

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
office@olartemoure.com

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-107976- -00005-0000
Fecha: 2012-10-25 17:25:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 519 TRASLADOINFORME Folios: 32

ASUNTO	Radicación	09-107976
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	2 - 196 17
	Folios	32

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I ☒ Cap. II	☐

No. Solicitud Internacional PCT/EP2008/053891
Fecha de Presentación Internacional 01/Abril/2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 97 a 210	01/Noviembre/2009
Reivindicaciones:	Folios 211 a 230	01/Noviembre/2009
Prioridad:	EP 07105572.7	03/Abril/2007

2. Análisis de la Prioridad

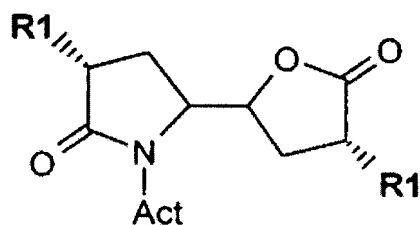
Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Métodos e intermediarios para preparar compuestos de lactama lactona de 8 átomos de carbono activos como inhibidores de renina" modificado en el folio 241

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una ruta sintética alternativa para la preparación de compuestos lactama-lactona C8, para asegurar su fabricación de una manera simple y eficiente.

Para resolver este problema técnico la solicitud en estudio proporciona un proceso para la preparación de compuestos lactama-lactona C8 de la formula I, mediante la utilización de reacciones organocatalíticas de Michael y Henry.



Fórmula I

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C231/12, C07C231/18, C07C237/20, C07C271/16, C07C205/15, C07C205/29, C07C205/45, C07C205/51, C07D207/16, C07D207/26, C07C47/277, C07D403/04, C07F7/18.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa porque la fórmula estructural del intermediario IV es muy general. Se sugiere al señor solicitante definirlo como el compuesto de fórmula (IVa) en la reivindicación 5 y el compuesto de fórmula (IVb) en la reivindicación 6 o incluir estos compuestos en la reivindicación 1.

Las reivindicaciones 2 y 3 son reivindicaciones independientes porque no dependen de la reivindicación 1. La reivindicación 4 depende de la reivindicación 3. Las reivindicaciones 5 a 8 y 48 dependen de la reivindicación 1. Las reivindicaciones 49 y 50 dependen de la reivindicación 2. Asimismo, la reivindicación 18 tiene falsa dependencia a las reivindicaciones 11 a 13 y 15 a 17 ya que la reivindicación 18 es independiente porque la reacción de los productos intermedios (VI) y (VIII), produce el producto final (IX), el cual es diferente a los productos finales de las reivindicaciones 11 a 13 y 15 a 17. Se le sugiere al señor solicitante cambiar la dependencia de las reivindicaciones teniendo en cuenta que la dependencia está dada porque todas las características esenciales de la reivindicación independiente están presentes en la reivindicación dependiente.

En la solicitud existen las siguientes reivindicaciones independientes de proceso:

- Rv. 1 proceso: (XII) + (IV) Reacción de Michael= (V)
- Rv. 2 proceso: (V) + reducción = (VI)
- Rv. 9 proceso: (VI) + GP (bencilo) = (VII)
- Rv. 14 proceso: (VII) + Reacción de Nef = (VIII)
- Rv. 18 proceso: (VI) ó (VII) + (VIII) = (IX)
- Rv. 24 proceso: (IX) + hidrogenación = (X)
- Rv. 33 proceso: (X) + oxidación = (I)
- Rv. 34 proceso: (VIII) + reducción = (XIV)

Rv. 35 proceso: (XV) + Reacción de Henry = (XVI)
Rv. 37 proceso: (XVI) + hidrogenación = (XVII)
Rv. 40 proceso: (XVII) + oxidación = (XVIII)

Se sugiere al señor solicitante agrupar las etapas o subprocesos en el capítulo reivindicatorio contemplando los procesos necesarios para preparar los productos finales o compuestos de interés de fórmulas generales (I) y (XVIII) desde los productos de partida e incluir las etapas necesarias con sus productos intermedios. Por ejemplo un esquema general del proceso desde los productos de partida hasta los productos finales incluyendo las etapas y condiciones de reacción está en un conjunto que reúne las reivindicaciones 1, 2, 3, 9, 14, 35 y 40.

Las reivindicaciones 5 y 6 reclaman el compuesto (IVa) y (IVb) pero se encabeza en términos de procedimiento. Se le recuerda al señor solicitante un procedimiento se caracteriza por su etapas y condiciones y no por la estructura química.

Las siguientes reivindicaciones reclaman productos finales:

- Rv. 45 se reclaman los compuestos (IA), (IC) y (ID)
- Rv. 46 se reclaman los compuestos (IB), (IE) y (IF)
- Rv. 47 se reclaman los compuestos (I)
- Rv. 51 se reclaman los compuestos (XVIII)
- Rv. 52 se reclaman los compuestos (XVIII A), (XVIII C) o (XVIII D)
- Rv. 53 se reclaman los compuestos (XVIII B), (XVIII E) o (XVIII F)

Por lo anterior, se deduce que los productos finales de interés para el señor solicitante son: (IA), (IC), (ID), (IB), (IE), (IF), (XVIII A), (XVIII C), (XVIII D), (XVIII B), (XVIII E) y (XVIII F).

Las reivindicaciones 34 y 35 no son claras porque el compuesto de fórmula (XIV) tiene estructuras diferentes en cada reivindicación. Se sugiere al señor solicitante aclarar cuál es la fórmula estructural correspondiente a (XIV).

Las reivindicaciones 52 y 53 no son claras porque tienen la definición de la abreviación "Act" pero en las estructuras no aparece la abreviación "Act". Se sugiere al señor solicitante hacer las aclaraciones a las que haya lugar.

La reivindicación 50 no es clara porque define el compuesto de la fórmula (V) o (VI) de acuerdo con la reivindicación 50. Se sugiere al señor solicitante corregir la dependencia.

En la definición de los radicales más representativos de la fórmula (I), de acuerdo con lo que se encuentra debidamente sustentado en el capítulo descriptivo, se encuentra que siempre varían entre los siguientes sustituyentes:

Radical	Soporte en la descripción
R ¹	isopropilo
PG	Hidroxi, bencilo

Por lo tanto se sugiere al solicitante presentar una generalización razonable y eliminar aquellas definiciones que exceden el sustento descriptivo.

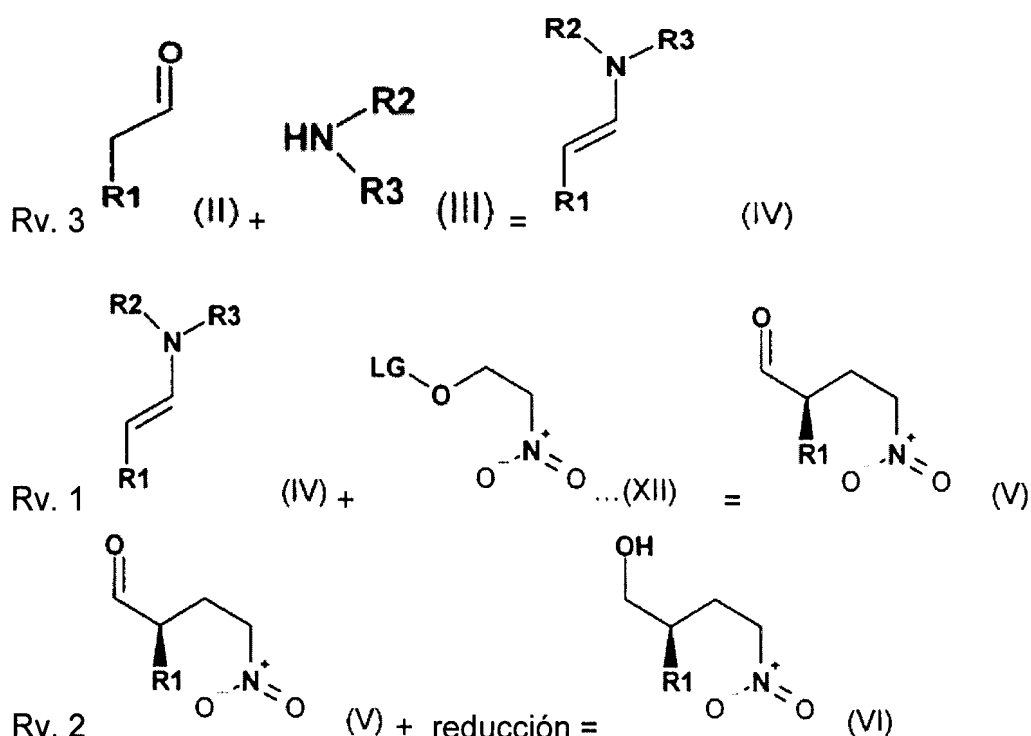
Las reivindicaciones 4 a 7 y 10 son procedimientos definidos por el producto o compuesto. Se sugiere al solicitante que defina el procedimiento de síntesis por sus etapas y no por las características del producto a obtener. Asimismo se
Primer Artículo 45-Expediente 09 107976

sugiere organizar el proceso de preparación compuestos lactama-lactona de manera secuencial, mostrando de manera clara los compuestos de partida, las condiciones de reacción, las etapas de manera sistemática hasta llegar a los compuestos de fórmula I o compuestos finales, para que la reivindicación independiente supere las objeciones de claridad.

Las reivindicaciones 41 a 44 no son claras porque reclaman procesos para la preparación del compuesto (XI) pero no definen los pasos de los procesos sino que relacionan la fabricación de productos intermedios de forma aislada y no definen cual es la etapa inicial y la etapa final de una forma sistemática y ordenada. Se sugiere al señor solicitante definir claramente las etapas, productos intermedios y condiciones de reacción para obtener el compuesto (XI).

5. Unidad de invención (Art 25 D 486)

El concepto común definido en el proceso para la preparación compuestos lactama-lactona C8 consiste en las etapas:

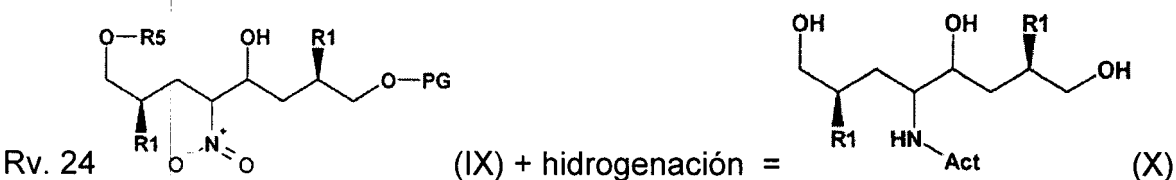
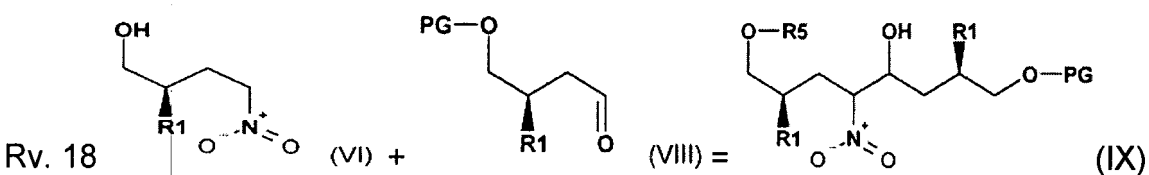
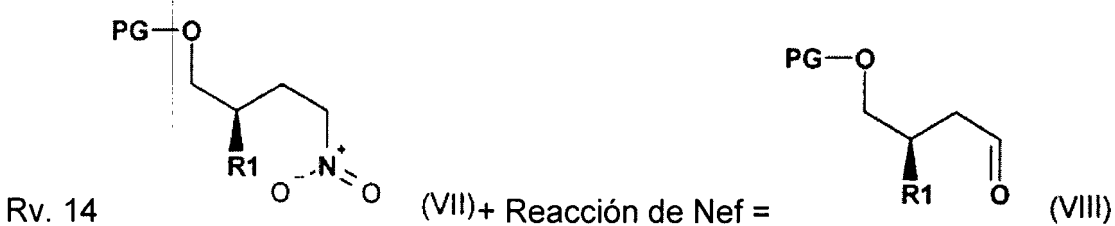
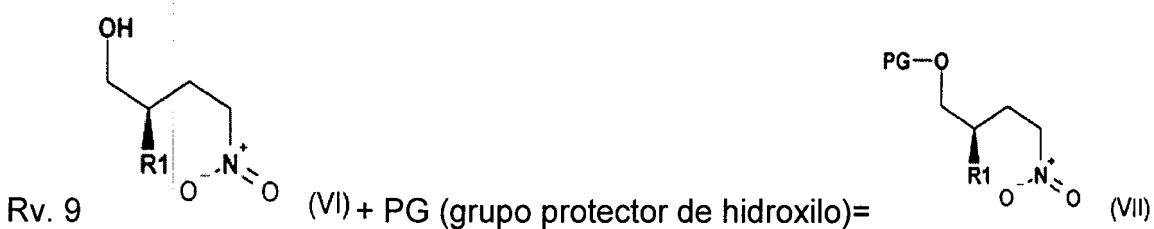
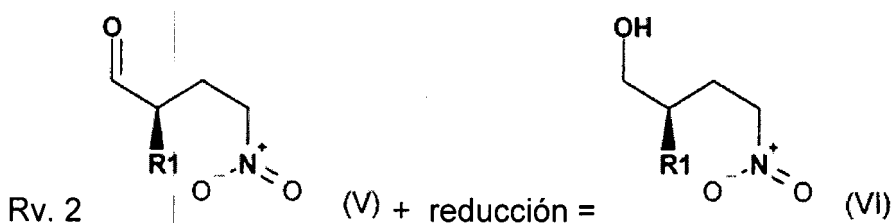
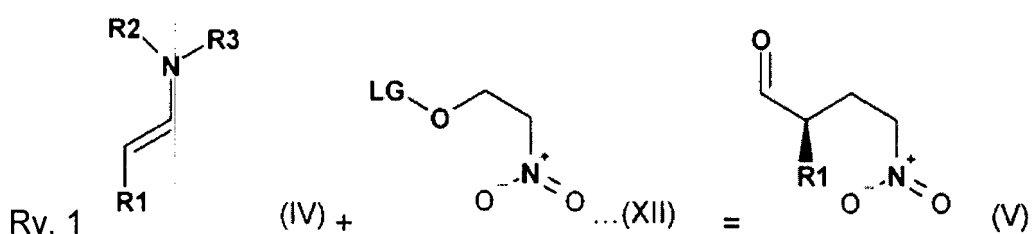
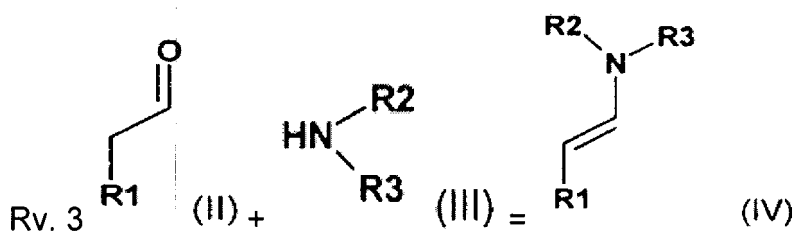


No hay unidad de invención para el proceso para la preparación de los compuestos lactonas-lactamas, porque las etapas no están concatenadas y no existe una interrelación técnica entre los productos intermedios y el producto final en el capítulo reivindicatorio, es decir, se tiene una gran cantidad de intermedios para llegar al producto final y con diferentes elementos estructurales, pero no todos los productos intermedios están involucrados en un mismo proceso para preparar el producto final. Por tanto, el proceso de preparación de los compuestos lactama-lactona no comparte un concepto común inventivo y se encuentran 3 grupos inventivos.¹

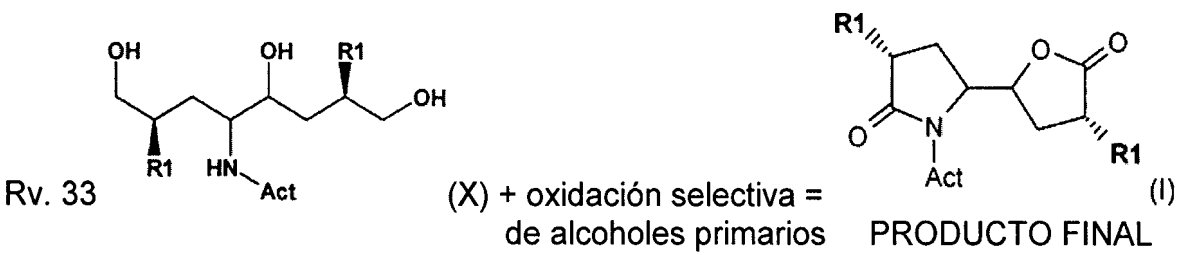
¹ Organización mundial de la propiedad intelectual. Tratado de cooperación en materia de patentes (pct). Directrices de búsqueda internacional y de examen preliminar internacional del PCT. 11 de marzo de 2004. Pág. 90, 91 y 100 a 103.

Los grupos inventivos están definidos a priori, por las siguientes características esenciales:

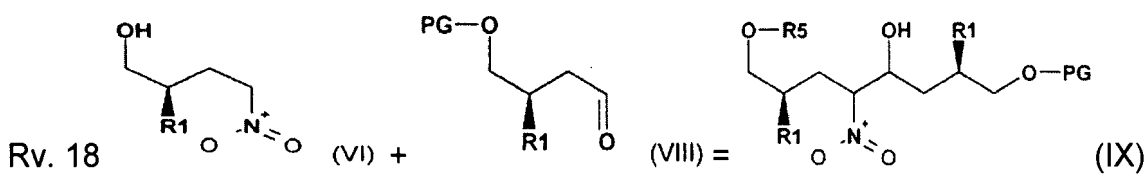
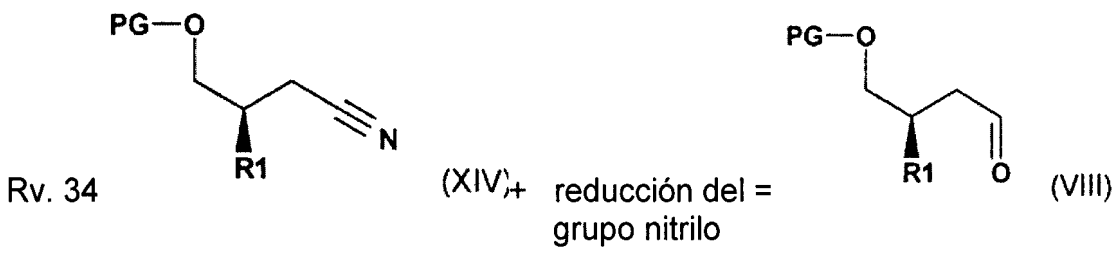
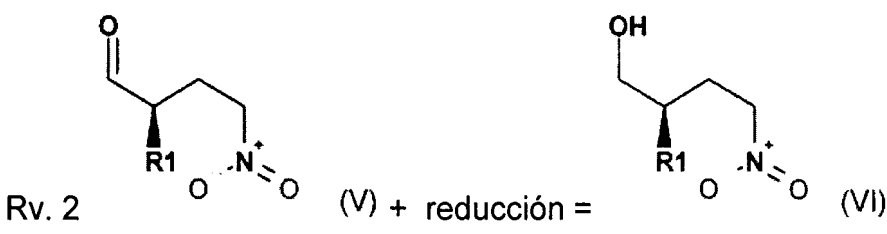
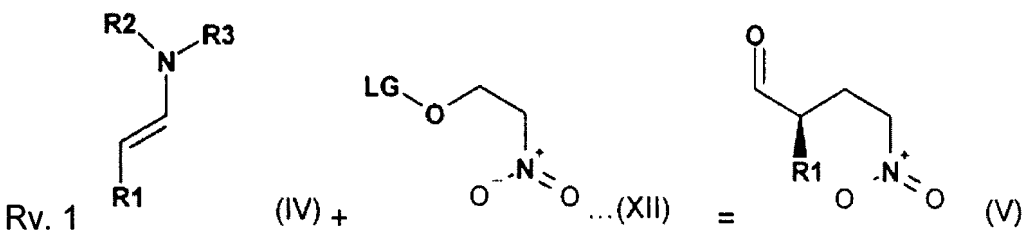
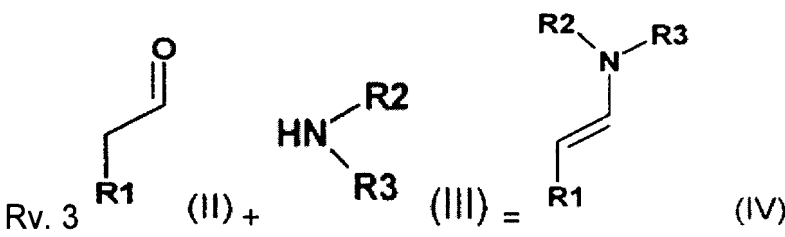
Grupo Inventivo 1°:

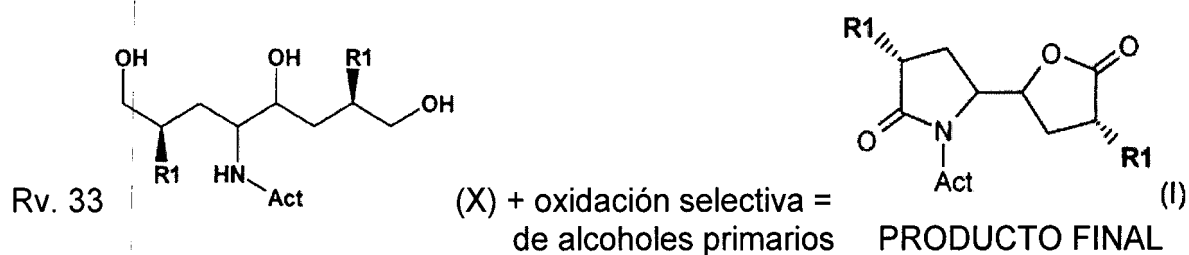
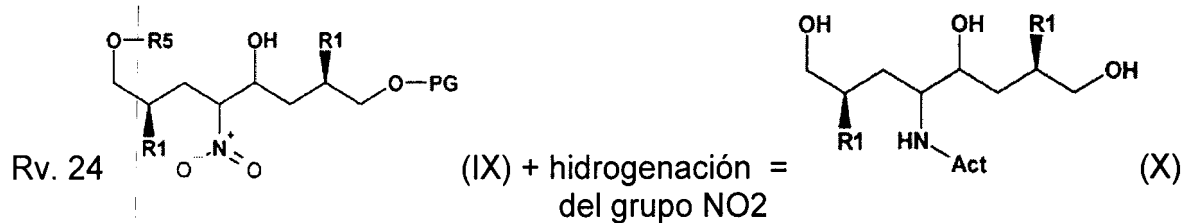


del grupo NO2

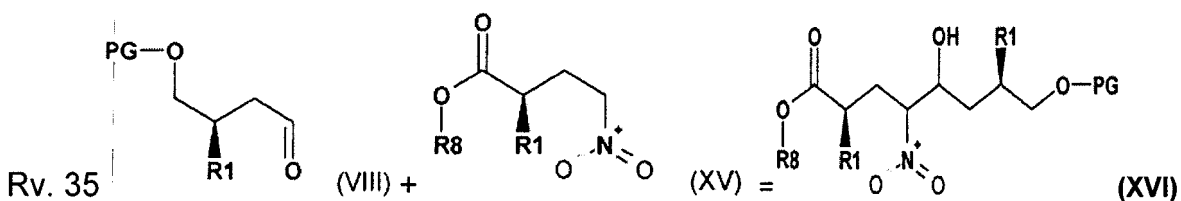
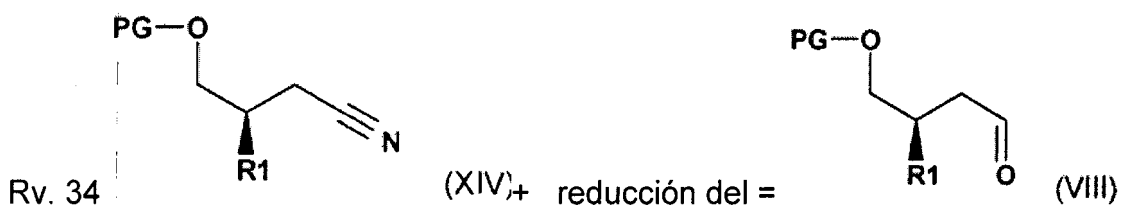
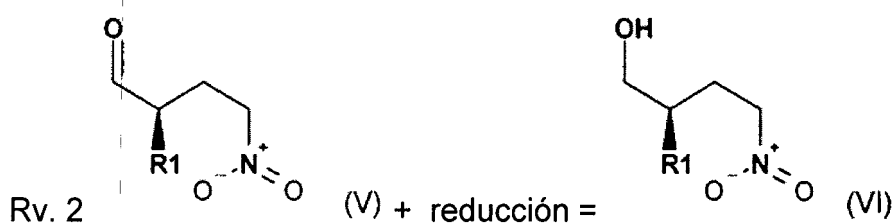
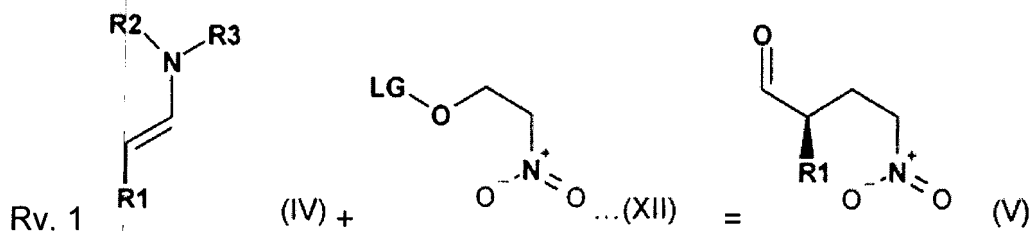
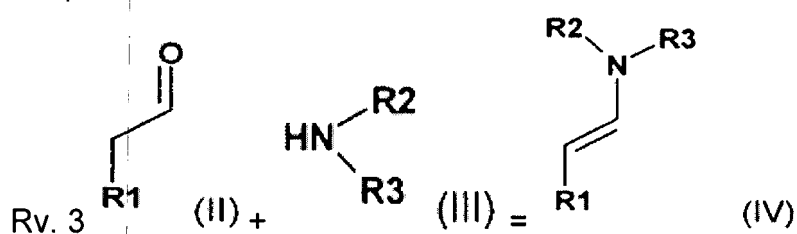


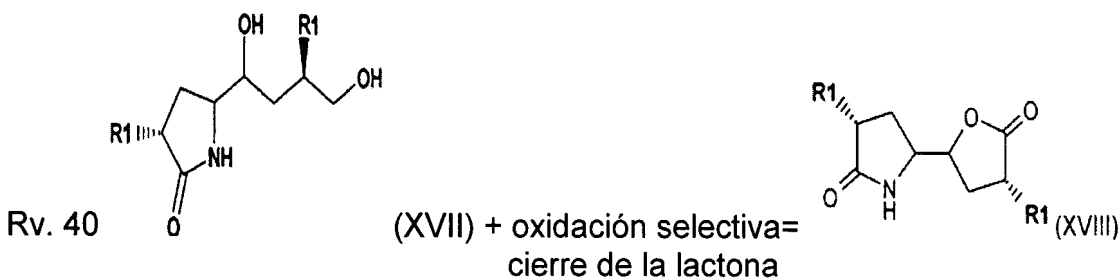
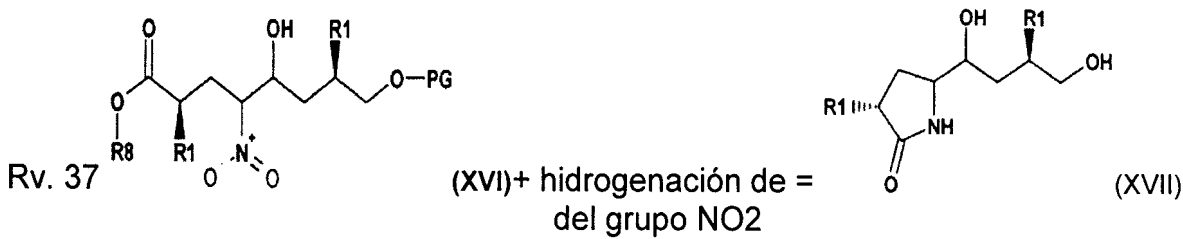
Grupo Inventivo 2°:





Grupo Inventivo 3°:





PRODUCTO FINAL

Se sugiere presentar las Solicitudes Divisionales que considere necesarias, ó limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de prioridad (03/Abril/2007) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación	Fecha de prioridad
D1	Hurd c. Journal of the american chemical society, american chemical society, Washington, vol. 74	ring-chain tautomerism of hydroxy aldehydes	05/Noviembre/1952	----
D2	Paquette Leo. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. J. Org. Chem. 2003, 68, 6096-6107	Convergent Enantioselective Synthesis of Vinigrol, anArchitecturally Novel Diterpenoid with Potent Platelet Aggregation Inhibitory and Antihypertensive Properties. 1. Application of Anionic Sigmatropy to Construction of the Octalin Substructure	14/Abril/2003	----
D3	US6683075	Cycloalkyl, lactam, lactone and related compounds, pharmaceutica	27/enero/2004	----
D4	CO2008-38593	Derivados de 3-alkuil-5-(4-	-----	17/octubre/2005

		alquil-5-oxo-tetrahidrofuran-2-il)-pirrolidin-2-ona como intermediarios en la síntesis de inhibidores de renina		
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D1<http://www.sinab.unal.edu.co:2108/ehost/search/basic?sid=cb6aed1b-c39d-4d23-bf56-b5bf74cbf414%40sessionmgr13&vid=1&hid=9>
Divulga el 4-metoxibutanal (Pág. 5324-5329).

D2<http://www.sinab.unal.edu.co:2139/action/showPublications?display=journals>
Divulga un compuesto con los grupos funcionales alcoxi y aldehído y cadena carbonada de 4 átomos (Pág. 6096-6107).

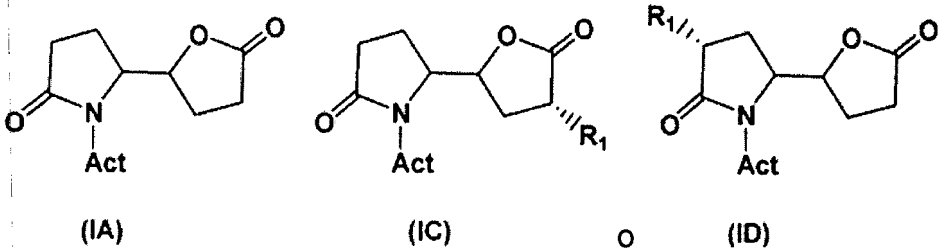
D3<http://www.google.com/patents/US6683075?printsec=abstract&dq=lactone+lactam+reaction+michael&ei=VexDUKPtG4b88gT2vIGgDg#v=onepage&q=lactone%20lactam%20reaction%20michael&f=false>
Divulga métodos de preparación de lactonas lactamas por medio de la adición de un carbanion a una amina en una reacción de adición nucleófila para producir un producto intermedio (columna 115).

D4. Divulga los compuesto lactona-lactama con formulas (II) y (VI) Fl. 309, 314 y 315

7. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 45 consiste en un compuesto de fórmula I o una sal del mismo, el cual tiene una de las siguientes estructuras:



en donde R1 es hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o bencilo, y Act es un grupo activador seleccionado a partir de un grupo protector de amino, en particular uno que, junto con el átomo de nitrógeno, forma un carbamato.

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
Compuesto de fórmula ID	Compuesto de fórmula VI
(ID)	(VI)

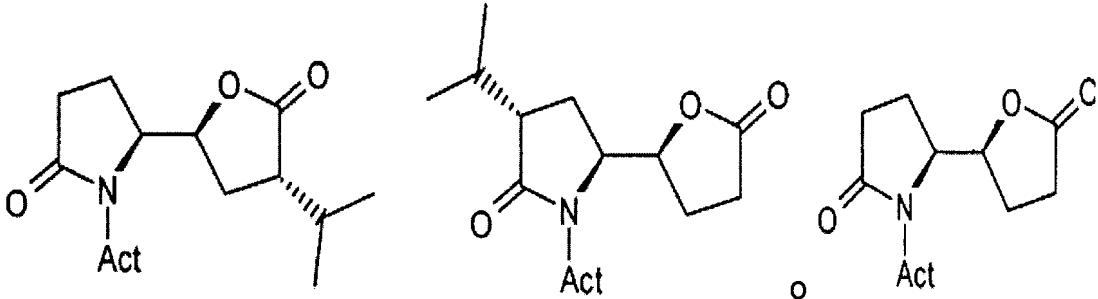
	R4=H
R ¹ = alquilo, cicloalquilo	R3= alquilo, cicloalquilo Fl. 314 y 315

Las características técnicas esenciales de la estructura de la reivindicación 45 habían sido divulgadas previamente en D4, el cual da a conocer los compuestos lactona-lactama con formula (VI) Fl. 314 y 315, tal como se presenta en el cuadro anterior.

En consecuencia, la reivindicación 45 no es nueva, según lo divulgado en el documento D4.

La reivindicación dependiente 46 que reivindica los compuestos (IB), (IE) y (IF) no menciona alguna característica que haga nuevos a los compuestos de fórmula estructural (ID) definidos en la reivindicación 45, por lo cual tampoco se considera que la reivindicación sea nueva.

La reivindicación 47 consiste en un compuesto de fórmula I o una sal del mismo, el cual tiene una de las siguientes estructuras:



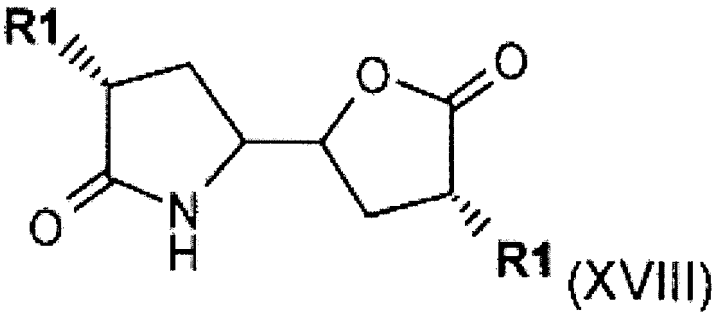
en donde Act es un grupo activador seleccionado a partir de un grupo protector de amino, en particular uno que, junto con el átomo de nitrógeno, forma un carbamato.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica:	
Características esenciales	D1
<u>Compuesto de fórmula I</u> 	<u>Compuesto de fórmula VI</u> R4=H
	R3= alquilo, cicloalquilo Fl. 314 y 315

Las características técnicas esenciales de la estructura de la reivindicación 47 habían sido divulgadas previamente en D4, el cual da a conocer los compuestos lactona-lactama con formula (VI) Fl. 314 y 315, tal como se presenta en el cuadro anterior.

En consecuencia, la reivindicación 47 no es nueva, según lo divulgado en el documento D4.

La reivindicación 51 consiste en un compuesto de fórmula (XVIII):



en donde R1 es, independientemente uno de otro, hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o bencilo o una sal del mismo.

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
<u>Compuesto de fórmula (XVIII)</u> R1 (XVIII)	<u>Compuesto de fórmula (II):</u> R4=H
R ¹ = alquilo, cicloalquilo	R3= alquilo, cicloalquilo
R ¹ = alquilo, cicloalquilo	R4= alquilo, cicloalquilo Fl. 309

Las características técnicas esenciales de la estructura de la reivindicación 51 habían sido divulgadas previamente en D4, el cual da a conocer los compuestos lactona-lactama con formula (II) Fl. 309, tal como se presenta en el cuadro anterior.

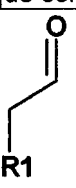
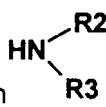
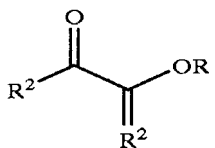
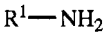
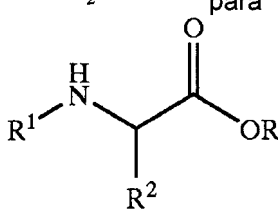
En consecuencia, la reivindicación 51 no es nueva, según lo divulgado en el documento D4.

Las reivindicaciones dependientes 52 y 53 no mencionan alguna característica que haga nuevos a los compuestos de fórmula estructural (XVIII) definidos en la reivindicación 51, por lo cual que se considera que tampoco son nuevas.

Nivel Inventivo (Art18 D486)

La reivindicación 3 consiste en un proceso (Fl. 212 a 213)

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D3
Proceso que comprende:	Proceso que comprende:
Reacción de  con  para producir de la fórmula IV) (compuestos	Reacción de  con  para producir  (columna 115).

El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1.

D1 divulga métodos de preparación de lactonas lactamas por medio de la adición de un carbanion a una amina en una reacción de adición nucleófila para producir un producto intermedio (columna 115).

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D1 consiste en que la invención tiene una amina secundaria.

No se evidencia que por el hecho de tener una amina secundaria, se tenga un efecto técnico inesperado.

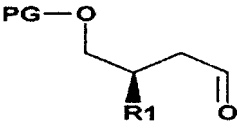
Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “cómo modificar la reacción de adición nucleófila conocido en D1 para conseguir una reacción de preparación de compuestos de la fórmula IV”.

Sin embargo, es conocido una reacción de adición nucleófila se puede realizar con aminas secundarias o primarias porque es posible usar diferentes bases que reaccionen con el carbanion presente en la reacción.²

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a emplear una amina secundaria. Por lo cual se considera obvia.

Conclusión:
La reivindicación 3 no cumple con el requisito de nivel inventivo (Art. 18).

La reivindicación 15 consiste en un compuesto de la fórmula (VIII):

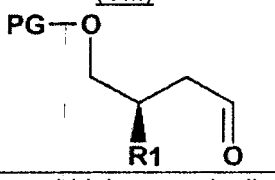
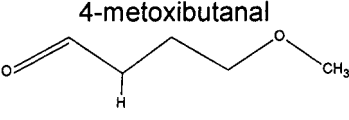
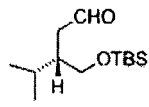


en donde:

² Morrison R. Química organica. Quinta edición. Editorial Addison Wesley. 1987. Pág. 1069 a 1071
Primer Artículo 45-Expediente 09 107976

R1 es hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o bencilo;
PG es un grupo protector de hidroxilo;
o una sal del mismo

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
<u>compuesto de la fórmula (VIII)</u> 	<u>4-metoxibutanal</u> 	<u>compuesto 11</u> 
R1 es hidrógeno, alquilo, cicloalquilo o bencilo	H	H
PG es un grupo protector de hidroxilo o una sal del mismo	CH3 (Pág. 5327, Columna 2, línea 9).	TBS (trimetilsililo) (Pág. 6098).

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1.

D1 divulga el 4-metoxibutanal (Pág. 5327, Columna 2, línea 9).

D2 divulga un compuesto con los grupos funcionales alcoxi y aldehído y cadena carbonada de 4 átomos (Pág. 6098).

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D1 consiste en que la invención tiene un grupo protector o sal del mismo.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D2 consiste en que la invención tiene un átomo de hidrógeno en el carbono 3.

No se evidencia que por el hecho de tener un grupo protector, se tenga un efecto técnico inesperado.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “cómo modificar el metoxibutanal conocido en D1 para conseguir compuestos de la fórmula VIII”.

Sin embargo, es conocido en el documento D2 la utilización de un grupo protector en el grupo metoxi.

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a emplear un grupo protector en el grupo metoxi. Por lo cual se considera obvia.

Conclusión:

La reivindicación 15 no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 16 y 17 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

8. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Hurd c. Journal of the american chemical society, american chemical society, Washington, vol. 74	15 a 17	Nivel inventivo
D2	Paquette Leo. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. J. Org. Chem. 2003, 68, 6096-6107	15 a 17	Nivel inventivo
D3	US6683075	3	Nivel inventivo
D4	CO2008-38593	45 a 53	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 30 Oct. 2012

Elaborado por: Ruth Angélica Lizarazo Pedraza
Revisado por: Consuelo Leguizamón Leguizamón
Aprobado por: José Luis Salazar López

The semicarbazone was prepared in aqueous ethanol and then recrystallized from methanol; m.p. 214.9–215.9° (cor.).

Anal. Calcd. for $C_{15}H_{21}N_3O_3$: C, 61.83; H, 7.27; N, 14.45. Found: C, 62.01; H, 7.43; N, 14.45.

The eluate fractions contained 35 to 65% benzene, were concentrated individually to give oily material, which were bulked, dissolved in ethanol and treated with 12 g. of semicarbazide hydrochloride and 18 g. of sodium acetate. Water was added until practically no solid remained and the solution was then heated at gentle reflux for two hours. At the end of the heating period crystals began to appear. The solution was cooled and filtered. The dried substance weighed 8.01 g. and melted at 178–184°. After recrystallization from methanol there was obtained 6.29 g. of white crystals, m.p. 185–186.4° (cor.). This was the semicarbazone of 1,4-dimethoxy-5-methyl-6-tetralone.

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.79; H, 7.01; N, 15.27.

A mixture of the semicarbazones of the monomethyl- and dimethyltetralones melted at 172–180°.

