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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-002061- -00011-0000

Fecha: 2008-05-27 16:44:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 16

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE:	
	☐ Corrección de Error Material	☒ Modificación a una solicitud
2	SOLICITANTE Nombre: SHIRE CANADA INC. Sociedad constituida y existente bajo las leyes de Canadá Dirección: 2250, BOUL Alfred-Nobel Bur 500, Ville St-Laurent, Québec H4S 2C9, Canadá Domicilio: Ville St-Laurent, Québec H4S 2C9, Canadá Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@camyp.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3	REPRESENTANTE O APODERADO Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 438.019 TP 31.929
4	Número de expediente: 04.002.061	
5	Descripción de la corrección o modificación solicitada: Atentamente solicito a su Despacho ordenar la anotación en los libros de Propiedad Industrial el cambio de nombre de la sociedad SHIRE BIOCHEM, INC. por el de SHIRE CANADA INC. Para este efecto, presento el documento que certifica el cambio de nombre debidamente legalizado y traducido, así como el poder	
6	Comprobante de pago No. 08-34.036 Fecha: abril 28 de 2008	
7	Anexos ☒ Comprobante de pago de la tasa por \$103.000, por concepto de modificaciones. ☒ Documento que certifica el cambio de nombre debidamente legalizado y traducido ☒ Poderes, si fuere el caso	
8	NOMBRE: EMILIO FERRERO	FIRMA: C.C. 438.019 de Usaquén T.P.A. 31.929

Canada



Industry Canada

Industrie Canada

**Certificate
of Amendment**

**Canada Business
Corporations Act**

**Certificat
de modification**

**Loi canadienne sur
les sociétés par actions**

232
252

SHIRE CANADA INC.

384940-6

Name of corporation-D énomination de la société

Corporation number-Numéro de la société

I hereby certify that the articles of the
above-named corporation were amended:

Je certifie que les statuts de la société
susmentionnée ont été modifiés:

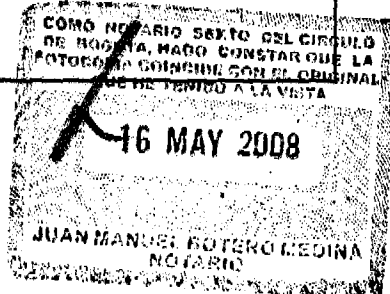
- a) under section 13 of the *Canada Business Corporations Act* in accordance with the attached notice;
- b) under section 27 of the *Canada Business Corporations Act* as set out in the attached articles of amendment designating a series of shares;
- c) under section 179 of the *Canada Business Corporations Act* as set out in the attached articles of amendment;
- d) under section 191 of the *Canada Business Corporations Act* as set out in the attached articles of reorganization;

- ☐ a) en vertu de l'article 13 de la *Loi canadienne sur les sociétés par actions*, conformément à l'avis ci-joint;
- ☐ b) en vertu de l'article 27 de la *Loi canadienne sur les sociétés par actions*, tel qu'il est indiqué dans les clauses modificatrices ci-jointes désignant une série d'actions;
- ☒ c) en vertu de l'article 179 de la *Loi canadienne sur les sociétés par actions*, tel qu'il est indiqué dans les clauses modificatrices ci-jointes;
- ☐ d) en vertu de l'article 191 de la *Loi canadienne sur les sociétés par actions*, tel qu'il est indiqué dans les clauses de réorganisation ci-jointes;

Richard G. Shaw
Director - Directeur

September 18, 2007 / le 18 septembre 2007

Date of Amendment - Date de modification



Canada

283
-237

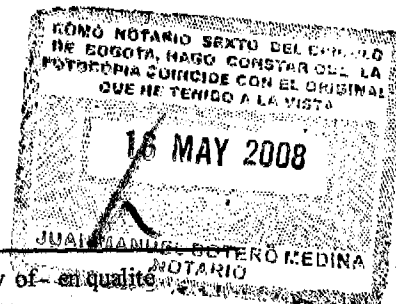
 Industry Canada **Industrie Canada** **ELECTRONIC TRANSACTION** **RAPPORT DE LA TRANSACTION**
REPORT **ÉLECTRONIQUE**
Canada Business **Loi canadienne sur les** **ARTICLES OF AMENDMENT** **CLAUSES MODIFICATRICES**
Corporations Act **sociétés par actions** **(SECTIONS 27 OR 177)** **(ARTICLES 27 OU 177)**

Processing Type - Mode de traitement: E-Commerce/Commerce-É

1. Name of Corporation - Dénomination de la société SHIRE BIOCHEM INC.	2. Corporation No. - N° de la société 384940-6
---	---

3. The articles of the above-named corporation are amended as follows:
Les statuts de la société mentionnée ci-dessus sont modifiés de la façon suivante:

The corporation changes its name to:
SHIRE CANADA INC.



Date	Name - Nom	Signature	Capacity of - en qualité
2007-09-18	CLAUDE PERRON		DIRECTOR

Page 1 of 1

Canada

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TRADUCCIÓN OFICIAL No.08/1045 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio del Interior y Justicia, por Resolución No. 323 de 1980 (Se traduce Documento sobre Ley de Sociedades Comerciales de Canada Certificado de Reforma escrito en inglés.)

Industria Canada

Certificado de Reforma

Ley de Sociedades Comerciales en Canada

SHIRE CANADA, INC.

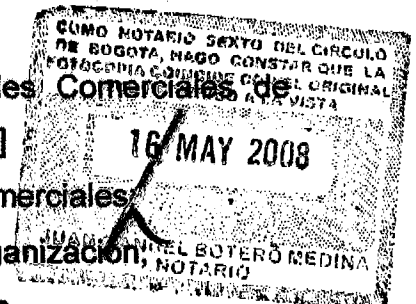
384940-6

Nombre de la sociedad-Denominación

Número de la Sociedad

Por el presente certifico que los estatutos de la sociedad mencionada arriba se reformaron:

- a) Bajo la sección 13 de la Ley de Sociedades Comerciales de Canada de Conformidad con el anuncio adjunto.
- b) Bajo la sección 27 de la Ley de Sociedades Comerciales de Canada; Según lo indicado en los artículos adjuntos de reforma, designando la Serie de las acciones;
- c) Bajo la sección 179 de la Ley de Sociedades Comerciales de Canada; [X]
- d) Bajo la sección 191 de la Ley de Sociedades Comerciales de Canada según los adjuntos artículos de reorganización;



(Firmado) Richard G. Shaw

Fecha de la Reforma

Director

Septiembre 18, 2007

Hilda Aguilera de Piedrahita
08.1045
TRADUCCION OFICIAL No. 08.1045
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES No 323 DEL MIN DE JUSTICIA

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Canada

Industria Canada Informe sobre Transacción Electrónica

Ley de Sociedades Comerciales de Canadá Artículos Reformados

(.Secciones 27 o 177)

Tipo de Procesamiento E Comercio E 2 Tipo No. de la Sociedad

1 Nombre de la Sociedad Designación 384940-6

SHIRE BIOCHEM INC.

3 Estatutos de la sociedad mencionada arriba, como sigue:

La sociedad cambia su nombre por

SHIRE CANADA INC.

Fecha	Nombre	Firma	En Calidad de
-------	--------	-------	---------------

2007-09-18	Claude Ferron		Director
------------	---------------	--	----------

Pagina 1 de 1

CANADA

Industria Ley de Sociedades Comerciales de Canada

YO CERTIFICO QUE LA ADJUNTA ES UNA COPIA FIEL DEL DOCUMENTO

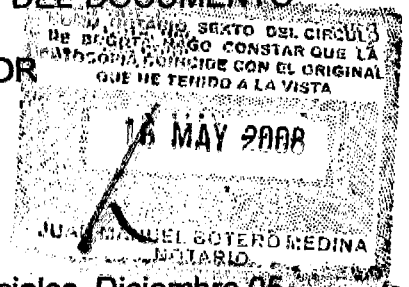
QUE SE ENCUENTRA EN LOS ARCHIVOS DEL DIRECTOR

(Firmado) Ilegible

Director Encargado – Director Adjunto

(Sello en Tinta de La Oficina de Ley de Sociedades Comerciales Diciembre 05,

2007)



TRADUCCION OFICIAL No. 08-1045
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

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Sello en Tinta: Certificado por el Departamento de Relaciones Exteriores de la Oficina Extranjera de la Ley de Sociedades Comerciales de Canadá, (Hay dos (2) firmas ilegibles) Sello con firma Suscrita por el Director Adjunto de la Oficina)

Sello en Tinta de Autenticación de Firma:

CONSULADO DE COLOMBIA

No. 069 Ottawa, Canadá a 14 de Abril de 2008

Visto en este Consulado para autenticar la firma de

**MARIO NUÑEZ SUAREZ OFICIAL
DE AUTENTICACIONES DE CANADA**

US\$ 25.00

CONSUL DE COLOMBIA

Rafael Guillermo Arismendy J.

Primer Secretario Encargado de las Funciones Consulares de la

Embajada Colombiana.

(Firmado) Ilegible

Sello en máquina: Ministerio de Relaciones Exteriores

2008 Mayo 7 Hora AM: 11.42

(Firma) Jefe de Legalizaciones Bogotá D.C.

No.: 758865

Es Traducción Fiel y Completa de la cual se deja copia en los

archivos de esta oficina para su confrontación y a la cual me remito, habiendo tenido el original del documento a la vista.

Colo-16516-845.001-4 Solicit. JM Crts, 2,564

TRADUCCION OFICIAL No. 68-1045
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
VIA NO. 323 DEL MIN. DE JUSTICIA



Consulado de Colombia

CERTIFICACION No. 051/ 2008

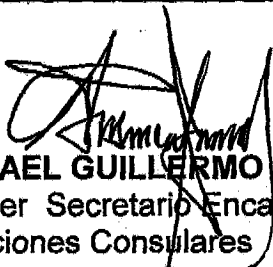
**EL SUSCRITO PRIMER SECRETARIO ENCARGADO DE FUNCIONES
CONSULARES, DE LA EMBAJADA DE COLOMBIA EN OTTAWA,**

VISTOS LOS DOCUMENTOS PRESENTADOS,

CERTIFICA:

1. Que el señor MARIO NUÑEZ SUAREZ, quien autoriza los documentos autenticados en la Provincia de Ontario, ejercía legalmente en la fecha indicada, como Oficial de Autenticaciones de la División legal del Ministerio de Asuntos Exteriores y de Comercio de Canadá, y que las firmas y sellos que en los documentos aparecen como suyos son los que usa y acostumbra en sus actos oficiales.
2. Que tuvo a la vista las pruebas de que la entidad SHIRE CANADA INC. registrada en el 2250 Boul. Alfred Nobel, Bur, 500, Ville St. Laurent, Québec H4S – 2C9 existe legalmente, y que actualmente ejerce su objeto social de acuerdo con las leyes canadienses.
3. Que el señor ANTONIO JAVIER AVELEDO, en su calidad de Representante de Propiedad Intelectual de SHIRE CANADA INC., está autorizado legalmente para representar a esa entidad en este acto y otorgar el poder.

Se expide a solicitud del interesado a los siete (14) días del mes de abril del año dos mil ocho (2008).

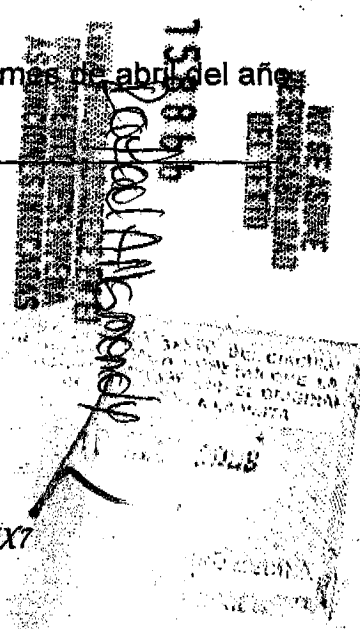

RAFAEL GUILLERMO ARISMENDY J.
Primer Secretario Encargado de las
Funciones Consulares

DERECHOS CONSULARES US\$ 110.00

360 Albert Street, Suite 1002, Ottawa Ontario K1R 7X7

Tel: (613) 230-3760 Fax: (613) 230-4416

<http://www.embajadacolombia.ca>



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CAVELIER

ABOGADOS
EDIFICIO SISKI
CARRERA 4ª N° 72-35
BOGOTÁ, 8 - COLOMBIA

179

Representación y Poder con certificado consular 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 consular certificate for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

PHAR-125-007 COLO ✓

Yo (nosotros), abajo firmado (s) (I (we), the undersigned
SHIRE CANADA INC.

domiciliado (s) en/of 2250, BOUL. ALFRED-NOBEL
BUR. 500, VILLE ST-LAURENT, QUEBEC, H4S 2C9

por el presente nombramos a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620 domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia 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 suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndolos por el solo 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 (autorizo) 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, 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, 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

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; 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 contentions 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; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of 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 these 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.

© Roxanne Daviault
Notaire

FEB 28 2008

ORIGINAL

COPIE CERTIFIÉE
CONFORME

16 MAY 2008

ROXANNE DAVIAULT
NOTAIRE

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promuevan. Y para que en todos los asuntos arriba determinados, puedan
sustituir este mandato, transigir, conciliar, admitir los hechos del proceso,
desistír, cancelar, recibir, renunciar, y ratificar los actos de agentes
oficiosos.

compromisa, conciliate, admit the facts of the case, desist, cancel, receive,
resign, and ratify acts done by representatives without a power of attorney.

Patent Application No. 04.002.061

Dado y firmado hoy/Given and signed this _____
en/in VILLE ST-LAURENT, QUEBEC _____
por/by _____
Antonio Aveledo, Intellectual Property Advisor

Firma

Signature

Antonio Aveledo

FEB 28 2008

Roxanne Daviault

Me Roxanne Daviault
Notaire

CONSULADO DE COLOMBIA

No. 068 Ottawa, Canadá, a 14 de ABRIL de 2008
Visto en este Consulado para autenticar la firma de
MARIO NÚÑEZ SUAREZ
quien en la Fecha ejercía las funciones de
OFICIAL DE AUTENTICACIONES M.R.E DE CANADA

US\$25.00 Cónsul de Colombia

Rafael Guillermo Arrienda
RAFAEL GUILLERMO ARRIENDA
Primer Secretario Encargado de las Funciones Consulares
Ottawa, Canada

HAUSE ASOME
RESPONSABILIDAD
DEL TITULO

750 967
Rafael Arrienda
COLUMBIAN CONSUL IN OTTAWA
AS-FUNCTIONS IN CHARGE

© CAVELIER ABOGADOS
WFP00003-179

MINISTERIO DE
RELACIONES EXTERIORES

2008 MAY 17 10:43

SECCION DE LEGALIZACION
BOGOTA D.C.

