.50 (3H, d, J=7.08 Hz), 1.37 (9H, s).

EJEMPLO DE REFERENCIA 81

Ester ter-butílico de ácido (1R, 5R)-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 167]



Ester ter-butílico de ácido (1S,5S)-7-hidroxi-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (1.0 g, 2.89 mmoles) se disolvió en cloruro de metileno (15 ml). Trifluoruro de bis (2-metoxietil)aminoazufre (BAST) (0.59 ml) se añadió bajo enfriamiento con hielo, y la mezcla se agitó a la misma temperatura durante una hora. La solución de reacción se lavó con bicarbonato de sodio saturado acuoso, se secó sobre sulfato de magnesio, y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (hexano: acetato de etilo = 10:1 →

847

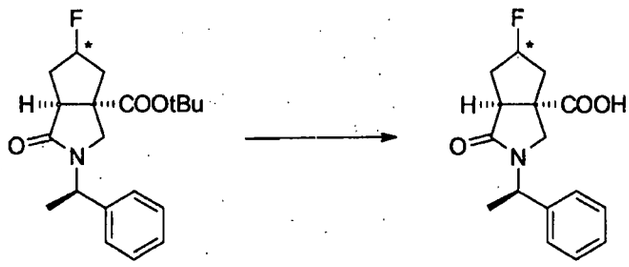
4:1 → 1:1) para dar 711 mg (71%) del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.50 (1H, q, J=7.1 Hz), 5.24 (1H, dt, J=52.2, 3.2 Hz), 3.48 (1H, d, J=10.0 Hz), 3.26-3.21 (2H, m), 2.61-2.37 (2H, m), 2.21-2.04 (2H, m), 1.48 (3H, d, J=7.1 Hz), 1.36 (9H, s).

EJEMPLO DE REFERENCIA 82

Acido (1R, 5R)-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 168]



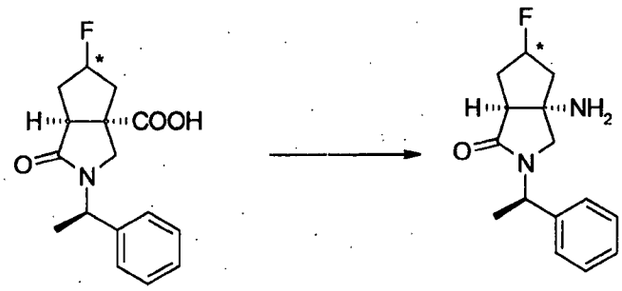
Ester ter-butílico de ácido (1R,5R)-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (705 mg, 2.03 mmoles) se disolvió en cloruro de metileno (4 ml). Se añadió ácido trifluoroacético (4 ml) bajo enfriamiento con hielo, y después la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida. Se añadió tolueno al residuo, y la mezcla se concentró bajo presión reducida nuevamente para dar 595 mg (cuantitativo) del compuesto del título como un sólido blanco.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.14 (5H, m), 5.48 (1H, q, J=7.08 Hz), 5.32-5.19 (1H, m), 3.61 (1H, d, J=10.74 Hz), 3.43 (1H, d, J=10.01 Hz), 3.33 (1H, d, J=10.50 Hz), 2.64-2.05 (4H, m), 1.49 (3H, d, J=7.08 Hz).

EJEMPLO DE REFERENCIA 83

(1R,5S)-1-Amino-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 169]



Tolueno (10 ml) y trietilamina (565 µl, 4.05 mmoles) se añadieron a ácido (1R,5R)-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (590 mg, 2.03 mmoles). Después, se añadió difenilfosforil azida (567 µl) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Posteriormente, la solución de reacción se calentó a reflujo durante una hora y se mezcló con una mezcla de acetato de etilo-bicarbonato de sodio saturado acuoso. La capa orgánica se secó sobre sulfato de magnesio y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se disolvió en dioxano (10 ml). Se añadió ácido clorhídrico 6N (10 ml) y la mezcla se calentó con agitación a 70°C durante dos horas. Después de lavar con éter, la capa acuosa se hizo básica con una solución 10 M de hidróxido de sodio, seguido por extracción con tolueno cinco veces. El extracto se secó sobre sulfato de magnesio y se filtró, y después el solvente se evaporó bajo presión reducida para dar 476 mg (90%) del compuesto del título como un aceite incoloro. El producto se usó para el siguiente paso sin purificación.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.16 (5H, m), 5.53 (1H, q,

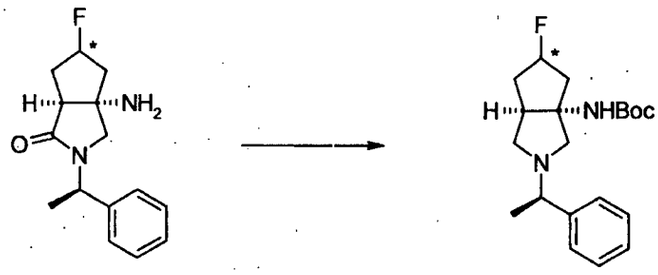
849

J=7.00 Hz), 5.20 (1H, dt, J=52.70, 4.40 Hz), 3.49 (1H, d, J=10.30 Hz), 2.86 (1H, d, J=10.30 Hz), 2.66 (1H, d, J=10.00 Hz), 2.52-2.19 (3H, m), 1.93 (1H, ddd, J=39.50, 15.00, 4.10 Hz), 1.52 (2H, brs), 1.47 (3H, d, J=7.10 Hz).

EJEMPLO DE REFERENCIA 84

(1R, 5S)-1-(ter-Butoxicarbonilamino)-7-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 170]



(1R,5S)-1-Amino-7-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (537 mg, 2.05 mmoles) se disolvió en tolueno (20 ml). Se añadió Red-Al™ (65% solución en tolueno) (2.53 ml, 8.12 mmoles) en una atmósfera de argón, la mezcla se agitó a 80°C durante una hora. Una solución 5 M de hidróxido de sodio se añadió a la solución de reacción, seguido por extracción con tolueno. El extracto se secó sobre sulfato de magnesio y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo se disolvió en tolueno (20 ml). Dicarbonato de di-ter-butilo (475 mg, 2.18 mmoles) se añadió, y la mezcla se agitó a 50°C durante una hora. El solvente se evaporó bajo presión reducida, y después el residuo se purificó por cromatografía sobre gel de sílice (hexano : acetato de etilo = 9:1 → 8:2 → 7:3) para dar 450 mg (71%) del compuesto del título como un aceite incoloro.

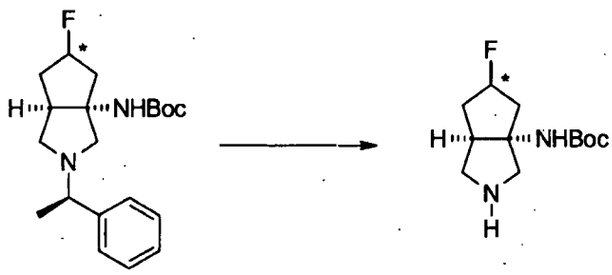
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.20 (5H, m), 5.20 (1H, d,

J=54.00 Hz), 4.90 (1H, brs), 3.22 (1H, q, J=6.50 Hz), 2.92 (1H, d, J=7.60 Hz), 2.58 (1H, d, J=9.80 Hz), 2.48-2.20 (4H, m), 1.79 (1H, t, J=16.80 Hz), 1.43 (9H, s), 1.33 (3H, d, J=6.60 Hz).

EJEMPLO DE REFERENCIA 85

(1R,5S)-1-(ter-Butoxicarbonilamino)-7-fluoro-3-biciclo [3.3.0] octano

[Fórmula 171]



(1R,5S)-1-(ter-Butoxicarbonilamino)-7-fluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (450 mg, 1.29 mmoles) se disolvió en metanol (15 ml). Se añadió una cantidad catalítica de un catalizador de 10% de paladio-carbón (50% húmedo) y la mezcla se agitó en una atmósfera de hidrógeno a 40°C durante 12 horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 316 mg (cuantitativo) del compuesto del título como un aceite incoloro.

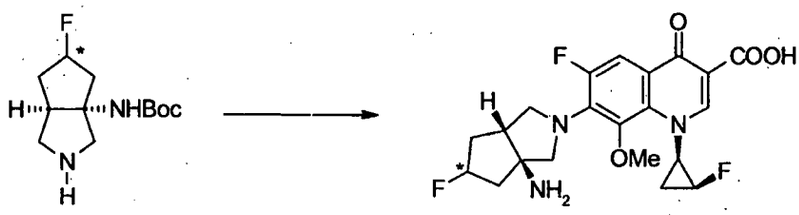
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 5.24 (1H, d, J=53.71 Hz), 5.07 (1H, s), 3.48-3.42 (1H, m), 3.23 (2H, dd, J=14.77, 12.33 Hz), 2.93-2.87 (1H, m), 2.76 (1H, brs), 2.44-2.16 (3H, m), 1.95-1.86 (1H, m), 1.44 (9H, s).

851

EJEMPLO 19

Acido 7-{(1R,5S)-1-amino-7-fluoro-3-azabiciclo[3.3.0] octan-3-il}-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 172]



(1R,5S)-1-(ter-Butoxicarbonilamino)-7-fluoro-3-azabiciclo[3.3.0] octano (296 mg, 1.21 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (437 mg, 1.21 mmoles) se disolvieron en sulfóxido de dimetilo (6 ml). Se añadió trietilamina (203 μl, 1.45 mmoles) y la mezcla se agitó a 40°C durante un día. Se añadió agua a la solución de reacción, y los cristales precipitados se recogieron por filtración, se lavaron con agua, y se secaron para dar un polvo amarillo. Este se disolvió en etanol (35 ml)-agua (9 ml). Se añadió trietilamina (202 μl) y la mezcla se calentó a reflujo durante cuatro horas. El solvente se evaporó bajo presión reducida, y el residuo se mezcló con una mezcla de acetato de etilo y una solución de ácido cítrico al 10%. La capa orgánica se secó sobre sulfato de magnesio y se filtró. El filtrado se evaporó bajo presión reducida. Después, ácido clorhídrico concentrado (9 ml) se añadió al residuo, y la mezcla se agitó a temperatura ambiente durante dos horas. La solución de reacción se diluyó con ácido clorhídrico concentrado, después se transfirió a un embudo de separación, y se lavó con cloroformo tres veces. Posteriormente, la capa de ácido clorhídrico se ajustó a pH 12 con a solución 12 M de hidróxido de sodio bajo enfriamiento

con hielo. La capa se ajustó de manera adicional a pH 7.4 con ácido clorhídrico 1 M y ácido clorhídrico 0.01 M, seguido por extracción con cloroformo-metanol (9:1). Después, la capa acuosa se ajustó a pH 7.4 nuevamente y se llevó a cabo una operación de extracción. Después de repetir esta operación cinco veces, la capa orgánica se secó sobre sulfato de magnesio y se filtró, y el filtrado se evaporó bajo presión reducida. Se añadió etanol al residuo, y el solvente se evaporó bajo presión reducida. El residuo se secó bajo presión reducida para dar 220 mg (42%) del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 7.66 (1H, d, J=13.70 Hz), 5.45-5.31 (1H, brm), 5.04-4.86 (1H, brm), 4.06-4.01 (1H, m), 3.87 (1H, t, J=8.90 Hz), 3.73-3.51 (6H, m), 2.52-2.25 (3H, m), 2.15-1.89 (2H, m), 1.64-1.47 (2H, m).

Análisis calculado para $C_{21}H_{22}F_3N_3O_4 \cdot 1.0H_2O \cdot 0.4EtOH$: C, 55.26; H, 5.62; F, 12.03; N, 8.87.

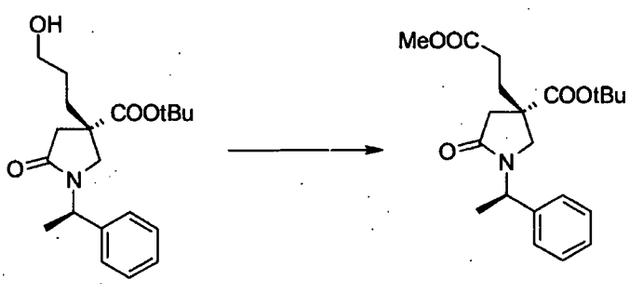
Encontrado: C, 55.05; H, 5.35; F, 12.32; N, 8.76.

EM (ESI) m/z: 438 $(M+H)^+$.

EJEMPLO DE REFERENCIA 86

Ester ter-butílico de ácido (3S)-3-(2-metoxicarbonil-1-etil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 173]



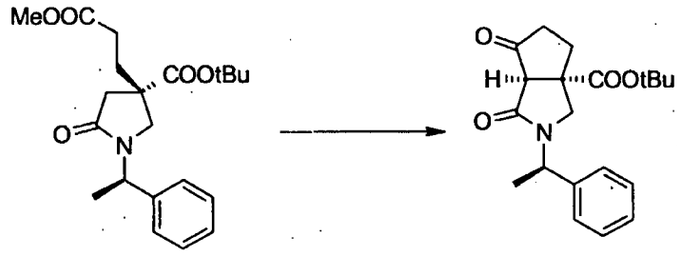
Tetracloruro de carbono (550 ml), acetonitrilo (550 ml), y agua (550 ml) se disolvieron en éster ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (38.2 g, 0.110 moles), y cloruro de rutenio (III) hidratado (456 mg, 2.20 mmoles) y peryoduro de sodio (94.1 g, 0.440 moles) se añadieron secuencialmente. La mezcla se agitó en un baño de agua con un circulador termostático a 15°C durante 2.5 horas mientras se mantenía la temperatura interna a 20 a 25°C. La solución de reacción se enfrió en un baño de hielo y una solución de ácido clorhídrico 1N (2.2 l) se añadió a una temperatura interna de 10°C o menor, seguido por extracción con 2 l de cloroformo. La capa acuosa se extrajo con cloroformo (1 l x 3). Después, las capas orgánicas se combinaron, se lavaron con salmuera (2 l x 2), y se secaron sobre sulfato de sodio anhidro. Después de filtración, el solvente se concentró bajo presión reducida. El crudo resultante se disolvió en N,N-dimetilformamida (370 ml). Se añadieron bicarbonato de sodio (37.9 g, 0.451 moles) y yoduro de metilo (70.7 g, 0.498 moles) con agitación a temperatura ambiente, y la mezcla se agitó durante tres días. La solución de reacción se vació en agua con hielo (1.8 l), seguido por extracción con acetato de etilo (1.8 l, 0.5 l). Las capas orgánicas se combinaron, se lavaron con salmuera, y después se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida, el residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 1:1), y la fracción que contenía la sustancia objetivo se concentró bajo presión reducida. El sólido resultante se disolvió en acetato de etilo, se lavó con una solución de tiosulfato de sodio al 10%, y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida, y el sólido resultante se secó para dar 35.0 g del compuesto del título como un sólido café-amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.25 (5H, m), 5.48 (1H, q, J=7.1 Hz), 3.68 (3H, s), 3.33 (1H, d, J=10.3 Hz), 3.13 (1H, d, J=10.3 Hz), 2.93 (1H, d, J=16.8 Hz), 2.34-2.20 (3H, m), 2.13-1.94 (2H, m), 1.51 (3H, d, J=7.1 Hz), 1.32 (9H, s).

EJEMPLO DE REFERENCIA 87

Ester ter-butílico de ácido {(1S,5R)-4,6-dioxo-3-[(1R)-1-feniletil]-3-azabiciclo [3,3, 0] octan-1-il}carboxílico

[Fórmula 174]



Ester ter-butílico de ácido (3S)-3-(2-metoxicarbonil-1-etil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (35.0 g, 93.2 mmoles) se disolvió en tetrahidrofurano (1 l). Una solución 2 M de diisopropilamida de litio/ heptano/tetrahidrofurano/etilbenceno (100 ml, 200 mmoles) se añadió gota a gota en una atmósfera de nitrógeno a una temperatura interna de -69°C durante 30 minutos. Después de agitación a la misma temperatura durante una hora, la solución de reacción se vació en una solución de ácido clorhídrico 1N (2 l) en un baño de hielo, seguido por extracción con acetato de etilo (2 l, 1 l). Las capas orgánicas se combinaron, se lavaron con salmuera, y se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida, y el sólido precipitado se recogió por filtración para dar 22.2 g del compuesto del título como cristales rojo pálido. El filtrado además se concentró

para dar 2.88 g del compuesto del título como cristales rojo pálido. El filtrado se concentró bajo presión reducida, y el residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 1:1) para dar 2.09 g del compuesto del título como cristales incoloros.

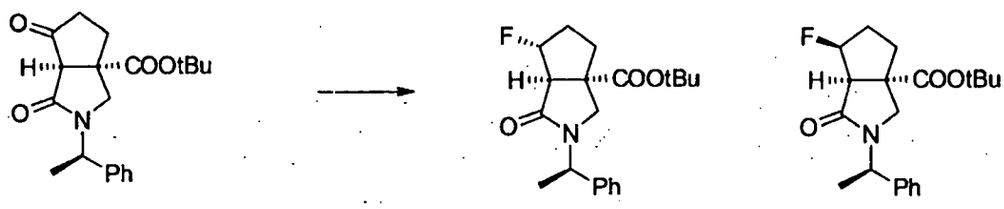
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 5.50 (1H, q, J=7.1 Hz), 3.38 (1H, d, J=10.5 Hz), 3.23 (1H, d, J=10.5 Hz), 2.55-2.35 (3H, m), 2.05-1.94 (1H, m), 1.53 (3H, d, J=7.1 Hz), 1.38 (9H, s).

EJEMPLO DE REFERENCIA 88

Ester ter-butílico de ácido {(1S,5R,6R)-6-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3,3,0]octan-1-il}carboxílico;

éster ter-butílico de ácido {(1S,5R,6S)-6-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3,3,0]octan-1-il} carboxílico

[Fórmula 175]



Ester ter-butílico de ácido {(1S,5R)-4,6-dioxo-3-[(1R)-1-feniletil]-3-azabiciclo [3,3,0]octan-1-il}carboxílico (1.30 g, 3.88 mmoles) se disolvió en tetrahidrofurano (40 ml). Borohidruro de sodio (185 mg, 4.92 mmoles) se añadió a 0°C, y la mezcla se agitó durante una hora. Una solución saturada de cloruro de amonio se añadió a la solución de reacción, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y después se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en

diclorometano (20 ml). Se añadió trifluoruro de [bis (2-metoximetil) amino] azufre (1.73 g, 7.82 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó durante dos horas. La solución de reacción se vació en bicarbonato de sodio saturado acuoso, en un baño de hielo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con una solución saturada de tiosulfato de sodio y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (30% acetato de etilo/hexano) para dar 797 mg del isómero (6R)-fluoro del título como un aceite incoloro y 170 mg del isómero (6S)-fluoro del título como un aceite incoloro.

Isómero (6R)-fluoro:

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.46 (1H, q, J=7.08 Hz), 5.28 (1H, d, J=51.76 Hz), 3.48 (1H, d, J=22.71 Hz), 3.41 (1H, d, J=10.50 Hz), 3.08 (1H, d, J=10.50 Hz), 2.57-2.49 (1H, m), 2.21-2.12 (1H, m), 1.83-1.58 (2H, m), 1.50 (3H, d, J=7.08 Hz), 1.35 (9H, s).

EM (EI); m/z: 348 $(M+H)^+$.

Isómero (6S)-fluoro:

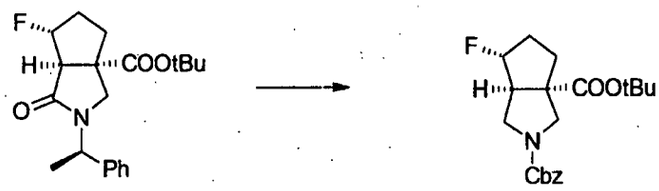
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.26 (5H, m), 5.49-5.40 (2H, m), 3.51 (1H, d, J=10.24 Hz), 3.41 (1H, d, J=29.76 Hz), 3.21 (1H, d, J=10.00 Hz), 2.46-2.44 (1H, m), 2.23-2.20 (1H, m), 2.03-1.93 (1H, m), 1.88-1.82 (1H, m), 1.52 (3H, d, J=6.83 Hz), 1.32 (9H, s).

EM (EI) ; m/z: 348 $(M+H)^+$.

EJEMPLO DE REFERENCIA 89

Ester ter-butílico de ácido {(1S,5S,6R)-3-benciloxicarbonil-6-f luoro-3-azabiciclo [3,3,0] octan-1-il}carboxílico

[Fórmula 176]



Ester ter-butílico de ácido {(1S,5R,6R)-6-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3,3,0] octan-1-il}carboxílico (420 mg, 1.21 mmoles) se disolvió en tetrahidrofurano (20 ml), y un complejo de borano 1M-tetrahidrofurano (3.63 ml, 3.63 mmoles) se añadió gota a gota en una atmósfera de nitrógeno. Después de cinco horas, un complejo de borano 1M-tetrahidrofurano (3.63 ml, 3.63 mmoles) se añadió; después de 15 horas, un complejo de borano 1M-tetrahidrofurano (3.63 ml, 3.63 mmoles) se añadió adicionalmente. Después de agitar durante tres horas, etanol (18 ml), agua (2 ml), y trietilamina (2 ml) se añadieron, y la mezcla se agitó a 80°C durante dos horas. La solución de reacción se evaporó bajo presión reducida, y una solución saturada de cloruro de amonio se añadió al residuo resultante, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y después se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en diclorometano (3 ml). Se añadió cloruro de benciloxicarbonilo (1.03 g, 6.04 mmoles) y la mezcla se agitó durante 16 horas. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (30% de acetato de etilo/hexano) para dar 367 mg

del compuesto del título como un aceite incoloro.

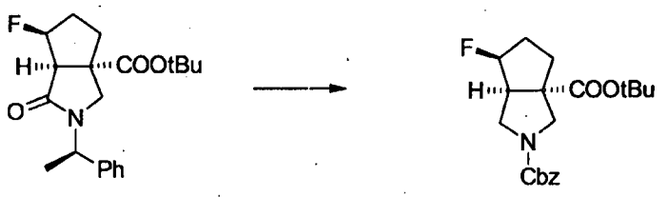
^{1}H-RMN (400 MHz, $CDCl_3$) δ 7.38-7.26 (5H, m), 5.12 (2H, s), 4.85 (1H, d, J=52.44 Hz), 3.86 (1H, d, J=11.71 Hz), 3.77-3.73 (1H, m), 3.40-3.35 (2H, m), 3.16-3.10 (1H, m), 2.46-2.42 (1H, m), 2.03-1.82 (3H, m), 1.45 (9H, s).

EM (EI) m/z: 386 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 90

Ester ter-butílico de ácido {(1S,5S,6S)-3-benciloxicarbonil-6-fluoro-3-azabiciclo [3,3,0] octan-1-il}carboxílico

[Fórmula 177]



Ester ter-butílico de ácido {(1S,5R,6S)-6-fluoro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3,3,0] octan-1-il}carboxílico (402 mg, 1.16 mmoles) se disolvió en tetrahidrofurano (20 ml), y un complejo de borano 1M-tetrahidrofurano (5.79 ml, 5.79 mmoles) se añadió gota a gota en una atmósfera de nitrógeno. Después de dos horas, se añadió un complejo de borano 1M-tetrahidrofurano (3.47 ml, 3.47 mmoles); después de 14 horas, un complejo de borano 1M-tetrahidrofurano (3.47 ml, 3.47 mmoles) se añadió adicionalmente. Después de agitar durante 2.5 horas, etanol (18 ml), agua (2 ml), y trietilamina (2 ml) se añadieron, y la mezcla se agitó a 80°C durante dos horas. La solución de reacción se evaporó bajo presión reducida, y una solución saturada de cloruro de amonio se añadió al residuo resultante, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y después se secó sobre

sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en diclorometano (2.8 ml). Se añadió cloruro de benciloxicarbonilo (1.03 g, 6.04 mmoles) y la mezcla se agitó a 40°C durante 14 horas. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (25% acetato de etilo/hexano) para dar 359 mg del compuesto del título como un aceite incoloro.

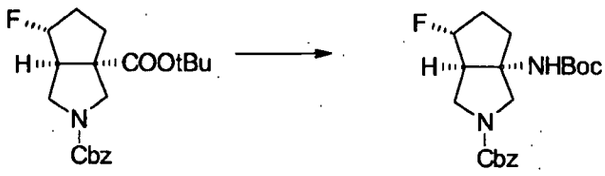
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.29 (5H, m), 5.13 (2H, s), 5.06 (1H, d, J=49.84 Hz), 3.99 (1H, dd, J=20.12, 11.59 Hz), 3.79 (1H, d, J=11.95 Hz), 3.58-3.55 (1H, m), 3.38 (1H, dd, J=46.71, 11.34 Hz), 3.00 (1H, brd, J=25.37 Hz), 2.26-1.94 (4H, m), 1.43 (9.0H, s).

EM (EI) m/z: 386 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 91

Ester bencílico de ácido {(1S,5R,6R)-1-ter-butoxicarbonilamino-6-fluoro-3-azabiciclo [3, 3, 0] octan-3-il}carboxílico

[Fórmula 178]



Ester ter-butílico de ácido {(1S,5S,6R)-3-benciloxicarbonil-6-fluoro-3-azabiciclo [3,3,0] octan-1-il}carboxílico (362 mg, 1.00 mmoles) se disolvió en diclorometano (10 ml). Se añadió ácido trifluoroacético (2.5 ml) y la mezcla se agitó durante 15 horas. El solvente se evaporó bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió al residuo resultante, y la mezcla se

860

lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo. El extracto se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (10 ml). Se añadieron trietilamina (202 mg, 1.99 mmoles) y difenilfosforil azida (339 mg, 1.20 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó a 100°C durante dos horas. La solución de reacción se concentró bajo presión reducida. Después, dioxano (20 ml) y ácido clorhídrico 6N (20 ml) se añadieron, y la mezcla se agitó a 40°C durante tres horas. Después de concentración bajo presión reducida y destilación azeotrópica con etanol, se añadió una solución de hidróxido de sodio 1N, seguida por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. Dicarbonato de di-ter-butilo (1087 mg, 4.98 mmoles) se añadió al residuo resultante, y la mezcla se agitó a 50°C durante dos horas. La solución de reacción se purificó por cromatografía en columna sobre gel de sílice (20% acetato de etilo/hexano) para dar 125 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.11 (2H, s), 4.95-4.80 (2H, m), 3.88-3.63 (3H, m), 3.28-3.24 (1H, m), 2.83-2.75 (1H, m), 2.12-1.98 (4H, m), 1.44 (9H, s).

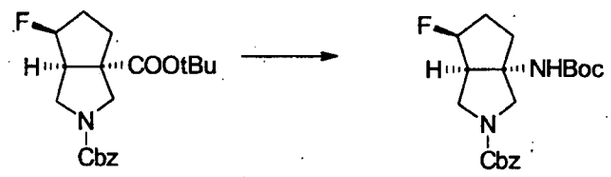
EM (EI) m/z: 401 $(M+Na)^+$.

861

EJEMPLO DE REFERENCIA 92

Ester bencílico de ácido {(1S,5R,6S)-1-ter-butoxicarbonilamino-6-fluoro-3-azabiciclo [3,3,0] octan-3-il}carboxílico

[Fórmula 179]



Ester ter-butílico de ácido {(1S,5S,6S)-3-benciloxicarbonil-6-fluoro-3-azabiciclo [3,3,0] octan-1-il}carboxílico (354 mg, 0.97 mmoles) se disolvió en diclorometano (10 ml). Se añadió ácido trifluoroacético (3 ml) y la mezcla se agitó durante 21 horas. El solvente se evaporó bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió al residuo resultante, y la mezcla se lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo. El extracto se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (8 ml). Se añadieron trietilamina (197 mg, 1.95 mmoles) y difenilfosforil azida (359 mg, 1.27 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó durante una hora. Posteriormente, ter-butanol (8 ml) se añadió, y la mezcla se agitó a 100°C durante 19 horas. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (25% acetato de etilo/hexano) para dar 136 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.26 (5H, m), 5.13 (2H, s), 5.05 (1H, d, J=58.77 Hz), 4.68 (1H, brs), 3.77 (1H, d, J=10.46 Hz), 3.71-3.60 (2H, m),

862

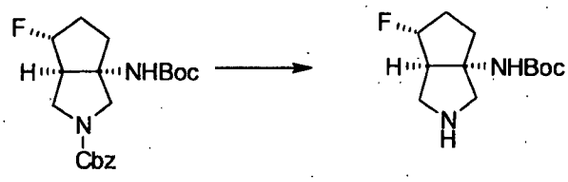
3.57-3.44 (1H, m), 3.11-2.86 (1H, m), 2.29-2.02 (4H, m), 1.43 (9H, s).

EM (EI) ; m/z: 401 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 93

(1S, 5R,6R)-1-ter-Butoxicarbonilamino-6-fluoro-3-azabiciclo [3,3,0] octano

[Fórmula 180]



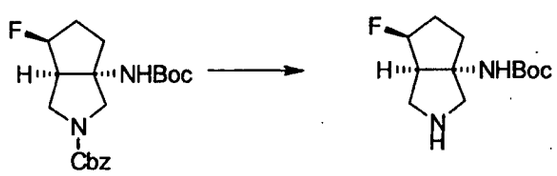
Ester bencílico de ácido {(1S,5R,6R)-1-ter-butoxicarbonilamino-6-fluoro-3-azabiciclo [3,3,0] octan-3-il}carboxílico (120 mg, 0.32 mmoles) se disolvió en metanol (10 ml). Se añadió 10% de paladio-carbón (M, húmedo) (50 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el filtrado se concentró bajo presión reducida para dar 77.5 mg del compuesto del título como un aceite incoloro.

EM (EI); m/z: 245 $(M+H)^+$.

EJEMPLO DE REFERENCIA 94

(1S,5R,6S)-1-ter-Butoxicarbonilamino-6-fluoro-3-azabiciclo [3,3,0]octano

[Fórmula 181]



863

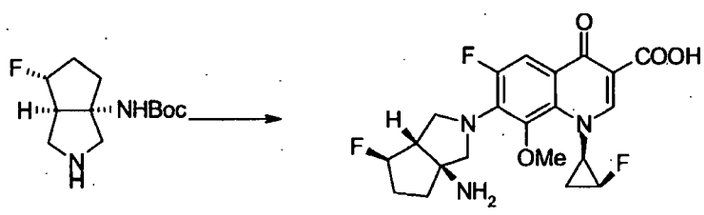
Ester bencílico de ácido {(1S,5R,6S)-1-ter-butoxicarbonilamino-6-fluoro-3-azabiciclo[3,3,0] octan-3-il}carboxílico (132 mg, 0.35 mmoles) se disolvió en metanol (10 ml). Se añadió 10% de paladio-carbón (M, húmedo) (50 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el filtrado se concentró bajo presión reducida para dar 85 mg del compuesto del título como un aceite incoloro.

EM (EI); m/z: 245 $(M+H)^+$.

EJEMPLO 20

Acido 7-{(1S,5R,6R)-1-amino-6-fluoro-3-azabiciclo [3,3,0] octan-3-il}-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 182]



(1S,5R,6R)-1-ter-Butoxicarbonilamino-6-fluoro-3-azabiciclo[3,3,0] octano (77.5 mg, 0.32 mmoles) se disolvió en sulfóxido de dimetilo (2 ml). Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (120.2 mg, 0.33 mmoles) y trietilamina (96.3 mg, 0.95 mmoles) se añadieron, y la mezcla se agitó a 40°C durante 18 horas. Después, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de

reacción, y la mezcla se agitó a 80°C durante tres horas. El solvente se evaporó bajo presión reducida, y una solución de ácido cítrico al 10% se añadió al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (5% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.5 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El sólido resultante se lavó con éter dietílico y se secó bajo presión reducida para dar 96 mg del compuesto del título como un sólido incoloro, p.f.: 179-181°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, s), 7.71 (1H, d, J=13.67 Hz), 5.10-5.07 (1H, m), 5.09 (1H, d, J=52.00 Hz), 4.07-4.04 (1H, m), 3.88 (1H, t, J=9.64 Hz), 3.68-3.63 (4H, m), 3.57 (1H, dd, J=16.97, 10.62 Hz), 3.45 (1H, d, J=11.72 Hz), 2.63-2.56 (1H, m), 2.10-2.01 (4H, m), 1.61-1.51 (2H, m).

Análisis calculado para $C_{21}H_{22}F_3N_3O_4 \cdot 0.5H_2O$: C, 56.50; H, 5.19; N, 9.41; F, 12.77.

Encontrado: C, 56.28; H, 5.17; N, 9.03; F, 12.47.

EM (EI) ; m/z: 438 $(M+H)^+$.

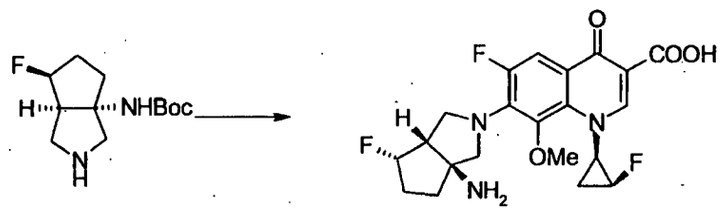
IR (ATR) ν: 3390, 2943, 2872, 1720, 1618, 1512, 1452, 1360, 1321, 1277, 1213 cm^{-1}.

865

EJEMPLO 21

Acido 7-[(1S,5R,6S)-1-amino-6-fluoro-3-azabiciclo [3,3,0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 183]



(1S,5R,6S)-1-ter-Butoxicarbonilamino-6-fluoro-3-azabiciclo[3,3,0] octano (85.2 mg, 0.35 mmoles) se disolvió en sulfóxido de dimetilo (2 ml). Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (132.2 mg, 0.37 mmoles) y trietilamina (105.9 mg, 1.05 mmoles) se añadieron, y la mezcla se agitó a 40°C durante 15 horas. Después, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante tres horas. El solvente se evaporó bajo presión reducida, y una solución de ácido cítrico al 10% se añadió al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (5% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.5 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo

866

presión reducida. El sólido resultante se lavó con éter dietílico y se secó bajo presión reducida para dar 101 mg del compuesto del título como un sólido incoloro, p.f.: 117-119°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.45 (1H, s), 7.70 (1H, d, J=14.15 Hz), 5.28 (1H, d, J=53.41 Hz), 5.07-4.73 (1H, m), 4.05-4.02 (1H, m), 3.84-3.64 (6H, m), 3.47 (1H, d, J=10.73 Hz), 2.59-2.53 (1H, m), 2.26-2.06 (3H, m), 1.79-1.78 (1H, m), 1.58-1.46 (2H, m).

Análisis calculado para $C_{21}H_{22}F_3N_3O_4 \cdot H_2O$: C, 55.38; H, 5.31; N, 9.23; F, 12.51.

Encontrado: C, 55.43; H, 5.46; N, 9.00; F, 12.21.

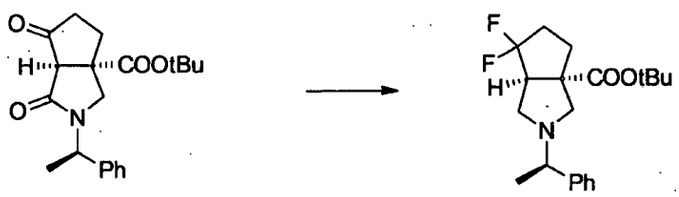
EM (EI) m/z: 438 $(M+H)^+$.

IR (ATR) ν: 2966, 2839, 1720, 1614, 1576, 1537, 1508, 1446, 1362, 1319, 1271, 1207 cm^{-1}.

EJEMPLO DE REFERENCIA 95

Ester ter-butílico de ácido {(1S,5S)-6,6-difluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3,3, 0] octan-1-il}carboxílico

[Fórmula 184]



Ester ter-butílico de ácido {(1S,5R)-4,6-dioxo-3-[(1R)-1-feniletil]-3-azabiciclo [3,3,0]octan-1-il}carboxílico (500 mg, 1.46 mmoles) se disolvió en diclorometano (20 ml). Trifluoruro de [bis (2-metoximetil) amino] azufre (966.3 mg, 4.37 mmoles) se añadió en una atmósfera de nitrógeno a 0°C, y la mezcla

867

se agitó a 20°C durante 17 horas. La solución de reacción se vació en bicarbonato de sodio saturado acuoso en un baño de hielo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con una solución saturada de tiosulfato de sodio y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (25% acetato de etilo/hexano). El crudo resultante se disolvió en tetrahidrofurano (15 ml). Un complejo de borano 1 M-tetrahidrofurano (4.37 ml, 4.37 mmoles) se añadió en una atmósfera de nitrógeno, y la mezcla se agitó durante 16 horas. Un complejo de borano 1 M-tetrahidrofurano (4.37 ml, 4.37 mmoles) se añadió, y la mezcla se agitó durante nueve horas. Un complejo de borano 1 M-tetrahidrofurano (4.37 ml, 4.37 mmoles) se añadió adicionalmente, y la mezcla se agitó durante 16 horas. Etanol (45 ml), agua (5 ml), y trietilamina (5 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante cuatro horas. Después, el solvente se evaporó bajo presión reducida, y una solución saturada de cloruro de amonio se añadió al residuo. La capa orgánica se extrajo con acetato de etilo, se lavó con agua y salmuera, y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (15% acetato de etilo/hexano) para dar 375.8 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 3.28 (1H, d, J=9.77 Hz), 3.13 (1H, q, J=6.51 Hz), 3.01 (1H, dd, J=19.04, 7.08 Hz), 2.60 (1H, d, J=9.28 Hz), 2.39-2.30 (3H, m), 2.15-2.09 (2H, m), 1.80-1.75 (1H, m), 1.41 (9H, s), 1.33 (3H, d, J=6.59 Hz).

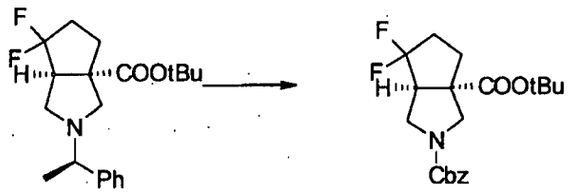
EM (EI) m/z: 352 $(M+H)^+$.

868

EJEMPLO DE REFERENCIA 96

Ester ter-butílico de ácido {(1S,5S)-3-benciloxicarbonil-6,6-difluoro-3-azabiciclo [3,3,0]octan-1-il}carboxílico

[Fórmula 185]



Ester ter-butílico de ácido {(1S,5S)-6,6-difluoro-3-[(1R)-1-feniletil]-3-azabiciclo [3,3,0] octan-1-il}carboxílico (370.0 mg, 1.05 mmoles) se disolvió en diclorometano (3 ml). Se añadió cloruro de benciloxicarbonilo (898 mg, 5.26 mmoles) y la mezcla se agitó a 40°C durante 17 horas. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (20% acetato de etilo/hexano) para dar 338 mg del compuesto del título como un aceite incoloro.

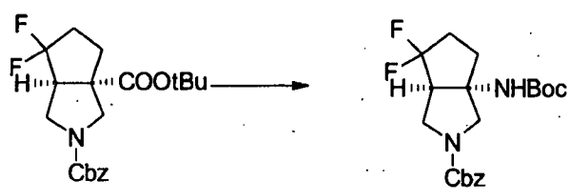
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.26 (5H, m), 5.13 (2H, s), 3.86 (2H, d, J=11.71 Hz), 3.54-3.42 (2H, m), 3.16-3.07 (1H, m), 2.37-2.11 (3H, m), 1.88-1.82 (1H, m), 1.45 (9H, s).

EM (EI) m/z : 404 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 97

Ester bencílico de ácido {(1S, 5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3,3,0] octan-3-il}carboxílico

[Fórmula 186]



869

Ester ter-butílico de ácido {(1S,5S)-3-benciloxicarbonil-6,6-difluoro-3-azabiciclo [3,3,0] octan-1-il}carboxílico (332.0 mg, 0.87 mmoles) se disolvió en diclorometano (10 ml). Se añadió ácido trifluoroacético (2 ml) y la mezcla se agitó durante 23 horas. La solución de reacción se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, y la mezcla se lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (10 ml). Trietilamina (176.2 mg, 1.74 mmoles) y difenilfosforil azida (370.4 mg, 1.31 mmoles) se añadieron en una atmósfera de nitrógeno, y la mezcla se agitó a 100°C durante 20 horas. La solución de reacción se concentró bajo presión reducida. Después, dioxano (10 ml) y ácido clorhídrico 6N (10 ml) se añadieron, y la mezcla se agitó a 40°C durante 1.5 horas. Después de concentración bajo presión reducida y destilación azeotrópica con etanol, se añadió una solución de hidróxido de sodio 1N, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. Dicarbonato de di-ter-butilo (949.9 mg, 4.35 mmoles) se añadió al residuo resultante, y la mezcla se agitó a 50°C durante 16 horas. La solución de reacción se purificó por cromatografía en columna sobre gel de sílice (25% acetato de etilo/hexano) para dar 67.0 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.17 (5H, m), 5.13 (2H, s), 4.80 (1H, S), 3.84-3.80 (1H, m), 3.71-3.65 (3H, m), 3.06-2.96 (1H, m), 2.39-2.31 (1H, m), 2.16-2.08 (3H, m), 1.44 (9H, s).

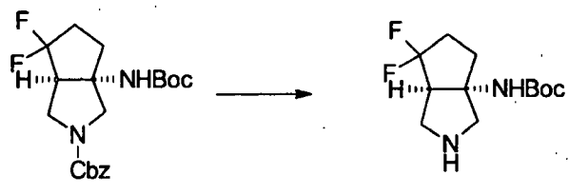
EM (EI) m/z: 397 $(M+H)^+$.

870

EJEMPLO DE REFERENCIA 98

(1S,5R)-1-ter-Butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3,3,0] octano

[Fórmula 187]



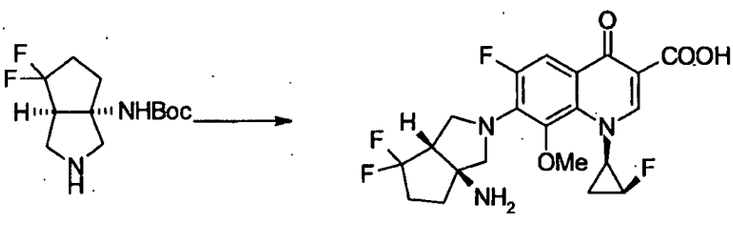
Ester bencílico de ácido [(1S,5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3,3,0] octan-3-il] carboxílico (65.0 mg, 0.16 mmoles) se disolvió en metanol (10 ml). Se añadió 10% de paladio-carbón (50% húmedo) (20 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante una hora. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el filtrado se concentró bajo presión reducida para dar 43 mg del compuesto del título como un sólido incoloro.

EM (EI); m/z: 263 $(M+H)^+$.

EJEMPLO 22

Acido 7-[(1S,5R)-1-amino-6,6-difluoro-3-azabiciclo[3,3,0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 188]



871

(1S,5R)-1-ter-Butoxicarbonilamino-6,6-difluoro-3-azabiciclo[3,3,0] octano (43.0 mg, 0.16 mmoles) se disolvió en sulfóxido de dimetilo (1.8 ml). Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (62.2 mg, 0.17 mmoles) y trietilamina (49.8 mg, 0.49 mmoles) se añadieron, y la mezcla se agitó a 40°C durante 16 horas. Después, etanol acuoso al 90% (20 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante 2.5 horas. El solvente se evaporó bajo presión reducida, y una solución de ácido cítrico al 10% se añadió al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El sólido resultante se disolvió en etanol-amoniaco acuoso, y la solución se calentó y se agitó. Después de vaporización de amoniaco, los cristales precipitados se recogieron por filtración y se secaron bajo presión reducida para dar 15.2 mg del compuesto del título como un sólido amarillo pálido, p.f.: 239-241°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 7.73 (1H, d, J=13.67 Hz), 5.07-4.91 (1H, m), 4.08-4.05 (1H, m), 3.91-3.88 (1H, m), 3.79-3.77 (1H, m), 3.72-3.70 (1H, m), 3.68 (3H, s), 3.55 (1H, d, J=10.74 Hz), 2.67-2.62

872

(1H, m), 2.36-2.33 (2H, m), 2.16-2.12 (1H, m), 1.96-1.89 (1H, m), 1.64-1.51 (2H, m).

Análisis calculado para $C_{21}H_{21}F_4N_3O_4 \cdot 0.25H_2O$: C, 54.84; H, 4.71; N, 9.14; F, 16.52.

Encontrado: C, 54.97, H, 4.53; N, 9.09; F, 16.53

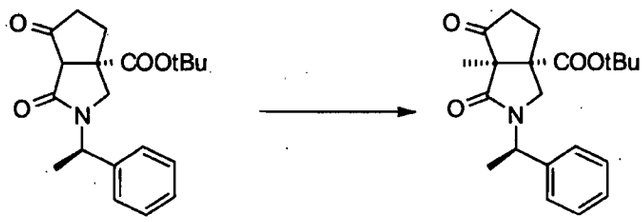
EM (EI); m/z: 456 $(M+H)^+$.

IR (ATR) ν: 3392, 3031, 2883, 1718, 1618, 1510, 1450, 1360, 1333, 1306, 1250 cm^{-1}.

EJEMPLO DE REFERENCIA 99

Ester ter-butílico de ácido (1S,5R)-5-metil-4,6-dioxo-3-[(1R)-1-fenil etil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 189]



N,N-Dimetilformamida (2.0 ml) se añadió a hidruro de sodio (152 mg, 3.48 mmoles) en una atmósfera de argón. Una solución de éster ter-butílico de ácido (1S,5R)-4,6-dioxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (1.00 g, 2.91 mmoles) en N, N-dimetilformamida (8.0 ml) se añadió gota a gota a esta suspensión bajo enfriamiento con hielo, y la mezcla se agitó a 0°C durante 30 minutos. Subsecuentemente, yoduro de metilo (0.217 ml, 3.49 mmoles) se añadió gota a gota bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2.5 horas. La solución de reacción se enfrió con hielo y después la reacción se extinguió con agua, seguida por extracción con

873

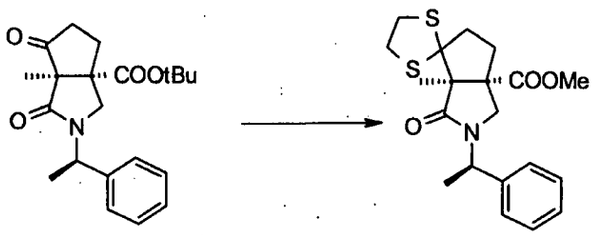
acetato de etilo. Después, la capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 2:1 → 1:1) para dar 0.79 g del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.41-7.23 (5H, m), 5.48 (1H, q, J=6.62 Hz), 3.40 (1H, d, J=10.54 Hz), 3.13 (1H, d, J=10.54 Hz), 2.63-2.40 (3H, m), 1.96-1.83 (1H, m), 1.54 (3H, d, J=7.11 Hz), 1.39 (9H, s), 1.22 (3H, s).

EJEMPLO DE REFERENCIA 100

Ester metílico de ácido (1S,5R)-6,6-etanodiildimercapto-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 190]



Ester ter-butílico de ácido (1S,5R)-5-metil-4,6-dioxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0]octan-1-ilcarboxílico (0.28 g, 0.78 mmoles) se disolvió en tolueno (14 ml). Se añadieron ácido toluensulfónico monohidratado (155 mg, 0.81 mmoles) y etanoditiol (0.14 ml, 1.7 mmoles) y la mezcla se calentó a reflujo durante nueve horas. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (diclorometano:metanol = 98:2) para dar el ácido carboxílico en la posición 1 objetivo (289 mg) como un sólido amarillo pálido. El ácido carboxílico

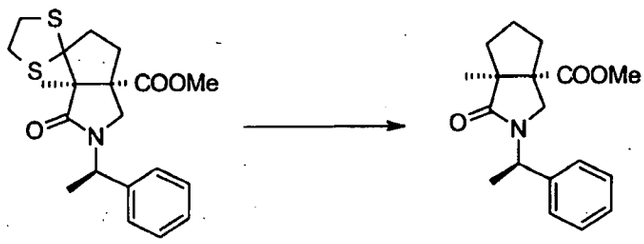
(289 mg) se disolvió en tetrahidrofurano (10 ml) y metanol (3.0 ml). Se añadió trimetilsililldiazometano (1.7 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante dos horas. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 3:2) para dar 267 mg del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.23 (5H, m), 5.52 (1H, q, J=6.86 Hz), 3.60 (3H, s), 3.55 (1H, d, J=10.05 Hz), 3.44-3.31 (1H, m), 3.28-3.19 (1H, m), 3.16 (1H, d, J=10.05 Hz), 2.79-2.70 (1H, m), 2.54-2.44 (1H, m), 2.26-2.15 (1H, m), 1.81-1.70 (1H, m), 1.59-1.52 (2H, m), 1.56 (3H, d, J=7.11 Hz), 1.33 (3H, s).

EJEMPLO DE REFERENCIA 101

Ester metílico de ácido (1S,5R)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico

[Fórmula 191]



Ester metílico de ácido (1S,5R)-6,6-etanodiildimercapto-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (266 mg, 0.68 mmoles) se disolvió en etanol (10 ml). Níquel de Raney (2.0 ml) se añadió gota a gota, y la mezcla se calentó a reflujo durante 5.5 horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida.

875

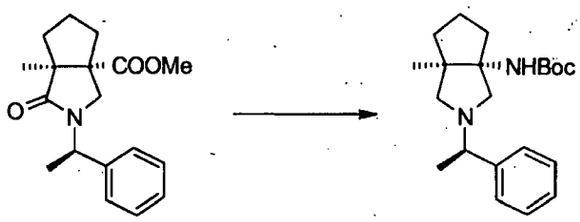
El residuo resultante se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 7:3 → 1:1) para dar 133 mg del compuesto del título como un sólido amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.24 (5H, m), 5.56-5.44 (1H, m), 3.64 (3H, s), 3.51 (1H, d, J=10.05 Hz), 3.02-2.96 (1H, m), 2.49-2.26 (2H, m), 1.91-1.44 (4H, m), 1.52 (3H, d, J=7.35 Hz), 1.12 (3H, s).

EJEMPLO DE REFERENCIA 102

(1S, 5S)-1-(ter-Butoxicarbonilamino)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 192]



Ester metílico de ácido (1S,5R)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (130 mg, 0.43 mmoles) se disolvió en metanol (5.0 ml). Una solución de hidróxido de sodio 1N (1.5 ml) se añadió gota a gota bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante cuatro horas. Después, una solución de hidróxido de sodio 1N (1.5 ml) se añadió gota a gota, y la mezcla se agitó a temperatura ambiente durante 15 horas. Hidróxido de sodio (93 mg) se añadió adicionalmente, y la mezcla se agitó a temperatura ambiente durante seis horas. Hidróxido de sodio (90 mg) se añadió nuevamente, y la mezcla se agitó a temperatura ambiente durante cuatro horas y después a 50°C durante una hora. La solución de reacción se hizo débilmente ácida con ácido clorhídrico, y el solvente se evaporó bajo presión

reducida. El residuo resultante se extrajo con diclorometano y ácido clorhídrico diluido. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en tolueno (5.0 ml). Trietilamina (0.132 ml, 0.95 mmoles) y difenilfosforil azida (0.111 ml, 0.52 mmoles) se añadieron, y la mezcla se calentó a reflujo durante tres horas. La solución de reacción se extrajo con acetato de etilo y bicarbonato de sodio saturado acuoso. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. 1,4-Dioxano (2.0 ml) y ácido clorhídrico 6N (2.0 ml) se añadieron al residuo resultante, y la mezcla se agitó a 50°C durante 15 horas. Después de extracción con agua y acetato de etilo, la capa acuosa se hizo alcalina con una solución saturada de hidróxido de sodio y se extrajo con cloroformo dos veces. Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron, y después el solvente se evaporó bajo presión reducida. Se añadieron tolueno (3.0 ml) y Red-Al™ (65% solución en tolueno) (0.50 ml) secuencialmente al residuo resultante, y la mezcla se agitó a 80°C durante 2.5 horas. Una solución de hidróxido de sodio 3N se añadió a la solución de reacción bajo enfriamiento con hielo, y las capas se separaron con tolueno. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en diclorometano (10 ml) y metanol (5.0 ml). Se añadió dicarbonato de di-ter-butilo (560 mg, 2.57 mmoles) y la mezcla se agitó a temperatura ambiente durante 16 horas. La solución de reacción se sometió a cromatografía en columna sobre gel de sílice (diclorometano : metanol = 98:2) para dar 77 mg del compuesto del título como un sólido amarillo pálido.

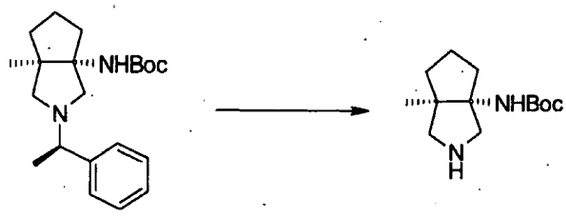
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.16 (5H, m), 4.79 (1H, brs),

3.17-3.00 (1H, m), 2.74-2.58 (2H, m), 2.53-2.44 (1H, m), 2.27-2.13 (1H, m), 2.08-1.89 (2H, m), 1.74-1.62 (2H, m), 1.60-1.24 (2H, m), 1.41 (9H, s), 1.28 (3H, d, J=6.59 Hz), 1.07 (3H, s).

EJEMPLO DE REFERENCIA 103

(1S, 5S)-1-(tert-Butoxicarbonilamino)-5-metil-4-oxo-3-azabiciclo [3.3.0] octano

[Fórmula 193]



(1S,5S)-1-(ter-Butoxicarbonilamino)-5-metil-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (77 mg, 0.22 mmoles) se disolvió en etanol (6.0 ml). Se añadió 10% de paladio-carbón (50% húmedo) (69 mg) y la mezcla se agitó en una atmósfera de hidrógeno a 45°C durante 19.5 horas. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida para dar 50 mg del compuesto del título como un aceite amarillo pálido.

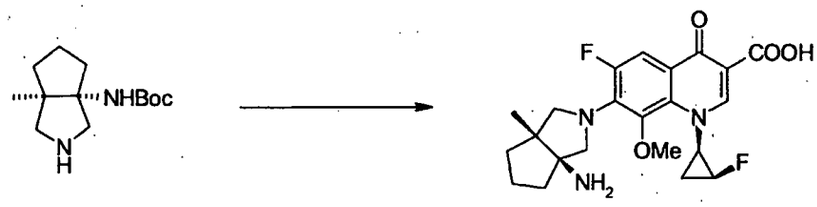
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.68 (1H, brs), 3.36-3.19 (1H, m), 3.00-2.58 (4H, m), 2.40-1.89 (4H, m), 1.81-1.26 (2H, m), 1.44 (9H, s), 1.07 (3H, s).

818

EJEMPLO 23

Acido 7-[(1R,5R)-1-amino-3-aza-5-metilbiciclo[3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropano]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 194]



Trietilamina (0.092 ml, 0.66 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropane]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (79.1 mg, 0.22 mmoles) se añadieron a una solución de (1R,5R)-1-(ter-butoxicarbonilamino)-5-metil-3-azabiciclo [3.3.0] octano (50.1 mg, 0.21 mmoles) en sulfóxido de dimetilo (2.0 ml). La mezcla se agitó a 45°C durante 24 horas. Etanol (3.0 ml), agua (1.0 ml), y trietilamina (1.0 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 2.5 horas. El solvente se evaporó bajo presión reducida, y el residuo resultante se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua dos veces y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo resultante se sometió a cromatografía en columna sobre gel de sílice (diclorometano : metanol = 99:1). El aceite resultante (92.5 mg) se disolvió en ácido clorhídrico concentrado (1.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 0.5 horas. La solución de reacción se lavó con cloroformo dos veces, y después la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se

ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por recristalización a partir de etanol para dar 47 mg del compuesto del título como un sólido amarillo pálido, p.f.: 109-113°C (dec.).

$[\alpha]_D^{24}$+78.2° (c=0.135, NaOH0.1N).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.45 (1H, s), 7.66 (1H, d, J=14.5 Hz), 4.79-4.85 (1H, m), 4.00-4.10 (1H, m), 3.61 (3H, s), 3.51-3.75 (3H, m), 3.34-3.44 (1H, m), 1.94-2.07 (1H, m), 1.43-1.93 (7H, m), 1.10 (3H, s).

EM (FAB) ; m/z: 434 $(M+H)^+$.

Análisis calculado para $C_{22}H_{25}F_2N_3O_4 \cdot 2H_2O$: C, 56.28; H, 6.23; F, 8.09; N, 8.95.

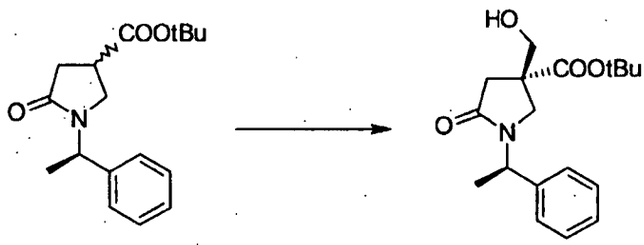
Encontrado: C, 56.57; H, 6.24; F, 8.19; N, 9.01.

IR (ATR) ν: 2942, 2877, 1612, 1573, 1448, 1434, 1392, 1349, 1342, 1311, 1301, 1290, 1272, 821, 804 cm^{-1}.

EJEMPLO DE REFERENCIA 104

Ester ter-butílico de ácido (3S)-3-hidroximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 195]



Ester ter-butílico de ácido 5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-

carboxílico (4 g, 13.82 moles) se disolvió en N,N-dimetilformamida (40 ml), y paraformaldehído (0.83 g, 27.65 mmoles) se suspendió en la solución. Hidruro de sodio (0.60 g, 13.82 mmoles) se añadió a temperatura ambiente, y la mezcla se agitó durante 30 minutos. Después, la solución de reacción se vació en una solución de ácido cítrico al 10% (150 ml) a 0°C. La mezcla se extrajo con acetato de etilo (300 ml). La capa orgánica se lavó con agua (100 ml x 2) y salmuera (100 ml), se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (30% acetato de etilo/hexano → 80% acetato de etilo/hexano) para dar 1.03 g del compuesto del título como un sólido incoloro.

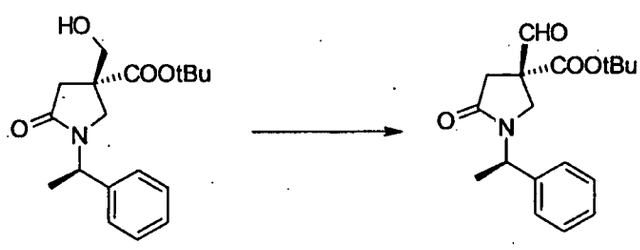
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.28 (5H, m), 5.51 (1H, q, J=7.16 Hz), 3.77 (1H, dd, J=11.23, 5.37 Hz), 3.61 (1H, dd, J=11.23, 7.81 Hz), 3.39 (1H, d, J=10.50 Hz), 3.21 (1H, d, J=10.25 Hz), 2.78 (1H, d, J=17.09 Hz), 2.51 (1H, dd, J=7.81, 5.37 Hz), 2.40 (1H, d, J=17.33 Hz), 1.53 (3H, d, J=7.33 Hz), 1.35 (9H, s).