1,4-Dimethoxy-5-methyl-6-tetralone from the corresponding Semicarbazone.—The above semicarbazone (6.25 g.) was gently warmed with 15 ml. of acetic acid until solution was complete. The solution was diluted with 10 ml. of water and 3 g. of redistilled pyruvic acid in 5 ml. of water was added. The whole was refluxed one-half hour and then was diluted with 15 ml. of water. An oil separated and when the mixture was cooled a crystalline solid, presumably pyruvic acid semicarbazone, separated also. The mixture was extracted twice with ether and the combined oil layers were washed with sodium bicarbonate solution and then with water. The ether solution was dried and distilled. After removal of the volatile solvent the residue boiled at 128–130° (0.3 mm.). The 1,4-dimethoxy-5-methyltetralone could not be induced to crystallize.

Anal. Calcd. for $C_{14}H_{19}O_3$: C, 70.89; H, 7.32. Found: C, 70.80; H, 7.38.

RENSSELAER, N. Y.

CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY¹

Ring-Chain Tautomerism of Hydroxy Aldehydes

BY CHARLES D. HURD AND WILLIAM H. SAUNDERS, JR.

RECEIVED APRIL 21, 1952

A study of the ultraviolet absorption spectra of some simple ω -hydroxy aldehydes has disclosed that in aqueous dioxane 4-hydroxybutanal and 5-hydroxypentanal exist predominantly as the cyclic hemiacetals, containing an estimated 11.4 and 6.1%, respectively, of free aldehyde at 25°. The higher members studied exist as 80–90% free aldehyde. These values were obtained by comparing the extinction coefficients at the carbonyl maximum with those of the corresponding ω -methoxy aldehydes. A number of hydroxy and methoxy aldehydes not previously reported in the literature were prepared, some of these by a new synthetic procedure involving a cyclic acyloin as the starting material.

The position of equilibrium of acyclic $\rightleftharpoons$ cyclic forms of hydroxy aldehydes has been qualitatively known to be essentially at the acyclic stage for β -hydroxy aldehydes¹ (aldols) and at the cyclic stage for γ - and δ -hydroxy aldehydes. The latter includes aldoses² as well as simple hydroxy aldehydes.³ There is evidence for cyclization also with 9-hydroxynonanal and 4-methyl-6-hydroxyhexanal.⁴

Quantitative approaches to this problem have been surprisingly few. These include "instantaneous" combination with hydrogen cyanide,⁵ reduction of the acyclic form at the dropping mercury electrode,⁶ and absorption spectra. Solutions of glucose do not show a maximum in the carbonyl band region of the ultraviolet⁷ except under strongly acid conditions, presumably because of the very small quantity of free aldehyde present. 5-Hydroxypentanal,⁸ however, shows a maximum at 290 m μ and from the intensity of this band it was estimated that the equilibrium mixture contained about 5% of free aldehyde.

It seemed reasonable to suppose that this approach would be capable of further refinement and

extension to other simple hydroxy aldehydes. With this in mind, a study of the ultraviolet absorption of a number of simple ω -hydroxy aldehydes was undertaken. The corresponding ω -methoxy aldehydes were chosen as standards, it being assumed that they would show essentially the same carbonyl absorption as would the hydroxy aldehydes if they were entirely in the open-chain form. The ω -hydroxy and ω -methoxy aldehydes prepared were those having 4, 5, 6, 8, 9 and 10 carbon atoms between the carbonyl oxygen and the hydroxy (or methoxy) group. Of these, 4-hydroxybutanal, 5-hydroxypentanal, 9-hydroxynonanal, 4-methoxybutanal and 5-methoxypentanal were compounds known prior to this investigation.

Ozonolysis of 4-penten-1-ol and 9-octadecen-1-ol according to the directions of Helferich and Schäfer⁹ yielded 4-hydroxybutanal and 9-hydroxynonanal, respectively. Methylation, then ozonolysis of the resulting unsaturated ethers gave rise to 4-methoxybutanal and 9-methoxynonanal. The same approach was used in the preparation of 10-hydroxy- and 10-methoxydecanal, 10-undecen-1-ol being the starting material.

5-Hydroxypentanal was synthesized from dihydropyran.⁸ A synthesis of 5-methoxypentanal was devised to replace the previous method, ozonolysis of the difficultly obtainable 6-methoxy-1-hexene.⁹ Mercaptalation¹⁰ of 5-hydroxypentanal to

(1) C. D. Hurd and J. L. Abernethy, *This Journal*, **63**, 1966 (1941).

(2) W. W. Pigman and R. M. Goepf, "Chemistry of the Carbohydrates," Academic Press, Inc., New York, N. Y., 1940, Chapter II.

(3) B. Helferich and co-workers, *Ber.*, **52**, 1123, 1800 (1919); **54**, 930, 2640 (1921); **55**, 702 (1922); **56**, 2088 (1923).

(4) B. Helferich and W. Schäfer, *ibid.*, **57**, 1911 (1924); B. Helferich and G. Sparnberg, *ibid.*, **64**, 104 (1931).

(5) F. Lippich, *Biochem. Z.*, **248**, 280 (1932).

(6) S. M. Cantor and Q. P. Peniston, *This Journal*, **62**, 2113 (1940); P. Delahay and J. E. Strassner, *ibid.*, **74**, 893 (1952).

(7) E. Pacsu and L. A. Hiller, *ibid.*, **70**, 523 (1948).

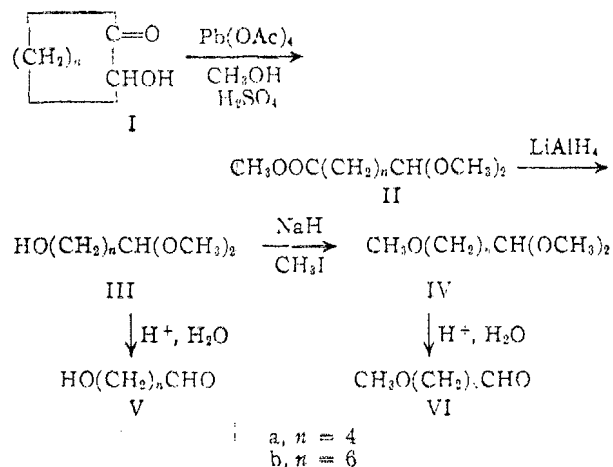
(8) L. E. Schniepp and H. H. Geller, *ibid.*, **68**, 1040 (1946).

(9) R. Pummerer and M. Schönmayrgruber, *Ber.*, **72**, 1834 (1939).

(10) This sequence of reactions was adapted from procedures for the preparation of open-chain aldose derivatives. See E. Fischer, *ibid.*, **27**, 647 (1894); P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **60**, 173 (1926); M. L. Wolfrom, *This Journal*, **51**, 2188 (1920).

5-hydroxyvaleraldehyde ethyl mercaptal, then methylation, yielded 5-methoxyvaleraldehyde ethyl mercaptal which was converted readily to 5-methoxypentanal.

The remaining two pairs of the series were prepared by a new synthesis starting with the cyclic acyloin possessing the same number of carbon atoms as the desired product. The cyclic acyloin Ia (adipoin) was obtained by hydrolysis of 2-



chlorocyclohexanone¹¹ while suberoin, Ib, was produced by the action of metallic sodium on methyl suberate in boiling xylene according to the general procedure of Prelog.¹² The acetal-esters IIa and IIb were obtained by treating methanolic solutions of the acyloins with lead tetraacetate¹³ followed by addition of sulfuric acid to catalyze the reaction of the aldehydic acids with methanol. IIb was contaminated with a yellow liquid, presumably 1,2-cyclooctanedione carried over from the impure Ib. The reduction and methylation steps proceeded smoothly but some difficulty was encountered in the acid hydrolysis of the hydroxy acetals IIIa and IIIb, since the acid promoted formation of condensation products by the hydroxy aldehydes Va and Vb. Even under the very mild conditions of treatment with cold saturated tartaric acid solution,¹⁴ IIIb gave only a 37% yield of Vb along with a higher-boiling residue. This tendency to form condensation products was much less troublesome in the preparation of the methoxy aldehydes VIa and VIb.

The hydroxy aldehydes of six carbons and more were waxy solids insoluble in all common solvents in the cold but soluble in many on heating. Their dual nature is reflected in rather indefinite and variable melting points. The most striking example is 6-hydroxyhexanal, whose melting point ranged from 57 to 86° and varied with the age of the sample and the rate of heating.

In choosing a solvent for the spectrophotometric measurements on the hydroxy aldehydes, it was hoped that an inert solvent could be used so that

there would be no uncertainties in results due to interaction of compound and solvent. Dioxane was the first tried, but a satisfactory equilibrium could not be established in this medium. The solvents finally chosen were 95% ethanol and a 3:1 mixture of dioxane and water, in both of which satisfactory equilibration occurred within a few days. The methoxy aldehydes underwent extensive interaction with the former, presumably hemiacetal formation,¹⁵ so that no comparison could be made in alcohol. In the dioxane-water mixture such interactions appeared to be quite small and a comparison could be made. The failure to attain equilibrium in inert solvents is probably associated with the necessity of having some medium which will effect the transfer of a proton from the hydroxyl group to the carbonyl oxygen in the ring closure and effect the reverse process in the ring opening.¹⁶

Solutions of the hydroxy and methoxy aldehydes were measured in 75% dioxane, the measurements on the hydroxy aldehydes being made at 25 and 35°. From the extinction coefficients the percentage of free aldehyde was estimated as in the following example: 4-methoxybutanal had ϵ 17.4 and 4-hydroxybutanal had ϵ 1.99 at 25°, from which the percentage of free aldehyde at 25° is 11.4 ($1.99/17.4 \times 100$). These results are recorded in Table I, the extinction coefficients of the hydroxy aldehydes in both 75% dioxane and in 95% ethanol being included for convenient comparison. No suitable solvent could be found for measurements on 10-hydroxydecanal. The diffuse and irreproducible maxima shown by this compound in various solvents suggest that it tends to exist as a colloid rather than as a true solution.

For an equilibrium between cyclic and acyclic structures, one would expect the two main factors influencing the position of the equilibrium to be the probability of ring formation and the amount of strain in the resulting ring.¹⁷ The greater stability of the six-membered ring as compared to the five-membered ring is as expected, since the former is highly stable in the preferred chair form, while the latter is under considerable strain arising from hydrogen-hydrogen repulsions.¹⁸ This order is also in accord with the observation that the pyranose structure is almost invariably favored in simple sugars.² There is much evidence that strain is also present in the medium-size rings, such strain being ascribed chiefly to hydrogen-hydrogen repulsions in the unfavorable constellations required by the geometry of these rings.^{18,19} Since both the ring strain and probability factors favor the open-chain form beyond the six-membered ring, a large increase in free aldehyde from 5-hydroxypentanal

(15) A. M. Buswell, E. C. Dunlop, W. H. Rodebush and J. B. Swartz, *THIS JOURNAL*, **62**, 325 (1940).

(16) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 159-160.

(17) L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz and M. Stoll, *Helv. Chim. Acta*, **9**, 499 (1926), postulate these same factors to explain the variation in yields of cyclic ketones from the pyrolysis of salts of dicarboxylic acids.

(18) H. C. Brown, R. S. Fletcher and R. Johannesen, *THIS JOURNAL*, **73**, 212 (1951). See also K. Pitzer, *Science*, **101**, 672 (1945).

(19) V. Prelog, *J. Chem. Soc.*, 424 (1950); Abstracts of Papers presented at American Chemical Society Meeting, New York, N. Y., September, 1951.

(11) A. Kätz, K. Blöndemann, R. Rosenbusch and E. Siringhaus, *Ann.*, **400**, 62 (1913).

(12) V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

(13) E. Baer, *THIS JOURNAL*, **64**, 1416 (1942), has reported the cleavage of some cyclic acyloins, including Ia, with lead tetraacetate in acetic acid.

(14) O. Fischer and K. Löwenberg, *Ann.*, **494**, 272 (1932).

TABLE I

n	Free aldehyde ^a (in 75% dioxane), %		Concn. ^b	In 75% dioxane		Extinction coefficients ^c		In 95% ethanol		m μ ^d
	At 25°	At 35°		m μ	cm ²	cm ²	Concn. ^b	m μ	cm ²	
3	11.4	13.4	0.141	286	1.99	2.34	0.203	286	1.00	1.24
4	6.1	6.8	.222	287	1.17	1.30	.415	285	0.42	0.57
5	8.5	8.9	.0308	288	16.6	17.2	.0404	286	3.44	4.43
7	80		.0140	289	16.1		.0191	287	4.08	5.08
8	91		.0178	288	19.1		.0173	284	6.52	7.20 ^d
$\text{CH}_3\text{O}(\text{CH}_2)_n\text{CHO}$										
3			0.0367	286	17.4 ^e					
4			.0383	288	19.2					
5			.0257	289	19.4					
7			.0209	289	20.1					
8			.0361	287	21.1					
9			.0208	290	21.6					

^a Though most values are given to three significant figures, the actual precision is in most observations ± 2 to 3%. ^b In moles per liter. ^c No appreciable temperature effect. ^d Measurement at 30°. ^e Measurements made on freshly distilled samples because of sensitivity to oxidation by air. No temperature control was used since the absorption was found to be quite insensitive to temperature.

to 6-hydroxyhexanal is to be anticipated, though the great magnitude of the change is somewhat surprising. The reversal of the order between 6-hydroxyhexanal and 8-hydroxyoctanal in 75% dioxane would not be predicted, and may be caused by an error or failure to attain true equilibrium, although repeated runs yielded essentially the same results. It will be noted that the expected order is observed in 95% ethanol. The more gradual increase in free aldehyde with chain length (as measured by the extinction coefficients) observed in 95% ethanol probably is the result of a greater variation in solvent interaction with the aldehydic form rather than any large solvent effect on the equilibrium itself.

It might be pointed out that this method is less capable of giving good results on the higher members, since the values are much more closely spaced and hence the same relative error could cause a more significant variation in percentage of free aldehyde. Uncertainties as to the solvent interactions preclude any detailed thermodynamic analysis of the results of these studies, since more than one equilibrium is involved. The possibility of some intermolecular hemiacetal formation by the hydroxy aldehyde should also be mentioned. However, the fact that measurements were made in rather dilute solutions in hydroxylic media makes it probable that this reaction is negligible, particularly in comparison with the reaction between aldehyde and solvent. In spite of these difficulties, this approach still seems capable of yielding valuable semi-quantitative information where relatively large differences are involved and the percentage of free aldehyde is neither very small nor very large.

Experimental

5-Hydroxypentanal was prepared according to the directions of Schniepp and Geller.⁸ From 50 g. of dihydropyran there was obtained 29 g. (48%) of 5-hydroxypentanal, b.p. 83–88° (15 mm.). Redistillation yielded a sample of b.p. 81° (12 mm.), n_D^{20} 1.4530 (lit.⁸ n_D^{25} 1.4514).⁸

5-Hydroxyvaleraldehyde Ethyl Mercaptan.—To a solution of 10.2 g. (0.1 mole) of 5-hydroxypentanal in 20 ml. of 8 N hydrochloric acid was added, while shaking and cooling the flask, 13.6 g. (0.22 mole) of ethyl mercaptan. The flask

was stoppered and shaken at intervals for one hour. The mixture was then extracted with three 15-ml. portions of ether, the extracts washed successively with 20 ml. of 5% sodium hydroxide and 20 ml. of saturated sodium chloride, and dried over sodium sulfate. Removal of the ether and vacuum distillation of the residue yielded 18.8 g. (90%) of the desired mercaptan, b.p. 153–158° (8 mm.). An analytical sample had b.p. 110° (0.5 mm.), n_D^{20} 1.5177.

Anal. Calcd. for $\text{C}_6\text{H}_{12}\text{OS}_2$: C, 51.87; H, 9.67. Found: C, 51.59; H, 9.65.

5-Methoxypentanal.—A solution of 9.0 g. of 5-methoxyvaleraldehyde ethyl mercaptan in a mixture of 10 cc. of water and 40 cc. of acetone was placed in a 200-cc., 3-neck, r.b. flask fitted with sealed stirrer, reflux condenser and dropping funnel. There was added 20 g. of cadmium carbonate and through the dropping funnel, with stirring, was added a solution of 27 g. of mercuric chloride in 30 cc. of acetone during 15 minutes. After 24 hours of stirring, the solid matter was separated and washed thrice with acetone. The filtrate and washings were combined and heated under reduced pressure at 40–50° to remove most of the acetone. The resulting water solution of the product was extracted with four 30-cc. portions of ether, some separation of solid occurring during this process. After drying over sodium sulfate, the product was distilled under reduced pressure. The material darkened as the distillation proceeded, but the product came over clear and colorless.

There was obtained 2.5 g. (53%) of material boiling at 81–83° (40 mm.). Redistillation yielded a center cut of b.p. 67° (20 mm.), n_D^{20} 1.4159 (lit.⁹ b.p. 59° (14.5 mm.), n_D^{20} 1.4162).

2-Hydroxycyclohexanone (Adipoin).—This was obtained in 48% yield by hydrolysis of 2-chlorocyclohexanone¹⁰ as directed by Kötze, *et al.*¹¹ The colorless crude product was used without further purification.

Methyl 6,6-Dimethoxyhexanoate.—To a solution of 20 g. of 2-hydroxycyclohexanone in 200 cc. of methanol there was added, with shaking and cooling, small portions of lead tetraacetate until a slight molar excess persisted for ten minutes, as shown by starch-iodide paper. This required about 80 g. of the tetraacetate. The excess was then destroyed by the addition of a few drops of glycerol and a solution of 32 g. of concd. sulfuric acid in 80 cc. of methanol was added.

After the mixture had stood in a stoppered flask for two days, lead sulfate was removed by suction filtration through celite and washed with three 25-cc. portions of methanol. The filtrate and washings were combined and poured, with vigorous stirring, into 300 cc. of 30% sodium carbonate solution. Some solid separated which was separated. The clear solution was extracted with four 200-cc. portions of ether and the combined extracts washed with 100 cc. of water. After drying over sodium sulfate, the ether and re-

(20) M. S. Newman, M. D. Furhman and H. Hipsher, *Org. Syntheses*, **25**, 22 (1945).

TABLE II
 RESULTS OF METHYLATION REACTIONS

Name	Yield, %	n_D^{20}	B.p., °C.	Mm.	n_D^{20}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Methoxy-1-pentene ^a	71	96		750	1.4027	...	...	...	...
5-Methoxyvaleraldehyde ethyl mercaptal	73	140-145		10					
		89		0.6	1.4959	54.00	54.00	9.97	10.04
1,1,6-Trimethoxyhexane	73	101-104		19					
		96		13	1.4189	61.33	61.39	11.44	11.14
1,1,8-Trimethoxyoctane	89	95-98		3.6	1.4258 ^b	64.66	64.83	11.84	11.66
1-Methoxy-9-octadecene	80	135-145		0.8					
11-Methoxy-1-undecene	78	115-120		18					
		89		2.8	1.4342	78.19	77.91	13.13	13.30

^a Lit.⁵ gives b.p. 96-98°, n_D^{20} 1.4032. ^b At 21.5°. ^c Unsatisfactory analysis even after redistillation, but ozonolysis of this material was satisfactory.

maining methanol were distilled off. A small amount of water always separated at this point and had to be removed and extracted once or twice with ether. The ether extracts were again dried and the ether removed.

Vacuum distillation of the residue yielded 21.7 g. (65%) of a colorless liquid of b.p. 79-83° (1.8 mm.). A portion of this was redistilled through a 7-cm. vacuum-jacketed Vigreux column to yield a liquid of b.p. 83° (2.2 mm.), n_D^{20} 1.4262.

Anal. Calcd. for $C_9H_{18}O_4$: C, 56.84; H, 9.54. Found: C, 56.93; H, 9.36.

6,6-Dimethoxy-1-hexanol.—A solution of 21.3 g. of methyl 6,6-dimethoxyhexanoate in 30 ml. of dry ether was added with stirring over 1.5 hours to 3.0 g. of lithium aluminum hydride in 100 ml. of dry ether, taking the usual precautions for exclusion of moisture. The processing followed the procedure of Amundsen and Nelson.²¹ A yield of 16.5 g. (91%) of 6,6-dimethoxy-1-hexanol, b.p. 83-88° (0.9 mm.), was obtained. Redistillation gave an analytical sample of b.p. 84° (1.0 mm.), n_D^{20} 1.4358.

Anal. Calcd. for $C_8H_{18}O_3$: C, 59.24; H, 11.18. Found: C, 59.33; H, 11.14.