Continued at the Department of Foreign Affairs and
International Trade for legalization of the
Foregoing Signature of *Mario Núñez Suarez*
Certifié par le Ministère des Affaires étrangères et
du Commerce international aux fins de légaliser
la signature en dessous de *Mario Núñez Suarez*
Deputy Minister of
Foreign Affairs
Sous-ministre des
Affaires étrangères

CANADA

16 MAY 2008
JUAN MANUEL BOTERO MEDINA
NOTARIO

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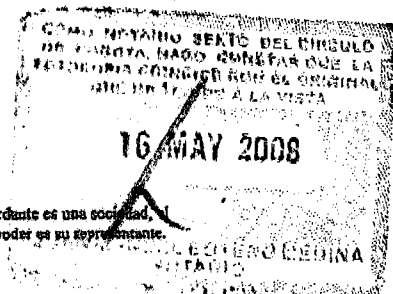
AUTENTICACION

El Señor Cónsul de Colombia debe expedir un certificado consular sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darle. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

AUTHENTICATION

The Colombia Consul must issue a consular certificate, on (1) the legal existence of the company which grants the Power-of-Authority, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Authority is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



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-241)

Traducción Oficial No. 08.1044 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial en los idiomas inglés-español-inglés, debidamente reconocida por el Ministerio del Interior y de Justicia, por Resolución 323 de 1980, y autorizada por el Ministerio de Relaciones Exteriores.

(Se traduce un Poder de Representación y autenticación notarial para patentes, modelos de utilidad diseños industriales, marcas, nombres comerciales, emblemas, nombres de dominio, licencias,

© cavalier abogados
carrera 4 No. 72-35
Bogotá,

179 Yo, (Nosotros, abajo firmados)

SHIRE CANADA, INC.

Domiciliado(s) en/de 2250, BOUL, ALFRED- NOBEL

Bur.500, Ville St. Laurent, Quebec H4S 2C9

Canada

En obediencia al parágrafo 1º. Del Artículo 543 del Código de Comercio, por el presente nombramos a EMILIO FERRERO, tpa. 31929, LUZ CLEMENCIA DE PAEZ, t.p.a. No. 23.555 y DANIEL PEÑA t.p.a. 65620 domiciliados en la Carrera 4ª, No. 72-35. Bogotá, Colombia, en obediencia 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 impedimento temporal o definitivo. La misma regla se aplicará cuando el segundo representante suplente deba reemplazar al primero, o cuando el tercero deba reemplazar al segundo. En tales casos, el representante principal, o el primero o segundo representantes suplentes, a su turno o ambos de ellos deberán ejercer la representación en su orden, uno u otros, según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el

Hilda Aguilera de Piedrahita

08-1044
TRADUCCION OFICIAL
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. NO. 323 DEL MIN. DE JUSTICIA

ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero conferimos a los dichos abogados para que nos representen en cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como tribunales de arbitramento, en todo lo concerniente a: a) obtención de patentes de invención, modelos de utilidad, diseños industriales; 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, cancelación voluntaria y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal protección al consumidor, cancelación administrativa protección del consumidor, oposiciones y procesos que promovamos o se nos promuevan; protección de derechos industriales y en general juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos. 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.

Dado y firmado hoy día

Solicitud de Patente No.04.002.061

En VILLE ST. LAURENT, QUEBEC,

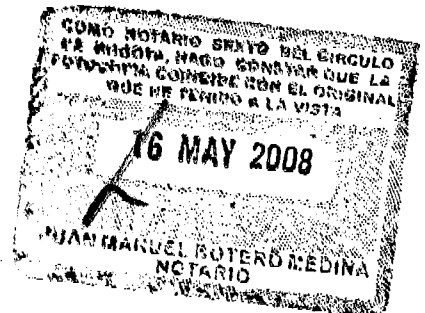
(Firma) ANTONIO AVELEDO, Asesor en Propiedad Intelectual

Febrero 28, 2008

(Firmado) Me. Roxanne Daviault Notario Público

Copia Certificada, Conforme

Original (Hay Firma Ilegible)



Consulado de Colombia

CERTIFICACION No. 051/2008

[Handwritten signature]
TRADUCCION OFICIAL No. 08.1044
HILDA AGUILERA DE PIEDRANTO
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

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243
EI SUSCRITO PRIMER SECRETARIO ENCARGADO DE FUNCIONES
CONSULARES, DE LA EMBAJADA DE COLOMBIA EN OTTAWA,
VISTOS LOS DOCUMENTOS PRESENTADOS,

CERTIFICA:

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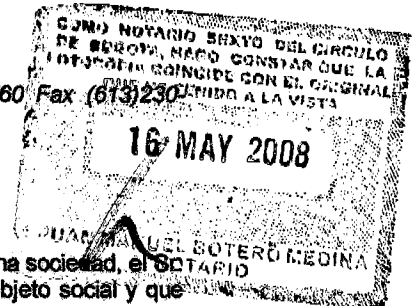
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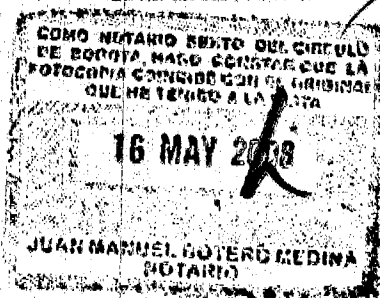
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
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		TOTAL :	\$ 103,000.00

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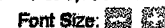
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Tetrahedron Letters

Volume 35, Issue 27, 4 July 1994, Pages 4739-4742

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PDF (298 K)

doi:10.1016/S0040-4039(00)76955-3



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Synthesis of optically active 2',3'-dideoxy-3'-oxa-4'-thio-ribonucleoside analogues by transposition of a leaving group on chiral oxathiolanes via a reductive-oxidative process

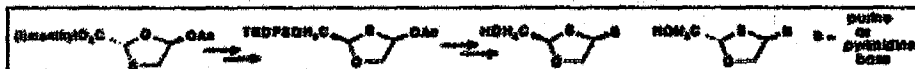
Wei Wang^a, Hailun Jin^a and Tarek S. Mansour^a^aBiochem Therapeutic Inc., 275 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4A7

Received 10 March 1994; revised 3 May 1994; accepted 6 May 1994. Available online 8 June 2001.

Abstract

The synthesis of chiral nucleoside analogues with a unique structural feature is reported. The strategy is based on a reductive-oxidative process to complete the transposition of the leaving group in chiral oxathiolanes with known configuration.

Reductive-oxidative transformation of chiral oxathiolanes has led to the transposition of the existing leaving group and provided the access to a series of novel chiral nucleoside analogues.



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SYNTHESES AND ANTIVIRAL ACTIVITIES OF 1,3-DIOXOLANYL-, 1,3-OXATHIOLANYL- AND 1,3-DITHIOLANYLNUCLEOSIDES WITH 2-HYDROXYMETHYL SUBSTITUENTS

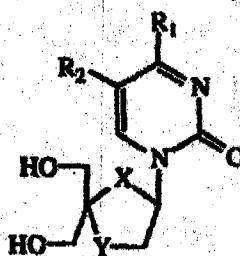
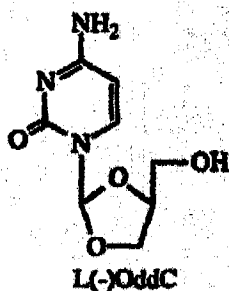
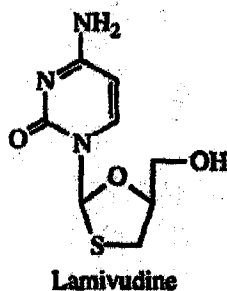
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Abstract: Novel 1,3-dioxolanyl-, 1,3-oxathiolanyl- and 1,3-dithiolanylnucleosides with 2-hydroxymethyl substituents (1a-4b) were each synthesized with good yields through the condensation of dinucleophiles (oxygen and/or sulfur) with 1,3-dibenzoxy-2-propanone methyl ketal as a key step. © 1997 Elsevier Science Ltd.

Recently, several nucleosides possessing more than one heteroatom in the sugar ring have been reported to exhibit good antiviral activity.¹⁻⁴ Among these, (-)-L-β-1,3-oxathiolanylcytosine (3TC, Lamivudine) has been approved for the treatment of AIDS and will soon be approved by the Food and Drug Administration (FDA) for anti-HBV agent.^{5,6}

Lamivudine is the first L-nucleoside to be approved by FDA and is much less cytotoxic than its enantiomer, D-isomer. Another L-nucleoside, (-)-L-β-1,3-dioxolanylcytosine (L(-)OddC) was found to be highly potent against HIV and HBV as well as highly cytotoxic and is being developed as an anticancer agent.^{7,8}



- 1a (X=O, Y=O, R₁=OH, R₂=CH₃)
 1b (X=O, Y=O, R₁=NH₂, R₂=H)
 2a (X=O, Y=S, R₁=OH, R₂=CH₃)
 2b (X=O, Y=S, R₁=NH₂, R₂=H)
 3a (X=S, Y=O, R₁=OH, R₂=CH₃)
 3b (X=S, Y=O, R₁=NH₂, R₂=H)
 4a (X=S, Y=S, R₁=OH, R₂=CH₃)
 4b (X=S, Y=S, R₁=NH₂, R₂=H)

For structure-activity relationship study, substituents are bonded onto the dioxolane or oxathiolane ring, and a comparison is made between the biological activity of the new compound with that of its parent. Therefore, we decided to synthesize 2-hydroxymethyl analogues of 1,3-dioxolanyl- and 1,3-oxathiolanyl nucleosides, since oxetanocin A⁹ and its ring-enlarged analogues¹⁰ showed good antiviral activity.

A concurrent investigation of synthesis of 4'-thio analogues of 4'-hydroxymethyl-3'-oxa- and 3'-thianucleosides and a comparison of the antiviral activities of each were carried out, since 4'-thionucleosides, possessing hetero atoms such as oxygen or sulfur atom at the 3'-position were reported to show good to excellent antiviral activity.¹¹⁻¹³

SYNTHESIS AND ANTIVIRAL ACTIVITIES OF 1,3-DIOXOLAN-2-YL- AND 1,3-DITHIOLAN-2-YL-NUCLEOSIDES WITH 4-HYDROXYMETHYL SUBSTITUENTS

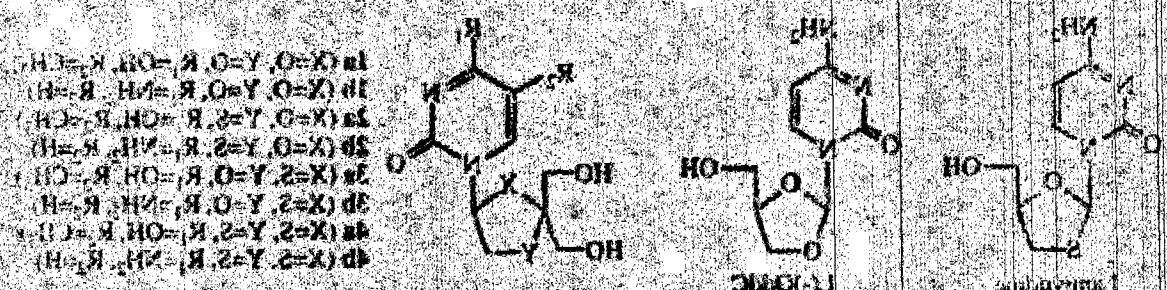
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Department of Chemistry, Seoul National University, Seoul 151-747, Korea; College of Pharmacy, Ewha Woman's University, Seoul 120-750, Korea; Applied Science and Technology, Seoul 130-030, Korea; and Department of Applied Science, Ewha Woman's University, Seoul 120-750, Korea

Abstract: A series of 1,3-dioxolane-2-yl- and 1,3-dithiolane-2-yl- nucleosides with 4-hydroxymethyl substituents (1a-13) were synthesized and their antiviral activities were evaluated. The results showed that 1,3-dioxolane-2-yl- nucleoside (1a) was the most active compound in the series.

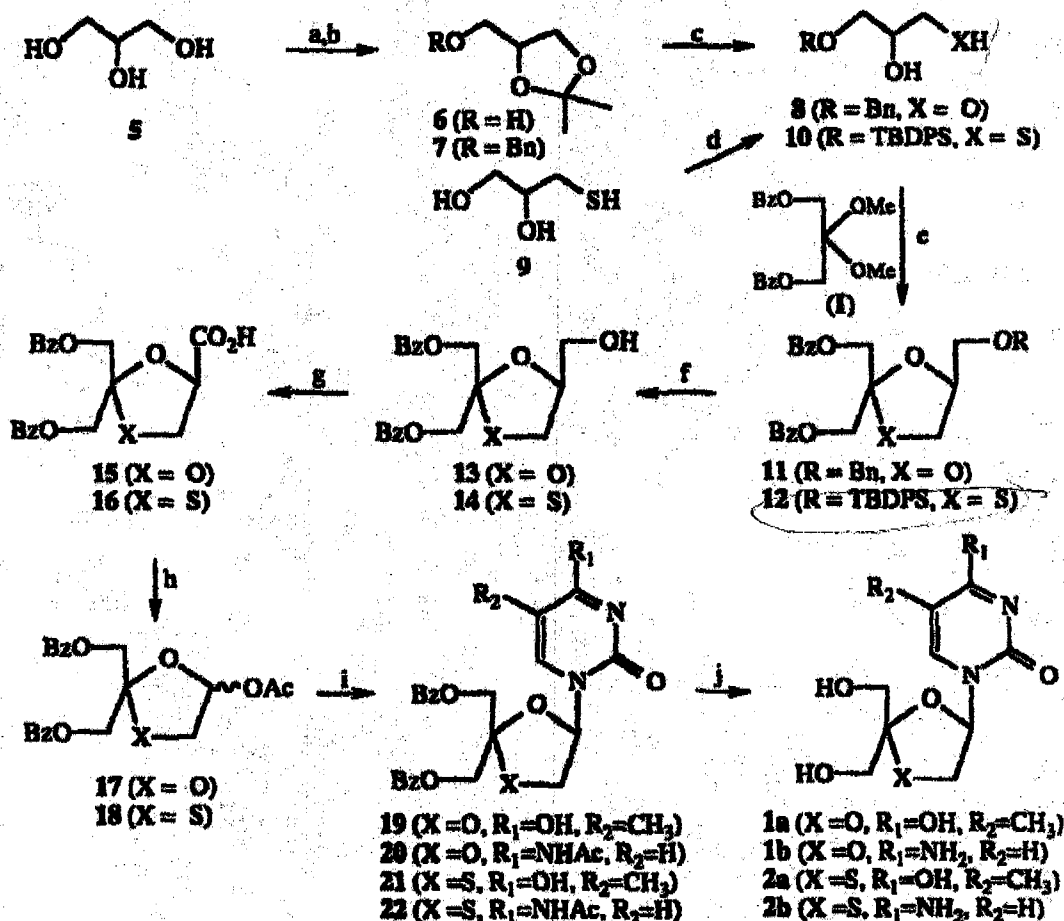
Recently, several nucleosides possessing more than one heteroatom in the sugar ring have been reported to exhibit good antiviral activity. Among these, (-)-1,3-bis(hydroxymethyl)-2-thio-2,3-dihydro-1,4-dioxane (1a) was reported for the treatment of AIDS and will soon be approved by the Food and Drug Administration (FDA) for use in AIDS therapy.