EM (EI); m/z: 320 $(M+H)^+$.

EJEMPLO DE REFERENCIA 105

Ester ter-butílico de ácido (3S)-3-formil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 196]



881

Ester ter-butílico de ácido (3S)-3-hidroximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (4.0 g, 12.52 mmoles) se disolvió en diclorometano. Trietilamina (6.34 g, 62.62 mmoles), sulfóxido de dimetilo (3.91 g, 50.09 mmoles), y un complejo de SO_3-piridina (3.99 g, 25.05 mmoles) se añadieron secuencialmente a 0°C, y la mezcla se agitó durante 17 horas. La solución de reacción se concentró bajo presión reducida, y se añadió agua al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (60% acetato de etilo/hexano) para dar 2.85 g del compuesto del título como un sólido incoloro.

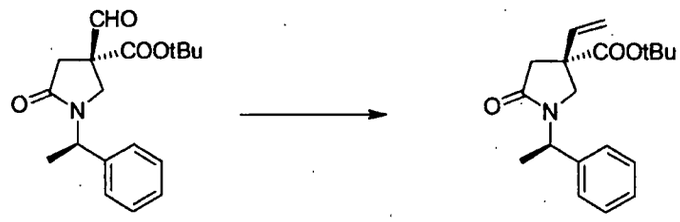
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 9.62 (1H, s), 7.35-7.28 (5H, m), 5.47 (1H, q, J=7.00 Hz), 3.79 (1H, t, J=9.52 Hz), 3.24 (1H, d, J=10.50 Hz), 2.93 (1H, d, J=17.33 Hz), 2.85 (1H, d, J=17.33 Hz), 1.53 (3H, d, J=7.08 Hz), 1.38 (9H, s).

EM (EI); m/z: 318 $(M+H)^+$.

EJEMPLO DE REFERENCIA 106

Ester ter-butílico de ácido (3R)-5-oxo-1-[(1R)-1-feniletil]-3-vinilpirrolidin-3-carboxílico

[Fórmula 197]



Bromuro de metiltrifenilfosfonio (187.4 mg, 0.52 mmoles) se disolvió en tetrahidrofurano. Una solución 2.62 M de n-butillitio en hexano (0.16

ml, 0.42 mmoles) se añadió gota a gota en una atmósfera de nitrógeno a -78°C, y la mezcla se agitó durante una hora. Después de calentar a 0°C, una solución de éster ter-butílico de ácido (3S)-3-formil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (111 mg, 0.35 mmoles) en tetrahidrofurano se añadió gota a gota, y la mezcla se agitó durante una hora. Una solución saturada de cloruro de amonio se añadió a la solución de reacción, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (25% acetato de etilo/hexano) para dar 54 mg del compuesto del título como un aceite amarillo.

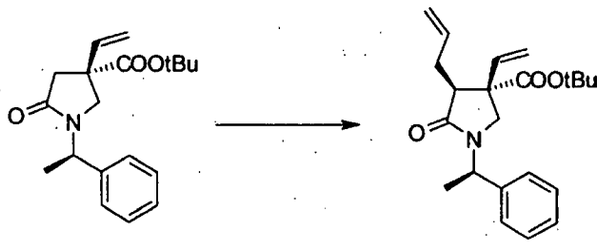
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.26 (5H, m), 5.96 (1H, dd, J=17.33, 10.74 Hz), 5.52-5.45 (1H, m), 5.21-5.17 (2H, m), 3.45 (1H, d, J=10.25 Hz), 3.26 (1H, d, J=10.01 Hz), 3.01 (1H, d, J=16.60 Hz), 2.54 (1H, d, J=16.60 Hz), 1.50 (3H, d, J=7.08 Hz), 1.33 (9H, s).

EM (EI) m/z: 318 $(M+H)^+$.

EJEMPLO DE REFERENCIA 107

Ester ter-butílico de ácido (3S,4S)-4-alil-5-oxo-1-[(1R)-1-feniletil]-3-vinilpirrolidin-3-carboxílico

[Fórmula 198]



Ester ter-butílico de ácido (3R)-5-oxo-1-[(1R)-1-feniletil]-3-

883

vinilpirrolidin-3-carboxílico (236.0 mg, 0.75 mmoles) y bromuro de alilo. (271.6 mg, 2.24 mmoles) se disolvieron en tetrahidrofurano. Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (1.12 ml, 1.12 mmoles) se añadió gota a gota en una atmósfera de nitrógeno a 0°C. Después de agitar durante 1.5 horas, se añadió una solución saturada de cloruro de amonio, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (10% acetato de etilo/hexano) para dar 135 mg del compuesto del título como un aceite incoloro.

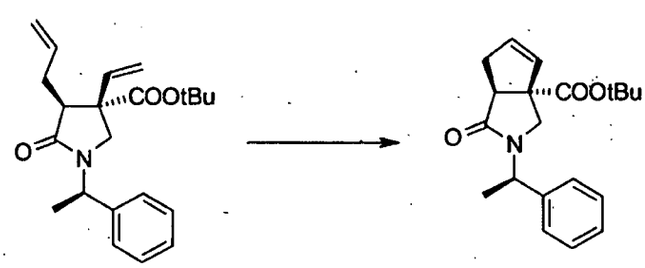
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.26 (5H, m), 5.98-5.82 (2H, m), 5.47 (1H, q, J=7.00 Hz), 5.24-4.97 (4H, m), 3.35-3.25 (2H, m), 3.03 (1H, t, J=6.82 Hz), 2.48-2.41 (1H, m), 2.39-2.32 (1H, m), 1.54 (3H, d, J=7.08 Hz), 1.33 (9H, s).

EM (EI) ; m/z: 356 $(M+H)^+$.

EJEMPLO DE REFERENCIA 108

Ester ter-butílico de ácido [(1S,5S)-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico

[Fórmula 199]



Ester ter-butílico de ácido (3S,4S)-4-alil-5-oxo-1-[(1R)-1-feniletil]-3-

vinilpirrolidin-3-carboxílico (130.0 mg, 0.37 mmoles) se disolvió en benceno (8 ml). Se añadió el catalizador Grubbs de segunda generación (31.0 mg, 0.04 mmoles) y la mezcla se agitó a temperatura ambiente durante dos horas. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (15% acetato de etilo/hexano) para dar 93.2 mg del compuesto del título como un aceite amarillo.

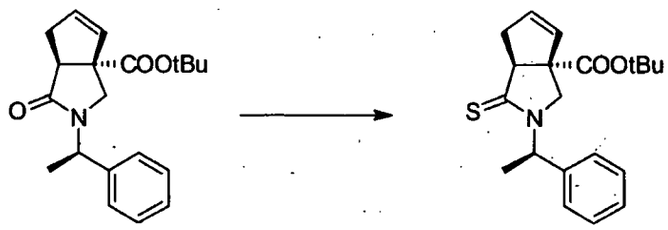
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.28 (5H, m), 5.94-5.91 (1H, m), 5.60-5.59 (1H, m), 5.51 (1H, q, J=7.16 Hz), 3.34-3.24 (3H, m), 2.81-2.79 (2H, m), 1.45 (3H, d, J=7.32 Hz), 1.38 (9H, s).

EM (EI) m/z: 328 $(M+H)^+$.

EJEMPLO DE REFERENCIA 109

Ester ter-butílico de ácido [(1S,5S)-3-[(1R)-1-feniletil]-4-tioxo-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico

[Fórmula 200]



Ester ter-butílico de ácido [(1S,5S)-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico (88.0 mg, 0.27 mmoles) se disolvió en tolueno (8 ml). Se añadió reactivo de Lawesson (81.5 mg, 0.20 mmoles) y la mezcla se agitó a 80°C durante cuatro horas. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (10% acetato de etilo/hexano) para dar 91.6 mg del compuesto del título como un aceite amarillo.

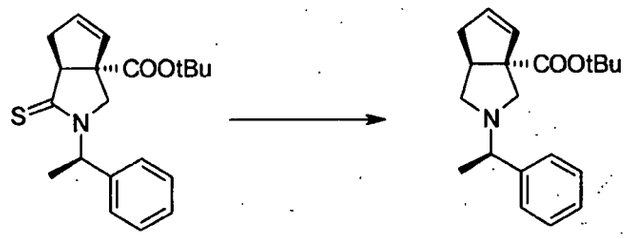
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.26 (5H, m), 6.41 (1H, q, J=7.08 Hz), 5.95-5.94 (1H, m), 5.55-5.54 (1H, m), 3.74 (1H, d, J=8.30 Hz), 3.60 (1H, d, J=11.96 Hz), 3.49 (1H, d, J=12.21 Hz), 3.15 (1H, d, J=17.09 Hz), 3.02-2.98 (1H, m), 1.51 (3H, d, J=7.08 Hz), 1.36 (9H, s).

EM (EI) m/z: 344 $(M+H)^+$.

EJEMPLO DE REFERENCIA 110

Ester ter-butílico de ácido [(1S,5S)-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico

[Fórmula 201]



Ester ter-butílico de ácido [(1S,5S)-3-[(1R)-1-feniletil]-4-tioxo-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico (88.2 mg, 0.27 mmoles) se disolvió en etanol. Se añadió níquel de Raney y la mezcla se agitó durante una hora. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. El residuo resultante se sometió a cromatografía en columna sobre gel de sílice (10% acetato de etilo/hexano) para dar 55.4 mg del compuesto del título como un aceite incoloro.

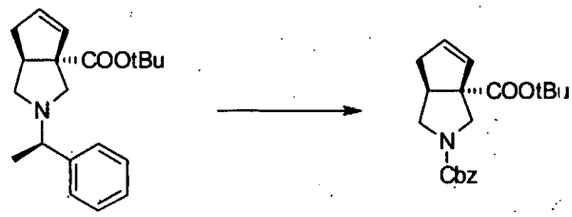
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.21 (5H, m), 5.74 (1H, brs), 5.54 (1H, brs), 3.15 (1H, q, J=6.75 Hz), 3.04 (1H, brs), 2.72-2.70 (2H, m), 2.61 (1H, t, J=7.81 Hz), 2.53-2.51 (2H, m), 2.18 (1H, d, J=16.85 Hz), 1.41 (9H, s), 1.32 (3H, d, J=6.59 Hz).

EM (EI) m/z: 314 $(M+H)^+$.

EJEMPLO DE REFERENCIA 111

Ester ter-butílico de ácido [(1S,5S)-3-benciloxicarbonil-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico

[Fórmula 202]



Ester ter-butílico de ácido [(1S,5S)-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico (370 mg, 1.18 mmoles) se disolvió en dicloroetano (3 ml). Se añadió cloruro de benciloxicarbonilo (1.01 g, 5.90 mmoles) y la mezcla se agitó a 40°C durante tres horas. La solución de reacción se concentró bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (10% acetato de etilo/hexano) para dar 385 mg del compuesto del título como un aceite incoloro.

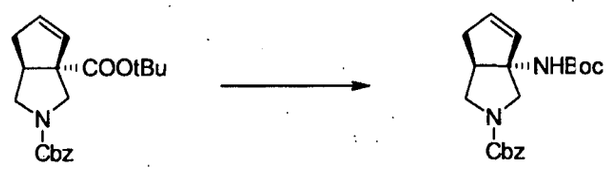
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.29 (5H, m), 5.79 (1H, brs), 5.64 (1H, brs), 5.12 (2H, s), 3.79-3.68 (3H, m), 3.21-3.12 (2H, m), 2.74 (1H, dd, J=17.44, 6.22 Hz), 2.19 (1H, t, J=18.54 Hz), 1.43 (9H, s).

EM; (EI) m/z: 366 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 112

Ester bencílico de ácido [(1S,5R)-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-7-en-3-il] carboxílico

[Fórmula 203]



Ester ter-butílico de ácido [(1S,5S)-3-benciloxicarbonil-3-azabiciclo [3.3.0] oct-7-en-1-il] carboxílico (380 mg, 1.11 mmoles) se disolvió en diclorometano (8 ml). Se añadió ácido trifluoroacético (1.5 ml) y la mezcla se agitó durante un día. La solución de reacción se concentró bajo presión reducida, y una solución de hidróxido de sodio 1N (100 ml) se añadió, y la mezcla se lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo (200 ml x 2). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (10 ml). Se añadieron trietilamina (223.3 mg, 2.21 mmoles) y difenilfosforil azida (469.5 mg, 1.66 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó a 80°C durante 20 horas. La solución de reacción se concentró bajo presión reducida. Después, 1,4-dioxano (10 ml) y ácido clorhídrico 6N (10 ml) se añadieron, y la mezcla se agitó durante tres días. Después de concentración bajo presión reducida y destilación azeotrópica con etanol, se añadió una solución de hidróxido de sodio 1N, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. Dicarbonato de di-ter-butilo (1204 mg, 5.52 mmoles) se añadió al residuo resultante, y la mezcla se agitó a 50°C durante 16 horas. La solución de reacción se purificó por cromatografía en columna sobre gel de sílice (20% acetato de etilo/hexano) para dar 92.1 mg del compuesto del título como un aceite incoloro.

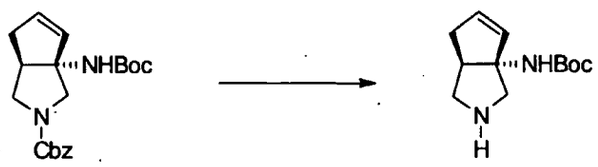
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.25 (5H, m), 5.84 (1H, s), 5.78 (1H, s), 5.10 (2H, s), 4.70 (1H, s), 3.87 (1H, dd, J=11.23, 8.79 Hz), 3.79-3.76 (2H, m), 3.24-3.21 (1H, m), 2.87-2.72 (2H, m), 2.21-2.18 (1H, m), 1.43 (9H, s).

EM (EI); m/z: 359 $(M+H)^+$.

EJEMPLO DE REFERENCIA 113

(1S, 5R)-1-ter-Butoxicarbonilamino-3-azabiciclo [3.3.0] oct-7-eno

[Fórmula 204]



Ester bencílico de ácido [(1S,5R)-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-7-en-3-il] carboxílico (85.0 mg, 0.24 mmoles) se disolvió en tetrahidrofurano (20 ml). Después de hacerlo burbujear con amoniaco líquido (20 ml) a -78°C, se añadió sodio (17.1 mg, 0.71 mmoles) y la mezcla se agitó durante una hora. Se añadió una solución saturada de cloruro de amonio (6 gotas) y después el amoniaco se vaporizó en un baño de agua con hielo. Una solución de hidróxido de sodio 1N se añadió, seguido por extracción con cloroformo dos veces. Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el filtrado se concentró bajo presión reducida para dar 52.9 mg del compuesto del título como un sólido incoloro.

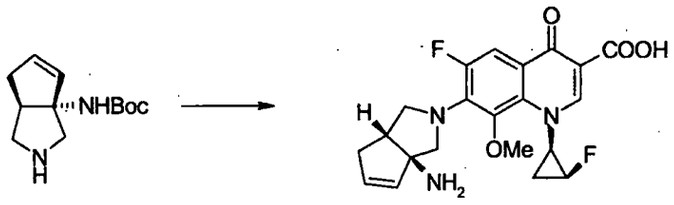
EM (EI) m/z: 225$(M+H)^+$.

889

EJEMPLO 24

Acido 7-[(1S,5R)-1-amino-3-azabiciclo [3.3.0] oct-7-en-3-il]-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico

[Fórmula 205]



(1S,5R)-1-ter-Butoxicarbonilamino-3-azabiciclo [3.3.0] oct-7-eno (52.9 mg, 0.24 mmoles) se disolvió en sulfóxido de dimetilo (2 ml). Se añadieron ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (89.4 mg, 0.25 mmoles) y trietilamina (71.6 mg, 0.71 mmoles) y la mezcla se agitó a 40°C durante 20 horas. Después, etanol acuoso al 90% (20 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante dos horas. El solvente se evaporó bajo presión reducida y una solución de ácido cítrico al 10% se añadió, seguida por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 8 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se lavó con etanol-éter dietílico y se secó bajo presión reducida para

889

dar 57.8 mg del compuesto del título como un sólido amarillo pálido, p.f.: 206-208°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, s), 7.69 (1H, d, J=13.67 Hz), 5.90 (1H, brs), 5.69 (1H, brs), 4.96 (1H, d, J=60.79 Hz), 4.08-4.04 (1H, m), 3.77 (1H, t, J=8.91 Hz), 3.70 (3H, d, J=10.25 Hz), 3.64 (1H, s), 3.59-3.57 (1H, m), 3.54-3.51 (1H, m), 2.91-2.87 (1H, m), 2.55-2.53 (1H, m), 2.30 (1H, d, J=17.09 Hz), 1.63-1.55 (2H, m).

Análisis calculado para $C_{21}H_{21}F_2N_3O_4 \cdot 0.25H_2O \cdot 0.5EtOH$: C, 59.39; H, 5.55; N, 9.44; F, 8.54.

Encontrado: C, 59.32; H, 5.44; N, 9.50; F, 8.28.

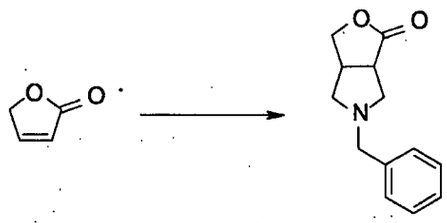
EM (EI); m/z: 418 $(M+H)^+$.

IR (ATR) ν: 2929, 2848, 2758, 1726, 1614, 1577, 1537, 1504, 1435, 1392, 1352, 1315, 1269 cm^{-1}.

EJEMPLO DE REFERENCIA 114

(1R*, 5S*)-7-Bencil-3-oxa-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 206]



(±)-cis

Se añadió ácido trifluoroacético (0.136 ml) a una solución de N-bencil-N-(metoximetil)-N-trimetilsililamina (43.9 g, 185 mmoles) y γ-crotonolactona (12.5 g, 176 mmoles) en 1,2-diclorometano (176 ml), y la mezcla se agitó en una atmósfera de nitrógeno a temperatura ambiente durante cuatro

890

horas. Una solución saturada de bicarbonato de sodio (250 ml) se añadió a la solución de reacción, seguido por extracción con cloroformo (200 ml x 2). La capa orgánica se lavó con salmuera (400 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 84:16 → 80:20 → 75:25 → 66:34 → 50:50) para dar 37.1 g del compuesto del título.

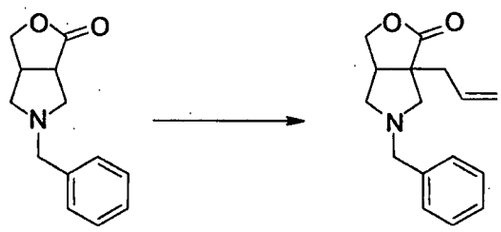
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.30-7.26 (5H, m), 4.48 (1H, t, J=8.58 Hz), 4.08 (1H, dd, J=9.19, 3.55 Hz), 3.69 (1H, d, J=13.24 Hz), 3.54 (1H, d, J=13.24 Hz), 3.26 (1H, d, J=9.31 Hz), 3.08-2.98 (2H, m), 2.80 (1H, d, J=9.56 Hz), 2.49-2.38 (2H, m).

EM (ESI) m/z: 218 $(MH-H)^+$.

EJEMPLO DE REFERENCIA 115

1-Alil-7-bencil-3-oxa-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 207]



(±)-cis

Bromuro de alilo (2.48 ml, 29.3 mmoles) se añadió a una solución de (1R*, 5S*)-7-bencil-3-oxa-7-azabiciclo [3.3.0] octan-2-ona (4.25 g, 19.6 mmoles) en tetrahidrofurano (98 ml) con agitación bajo enfriamiento con hielo con sal. Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (23.5 ml, 23.5 mmoles) se añadió gota a gota bajo enfriamiento con hielo-

891

acetona. La mezcla se agitó durante dos horas mientras se calentaba gradualmente a temperatura ambiente. Una solución saturada de cloruro de amonio (200 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (100 ml x 2). La capa orgánica se lavó con agua (250 ml) y salmuera (250 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25 → 66:34 → 50:50) para dar 1.51 g del compuesto del título.

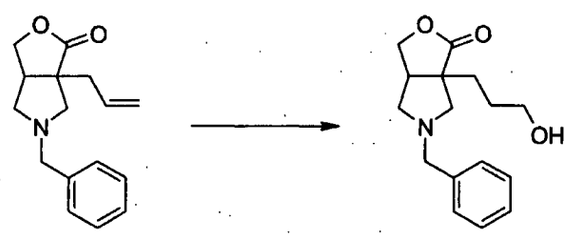
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.21 (5H, m), 5.80-5.70 (1H, m), 5.20-5.14 (2H, m), 4.35 (1H, t, J=8.95 Hz), 4.03 (1H, dd, J=9.19, 3.55 Hz), 3.63 (1H, d, J=13.24 Hz), 3.51 (1H, d, J=13.24 Hz), 3.26 (1H, d, J=9.07 Hz), 2.81 (1H, d, J=9.56 Hz), 2.73-2.71 (1H, m), 2.57 (1H, dd, J=13.73, 6.62 Hz), 2.49 (1H, dd, J=9.44, 6.74 Hz), 2.30 (1H, dd, J=13.85, 8.21 Hz), 2.23 (1H, d, J=9.07 Hz).

EM (ESI); m/z: 258 $(M+H)^+$.

EJEMPLO DE REFERENCIA 116

7-Bencil-1-(3-hidroxipropil)-3-oxa-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 208]



Una solución de 1-alil-7-bencil-3-oxa-7-azabiciclo [3.3.0] octan-2-ona (11.0 g, 42.7 mmoles) en tetrahidrofurano (142 ml) se enfrió con hielo-acetona. Una solución 0.5 moles/l de 9-borabiciclo[3.3.1]nonano en

892

tetrahidrofurano (264 ml, 132 mmoles) se añadió en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante dos horas. Después de enfriar con hielo-acetona, se añadieron una solución 1 mol/l de hidróxido de sodio (142 ml) y una solución de peróxido de hidrógeno al 30% en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante una hora. La capa orgánica de la solución de reacción se concentró bajo presión reducida y se extrajo con cloroformo (300 ml x 1, 250 ml x 1). La capa orgánica se lavó con salmuera (600 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 66:34 → 50:50 → 34:66 → 20:80) para dar 12.9 g de un residuo que contenía el compuesto del título que se usó directamente para la siguiente reacción.

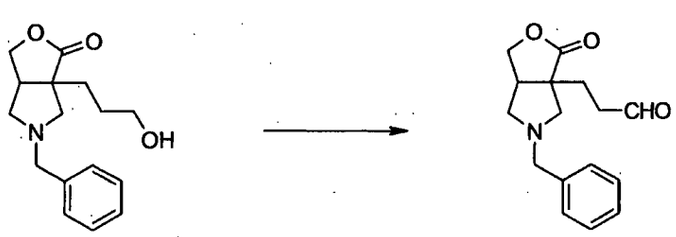
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.22 (5H, m), 4.41 (1H, t, J=8.82 Hz), 4.05 (1H, dd, J=9.19, 3.55 Hz), 3.81 (1H, t, J=8.95 Hz), 3.68-3.63 (3H, m), 3.51 (1H, d, J=13.24 Hz), 3.29 (1H, d, J=9.31 Hz), 2.83 (1H, d, J=9.56 Hz), 2.69 (1H, s), 2.49 (1H, t, J=7.84 Hz), 2.19 (1H, t, J=8.58 Hz), 1.93-1.82 (3H, m).

EM (ESI) ; m/z: 276 $(M+H)^+$.

EJEMPLO DE REFERENCIA 117

7-Bencil-3-oxa-1-(3-oxopropil)-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 209]



893

Una solución de diclorometano (113 ml) se enfrió con hielo seco-metanol en una atmósfera de nitrógeno. Cloruro de oxalilo (11.2 ml, 128 mmoles) y sulfóxido de dimetilo (15.2 ml, 214 mmoles) se añadieron, y la mezcla se agitó bajo enfriamiento durante 30 minutos. Se añadió una solución del residuo que contenía 7-bencil-1-(3-hidroxipropil)-3-oxa-7-azabiciclo[3.3.0] octan-2-ona (12.9 g, 42.7 mmoles) en diclorometano (100 ml) y la mezcla se agitó bajo enfriamiento con hielo durante una hora. Trietilamina (35.8 ml, 256 mmoles) se añadió bajo enfriamiento con hielo, y la mezcla se agitó bajo enfriamiento durante una hora y después a temperatura ambiente durante una hora. Una solución saturada de cloruro de amonio (200 ml) se añadió a la solución de reacción, seguido por extracción con cloroformo (150 ml x 2). La capa orgánica se lavó con salmuera (450 ml) y después se secó sobre sulfato de sodio anhidro Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 90:10 → 66:34 → 50:50) para dar 8.91 g de un residuo que contenía el compuesto del título que se usó directamente para la siguiente reacción.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 9.77 (1H, s), 7.32-7.22 (5H, m), 4.42 (1H, t, J=8.95 Hz), 4.06 (1H, dd, J=9.31, 3.68 Hz), 3.62 (1H, d, J=12.99 Hz), 3.53 (1H, d, J=13.24 Hz), 3.30 (1H, d, J=9.31 Hz), 2.84 (1.0H, d, J=9.31 Hz), 2.73-2.62 (2.0H, m), 2.55-2.51 (2.0H, m), 2.04-2.00 (2H, m).

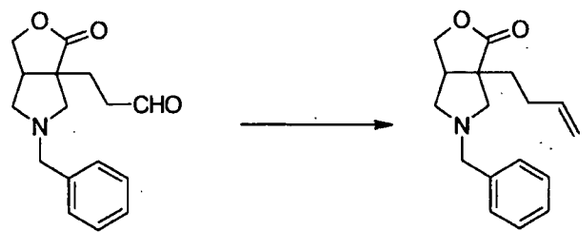
EM (ESI); m/z: 274 $(M+H)^+$.

894

EJEMPLO DE REFERENCIA 118

7-Bencil-1-(3-buten-1-il)-3-oxa-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 210]



Tetrahidrofurano (45.7 ml) se añadió a yoduro de metiltrifenilfosfonio (6.16 g, 15.2 mmoles) en una atmósfera de nitrógeno. Una solución 1.57 moles/l de butillitio en hexano (14.0 ml, 22.0 mmoles) se añadió bajo enfriamiento con hielo, y después la solución de reacción se agitó durante 15 minutos. Una solución del residuo que contenía 7-bencil-3-oxa-1-(3-oxopropil)-7-azabiciclo [3.3.0]octan-2-ona (5.00 g, 18.3 mmoles) en tetrahidrofurano (45.7 ml) se añadió gota a gota a la misma bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. Se añadió agua (150 ml) a la solución de reacción, seguido por extracción con acetato de etilo (150 ml). La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano :acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25) para dar 1.09 g del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.22 (10.8H, m), 5.83-5.73 (1H, m), 5.07-4.96 (2.1H, m), 4.40 (1H, t, J=8.95 Hz), 4.04 (1H, dd, J=9.19, 3.55 Hz), 3.63 (1H, d, J=12.99 Hz), 3.50 (1H, d, J=13.24 Hz), 3.29 (1H, d, J=9.31 Hz), 2.83 (1H, d, J=9.56 Hz), 2.71-2.69 (1H, m), 2.47 (1H, dd, J=9.56, 6.62 Hz), 2.23-2.02 (3H, m), 1.92-1.88 (1H, m), 1.69-1.65 (1H, m).

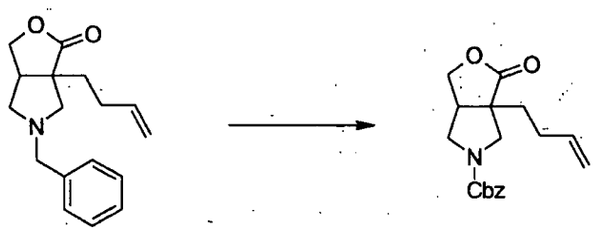
895

EM (ESI); m/z: 272 $(M+H)^+$.

EJEMPLO DE REFERENCIA 119

7-Benciloxicarbonil-1-(3-buten-1-il)-3-oxa-7-azabiciclo [3.3.0] octan-2-ona

[Fórmula 211]



Cloroformiato de bencilo (1.72 ml, 12.0 mmoles) se añadió a una solución de 7-bencil-1-(3-buten-1-il)-3-oxa-7-azabiciclo [3.3.0] octan-2-ona (1.09 g, 4.02 mmoles) en diclorometano (13.4 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante cinco días. La solución de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 84:16 → 80:20 → 75:25 → 66:34 → 50:50) para dar 1.13 g del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.82-5.72 (1H, m), 5.12-5.00 (4H, m), 4.42 (1H, t, J=8.33 Hz), 4.12 (1H, brs), 4.00 (1H, d, J=11.77 Hz), 3.83 (1H, dd, J=11.77, 8.33 Hz), 3.44 (2H, d, J=37.75 Hz), 2.95-2.89 (1H, m), 2.26-2.17 (1H, m), 2.10-2.06, (1H, m), 1.90-1.76 (2H, m).

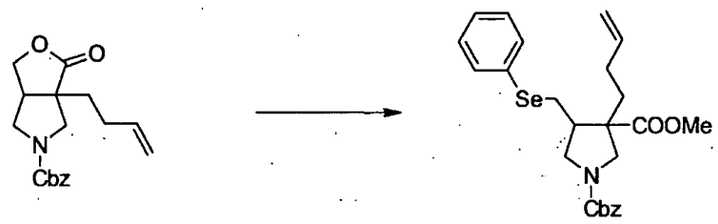
EM (ESI); m/z: 316 $(M+H)^+$.

896

EJEMPLO DE REFERENCIA 120

Ester metílico de ácido 1-benciloxicarbonil-3-(3-buten-1-il)-4-fenilselenilmetil-1-3-carboxílico

[Fórmula 212]



N,N-Dimetilformamida (16.3 ml) se añadió a difenil diselenida (946 mg, 3.03 mmoles) en una atmósfera de nitrógeno. Después, la mezcla se despresurizó al vacío y se desgasificó por congelamiento (x 3) mientras se enfriaba con nitrógeno líquido. Se añadió Borohidruro de sodio (229 mg, 6.05 mmoles) a la misma a temperatura ambiente. La mezcla se agitó a temperatura ambiente hasta que se completó la generación de gas, y después se despresurizó al vacío y se desgasificó por congelamiento (x 3) para preparar una solución de reacción A.

De manera separada, una solución de 7-bencil-1-(3-buten-1-il)-3-oxa-7-azabiciclo[3.3.0]octan-2-ona (955 mg, 3.03 mmoles) en N,N-dimetilformamida (14.0 ml) se despresurizó al vacío y se desgasificó por congelamiento (tres veces) mientras se enfriaba con nitrógeno líquido para preparar una solución de reacción B.

La solución de reacción B se añadió a la solución de reacción A, y la mezcla se agitó a 100°C durante una hora. La solución de reacción se enfrió a temperatura ambiente y después se añadió ácido clorhídrico 1N (10 a 20 ml) seguido por extracción con acetato de etilo (100 ml x 2). La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. Después de

filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2 → 97:3 → 96:4) para dar 2.08 g del compuesto del título que se usó directamente para el paso de esterificación. Se añadió trimetilsilildiazometano (9.09 ml) a una solución de 2.08 g del residuo en metanol (30.3 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 20 minutos. La solución de reacción se concentró bajo presión reducida. Después, el residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25) para dar 485 mg del compuesto del título.

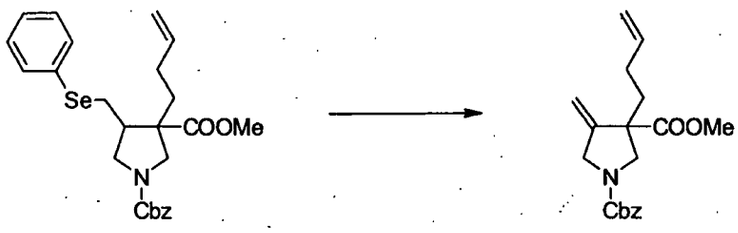
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.49-7.23 (5H, m), 5.73-5.69 (1H, m), 5.16-5.09 (2H, m), 4.98-4.95 (2H, m), 3.98 (1H, dd, J=21.33, 11.28 Hz), 3.80 (1H, ddd, J=24.08, 10.97, 7.05 Hz), 3.70 (3H, s), 3.32-3.21 (2H, m), 3.12 (1H, dd, J=12.38, 3.06 Hz), 2.49 (1H, t, J=12.01 Hz), 2.34-2.29 (1H, m), 2.10-2.05 (1H, m), 1.96-1.92 (2H, m), 1.38-1.35 (1H, m).

EM (ESI); m/z: 378 $(M+H)^+$.

EJEMPLO DE REFERENCIA 121

Ester metílico de ácido 1-benciloxicarbonil-3-(3-buten-1-il)-4-metilenepirrolidin-3-carboxílico

[Fórmula 213]



Una solución de peryoduro de sodio 0.5N (4.99 ml, 2.50 mmoles)

898

se añadió a una solución de éster metílico de ácido 1-benciloxicarbonil-3-(3-buten-1-il)-4-fenilselenilmetil-3-carboxílico (485 mg, 0.997 mmoles) en tetrahidrofurano (9.97 ml). La mezcla se agitó a temperatura ambiente durante cinco horas y después a 40°C a 50°C durante 24 horas. Se añadió agua (50 ml) a la solución de reacción, seguido por extracción con acetato de etilo (50 ml x 2). La capa orgánica se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25) para dar 285 mg del compuesto del título.

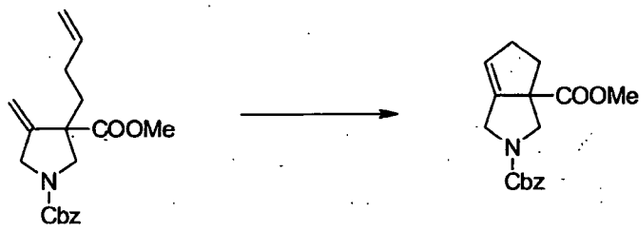
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.42-7.28 (5H, m), 5.79-5.75 (1H, m), 5.20-5.15 (4H, m), 5.03-4.98 (2H, m), 4.21-4.13 (3H, m), 3.69 (3H, s), 3.41 (1H, dd, J=19.49, 11.40 Hz), 2.17-2.10 (1H, m), 2.04-2.02 (2H, m), 1.68-1.64 (1H, m).

EM (ESI) m/z: 330 $(M+H)^+$.

EJEMPLO DE REFERENCIA 122

Ester metílico de ácido {3-benciloxicarbonil-3-azabiciclo [3.3.0] oct-5-en-1-il}carboxílico

[Fórmula 214]



El catalizador Grubbs de segunda generación (29.6 mg, 0.871 mmoles) se añadió a una solución de éster metílico de ácido 1-benciloxicarbonil-3-(3-buten-1-il)-4-metilenopirrolidin-3-carboxílico (286 mg, 0.871 mmoles) en

899

diclorometano (8.71 ml) en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 19 horas, y se añadió el diclorometano (17.4 ml). Después de agitación a 45°C durante seis horas, la solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano :acetato de etilo = 100:0 → 95:5 → 87:13 → 85:15 → 83:17 → 80:20 → 75:25 → 66:34) para dar 187 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.72 (1H, d, J=13.73 Hz), 5.17-5.12 (2H, m), 4.20 (1H, dd, J=10.79, 2.70 Hz), 4.04-3.94 (2H, m), 3.68 (3H, d, J=1.47 Hz), 3.07 (1H, dd, J=10.79, 7.11 Hz), 2.95-2.87 (1H, m), 2.63-2.48 (2H, m), 1.88-1.83 (1H, m).

EM (ESI) m/z: 302 $(M+H)^+$.

EJEMPLO DE REFERENCIA 123

Acido {3-benciloxicarbonil-3-azabiciclo [3.3.0] oct-5-en-1-il}carboxílico

[Fórmula 215]



Una solución de hidróxido de sodio 1N (1.86 ml) se añadió a una solución de éster metílico de ácido {3-benciloxicarbonil-3-azabiciclo [3.3.0]oct-5-en-1-il}carboxílico (187 mg, 0.620 mmoles) en metanol (6.20 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 16 horas. La solución de reacción se concentró bajo presión reducida y después se lavó con éter dietílico (50 ml x 2). La capa acuosa se hizo ácida con ácido clorhídrico 1N bajo enfriamiento con hielo, seguido por extracción con acetato de

900

etilo (100 ml x I, 80 ml x 1). La capa orgánica se lavó con agua (80 ml) y salmuera (80 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 186 mg (cuantitativo) del compuesto del título.

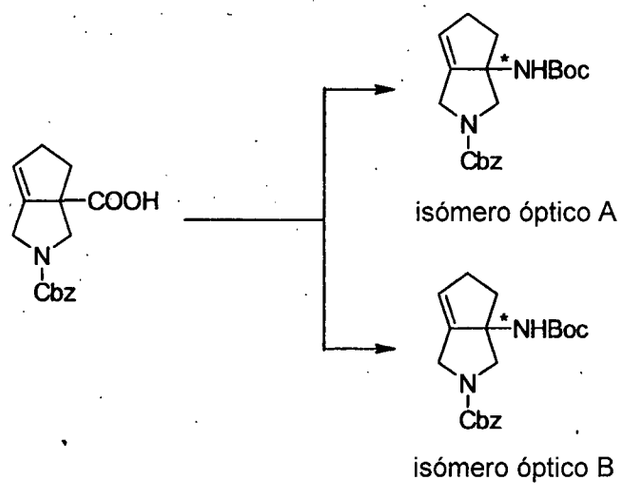
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.30 (5H, m), 5.77 (1H, d, J=17.16 Hz), 5.21-5.10 (2H, m), 4.25 (1H, dd, J=10.91, 5.02 Hz), 4.02 (2H, t, J=17.53 Hz), 3.09 (1H, dd, J=10.91, 7.72 Hz), 2.93 (1H, brs), 2.60-2.54 (2H, m), 1.93-1.83 (1H, m).

EM (ESI); m/z: 288 $(M+H)^+$.

EJEMPLO DE REFERENCIA 124

3-Benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (isómero óptico A, isómero óptico B)

[Fórmula 216]



Se añadieron trietilamina (0.181 ml, 1.30 mmoles) y difenilfosforil azida (0.181 ml, 0.840 mmoles) a una solución de ácido {3-benciloxicarbonil-3-azabiciclo [3.3.0] oct-5-en-1-il}carboxílico (186 mg, 0.647 mmoles) en tolueno (3.23 ml) en una atmósfera de nitrógeno. La mezcla se agitó a temperatura

901

ambiente durante 30 minutos y después a 100°C durante 30 minutos. La solución de reacción se concentró bajo presión reducida, y trietilamina se destiló azeotrópicamente con tolueno (x 3). 1,4-Dioxano (1.62 ml) y ácido clorhídrico 6N (1.62 ml) se añadieron al residuo resultante, y la mezcla se agitó a 50°C durante una hora. La solución de reacción se destiló con agua (6.5 ml), y la capa orgánica se evaporó por concentración bajo presión reducida. El residuo se lavó con éter dietílico (20 ml x 2). La capa acuosa se hizo alcalina con una solución de hidróxido de sodio 1N bajo enfriamiento con hielo, seguido por extracción con cloroformo (40 ml x l, 30 ml x 1). La capa orgánica se lavó con agua (40 ml) y salmuera (40 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. Se añadió diclorometano (3.23 ml) al residuo resultante, y se añadió dicarbonato de di-ter-butilo (283 mg, 1.30 mmoles) en una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 17 horas, la solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano :acetato de etilo = 100:0 → 90:10 → 84:16 → 80:20 → 75:25) para dar 120 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m), 5.74 (1H, d, J=7.48 Hz), 5.17-5.11 (2H, m), 4.58 (1H, s), 4.26 (1H, dd, J=25.37, 11.40 Hz), 4.02-4.01 (2H, m), 3.14 (1H, dd, J=11.28, 8.82 Hz), 2.80 (1H, brs), 2.55-2.52 (1H, m), 2.37 (1H, brs), 1.94-1.91 (1H, m), 1.43 (9H, s).

El racemato 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (108 mg, 0.301 mmoles) obtenido como se describió antes se resolvió ópticamente mediante una columna ópticamente activa (CHIRALCEL OJ, 20 mm de diámetro x 250 mm, hexano : alcohol isopropílico = 90:10, velocidad de flujo = 20 ml/min, resolviendo 20 mg cada vez) para dar 3-

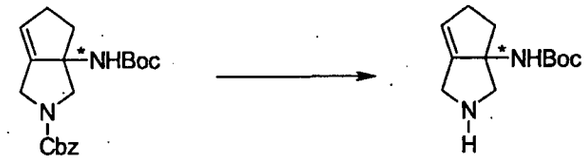
902

benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0]oct-5-eno (isómero óptico A) (50.5 mg, 1.41 mmoles, tiempo de retención = 8.0 min) y su enantiómero 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (isómero óptico B) (55.6 mg, 0.155 mmoles, tiempo de retención = 11.5 min).

EJEMPLO DE REFERENCIA 125

1-ter-Butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (derivado del isómero óptico A)

[Fórmula 217]



isómero óptico A

Una solución de 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (isómero óptico A) (50.5 mg, 0.141 mmoles) en tetrahidrofurano (1.41 ml) se hizo burbujear con amoniaco gaseoso bajo enfriamiento con hielo seco-acetona para añadir 30 a 40 ml de amoniaco líquido a la solución. Se añadió sodio (17.0 mg, 0.709 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó durante 10 minutos. Una solución saturada de cloruro de amonio (3 gotas) se añadió a temperatura ambiente, y la mezcla se agitó a temperatura ambiente para evaporar el amoniaco. Una solución de hidróxido de sodio 1N (12.0 ml) se añadió, seguido por extracción con cloroformo (40 ml x 1, 20 ml x 1) y la capa inferior de cloroformo/metanol/agua = 7/3/1 (40 ml x 1, 20 ml x 1). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el filtrado se concentró

bajo presión reducida para dar 33 mg (cuantitativo) del compuesto del título.

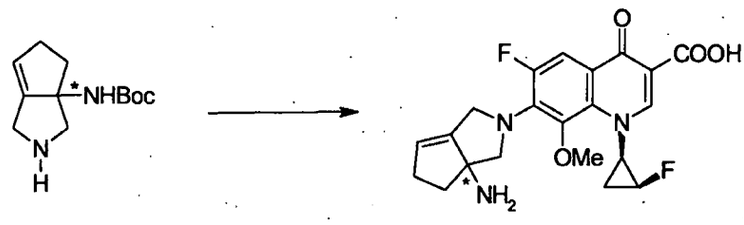
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 5.58 (1H, brs), 4.62 (1H, brs), 3.47 (3H, tt, J=14.34, 9.68 Hz), 2.96-2.87 (1H, m), 2.61-2.57 (2H, m), 2.28-2.25 (1H, m), 1.85 (1H, dt, J=16.42, 6.62 Hz), 1.45 (9H, s).

EM (ESI) m/z: 225 $(M+H)^+$.

EJEMPLO 25

Acido 7-[1-amino-3-azabiciclo [3.3.0] oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico A)

[Fórmula 218]



Trietilamina (0.0595 ml, 0.426 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-6,7-difluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (51.2 mg, 0.142 mmoles) se añadieron a una solución de 1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0]oct-5-eno (derivado del isómero óptico A) (33.0 mg, 0.135 mmoles) en sulfóxido de dimetilo (0.284 ml). La mezcla se agitó a temperatura ambiente durante dos horas y a 40°C durante 14 horas. Una solución mixta de etanol : agua = 4:1 (5 ml) y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de ácido cítrico al 10% (15 ml), agua (15 ml), y salmuera (15 ml). La capa orgánica se secó

sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). 61.4 mg del residuo resultante se disolvieron en ácido clorhídrico concentrado (1 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (15 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml), cloroformo/metanol = 10/1 (80 ml), y la capa inferior de cloroformo/metanol/agua = 7/3/1 (80 ml x 3). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se disolvió en etanol caliente (5 ml) y una solución de amoniaco al 28% (1 a 2 ml), y el material insoluble se removieron por filtración. El solvente se evaporó gradualmente bajo presión reducida mientras se calentaba con agitación. Adicionalmente, amoniaco se destiló azeotrópicamente con etanol (3 a 5 ml) (x 10). El etanol se concentró hasta que los cristales se precipitaron, seguido por agitación a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración, se lavaron con etanol y éter dietílico, y después se secaron bajo presión reducida a 60°C para dar 9.65 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.40 (1H, d, J=3.19 Hz), 7.69 (1H, d, J=14.46 Hz), 5.62 (1H, s), 5.12-4.96 (1H, m), 4.50 (1H, d, J=12.50 Hz), 4.04-4.01 (2H, m), 3.60 (5H, dd, J=16.67, 9.31 Hz), 2.91 (1H, s), 2.62-2.59 (1H, m), 2.15-2.07 (1H, m), 1.99-1.92 (1H, m), 1.58-1.54 (1H, m), 1.48-1.37 (1H, m).

Análisis calculado para $C_{21}H_{21}F_2N_3O_4 \cdot 1.5H_2O$: C, 56.75; H, 5.44; N, 99.45.

Encontrado: C, 56.53; H, 4.96; N, 9.01.

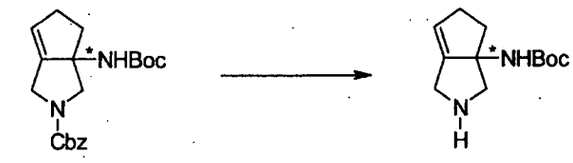
EM (ESI); m/z: 418 $(M+H)^+$.

IR (ATR) ν: 2935, 2852, 2755, 2657, 2572, 2103, 1716, 1614, 1569, 1531, 1498, 1463, 1455, 1361, 1324, 1116, 1043, 943, 919, 808 cm^{-1}.

EJEMPLO DE REFERENCIA 126

1-ter-Butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (derivado del isómero óptico B)

[Fórmula 219]



isómero óptico B

Una solución de 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (isómero óptico B) (54.7 mg, 0.153 mmoles) en tetrahidrofurano (1.53 ml) se hizo burbujear con amoniaco gaseoso bajo enfriamiento con hielo seco-acetona para añadir 30 a 40 ml de amoniaco líquido a la solución. Se añadió sodio (18.4 mg, 0.767 mmoles) en una atmósfera de nitrógeno, y la mezcla se agitó durante 10 minutos. Una solución saturada de cloruro de amonio (10 gotas) se añadió a temperatura ambiente, y la mezcla se agitó a temperatura ambiente para evaporar el amoniaco. Una solución de hidróxido de sodio 1N (3 a 4 ml) se añadió, y la mezcla se concentró bajo presión reducida.

Se añadió cloroformo/metanol = 10/1 (10 a 20 ml). Después de tratamiento ultrasónico, el material insoluble se removió por filtración. El filtrado se concentró bajo presión reducida para dar 150 mg de un residuo que contenía

906

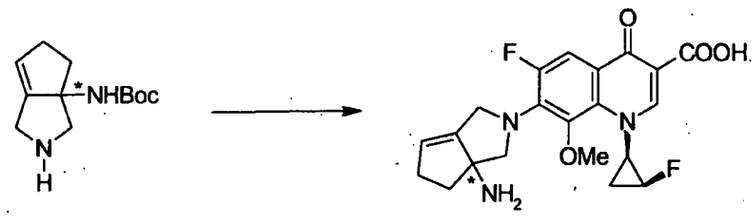
el compuesto del título, que se usó directamente para la siguiente reacción.

EM(ESI) m/z: 225$(M+H)^+$.

EJEMPLO 26

Acido 7-[1-amino-3-azabiciclo[3.3.0] oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico B)

[Fórmula 220]



Trietilamina (0.0641 ml, 0.460 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (58.0 mg, 0.161 mmoles) se añadieron a una solución del residuo que contenía 1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] oct-5-eno (derivado del isómero óptico B) (150 mg, 0.153 mmoles) en sulfóxido de dimetilo (0.306 ml). La mezcla se agitó a temperatura ambiente durante 1.5 horas. Se añadieron sulfóxido de dimetilo (0.306 ml) y trietilamina (0.0641 ml, 0.460 mmoles) y la mezcla se agitó a 40°C durante un día. Acido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (174 mg, 0.483 mmoles) se añadió a la solución de reacción, y la mezcla se agitó a 40°C durante 15 horas. Una solución mixta de etanol:agua = 4:1 (5 ml) y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30

907

ml) y se lavó con una solución de ácido cítrico al 10% (20 ml), agua (20 ml), y salmuera (20 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). 194 mg del residuo resultante se disolvieron en ácido clorhídrico concentrado (1 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar lavando con cloroformo (30 ml x 5), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml), cloroformo/metanol = 10/1 (80 ml), y la capa inferior de cloroformo/metanol/agua = 7/3/1 (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por CCDP (capa inferior de cloroformo/metanol/agua = 7/3/1). Cloroformo/metanol (10/1) se añadió al residuo resultante, y el material insoluble se removió por filtración. El filtrado se concentró bajo presión reducida. Se añadió etanol (1 ml) al residuo resultante, y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió éter dietílico (2 ml) y los cristales precipitados se recogieron por filtración, se lavaron con etanol y éter dietílico, y después se secaron bajo presión reducida a 50°C para dar 2.38 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.50 (1H, s), 7.70 (1H, d, J=14.46 Hz), 5.62 (1H, s), 5.05-4.90 (1H, m), 4.65-4.59 (1H, m), 4.11 (1H, s), 3.93 (1H, d, J=14.95 Hz), 3.70 (1H, d, J=10.05 Hz), 3.62 (3H, s), 3.53 (1H, d, J=10.79 Hz), 3.00-2.82 (1H, m), 2.67-2.56 (1H, m), 2.15-2.12 (1H, m), 2.00-1.95 (1H, m), 1.72-1.58 (2H, m).

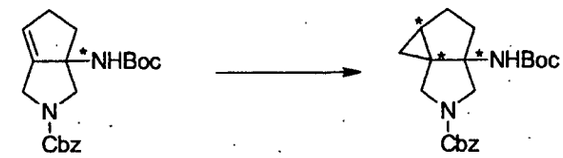
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EM (ESI); m/z: 418 $(M+H)^+$.

EJEMPLO DE REFERENCIA 127

6-ter-Butoxicarbonilamino-8-benciloxicarbonil-8-azatriciclo[4.3.0.0^{1,3}] nonano (derivado del isómero óptico A)

[Fórmula 221]



isómero óptico A

Una solución de diclorometano (3.52 ml) se enfrió con hielo-acetona. Una solución 1.0 M de dietilzinc en n-hexano (0.88 ml, 0.88 mmoles) y diyodometano (0.071 ml, 0.881 mmoles) se añadieron lentamente en una atmósfera de nitrógeno, y la mezcla se agitó durante 20 minutos bajo enfriamiento. Una solución de 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.2.0]oct-5-eno (isómero óptico A) (126 mg, 0.352 mmoles) en diclorometano (3.52 ml) se añadió lentamente bajo enfriamiento, la mezcla se agitó a temperatura ambiente durante 24 horas. Una solución saturada de bicarbonato de sodio acuoso (10 ml) y una solución de tiosulfato de sodio al 10% (10 ml) se añadieron bajo enfriamiento con hielo-acetona, y la mezcla se agitó hasta que desapareció el color bermellón. La capa orgánica se extrajo con cloroformo (50 ml x 1, 40 ml x 1). La capa orgánica se lavó con salmuera (80 ml), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. Acetonitrilo (7.04 ml) y dicarbonato de di-ter-butilo (384 mg, 1.76 mmoles) se añadieron secuencialmente a 212 mg del residuo resultante en una atmósfera de nitrógeno. Después de agitar a

909

temperatura ambiente durante 19 horas, la solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25) para dar 95.2 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.31 (5H, m), 5.17-5.11 (2H, m), 4.93 (1H, brs), 4.21-4.11 (1H, m), 3.75 (1H, dd, J=10.91, 6.74 Hz), 3.32-3.12 (2H, m), 2.47-2.31 (1H, m), 1.97-1.88 (1H, m), 1.81-1.78 (1H, m), 1.43 (9H, s), 1.35-1.31 (1H, m), 1.19-1.16 (1H, m), 0.82-0.76 (2H, m).

EM (ESI); m/z: 395 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 128

6-ter-Butoxicarbonilamino-8-benciloxicarbonil-8-azatriciclo[4.3.0.0^{1,3}]nonano (derivado del isómero óptico B)

[Fórmula 222]



isómero óptico B

Una solución de diclorometano (4.18 ml) se enfrió con hielo-acetona. Una solución 1.0 M de dietilzinc en n-hexano (1.05 ml, 1.05 mmoles) y diyodometano (0.0842 ml, 1.05 mmoles) se añadieron lentamente en una atmósfera de nitrógeno, y la mezcla se agitó durante 20 minutos bajo enfriamiento. Una solución de 3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.2.0] oct-5-eno (isómero óptico B) (150 mg, 0.418 mmoles) en diclorometano (4.18 ml) se añadió lentamente bajo enfriamiento, la mezcla se agitó a temperatura ambiente durante 22 horas. Una solución saturada de

910

bicarbonato de sodio acuoso (10 ml) y una solución de tiosulfato de sodio al 10% (10 ml) se añadieron bajo enfriamiento con hielo-acetona, y la mezcla se agitó hasta que desapareció el color bermellón. La capa orgánica se extrajo con cloroformo (60 ml x 1, 50 ml x 1). La capa orgánica se lavó con salmuera (60 ml), se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró después bajo presión reducida. Acetonitrilo (8.36 ml) y dicarbonato de di-ter-butilo (274 mg, 1.25 mmoles) se añadieron secuencialmente a 256 mg del residuo resultante en una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 13 horas, la solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 84:16 → 80:20 → 75:25) para dar 113 mg del compuesto del título.

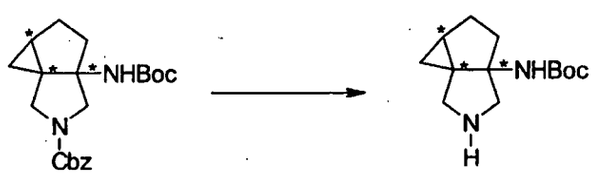
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.13 (2H, t, J=6.74 Hz), 4.93 (1H, d, J=16.18 Hz), 4.23-4.09 (1H, m), 3.75 (1H, dd, J=11.03, 6.62 Hz), 3.27-3.19 (2H, m), 2.43 (1H, brs), 1.98-1.88 (1H, m), 1.82-1.74 (2H, m), 1.43 (9H, s), 1.37-1.22 (1H, m), 1.22-1.14 (1H, m), 0.81-0.77 (2H, m).

EM (ESI); m/z: 395 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 129

6-ter-Butoxicarbonilamino-8-azatriciclo [4.3.0.0^{1,3}] nonano (derivado del isómero óptico A)

[Fórmula 223]



911

Un catalizador de 10% de paladio-carbón (47.6 mg, 50 % en peso) se añadió a una solución de 6-ter-butoxicarbonilamino-8-benciloxicarbonil-8-azatriciclo [4.3.0.0^{1,3}] nonano (derivado del isómero óptico A) (95.2 mg, 0.255 mmoles) en metanol (2.55 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó a temperatura ambiente durante una hora. Se añadió un catalizador de 10% de paladio-carbón (28.6 mg, 30 % en peso). Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó a temperatura ambiente durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 56.0 mg del compuesto del título como un aceite negro.

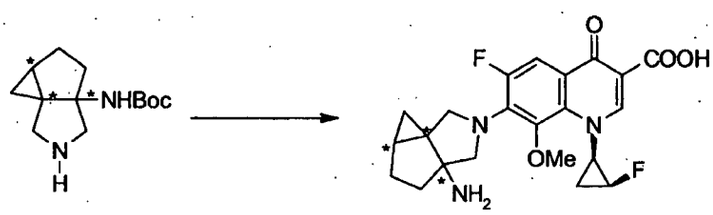
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.98 (1H, brs), 3.63 (1H, s), 3.46-3.44 (1H, m), 2.92 (2H, dd, J=30.52, 11.15 Hz), 2.37 (1H, brs), 2.00-1.96 (1H, m), 1.76-1.70 (1H, m), 1.44 (9H, s), 1.35-1.25 (1H, m), 1.21-1.15 (1H, m), 0.86-0.69 (2H, m).

EM (ESI); m/z: 239 $(M+H)^+$.

EJEMPLO 27

Acido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico A)

[Fórmula 224]



912

Trietilamina (0.0984 ml, 0.705 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (89.1 mg, 0.247 mmoles) se añadieron a una solución de 6-ter-butoxicarbonilamino-8-azatriciclo [4.3.0.$0^{1,3}$] nonano (derivado del isómero óptico A) 56.0 mg (0.235 mmoles) en sulfóxido de dimetilo (0.470 ml). La mezcla se agitó a 35°C durante 19 horas. Una solución mixta de etanol:agua = 4:1 (5.0 ml) y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (35 ml) y se lavó con una solución de ácido cítrico al 10% (25 ml), agua (25 ml), y salmuera (25 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1). 80.5 mg del residuo resultante se disolvieron en ácido clorhídrico concentrado (1 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (30 ml x 4), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (60 ml x 2) y cloroformo/metanol = 10/1 (60 ml x 3). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se purificó por CCDP (capa inferior de cloroformo/metanol/agua = 7/3/1). El residuo resultante se disolvió en cloroformo/metanol = 10/1 (10 ml). El material insoluble se removió por filtración, y después el filtrado se concentró bajo presión reducida. El residuo resultante se disolvió en etanol caliente (20 to 30 ml), y después se concentró bajo presión reducida y se secó. Se añadieron etanol (0.5 ml) y éter

913

dietílico (5 ml) al residuo resultante, y la mezcla se trató ultrasónicamente y se enfrió con hielo. Después, los cristales precipitados se recogieron por filtración y se lavaron con éter dietílico. Los cristales se secaron bajo presión reducida a 45°C para dar 21.0 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.38 (1H, d, J=2.94 Hz), 7.67 (1H, d, J=14.22 Hz), 5.12-4.96 (1H, m), 4.32-4.29 (1H, m), 4.04-3.99 (1H, m), 3.80 (1H, d, J=10.30 Hz), 3.61 (3H, s), 3.44 (1H, d, J=10.54 Hz), 3.31 (1H, d, J=10.30 Hz), 2.02-1.89 (2H, m), 1.77 (1H, dd, J=12.62, 8.46 Hz), 1.58-1.24 (4H, m), 0.82 (2H, dt, J=23.78, 5.82 Hz).

Análisis calculado para $C_{22}H_{23}F_2N_3O_4$: C, 57.64; H, 5.72; F, 8.29; N, 9.17.

Encontrado: C, 57.70; H, 5.77; F, 8.57; N, 9.09.

EM (ESI) ; m/z: 432 $(M+H)^+$.