6-Hydroxyhexanal.—Ten grams of 6,6-dimethoxy-1-hexanol and 15 ml. of 1:10 hydrochloric acid were mixed and warmed gently on the steam-bath for ten minutes. The solution was made weakly alkaline (pH 7-8) by the addition of solid potassium carbonate, saturated with sodium chloride and extracted with five 10-ml. portions of ether. The ether solution was dried over magnesium sulfate, the ether removed and the residue distilled *in vacuo* to yield 3.7 g. (52%) of 6-hydroxyhexanal, b.p. 72-77° (0.9 mm.). A center cut of b.p. 73° (0.9 mm.) was analyzed. Both fractions solidified on standing.

Anal. Calcd. for $C_6H_{12}O_3$: C, 62.03; H, 10.42. Found: C, 61.65; H, 10.39.

Melting points of the solidified product ranged from 57-86° for different runs, increasing with the age of the sample, and generally covered about a 10° range unless the temperature was raised very slowly. The solid was insoluble in all common solvents at room temperature. Although it dissolved in a variety of solvents on heating, it separated with reluctance on cooling and no suitable medium for recrystallization could be found. A Rast molecular weight determination in camphor gave values of 115 and 119, as compared to 116 calculated for $C_6H_{12}O_3$.

6-Methoxyhexanal.—The same hydrolytic and processing procedures were applied as for 6-hydroxyhexanal, starting with 1,1,6-trimethoxyhexane. The yield of 6-methoxyhexanal, b.p. 82-85° (19 mm.) was 70%. An analytical sample had b.p. 82° (18 mm.), n_D^{20} 1.4205.

Anal. Calcd. for $C_7H_{14}O_3$: C, 64.58; H, 10.84. Found: C, 64.07; H, 10.91.

Preparation of Aldehydes by Ozonolysis.—Helfferich's directions²² were followed for ozonizing 4-penten-1-ol²³ and 9-octadecen-1-ol. The 4-hydroxybutanal obtained had these constants: b.p. 57.5-58° (9 mm.), n_D^{20} 1.4450. Helfferich reported no b.p. but did give n_D^{20} 1.4291. Paul²⁴

obtained the compound by periodate cleavage and by lead tetraacetate cleavage of 1,2,5-pentanetriol and reported b.p. 59-60° (8 mm.), n_D^{20} 1.4403. In the present work difficulty was encountered in purification when any unreacted 4-penten-1-ol remained in the reaction mixture.

The 9-hydroxynonanal obtained melted at 58-59° (lit.⁴ 58°) after several recrystallizations from xylene-ligroin. On standing, the m.p. increased to 62-64°.

4-Methoxybutanal.—To ozonize 5-methoxy-1-pentene, 5.2 g. of it in 20 ml. of methylene chloride was chilled to -78° and subjected to a stream of ozonized oxygen for three hours. It was then added to a mixture of 10 ml. of glacial acetic acid, 20 ml. of ether and 1 g. of water. Four grams of zinc dust was added in small portions. Decomposition of the ozonide was completed by refluxing for 1.5 hours. The mixture was filtered, the residue washed thrice with ether, and the combined filtrate and washings washed with concentrated potassium carbonate solution. After drying with magnesium sulfate, the solvent was removed and the residue distilled under reduced pressure. The yield of 4-methoxybutanal, b.p. 56-61° (40 mm.), was 2.2 g. or 42%. On redistillation there was obtained a sample of b.p. 66° (50 mm.), n_D^{20} 1.4101 (lit. b.p. 138-140°, n_D^{20} 1.4073²⁵).

9-Methoxynonanal.—An ozone stream was passed through a solution of 11.6 g. of crude 1-methoxy-9-octadecene in 15 g. of glacial acetic acid. After processing with zinc dust, washing, etc., distillation gave a forerun of pentaldehyde, followed by 2.7 g. (38%) of 9-methoxynonanal, b.p. 100-110° (4 mm.). Redistillation yielded an analytical sample of b.p. 91° (1.7 mm.), n_D^{20} 1.4326.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 69.70; H, 11.70. Found: C, 70.00; H, 12.04.

10-Hydroxydecanal.—A solution of 6 g. of 10-undecen-1-ol in 12 ml. of glacial acetic acid was ozonized similarly. From the products was obtained 5.7 g. of a viscous oil which on cooling turned to a waxy solid. The crude product was recrystallized five times from a xylene-ligroin mixture to yield a powdery solid of m.p. 68-70°. This value increased to 71-73° on standing for several weeks.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 69.70; H, 11.70. Found: C, 69.71; H, 11.97.

10-Methoxydecanal.—11-Methoxy-1-undecene (in acetic acid) was ozonized similarly. From 6.5 g. there was obtained 4.5 g. (69%) of 10-methoxydecanal, b.p. 75-80° (0.5 mm.). Redistillation gave a center cut of b.p. 78° (0.5 mm.), n_D^{20} 1.4357.

Anal. Calcd. for $C_{11}H_{22}O_3$: C, 70.92; H, 11.91. Found: C, 71.44; H, 12.12.

Methylations.—In a 3-neck, r.b. flask fitted with a sealed stirrer, reflux condenser and dropping funnel was placed 0.1 mole of sodium hydride and 50 cc. of dry ether. Then, with stirring, 0.1 mole of the alcohol (4-penten-1-ol, 5-hydroxyvaleraldehyde ethyl mercaptal, 6,6-dimethoxy-1-hexanol, 8,8-dimethoxy-1-octanol, 9-octadecen-1-ol, 10-undecen-1-ol) was added at such a rate as to keep the evolution of hydrogen under control. After 24 hours the ether was removed and to the gray-brown paste was added 0.12-0.2 mole of methyl iodide. Heat of reaction caused gentle refluxing. Stirring was continued for 1.5 hours or longer, then 30 cc. of dry ether was added. After filtration and rinsing of the precipitate with ether the filtrate was distilled. Results are collected in Table II.

(21) L. H. Amundsen and L. S. Nelson, *THIS JOURNAL*, **73**, 242 (1951).

(22) Obtained as in *Org. Syntheses*, **28**, 84 (1945).

(23) R. Paul, *Compt. rend.*, **218**, 303 (1942); R. Paul and S. Tchelitcheff, *Bull. soc. chim.*, [5] **16**, 197 (1948).

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High Dilution Reflux Cycle.—This apparatus was prepared for use in the next synthesis. A 2-liter, 3-neck, r.b. flask was fitted with a sealed Hershberg stirrer, a gas inlet tube through which a slow stream of dry, pure²⁴ nitrogen was admitted and a high dilution reflux cycle. The last consisted of three parts: (1) a side-arm tube about 30 × 150 mm.; (2) above this and fitted to it, a reflux condenser; (3) attached at the top of the latter, a dropping funnel and gas vent.

The side arm was equipped with a stopcock at the bottom for convenience in draining, and with a 24/40 female joint at the top to accommodate the condenser. The side-arm, near the top of the tube, was of 12 mm. diameter, and was bent to fit into one neck of the flask. The tube contained a funnel to force the condensed vapor to flow to the bottom of the tube before returning to the flask.

The gas vent was simply a tube which conveyed the escaping gas through a layer of xylene in a test-tube, thus forming a seal. The reflux cycle is sketched in Fig. 1.

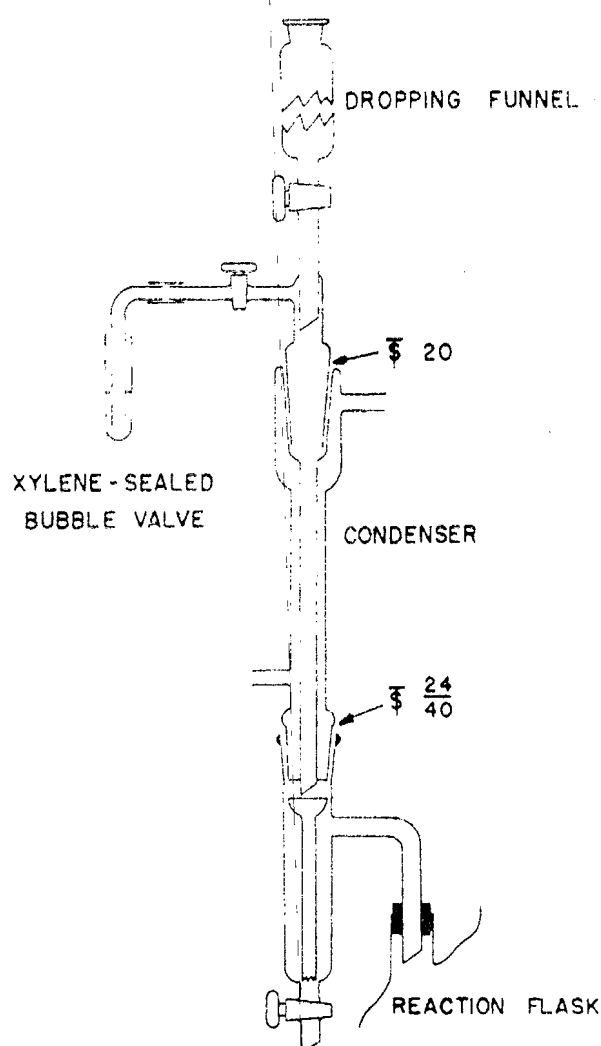


Fig. 1.—Reflux cycle.

2-Hydroxycyclooctanone (Suberoin).—Except for the design of the dilution cycle, the procedure essentially followed the general directions of Prelog and collaborators.¹² The flask was charged with 800 ml. of dry xylene and a little was distilled off to remove any moisture. There was added 37 g. (1.6 moles) of clear sodium and the sodium dispersed by rapid stirring in the refluxing (135–137°) xylene. A solution of 76 g. (0.38 mole) of methyl suberate in 70 ml. of dry xylene was added through the dilution cycle over seven hours. After it had been stirred with refluxing for two more hours the mixture was cooled and processed.¹² The xylene was removed from the dried solution through a

Vigreux column under reduced pressure and the residue distilled *in vacuo*. There was obtained 25.4 g. (47%) of a pale yellow semi-solid, b.p. 90–100° (5 mm.). Attempts at further purification by distillation and recrystallization failed. On standing the product decomposed slowly to suberic acid, identified by m.p. and mixed m.p.

The 2,4-dinitrophenylsazone was prepared from 0.4 g. of suberoin and a solution of 0.4 g. of 2,4-dinitrophenylhydrazine in strongly acidic aqueous ethanol.²⁵ Recrystallization of the product from chloroform–ethanol yielded orange-red needles melting with decomp. at 215–216° (cor.).

Anal. Calcd. for $C_{12}H_{18}N_2O_8$: N, 22.39. Found: N, 22.32.

Methyl 8,8-dimethoxyoctanoate was prepared according to the procedure given for methyl 6,6-dimethoxyhexanoate. From 15 g. of 2-hydroxycyclooctanone (contaminated with the yellow diketone) in 150 ml. of methanol and 50–55 g. of lead tetraacetate there was obtained 14.9 g. (65%) of a pale yellow oil, b.p. 105–110° (1.7 mm.). Redistillation yielded a colorless center cut, b.p. 81° (0.5 mm.), n_D^{20} 1.4321.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 60.52; H, 10.16. Found: C, 60.20; H, 9.96.

8,8-Dimethoxy-1-octanol.—The reaction of 17 g. of methyl 8,8-dimethoxyoctanoate (pale yellow material obtained in the first distillation) in 20 ml. of dry ether with 2.3 g. of lithium aluminum hydride in 100 ml. of dry ether, followed by the aforementioned processing,²³ yielded 11.3 g. (76%) of 8,8-dimethoxy-1-octanol as a colorless oil, b.p. 105–110° (0.6 mm.). An analytical sample had b.p. 90° (0.4 mm.), n_D^{20} 1.4426.

Anal. Calcd. for $C_{11}H_{22}O_3$: C, 63.11; H, 11.66. Found: C, 63.24; H, 11.74.

8-Hydroxyoctanal.—Hydrolysis of 8,8-dimethoxy-1-octanol with dilute hydrochloric acid gave poor yields of the aldehyde (21%), so a modification of the procedure devised by Fischer¹⁴ for the hydrolysis of sensitive acetals was used.

There was mixed 5.0 g. (0.026 mole) of redistilled (b.p. 95–99° at 0.4 mm.) 8,8-dimethoxy-1-octanol and 5 cc. of saturated tartaric acid solution. The mixture was shaken until it became homogeneous (about one minute) and allowed to stand for 15 minutes. On the addition of 10 cc. of saturated sodium chloride solution, the aldehyde separated. It was extracted with three 15-cc. portions of ether and the combined extracts were washed with 10 cc. of 5% potassium carbonate solution. After drying over magnesium sulfate, the mixture was distilled.

There was obtained 1.4 g. (47% of the theoretical) of material boiling 90–100° (0.5 mm.). This was viscous and it slowly turned semi-solid. In addition 0.6 g. came over in the range 110–150° (0.5 mm.). No suitable medium for recrystallization of the first fraction could be found, but purification was accomplished by grinding the 90–100° (0.5 mm.) fraction with dry ether in a mortar, filtering, and washing the residue repeatedly with dry ether. In this manner there was obtained a powdery white solid of m.p. 63–65°. This m.p. decreased after a week to 59–63°. Repeated ether treatment gave a sample melting at 66–68°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.10; H, 11.47.

8-Methoxyoctanal.—The procedure given for 8-hydroxyoctanal was followed using 7.0 g. of 1,1,8-trimethoxyoctane and 20 ml. of saturated tartaric acid except the heterogeneous mixture was shaken at intervals for one hour and then worked up as described above to yield 3.9 g. (72%) of 8-methoxyoctanal, b.p. 81–86° (3.2 mm.). This product gave a poor analysis, so it was further purified through its bisulfite addition compound, giving a liquid of b.p. 67° (1.2 mm.), n_D^{20} 1.4282.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.32; H, 11.47. Found: C, 68.52; H, 11.58.

2,4-Dinitrophenylhydrazones of all aldehydes not previously reported were prepared. Melting points and analyses are recorded in Table III.

Spectrophotometric measurements were made on a Beckman DU spectrophotometer. For the hydroxy aldehydes the cell compartment was kept at the stated temperature $\pm 0.1^\circ$. The 95% ethanol was a commercial grade while

(25) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 50.

(24) L. Fieser, *This Journal*, **46**, 2639 (1924).

TABLE III
 2,4-DINITROPHENYLHYDRAZONES^a

Aldehyde	M.p. of DNP, °C.	Nitrogen, % Calcd.	Nitrogen, % Found
5-Methoxypentanal	79-79.5	18.91	19.10
6-Hydroxyhexanal	104-105	18.91	19.09
6-Methoxyhexanal	74-74.5	18.06	18.36
8-Hydroxyoctanal	91-93	17.28	17.33
8-Methoxyoctanal	73-74	16.56	16.48
9-Methoxynonanal	73-74	15.90	15.98
10-Hydroxydecanal	80 ^b		
	101-103	15.90	16.33
10-Methoxydecanal	77	15.29	15.25

^a These derivatives were prepared by standard procedures as given by Shriner and Fuson²⁵ and A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., Inc., New York, N. Y., 1948, p. 342. ^b Double m.p. sintered at 80° and melted 101-108°.

"75% dioxane" was prepared by mixing three volumes of dried and purified²⁶ dioxane with one volume of distilled

(26) L. Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., New York, N. Y., 1941, p. 369.

water. The samples measured were generally the same as those submitted for analysis or were purified as described under their preparation. Equilibrium conditions in solutions of the hydroxy aldehydes were obtained within one to three days. Initial absorption was usually considerably lower than that at equilibrium. The existence of equilibrium was verified by rechecks on different solutions or by returning to the original temperature after measurements at another temperature. The equilibria were quite mobile once established, about one-half hour at a given temperature generally being sufficient for the attainment of stable readings. The precision of the results may vary somewhat, since a few of the measurements were made at high transmittancies where the spectrophotometer is less accurate.²⁷ Data on the methoxy aldehydes are given in Table I.

Acknowledgments.—One of us (W. H. S.) is indebted to the Allied Chemical and Dye Corporation for financial aid in the form of a fellowship, 1950-1951. Microanalysis for carbon, hydrogen, nitrogen were performed by Misses C. Brauer and J. Sorensen.

(27) G. H. Ayres, *Anal. Chem.*, **21**, 652 (1949).

EVANSTON, ILLINOIS

(CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE)

Rates of Chromic Acid Oxidation of Some Cyclanols^{1,2}

BY HENRY G. KUIVILA AND WILLIAM J. BECKER, III

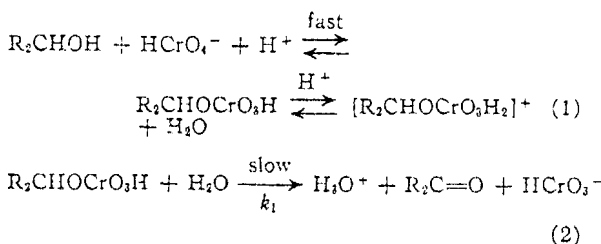
RECEIVED MAY 19, 1952

The rates of chromic acid oxidation of isopropyl alcohol and four cyclanols follow the order $C_8H_{15}OH > C_7H_{13}OH > C_6H_{11}OH > C_5H_9OH > C_4H_9OH > C_3H_7OH$.

It is well known that the rates and equilibria of reactions involving alicyclic compounds often vary profoundly with ring size. Several factors appear to be involved. Some of these have been embraced in the concept of I-strain by Brown and co-workers.³ Thus a quadricovalent cyclopropane derivative will be less strained due to the bond angles imposed by the ring structure than a tricovalent (e.g., ion, radical or ketone) or pentavalent (transition state in an S_N2 displacement) species. Transformation from the first to either of the latter two is therefore relatively difficult; the reverse transformation is relatively easy. A similar argument applies to cyclobutane derivatives where the differences in strain are smaller. However, complications can be introduced, for example, by the fact that the cations from some cyclobutyl and cyclopropylmethyl derivatives may be identical.⁴ For the 5- and 7-membered rings torsional forces due to hydrogen-hydrogen repulsions^{5,5} appear to account for the greater ease of the quadricovalent-to-tricovalent transformation of a carbon atom compared

with the 6-membered ring; in the latter hydrogen-hydrogen repulsions are at a minimum because of the possibility of a completely "staggered" configuration.

In order to obtain additional quantitative information on the reactivities of alicyclic derivatives we have measured the rates of chromic acid oxidation of isopropyl alcohol and the series cyclobutanol through cyclooctanol. As a result of the elegant investigations of Westheimer and co-workers⁶ the mechanisms of oxidation of secondary alcohols are fairly well understood. The slow step in the reaction involves participation by the alcohol, acid chromate ion and one or two protons as kinetically distinguishable species in water. Furthermore, removal of the hydrogen on the carbinol carbon is part of this step, as evidenced by the fact that 2-deutero-2-propanol reacts only about one-sixth as fast as ordinary 2-propanol.^{6b} The mechanisms may be represented as



(1) Taken in part from the Master's Thesis of W. J. Becker, III, June, 1951.

(2) The authors gratefully acknowledge the assistance provided by a Frederick Gardner Cottrell grant of the Research Corporation.

(3) H. C. Brown and M. Gerstein, *THIS JOURNAL*, **72**, 2926 (1950); H. C. Brown, R. S. Fletcher and R. B. Johanssen, *ibid.*, **73**, 212 (1951). The latter paper contains a summary of pertinent data for 5-, 6- and 7-membered ring compounds. See also H. C. Brown and M. Borkowski, *ibid.*, **74**, 1897 (1952).

(4) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509, 3542 (1951).

(5) K. S. Pitzer, *Science*, **101**, 672 (1945); J. Kilpatrick, K. S. Pitzer and R. Spitzer, *THIS JOURNAL*, **69**, 2483 (1947); C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2488 (1947).

(6) (a) F. H. Westheimer and A. Novick, *J. Chem. Phys.*, **11**, 506 (1943); (b) F. Westheimer and N. Nicolaidis, *THIS JOURNAL*, **71**, 25 (1949); (c) F. Holloway, M. Cohen and F. H. Westheimer, *ibid.*, **73**, 65 (1951).

Convergent Enantioselective Synthesis of Vinigrol, an Architecturally Novel Diterpenoid with Potent Platelet Aggregation Inhibitory and Antihypertensive Properties. 1. Application of Anionic Sigmatropy to Construction of the Octalin Substructure

Leo A. Paquette,* Ronan Guevel,^{1a} Shuichi Sakamoto,^{1b} In Ho Kim,^{1c} and Jason Crawford^{1d}

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

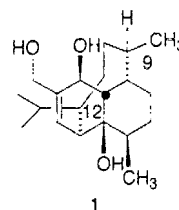
paquette.1@osu.edu

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The coupling of building blocks **15** and **36e** in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$ at 0 °C proceeds with an exo stereoselectivity (3.2:1) considerably more advantageous for the acquisition of carbinol **37e** than in the absence of the additive (exo/endo = 1:5.7). The pivotal transformation that sets all of the relevant stereocenters of the *cis* octalin **55** is the oxyanionic accelerated [3,3] sigmatropic rearrangement of **37e**. A salient feature is the structurally enforced adoption of a boatlike transition state that serves to properly set four vicinal methine hydrogens in an all *cis* arrangement. The ensuing conversion of **55** into iodo sulfone **62** has permitted X-ray crystallographic confirmation of all absolute stereochemical assignments since the isopropyl substituent was initially installed enantioselectively via the Evans oxazolidinone protocol. No intramolecular anionic cyclization of **62** to generate the tricyclic framework was seen. This absence of reactivity is attributed to conformational factors that inhibit attainment of the proper $\text{S}_{\text{N}}2$ reaction trajectory.