Lamivudine is the first F-nucleoside to be approved by FDA and is much less cytotoxic than the monomeric D-thymine. Another F-nucleoside, (-)-1,3-bis(hydroxymethyl)-2-thio-2,3-dihydro-1,4-dioxane (1b) was found to be highly cytotoxic and is being developed as an anticancer agent.



For structure-activity relationship study, substituents are bonded onto the dioxolane or dithiolane ring. A comparison is made between the biological activity of the new compounds with that of the parent. Therefore, we decided to synthesize 1,3-dioxolane-2-yl- and 1,3-dithiolane-2-yl- nucleosides, since nucleoside A and its ring-substituted analogues showed good antiviral activity.

A systematic investigation of synthesis of 4-hydroxymethyl-2-thio-2,3-dihydro-1,4-dioxane (1a) and its ring-substituted analogues and a comparison of the antiviral activities of each were carried out, since 4-hydroxymethyl-2-thio-2,3-dihydro-1,4-dioxane (1a) was reported to show good to excellent antiviral activity.

248
248Scheme 1^a

sililado

Reagents^a: a) $\text{CH}_3\text{C}(\text{OMe})_2\text{CH}_3$, cHCl , RT, 15 h, 87%. b) NaH , BnBr , DMF, RT, 15 h, 98%.
 c) cHCl , MeOH , reflux, 1 h, 77%. d) $t\text{-BDPSCl}$, imidazole, THF, RT, 30 min, 86%.
 e) cat. $p\text{-TsOH}$, toluene, reflux, 76% for 13, 53% for 14. f) H_2 , 10% Pd/C , RT, 15 h, 78% for 15, $n\text{-Bu}_4\text{NF}$, THF, RT, 20 min, 86% for 16. g) PDC , DMF, 45–50°C, 15 h.
 h) $\text{Pb}(\text{OAc})_4$, pyridine, THF, 0°C to RT, 30 min, 50% from 15 for 19, 49% from 16 for 20. i) persilylated bases, TMSOTf , 1,2- DCE , -20°C to RT, 2 h, 74% for 19, 46% for 20, 69% for 21, 55% for 22. j) NaOMe , CH_2Cl_2 , RT, 30 min, 97% for 1a, 95% for 1b, 80% for 2a, 99% for 2b.

This paper describes the syntheses and antiviral activities of racemic 1,3-dioxolanyl-, 1,3-oxathiolanyl- and 1,3-dithiolanyl nucleosides (1a–4b) with 2-hydroxymethyl substituents through the condensation reaction of dinucleophiles (oxygen and/or sulfur) with 1,3-dibenzoyl-2-propanone methyl ketal. In order to produce the target nucleosides (1a–2b), sugar acetate was first synthesized and then condensed with heterocyclic bases. (Scheme 1).

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1,2-Diol of DL-glycerin (5) was protected as acetonide (6) and underwent benzylation to produce a benzyl derivative (7). The isopropylidene group of 7 was removed under acidic conditions to yield the diol 8. The another dinucleophile 10 was synthesized from 3-mercapto-1,2-propanediol (9) after treatment with tert-butyldiphenylsilyl chloride in DMF. The intermediates 8 and 10 were condensed with 1,3-dibenzoxy-2-propanone methyl ketal (I) in the presence of catalytic amount of acid to give 3'-oxa- and 3'-thiasugars 11 and 12, respectively. 1,3-Dibenzoxy-2-propanone methyl ketal (I) could be readily synthesized from 1,3-dihydroxypropane-2-one dimer. Treatment of 1,3-dihydroxypropane-2-one dimer with trimethyl orthoformate and p-TsOH yielded the ketal derivative (82%), which was benzyolated using NaH and benzoyl chloride to give the intermediate (I) in an 89% yield. Compounds 11 and 12 were deprotected using H₂ in Pd/C and n-Bu₄NF to yield the alcohol derivatives 13 and 14, respectively. Treatment of 13 and 14 with pyridinium dichromate (PDC) in DMF¹⁴ produced acid derivatives 15 and 16, which underwent oxidative decarboxylation with lead tetraacetate to give the key intermediates 17 and 18, respectively. Lewis acid (TMSOTf) catalyzed the condensation of the sugar 17 with persilylated bases (thymine and N-acetylcytosine) in 1,2-dichloroethane at room temperature and yielded the protected 3'-oxanucleosides 19 and 20. 3'-Thianucleosides 21 and 22 were similarly prepared. Protecting groups of the 3'-oxa- and 3'-thianucleosides were removed using sodium methoxide in CH₂Cl₂ to afford the final nucleosides 1a-2b.^{15,16}

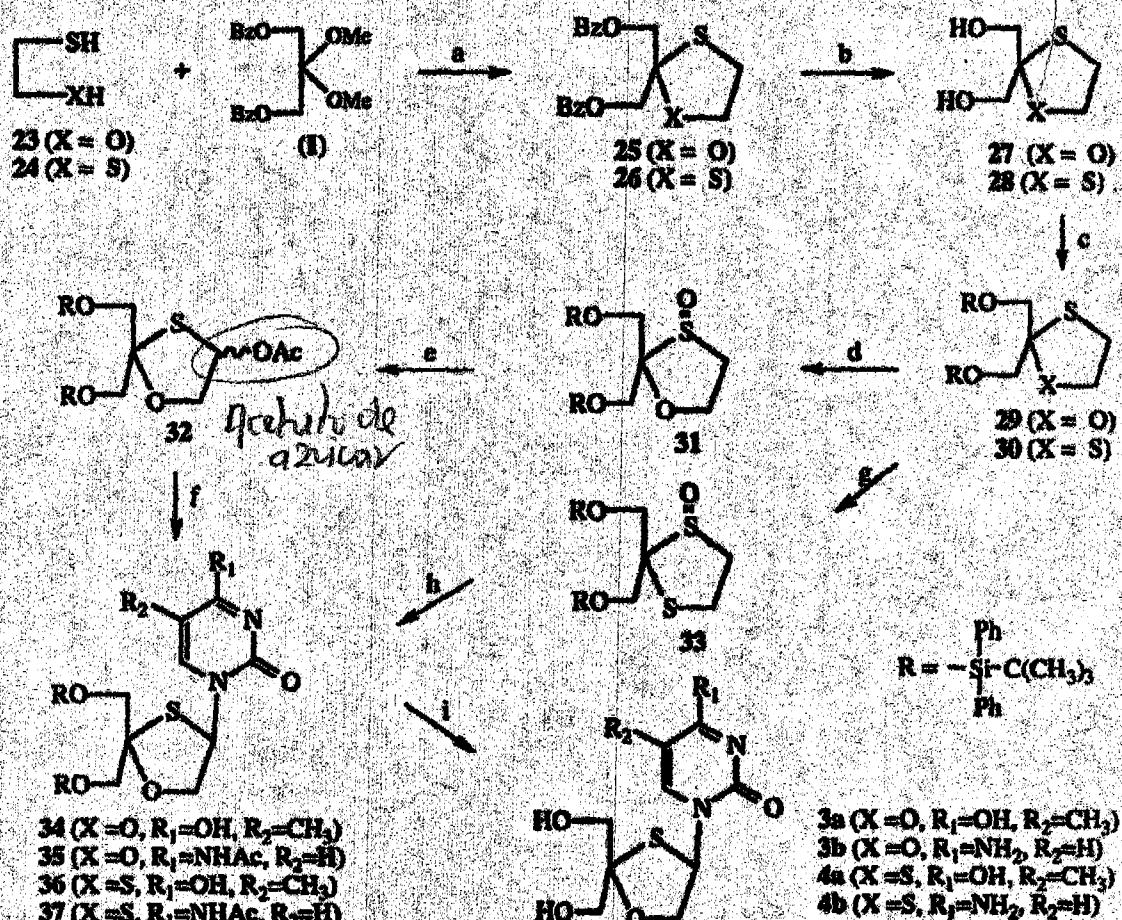
Syntheses of racemic 1,3-oxathiolanyl- and 1,3-dithiolanyl nucleosides (3a-4b) with 2-hydroxymethyl group were accomplished utilizing a Pummerer rearrangement¹⁷ of the sulfoxide as a key step and are described in detail in Scheme 2. Dinucleophiles, 2-mercaptoethanol (23) and 1,2-ethanedithiol (24) were condensed with methyl ketal (I) in the presence of a catalytic amount of p-TsOH to give 1,3-oxathiolane ring (25) and 1,3-dithiolane ring (26) in 73% yields, respectively. Treatment of benzoates (25 and 26) with methanolic ammonia yielded diol derivatives (27 and 28) which were protected with t-butyldiphenyl silyl group to give 29 and 30, respectively. The sulfur atom of compound 29 was oxidized to sulfoxide 31 by treating with m-CPBA at 0 °C. A Pummerer rearrangement of sulfoxide was utilized to synthesize the sugar acetate ready for the condensation with pyrimidine bases.¹⁷ Thus, treatment of sulfoxide 31 with sodium acetate and acetic anhydride at 120 °C produced acetate 32 in a 34% yield.

Condensation reactions of 32 with persilylated pyrimidine bases such as thymine and N-acetylcytosine in 1,2-dichloroethane, which used TMSOTf as a Lewis acid catalyst at room temperature, yielded the protected nucleosides 34 and 35 in 38% to 49% yields. On the other hand, the production of 1,3-dithiolanyl nucleosides by a direct condensation reaction of sulfoxide with persilylated pyrimidine bases, through a Pummerer type rearrangement, was utilized instead of preparing a sugar acetate like 1,3-oxathiolanyl nucleosides 34 and 35.^{18,19} Thus, compound 30 was oxidized to sulfoxide 33 by treating with m-CPBA in methylene chloride at -78 °C. Reaction of sulfoxide 33 with persilylated pyrimidine bases such as thymine and N-acetylcytosine in 1,2-dichloroethane, using TMSOTf as a Lewis acid catalyst at 50 °C, yielded the protected nucleosides 36 and 37 in 53% to 86% yields. Silyl groups of protected nucleosides 34-37 were removed using tetrabutylammonium fluoride to give 3a-4b.^{20,21} The silyl groups remained intact at room temperature and were only removed under conditions of elevated temperature (45 °C) and a longer reaction time (15 h).

1,2-Diol of *DL*-glyceral (8) was protected as acetone (9) and underwent acetylation to produce a methyl derivative (10). The hydrophilic group of 10 was removed under acidic conditions to yield the diol 8. The product dithiolanynucleoside 10 was synthesized from 3-methyl-1,3-propanediol (9) after treatment with tetrahydrofuran (THF). The intermediates 8 and 10 were condensed with 1,3-dithiolan-2-yl phosphonate methyl ketol (11) in the presence of catalytic amount of acid to give 3'-oxa- and 3'-thiaguanine 11 and 12, respectively. 1,3-Dithiolan-2-yl phosphonate methyl ketol (11) could be readily synthesized from 1,3-dithiolan-2-yl phosphonate-3-one dimer with dimethyl sulfoxide (DMSO). Treatment of 1,3-dithiolan-2-yl phosphonate-3-one dimer with dimethyl sulfoxide (DMSO) and *p*-TsOH yielded the ketol derivative (85%) which was benzoylated using *N*Me and benzoyl chloride to give the intermediate (12) in an 85% yield. Compounds 11 and 12 were deprotected using H_2 in Pd/C and a 2:1 to 1:1 ratio of alcohol/ether, respectively. Treatment of 13 and 14 with pyridine and dithionine (DTN) yielded the alcohol derivatives 13 and 14, respectively. Treatment of 13 and 14 with pyridine and dithionine (DTN) produced acid derivatives 15 and 16, which underwent oxidative desulfurization with acid to give the key intermediates 17 and 18, respectively. Lewis acid (TMOT) catalyzed the condensation of the sugar 17 with benzylated bases (thymine and *N*-acetylcytosine) in 1,2-dichloroethane at room temperature and yielded the protected 3'-oxanucleosides 19 and 20. 3'-Thiannucleosides 21 and 22 were similarly prepared. Protecting groups of the 3'-oxa- and 3'-thiannucleosides were removed using sodium methoxide in CH₂Cl₂ to obtain the final nucleosides 1a-2b (15).

Synthesis of nucleoside 1,3-oxanucleosides (3a-4b) and 1,3-dithiolanynucleosides (3c-4b) with 3'-hydroxymethyl group were accomplished utilizing a *pin-methyl* rearrangement of the nucleoside as a key step and the reaction of 2-thione-2,4-dithiolan-3-yl phosphonate (23) and 1,3-dithiolan-2-yl phosphonate (24) were condensed with methyl ketol (11) in the presence of a catalytic amount of *p*-TsOH to give 1,3-oxadiazole ring (25) and 1,3-dithiolan-2-yl phosphonate (26) in 75% yields, respectively. Treatment of benzoyl (25 and 26) with methanolic ammonium hydroxide (27 and 28) which were protected with a benzylidene group to give 29 and 30, respectively. The sulfur atom of compound 29 was oxidized to sulfoxide 31 by treating with *m*-CPBA and the *pin-methyl* rearrangement of sulfoxide was utilized to synthesize the sugar acetate ready for the condensation with pyrimidine bases. Thus, treatment of sulfoxide 31 with sodium acetate and acetic anhydride at 120°C produced acetone 32 in a 34% yield.

Condensation reactions of 32 with benzylated pyrimidine bases such as thymine and *N*-acetylcytosine in 1,2-dichloroethane, which used TMOT as a Lewis acid catalyst at room temperature, yielded the protected nucleosides 34 and 35 in 38% to 49% yields. On the other hand, the production of 1,3-dithiolanynucleosides by a direct condensation reaction of sulfoxide with benzylated pyrimidine bases, through a *pin-methyl* rearrangement, was utilized instead of preparing a sugar acetate like 1,3-oxadiazole nucleosides 34 and 35. Thus, compound 30 was oxidized to sulfoxide 33 by treating with *m*-CPBA in methylene chloride at 78°C. Reaction of sulfoxide 33 with benzylated pyrimidine bases such as thymine and *N*-acetylcytosine in 1,2-dichloroethane, using TMOT as a Lewis acid catalyst at 20°C, yielded the protected nucleosides 36 and 37 in 23% to 86% yields. 23% of protected nucleosides 34-37 were removed using tetraethylammonium fluoride to give 3a-4b (31). The silyl groups remained intact at room temperature and were only removed under conditions of elevated temperature (45°C) and a longer reaction time (12 h).

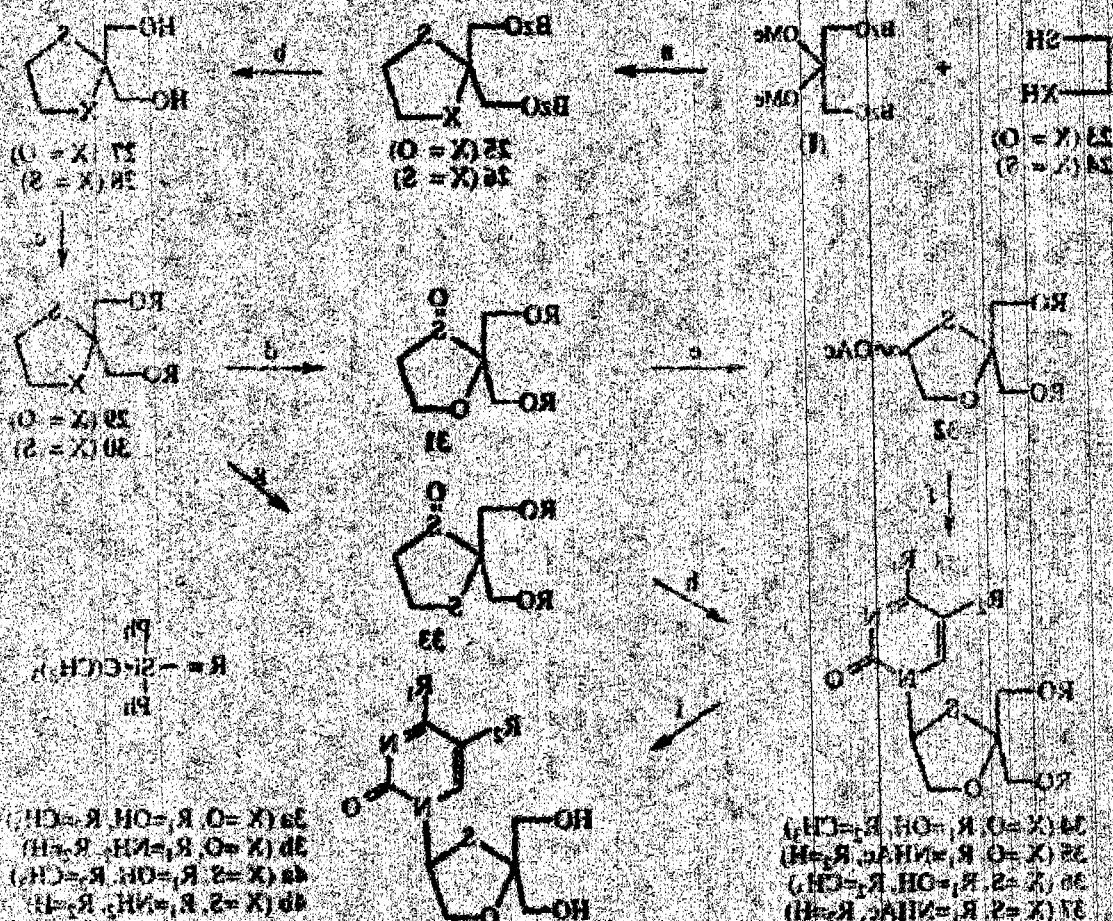
Scheme 2^a

Reagents^a: a) p-TsOH, toluene, reflux, 3 h, 73%. b) NH₃, MeOH, RT, 3 d, 88%.
 c) t-BDPSCl, imidazole, THF, RT, 40 min, 89%. d) mCPBA, CH₂Cl₂, 0°C, 30 min.
 e) NaOAc, Ac₂O, reflux, 3 days, 34%. f) persilylated bases, TMSOTf, 1,2-DCE, -20°C to RT, 2 h, 49% for 34, 38% for 35. g) mCPBA, CH₂Cl₂, -78°C, 1 h, 75%.
 h) persilylated bases, TMSOTf, 1,2-DCE, -20°C to 50°C, 18-48 h, 61% for 36, 86% for 37.
 i) n-Bu₄NF, THF, 45°C, 15 h, 90% for 3a, 70% for 3b, 74% for 4a, 86% for 4b.

It was interesting to note that the silyl and acetate groups were removed simultaneously using tetrabutylammonium fluoride in the cases of 35 and 37.

Antiviral assay against several viruses such as HIV, HSV-1, HSV-2, poliovirus and VSV were performed on the final nucleosides 3a-4e. Most compounds did not show any significant antiviral activity except compound 1b, which only exhibited a weak anti-HIV activity in MT-4 cells. It is presumed that a lack of recognition by kinases due to intramolecular hydrogen bonding between two hydroxyl groups, disallowing the formation of

Scheme 3



Reagents: a) p -TolOH, reflux, 3 h, 73%; b) NH_4^+ , MeOH, RT, 1.5, 88%;
 c) t -BuPSCl, imidazole, THF, RT, 40 min, 88%; d) MCPBA, CH_2Cl_2 , 0°C, 30 min;
 e) N -OAc, Ac₂O, reflux, 3 days, 74%; f) benzylated base, TMSOTf, 1,2-DCE, -50°C to
 RT, 2 h, 40% for 34, 38% for 35; g) MCPBA, CH_2Cl_2 , -78°C, 1 h, 72%.
 h) benzylated base, TMSOTf, 1,2-DCE, -50°C to 20°C, 18-48 h, 81% for 36, 86% for 37.
 i) n -Bu₄NF, THF, 45°C, 12 h, 90% for 38, 70% for 39, 74% for 40, 56% for 41.

It was interesting to note that the allyl and acetate groups were removed simultaneously using
 tetrabutylammonium fluoride in the cases of 35 and 37.
 Antiviral assays against several viruses such as HIV, HSV-1, HSV-2, poliovirus and VSV were performed
 on the final nucleosides 38-40. Most compounds did not show any significant antiviral activity except compound
 39, which only exhibited a weak anti-HIV activity in MT-4 cells. It is presumed that a lack of recognition by
 kinases due to intramolecular hydrogen bonding between two hydroxyl groups, disallowing the formation of

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triphosphates, may be responsible for an absence of antiviral activity. Our laboratory is now testing the affinity of 1a-4b to the kinases and synthesizing the triphosphates of 1a-4b to test against HIV-1 to determine if an absence of antiviral activity is due to a lack of recognition by kinases. The results will soon be published elsewhere.

Acknowledgments: This study was supported by grants of the Korea Science and Engineering Foundation (KOSEF 96-0403-01-01-3) and Good Health R&D Project, Ministry of Health & Welfare. The authors wish to thank Dr. C.-K. Lee, Korea Research Institute of Chemical Technology for the antiviral testing.

References and Notes:

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15. Compound 1b: white solid, mp 202-205°C; MS *m/e* 243 (M⁺); UV (MeOH) $\lambda_{\max}$ 270 nm (ϵ 8,000) (pH 7); ¹H NMR (DMSO-d₆, 300 MHz) δ 7.87 (d, 1 H, *J* = 6.6 Hz, H-6), 7.21 (br s, 1 H, NH₂), 7.09 (br

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1) ¹H NMR (DMSO-d₆, 300 MHz) δ 7.87 (d, 1 H, J = 6.6 Hz, H-6), 7.51 (br s, 1 H, NH), 7.00 (m, 1 H, H-5), 6.80 (m, 1 H, H-4), 6.60 (m, 1 H, H-3), 6.40 (m, 1 H, H-2), 6.20 (m, 1 H, H-1), 5.80 (m, 1 H, H-10), 5.60 (m, 1 H, H-9), 5.40 (m, 1 H, H-8), 5.20 (m, 1 H, H-7), 5.00 (m, 1 H, H-6), 4.80 (m, 1 H, H-5), 4.60 (m, 1 H, H-4), 4.40 (m, 1 H, H-3), 4.20 (m, 1 H, H-2), 4.00 (m, 1 H, H-1), 3.80 (m, 1 H, H-10), 3.60 (m, 1 H, H-9), 3.40 (m, 1 H, H-8), 3.20 (m, 1 H, H-7), 3.00 (m, 1 H, H-6), 2.80 (m, 1 H, H-5), 2.60 (m, 1 H, H-4), 2.40 (m, 1 H, H-3), 2.20 (m, 1 H, H-2), 2.00 (m, 1 H, H-1), 1.80 (m, 1 H, H-10), 1.60 (m, 1 H, H-9), 1.40 (m, 1 H, H-8), 1.20 (m, 1 H, H-7), 1.00 (m, 1 H, H-6), 0.80 (m, 1 H, H-5), 0.60 (m, 1 H, H-4), 0.40 (m, 1 H, H-3), 0.20 (m, 1 H, H-2), 0.00 (m, 1 H, H-1).

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- s, 1 H, NH_b), 6.24 (dd, 1 H, $J = 3.2, 5.8$ Hz, $1'\text{-H}$), 5.72 (d, 1 H, $J = 6.3$ Hz, H-5), 5.08 (t, 1 H, $J = 5.9$ Hz, OH), 4.97 (t, 1 H, $J = 5.6$ Hz, OH), 4.44 (dd, 1 H, $J = 6.0, 9.0$ Hz, $2'\text{-H}_a$), 3.90 (dd, 1 H, $J = 3.3, 9.0$ Hz, $2'\text{-H}_b$), 3.37-3.54 (m, 4 H, 2 $\times$ $\text{CH}_2\text{-OH}$); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 165.69, 155.29, 140.93, 112.18, 93.97, 82.30, 70.48, 61.91, 61.59. Normal sugar numbering system was used for the interpretation of ^1H NMR. Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_5$: C, 44.40; H, 5.35; N, 17.28. Found: C, 44.00; H, 5.27; N, 17.04.
16. Compound 2b: white solid, mp 201-205 $^\circ\text{C}$; MS m/e 258 (M^+); UV (MeOH) λ_{max} 270 nm (ϵ 7,500) (pH 7); ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.84 (d, 1 H, $J = 7.6$ Hz, H-6), 7.24 (br s, 2 H, NH_2), 6.31 (t, 1 H, $J = 5.6$ Hz, $1'\text{-H}$), 5.73 (d, 1 H, $J = 7.6$ Hz, H-5), 5.23 (br s, 1 H, OH), 5.16 (br s, 1 H, OH), 3.71 (d, 1 H, $J = 12.0$ Hz, $\text{CH}_2\text{-OH}$), 3.63 (d, 1 H, $J = 11.2$ Hz, $\text{CH}_2\text{-OH}$), 3.60 (d, 1 H, $J = 11.2$ Hz, $\text{CH}_2\text{-OH}$), 3.33-3.47 (m, 2 H, $2'\text{-H}_a$, $\text{CH}_2\text{-OH}$), 2.96 (dd, 1 H, $J = 11.6$ Hz, $2'\text{-H}_b$); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 165.59, 154.66, 140.84, 97.34, 94.17, 87.17, 64.42, 63.95, 36.11. Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.39; H, 4.95; N, 15.86.
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20. Compound 3b: white solid, mp 201-205 $^\circ\text{C}$; MS m/e 259 (MH^+); UV (MeOH) λ_{max} 270 nm (ϵ 8,500) (pH 7); ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.93 (d, 1 H, $J = 3.2$ Hz, H-6), 7.18 (br s, 1 H, NH_a), 7.10 (br s, 1 H, NH_b), 6.21 (d, 1 H, $J = 4.8$ Hz, $1'\text{-H}$), 5.73 (d, 1 H, $J = 3.2$ Hz, H-5), 5.23 (t, 1 H, $J = 6.0$ Hz, OH), 5.11 (dd, 1 H, $J = 5.2, 6.8$ Hz, OH), 4.33 (d, 1 H, $J = 11.2$ Hz, $2'\text{-H}_a$), 4.25 (dd, 1 H, $J = 4.8, 10.8$ Hz, $2'\text{-H}_b$), 3.80 (dd, 1 H, $J = 4.8, 11.6$ Hz, CH_2OH); 3.63-3.67 (m, 2 H, CH_2OH , CH_2OH); 3.39 (dd, 1 H, $J = 6.8, 12.0$ Hz, CH_2OH); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 165.39, 155.21, 140.04, 100.51, 94.53, 74.70, 63.07, 62.62, 61.79. Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.90; H, 5.27; N, 16.04.
21. Compound 4b: white solid, mp 200-204 $^\circ\text{C}$; MS m/e 275 (M^+); UV (MeOH) λ_{max} 270 nm (ϵ 9,000) (pH 7); ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.16 (d, 1 H, $J = 7.6$ Hz, H-6), 7.19 (br s, 1 H, NH_a), 7.11 (br s, 1 H, NH_b), 6.44 (pseudo t, 1 H, $J = 2.7, 4.7$ Hz, $1'\text{-H}$), 5.73 (d, 1 H, $J = 7.6$ Hz, H-5), 5.49 (t, 1 H, $J = 5.5$ Hz, OH), 5.31 (t, 1 H, $J = 5.7$ Hz, OH), 3.81 (d, 2 H, $J = 5.1$ Hz, CH_2OH), 3.53-3.67 (m, 3 H, $2'\text{-H}_a$, CH_2OH); 3.30-3.40 (m, 1 H, $2'\text{-H}_b$). Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_3\text{S}_2$: C, 39.27; H, 4.73; N, 15.27. Found: C, 39.67; H, 4.95; N, 15.66.

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Compound 5b: white solid, mp 201-202°C; MS m/z 328 (M+); UV (MeOH) λ_{max} 210 nm (ϵ 2500) (m); 1H NMR (DMSO- d_6 , 400 MHz) δ 7.84 (d, 1 H, J = 7.6 Hz, H-6), 7.34 (d, 2 H, H-5, H-7), 6.31 (d, 1 H, J = 7.6 Hz, H-1), 5.73 (d, 1 H, J = 7.6 Hz, H-2), 3.73 (m, 2 H, OH), 2.16 (m, 2 H, OH), 3.71 (d, 1 H, J = 12.0 Hz, CH-OH), 3.63 (d, 1 H, J = 11.3 Hz, CH-OH), 3.60 (d, 1 H, J = 11.3 Hz, CH-OH), 3.33-3.47 (m, 2 H, 2 H, CH-OH), 2.66 (dd, 1 H, J = 11.6 Hz, 2 H, CH-OH). (DMSO- d_6 , 100 MHz) δ 165.29, 124.66, 140.84, 97.24, 97.17, 67.45, 67.35, 36.11. Calcd for $C_{14}H_{14}O_5$: C 61.70, H 5.02, N 16.32. Found: C 61.39, H 4.92, N 15.66.

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Compound 2b: white solid, mp 201-202 °C; MS m/z 320 (M⁺); UV (MeOH) λ_{max} 270 nm (ε 2.500);
 (d₁) 1 H NMR (DMSO-d₆, 400 MHz): δ 7.93 (d, 1 H, ³J = 3.2 Hz, H-6'), 7.18 (d, 1 H, H-6'), 7.10
 (d, 1 H, H-6'), 6.31 (d, 1 H, ³J = 4.8 Hz, 1-H), 5.77 (d, 1 H, ³J = 3.2 Hz, H-5'), 5.33 (d, 1 H, ³J =
 6.0 Hz, OH), 5.11 (dd, 1 H, ³J = 5.2 Hz, OH), 4.33 (d, 1 H, ³J = 11.2 Hz, 2-H), 4.22 (dd, 1 H, ³J =
 4.8, 10.8 Hz, 3-H), 3.80 (dd, 1 H, ³J = 4.8, 11.0 Hz, CH₂OH), 3.63-3.67 (m, 2 H, CH₂OH),
 CH₂OH), 3.39 (dd, 1 H, ³J = 6.8, 15.0 Hz, CH₂OH); IR NMR (DMSO-d₆, 100 MHz): δ 163.39,
 152.51, 140.04, 100.31, 94.33, 74.70, 63.07, 62.65, 61.75. Calcd for C₁₁H₁₃N₃O₂: C, 61.50, H,
 5.03, N, 19.33. Found: C, 61.90, H, 5.37, N, 19.04.

12.37 Found: C 38.6%, H 4.92%, N 13.66%.
 C₁₀H₅-H₂-CH₂OH; 3.30-3.40 (m, 1 H, T-H₂). Calcd for C₁₀H₁₃N₃O₂: C, 39.57%; H, 4.73%; N, 13.70%.
 H-1 = 7.5 Hz (OH), 2.31 (t, 1 H, 1 = 5.2 Hz, OH), 3.81 (q, 2 H, 1 = 5.1 Hz, CH₂OH), 3.23-3.87 (m, 1 H, NH₂), 6.44 (pseudo t, 1 H, 1 = 5.2, 4.3 Hz, 1-H), 5.23 (q, 1 H, 1 = 5.5 Hz, H-3), 2.49 (t, 1 H, NH₂).
 13C-NMR (DMSO-d₆, 300 MHz): 8.16 (d, 1 H, 1 = 7.6 Hz, H-6), 7.19 (t, 2 H, NH₂), 7.11 (m, 1 H, NH₂).
 Compound 4b: white solid, mp 200-204 °C; MS m/z 275 (M⁺); UV (MeOH) λ_{max} 270 nm (ε 4900). 1H-NMR (DMSO-d₆, 300 MHz): 8.16 (d, 1 H, 1 = 7.6 Hz, H-6), 7.19 (t, 2 H, NH₂), 7.11 (m, 1 H, NH₂).
 13C-NMR (DMSO-d₆, 300 MHz): 8.16 (d, 1 H, 1 = 7.6 Hz, H-6), 7.19 (t, 2 H, NH₂), 7.11 (m, 1 H, NH₂).
 12.37 Found: C 38.6%, H 4.92%, N 13.66%.

(K: 1971-1972; 1973-1974; 1975-1976; 1977-1978; 1979-1980; 1981-1982; 1983-1984; 1985-1986; 1987-1988; 1989-1990; 1991-1992; 1993-1994; 1995-1996; 1997-1998; 1999-2000; 2001-2002; 2003-2004; 2005-2006; 2007-2008; 2009-2010; 2011-2012; 2013-2014; 2015-2016; 2017-2018; 2019-2020; 2021-2022; 2023-2024; 2025-2026; 2027-2028; 2029-2030; 2031-2032; 2033-2034; 2035-2036; 2037-2038; 2039-2040; 2041-2042; 2043-2044; 2045-2046; 2047-2048; 2049-2050; 2051-2052; 2053-2054; 2055-2056; 2057-2058; 2059-2060; 2061-2062; 2063-2064; 2065-2066; 2067-2068; 2069-2070; 2071-2072; 2073-2074; 2075-2076; 2077-2078; 2079-2080; 2081-2082; 2083-2084; 2085-2086; 2087-2088; 2089-2090; 2091-2092; 2093-2094; 2095-2096; 2097-2098; 2099-2100; 2101-2102; 2103-2104; 2105-2106; 2107-2108; 2109-2110; 2111-2112; 2113-2114; 2115-2116; 2117-2118; 2119-2120; 2121-2122; 2123-2124; 2125-2126; 2127-2128; 2129-2130; 2131-2132; 2133-2134; 2135-2136; 2137-2138; 2139-2140; 2141-2142; 2143-2144; 2145-2146; 2147-2148; 2149-2150; 2151-2152; 2153-2154; 2155-2156; 2157-2158; 2159-2160; 2161-2162; 2163-2164; 2165-2166; 2167-2168; 2169-2170; 2171-2172; 2173-2174; 2175-2176; 2177-2178; 2179-2180; 2181-2182; 2183-2184; 2185-2186; 2187-2188; 2189-2190; 2191-2192; 2193-2194; 2195-2196; 2197-2198; 2199-2200; 2201-2202; 2203-2204; 2205-2206; 2207-2208; 2209-2210; 2211-2212; 2213-2214; 2215-2216; 2217-2218; 2219-2220; 2221-2222; 2223-2224; 2225-2226; 2227-2228; 2229-2230; 2231-2232; 2233-2234; 2235-2236; 2237-2238; 2239-2240; 2241-2242; 2243-2244; 2245-2246; 2247-2248; 2249-2250; 2251-2252; 2253-2254; 2255-2256; 2257-2258; 2259-2260; 2261-2262; 2263-2264; 2265-2266; 2267-2268; 2269-2270; 2271-2272; 2273-2274; 2275-2276; 2277-2278; 2279-2280; 2281-2282; 2283-2284; 2285-2286; 2287-2288; 2289-2290; 2291-2292; 2293-2294; 2295-2296; 2297-2298; 2299-2300; 2301-2302; 2303-2304; 2305-2306; 2307-2308; 2309-2310; 2311-2312; 2313-2314; 2315-2316; 2317-2318; 2319-2320; 2321-2322; 2323-2324; 2325-2326; 2327-2328; 2329-2330; 2331-2332; 2333-2334; 2335-2336; 2337-2338; 2339-2340; 2341-2342; 2343-2344; 2345-2346; 2347-2348; 2349-2350; 2351-2352; 2353-2354; 2355-2356; 2357-2358; 2359-2360; 2361-2362; 2363-2364; 2365-2366; 2367-2368; 2369-2370; 2371-2372; 2373-2374; 2375-2376; 2377-2378; 2379-2380; 2381-2382; 2383-2384; 2385-2386; 2387-2388; 2389-2390; 2391-2392; 2393-2394; 2395-2396; 2397-2398; 2399-2400; 2401-2402; 2403-2404; 2405-2406; 2407-2408; 2409-2410; 2411-2412; 2413-2414; 2415-2416; 2417-2418; 2419-2420; 2421-2422; 2423-2424; 2425-2426; 2427-2428; 2429-2430; 2431-2432; 2433-2434; 2435-2436; 2437-2438; 2439-2440; 2441-2442; 2443-2444; 2445-2446; 2447-2448; 2449-2450; 2451-2452; 2453-2454; 2455-2456; 2457-2458; 2459-2460; 2461-2462; 2463-2464; 2465-2466; 2467-2468; 2469-2470; 2471-2472; 2473-2474; 2475-2476; 2477-2478; 2479-2480; 2481-2482; 2483-2484; 2485-2486; 2487-2488; 2489-2490; 2491-2492; 2493-2494; 2495-2496; 2497-2498; 2499-2500; 2501-2502; 2503-2504; 2505-2506; 2507-2508; 2509-2510; 2511-2512; 2513-2514; 2515-2516; 2517-2518; 2519-2520; 2521-2522; 2523-2524; 2525-2526; 2527-2528; 2529-2530; 2531-2532; 2533-2534; 2535-2536; 2537-2538; 2539-2540; 2541-2542; 2543-2544; 2545-2546; 2547-2548; 2549-2550; 2551-2552; 2553-2554; 2555-2556; 2557-2558; 2559-2560; 2561-2562; 2563-2564; 2565-2566; 2567-2568; 2569-2570; 2571-2572; 2573-2574; 2575-2576; 2577-2578; 2579-2580; 2581-2582; 2583-2584; 2585-2586; 2587-2588; 2589-2590; 2591-2592; 2593-2594; 2595-2596; 2597-2598; 2599-2600; 2601-2602; 2603-2604; 2605-2606; 2607-2608; 2609-2610; 2611-2612; 2613-2614; 2615-2616; 2617-2618; 2619-2620; 2621-2622; 2623-2624; 2625-2626; 2627-2628; 2629-2630; 2631-2632; 2633-2634; 2635-2636; 2637-2638; 2639-2640; 2641-2642; 2643-2644; 2645-2646; 2647-2648; 2649-2650; 2651-2652; 2653-2654; 2655-2656; 2657-2658; 2659-2660; 2661-2662; 2663-2664; 2665-2666; 2667-2668; 2669-2670; 2671-2672; 2673-2674; 2675-2676; 2677-2678; 2679-2680; 2681-2682; 2683-2684; 2685-2686; 2687-2688; 2689-2690; 2691-2692; 2693-2694; 2695-2696; 2697-2698; 2699-2700; 2701-2702; 2703-2704; 2705-2706; 2707-2708; 2709-2710; 2711-2712; 2713-2714;

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Catalytic asymmetric synthesis of cyclopropane-carboxylic acids: an application of chiral copper carbenoid reaction

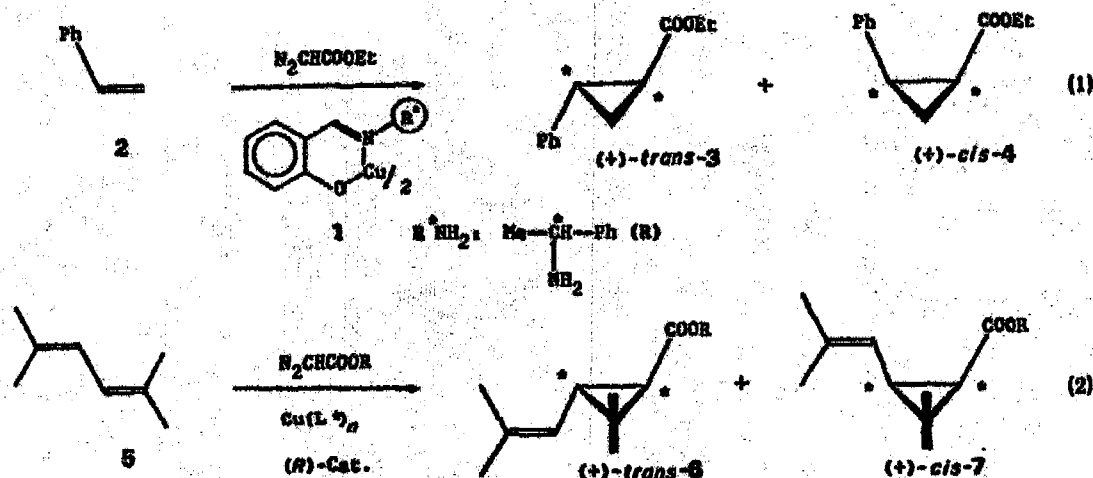
Tadatoshii Aratani

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Abstract - Reaction of alkyl diazoacetate with an olefin catalyzed by a chiral copper complex gives an optically active alkyl cyclopropanecarboxylate. This chiral copper carbenoid reaction was successfully applied to the synthesis of industrially valuable cyclopropanecarboxylic acids: (+)-*trans*-chrysanthemic acid, (+)-*cis*-permethrinic acid and (+)-2,2-dimethylcyclopropanecarboxylic acid. A series of effective catalysts, chiral Schiff base-copper complexes, was prepared starting with an optically active α -amino acid to achieve more than 90% e.e. of the products. The chirality of the products was correlated with that of the catalyst on the basis of metallacyclobutane intermediates.

CHIRAL COPPER CARBENOID REACTION (ref. 1) AND ITS APPLICATION TO CHRYSANTHEMIC ACID SYNTHESIS

In 1966, the first example of asymmetric catalysis (ref. 2) by means of a soluble transition metal complex was reported by Prof. Nozaki and his coworkers. They decomposed ethyl diazoacetate in styrene in the presence of chiral copper complex (1) as a catalyst to give the products, *trans*- and *cis*-2-phenyl-cyclopropanecarboxylate (3 and 4), both in an optically active form (Eq 1). This finding demonstrated that the carbene derived from ethyl diazoacetate is not free but is combined with the chiral copper complex to form a carbene-copper complex (ref. 3), which is responsible for the asymmetric induction. Furthermore, the reaction provided a new method for the preparation of optically active cyclopropane derivatives of practical value, although the enantiomeric excess (e.e.) attained at that time was less than 10%.



Chrysanthemic acid, 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylic acid (6, 7; R = H) is an acid component of pyrethroid, an insecticide of high activity and low mammalian toxicity (ref. 4). There is a close correlation between the chirality of a molecule and its biological activities. Among the four optical isomers of chrysanthemic acid, the most effective isomer is shown to be (+)-*trans* isomer, which is followed by (+)-*cis* isomer. (-)-*Trans* and (-)-*cis* isomers are almost ineffective (ref. 5). The natural chrysanthemic acid also has the (+)-*trans* configuration.

As an application of the chiral copper carbenoid reaction, alkyl diazoacetate was reacted with 2,5-dimethyl-2,4-hexadiene (5) in the presence of chiral copper catalyst to give an optically active alkyl chrysanthemate (Eq 2). The first problem to be solved was a choice of a suitable catalyst to achieve high e.e. of the product.

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Catalytic asymmetric synthesis of cyclopropane-carboxylic acids: an application of chiral copper-carbenoid reaction

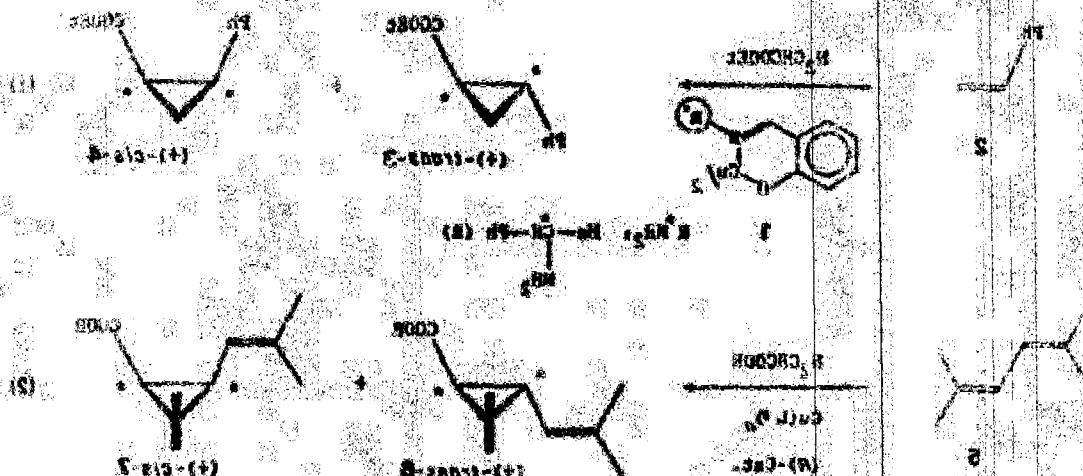
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Abstract - Reaction of alkyl diazoacetate with an olefin catalyzed by a chiral copper-carbenoid complex gives an optically active alkyl cyclopropanecarboxylate. This chiral copper-carbenoid reaction was successfully applied to the synthesis of optically active cyclopropane-carboxylic acids. (+)-trans-cyclopropanecarboxylic acid, (+)-cis-cyclopropanecarboxylic acid, (+)-2,3-dimethylcyclopropanecarboxylic acid, and (+)-2,3-dimethyl-2-cyclopropanecarboxylic acid were prepared. A series of effective chiral Schiff base-copper complexes was prepared. A reaction with an optically active amino acid to achieve more than 90% e.e. of the product. The character of the products was correlated with that of the copper-carbenoid complex. The character of the products was correlated with that of the copper-carbenoid complex.

CHIRAL COPPER CARBENOID REACTION (I) AND ITS APPLICATION TO CHIRAL CYCLOPROPANE CARBOXYLIC ACID SYNTHESIS

In 1952, the first example of asymmetric catalysis (1) by means of a soluble transition metal complex was reported by E. J. Corey and his coworkers. They described ethyl diazoacetate in the presence of chiral copper complex (I) as a catalyst to give the product, trans- and cis-2,3-dimethylcyclopropanecarboxylate (2 and 3), both in an optically active form (2d, 3). This reaction demonstrated that the carbene derived from ethyl diazoacetate is not free but is coordinated with the chiral copper complex to form a copper-carbenoid complex (I), which is responsible for the asymmetric induction. Furthermore, the reaction provided a new method for the preparation of optically active cyclopropane derivatives of practical value, although the enantiomeric excess (e.e.) obtained at that time was less than 10%.



Cyclopropane carboxylic acid, 2,3-dimethyl-2-(3-methylpropenyl)-cyclopropanecarboxylic acid (4a, 4b) is an acid component of pyrethrin, an insecticide of high activity and low mammalian toxicity (5). There is a close correlation between the chirality of a molecule and its biological activities. Among the four optical isomers of cyclopropane carboxylic acid, the most effective isomer is shown to be (+)-trans isomer, (+)-trans and (+)-cis isomers are almost ineffective (6). The natural cyclopropane carboxylic acid also has the (+)-trans configuration.

An application of the chiral copper carbenoid reaction, alkyl diazoacetate was reacted with 2,3-dimethyl-2-butene (5) in the presence of chiral copper catalyst to give an optically active alkyl cyclopropanecarboxylate (6). The first problem to be solved was a choice of a suitable catalyst to achieve high e.e. of the product.

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NOVEL COPPER CATALYSTS AND IMPROVEMENT OF STEREOSELECTIVITY (ref. 8)

An extensive search was carried out to devise a series of effective catalysts. The catalyst was prepared according to the reactions of Eq 3. An ester of optically active α -amino acid (8) was reacted with an excess of Grignard reagent to give an amino alcohol (9) with complete retention of configuration (ref. 7). Schiff base of 9 with salicylaldehyde was treated with cupric acetate followed by sodium hydroxide to give a copper chelate (10) as an air-stable green mass. The complex 10 was shown to have a dimeric structure, in which the Schiff base was incorporated as a tridentate ligand (ref. 8). An example of X-ray crystallographical analysis is shown in Fig. 1 (ref. 9).

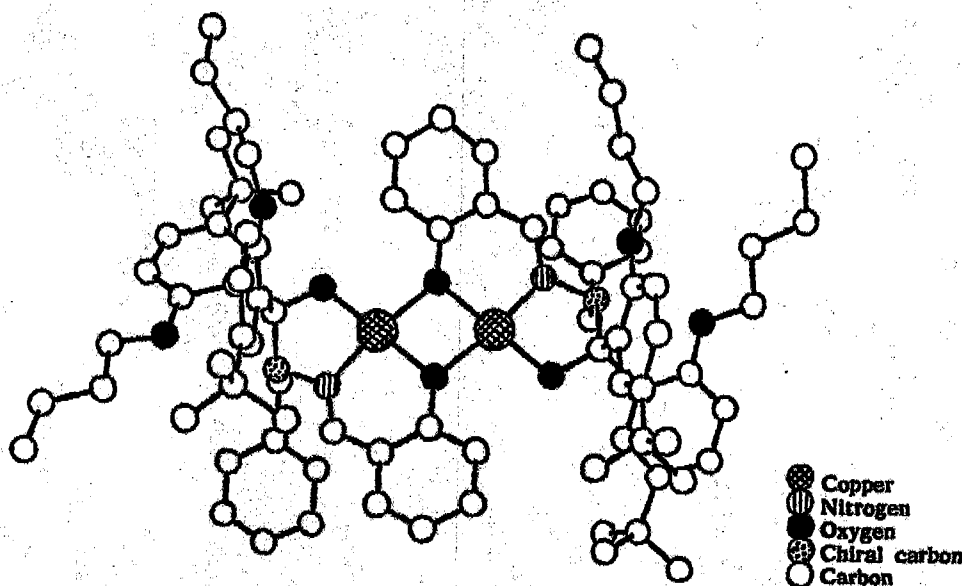
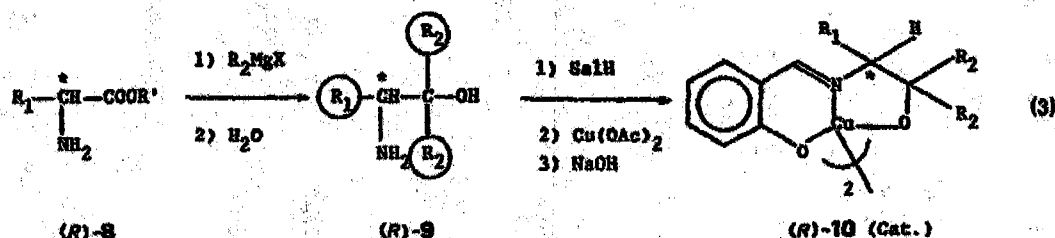


Fig. 1. X-ray crystallographical analysis of a copper complex, R-7644
(10, R configuration, R_1 = benzyl, R_2 = 2-butoxy-5-*t*-butyl-phenyl).

The complex 10 has two substituents R_1 and R_2 . R_1 comes from the α -amino acid and R_2 comes from the Grignard reagent (Eq 3). By combining different α -amino acids and Grignard reagents, a variety of copper chelates were prepared and the products were examined as catalysts in the chrysanthemic syntheses (Eq 2). Results shown in Fig. 2 were obtained when ethyl diazoacetate was employed as a diazo ester. The e.e. of chrysanthemic acid increased with the bulkiness of the substituent R_2 . The highest e.e. achieved was ca. 70% when R_1 was methyl, and R_2 was 5-*t*-butyl-2-octyloxy-phenyl. Hereafter, this catalyst having R configuration is named R-1648.

Optical isomers of chrysanthemic acid were analyzed by GC after conversion to the diastereomeric (+)-2-octyl esters (ref. 10). Table 1 shows the composition of chrysanthemic acid produced by the use of R-1648. The catalyst of R configuration favors the formation of (+)-*trans* and (+)-*cis* isomer over that of (-)-*trans* and (-)-*cis* isomer, respectively. Ethyl diazoacetate gave nearly equal amount of *cis* and *trans* isomers. A remarkable improvement of stereoselectivity was brought about by changing ethyl diazoacetate to bulkier alkyl diazoacetate. The selected alkyl was the 1-menthyl group which gave a *cis/trans* product ratio of 7/93, and a 94% e.e. for the *trans* isomer. Reaction of other alkyl diazoacetates in the presence of R-1648 gave the results shown in Fig. 3. The bulkier the alkyl group of diazoacetate is, the higher the *trans* content of the product and the e.e. of *trans* isomer are.

NOVEL COPPER CATALYSTS AND IMPROVEMENT OF STEREOSPECIFICITY (rel. 6)

An extensive search was carried out to devise a series of effective catalysts. The catalyst was prepared according to the reaction of **10**. An ester of optically active α -amino acid (**11**) was reacted with an excess of Gilman reagent to give an amino alcohol (**12**) with optical rotation of configuration (rel. 2). **12** was then treated with acetic anhydride followed by sodium hydride to give a copper chelate (**13**) as an air-stable green mass. The complex **13** was shown to have a dimeric structure, in which the Schiff base was incorporated as a tridentate ligand (rel. 4). An example of X-ray crystallographical analysis is shown in Fig. 1 (rel. 5).

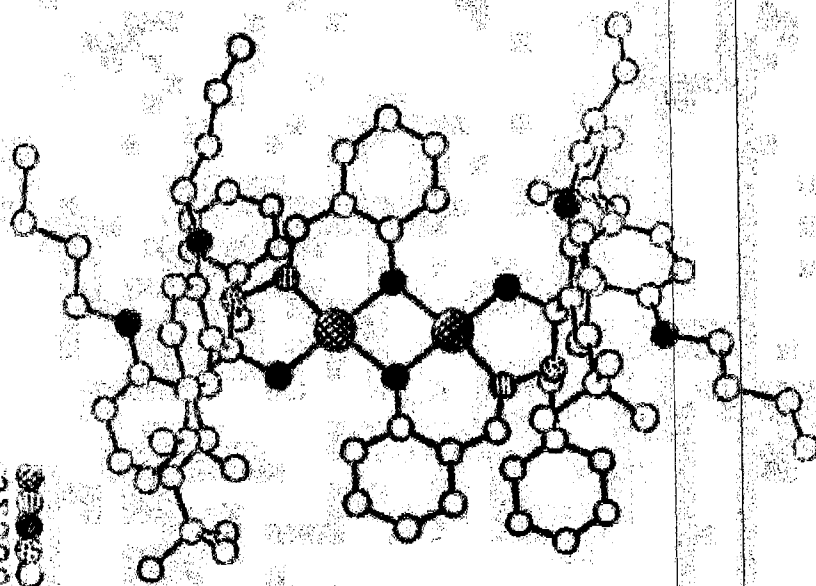
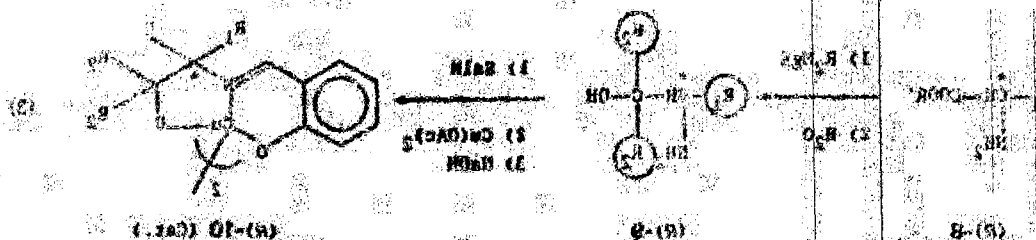


Fig. 1. X-ray crystallographical analysis of a copper complex **13-1044**. (10) R configuration, R' = benzyl, R'' = 2-butoxy-2-butyl-phenyl.

The complex **13** has two substituents R and R'. R comes from the α -amino acid and R' comes from the Gilman reagent (**11**). By combining different α -amino acids and Gilman reagents, a variety of copper chelates were prepared and the products were examined as catalysts in the chiral asymmetric synthesis (**12**). Results shown in Fig. 2 were obtained when ethyl diazoacetate was employed as a chiral ester. The e.e. of chrysanthemic acid increased with the bulkiness of the substituent R'. The highest e.e. achieved was ca. 10% when R was methyl and R' was 2-butoxy-2-butyl-phenyl. Hereafter, this catalyst having R configuration is named **R-1043**.

Optical isomers of chrysanthemic acid were analyzed by GC after conversion to the diastereomeric (+)-2-octyl esters (rel. 10). Table 1 shows the composition of chrysanthemic acid produced by the use of **R-1043**. The catalyst of R configuration favors the formation of (+)-trans and (-)-cis isomers over that of (-)-trans and (-)-cis isomers, respectively. Ethyl diazoacetate gave nearly equal amount of cis and trans isomers. A remarkable improvement of stereospecificity was brought about by changing ethyl diazoacetate to butyl allyl diazoacetate. The selected alkyl was the 1-methyl group which gave a cis/trans product ratio of 7:93, and a 94% e.e. for the trans isomer. Reaction of other alkyl diazoacetates in the presence of **R-1043** gave the results shown in Fig. 3. The bulkier the alkyl group of diazoacetate, the higher the trans content of the product and the e.e. of trans isomer are.

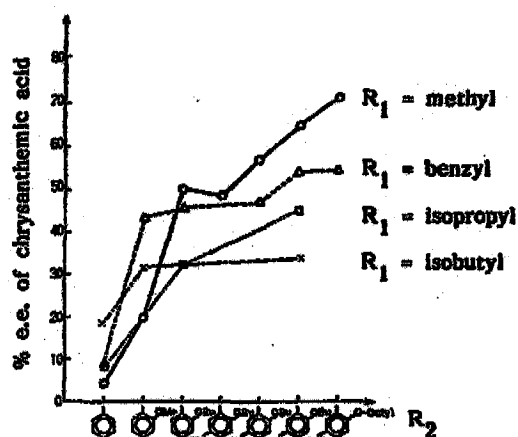
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Fig. 2. Search for the catalyst.

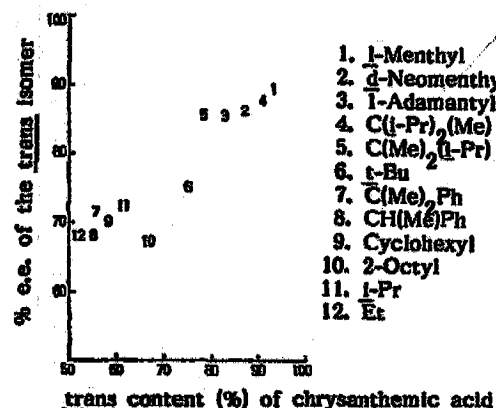


Fig. 3. Search for alkyl diazoacetate.

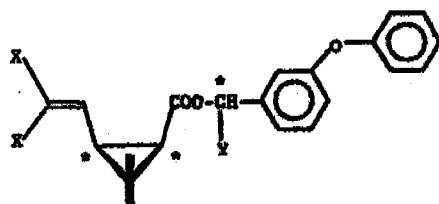
TABLE 1. Asymmetric synthesis of alkyl chrysanthemate

Alkyl	% Composition of chrysanthemic acid				cis/trans	% e.e.	
	(-)-cis	(+)-cis	(-)-trans	(+)-trans		cis	trans
Ethyl	9.2	39.4	8.1	43.3	49/51	62	68
l-Menthyl	2.0	5.4	2.7	89.9	7/93	46	94
d-Menthyl	5.8	22.6	3.4	68.2	28/72	59	90
dl-Menthyl	2.3	16.3	4.1	77.3	19/81	75	90

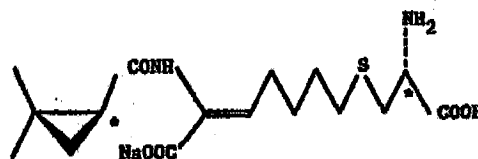
ASYMMETRIC SYNTHESIS OF CYCLOPROPANE CARBOXYLIC ACIDS

(ref. 11)

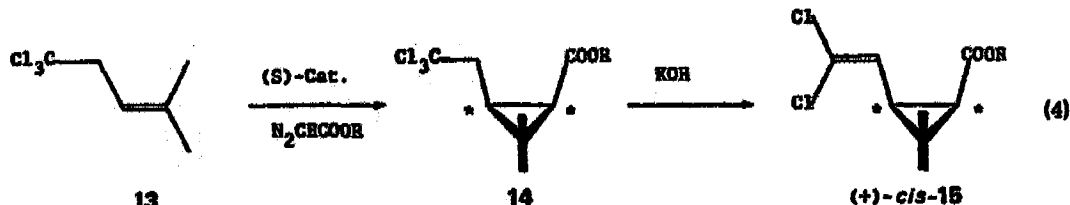
Permethrinic acid, 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid (15), is another kind of acid component producing pyrethroids (11) of higher potency and photostability (ref. 12). The most effective isomer of permethrinic acid is shown to be (+)-1R-cis isomer. A stereoselective route to this isomer was explored using chiral catalysts at hand.



11, Permethrin (X = Cl, Y = H)



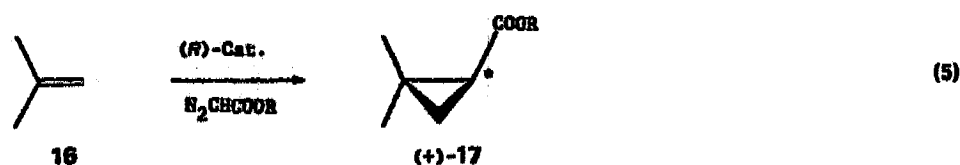
12, Cilastatin (MK-0791)



13

14

(+)-cis-15



16

(+)-17

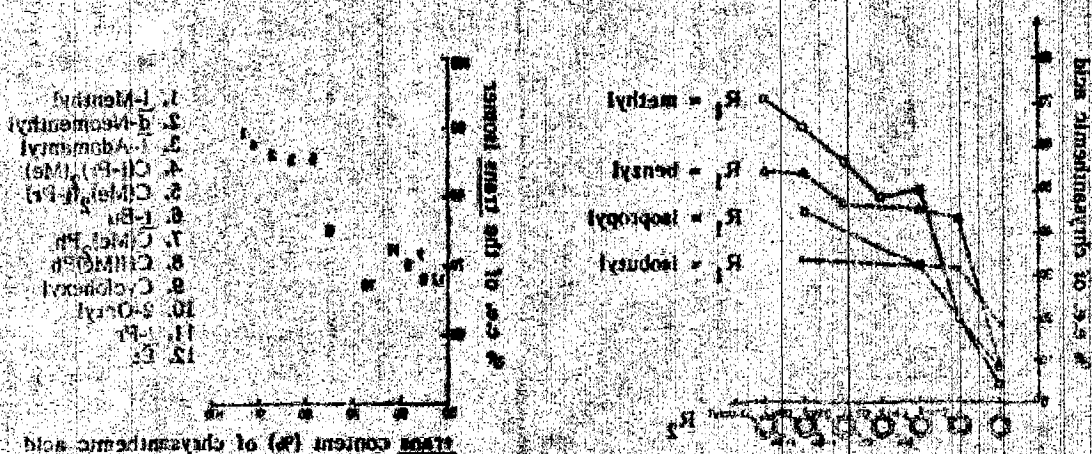


Fig. 2. Search for the catalyst.

Fig. 2. Search for the catalyst.

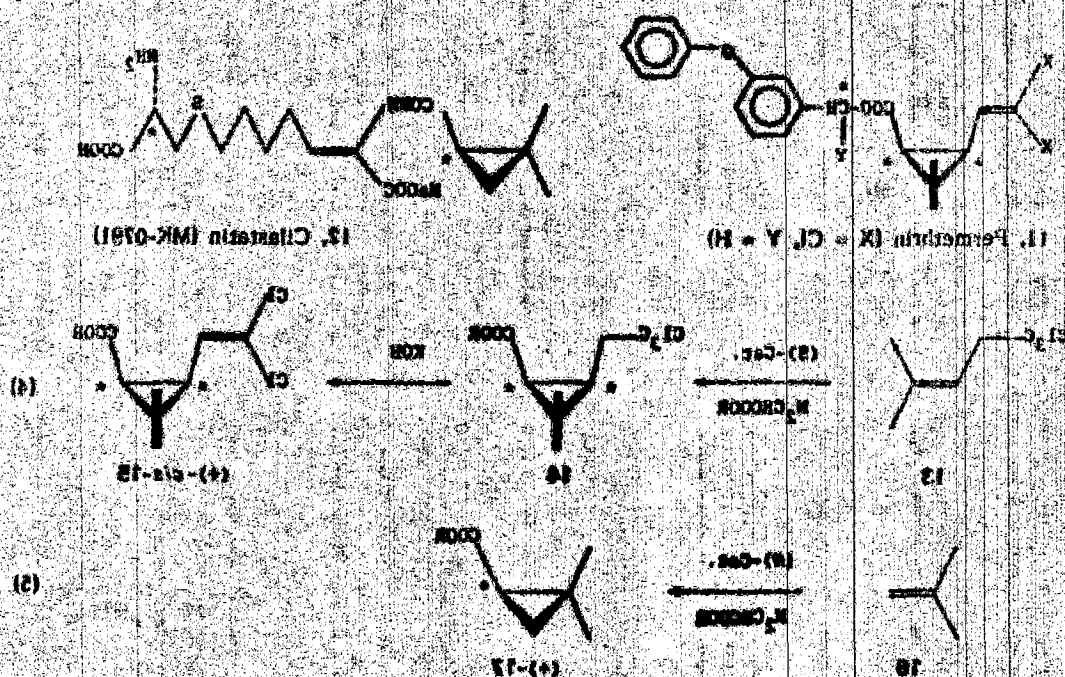
TABLE I. Asymmetric synthesis of alkyl cyclopropanecarboxylic acids

Alkyl	Composition of cyclopropanecarboxylic acid			
	(-)-cis (+)-trans	(-)-trans (+)-cis	cis:trans	cis:trans
Et	9.3	29.4	42.3	48.51
i-Pr	5.9	2.4	88.0	7.93
n-Pr	2.8	22.6	88.3	20.73
i-Bu	2.3	16.3	77.3	19.81

ASYMMETRIC SYNTHESIS OF CYCLOPROPANE CARBOXYLIC ACIDS

(ref. 12)

Permethrin acid, 3-(2,2-dichlorovinyl)-2-methyl-cyclopropanecarboxylic acid (12), is another kind of acid component producing pyrethroids (11) of higher potency and bioactivity (ref. 12). The most effective isomer of permethrin acid is shown to be (-)-1R-cis isomer. A stereoselective route to this isomer was explored using chiral catalysts as here.



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Ethyl diazoacetate was reacted with 2-methyl-5,5,5-trichloro-2-pentene (13; ref. 13) in the presence of the catalyst of S configuration, S-1848, to give ethyl 2,2-dimethyl-3-(2,2,2-trichloroethyl)-cyclopropanecarboxylate (14), whose dehydrochlorination and hydrolysis with potassium hydroxide afforded (+)-permethrinic acid (Eq 4). Analysis of the product revealed that cis/trans ratio was 85/15 and e.e. of the cis isomer was 91%. This stereoselectivity makes a sharp contrast to that of chrysanthemate synthesis (Eq 2). First, thermodynamically less stable isomer, cis, is preferred in Eq 4 whereas thermodynamically more stable isomer, trans, is preferred in Eq 2. Second, preference of the same 1R configuration in the product requires S-catalyst in Eq 4 and the antipodal R-catalyst in the chrysanthemate synthesis. Since similar selectivity of Eq 4 was observed in the reaction of 2-methyl-2-butene (21; Table 2), these discrepancies cannot be attributed to the participation of chlorine atom of 13. An explanation will be given in the final section.

The third compound of practical importance comes from pharmaceutical field. Imipenem (MK-0787), N-formimidoyl-thienamycin, is one of the most promising β -lactam antibiotics recently developed (ref. 14). In spite of its high and wide antibacterial activity and strong resistance to β -lactamase degradation, Imipenem was susceptible to renal metabolism in animal species and in man. This metabolism can be suppressed by coadministration with Cilastatin (12), an enzyme inhibitor for dehydropeptidase I (ref. 15). (+)1S-2,2-Dimethyl-cyclopropanecarboxylic acid (DCCA, 17; R = H) is a key intermediate in the production of Cilastatin.

Ethyl diazoacetate was reacted with isobutylene in the presence of the catalyst, R-7644 (Fig. 1), to give ethyl ester of (+)-DCCA in 92% e.e. (Eq 5). This reaction was proved to work well in a factory scale. Other examples of asymmetric catalysis of practical usage include L-DOPA synthesis by Monsanto (ref. 16) and L-menthol production by Takasago (ref. 17).

The chiral catalyst 10 is useful in the preparation of optically active cyclopropanecarboxylic acids of a wide range (ref. 18). For example, L-menthyl diazoacetate was reacted with olefins in the presence of R- and S-1648 to give the corresponding cyclopropanecarboxylates in high e.e. The e.e. of the products was directly analyzed by GC and the absolute configuration was determined according to the literature. Results are summarized in Table 2.

TABLE 2. Asymmetric synthesis of substituted cyclopropanecarboxylic acids

Olefin	Catalyst Confign	Product <u>cis/trans</u>	~% e.e.~		~Confign~	
			<u>cis</u>	<u>trans</u>	<u>cis</u>	<u>trans</u>
Styrene (2)	R	14/86	(+)54	(+)69	1S,2R	1S,2S
	S	18/82	(-)78	(-)81	1R,2S	1R,2R
1-Octene (18)	R	17/83	(+)46	(+)76	1S,2R	1S,2S
	S	22/78	(-)64	(-)84	1R,2S	1R,2R
<u>trans</u> -4-Octene (19)	R	-	-	(+)82	-	2S,3S
	S	-	-	(-)84	-	2R,3R
<u>trans</u> -Anethole	R	9/91	(+)44	(+)81	-	-
	S	12/88	(-)60	(-)89	-	-
1,1-Diphenylethylene (20)	R	-	-	(+)75	-	1S
	S	-	-	(-)64	-	1R
α -Methylstyrene	R	40/60	86	68	-	-
	S	36/64	68	58	-	-
2-Methyl-2-butene (21)	R	79/21	(+)ND	(+)ND	1S,3R	1S,3S
	S	77/23	(-)ND	(-)ND	1R,3S	1R,3R

STEREOCHEMISTRY OF CHIRAL COPPER CARBENOID REACTION

In this section, an attempt will be made to correlate the chirality of the products with that of the catalyst to deduce an empirical rule which predicts the absolute configuration of a new product (ref. 19). A mechanism is proposed to explain the mode of chirality transfer. Reactions employing the catalyst 10 of S configuration are considered throughout the following discussions. Enantio-preferences observed in Eqs 2, 4 and 5 and Table 2 are interpreted as follows. If prochiral olefins are placed on the plane as shown in Fig. 4, the carbene derived from alkyl diazoacetate prefers to cyclopropanate the olefins from the front side of the plane with the alkoxycarbonyl substituent downward. When geometrical isomers of the product exist, the arrangement of the top gives the trans product and that of the bottom gives the cis product. Since the arrangements of top and bottom are upside down each other, both cis and trans products have the same absolute configuration at the carbene carbon atom. Thus, the olefin 5 gives 1S-trans- and 1S-cis-chrysanthemate (Eq 2; S Cat.) and the olefin 13 gives 1R-trans- and 1R-cis-15 (permethrinic acid precursor; Eq 4). What is the common feature of the arrangements of Fig. 4? This problem can be solved in terms of electronic factor of the olefin rather than steric one. Of the two olefinic carbon atoms, the carbon atom, α , capable to produce more stabilized carbonium ion is placed on the right side and the other, β , is placed on the left side (ref. 20). The order of stability of carbo-cation has been established as follows: benzylic $\sim$ allylic $\sim$ tertiary $\sim$ secondary $\sim$ primary. The conclusion is shown in Eq 6.

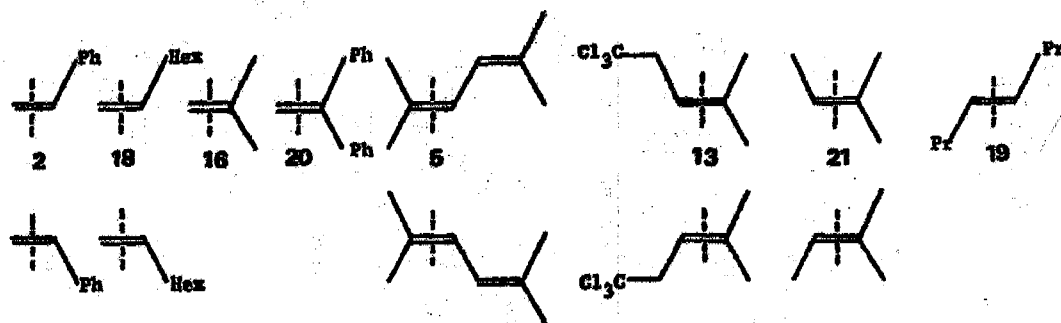
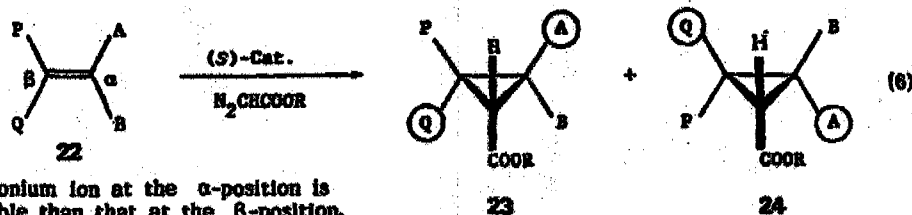
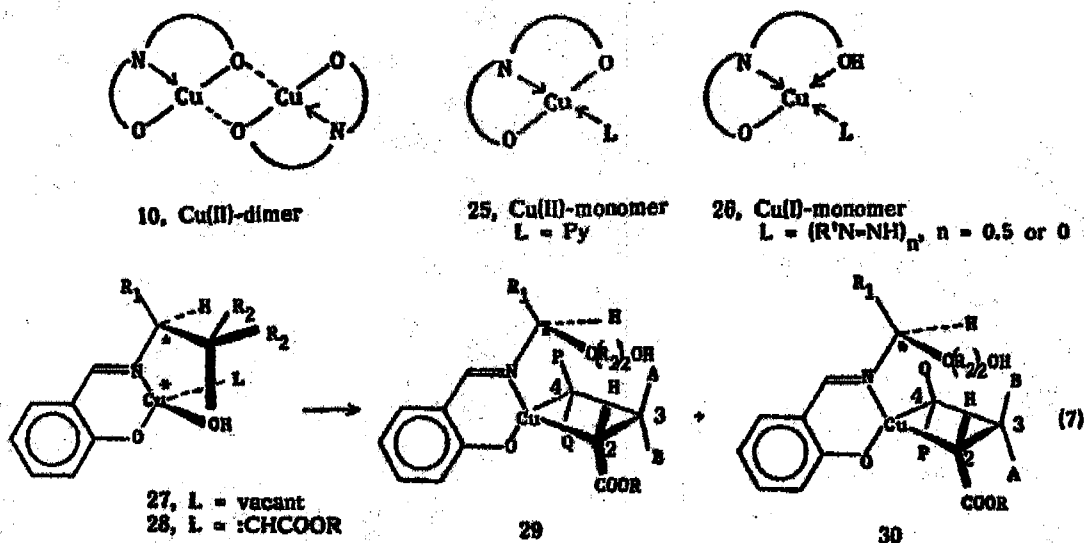
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Fig. 4. The preferred arrangement of olefins for cyclopropanation



The carbonium ion at the α -position is more stable than that at the β -position.

There are strong evidences indicating that the original structure of copper complex 10 is not retained during the catalysis. First, the complex 10 should be activated before use. Thus, addition of alkyl diazoacetate to a solution of 10 at room temperature did not induce any changes. When the mixture was warmed up to 70-80 °C, a vigorous evolution of nitrogen gas took place and the color of the solution turned from green to brown. Subsequent addition of diazoacetate to the solution gave a smooth evolution of nitrogen gas. Second, a mononuclear complex (25), which was derived from the binuclear complex 10 upon the addition of a monodentate neutral ligand such as pyridine, gave the same result as 10 in the asymmetric synthesis. Finally, we found that reduction of cupric complex 10 with a substituted hydrazine gave a pale yellow cuprous complex (26; ref. 21), which induced an instantaneous decomposition of diazoacetate at room temperature. In conclusion, we are safe to assume that the actual catalyst responsible for the asymmetric induction is a mononuclear cuprous complex such as 27, in which copper is supposed to have a tetrahedral configuration and one of four coordination sites is left vacant.



Alkyl diazoacetate will attack the vacant site of 27 from the less hindered side (back side of the plane) to give a carbene-copper complex 28 with the evolution of nitrogen gas. Subsequent attack of an olefin occurs again from the back side of the plane (re-face) to give metallacyclobutanes (29 and 30; ref. 22), in which alkoxy carbonyl group comes to the bottom side of the metallacycle to avoid repulsion with the bulky $C(R_2)_2OH$ group. Nucleophilic nature of the attack of olefin controls regioselectivity in the metallacycle formation. Copper atom forms a bond with β -carbon atom of the olefin 22 rather than α -carbon atom. Collapse of the metallacycles 29 and 30 into the products 23 and 24, respectively, regenerates the true catalyst 27 to complete a catalysis cycle.

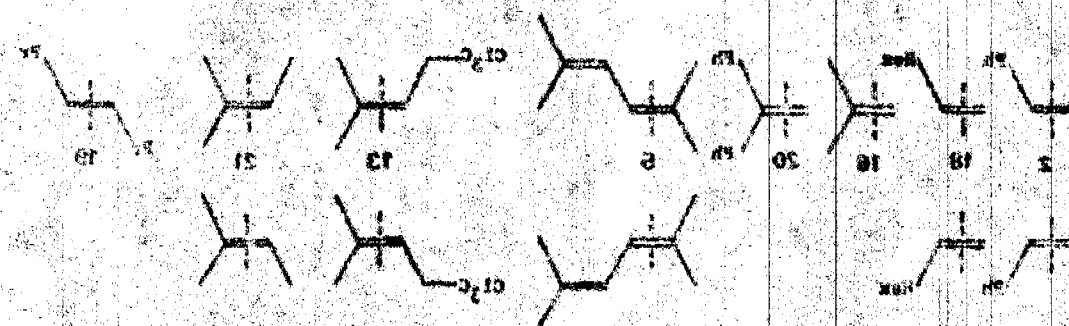
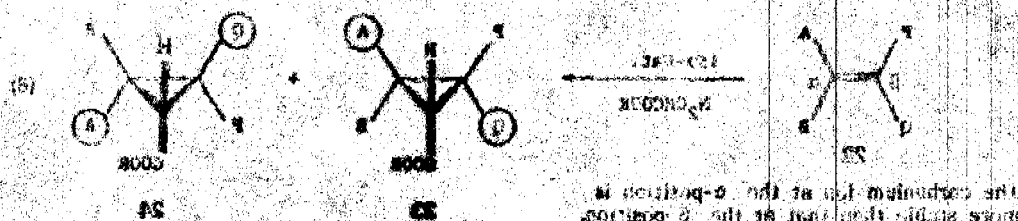
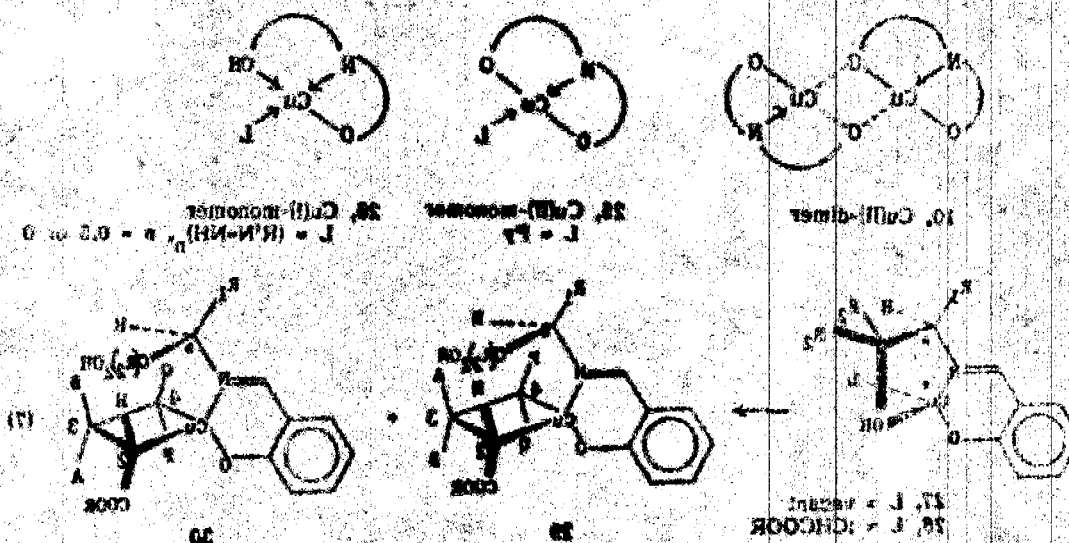


Fig. 4 The preferred arrangement of olefin for cyclopropanation



There are strong evidence indicating that the original structure of copper complex 10 is not retained during the catalytic cycle. First, the complex 10 could be activated before use. Thus, addition of allyl diazoacetate to a solution of 10 at room temperature did not induce any changes. When the mixture was warmed up to 10-20 °C, a vigorous evolution of nitrogen was observed and the color of the solution turned from green to brown. Subsequent addition of diazoacetate to the solution gave a smooth evolution of nitrogen gas. Second, a monodentate neutral ligand such as pyridine, gave the same result as 10 in the asymmetric synthesis. Finally, we found that reduction of copper complex 10 with a substituted hydrazine gave a pale yellow cuprous complex (50, ref. 21), which indicated an irreversible decomposition of diazoacetate at room temperature. In conclusion, we are able to assume that the actual catalyst responsible for the asymmetric induction is a mononuclear cuprous complex such as 27, in which copper is supposed to have a tetrahedral configuration and one of four coordination sites is left vacant.



Allyl diazoacetate will attack the vacant site of 27 from the less hindered side (back side of the plane) to give a cupro-copper complex 28 with the evolution of nitrogen gas. Subsequent attack of allyl diazoacetate from the back side of the plane (face) to give metallacyclobutane. No attack occurs again from the bottom side of the metallacyclobutane to the metallacyclobutane to which allyl diazoacetate group comes to the bottom side of the metallacyclobutane. Inoculative nature of the attack of allyl diazoacetate to the metallacyclobutane formation. Copper atom forms a bond with β -carbon atom of the allyl diazoacetate rather than α -carbon atom. Collapse of the metallacyclobutane 29 and 30 into the products 23 and 24, respectively, regenerates the true catalyst 27 to complete a catalytic cycle.

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Geometry of the four-membered intermediate (29/30) is transferred into that of the three-membered products (23/24). Here is the reason why thermodynamically less stable cis product is favored in our permethrinic acid synthesis (Eq 4). The 2,4-cis-disubstituted metallacyclobutane 30 (A = B = methyl, P = trichloroethyl and Q = hydrogen), which is derived from the olefin 13, should be more stable than the 2,4-trans isomer 29. In Ciba-Geigy's cis-permethrinic acid synthesis (ref. 23), stability of the four-membered intermediate, cis-2-chloro-3,3-dimethyl-4-trichloroethyl-cyclobutanone is ascribed to a puckered conformation of cyclobutanone ring to release repulsion of two substituents at the 2,4-cis positions.

It is hoped that future experiments will prove the validity of stereochemical prediction (Eq 6) and the correctness of mechanistic pathway speculated herein (ref. 24).

ACKNOWLEDGEMENTS

The author would like to express his hearty gratitude to the people who have participated in this work. Special thanks are due to Mr. Yukio Yoneyoshi, Mr. Hiroshi Yoshihara and Dr. Tsuneyuki Nagase for their valuable contribution and encouragement. He is also indebted to the Catalysis Society of Japan and Kagaku-Dojin, Kyoto for permission to reproduce Figures and formulas.

Geometry of the four-membered intermediate (23/20) is transferred into that of the three-membered product (23/21). Here is the reason why thermodynamically less stable cis product is favored in our pericyclic acid synthesis (cf. 4). The 2,4-cis-disubstituted metallocyclobutane 20 (A = B = methyl), P = trichloromethyl and Q = hydrogen), which is derived from the olefin 13, should be more stable than the 2,4-trans isomer 20. In Ciba-Gigley's cis-permethrinic acid synthesis (ref. 23), stability of the four-membered intermediate, cis-2-chloro-2,3-dimethyl-4-trichloromethyl-cyclobutane is ascribed to a preferred conformation of cyclobutane ring to release repulsion of two substituents at the 2,4-cis position.

It is hoped that future experiments will prove the validity of stereochemical prediction (Ed 6) and the correctness of mechanistic pathway speculated herein (ref. 24).

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