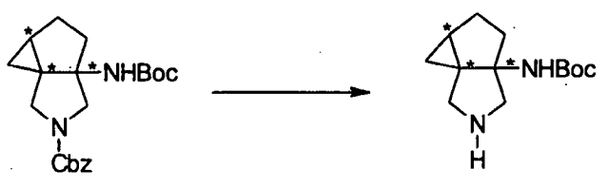
IR (ATR) ν: 2935, 2869, 1725, 1616, 1432, 1363, 1319, 1182, 1137, 1045, 943, 923, 806 cm^{-1}.

EJEMPLO DE REFERENCIA 130

6-ter-Butoxicarbonilamino-8-azatriciclo [4.3.0.0^{1,3}] nonano

(derivado del isómero óptico B)

[Fórmula 225]



Un catalizador de 10% de paladio-carbón (27.7 mg, 30 % en peso) se añadió a una solución de 6-ter-butoxicarbonilamino-8-benciloxicarbonil-8-

914

azatriciclo [4.3.0.0^{1,3}] nonano (derivado del isómero óptico B) (92.3 mg, 0.248 mmoles) en metanol (2.48 ml) en una atmósfera de nitrógeno. La mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante una hora. Se añadió un catalizador de 10% de paladio-carbón (18.5 mg, 20% en peso) y la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante 2.5 horas. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 64.4 mg de un residuo que contenía el compuesto del título.

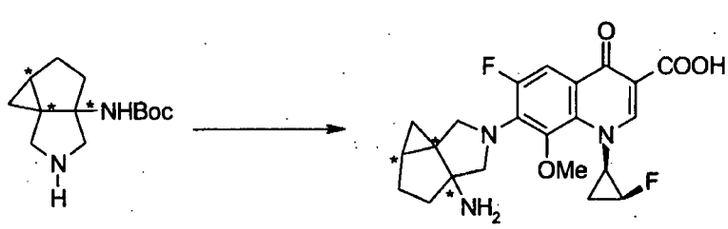
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.87 (1H, brs), 3.50 (1H, brs), 3.29 (1H, d, J=11.03 Hz), 3.14-3.12 (1H, m), 2.76 (2H, dd, J=19.12, 11.28 Hz), 2.47-1.66 (3H, m), 1.43 (9H, s), 1.32 (1H, dd, J=24.14, 10.17 Hz), 1.08-1.04 (1H, m), 0.82-0.67 (2H, m).

EM (ESI); m/z: 239 $(M+H)^+$.

EJEMPLO 28

Acido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico B)

[Fórmula 224]



Trietilamina (0.104 ml, 0.745 mmoles) y ácido 1-[(1R,2S)-2-fluorociclopropan-1-il]-6,7-difluoro-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (89.5 mg, 0.248 mmoles) se añadieron a una

915

solución de 64.4 mg del residuo que contenía 6-ter-butoxicarbonilamino-8-azatriciclo [4.3.0.$0^{1,3}$]nonano (0.248 equivalentes mmolares) en sulfóxido de dimetilo (0.496 ml), y la mezcla se agitó a 35°C durante 17 horas. Uha solución mixta de etanol:agua = 4:1 (5.0 ml) y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (35 ml) y se lavó con una solución de ácido cítrico al 10% (25 ml), agua (25 ml), y salmuera (25 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1). 75.5 mg del residuo resultante se disolvieron en ácido clorhídrico concentrado (1 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (30 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml x 1, 70 ml x 1, 50 ml x 1). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en etanol caliente (10 ml), y el material insoluble se removió por filtración. El solvente se evaporó gradualmente bajo presión reducida mientras se calentaba con agitación. Después, la solución se concentró hasta que el etanol fue de aproximadamente 0.5 ml, y después se regresó a temperatura ambiente. Se añadió éter dietílico (5 ml) y la mezcla se enfrió con hielo. Después, los cristales precipitados se recogieron por filtración y después se lavaron con éter dietílico. Los cristales se secaron bajo presión reducida a 50°C para dar 25.9 mg del compuesto del título.

916.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.50 (1H, s), 7.67 (1H, d, J=14.71 Hz), 4.99-4.93 (1H, m), 4.39 (1H, dd, J=10.30, 3.43 Hz), 4.09 (1H, q, J=6.21 Hz), 3.87 (1H, dd, J=10.54, 2.94 Hz), 3.63 (3H, s), 3.37 (1H, d, J=10.54 Hz), 3.23 (1H, d, J=10.30 Hz), 2.01-1.95 (2H, m), 1.79-1.58 (3H, m), 1.34-1.17 (2H, m), 0.82 (2H, dt, J=22.22, 5.94 Hz).

Análisis calculado para $C_{22}H_{23}F_2N_3O_4 \cdot 0.5H_2O$: C, 59.99; H, 5.49; F, 8.63; N, 9.54.

Encontrado: C, 60.28; H, 5.34; F, 8.57; N, 9.52.

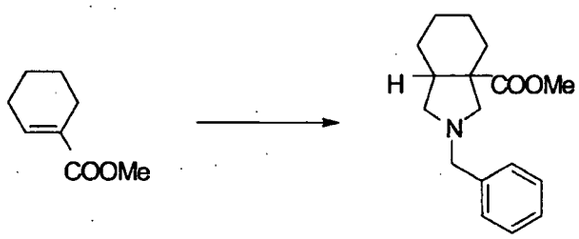
EM (ESI) ; m/z: 432 $(M+H)^+$.

IR (ATR) ν: 2937, 2863, 1716, 1616, 1508, 1434, 1321, 1187, 1120, 1054, 939, 889, 804 cm^{-1}.

EJEMPLO DE REFERENCIA 131

Ester metílico de ácido [(1R*,6R*)-8-bencil-3-azabiciclo [4.3.0] nonan-1-il] carboxílico

[Fórmula 227]



(±)-cis

Una cantidad catalítica de ácido trifluoroacético se añadió a una solución de éster metílico de ácido 1-ciclohexen-1-carboxílico (25.0 g, 178 mmoles) y N-bencil-N-(metoximetil)-N-trimetilsililmetilamina (46.6 g, 196 mmoles) en 1,2-dicloroetano (178 ml) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante dos horas. Una solución saturada de

917

bicarbonato de sodio (200 ml) se añadió a la solución de reacción, seguido por extracción con cloroformo (150 ml x 1, 100 ml x l). La capa orgánica se lavó con salmuera (450 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 90:10 → 85:15 → 75:25) para dar 21.3 g del compuesto del título.

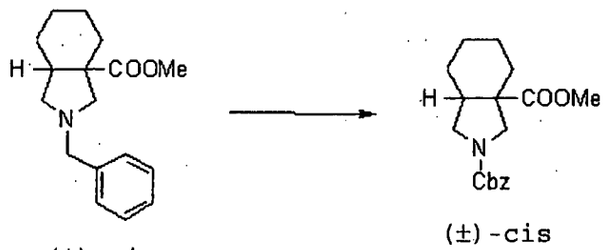
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.24 (5H, m), 3.70-3.65 (5H, m), 2.92 (1H, d, J=9.31 Hz), 2.73-2.68 (3H, m), 1.93 (1H, td, J=9.01, 4.82 Hz), 1.79-1.65 (2H, m), 1.53-1.21 (6H, m).

EM (ESI); m/z: 274 $(M+H)^+$.

EJEMPLO DE REFERENCIA 132

Ester metílico de ácido [(1R*,6R*)-S-benciloxicarbonil-3-azabiciclo [4.3.0] nonan-1-il] carboxílico

[Fórmula 228]



(±)-cis (±)-cis

Cloroformiato de bencilo (33.4 ml, 234 mmoles) se añadió a una solución de éster metílico de ácido [(1R*,6R*)-8-bencil-8-azabiciclo [4.3.0] nonan-1-il]carboxílico (21.3 g, 77.9 mmoles) en diclorometano (259 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 15 horas. La solución de reacción se concentró bajo presión reducida. Después, el

residuo (58.0 g) se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 95:5 → 90:10 → 80:20 → 75:25) para dar 17.5 g del compuesto del título.

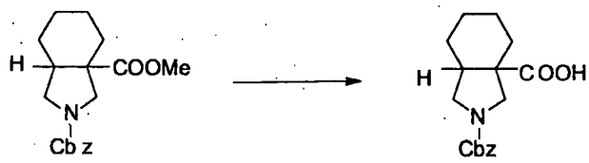
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.13 (2H, m), 3.71 (3H, d, J=3.19 Hz), 3.63 (1H, dd, J=10.91, 8.21 Hz), 3.52-3.28 (3H, m), 2.72-2.64 (1H, m), 1.93 (1H, m), 1.75 (1H, dq, J=20.41, 5.23 Hz), 1.63-1.38 (6H, m).

EM (ESI); m/z: 318 $(M+H)^+$.

EJEMPLO DE REFERENCIA 133

Acido [(1R*,6R*)-8-benciloxicarbonil-8-azabiciclo [4.3.0] nonan-1-il] carboxílico

[Fórmula 229]



(±)-cis (±)-cis

Una solución 1 mol/l de hidróxido de sodio (70.8 ml) y tetrahidrofurano (78.8 ml) se añadieron a una solución de éster metílico de ácido [(1R*,6R*)-8-benciloxicarbonil-8-azabiciclo [4.3.0]nonan-1-il] carboxílico (7.50 g, 23.6 mmoles) en metanol (78.8 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante tres días. La solución de reacción se concentró bajo presión reducida y después se lavó con éter dietílico (50 ml x 2). La capa acuosa se hizo ácida con 3 moles/l de ácido clorhídrico (28 ml) bajo enfriamiento con hielo, seguido por extracción con acetato de etilo (100 ml x 2). La capa orgánica se lavó con salmuera (250 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión

919

reducida para dar 6.70 g del compuesto del título.

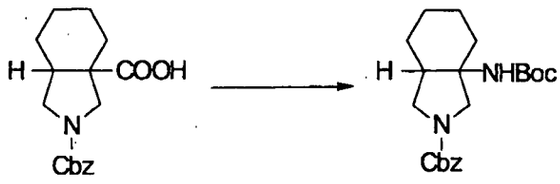
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5, en), 5.13 (2H, m), 3.70 (1H, dd, J=10.91, 4.78 Hz), 3.51 (2H, m), 3.40-3.30 (1H, m), 2.68 (1H, m), 2.00-1.96 (1H, m), 1.78-1.76 (1H, m), 1.65-1.60 (1H, m), 1.51-1.45 (5H, m).

EM (ESI); m/z: 304 $(M+H)^+$.

EJEMPLO DE REFERENCIA 134

(1R*,6S*)-8-Benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano

[Fórmula 230]



Trietilamina (6.17 ml, 44.2 mmoles) y difenilfosforil azida (6.19 ml, 28.7 mmoles) se añadieron a una solución de ácido [(1R*,6R*)-8-benciloxicarbonil-8-azabiciclo [4.3.0] nonan-1-il] carboxílico (6.70 g, 22.1 mmoles) en tolueno (110 ml) mientras se agitaba bajo enfriamiento con hielo en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 40 minutos y después a 90°C durante una hora. La solución de reacción se diluyó con acetato de etilo (150 ml) a temperatura ambiente, se lavó con una solución saturada de bicarbonato de sodio (200 ml), agua (200 ml), y salmuera (200 ml), y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. Se añadieron 1,4-dioxano (55.0 ml) y 6 moles/l de ácido clorhídrico (55.0 ml) al residuo resultante, y la mezcla se agitó a 50°C durante dos horas. La solución de reacción se destiló con agua (55.0 ml) y se concentró bajo presión reducida. Después, el residuo se secó

920

azeotrópicamente con etanol (x 5). Diclorometano (110 ml) se añadió al sólido blanco precipitado (7.41 g). Trietilamina (15.4 ml, 110 mmoles) y di-ter-butoxicarbonilo (9.65 g, 44.2 moles) se añadieron en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 15 horas. La solución de reacción se concentró bajo presión reducida, y se añadió acetato de etilo (150 ml). La mezcla se lavó con agua (200 ml) y salmuera (200 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 83:17 → 66:34) para dar 6.65 g del compuesto del título.

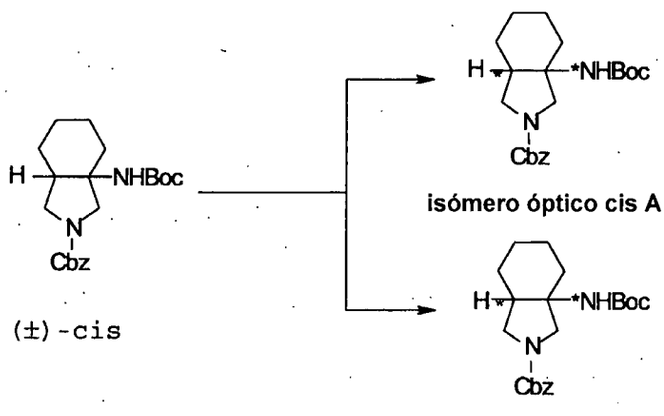
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 5.13 (2H, s), 4.55 (1H, d, J=13.97 Hz), 3.69 (1H, d, J=11.28 Hz), 3.58-3.45 (2H, m), 3.30 (1H, ddd, J=21.33, 10.66, 6.74 Hz), 2.03-1.99 (1H, m), 1.66-1.43 (17H, m).

EM (ESI) ; m/z: 374 $(M+H)^+$.

EJEMPLO DE REFERENCIA 135

(1R, 6S)-/ (1S,6R)-8-Benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (isómero óptico A, isómero óptico B)

[Fórmula 231]



921

El racemato (1R*,6S*)-8-benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (6.65 g, 17.8 mmoles) se resolvió ópticamente mediante una columna ópticamente activa (CHIRALPAK AD, 20 mm de diámetro x 250 mm, hexano : alcohol isopropílico = 95:5, velocidad de flujo = 20 ml/min) para dar 8-benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano ópticamente activo (isómero óptico A) (427 mg, 1.14 mmoles, tiempo de retención = 14.2 min) y su enantiómero ópticamente activo 8-benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (isómero óptico B) (415 mg, 1.11 mmoles, tiempo de retención = 19.4 min).

EJEMPLO DE REFERENCIA 136

1-ter-Butoxicarbonilamino-3-azabiciclo [4.3.0] nonano (derivado del isómero óptico A)

[Fórmula 232]



isómero óptico cis A

Un catalizador de 10% de paladio-carbón (80.0 mg, 20 % en peso) se añadió a una solución de 8-benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (isómero óptico A) (400 mg, 1.07 mmoles) en metanol (10.7 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a

922

temperatura ambiente durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar el compuesto del título cuantitativamente.

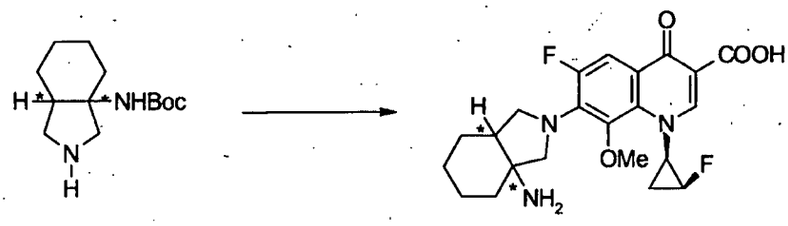
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.61 (1H, brs), 3.18-3.12 (2H, m), 3.02 (1H, d, J=11.28 Hz), 2.81 (1H, dd, J=10.66, 6.74 Hz), 2.16 (1H, brs), 2.01 (1H, brs), 1.57-1.43 (8H, m), 1.43 (9H, s).

EM (ESI); m/z: 241 $(M+H)^+$.

EJEMPLO 29

Acido 7-[1-amino-8-azabiciclo [4.3.0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4 oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico A)

[Fórmula 233]



Trietilamina (0.407 ml, 2.92 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (351 mg, 0.972 mmoles) se añadieron a una solución de 1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (derivado del isómero óptico A) (277 mg, 1.07 mmoles) en sulfóxido de dimetilo (1.94 ml), y la mezcla se agitó a 35°C durante 17 horas. Una solución mixta de etanol : agua = 4:1 (20 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo

presión reducida. El residuo se disolvió en acetato de etilo (40 ml) y se lavó con una solución de ácido cítrico al 10% (50 ml), agua (50 ml), y salmuera (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). 456 mg del residuo resultante se disolvió en ácido clorhídrico concentrado (3.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. La solución de reacción se ajustó a pH 13.6 con una solución saturada de hidróxido de sodio, y la solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (100 ml), cloroformo/metanol = 10/1 (150 ml x 1, 100 ml x 2), y la capa inferior de cloroformo/metanol/agua = 7/3/1 (150 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en etanol caliente (67.5 ml), y el material insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. La solución se concentró hasta que el etanol fue de 10 ml, y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración y después se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C para dar 271 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.42 (1H, d, J=1.96 Hz), 7.65 (1H, d, J=14.71 Hz), 4.97 (1H, dt, J=49.76, 17.89 Hz), 4.05-4.00 (1H, m), 3.84 (1H, t, J=7.48 Hz), 3.71 (1H, d, J=10.30 Hz), 3.60 (4H, t, J=12.01 Hz), 3.36 (1H, d, J=8.33 Hz), 2.01 (1H, m), 1.77 (2H, m), 1.60-1.41 (8H, m).

Análisis calculado para $C_{22}H_{25}F_2N_3O_4 \cdot 0.5H_2O$: C, 59.72; H, 5.92; F, 8.59; N, 9.50.

924

Encontrado: C, 59.91; H, 5.97; F, 8.68; N, 9.39.

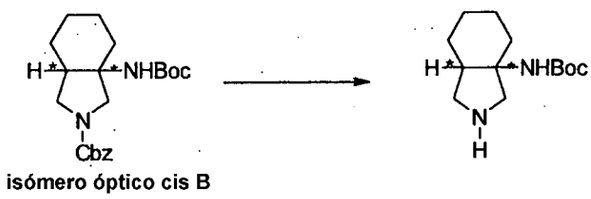
EM (ESI); m/z: 434 $(M+H)^+$.

IR (ATR) ν: 2927, 2856, 1724, 1616, 1508, 1430, 1324, 1268, 1186, 1120, 1049, 925, 877, 806 cm^{-1}.

EJEMPLO DE REFERENCIA 137

1-ter-Butoxicarbonilamino-3-azabiciclo [4.3.0] nonano (derivado del isómero óptico B)

[Fórmula 234]



isómero óptico cis B

Un catalizador de 10% de paladio-carbón (83.0 mg, 20% en peso) se añadió a una solución de 8-benciloxicarbonil-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (isómero óptico B) (415 mg, 1.11 mmoles) en metanol (11.1 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar el compuesto del título cuantitativamente.

^{1}H-RMN ($CDCl_3$) δ: 4.60 (1H, brs), 3.17-3.12 (2H, m), 3.02 (1H, d, J=11.52 Hz), 2.81 (1H, brs), 2.15 (1H, brs), 2.00 (1H, s), 1.63-1.36 (8H, m), 1.43 (9H, s).

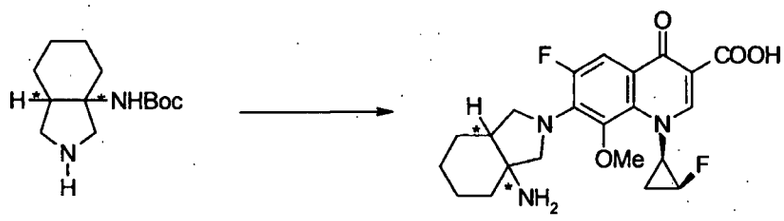
EM (ESI); m/z: 241 $(M+H)^+$.

925

EJEMPLO 30

Acido 7-[1-amino-8-azabiciclo [4.3.0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico (sustituyente en la posición 7: derivado del isómero óptico B)

[Fórmula 235]



Trietilamina (0.422 ml, 3.03 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (364 mg, 1.01 mmoles) se añadieron a una solución de 1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (derivado del isómero óptico B) (273 mg, 1.11 mmoles) en sulfóxido de dimetilo (1.94 ml), y la mezcla se agitó a 35°C durante 17 horas. Una solución mixta de etanol : agua = 4:1 (20 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (40 ml) y se lavó con una solución de ácido cítrico al 10% (50 ml), agua (50 ml), y salmuera (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). 536 mg del residuo resultante se disolvió en ácido clorhídrico concentrado (3.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (20

926

ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7 con ácido clorhídrico, seguido por extracción con cloroformo/metanol = 10/1 (150 ml x 1, 100 ml x 2). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en etanol caliente (67.5 ml), y el material insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. La solución se concentró hasta que el etanol fue de 10 ml, y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración y se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C para dar 315 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.45 (1H, d, J=1.47 Hz), 7.64 (1H, d, J=14.95 Hz), 5.04-4.84 (1H, m), 4.06-3.99 (2H, m), 3.88 (1H, dd, J=10.54, 2.21 Hz), 3.57 (3H, s), 3.42 (1H, d, J=10.54 Hz), 3.20 (1H, d, J=8.82 Hz), 1.94 (1H, m), 1.83 (1H, m), 1.73 (1H, m), 1.67-1.46 (6H, m), 1.33 (2H, m).

Análisis calculado para $C_{22}H_{25}F_2N_3O_4 \cdot 0.75H_2O$: C, 59.12; H, 5.98; F, 8.50; N, 9.40.

Encontrado: C, 59.05; H, 6.12; F, 8.36; N, 9.20.

EM (ESI); m/z: 434 $(M+H)^+$.

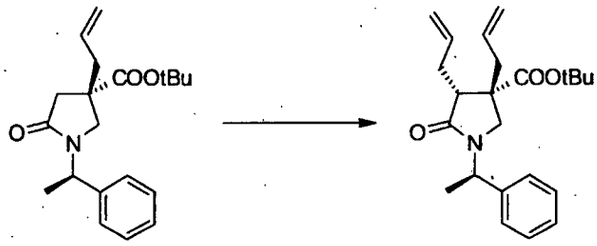
IR (ATR) ν: 2927, 2859, 1724, 1616, 1573, 1509, 1432, 1369, 1355, 1319, 1267, 1118, 1049, 933, 879, 804 cm^{-1}.

927

EJEMPLO DE REFERENCIA 138

Ester ter-butílico de ácido (3S,4R)-3,4-dialil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 236]



Bromuro de alilo (1.36 ml, 16.1 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.05 g, 12.3 mmoles) en tetrahidrofurano (41.0 ml) con agitación bajo enfriamiento en hielo con sal. Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (16.0 ml, 16.0 mmoles) se añadió gota a gota con agitación bajo enfriamiento en hielo con sal, y la mezcla se agitó bajo enfriamiento en hielo con sal durante 15 minutos. Una solución saturada de cloruro de amonio (40 ml) y agua (20 ml) se añadieron a la solución de reacción, seguida por extracción con acetato de etilo (40 ml x 1, 20 ml x 1). La capa orgánica se lavó con salmuera (140 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 89:11 → 88:12 → 87:13 → 83:17 → 80:20 → 75:25) para dar 2.02 g del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32 (5H, m), 5.77-5.62 (2H, m), 5.48 (1H, q, J=7.11 Hz), 5.13 (2H, dd, J=13.36, 11.89 Hz), 5.02 (1H, t, J=9.07 Hz), 4.91 (1H, dd, J=5.52, 2.76 Hz), 3.21 (1H, d, J=10.54 Hz), 3.09 (1H, d, J=10.79

928

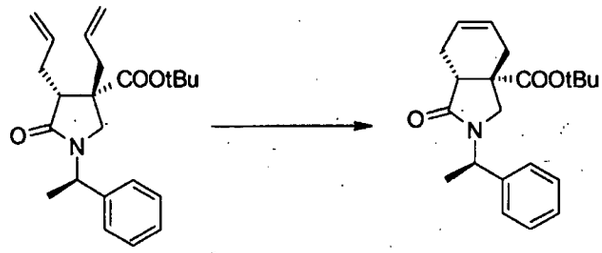
Hz), 2.56 (1H, dd, J=14.34, 6.01 Hz), 2.40 (3H, d, J=4.41 Hz), 2.27 (1H, dd, J=13.73, 8.33 Hz), 1.50 (3H, d, J=7.11 Hz), 1.40 (9H, s).

EM (ESI); m/z: 370 $(M+H)^+$.

EJEMPLO DE REFERENCIA 139

Ester ter-butílico de ácido [(1S,6R)-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-en-1-il] carboxílico

[Fórmula 237]



El catalizador Grubbs de segunda generación (91.9 mg, 0.108 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S,4R)-3,4-dialil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (2.00 g, 5.41 mmoles) en diclorometano (54.1 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 80:20 → 75:25 → 66:34 → 50:50) para dar 1.61 g del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.21 (5H, m), 5.75 (1H, m), 5.67-5.62 (1H, m), 5.49 (1H, q, J=7.19 Hz), 3.22 (2H, dd, J=13.97, 10.05 Hz), 2.74 (1H, dd, J=16.42, 5.15 Hz), 2.62-2.54 (1H, m), 2.49 (1H, d, J=5.39 Hz), 2.42 (1H, m), 2.15-2.08 (1H, m), 1.48 (3H, d, J=7.11 Hz), 1.18 (9H, s).

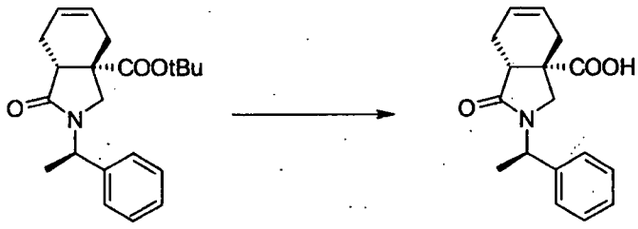
EM (ESI); m/z: 342 $(M+H)^+$.

929

EJEMPLO DE REFERENCIA 140

Acido [(1S,6R)-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-en-1-il] carboxílico

[Fórmula 238]



Se añadió ácido trifluoroacético (18.0 ml) a una solución de éster ter-butílico de ácido [(1S,6R)-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-en-1-il]carboxílico (2.04 g, 5.99 mmoles) en diclorometano (18.0 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1.5 horas. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (x 3). Una solución 1 mol/l de hidróxido de sodio (15.0 ml) se añadió al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con éter dietílico (40 ml x 2). La capa acuosa se hizo ácida con 1 mol/l de ácido clorhídrico (20 ml) bajo enfriamiento con hielo. Después, los cristales precipitados se recogieron por filtración y se lavaron con 0.5 mol/l de ácido clorhídrico, acetato de etilo, y éter dietílico. Los cristales resultantes se secaron bajo presión reducida a 50°C durante la noche para dar 1.40 g del compuesto del título como cristales blancos. La capa acuosa del filtrado se extrajo con acetato de etilo (50 ml). Las capas orgánicas se combinaron, se lavaron con agua (150 ml) y salmuera (150 ml), y se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 250 mg del compuesto del título

930

como cristales blancos.

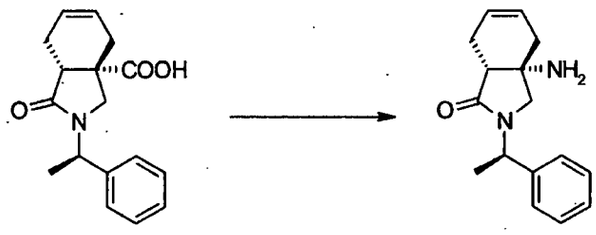
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.23 (5H, m), 5.81 (1H, m), 5.69 (1H, m), 5.51 (1H, q, J=7.11 Hz), 3.27 (1H, d, J=10.05 Hz), 3.18 (1H, d, J=10.05 Hz), 2.74 (1H, dd, J=16.67, 4.90 Hz), 2.59 (1H, m), 2.47 (1H, m), 2.22 (1H, d, J=16.67 Hz), 2.14 (1H, brs), 1.49 (3H, d, J=7.11 Hz).

EM (ESI); m/z: 286 $(M+H)^+$.

EJEMPLO DE REFERENCIA 141

(1S, 6R)-1-Amino-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-eno

[Fórmula 239]



Trietilamina (1.61 ml, 11.5 mmoles) y difenilfosforil azida (1.62 ml, 7.52 mmoles) se añadieron a una solución de ácido [(1S,6R)-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-en-1-il] carboxílico (1.65 g, 5.78 mmoles) en tolueno (28.9 ml) en una atmósfera de nitrógeno con agitación bajo enfriamiento con hielo, y la mezcla se agitó a 100°C durante 30 minutos. La solución de reacción se concentró bajo presión reducida, y trietilamina se destiló azeotrópicamente con tolueno (x 3). 1,4-Dioxano (14.4 ml) y 4 moles/l de ácido clorhídrico (14.4 ml) se añadieron al residuo resultante, y la mezcla se agitó a 50°C durante seis horas. La solución de reacción se diluyó con agua (30.0 ml) y se lavó con acetato de etilo (50 ml x 2). Una solución 1 mol/l de hidróxido de sodio (55.0 ml) se añadió a la capa acuosa, seguido por extracción con cloroformo (100 ml x 1, 80 ml x 1). La capa orgánica se lavó con salmuera (150

931

ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 1.24 g del compuesto del título como un compuesto amorfo.

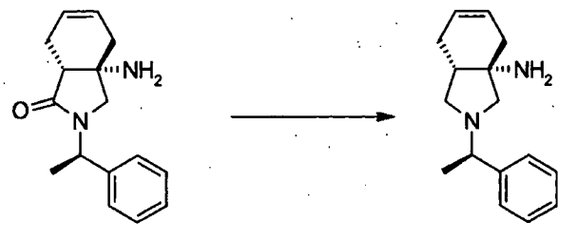
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.23 (5H, m), 5.81-5.77 (1H, m), 5.67-5.62 (1H, m), 5.53 (1H, q, J=7.11 Hz), 3.70 (2H, s), 3.23 (1H, d, J=9.80 Hz), 2.96 (1H, d, J=9.80 Hz), 2.45 (2H, m), 2.33 (1H, m), 2.27-2.16 (1H, m), 2.10 (1H, dd, J=16.79, 5.02 Hz), 1.50 (3H, d, J=7.11 Hz).

EM (ESI); m/z: 257 $(M+H)^+$.

EJEMPLO DE REFERENCIA 142

(1S,6S)-1-Amino-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-eno

[Fórmula 240]



Una solución al 65% de hidruro de sodio-bis(2-metoxietoxi) aluminio en tolueno (2.87 ml, 9.56 mmoles) se añadió a una solución de (1S,6R)-1-amino-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-eno (612 mg, 2.39 mmoles) en tolueno (11.9 ml), y la mezcla se agitó a 80°C durante una hora. Una solución de 5 moles/l de hidróxido de sodio (15.0 ml) se añadió a la solución de reacción con agitación bajo enfriamiento con hielo, seguido por extracción con tolueno (30 ml x 2). La capa orgánica se lavó con salmuera (90 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 450 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.19 (5H, m), 5.72-5.59 (2H, m),

932

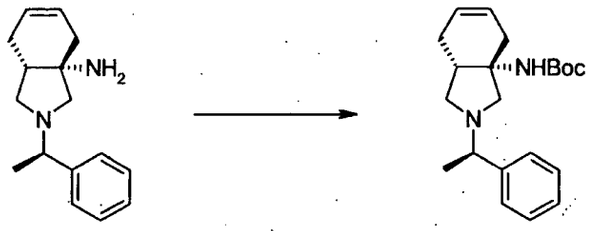
3.58 (1H, q, J=6.54 Hz), 2.86 (1H, d, J=9.07 Hz), 2.70 (1H, dd, J=9.56, 8.09 Hz), 2.54-2.48 (2H, m), 2.22-1.73 (5H, m), 1.33 (3H, d, J=6.62 Hz).

EM (ESI); m/z: 243 $(M+H)^+$.

EJEMPLO DE REFERENCIA 143

(1S, 6S)-1-ter-Butoxicarbonilamino-S-[(1R)-1-feniletil] 8-azabiciclo [4.3.0] non-3-eno

[Fórmula 241]



Dicarbonato de di-ter-butilo (689 mg, 3.16 mmoles) se añadió a una solución de (1S, 6S)-1-amino-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-eno (450 mg, 1.86 mmoles) en diclorometano (9.3 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 16 horas. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano :acetato de etilo = 100:0 → 90:10 → 80:20 → 66:34 → 50:50 → 25:75 → 16:84) para dar 456 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.29-7.18 (5H, m), 5.69-5.59 ($2H_1$ m), 4.43 (1H, s), 3.62 (1H, q, J=6.54 Hz), 3.53 (1H, d, J=10.54 Hz), 3.04 (1H, dd, J=8.95, 7.23 Hz), 2.89 (1H, d, J=18.38 Hz), 2.60 (1H, d, J=11.03 Hz), 2.52 (1H, dd, J=11.28, 9.31 Hz), 2.26-2.08 (2H, m), 1.99-1.83 (2H, m), 1.44 (9H, s), 1.32 (3H, d, J=6.62 Hz).

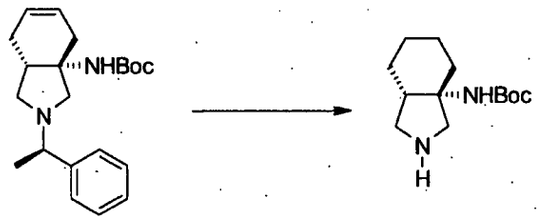
EM (ESI); m/z: 343 $(M+H)^+$.

933

EJEMPLO DE REFERENCIA 144

(1S,6S)-1-ter-Butoxicarbonilamino-8-azabiciclo [4.3.0] nonano

[Fórmula 242]



Un catalizador de 10% de paladio-carbón (406 mg, 100% en peso) se añadió a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0]non-3-eno (406 mg, 1.18 mmoles) en etanol (11.8 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno t 40°C a 50°C durante siete horas. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar el compuesto del título cuantitativamente.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.24 (1H, brs), 3.59 (1H, brs), 3.01 (1H, dd, J=9.80, 7.60 Hz), 2.67-2.62 (2H, m), 2.52 (1H, d, J=11.28 Hz), 1.79-1.53 (9H, m), 1.44 (9H, s).

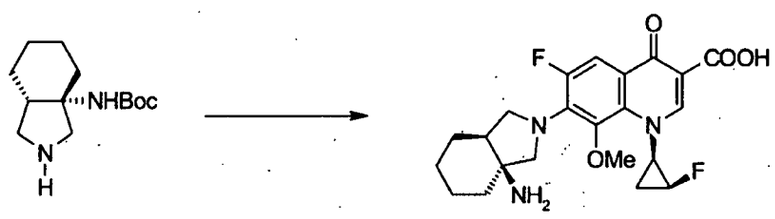
EM (ESI); m/z: 241 $(M+H)^+$.

EJEMPLO 31

Acido 7-[(1S,6S)-1-amino-8-azabiciclo [4.3.0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico

934

[Fórmula 243]



Trietilamina (0.449 ml, 3.22 mmoles) y ácido 1-[(1R,2S)-2-fluorociclopropan-1-il]-6,7-difluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (387 mg, 1.07 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (301 mg, 1.18 mmoles) en sulfóxido de dimetilo (2.14 ml), y la mezcla se agitó a 35°C durante 15 horas. Una solución mixta de etanol:agua = 4:1 (20 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 1.5 horas. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de ácido cítrico al 10% (40 ml), agua (40 ml), y salmuera (40 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se disolvieron 506 mg del residuo resultante en ácido clorhídrico concentrado (3.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (20 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (150 ml) y cloroformo/metanol = 10/1 (100 ml x 2). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en etanol caliente (45 ml), y el material

935

insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. La solución se concentró hasta que el etanol fue de 10 ml, y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración y después se lavó con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C a 60°C para dar 126 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.35 (1H, d, J=3.92 Hz), 7.65 (1H, d, J=14.71 Hz), 5.15-4.96 (1H, m), 3.99 (1H, dt, J=10.21, 4.47 Hz), 3.62 (3H, m), 3.54 (3H, s), 3.44 (1H, t, J=8.46 Hz), 3.27 (1H, d, J=9.56 Hz), 1.87-1.28 (11H, m).

Análisis calculado para $C_{22}H_{25}F_2N_3O_4 \cdot 0.25H_2O$: C, 60.33; H, 5.87; F, 8.68; N, 9.59.

Encontrado: C, 60.27; H, 5.84; F, 8.60; N, 9.58.

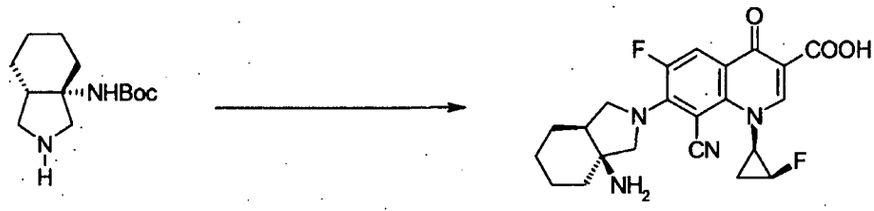
EM (ESI); m/z: 434 $(M+H)^+$.

IR (ATR) ν: 2929, 2859, 1722, 1617, 1508, 1432, 1363, 1319, 1045, 925, 804 cm^{-1}.

EJEMPLO 32

Acido 7-[(1S,6S)-1-amino-8-azabiciclo [4.3.0] nonan-8-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-4-oxoquinolin-3-carboxílico

[Fórmula 244]



Trietilamina (478 μl, 3.42 mmoles) y éster etílico de ácido 8-ciano-

936

6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-4-oxoquinolin-3-carboxílico (384 mg, 1.14 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0]nonano (302 mg, 1.26 mmoles) en acetonitrilo (2.28 ml) en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante una hora y después a 45°C durante una hora. La solución de reacción se concentró bajo presión reducida. Después, el residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 90:10 → 66:34 → 50:50 → 40:60 → 30:70) para dar un compuesto amorfo amarillo pálido. Una solución 1 mol/l de hidróxido de sodio (4.64 ml) se añadió a una solución de 644 mg del compuesto amorfo en etanol (5.80 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. Después, tetrahidrofurano (8.70 ml) se añadió, y la mezcla se agitó a temperatura ambiente durante una hora. Una solución de ácido cítrico al 10% (15 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (50 ml x l, 40 ml x 1). La capa orgánica se lavó con salmuera (80 ml), se secó sobre sulfato de sodio anhidro, y después se filtró. El filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se disolvieron 554 mg del residuo resultante en ácido clorhídrico concentrado (2 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 10 minutos. La solución se lavó con cloroformo (25 ml x 2). La solución de reacción se ajustó a pH 12.5 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con la capa inferior de cloroformo/metanol/agua = 7/3/1 (200 ml x 3). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo

presión reducida. Se añadieron etanol caliente (80 ml) y 28% amoniaco acuoso (5 ml) al residuo, y el material insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. El amoniaco se removió azeotrópicamente con etanol varias veces. La solución se concentró a aproximadamente a 20 ml y después se agitó a temperatura ambiente. Los cristales precipitados se recogieron por filtración y después se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C durante la noche para dar 341 mg del compuesto del título como cristales amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.29 (1H, d, J=3.92 Hz), 7.85 (1H, d, J=15.44 Hz), 5.18 (1H, ddd, J=66.61, 6.92, 4.47 Hz), 4.01-3.88 (3H, m), 3.70-3.65 (1H, m), 3.46 (1H, t, J=5.27 Hz), 1.95-1.32 (11H, m).

Análisis calculado para $C_{22}H_{22}F_2N_4O_3 \cdot 1.25H_2O \cdot 0.25EtOH$: C, 58.91; H, 5.71; F, 8.28; N, 12.21.

Encontrado: C, 58.71; H, 5.66; N, 11.96.

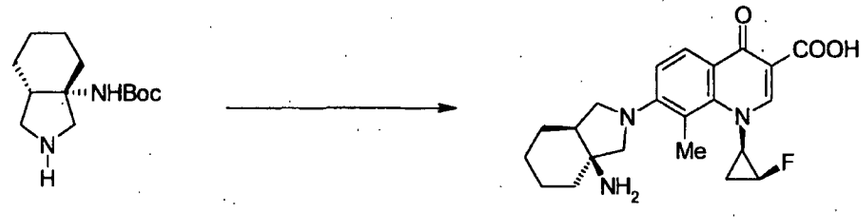
EM (ESI); m/z: 429 $(M+H)^+$.

IR (ATR) ν: 3623, 2938, 2886, 2202, 1641, 1610, 1556, 1535, 1515, 1490, 1461, 1353, 1342, 1301, 1261 cm^{-1}.

EJEMPLO 33

Acido 7-[(1S,6S)-1-amino-8-azabiciclo[4.3.0] nonan-8-il]-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 245]



938

Trietilamina (0.277 ml, 1.98 mmoles) y ácido 7-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (185 mg, 0.663 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (175 mg, 0.728 mmoles) en sulfóxido de dimetilo (1.33 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a 75°C durante 12 días. La solución de reacción se diluyó con acetato de etilo (45 ml) y después se lavó con una solución de ácido cítrico al 10% (40 ml), agua (40 ml), y una solución saturada de hidróxido de sodio (40 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se disolvieron 260 mg (0.578 mmoles) del residuo resultante en ácido clorhídrico concentrado (2.5 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 10 minutos. Después de lavar con cloroformo (50 ml x 2), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 2) y cloroformo/metanol = 10/1 (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por CCDP (revelada con la capa inferior de cloroformo/metanol/agua = 7/3/1). Después de que la parte fluorescente se recogió, se añadió la capa inferior de cloroformo/metanol/agua = 7/3/1 (70 ml). Después de tratamiento ultrasónico, el gel de sílice se filtró. El filtrado se concentró bajo presión reducida y después se secó bajo vacío. Se añadieron etanol (1 ml), éter dietílico, y 2-propanol al residuo. Eter dietílico se añadió. Después de repetir tratamiento ultrasónico y

939

enfriamiento con hielo varias veces, la mezcla se agitó a 40°C durante 30 minutos. Después de agitar a temperatura ambiente durante dos horas, los cristales se recogieron por filtración y se secaron bajo presión reducida para dar 88.7 mg del compuesto del título como cristales amarillo pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.40 (1H, d, J=3.68 Hz), 7.98 (1H, d, J=8.82 Hz), 7.07 (1H, d, J=9.31 Hz), 5.17-4.94 (1H, m), 4.06 (1H, dd, J=13.97, 5.64 Hz), 3.55 (2H, dd, J=19.36, 10.30 Hz), 3.22 (1H, t, J=8.09 Hz), 3.13 (1H, d, J=9.56 Hz), 2.43 (3H, s), 1.92-1.19 (11H, m).

Análisis calculado para $C_{22}H_{26}FN_3O_3 \cdot 0.25H_2O$: C, 65.41; H, 6.61; F, 4.70; N, 10.40.

Encontrado: C, 65.18; H, 6.60; N, 10.48.

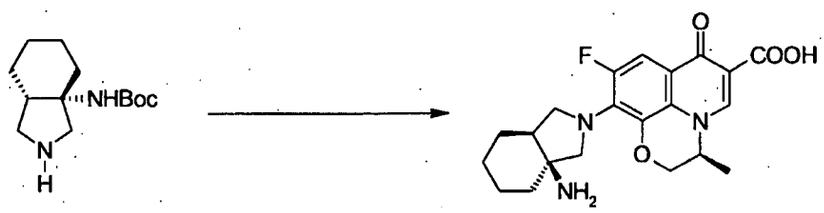
EM (ESI) ; m/z: 400 $(M+H)^+$.

IR (ATR) ν: 3380, 2927, 2863, 1712, 1614, 1509, 1428, 1396, 1359, 1348, 1340, 1315, 1301, 1035, 927 cm^{-1}.

EJEMPLO 34

Acido 10-[(1S,6S)-1-amino-8-azabiciclo [4.3.0] nonan-8-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de] [1,4] benzoxazin-6-carboxílico

[Fórmula 246]



Trietilamina (0.208 ml, 1.49 mmoles) y ácido 9,10-difluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazin-6-carboxílico-quelato de BF_2 (164 mg, 0.498 mmoles) se añadieron a una solución de

940

(1S,6S)-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] nonano (126 mg, 0.524 mmoles) en sulfóxido de dimetilo (0.996 ml), y la mezcla se agitó a 35°C durante 15 horas. Una solución mixta de etanol:agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante tres horas. La solución de reacción se concentró bajo presión reducida, y después una solución de ácido cítrico al 10% (30 ml) se añadió al residuo, seguido por extracción con acetato de etilo (30 ml). La parte de interfase se extrajo con cloroformo. La capa orgánica se lavó con agua (30 ml) y salmuera (30 ml), respectivamente, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se disolvieron 169 mg del residuo resultante en ácido clorhídrico concentrado (1 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (20 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 2) y cloroformo/metanol = 10/1 (100 ml x 3). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo (130 mg) se disolvió en etanol/28% de amoniaco acuoso = 7/1 (60 ml), y el material insoluble se removió por filtración. El filtrado se calentó con agitación para evaporar gradualmente el solvente. El amoniaco se removió azeotrópicamente con etanol varias veces. La solución se concentró a 10 ml y después se regresó a temperatura ambiente. Los cristales precipitados se recogieron por filtración, se lavaron con etanol y éter dietílico, y después se secaron bajo presión reducida para dar 109 mg del compuesto del título como cristales amarillo pálido.

941

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.30 (1H, s), 7.51 (1H, d, J=14.46 Hz), 4.62-4.54 (1H, m), 4.45 (1H, dd, J=11.40, 2.08 Hz), 4.26 (1H, dd, J=11.28, 2.21 Hz), 3.74 (1H, dd, J=10.05, 3.43 Hz), 3.70-3.64 (1H, m), 3.43 (1H, t, J=8.33 Hz), 3.34 (1H, d, J=8.33 Hz), 1.87-1.63 (5H, m), 1.56-1.22 (4H, m), 1.52 (3H, d, J=6.86 Hz).

Análisis calculado para $C_{21}H_{24}FN_3O_4 \cdot 0.25H_2O$: C, 62.13; H, 6.08; F, 4.68; N, 10.35.

Encontrado: C, 62.03; H, 6.10; N, 10.31.

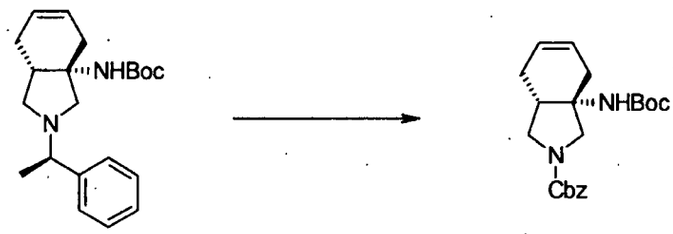
EM (ESI); m/z: 402 $(M+H)^+$.

IR (ATR) ν: 3590, 3295, 3222, 2929, 2883, 1614, 1554, 1471, 1344, 1311, 1259, 1234, 1110, 1041, 985, 815 cm^{-1}.

EJEMPLO DE REFERENCIA 145

(1S, 6S)-8-Benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [4.3.0] non-3-eno

[Fórmula 247]



Cloroformiato de bencilo (0.600 ml, 4.20 mmoles) se añadió a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] non-3-eno (479 mg, 1.40 mmoles) en diclorometano (4.66 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 17 horas. La solución de reacción se concentró bajo presión reducida. Después, el residuo se purificó por cromatografía en columna sobre gel de sílice (hexano :

942

acetato de etilo = 100:0 → 95:5 → 90:10 → 75:25 → 66:34) para dar 401 mg del compuesto del título.

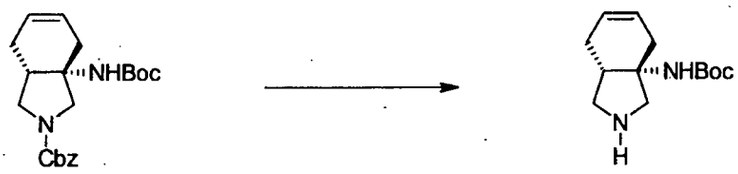
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.43-7.18 (5H, m), 5.76-5.58 (2H, m), 5.19-5.09 (2H, m), 4.54-4.32 (2H, m), 3.70 (1H, dd, J=18.02, 7.97 Hz), 3.17-2.97 (3H, m), 2.39-1.47 (4H, m), 1.41 (9H, s).

EM (ESI); m/z: 395 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 146

(1S,6S)-1-ter-Butoxicarbonilamino-8-azabiciclo [4.3.0] non-3-eno

[Fórmula 248]



Una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-benciloxicarbonil-8-azabiciclo [4.3.0] non-3-eno (400 mg, 1.07 mmoles) en tetrahidrofurano (5.35 ml) se hizo burbujear con amoniaco gaseoso bajo enfriamiento con hielo seco-metanol durante 10 minutos para añadir 30 a 40 ml de amoniaco líquido a la solución. Se añadió sodio (128 mg, 5.34 mmoles) y la mezcla se agitó durante 10 minutos. Una solución saturada de cloruro de amonio (15 gotas) se añadió a temperatura ambiente, y la mezcla se agitó a temperatura ambiente para evaporar el amoniaco. Una solución 1 mol/l de hidróxido de sodio (15.0 ml) se añadió, seguido por extracción con cloroformo (30 ml x 2). La capa acuosa se concentró bajo presión reducida. una solución 1 mol/l de hidróxido de sodio (5.0 ml) se añadió, seguido por extracción con la capa inferior de cloroformo/metanol/agua = 7/3/1 (35 ml x 2). Las capas

orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el filtrado se concentró bajo presión reducida para dar 136 mg del compuesto del título como un compuesto amorfo blanco.

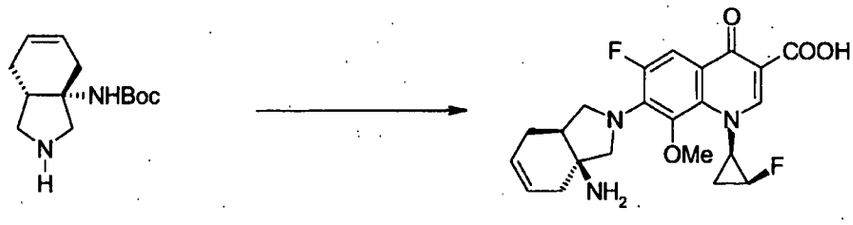
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 5.74-5.63 (2H, m), 4.44-4.36 (1H, m), 3.12 (1H, dd, J=9.93, 7.72 Hz), 3.02-2.88 (2H, m), 2.72 (1H, t, J=10.79 Hz), 2.60 (2H, d, J=11.52 Hz), 2.30 (1H, t, J=11.52 Hz), 2.18-1.82 (4H, m), 1.39 (9H, s).

EM (ESI); m/z: 239 $(M+H)^+$.

EJEMPLO 35

Acido 7-[(1S,6S)-1-amino-8-azabiciclo [4.3.0] non-3-en-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 249]



Trietilamina (0.217 ml, 1.55 mmoles) y ácido 1-[(1R,2S)-2-fluorociclopropan-1-il]-6,7-difluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (187 mg, 0.518 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-8-azabiciclo [4.3.0] non-3-eno (136 mg, 0.571 mmoles) en sulfóxido de dimetilo (2.04 ml), y la mezcla se agitó a 35°C durante 16 horas. Una solución mixta de etanol : agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de

ácido cítrico al 10% (30 ml), agua (30 ml), y salmuera (30 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). 242 mg del residuo resultante se disolvieron en ácido clorhídrico concentrado (2.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 10 minutos. Después de lavar con cloroformo (25 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo/metanol = 10/1 (150 ml x 1, 75 ml x 1, 50 ml x 1). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en 2-propanol caliente (40 ml), y el material insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. La solución se concentró a 10 ml y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración, se lavaron con 2-propanol y éter dietílico, y después se secaron bajo presión reducida para dar 129 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.36 (1H, d, J=3.68 Hz), 7.66 (1H, d, J=14.46 Hz), 5.88-5.72 (2H, m), 5.15-4.94 (1H, m), 4.05-3.98 (1H, m), 3.80-3.61 (3H, m), 3.57 (3H, s), 3.45 (1H, d, J=9.31 Hz), 2.48-1.97 (5H, m), 1.55-1.48 (1H, m), 1.45-1.29 (1H, m).

Análisis calculado para $C_{22}H_{23}F_2N_3O_4 \cdot 0.5H_2O \cdot iPrOH$: C, 59.99; H, 6.44; F, 7.59; N, 8.39.

Encontrado: C, 59.95; H, 6.30; F, 7.61; N, 8.25.

EM (ESI); m/z: 432 $(M+H)^+$.

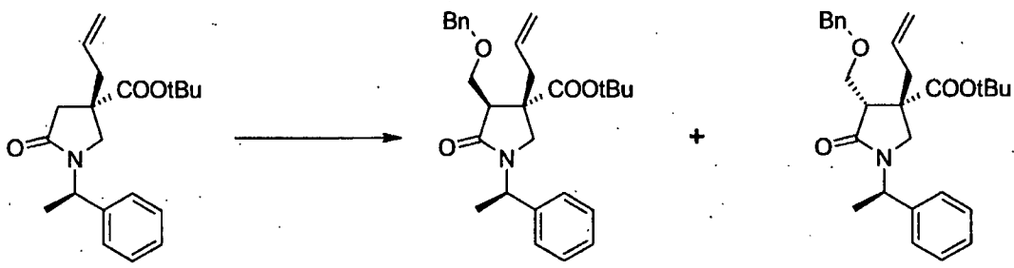
945

IR (ATR) ν: 2962, 1725, 1612, 1450, 1436, 1386, 1351, 1309, 1035, 819 cm^{-1}.

EJEMPLO DE REFERENCIA 147

Ester ter-butílico de ácido (3S,4R)-3-alil-benciloximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico; éster ter-butílico de ácido (3S,4S)-3-alil-4-benciloximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 250]



Bromuro de alilo (11.0 ml, 79.1 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S)-3-alil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (20.0 g, 60.7 mmoles) en tetrahidrofurano (303 ml) con agitación bajo enfriamiento con hielo con sal. Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (78.9 ml, 78.9 mmoles) se añadió gota a gota con agitación bajo enfriamiento con hielo con sal, y la mezcla se agitó bajo enfriamiento con hielo durante 10 minutos. Una solución saturada de cloruro de amonio (300 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (200 ml). La capa orgánica se lavó con salmuera (600 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 84:16 → 75:25 → 66:34) para dar 9.81 g del isómero (3S,4R) del compuesto del título y 6.76 g del

946

isómero (3R, 4S) del compuesto del título.

Isómero (3S,4R):

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.21 (10H, m), 5.75-5.59 (1H, m), 5.51-5.41 (1H, m), 5.17-5.08 (1H, m), 5.06-4.97 (1H, m), 4.71 (1H, s), 4.50 (1H, dd, J=22.31, 11.77 Hz), 3.97-3.95 (1H, m), 3.85-3.83 (1H, m), 3.35-3.04 (2H, m), 2.64-2.61 (1H, m), 2.45-2.37 (1H, m), 1.49 (1H, dd, J=7.11, 4.66 Hz), 1.42 (3H, d, J=7.35 Hz), 1.28 (9.H, s).

EM (ESI); m/z: 450 $(M+H)^+$.

Isómero (3R, 4S):

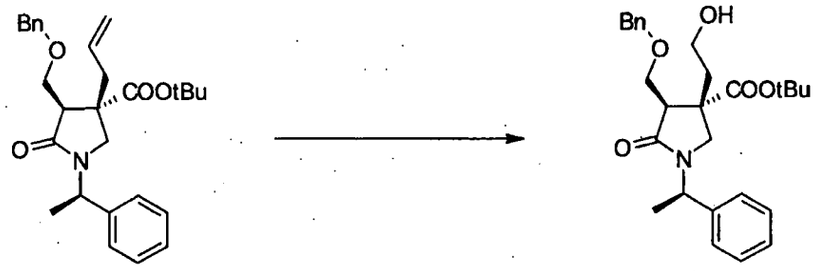
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.27-6.96 (10H, m), 5.76-5.65 (1H, m), 5.52 (1H, q, J=7.03 Hz), 5.17-5.12 (2H, m), 4.42-4.35 (2H, m), 3.50 (1H, d, J=10.05 Hz), 3.04 (1H, d, J=10.05 Hz), 2.52 (1H, dd, J=13.73, 6.37 Hz), 2.45 (1H, t, J=2.82 Hz), 2.36 (1H, dd, J=13.73, 8.09 Hz), 1.51 (3H, d, J=7.11 Hz), 1.38 (9H, s).

EM (ESI); m/z: 450 $(M+H)^+$.

EJEMPLO DE REFERENCIA 148

Ester ter-butílico de ácido (3S,4R)-4-benciloximetil-3-hidroxietil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 251]



Una solución de éster ter-butílico de ácido (3S,4R)-3-alil-4-benciloximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (8.00 g, 17.8

mmoles) en metanol (177 ml) se hizo burbujear con oxígeno durante 10 minutos. Después de hacerlo burbujear con ozono durante 30 minutos con agitación bajo enfriamiento con hielo seco-metanol, el ozono se removió por burbujeo con nitrógeno. Se añadió Borohidruro de sodio (1.68 g, 44.4 mmoles) bajo enfriamiento con hielo-acetona, y la mezcla se agitó bajo enfriamiento durante 1.5 horas. Una solución saturada de cloruro de amonio (150 ml) se añadió a la solución de reacción, y el metanol se evaporó por concentración bajo presión reducida. La mezcla se extrajo con acetato de etilo (200 ml x 1, 150 ml x 1). La capa orgánica se lavó con salmuera (300 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 66:34 → 50:50) para dar 3.79 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.22 (5H, m), 5.46 (1H, q, J=7.03 Hz), 4.50 (2H, dd, J=17.28, 11.64 Hz), 3.97 (1H, dd, J=9.80, 4.41 Hz), 3.84 (1H, dd, J=9.80, 2.45 Hz), 3.60 (2H, t, J=6.37 Hz), 3.42 (1H, d, J=9.31 Hz), 3.26 (1H, d, J=9.31 Hz), 3.10 (1H, dd, J=4.41, 2.45 Hz), 2.11 (1H, dt, J=15.52, 5.58 Hz), 1.99-1.93 (1H, m), 1.41 (3H, d, J=7.35 Hz), 1.28 (9H, s).

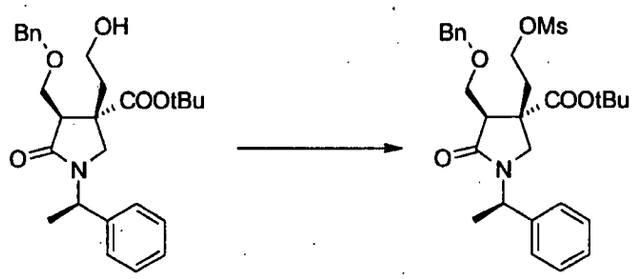
EM (ESI); m/z: 454 $(M+H)^+$.