Fungi have been the source of a wide variety of structurally unique and pharmacologically active compounds. In 1987/1988, a group of scientists from the Fujisawa Pharmaceutical Co. reported the isolation from *Virgaria nigra* and the structural elucidation of a diterpenoid, the antihypertensive and platelet-inhibiting properties of which held unusual promise.² Spectroscopic studies, capped by an X-ray crystallographic analysis, established this substance, named vinigrol, to possess a totally unprecedented decahydro-1,5-butanonaphthalene framework as defined by **1**. These unusual structural features, and the subsequent discovery that vinigrol is also a powerful tumor necrosis factor antagonist and an agent capable of arresting the progression of the AIDS-related complex to AIDS,⁴ have fueled interest in **1** as a challenging synthetic objective.^{4–6} Despite the application

of several imaginative strategies to this problem, a *de novo* route to **1** has not yet been achieved. Herein we describe, with full experimental detail, a route to an advanced precursor of vinigrol. The present investigation highlights the utility of anionic oxy-Cope chemistry for constructing an extensively functionalized octalin ring system having the dual *R* configuration present in appendages housing both C9 and C12.



Results and Discussion

Retrosynthetic Analysis. In line with our long range plan to advance to **1** in nonracemic fashion, the strategy as defined in Scheme 1 was based on the expectation that the cyclization of **3** or a close relative thereof would lead via **2** to the enantiopure diterpenoid target. With the focus on **3**, proper access to this intermediate by methodology capable of accommodating the proper juxtapositioning of six contiguous stereogenic centers was accorded attention. It was reasoned that this important objective

(1) Current addresses: (a) CRIT Pharma, 24 Avenue Jean Jaures, 69153 Decines, France. (b) Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba Ibaraki, 205-8585 Japan. (c) Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD 20892. (d) AnorMED Inc., 200-20353 64th Ave., Langley, B.C., Canada V2Y 1N5.

(2) (a) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292. (b) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 2b. (c) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.

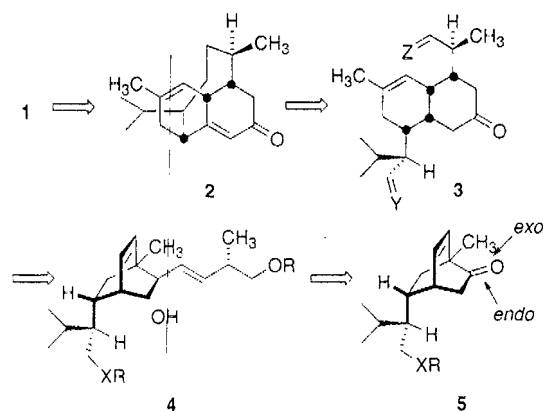
(3) Norris, D. B.; Depledge, P.; Jackson, A. P. PCT Int. Appl. W0 91 07 953; *Chem Abstr.* **1991**, *115*, 64776h.

(4) (a) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1993**, *58*, 2349. (b) Devaux, J.-F.; Fraisse, P.; Hanna, I.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 9471. (c) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062. (d) Centric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139.

(5) Mehta, G.; Subba Reddy, K. *Synlett* **1996**, 625.

(6) (a) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (b) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 11369.

SCHEME 1



could be realized in a single step by anionic oxy-Cope rearrangement⁷ of the tertiary bicyclo[2.2.2]octenol **4**. Another attractive feature of **4** is the convenient allowance provided by it for convergent assembly. Thus, we envisioned that ketones such as **5** and appropriately substituted vinylic halides would serve as reaction partners. Proper delineation of the stereoselectivity associated with the coupling of these building blocks was also mandated. Nucleophilic addition to **5** from the π surface opposite the unsaturated bridge would give rise to a diastereomer having olefinic centers too remote for possible engagement in charge-accelerated [3,3]sigmatropic rearrangement. We therefore hoped to skirt its formation. The degree of control available from solvent, temperature, and precise nature of the organometallic reagent was not a priori predictable, and we planned to launch a systematic study in order to define conditions leading to maximum exo stereoselectivity. The impact of changes in the chemical nature of the XR substituent was also to be probed.

Synthesis of Representative Bicyclo[2.2.2]octenones. After brief, unprofitable encounters with routes to **5** based on Diels–Alder and Ireland–Claisen protocols as key transformations,⁸ attention was directed instead to a pathway featuring a Michael–Michael sequence for elaboration of the structural framework. The route began by acylation of the lithiated form of (*S*)-oxazolidinone **6**⁹ with isovaleryl chloride (Scheme 2).¹⁰ Excellent levels of diastereoselectivity (dr > 95:5) were subsequently realized in the alkylation¹¹ of **7** with allyl bromide. Traces of the minor reaction component were conveniently removed by preparative HPLC to give **8** of very high quality (>99% ee). Some difficulties were experienced in removing the chiral auxiliary resident in **8**.¹² The use of LiAlH₄ resulted in the formation of a significant amount of ring-cleaved amino alcohol. Although Damon's two-step procedure

involving the use of lithium benzyl mercaptide was effective on a 100 mg scale,¹³ only a 12% yield of **9** was realized at the 10 g level. In contrast, the hindered acyl oxazolidinone responded well to the action of lithium borohydride in THF containing 1 equiv of ethanol.¹⁴ The absence of racemization during formation of alcohol **9** was ascertained by Mosher ester analysis.¹⁵ (>97% ee)

Protection of **9** as the *tert*-butyldimethylsilyl ether followed by ozonolysis afforded aldehyde **11**. While the direct alkylation of aldehydes is recognized to be sluggish and competitive with concomitant operation of unwanted aldol condensations or Cannizzaro type reactions,¹⁶ prior conversion to an enamine, hydrazone, or imine derivative has been reported to allow alkylations to proceed efficiently.¹⁷ From these options, the pyrrolidine enamine alternative proved most successful in conjunction with methyl vinyl ketone, giving rise to **12** in 84% yield. The best conditions uncovered for the cyclization of the resulting keto aldehyde were adapted from those developed in Burke's quadron synthesis.¹⁸ Following the heating of **12** with potassium hydroxide and dibenzo-18-crown-6 in benzene, there was isolated 16% of **13** (dr = 1.7:1) and 47% of the intermediate β -hydroxy ketones. Resubmission of the latter to the basic reaction conditions resulted in an increase of the overall yield of cyclohexenones to 80%.

Following the α' -monomethylation of **13**, compound **14** so obtained was subjected to a double-Michael reaction¹⁹ involving phenyl vinyl sulfoxide as the co-reactant. Without purification, the intermediate bicyclic adducts were heated in toluene containing calcium carbonate in order to induce the direct thermal extrusion of benzene sulfenic acid.²⁰ Although the overall yield in which **15** and **16** were formed was modest (41%), these diastere-

(7) (a) Paquette, L. A. *Tetrahedron* **1997**, 53, 13971. (b) Paquette, L. A. *Synlett* **1990**, 67. (c) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 609.

(8) Guevel, R. Ph.D. Dissertation, The Ohio State University, 1994.

(9) (a) Evans, D. A.; Bartoli, J.; Shih, I. L. *J. Am. Chem. Soc.* **1981**, 103, 2127. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, 104, 1737.

(10) (a) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, 52, 2, 3759. (b) Iscki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, 34, 2169. (c) Thom, C.; Kocienski, P. *Synthesis* **1992**, 882.

(11) (a) Tumble, J. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, 108, 6397. (b) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1988**, 29, 6257. (c) Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, 54, 1178.

(12) (a) Evans, D. A.; Bilodeau, M. L.; Somers, J. C.; Gandy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, 56, 5750. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, 114, 2260. (c) Mayonke, B. J.; Lu, Z.; Kyla, D. J. *Tetrahedron Lett.* **1993**, 34, 2255.

(13) (a) Damon, R. E.; Cuppolo, G. M. *Tetrahedron Lett.* **1990**, 31, 2849. (b) Shapiro, G.; Chengzhi, C. *Tetrahedron Lett.* **1992**, 33, 2447.

(14) (a) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. L.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 20, 307. (b) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1992**, 33, 4369.

(15) (a) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, 32, 7165. (b) Dale, J. A.; Dall, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543.

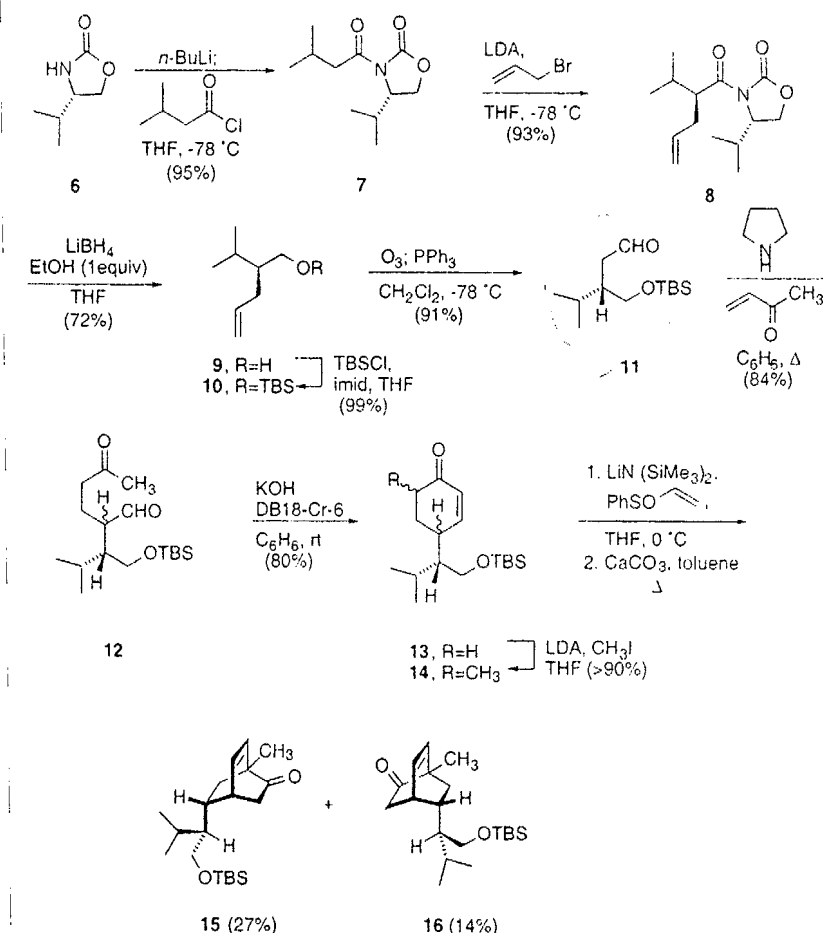
(16) (a) House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, 39, 3102. (b) Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273. (17) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

(18) Burke, S. D.; Muirshaw, C. W.; Saunders, J. O.; Opinger, I. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984**, 106, 4558.

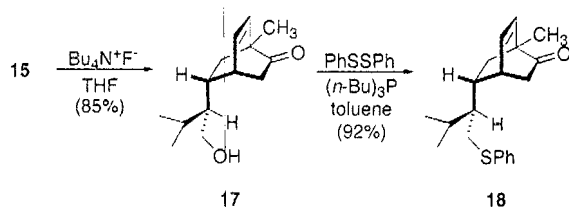
(19) (a) Ihara, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, 25, 3235. (b) For activation of sulfoxide in Diels–Alder reactions, see: Ronan, B.; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, 3, 115. (c) For a review on MIMIRC, see: Posner, G. H. *Chem. Rev.* **1986**, 86, 831. (d) For a review on the intramolecular double Michael reaction, see: Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1010. (e) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, 371. (f) Brown, P. J.; Jones, D. N.; Khan, M. A.; Meanwell, N. A.; Richards, P. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2049. (g) Jones, D. N.; Meanwell, N. A.; Mirza, S. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 145. (h) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1340. (i) Seki, K.; Ohno, T.; Oishi, T.; Ban, Y. *Tetrahedron Lett.* **1975**, 723. (j) Goy, R. M.; Chan, D. M. T. *Tetrahedron Lett.* **1975**, 1441. (k) Goy, R. M.; Chan, D. M.; Nagan, Y. M. A.; Rastan, M. H.; Komersar, K. M. *J. Org. Chem.* **1980**, 45, 1852. (l) Montgomery, T.; Sengul, J. L. *J. Org. Chem.* **1993**, 58, 5470.

(20) (a) Koppel, C. A.; Kinnick, M. D. *J. Org. Chem.* **1975**, 40, 173. (b) Kametani, T.; Yukuwa, H.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 571. (c) De Groot, A.; Jansen, B. J. M.; Keeney, J. T. A.; Tedjo, L. M. *Tetrahedron Lett.* **1981**, 22, 413.

SCHEME 2



SCHEME 3



omeric β,γ unsaturated ketones were conveniently amenable to chromatographic separation.

Deprotection of **15** with TBAF smoothly gave **17** and made possible the ensuing conversion to the phenylthio derivative **18** through the combined action of diphenyl disulfide and tri-*n*-butylphosphine²¹ (Scheme 3). We were now in a good position to examine the possible role of different heteroatomic groups on π -face diastereoselection.

Construction of the Nucleophilic Synthons. A rich collection of *O*-substituted derivatives of methyl (*R*)-2-(hydroxymethyl) propionate has been described in the prior art.²² Of these, **19a–c** were selected for evaluation (Scheme 4). Reduction of these esters with LiAlH_4 or Dibal-H furnished the corresponding alcohols. Subsequent careful oxidation of intermediates **20** under Swern conditions²³ or with the perruthenate reagent²⁴ was implemented without any obvious epimerization. However, stereochemical integrity could not be ensured if the

aldehydes were stored for any extended time period, even at low temperatures. Immediate submission of **21** to the Takai reaction²⁵ was observed to lead almost exclusively to the *E* vinyl iodide **22**. At this point, effort was expended for the purpose of determining the extent of configurational loss during the reaction sequence. To this end, the unstable vinyl iodide **22a** was hydrogenated over plati-

(22) (a) Tsukuda, T.; Kakisawa, H. *Tetrahedron Lett.* **1989**, 30, 4245 (SEM); (b) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, 57, 5207 (Bn); (c) Rinehart, K. L.; Harada, K.-I.; Namikoshi, C. C.; Harris, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, A. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, 110, 8557 (EE); (d) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, 112, 6348 (TBDMS, TBDPS, Bn); (e) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, 37, 3873; (f) Meyers, A. I.; Babick, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Henschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. L.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, 105, 5015; (g) White, J. D.; Angello, J. C.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem.* **1992**, 57, 1270 (SEM); (h) Ruma, D.; Johnson, L. L.; Plamondon, L.; Mwya, T.; Schaeffer, S. L. *J. Org. Chem.* **1992**, 57, 5050 (Bn); (i) See: *Aldrichim. Acta* **1984**, 17, 42; (j) Nagashima, Y.; Kamezawa, M.; Tachibana, H.; Minakata, Y.; Fujita, T.; Kawa, K.; Sakai, T. *J. Chem. Soc., Perkin, Trans. 1* **1993**, 557; (k) Baker, R.; O'Mahony, M.; Swain, C. J. *Tetrahedron Lett.* **1986**, 27, 3079 (TBDPS); (l) Bockman, R. A.; Chavette, A. B.; Asherom, I.; Johnston, B. *J. Am. Chem. Soc.* **1987**, 109, 7553 (MOM); (m) Hori, K.; Hikoguchi, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, L. *J. Org. Chem.* **1992**, 57, 2388; (n) Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, 32, 1749.

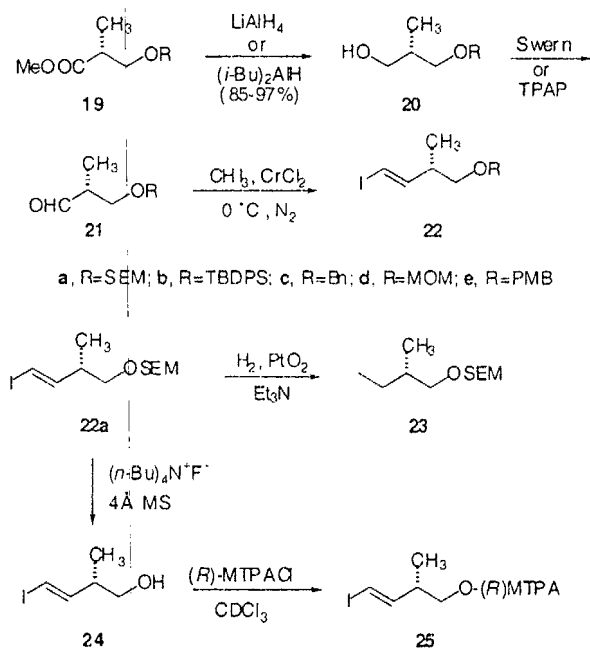
(23) (a) Manerzo, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480; (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, 34, 1651; (c) For this specific example, consult: Shimizu, S.; Nakamura, S.; Nishida, M.; Shibasaki, M. *Tetrahedron* **1996**, 52, 13363.

(24) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

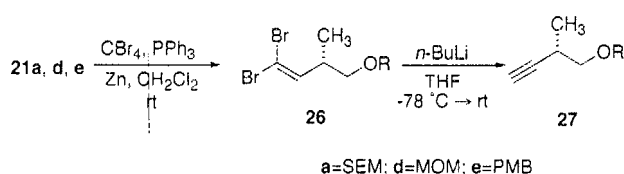
(25) Takai, K.; Nitta, K.; Urimoto, K. *J. Am. Chem. Soc.* **1987**, 109, 951.

(21) (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409; (b) Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, 51, 858.

SCHEME 4



SCHEME 5

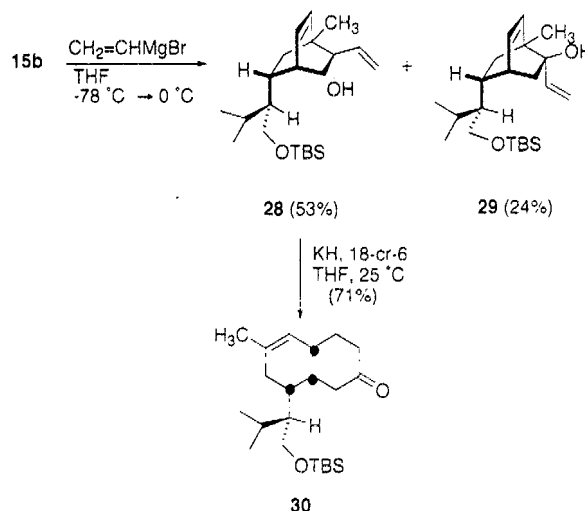


num oxide in the presence of triethylamine.^{26a} This process gave rise to **23**, which was independently prepared from pure (*S*)-(-)-2-methyl-1-butanol.²⁷ Comparison of $[\alpha]_D$ values indicated the enantiomeric excess to be 75%. The same sample of **22a** was treated as well with anhydrous tetra-*n*-butylammonium fluoride at 80 °C under reduced pressure^{26b} to provide alcohol **24**. Mosher ester analysis of **25** by ¹H and ¹⁹F NMR established more reliably that the enantiomeric excess was greater than 90% and therefore suited for further deployment. Parallel behavior was seen with **22b** and **22c**.

To gain greater quantitative appreciation of the stereoselectivity of nucleophilic capture by bicyclic ketones **15** and **18**, the alkynes **27a**, **27d**, and **27e** were also produced (Scheme 5). The Corey–Fuchs procedure²⁸ was selected among several options and found to be satisfactory for our purposes.

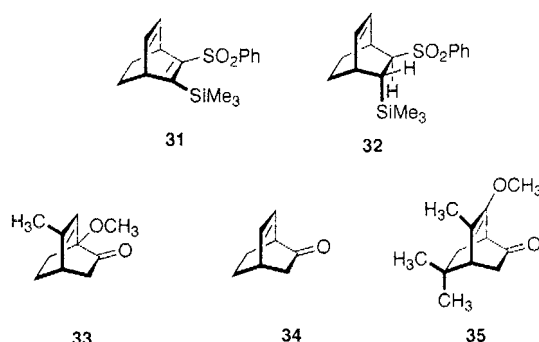
Stereochemical Course of the Coupling Reactions. The ultimate acquisition of **4** requires that 1,2-addition to the carbonyl group in **15** and **18** occur predominantly from the direction syn to the double bond. The consequences of methyl substitution at the proximal bridgehead site and of the endo-oriented side chain on reaction trajectories were not known. Consequently, feasibility studies involving vinylmagnesium bromide were initially undertaken. The conversion to **28** and **29**,

SCHEME 6



realized in anhydrous THF at -78 to 0 °C, proceeded with minimal competing enolization. Column chromatography conveniently separated the less polar **28** (53%) from its more polar counterpart **29** (24%) (Scheme 6). The exo orientation of the vinyl substituent in **28** was easily recognized on the basis of NOE studies. The significant amount of **29** formed under these circumstances was not entirely expected because of the postulate that the bulky group projected to the endo surface might well sterically impede approach from this direction.

The literature precedent in this area is limited and rather disparate. At one extreme such as that involving the conjugate reduction of **31** with LiAlH₄, hydride delivery occurs stereospecifically from the exo direction to give **32**.²⁹ In a related alkylation example, treatment of ketone **33** with LDA and 1-iodobutane produced the exo product (75%), equilibration of which with methanolic sodium hydroxide produced a 73/27 exo:endo mixture.³⁰ Where direct addition to the carbonyl is involved, product ratios are significantly less imbalanced. For example, the coupling of vinylmagnesium bromide to parent ketone **34** gives rise to a 2:1 mixture of the exo adduct and its epimer.³¹ Higher levels of substitution as in **35**, a ketone more structurally allied to **15b**, have little obvious impact on product distribution. The exposure of **35** to 2-lithiodihydropyran has been reported to lead to a 1.5:1 distribution of exo and endo carbinols.³²



(26) (a) Paquette, L. A.; Barrett, J. H.; Spitz, R. P.; Pitcher, R. *J. Am. Chem. Soc.* **1965**, 87, 3417. (b) Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, 109, 3017.

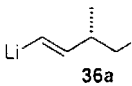
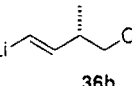
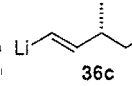
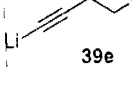
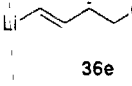
(27) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, 21, 3343.

(28) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, 115, 11393.

(29) (a) Williams, R. V.; Chaudhri, K.; Gadgil, V. R. *J. Chem. Soc. Chem. Commun.* **1994**, 1739. (b) Williams, R. V.; Gadgil, V. R.; Garner, G. G.; Williams, J. D.; Viji, A. *Tetrahedron Lett.* **1999**, 40, 2689.

(30) Kim, D.; Hoog, S. W.; Park, C. W. *J. Chem. Soc. Chem. Commun.* **1997**, 2263.

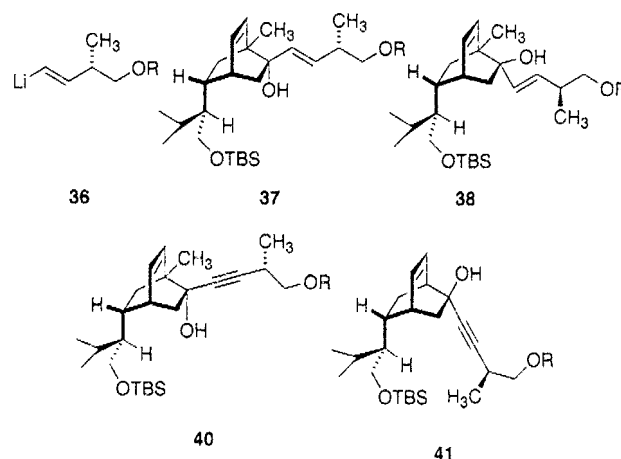
TABLE 1. Stereochemical Course of 1,2-Addition to Bicyclo[2.2.2]octenones **15** and **18** (THF, -78°C)

expt	ketone	organometallic reagent	yield, %	exo/endo ratio
1	15	$\text{CH}_2=\text{CHMgBr}$	77	2.2:1
2	15		72	1:3.5
3	15		73	1:3.6
4	15		93	1:4.8
5	15		47	1:5.7
6	18		58	1:3.5
7	15	27e , $\text{C}_2\text{H}_5\text{MgBr}$, THF	30	1:1.8
8	15	27e , Mg , $\text{Br}-\text{CH}_2\text{CH}_2-\text{Br}$, THF, $15-30^{\circ}\text{C}$, 2 h	33	1.5:1
9	15	22e , $t\text{-BuLi}$; $\text{MgBr}_2\cdot\text{OEt}_2$, ether, $-78^{\circ}\text{C} \rightarrow 0^{\circ}\text{C}$	60	1.9:1
10	15	22e , $t\text{-BuLi}$; $\text{MgBr}_2\cdot\text{OEt}_2$, ether, 0°C , 2 h	83	3.2:1

As a result of the above, we defined as an interim goal a clearer definition of those conditions most conducive to production of the appropriate exo isomers. The compatibility of those structural feature resident in **28** to a potential synthesis of vinigrol was brought to the fore when its sigmatropic rearrangement to **30** was found to occur readily at room temperature in the presence of potassium hydride and 18 crown-6 in tetrahydrofuran.

The ready availability of the lithiated alkenes **36** by metal-halogen exchange involving *tert*-butyllithium in THF at -78°C ³¹ prompted their initial exploitation. Following chromatographic separation of the less polar **37** from the more polar **38**, it was possible to ascertain by NOE analysis that the preferred α -facial stereoselectivity was in fact opposite to that observed with vinyl-magnesium bromide (Table 1). The proportion of **38** varied from 3.5:1 when R was the SEM protecting group to 5.7:1 for the *p*-methoxybenzyl (PMB) derivative. Recourse to HMPA as cosolvent on the basis of its capability to disrupt lithium aggregates³⁴ had no effect

on the isomer distribution. The replacement of THF by ether led to extensive enolization of **15** and **18**, resulting in low-yielding conversion to addition products. The ability of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to influence facial selectivity is well recognized.³⁵ However, the precomplexation of **18** with MAD did not result in a change of product composition at very short exposure times. When reactions were allowed to proceed beyond 20 min at -78°C , extensive decomposition was noted.



Although recourse to the vinyl cerates³⁶ and zincates³⁷ was also ineffective and lithium acetylides afforded no advantage, Grignard reagents proved more ideally suited to preferred exo addition, provided that proper conditions were employed (Table 1, expts 7–10). Although the direct entrainment method involving the metalation of alkyne **27e** with ethylmagnesium bromide in THF failed to give rise to a useful distribution of **40** and **41** (expt 7), significant improvements were noted when sonication of the vinyl iodides in the presence of magnesium metal and 1,2-dibromoethane was utilized (expt 8). More serviceable yet were those conditions involving exposure of the vinyl iodide **22e** to *tert*-butyllithium followed by magnesium bromide etherate (expts 9 and 10). The 3.2:1 exo/endo ratio observed in the last of these experiments accorded us the opportunity to access reasonable quantities of **37e** for the continuation of our studies as discussed in the sequel.

Probe of Possible Cyanohydrin and Enol Ether Alternatives. Although the preceding results proved to be reproducible, we simultaneously probed other possible means for stereocontrolled carbinol synthesis. The alternative interim goal was the construction of α -hydroxy aldehydes of the type **46**, **47**, or **52**, which possess an exo carbonyl group potentially suited to Wittig and related condensations. To this end, **15** was treated with *tert*-butyldimethylsilyl cyanide³⁸ in the presence of a catalytic

(34) Chang, N.-Y.; Day, H. M.; Li, W. F. *J. Org. Chem.* **1989**, 54, 4083.

(35) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, 107, 1672; (b) Hirakawa, T.; Shino, T.; Kato, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 217; (c) Preparation of MAD: Sere, A. J.; Rebois, J. J.; Swerton, J. S. *J. Org. Chem.* **1989**, 54, 1413.

(36) (a) Inamoto, T.; Sagami, Y.; Takayama, N. *Tetrahedron Lett.* **1984**, 25, 4233; (b) Inamoto, T.; Sugiyama, Y. *J. Organomet. Chem.* **1985**, 285, C21; (c) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, 45, 107; (d) Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, 33, 4759.

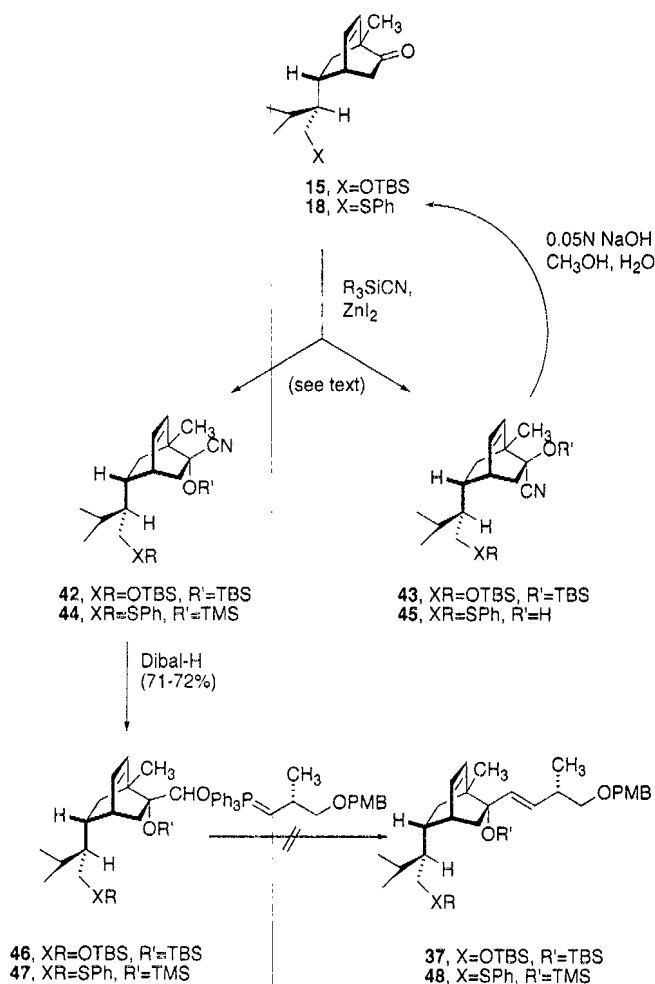
(37) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, 120, 11198.

(31) Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, 86, 5019.

(32) (a) Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, 28, 5441; (b) For a more recent pertinent example, consult: Kim, D.; Shim, P. J.; Lee, J.; Park, C. W.; Hong, S. W.; Kim, S. *J. Org. Chem.* **2000**, 65, 4864.

(33) Evans, D. A.; Thomas, R. C.; Walker, J. A. *Tetrahedron Lett.* **1976**, 1427.

SCHEME 7



amount of zinc iodide. Chromatography on silica gel was necessary to separate the nonpolar adducts **42** and **43**, which were formed quantitatively in a reasonably favorable 2:1 ratio. These isomers were distinguished spectroscopically and on the basis of the readiness with which **43** was converted to **15** in the presence of 0.05 N NaOH in aqueous methanol (Scheme 7).

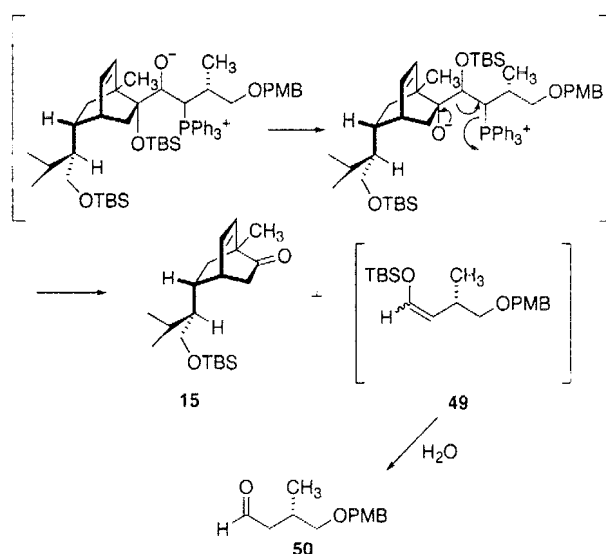
The desired isomer **42** proved inert to these conditions during overnight stirring.

Therefore, the recycling process could, if warranted, be used advantageously to produce exclusively the exo nitrile **42**, the reduction of which to aldehyde **46** with Dibal-H was conveniently accomplished in 72% yield.

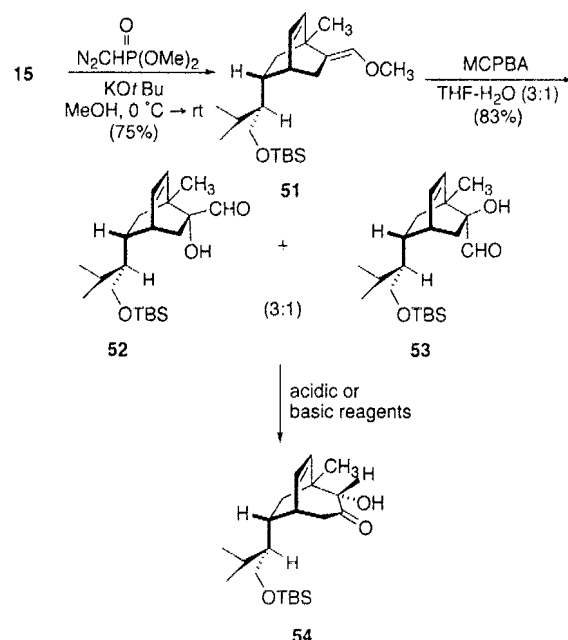
Comparable exposure of **18** to trimethylsilyl cyanide³⁹ gave rise to a less favorable 1.4:1 mixture of **44** and **45**. As expected, these adducts and the derived aldehyde **47** proved to be somewhat more sensitive compounds as a result of the sterically smaller, more reactive nature of the protecting group. The hydrolysis leading to **45** during chromatography is noteworthy.

The attempted homologation of **46** and **47** to **37** and **48**, respectively, proved to be unsuccessful. Neither Wittig methylenation nor Julia olefination⁴⁰ resulted in

SCHEME 8



SCHEME 9



generation of the desired olefin. In the first instance, modest amounts of aldehyde **50** were isolated in addition to the starting ketone **15**. On this basis, it would appear that the mechanistic pathway shown in Scheme 8 may be operative.⁴¹ This fragmentative option results in the expulsion of silyl enol ether **49**, the hydrolysis of which gave rise to **50**.

Our requirements for highly controlled exo orientation of the unsaturated side chain at C-2 of the bicyclooctanol were also met by homologation of **15** to enol ether **51** with dimethyl diazomethylphosphonate⁴² and oxidation of the latter with *m*-chloroperbenzoic acid⁴³ (Scheme 9). These conditions afforded **52** and **53** as a 3:1 mixture in good

(41) Maryanoff, B. F.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(42) Gilbert, J. C.; Weerasooriya, V.; Wiesbauer, B. *Org. Synth. Coll. Vol.* **1980**, *21*, 5003.

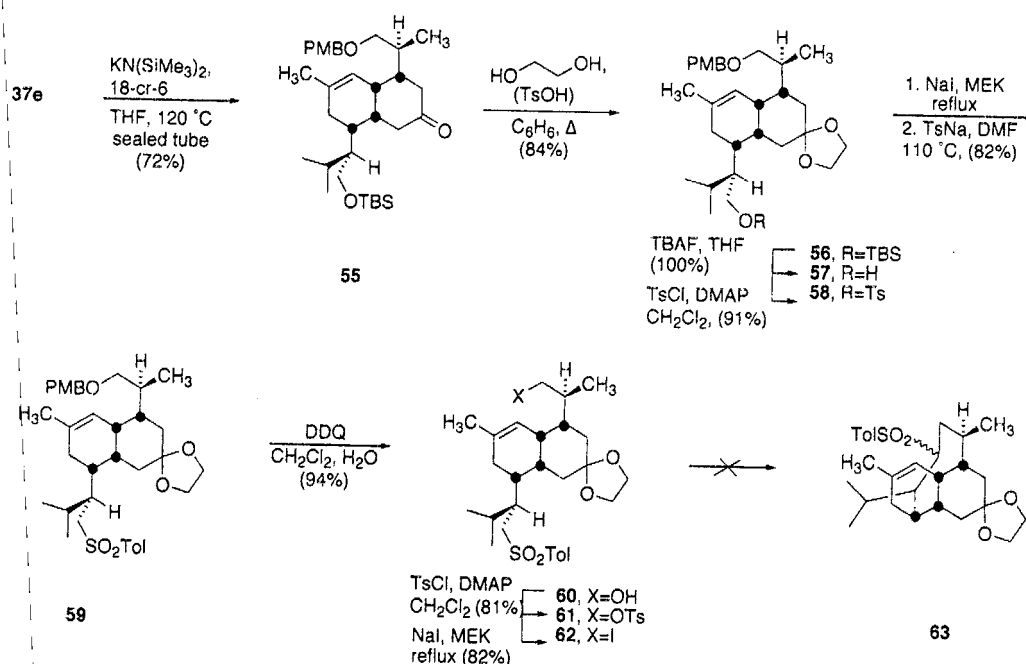
(43) (a) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. (b) Martin, S. F.; Asserq, J. M.; Austin, R. F.; Dattarayana, A. P.; Fishbaugh, J. R.; Gluchowski, C.; Guinn, D. L.; Hartmann, M.; Tanaka, T.; Wagner, R.; White, J. B. *Tetrahedron* **1995**, *51*, 3455.

(38) Narasaka, K.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1991**, 423.

(39) (a) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 581. (b) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

(40) Marko, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089 and relevant references therein.

SCHEME 10



yield. The sensitivity of these compounds to acidic and basic conditions precluded their chromatographic separation. Furthermore, all attempts to protect their tertiary hydroxyl group or to effect chain extension generally resulted in operation of an α -ketol rearrangement to give **54**. This result prompted cessation of this phase of the effort and solidified the stance that further advance would be made via the route defined by experiment 10 in Table 1.

Construction of the Octalin Core. Given the ease with which **28** was noted to undergo oxyanionic sigmatropy to form **30**, the expectation was that **37e** and its congeners would likewise rearrange at or slightly above room temperature. Quite to the contrary, exposure of **37e** to potassium hexamethyldisilazide and 18-crown-6 in THF between -78 and 30 $^\circ\text{C}$ induced only gradual degradation of the carbinol. After considerable experimentation, it was determined that rapid heating of such samples to 120 $^\circ\text{C}$ in sealed tubes for 1 h with subsequent rapid cooling provided **55** in yields exceeding 70% (Scheme 10). That a structurally enforced boatlike transition state had been adopted to set the four contiguous methine hydrogens of the newly crafted octalin ring system in a rigorous all-*cis* relationship was ultimately confirmed by X-ray crystallographic studies (see below).

To develop the functional group array in **55** while simultaneously addressing the unconfirmed stereochemical issues, we chose to venture forward via the acetal **56**. Following temporary masking of the ketone carbonyl in this manner, desilylation was implemented and the hydroxyl group so uncovered was transformed via tosylate **58** to sulfone **59**. A comparable few steps transformed the *p*-methoxybenzyloxy terminated side chain into a primary iodide. These advances made available the highly crystalline substance **62**, single crystal X ray analysis of which confirmed the original stereochemical assumptions while simultaneously defining its solid state conformational features (Figure 1). This rigorous evidence establishes all stereogenic centers to be of the proper vinigrol absolute configuration as a consequence

of their relative relationship to C-17, which was installed in enantiocontrolled fashion. Beyond that, the pair of heavily functionalized side chains are clearly seen to be strongly directed to the equatorial plane. A major consequence of this orientational preference, the origins of which are obviously steric in nature, is to position the incipient nucleophilic center neighboring the sulfone sulfur (viz. C-21) remotely from the electrophilic carbon bonded to iodine (C-15). Although it is quite likely that this conformation of **62** or a closely related variant is also preferentially adopted in solution, no information is available concerning the topological flexibility of this *cis*-octalin. *cis*-Decalins are well recognized to be mobile systems subject to being biased toward one of two chair-chair arrangements depending on the locus of substitution.⁴⁴ In *cis*-octalins, the situation is somewhat more complex since the double bond introduces an added degree of rigidification.