EJEMPLO DE REFERENCIA 149

Ester ter-butílico de ácido (3S,4R)-3-benciloximetil-3-metansulfoniloxietil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

948

[Fórmula 252]



Trietilamina (2.79 ml, 19.9 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S,4R)-4-benciloximetil-3-hidroxietil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.57 g, 10.0 mmoles) en diclorometano (50.0 ml) en una atmósfera de nitrógeno. Cloruro de metansulfonilo (1.17 ml, 15.1 mmoles) se añadió bajo enfriamiento con hielo-acetona, y la mezcla se agitó a temperatura ambiente durante 15 minutos. Se añadió agua (150 ml) a la solución de reacción, seguido por extracción con cloroformo (150 ml x 1, 80 ml x 1). La capa orgánica se lavó con salmuera (200 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 7.09 g de un residuo que contenía el compuesto del título, que se usó directamente para el siguiente paso sin purificación adicional.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.25 (10H, m), 5.45 (1H, q, J=7.11 Hz), 4.50 (2H, dd, J=17.16, 11.52 Hz), 4.23-4.20 (1H, m), 4.14-4.11 (1H, m), 3.99 (1H, dd, J=9.93, 4.29 Hz), 3.81 (1H, dd, J=9.93, 2.57 Hz), 3.37 (1H, d, J=9.56 Hz), 3.25 (1H, d, J=9.56 Hz), 3.08 (1H, dd, J=4.41, 2.45 Hz), 2.90 (3H, s), 2.33-2.26 (1H, m), 2.21-2.17 (1H, m), 1.42 (3H, d, J=7.11 Hz), 1.28 (9H, s).

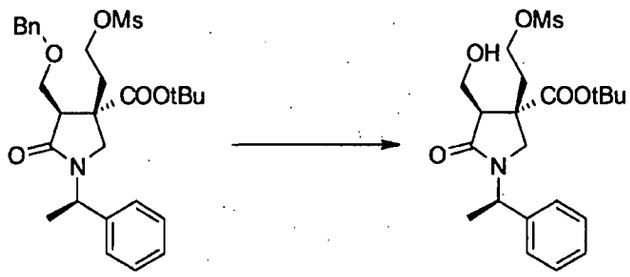
EM (ESI); m/z: 532 $(M+H)^+$.

949

EJEMPLO DE REFERENCIA 150

Ester ter-butílico de ácido (3S,4R)-4-hidroximetil-3-metansulfoniloxietil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 253]



Un catalizador de 20% de hidróxido de paladio-carbón (7.09 g, 100 % en peso) se añadió a una solución de éster ter-butílico de ácido (3S,4R)-3-benciloximetil-3-metansulfoniloxietil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (7.09 g) en etanol (100 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante una hora y a 50°C durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite, se concentró bajo presión reducida, y se secó bajo presión reducida para dar 4.49 g de un residuo que contenía el compuesto del título, que se usó directamente para el siguiente paso sin purificación adicional.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.30-4.19 (2H, m), 4.11-3.96 (2H, m), 3.34 (2H, dd, J=26.72, 10.54 Hz), 2.99 (3H, s), 2.98-2.95 (1H, m), 2.31-2.24 (1H, m), 2.17-2.10 (1H, m), 1.56 (3H, d, J=7.11 Hz), 1.37 (9H, s).

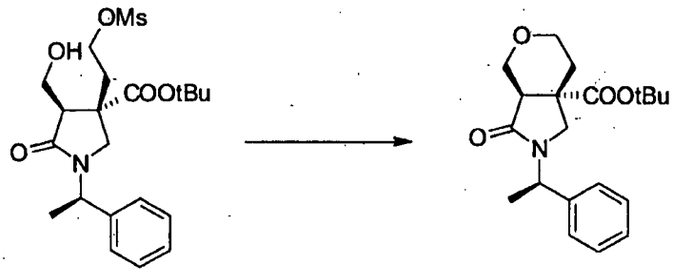
EM (ESI); m/z: 442 $(M+H)^+$.

950

EJEMPLO DE REFERENCIA 151

Ester ter-butílico de ácido (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico

[Fórmula 254]



Una solución de éster ter-butílico de ácido (3S,4R)-4-hidroximetil-3-metansulfoniloxietil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.49 g) en piridina (100 ml) se agitó en una atmósfera de nitrógeno a 50°C durante 15 horas. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 66:34 → 50:50 → 10:90) para dar 1.75 g del compuesto del título como cristales blancos.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.23 (5H, m), 5.58 (1H, q, J=7.11 Hz), 4.38 (1H, d, J=11.77 Hz), 3.83-3.79 (1H, m), 3.71 (1H, dd, J=12.01, 3.92 Hz), 3.42 (1H, td, J=12.01, 2.21 Hz), 3.04 (1H, d, J=10.05 Hz), 2.96 (1H, d, J=9.80 Hz), 2.62 (1H, d, J=3.43 Hz), 1.97 (1H, d, J=14.22 Hz), 1.75 (1H, ddd, J=15.44, 10.79, 3.19 Hz), 1.54 (3H, d, J=7.11 Hz), 1.44 (9H, s).

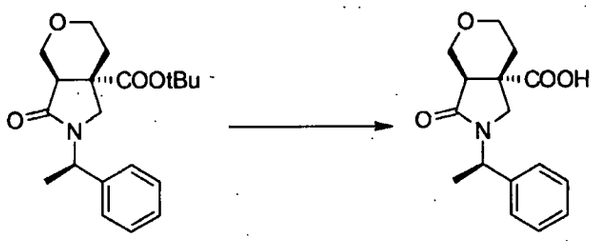
EM (ESI) ; m/z: 346 $(M+H)^+$.

EJEMPLO DE REFERENCIA 152

Acido (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico

951

[Fórmula 255]



Se añadió ácido trifluoroacético (6.63 ml) a una solución de éster ter-butílico de ácido (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico (763 mg, 2.21 mmoles) en diclorometano (6.63 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1.5 horas. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (tres veces). Una solución 1 mol/l de hidróxido de sodio (20 ml) se añadió al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con éter dietílico (50 ml x 2). La capa acuosa se hizo ácida con 1 mol/l de ácido clorhídrico (20 ml) bajo enfriamiento con hielo, seguido por extracción con acetato de etilo (60 ml x 1, 50 ml x 1). Las capas orgánicas se combinaron, se lavaron con salmuera (90 ml), y se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 637 mg del compuesto del título como cristales blancos.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.43-7.24 (5H, m), 5.58 (1H, q, J=7.11 Hz), 4.41 (1H, d, J=12.26 Hz), 3.83 (1H, dd, J=12.13, 2.82 Hz), 3.70 (1H, dd, J=12.01, 3.68 Hz), 3.44 (1H, td, J=12.13, 1.88 Hz), 3.11 (1H, d, J=10.05 Hz), 3.02 (1H, d, J=10.05 Hz), 2.69 (1H, d, J=3.43 Hz), 2.09-2.05 (1H, m), 1.84-1.76 (1H, m), 1.55 (3H, d, J=7.11 Hz).

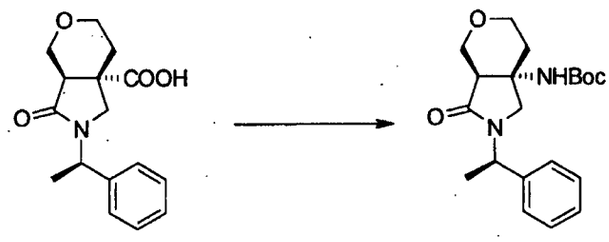
EM (ESI); m/z: 290 $(M+H)^+$.

952

EJEMPLO DE REFERENCIA 153

(1S,6R)-1-ter-Butoxicarbonilamino-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano

[Fórmula 256]



Trietilamina (0.720 ml, 5.16 mmoles) y difenilfosforil azida (0.723 ml, 3.35 mmoles) se añadieron a una solución de ácido (1S,6R)-{4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico (747 mg, 2.58 mmoles) en tolueno (12.9 ml) en una atmósfera de nitrógeno con agitación bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 30 minutos y después a 100°C durante 30 minutos. La solución de reacción se concentró bajo presión reducida, y trietilamina se destiló azeotrópicamente con tolueno (x 3). 1,4-Dioxano (6.45 ml) y 6 mol/l de ácido clorhídrico (6.45 ml) se añadieron al residuo resultante, y la mezcla se agitó a 50°C durante una hora. La solución de reacción se diluyó con agua (15 ml) y se lavó con acetato de etilo (50 ml x 2). La capa acuosa se hizo alcalina con una solución 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo, seguido por extracción con cloroformo (50 ml x 2). La capa orgánica se lavó con salmuera (80 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. Diclorometano (14.9 ml) se añadió al residuo resultante, dicarbonato de di-ter-butilo (813 mg, 3.73 mmoles) se añadió en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante cuatro días. La solución de reacción se concentró bajo presión reducida. El residuo

resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 95:5 → 90:10 → 75:25 → 60:40 → 50:50) para dar 470 mg (51%) del compuesto del título.

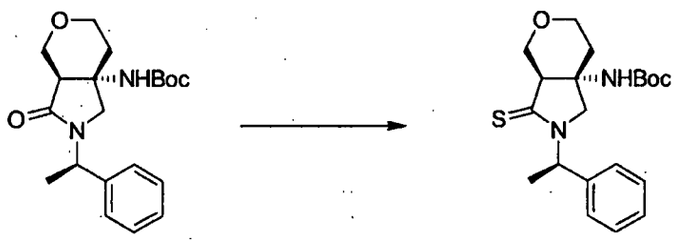
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.25 (5H, m), 5.58 (1H, q, J=7.19 Hz), 4.81 (1H, brs), 4.31 (1H, dd, J=12.26, 1.72 Hz), 3.77 (1H, td, J=7.54, 4.09 Hz), 3.61 (1H, dd, J=12.26, 3.92 Hz), 3.48 (2H, m), 3.09 (1H, d, J=10.05 Hz), 2.39 (1H, brs), 2.16-2.05 (1H, m), 1.81 (1H, ddd, J=15.26, 10.85, 3.62 Hz), 1.53 (3H, d, J=7.11 Hz), 1.39 (9H, s).

EM (ESI); m/z: 361 $(M+H)^+$.

EJEMPLO DE REFERENCIA 154

(1S,6R)-1-ter-Butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-7-tioxo-8-azabiciclo [4.3.0] nonano

[Fórmula 257]



Reactivo de Lawesson se añadió a una solución de (1S, 6R)-1-ter-butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-7-oxo-8-azabiciclo[4.3.0] nonano (470 mg, 1.30 mmoles) en tetrahidrofurano (13.0 ml), y la mezcla se agitó a 60°C durante 2.5 horas. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 95:5 → 90:10 → 80:20 → 75:25 → 66:34) para dar un residuo que contenía el compuesto del título, que se usó directamente para el siguiente paso.

954

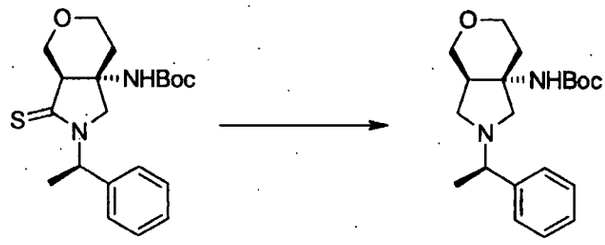
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.29 (5H, m), 6.97 (1H, dt, J=12.83, 4.60 Hz), 6.44 (1H, q, J=7.03 Hz), 4.39 (1H, d, J=9.31 Hz), 3.87-3.82 (3H, m), 3.72-3.57 (2H, m), 2.70 (1H, brs), 2.03-1.94 (1H, m), 1.90-1.79 (1H, m), 1.60 (3H, d, J=7.11 Hz), 1.36 (9H, s).

EM (ESI); m/z: 377 $(M+H)^+$.

EJEMPLO DE REFERENCIA 155

(1S, 6R)-1-ter-Butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano

[Fórmula 258]



Níquel de Raney (14.2 ml) se añadió a una solución de (1S, 6R)-1-ter-butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-7-tioxo-8-azabiciclo [4.3.0] nonano (700 mg) en etanol (28.4 ml) en una atmósfera de nitrógeno. La mezcla se agitó vigorosamente a temperatura ambiente durante una hora. La solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 423 mg del compuesto del título cuantitativamente.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.20 (5H, m), 4.66 (1H, brs), 3.75-3.40 (4H, m), 2.90 (2H, s), 2.78-2.69 (2H, m), 2.20-1.96 (3H, m), 1.41 (9H, s), 1.34 (3H, d, J=6.59 Hz).

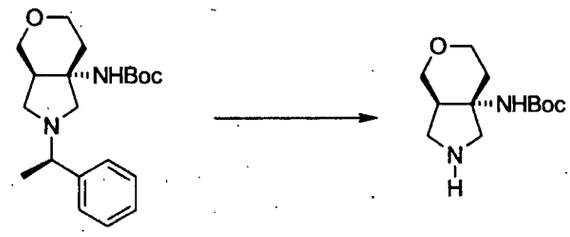
EM (ESI) ; m/z: 347 $(M+H)^+$.

955

EJEMPLO DE REFERENCIA 156

(1S, 6S)-1-ter-Butoxicarbonilamino-4-oxabiciclo [4.3.0] nonano

[Fórmula 259]



Un catalizador de 10% de paladio-carbón (205 mg) se añadió a una solución de (1S, 6R)-1-ter-butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano (205 mg, 0.592 mmoles) en etanol (5.92 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante 45 minutos y a 50°C durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida. Un catalizador de 10% de paladio-carbón (205 mg) se añadió a una solución del residuo resultante en etanol (5.92 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó a 50°C durante 16 horas. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida. Un catalizador de 20% de hidróxido de paladio-carbón (205 mg) se añadió a una solución del residuo resultante en etanol (5.92 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a 50°C durante una hora. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite, se concentró

956

bajo presión reducida, y se secó bajo presión reducida para dar 128 mg del compuesto del título como un aceite color bermellón pálido.

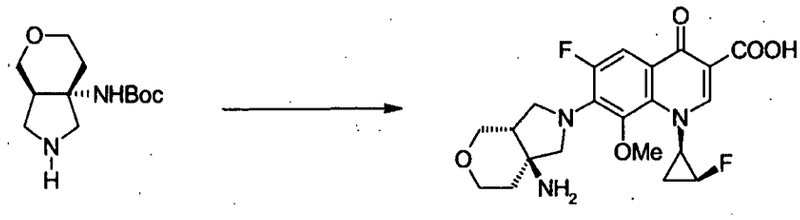
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.83 (1H, brs), 3.68-3.57 (4H, m), 3.30-3.19 (3H, m), 3.00-2.98 (1H, m), 2.14-1.96 (3H, m), 1.44 (9H, s).

EM (ESI); m/z: 243 $(M+H)^+$.

EJEMPLO 36

Acido 7-[(1S,6R)-1-amino-4-oxa-8-azabiciclo [4.3.0] nonan-8-il]-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 260]



Trietilamina (0.198 ml, 1.42 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (171 mg, 0.474 mmoles) se añadieron a una solución de (1S, 6R)-8-aza-1-ter-butoxicarbonilamino-4-oxabiciclo [4.3.0] nonano (126 mg, 0.520 mmoles) en sulfóxido de dimetilo (0.948 ml), y la mezcla se agitó a 35°C durante 16 horas. Una solución mixta de etanol:agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de ácido cítrico al 10% (30 ml), agua (30 ml), y salmuera (30 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo

957

presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2).Se añadió ácido trifluoroacético (0.694 ml, 3 v/p) a una solución de 125 mg del residuo resultante en diclorometano (2.31 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (x 3). Se añadió ácido clorhídrico a pH 1 (20.0 ml) al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con éter dietílico (40 ml x 4). La capa acuosa se ajustó a pH 12 con una solución 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo. La solución básica se ajustó a pH 7.4 con 1 mol/l de ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 2) y cloroformo/metanol = 10/1 (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en etanol caliente (10 ml), y el material insoluble se removió por filtración. El solvente se evaporó gradualmente mientras se calentaba con agitación. El residuo se concentró hasta que el etanol fue de 3 a 4 ml, y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración, se lavaron con etanol y éter dietílico, y después se secaron bajo presión reducida a 60°C para dar 20.5 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.45 (1H, s), 7.68 (1H, d, J=14.71 Hz), 5.08-4.92 (1H, m), 4.07 (1H, dd, J=13.73, 6.13 Hz), 3.92 (1H, dd, J=12.50, 3.68 Hz), 3.83 (4H, dd, J=13.85, 8.95 Hz), 3.73-3.58 (6H, m), 2.20-2.13 (1H, m), 2.06-1.99 (1H, m), 1.68-1.49 (3H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_5 \cdot 0.75H_2O$: C, 56.18; H, 5.50; N, 9.36.

958

Encontrado: C, 56.15; H, 5.46; N, 9.65.

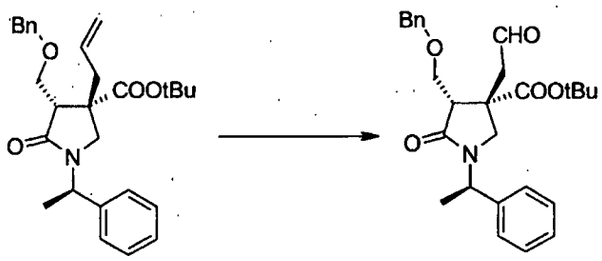
EM (ESI); m/z: 436 $(M+H)^+$.

IR (ATR) ν: 2937, 2892, 2856, 1724, 1625, 1515, 1454, 1324, 1137, 1099, 1054, 985, 927, 887, 802 cm^{-1}.

EJEMPLO DE REFERENCIA 157

Ester ter-butílico de ácido (3S,4S)-4-benciloximetil-5-oxo-3-(2-oxoetil)-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 261]



Una solución de éster ter-butílico de ácido (3S,4S)-3-alil-4-benciloximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (6.76 g, 15.0 mmoles) en metanol (150 ml) se hizo burbujear con oxígeno durante cinco minutos. Después de hacerlo burbujear con ozono durante 1.5 horas con agitación bajo enfriamiento con hielo seco-metanol, el ozono se removió por burbujeo con nitrógeno. Sulfuro de dimetilo (5.64 ml, 76.8 mmoles) se añadió bajo enfriamiento, y la mezcla se agitó durante 19 horas. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 90:10 → 80:20 → 75:25 → 66:34 → 50:50) para dar 4.58 g del compuesto del título como un aceite transparente.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 9.74 (1H, s), 7.37-7.15 (5H, m), 5.47

959

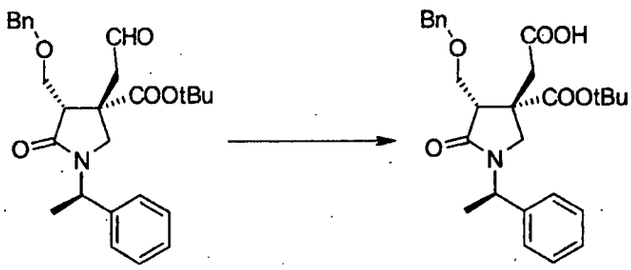
(1H, q, J=7.19 Hz), 4.42 (2H, s), 3.92 (1H, dd, J=9.80, 3.68 Hz), 3.81 (1H, dd, J=9.56, 6.62 Hz), 3.68 (1H, d, J=10.54 Hz), 3.21 (1H, t, J=8.58 Hz), 3.13 (1H, d, J=10.54 Hz), 2.70 (1H, dd, J=6.37, 3.68 Hz), 2.61 (1H, d, J=17.16 Hz), 1.50 (3H, d, J=7.11 Hz), 1.27 (9H, s).

EM (ESI); m/z: 452 $(M+H)^+$.

EJEMPLO DE REFERENCIA 158

Ester ter-butílico de ácido (3S,4S)-4-benciloximetil-3-carboximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico

[Fórmula 262]



2-Metil-2-buteno se añadió a una solución de éster ter-butílico de ácido (3S,4S)-4-benciloximetil-5-oxo-3-(2-oxoetil)-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.58 g, 10.1 mmoles) en alcohol ter-butílico (25.2 ml) bajo enfriamiento con hielo, y la mezcla se agitó. Clorito de sodio (2.29 g, 25.3 mmoles) se añadió a una solución de fosfato diácido de sodio dihidratado (4.10 g, 26.3 mmoles) en agua (20.2 ml) para preparar de manera separada una solución. Esta solución se añadió a la solución anterior bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. El sólido precipitado se recogió por filtración, se lavó con agua y hexano, y después se secó bajo presión reducida a 40°C para dar 3.93 g del compuesto del título como cristales en polvo blancos.

960

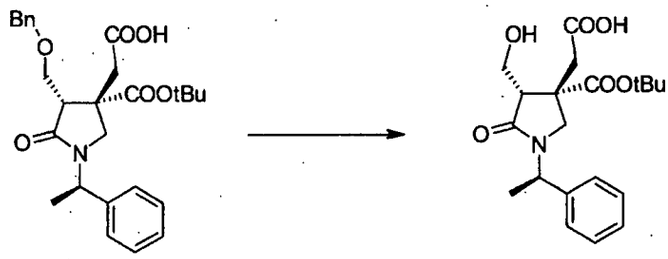
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.30-7.14 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.42 (2H, s), 3.90 (1H, dd, J=9.68, 3.55 Hz), 3.82 (1H, dd, J=9.56, 6.13 Hz), 3.69 (1H, d, J=10.54 Hz), 3.27 (1H, d, J=10.79 Hz), 3.10 (1H, d, J=16.18 Hz), 2.70 (1H, dd, J=6.13, 3.68 Hz), 2.58 (1H, d, J=16.18 Hz), 1.79 (1H, brs), 1.52 (3H, d, J=7.11 Hz), 1.29 (9H, s).

EM (ESI); m/z: 468 $(M+H)^+$.

EJEMPLO DE REFERENCIA 159

Ester ter-butílico de ácido (3S,4S)-3-carboximetil-4-hidroximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 263]



Un catalizador de 10% de paladio-carbón (3.93 g) se añadió a una solución de éster ter-butílico de ácido (3S,4S)-4-benciloximetil-3-carboximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (3.93 g, 8.41 mmoles) en metanol (84.0 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante tres días. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 2.54 g del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.27 (5H, m), 5.44 (1H, q, J=7.11 Hz), 3.88 (1H, dd, J=11.28, 7.60 Hz), 3.80 (1H, dd, J=11.28, 5.39 Hz),

961

3.69 (1H, d, J=10.79 Hz), 3.26 (1H, d, J=10.79 Hz), 3.05 (1H, d, J=16.91 Hz), 2.68 (1H, dd, J=7.35, 5.39 Hz), 2.59 (1H, d, J=16.91 Hz), 1.53 (3H, d, J=7.11 Hz), 1.28 (9H, s).

EM (ESI); m/z: 378 $(M+H)^+$.

EJEMPLO DE REFERENCIA 160

Ester ter-butílico de ácido {(1S, 6S)-4-oxa-3,7-dioxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico

[Fórmula 264]



Trietilamina (1.32 ml, 9.46 mmoles) y cloruro de 2,4,6-triclorobenzoilo (1.16 ml, 7.45 mmoles) se añadieron a una solución de éster ter-butílico de ácido (3S,4S)-3-carboximetil-4-hidroximetil-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (2.54 g, 6.73 mmoles) en tetrahidrofurano (44.8 ml) en una atmósfera de nitrógeno. Después de agitar a temperatura ambiente durante 30 minutos, se añadieron tolueno (179 ml) y después 4-dimetilamino piridina (1.23 g, 10.1 mmoles). Después de agitar a temperatura ambiente durante 18 horas, la solución de reacción se diluyó con acetato de etilo (100 ml) y se lavó con 1 mol/l de ácido clorhídrico (150 ml), agua (150 ml), una solución saturada de bicarbonato de sodio (150 ml), agua (150 ml), y salmuera (150 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por

962

cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 80:20 → 66:34 → 50:50 → 34:66 → 25:75) para dar 2.06 g del compuesto del título.

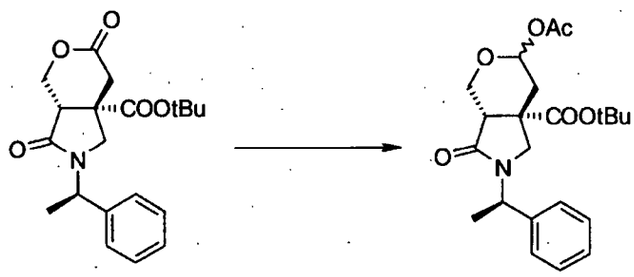
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.27 (5H, m), 5.43 (1H, q, J=7.19 Hz), 4.76-4.72 (2H, m), 3.34-3.20 (3H, m), 2.90 (1H, dd, J=10.42, 7.97 Hz), 2.56 (1H, d, J=16.91 Hz), 1.52 (3H, d, J=7.35 Hz), 1.24 (9H, s).

EM (ESI) ; m/z: 360 $(M+H)^+$.

EJEMPLO DE REFERENCIA 161

Ester ter-butílico de ácido {(1S,6S)-3-acetoxi-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico

[Fórmula 265]



Una solución 0.97 mol/l de hidruro de diisobutilaluminio en hexano (1.65 ml, 1.60 mmoles) se añadió a una solución de éster ter-butílico de ácido {(1S,6S)-4-oxa-3,7-dioxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico (500 mg, 1.39 mmoles) en diclorometano (6.95 ml) con agitación bajo enfriamiento con hielo seco-metanol. Después de agitar bajo enfriamiento durante una hora, una solución de 0.97 moles/l de hidruro de diisobutilaluminio en hexano (0.716 ml, 0.695 mmoles) se añadió. Después de agitar bajo enfriamiento durante dos horas, se añadieron una solución de piridina (0.338 ml, 4.18 mmoles) y 4-dimetilaminopiridina (204 mg, 1.67 mmoles) en diclorometano

963

(3.5 ml) y una solución de anhídrido acético (0.526 ml, 5.56 mmoles) en diclorometano (1.8 ml). La mezcla se agitó bajo enfriamiento durante una hora y después se enfrió con hielo, y una solución saturada de cloruro de tetraamonio (20 ml) se añadió. Después de agitar bajo enfriamiento con hielo durante 30 minutos, la solución de reacción se extrajo con acetato de etilo (50 ml x 1, 40 ml x 1). La capa orgánica se lavó con ácido cítrico al 10% (60 ml), agua (60 ml), una solución saturada de bicarbonato de sodio (60 ml), y salmuera (60 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 66:34 → 60:40 → 50:50) para dar 350 mg del compuesto del título como un sólido blanco.

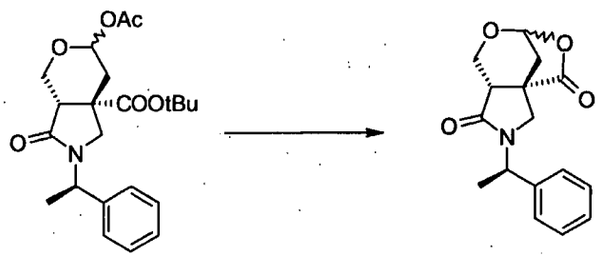
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.35-7.23 (5H, m), 5.74 (1H, dd, J=7.35, 4.17 Hz), 5.45 (1H, dd, J=20.84, 10.42 Hz), 4.29-4.14 (2H, m), 2.70-2.60 (2H, m), 2.09 (3H, s), 1.67 (1H, dd, J=12.62, 7.23 Hz), 1.48 (3H, d, J=7.11 Hz), 1.23 (9H, s).

EM (ESI); m/z: 404 $(M+H)^+$.

EJEMPLO DE REFERENCIA 162

(1S, 5S)-3-Aza-4,10-dioxo-3-[(1R)-1-feniletil]-7,9-dioxatriciclo [6.2.1.0^{1,5}] undecano

[Fórmula 266]



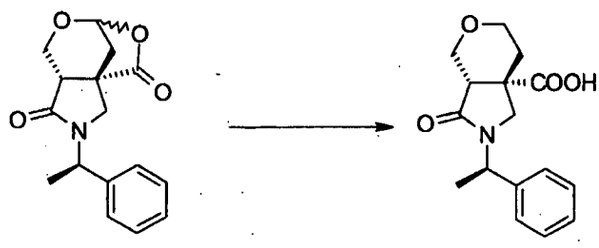
Una solución de éster ter-butílico de ácido {(1S,6S)-3-acetoxi-7-oxa-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico (663 mg, 1.64 mmoles) en acetonitrilo (8.20 ml) se enfrió con hielo-acetona. Trietilsilano (0.787 ml, 4.93 mmoles) y triflato de trimetilsililo (0.595 ml, 3.29 mmoles) se añadieron en una atmósfera de nitrógeno, y la mezcla se agitó bajo enfriamiento durante 15 minutos. Una solución saturada de bicarbonato de sodio (50 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (100 ml x 1, 60 ml x 1). La capa orgánica se lavó con agua (50 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 80:20 → 75:25 → 66:34 → 50:50 → 34:66) para dar 413 mg del compuesto del título como un aceite transparente.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.17 (5H, m), 5.45 (1H, q, J=7.03 Hz), 4.25 (1H, dd, J=11.28, 4.17 Hz), 4.18-4.10 (1H, m), 3.97-3.92 (2H, m), 3.31-3.25 (2H, m), 2.61 (1H, dd, J=10.66, 4.29 Hz), 2.19 (1H, d, J=13.24 Hz), 1.80 (1H, td, J=12.62, 4.66 Hz), 1.48 (3H, d, J=7.11 Hz).

EJEMPLO DE REFERENCIA 163

Acido {(1S,6S)-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il}carboxílico

[Fórmula 267]



965

Una solución de (1S,5S)-3-aza-4,10-dioxo-3-[(1R)-1-feniletil]-7,9-dioxatriciclo [6.2.1.$0^{1,5}$] undecano (413 mg, 1.44 mmoles) en diclorometano (7.20 ml) se enfrió con hielo seco-metanol. Trietilsilano (0.690 ml, 4.32 mmoles) y una solución de 1.0 mol/l de tetraclorotitanio en diclorometano (2.88 ml, 2.88 mmoles) se añadieron en una atmósfera de nitrógeno, y la mezcla se agitó bajo enfriamiento durante 30 minutos. Una solución saturada de bicarbonato de sodio (50 ml) se añadió a la solución de reacción, y la mezcla se lavó con acetato de etilo (100 ml x 2). La capa acuosa se hizo ácida con 6 moles/l de ácido clorhídrico y 1 mol/l de ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 1, 60 ml x 1). La capa orgánica se lavó con agua (100 ml) y salmuera (150 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida y se secó bajo presión reducida para dar 235 mg del compuesto del título como cristales blancos.

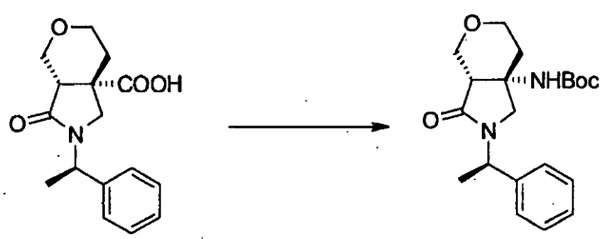
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.23 (5H, m), 5.46 (1H, d, J=7.35 Hz), 4.26 (1H, dd, J=11.03, 4.41 Hz), 3.97-3.91 (2H, m), 3.33-3.24 (3H, m), 2.60 (1H, dd, J=10.66, 4.29 Hz), 2.19 (1H, d, J=12.50 Hz), 1.85-1.67 (2H, m), 1.49 (3H, d, J=7.11 Hz).

EM (ESI); m/z: 290 $(M+H)^+$.

EJEMPLO DE REFERENCIA 164

(1S,6S)-1-ter-Butoxicarbonilamino-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano

[Fórmula 268]



Trietilamina (0.330 ml, 2.36 mmoles) y difenilfosforil azida (0.330 ml, 1.53 mmoles) se añadieron a una solución de ácido [(1S,6S)-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonan-1-il] carboxílico (340 mg, 1.18 mmoles) en tolueno (5.90 ml) en una atmósfera de nitrógeno con agitación bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 30 minutos y después a 100°C durante una hora. La solución de reacción se concentró bajo presión reducida, y trietilamina se destiló azeotrópicamente con tolueno (x 3). 1,4-Dioxano (2.95 ml) y 6 moles/l de ácido clorhídrico (2.95 ml) se añadieron al residuo resultante, y la mezcla se agitó a 50°C durante una hora. La solución de reacción se diluyó con agua (9.0 ml) y se lavó con éter dietílico (40 ml x 2). La capa acuosa se hizo alcalina con una solución 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo, seguido por extracción con cloroformo (80 ml x 1, 60 ml x 1). La capa orgánica se lavó con agua (80 ml) y salmuera (80 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. Diclorometano (5.90 ml) se añadió al residuo resultante, y dicarbonato de di-ter-butilo (773 mg, 3.54 mmoles) se añadió en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 14 horas y a 50°C durante siete horas, se añadió dicarbonato de di-ter-butilo (515 mg, 2.36 mmoles). Después de agitación a 50°C durante 17 horas, la solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 100:0 → 90:10 → 80:20 → 66:34 → 60:40) para dar 320 mg del compuesto del título.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.34-7.23 (5H, m), 5.44 (1H, q, J=6.95 Hz), 4.53 (1H, brs), 4.16-4.11 (1H, m), 3.81 (1H, dd, J=12.13, 3.80 Hz), 3.62 (3H, tt, J=14.83, 6.37 Hz), 3.15 (1H, d, J=10.30 Hz), 2.69 (1H, dd, J=11.52,

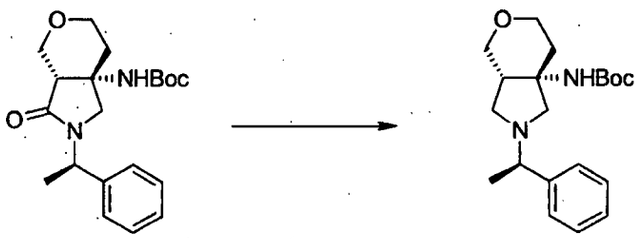
4.41 Hz), 1.71 (1H, td, J=12.68, 4.98 Hz), 1.49 (3H, d, J=7.11 Hz), 1.26 (9H, s).

EM (ESI) ; m/z: 361 $(M+H)^+$.

EJEMPLO DE REFERENCIA 165

(1S,6S)-1-ter-Butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano

[Fórmula 269]



Una solución de (1S,6S)-1-ter-butoxicarbonilamino-4-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano (331 mg, 0.918 mmoles) en tetrahidrofurano (3.0 ml) se enfrió con hielo-acetona. Una solución de 1.2 moles/l de borano en tetrahidrofurano (3.83 ml, 4.59 mmoles) se añadió en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 19 horas. Después de enfriar con hielo-acetona nuevamente, una solución de 1.2 moles/l de borano en tetrahidrofurano (3.83 ml, 4.59 mmoles) se añadió en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida. Después, una solución mixta de etanol : agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron, y la mezcla se calentó a reflujo durante 1.5 horas. La solución de reacción se concentró bajo presión reducida y una solución saturada de bicarbonato de sodio (50 ml) se añadió al residuo, seguido por extracción con cloroformo (50 ml x 1, 40 ml x 1). La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se

968

concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → → 90:10 → 60:40 → 50:50 → 34:66 → 25:75 → 16:84 → 10:90 → 5:95 → 2:98 → 0:100) para dar 255 mg del compuesto del título.

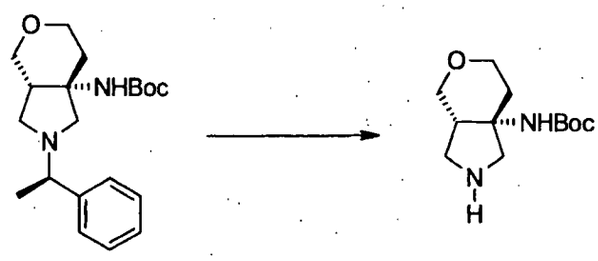
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.31-7.21 (5H, m), 4.35 (1H, s), 3.81 (2H, ddd, J=22.43, 11.64, 4.04 Hz), 3.62 (2H, td, J=11.95, 2.37 Hz), 3.49 (1H, t, J=11.52 Hz), 3.37 (1H, d, J=10.05 Hz), 2.91 (1H, t, J=8.33 Hz), 2.55-2.42 (2H, m), 2.17 (1H, t, J=5.88 Hz), 1.56-1.50 (1H, m), 1.47 (9H, s), 1.32 (3H, d, J=6.37 Hz).

EM (ESI); m/z : 347 $(M+H)^+$.

EJEMPLO DE REFERENCIA 166

(1S,6S)-1-ter-Butoxicarbonilamino-4-oxa-8-biciclo [4.3.0] nonano

[Fórmula 270]



Un catalizador de 20% de hidróxido de paladio-carbón (262 mg) se añadió a una solución de (1S,6S)-1-ter-butoxicarbonilamino-4-oxa-8-[(1R)-1-feniletil]-8-azabiciclo [4.3.0] nonano (262 mg, 0.756 mmoles) en etanol (7.56 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó en una atmósfera de hidrógeno a 45°C durante 2.5 horas. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite, se concentró bajo presión reducida, y se

secó bajo presión reducida para dar 183 mg del compuesto del título.

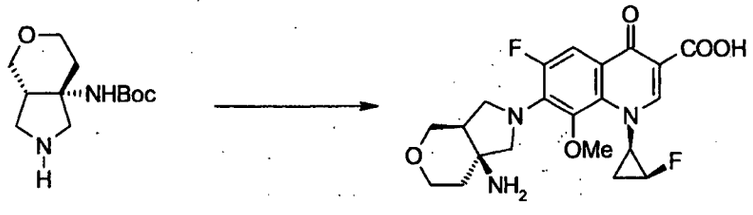
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.33 (1H, brs), 3.95 (1H, dd, J=11.64, 4.29 Hz), 3.84 (1H, dd, J=12.50, 4.66 Hz), 3.72 (1H, q, J=7.03 Hz), 3.62-3.55 (2H, m), 3.49 (1H, t, J=11.64 Hz), 3.06 (1H, dd, J=9.93, 7.97 Hz), 2.68-2.57 (3H, m), 2.13-2.04 (1H, m), 1.57 (1H, td, J=12.93, 4.74 Hz), 1.45 (9H, s).

EM (ESI); m/z: 243 $(M+H)^+$.

EJEMPLO 37

Acido 7-[(1S,6S)-1-amino-4-oxa-8-azabiciclo [4.3.0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 271]



Trietilamina (0.165 ml, 1.18 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (142 mg, 0.393 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-4-oxa-8-biciclo[4.3.0]nonano (142 mg, 0.421 mmoles) en sulfóxido de dimetilo (0.787 ml), y la mezcla se agitó a temperatura ambiente durante 14 horas. Una solución mixta de etanol:agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de ácido cítrico al 10% (30 ml), agua (30 ml), y salmuera (30 ml). La

capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se añadió ácido trifluoroacético (0.975 ml, 3 v/p) a una solución de 174 mg del residuo resultante en diclorometano (3.25 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante dos horas. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (x 3). Se añadió ácido clorhídrico 1N (25.0 ml) al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con éter dietílico (50 ml x 5). La capa acuosa se ajustó a pH 12 con una solución de 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo. La solución básica se ajustó a pH 7.4 con 1 mol/l de ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 2, 50 ml x 2). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo se disolvió en cloroformo/metanol = 10/1, y el material insoluble se removió por filtración. El filtrado se concentró bajo presión reducida y se disolvió en etanol caliente. El solvente se evaporó gradualmente mientras se calentaba con agitación. Después, la solución se concentró hasta que el etanol fue de aproximadamente 10 ml, y se agitó a temperatura ambiente durante tres horas. Los cristales precipitados se recogieron por filtración y después se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C durante la noche para dar 55.3 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.36 (1H, d, J=3.68 Hz), 7.67 (1H, d, J=14.46 Hz), 5.15-4.96 (1H, m), 4.00 (3H, ddd, J=20.71, 11.03, 4.53 Hz), 3.84-3.63 (4H, m), 3.58 (3H, s), 3.53 (1H, t, J=8.58 Hz), 3.39 (1H, d, J=9.31 Hz),

471

2.32-2.20 (1H, m), 1.99-1.85 (2H, m), 1.58-1.43 (1H, m), 1.43-1.27 (1H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_5 \cdot 0.25H_2O$: C, 57.33; H, 5.38; N, 9.55.

Encontrado: C, 57.55; H, 5.40; N, 9.47.

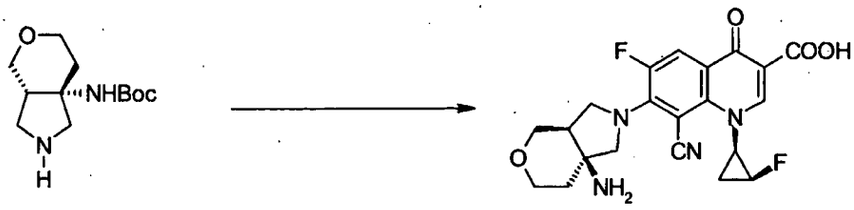
EM (ESI); m/z: 436 $(M+H)^+$.

IR (ATR) ν: 3052, 2927, 2869, 1727, 1614, 1594, 1508, 1446, 1428, 1363, 1322, 1110, 1078, 1043, 989, 948, 910, 809 cm^{-1}.

EJEMPLO 38

Acido 7-[(1S,6S)-1-amino-4-oxa-8-azabiciclo [4.3.0] nonan-8-il]-8-ciano-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-4-oxoquinolin-3-carboxílico

[Fórmula 272]



Trietilamina (0.263 ml, 1.88 mmoles) y 8-ciano-6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-4-oxoquinolin-3-carboxilato de etilo (211 mg, 0.627 mmoles) se añadieron a una solución de (1S,6S)-1-ter-butoxicarbonilamino-4-oxa-8-azabiciclo [4.3.0] nonano (151 mg, 0.628 mmoles) en acetonitrilo (1.25 ml) en una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 18 horas. La solución de reacción se concentró bajo presión reducida. Después, el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 90:10 → 60:40 → 50:50 → 34:66 → 25:75 → 16:84). Una solución de 1 mol/l

de hidróxido de sodio (1.94 ml) se añadió a una solución del residuo resultante en etanol (2.42 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. Una solución de ácido cítrico al 10% (30 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (40 ml x 1, 30 ml x 1). La capa orgánica se lavó con salmuera (45 ml) y después se secó sobre sulfato de sodio anhidro y se filtró. El filtrado se concentró después bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se añadió ácido trifluoroacético (1.38 ml, 3 v/p) a una solución de 243 mg del residuo resultante en diclorometano (4.58 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2.5 horas. La solución de reacción se concentró bajo presión reducida. Después, ácido clorhídrico a pH 1 se añadió al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con cloroformo (40 ml x 3). La capa acuosa se ajustó a pH 12 con una solución de 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo. La solución básica se ajustó a pH 7.4 con 1 mol/l de ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 1, 70 ml x 1, 50 ml x 1). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. La capa acuosa se concentró bajo presión reducida. El residuo resultante se disolvió en cloroformo/metanol = 10/1, y el material insoluble se removió por filtración (x 2). Los residuos obtenidos de la capa orgánica y la capa acuosa se purificaron por CCDP (capa inferior de cloroformo/metanol/agua = 7/3/1), respectivamente. Estas se combinaron y se disolvieron en diclorometano (20 ml), y el diclorometano se removió azeotrópicamente con etanol (tres veces). Se añadió etanol (5 ml) al residuo resultante, y la mezcla se trató ultrasónicamente y después se enfrió. El sólido

973

precipitado se recogió por filtración, se lavó con etanol y éter dietílico, y se secó bajo presión reducida a 60°C para dar 122 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.30 (1H, d, J=3.92 Hz), 7.90 (1H, d, J=15.44 Hz), 5.19 (1H, dd, J=63.24, 3.43 Hz), 4.06-3.97 (5H, m), 3.81-3.74 (3H, m), 3.58 (1H, d, J=10.30 Hz), 2.33-2.31 (1H, m), 2.03-1.73 (3H, m), 1.61-1.49 (1H, m).

Análisis calculado para $C_{21}H_{20}F_2N_4O_4 \cdot 0.25H_2O$: C, 58.00; H, 4.75; F, 8.74; N, 12.88.

Encontrado: C, 58.07; H, 4.60; F, 8.70; N, 12.74

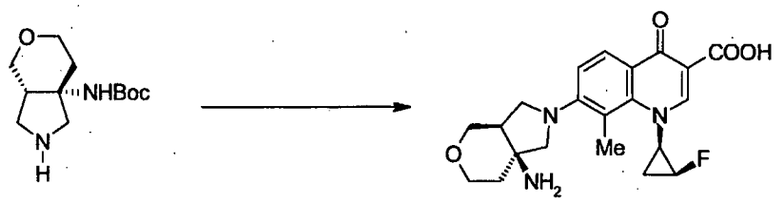
EM (ESI) ; m/z: 431 $(M+H)^+$.

IR (ATR) ν: 3081, 2960, 2873, 2211, 1725, 1629, 1446, 1400, 1307, 1261, 927, 912, 804 cm^{-1}.

EJEMPLO 39

Acido 7-[(1S,6S)-1-amino-4-oxa-8-azabiciclo [4.3.0] nonan-8-il]-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 273]



Trietilamina (0.0737 ml, 0.528 mmoles) y ácido 7-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (49.0 mg, 0.175 mmoles) se añadieron a (1S,6S)-1-ter-butoxicarbonilamino-4-oxa-8-azabiciclo [4.3.0] nonano (42.2 mg, 0.176 mmoles) en sulfóxido de dimetilo (0.352 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a 75°C durante

dos días. Sulfóxido de dimetilo (0.352 ml) y trietilamina (0.147 ml, 1.06 mmoles) se añadieron a la solución de reacción, y la mezcla se agitó a 75°C durante cuatro días. Sulfóxido de dimetilo (0.352 ml) y trietilamina (0.147 ml, 1.06 mmoles) se añadieron a la solución de reacción, y la mezcla se agitó a 75°C durante dos días. Acido 7-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (24.6 mg, 0.0881 mmoles) y trietilamina (0.147 ml, 1.06 mmoles) se añadieron a la solución de reacción, y la mezcla se agitó durante cinco días. La solución de reacción se diluyó con acetato de etilo (30 ml) y después se lavó con una solución de ácido cítrico al 10% (25 ml), agua (25 ml), y una solución saturada de hidróxido de sodio (25 ml). Adicionalmente, la capa orgánica se extrajo nuevamente de la solución de ácido cítrico al 10% de lavado y el agua de lavado con acetato de etilo (40 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). Se añadió ácido trifluoroacético (0.402 ml, 3 v/p) a una solución de 67.5 mg del residuo resultante en diclorometano (1.32 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (x 3). Se añadieron 6 moles/l de ácido clorhídrico al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con cloroformo (30 ml x 5). La capa acuosa se ajustó a pH 12 con una solución de 1 mol/l de hidróxido de sodio bajo enfriamiento con hielo. La solución básica se ajustó a pH 7.4 con 1 mol/l de ácido clorhídrico, seguido por extracción con cloroformo (100 ml x 2) y cloroformo/metanol = 10/1 (50 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el

975

filtrado se concentró bajo presión reducida. El residuo se purificó por CCDP (capa inferior de of cloroformo / metanol / agua = 7/3/1) y se concentró bajo presión reducida. El residuo resultante se disolvió en etanol caliente, y el material insoluble se removió por filtración. El filtrado se concentró bajo presión reducida, se disolvió en etanol caliente (1 ml), se trató ultrasónicamente, y se enfrió con agua con hielo. Después, la suspensión se lavó con éter dietílico (10 ml). Después de agitar a temperatura ambiente durante la noche, los cristales precipitados se recogieron por filtración, se lavaron con etanol y éter dietílico, y después se secaron bajo presión reducida a 60°C para dar 12.4 mg del compuesto del título.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.41 (1H, d, J=3.68 Hz), 8.00 (1H, d, J=8.58 Hz), 7.09 (1H, d, J=8.82 Hz), 5.16-4.96 (1H, m), 4.10-3.95 (3H, m), 3.83-3.77 (2H, m), 3.66 (1H, d, J=9.80 Hz), 3.59 (1H, t, J=10.91 Hz), 3.26 (2H, dd, J=15.32, 8.70 Hz), 2.45 (3H, s), 2.33-2.23 (1H, m), 2.02-1.87 (3H, m), 1.68-1.57 (1H, m), 1.33-1.21 (1H, m).

Análisis calculado para $C_{21}H_{24}FN_3O_4 \cdot 1.5H_2O$: C, 58.87; H, 6.35; N, 9.81,

Encontrado: C, 58.97; H, 5.98; N, 9.40.

EM (ESI); m/z: 402 $(M+H)^+$.

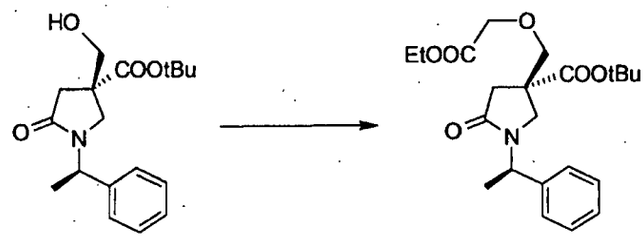
IR (ATR) ν: 2937, 2865, 1710, 1608, 1508, 1428, 1388, 1349, 1315, 1257, 794 cm^{-1}.

EJEMPLO DE REFERENCIA 167

Ester ter-butílico de ácido (3S)-3-etoxicarbonilmetoximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 274]

976.



Ester ter-butílico de ácido (3S)-3-hidroximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (2.0 g, 6.26 mmoles) y bromoacetato de etilo (2.09 g, 12.52 mmoles) se disolvieron en tetrahidrofurano (40 ml). Hidruro de sodio (0.33 g, 7.51 mmoles) se añadió a 0°C, y la mezcla se agitó a temperatura ambiente durante 18 horas. Una solución saturada de cloruro de amonio (100 ml) se añadió a la solución de reacción a 0°C, seguido por extracción con acetato de etilo (300 ml). La capa orgánica se lavó con agua (100 ml) y salmuera (100 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (40% acetato de etilo/hexano) para dar 1.74 g del compuesto del título como un aceite incoloro.

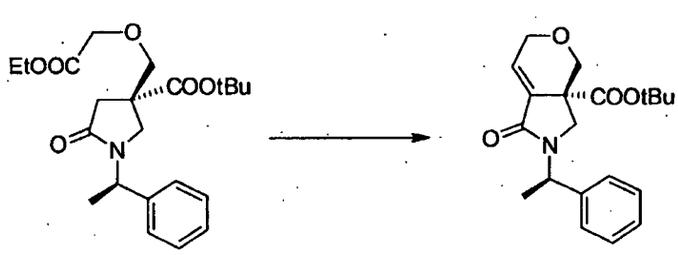
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.30 (5H, m), 5.49 (1H, q, J=6.99 Hz), 4.21 (2H, q, J=7.15 Hz), 4.08 (2H, s), 3.68 (2H, brs), 3.46 (1H, d, J=10.24 Hz), 3.31 (1H, d, J=10.24 Hz), 2.80 (1H, d, J=17.07 Hz), 2.56 (1H, d, J=17.07 Hz), 1.53 (3H, d, J=7.32 Hz), 1.35 (9H, s), 1.28 (3H, t, J=7.19 Hz).

EM (EI) m/z: 406 $(M+H)^+$.

EJEMPLO DE REFERENCIA 168

Ester ter-butílico de ácido {(1S)-3-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4,3,0] non-5-en-1-il}carboxílico

[Fórmula 275]



Ester ter-butílico de ácido (3S)-3-etoxicarbonilmetoximetil-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (9.31 g, 25.9 mmoles) se disolvió en tetrahidrofurano (200 ml). Una solución 1 M de hexametildisilazida de litio en tetrahidrofurano (64.7 ml) se añadió gota a gota en una atmósfera de nitrógeno a 0°C, y la mezcla se agitó durante 1.5 horas. Una solución saturada de cloruro de amonio (300 ml) se añadió, seguida por extracción con acetato de etilo (900 ml). La capa orgánica se lavó con agua (300 ml) y salmuera (100 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tetrahidrofurano (200 ml). Borohidruro de sodio (1.27 g, 33.67 mmoles) se añadió a 0°C, y la mezcla se agitó durante una hora. Una solución saturada de cloruro de amonio (200 ml) se añadió a la solución de reacción, seguida por extracción con acetato de etilo (600 ml). La capa orgánica se lavó con agua (200 ml) y salmuera (200 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (40% acetato de etilo/hexano). El concentrado se disolvió en diclorometano (150 ml). Se añadió trietilamina (5.69 ml, 41.02 mmoles) y cloruro de metansulfonilo (1.90 ml, 24.61 mmoles) se añadió gota a gota a -10°C. Después de agitar durante una hora, una solución saturada de cloruro de amonio (200 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (600 ml). La capa orgánica se lavó con agua (200 ml) y salmuera (200 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (150 ml). Se añadió DBU (12.24 ml, 82.03 mmoles) y la mezcla se agitó a 40°C durante 15 horas. La solución de reacción se concentró bajo presión reducida y después una solución saturada de cloruro

978

de amonio (150 ml) se añadió, seguido por extracción con acetato de etilo (400 ml). La capa orgánica se lavó con agua (150 ml) y salmuera (150 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (75% de acetato de etilo/hexano) para dar 3.28 g del compuesto del título como un sólido incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.32-7.29 (5H, m), 6.60 (1H, t, J=2.32 Hz), 5.57 (1H, q, J=7.16 Hz), 4.50-4.45 (2H, m), 4.24 (1H, dd, J=18.55, 2.44 Hz), 3.26 (1H, d, J=10.25 Hz), 3.21 (1H, d, J=10.01 Hz), 3.13 (1H, d, J=10.01 Hz), 1.51 (3H, d, J=7.08 Hz), 1.27 (9H, s).

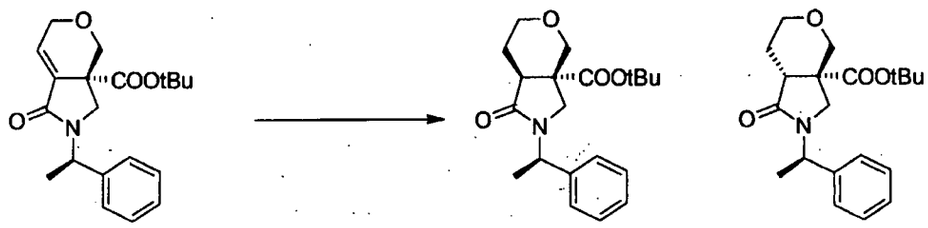
EM (EI) m/z: 344 $(M+H)^+$.

EJEMPLO DE REFERENCIA 169

Ester ter-butílico de ácido {(1S,6S)-3-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4,3, 0] nonan-1-il}carboxílico;

éster ter-butílico de ácido {(1S, 6R)-3-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4,3,0] nonan-1-il}carboxílico

[Fórmula 276]



Ester ter-butílico de ácido {(1S)-3-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo[4,3,0] non-5-en-1-il}carboxílico (231 mg, 0.67 mmoles) se disolvió en tetrahidrofurano. Se añadió 10% de paladio-carbón (50% húmedo) (100 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante cuatro horas. El

979

catalizador se removió por filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (20% de acetato de etilo/hexano → 50%) para dar 187 mg del isómero (1S,6S) del compuesto del título como un sólido incoloro y 44 mg del isómero (1S,6R) del compuesto del título como un sólido incoloro.

Isómero (1S, 6S):

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.29-7.24 (5H, m), 5.48 (1H, q, J=7.24 Hz), 4.41 (1H, d, J=10.24 Hz), 4.10 (1H, dd, J=10.98, 4.39 Hz), 3.38-3.33 (2H, m), 3.17 (1H, d, J=9.76 Hz), 3.08 (1H, d, J=10.00 Hz), 2.28-2.19 (2H, m), 1.96-1.92 (1H, m), 1.46 (3H, d, J=7.32 Hz), 1.23 (9H, s).

EM (EI) m/z: 346 $(M+H)^+$.

Isómero (1S,6R):

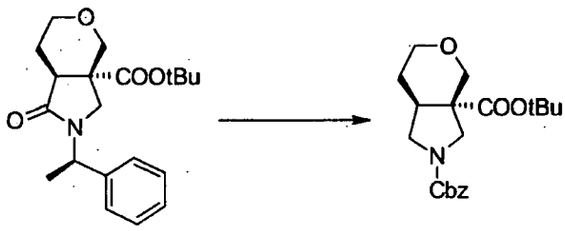
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.26 (5H, m), 5.54 (1H, q, J=7.07 Hz), 4.12 (1H, d, J=11.71 Hz), 3.82-3.77 (1H, m), 3.39 (1H, m), 3.29 (1H, d, J=11.71 Hz), 3.02 (1H, t, J=4.63 Hz), 2.91 (2H, dd, J=18.29, 10.24 Hz), 2.03-2.01 (2H, m), 1.53 (3H, d, J=7.07 Hz), 1.41 (9H, s).

EM (EI) m/z: 346 $(M+H)^+$.

EJEMPLO DE REFERENCIA 170

Ester ter-butílico de ácido [(1S,6S)-3-oxa-8-benciloxicarbonil-8-azabiciclo [4,3,0] nonan-1-il] carboxílico

[Fórmula 277]



980

Ester ter-butílico de ácido [(1S,6S)-3-oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4,3, 0] nonan-1-il] carboxílico (3.36 g, 9.73 mmoles) se disolvió en tetrahidrofurano (50 ml), y una solución 1 M de un complejo de borano-tetrahidrofurano en tetrahidrofurano (48.63 ml) se añadió gota a gota en una atmósfera de nitrógeno. Después de agitar durante tres días, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de reacción y la mezcla se agitó a 80°C durante dos horas. La solución de reacción se concentró bajo presión reducida y después una solución saturada de cloruro de amonio (100 ml) se añadió, seguido por extracción con acetato de etilo (300 ml). La capa orgánica se lavó con agua (100 ml) y salmuera (100 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo se sometió a cromatografía en columna corta de gel de sílice (35% de acetato de etilo/hexano). El crudo resultante se disolvió en 1,2-dicloroetano (18 ml). Se añadió cloruro de benciloxicarbonilo (3.40 g, 19.91 mmoles) y la mezcla se agitó a 40°C durante un día. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (35% de acetato de etilo/hexano) para dar 2.39 g del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.24 (5H, m), 5.14 (2H, s), 3.88 (1H, dd, J=20.63, 11.84 Hz), 3.77-3.54 (6H, m), 3.48 (1H, t, J=10.50 Hz), 3.41-3.33 (1H, m), 2.81-2.70 (1H, m), 1.93-1.80 (1H, m), 1.44 (9H, s).

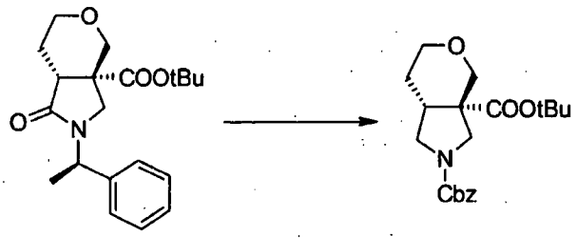
EM (EI) m/z: 384 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 171

Ester ter-butílico de ácido {(1S,6R)-8-benciloxicarbonil-3-oxa-8-azabiciclo [4, 3, 0] nonan-1-il}carboxílico

981

[Fórmula 278]



Ester ter-butílico de ácido {(1S,6R)-3-Oxa-7-oxo-8-[(1R)-1-feniletil]-8-azabiciclo [4,3,0] nonan-1-il}carboxílico (709 mg, 2.05 mmoles) se disolvió en tetrahidrofurano (20 ml), y una solución 1 M de un complejo de borano-tetrahidrofurano en tetrahidrofurano (10.26 ml) se añadió gota a gota en una atmósfera de nitrógeno. Después de agitar durante tres días, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante dos horas. La solución de reacción se concentró bajo presión reducida y después una solución saturada de cloruro de amonio (80 ml) se añadió, seguido por extracción con acetato de etilo (240 ml). La capa orgánica se lavó con agua (80 ml) y salmuera (80 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (35% de acetato de etilo/hexano). La fracción resultante se concentró bajo presión reducida, y el residuo se disolvió en 1,2-dicloroetano (4 ml). Cloruro de benciloxicarbonilo (788 mg, 4.62 mmoles) se añadió, y la mezcla se agitó a 40°C durante cuatro días. La solución de reacción se concentró bajo presión reducida, y el residuo se purificó por cromatografía en columna sobre gel de sílice (40% de acetato de etilo/hexano) para dar 435 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.33-7.28 (5H, m), 5.13 (2H, d,

982

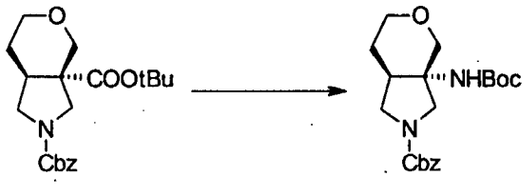
J=3.42 Hz), 4.48 (1H, dd, J=20.75, 10.50 Hz), 4.10-4.07 (1H, m), 3.77 (1H, dd, J=24.05, 11.11 Hz), 3.62-3.52 (2H, m), 3.38 (1H, td, J=11.66, 2.77 Hz), 3.22 (1H, dd, J=10.50, 6.84 Hz), 3.07 (1H, dd, J=10.99, 3.42 Hz), 2.24-2.21 (1H, m), 1.98-1.96 (1H, m), 1.63-1.60 (1H, m), 1.44 (9H, s).

EM (EI); m/z: 384 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 172

Ester bencílico de ácido [(1S,6R)-1-ter-butoxicarbonilamino-3-oxa-8-azabiciclo [4,3,0] nonan-8-il] carboxílico

[Fórmula 279]



Ester ter-butílico de ácido {(1S,6S)-8-Benciloxicarbonil-3-oxa-8-azabiciclo [4,3,0] nonan-1-il}carboxílico (2.30 g, 6.94 mmoles) se disolvió en diclorometano (20 ml). Se añadió ácido trifluoroacético (10 ml) y la mezcla se agitó durante un día. La solución de reacción se concentró bajo presión reducida, y una solución de hidróxido de sodio 1N (100 ml) se añadió, y la mezcla se lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo (200 ml x 2). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en acetonitrilo (40 ml). Se añadió 1,1-carbonilbis-1H-imidazol (1.55 g, 9.53 mmoles) en una atmósfera de nitrógeno a 0°C, y la mezcla se agitó durante una hora y después se hizo burbujear con amoniaco gaseoso a temperatura ambiente. Acetato de

983

etilo y agua se añadieron, y la mezcla se lavó con salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (acetato de etilo). El crudo resultante se disolvió en ter-butanol (50 ml). Tetraacetato de plomo (3.98 g, 8.97 mmoles) se añadió, y la mezcla se agitó en una atmósfera de nitrógeno a 80°C durante una hora. Bicarbonato de sodio (3.52 g, 41.86 mmoles) y acetato de etilo se añadieron a la solución de reacción, y la mezcla se filtró a través de Celite. Después, el filtrado se lavó con bicarbonato de sodio saturado acuoso y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (30% de acetato de etilo/hexano) para dar 1.70 g del compuesto del título como un aceite incoloro.

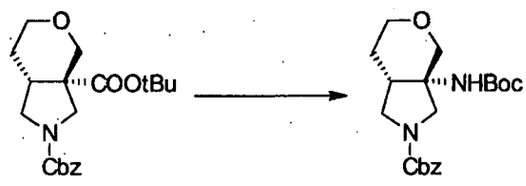
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.31 (5H, m), 5.13 (2H, s), 4.66 (1H, d, J=7.57 Hz), 3.86-3.57 (7H, m), 3.36 (1H, dq, J=23.01, 5.45 Hz), 2.63-2.55 (1H, m), 1.87-1.79 (1H, m), 1.54-1.50 (1H, m), 1.43 (9H, s).

EM (EI) m/z: 399 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 173

Ester bencílico de ácido {(1S,6S)-1-ter-butoxicarbonilamino-3-oxa-8-biciclo [4,3,0] nonan-8-il}carboxílico

[Fórmula 280]



984

Ester ter-butílico de ácido {(1S,6R)-8-benciloxicarbonil-3-oxa-8-biciclo [4,3,0] nonan-1-il}carboxílico (725 mg, 2.01 mmoles) se disolvió en diclorometano (20 ml). Se añadió ácido trifluoroacético (4 ml) y la mezcla se agitó durante 15 horas. La solución de reacción se concentró bajo presión reducida, y se añadió una solución de hidróxido de sodio 1N (50 ml) y la mezcla se lavó con cloroformo. La capa acuosa se hizo ácida con una solución de ácido clorhídrico, seguido por extracción con cloroformo (50 ml x 2). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se disolvió en tolueno (20 ml). Trietilamina (406 mg, 4.01 mmoles) y difenilfosforil azida (740 mg, 2.61 mmoles) se añadieron en una atmósfera de nitrógeno, y la mezcla se agitó a 110°C durante 1.5 horas. La solución de reacción se concentró bajo presión reducida. Después, dioxano (20 ml) y ácido clorhídrico 6N (20 ml) se añadieron, y la mezcla se agitó a 50°C durante dos horas. Después de concentración bajo presión reducida y destilación azeotrópica con etanol, una solución de hidróxido de sodio 1N (50 ml) se añadió, seguido por extracción con cloroformo (100 ml x 2). Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida. Dicarbonato de di-ter-butilo (2189 mg, 10.03 mmoles) se añadió al residuo resultante, y la mezcla se agitó a 50°C durante 1.5 horas. La solución de reacción se purificó por cromatografía en columna sobre gel de sílice (60% de acetato de etilo/hexano) para dar 623 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.52-7.26 (5H, m), 5.13 (2H, s), 4.55 (1H, dd, J=19.51, 11.22 Hz), 4.45 (1H, d, J=10.73 Hz), 4.25 (1H, t, J=12.44 Hz), 4.13-4.08 (1H, m), 3.70-3.62 (1H, m), 3.36-3.34 (1H, m), 3.16-3.09 (3H, m), 2.02-1.97 (1H, m), 1.69-1.62 (2H, m), 1.43 (9H, s).

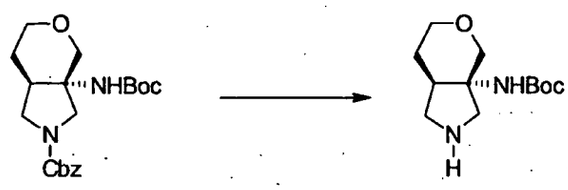
985

EM (EI) m/z: 399 $(M+Na)^+$.

EJEMPLO DE REFERENCIA 174

(1S,6R)-1-ter-Butoxicarbonilamino-3-oxa-8-azabiciclo [4,3,0] nonano

[Fórmula 281]



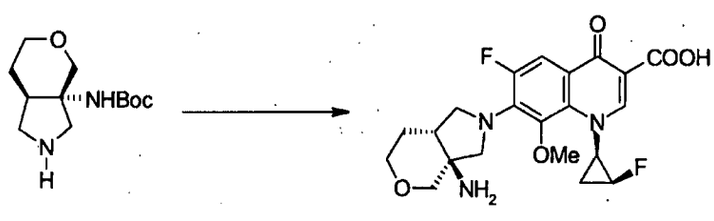
Ester bencílico de ácido [(1S,6R)-1-ter-butoxicarbonilamino-3-oxa-8-azabiciclo [4,3,0] nonan-8-il] carboxílico (401 mg, 1.07 mmoles) se disolvió en metanol (20 ml). Se añadió 10% de paladio-carbón (50% húmedo) (200 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante 2.5 horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, seguida por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida para dar 256 mg del compuesto del título como un sólido incoloro.

EM(EI) m/z: 243$(MH-H)^+$.

EJEMPLO 40

Acido 7-[(1S,6R)-1-amino-3-oxa-8-azabiciclo [4,3,0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 282]



986

(1S,6R)-8-Aza-1-ter-butoxicarbonilamino-3-oxabiciclo[4,3,0] nonano (252 mg, 1.04 mmoles) se disolvió en sulfóxido de dimetilo (8 ml). Se añadieron ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (450.6 mg, 1.25 mmoles) y trietilamina (315.7 mg, 3.12 mmoles) y la mezcla se agitó a 40°C durante 17 horas. Después, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante cinco horas. El solvente se evaporó bajo presión reducida, y después una solución de ácido cítrico al 10% se añadió al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). La fracción resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 8 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se lavó con etanol y éter dietílico y se secó bajo presión reducida para dar 302 mg del compuesto del título como cristales amarillo pálido, p.f.: 132-134°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.41 (1H, s), 7.66 (1H, d, J=14.63 Hz), 4.99 (1H, d, J=63.90 Hz), 4.04-4.03 (2H, m), 3.91-3.88 (1H, m), 3.82 (2H, t, J=11.22 Hz), 3.68-3.62 (2H, m), 3.59 (3H, s), 3.51 (1H, d, J=11.95 Hz), 3.37 (1H, d, J=10.98 Hz), 2.23-2.20 (1H, m), 1.93-1.91 (1H, m), 1.57-1.47 (3H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_5 \cdot 0.5H_2O$ $0.4CHCl_3$: C, 55.42;

H, 5.30; N, 9.06; F, 8.19.

Encontrado: C, 55.19; H, 5.19; N, 9.09; F, 8.32.

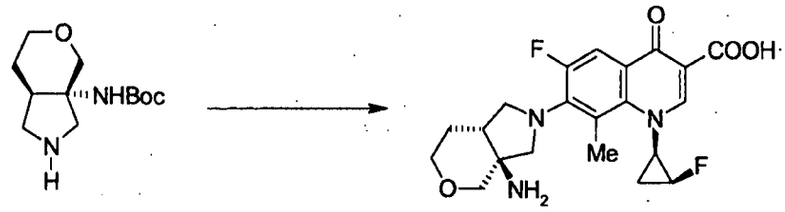
EM (EI) m/z: 436 $(M+H)^+$.

IR (ATR) ν: 2943, 2887, 2845, 1720, 1622, 1516, 1452, 1346, 1323, 1275 cm^{-1}.

EJEMPLO 41

Acido 7-[(1S, 6R)-1-amino-3-oxa-8-azabiciclo [4,3,0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 283]



(1S,6R)-1-ter-Butoxicarbonilamino-3-oxa-8-azabiciclo[4,3,0] nonano (187 mg, 0.77 mmoles) se disolvió en sulfóxido de dimetilo (4 ml). Se añadieron 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico-quelato de BF_2 (316.5 mg, 0.92 mmoles) y trietilamina (93.6 mg, 0.92 mmoles) y la mezcla se agitó durante 14 días. Después, etanol acuoso al 90% (18 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante dos horas. El solvente se evaporó bajo presión reducida, y una solución de ácido cítrico al 10% se añadió al residuo resultante, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida. Después, el residuo se purificó por CCDP (5% de metanol/cloroformo), y la fracción resultante se

disolvió en ácido clorhídrico concentrado y se lavó con cloroformo dos veces. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.9 con ácido clorhídrico, seguido por extracción con 5% de metanol/cloroformo dos veces. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. Los cristales precipitados se recogieron por filtración y se secaron bajo presión reducida para dar 51 mg del compuesto del título como cristales incoloros, p.f.: 158-160°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.44 (1H, d, J=3.17 Hz), 7.67 (1H, d, J=14.16 Hz), 5.01 (1H, d, J=64.94 Hz), 4.16 (1H, t, J=6.71 Hz), 4.07 (1H, dt, J=9.93, 4.46 Hz), 4.01 (1H, d, J=10.01 Hz), 3.95-3.92 (1H, m), 3.85 (1H, d, J=11.96 Hz), 3.62-3.54 (1H, m), 3.47 (1H, d, J=11.72 Hz), 3.17 (1H, d, J=9.77 Hz), 3.06 (1H, d, J=10.01 Hz), 2.48 (3H, s), 2.20-2.15 (1H, m), 1.89-1.82 (1H, m), 1.65-1.60 (2H, m), 1.26-1.19 (1H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 0.75H_2O \cdot 0.25EtOH$: C, 58.10; H, 5.90; N, 9.45; F, 8.55.

Encontrado: C, 58.35; H, 5.86; N, 9.19; F, 8.53.

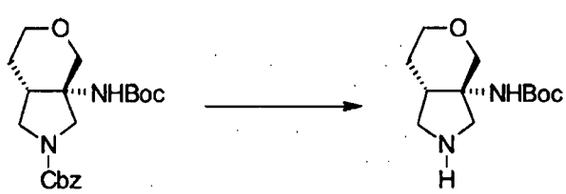
EM (EI) m/z: 420 $(M+H)^+$.

IR (ATR) ν: 3365, 2945, 2839, 1716, 1616, 1510, 1466, 1454, 1431, 1342, 1311, 1265, 1215 cm^{-1}.

EJEMPLO DE REFERENCIA 175

(1S, 6S)-1-ter-Butoxicarbonilamino-3-oxa-8-azabiciclo [4,3,0] nonano

[Fórmula 284]



989

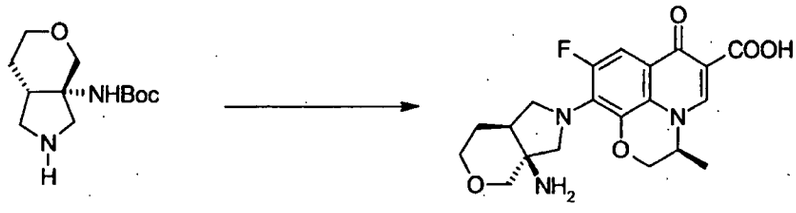
Ester bencílico de ácido {(1S,6S)-1-ter-Butoxicarbonilamino-3-oxa-8-biciclo [4,3,0] nonan-8-il}carboxílico (610 mg, 1.62 mmoles) se disolvió en metanol (20 ml). Se añadió 10% de paladio-carbón (50% húmedo) (200 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante tres horas. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1N se añadió, seguido por extracción con cloroformo. Después de secado sobre sulfato de sodio anhidro y filtración, el solvente se evaporó bajo presión reducida para dar 362 mg del compuesto del título como un sólido incoloro.

EM (EI) m/z: 243 $(M+H)^+$.

EJEMPLO 42

Acido 10-[(1S,6S)-1-amino-3-oxa-8-azabiciclo [4,3,0] nonan-8-il]-9-fluoro-2, 3-dihidro-3-metil-(S)-7-oxo-7H-pirido [1,2,3-de] [1,4]benzoxazin-6-carboxílico

[Fórmula 285]



(1S,6S)-1-ter-Butoxicarbonilamino-3-oxa-8-azabiciclo[4,3,0] nonano (147.7 mg, 0.61 mmoles) se disolvió en sulfóxido de dimetilo (2.5 ml). Se añadieron 9,10-difluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de] [1,4] benzoxazin-6-carboxílico-quelato de BF_2 (211.3 mg, 0.64 mmoles) y trietilamina (185.7 mg, 1.83 mmoles) y la mezcla se agitó a 40°C durante 18 horas. Después, etanol acuoso al 90% (33 ml) y trietilamina (3 ml) se añadieron a la

490

mezcla de reacción, la cual se agitó a 80°C durante cuatro horas. El solvente se evaporó bajo presión reducida y una solución de ácido cítrico al 10% se añadió, seguida por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). La fracción resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol-amoniaco acuoso, y la solución se calentó y se agitó. Después de vaporización del amoniaco, los cristales precipitados se recogieron por filtración y se secaron bajo presión reducida para dar 180 mg del compuesto del título como cristales incoloros, p.f.: >300°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.31 (1H, s), 7.51 (1H, d, J=14.63 Hz), 4.58 (1H, d, J=7.07 Hz), 4.45 (1H, dd, J=11.34, 1.83 Hz), 4.27 (1H, d, J=11.22 Hz), 4.08 (1H, dd, J=11.22, 3.66 Hz), 3.93 (1H, d, J=10.49 Hz), 3.78 (1H, dd, J=10.37, 3.05 Hz), 3.75-3.68 (1H, m), 3.55 (1H, d, J=10.98 Hz), 3.49-3.43 (2H, m), 3.29 (1H, d, J=10.00 Hz), 2.04-2.01 (1H, m), 1.81-1.72 (2H, m), 1.52 (3H, d, J=6.59 Hz).

Análisis calculado para $C_{20}H_{22}FN_3O_5 \cdot 1.5H_2O$: C, 55.81; H, 5.85; N, 9.76; F, 4.41.

Encontrado: C, 55.80; H, 5.89; N, 9.74; F, 4.34.

EM (EI) m/z: 404 $(M+H)^+$.

IR (ATR) ν: 3498, 3407, 3224, 3045, 2956, 2877, 1616, 1573,

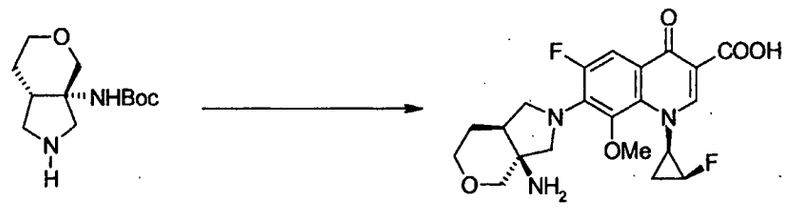
991

1523, 1473, 1379, 1352, 1306, 1261 cm^{-1}.

EJEMPLO 43

Acido 7-[(1S,65)-1-amino-8-aza-3-oxabiciclo [4,3,0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 286]



(1S,6S)-8-Aza-1-ter-butoxicarbonilamino-3-oxabiciclo[4,3,0] nonano (108.8 mg, 0.45 mmoles) se disolvió en sulfóxido de dimetilo (4 ml). Se añadieron 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-quelato de BF_2 (210.7 mg, 0.58 mmoles) y trietilamina (136.3 mg, 1.35 mmoles) y la mezcla se agitó a 40°C durante 18 horas. Después, etanol acuoso al 90% (30 ml) y trietilamina (3 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 80°C durante cinco horas. El solvente se evaporó bajo presión reducida, y una solución de ácido cítrico al 10% se añadió al residuo, seguido por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). El crudo resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.4 con ácido

992

clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se purificó por recristalización a partir de etanol y se secó bajo presión reducida para dar 121 mg del compuesto del título como cristales amarillo pálido, p.f.: 190-192°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.36 (1H, d, J=3.66 Hz), 7.65 (1H, d, J=14.40 Hz), 5.06 (1H, dd, J=64.09, 3.54 Hz), 4.09 (1H, dd, J=11.35, 4.03 Hz), 4.02-3.95 (2H, m), 3.67-3.51 (8H, m), 3.24 (1H, d, J=10.25 Hz), 2.14-2.11 (1H, m), 1.88-1.71 (2H, m), 1.54-1.48 (1H, m), 1.36-1.32 (1H, m).

Análisis calculado para $C_{21}H_{23}F_2N_3O_5 \cdot 0.25H_2O$: C, 57.33; H, 5.38; N, 9.55; F, 8.64.

Encontrado: C, 57.28; H, 5.39; N, 9.27; F, 8.48.

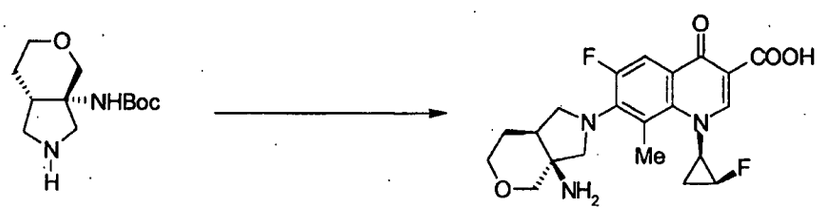
EM (EI) m/z: 436 $(M+H)^+$.

IR (ATR) ν: 3502, 3374, 3091, 2948, 2881, 2850, 1716, 1617, 1513, 1450, 1365, 1321, 1309, 1268, 1223 cm^{-1}.

EJEMPLO 44

Acido 7-[(1S, 6S)-1-amino-3-oxa-8-azabiciclo[4,3,0] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 287]



(1S,6S)-1-ter-Butoxicarbonilamino-3-oxa-8-azabiciclo[4,3,0] nonano (184.7 mg, 0.76 mmoles) se disolvió en sulfóxido de dimetilo (4 ml). Se

993

añadieron ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metil-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (289.4 mg, 0.84 mmoles) y trietilamina (115.7 mg, 1.14 mmoles) y la mezcla se agitó durante siete días. Después, etanol acuoso al 90% (22 ml) y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se agitó a 75°C durante dos horas. El solvente se evaporó bajo presión reducida y una solución de ácido cítrico al 10% se añadió, seguida por extracción con acetato de etilo. La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna corta de gel de sílice (3% de metanol/cloroformo). La fracción resultante se disolvió en ácido clorhídrico concentrado y se lavó con cloroformo. La capa acuosa se ajustó a pH 12 con hidróxido de sodio acuoso a 0°C y después se ajustó a pH 7.5 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en etanol-amoniaco acuoso, y la solución se calentó y se agitó. Después de vaporización del amoniaco, los cristales precipitados se recogieron por filtración y se secaron bajo presión reducida para dar 94.7 mg del compuesto del título como cristales incoloros. p.f.: 159-161°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.42 (1H, s), 7.67 (1H, d, J=14.15 Hz), 5.03 (1H, d, J=60.24 Hz), 4.10-4.08 (2H, m), 3.96 (1H, d, J=10.49 Hz), 3.82 (1H, d, J=9.27 Hz), 3.68 (1H, t, J=10.49 Hz), 3.61 (1H, d, J=10.49 Hz), 3.49 (1H, t, J=11.10 Hz), 3.26 (1H, t, J=8.17 Hz), 3.08 (1H, d, J=9.51 Hz), 2.45 (3H, s), 2.21-2.18 (1H, m), 1.84-1.57 (3H, m), 1.23 (1H, d, J=26.10 Hz).

Análisis calculado para $C_{21}H_{23}F_2N_3O_4 \cdot 1.25H_2O$: C, 57.07; H, 5.82; N, 9.51; F, 8.60.

994

Encontrado: C, 56.87; H, 5.99; N, 9.49; F, 8.43.

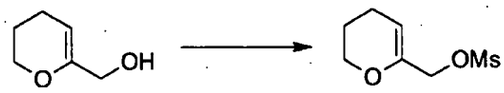
EM (EI) m/z: 420 $(M+H)^+$.

IR (ATR) ν: 3518, 3251, 3059, 2935, 2885, 1720, 1614, 1540, 1508, 1441, 1387, 1358, 1325, 1306, 1273 cm^{-1}.

EJEMPLO DE REFERENCIA 176

Metansulfonato de (5,6-dihidro-4H-piran-2-il) metilo

[Fórmula 288]



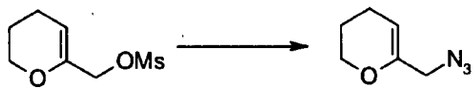
Cloruro de metansulfonilo (17.9 ml, 232 mmoles) se añadió gota a gota a una solución de (5,6-dihidro-4H-piran-2-il)metanol (25.51 g, 193 mmoles) [véase Synlett, Vol. 5, p. 533 (1997)] y trietilamina (40.4 ml, 290 mmoles) en diclorometano (600 ml) bajo enfriamiento con hielo con sal durante 15 minutos. Después de agitación a la misma temperatura durante dos horas, trietilamina (18.8 ml, 135 mmoles) y cloruro de metansulfonilo (7.5 ml, 97 mmoles) se añadieron, y la mezcla se agitó adicionalmente durante 30 minutos. Se añadió agua (300 ml) a la solución de reacción, seguido por extracción con acetato de etilo (1.5 l). La capa orgánica resultante se lavó con agua (300 ml) y salmuera (300 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró, y el solvente se evaporó bajo presión reducida. El compuesto del título crudo resultante se usó para la siguiente reacción sin purificación.

995

EJEMPLO DE REFERENCIA 177

2-Azidometil-5,6-dihidro-4H-pirano

[Fórmula 289]



Agua (35 ml) y azida de sodio (15.1 g, 232 mmoles) se añadieron a una solución del metansulfonato de (5,6-dihidro-4H-piran-2-il) metilo crudo (aproximadamente 193 mmoles) en N,N-dimetilformamida (350 ml), y la mezcla se agitó a temperatura ambiente durante 20 horas. Se añadió agua (300 ml) a la solución de reacción, seguido por extracción con acetato de etilo (1.5 L). La capa orgánica resultante se lavó con agua (3 x 200 ml) y salmuera (200 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró y el solvente se evaporó bajo presión reducida a aproximadamente 300 ml. La solución del compuesto del título crudo resultante se usó para la siguiente reacción sin purificación.

EJEMPLO DE REFERENCIA 178

2-Aminometil-5,6-dihidro-4H-pirano

[Fórmula 290]



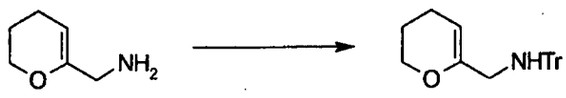
Tetrahidrofurano (500 ml), agua (50 ml), y trifenilfosfina (35.4 g, 135 mmoles) se añadieron secuencialmente al 2-azidometil-5,6-dihidro-4H-pirano crudo (aproximadamente 193 mmoles), y la mezcla se calentó con

agitación en un baño de aceite a 60°C durante dos horas. Acetato de etilo (1 l) se añadió a la solución de reacción, y la capa acuosa se removió. Después, la capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y el solvente se evaporó bajo presión reducida. El compuesto del título crudo resultante se usó para la siguiente reacción sin purificación adicional.

EJEMPLO DE REFERENCIA 179

2-(Tritilamino)metil-5,6-dihidro-4H-pirano

[Fórmula 291]



Trietilamina (37.7 ml, 270 mmoles) y cloruro de tritilo (41.4 g, 149 mmoles) se añadieron secuencialmente a una solución de 2-aminometil-5,6-dihidro-4H-pirano crudo (aproximadamente 193 mmoles) en diclorometano (500 ml), y la mezcla se agitó a temperatura ambiente durante 11 horas. La solución de reacción se diluyó con diclorometano (500 ml), se lavó con agua (2 x 500 ml) y salmuera (500 ml), y después se secó sobre sulfato de sodio anhidro y se filtró. El solvente se evaporó bajo presión reducida. Después, el residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etil:hexano = 5:95 → 10:90) para dar 22.2 g (cuatro pasos, 32%) del compuesto del título como un sólido gomoso transparente incoloro.

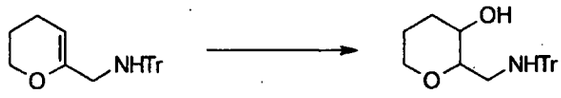
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.16-7.49 (15H, m), 4.81 (1H, brs), 3.97 (2H, t, J=5.1 Hz), 2.66 (2H, brs), 2.02-2.04 (2H, m), 1.76-1.82 (2H, m).

997

EJEMPLO DE REFERENCIA 180

2-(Tritilamino)metil-3,4,5,6-tetrahidro-2H-piran-3-ol

[Fórmula 292]



Una solución de un complejo de borano-tetrahidrofurano en tetrahidrofurano (1 M, 187 ml, 187 mmoles) se añadió gota a gota a una solución de 2-(tritilamino)metil-5,6-dihidro-4H-pirano (22.2 g, 62.4 mmoles) en tetrahidrofurano (180 ml) a temperatura ambiente durante 20 minutos. Después de agitar a temperatura ambiente durante 2.5 horas, la solución de reacción se enfrió con hielo, y una solución de hidróxido de sodio 3N (208 ml, 624 mmoles) se añadió gota a gota durante 10 minutos. Subsecuentemente una solución de peróxido de hidógeno al 31% (69 ml, 629 mmoles) se añadió gota a gota a la misma temperatura durante 10 minutos, y después la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se extrajo con éter dietílico (2 x 300 ml). Las capas orgánicas combinadas se lavaron con agua (300 ml) y salmuera (300 ml), y después se secaron sobre sulfato de sodio anhidro y se filtraron. El solvente se evaporó bajo presión reducida, y después el residuo se suspendió en un solvente mixto de diclorometano/hexano (1:1, 80 ml). El material insoluble se removió por filtración, y después el filtrado se evaporó bajo presión reducida para dar 18.54 g (80%) del compuesto del título como un sólido gomoso amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.41-7.46 (6H, m), 7.26-7.33 (6H, m), 7.18-7.23 (3H, m), 3.81-3.84 (1H, m), 3.73-3.76 (1H, m), 3.60-3.66 (1H, m), 3.25-3.32 (1H, m), 3.05-3.10 (1H, m), 2.64 (1H, dd, J=11.6, 7.7 Hz), 2.35 (1H, dd,

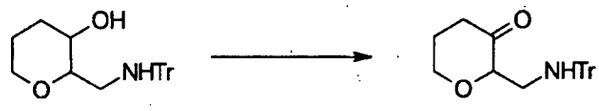
498

J=11.7, 4.9 Hz), 2.13-2.21 (1H, m), 1.83-1.86 (1H, m), 1.62-1.68 (1H, m), 1.38-1.48 (1H, m).

EJEMPLO DE REFERENCIA 181

2-(Tritilamino) metil-5,6-dihidro-2H-piran-3 (4H)-ona

[Fórmula 293]



Una solución de un complejo de trióxido de azufre-piridina (23.7 g, 149 mmoles) en sulfóxido de dimetilo (150 ml) se añadió a una solución de 2-(tritilamino) metil-3,4,5,6-tetrahidro-2H-piran-3-ol (18.54 g, 49.6 mmoles) y trietilamina (45 ml, 323 mmoles) en sulfóxido de dimetilo (150 ml) en una atmósfera de nitrógeno a temperatura ambiente. La mezcla se agitó a la misma temperatura durante 10 horas. La solución de reacción se vació en agua con hielo (1 l), seguido por extracción con acetato de etilo (2 x 1 l). Después, las capas orgánicas se combinaron y se lavaron con agua (2 x 1 l) y salmuera (1 l). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : hexano = 5:95 → 10:90 → 20:80) para dar 9.56 g (52%) del compuesto del título como un sólido gomoso transparente incoloro.

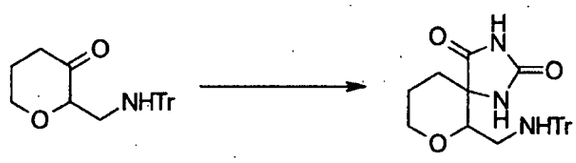
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.44-7.47 (6H, m), 7.15-7.28 (9H, m), 3.93-4.00 (2H, m), 3.65-3.72 (1H, m), 2.41-2.61 (4H, m), 1.99-2.20 (2H, m).

999

EJEMPLO DE REFERENCIA 182

6-(Tritilamino)metil-7-oxa-1,3-diazaespiro [4.5] decano-2,4-diona

[Fórmula 294]



Una mezcla de 2-(tritilamino)metil-5,6-dihidro-2H-piran-3 (4H)-ona (9.56 g, 25.7 mmoles), cianuro de sodio (2.52 g, 51.4 mmoles), cloruro de amonio (2.75 g, 51.4 mmoles), carbonato de amonio (10.18 g, 128.7 mmoles), amoniaco acuoso concentrado (50 ml), y etanol (50 ml) se agitó en una atmósfera de nitrógeno en un baño de aceite a 60°C durante 4.5 horas. Se añadió carbonato de amonio (10.18 g, 128.7 mmoles) y la mezcla se agitó a la misma temperatura durante 19.5 horas adicionales. La solución de reacción resultante se concentró bajo presión reducida, y el residuo se extrajo con acetato de etilo (300 ml, 100 ml). Después, las capas orgánicas se combinaron y se lavaron con agua (2 x 100 ml) y salmuera (100 ml). La capa orgánica resultante se secó sobre sulfato de magnesio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida para dar 11.35 g (cuantitativo) del compuesto del título como un compuesto amorfo incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.65 (1H, s), 7.38-7.49 (6H, m), 7.15-7.30 (9H, m), 5.79 (1H, s), 3.97 (1H, dm, J=13.2 Hz), 3.68 (1H, dd, J=7.1, 5.1 Hz), 3.51 (1H, dt, J=11.2, 4.4 Hz), 2.34 (1H, dd, J=12.1, 5.0 Hz), 2.18-2.23 (1H, m), 2.05-2.14 (1H, m), 1.81 (1H, brd, J=13.4 Hz), 1.55-1.70 (2H, m).

1000

EJEMPLO DE REFERENCIA 183

Acido (2R*,3R*)-3-amino-2-(ter-butoxicarbonilamino) metil-3,4,5,6-tetrahidro-2H-piran-3-carboxílico

[Fórmula 295]



6-(Tritilamino)metil-7-oxa-1,3-diazaespiro [4.5] decano-2,4-diona (10.69 g, 24.2 mmoles) se disolvió en ácido trifluoroacético (50 ml) a temperatura ambiente, y la mezcla se agitó durante 15 minutos. Se añadió agua (50 ml) a la solución de reacción, y el solvente se evaporó bajo presión reducida. Después, se añadió agua (200 ml) al residuo, y la mezcla se lavó con éter dietílico (2 x 100 ml).

Hidróxido de sodio (40 g, 1.0 mol) se añadió a la solución resultante (aproximadamente 250 ml), y la mezcla se calentó a reflujo en un baño de aceite a 130°C durante 16 horas. La solución de reacción se enfrió con hielo y después se ajustó a pH 7.0 añadiendo gradualmente ácido clorhídrico concentrado, y el solvente se evaporó bajo presión reducida.

El residuo resultante se suspendió en una solución de hidróxido de sodio 1N (75 ml) y 1,4-dioxano (150 ml). Dicarbonato de di-ter-butilo (52.8 g, 242 mmoles) se añadió a temperatura ambiente, y la mezcla se agitó a la misma temperatura durante cinco días. El solvente se concentró bajo presión reducida. Después, el residuo se suspendió en una solución de hidróxido de sodio 1N (300 ml), y la mezcla se lavó con éter diisopropílico (3 x 300 ml). Se añadió gradualmente ácido clorhídrico concentrado a la capa acuosa resultante bajo enfriamiento con hielo para ajustar la capa acuosa a pH 7.0. El solvente se

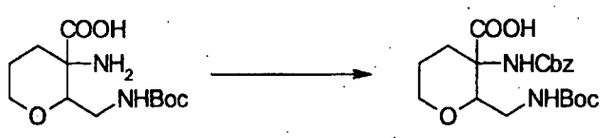
evaporó bajo presión reducida. El residuo se suspendió en metanol (100 ml), y después la mayor parte del cloruro de sodio se removió por filtración (dos veces). Posteriormente, el residuo se purificó por un resina de intercambio de iones HP-20 (se eluyó con metanol) para dar 1.21 g (tres pasos, 18%) del compuesto del título como un sólido café pálido.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 3.99-4.03 (1H, m), 3.69-3.73 (1H, m), 3.53 (1H, t, J=12.0 Hz), 3.00-3.12 (2H, m), 2.00-2.06 (1H, m), 1.70-1.87 (2H, m), 1.52-1.56 (1H, m), 1.43 (9H, s).

EJEMPLO DE REFERENCIA 184

Acido (2R*,3R*)-3-(Benciloxicarbonilamino)-2-(ter-butoxicarbonilamino) metil-3,4,5,6-tetrahidro-2H-piran-3-carboxílico

[Fórmula 296]



N-(Benciloxicarboniloxi) succinimida (1.49 g, 5.98 mmoles) se añadió a una solución de ácido (2R*,3R*)-3-amino-2-(ter-butoxicarbonilamino)metil-3,4,5,6-tetrahidro-2H-piran-3-carboxílico (1.09 g, 3.99 mmoles) y trietilamina (1.11 ml, 7.96 mmoles) en tetrahidrofurano (10 ml)/agua (10 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 horas. La solución de reacción se diluyó con acetato de etilo (150 ml) y se lavó con ácido clorhídrico 1N (50 ml). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (metanol : cloroformo = 2:98 → 5:95) y después se disolvió en una

solución de hidróxido de sodio 1N (50 ml) y se lavó con éter dietílico (2 x 20 ml) para remover el alcohol bencílico resultante. La capa acuosa resultante se ajustó a pH 1 a 2 con ácido clorhídrico concentrado, seguido por extracción con diclorometano (2 x 80 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, y se filtraron. Después, el solvente se evaporó bajo presión reducida para obtener 1.08 g (66%) del compuesto del título como un sólido blanco.

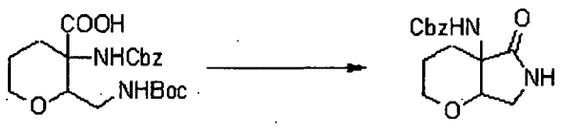
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.28 (5H, m), 5.53 (1H, brs), 5.20-5.07 (2H, m), 4.94 (1H, brs), 3.99 (1H, dd, J=11.1, 4.5 Hz), 3.65 (1H, m), 3.55-3.30 (2H, m), 3.17 (1H, m), 2.59 (1H, m), 2.06 (1H, m), 1.73 (1H, m), 1.57-1.51 (1H, m), 1.43 (9H, m).

EM (ESI); m/z: 309 $(M\text{-}Boc+2H)^+$.

EJEMPLO DE REFERENCIA 185

(1R*,6R*)-6-(Benciloxicarbonilamino)-2-oxa-7-oxo-8-azabiciclo [4.3.0] nonano

[Fórmula 297]



(±)-trans

e disolvió ácido (2R*,3R*)-3-(benciloxicarbonilamino)-2-(ter-butoxicarbonilamino)metil-3,4,5,6-tetrahidro-2H-piran-3-carboxílico (1.08 g, 2.64 mmoles) en una solución de cloruro de hidrógeno 4N en 1,4-dioxano a temperatura ambiente. La mezcla se agitó a la misma temperatura durante 20 minutos, y después el solvente se evaporó bajo presión reducida. El residuo

1003

resultante se destiló azeotrópicamente con dioxano (dos veces) para dar 921 mg (cuantitativo) de un residuo. Se disolvieron 691 mg (2.00 mmoles) del residuo resultante y N,N-diisopropiletilamina (1.75 ml, 10.0 mmoles) en diclorometano (25 ml). Cloruro de bis(2-oxo-3-oxazolidinil)fosfinil (1.02 g, 4.01 mmoles) se añadió a temperatura ambiente, y la mezcla se agitó a la misma temperatura durante 18 horas. La solución de reacción se diluyó con cloroformo (50 ml) y secuencialmente se lavó con ácido clorhídrico 1N (30 ml), agua (30 ml), una solución saturada de bicarbonato de sodio (30 ml), y salmuera (30 ml). La capa orgánica resultante se secó sobre sulfato de sodio anhidro y se filtró. Después, el solvente se evaporó bajo presión reducida a temperatura ambiente. El residuo se purificó por cromatografía en columna sobre gel de sílice (metanol : cloroformo = 2:98 → 5:95) para dar 834 mg (cuantitativo) del compuesto del título como un sólido gomoso café pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.23 (5H, m), 5.60 (1H, brs), 5.42 (1H, brs), 5.12 (2H, s), 4.06 (1H, dd, J=11.7, 5.4 Hz), 3.67-3.55 (2H, m), 3.43-3.38 (1H, m), 3.33 (1H, t, J=4.2 Hz), 2.76-2.68 (1H, m), 1.94-1.82 (1H, m), 1.65-1.55 (2H, m).

EM (ESI) ; m/z: 291 $(M+H)^+$.

EJEMPLO DE REFERENCIA 186

(1R*,6R*)-8-Bencil-6-(benciloxicarbonilamino)-2-oxa-7-oxo-8-azabiciclo [4.3.0] nonano

[Fórmula 298]



(±)-trans (±)-trans

1004

Hidruro de sodio (55% de dispersión en aceite mineral, 111 mg, 2.54 mmoles) se añadió a una solución de (1R*,6R*)-6-(benciloxicarbonilamino)-2-oxa-7-oxo-8-azabiciclo [4.3.0]nonano (818 mg, aproximadamente 1.96 mmoles) en N,N-dimetilformamida bajo enfriamiento con hielo, y la mezcla se agitó a la misma temperatura durante 20 minutos. Después, bromuro de bencilo (0.304 ml, 2.56 mmoles) se añadió, y la mezcla se agitó a temperatura ambiente durante 20 minutos. La solución de reacción se vació en una solución de ácido cítrico al 10% (30 ml), seguido por extracción con acetato de etilo (100 ml). La capa orgánica resultante se lavó con agua (2 x 30 ml) y salmuera (30 ml). Esta se secó sobre sulfato de sodio anhidro y se filtró, y después el solvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (acetato de etilo : cloroformo = 50:50 → metanol : cloroformo = 1:99 → 2:98) para dar 224 mg (0.59 mmoles, tres pasos, 30%) del compuesto del título como un sólido gomoso transparente incoloro.

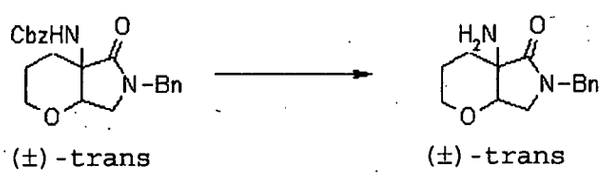
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.16 (5H, m), 5.38 (1H, brs), 5.20-5.09 (2H, m), 4.46 (2H, s), 4.02 (1H, dd, J=11.5, 5.7 Hz), 3.57-3.50 (2H, m), 3.23 (1H, t, J=9.2 Hz), 3.13 (1H, dd, J=9.2, 6.7 Hz), 2.75 (1H, m), 1.94-1.84 (1H, m), 1.68-1.61 (1H, m), 1.56-1.53 (1H, m),

EM (ESI); m/z: 381 $(M+H)^+$.

EJEMPLO DE REFERENCIA 187

(1R*,6R*)-6-Amino-8-bencil-2-oxa-7-oxo-8-azabiciclo [4.3.0] nonano

[Fórmula 299]



(±)-trans (±)-trans

1065

Un catalizador de 10% de paladio-carbón (50% húmedo, 80 mg) se añadió a una solución de (1R*,6R*)-8-bencil-6-(benciloxicarbonilamino)-2-oxa-7-oxo-8-azabiciclo [4.3.0] nonano (220 mg, 0.58 mmoles) en metanol (10 ml), y la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante 1.5 horas. La solución de reacción se filtró, y el filtrado se concentró bajo presión reducida para dar 143 mg (cuantitativo) del compuesto del título como un sólido gomoso transparente incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.24 (5H, m), 4.58 (1H, d, J=15.1 Hz), 4.38 (1H, d, J=14.9 Hz), 4.09 (1H, dd, J=11.6, 5.5 Hz), 3.58-3.40 (3H, m), 3.17 (1H, dd, J=8.1, 6.1 Hz), 2.53 (2H, brs), 2.15-2.04 (2H, m), 1.79-1.72 (1H, m), 1.60-1.55 (1H, m).

EM (ESI); m/z: 247 $(M+H)^+$.

EJEMPLO DE REFERENCIA 188

(1R*,6S*)-8-Bencil-6-(ter-butoxicarbonilamino)-2-oxa-8-azabiciclo [4.3.0] nonano

[Fórmula 300]



Hidruro de litio-aluminio (65 mg, 1.71 mmoles) se añadió a una solución de (1R*,6R*)-6-amino-8-bencil-2-oxa-7-oxo-8-azabiciclo [4.3.0] nonano (140 mg, 0.57 mmoles) en tetrahidrofurano (6 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 30 minutos. La solución de

1006

reacción se enfrió con hielo. Se añadieron secuencialmente agua (0.06 ml), una solución de hidróxido de sodio al 15% (0.06 ml), y agua (0.18 ml) cuidadosamente, y la mezcla se agitó a temperatura ambiente durante la noche. Posteriormente, se añadió sulfato de magnesio anhidro y la mezcla se agitó durante 10 minutos. La mezcla resultante se filtró a través de Celite, y después el filtrado se concentró bajo presión reducida.

El residuo resultante se disolvió en diclorometano (3 ml). Se añadió dicarbonato de di-ter-butilo (252 mg, 1.15 mmoles) y la mezcla se agitó a temperatura ambiente durante cuatro horas. El solvente se evaporó bajo presión reducida, y después el residuo resultante se purificó por CCDP (metanol : cloroformo = 2:98) para dar 50 mg (0.152 mmoles, dos pasos, 26%) del compuesto del título como un sólido gomoso transparente incoloro.

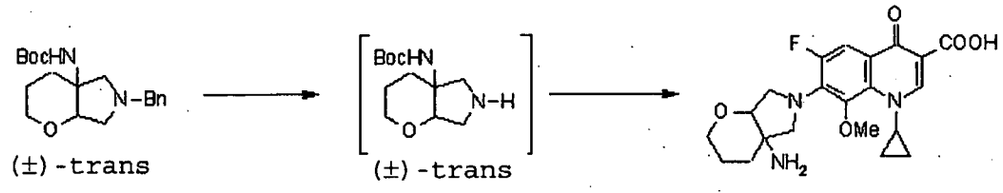
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.30-7.20 (5H, m), 4.93 (1H, brs), 4.02 (1H, dd, J=11.6, 5.2 Hz), 3.81 (2H, s), 3.61-3.48 (3H, m), 3.07 (1H, t, J=8.0 Hz), 2.71-2.67 (2H, m), 2.52 (1H, m), 1.90-1.55 (3H, m), 1.47 (9H, s).

EM (ESI); m/z: 333 $(M+H)^+$.

EJEMPLO 45

Acido 7-[(1R*,6S*)-6-amino-2-oxa-8-azabiciclo [4.3.0] nonan-3-il]-1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 301]



Un catalizador de 10% de paladio-carbón (50% húmedo, 50 mg) se

1067

añadió a una solución de (1R*,6S*)-8-bencil-6-(ter-butoxicarbonilamino)-2-oxa-8-azabiciclo [4.3.0] nonano (50 mg, 0.152 mmoles) en metanol (10 ml), y la mezcla se agitó en una atmósfera de hidrógeno a temperatura ambiente durante 1.5 horas. El catalizador se removió por filtración, y después el solvente se evaporó bajo presión reducida para dar 45 mg de (1R*,6S*)-6-(ter-butoxicarbonilamino)-2-oxa-8-azabiciclo [4.3.0] nonano.

Una mezcla del (1R*,6S*)-6-(ter-butoxicarbonilamino)-2-oxa-8-azabiciclo [4.3.0] nonano resultante (45 mg), ácido 1-ciclopropil-6,7-difluoro-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (572 mg, 1.67 mmoles), trietilamina (0.128 ml, 0.92 mmoles) y sulfóxido de dimetilo (0.5 ml) se agitó en un baño de aceite a 40°C durante 19 horas. Enseguida, etanol (16 ml), agua (4 ml), y trietilamina (2 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo en un baño de aceite a 110°C durante 2.5 horas. El solvente se evaporó bajo presión reducida, y después una solución de ácido cítrico al 10% (20 ml) se añadió al residuo resultante, seguido por extracción con acetato de etilo (60 ml). La capa orgánica se lavó con agua (20 ml x 2) y salmuera (20 ml), se secó sobre sulfato de sodio anhidro, y se filtró. Después, el solvente se evaporó bajo presión reducida. El residuo resultante se disolvió en ácido clorhídrico concentrado (10 ml) a temperatura ambiente. La solución ácida resultante se transfirió a un embudo de separación y después se lavó con cloroformo (5 x 30 ml, 3 x 50 ml). La capa acuosa se ajustó a pH 12.0 con una solución de hidróxido de sodio 10 moles/l bajo enfriamiento con hielo y después se ajustó a pH 7.4 con ácido clorhídrico. Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se suspendió en metanol y se filtró, y el filtrado se evaporó bajo presión reducida. Después, el residuo se suspendió nuevamente en metanol y se filtró, y el filtrado se evaporó bajo presión reducida.

1068

El residuo resultante se purificó por CCDP (solvente de capa inferior de cloroformo:metanol:agua = 7:3:1) y se cristalizó adicionalmente usando éter dietílico y se purificó para dar 10 mg (16%) del compuesto del título como un polvo amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 8.78 (1H, s), 7.79 (1H, d, J=12.9 Hz), 4.20-3.60 (5H, m), 3.58 (3H, s), 3.50-3.40 (3H, m), 2.02 (2H, m), 1.80-1.60 (2H, m), 1.35-1.05 (3H, m), 0.81 (1H, m).

Análisis. calculado para $C_{21}H_{24}FN_3O_5 \cdot 0.25H_2O \cdot 0.25Et_2O$: C, 59.99; H, 6.18; N, 9.54.

Encontrado: C, 59.94; H, 5.94; N, 9.12.

EM (EI) m/z: 417 (M^+).

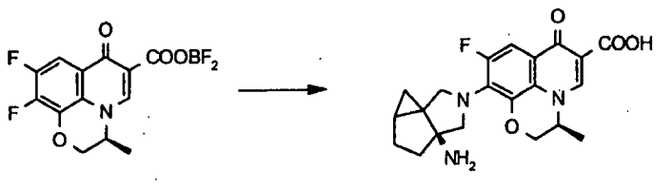
HRMS (FAB) Calculado para $C_{21}H_{24}FN_3O_5$: 417.1700.

Encontrado: 417.1695.

EJEMPLO 46

Acido (3S)-10-[6-Amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de] [1,4] benzoxazin-6-carboxílico

[Fórmula 302]



Trietilamina (0.266 ml, 1.91 mmoles) y ácido (3S)-9,10-difluoro-2,3-dihidro-3-metil-7-oxo-7H-pirido[1,2,3-de] [1,4]benzoxazin-6-carboxílico-quelato de BF_2 (209 mg, 0.635 mmoles) se añadieron a una solución de 6-ter-butoxicarbonilamino-8-azatriciclo[4.3.0.0^{1,3}] nonano (160 mg, 0.666 mmoles) en

sulfóxido de dimetilo (1.27 ml), y la mezcla se agitó a 35°C durante 16 horas. Una solución mixta de etanol:agua = 4:1 (10 ml) y trietilamina (1 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante 2.5 horas. La solución de reacción se concentró bajo presión reducida, y después una solución de ácido cítrico al 10% (40 ml) se añadió al residuo, seguido por extracción con acetato de etilo (50 ml). La parte de interfaz se extrajo con cloroformo. La capa orgánica se lavó con agua (40 ml) y salmuera (40 ml), respectivamente, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99.5:0.5 → 99:1 → 98:2 → 96:4 → 92:8). El residuo resultante (224 mg) se disolvió en ácido clorhídrico concentrado (1.5 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (25 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml x 3, 60 ml x 1). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo (190 mg) se disolvió en etanol caliente (aproximadamente 100 ml), y el material insoluble se removió por filtración a través de un papel filtro acanalado. El solvente se evaporó gradualmente calentando el filtrado con agitación. La solución se concentró a aproximadamente 10 a 20 ml y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración y se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 60°C durante la noche para dar 120 mg del compuesto del título como cristales amarillo pálido.

^{1}H-RMN (NaOD0.1N) δ: 8.32 (1H, s), 7.53 (1H, d, J=14.46 Hz), 4.61-4.59 (1H, m), 4.48 (1H, dd, J=11.52, 1.96 Hz), 4.32-4.30 (2H, m), 3.85 (1H, dd, J=10.54, 2.70 Hz), 3.49 (1H, d, J=9.80 Hz), 3.29 (1H, d, J=10.30 Hz), 1.95-1.91 (2H, m), 1.75 (1H, dd, J=12.50, 8.58 Hz), 1.52 (3H, d, J=6.86 Hz), 1.31-1.17 (3H, m), 0.82-0.76 (2H, m).

Análisis. calculado para $C_{21}H_{22}FN_3O_4$: C, 63.15; H, 5.55; F, 4.76; N, 10.52.

Encontrado: C, 62.94; H, 5.53; F, 4.62; N, 10.40.

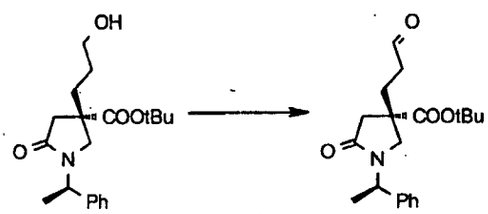
EM (ESI) m/z: 400 $(M+H)^+$.

IR (ATR): 3370, 2933, 2877, 1708, 1618, 1523, 1463, 1444, 1396, 1353, 1311, 1274, 1228, 1145, 1085, 1045, 985, 970, 956, 860, 831, 800 cm^{-1}.

EJEMPLO DE REFERENCIA 189

Ester ter-butílico de ácido (3S)-3-(3-oxo-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 303]



Diclorometano (35 ml) se enfrió con hielo seco-metanol en una atmósfera de nitrógeno. Cloruro de oxalilo (3.45 ml, 39.5 mmoles) y sulfóxido de dimetilo (4.68 ml, 66.0 mmoles) se añadieron, y la mezcla se agitó bajo enfriamiento durante 15 minutos. Una solución de éster ter-butílico de ácido (3S)-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (4.58 g, 13.2 mmoles) en diclorometano (31 ml) se añadió, y la mezcla se agitó bajo

enfriamiento durante una hora. Se añadió trietilamina (11.1 ml, 79.5 mmoles) bajo enfriamiento, y la mezcla se agitó bajo enfriamiento durante una hora y después a temperatura ambiente durante una hora. Una solución saturada de cloruro de amonio (100 ml) se añadió a la solución de reacción, seguido por extracción con cloroformo (100 ml x 1, 80 ml x 1). La capa orgánica se lavó con salmuera (120 ml) y después se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 66:34 → 60:40 → 50:50 → 40:60 → 34:66 → 25:75) para dar 4.59 g del compuesto del título como cristales blancos.

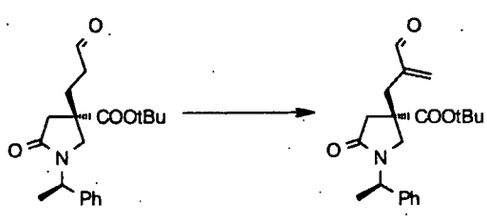
^{1}H-RMN ($CDCl_3$) δ: 9.76 (1H, s), 7.35-7.24 (5H, m), 5.49 (1H, q, J=7.19 Hz), 3.34 (1H, d, J=10.05 Hz), 3.13 (1H, d, J=10.05 Hz), 2.94 (1H, d, J=16.91 Hz), 2.44 (2H, dt, J=11.52, 4.72 Hz), 2.29 (1H, d, J=16.91 Hz), 2.12-2.05 (1H, m), 1.99-1.91 (1H, m), 1.52 (3H, d, J=7.11 Hz), 1.32 (9H, s).

EM (ESI) m/z: 346 $(M+H)^+$.

EJEMPLO DE REFERENCIA 190

Ester ter-butílico de ácido (3S)-3-(3-oxo-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 304]



1,8-Diazabiciclo[5.4.0]-7-undeceno (2.17 ml, 14.5 mmoles) y sal de Eschenmoser (3.66 g, 19.8mmol) se añadieron a una solución de éster ter-

butílico de ácido (3S)-3-(3-oxo-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico en diclorometano (88.0 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 16 horas. Posteriormente, sal de Eschenmoser (1.22 g, 6.59 mmoles) se añadió, y la mezcla se agitó a temperatura ambiente durante tres horas. Una solución saturada de cloruro de amonio (150 ml) se añadió a la solución de reacción, seguido por extracción con cloroformo (100 ml x 1, 150 ml x 1). La capa orgánica se lavó con salmuera (200 ml) y después se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 66:34 → 60:40 → 50:50 → 34:66) para dar 3.14 g del compuesto del título como cristales blancos.

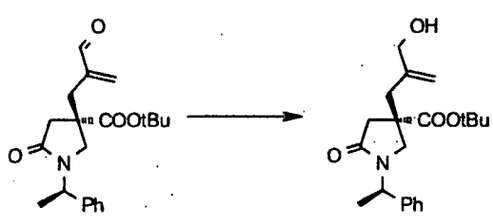
^{1}H-RMN ($CDCl_3$) δ: 9.51 (1H, s), 7.34-7.24 (5H, m), 6.31 (1H, s), 6.12 (1H, s), 5.47 (1H, q, J=7.08 Hz), 3.31 (1H, d, J=10.50 Hz), 3.22 (1H, d, J=10.25 Hz), 2.89 (1H, d, J=17.09 Hz), 2.75-2.64 (2H, m), 2.41 (1H, d, J=17.09 Hz), 1.51 (3H, d, J=7.08 Hz), 1.30 (9H, s).

EM (ESI) m/z: 358 $(M+H)^+$.

EJEMPLO DE REFERENCIA 191

Ester ter-butílico de ácido (3S)-3-(3-hidroxi-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 305]



4013

Etanol (43.9 ml) se añadió a Borohidruro de sodio (644 mg, 17.0 mmoles) en una atmósfera de nitrógeno, y la mezcla se enfrió con hielo-acetona. Cloruro de cerio heptahidratado (6.55 g, 17.6 mmoles) y éster ter-butílico de ácido (3S)-3-(3-oxo-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico (3.14 g, 6.55 mmoles) se añadieron bajo enfriamiento. La mezcla se agitó bajo enfriamiento durante una hora, y después cloruro de cerio heptahidratado (1.64 g, 4.40 mmoles) y Borohidruro de sodio (166 mg, 4.39 mmoles) se añadieron. La mezcla se agitó bajo enfriamiento durante 30 minutos y después se enfrió con hielo. Una solución saturada de cloruro de amonio (150 ml) se añadió a la solución de reacción. La mezcla se concentró bajo presión reducida y se removió etanol. La mezcla se extrajo con acetato de etilo (150 ml x 1, 100 ml x 1). La capa orgánica se lavó con salmuera (200 ml) y después se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 90:10 → 66:34 → 50:50 → 34:66 → 25:75 → 17:83 → 5:95) para dar 2.83 g del compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 7.35-7.23 (5H, m), 5.49 (1H, q, J=7.11 Hz), 5.15 (1H, d, J=1.23 Hz), 4.87 (1H, d, J=1.23 Hz), 3.98 (2H, d, J=6.37 Hz), 3.33 (1H, d, J=10.30 Hz), 3.22 (1H, d, J=10.30 Hz), 2.94 (1H, d, J=17.16 Hz), 2.62 (1H, d, J=14.95 Hz), 2.46 (1H, d, J=15.44 Hz), 2.44 (1H, d, J=17.16 Hz), 1.72 (1H, t, J=6.25 Hz), 1.52 (3H, d, J=7.11 Hz), 1.32 (9H, s).

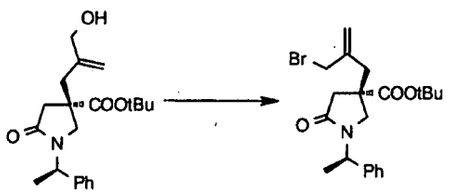
EM (ESI) m/z: 360 $(M+H)^+$.

1014

EJEMPLO DE REFERENCIA 192

Ester ter-butílico de ácido (3S)-3-(3-bromo-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 306]



Tetrabromuro de carbono (3.24 g, 9.77 mmoles) y trifenilfosfina (2.57 g, 9.80 mmoles) se añadieron a una solución de éster ter-butílico de ácido (3S)-3-(3-hidroxi-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico en diclorometano (113 ml) bajo enfriamiento con agua con hielo en una atmósfera de nitrógeno. La mezcla se agitó bajo enfriamiento con agua con hielo durante 15 minutos y después se concentró bajo presión reducida para remover el solvente. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 95:5 → 90:10 → 80:20 → 75:25 → 66:34) para dar 3.22 g del compuesto del título como cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 7.34-7.22 (5H, m), 5.48 (1H, q] J=7.19 Hz), 5.26 (1H, s), 4.89 (1H, s), 3.88 (2H, s), 3.36 (1H, d, J=10.05 Hz), 3.21 (1H, d, J=10.30 Hz), 2.99 (1H, d, J=16.91 Hz), 2.72 (1H, d, J=15.44 Hz), 2.57 (1H, d, J=15.44 Hz), 2.44 (1H, d, J=16.91 Hz), 1.51 (3H, d, J=7.35 Hz), 1.30 (9H, s).

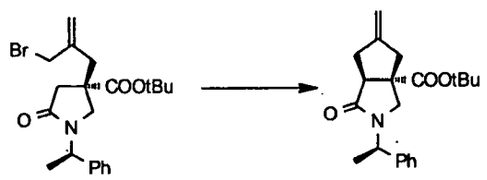
EM (ESI) m/z: 422 (M^+).

1015

EJEMPLO DE REFERENCIA 193

Ester ter-butílico de ácido [(1S,5S)-7-metilen-4-oxo-3-[(1R)-1-fenil etil]-3-aza-biciclo [3.3.0] octan-1-il] carboxílico

[Fórmula 307]



Una solución 1 M de hexametildisilazida de litio en THF (9.15 ml, 9.15 mmoles) se añadió a una solución de éster ter-butílico de ácido (3S)-3-(3-bromo-2-metilen-1-propil)-5-oxo-1-[(1R)-1-feniletil] pirrolidin-3-carboxílico (3.22 g, 7.62 mmoles) en tetrahidrofurano (76.2 ml) bajo enfriamiento con hielo-acetona en una atmósfera de nitrógeno, y la mezcla se agitó durante 10 minutos. Una solución de ácido cítrico al 10% (120 ml) se añadió a la solución de reacción, seguido por extracción con acetato de etilo (100 ml x 2). La capa orgánica se lavó con salmuera (200 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 83:17 → 80:20 → 75:25) para dar 2.47 g del compuesto del título como cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 7.34-7.23 (5H, m), 5.46 (1H, q, J=7.11 Hz), 4.88 (2H, d, J=1.72 Hz), 3.31 (1H, d, J=10.30 Hz), 3.13 (2H, t, J=6.37 Hz), 3.08 (2H, d, J=10.30 Hz), 2.89 (1H, d, J=15.69 Hz), 2.72 (2H, d, J=6.13 Hz), 2.30 (1H, d, J=15.93 Hz), 1.47 (3H, d, J=7.11 Hz), 1.35 (9H, s).

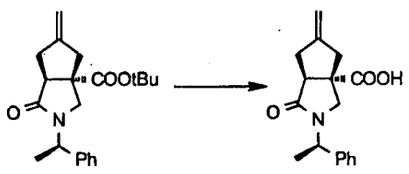
EM (ESI) m/z: 342 $(M+H)^+$.

1016

EJEMPLO DE REFERENCIA 194

Acido [(1S,5S)-7-metilen-4-oxo-3-[(1R)-1-fenil etil]-3-azabiciclo [3.3.0] octan-1-il] carboxílico

[Fórmula 308]



Ácido trifluoroacético (26.0 ml) se añadió a una solución de éster ter-butílico de ácido [(1S,5S)-7-metilen-4-oxo-3-[(1R)-1-feniletil]-3-aza-biciclo [3.3.0]octan-1-il] carboxílico (2.47 g, 8.66 mmoles) en diclorometano (26.0 ml) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante una hora. La solución de reacción se concentró bajo presión reducida, y ácido trifluoroacético se destiló azeotrópicamente con tolueno (x 3). Una solución 1 mol/l de hidróxido de sodio (15.0 ml) se añadió al residuo resultante bajo enfriamiento con hielo, y la mezcla se lavó con éter dietílico (60 ml x 2). La capa acuosa se hizo ácida con 6 moles/l de ácido clorhídrico (4 ml) bajo enfriamiento con hielo, seguido por extracción con acetato de etilo (100 ml x 2). Las capas orgánicas se combinaron, se lavaron con agua (100 ml) y salmuera (100 ml), y se secaron sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 2.15 g del compuesto del título como cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 7.36-7.24 (5H, m), 5.48 (1H, q, J=7.03 Hz), 4.93 (2H, s), 3.40 (1H, d, J=10.30 Hz), 3.27 (1H, dd, J=7.48, 4.78 Hz), 3.16 (1H, d, J=10.54 Hz), 3.02 (1H, d, J=15.93 Hz), 2.77 (2H, d, J=5.39 Hz), 2.38 (1H, d, J=15.93 Hz), 1.50 (3H, d, J=7.11 Hz).

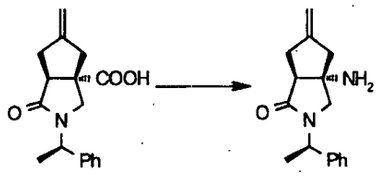
1017

EM (ESI) m/z: 342 $(M+H)^+$.

EJEMPLO DE REFERENCIA 195

(1S,5S)-1-Amino-7-metilen-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 309]



Trietilamina (0.489 ml, 3.50 mmoles) y difenilfosforil azida (0.491 ml, 2.28 mmoles) se añadieron a una solución de ácido [(1S,5S)-7-metilen-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-il] carboxílico (500 mg, 1.75 mmoles) en tolueno (8.75 ml) en una atmósfera de nitrógeno con agitación bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 30 minutos y después a 100°C durante 30 minutos. La solución de reacción se concentró bajo presión reducida, y trietilamina se removió azeotrópicamente con tolueno (x 3). Se añadieron 1,4-dioxano (4.37 ml) y 6 moles/l de ácido clorhídrico (4.37 ml) al residuo resultante, y la mezcla se agitó a 50°C durante una hora. La solución de reacción se diluyó con agua (18.0 ml) y se lavó con éter dietílico (60 ml x 2). La capa acuosa se hizo alcalina con una solución de 1 mol/l de hidróxido de sodio, seguido por extracción con cloroformo (80 ml x 1, 70 ml x 1). La capa orgánica se lavó con agua (80 ml) y salmuera (80 ml) y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 238 mg del compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 7.38-7.24 (5H, m), 5.53 (1H, q, J=7.11 Hz),

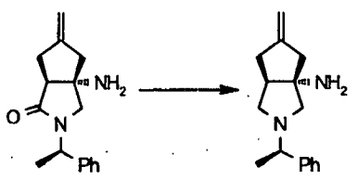
4.92 (2H, brs), 3.25 (1H, d, J=10.05 Hz), 2.79-2.73 (3H, m), 2.58 (1H, dd, J=9.44, 4.04 Hz), 2.40 (2H, dd, J=35.17, 15.57 Hz), 1.48 (3H, d, J=7.11 Hz).

EM (ESI) m/z: 257 $(M+H)^+$.

EJEMPLO DE REFERENCIA 196

(1S,5R)-1-Amino-7-metilen-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 310]



Una solución al 65% de hidruro bis(2-metoxietoxi) aluminio-sodio en tolueno (0.539 ml, 1.79 mmoles) se añadió a una solución de (1S,5S)-1-amino-7-metilen-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (115 mg, 0.449 mmoles) en tolueno (2.24 ml), y la mezcla se agitó a temperatura ambiente durante 30 minutos y a 80°C durante 30 minutos. Una solución de 5 moles/l de hidróxido de sodio (15.0 ml) se añadió a la solución de reacción con agitación bajo enfriamiento con hielo, seguido por extracción con tolueno (30 ml x 1, 20 ml x 1). La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. Después de filtración, el filtrado se concentró bajo presión reducida para dar 106 mg del compuesto del título.

^{1}H-RMN ($CDCl_3$) δ: 7.38-7.19 (5H, m), 4.80-4.78 (2H, m), 3.14 (1H, q, J=6.45 Hz), 2.78 (1H, t, J=8.21 Hz), 2.65-2.56 (2H, m), 2.47 (1H, d, J=14.71 Hz), 2.33 (1H, d, J=9.07 Hz), 2.22 (1H, d, J=14.95 Hz), 2.13-2.06 (3H, m), 1.31 (3H, d, J=6.62 Hz).

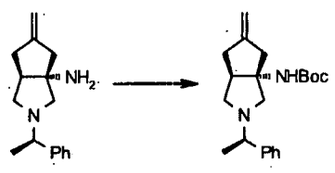
EM (ESI) m/z: 243 $(M+H)^+$.

1419

EJEMPLO DE REFERENCIA 197

(1S, 5R)-1-ter-Butoxicarbonilamino-7-metilen-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 311]



Dicarbonato de di-ter-butilo (191 mg, 0.875 mmoles) se añadió a una solución de (1S,5R)-1-amino-7-metilen-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (106 mg, 0.437 mmoles) en diclorometano (2.18 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 22 horas. La solución de reacción se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:0 → 95:5 → 90:10 → 88:12 → 84:16 → 80:20 → 75:25) para dar 203 mg del compuesto del título como un aceite transparente.

^{1}H-RMN ($CDCl_3$) δ: 7.29-7.22 (5H, m), 4.86 (1H, brs), 4.79 (2H, d, J=7.84 Hz), 3.16 (1H, q, J=6.45 Hz), 2.92 (1H, d, J=9.07 Hz), 2.76 (4H, t, J=8.58 Hz), 2.67-2.57 (4H, m), 2.40 (2H, d, J=9.56 Hz), 2.08-1.99 (2H, m), 1.43 (9H, s), 1.31 (3H, d, J=6.62 Hz).

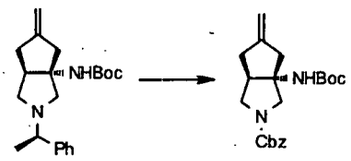
EM (ESI) m/z: 343 $(M+H)^+$.

EJEMPLO DE REFERENCIA 198

(1S,5R)-3-Benciloxicarbonil-1-ter-butoxicarbonilamino-7-metilen-3-azabiciclo [3.3.0] octano

[Fórmula 312]

1020



Cloroformiato de bencilo (0.250 ml, 1.75 mmoles) se añadió a una solución del residuo que contenía (1S,5R)-1-ter-butoxicarbonilamino-7-metilen-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (200 mg, equivalente a 0.437 mmoles) en diclorometano (1.94 ml) en una atmósfera de nitrógeno, y la mezcla se agitó a temperatura ambiente durante 15 horas y a 40°C durante cuatro horas. La solución de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 87:13 → 86:14 → 83:17 → 80:20 → 75:25) para dar 95.1 mg del compuesto del título como un aceite transparente.

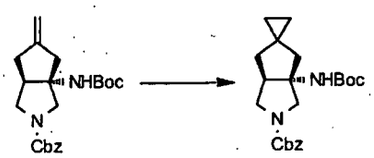
^{1}H-RMN ($CDCl_3$) δ: 7.36-7.30 (7H, m), 5.12 (2H, s), 4.92 (2H, d, J=8.82 Hz), 4.67 (1H, brs), 3.74-3.72 (2H, m), 3.56 (1H, d, J=11.77 Hz), 3.27-3.24 (1H, m), 2.72-2.68 (4H, m), 2.19-2.17 (1H, m), 1.43 (9H, s).

EM (ESI) m/z: 373 $(M+H)^+$.

EJEMPLO DE REFERENCIA 199

(1S, 5R)-3-Benciloxicarbonil-1-ter-butoxicarbonilaminoespiro (3-azabiciclo [3.3.0] octano-7,1'-ciclopropano)

[Fórmula 313]



N-Metil-N'-nitro-N-nitrosoguanidina (mezcla de 50% con agua, 6 g)

1021

se añadió a una solución de dos capas de una solución de hidróxido de potasio al 40% (18 ml) y éter dietílico (60 ml) en un sistema abierto bajo enfriamiento con agua con hielo para preparar una solución de diazometano en éter dietílico.

Acetato de paladio (5.26 mg, 0.0234 mmoles) se añadió a (1S,5R)-3-benciloxicarbonil-1-ter-butoxicarbonilamino-7-metilen-3-azabiciclo [3.3.0]octano (175 mg, 0.469 mmoles) en éter dietílico (4.69 ml) en un sistema abierto bajo enfriamiento con hielo. La solución de diazometano en éter dietílico preparada previamente (20 ml) se añadió lentamente a esta solución bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 16 horas. Después de filtración a través de Celite, el filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:0 → 95:5 → 90:10 → 88:12 → 87:13 → 86:14 → 85:15 → 83:17 → 80:20 → 75:25) para dar 138 mg del compuesto del título como un aceite transparente.

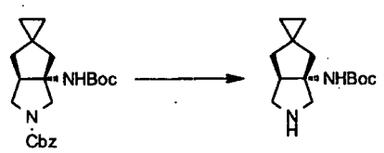
^{1}H-RMN ($CDCl_3$) δ: 7.38-7.28 (5H, m), 5.13 (2H, s), 4.80 (1H, d, J=9.31 Hz), 3.77-3.72 (3H, m), 3.37-3.35 (1H, m), 2.66 (1H, s), 2.05-1.97 (3H, m), 1.60 (1H, s), 1.43 (10H, s), 0.47-0.46 (4H, m).

EM (ESI) m/z: 387 $(M+H)^+$.

EJEMPLO DE REFERENCIA 200

(1S, 5R)-1-ter-Butoxicarbonilaminoespiro (3-azabiciclo [3.3.0] octano-7,1'-ciclopropano)

[Fórmula 314]



1022

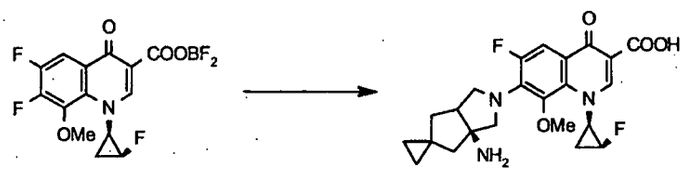
Un catalizador de 10% de paladio-carbón (45.6 mg, 30% en peso) se añadió a una solución de (1S,5R)-3-benciloxicarbonil-1-ter-butoxicarbonilaminoespiro (3-azabiciclo [3.3.0] octano-7,1'-ciclopropano) (152 mg, 0.393 mmoles) en metanol (3.93 ml) en una atmósfera de nitrógeno. Después de que la atmósfera se reemplazó con hidrógeno, la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de que la atmósfera se reemplazó con nitrógeno, la solución de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 97.9 mg del compuesto del título como un aceite transparente.

EM (ESI) m/z: 253 $(M+H)^+$.

EJEMPLO 47

Acido 7-[(1S,5R)-1-aminoespiro (3-azabiciclo [3.3.0] octano-7,1'-ciclopropan)-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-8-metoxi-4-oxo-1,4-dihidroquinolin-3-carboxílico

[Fórmula 315]



Trietilamina (0.162 ml, 0.388 mmoles) y ácido 1-[(1R,2S)-2-fluorociclopropan-1-il]-6,7-difluoro-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (140 mg, 0.388 mmoles) se añadieron a una solución de (1S,5R)-1-ter-butoxicarbonilaminoespiro(3-azabiciclo[3.3.0] octano-7,1'-ciclopropano) (97.9 mg, 0.388 mmoles) en sulfóxido de dimetilo (0.776 ml), y la mezcla se agitó a 35°C durante 14 horas. Una solución mixta de etanol : agua =

1023

4:1 (10.0 ml) y trietilamina (1.0 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. La solución de reacción se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (30 ml) y se lavó con una solución de ácido cítrico al 10% (30 ml), agua (30 ml), y salmuera (30 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y después se filtró, y el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (cloroformo:metanol = 100:0 → 99:1 → 98:2). El residuo resultante (165 mg) se disolvió en ácido clorhídrico concentrado (1.0 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (25 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml x 5) y cloroformo/metanol = 10/1 (60 ml x 1). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se disolvió en etanol caliente (20 ml), y el material insoluble se removió por filtración a través de un papel filtro acanalado. El solvente se evaporó gradualmente calentando el filtrado con agitación. La solución se concentró a aproximadamente 5 ml y después se agitó a temperatura ambiente durante la noche. Los cristales precipitados se recogieron por filtración y se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C durante la noche para dar 86.0 mg del compuesto del título como cristales amarillo pálido.

^{1}H-RMN (NaOD 0.1N) δ: 8.46 (1H, s), 7.70 (1H, d, J=14.15 Hz), 5.06-5.04 (1H, m), 4.09-4.04 (1H, m), 3.92-3.86 (1H, m), 3.70-3.68 (4H, m), 3.58 (1H, d, J=10.73 Hz), 3.53-3.49 (1H, m), 2.54-2.46 (1H, m), 2.15-2.09 (1H, m),

1024

1.86-1.76 (2H, m), 1.67-1.46 (3H, m), 0.57-0.45 (4H, m).

Análisis. calculado para $C_{23}H_{25}F_2N_3O_4O$ $0.5H_2O$: C, 60.79; H, 5.77; F, 8.36; N, 9.25.

Encontrado: C, 60.82; H, 5.73; F, 8.17; N, 9.23.

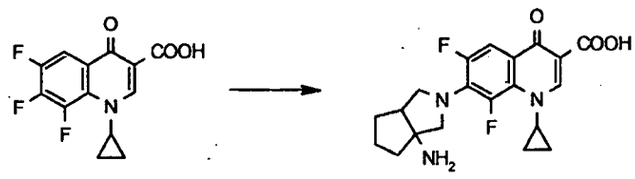
EM (ESI) m/z: 446 $(M+H)^+$.

IR (ATR) : 2931, 2850, 1725, 1616, 1508, 1434, 1342, 1315, 1270, 1209, 1186, 1120, 1052, 1014, 987, 927, 881, 850, 806, 746 cm^{-1}.

EJEMPLO 48

Acido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0] octan-3-il]-1-ciclopropil-6,8-difluoro-1,4-dihidro-4-oxoquinolin-3-carboxílico

[Fórmula 316]



Un catalizador de 10% de paladio-carbón (M, aproximadamente 50% húmedo, 72.6 mg) se añadió a una solución de (+)-(1S,5R)-3-benciloxicarbonil-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0]octano (363 mg, 1.01 mmoles) en metanol (10.1 ml), y la mezcla se agitó en una atmósfera de hidrógeno en un balón de hule a temperatura ambiente durante 45 minutos. El catalizador se removió por filtración, y después el solvente se evaporó bajo presión reducida para dar 229 mg de un residuo que contenía (1S,5R)-1-(ter-butoxicarbonilamino)-3-azabiciclo [3.3.0]octano como un sólido gomoso transparente incoloro.

Trietilamina (0.423 ml, 3.03 mmoles) y ácido 1-ciclopropil-6,7,8-

trifluoro-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico (272 mg, 0.960 mmoles) se añadieron a una solución del residuo que contenía (1S,5R)-1-ter-butoxicarbonilamino-3-azabiciclo [3.3.0] octano obtenido antes (229 mg) en acetonitrilo (3.84 ml) en una atmósfera de nitrógeno, y la mezcla se calentó a reflujo durante seis horas. La solución de reacción se enfrió con hielo, y después los cristales precipitados se recogieron por filtración y se lavaron con acetonitrilo y éter dietílico. Los cristales se secaron bajo presión reducida a 50°C durante la noche. El residuo resultante (410 mg) se disolvió en ácido clorhídrico concentrado (3 ml) bajo enfriamiento con hielo, y después la solución se agitó a temperatura ambiente durante 15 minutos. Después de lavar con cloroformo (40 ml x 3), la capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo (80 ml x 2) y cloroformo/metanol = 10/1 (100 ml x 6). La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró, y después el filtrado se concentró bajo presión reducida. Etanol caliente (150 ml) y amoniaco acuoso al 28% (3 a 5 ml) se añadieron al residuo, y el material insoluble se removió por filtración a través de un papel filtro acanalado. El solvente se evaporó gradualmente mientras se calentaba con agitación. El amoniaco se removió azeotrópicamente con etanol varias veces. La solución se concentró a aproximadamente 10 ml y después se agitó a temperatura ambiente durante cuatro horas. Los cristales precipitados se recogieron por filtración y se lavaron con etanol y éter dietílico. Los cristales se secaron bajo presión reducida a 45°C durante la noche para dar 289 mg del compuesto del título como cristales amarillo pálido.

^{1}H-RMN (NaOD0.1N) δ: 8.44 (1H, s), 7.62 (1H, d, J=13.73 Hz), 3.97-3.86 (2H, m), 3.59 (1H, d, J=10.30 Hz), 3.49 (1H, d, J=10.30 Hz), 3.32 (1H,

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d, J=5.64 Hz), 2.31-2.26 (1H, m), 2.02 (1H, dt, J=20.43, 7.48 Hz), 1.90-1.84 (1H, m), 1.81-1.74 (2H, m), 1.70-1.63 (1H, m), 1.51-1.48 (1H, m), 1.19 (2H, t, J=7.11 Hz), 1.07 (2H, s).

Análisis. calculado para $C_{20}H_{21}F_2N_3O_3 0.75H_2O$: C, 59.62; H, 5.63; F, 9.43; N, 10.43.

Encontrado: C, 59.69; H, 5.58; F, 9.31; N, 10.35.

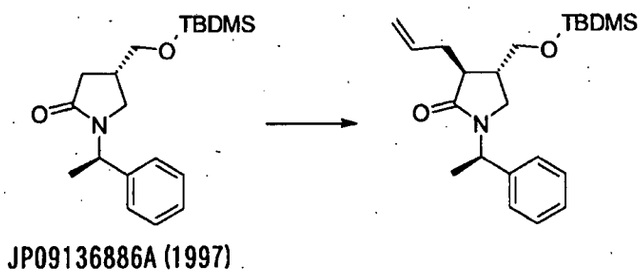
EM (ESI) m/z: 390 $(M+H)^+$.

IR (ATR): 2956, 1612, 1573, 1542, 1508, 1459, 1402, 1351, 1317, 1274, 1201, 1166, 1106, 1031, 979, 817, 732 cm^{-1}.

EJEMPLO DE REFERENCIA 201

(3S,4S)-3-alil-4-(ter-butildimetilsililoxi) metil-2-oxo-1-[(1R)-1-feniletil] pirrolidina

[Fórmula 317]



JP09136886A (1997)

(4S)-4-(ter-Butildimetilsililoxi)metil-2-oxo-1-[(1R)-1-feniletil] pirrolidina (333.5 g, 1.00 mol) y bromuro de alilo (90.9 ml, 1.05 moles) se disolvieron en tetrahidrofurano (1.10 l). Hexametildisilazida de litio (solución 1.0 M en tetrahidrofurano) (1.10 l, 1.10 moles) se añadió gota a gota a -15°C, y la mezcla se agitó a -5°C durante una hora. La solución de reacción se extrajo con una solución saturada de cloruro de amonio y acetato de etilo. Después, la capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro.

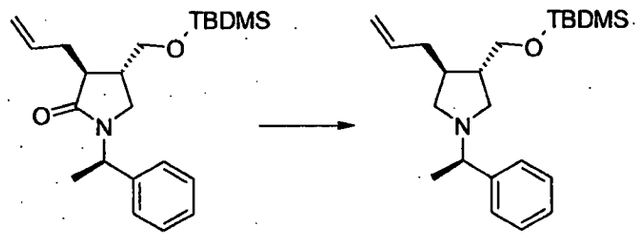
Posteriormente, el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 4:1 → 2:1) para dar 327 g del compuesto del título como un jarabe incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.42-7.32 (5H, m), 5.93-5.80 (1H, m), 5.57 (1H, q, J=7.1 Hz), 5.22-5.12 (2H, m), 3.56 (1H, dd, J=10.0, 4.9 Hz), 3.48-3.43 (1H, m), 3.34 (1H, dd, J=10.3, 8.1 Hz), 2.82 (1H, dd, J=9.8, 5.9 Hz), 2.65-2.57 (1H, m), 2.48-2.40 (2H, m), 2.32-2.24 (1H, m), 1.59 (3H, d, J=7.6 Hz), 0.86 (9H, s), 0.00 (6H, s).

EJEMPLO DE REFERENCIA 202

(3S,4S)-3-Alil-4-(ter-butildimetilsililoxi) metil-1-[(1R)-1-feniletil] pirrolidina

[Fórmula 318]



Una solución al 65% de Red-Al™ en tolueno (788 ml, 2.63 moles) se añadió gota a gota a una solución de (3S,4S)-3-alil-4-(ter-butildimetilsililoxi)metil-2-oxo-1-[(1R)-1-feniletil] pirrolidina (327 g, 875 mmoles) en tolueno (1500 ml) en una atmósfera de nitrógeno durante una hora. La solución de reacción se agitó a 45°C durante cinco horas y después se enfrió a 0°C, y se añadió una solución al 20% de tartrato de sodio-(+)-potasio tetrahidratado (2.00 l). La solución de reacción se vació en una mezcla de acetato de etilo y salmuera, seguido por extracción con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y

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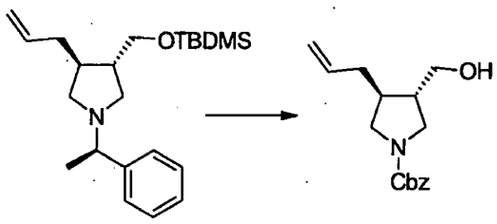
después se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 20:1 → 4:1) para dar 213 g del compuesto del título como un jarabe incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.29-7.10 (5H, m), 5.73-5.63 (1H, m), 4.97-4.87 (2H, m), 3.49 (2H, d, J=6.8 Hz), 3.09 (1H, q, J=6.6 Hz), 2.57-2.49 (2H, m), 2.39 (1H, t, J=8.5 Hz), 2.20-2.13 (1H, m), 2.09-2.00 (2H, m), 1.91-1.83 (1H, m), 1.78-1.68 (1H, m), 1.28 (3H, d, J=6.6 Hz), 0.85 (9H, s), 0.27 (6H, d, J=1.0 Hz).

EJEMPLO DE REFERENCIA 203

(3S,4S)-3-Alil-1-benciloxicarbonil-4-hidroximetilpirrolidina

[Fórmula 319]



(3S,4S)-3-Alil-4-(ter-butildimetilsililoxi)metil-1-[(1R)-1-feniletil] pirrolidina (213 g, 592 mmoles) se disolvió en diclorometano (420 ml). Cloroformiato de bencilo (169.2 ml, 1.19 mol) se añadió gota a gota, y la mezcla se agitó a 55°C durante 10 horas y después a temperatura ambiente durante 14 horas. Una solución 1 M de ácido clorhídrico en etanol (250 ml, 250 mmoles) se añadió adicionalmente a la solución de reacción y la mezcla se agitó a temperatura ambiente durante 24 horas. La solución de reacción se extrajo con una solución saturada de bicarbonato de sodio y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y después se concentró bajo presión reducida. El residuo resultante se purificó por

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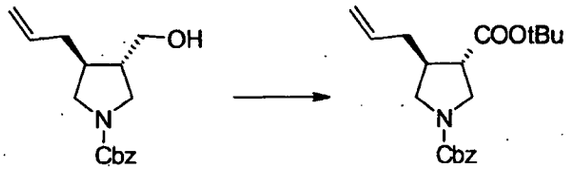
cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 10:1 → 1:1) para dar 140 g del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.75 (1H, brs), 5.13-5.02 (4H, m), 3.76-3.54 (4H, m), 3.31-3.23 (1H, m), 3.15-3.07 (1H, m), 2.32-2.26 (1H, m), 2.14-2.03 (3H, m).

EJEMPLO DE REFERENCIA 204

Ester ter-butílico de ácido (3S,4S)-4-alil-1-benciloxicarbonilpirrolidin-3-carboxílico

[Fórmula 320]



Dicloruro de oxalilo (48.0 ml, 559 mmoles) se disolvió en diclorometano (1000 ml). Sulfóxido de dimetilo (39.7 ml, 559 mmoles) se añadió gota a gota a -70°C, y la mezcla se agitó durante 15 horas. Una solución de (3S,4S)-3-alil-1-benciloxicarbonil-4-hidroximetilpirrolidina (140 g, 508 mmoles) en diclorometano (400 ml) se añadió gota a gota a la solución de reacción y la mezcla se agitó durante 50 minutos. Trietilamina (354 ml, 2.54 mol) se añadió gota a gota a la solución de reacción, y después la mezcla se agitó a-10°C durante 10 minutos. La solución de reacción se extrajo con agua y diclorometano. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro, y se concentró bajo presión reducida.

El residuo resultante se disolvió en una solución mixta de alcohol ter-butílico (250 ml) y tetrahidrofurano (750 ml). Se añadió 2-metil-2-buteno (538

1030

ml, 5.08 moles) y después una suspensión de clorito de sodio (60.3 g, 533 mmoles) y fosfato diácido de sodio dihidratado (238 g, 1.52 mol) en agua (250 ml) se añadió a 0°C, y la mezcla se agitó a temperatura ambiente durante 20 horas. La solución de reacción se concentró bajo presión reducida, y después una solución de ácido clorhídrico 1N se añadió, seguida por extracción con éter dietílico. La capa orgánica se lavó con una solución de tiosulfato de sodio al 5% y salmuera, y después se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida.

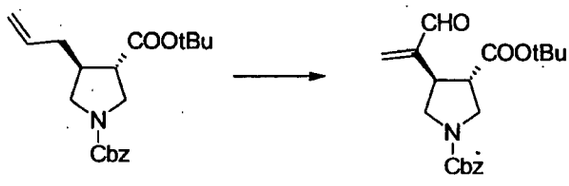
El residuo resultante se disolvió en diclorometano (1000 ml). N,N'-Diisopropil-O-ter-butilisourea (509 g, 2.54 mol) se añadió gota a gota, y la mezcla se agitó a 50°C durante cuatro horas y después a temperatura ambiente durante 15 horas. El sólido precipitado se filtró, y después el filtrado se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 10:1 → 4:1) para dar 126 g del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.36-7.31 (5H, m), 5.81-5.65 (1H, m), 5.14-5.07 (2H, m), 5.06-5.00 (2H, m), 3.77-3.63 (2H, m), 3.58-3.49 (1H, m), 3.13-3.01 (1H, m), 2.71-2.59 (1H, m), 2.48 (1H, brs), 2.36-2.26 (1H, m), 2.16-2.04 (1H, m), 1.45 (9H, s).

EJEMPLO DE REFERENCIA 205

Ester ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-(1-formilvinil) pirrolidin-3-carboxílico

[Fórmula 321]



1031

Ester ter-butílico de ácido (3S,4S)-4-alil-1-benciloxicarbonilpirrolidin-3-carboxílico (70.0 g, 203 mmoles) se disolvió en una solución mixta de tetrahidrofurano (350 ml) y agua (350 ml). Metaperyodato de sodio (86.7 g, 406 mmoles) y tetróxido de osmio (una cantidad catalítica) se añadieron secuencialmente, y la mezcla se agitó a temperatura ambiente durante 20 horas. Una solución de bisulfito de sodio al 10% se añadió a la solución de reacción, seguida por extracción con diclorometano. La capa orgánica se lavó con agua y salmuera, y después se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida.

El residuo resultante se disolvió en diclorometano (700 ml). Yoduro de N,N-dimetilmetilenamonio (56.3 g, 305 mmoles) y 1,8-diazabiciclo [5.4.0] undeceno (33.4 ml, 223 mmoles) se añadieron gota a gota, y la mezcla se agitó a temperatura ambiente durante 59 horas. Una solución saturada de cloruro de amonio se añadió a la solución de reacción, seguida por extracción con acetato de etilo. La capa orgánica se lavó con salmuera, y después se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano:acetato de etilo = 24:1 → 4:1) para dar 56.7 g del compuesto del título como un aceite incoloro.

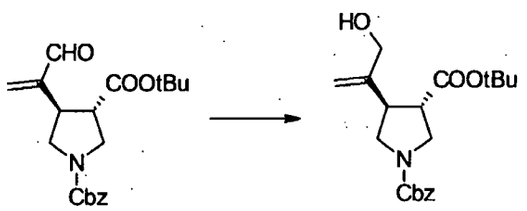
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 9.55 (1H, d, J=5.1 Hz), 7.40-7.28 (5H, m), 6.38 (1H, d, J=2.0 Hz), 6.15 (1H, d, J=3.2 Hz), 5.13 (2H, d, J=4.1 Hz), 3.89-3.74 (2H, m), 3.60 (1H, t, J=9.6 Hz), 3.49-3.41 (1H, m), 3.29 (1H, dt, J=30.0, 9.7 Hz), 3.15-3.07 (1H, m), 1.41 (9H, s).

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EJEMPLO DE REFERENCIA 206

Ester ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-[1-(hidroximetil)vinil] pirrolidin-3-carboxílico

[Fórmula 322]



Cloruro de cerio (III) heptahidratado (57.0 g, 153 mmoles) se disolvió en etanol (700 ml). Se añadió Borohidruro de sodio (5.79 g, 153 mmoles) a 0°C, y la mezcla se agitó durante 10 minutos. Una solución de éster ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-(1-formilvinil)pirrolidin-3-carboxílico (55.0 g, 153 mmoles) en etanol (700 ml) se añadió gota a gota a la solución de reacción a 0°C, y la mezcla se agitó a temperatura ambiente durante tres horas. La solución de reacción se extrajo con una solución de ácido cítrico al 10%, agua, y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 24:1 → 2:1) para dar 42.2 g del compuesto del título como un aceite incoloro.

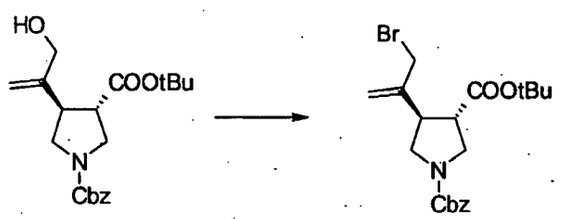
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.20 (1H, brs), 5.17-5.10 (2H, m), 5.04 (1H, d, J=5.4 Hz), 4.16-4.09 (3H, m), 3.87-3.77 (2H, m), 3.52 (1H, dd, J=17.2, 8.9 Hz), 3.29 (1H, q, J=10.9 Hz), 3.18-2.98 (2H, m), 1.43 (9H, s).

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EJEMPLO DE REFERENCIA 207

Ester ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-[1-(bromometil) vinil] pirrolidin-3-carboxílico

[Fórmula 323]



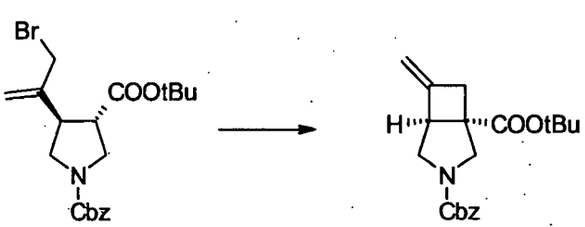
Ester ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-[1-(hidroximetil)vinil]pirrolidin-3-carboxílico (30.0 g, 83.0 mmoles) se disolvió en diclorometano (300 ml). Trifenilfosfina (23.2 g, 87.2 mmoles) y tetrabromuro de carbono (29.4 g, 87.2 mmoles) se añadieron, y la mezcla se agitó a temperatura ambiente durante 30 minutos. La solución de reacción se concentró bajo presión reducida. Después, el residuo resultante se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:1 → 1:1) para dar 26.9 g del compuesto del título como un aceite incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.34 (1H, s), 5.16-5.12 (3H, m), 3.99 (2H, q, J=10.6 Hz), 3.91-3.78 (2H, m), 3.59-3.53 (1H, m), 3.34-3.22 (2H, m), 3.08-2.96 (1H, m), 1.44 (9H, s).

EJEMPLO DE REFERENCIA 208

Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-metilen-3-azabiciclo [3.2.0] heptano-1-carboxílico

[Fórmula 324]



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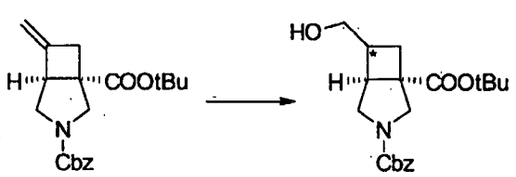
Ester ter-butílico de ácido (3S,4R)-1-benciloxicarbonil-4-[1-(bromometil)vinil] pirrolidin-3-carboxílico (22.8 g, 53.7 mmoles) y 1,3-dimetil-3,4,5,6-tetrahidro-2 (1H)-pirimidinona (19.5 ml, 161 mmoles) se disolvieron en una solución mixta de tetrahidrofurano (220 ml) y tolueno (220 ml). Hexametildisilazida de litio (solución 1.0 M en tetrahidrofurano) (80.6 ml, 80.6 mmoles) se añadió gota a gota a -78°C, y después la mezcla se agitó a temperatura ambiente durante cinco minutos. La solución de reacción se extrajo con una solución saturada de cloruro de amonio y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 24:1 → 2:1) para dar 8.34 g del compuesto del título como un jarabe incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.37-7.24 (5H, m), 5.14 (2H, d, J=2.4 Hz), 4.98-4.88 (2H, m), 3.93-3.76 (2H, m), 3.66 (1H, d, J=11.7 Hz), 3.59-3.54 (1H, m), 3.45-3.38 (1H, m), 3.24 (1H, dt, J=16.4, 2.6 Hz), 2.67-2.57 (1H, m), 1.46 (9H, s).

EJEMPLO DE REFERENCIA 209

Ester ter-butílico de ácido (1S, 5S,6R)-/ (1S, 5S, 6S)-3-benciloxicarbonil-6-hidroximetil-3-azabiciclo[3.2.0]heptano-1-carboxílico

[Fórmula 325]



Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-metileno-3-

1035

azabiciclo [3.2.0] heptano-1-carboxílico (2.00 g, 5.82 mmoles) se disolvió en tetrahidrofurano (40 ml). Un dímero de 9-borabiciclo [3.3.1] nonano (solución 0.5 M en tetrahidrofurano) (17.5 ml, 8.73 mmoles) se añadió gota a gota, y después la mezcla se agitó durante dos horas. Una solución 3 M de hidróxido de sodio (3.49 ml, 10.5 mmoles) y peróxido de hidrógeno acuoso al 30% (2.47 ml) se añadieron gota a gota a la solución de reacción a 0°C, y después la mezcla se agitó a temperatura ambiente durante 16 horas. La solución de reacción se extrajo con agua y acetato de etilo. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:1 → 1:2) para dar 1.58 g de un isómero A (isómero menos polar) del compuesto del título y 50.0 mg de un isómero B (isómero más polar) del compuesto del título como jarabes incoloros.

Isómero A; ^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.30 (5H, m), 5.17 (2H, s), 4.00 (1H, d, J=12.4 Hz), 3.75-3.54 (4H, m), 3.42 (1H, d, J=11.7 Hz), 3.29 (1H, dd, J=12.6, 7.9 Hz), 3.09 (1H, t, J=8.2 Hz), 2.74-2.64 (1H, m), 2.67-2.54 (1H, m), 1.47 (9H, s).

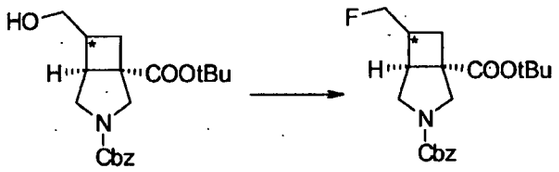
Isómero B; ^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.28 (5H, m), 5.17 (2H, s), 3.86-3.56 (6H, m), 3.38 (1H, dd, J=11.6, 6.0 Hz), 2.85-2.78 (1H, m), 2.32-2.22 (1H, m), 2.19-2.09 (1H, m), 1.45 (9H, s).

EJEMPLO DE REFERENCIA 210

Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-fluorometil-3-azabiciclo [3.2.0] heptano-1-carboxílico (derivado del Isómero A)

L936

[Fórmula 326]



Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-hidroximetil-3-azabiciclo [3.2.0] heptano-1-carboxílico (Isómero A) (1.51 g, 4.18 mmoles) se disolvió en diclorometano (30 ml). Trietilamina (1.28 ml, 9.20 mmoles) y cloruro de clorometilsulfonilo (746 μl, 8.36 mmoles) se añadieron gota a gota a 0°C, y después la mezcla se agitó durante 15 minutos. La solución de reacción se extrajo con una solución saturada de cloruro de amonio y acetato de etilo a 0°C. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida.

El residuo resultante se disolvió en tetrahidrofurano (20 ml). Fluoruro de tetrabutilamonio (solución 1.0 M en tetrahidrofurano) (16.7 ml, 16.7 mmoles) se añadió gota a gota a 0°C, y después la mezcla se agitó durante 16 horas. La solución de reacción se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 100:1 → 1:1) para dar 1.01 g del compuesto del título como un jarabe incoloro.

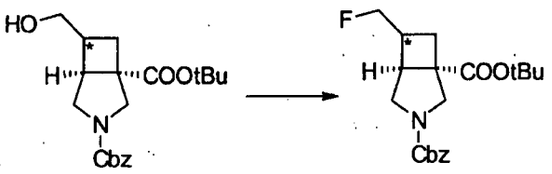
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m), 5.18 (2H, s), 4.48-4.26 (2H, m), 3.99 (1H, d, J=12.7 Hz), 3.72 (1H, brs), 3.43 (1H, d, J=12.6 Hz), 3.31 (1H, dd, J=13.2, 7.8 Hz), 3.11 (1H, t, J=8.0 Hz), 2.96-2.79 (1H, m), 2.62-2.53 (1H, m), 1.69-1.60 (1H, m), 1.48 (9H, s).

1037

EJEMPLO DE REFERENCIA 211

Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-fluorometil-3-azabiciclo [3.2.0] heptano-1-carboxílico (derivado del Isómero B)

[Fórmula 327]



Ester ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-hidroximetil-3-azabiciclo [3.2.0] heptano-1-carboxílico (Isómero B) (180 mg, 498 μmoles) se disolvió en diclorometano (4 ml). Trietilamina (153 μl, 1.10 mmoles) y cloruro de clorometilsulfonilo (89.0 μl, 996 μmoles) se añadieron gota a gota a 0°C, y después la mezcla se agitó durante 15 minutos. La solución de reacción se extrajo con una solución saturada de cloruro de amonio y acetato de etilo a 0°C. Después, la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida.

El residuo resultante se disolvió en tetrahidrofurano (4 ml). Fluoruro de tetrabutilamonio (solución 1.0 M en tetrahidrofurano) (1.99 ml, 1.99 mmoles) se añadió gota a gota a 0°C, y después la mezcla se agitó durante dos horas. La solución de reacción se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 100:1 → 1:1) para dar 80.6 mg del compuesto del título como un jarabe incoloro.

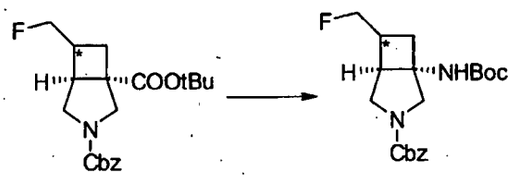
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m), 5.17 (2H, s), 4.52-4.31 (2H, m), 3.89-3.56 (3H, m), 3.38 (1H, dd, J=12.0, 6.6 Hz), 2.89 (1H, t, J=5.6 Hz), 2.40-2.25 (2H, m), 2.06-2.02 (1H, m), 1.46 (9H, s).

1038

EJEMPLO DE REFERENCIA 212

(1S,5R)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-6 fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero A)

[Fórmula 328]



Se añadió gota a gota ácido trifluoroacético (4 ml) a una solución de éster ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-fluorometil-3-azabiciclo [3.2.0] heptano-1-carboxílico (derivado del Isómero A) (887 mg, 2.44 mmoles) en diclorometano (4 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante dos horas. La solución de reacción se concentró bajo presión reducida, y después una solución 1 M de hidróxido de sodio se añadió al residuo bajo enfriamiento con hielo. La solución se lavó con éter dietílico, y después la capa acuosa se ajustó a pH 2 a 3 con ácido clorhídrico concentrado bajo enfriamiento con hielo, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida.

1,1'-Carbonilbis-1*H*-imidazol (594 mg, 3.66 mmoles) se añadió a una solución del residuo resultante en acetonitrilo (16 ml), y la mezcla se agitó durante una hora. La solución de reacción se hizo burbujear con amoniaco gaseoso durante 1.5 horas. Después, se añadió agua a la solución de reacción, seguido por extracción con cloroformo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida.

Tetraacetato de plomo (2.16 g, 4.88 mmoles) se añadió a una

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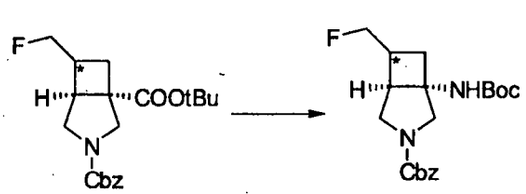
solución del residuo resultante en alcohol ter-butílico (16 ml), y la mezcla se calentó con agitación a 80°C durante 15 minutos. Después de dejar enfriar, se añadieron bicarbonato de sodio (2.50 g) y éter dietílico a la solución de reacción, y la mezcla se agitó bajo enfriamiento con hielo durante 30 minutos. El material insoluble se removió por filtración a través de Celite, y después el filtrado se lavó con una solución saturada de bicarbonato de sodio y salmuera. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 7:1 → 1:1) para dar 754 mg del compuesto del título como un jarabe incoloro.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.40-7.29 (5H, m), 5.16 (2H, s), 4.89-4.79 (1H, m), 4.53-4.27 (2H, m), 3.91 (1H, d, J=12.5 Hz), 3.77 (1H, d, J=11.5 Hz), 3.51-3.40 (1H, m), 3.33-3.26 (1H, m), 3.00-2.86 (2H, m), 2.37-2.23 (1H, m), 1.87 (1H, dd, J=13.1, 6.7 Hz), 1.45 (9H, s).

EJEMPLO DE REFERENCIA 213

(1S,5R)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero B)

[Fórmula 329]



Acido trifluoroacético (3 ml) se añadió gota a gota a una solución de éster ter-butílico de ácido (1S,5S)-3-benciloxicarbonil-6-fluorometil-3-azabiciclo [3.2.0] heptano-1-carboxílico (derivado del Isómero B) (660 mg, 1.82

1040

mmoles) en diclorometano (3 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante dos horas. La solución de reacción se concentró bajo presión reducida, y después una solución 1 M de hidróxido de sodio se añadió al residuo bajo enfriamiento con hielo. La solución se lavó con éter dietílico, y después la capa acuosa se ajustó a pH 2 a 3 con ácido clorhídrico concentrado bajo enfriamiento con hielo, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida.

1,1'-Carbonilbis-1*H*-imidazol (443 mg, 2.73 mmoles) se añadió a una solución del residuo resultante en acetonitrilo (12 ml), y la mezcla se agitó durante una hora. La solución de reacción se hizo burbujear con amoniaco gaseoso durante 1.5 horas. Después, se añadió agua a la solución de reacción, seguido por extracción con cloroformo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida.

Tetraacetato de plomo (1.61 g, 3.64 mmoles) se añadió a una solución del residuo resultante en alcohol ter-butílico (12 ml), y la mezcla se calentó con agitación a 80°C durante 15 minutos. Después de dejar enfriar, se añadieron bicarbonato de sodio (2.00 g) y éter dietílico a la solución de reacción, y la mezcla se agitó bajo enfriamiento con hielo durante 30 minutos. El material insoluble se filtró a través de Celite, y después el filtrado se lavó con una solución saturada de bicarbonato de sodio y salmuera. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (hexano : acetato de etilo = 16:1 → 1:1) para dar 590 mg del compuesto del título como un jarabe incoloro.

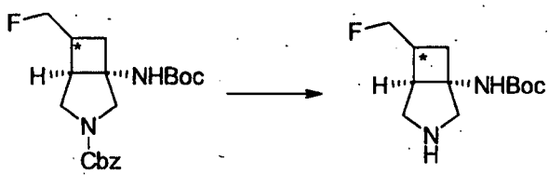
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.15 (2H, s), 4.89-

4.74 (1H, m), 4.58-4.32 (2H, m), 3.91 (1H, d, J=11.7 Hz), 3.76-3.46 (3H, m), 2.83-2.66 (1H, m), 2.31 (1H, dd, J=10.7, 8.8 Hz), 2.19-2.05 (2H, m), 1.43 (9H, s).

EJEMPLO DE REFERENCIA 214

(1S,5R)-1-(ter-Butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero A)

[Fórmula 330]



(1S,5R)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero A) (625 mg, 1.65 mmoles) se disolvió en tetrahidrofurano (12 ml). Se añadió 20% de hidróxido de paladio-carbón (50% húmedo) (200 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante una hora. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución 1 M de hidróxido de sodio se añadió al residuo bajo enfriamiento con hielo, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para dar 403 mg del compuesto del título como un jarabe incoloro.

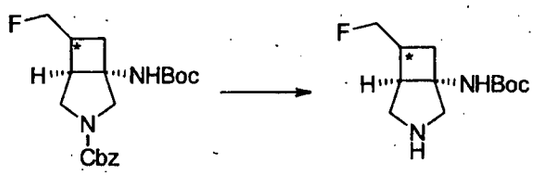
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.89-4.78 (1H, m), 4.66-4.39 (2H, m), 3.15 (1H, d, J=11.5 Hz), 3.07-2.78 (4H, m), 2.71 (1H, d, J=10.3 Hz), 2.34-2.26 (1H, m), 1.90 (1H, dd, J=12.7, 8.3 Hz), 1.46 (9H, s).

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EJEMPLO DE REFERENCIA 215

(1S, 5R)-1-(ter-Butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero B)

[Fórmula 331]



(1S,5R)-3-Benciloxicarbonil-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero B) (305 mg, 806 μmoles) se disolvió en tetrahidrofurano (6 ml). Se añadió 20% de hidróxido de paladio-carbón (50% húmedo) (100 mg) y la mezcla se agitó en una atmósfera de hidrógeno durante una hora. El catalizador se removió por filtración, y después el filtrado se concentró bajo presión reducida. Una solución de hidróxido de sodio 1 M se añadió al residuo bajo enfriamiento con hielo, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para dar 196 mg del compuesto del título como un jarabe incoloro.

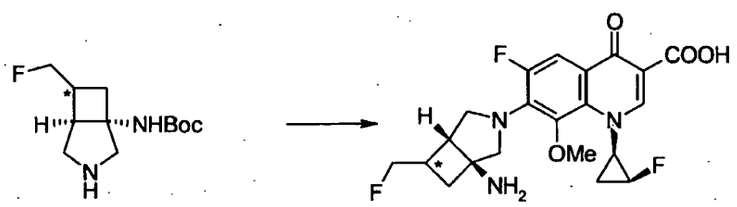
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 4.82 (1H, brs), 4.58-4.39 (2H, m), 3.16 (1H, d, J=11.2 Hz), 3.06 (1H, dd, J=11.1, 5.2 Hz), 2.85 (2H, dd, J=19.3, 11.7 Hz), 2.65-2.53 (1H, m), 2.27-1.86 (3H, m), 1.44 (9H, s).

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EJEMPLO 49

Acido 7-[(1S,5R)-1-amino-6-fluorometil-3-azabiciclo [3.2.0] heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluoro-1-ciclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico (derivado del Isómero A)

[Fórmula 332]



Trietilamina (143 μl, 1.03 mmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-fluoro-1-ciclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico -quelato de BF_2 (309 mg, 855 μmoles) se añadieron a una solución de (1S,5R)-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero A) (209 mg, 855 μmoles) en sulfolano (3 ml). La mezcla se agitó a 40°C durante 87 horas. Etanol (20 ml), agua (2 ml), y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante dos horas. El solvente se evaporó bajo presión reducida, y después el residuo resultante se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua tres veces y salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (cloroformo:metanol = 99:1 → 9:1). El aceite resultante (1.02 g) se disolvió en ácido clorhídrico concentrado (5 ml) bajo enfriamiento con hielo, y la solución se agitó a temperatura ambiente durante 15 minutos. La solución de reacción se lavó con cloroformo cinco veces, y después la capa acuosa se ajustó a pH 11 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico,

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seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por CCDP (usando la capa inferior de cloroformo:metanol :agua = 7:3:1 como un solvente de revelado), y después la fracción resultante se concentró bajo presión reducida. El residuo resultante se recristalizó a partir de etanol para dar 120 mg del compuesto del título como un sólido blanco. p.f.: 122-125°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.47 (1H, brs), 7.74 (1H, d, J=13.4 Hz), 5.00 (1H, d, J=64.5 Hz), 4.70-4.49 (2H, m), 4.09-4.01 (1H, m), 3.75-3.54 (6H, m), 3.14 (1H, d, J=10.5 Hz), 3.02-2.89 (1H, m), 2.65 (1H, t, J=7.8 Hz), 2.16 (1H, t, J=11.8 Hz), 2.00 (1H, dd, J=12.7, 7.8 Hz), 1.67-1.41 (2H, m).

Análisis. calculado para $C_{21}H_{22}F_3N_3O_4 \cdot 2.5H_2O$: C, 52.28; H, 5.64; N, 8.71.

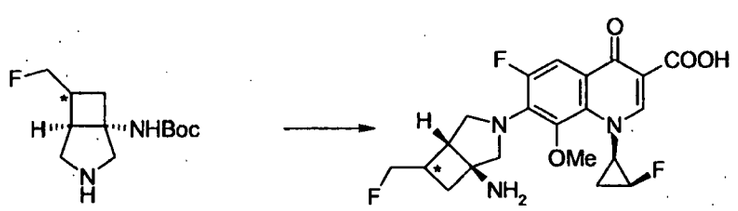
Encontrado: C, 52.03; H, 5.50; N, 8.47.

IR (KBr) ν: 3404, 2963, 1731, 1619, 1579, 1541, 1452, 1392, 1360, 1320, 1293, 1270, 1053 cm^{-1}.

EJEMPLO 50

Acido 7-[(1S,5R)-1-amino-6-fluorometil-3-azabiciclo [3.2.0] heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluoro-1-ciclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico (derivado del Isómero B)

[Fórmula 333]



Trietilamina (135 μl, 967 μmoles) y ácido 6,7-difluoro-1-[(1R,2S)-2-

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fluoro-1-ciclopropil]-8-metoxi-1,4-dihidro-4-oxoquinolin-3-carboxílico-quelato de BF_2 (291 mg, 806 μmoles) se añadieron a una solución de (1S,5R)-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero B) (196 mg, 806 μmoles) en sulfolano (2 ml). La mezcla se agitó a 40°C durante 111 horas. Etanol (10 ml), agua (1 ml), y trietilamina (0.5 ml) se añadieron a la solución de reacción, y la mezcla se calentó a reflujo durante una hora. El solvente se evaporó bajo presión reducida, y después el residuo resultante se extrajo con una solución de ácido cítrico al 10% y acetato de etilo. Después, la capa orgánica se lavó con agua tres veces y salmuera, se secó sobre sulfato de sodio anhidro, y se concentró bajo presión reducida. El residuo se sometió a cromatografía en columna sobre gel de sílice (cloroformo:metanol = 99:1 → 9:1). El aceite resultante-(515 mg) se disolvió en ácido clorhídrico concentrado (5 ml) bajo enfriamiento con hielo, y después la solución se agitó a temperatura ambiente durante 15 minutos. La solución de reacción se lavó con cloroformo cinco veces, y después la capa acuosa se ajustó a pH 11 con una solución saturada de hidróxido de sodio. La solución básica se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por CCDP (usando la capa inferior de cloroformo:metanol:agua = 7:3:1 como un solvente de revelado), y después la fracción resultante se concentró bajo presión reducida. El residuo resultante se recristalizó a partir de etanol para dar 125 mg del compuesto del título como un sólido blanco, p.f.: 193-195°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.48 (1H, brs), 7.73 (1H, d, J=13.7 Hz), 4.98 (1H, d, J=65.2 Hz), 4.68-4.48 (2H, m), 4.10-4.04 (1H, m), 3.76-3.67 (5H, m), 3.58-3.52 (1H, m), 3.22 (1H, d, J=10.5 Hz), 2.46-2.41 (1H, m),

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2.40-2.22 (2H, m), 1.96-1.87 (1H, m), 1.69-1.44 (2H, m).

Análisis. calculado para $C_{21}H_{22}F_3N_3O_4$: C, 57.66; H, 5.07; F, 13.03; N, 9.61.

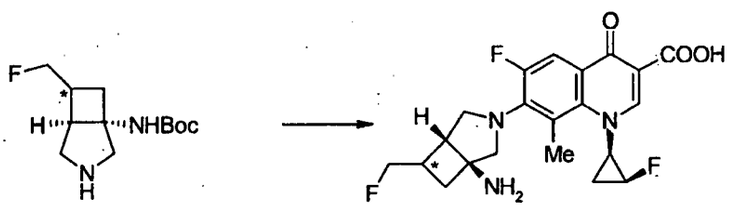
Encontrado: C, 57.42; H, 5.07; F, 12.98; N, 9.53.

IR (KBr) ν: 3393, 3086, 3063, 3034, 2954, 2930, 2897, 2872, 1720, 1621, 1514, 1452, 1395, 1365, 1344, 1318, 1288, 1273, 1186, 1123, 1108, 1060, 1038, 1020 cm^{-1}.

EJEMPLO 51

7-[(1S, 5R)-1-Amino-6-fluorometil-3-azabiciclo [3.2.0] heptan-3-il]-6-fluoro-1-[(1R, 2S)-2-fluoro-1-ciclopropil]-8-metil-1, 4-dihidro-4-oxoquinolin-3-carboxílico ácido (derivado del Isómero A)

[Fórmula 334]



Una solución de (1S,5R)-1-(ter-butoxicarbonilamino)-6-fluorometil-3-azabiciclo [3.2.0] heptano (derivado del Isómero A) (157 mg, 643 μmoles), éster etílico de ácido 7-bromo-6-fluoro-1-[(1R,2S)-2-fluoro-1-ciclopropil]-8-metil-1,4-dihidro-4-oxoquinolin-3-carboxílico (226 mg, 643 μmoles), rac-2,2'-bis(difenilfosfino)-1,1'-dinaftilo (273 mg, 438 μmoles), tris (dibencilidenacetona) dipaladio (0) (134 mg, 146 μmoles), y carbonato de cesio (381 mg, 1.17 mmoles) en dioxano (5.00 ml) se agitó en una atmósfera de argón a temperatura ambiente durante 30 minutos y a 100°C durante 16 horas. Se añadió agua a la solución de reacción, seguido por extracción con acetato de etilo y cloroformo.

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Después, la capa orgánica se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida, y el residuo resultante se sometió a cromatografía en columna sobre gel de sílice (hexano: acetato de etilo = 7:1 → acetato de etilo).

Una solución de hidróxido de sodio 1N (1.21 ml) se añadió a una solución de la espuma amarilla pálida resultante en etanol (5 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 30 horas. Una solución de ácido cítrico al 10% se añadió a la solución de reacción a 0°C, seguido por extracción con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio anhidro y después se concentró bajo presión reducida. El residuo resultante se disolvió en ácido clorhídrico concentrado (5 ml) a 0°C. La mezcla se agitó durante 15 minutos y después se lavó con cloroformo cinco veces. La capa acuosa se ajustó a pH 12 con una solución saturada de hidróxido de sodio a 0°C y después se ajustó a pH 7.4 con ácido clorhídrico, seguido por extracción con cloroformo. La capa orgánica se secó sobre sulfato de sodio anhidro y después se concentró bajo presión reducida. El residuo se purificó por CCDP (usando la capa inferior de cloroformo:metanol:agua = 7:3:1 como un solvente de revelado). Después, la fracción resultante se recristalizó a partir de etanol para dar 28.5 mg del compuesto del título como un sólido blanco. p.f.: 130-133°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.46 (1H, d, J=3.2 Hz), 7.73 (1H, d, J=13.8 Hz), 5.01 (1H, d, J=64.2 Hz), 4.78-4.46 (2H, m), 4.13-4.06 (1H, m), 3.91-3.84 (1H, m), 3.51 (1H, d, J=9.6 Hz), 3.34 (1H, d, J=11.0 Hz), 2.99-2.87 (2H, m), 2.71-2.64 (4H, m), 2.24-2.12 (2H, m), 1.66-1.55 (1H, m), 1.29-1.16 (1H, m).

Análisis. calculado para $C_{21}H_{22}F_3N_3O_3 \cdot 2.25H_2O \cdot 0.25$IPA: C, 54.77; H, 6.02; F, 11.95; N, 8.81.

1048

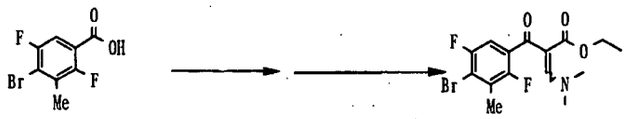
Encontrado: C, 54.82, H, 5.71; F, 11.84; N, 8.85.

IR (KBr) ν: 3414, 2970, 1723, 1616, 1580, 1546, 1508, 1458, 1434, 1394, 1363, 1320, 1103, 1023 cm^{-1}.

EJEMPLO DE REFERENCIA 216

2-(4-Bromo-2, 5-difluoro-3-metilbenzoil)-3-dimetilaminoacrilato de etilo

[Fórmula 335]



Acido 2,5-difluoro-4-bromo-3-metilbenzoico (10.7 g, 42.4 mmoles) se disolvió en tolueno (160 ml). Se añadieron cloruro de tionilo (5.00 ml, 63.9 mmoles) y dimetilformamida (5.0 ml) y la mezcla se calentó a reflujo durante dos horas. El solvente se evaporó bajo presión reducida, y el residuo se disolvió en tetrahidrofurano (300 ml). Se añadieron 3-dimetilaminoacrilato de etilo (7.30 ml, 50.9 mmoles) y trietilamina (7.60 ml, 54.5 mmoles) y la mezcla se calentó a reflujo durante tres horas. El solvente se evaporó bajo presión reducida, y diclorometano y agua se añadieron al residuo para separar las capas. Después, la capa orgánica se secó sobre sulfato de sodio anhidro, y el solvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía en columna instantánea (hexano : acetato de etilo = 2:1 → 1:1 flecha 1:2) para dar el compuesto del título (11.35 g) como un aceite amarillo.

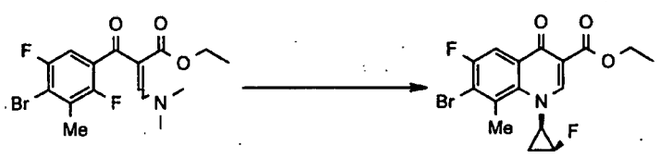
^{1}H-RMN ($CDCl_3$) δ: 7.81-7.74 (1H, m), 7.27-7.16 (1H, m), 4.00 (2H, q, J=7.1 Hz), 3.31 (3H, br s), 2.89 (3H, br s), 2.35 (3H, d, J=2.9 Hz), 0.97 (3H, t, J=7.1 Hz).

1049

EJEMPLO DE REFERENCIA 217

7-Bromo-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metil-4-oxo-1,4-dihidro-3-quinolincarboxilato de etilo

[Fórmula 336]



2-(4-Bromo-2,5-difluoro-3-metilbenzoil)-3-dimetilaminoacrilato de etilo (11.4 g, 30.2 mmoles) se disolvió en diclorometano (200 ml). Tosilato de (1R,2S)-2-fluorociclopropilamina (8.24 g, 33.3 mmoles) se añadió, y la mezcla se enfrió a -25°C. Trietilamina (6.60 ml, 47.4 mmoles) se añadió gota a gota a la solución de reacción a -25°C, y la mezcla se agitó a -15°C durante una hora y a 0°C durante 2.5 horas. El solvente se evaporó bajo presión reducida, y acetato de etilo y agua se añadieron al residuo para separar las capas. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida para dar un aminoacrilato como un aceite amarillo. El aminoacrilato resultante se disolvió en N,N-dimetilformamida (350 ml). Se añadió carbonato de cesio (19.8 g, 60.9 mmoles) y la mezcla se agitó a temperatura ambiente durante 12 horas. El solvente se evaporó bajo presión reducida, y acetato de etilo y agua se añadieron al residuo para separar las capas. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro, y el solvente se evaporó bajo presión reducida. El residuo se sometió cromatografía en columna instantánea (hexano : acetato de etilo = 9:1 → 1:1 → 1:2) para dar el compuesto del título (2.98 g) como un polvo incoloro.

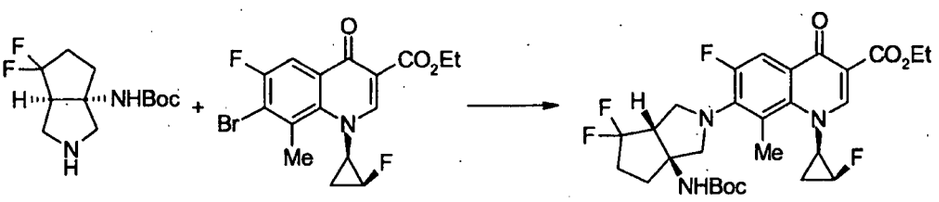
^{1}H-RMN ($CDCl_3$) δ: 8.56 (1H, d, J=3.2 Hz), 8.06 (1H, d, J=8.1 Hz), 4.98-4.73 (1H, m), 4.40 (2H, q, J=7.1 Hz), 3.91-3.82 (1H, m), 2.85 (3H, s), 1.61-

1.22 (2H, m), 1.41 (3H, t, J=7.1 Hz).

EJEMPLO DE REFERENCIA 218

7-[(1S,5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxilato de etilo

[Fórmula 337]



Una mezcla de (1S, 5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo[3.3.0] octano (318 mg, 1.21 mmoles), 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxilato de etilo (426 mg, 1.10 mmoles), 1,1'-bis (difenilfosfino) ferroceno (183 mg, 0.331 mmoles), tris (dibencilidenecetona) dipaladio (0) (101 mg, 0.110 mmoles) y carbonato de cesio (718 mg, 2.20 mmoles) en dioxano (5.51 ml) se agitó a temperatura ambiente durante 30 minutos, y a 100°C durante 11 horas bajo atmósfera de argón. La mezcla se diluyó con agua, y se extrajo con acetato de etilo y cloroformo (3x). La capa orgánica combinada se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice (acetato de etilo/hexano = 10:90 → 50:50 → 67:33 → acetato de etilo) para dar 436 mg del compuesto del título como una espuma amarilla pálida.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 2.9 Hz), 7.96 (1H, d, J = 12.9 Hz), 4.99 (1H, brs), 4.94-4.72 (1H, m), 4.39 (2H, q, J = 7.1 Hz), 3.91-

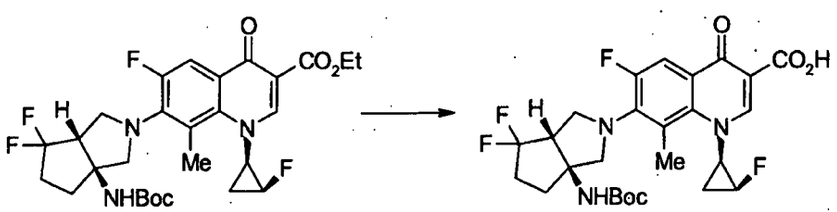
3.79 (2H, m), 3.62 (2H, s), 3.49-3.41 (1H, m), 2.91-2.76 (1H, m), 2.62 (3H, s), 2.42-2.12 (4H, m), 1.45 (9H, s), 1.61-1.43 (1H, m), 1.41 (3H, t, J = 7.1 Hz), 1.34-1.21 (1H, m).

EM(ESI) m/z: 568 $(M+H)^+$.

EJEMPLO DE REFERENCIA 219

Acido 7-[(1S,5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 338]



A una solución de 7-[(1S,5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxilato de etilo (436 mg, 0.769 mmoles) en etanol (5 ml) se añadió 1 mol/l de solución acuosa de hidróxido de sodio (0.845 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 13 horas. A la mezcla se añadió adicionalmente 1 mol/l de solución acuosa de hidróxido de sodio (0.845 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 4 horas. A la mezcla se añadió solución acuosa al 10% de ácido cítrico, y el etanol se destiló bajo presión reducida. El residuo se diluyó con agua y se extrajo con diclorometano (3x). La capa orgánica combinada se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice (acetato de etilo/hexano =

1052

1:3 → 1:1 → 2:1 → acetato de etilo) para dar 342 mg del compuesto del título como una espuma incolora.

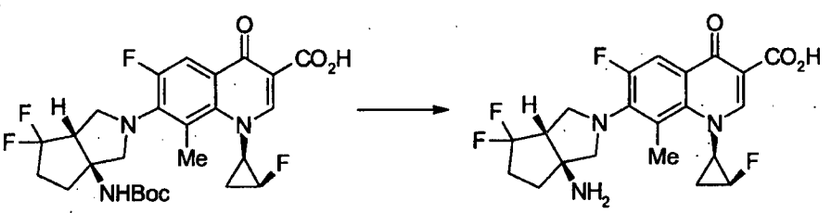
^{1}H-RMN ($CDCl_3$) δ: 14.98 (1H, s), 8.78 (1H, d, J = 2.9 Hz), 7.95 (1H, d, J = 12.7 Hz), 5.03-4.77 (2H, m), 4.02-3.87 (2H, m), 3.77-3.64 (2H, m), 3.57-3.49 (1H, m), 2.98-2.83 (1H, m), 2.66 (3H, s), 2.43-2.12 (4H, m), 1.70-1.53 (1H, m), 1.46 (9H, s), 1.40-1.26 (1H, m).

EM (ESI) m/z: 540 $(M+H)^+$.

EJEMPLO 52

Acido 7-[(1S,5R)-1-amino-6,6-difluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-(fluorociclopropl]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 339]



Acido 7-[(1S,5R)-1-ter-butoxicarbonilamino-6,6-difluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R, 2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (414 mg, 0.767 mmoles) se disolvió en ácido clorhídrico concentrado (4 ml) a 0°C y la mezcla se agitó a 0°C durante una hora. La solución acuosa se lavó con cloroformo (3 x). La mezcla se basificó a pH 12 con solución acuosa saturada de hidróxido de sodio, y después se neutralizó a pH 7.4 a 0°C. La solución se extrajo con cloroformo (5 x). La capa orgánica combinada se secó con sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se recristalizó a partir de etanol para

1053

dar 219 mg del compuesto del título como un sólido blanco.

Punto de fusión: 211-212°C.

^{1}H-RMN (400MHz, NaOD 0.1N) δ: 8.52-8.46 (1H, m), 7.79-7.67 (1H, m), 5.12-4.88 (1H, m), 4.18-4.05 (1H, m), 3.91-3.79 (1H, m), 3.68-3.55 (1H, m), 3.52-3.40 (1H, m), 3.36-3.25 (1H, m), 2.71-2.58 (4H, m), 2.45-2.28 (2H, m), 2.24-2.12 (1H, m), 1.97-1.85 (1H, m), 1.69-1.54 (1H, m), 1.38-1.17 (1H, m).

Análisis. calculado para $C_{21}H_{21}F_4N_3O_3 \cdot 0.2H_2O$: C, 56.93; H, 4.87; N, 9.49; F, 17.15.

Encontrado: C, 56.91, H, 4.83; N, 9.47; F, 17.55

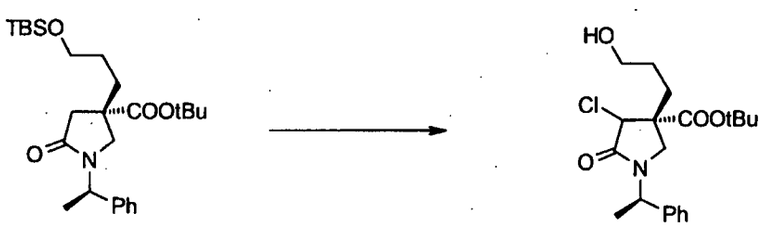
EM (ESI) m/z: 440 $(M+H)^+$.

IR (ATR) ν: 3391, 3061, 2962, 2871, 1714, 1615, 1510, 1460, 1434, 1356, 1336, 1301, 1235, 1207, 1177, 1157, 1140, 1075, 1061, 1045, 1015 cm^{-1}.

EJEMPLO DE REFERENCIA 220

Acido (3S)-4-cloro-3-(3-hidroxi-1-propil)-5-oxo-1-[(1R)-1-feniletill pirrolidin-3-carboxílico de ter-butilo

[Fórmula 340]



Bajo atmósfera de nitrógeno, a una solución de ácido (3S)-3-[3-(ter-butildimetilsililoxi)propan-1-il]-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico de ter-butilo (960 mg, 2.08 mmoles) en THF (15 ml) se añadió bis (trimetilsilil) amida de litio 1.0M en solución de THF (2.29 ml, 2.29 mmoles) a

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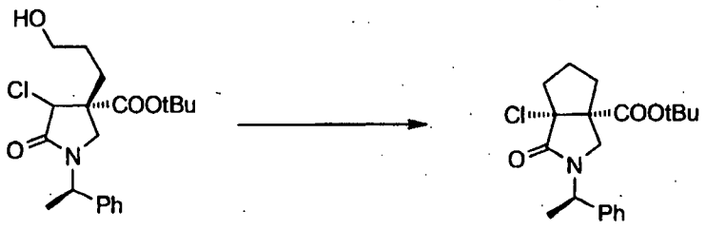
-78°C, y la mezcla se agitó durante 30 minutos. Después, se añadió N-clorosuccinimida (333 mg, 2.50 mmoles) y la mezcla se agitó durante 1 hora a -60°C, y se agitó adicionalmente durante 10 minutos a 0°C. A la mezcla se añadieron solución acuosa saturada de cloruro de amonio y acetato de etilo. La capa orgánica separada se lavó con agua y salmuera. La solución se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. A 0°C, a una solución de este residuo en THF (20 ml) se añadieron ácido acético (0.24 ml, 4.16 mmoles) y fluoruro de tetrabutilamonio 1.0M en solución de THF (4.16 ml, 4.16 mmoles), la mezcla se agitó durante 16 horas a temperatura ambiente. A la mezcla se añadieron solución acuosa al 10% de ácido cítrico y acetato de etilo. La capa orgánica separada se lavó con agua y salmuera. La solución se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice (acetato de etilo/hexano = 1:1 → 1:2) para dar 506 mg del compuesto del título como un aceite amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 7.34-7.26 (5H, m), 5.49-5.40 (1H, m), 4.75 (1H, s), 3.68-3.61 (2H, m), 3.39-3.34 (2H, m), 3.24 (0.75H, d, J = 10.0 Hz), 3.14 (0.25H, d, J = 10.9 Hz), 1.95-1.80 (2H, m), 1.68-1.40 (2H, m), 1.52 (3H, d, J = 7.1 Hz), 1.28 (9H, s).

EJEMPLO DE REFERENCIA 221

Acido (1S,5R)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico de ter-butilo

[Fórmula 341]



1055

A 0°C, a una solución de ácido (3S)-4-cloro-3-(3-hidroxipropan-1-il)-5-oxo-1-[(1R)-1-feniletil]pirrolidin-3-carboxílico de ter-butilo (500 mg, 1.31 mmoles) en diclorometano (10 ml) se añadieron tetrabromuro de carbono (434 mg, 1.31 mmoles) y trifenilfosfina (344 mg, 1.31 mmoles). Después de agitar la mezcla durante 2 horas a temperatura ambiente, tetrabromuro de carbono (143 mg, 0.431 mmoles) y trifenilfosfina (114 mg, 0.434 mmoles) se añadieron a la mezcla. Después de agitar durante 2 horas, tetrabromuro de carbono (72 mg, 0.216 mmoles) y trifenilfosfina (57 mg, 0.217 mmoles) se añadieron y la mezcla se agitó durante 16 horas. El solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice corta (15% acetato de etilo/hexano) para dar un aceite incoloro. Bajo atmósfera de nitrógeno, a una solución de este aceite en THF (12 ml) se añadió bis (trimetilsilil) amida de litio 1.0M en solución de THF (1.46 ml, 1.46 mmoles) a –78°C, y la mezcla de reacción se calentó a 0°C durante 2 horas. A la mezcla se añadieron solución acuosa saturada de cloruro de amonio y acetato de etilo. La capa orgánica separada se lavó con agua y salmuera. La solución se secó sobre sulfato de sodio anhidro y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice (15% de acetato de etilo/hexano) para dar 337 mg del compuesto del título como un sólido amarillo pálido.

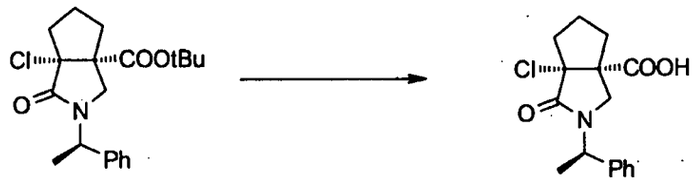
^{1}H-RMN ($CDCl_3$) δ: 7.37-7.26 (5H, m), 5.54 (1H, q, J = 7.1 Hz), 3.51 (1H, d, J = 10.7 Hz), 3.02 (1H, d, J = 10.7 Hz), 2.76-2.71 (1H, m), 2.52-2.45 (1H, m), 2.38-2.30 (1H, m), 2.02-1.96 (1H, m), 1.74-1.60 (2H, m), 1.53 (3H, d, J= 7.1 Hz), 1.45 (9H, s).

1056

EJEMPLO DE REFERENCIA 222

Acido (1S,5R)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3.3.0]octan-1-ilcarboxílico

[Fórmula 342]



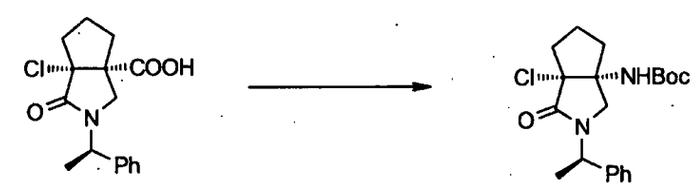
Una mezcla de ácido (1S,5R)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico de ter-butilo (332 mg, 0.912 mmoles) y ácido trifluoroacético (2 ml) en diclorometano (4 ml) se agitó durante 14.5 horas a temperatura ambiente. El solvente se destiló bajo presión reducida. Al residuo se añadió éter dietílico (3 ml), y después el precipitado se recogió por filtración para dar 245 mg del compuesto del título como un sólido incoloro.

^{1}H-RMN ($CDCl_3$) δ: 7.38-7.26 (5H, m), 5.50 (1H, q, J = 7.1 Hz), 3.53 (1H, d, J = 10.7 Hz), 3.07 (1H, d, J = 10.8 Hz), 2.78-2.73 (1H, m), 2.63-2.56 (1H, m), 2.41-2.33 (1H, m), 2.05-2.01 (1H, m), 1.79-1.63 (2H, m), 1.54 (3H, d, J = 7.1 Hz).

EJEMPLO DE REFERENCIA 223

(1R,5R)-1-(ter-Butoxicarbonilamino)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 343]



1057

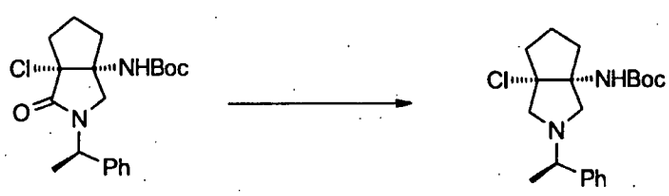
Una solución de ácido (1S,5R)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octan-1-ilcarboxílico (239 mg, 0.777 mmoles), trietilamina (0.215 ml, 1.55 mmoles) y difenilfosforil azida (0.184 ml, 0.855 mmoles) en tolueno (6 ml) se agitó durante 30 minutos a 80°C. El solvente se destiló bajo presión reducida. A una solución del residuo en 1,4-dioxano (5 ml) se añadió solución acuosa 6N de ácido clorhídrico (5 ml). La mezcla se agitó durante 5 horas a 50°C. El solvente se destiló bajo presión reducida. Al residuo se añadió solución acuosa 1N de hidróxido de sodio. La solución se extrajo con $CHCl_3$ dos veces, y las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro y el solvente se destiló bajo presión reducida. Una mezcla del residuo y dicarbonato de di-ter-butilo (847 mg, 3.89 mmoles) se agitó durante 3 horas a 50°C y la mezcla se purificó por cromatografía en columna instantánea de gel de sílice (15% de acetato de etilo/hexano) para dar 222 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 7.37-7.26 (5H, m), 5.50 (1H, q, J = 6.9 Hz), 5.25 (1H, brs), 3.66 (1H, brd, J = 10.0 Hz), 2.96 (1H, d, J = 6.8 Hz), 2.76-2.69 (1H, m), 2.55-2.51 (1H, m), 2.18-2.08 (1H, m), 1.98-1.84 (2H, m), 1.51 (3H, d, J = 7.1 Hz), 1.65-1.50 (1H, m), 1.40 (9H, s).

EJEMPLO DE REFERENCIA 224

(1R, 5R)-1-(ter-Butoxicarbonilamino)-5-cloro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano

[Fórmula 344]



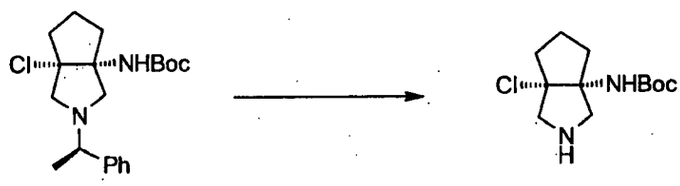
Bajo atmósfera de nitrógeno, a una solución de (1R, 5R)-1-(ter-butoxicarbonilamino)-5-cloro-4-oxo-3-[(1R)-1-feniletil]-3-azabiciclo[3.3.0] octano (217 mg, 0.573 mmoles) en THF (10 ml) se añadió complejo de borano 1.0M-THF en solución de THF (1.72 ml, 1.72 mmoles) a temperatura ambiente. Después de agitar durante 14 horas, se añadió complejo de borano 1.0M-THF en solución de THF (0.86 ml, 0.86 mmoles). La mezcla se calentó a 50°C, y se agitó durante 18 horas. A la mezcla se añadió adicionalmente complejo de borano 1.0M-THF en solución de THF (0.86 ml, 0.86 mmoles) y la mezcla se agitó durante 24 horas a 50°C. Después de enfriarse a 0°C, a la mezcla se añadieron agua (1 ml), EtOH (9 ml) y trietilamina (1 ml). La mezcla se calentó a 80°C, y se agitó durante 2 horas. El solvente se destiló bajo presión reducida. Al residuo se añadieron solución acuosa saturada de cloruro de amonio y acetato de etilo. La capa orgánica separada se lavó con agua y salmuera. La solución se secó sobre sulfato de sodio anhidro y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía en columna instantánea de gel de sílice (10% de acetato de etilo/hexano) para dar 67.3 mg del compuesto del título como un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 7.29-7.19 (5H, m), 5.53 (1H, brs), 3.22 (1H, q, J = 6.8 Hz), 3.07 (1H, brd, J = 8.8 Hz), 2.93 (1H, brd, J = 8.7 Hz), 2.82-2.71 (1H, m), 2.64-2.57 (1H, m), 2.27-2.15 (2H, m), 2.09-2.06 (2H, m), 1.74-1.67 (2H, m), 1.55 (9H, s), 1.31 (3H, d, J = 6.6 Hz).

EJEMPLO DE REFERENCIA 225

(1R, 5R)-1-(ter-Butoxicarbonilamino)-5-cloro-3-azabiciclo [3.3.0] octano

[Fórmula 345]



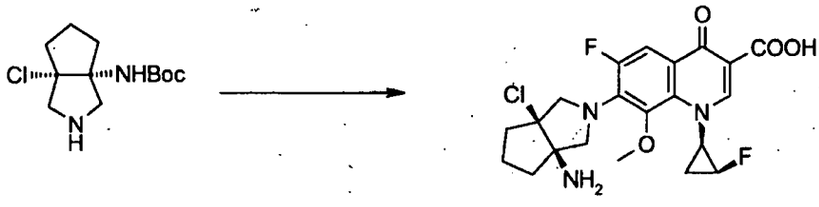
Bajo atmósfera de hidrógeno, una mezcla de (1R,5R)-1-(ter-butoxicarbonilamino)-5-cloro-3-[(1R)-1-feniletil]-3-azabiciclo [3.3.0] octano (63.0 mg, 0.173 mmoles), 10% de Pd-C (50% en peso, M, 32 mg) en metanol (6 ml) se agitó durante 4 horas a temperatura ambiente y durante 19 horas a 40°C. Después de remover el catalizador por filtración, el filtrado se destiló bajo presión reducida.

EM (ESI) m/z : 261 $(M + H)^+$.

EJEMPLO 53

Acido 7-[(1R,5R)-1-amino-5-cloro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 346]



Una mezcla de (1R,5R)-1-(ter-butoxicarbonilamino)-5-cloro-3-azabiciclo [3.3.0] octano (45.0 mg, 0.173 mmoles), complejo de ácido 6,7-difluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-difluoroboro (62.3 mg, 0.173 mmoles) y trietilamina (0.0598 ml, 0.433 mmoles) en sulfóxido de dimetilo (3 ml) se agitó durante 45 horas a 45°C. A la mezcla se añadieron agua (1 ml), EtOH (9 ml) y trietilamina (1 ml). La mezcla se agitó durante 1.5 horas a 80°C. Después de enfriarse a temperatura ambiente, el solvente se destiló bajo presión reducida. Al residuo se añadieron solución acuosa al 10% de ácido cítrico y acetato de etilo. La capa orgánica separada se

LOGO

lavó con H_2O y salmuera. La solución se secó sobre sulfato de sodio anhidro y el solvente se destiló bajo presión reducida. El residuo se purificó por TLC (5% de MeOH/$CHCl_3$) para dar 48.0 mg del compuesto N-Boc protegido como un aceite amarillo. A este aceite se añadió ácido clorhídrico y la mezcla se agitó durante 30 minutos a temperatura ambiente. La mezcla se basificó a pH 12 con solución acuosa de hidróxido de sodio, y después se neutralizó a pH 7.8 a 0°C. La solución se extrajo con cloroformo dos veces. Las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se secó bajo presión reducida para dar 33.9 mg del compuesto del título como un sólido amarillo pálido.

Punto de fusión: 161-163°C.

^{1}H-RMN (400MHz, NaOD 0.1N) δ: 8.48 (1H, s), 7.70 (1H, d, J = 14.2 Hz), 5.07-4.85 (1H, m), 4.19-4.08 (2H, m), 3.92 (1H, d, J = 11.8 Hz), 3.76-3.63 (5H, m), 2.48-2.41 (1H, m), 2.30-2.25 (1H, m), 2.08-1.87 (4H, m), 1.70-1.51 (2H, m), 1.19 (1.8H, t, J = 7.2 Hz).

Análisis calculado para $C_{21}H_{22}ClF_4N_3O_3 \cdot 0.6EtOH$: C, 55.38; H, 5.36; N, 8.73; F, 7.89; Cl, 7.36.

Encontrado: C, 55.24, H, 4.91; N, 8.85; F, 8.27; Cl, 6.92.

EM (ESI) m/z: 454 $(M + H)^+$.

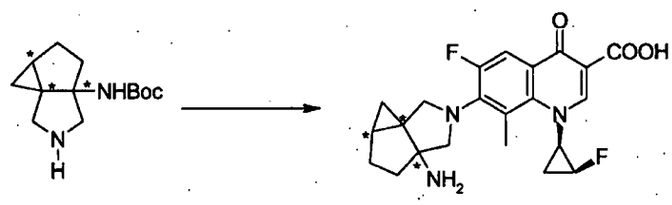
IR (ATR) ν: 3384, 3075, 2880, 1728, 1621, 1513, 1453, 1360, 1318, 1188, 1136, 1120, 1103, 1056 cm^{-1}.

EJEMPLO 54

Acido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-8-metil-4-oxo-1,4-dihidroquinolin-3-carboxílico ácido (posición 7: derivado del isómero óptico A)

1061

[Fórmula 347]



A una solución de tris (dibencilidenacetona) dipaladio (0) (332 mg, 0.363 mmoles) y 4,5-bis(difenil)fosfino-9,9-dimetilxanteno (462 mg, 0.798 mmoles) en 1,4-dioxano (9.06 ml) se añadieron 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metil-1,4-dihidro-4-oxoquinolin-3-carboxilato de etilo (350 mg, 0.906 mmoles), 6-ter-butoxicarbonilamino-8-azatriciclo[4.3.0.$0^{1,3}$] nonano (216 mg, 0.906 mmoles) y carbonato de cesio (355 mg, 1.09 mmoles) y la mezcla se agitó a 90°C durante 22 horas bajo atmósfera de nitrógeno. La mezcla de reacción se diluyó con agua (80 ml) y se extrajo con acetato de etilo (90 ml). La capa orgánica se lavó con solución acuosa saturada de cloruro de sodio (80 ml) y se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (cloroformo-metanol; 100:0 → 99:1 → 98:2) para dar un sólido amarillo pálido. A una solución de este sólido en etanol (3.32 ml) se añadió 1 mol/l solución acuosa de hidróxido de sodio (1.50 ml) en un baño de hielo y la mezcla se agitó a temperatura ambiente durante 14 horas. A esta solución de reacción se añadió 1 mol/l de solución acuosa de ácido clorhídrico (1.50 ml) en un baño de hielo y la capa orgánica se concentró bajo presión reducida. La solución acuosa se diluyó con agua (30 ml) y se extrajo con acetato de etilo (40 ml). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (cloroformo-metanol; 100:0 → 99:1 → 98:2) para dar un sólido amarillo pálido. El sólido se

1062

disolvió en ácido clorhídrico concentrado (1.0 ml) en un baño de hielo y la solución acuosa se lavó con cloroformo (25 ml x 3). A la capa acuosa se añadió solución saturada de hidróxido de sodio para ajustar pH a 12.0 y lac solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (120 ml x 1, 80 ml x 2). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol para dar el compuesto del título 68.1 mg (18%) as sólido amarillo pálido. p.f.: 145-149°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.43 (1H, d, J = 3.2 Hz), 7.70 (1H, d, J = 14.2 Hz), 5.12-4.92 (1H, m), 4.29 (1H, d, J = 9.2 Hz), 4.12-4.07 (1H, m), 3.91-3.88 (1H, m), 3.24 (1H, d, J = 9.6 Hz), 3.08 (1H, d, J = 9.2 Hz), 2.54 (3H, s), 2.08-1.97 (1H, m), 1.92-1.87 (1H, m), 1.79-1.74 (1H, m), 1.65-1.55 (1H, m), 1.32-1.19 (3H, m), 0.84-0.76 (2H, m).

Análisis calculado para $C_{22}H_{23}F_2N_3O_3 \cdot 1.5H_2O$: C, 59.72; H, 5.92; F, 8.59; N, 9.50.

Encontrado: C, 59.72; H, 5.65; F, 59.08; N, 9.47.

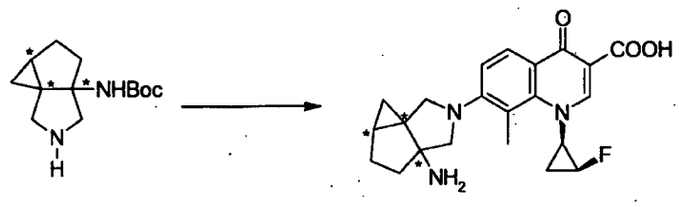
EM (ESI) m/z: 416 $(M + H)^+$.

IR (ATR): 2939, 2867, 1719, 1612, 1542, 1507, 1460, 1428, 1354, 1314, 1284, 1184, 1136, 1024, 967, 921, 884, 806 cm^{-1}

EJEMPLO 55

Acido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-1-[(1R,2S)-2-fluorociclopropan-1-il]-8-metil-4-oxo-1,4-dihidroquinolin-3-carboxílico (posición 7: derivado del isómero óptico A)

[Fórmula 348]



1063

A una solución de 6-ter-butoxicarbonilamino-8-azatriciclo[4.3.0.0^{1,3}]nonano (290 mg, 1.22 mmoles) en sulfóxido de dimetilo (2.42 ml) se añadieron trietilamina (0.507 ml, 3.63 mmoles) y ácido 7-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (337 mg, 1.21 mmoles) y la mezcla se agitó a 70°C durante 13 días bajo atmósfera de nitrógeno. La solución de reacción se diluyó con acetato de etilo y se lavó con solución acuosa al 10% de ácido cítrico (50 ml), agua (60 ml), y solución acuosa saturada de cloruro de sodio (60 ml). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (cloroformo-metanol; 100:0 → 99:1 → 98:2 → 95:5) para dar un sólido amarillo pálido. El sólido se disolvió en ácido clorhídrico concentrado (1.0 ml) en un baño de hielo y la solución acuosa se lavó con cloroformo (30 ml x 5) A la capa acuosa se añadió solución acuosa saturada de hidróxido de sodio para ajustar pH a 12.0 y la solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (80 ml x 4) y 10% de metanol-cloroformo (80 ml x 1, 50 ml x 1). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol para dar el compuesto del título 138 mg (29%) como un sólido amarillo pálido, p.f.: >254°C (decomp.).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.42 (1H, d, J = 3.9 Hz), 8.00 (1H, d, J = 9.3 Hz), 7.14 (1H, d, J = 9.0 Hz), 5.13-4.94 (1H, m), 4.32 (1H, d, J = 10.0 Hz), 4.10-4.04 (1H, m), 3.73 (1H, d, J= 10.3 Hz), 3.23 (1H, d, J = 10.0 Hz), 3.00 (1H, d, J = 10.3 Hz), 2.46 (3H, s), 2.04-1.92 (2H, m), 1.79-1.73 (1H, m), 1.66-1.55 (1H, m), 1.35-1.17 (3H, m), 0.86-0.77 (2H, m).

Análisis calculado para $C_{22}H_{24}FN_3O_3$ 0.25H_2O: C, 65.74; H, 6.14; F,

4.73; N, 10.45.

Encontrado: C, 65.84; H, 6.28; F, 5.00; N, 10.41.

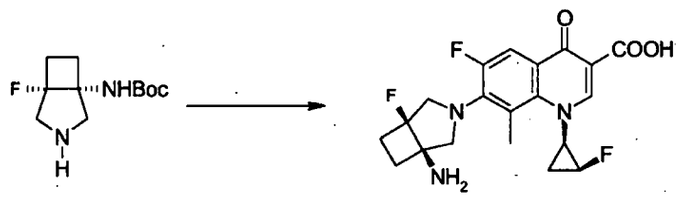
EM (ESI) m/z: 398 $(M + H)^+$.

IR (ATR): 3376, 3030, 2989, 2929, 2858, 1703, 1614, 1547, 1510, 1450, 1430, 1387, 1354, 1337, 1313, 1295, 1266, 1230, 1189, 1177, 1153, 1138, 1090, 1079, 1054, 1022, 998, 990, 923 cm^{-1}.

EJEMPLO 56

Acido 7-{(1R,5S)-1-amino-5-fluoro-3-azabiciclo[3.2.0]heptan-3-il}-6-fluoro-1-[(1R, 2S)-2-fluorociclopropan-1-il]-8-metil-4-oxo-1,4-dihidroquinolin-3-carboxílico

[Fórmula 349]



A una solución de tris(dibencilidenacetona) dipaladio (0) (414 mg, 0.452 mmoles) y 4,5-bis(difenil)fosfino-9,9-dimetilxanteno (522 mg, 0.902 mmoles) en 1,4-dioxano (20.0 ml) se añadieron 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metil-1,4-dihidro-4-oxoquinolin-3-carboxilato de etilo (1.28 g, 3.31 mmoles), (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo [3.2.0] heptano (693 mg, 3.01 mmoles) y carbonato de cesio (1.96 g, 6.02 mmoles) y la mezcla se agitó a 95°C durante 14 horas bajo atmósfera de nitrógeno. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en

columna sobre gel de sílice (n-hexano-acetato de etilo; 100:0 → 95:5 → 90:10 → 75:25 → 5:95 → 0:100) para dar un sólido amarillo pálido. A una solución de este sólido en etanol (15.9 ml) se añadió 1 mol/l de solución acuosa de hidróxido de sodio (5.98 ml) en un baño de hielo y la mezcla se agitó a temperatura ambiente durante 13 horas. A esta solución de reacción se añadió 1 mol/l de solución acuosa de ácido clorhídrico (5.98 ml) en un baño de hielo y la capa orgánica se concentró bajo presión reducida. La solución acuosa se diluyó con agua (80 ml) y se extrajo con acetato de etilo (100 ml x 1, 80 ml x 1). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (cloroformo-metanol; 100:0 → 99:1 → 98:2→ 97:3 → 96:4→ 95:5 flecha 94:6-» 93:7) para dar un sólido amarillo pálido. El sólido se disolvió en ácido clorhídrico concentrado (3.0 ml) en un baño de hielo y la solución acuosa se lavó con cloroformo (40 ml x 4). A la capa acuosa se añadió solución saturada de hidróxido de sodio para ajustar pH a 12.0 y la solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (250 ml x 4). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de etanol para dar el compuesto del título 690 mg (56%) como sólido amarillo pálido, p.f.: >272°C (decomp.).

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.49 (1H, d, J = 2.2 Hz), 7.70 (1H, dd, J = 13.2, 4.2 Hz), 5.08-4.88 (1H, m), 4.12-4.06 (1H, m), 3.69-3.56 (2H, m), 3.42-3.39 (1H, m), 3.21-3.18 (1H, m), 2.64 (3H, d, J = 5.1 Hz), 2.54-2.39 (1H, m), 2.31-2.20 (1H, m), 2.12-1.93 (2H, m), 1.66-1.56 (1H, m), 1.32-1.19 (1H, m).

Análisis calculado para $C_{20}H_{20}F_3N_3O_3$: C, 58.96; H, 4.95; F, 13.99; N, 10.31.

1066

Encontrado: C, 58.76; H, 4.88; F, 14.11; N, 10.28.

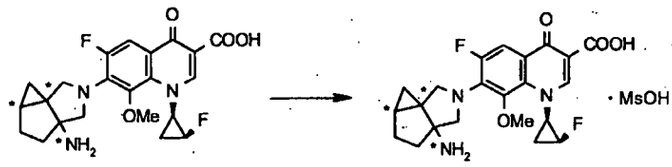
EM (ESI) m/z: 408 $(M + H)^+$.

IR (ATR): 3089, 2980, 2936, 2862, 2837, 1719, 1614, 1544, 1506, 1474, 1454, 1432, 1350, 1318, 1268, 1231, 1213, 1181, 1159, 1140, 1093, 1058, 1047, 1021, 1009, 977, 962, 930, 898, 864, 837, 805 cm^{-1}.

EJEMPLO 57

Metansulfonato de ácido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-8-metoxi-4-oxo-1,4-dihidroquinolin-3-carboxílico

[Fórmula 350]



A una suspensión de ácido 7-[6-amino-8-azatriciclo [4.3.0.0^{1,3}] nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan-1-il]-8-metoxi-4-oxo-1,4-dihidroquinolin-3-carboxílico (2.24 g, 4.82 mmoles) en etanol (48.2 ml) se añadió ácido metansulfónico (0.316 ml, 4.87 mmoles) y la mezcla se agitó a temperatura ambiente durante 15 horas. A esta solución de reacción se añadió agua (5 ml) y la mezcla se concentró bajo presión reducida. A este residuo se añadió 2-propanol (20 ml) y la mezcla se agitó a temperatura ambiente durante 15 horas. Los sólidos precipitados se recogieron por filtración. Los sólidos se lavaron con una cantidad en exceso de 2-propanol para dar el compuesto del título 2.41 g (95%) como sólido amarillo pálido. p.f.: 202-204°C.

^{1}H-RMN (400 MHz, NaOD 0.1N) δ: 8.39 (1H, d, J = 2.9 Hz), 7.64 (1H, d, J = 14.4 Hz), 5.09-4.93 (1H, m), 4.21 (1H, dd, J = 10.0, 2.7 Hz), 3.97 (1H,

1067

dt, J = 10.0, 4.6 Hz), 3.72 (1H, dd, J = 10.6, 2.7 Hz), 3.53 (3H, s), 3.39 (1H, d, J = 10.3 Hz), 3.18 (1H, d, J = 10.3 Hz), 2.83 (3H, s), 1.99-1.85 (2H, m), 1.73 (1H, dd, J = 12.2, 8.5 Hz), 1.56-1.46 (1H, m), 1.39-1.23 (2H, m), 1.17-1.13 (1H, m), 0.79-0.74 (2H, m).

Análisis calculado para $C_{22}H_{23}F_2N_3O_4$ CH_4O_3S $0.5H_2O$: C, 51.49; H, 5.26; F, 7.08; N, 7.83; S, 5.98.

Encontrado: C, 51.21; H, 5.20; F, 7.44; N, 7.82; S, 6.00.

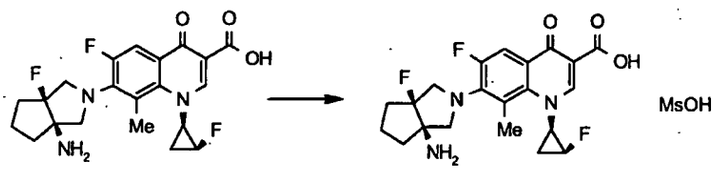
EM (ESI) m/z: 432 $(M + H)^+$.

IR (ATR): 3412, 2944, 2878, 1694, 1617, 1597, 1536, 1513, 1437, 1361, 1330, 1315, 1297, 1273, 1219, 1167, 1135, 1109, 1040, 952, 925, 883, 805 cm^{-1}.

EJEMPLO 58

Metansulfonato de ácido 7-[(1R,5S)-1-amino-5-fluoro-3-azabiciclo [3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 351]



A una suspensión de ácido 7-[(1R,5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico (4.50 g, 10.7 mmoles) en etanol (90 ml) se añadió ácido metansulfónico (0.695 ml, 10.7 mmoles), y la mezcla se agitó a temperatura ambiente durante 30 minutos. La mezcla se diluyó con agua (20

P068

ml), y se destiló bajo presión reducida. El residuo se purificó suspendiendo en 2-propanol para dar 4.96 g del compuesto del título como un polvo amarillo pálido.

^{1}H-RMN (400MHz, NaOD 0.1N) δ: 8.48 (1H, d, J=2.9Hz), 7.72 (1H, d, J=13.7Hz), 5.11-4.86 (1H,m), 4.15-4.07 (1H, m), 3.93-3.81 (1H,m), 3.60-3.31 (3H, m), 2.82 (3H, s),.62 (3H, s), 2.16-1.98 (3H, m), 1.92-1.55 (4H, m), 1.33-1.19 (1H, m).

EM(FAB); m/z: 422 $(M+H)^+$.

Análisis calculado para $C_{21}H_{22}F_3N_3O_3 \cdot CH_3SO_3H \cdot 1.75H_2O$: C, 48.13, H, 5.42; F, 10.38, N, 7.65; S, 5.84.

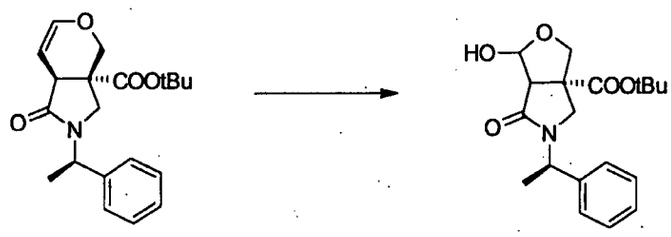
Encontrado: C, 47.81; H, 5.09; F, 10.43; N, 7.63; S, 5.75.

IR (ATR) ν: 3442, 2871, 1709, 1615, 1509, 1432, 1370, 1319, 1265, 1161, 1038, 971, 929, 892, 853, 806 cm^{-1}.

EJEMPLO DE REFERENCIA 226

Ester ter-butílico de ácido (3aS)-1-hidroxi-6-oxo-5-[(R)-1-feniletil] tetrahidrofuro [3,4-c] pirrol-3a-carboxílico

[Fórmula 352]



Una mezcla de éster ter-butílico de ácido (3aS, 7aS)-1-oxo-2-[(R)-1-feniletil]-1,2,3,7a-tetrahidropirano[3,4-c]pirrol-3a-carboxílico (4.0 g, 11.6 mmoles), N-óxido de N-metilmorfolina (2.95 g, 22.0 mmoles) y tetróxido de osmio (cat.) se disolvió en ter-butanol (20 ml) y agua (10 ml), y se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se diluyó con

L069

AcOEt y se añadió tiosulfato de sodio acuoso al 10%. Las capas se separaron y la capa acuosa se extrajo con AcOEt. Los extractos combinados se lavaron con $NaHCO_3$ ac. sat., salmuera, se secaron (Na_2SO_4), y se concentraron al vacío, dando un aceite café oscuro (4.4 g). El producto crudo (2.6 g) se disolvió en tetrahidrofurano (60 ml) y agua (30 ml), y se añadió peryodato de sodio (2.6 g). La mezcla de reacción se agitó a temperatura ambiente durante 18 hr, y se diluyó con AcOEt y agua. Las capas se separaron y la capa acuosa se extrajo con AcOEt. Los extractos combinados se lavaron con $NaHCO_3$ ac. sat., salmuera, se secaron (Na_2SO_4), y se concentraron al vacío. El residuo se disolvió en etanol y tetrahidrofurano (20 ml; 17:3) y NaOH ac. 1N (5.2 ml) se añadió gota a gota a 0°C. La mezcla se agitó a temperatura ambiente durante 3 hr, tiempo después del cual NaOH ac. 1N adicional (2.2 ml) se añadió y la mezcla de reacción se agitó durante 1 hr más. El solvente se removió al vacío y el residuo resultante se dividió entre AcOEt y agua, y la capa acuosa se extrajo. Los extractos combinados se lavaron con $NaHCO_3$ ac. sat., salmuera, se secaron (Na_2SO_4), y se concentraron al vacío. El residuo resultante se purificó por cromatografía sobre gel de sílice eluyendo con 50% de AcOEt en hexano para dar el compuesto del título (1.10 g) como un sólido blanco.

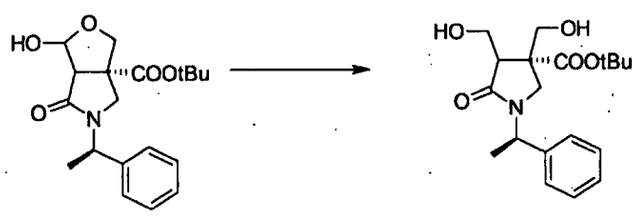
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.71 (1H, d, J = 7.3 Hz), 5.66-5.44 (1.2H, m), 4.96 (0.2H, d, J = 7.3 Hz), 4.49 (0.8H, d, J = 9.6 Hz), 4.25 (0.2H, d, J = 9.6 Hz), 4.00 (0.2H, d, J = 9.2 Hz), 3.90 (0.8H, d, J = 9.2 Hz), 3.64 (0.8H, d, J = 7.3 Hz), 3.38-3.24 (3H, m), 1.54-1.38 (12H, m).

EM (ESI) m/z :348 $(M + H)^+$.

EJEMPLO DE REFERENCIA 227

Ester ter-butílico de ácido (3S)-3,4-bis(hidroximetil)-5-oxo-1-[(R)-1-feniletil] pirrolidin-3-carboxílico

[Fórmula 353]



A una solución enfriada (-20°C) de éster ter-butílico de ácido (3aS)-1-hidroxi-6-oxo-5-[(R)-1-feniletil]tetrahidrofuro[3,4-c]pirrol-3a-carboxílico (350 mg, 1.01 mmoles) en tetrahidrofurano y etanol (10 ml; 4:1), Borohidruro de sodio (38.0 mg, 1.00 mmoles) se añadió en porciones, y la mezcla se agitó a la misma temperatura durante 5.5 hr. La mezcla de reacción se concentró al vacío y recogió en AcOEt y agua. Las capas se separaron y la capa acuosa se extrajo con AcOEt. Los extractos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con 90% de AcOEt en hexano para dar el compuesto del título (153 mg) como un aceite incoloro.

^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.50 (1H, q, J = 7.0 Hz), 4.19-3.80 (4H, m), 3.40-3.05 (5H, m), 1.52 (3H, d, J = 7.0 Hz), 1.40 (9H, s).

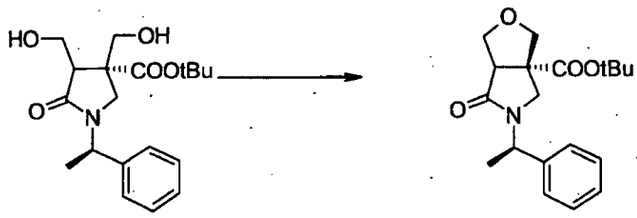
EM (ESI) m/z:350 $(M + H)^+$.

EJEMPLO DE REFERENCIA 228

Ester ter-butílico de ácido (3aS)-6-oxo-5-[(R)-1-feniletil]tetrahidrofuro [3,4-c] pirrol-3a-carboxílico

[Fórmula 354]

2071



A una solución enfriada (0°C) de éster ter-butílico de ácido (3S)-3,4-bis(hidroximetil)-5-oxo-1-[(R)-1-feniletil]pirrolidin-3-carboxílico (710 mg, 2.03 mmoles) y trifenilfosfina (450 mg, 2.64 mmoles) en tetrahidrofurano (10 ml) se añadió una solución de azodicarboxilato de dietilo al 40% en tolueno (1.06 ml, 2.33 mmoles) gota a gota. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 6 hr. La mezcla se concentró al vacío. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con AcOEt al 40% en hexano para dar el compuesto del título (435 mg) como un sólido blanco.

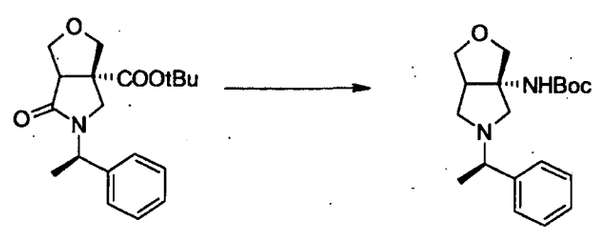
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.39-7.25 (5H, m), 5.48 (1H, q, J = 7.2 Hz), 4.32-4.26 (1H, m), 4.01 (1H, d, J = 9.6 Hz), 3.97-3.91 (1H, m), 3.85 (1H, d, J = 9.6 Hz), 3.43 (1H, d, J = 10.1 Hz), 3.37-3.32 (1H, m), 3.26 (1H, d, J = 10.1 Hz), 1.54 (3H, d, J = 6.9 Hz), 1.38 (9H, br s).

EM (ESI) m/z:332 $(M + H)^+$.

EJEMPLO DE REFERENCIA 229

Ester ter-butílico de ácido [(3aS)-5-[(R)-1-feniletil] tetrahidrofuro [3,4-c] pirrol-3a-il] carbámico

[Fórmula 355]



A una solución de éster ter-butílico de ácido [(3aS)-6-oxo-5-[(R)-1-feniletil] tetrahidrofuro [3,4-c] pirrol-3a-il] carbámico (820 mg, 2.47 mmoles) en diclorometano (8 ml) se añadió ácido trifluoroacético (8 ml), y la mezcla se agitó a temperatura ambiente durante 2 hr. El solvente se removió al vacío y se bombeó a sequedad, dando un sólido blanco (680 mg).

1,1'-carbonibis-1H-imidazol (480 mg, 2.94 mmoles) se añadió a una solución del producto crudo (540 mg) en acetonitrilo (10 ml) a 0°C, y la mezcla se agitó durante 1 hr a la misma temperatura y después se calentó a temperatura ambiente. Amoniaco gaseoso se hizo burbujear a través de la mezcla de reacción durante 30 min y el solvente se concentró al vacío. El residuo resultante se recogió en diclorometano, se lavó con HCl 1N, $NaHCO_3$ ac. sat. y salmuera, se secó (Na_2SO_4), y se concentró al vacío para dar un sólido blanco (536 mg).

A una suspensión del sólido blanco (536 mg) en ter-butanol (20 ml) se añadió tetraacetato de plomo (1.73 g, 3.90 mmoles), y la mezcla se calentó a 100°C durante 5 hr. La mezcla de reacción se dejó enfriar a temperatura ambiente, se diluyó con éter dietílico (200 ml) y se añadió bicarbonato de sodio (3 g). Después de agitar durante 30 min, el precipitado se filtró. El filtrado se concentró al vacío, y el residuo se recogió en diclorometano, se lavó con $NaHCO_3$ ac. sat. y salmuera, se secó (Na_2SO_4), y se concentró al vacío. El producto crudo se obtuvo como un sólido blanco (620 mg).

Se añadió ácido trifluoroacético (6 ml) a una solución del producto crudo (200 mg) en diclorometano (6 ml), y la mezcla de reacción se agitó durante 1 hr, después el solvente se removió al vacío y se bombeó a sequedad. Esto se llevó al siguiente paso.

A una solución de este material en tolueno (6 ml) se añadió

lentamente hidruro de bis(2-metoxietoxi)aluminio-sodio (65% en solución de tolueno, 690 µl, 2.3 mmoles), y la mezcla se calentó a 60°C durante 1 hr. La mezcla de reacción se enfrió a temperatura ambiente, después NaOH ac. 5N se añadió y se agitó durante 1 hr. Las capas se separaron y la capa acuosa se extrajo con tolueno. Los extractos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron al vacío. El producto crudo (540 mg) se llevó a cabo sin purificación.

Dicarbonato de di-ter-butilo (589 mg) se añadió a una solución del producto crudo en diclorometano (6 ml), y la mezcla se agitó durante 18 hr y el solvente se removió al vacío. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con AcOEt al 30% en hexano para dar el compuesto del título (150 mg) como un sólido blanco.

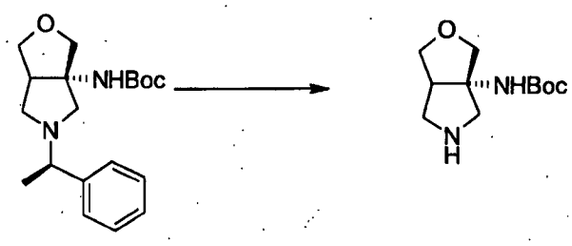
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.31-7.21 (5H, m), 5.00 (1H, s), 4.09-3.78 (3H, m), 3.53 (1H, dd, J = 8.7, 4.6 Hz), 3.27 (1H, q, J = 6.7 Hz), 2.78-2.65 (3H, m), 2.50-2.36 (2H, m), 1.42 (9H, s), 1.33 (3H, d, J = 6.4 Hz).

EM (ESI) m/z: 333 $(M + H)^+$

EJEMPLO DE REFERENCIA 230

Ester ter-butílico de ácido (3aS)-(ttrahidrofuro [3,4-c] pirrol-3a-il) carbámico

[Fórmula 356]



Ester ter-butílico de ácido (3aS)-5-[(R)-1-feniletil] tetrahidrofuro [3,4-c]pirrol-3a-il] carbámico (355 mg, 1.06 mmoles) se disolvió en dioxano (10

2074

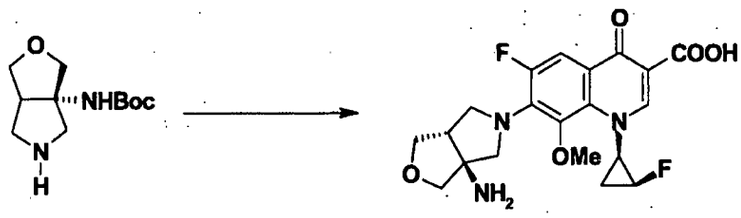
ml) y se añadió catalizador de hidróxido de paladio al 20% (20 % en peso Pd sobre carbón, húmedo; cat.). La mezcla se agitó vigorosamente bajo una atmósfera de hidrógeno a 40°C durante 24 hr. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida. El residuo se recogió en diclorometano, y se lavó con NaOH ac. 1N y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y el solvente se removió al vacío para dar el compuesto del título crudo (243 mg) como un jarabe incoloro.

EM (ESI) m/z: 229 $(M + H)^+$.

EJEMPLO 59

Acido 7-[(3aS)-3a-aminotetrahidrofuro[3,4-c]pirrol-5-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 357]



A una solución de complejo de ácido 6,7-difluoro-1-[(2S,1R)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-difluoroboro (426 mg, 1.18 mmoles) en sulfóxido de dimetilo (6 ml) se añadieron éster ter-butílico de ácido (S)-(tetrahidro-2-oxa-5-azaciclopropa[c]pentalen-3a-il) carbámico (270 mg, 1.18 mmoles) y trietilamina (0.50 ml, 3.54 mmoles), y la mezcla se agitó a 40°C durante 17 hr. La solución de reacción se concentró al vacío, y el concentrado se disolvió en una solución mixta de etanol y agua (9:1) (150 ml). Después de añadir trietilamina (5 ml), la mezcla se calentó bajo reflujo durante 5 hr. La mezcla de reacción se concentró bajo presión reducida, y el

concentrado se disolvió en AcOEt (100 ml x 2), y se lavó con ácido cítrico ac. al 10% (100 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. Después de purificación por cromatografía en columna sobre gel de sílice (3% de MeOH en $CHCl_3$), el sólido obtenido se disolvió en ácido clorhídrico concentrado (5 ml) en un baño de hielo, y la solución acuosa se lavó con cloroformo (50 ml x 3). A la capa acuosa se añadió 10 mol/l de solución acuosa de hidróxido de sodio para ajustar pH a 12.0, y la solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (100 ml x 6) y los extractos combinados se secaron con sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía preparativa, y se purificó adicionalmente por recristalización a partir de etanol, y subsecuentemente, se secó bajo presión reducida para dar el compuesto del título (220 mg) como cristales amarillo pálido. p.f.: 201-202°C.

^{1}H-RMN (400MHz, $CDCl_3$) δ: 8.76 (1H, d, J = 1.4 Hz), 7.87 (1H, d, J = 12.8 Hz), 4.92-4.71 (1H, m), 4.27 (1H, dd, J = 9.2, 7.3 Hz), 3.93-3.57 (11H, m), 2.57-2.49 (1H, m), 1.68-1.47 (2H, m).

Análisis calculado para $C_{20}H_{21}F_2N_3O_5$ H_2O:C, 54.67; H, 5.28, N, 9.56; F, 8.65.

Encontrado: C, 54.52; H, 5.18; N, 9.58; F, 8.73.

EM (ESI) m/z: 422 $(M + H)^+$.

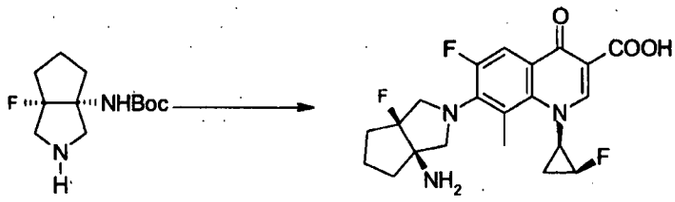
IR (ATR) ν: 3301, 2974, 2847, 1722, 1614, 1580, 1516, 1447, 1403, 1378, 1365, 1355, 1340, 1316, 1289, 1265 cm^{-1}.

1078.

EJEMPLO 60

Acido 7-[(1R, 5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0] octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropan]-1,4-dihidro-8-metil-4-oxoquinolin-3-carboxílico

[Fórmula 358]



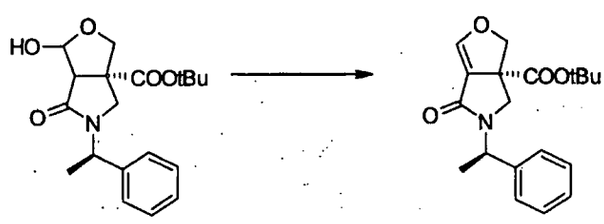
A una solución de tris (dibencilideneacetona) dipaladio (0) (7.75 g, 8.46 mmoles), 4,5-bis(difenil)fosfino-9,9-dimetilxanteno (14.7 g, 25.4 mmoles), 7-bromo-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-8-metil-1,4-dihidro-4-oxoquinolin-3-carboxilato de etilo (14.2 g, 36.8 mmoles) y (1R,5S)-1-(ter-butoxicarbonilamino)-5-fluoro-3-azabiciclo [3.3.0] octano (6.90 g, 28.2 mmoles) en 1,4-dioxano (345 ml) se añadieron carbonato de cesio (18.4 g, 56.5 mmoles) y la mezcla se agitó a 110°C durante 23 horas bajo atmósfera de nitrógeno. La mezcla de reacción se diluyó con agua (400 ml) y se extrajo con acetato de etilo (600 ml x 1, 250 ml x 1). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (cloroformo-metanol; 100:0 → 99.5:0.5 → 99.25:0.75 → 99:1) para dar un sólido. A una solución de este sólido en etanol (273 ml) se añadió 1 mol/l de solución acuosa de hidróxido de sodio (68.2 ml) en un baño de hielo y la mezcla se agitó a temperatura ambiente durante 1 hora. A esta solución de reacción se añadió etanol (327 ml) y 1 mol/l de solución acuosa de hidróxido de sodio (27.3 ml) y la mezcla se agitó a temperatura ambiente durante 13 horas. A esta solución de reacción se añadió 1 mol/l de solución acuosa de ácido clorhídrico

(95.5 ml) en un baño de hielo y la capa orgánica se concentró bajo presión reducida. La solución acuosa se diluyó con agua (150 ml) y se extrajo con cloroformo (250 ml x 1, 150 ml x 1). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice (n-hexano-acetato de etilo; 100:0 → 2:1 → 1:1 → 1:1.5 → 1:1.7 → 1:1.85 → 1:2 → 1:5 → 1:9 → 0:100) para dar un sólido amarillo pálido. El sólido se disolvió en ácido clorhídrico concentrado (30 ml) en un baño de hielo y la solución acuosa se lavó con cloroformo (100 ml x 5). A la capa acuosa se añadió solución saturada de hidróxido de sodio para ajustar pH a 12.0. A la solución se añadió agua (1.8 l) y la solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (1.5 l x 1, 800 ml x 1). La capa orgánica se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo se purificó por recristalización a partir de 2-propanol/metanol=10/1 para dar el compuesto del título 6.14 g (52%) como sólido amarillo pálido. Y todos los datos espectroscópicos de este compuesto probaron concordar bien con los del ejemplo 17.

EJEMPLO DE REFERENCIA 231

Ester ter-butílico de ácido (3aS)-6-oxo-5-[(R)-1-feniletil]-5,6-dihidro-4H-furo [3,4-c] pirrol-3a-carboxílico

[Fórmula 359]



A una solución de éster ter-butílico de ácido (3aS)-(tetrahidrofuro [3,4-c]pirrol-3a-il)carboxílico (8.80 g, 25.0 mmoles) y trietilamina (7.8 ml) en diclorometano (75 ml) se añadió gota a gota cloruro de metansulfonilo (3.13 ml, 40.0 mmoles) a -10°C y la mezcla se agitó durante 1.5 hr a la misma temperatura y después se añadió trietilamina adicional (7.8 ml). La mezcla de reacción se calentó a 40°C y se agitó durante 5 días. Después de enfriar a temperatura ambiente, el solvente se removió al vacío y el residuo se purificó por cromatografía sobre gel de sílice eluyendo con una solución mixta de AcOEt, hexano y trietilamina (40:60:0.5) para dar el compuesto del título como un sólido blanco (2.56 g).

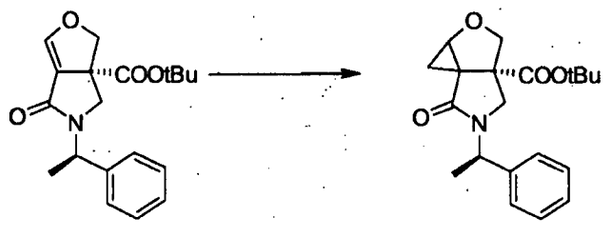
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 7.08 (1H, s), 5.48 (1H, q, J = 6.9 Hz), 5.03 (1H, d, J= 9.6 Hz), 4.25 (1H, d, J = 9.6 Hz), 3.43 (1H, d, J = 10.1 Hz), 3.26 (1H, d, J = 10.1 Hz), 1.38 (3H, d, J = 6.9 Hz), 1.30 (9H, s).

EM (ESI) m/z:330 $(M+H)^+$.

EJEMPLO DE REFERENCIA 232

Ester ter-butílico de ácido (S)-6-oxo-5-[(R)-1-feniletil] tetrahidro-2-oxa-5-azaciclopropa [c] pentalen-3a-carboxílico

[Fórmula 360]



A una solución de dietil zinc (solución en hexano 1M, 22.3 ml) en diclorometano (75 ml) se añadió gota a gota diyodometano (1.79 ml, 22.3 mmoles) a -10°C, y la mezcla se agitó durante 15 min a la misma temperatura. Una solución de éster ter-butílico de ácido (S)-6-oxo-5-[(R)-1-feniletil]-5,6-

dihidro-4H-furo[3,4-c]pirrol-3a-carboxílico en diclorometano se añadió a -10°C, y la mezcla resultante se agitó durante 8 hr a temperatura ambiente. La mezcla de reacción se extinguió con ácido cítrico ac. al 10%. Las capas se separaron y la capa acuosa se extrajo con diclorometano. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ ac. sat. y salmuera, se secaron (Na_2SO_4) y se concentraron al vacío. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con 30% de AcOEt en hexano para dar el compuesto del título (1.96 g) como un sólido blanco.

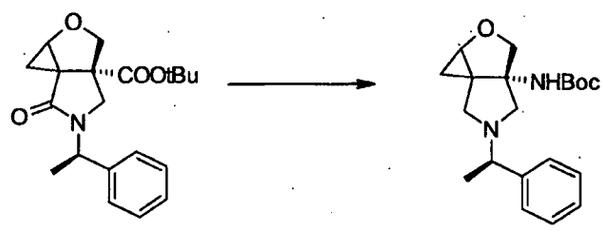
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.38-7.25 (5H, m), 5.54 (1H, q, J = 7.0 Hz), 4.45 (1H, d, J = 9.2 Hz), 4.24 (1H, dd, J = 5.5, 2.8 Hz), 4.14 (1H, d, J = 9.2 Hz), 3.51 (1H, d, J = 10.1 Hz), 3.40 (1H, d, J = 10.1 Hz), 1.73-1.67 (1H, m), 1.58-1.53 (4H, m), 1.33 (9H, s).

EM (ESI) m/z: 344 $(M + H)^+$

EJEMPLO DE REFERENCIA 233

Ester ter-butílico de ácido [(S)-5-[(R)-1-feniletil] tetrahidro-2-oxa-5-azaciclopropa [c] pentalen-3a-il] carbámico

[Fórmula 361]



A una solución de éster ter-butílico de ácido (S)-6-oxo-5-[(R)-1-feniletil] tetrahidro-2-oxa-5-azaciclopropa [c]pentalen-3a-carboxílico (880 mg, 2.56 mmoles) en diclorometano (7 ml) se añadió ácido trifluoroacético (8 ml), y la mezcla se agitó a temperatura ambiente durante 2 hr. El solvente se removió al

vacío para dar un sólido blanco (800 mg).

1,1'-carbonibis-1H-imidazol (677 mg, 4.18 mmoles) se añadió a una solución del sólido blanco (800 mg) en acetonitrilo (15 ml) a -0°C, y la mezcla se agitó durante 1 hr a la misma temperatura y después se dejó calentar a temperatura ambiente. Amoniaco gaseoso se hizo burbujear a través de la mezcla de reacción durante 30 min y el solvente se concentró al vacío. El residuo resultante se recogió en diclorometano, se lavó con HCl 1N, $NaHCO_3$ ac. sat. y salmuera, se secó (Na_2SO_4), y se concentró al vacío para dar un sólido blanco (750 mg).

A una suspensión del sólido blanco (120 mg) en ter-butanol (5 ml) se añadió tetraacetato de plomo (558 mg, 1.26 mmoles), y la mezcla se calentó a 100°C durante 5 hr. La mezcla de reacción se dejó enfriar a temperatura ambiente, se diluyó con éter dietílico (50 ml) y se añadió bicarbonato de sodio (1 g). Después de agitar durante 30 min, los sólidos se filtraron. El filtrado se removió al vacío, y el residuo se recogió en diclorometano, se lavó con $NaHCO_3$ ac. sat. y salmuera, se secó (Na_2SO_4), y se concentró al vacío. El producto crudo se recogió sin purificación adicional.

Se añadió ácido trifluoroacético (6 ml) a una solución del producto crudo en diclorometano (5 ml), y la mezcla de reacción se agitó durante 1 hr, después el solvente se removió al vacío, y se bombeó a sequedad. Este se llevó adelante al siguiente paso.

A una solución de este material en tolueno (4 ml) se añadió lentamente hidruro de bis (2-metoxietoxi)aluminio-sodio (solución de tolueno al 65%, 600 µl, 2.0 mmoles), y la mezcla se calentó a 60°C durante 1 hr. La mezcla de reacción se enfrió a temperatura ambiente y se añadió NaOH ac. 5N, y después se agitó durante 1 hr. Las capas se separaron y la capa acuosa se

extrajo con tolueno. Los extractos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron al vacío. El producto crudo se llevó sin purificación.

Se añadió dicarbonato de di-ter-butilo (163 mg) a una solución del producto crudo en diclorometano (6 ml), y la mezcla se agitó durante 18 hr y el solvente se removió al vacío. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con 25% de AcOEt en hexano para dar el compuesto del título (140 mg) como un sólido blanco.

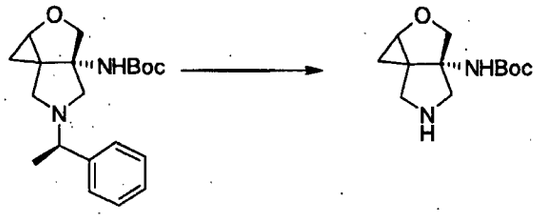
^{1}H-RMN (400MHz, $CDCl_3$) δ: 7.36-7.19 (5H, m), 4.92 (1H, s), 4.20 (1H, d, J = 9.6 Hz), 3.98-3.85 (2H, m), 3.43 (1H, q, J = 6.6 Hz), 2.99 (1H, d, J = 8.7 Hz), 2.81-2.62 (3H, m), 1.40 (9H, s), 1.35 (3H, d, J = 6.6 Hz), 1.19 (1H, d, J = 6.4 Hz), 0.91 (1H, t, J = 5.7 Hz).

EM (ESI) m/z: 345 $(M + H)^+$.

EJEMPLO DE REFERENCIA 234

Ester ter-butílico de ácido (S)-(tetrahidro-2-oxa-5-azaciclopropa [c] pentalen-3a-il) carbámico

[Fórmula 362]



Un éster ter-butílico de ácido [(S)-5-[(R)-1-feniletil] tetrahidro-2-oxa-5-azaciclopropa [c]pentalen-3a-il] carbámico (480 mg, 1.39 mmoles) se disolvió en dioxano (10 ml) y se añadió catalizador de hidróxido de paladio al 20% (20 % en peso Pd sobre carbón, húmedo; cat.). La mezcla se agitó vigorosamente bajo

L082

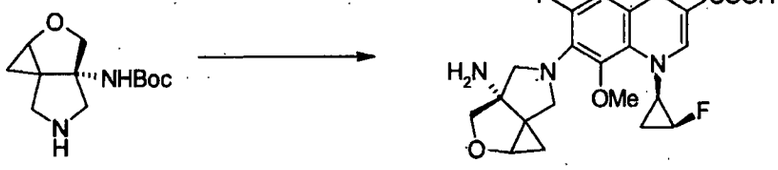
una atmósfera de hidrógeno a temperatura ambiente durante 3 días. Después de remover el catalizador por filtración, el filtrado se concentró bajo presión reducida. El residuo se recogió en diclorometano, y se lavó con NaOH ac. 1N y salmuera. La capa orgánica se secó sobre sulfato de sodio anhidro y el solvente se removió al vacío para dar el compuesto del título crudo como un sólido blanco (280 mg).

EM (ESI) m/z: 241$(M + H)^+$.

EJEMPLO 61

Acido 7-[(3aS)-3a-amino-5-aza-oxatetrahidrociclopentalen-5-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico

[Fórmula 363]



A una solución de complejo de ácido 6,7-difluoro-1-[(2S,1R)-2-fluorociclopropil]-1,4-dihidro-8-metoxi-4-oxoquinolin-3-carboxílico-difluoroboro (361 mg, 1.00 mmol) en sulfóxido de dimetilo (5 ml) se añadieron éster ter-butílico de ácido (S)-(tetrahidro-2-oxa-5-azaciclopropa[c]pentalen-3a-il) carbámico (250 mg, 1.08 mmoles) y trietilamina (0.50 ml, 3.54 mmoles), y la mezcla se agitó a temperatura ambiente durante 2 días. La solución de reacción se concentró al vacío, y el concentrado se disolvió en una solución mixta de etanol y agua (9:1) (150 ml). Después de añadir trietilamina (5 ml), la mezcla se calentó bajo reflujo durante 5 hr. La mezcla de reacción se concentró bajo

1083

presión reducida, y el concentrado se disolvió en AcOEt (100 ml x 2), y se lavó con ácido cítrico ac. al 10% (100 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. Después de purificación por cromatografía sobre gel de sílice (5% de MeOH en $CHCl_3$), el residuo se disolvió en ácido clorhídrico concentrado (5 ml) en un baño de hielo, y la solución acuosa se lavó con cloroformo (50 ml x 3). A la capa acuosa se añadió 10 mol/l de solución acuosa de hidróxido de sodio para ajustar pH a 12.0, y la solución acuosa básica se ajustó con ácido clorhídrico a pH 7.4. La solución se extrajo con cloroformo (100 ml x 6) y los extractos combinados se secaron con sulfato de sodio anhidro, y el solvente se destiló bajo presión reducida. El residuo se purificó por cromatografía preparativa, y se purificó adicionalmente por recristalización a partir de etanol, y subsecuentemente, se secó bajo presión reducida para dar el compuesto del título (135 mg) como cristales de aguja amarillo pálidos, p.f.: 189-191°C.

^{1}H-RMN (400MHz, NaOD 0.1N) δ: 8.42 (1H, d, J = 2.8 Hz), 7.71 (1H, d, J = 13.8 Hz), 5.13-4.89 (1H, m), 4.17-4.01 (4H, m), 3.94 (1H, dd, J = 10.5, 2.3 Hz), 3.67 (3H, s), 3.64-3.47 (3H, m), 1.63-1.37 (3H, m), 1.02 (1H, dd, J = 7.8, 5.5 Hz).

Análisis calculado para $C_{21}H_{21}F_2N_3O_5$ $1.25H_2O$: C, 55.32; H, 5.20; N, 9.22, F, 8.33.

Encontrado: C, 55.48, H, 5.12, N, 9.00; F, 8.61.

EM (ESI) m/z: 434 $(M + H)^+$.

IR (ATR) ν: 3358, 3076, 2941, 2879, 1721, 1620, 1513, 1437, 1367, 1323, 1274 cm^{-1}.

P084

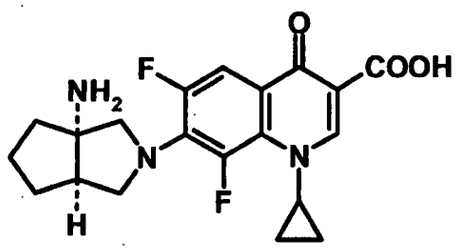
EJEMPLO DE PRUEBA 1

Se midió la actividad antibacterial de los compuestos de la presente invención de conformidad con el método estándar especificado por la Sociedad Japonesa de Quimioterapia. Los resultados se muestran como MIC (μg/ml) (cuadro 2).

Para comparación con los valores MIC de los compuestos de la presente invención, el cuadro 2 también muestra valores MIC de ácido 7-[3-(R)-(1-aminociclopropil)pirrolidin-1-il]-8-ciano-1-[2-(S)-fluoro-1-(R)-ciclopropil]-1,4-dihidro-4-oxoquinolin-3-carboxílico descrito en WO 02/40478 (fármaco de control 1: la siguiente fórmula), levofloxacin (LVFX), ciprofloxacin (CPFX), y moxifloxacin (MXFX).

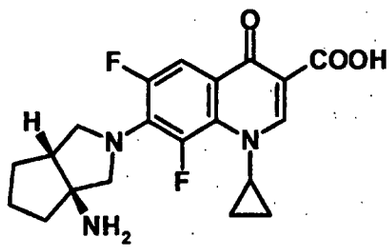
El compuesto específicamente ejemplificado en EP-A-343524 descrito en la sección "Descripción de la técnica relacionada", representado por la siguiente fórmula:

[Fórmula 364]



tiene uno de dos isómero ópticos como su sustituyente en la posición 7. Los inventores de la presente sintetizaron un compuesto representado por la siguiente fórmula:

[Fórmula 365]



que tiene un grupo (1S,5R)-1-amino-3-azabiciclo [3.3.0] octan-3-ilo que es un isómero altamente activo como su sustituyente en la posición 7. El compuesto representado por la fórmula 365 confirmó ser positivo para la inducción de micronúcleos en una prueba de micronúcleo de médula ósea de ratón después de administración intravenosa. Es decir, se sugiere que el compuesto es genotóxico. Además, se encontró que el compuesto es positivo para fototoxicidad en una prueba de fototoxicidad en ratón después de administración intravenosa. Por otra parte, se encontró que el compuesto descrito en el ejemplo 11, que es un compuesto representativo de la presente invención era negativo en las dos pruebas anteriores. Es decir, se sugiere que el compuesto es débilmente genotóxico y no fototóxico y por lo tanto altamente seguro como una medicina para humanos.

CUADRO 2

Actividad antibacterial

Bacteria/compuesto (No. de Ejemplo)	2	5	10	11	15	17	24	25	27
E. coli NIHJ	0.025	0.025	0.025	0.025	0.006	≤0.003	0.025	0.012	0.012
K. pneumoniae TIPO 1	0.1	0.1	0.2	0.1	0.05	0.012	0.1	0.05	0.1
P. mirabilis 08103	0.012	0.025	0.05	0.05	0.025	0.006	0.025	0.025	0.05
E.cloacae 03400	0.025	0.025	0.025	0.012	0.025	0.006	0.025	0.012	0.025
S. marcescens 10100	0.2	0.2	0.2	0.1	0.2	0.05	0.2	0.1	0.2
P. aeruginosa PAOI	0.78	0.78	0.78	0.78	0.78	0.2	0.39	0.39	0.78
H. influenzae ATCC49247	0.006	0.012	0.012	0.006	≤0.003	≤0.003	0.006	0.006	0.006
M (B). Caterrhalis ATCC25238	0.025	0.05	0.025	0.025	0.025	0.006	0.05	0.025	0.05
S. aureus FDA 209-P	≤0.003	0.006	0.006	0.012	0.012	0.006	0.025	0.025	0.012
S. epidermidis 56500	0.012	0.025	0.025	0.05	0.05	0.025	0.1	0.1	0.05
S. pneumoniae J24	0.012	0.025	0.025	0.05	0.05	0.025	0.05	0.05	0.025
S. pyogenes JCM5674 (ATCC12344)	0.025	0.05	0.025	0.025	0.05	0.025	0.1	0.05	0.05
E. faecalis 19433	0.05	0.1	0.1	0.1	0.2	0.05	0.1	0.2	0.1
S. aureus 870307	0.1	0.2	0.1	0.78	0.39	0.2	0.78	0.39	0.2
S. pneumoniae 104835	0.1	0.2	0.2	0.39	0.39	0.1	0.39	0.39	0.2

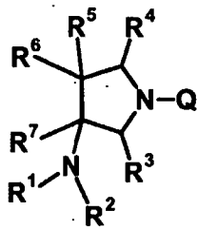
Bacteria/compuesto (No. de Ejemplo)	31	34	35	37	43	44	LVFX	CPFX	MXFX
E. coli NIHJ	0.006	0.006	0.006	0.006	0.006	≤0.003	0.012	≤0.003	0.012
K. pneumoniae TIPO 1	0.05	0.025	0.05	0.1	0.05	0.025	0.05	0.025	0.1
P. mirabilis 08103	0.012	0.012	0.025	0.05	0.025	0.025	0.025	0.012	0.025
E.cloacae 03400	0.012	0.006	0.012	0.025	0.012	0.006	0.012	0.006	0.012
S. marcescens 10100	0.1	0.05	0.1	0.2	0.2	0.05	0.05	0.025	0.2
P. aeruginosa PAOI	0.39	0.2	0.39	1.56	0.78	0.39	0.39	0.05	0.78
H. influenzae ATCC25238	0.012	0.006	0.012	≤0.003	0.006	≤0.003	0.012	0.006	0.012
M(B). Caterrhalis ATCC49247	0.025	0.012	0.025	0.025	0.025	0.006	0.025	0.025	0.05
S. aureus FDA 209-P	0.012	0.025	0.025	0.006	0.012	0.012	0.1	0.1	0.05
S. epidermidis 56500	0.05	0.05	0.05	0.012	0.05	0.025	0.39	0.2	0.1
S. pneumoniae J24	0.025	0.1	0.05	0.05	0.1	0.05	0.78	0.78	0.1
S. pyogenes JCM5674 (ATCC12344)	0.025	0.05	0.05	0.05	0.05	0.05	0.39	0.39	0.2
E. faecalis 19433	0.1	0.1	0.2	0.1	0.2	0.1	0.78	0.78	0.2
S. aureus 870307	0.1	0.39	0.2	0.05	0.2	0.2	6.25	>6.25	0.78
S. pneumoniae 104835	0.2	0.39	0.39	0.39	0.78	0.39	>6.25	>6.25	3.13

1687

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un compuesto representado por la siguiente fórmula (I), una sal, o un hidrato del mismo:



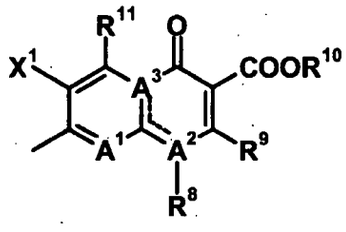
I

en donde R^1 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, o un grupo carbonilo sustituido derivado de un aminoácido, un dipéptido, o un tripéptido, dicho grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un grupo ciano, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y dicho grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno; R^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, o un grupo cicloalquilo que tiene 3 a 6 átomos de carbono, dicho grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y dicho grupo cicloalquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que

P088

tiene 1 a 6 átomos de carbono, un grupo amino, un grupo hidroxi, y un átomo de halógeno; R^3 y R^4 independientemente representan un átomo de hidrógeno o un grupo alquilo que tiene 1 a 6 átomos de carbono, dicho grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono; R^5 representa un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquinilo que tiene 2 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, o un grupo heteroarilo que puede tener un sustituyente, dicho grupo alquilo, grupo alquenilo, y grupo alquinilo puede ser lineal o ramificado, el grupo alquilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo hidroxi, un grupo amino, un átomo de halógeno, un grupo alquiltio que tiene 1 a 6 átomos de carbono, y un grupo alcoxi que tiene 1 a 6 átomos de carbono, y el grupo alquenilo puede tener uno o más sustituyentes seleccionados del grupo que consiste de un átomo de halógeno y un grupo alcoxi que tiene 1 a 6 átomos de carbono; R^6 y R^7 tomados junto con los átomos de carbono a los cuales están unidos forman una estructura cíclica de cuatro a siete miembros, la estructura cíclica representando una estructura parcial que junto con el anillo de pirrolidina forma una estructura cíclica fusionada (bicíclica), la estructura cíclica de cuatro a siete miembros puede contener a doble enlace y puede contener un átomo de oxígeno o un átomo de azufre como un átomo constituyente de anillo, R^5 puede ser a grupo metileno tomado junto con R^6 para formar una estructura cíclica fusionada de tres miembros, y además esta estructura cíclica fusionada puede ser ubicada en otra

parte de la estructura cíclica fusionada (bicíclica), y el anillo formado como se describió antes puede ser ubicado en otra parte de la estructura cíclica fusionada (bicíclica), y dicha estructura cíclica de cuatro a siete miembros puede tener uno o más sustituyentes seleccionados del grupo que consiste de un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquenilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo alquinilo que tiene 2 a 6 átomos de carbono que puede tener un sustituyente, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo exometileno que puede tener un sustituyente, un grupo espiroalquilo que puede tener un sustituyente, un grupo arilo que tiene 6 a 10 átomos de carbono que puede tener un sustituyente, un grupo heteroarilo que puede tener un sustituyente, un grupo alcoxiimino que tiene 1 a 6 átomos de carbono que puede tener un sustituyente, un átomo de halógeno, un grupo hidroxi, un grupo ciano y un grupo hidroxiimino; o una cadena de polimetileno de 2 a 5 átomos de carbono se puede unir para formar un sistema de anillo espirocíclico; y Q representa una estructura parcial representada por la siguiente fórmula (II):



II

en donde R^8 representa un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alquenilo que tiene 2 a 6 átomos de carbono, un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono, un grupo cicloalquilo que tiene 3 a 6 átomos de carbono que puede tener un sustituyente, un grupo fenilo halógeno-sustituido que puede tener un sustituyente, un grupo heteroarilo halógeno-

1090

sustituido que puede tener un sustituyente, un grupo alcoxi que tiene 1 a 6 átomos de carbono, o un grupo alquilamino que tiene 1 a 6 átomos de carbono; R^9 representa un átomo de hidrógeno o un grupo alquiltio que tiene 1 a 6 átomos de carbono, o R^9 y R^8 tomados junto con los átomos a los cuales están unidos forman una estructura cíclica, dicha estructura cíclica puede contener un átomo de azufre as un átomo constituyente de anillo y puede tener un grupo alquilo que tiene 1 a 6 átomos de carbono o un grupo alquilo halógeno-sustituido que tiene 1 a 6 átomos de carbono como un sustituyente; R^{10} representa un átomo de hidrógeno, un grupo fenilo, un grupo acetoximetilo, un grupo pivailoximetilo, un grupo etoxicarbonilo, un grupo colina, un grupo dimetilaminoetilo, un grupo 5-indanilo, un grupo ftalidinilo, un 5-alquil-2-oxobutilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoximetilo que tiene 2 a 7 átomos de carbono, o un grupo fenilalquilo formado por un grupo alquileno que tiene 1 a 6 átomos de carbono y un grupo fenilo; R^{11} representa un átomo de hidrógeno, un grupo amino, un grupo hidroxi, un grupo tiol, un grupo halogenometilo, o un grupo alquilo que tiene 1 a 6 átomos de carbono, el grupo amino puede tener uno o dos sustituyentes seleccionados del grupo que consiste de un grupo formilo, un grupo alquilo que tiene 1 a 6 átomos de carbono, y un grupo acilo que tiene 2 a 5 átomos de carbono; X^1 representa un átomo de halógeno o un átomo de hidrógeno; A^1 representa un átomo de nitrógeno o una estructura parcial representada por la fórmula (III):



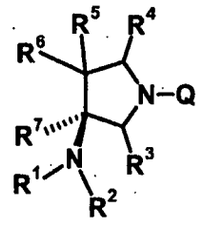
III

en donde X^2 representa un átomo de hidrógeno, un grupo alquilo que tiene 1 a 6 átomos de carbono, un grupo alcoxi que tiene 1 a 6 átomos de carbono, un grupo ciano, un átomo de halógeno, un metilo halógeno-sustituido, o un grupo

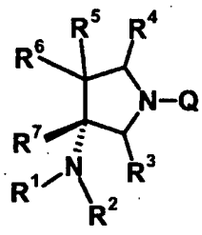
1091

halogenometoxi, o X^2 y R^8 tomados junto con su parte de conexión de la estructura de base madre forman una estructura cíclica, dicha estructura cíclica puede contener un átomo de oxígeno, un átomo de nitrógeno, o un átomo de azufre como un átomo constituyente de anillo, y puede ser sustituido con un grupo alquilo que tiene 1 a 6 átomos de carbono que puede tener un sustituyente; y A^2 y A^3 cada uno representa un átomo de nitrógeno o un átomo de carbono, y A^1, A^2, A^3, R^8 y el átomo de carbono al cual A^2 y A^3 están unidos juntos representan una estructura parcial: >C=C(-A^1=)-N(-R^8)- o una estructura parcial: >N-C(-A^1=)=C(-R^8)-.

2.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula:



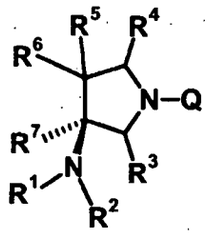
o la siguiente fórmula:



en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, y Q son como se define en la reivindicación 1.

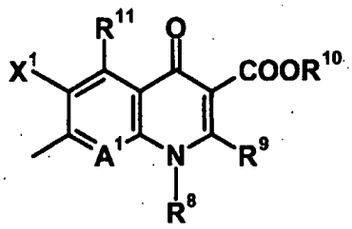
3.- El compuesto de conformidad con la reivindicación 1 o una sal del mismo, o un hidrato del mismo, caracterizado además porque el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula :

1092

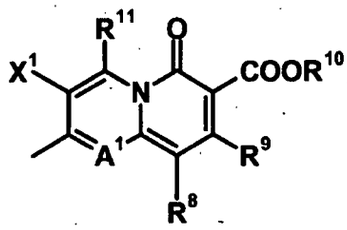


en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, y Q son como se define en la reivindicación 1.

4.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque Q representado por la fórmula (II) en el compuesto representado por la fórmula (I) tiene una estructura representada por la siguiente fórmula:

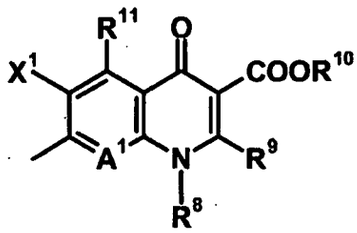


o la siguiente fórmula:



en donde R^8, R^9, R^{10}, R^{11}, X^1, y A^1 son como se define en la reivindicación 1.

5.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque Q representado por la fórmula (II) en el compuesto representado por la fórmula (I) tiene una estructura representada por la siguiente fórmula:



L093

en donde R^8, R^9, R^{10}, R^{11}, X^1, y A^1 son como se define en la reivindicación 1.

6.- El compuesto de conformidad con la reivindicación 1, 2 ó 3, una sal, o un hidrato del mismo, caracterizado además porque R^1 y R^2 en la fórmula (I) son cada uno un átomo de hidrógeno.

7.- El compuesto de conformidad con la reivindicación 1, 2 ó 3, una sal, o un hidrato del mismo, caracterizado además porque uno de R^1 y R^2 en la fórmula (I) es un átomo de hidrógeno y el otro es un sustituyente seleccionado de un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo fluoroetilo, un cianoetilo, un grupo ciclopropilo y un grupo ciclobutilo.

8.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7, una sal, o un hidrato del mismo, caracterizado además porque R^3 y R^4 en la fórmula (I) son cada uno un átomo de hidrógeno.

9.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8, una sal, o un hidrato del mismo, caracterizado además porque R^5 en la fórmula (I) es un átomo de hidrógeno, un átomo de flúor, un átomo de cloro, un grupo metilo, un grupo etilo, un grupo isopropilo, un grupo ciclopropilo, un grupo fluorometilo, un grupo fluoroetilo, un grupo trifluorometilo, un grupo metoximetilo, un grupo vinilo, un grupo etinilo, un grupo metoxi, un grupo fenilo o un oxazol-2-ilo.

10.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cuatro miembros que puede ser sustituido por uno o más sustituyentes.

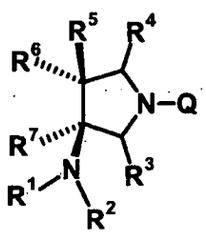
L094

11.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que puede ser sustituido por uno o más sustituyentes.

12.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9 y 11, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que contiene un doble enlace como una estructura constituyente que puede ser sustituida por uno o más sustituyentes.

13.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9 y 11 a 12, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros que contiene un átomo de oxígeno como un átomo constituyente de anillo.

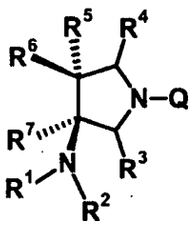
14.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9 y 11 a 13, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros y se fusiona con el anillo de pirrolidina para formar una estructura bicíclica cis-fusionada representada por la siguiente fórmula:



L095

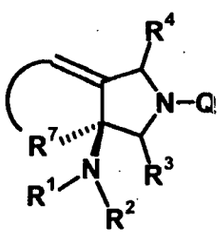
en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, y Q son como se define en la reivindicación 1.

15.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9 y 11 a 13, una sal, o un hidrato del mismo, caracterizado además porque la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos en la fórmula (I) es un anillo de cinco o seis miembros y se fusiona con el anillo de pirrolidina para formar una estructura bicíclica trans-fusionada representado por la siguiente fórmula:



en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, y Q son como se define en la reivindicación 1.

16.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9 y 11 a 13, una sal, o un hidrato del mismo, caracterizado además porque en la fórmula (I), la estructura cíclica formada al tomar R^6 y R^7 junto con los átomos de carbono a los cuales están unidos es un anillo de cinco o seis miembros, R^5 y R^6 se toman juntos para formar una estructura parcial de doble enlace, y la estructura cíclica resultante está representado por la siguiente fórmula:



en donde R^1, R^2, R^3, R^4, R^7, y Q son como se definió antes.

17.- El compuesto de conformidad con cualquiera de las

1096

reivindicaciones 1 a 16, una sal, o un hidrato del mismo, caracterizado además porque X^1 es un átomo de hidrógeno o un átomo de flúor en la estructura parcial Q en la fórmula (I) representado por la fórmula (II).

18.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 17, una sal, o un hidrato del mismo, caracterizado además porque X^1 es un átomo de flúor en la estructura parcial Q en la fórmula (I) representado por la fórmula (II).

19.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, una sal, o un hidrato del mismo, caracterizado además porque A^1 es un átomo de nitrógeno en la estructura parcial Q en la fórmula (I) representado por la fórmula (II).

20.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, una sal, o un hidrato del mismo, caracterizado además porque A^1 es una estructura parcial representada por la fórmula (III) en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

21.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, una sal, o un hidrato del mismo, caracterizado además porque X^2 en la fórmula (III) es un grupo metilo, un grupo etilo, un grupo metoxi, un grupo difluorometoxi, un grupo ciano o un átomo de cloro.

22.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, una sal, o un hidrato del mismo, caracterizado además porque X^2 en la fórmula (III) es un grupo metilo o un grupo metoxi.

23.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 22, una sal, o un hidrato del mismo, caracterizado además porque R^8 es un 1,2-cis-2-halogenociclopropilo en la estructura parcial Q en la fórmula (I) representado por la fórmula (II).

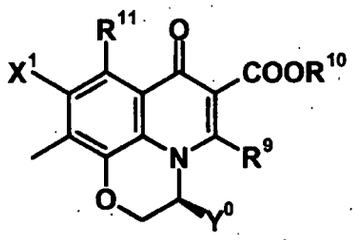
1697

24.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 22, una sal, o un hidrato del mismo, caracterizado además porque R^8 es un 1,2-cis-2-halogenociclopropilo estereoquímicamente individual en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

25.- El compuesto de conformidad con la reivindicación 24, una sal, o un hidrato del mismo, caracterizado además porque el 1,2-cis-2-halogenociclopropilo de R^8 es un grupo (1R,2S)-2-halogenociclopropilo en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

26.- El compuesto de conformidad con la reivindicación 25, una sal, o un hidrato del mismo, caracterizado además porque el (1R,2S)-2-halogenociclopropilo de R^8 es un grupo (1R,2S)-2-fluorociclopropilo en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

27.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque Q en el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula:

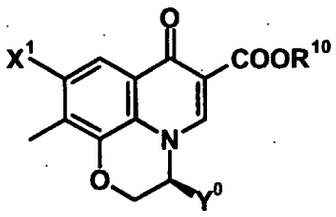


en donde R^9 , R^{10}, R^{11}, y X^1 son como se define en la reivindicación 1 y Y^0 es un grupo metilo o un grupo fluorometilo.

28.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 27, una sal, o un hidrato del mismo, caracterizado además porque R^9 es un átomo de hidrógeno en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

1698

29.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque Q en el compuesto representado por la fórmula (I) es un compuesto representado por la siguiente fórmula (IV):



IV

en donde R^{10} y X^1 son como se define en la reivindicación 1 y Y^0 es un grupo metilo o un grupo fluorometilo.

30.- El compuesto de conformidad con la reivindicación 29 o una sal del mismo, o un hidrato del mismo, caracterizado además porque Y^0 en la fórmula (IV) es un grupo metilo.

31.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 30, una sal, o un hidrato del mismo, caracterizado además porque R^{10} es un átomo de hidrógeno en la estructura parcial Q en la fórmula (I) representada por la fórmula (II).

32.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 31, una sal, o un hidrato del mismo, caracterizado además porque el compuesto representado por la fórmula (I) es un compuesto estereoquímicamente individual.

33.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque Q en la fórmula (I) tiene la siguiente estructura: un grupo 7-carboxi-9-ciclopropilo-3-fluoro-6(H)-6-oxopirido[1,2-a]pirimidin-4-ilo; un grupo 3-carboxi-1-ciclopropilo-7-fluoro-9-metil-4(H)-4-oxoquinolizin-8-ilo; un grupo 5-carboxi-9-fluoro-2,3-dihidro-3-(R)-metil-6(H)-

6-oxopirano[2,3,4-ij]quinolizin-10-ilo; un grupo 1-(6-amino-3,5-difluoropiridin-2-il)-8-cloro-3-carboxi-6-fluoro-1,4-dihidro-4-quinolin-7-ilo; un grupo 1-(6-amino-3, 5-difluoropiridin-2-il)-3-carboxi-6-fluoro-1,4-dihidro-8-metil-4-quinolin-7-ilo; un grupo 6-carboxi-9-fluoro-3-(R)-fluorometil-2,3-dihidro-metil-7(H)-7-oxopirido [1,2,3-de][1,4]benzoxazin-10-ilo; un grupo 6-carboxi-9-fluoro-2,3-dihidro-3-(S)-metil-7(H)-7-oxopirido [1,2,3-de][1,4]benzoxazin-10-ilo; un grupo 8-amino-6-carboxi-9-fluoro-2,3-dihidro-3-(S)-metil-7(H)-7-oxopirido [1,2,3-de][1,4]benzoxazin-10-ilo; un grupo 3-carboxi-8-cloro-1-ciclopropilo-6-fluoro-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-cloro-1-ciclopropilo-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-ciano-1-ciclopropilo-6-fluoro-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-ciano-1-ciclopropilo-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropilo-6-fluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropilo-1,4-dihidro-8-metoxi-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropilo-6-fluoro-8-difluorometoxi-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropil-8-difluorometoxi-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropilo-6-fluoro-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-ciclopropil-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo; un grupo 5-amino-3-carboxi-1-ciclopropilo-6-fluoro-1,4-dihidro-8-metoxi-4-oxoquinolin-7-ilo; un grupo 5-amino-3-carboxi-1-ciclopropilo-6-fluoro-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-cloro-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-cloro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-8-ciano-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolin-

7-ilo; un grupo 3-carboxi-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-8-difluorometoxi-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-[(1R,2S)-2-fluorociclopropilo]-8-difluorometoxi-1,4-dihidro-4-oxoquinolin-7-ilo; un grupo 3-carboxi-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo; un grupo 3-carboxi-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo; un grupo 5-amino-3-carboxi-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolin-7-ilo; o un grupo 5-amino-3-carboxi-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolin-7-ilo.

34.- El compuesto de conformidad con la reivindicación 1, una sal, o un hidrato del mismo, caracterizado además porque la estructura parcial sustituida en Q en la fórmula (I) tiene la siguiente estructura: un grupo (1R,5S)-1-amino-5-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5S,6R)-1-amino-6-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5S,6S)-1-amino-6-fluoro-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5S)-1-amino-6,6-difluoro-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5R,6R)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5R,6R)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo (1S,5R,6S)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-ilo; un grupo espiro[(1S,5S)-1-amino-3-azabiciclo[3.2.0]heptano-6,1'-ciclopropan]-3-ilo; un grupo (1S,5R)-1-amino-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5S)-1-amino-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1R,5S)-1-amino-5-fluoro-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1R,5R)-1-amino-5-fluoro-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5R,6S)-1-amino-6-fluoro-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5R)-1-amino-6,6-difluoro-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5R,7S)-1-amino-7-fluoro-3-azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5R,7R)-1-amino-7-fluoro-3-

azabiciclo[3.3.0]octan-3-ilo; un grupo (1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-ilo; un grupo (1S,5R)-1-amino-7-metil-3-azabiciclo[3.3.0]oct-7-en-3-ilo; un grupo (1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-ilo; un grupo (1S)-1-amino-6-metil-3-azabiciclo[3.3.0]oct-5-en-3-ilo; un grupo (1R,5R)-1-amino-3-oxa-5-azabiciclo[3.3.0]octan-5-ilo; un grupo (1R,5S)-1-amino-3-oxa-5-azabiciclo[3.3.0]octan-5-ilo; un grupo (1R,5R)-1-amino-4-oxa-5-azabiciclo[3.3.0]octan-5-ilo; un grupo (1R,5S)-1-amino-4-oxa-5-azabiciclo[3.3.0]octan-5-ilo; un grupo 6-amino-8-azatriciclo [4.3.0.$0^{1,3}$]nonan-8-ilo; un grupo (1S,5R)-1-amino-3-azabiciclo[4.3.0]nonan-3-ilo; un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-ilo; un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]non-7-en-3-ilo; un grupo (1S,5S)-1-amino-3-azabiciclo[4.3.0]non-8-en-3-ilo; un grupo (1S)-1-amino-3-azabiciclo[4.3.0]non-5-en-3-ilo; un grupo (1R,6S)-1-amino-5-oxa-8-azabiciclo[4.3.0]nonan-8-ilo; un grupo (1S,6S)-1-amino-4-oxa-8-azabiciclo[4.3.0]nonan-8-ilo; o un grupo (1S,6S)-1-amino-3-oxa-8-azabiciclo[4.3.0]nonan-8-ilo.

35.- Un compuesto de la fórmula (I), una sal, o un hidrato del mismo como sigue: ácido 7-[(1S,5R,6R)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 10-[(1S,5R,6S)-1-amino-6-metil-3-azabiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico; ácido 7-[(1S,5R,6S)-1-amino-6-fluorometil-3-azabiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-

carboxílico; ácido 7-[(1S,5R,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido10-[(1S,5R,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico; ácido 7-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 10-[(1S,5S,6R)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico; ácido 7-[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 10 -[(1S,5S,6S)-1-amino-3-azabiciclo-6-fluorobiciclo[3.2.0]heptan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico;

ácido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 10-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4]benzoxazino-6-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-8-cloro-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-

1103

fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-fluorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-clorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1R,5S)-1-amino-3-aza-5-clorobiciclo[3.3.0]octan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5R)-1-amino-3-azabiciclo[3.3.0]oct-7-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 7-[(1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4- oxoquinolino-3-carboxílico; ácido 7-[(1S)-1-amino-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 7-[(1S)-1-amino-5-metil-3-azabiciclo[3.3.0]oct-5-en-3-il]-6-fluoro-1-[(1R,2S)-2-f luorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 10-[6-amino-8-azatriciclo [4.3.0.$0^{1,3}$]nonan-8-il]-9-fluoro-2,3-dihidro-3-(S)-metilo-7- oxo-7H-pirido[1,2,3-de][1,4] benzoxazino-6-carboxílico; ácido 7-[6-amino-8-azatriciclo[4.3.0.$0^{1,3}$]nonan-8-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico; ácido 7-[6-amino-8-azatriciclo[4.3.0.$0^{1,3}$]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4- oxoquinolino-3-carboxílico; ácido 7-[6-amino-8-azatriciclo[4.3.0.$0^{1,3}$]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metilo-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5S)-1-amino-3-

1 104

azabiciclo[4.3.0]nonan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3- carboxílico; ácido 7-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; ácido 10-[(1S,5S)-1-amino-3-azabiciclo[4.3.0]nonan-3-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido [1,2,3-de][1,4]benzoxazino-6-carboxílico; ácido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-8-cloro-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-8-ciano-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-4- oxoquinolino-3-carboxílico; ácido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metoxi-4-oxoquinolino-3-carboxílico; ácido 7-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0]nonan-8-il]-6-fluoro-1-[(1R,2S)-2-fluorociclopropilo]-1,4-dihidro-8-metil-4-oxoquinolino-3-carboxílico; o ácido 10-[(1S,6S)-1-amino-8-aza-3-oxabiciclo[4.3.0] nonan-8-il]-9-fluoro-2,3-dihidro-3-(S)-metil-7-oxo-7H-pirido[1,2,3-de][1,4]benzoxazino-6-carboxílico.

36.- Una medicina que comprende el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

37.- Un agente antibacteriano que comprende el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

38.- Un agente terapéutico para infecciones que comprende el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

39.- Un método para tratar enfermedades que comprende administrar el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

40.- Un método para tratar infecciones que comprende administrar el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

41.- Un método para producir una medicina que comprende añadir el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

42.- Un método para producir un agente antibacteriano que comprende añadir el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

43.- Un método para producir un agente terapéutico para infecciones que comprende añadir el compuesto de conformidad con cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo como un ingrediente activo.

44.- El uso del compuesto como se reclama en cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo para la producción de una medicina.

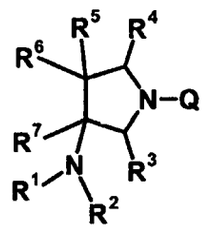
45.- El uso del compuesto como se reclama en cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo para la producción de un agente antibacteriano.

46.- El uso del compuesto como se reclama en cualquiera de las reivindicaciones 1 a 34, una sal, o un hidrato del mismo para la producción de un agente terapéutico para infecciones.

1 206

RESUMEN DE LA INVENCION

Se provee un agente antibacteriano sintético de quinolona que tiene excelentes propiedades como una medicina, que tiene fuerte actividad antibacteriana no sólo para bacterias Gram-negativas sino también para cocos Gram-positivos que tienen sensibilidad baja a agentes antibacterianos de quinolona, y que presenta alta seguridad y excelente farmacocinética; un compuesto representado por la fórmula (I) o una sal del mismo, o un hidrato del mismo; de manera específica, un derivado de quinolona de la fórmula (I)



(I)

en donde los sustituyentes R6 y R7 tomados junto con los átomos de carbono a los cuales están unidos forman una estructura cíclica que puede contener un átomo de oxígeno como un átomo constituyente de anillo, la estructura cíclica formando un sustituyente de pirrolidinilo bicíclico 5-4, 5-5 ó 5-6 fusionado, el sustituyente siendo unido a una estructura de base madre de quinolona Q que contiene una estructura de piridobenzoxazina.

FIG.1

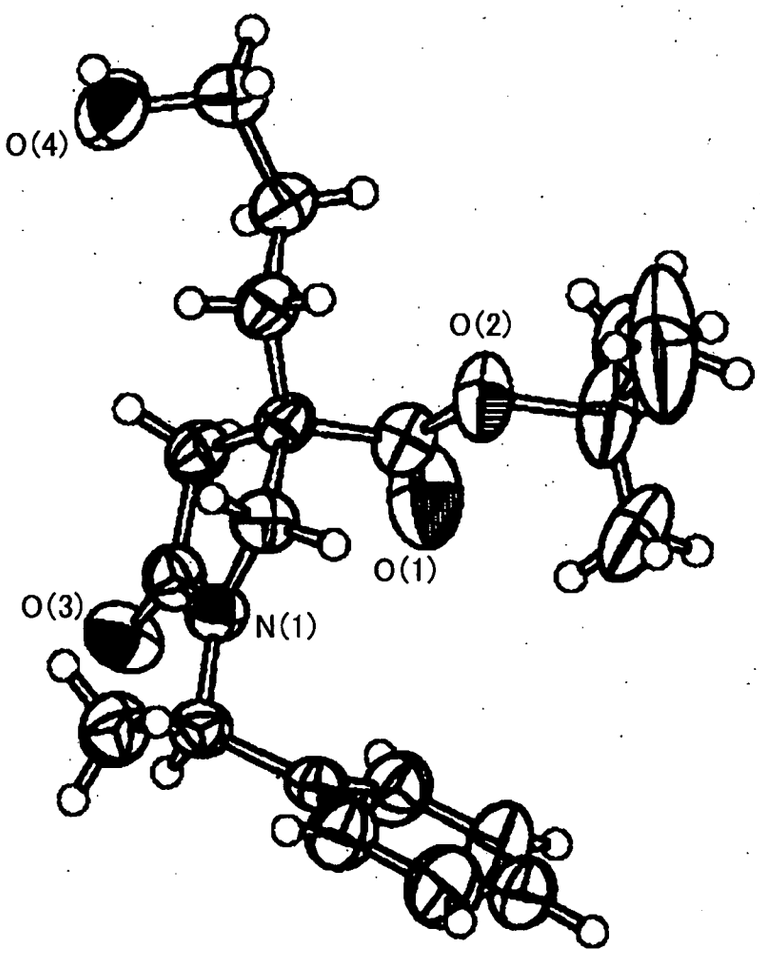
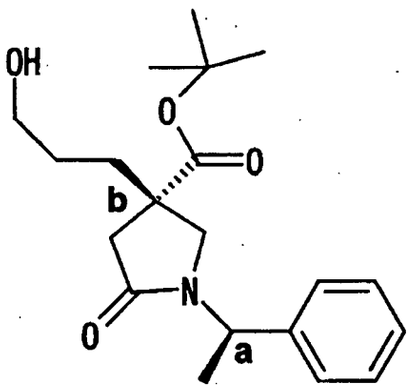


FIG.2



L1058

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/075434

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D491/052 C07D498/04 A61K31/47
A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 343 524 A (SHIONOGI & CO [JP]) 29 November 1989 (1989-11-29) cited in the application compounds I-24	1-6,8,9, 11,14, 18,20, 31,36-46
X	WO 96/23782 A (DAIICHI SEIYAKU CO [JP]; TAKEMURA MAKOTO [JP]; KIMURA YOUICHI [JP]; KA) 8 August 1996 (1996-08-08) cited in the application example 6	1-6, 8-10,17, 19-26, 28,31, 36-46
X	EP 0 812 838 A (DAINIPPON PHARMACEUTICAL CO [JP]) 17 December 1997 (1997-12-17) cited in the application examples 1-13,15,16	1-6, 8-10,17, 19-26, 28,31-46

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2008	07/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bakboord, Joan

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/075434

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& WO 95/21163 A (DAINIPPON PHARMACEUTICAL CO [JP]; SAKAMOTO MASATO [JP]; CHIBA KATSUMI) 10 August 1995 (1995-08-10)	
X	OGATA M ET AL: "SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW 7-(AMINOAZABICYCLOALKANYL)QUINOLONECARBOXYLIC ACIDS" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 26, no. 9, 1 December 1991 (1991-12-01), pages 889-906, XP000647511 ISSN: 0223-5234 compound 40	1-6,8,9, 11,14, 17,18, 20,28, 31,36-46
X	MA Z ET AL: "SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4H-4-OXOQUINOLIZINE DERIVATIVES: CONSEQUENCES OF STRUCTURAL MODIFICATION AT THE C-8 POSITION" JOURNAL OF MEDICINAL CHEMISTRY, US AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 42, 1 January 1999 (1999-01-01), pages 4202-4213, XP002936065 ISSN: 0022-2623 compound X	1-6,8,9, 11,14, 17,18, 20-22, 28,31, 32,36-46
X	WO 2005/049602 A (WARNER LAMBERT CO [US]; ELLSWORTH EDMUND LEE [US]; TAYLOR CLARKE BENTL) 2 June 2005 (2005-06-02) page 53, line 5 - page 45, line 4	1-9,11, 14,15, 17,18, 20-22, 28,31, 36-46
X	WO 96/39407 A (ABBOTT LAB [US]) 12 December 1996 (1996-12-12) examples 495,497,499,501,536	1-6, 8-11, 13-15, 17,18, 20-22, 28,31, 36-46
X	CIANCHETTA G. ET AL: "Chemometric studies on the bacterial activity of quinolones via an extended volsurf approach" JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, 2004, pages 3193-3201, XP002494591 compound 28	1-6,8,9, 11,12, 14,15, 17,18, 20,21, 23-26, 28,31, 32,36-46

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/075434

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 01 056673 A (DAINIPPON PHARMACEUTICAL CO) 3 March 1989 (1989-03-03) abstract	1

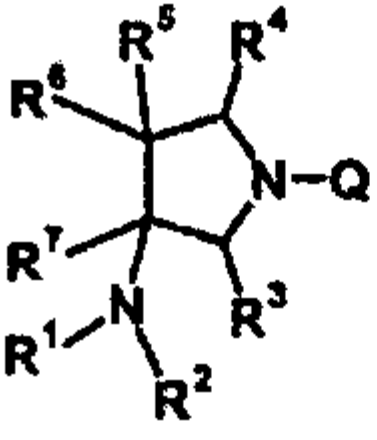
1112

INTERNATIONAL SEARCH REPORT

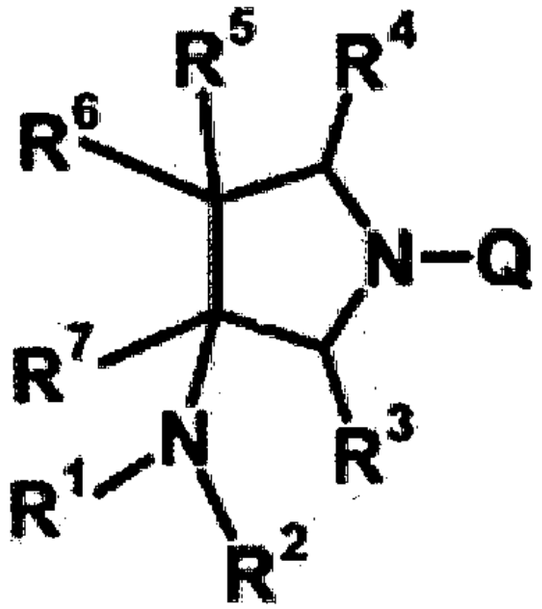
Information on patent family members

International application No
PCT/JP2007/075434

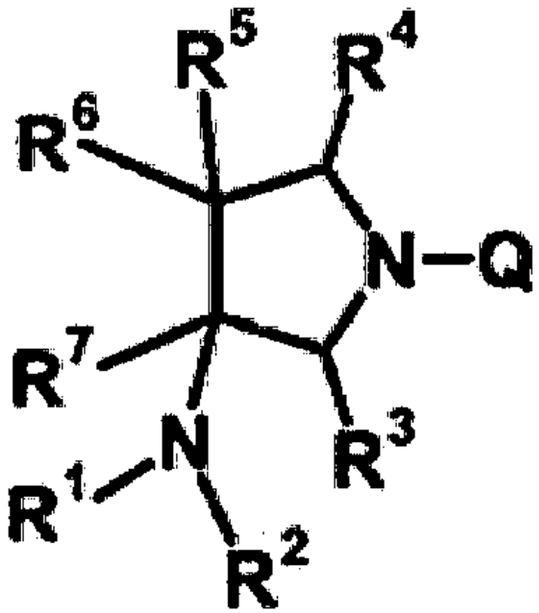
Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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WO 9623782	A	08-08-1996	AT	239720 T	15-05-2003
			CA	2212007 A1	08-08-1996
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			JP	6076400 B	28-09-1994



(I)



(I)



(I)

1114

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-081886- -00000-0000

Fecha: 2009-08-05 17:19:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1117

RECIBO OFICIAL DE CAJA : 09 - 53,098
FECHA : JULIO 21 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19805542	21/07/2009	22,635,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-02 PRORROGAS Y RENOVACIONES	30 PRORROGAS Y RENOVACIONES	643,000.00
		TOTAL : $	643,000.00

SON: SEISCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 15869-84105-2

1115

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-081886- -00000-0000
Fecha: 2009-08-05 17:19:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1117

RECIBO OFICIAL DE CAJA : 09 - 53,099
FECHA : JULIO 21 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19805542	21/07/2009	22,635,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-02 PRORROGAS Y RENOVACIONES	30 PRORROGAS Y RENOVACIONES	643,000.00
		TOTAL : $	643,000.00

SON: SEISCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Odo 15869-841-015-2

1116.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 53,130
FECHA : JULIO 21 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-081886- -00000-0000
Fecha: 2009-08-05 17:19:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1117

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19805542	21/07/2009	22,635,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD 1	99 OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
		TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

Odo 15869-84015-2

1117.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-081886- -00000-0000

Fecha: 2009-08-05 17:19:13 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1117

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 53,277
FECHA : JULIO 22 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	RECIBO DE CAJA			53119	21/07/2009	500,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 15869-841-015-2

1118

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

F

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-081886- -00000-0000
Fecha: 2009-08-05 17:19:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1117

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
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www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 1118

2020
Bogotá D.C.,

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
DAIICHI SANKYO COMPANY LIMITED

REFERENCIA	Radicación No.	9 81886
	Solicitud internacional	PCT/JP2007/075434
	Fecha inicio fase nacional	05/08/2009
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	8745
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 10 SET. 2009

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11