Attempted Tricycle Formation via Intramolecular Nucleophilic Displacement. The next major goal in the synthesis was cyclization to close the eight-membered ring. The various basic reagents that we chose to employ, ranging from potassium hexamethyldisilazide to potassium hydride, proved to be uniformly incapable of generating **63**. Depending on the specific conditions, either unreacted **62** was returned or elimination of HI was seen. Based on these results, it would appear that intramolecular nucleophilic attack is impeded by an inability of the reaction centers to orient themselves properly along the necessary collinear trajectory. We recognize that $\text{S}_{\text{N}}2$ displacement reactions represent perhaps the most stereoelectronically demanding carbon-carbon bond forming reactions. For that reason, recourse to this tactic for medium-ring construction has been most often applied only when favorable low energy conformations are populated.⁴⁵ MM2 transition structures based

(44) *Stereochemistry of Organic Compounds*; Eliel, E. L.; Wilen, S. H.; Mander, L. M., Eds.; John Wiley and Sons: New York, 1994; pp 776-781.

(45) Takahashi, T. *Stud. Nat. Prod. Chem.* **1991**, *8*, 173-204.

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(1.5:1 ratio of 2 diastereoisomers) and 987 mg (20%) of more polar unreacted **13** which can be recycled.

For **14**: IR (neat, cm^{-1}): 1690, 1625, 1480, 1400; ^1H NMR (250 MHz, CDCl_3) δ 7.01 (dd, $J = 10.3, 2.8$ Hz, 1H, minor), 6.90 (dd, $J = 10.2, 2.8$ Hz, 1H, major), 5.91 (m, 1H), 3.67 (m, 2H), 2.80 (m, 1H), 2.55 (m, 1H), 2.10 (m, 1H), 1.84 (m, 2H), 1.50 (m, 1H, major), 1.41 (m, 1H, minor), 1.15 (d, $J = 7$ Hz, 3H, minor), 1.13 (d, $J = 7$ Hz, 3H, major), 0.98 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H, major), 0.94 (d, $J = 6.8$ Hz, 3H, minor), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (62 MHz, CDCl_3) (major diastereoisomer) δ 203.2 (s), 155.1 (d), 127.7 (d), 61.5 (t), 49.8 (d), 39.3 (d), 33.4 (d), 32.1 (t), 27.1 (d), 25.8 (q, 3C), 21.8 (q), 19.9 (q), 18.1 (s), 15.5 (q), -5.6 (q, 2C); (minor isomer) δ 203.0 (s), 154.8 (d), 127.4 (d), 61.0 (t), 49.9 (d), 39.4 (d), 33.7 (t), 32.8 (d), 27.4 (d), 25.8 (q, 3C), 21.6 (q), 19.6 (q), 18.1 (s), 15.6 (q), -5.6 (q, 2C); MS m/z ($\text{M}^+ - \text{CH}_3$) calcd 295.2093, obsd 295.2119.

Anal. Calcd for $\text{C}_{18}\text{H}_{34}\text{O}_2\text{Si}$: C, 69.62; H, 11.04. Found: C, 69.88; H, 11.13.

(1S,4S,8R)-8-[(1R)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (15) and (1R,4R,8S)-8-[(1R)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (16). To a cold (0 °C) solution of hexamethyldisilazane (8.2 mL, 38.9 mmol) in THF (36 mL) was added *n*-butyllithium in hexanes (20.1 mL, 32.2 mmol). After 30 min, **14** (4.0 g, 12.9 mmol) dissolved in dry THF (515 mL) was introduced, and the brownish mixture was stirred at 0 °C for 30 min, treated with phenyl vinyl sulfoxide (4.12 g, 27.1 mmol) in THF (65 mL) via a syringe pump during 3 h at 3–6 °C, and quenched with saturated NH_4Cl solution (40 mL). The aqueous phase was extracted several times with ether, and the combined organic layers were dried and concentrated. The residue was taken up in ether, filtered through a pad of Celite, and concentrated. The residue was dissolved in toluene (40 mL), calcium carbonate (2.6 g, 26 mmol) was added, and the yellow suspension was heated at reflux for 24 h. After filtration of the cooled mixture through a pad of Celite, the filtrate was evaporated and the residue was chromatographed on silica gel (elution with 9% ethyl acetate in hexanes) to give 2.5 g (58%) of a mixture of **15** and **16**. Further purification by MPLC afforded 1.16 g (27%) of pure **15** and 609 mg (14%) of **16**.

For **15**: colorless solid; mp 38–40 °C; IR (neat, cm^{-1}) 1730, 1470, 1415, 1390; ^1H NMR (300 MHz, C_6D_6) δ 6.21 (dd, $J = 8, 7$ Hz, 1H), 5.83 (br d, $J = 8$ Hz, 1H), 3.55 (dd, $J = 10.5, 3$ Hz, 1H), 3.39 (dd, $J = 10.5, 5$ Hz, 1H), 2.48 (m, 1H), 2.01 (dd, $J = 18, 2$ Hz, 1H), 1.88–1.76 (series of m, 2H), 1.67 (septet $\times$ d, $J = 7, 3$ Hz, 1H), 1.59 (dd, $J = 13, 10.5$ Hz, 1H), 1.26 (s, 3H), 1.24 (dd, $J = 13, 6$ Hz, 1H), 0.99 (m, 1H), 0.92 (d, $J = 7$ Hz, 3H), 0.91 (s, 9H), 0.87 (d, $J = 7$ Hz, 3H), 0.00 (s, 6H); ^1H NMR (300 MHz, CDCl_3) δ 6.54 (dd, $J = 7.4, 7.1$ Hz, 1H), 5.83 (d, $J = 7.7$ Hz, 1H), 3.68 (dd, $J = 10.5, 3.5$ Hz, 1H), 3.61 (dd, $J = 10.5, 5$ Hz, 1H), 2.85 (br s, 1H), 2.17 (dd, $J = 18.5, 1.6$ Hz, 1H), 1.90 (ddd, $J = 18.5, 3.3, 1.6$ Hz, 1H), 1.88 (m, 1H), 1.69 (dd, $J = 13.2, 10.5$ Hz, 1H), 1.37 (dd, $J = 13.2, 6$ Hz, 1H), 1.24 (m, 2H), 1.19 (s, 3H), 0.99 (d, $J = 7$ Hz, 3H), 0.90 (d, $J = 7$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.4 (s), 138.4 (d), 133.9 (d), 61.7 (t), 49.3 (s), 48.6 (d), 37.2 (t), 36.3 (d), 34.5 (t), 33.8 (d), 27.9 (d), 26.0 (q, 3C), 21.8 (q), 18.3 (s), 18.1 (q), 17.8 (q), -5.5 (q), -5.6 (q); ^{13}C NMR (75 MHz, CDCl_3) δ 213.5 (s), 138.5 (d), 133.5 (d), 61.6 (t), 49.4 (s), 48.7 (d), 37.1 (t), 36.4 (d), 34.7 (t), 33.6 (d), 27.7 (d), 25.9 (q, 3C), 21.7 (q), 18.1 (s), 17.6 (q), 17.5 (q), -5.5 (q), -5.6 (q); MS m/z (M^+) calcd 336.2485, obsd 336.2481; $[\alpha]_D^{20} -273$ (c 1.35, CHCl_3).

Anal. Calcd for $\text{C}_{20}\text{H}_{36}\text{O}_2\text{Si}$: C, 71.37; H, 10.78. Found: C, 71.56; H, 10.87.

For **16**: IR (neat) 1730, 1470, 1415, 1390; ^1H NMR (300 MHz, C_6D_6) δ 6.33 (dd, $J = 8, 7$ Hz, 1H), 5.66 (br d, $J = 8$ Hz, 1H), 3.46 (dd, $J = 10.5, 3$ Hz, 1H), 3.40 (dd, $J = 10.5, 4.5$ Hz, 1H), 2.89 (m, 1H), 2.30 (dd, $J = 18, 2$ Hz, 1H), 1.96 (ddd, $J = 18, 3.5, 2$ Hz, 1H), 1.77 (m, 1H), 1.57 (septet $\times$ d, $J = 7, 3$ Hz, 1H), 1.12 (dd, $J = 13, 10.5$ Hz, 1H), 1.25 (s, 3H), 1.05 (m, 1H),

1.00 (dd, $J = 13, 6$ Hz, 1H), 0.92 (s, 9H), 0.87 (d, $J = 7$ Hz, 3H), 0.71 (d, $J = 7$ Hz, 3H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.7 (s), 138.9 (d), 133.5 (d), 61.3 (t), 49.2 (d), 49.1 (s), 38.7 (d), 37.0 (t), 34.9 (t), 34.5 (d), 28.5 (d), 25.9 (q, 3C), 22.4 (q), 18.2 (s), 18.1 (q), 17.1 (q), -5.3 (q), -5.6 (q); MS m/z (M^+) calcd 336.2485, obsd 336.2482; $[\alpha]_D^{20} +278$ (c 1.1, CHCl_3).

Anal. Calcd for $\text{C}_{20}\text{H}_{36}\text{O}_2\text{Si}$: C, 71.37; H, 10.78. Found: C, 71.51; H, 10.78.

(1S,4S,8R)-8-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (17). To a solution of **15** (200 mg, 0.6 mmol) in THF (20 mL) was added at 0 °C a 1 M solution of TBAF in THF (1.4 mL, 1.4 mmol). After being stirred at 0 °C for 5 h and at rt for 10 h, the reaction mixture was treated with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with ether (5 $\times$ 60 mL) and the combined organic layers were dried. Purification of the residue by chromatography (Florisil, elution with 10% ethyl acetate in petroleum ether) gave 113 mg (85%) of **17** as a colorless oil; IR (neat, cm^{-1}) 3416 (br), 1714, 1616, 1453; ^1H NMR (300 MHz, C_6D_6) δ 6.19 (dd, $J = 8, 7$ Hz, 1H), 5.63 (br d, $J = 8$ Hz, 1H), 3.35 (m, 2H), 2.44 (m, 1H), 1.99 (br d, $J = 18$ Hz, 1H), 1.76 (br d, $J = 18$ Hz, 1H), 1.64 (m, 2H), 1.47 (dd, $J = 13, 10.5$ Hz, 1H), 1.23 (br s, 1H), 1.22 (s, 3H), 1.15 (dd, $J = 13, 6$ Hz, 1H), 0.91 (d, $J = 7$ Hz, 3H), 0.91 (m, 1H), 0.80 (d, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 211.3 (s), 138.4 (d), 133.8 (d), 61.5 (t), 49.3 (s), 19.0 (d), 37.1 (t), 36.6 (d), 34.5 (t), 33.8 (d), 27.8 (d), 21.7 (q), 18.0 (q), 17.5 (q); MS m/z (M^+) calcd 222.1620, obsd 222.1619.

Anal. Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 75.63; H, 10.03. Found: C, 75.84; H, 10.03.

(1S,4S,8R)-8-[(1R)-1-(Phenylthiomethyl)-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-one (18). A solution of **17** (500 mg, 2.25 mmol) and diphenyl disulfide (970 mg, 4.44 mmol) in toluene (5 mL) was treated with tri-*n*-butylphosphine (1.1 mL, 4.4 mmol) stirred overnight at rt, and directly charged onto a column of silica gel. Elution with 0–10% of ethyl acetate in hexanes gave **18** (650 mg, 92%) as a white solid; mp 82.5–83.5 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.32–7.24 (m, 4H), 7.19–7.14 (m, 1H), 6.53 (t, $J = 7.4$ Hz, 1H), 5.83 (d, $J = 7.4$ Hz, 1H), 2.95 (dd, $J = 5.7, 12.4$ Hz, 1H), 2.89 (m, 1H), 2.82 (ddd, $J = 1.0, 3.6, 12.4$ Hz, 1H), 2.17 (ddd, $J = 1.0, 1.7, 18.5$ Hz, 1H), 2.11–1.80 (m, 3H), 1.69–1.49 (m, 1H), 1.40–1.35 (m, 2H), 1.18 (s, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 212.8, 138.2, 137.7, 133.7, 129.3 (2C), 128.8 (2C), 126.0, 49.2, 46.9, 39.6, 37.0, 34.5, 33.9 (2C), 28.4, 21.0, 17.5, 16.9; MS m/z (M^+) calcd 346.1780, obsd 346.1768; $[\alpha]_D^{20} +303$ (c 6.6, CHCl_3).

Anal. Calcd for $\text{C}_{26}\text{H}_{30}\text{OS}$: C, 76.38; H, 8.33. Found: C, 76.34; H, 8.37.

Methyl (2R)-3-(*p*-Methoxybenzyloxy)-2-methylpropionate (19c). To an ice cold suspension of sodium hydride (500 mg, 20 mmol) in dry ether (25 mL) was added dropwise a solution of *p*-methoxybenzyl alcohol (25 g, 0.20 mol) in dry ether (40 mL) over a 15 min period. After an additional 30 min, trichloroacetonitrile (19 mL, 0.89 mol) was introduced dropwise at ice-bath temperature. The mixture was stirred overnight and concentrated to leave the imidate as an oil (46.4 g, 90%).

To a mixture of methyl (*R*)-2-(hydroxymethyl)propionate (10.0 g, 0.085 mol) and the freshly prepared imidate (16 g, 0.16 mol, CH_2Cl_2) (20 mL) and petroleum ether (40 mL) was added at 0 °C a solution of triflic acid (0.024 mL, 0.094 mmol) in CH_2Cl_2 (2 mL) under N_2 . The reaction mixture was stirred for 30 min at rt, diluted with ice water, and filtered with the aid of hexanes, and the combined organic phases were washed with brine, dried and evaporated. Purification by chromatography on silica gel gave **19c** (9.6 g, 47%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.12 (d, $J = 9.0$ Hz, 2H), 6.76 (d, $J = 9.0$ Hz, 2H), 4.34 (s, 2H), 3.69 (s, 3H), 3.57 (s, 3H), 3.52 (dd, $J = 9.1, 7.4$ Hz, 1H), 3.35 (dd, $J = 9.1, 5.9$ Hz, 1H), 2.67 (ddd, $J = 7.4, 7.1, 5.9$ Hz, 1H), 1.06 (d, $J = 7.1$ Hz, 3H).

p-Methoxybenzyl (2S,3E)-4-Iodo-2-methyl-3-butenyl Ether (22e). A cold (-78°C) solution of **19e** (480 mg, 2.01 mmol) in dry ether (10 mL) was treated dropwise with a solution of diisobutylaluminum hydride in hexanes (2.1 mL of 1 M, 2.1 mmol), stirred at -78°C for 1.5 h, quenched with saturated NH_4Cl solution, and allowed to warm to rt. The product was extracted into ethyl acetate, the combined organic layers were washed with brine, dried, and evaporated, and the residual aldehyde (420 mg) was used immediately.

To a cold (0°C) suspension of dry chromium(II) chloride (1.4 g) in anhydrous THF (10 mL) and dioxane (4 mL) was added dropwise a solution of the above aldehyde and iodoform (1.5 g, 3.8 mmol) in dry THF (8 mL). The reaction mixture was stirred at 0°C for 1 h and at rt for 4 h prior to being quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and concentrated. Purification of the residue on silica gel (elution with 0–3% ethyl acetate in hexanes) gave 322 mg (42% over two steps) of **22e** as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.23 (d, $J = 8.9$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 6.51 (dd, $J = 7.4, 14.5$ Hz, 1H), 6.08 (d, $J = 14.5$ Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.30 (m, 2H), 2.50 (m, 1H), 1.02 (d, $J = 6.9$ Hz, 3H); MS m/z (M^+) calcd 332.0273, obsd 332.0266; $[\alpha]_D^{20} -4.2$ (c 0.17, CHCl_3).

(1S,2S,4S,8R)-2-[(1E,3S)-4-(p-Methoxybenzyloxy)-3-methyl-1-butenyl]-8-[(1R)-1-[(tert-butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-ol (37e) and (1S,2R,4S,8R)-2-[(1E,3S)-4-(4-Methoxybenzyloxy)-3-methyl-1-butenyl]-8-[(1R)-1-[(tert-butyldimethylsiloxy)methyl]-2-methylpropyl]-1-methylbicyclo[2.2.2]oct-5-en-2-ol (38e). **A. By Barbier-Type Reaction.** A mixture of magnesium turnings (270 mg, 0.81 mmol), 1,2-dibromoethane (0.03 mL, 0.35 mmol), **22e** (270 mg, 0.81 mmol), and **15** (95 mg, 0.28 mmol) in dry THF (3 mL) was sonicated for 2 h at 15 – 20°C . After being cooled to 0°C , the reaction mixture was quenched with saturated NH_4Cl solution (1 mL) and diluted with ether. The organic phase washed with brine, dried, and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 5% ethyl acetate in hexanes) to give 31 mg (20%) of **37e** and 20 mg (13%) of **38e**.

For **37e**: colorless oil; IR (CHCl_3 , cm^{-1}) 3400, 1627, 1439; ^1H NMR (300 MHz, C_6D_6) δ 7.28 (d, $J = 6.8$ Hz, 2H), 6.81 (d, $J = 6.8$ Hz, 2H), 6.27 (dd, $J = 8.0, 7.1$ Hz, 1H), 5.88 (d, $J = 8.0$ Hz, 1H), 5.58 (m, 2H), 4.31 (br s, 2H), 3.76 (dd, $J = 10.5, 2.5$ Hz, 1H), 3.72 (dd, $J = 10.5, 4.1$ Hz, 1H), 3.32 (s, 3H), 3.28 (m, 1H), 3.20 (m, 1H), 2.51 (br q, $J = 6.0$ Hz, 1H), 2.42 (br s, 1H), 2.02 (dd, $J = 13, 4.5$ Hz, 1H), 1.87 (m, 1H), 1.75 (m, 2H), 1.55 (ddd, $J = 13, 2.1, 1.3$ Hz, 1H), 1.40–1.20 (m, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.06 (d, $J = 6.3$ Hz, 3H), 1.02 (s, 3H), 0.96 (s, 9H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.4 (s), 138.4 (s), 138.1 (d), 135.8 (d), 129.0 (s), 128.7 (d, 2C), 127.4 (d), 113.7 (d, 2C), 77.2 (s), 75.2 (t), 72.6 (t), 62.3 (t), 54.4 (d), 47.7 (d), 41.9 (s), 38.0 (t), 36.9 (d), 36.1 (d), 34.0 (u), 32.7 (d), 27.9 (d), 25.6 (q, 3C), 21.8 (q), 18.9 (q), 18.4 (s), 17.5 (q), 17.4 (q), -5.5 (q), -5.7 (q); MS m/z ($\text{M}^+ - \text{C}_8\text{H}_9\text{O}$) calcd 421.3138, obsd 421.3128; $[\alpha]_D^{20} -71$ (c 1.8, CHCl_3).

Anal. Calcd for $\text{C}_{33}\text{H}_{44}\text{O}_5\text{Si}$: C, 73.01; H, 10.03. Found: C, 72.93; H, 10.07.

For **38e**: colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 6.55 (t, $J = 8.4$ Hz, 1H), 5.90 (d, $J = 8.4$ Hz, 1H), 5.63 (m, 2H), 3.62 (dd, $J = 6.9, 2.1$ Hz, 1H), 3.51 (dd, $J = 6.8, 3.1$ Hz, 1H), 3.39 (dd, $J = 8.1, 4.1$ Hz, 1H), 2.55 (br s, 1H), 2.41 (m, 1H), 1.85 (m, 3H), 1.55 (m, 1H), 1.26–1.20 (m, 1H), 1.21 (br s, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.88 (2s, 18H), 0.81 (d, $J = 7.1$ Hz, 3H), 0.05 (4s, 12H); MS m/z ($\text{M}^+ - \text{C}_8\text{H}_9\text{O}$) calcd 421.3138, obsd 421.3142.

B. Use of Magnesium Bromide Etherate at -78°C to 0°C . A cold (-78°C) solution of **22e** (186 mg, 0.56 mmol) in dry ether (3 mL) was treated with *tert*-butyllithium (0.75 mL of 1.7 M in pentane, 1.28 mmol) until a pale yellow color

appeared. After 10 min of stirring, magnesium bromide etherate (excess) and a solution of **15** (95 mg, 0.28 mmol) were introduced at this temperature, and the reaction mixture was allowed to warm to 0°C over 2 h. After the reaction mixture was quenched with saturated NH_4Cl solution (1 mL), the mixture was diluted with ether, and the organic phase was washed with brine, dried, and concentrated. Chromatography of the residue as above afforded 60 mg (39%) of **37e** and 32 mg (21%) of **38e**.

C. Use of Magnesium Bromide Etherate at 0°C . A cold (-78°C) solution of **22e** (101 mg, 0.30 mmol) in dry ether (2 mL) was treated with *tert*-butyllithium (0.4 mL of 1.7 M in pentane, 0.68 mmol) until a pale yellow color appeared. After 10 min of stirring, magnesium bromide etherate (excess) was introduced at this temperature and the reaction mixture was warmed directly to 0°C , stirred for 20 min, and treated with a solution of **15** (51 mg, 0.15 mmol) in THF (2 mL). After 2 h of stirring at 0°C , the above workup was applied, and there was isolated 52 mg (63%) of **37e** and 16 mg (20%) of **38e**.

Compound 55. To a cold (0°C) solution of **37e** (177 mg, 0.326 mmol) and 18-crown-6 (86 mg, 0.33 mmol) in dry THF (6 mL) was added potassium hexamethyldisilazide (2 mL of 0.5 M in toluene, 1 mmol). After being stirred for 5 min at 0°C , the yellowish mixture was directly heated at 120°C for 1 h in a sealed tube, returned to 0°C , quenched with saturated NH_4Cl solution, and diluted with ether. The organic phase was washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 8:1 ether/hexanes) to give 127 mg (72%) of **55**: colorless oil; IR (neat, cm^{-1}) 1710, 1510, 1460; ^1H NMR (300 MHz, CDCl_3) δ 7.24 (br d, $J = 8.6$ Hz, 2H), 6.86 (br d, $J = 8.6$ Hz, 2H), 5.35 (br s, 1H), 4.47 (d, $J = 11.6$ Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 3.79 (s, 3H), 3.69–3.62 (m, 2H), 3.48 (dd, $J = 9.1, 3.7$ Hz, 1H), 3.38 (dd, $J = 9.0, 6.2$ Hz, 1H), 2.61 (br s, 1H), 2.31 (br d, $J = 11.6$ Hz, 1H), 2.20–2.02 (m, 6H), 1.94–1.70 (m, 4H), 1.70 (br s, 3H), 1.12–1.07 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.05 (br s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 212.7, 159.1, 136.9, 130.7, 129.0 (2C), 118.1, 113.7 (2C), 73.1, 72.8, 60.4, 55.2, 46.7, 43.7, 41.5, 38.2, 37.3, 37.0, 36.6, 34.7, 32.1, 26.7, 25.9 (3C), 23.7, 21.7, 18.1, 17.5, 16.2, -5.5 , -5.7 ; MS m/z ($\text{M}^+ - \text{CH}_3$) calcd 527.3557, obsd 527.3536; $[\alpha]_D^{20} +5.9$ (c 1.60, CHCl_3).

Compound 56. A solution of **55** (185 mg, 0.34 mmol), ethylene glycol (0.38 mL, 6.8 mmol), and *p*-toluenesulfonic acid (19 mg, 0.1 mmol) in benzene (4 mL) was refluxed for 4 h under a Dean–Stark trap, cooled to rt, and quenched with saturated NaHCO_3 solution. After dilution with ether, the organic phase was washed with additional bicarbonate solution, dried, and evaporated. Chromatography of the residue on silica gel (elution with 10:1 hexanes/ethyl acetate) afforded 168 mg (84%) of **56**: colorless oil; IR (neat, cm^{-1}) 1610, 1510, 1450; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (br d, $J = 8.4$ Hz, 2H), 6.86 (br d, $J = 8.3$ Hz, 2H), 5.22 (br s, 1H), 4.47 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 3.93 (br s, 4H), 3.80 (s, 3H), 3.70–3.60 (m, 2H), 3.51 (dd, $J = 9.0, 3.5$ Hz, 1H), 3.32–3.26 (m, 1H), 2.40 (br s, 1H), 2.09–1.91 (m, 4H), 1.84–1.58 (m, 4H), 1.64 (br s, 3H), 1.43–1.16 (m, 4H), 1.05 (d, $J = 6.5$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.89 (br s, 9H), 0.88 (d, $J = 7.0$ Hz, 3H), 0.05 (br s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 135.9, 131.0, 129.0 (2C), 118.7, 113.6 (2C), 109.9, 73.5, 72.6, 64.1, 63.9, 60.9, 55.2, 46.9, 40.8, 38.1, 36.4, 34.5, 34.2, 34.0, 32.6, 29.3, 26.7, 25.9 (3C), 23.7, 21.6, 18.1, 17.8, 16.4, -5.5 , -5.6 ; MS m/z (M^+) calcd 586.4054, obsd 586.4023; $[\alpha]_D^{20} +10.2$ (c 1.40, CHCl_3).

Compound 57. A solution of **56** (54 mg, 0.092 mmol) in dry THF (4 mL) was treated with a 1 M solution of TBAF in THF (0.28 mL, 0.28 mmol), stirred at rt for 14 h, diluted with hexanes, and filtered through a short plug of silica gel. The evaporated filtrate was purified by chromatography (silica gel, elution with 2:1 hexanes/ethyl acetate) to give **57** (43 mg, 100%) as a colorless oil; IR (neat, cm^{-1}) 3420, 1600, 1500, 1430; ^1H NMR (300 MHz, CDCl_3) δ 7.24 (br d, $J = 8.4$ Hz, 2H), 6.85

(br d, $J = 8.6$ Hz, 2H), 5.21 (br s, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.37 (d, $J = 11.7$ Hz, 1H), 3.91 (br s, 4H), 3.79 (s, 3H), 3.77–3.67 (m, 2H), 3.49 (dd, $J = 9.0$, 3.6 Hz, 1H), 3.28 (dd, $J = 9.0$, 7.1 Hz, 1H), 2.37 (br s, 1H), 2.11–1.83 (m, 4H), 1.82–1.57 (m, 4H), 1.64 (br s, 3H), 1.43–1.18 (m, 5H), 1.02 (d, $J = 6.5$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 135.6, 130.9, 129.0 (2C), 118.9, 113.6 (2C), 109.8, 73.3, 72.6, 64.2, 63.9, 61.2, 55.2, 47.4, 40.7, 38.0, 36.5, 34.5, 34.1, 34.0, 32.7, 29.2, 26.5, 23.7, 21.6, 17.7, 16.4; MS m/z ($\text{M}^+ + \text{H}$) calcd 473.3267, obsd 473.3285; $[\alpha]_D^{25} +7.6$ (c 1.53, CHCl_3).

Compound 58. To a stirred solution of **57** (43 mg, 0.091 mmol) and DMAP (67 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) was added *p*-toluenesulfonyl chloride (52 mg, 0.27 mmol), and the mixture was stirred overnight at rt, quenched with saturated NaHCO_3 solution, and extracted with ether. The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 2.5:1 hexanes/ethyl acetate gave 52 mg (91%) of tosylate as a colorless gum: IR (neat, cm^{-1}) 1590, 1505, 1440, 1350; ^1H NMR (300 MHz, CDCl_3) δ 7.79 (br d, $J = 8.2$ Hz, 2H), 7.34 (br d, $J = 8.1$ Hz, 2H), 7.24 (br d, $J = 8.5$ Hz, 2H), 6.86 (br d, $J = 8.6$ Hz, 2H), 5.18 (br s, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.23 (d, $J = 11.7$ Hz, 1H), 4.09–3.29 (series of m, 2H), 3.89 (br s, 4H), 3.79 (s, 3H), 3.47 (dd, $J = 9.0$, 3.5 Hz, 1H), 3.26 (dd, $J = 8.8$, 7.2 Hz, 1H), 2.45 (s, 3H), 2.34 (br s, 1H), 2.00–1.80 (m, 3H), 1.76–1.48 (m, 5H), 1.54 (br s, 3H), 1.43–1.15 (m, 4H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 144.7, 135.0, 132.9, 130.8, 129.8 (2C), 129.0 (2C), 128.0 (2C), 119.0, 113.6 (2C), 109.6, 73.2, 72.6, 68.9, 64.1, 63.9, 55.2, 44.6, 40.6, 37.8, 35.9, 34.4, 34.0, 33.6, 32.1, 29.1, 26.2, 23.4, 21.6, 21.2, 17.2, 16.3; MS m/z ($\text{M}^+ - \text{CH}_3$) calcd 611.3043, obsd 611.3054; $[\alpha]_D^{25} +9.2$ (c 2.43, CHCl_3).

Compound 59. A mixture of **58** (52 mg, 0.083 mmol) and sodium iodide (24 mg, 0.83 mmol) in methyl ethyl ketone (5 mL) was refluxed for 1.5 h under N_2 , cooled to rt, diluted with ether, and washed with saturated sodium thiosulfate solution. The organic phase was dried and evaporated. The residue was taken up in DMF (4 mL), treated with sodium *p*-toluenesulfonate (148 mg, 0.83 mmol), and heated at 110 °C for 11 h. The cooled reaction mixture was diluted with ether and washed with brine. The aqueous phase was extracted with ether, and the combined organic layers were dried and concentrated. Purification of the product was accomplished by flash chromatography on silica gel (elution with 3:1 hexanes/ethyl acetate) to furnish 42 mg (82%) of **59** as a colorless gum: IR (neat, cm^{-1}) 1590, 1460, 1440; ^1H NMR (300 MHz, CDCl_3) δ 7.79 (br d, $J = 8.2$ Hz, 2H), 7.35 (br d, $J = 8.0$ Hz, 2H), 7.25 (br d, $J = 8.9$ Hz, 2H), 6.86 (br d, $J = 8.6$ Hz, 2H), 5.16 (br s, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.35 (d, $J = 11.7$ Hz, 1H), 3.95–3.86 (m, 4H), 3.78 (br s, 3H), 3.45 (dd, $J = 9.0$, 3.5 Hz, 1H), 3.25 (dd, $J = 8.9$, 7.0 Hz, 1H), 3.07 (dd, $J = 15.2$, 4.3 Hz, 1H), 2.86 (dd, $J = 15.2$, 3.7 Hz, 1H), 2.44 (s, 3H), 2.34 (br s, 1H), 2.13–2.04 (m, 1H), 1.93–1.90 (m, 2H), 1.80–1.49 (m, 5H), 1.54 (br s, 3H), 1.46–1.17 (m, 4H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.73 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 144.5, 137.6, 135.3, 130.8, 129.8 (2C), 129.0 (2C), 128.2 (2C), 118.8, 113.6 (2C), 109.5, 73.3, 72.6, 64.2, 64.0, 56.4, 55.2, 40.6, 40.01, 39.96, 38.1, 34.6, 34.4, 34.0, 32.5, 29.0, 27.1, 23.5, 21.5, 20.4, 16.3, 16.2; MS m/z (M^+) calcd 610.3328, obsd 610.3292; $[\alpha]_D^{25} +1.1$ (c 2.00, CHCl_3).

Compound 60. A mixture of **59** (42 mg, 0.069 mmol) and DDQ (23 mg, 0.1 mmol) in 18:1 $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (4 mL) was stirred at rt for 1.5 h, quenched with saturated NaHCO_3 solution, and diluted with ether. The aqueous phase was extracted with ether, and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (silica gel, elution with 1:1 hexanes/ethyl acetate) to provide 32 mg (94%) of **60** as a colorless gum: IR (neat, cm^{-1}) 3460, 1590, 1370; ^1H NMR (300 MHz, CDCl_3) δ 7.88 (br d,

$J = 8.3$ Hz, 2H), 7.35 (br d, $J = 8.2$ Hz, 2H), 5.18 (br s, 1H), 3.95–3.91 (m, 4H), 3.67 (dd, $J = 10.6$, 3.3 Hz, 1H), 3.47 (dd, $J = 10.5$, 6.0 Hz, 1H), 3.06 (dd, $J = 15.2$, 4.4 Hz, 1H), 2.85 (dd, $J = 15.2$, 3.8 Hz, 1H), 2.67 (d, $J = 8.7$ Hz, 2H), 2.44 (s, 3H), 2.35 (br s, 1H), 2.09–1.96 (m, 1H), 1.95–1.90 (m, 2H), 1.78–1.52 (m, 5H), 1.55 (s, 3H), 1.30–1.20 (m, 3H), 0.99 (d, $J = 6.2$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.5, 137.6, 135.8, 129.8 (2C), 128.2 (2C), 118.5, 109.5, 65.9, 64.2, 64.0, 56.4, 40.1, 40.0, 39.9, 38.1, 35.8, 34.7, 34.5, 32.5, 28.9, 27.1, 23.5, 21.6, 20.5, 16.2, 15.6; MS m/z (M^+) calcd 190.2753, obsd 190.2754; $[\alpha]_D^{25} -4.1$ (c 1.78, CHCl_3).

Compound 61. To a mixture of **60** (32 mg, 0.065 mmol) and DMAP (48 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added *p*-toluenesulfonyl chloride (37 mg, 0.19 mmol). After being stirred overnight at rt, the reaction mixture was quenched with saturated NaHCO_3 solution and extracted with ether. The combined organic layers were dried and concentrated to leave a residue that was purified by flash chromatography (silica gel, elution with 2.5:1 hexanes/ethyl acetate). There was isolated 34 mg (81%) of **61** as a colorless gum: IR (neat, cm^{-1}) 1590, 1440, 1340; ^1H NMR (300 MHz, CDCl_3) δ 7.79 (br d, $J = 8.3$ Hz, 2H), 7.75 (br d, $J = 8.4$ Hz, 2H), 7.35 (br d, $J = 8.1$ Hz, 2H), 7.31 (br d, $J = 8.1$ Hz, 2H), 4.98 (br s, 1H), 4.05 (dd, $J = 9.4$, 3.4 Hz, 1H), 3.93–3.85 (m, 5H), 3.97 (dd, $J = 15.2$, 4.3 Hz, 1H), 2.84 (dd, $J = 15.0$, 3.7 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.18 (br s, 1H), 2.04–1.96 (m, 1H), 1.94–1.67 (m, 4H), 1.66–1.47 (m, 3H), 1.53 (br s, 3H), 1.17–1.14 (m, 4H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.6, 144.5, 137.6, 136.4, 133.1, 129.9 (2C), 129.7 (2C), 128.2 (2C), 127.9 (2C), 117.5, 109.2, 73.2, 64.2, 64.1, 56.3, 39.93, 39.89, 39.82, 37.7, 34.5, 34.3, 33.3, 32.5, 28.9, 27.1, 23.5, 21.61, 21.57, 20.4, 16.2, 15.6; MS m/z (M^+) calcd 644.2841, obsd 644.2863; $[\alpha]_D^{25} -1.3$ (c 2.49, CHCl_3).

Compound 62. A mixture of **61** (42 mg, 0.019 mmol) and sodium iodide (28 mg, 0.19 mmol) in methyl ethyl ketone (3 mL) was heated at reflux temperature for 1.5 h, cooled to rt, diluted with ether, and washed with saturated sodium thiosulfate solution. The organic phase was dried and evaporated, and the residue was purified by flash chromatography (silica gel, elution with 4:1 hexanes/ethyl acetate) to furnish 9 mg (82%) of **62** as a white solid: mp 193 °C; IR (neat, cm^{-1}) 1580, 1420, 1360; ^1H NMR (300 MHz, CDCl_3) δ 7.80 (br d, $J = 8.2$ Hz, 2H), 7.36 (br d, $J = 8.0$ Hz, 2H), 5.10 (br s, 1H), 3.94 (br s, 4H), 3.34 (dd, $J = 9.8$, 2.6 Hz, 1H), 3.22 (dd, $J = 9.7$, 5.2 Hz, 1H), 3.08 (dd, $J = 15.2$, 4.3 Hz, 1H), 2.86 (dd, $J = 15.1$, 3.8 Hz, 1H), 2.45 (s, 3H), 2.38 (br s, 1H), 2.15–1.90 (m, 3H), 1.84–1.50 (m, 5H), 1.58 (br s, 3H), 1.46–1.20 (m, 4H), 1.01 (d, $J = 6.3$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.5, 137.7, 136.6, 129.9 (2C), 128.2 (2C), 117.6, 109.4, 64.3, 64.1, 56.4, 42.6, 40.04, 39.96, 37.5, 34.4, 34.3, 33.5, 32.6, 28.9, 27.2, 23.5, 21.6, 20.4, 19.7, 17.5, 16.2; MS m/z (M^+) calcd 600.1770, obsd 600.1761; $[\alpha]_D^{25} +7.6$ (c 0.87, CHCl_3).

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Supporting Information Available: Experimental details for those compounds not involved in the direct route to **62**, tables of the X-ray crystal data, atomic coordinates, and equivalent isotropic displacement parameters, and positional parameters for the hydrogen atoms of **62**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 411 PRESENTACION Folios: 302

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2008/000066

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE (71)

Nombre: NOVARTIS AGDirección: Lichtstrasse 35, CH-4056 BaselNacionalidad o Domicilio: SuizaLugar de Constitución: Suiza

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE APODERADO

Nombre: CARLOS R. OLARTEDirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10Teléfono: 601-7700 Fax: 601-7799E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTADirección: VER PAGINA ADJUNTANacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2006/009970 Fecha Octubre 16, 2006Publicación Internacional No. WO 2007/045420 Fecha Abril 26, 2007

6

Título (54) DERIVADOS DE 3-ALQUIL-5-(4-ALQUIL-5-OXO-TETRAHIDROFURAN-2-IL)-
PIRROLIDIN-2-ONA COMO INTERMEDIARIOS EN LA SINTESIS DE INHIBIDORES DE
RENINA**Clasificación Internacional (51)** C07D 405/04, C07D 207/26, C07D 307/32, C07F 1/02

Prioridad

(33) País de Origen

GB

(32) Fecha

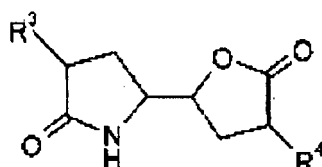
Octubre 17, 2005

(31) Número de Solicitud

0521083.6

CAPITULO REIVINDICATORIO MODIFICADO

1. Un compuesto de la Fórmula (II):



(II)

en donde:

R^3 es alquilo de 1 a 7 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono; y

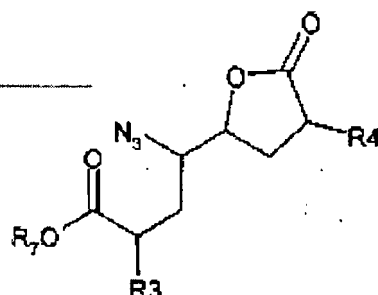
R^4 es alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, fenil- o naftil-alquilo de 1 a 4 átomos de carbono, cada uno insustituido o mono-, di-, o tri-sustituido por alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, OH, alquilo de 1 a 4 átomos de carbono-amino, di-alquilo de 1 a 4 átomos de carbono-amino, halógeno, y/o por trifluoro-metilo;

o una sal del mismo.

2. El compuesto de acuerdo con la reivindicación 1, en donde R^3 y R^4 son independientemente alquilo de 3 a 6 átomos de carbono ramificado.

3. El compuesto de acuerdo con la reivindicación 1 ó 2, el cual tiene la siguiente estereoquímica:

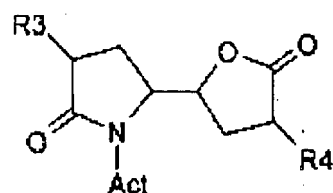




(V)

en donde R³ y R⁴ son como se definen para un compuesto de la Fórmula (II), y R⁷ es alquilo de 1 a 7 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono, o una sal del mismo; seguido por hidrogenación para convertir la fracción de azida hasta una amina, y para efectuar el cierre del anillo de lactama.

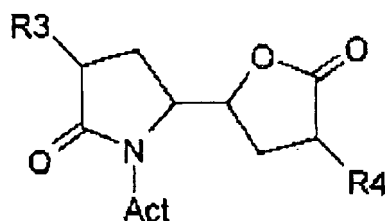
13. Un método para la preparación de un compuesto de la Fórmula (VI):



(VI)

en donde R³ y R⁴ son como se definen para un compuesto de la Fórmula (II), y Act es un grupo activador seleccionado a partir de un grupo protector de amino, en particular un carbamato, o una sal del mismo; que comprende introducir el grupo activador en el nitrógeno de un compuesto de la Fórmula (II), como se da en cualquiera de las reivindicaciones 1 a 4, o una sal del mismo.

14. Un compuesto de la Fórmula (VI):



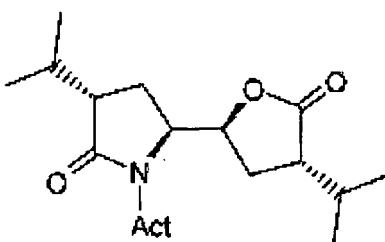
R^3 es alquilo de 1 a 7 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono;

R^4 es alquilo de 1 a 7 átomos de carbono, alqueno de 2 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, fenil- o naftil-alquilo de 1 a 4 átomos de carbono, cada uno insustituido o mono-, di-, o tri-sustituido por alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, OH, alquilo de 1 a 4 átomos de carbono-amino, di-alquilo de 1 a 4 átomos de carbono-amino, halógeno, y/o por trifluoro-metilo; y

Act es un grupo activador seleccionado a partir de un grupo protector de amino, en particular un carbamato;

o una sal del mismo.

15. El compuesto de acuerdo con la reivindicación 14, el cual tiene la Fórmula:



16. El compuesto de acuerdo con la reivindicación 14 ó 15, el cual tiene la Fórmula:

