



No. 08-031016- -00004-0000

Fecha: 2009-10-28 16:59:52 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSRVTER Folios: 42

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lengua Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 08.031.016

Solicitante: NOVARTIS AG

**SOLICITUD
PUBLICADA**

Apoderado: CARLOS REYNALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: SÍNTESIS DE

INHIBIDORES DE RENINA QUE INVOLUCRA UNA REACCIÓN DE CICLOADICIÓN.

Gaceta: 606

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: <u>GYNOPHARM S.A.</u>	IDENTIFICACIÓN	
	Dirección: <u>Carrera 14 N° 94-44 Piso 7 Torre b</u>	C.C. ☐ NIT ☒	
	Nacionalidad o Domicilio: <u>COLOMBIA</u>	C.E. ☐ Otro ☐	
	Lugar de Constitución: <u>BARRANQUILLA</u>	Cual <u> </u>	
	Teléfono: <u>2 36 84 95</u> Fax: <u> </u>	Numero <u>802,006,279-4</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: <u>CIELO ANGELA PEÑA RODRIGUEZ</u>	IDENTIFICACIÓN	
	Dirección: <u>CARRERA 13 No. 119-95</u>	C.C. ☒ NIT ☐	
	Teléfono: <u>(571)213 12 13</u> Fax: <u>(571)612 19 79</u>	C.E. ☐ Otro ☐	
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Numero <u>51.940.252</u> TP <u>82701</u>	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

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⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 08 31016
Asunto : Oposición a la solicitud de patente de Invención titulada
"SÍNTESIS DE INHIBIDORES DE RENINA QUE INVOLUCRA UNA REACCIÓN DE CICLOADICIÓN"
Solicitante : NOVARTIS AG
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 606 del 31 de julio de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en calidad de Agente Oficioso de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "SÍNTESIS DE INHIBIDORES DE RENINA QUE INVOLUCRA UNA REACCIÓN DE CICLOADICIÓN", cuyo titular es **NOVARTIS AG**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

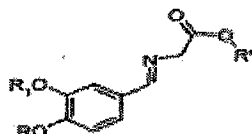
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular INHIBIDORES DE RENINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

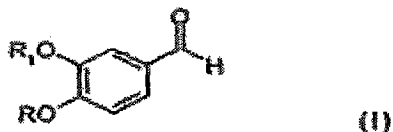
2.1. La solicitud objeto de la presente fue presentada el 28 de marzo de 2008 reivindicando prioridad bajo la solicitud GB20050019764 del 2005-09-28; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 605 del 30 de junio de 2009, cuya publicación internacional corresponde a la WO2007039183 del 2007-04-12.

2.2. La solicitud colombiana 08 31016 objeto de la presente oposición, se refiere a un proceso para la fabricación de un compuesto de la Fórmula III:

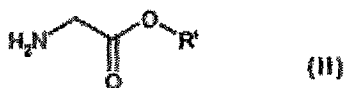


(III)

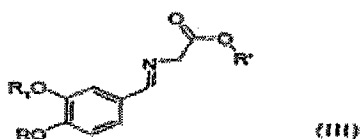
en donde: R es alquilo; R1 es alcoxi-alquilo; y R' es hidrógeno, alquilo, o aralquilo; o una sal del mismo; comprendiendo esta fabricación (de preferencia consistiendo en): hacer reaccionar un compuesto de la Fórmula I:



en donde R y R1 son como se definen para un compuesto de la Fórmula III, con un compuesto de glicina de la Fórmula II:



en donde R' es como se define para un compuesto de la Fórmula III, con el objeto de dar la funcionalidad de imina; y un compuesto de la Fórmula III:



en donde: R es alquilo; R1 es alcoxi-alquilo; R' es alquilo o aralquilo, de preferencia alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 3 átomos de carbono, fenilo, más preferiblemente alquilo de 1 a 4 átomos de carbono o bencilo, en especial etilo; o una sal del mismo; con el nombre de etil-éster del ácido {[1-[4-metoxi-3-(3-metoxi-propoxi)-fenil]-met-(E)-iliden]-amino}-acético, o una sal del mismo.

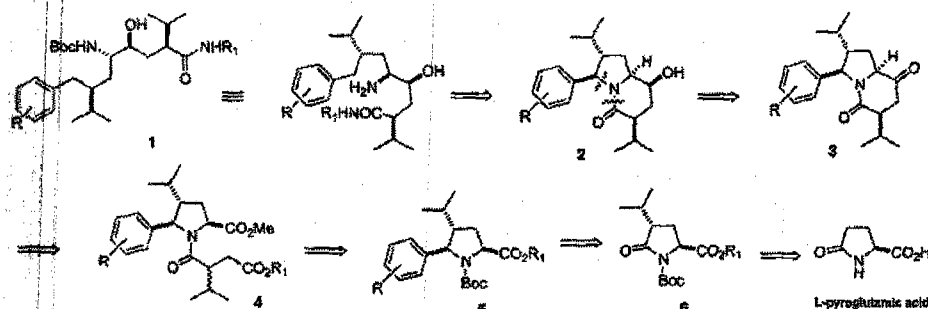
2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o*

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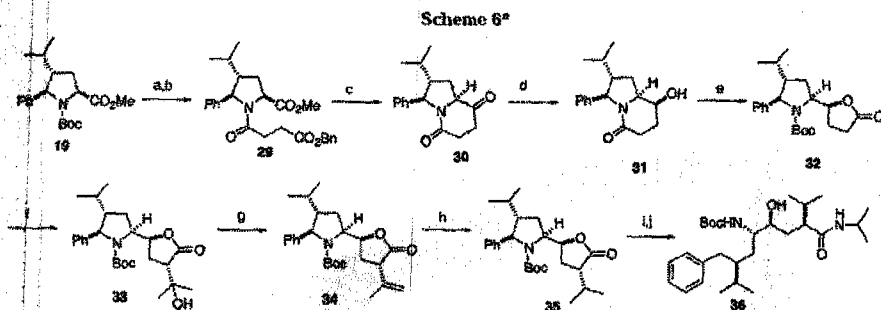
procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: Ayerbe, M. et al : "Stereocontrolled synthesis of highly substituted proline esters via [3+2] cycloaddition between N-metalated azomethine ylides and nitroalkenes. Origins of the metal effect on the stereochemical outcome", Journal of Organic Chemistry, vol.63, 1998, pages 1795-1805.
- D2: Hanessian, Stephen et al: "The power of visual imagery in synthesis planning. Stereocontrolled Approaches to CGP-60536B, a potent renin inhibitor", Journal of organic chemistry, 67(12), 2002, 4261-4274.

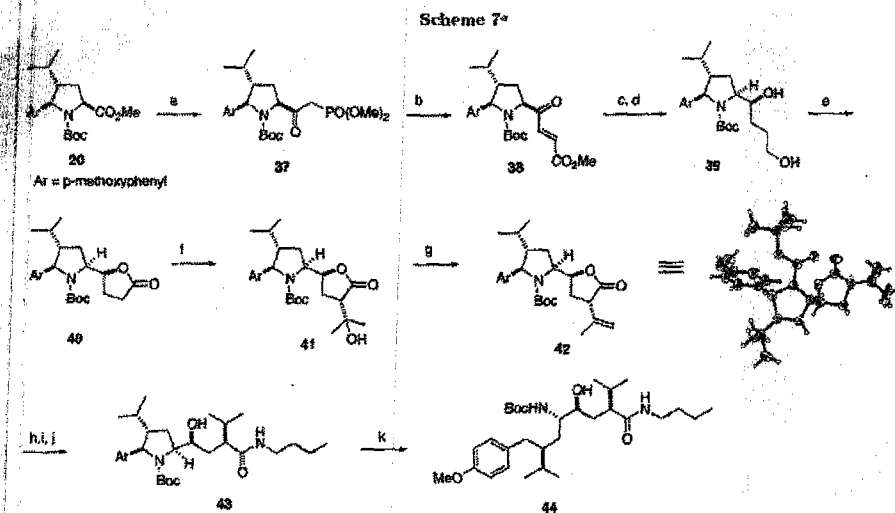
2.4. Ahora bien, el documento D1, particularmente en la página 1803, revela el procedimiento general de síntesis de una imina, a partir de un éster ácido metil amino (ácido carboxílico) y una amina. Ahora bien, el documento D2 revela dos estrategias hacia la síntesis estereocontrolada del compuesto: ácido 8-aril-3-hidroxi-4-amino-2,7- diisopropiloctanoico, con centros estereogénicos predeterminados, d manera que D1, guarda relación con un potente inhibidor de renina, el compuesto CGP-60536P (Alisquiren). Según D2, el análisis de retrosíntesis de una amida, el ácido 8-aril-2R-isopropil-3S-hidroxi-4S-amino-6S- isopropiloctanoico, se indica en la siguiente figura:



Este compuesto es un potente inhibidor de la renina. Otras reacciones se muestran en la siguiente figura:



^a Reagents and conditions: (a) TFA, benzene, quantitative; (b) BOP-Cl, Et₃N, Pr₂NEt, HO₂C(CH₂)₂CO₂Br, 85%; (c) sodium *tert*-butoxide, THF, -20 °C, then H₂, 10% Pd/C, 49%; (d) L-Selectride, -78 °C, THF, 66%; (e) concentrated HCl, MeOH, reflux, then Boc₂O, 60%; (f) LiHMDS, -78 °C, THF, then acetone, 85%; (g) PCl₅, DCM, 80%; (h) H₂, 10% Pd/C, EtOAc, 90%; (i) NH₂CHMe₂, AlMe₃, DCM; (j) H₂, 10% Pd/C, EtOAc, 60 psi, 3 days, 50% (two steps).



^a Reagents and conditions: (a) MePO(OMe)₂, ^tBuLi, THF, -78 °C, 88%; (b) CHOCOMe, LiCl, MeCN, Pr₂NEt, 68%; (c) H₂, 10% Pd/C, EtOAc, 90%; (d) NaBH₄, MeOH, 88%; (e) TEMPO, DCM, PhI(OAc)₂, 73%; (f) LiHMDS, THF, -78 °C, then acetone, 87%; (g) PCl₅, DCM, 80 °C, 80%; (h) H₂, 10% Pd/C, EtOAc, 90%; (i) ^tBuNH₂, AlMe₃, DCM, 75%; (j) H₂, 10% Pd/C, MeOH, 3 days, 80%.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 y D2 carece evidentemente de ALTURA O NIVEL INVENTIVO, dado que cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada la anterioridad D2 con lo indicado en el documento D1, para llegar a definir la síntesis de inhibidores de renina que involucra una reacción de cicloadición, conforme se define en el presente capítulo reivindicatorio.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 31016 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 28 de septiembre de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a la síntesis de inhibidores de renina que involucra una reacción de cicloadición, sobre el cual busca protección en el capítulo reivindicatorio.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada “SÍNTESIS DE INHIBIDORES DE RENINA QUE INVOLUCRA UNA REACCIÓN DE CICLOADICIÓN”, cuyo titular es NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 606 del 31 de julio de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: Ayerbe, M. et al : “Stereocontrolled synthesis of highly substituted proline esters via [3+2] cycloaddition between N-metalated azomethine ylides and nitroalkenes. Origins of the metal effect on the stereochemical outcome”, Journal of Organic Chemistry, vol.63, 1998, pages 1795-1805.
- D2: Hanessian, Stephen et al: “The power of visual imagery in synthesis planning. Stereocontrolled Approaches to CGP-60536B, a potent renin inhibitor”, Journal of organic chemistry, 67(12), 2002, 4261-4274.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: Ayerbe, M. et al: "Stereocontrolled synthesis of highly substituted proline esters via [3+2] cycloaddition between N-metalated azomethine ylides and nitroalkenes. Origins of the metal effect on the stereochemical outcome", Journal of Organic Chemistry, vol.63, 1998, pages 1795-1805.
 - D2: Hanessian, Stephen et al: "The power of visual imagery in synthesis planning. Stereocontrolled Approaches to CGP-60536B, a potent renin inhibitor", Journal of organic chemistry, 67(12), 2002, 4261-4274.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-031016- -00004-0000

Fecha: 2009-10-28 16:59:52 Dep. 2020 NUECREACIONE
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Act. 400 OPOSIOBSERVTER Folios: 42

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 101,492
FECHA : DICIEMBRE 30 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAD. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	14727985	18/12/2008	1,064,000.00
LAD. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	96103313	28/11/2008	1,064,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	105711141	26/12/2008	1,330,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-031016-00004-0000

Fecha: 2009-10-28 16:59:52 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 42

CERTIFICACION DE EXCEDENTE : 09 - 81,203

FECHA : OCTUBRE 28 DE 2009

XXXX CONSIGNACION XXXX

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GYNOPHARM S.A.	RECIBO DE CAJA			32048	29/04/2009	203,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			64132	31/08/2009	106,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			64138	31/08/2009	68,000.00

XXXX CONCEPTO XXXX

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	21,000.00
		TOTAL :	21,000.00

SON: VEINTIUNO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

Stereocontrolled Synthesis of Highly Substituted Proline Esters via [3 + 2] Cycloaddition between N-Metalated Azomethine Ylides and Nitroalkenes. Origins of the Metal Effect on the Stereochemical Outcome

Mirari Ayerbe, Ana Arrieta, and Fernando P. Cossio*

Kimika Fakultatea, Euskal Herriko Unibertsitatea, P.K. 1072, San Sebastián-Donostia, Spain

Anthony Linden

Organisch-chemisches Institut der Universität Zürich, Winterthurestrasse 190, CH-8057, Zürich, Switzerland

Received July 2, 1997 (Revised Manuscript Received January 5, 1998)

The [3 + 2] cycloaddition reaction between several *N*-metalated azomethine ylides and nitroalkenes has been studied using AgOAc and LiClO₄ as metalating reagents in the presence of triethylamine. The reaction is found to be very versatile and can be extended to homochiral nitroalkenes. In general, lithium and silver salts promote preferential formation of the *endo* and *exo* cycloadducts, respectively. The presence of a phenol moiety induces a shift toward the *exo*-cycloadduct even when lithium is used. A model based upon the experimental results obtained and SCF-MO calculations is proposed to explain the variable stereochemical outcome of these reactions.

Introduction

The importance of substituted prolines¹ in the design of new catalysts² or in the chemical synthesis of pharmacologically³ or biologically interesting⁴ molecules is well recognized. The [3 + 2] reaction of azomethine ylides and alkenes is one of the most useful methods for the preparation of these molecules in a convergent manner.⁵ Among the different versions of this reaction,⁶ the interaction between *N*-metalated azomethine ylides and π -deficient alkenes is specially promising, since, in general, it allows the synthesis of proline nuclei under mild conditions and with good chemical yields.⁷ In addition, the reaction is very versatile and consequently is well suited for combinatorial chemistry.⁸ Another

interesting feature of this reaction is that the stereocontrol observed is usually satisfactory. Thus, the reaction between α,β -unsaturated carbonyl compounds and *N*-metalated azomethine ylides derived from amino esters and aldehydes yields *endo*-cycloadducts⁹ as the major stereoisomers.¹⁰ However, Töke et al.¹¹ have observed a reversal of stereoselectivity in the 1,3-dipolar cycloaddition between several azomethine ylides and aryl nitroolefins. These authors reported that lithium metalation promotes the preferential formation of *endo* cycloadducts, whereas the use of silver salts favors the formation of *exo*-pyrrolidines as major stereoisomers.

Within this context and in connection to our ongoing research program on nitroalkene chemistry,¹² we present

(1) (a) Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* 1996, 7, 927. (b) Sharma, R.; Lubell, W. D. *J. Org. Chem.* 1996, 61, 202. (c) Collado, I.; Ezquerro, J.; Pedregal, C. *J. Org. Chem.* 1995, 60, 5011. (d) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* 1996, 123.

(2) (a) *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH Publishers: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(3) See, for example: (a) Waid, P. P.; Flynn, G. A.; Huber, E. W.; Sabol, J. S. *Tetrahedron Lett.* 1996, 37, 4091. (b) Khav, V. V.; Martinelli, M. J. *Tetrahedron Lett.* 1996, 37, 4323. (c) Kolodziej, S. A.; Nikiforovich, G. V.; Skeean, R.; Lignon, M.-F.; Martinez, J.; Marshall, G. R. *J. Med. Chem.* 1995, 38, 137.

(4) See for example: (a) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* 1996, 37, 3915. (b) Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villani, C.; Prato, M. *J. Am. Chem. Soc.* 1996, 118, 4072. (c) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 1278. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* 1993, 32, 1244.

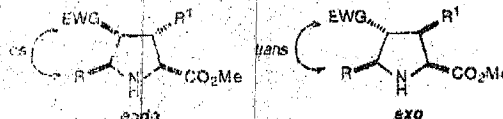
(5) (a) Huisgen, R. *Angew. Chem.* 1983, 2, 565. (b) Huisgen, R. *J. Org. Chem.* 1976, 41, 403.

(6) (a) Grigg, R. *Chem. Soc. Rev.* 1987, 16, 89. (b) Lowin, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; J. Wiley & Sons: New York, 1984; Vol. 1, pp 653-732. (c) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, pp 232-349. (d) Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, 1988; Vol. 1, pp 33-51.

(7) Kanemasa, S.; Tsuge, O. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, 1993; Vol. 3, pp 99-159.

(8) (a) Murphy, M. M.; Schmale, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* 1995, 117, 7029. (b) Hamper, B. C.; Dukeshner, D. R.; Smith, M. S. *Tetrahedron Lett.* 1996, 37, 3671. (c) Marx, M. A.; Grillo, A.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* 1997, 119, 8153.

(9) We denote the *endo* and *exo* stereoisomers as those in which the electron-withdrawing group at C4 and the substituent at the C5 position are in a *cis* and *trans* relationship, respectively.

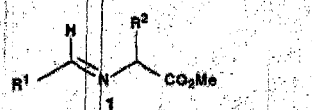


(10) See for example: (a) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* 1993, 58, 1384. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* 1993, 66, 2196. (c) Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* 1978, 2885. (d) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozi, K.; Takenaka, S.; Veno, K. *Chem. Lett.* 1986, 1271. (e) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozi, K.; Takenaka, S.; Veno, K. *Bull. Chem. Soc. Jpn.* 1997, 60, 4067.

(11) (a) Nyerges, M.; Balázs, L.; Bitter, L.; Kádás, I.; Kövesdi, I.; Töke, L. *Tetrahedron* 1995, 51, 6783. (b) Nyerges, M.; Rudas, M.; Tóth, G.; Hecsei, B.; Kádás, I.; Bitter, L.; Töke, L. *Tetrahedron* 1995, 51, 13321. (c) Nyerges, M.; Bitter, L.; Kádás, I.; Tóth, G.; Töke, L. *Tetrahedron Lett.* 1994, 35, 4413.

(12) (a) Ayerbe, M.; Cossio, F. P. *Tetrahedron Lett.* 1995, 36, 4447. (b) Ayerbe, M.; Morao, I.; Arrieta, A.; Linden, A.; Cossio, F. P. *Tetrahedron Lett.* 1997, 38, 2311.

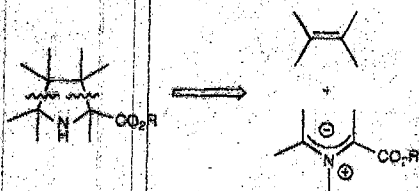
Chart 1



	R ¹	R ²
a	C ₆ H ₅	H
b	2-HO-C ₆ H ₄	H
c	2-OH-C ₆ H ₄	CH ₃
d	2-CH ₃ OC ₆ H ₄	H
e	2-CH ₃ OC ₆ H ₄	CH ₃
f	2-pyridyl	H
g	4-HO-3-CH ₃ OC ₆ H ₃	H



	R ³	R ⁴
a	H	4-Cl-C ₆ H ₄
b	H	4-CH ₃ OC ₆ H ₄
c	CH ₃	4-CH ₃ OC ₆ H ₄
d	H	(S)-CH(Obn)CH ₃

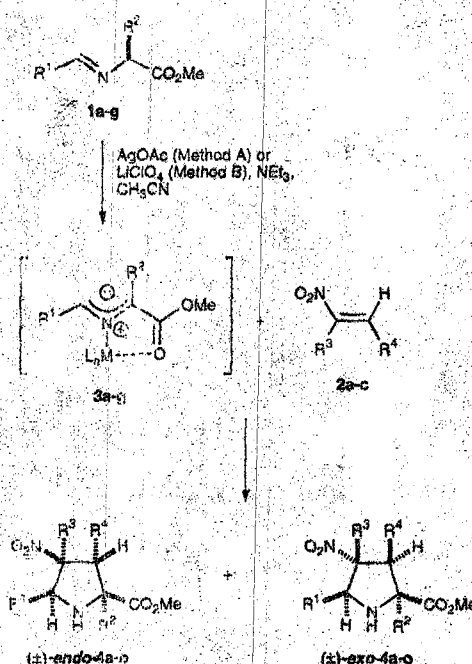
Scheme 1^a

^a The substituents at the different positions are not specified.

herein our results on the reaction between nitro olefins and azomethines. We have extended the reaction to highly substituted azomethine ylides and nitroalkenes, and we provide an explanation to the metal dependence of the stereochemical outcome of this important reaction.

Results and Discussion

To obtain structurally diverse cycloadducts, imines **1a-g** and nitroalkenes **2a-d** were selected (see Chart 1). In particular, compounds **1b-f** were studied because of the potential of the corresponding cycloadducts as tridentate ligands.² Nitroalkene **2d** was also selected in order to study the synthetic potential of the reaction when homochiral nitroalkenes are used as dipolarophiles. Lithium and silver azomethine ylides (see Scheme 2) derived from imines **1a-g** were generated from LiClO₄ and AgOAc, respectively, in the presence of triethylamine as base and acetonitrile as solvent. LiClO₄ has not been previously described as a source of N-lithiated azomethines. These reactive intermediates are usually generated by means of either the LiBr/NEt₃ or the LDA/NEt₃ systems.⁷ We have observed that LiClO₄ usually leads to cleaner crude reaction mixtures with respect to the above-mentioned lithium salts. The results obtained are collected in Table 1. We have found that when AgOAc is used to promote the formation of azomethine ylides, the reaction takes place faster than when formation of the dipoles is assisted by LiClO₄. For example, reaction between **1a** and **2b** in the presence of 0.15 equiv of AgOAc yields a mixture of *endo*- and *exo*-**4b** after 3 h of reaction at room temperature in a 69% yield (see Table

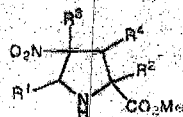
Scheme 2^a

^a Only one enantiomer of the cycloadducts **4** is drawn.

1, entry 2). In contrast, the same reaction in the presence of 0.15 equiv of LiClO₄ yields **4b** in a 30% yield with a *endo:exo* ratio of 33:37. When 5 equiv of LiClO₄ were used, the cycloadduct was obtained in a 47% yield and with higher stereocontrol (see Table 1, entry 2). This effect is more pronounced with more substituted substrates. Thus, when the **1c**+**2b** → **4e** transformation was performed in the presence of 0.15 equiv of LiClO₄, a reaction time of 20 h was required to obtain a 56:44 *cis:trans* mixture of cycloadducts **4e** in a 30% yield. When the same reaction was carried out with 5 equiv of LiClO₄, only 4 h were required to achieve a higher yield of **4e** (see Table 1, entry 5). Similar results were observed in other cases. Therefore, we decided to use 5 equiv of this salt in all cases, because of the lower reaction times required to achieve acceptable yields and/or the higher stereocontrol observed.

We have observed a preferential formation of the *exo*-cycloadduct when a silver azomethine ylide possessing a noncoordinating aromatic substituent reacts with an aromatic nitroalkene. In the case of the corresponding lithium azomethine, the *endo*-stereoisomer is formed preferentially under similar conditions. For instance, *exo*-**4a** is the major product in the reaction between **1a** and **2a** in the presence of AgOAc, whereas *endo*-**4a** is preferentially formed when LiClO₄ is used (see Table 1, entry 1). Similar results were obtained in the reaction between **1a** and **2b** (entry 2). When the same experiments were repeated using *N,N*-diisopropylethylamine as base instead of triethylamine, the same stereochemical outcome was observed. These results are in agreement with the observations of Tóke et al.¹¹ for structurally related compounds.

We have found that the above-mentioned trend can be modified when azomethines incorporating certain groups at the aromatic moiety are used. Thus, when imine **1b** derived from salicylaldehyde and glycine was allowed to

Table 1. [3 + 2] Cycloaddition between N-Metalated Azomethines Derived from Imines 1a–g and Nitroalkenes 2a–c Using Acetonitrile as Solvent and in the Presence of AgOAc and LiClO₄

entry	product	R ¹	R ²	R ³	R ⁴	method A (AgOAc)			method B (LiClO ₄)		
						time (h)	yield ^a (%)	endo:exo ^b	time (h)	yield ^a (%)	endo:exo ^b
1	4a	C ₆ H ₅	H	H	4-Cl-C ₆ H ₄	3	60	27:73	3	66	76:24
2	4b	C ₆ H ₅	H	H	4-CH ₃ OC ₆ H ₄	3	69	30:70	3	47	83:17
3	4c	2-HO-C ₆ H ₄	H	H	4-Cl-C ₆ H ₄	2.5	29 ^c	2:98	2.5	24 ^c	14:86
4	4d	2-HO-C ₆ H ₄	H	H	4-CH ₃ OC ₆ H ₄	2.5	41 ^c	2:98	2.5	45 ^c	2:98
5	4e	2-HO-C ₆ H ₄	CH ₃	H	4-CH ₃ OC ₆ H ₄	48	49 ^c	42:58	4	37 ^c	58:42
6	4f	2-HO-C ₆ H ₄	H	CH ₃	4-CH ₃ OC ₆ H ₄	17	24 ^c	30:70	17	24 ^c	55:45
7	4g	2-HO-C ₆ H ₄	CH ₃	CH ₃	4-CH ₃ OC ₆ H ₄	40	30 ^c	30:70	7.5	27 ^c	65:35
8	4h	2-H ₃ COC ₆ H ₄	H	H	4-Cl-C ₆ H ₄	2	62 ^c	33:67	2	38 ^c	43:57
9	4i	2-CH ₃ OC ₆ H ₄	H	H	4-CH ₃ OC ₆ H ₄	2	57 ^c	37:63	2	61	39:61
10	4j	2-CH ₃ OC ₆ H ₄	CH ₃	H	4-CH ₃ OC ₆ H ₄	16	60	36:64	16	56	73:27
11	4k	2-CH ₃ OC ₆ H ₄	CH ₃	CH ₃	4-CH ₃ OC ₆ H ₄	24	60	33:67	16	60	34:66
12	4l	2-pyridyl	H	H	4-Cl-C ₆ H ₄	4	25 ^c	33:67	2.5	54	65:35
13	4m	2-pyridyl	H	H	4-CH ₃ OC ₆ H ₄	4	61 ^c	22:78	2.5	52	68:32
14	4n	4-HO-3-CH ₃ OC ₆ H ₃	H	H	4-Cl-C ₆ H ₄	2	36 ^c	36:64	2	40 ^c	23:77
15	4o	4-HO-3-CH ₃ OC ₆ H ₃	H	H	4-CH ₃ OC ₆ H ₄	2	42 ^c	30:70	2	56	24:76

^a Yield of the major stereoisomer purified by column chromatography. ^b Diastereomeric ratio measured by 300 MHz ¹H-NMR on crude reaction mixtures. ^c Yield of the major stereoisomer purified by crystallization. ^d Yield of the exo isomer estimated from the mixtures obtained from the column chromatography. This isomer couldn't be isolated. ^e Yield of the endo isomer estimated from the mixtures obtained from the column chromatography. This isomer could not be isolated.

react with nitroalkenes 2a or 2b in the presence of AgOAc and 2 equiv of triethylamine, the *exo* cycloadducts 4c and 4d were obtained with excellent stereocontrol (*endo:exo* = 2:98). When the same reaction was carried out in the presence of LiClO₄, the *exo* cycloadducts were also the major stereoisomers (see Table 1, entries 3 and 4). This effect is significantly lower when the imine 1d, which incorporates a 2-methoxyphenyl group was used instead of 1b (see Table 1, entries 8 and 9). When azomethines derived from imine 1f which has a 2-pyridyl group were used, the "normal" sense of stereocontrol was observed, although the stereoselectivity was lower (see Table 1, entries 12 and 13). In all these systems, there is a Lewis basic center located at the *ortho* position, which is amenable to intramolecular coordination to the metallic center. To test if this effect can also operate intermolecularly, imine 1g, derived from vanillin and the methyl ester of glycine, was allowed to react with nitroalkenes 2a and 2b. The results are shown in entries 14 and 15 of Table 1. As can be seen, the ionized *para*-phenolic moiety also promotes preferential formation of the *exo* cycloadducts 4n and 4o in the presence of LiClO₄, although the effect is less pronounced than in the case of entries 3 and 4 (vide supra).

With these results in mind, we reasoned that the presence of additives incorporating highly coordinating moieties such as nitro or phenoxy groups might modify the stereochemical outcome of the reaction between aromatic nitroalkenes and N-lithium azomethines derived from 1a. We performed the experiments reported in Table 2 to verify this hypothesis. In effect, the presence of phenol (entry 4), 2,6-di-*tert*-butyl phenol (entry 5) and nitrobenzene (entry 7) reverses the stereochemical outcome observed in the reaction between imine 1a and nitroalkene 2a to form the cycloadducts *endo*- and *exo*-4a. As expected, the effect induced by the hindered 2,6-di-*tert*-butylphenol is less pronounced than that promoted by phenol itself (see Table 2, entries 4 and 5). In the case of using AgOAc, these additives have negli-

Table 2. Stereoselectivity in the [3 + 2] Cycloaddition between N-Metalated Azomethines Derived from Imine 1a and Alkene 2a in the Presence of Several Additives^a

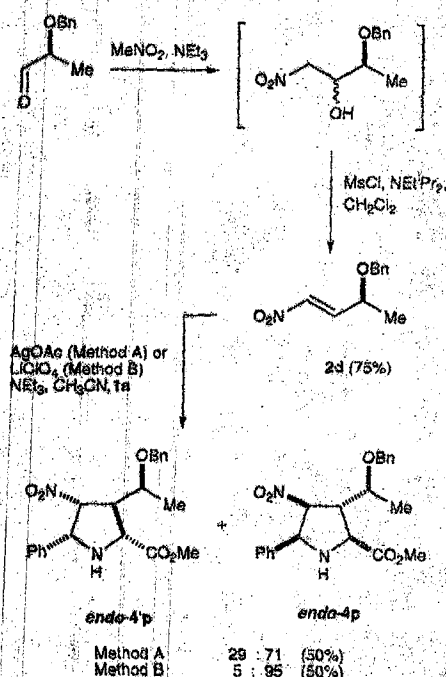
entry	MX	additive ^b	time (h)	endo-4a:exo-4a ^c
1	AgOAc	none	3	27:73
2	LiClO ₄	none	3	76:24
3	AgOAc	C ₆ H ₅ OH ^d	5	30:70
4	LiClO ₄	C ₆ H ₅ OH ^d	5	40:60
5	LiClO ₄	2,6-di- <i>tert</i> -Bu-PhOH ^d	2	51:49
6	AgOAc	C ₆ H ₅ NO ₂	5	27:73
7	LiClO ₄	C ₆ H ₅ NO ₂	5	36:64

All experiments were conducted using acetonitrile as solvent and triethylamine as base. ^a One equivalent of the additive was used. ^b Diastereomeric ratio determined by 300 MHz ¹H-NMR on crude reaction mixtures. ^c Two equivalents of triethylamine were used.

gible influence on the stereochemical outcome of the 1a+2a → 4a process (see Table 2, entries 1, 3, and 6).

According to our results azomethines derived from substituted amino esters such as alanine (see compounds 1c e in Chart 1) and (2S)-1-methyl-2-(arylnitro)ethylenes (see compound 2c in Chart 1) are much less reactive than the preceding reactants. For example, the reaction between 1c (R² = Me) and 2b to form 4e requires 48 h at room temperature in the presence of AgOAc, whereas the reaction between 1b (R² = H) and 2b takes place in only 2.5 h under the same conditions (see Table 1, entry 4). In any case, the use of highly substituted reactants is of preparative value, since the cycloadducts are readily purified and obtained in acceptable yields. In addition, in these highly substituted substrates the effect of *ortho*-phenolic groups is very attenuated with respect to their less substituted analogues. Thus, in the reaction of imine 1c with nitroalkene 2c to yield cycloadducts *endo*- and *exo*-4g (Table 1, entry 7) a loss of stereocontrol is observed with respect to the nonmethylated substrates (see Table 1, entry 4). When LiClO₄ is used, the proportion of *exo*-4g is higher than that obtained in the case of the 1a+2b → 4a process, although the *endo* cycloadduct is the major one.

Scheme 3



We next extended our study to the chiral nitroalkene **2d** (see Chart 1). This compound was prepared via the Henry reaction between (*S*)-2-(benzyloxy)propanal and nitromethane in the presence of a catalytic amount of triethylamine. The diastereomeric nitro alcohols¹³ thus formed were transformed in the corresponding mesylates¹⁴ and treated *in situ* with *N,N*-diisopropylethylamine to yield the nitroalkene **2d** in good yield.¹⁵ Reaction of this dipolarophile with azomethine ylides derived from **1a** lead to the diastereomeric pair **endo-4p** and **exo-4p** (see Scheme 3). Interestingly, this aliphatic nitroalkene yields *endo* cycloadducts using both lithium and silver azomethines, thus suggesting that the aryl group in nitroalkenes **2a–c** also plays a role in the stereochemical outcome of the reaction (*vide infra*). When lithium perchlorate was used instead of silver acetate, the observed diastereomeric ratio was 95:5 in favor of **endo-4p** (see Scheme 3). The major cycloadduct was purified by crystallization in ethyl acetate–hexanes. Despite the higher stereocontrol observed when the lithium azomethine ylide of **1a** was used, the chemical yield of **endo-4p** was similar to that obtained using AgOAc as the metalating reagent (see Scheme 3). Therefore, the reaction was found to be of preparative value and provides a useful access to the asymmetric synthesis of compounds of this kind.

The structure of cycloadducts **4a–p** was established by means of their ¹H NMR and ¹³C NMR spectra. The most significant coupling constants are reported in Table 1 of the Supporting Information. In two cases, the

relative stereochemistry was secured by X-ray diffraction analysis. The ORTEP diagrams of compounds **exo-4c** and **exo-4f** are shown in Figures 1 and 2 of the Supporting Information, respectively.¹⁶

In the case of compound **exo-4p**, its structure was assigned by NOE experiments, by analogy with structurally related compounds,¹⁷ and applying the *endo*-alkoxy rule developed by Houk.¹⁸ In several cases, oily cycloadducts were transformed in their solid *N*-acetylated derivatives¹⁹ in order to facilitate their purification. Thus, cycloadducts **endo-4h** and **exo-4h,j** were heated with trifluoroacetic acid, and the corresponding salts were acylated with acetic anhydride for 48 h to yield the acetamides **endo-5h** and **exo-5h,j** respectively (see Supporting Information for additional details).

The next step in our study was to elucidate the origins of the observed changes in the sense of stereocontrol. Given that under kinetic conditions this stereocontrol is determined by the differences in energy between the corresponding diastereomeric transition structures,²⁰ the computational tools nowadays available to the organic chemist are particularly convenient to address this particular problem. Since it was presumed that solvent and substituent effects should play a significant role, the PM3 semiempirical Hamiltonian²¹ was used, in view of its superior ability to model the particular features of the nitro group.²²

We located first the saddle point TS1 (Figure 1) associated with the [3 + 2] cycloaddition between ethylene and the lithium azomethine ylide of *N*-(formylmethyl)benzylidenearamine. This transition structure corresponds to a concerted *supra-supra* topology as would be expected from the Woodward–Hoffmann rules for thermal six-electron cycloadditions. However, inclusion of a nitro group induces a drastic change in the potential energy hypersurface. Thus, nitroalkene is highly π -deficient and behaves as a Michael acceptor rather than a dipolarophile. Therefore, the [3 + 2] cycloaddition actually consists of a tandem Michael–Henry reaction, as it is shown in Scheme 4. The first step is a nucleophilic attack of the lithium azomethine ylide on the nitroalkene to form the zwitterionic species denoted in Scheme 4 as INT, in which the C2–C3 bond is formed.²³ The second step is a nitronal process¹³ in which the nitronate moiety adds to the imine part of INT. This is in agreement with the fact that several authors^{7,24} have reported the formation of Michael adducts in the reaction

(16) Crystallographic data (excluding structure factors) for the structures **exo-6c** and **exo-4f** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EF, UK; fax: +44 (0)1223 336033; email: deposit@chem.cam.ac.uk.

(17) (a) Amadeo, R.; Cingolani, M.; Corzi, F.; Faimondi, L.; Pillati, T. *Tetrahedron Lett.* 1993, 2, 1229. (b) Pätz, M.; Galley, G.; Jones, P. G.; Chiriacovsky, A. *Tetrahedron Lett.* 1993, 34, 5707. (c) Galley, G.; Chiriacovsky, A.; Pätz, M. *J. Org. Chem.* 1993, 58, 5005.

(18) (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rendan, N. G.; Jager, V.; Schmidt, K.; Frisch, P. E. *J. Am. Chem. Soc.* 1984, 106, 3580. (b) Houk, K. N.; Wu, Y.-D.; Doh, H. Y.; Moses, S. R. *J. Am. Chem. Soc.* 1986, 108, 3754.

(19) Amoselli, G.; Lill, W. D. *J. Am. Chem. Soc.* 1996, 118, 12932.

(20) Schreiner, L. *Chem. Rev. (Washington, D.C.)* 1983, 83, 83. (21) (a) Schreiner, L. *P. J. Comput. Chem.* 1989, 10, 209. (b) Anders, E.; Koch, H.; Frensdorff, P. *J. Comput. Chem.* 1993, 14, 1301.

(22) Jorgensen, J. *J. Comput.-Aided Mol. Des.* 1990, 4, 1.

(23) For a related reaction mechanism involving azomethine ylides and α,β -unsaturated carbonyl compounds, see: Matsukawa, A.; Kawakami, K.; Kanemitsu, S.; Rudzinski, J. M. *J. Chem. Soc. Perkin Trans. 2* 1994, 2525.

(13) (a) For a recent review see: Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, pp 321–340. (b) For an study on the mechanism of this reaction, see Lecea, B.; Arrieta, A.; Morao, I.; Cossio, F. P. *Eur. J. Chem.* 1997, 3, 20.

(14) Melton, J.; McMurry, J. E. *J. Org. Chem.* 1975, 40, 2185.

(15) Pätz, M. et al. have prepared structurally related chiral nitroalkenes using different reaction conditions and have observed a lower stereocontrol. See Galley, G.; Hübner, J.; Anklam, S.; Jones, P. G.; Pätz, M. *Tetrahedron Lett.* 1996, 37, 6307.

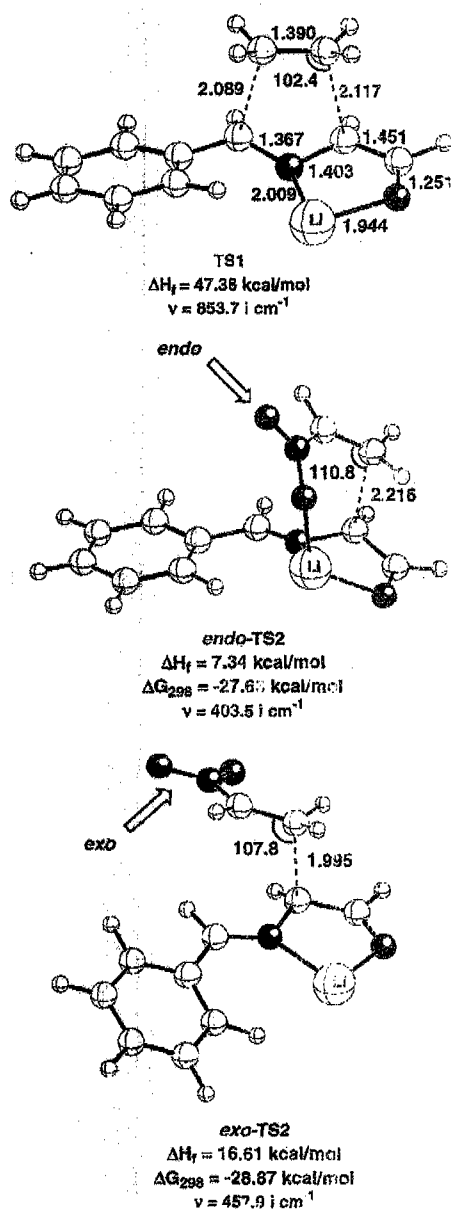
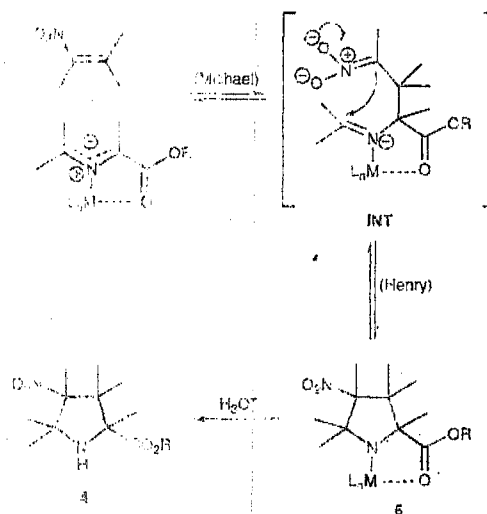


Figure 1. Computer plots of the transition structures **TS1**, **endo-TS2**, and **exo-TS2** computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. In this and the following figures, which incorporate ball-and-stick representations, unless otherwise noted, atoms are represented by increased order of shadowing as follows: H, C, O, N.

between π -deficient alkenes and azomethine ylides derived from alkyl aldehydes or ketones.

We tried to isolate and characterize several of these Michael intermediates in order to verify our computational results. However, in most cases the inherent instability of the intermediates precluded their isolation, although they were observed in the ^1H NMR spectra of several reaction mixtures. We reasoned that, since the more substituted nitronate is the lower its reactivity,¹³⁵ α -methyl nitroalkenes could be more convenient starting

Scheme 4



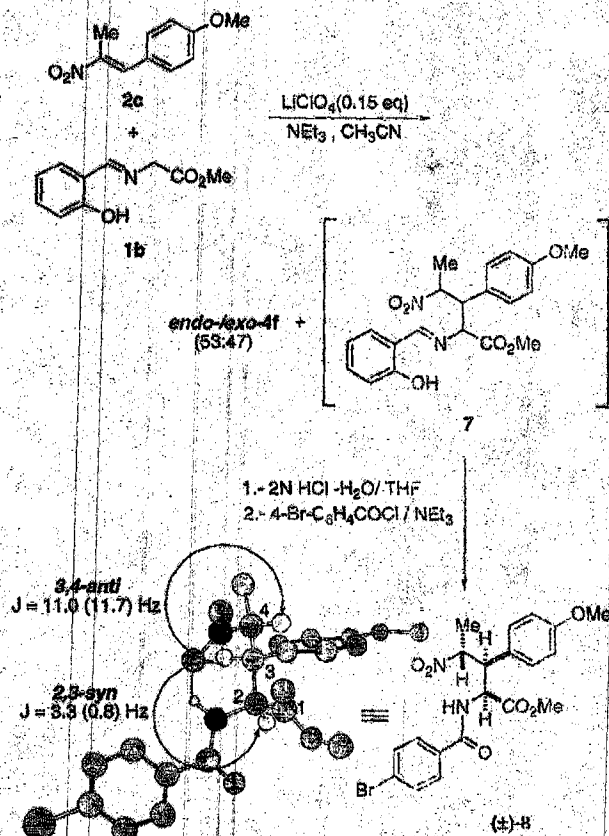
The possible substituents at the different positions are not specified.

materials. On the other hand, we have found that the reaction takes place more slowly when it is carried out in the presence of only 0.15 equiv of LiClO_4 (vide supra). Therefore, we repeated the reaction between **1b** and **2c** in the presence of 0.15 equiv of LiClO_4 (Scheme 5). After 16 h reaction at room temperature, a 53:47 mixture of *endo-exo-4f* and a mixture of Michael intermediates **7** was observed. The cycloadducts **4f** and the intermediates were found to be in a ca. 2:1 ratio in the crude reaction mixture, while ca. 25% of **2c** remained unreacted. When this mixture was allowed to react for additional 10 h, the ^1H NMR signals of **7** disappeared and only a mixture of cycloadducts **4f** was observed. In this case a complex mixture of pyrrolidines was obtained because of the partial loss of the trans relationship between the nitro and the 4-methoxyphenyl groups. All our attempts to isolate and characterize these intermediates in a pure form failed. However, hydrolysis of the imine moiety in **7** followed by in situ acylation with 4-bromobenzoyl chloride allowed the complete characterization of amide **8**, which was the major diastereomer observed in the crude reaction mixture. The overall yield of **8** from **1b** was 60%. Both the high δ value of the N-H signal and molecular mechanics optimizations (vide infra) indicate that in **8** there is a strong intramolecular hydrogen bond between the acidic hydrogen and the nitro group, thus yielding a pseudocyclic structure. Therefore, the relative stereochemistry of this product was established on the basis of the coupling constants between the contiguous methine protons (see Scheme 5). In summary, the observation of intermediate **7**, its conversion to the corresponding cycloadducts and the complete characterization of its derivative **8** provide experimental support for the stepwise mechanism predicted by our calculations.

Since no isomerization is observed either in the azomethine ylides or in the nitroalkene during the course of the reaction, the stereochemistry of the cycloadducts is determined by the approaching mode between both partners. In Figure 1 we have included the two diastereomeric *endo*- and *exo*-TS2 saddle points. In *endo*-TS2, the nitro group is coordinated to the lithium atom, with a Li-N bond length of 2.009 Å. In the latter saddle

(24) (a) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Chem. Lett.* 1986, 1271. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* 1989, 62, 869.

Scheme 5



* Numbers in parentheses correspond to computed coupling constants (see text). Nonrelevant hydrogen atoms have been omitted for clarity.

point, *exo*-TS2 the lithium atom is dicoordinated and therefore the stabilizing Li...ONO interaction is not present. In contrast, this transition structure is much more flexible and the $\Delta G_{298}^\ddagger$ value for *exo*-TS2 is calculated to be 1.24 kcal/mol lower than that obtained for *endo*-TS2 at the RHF/PM3 level (see Figure 1). These results are not in agreement with our experimental data, since we have observed that when azomethine ylides derived from benzaldehyde are used, the *endo* cycloadducts are obtained with a relatively low stereocontrol (*vide supra*). Therefore, we calculated additional transition structures taking into account as closely as possible the effects operating under the experimental conditions, namely the aryl substituent of the nitroalkene and the solvent. In Figure 2 we present the *endo*- and *exo*-TS3 transition structures, which incorporate two acetonitrile molecules. In *endo*-TS3, the lithium atom is pentacoordinated, and its surrounding ligands adopt a bipyramidal disposition, in which the nitrogens of the azomethine moiety and of one solvent molecule occupy the axial positions. In contrast, *exo*-TS3 shows a tetrahedrally coordinated lithium atom, with a close proximity between the methyl group of one acetonitrile molecule and the phenyl group of the nitroalkene. These combined effects result in a slightly higher stability of *endo*-TS3, whose $\Delta G_{298}^\ddagger$ calculated value is only 0.47 kcal/mol lower than that found for its *exo* congener. This result is in fair agreement with the diastereomeric excess experimentally found for dipoles of this type.

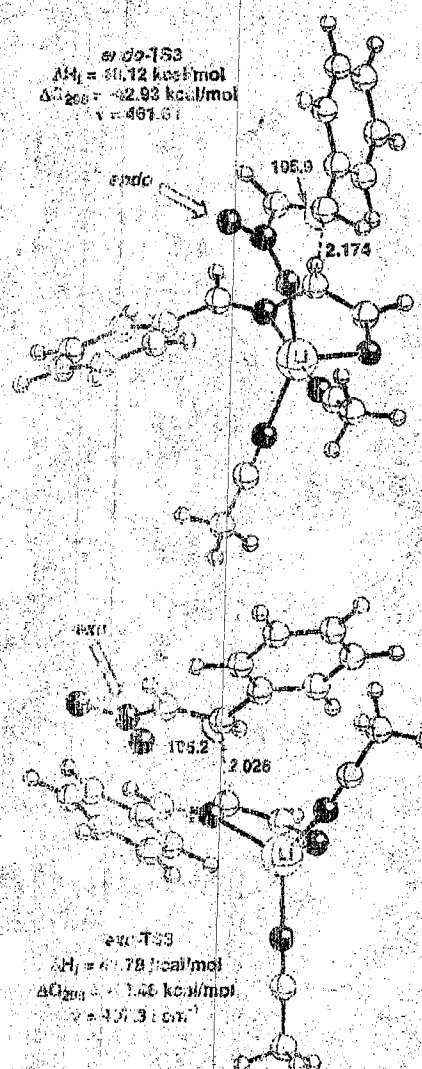


Figure 2. Computer plots of the transition structures *endo*-TS3 and *exo*-TS3 computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

We next investigated computationally the effect of the *ortho*-phenoxy group on the stereochemical outcome. Figure 3 shows the three transition structures found for the *ortho*-phenoxy analogues of TS2 saddle points in the RHF/PM3 energy hypersurface. Our calculations show that the phenoxy substituent has a remarkable effect.²⁵ The first saddle point is *endo*-TS4, whose chief geometric features are similar to those of *endo*-TS3. However, in this case there is a remarkable repulsive Coulombic interaction between the nitro and the phenoxy groups coordinated to the lithium atom. Thus, partitioning of the total energy reveals that the bicentric term between both groups is $\Delta E = +9.34 \text{ kcal/mol}$, which corresponds to an almost purely Coulombic repulsion. We have also located another saddle point which is associated with the formation of the corresponding *endo* cycloadduct. This transition structure is denoted as *endo*-TS4 in Figure 3.

²⁵ For a related lithium-iron complexes involving *o*-alkoxy groups, see: Guly, D. A.; Sawyer, R. J. *Am. Chem. Soc.* **1996**, *118*, 3479.

²⁶ (a) Bawin, M. T.; Liao, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 7201. (b) Albrecht, S.; Villanueva, J. J. *Heterocycl. Chem.* **1981**, *18*, 1189.

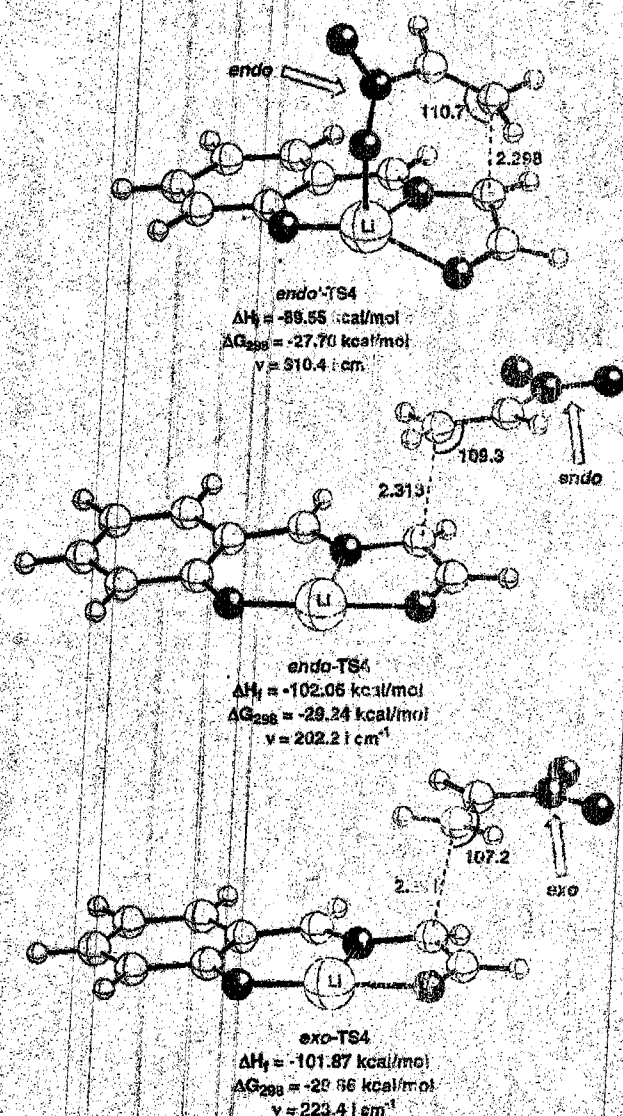


Figure 3. Computer plots of the transition structures *endo-TS4* and *endo-TS4* and *exo-TS4* computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

Both RHF/PM3 calculated heats of formation and free energies predict that this latter saddle point, despite having a tricoordinated lithium cation, is significantly more stable than *endo-TS4*. In addition, *endo-TS4* shows an almost perfect antiperiplanar arrangement between the N1-C2 and C3-C4 bonds, and the calculated C2...C3-C4 bond angle is found to be of 109.3°, a value in good agreement with the Bürgi-Dunitz trajectory²⁷ usually associated with nucleophilic attacks of organometallic compounds to electrophilic double bonds. Therefore, we can conclude that *endo-TS4* resembles the saddle point that one can expect for a Michael addition of an organometallic carbon nucleophile on a π -deficient olefin.

In addition, we have also located the transition structure *exo-TS4*, whose main geometric and energetic fea-

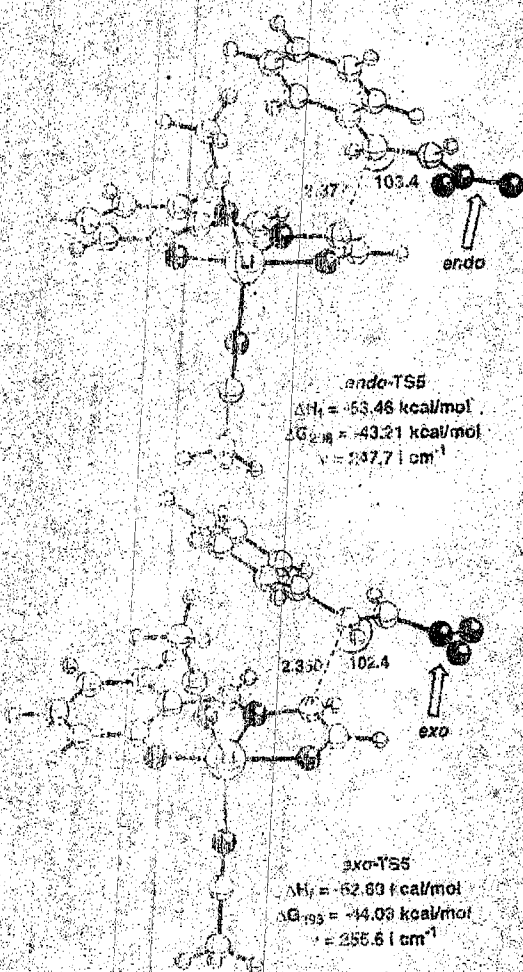


Figure 4. Computer plots of the transition structures *endo-TS5* and *exo-TS5* computed at the RHF/PM3 level. Bond distances and angles are given in angstroms and deg, respectively. See Figure 1 caption for additional details.

tures are also reported in Figure 3. This latter saddle point does not exhibit an antiperiplanar arrangement between the N1-C2 and C3-C4 and therefore has a heat of formation ca. 0.2 kcal/mol higher than that calculated for *endo-TS4*. However, the total entropy of *exo-TS4* is higher than that of its *endo* congener. Therefore, according to our calculations the free energy at 298 K of *exo-TS4* is predicted to be 0.42 kcal/mol more stable than *endo-TS4* at the RHF/PM3 level (see Figure 3).

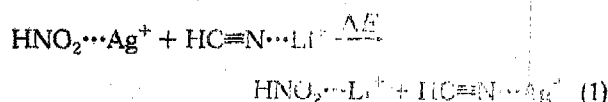
We have also calculated the transition structures including two molecules of the solvent and an additional phenyl ring for the lithiophilic moiety. The resulting diastereomeric *endo-TS5* and *exo-TS5* saddle points are depicted in Figure 4. Both transition structures are quite similar to each other. Thus, in both stationary points the lithium atom is pentacoordinated, the oxygen and nitrogen atoms occupying the axial and equatorial positions, respectively. Once again, in *endo-TS5* the arrangement between the N1-C2 and C3-C4 bonds is almost perfectly antiperiplanar, thus resulting in a lower heat of formation for this transition structure. In contrast, the entropic term of *exo-TS5* is higher than in its *endo* congener. As a result, the free energy at 298 K of *exo-TS5* is calculated to be 0.821 kcal/mol lower than that of *endo-TS5* (see Figure 4). Therefore, the free energy

(27) (a) Bürgi, H. B.; Lehn, J.-M.; Wipf, G. *J. Am. Chem. Soc.* 1974, 96, 1956. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J.-M. *Tetrahedron* 1974, 30, 1563.

balance favors formation of *exo*-TS5 with a stereocontrol higher than that calculated for the non-*ortho*-substituted analogues, in good agreement with our experimental results.

In summary, our computational studies provide a useful information on the origins of the stereocontrol of these cycloadditions. When nonionizable substituents are present, entropic factors, the aryl group of the dipolarophile (or Michael acceptor), and the solvent favor the preferential formation of the *endo* cycloadduct by coordination of the nitro group with the lithium atom. In contrast, when groups other than the nitro group but with high affinity for the lithium cation are present, the same factors shift the sense of stereoselection toward the preferential formation of the *exo* cycloadduct.

At this stage of our study, there was another aspect which remained unexplored, namely the preferential formation of *exo* cycloadducts when silver azomethine ylides are used. Given that silver is not para-*ortho*-directed in PM3, we used an indirect approach to address this problem. As we have previously found, a possible source of stereocontrol can arise from the competition between the nitro and cyano groups. Therefore, the sign of the energy associated with eq 1 can serve as an indicator of the relative affinity of lithium and silver cations for the



nitro and cyano groups. Given the number of electrons of silver cation, the relativistic compact effective potential developed by Stevens, Krauss, Basch and Jasien (SMMJ)²⁸ was used. At the MP2(FC)/SRB3-6-31+G*-NZPVT4 level (vide infra) the silver cation is calculated to be softer than the lithium cation, the difference in hardness being of $\Delta\eta = 1.01$ au. In addition, the computed value for ΔE is -2.74 kcal/mol, thus indicating a higher affinity of silver for the cyano group. Therefore, in the presence of acetonitrile as solvent, the cyano group can compete more efficiently with the nitro group when silver azomethines are used, thus resulting in the preferential formation of *exo* cycloadducts.

Conclusions

From the combined experimental and computational studies reported in this paper, the following conclusions can be drawn:

- The reaction between substituted nitrostyrenes and lithium azomethines having *o*-phenoxyl groups results in the preferential formation of the *endo* cycloadducts, both in the case of lithium or silver azomethine ylides.
- The reaction between chiral nitroalkenes and achiral lithium azomethines seems to be of preparative value, although the use of silver azomethines results in a lower stereocontrol.
- Computational studies suggest that the [3 + 2] cycloaddition is actually a tandem Michael–Henry process. In one case, a stable derivative of the reaction intermediate has been isolated and characterized.
- According to the computational studies, the stereochemical outcome of the reaction depends on the nature

of the substituents and on the competition between the coordinating ability of the nitro group and that of the solvent or of the auxiliary groups, if present.

In the future, it is most important, its hardness, is closely related to the stereochemical outcome of the reaction. Although, in principle, the nitro group shows more affinity for the lithium metal.

Experimental Section

Commercially available compounds were used as purchased, without further purification. LiClO₄ (ACS reagent) was used as received. LiClO₄ compounds are potentially explosive and should be used under the experimental conditions described in the literature (special care should be used). All solvents were dried and distilled according to standard protocols.²⁹ Nitroalkenes have been prepared following reported procedures.³⁰ Substituted azomethines were prepared as previously reported.³¹ All starting materials are uncorrected. Chemical shifts in CDCl₃ and DMSO-*d*₆ NMR spectra are reported as δ values and were compared to PM3 and Hartree–Fock calculations. Fluorine NMR spectra were performed using SiF₄ as the solvent and TMS as the reference. All spectra were recorded on Bruker Avance 400 NMR spectrometers. The samples were dried with Na₂SO₄ prior to recording and the solvent under reduced pressure.

MP2/6-31+G* Calculations. All semi-empirical calculations were performed as inputs of the PM3 transition.³² The parameters for the transition state of the reaction were used. All the calculations were performed using the eigenvalue-for-eigenvalue method implemented in the PM3 program.³³ All saddle points were confirmed by vibrational analysis³⁴ and showed one imaginary frequency. The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96.

MP2/6-31+G* Calculations. The minimum energy structure of the transition state was obtained using the GAUSS-94 program.³⁵ The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96. The vibrational frequencies were scaled by 0.96.

MP2/6-31+G* Calculations. The minimum energy structure of the transition state was obtained using the

(28) Stevens, W. J.; Krauss, M.; Basch, H.; Jasien, P. G. *J. Chem. Phys.* 1992, 97, 1292.

(29) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(30) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(31) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(32) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(33) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(34) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

(35) Perrin, D. D.; Perrin, F. W. *Quantitative Organic Chemistry*; Chapman and Hall: New York, 1985.

MM2⁴⁰ force field⁴⁰ as implemented in the MacroModel 5.0 suite of programs.⁴¹ The different possible diastereomers were optimized and then Monte Carlo⁴² simulations were performed on 1000 structures. The theoretical coupling constants included in Scheme 5 were performed on the more stable conformations using the Altona method.⁴³

General Procedure for the Preparation of the Imines 1a–g. To a solution of the corresponding amino acid methyl ester chlorhydrate (23 mmol) in CH₂Cl₂ (35 mL) were added MgSO₄ and of NEt₃ (3.5 mL, 25 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 1 h. Then the aldehyde was added and the resulting mixture was stirred for 16 h (except in the case of the imine 1f which only needed 7 h). Then the MgSO₄ was filtered out and the organic layer washed with water (2 × 25 mL), dried, and evaporated. The imines showed satisfactory ¹H NMR spectra and were used in subsequent reactions immediately without further purification.

Synthesis of (E)-3-(3-(Benzoyloxy)-1-nitro-1-butene (2d). A mixture of (S)-2-(benzyloxy)propanal (1.64 g, 10 mmol), nitromethane (2.7 mL, 50 mmol), and NEt₃ (0.2 mL) was stirred at room temperature for 5 h. The excess of nitromethane was removed by evaporation under reduced pressure. The nitroalcohol thus obtained, as a mixture of diastereomers was dissolved in CH₂Cl₂ (20 mL) and cooled to -70 °C. MsCl (0.9 mL, 12 mmol) was added dropwise followed by a solution of *N,N*-diisopropylethylamine (25 mL, 25 mmol) in CH₂Cl₂ (5 mL), keeping the reaction mixture below -50 °C. The mixture was stirred at -70 °C for 2.5 h and then allowed to reach room temperature. The solution was washed with water (5 mL), HCl 1 N (4 × 5 mL), and brine (5 mL), dried, and evaporated. The product was purified by flash column chromatography, yielding 75% of a pale yellow oil: bp 82–94 °C (0.04 mmHg); IR (film) 1523, 1351 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.19–7.17 (m, 2H), 4.61 (s, 2H), 4.32 (qd, 1H, *J* = 5.8 Hz, *J* = 3.3 Hz), 1.39 (d, 3H, *J* = 5.8 Hz); ¹³C NMR (δ ppm, CDCl₃) 142.8, 139.3, 137.3, 128.4, 127.8, 127.4, 70.9, 10.3; ¹⁹F NMR (δ ppm, CF₃CO₂H) -39.11 (*c* = 1.23, CH₂Cl₂).

General Procedure for the Reaction of the Imines 1 and the Nitroalkenes 2. Method A. As a typical example the reaction between imine 1a and nitroalkene 2a is described below. The imine 1a (0.83 g, 3 mmol) was solved in CH₃CN (50 mL), and then NEt₃ (0.7 mL, 5 mmol), the nitroalkene 2a (0.92 g, 5 mmol), and AgOAc (0.3 g, 0.75 mmol) were added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered through a Celite pad and washed with NH₄Cl saturated water solution (2 × 10 mL) and water (2 × 10 mL). After drying, the solution was evaporated, and the crude mixture separated by flash chromatography to give both *endo* and *exo* isomers which were crystallized separately in EtOH.

Method B. As a typical example the reaction between imine 1c and nitroalkene 2b is described below. The imine 1c (0.97 g, 5 mmol) was solved in CH₂Cl₂ (25 mL), and then NEt₃ (1.4 mL, 10 mmol), the nitroalkene 2b (0.90 g, 5 mmol), and LiClO₄ (2.66 g, 25 mmol) were added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with NH₄Cl saturated water solution (2 × 10 mL) and water (2 × 5 mL). The residue was dried and evaporated. The crude mixture was triturated in Et₂O to give a white powder as a mixture of *endo* and *exo* isomers of 4d which were separated by fractional crystallization in EtOH.

(39) Pople, J. A.; Schlegel, B. R.; Krishnan, R.; Devries, A. J.; Rawley, J. S.; Frisch, H.; Whiteside, R.; Houk, R. F.; J. H. Hahn, W. L. *J. Quantum Chem. Symp.* 1981, 15, 269.

(40) Allinger, N. L. *J. Am. Chem. Soc.* 1977, 99, 8127.

(41) MacroModel v5.0; Mohammedi, P.; Richards, N. G. S.; Guida, W. C.; Liskamp, R.; Lipton, M.; Saucy, C.; Chang, C. C.; Kricheldorf, T.; Still, W. C. *J. Comput. Chem.* 1990, 11, 440.

(42) (a) Chang, C.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* 1989, 111, 4379. (b) Saunders, M.; Houk, R. N.; Y.-P. Fan, W. C.; Lian, M.; Chang, C.; Guida, W. C. *J. Am. Chem. Soc.* 1990, 112, 1495.

(43) Haasnoot, C. A. G.; de Leeuw, A. A. *Magn. Reson. Chem.* 1980, 18, 2783.

The other reactions were performed according to the procedures described above. The reaction conditions as well as the results are listed in Table 1.

(2S,3S,4S)-3-(3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4a-*endo* isomer): mp 113–115 °C; IR (KBr) 1733, 1547, 1352 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 6.6 Hz, *J* = 3.9 Hz), 4.5–4.3 (m, 2H), 3.7 (t, 1H, *J* = 3.9 Hz), 4.08 (m, 1H), 2.79 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 173.4, 155.3, 154.3, 131.0, 129.4, 128.9, 128.8, 128.7, 126.4, 96.7, 87.2, 67.2, 54.2, 52.7; Anal. Calcd for C₁₄H₁₂ClN₂O₅: C, 59.9; H, 3.4; N, 7.7. Found: C, 60.3; H, 4.8; N, 7.02.

(2S,3S,4S)-3-(3-(4-Chlorophenyl)-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4a-*exo* isomer): mp 113–114 °C; IR (KBr) 1733, 1547, 1352 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 6.6 Hz, *J* = 3.9 Hz), 4.49 (dd, 1H, *J* = 2.8 Hz, *J* = 5.4 Hz), 4.32 (dd, 1H, *J* = 7.7 Hz, *J* = 3.3 Hz), 3.34 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 171.3, 157.5, 134.7, 134.0, 128.2, 129.0, 128.9, 126.8, 95.1, 67.2, 64.0, 54.7, 53.9; Anal. Calcd for C₁₄H₁₂ClN₂O₅: C, 59.91; H, 4.76; N, 7.73. Found: C, 60.50; H, 5.03; N, 7.12.

(2S,3S,4S)-3-(3-(4-Methoxyphenyl)-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4b-*endo* isomer): mp 59–60 °C; IR (KBr) 1732, 1553, 1364 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.68 (dd, 1H, *J* = 3.4 Hz, *J* = 2.3 Hz), 4.80 (s, 1H), 4.7–4.58 (m, 2H), 3.9 (s, 3H), 3.66 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 171.3, 159.2, 134.4, 130.4, 128.6, 128.5, 126.4, 114.1, 97.3, 95.5, 67.4, 54.7, 52.6; Anal. Calcd for C₁₆H₁₈N₂O₇: C, 60.02; H, 5.57; N, 7.86. Found: C, 60.9; H, 5.6; N, 7.92.

(2S,3S,4S)-3-(3-(4-Methoxyphenyl)-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4b-*exo* isomer): mp 144–145 °C; IR (KBr) 1731, 1542, 1350 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 7.0 Hz), 4.46 (d, 1H, *J* = 5.0 Hz), 4.32 (dd, 1H, *J* = 8.0 Hz), 3.77 (s, 3H), 3.34 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 172.0, 159.3, 132.7, 131.5, 129.0, 128.5, 127.7, 126.8, 114.1, 95.3, 67.4, 64.2, 54.2, 53.2, 51.9; Anal. Calcd for C₁₆H₁₈N₂O₇: C, 60.02; H, 5.57; N, 7.86. Found: C, 60.05; H, 5.75; N, 7.98.

(2S,3S,4R)-3-(3-(4-Chlorophenyl)-5-(2-hydroxyphenyl)-4-nitro-5-oxopyrrolidine (4c-*exo* isomer): mp 174–175 °C; IR (KBr) 1737, 1545, 1355 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.60 (s, 1H), 7.35 (d, 1H, *J* = 9.3 Hz), 7.21 (d, 1H, *J* = 9.3 Hz), 7.02 (s, 1H), 6.85 (d, 1H, *J* = 10.4 Hz), 4.41 (d, 1H, *J* = 9.1 Hz), 3.9 (s, 3H), 3.66 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 173.3, 155.8, 131.3, 132.3, 131.7, 129.4, 129.1, 124.0, 115.5, 110.7, 107.5, 68.9, 61.9, 52.3, 51.6; Anal. Calcd for C₁₆H₁₄ClN₂O₅: C, 59.39; H, 3.61; N, 7.00.

(2S,3S,4R)-3-(3-(4-Methoxyphenyl)-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4d-*exo* isomer): mp 130–132 °C; IR (KBr) 1732, 1545, 1350 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 9.3 Hz), 4.46 (d, 1H, *J* = 5.0 Hz), 4.32 (dd, 1H, *J* = 10.4 Hz), 4.40 (t, 1H, *J* = 5.0 Hz), 3.77 (s, 3H), 3.34 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 172.0, 159.3, 132.7, 131.5, 129.0, 128.5, 127.7, 126.8, 114.1, 95.3, 67.4, 64.2, 54.2, 53.2, 51.9; Anal. Calcd for C₁₆H₁₈N₂O₇: C, 60.02; H, 5.57; N, 7.86. Found: C, 60.05; H, 5.75; N, 7.98.

(2S,3S,4S)-3-(3-(4-Methoxyphenyl)-2-methyl-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4e-*endo* isomer): mp 131–133 °C; IR (KBr) 1732, 1545, 1350 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 9.3 Hz), 4.46 (d, 1H, *J* = 5.0 Hz), 4.32 (dd, 1H, *J* = 10.4 Hz), 4.40 (t, 1H, *J* = 5.0 Hz), 3.77 (s, 3H), 3.34 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 172.0, 159.3, 132.7, 131.5, 129.0, 128.5, 127.7, 126.8, 114.1, 95.3, 67.4, 64.2, 54.2, 53.2, 51.9; Anal. Calcd for C₁₆H₁₈N₂O₇: C, 60.02; H, 5.57; N, 7.86. Found: C, 60.05; H, 5.75; N, 7.98.

(2S,3S,4S)-3-(3-(4-Methoxyphenyl)-2-methyl-2-(methoxycarbonyl)-4-nitro-5-oxopyrrolidine (4e-*exo* isomer): mp 131–133 °C; IR (KBr) 1732, 1545, 1350 cm⁻¹; ¹H NMR (δ ppm, CDCl₃) 7.6–7.18 (m, 2H), 5.23 (dd, 1H, *J* = 9.3 Hz), 4.46 (d, 1H, *J* = 5.0 Hz), 4.32 (dd, 1H, *J* = 10.4 Hz), 4.40 (t, 1H, *J* = 5.0 Hz), 3.77 (s, 3H), 3.34 (s, 3H); ¹³C NMR (δ ppm, CDCl₃) 172.0, 159.3, 132.7, 131.5, 129.0, 128.5, 127.7, 126.8, 114.1, 95.3, 67.4, 64.2, 54.2, 53.2, 51.9; Anal. Calcd for C₁₆H₁₈N₂O₇: C, 60.02; H, 5.57; N, 7.86. Found: C, 60.05; H, 5.75; N, 7.98.

3H), 2.44 (dd, 1H), 1.76 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 153.6, 159.8, 157.0, 130.4, 128.9, 90.4, 87.9, 69.3, 59.9, 55.2, 52.5, 25.1. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 62.45; H, 5.70; N, 7.30.

(2*S*,3*S*,4*R*,5*S*)-5-(2-Hydroxyphenyl)-3-(methoxycarbonyl)-4-methyl-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*f*-endo isomer): mp 178–180 °C; IR 3550, 1732, 1529, 1386 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 11.05 (s, 1H), 5.41 (d, 1H, $J = 6.2$ Hz), 4.82 (dd, 1H, $J = 10.8$ Hz, $J = 3.8$ Hz), 3.77 (s, 3H), 3.64 (s, 3H), 3.59 (s, 1H), 3.27 (s, 1H), 1.28 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.7, 160.0, 157.9, 130.2, 129.9, 129.3, 123.2, 121.4, 119.7, 118.2, 114.3, 99.4, 79.0, 61.3, 59.9, 55.2, 52.7, 20.6. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 61.85; H, 5.68; N, 7.31.

(2*S*,3*S*,4*R*,5*S*)-5-(2-Hydroxyphenyl)-3-(methoxycarbonyl)-4-methyl-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*f*-exo isomer): mp 181–183 °C; IR 3348, 1733, 1330, 1387 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 10.60 (s, 1H), 5.31 (t, 1H, $J = 4.4$ Hz), 4.62 (dd, 1H, $J = 9.9$ Hz, $J = 4.4$ Hz), 4.55 (d, 1H, $J = 9.9$ Hz), 3.78 (s, 3H), 3.49 (s, 3H), 3.10 (s, 1H), 3.02 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.1, 159.4, 158.0, 130.7, 130.2, 129.3, 125.9, 118.7, 117.6, 113.9, 98.2, 70.9, 61.9, 55.2, 55.0, 52.2, 18.0. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 61.40; H, 5.32; N, 7.14.

(2*S*,3*R*,4*S*,5*S*)-2,4-Dimethyl-5-(2-hydroxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*g*-endo isomer): mp 123–125 °C; IR 3278, 1725, 1568, 1377 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 11.03 (s, 1H), 5.22 (d, 1H, $J = 5.9$ Hz), 4.54 (s, 1H), 3.91 (d, 1H, $J = 5.0$ Hz), 3.82 (s, 3H), 3.80 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 176.4, 159.4, 158.1, 132.8, 129.9, 129.3, 125.6, 119.7, 118.7, 117.4, 113.8, 99.5, 66.5, 66.3, 61.7, 55.2, 53.4, 24.2, 18.8. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.02; N, 7.00. Found: C, 63.47; H, 6.02; N, 6.91.

(2*S*,3*S*,4*R*,5*S*)-2,4-Dimethyl-5-(2-hydroxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*g*-exo isomer): mp 179–180 °C; IR 3378, 1716, 1534, 1375 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 11.10 (s, 1H), 5.38 (s, 1H), 4.27 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 2.52 (s, 3H), 1.75 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 174.2, 159.7, 158.4, 131.3, 130.2, 129.2, 124.5, 116.4, 117.7, 114.9, 113.8, 98.6, 69.0, 67.0, 63.7, 55.2, 52.5, 27.3, 19.1. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.53; H, 6.13; N, 6.89.

(2*S*,3*S*,4*R*,5*S*)-3-(4-Methoxyphenyl)-5-(3-methoxyphenyl)-4-nitropyrrolidine (4*h*-endo isomer): mp 94–97 °C; IR 3326, 1733, 1548, 1354 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.21 (dd, 1H, $J = 7.6$ Hz, $J = 6.2$ Hz), 4.03 (d, 1H, $J = 7.6$ Hz), 4.53 (dd, 1H, $J = 8.7$ Hz, $J = 6.2$ Hz), 3.76 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.2, 159.3, 157.2, 129.2, 129.2, 128.8, 128.4, 125.1, 121.0, 113.9, 110.7, 83.5, 61.5, 53.2, 31.3, 31.7. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 61.89; H, 5.70; N, 7.26.

(2*S*,3*R*,4*S*,5*S*)-2-(Methoxycarbonyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-2-methyl-4-nitropyrrolidine (4*i*-endo isomer): mp 122–123 °C; IR 3342, 1724, 1541, 1372 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.26 (d, 1H, $J = 6.8$ Hz), 4.96 (dd, 1H, $J = 6.8$ Hz, $J = 4.5$ Hz), 4.17 (d, 1H, $J = 4.5$ Hz), 3.86 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 2.94 (s, 1H), 1.01 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 175.4, 159.0, 157.0, 130.0, 128.9, 127.8, 126.4, 120.5, 115.8, 110.1, 97.0, 69.0, 60.1, 56.8, 55.2, 54.7, 52.9, 23.2. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.19; H, 5.81; N, 7.37.

(2*S*,3*R*,4*S*,5*S*)-2,4-Dimethyl-5-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-4-nitropyrrolidine (4*k*-endo isomer): mp 132–134 °C; IR 3332, 1731, 1510, 1348 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.13 (s, 1H), 5.17 (s, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.19 (s, 1H), 1.18 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 177.3, 158.9, 155.9, 132.6, 128.6, 128.0, 127.1, 125.7, 120.4, 113.2, 109.6, 98.3, 67.7, 63.4, 61.5, 55.1, 54.7, 52.7, 23.7, 20.0. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_6$: C, 63.74; H, 6.34; N, 6.92. Found: C, 63.05; H, 6.52; N, 6.98.

(2*S*,3*S*,4*R*,5*S*)-3-(4-Methoxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-5-(2-methoxyphenyl)-4-nitropyrrolidine (4*l*-endo isomer): mp 150–152 °C; IR 3344, 1725, 1536, 1334 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.31 (s, 1H), 4.50 (s, 1H), 3.24 (s, 3H), 3.10 (s, 3H), 3.03 (s, 3H), 2.75 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 175.9, 159.1, 157.3, 134.7, 134.2, 127.4, 125.0, 120.6, 115.6, 110.2, 103.0, 59.6, 66.3, 63.8, 61.2, 51.9, 21.9, 20.0. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_6$: C, 63.74; H, 6.34; N, 6.92. Found: C, 63.95; H, 6.16; N, 6.88.

(2*S*,3*R*,4*S*,5*S*)-5-(3-Chlorophenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*l*-endo isomer): mp 141–143 °C; IR 3277, 1714, 1546, 1362 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 3.35 (d, 1H, $J = 6.7$ Hz, $J = 4.5$ Hz), 4.06 (d, 1H, $J = 6.7$ Hz, $J = 4.5$ Hz), 3.74 (s, 3H), 4.10 (s, 3H), 3.26 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.4, 154.1, 149.4, 130.8, 131.0, 129.4, 128.4, 122.0, 95.9, 67.9, 67.0, 59.5, 52.5. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_6$: C, 56.43; H, 4.71; N, 11.86. Found: C, 57.25; H, 4.52; N, 11.41.

(2*S*,3*R*,4*S*,5*S*)-5-(4-Chlorophenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*l*-exo isomer): mp 140–142 °C; IR 3278, 1714, 1546, 1362 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 3.35 (d, 1H, $J = 6.7$ Hz, $J = 6.1$ Hz), 4.06 (d, 1H, $J = 6.7$ Hz, $J = 6.1$ Hz), 3.74 (s, 3H), 4.10 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.4, 154.1, 149.4, 130.8, 131.0, 129.4, 128.4, 122.0, 95.9, 67.9, 67.0, 59.5, 52.5. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_6$: C, 56.43; H, 4.71; N, 11.86. Found: C, 56.98; H, 4.39; N, 11.29.

(2*S*,3*R*,4*S*,5*S*)-5-(3-Methoxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*m*-exo isomer): mp 112–114 °C; IR 3290, 1742, 1550, 1368 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.43 (s, 1H), $J = 6.5$ Hz), 4.72 (d, 1H, $J = 6.5$ Hz), 4.50 (d, 1H, $J = 4.7$ Hz), 4.37 (d, 1H, $J = 8.7$ Hz, $J = 4.7$ Hz), 3.91 (s, 3H), 3.73 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 175.8, 159.2, 157.6, 130.7, 129.3, 128.6, 128.2, 123.3, 113.9, 98.6, 69.0, 63.6, 54.4, 51.9. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 63.05; H, 6.02; N, 6.91.

(2*S*,3*R*,4*S*,5*S*)-5-(3-Chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-2-(methoxycarbonyl)-4-nitropyrrolidine (4*n*-endo isomer): mp 147–149 °C; IR 3310, 1728, 1549, 1538 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.31 (s, 1H), 5.09 (t, 1H, $J = 4.8$ Hz), 4.37 (d, 1H, $J = 6.2$ Hz), 4.05 (d, 1H, $J = 6.2$ Hz), 3.34 (s, 3H), 3.30 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (δ ppm, CDCl_3) 171.9, 147.0, 146.2, 131.3, 127.1, 126.4, 123.2, 120.0, 110.7, 114.8, 108.3, 91.8, 67.4, 63.8, 61.2, 52.7, 21.9. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{ClN}_2\text{O}_6$: C, 56.09; H, 4.70; Cl, 3.49. Found: C, 56.82; H, 4.57; Cl, 3.67.

(2*S*,3*R*,4*S*,5*S*)-5-(2-Hydroxy-3-methoxyphenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*n*-exo isomer): mp 123–124 °C; IR 3312, 1725, 1547, 1534 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.15 (s, 1H), 5.15 (t, 1H, $J = 4.8$ Hz), 4.43 (d, 1H, $J = 6.0$ Hz), 4.32 (t, 1H, $J = 6.0$ Hz), 3.72 (s, 3H), 3.77 (s, 3H), 3.28 (s, 3H), 2.63 (s, 1H); ^{13}C NMR (δ ppm, CDCl_3) 176.5, 153.4, 147.0, 146.1, 129.6, 128.9, 127.8, 126.4, 120.5, 115.8, 110.1, 97.0, 69.0, 60.1, 56.8, 55.2, 54.7, 23.2. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.22; H, 5.89; N, 6.86.

(2*S*,3*R*,4*S*,5*S*)-5-(3-Chlorophenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*o*-endo isomer): mp 123–124 °C; IR 3312, 1725, 1547, 1534 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.15 (s, 1H), 5.15 (t, 1H, $J = 4.8$ Hz), 4.43 (d, 1H, $J = 6.0$ Hz), 4.32 (t, 1H, $J = 6.0$ Hz), 3.72 (s, 3H), 3.77 (s, 3H), 3.28 (s, 3H), 2.63 (s, 1H); ^{13}C NMR (δ ppm, CDCl_3) 176.5, 153.4, 147.0, 146.1, 129.6, 128.9, 127.8, 126.4, 120.5, 115.8, 110.1, 97.0, 69.0, 60.1, 56.8, 55.2, 54.7, 23.2. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.22; H, 5.89; N, 6.86.

(2*S*,3*R*,4*S*,5*S*)-5-(3-Chlorophenyl)-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (4*o*-exo isomer): mp 123–124 °C; IR 3312, 1725, 1547, 1534 cm^{-1} ; ^1H NMR (δ ppm, CDCl_3) 5.15 (s, 1H), 5.15 (t, 1H, $J = 4.8$ Hz), 4.43 (d, 1H, $J = 6.0$ Hz), 4.32 (t, 1H, $J = 6.0$ Hz), 3.72 (s, 3H), 3.77 (s, 3H), 3.28 (s, 3H), 2.63 (s, 1H); ^{13}C NMR (δ ppm, CDCl_3) 176.5, 153.4, 147.0, 146.1, 129.6, 128.9, 127.8, 126.4, 120.5, 115.8, 110.1, 97.0, 69.0, 60.1, 56.8, 55.2, 54.7, 23.2. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$: C, 62.98; H, 6.05; N, 7.00. Found: C, 62.22; H, 5.89; N, 6.86.

The Power of Visual Imagery in Synthesis Planning. Stereocontrolled Approaches to CGP-60536B, a Potent Renin Inhibitor

Stephen Hanessian,* Stephen Claridge, and Shawn Johnstone

Department of Chemistry, Université de Montréal, C.P. 6128, Succursale Centre-ville,
Montréal, Québec H3C 3J7, Canada

stephen.hanessian@umontreal.ca

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Two strategies were developed toward the stereocontrolled synthesis of 8-aryl-3-hydroxy-4-amino-2,7-diisopropyloctanoic acids with predetermined stereogenic centers. This is a generic motif in a new class of potent inhibitors of the enzyme renin, exemplified by CGP-60536B. The synthesis relies on the utilization of L-pyroglutamic acid as chiron, and proceeds through the incorporation of required functionality by exploiting internal induction. One of the strategies shows the power of visual imagery in synthesis planning, akin to a Dali-like representation of objects that can be viewed in more than one way. Thus, the entire carbon skeleton of the target molecule is encompassed in a partially functionalized bicyclic indolizidinone precursor. In a second strategy, an intermediate common to the first approach is elaborated into an appended γ -lactone which is alkylated through enolate chemistry and ultimately transformed into the intended target compound. X-ray crystallography was used to corroborate the structures and stereochemistries of several intermediates.

Introduction

The aspartic protease renin¹ has been associated with the cascade of events involving the selective cleavage of a Leu-Val bond in angiotensinogen to angiotensin I, in the so-called renin-angiotensin system (RAS). Further enzymatic cleavage produces the octapeptide angiotensinogen II, a vasoconstricting peptide resulting eventually in hypertension in man.² A major advance was made in 1982 when renin inhibitors were synthesized on the basis of a transition-state structure to replace the scissile bond.³ Dipeptide hydroxyethylene and related isosteres of the Leu-Val bond in the natural substrate were actively pursued by many groups.⁴ Intensive efforts on the chemical and biological fronts followed over the past two decades, leading to a better understanding of the molecular events involved in the release of renin in animal models, and its inhibition by designed transition-state-based inhibitors.⁵ Nonpeptidic inhibitors of renin based on substituted piperidines with remarkable activity have been reported.⁶ The amide backbone of renin

inhibitors has been replaced with nonpeptidic vinyllogous amides showing low micromolar inhibition *in vitro*.⁷ Several drug candidates were successfully developed

* To whom correspondence should be addressed. Phone: (514) 343-6738. Fax: (514) 343-5728.

(1) (a) Reid, I. A.; Morris, R. J.; Ganong, W. F. *Annu. Rev. Physiol.* **1978**, *40*, 377. (b) Skeggs, L. T.; doven, F. E.; Levins, M.; Lentz, K.; Kahn, J. R. In *The Renin-Angiotensin System*; Johnson, J. A., Anderson, R. R., Eds.; Plenum Press: New York, 1980; p 1. (c) McGregor, G. A.; Markandu, N. D.; Roulston, J. E.; Jones, J. C.; Morton, J. J. *Nature* **1981**, *291*, 329.

(2) (a) Antonaccio, M. J. *Annu. Rev. Pharmacol. Toxicol.* **1982**, *22*, 57. (b) Patchett, A. A.; Cordes, E. H. *Adv. Enzymol.* **1985**, *57*, 1. (c) Vallotton, M. B. *Trends Pharmacol. Sci.* **1987**, *8*, 69. (d) Boger, J. *Trends Pharmacol. Sci.* **1987**, *8*, 370.

(3) (a) Szelke, M.; Jones, D. M.; Atrash, B.; Hallett, A.; Leckie, B. J. In *Peptides, Structure and Function*, Proceedings of the Eight American Peptide Symposium; Hruby, V. J., Rich, D. H., Eds.; Pierce Chemical Co.: Rockford, IL, 1983; p 379. (b) Foundling, S. I.; Cooper, J.; Watson, F. E.; Cleasby, A.; Pearl, L. H.; Sibanda, B. L.; Hemmings, A.; Wood, S. P.; Blundell, T. L.; Valler, M. J.; Norey, C. G.; Kay, J.; Boger, J.; Dunn, B. M.; Leckie, B. J.; Jones, D. M.; Atrash, B.; Hallett, A.; Szelke, M. *Nature* **1987**, *327*, 349.

(4) For selected examples, see: (a) Evans, B. E.; Rittle, K. E.; Honnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (b) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828. (c) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374. (d) Bolis, G.; Fung, A. K. L.; Greer, J.; Kleinert, H. D.; Marcotte, P. A.; Perum, T. J.; Plattner, J. J.; Stein, H. H. *J. Med. Chem.* **1987**, *30*, 1729. (e) Thaisrivongs, S.; Fals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976. (f) Bühlmyer, P.; Caselli, A.; Fuhrer, W.; Göschke, R.; Rasetti, V.; Rüeger, H.; Stanton, J. L.; Criscione, L.; Wood, J. M. *J. Med. Chem.* **1988**, *31*, 1839. (g) Wuts, P. G. M.; Putt, S. R.; Ritter, A. R. *J. Org. Chem.* **1988**, *53*, 4503. (h) Luly, J. R.; BaMaung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H. H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Green, J.; Perum, T. J.; Plattner, J. J. *J. Med. Chem.* **1988**, *31*, 2264. (i) Nishi, T.; Kataoka, M.; Morisawa, Y. *Chem. Lett.* **1989**, 1993. (j) Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178. (k) Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* **1989**, *30*, 3845. (l) Chakravaty, P. K.; de Laszlo, S. E.; Samella, C. S.; Springer, J. P.; Schuda, P. F. *Tetrahedron Lett.* **1989**, *30*, 415. (m) Shiozaki, M.; Hata, T.; Furukawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3669. (n) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. (o) D'Aniello, F.; Géhanne, S.; Taddei, M. *Tetrahedron Lett.* **1992**, *33*, 5621. (p) Baker, W. R.; Condon, S. L. *Tetrahedron Lett.* **1992**, *33*, 1581. (q) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 547. (r) Pegorier, L.; Larchevesque, M. *Tetrahedron Lett.* **1992**, *33*, 1581.

(5) For selected reviews, see: (a) Kleinert, H. D. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1087. (b) Middlemiss, D.; Watson, S. P. *Tetrahedron* **1994**, *50*, 13049. (c) O'Carroll, T. D.; Abou-Gharbia, M. *Drugs Future* **1991**, *16*, 37. (d) Hutchins, C.; Greer, J. *Crit. Rev. Biochem. Mol. Biol.* **1991**, *26*, 77. (e) Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173. (f) McAreavey, D.; Robertson, J. J. S. *Drugs* **1990**, *40*, 326. (g) Greenlee, W. J. *Pharm. Res.* **1987**, *4*, 364. (h) Antonaccio, M. J.; Wright, J. J. *Prog. Drug Res.* **1987**, *31*, 161. (i) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263.

(6) (a) Vieira, E.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H. P.; Müller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. *Biochem. Med. Chem. Lett.* **1999**, *9*, 1397. (b) Oefner, C.; Binggeli, A.; Breu, V.; Bur, D.; Clozel, J.-P.; D'Arcy, A.; Dorn, A.; Fischli, W.; Grüniger, F.; Güller, R.; Hirth, G.; Märki, H. P.; Mathews, S.; Müller, M.; Ridley, R. G.; Stadler, H.; Vietra, E.; Wilhelm, M.; Winkler, F. K.; Wostl, W. *Chem. Biol.* **1999**, *6*, 127.

(7) Smith, A. B., III; Akaishi, R.; Jones, D. R.; Keenan, T. P.; Guzman, M. C.; Holcomb, R. C.; Sprengeler, P. A.; Wood, J. L.; Hirschmann, R.; Holloway, M. K. *Biopolymers* **1995**, *37*, 29.

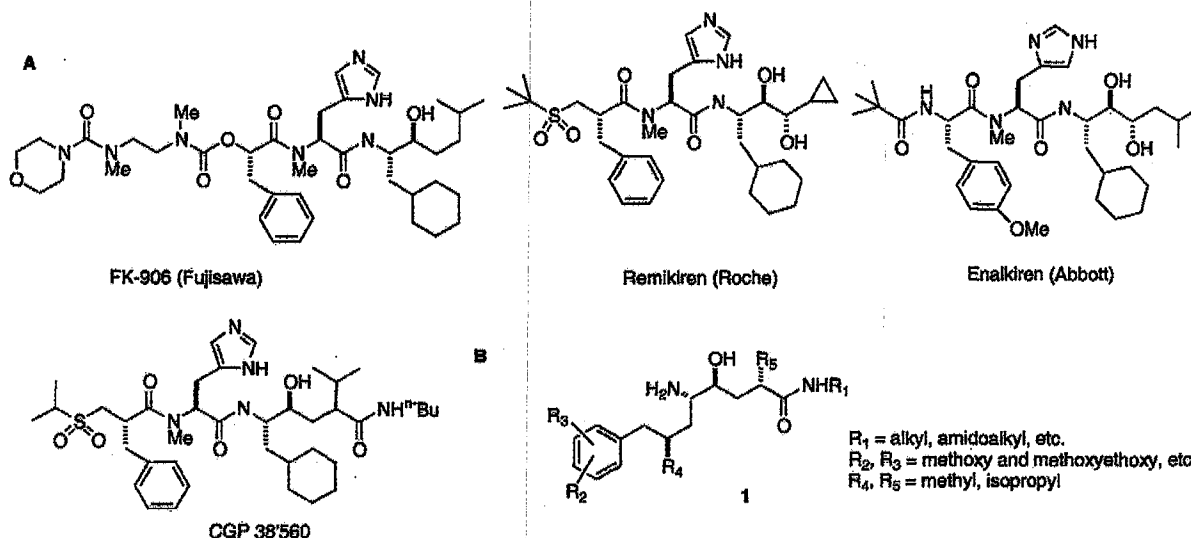


Figure 1.

worldwide, culminating with compounds that exhibited potent in vitro and in vivo activities, although good bioavailability remained as a major challenge. Unfortunately, these programs were eventually terminated virtually in every pharmaceutical company, primarily for strategic marketing reasons. Although good pharmacokinetics and excellent antihypertensive activity were achieved with some compounds in experimental animals, a major obstacle was concerned with oral bioavailability in man, and in devising cost-effective syntheses. The structures of some of these compounds, harboring four or more stereogenic centers, with heterocyclic, alkyl, and hydroxy appendages on a peptidic backbone are shown in Figure 1A. More recently, a new class of inhibitors having the general structure 1 (Figure 1B), and exhibiting sub-nanomolar specific binding affinity to human renin, with excellent oral activity in primates, was reported.⁸ The generic structure 1, varying in the nature of the aromatic substituents, the amide moiety, and the alkyl groups, represents a novel carbon backbone with unique binding affinities to renin. Of particular significance was the nonpeptidic nature of the truncated tetrasubstituted 8-aryloctanoic acid amide backbone in 1, in which the P_1 - P_4 units of peptide-type inhibitors (Figure 1B) were modified by directly linking P_1 - P_3 moieties as shown in another series.^{9,10} X-ray crystal structure data of recombinant glycosylated renin with a representative analogue of 1 revealed favorable hydrophobic and hydrogen-bonding interactions within the S_3 - S_2 subsites, which were not utilized by peptidic inhibitors.¹¹ Extensive optimization of the backbone appendages in the 8-aryloctanoic acid motif revealed a distinct preference for two isopropyl groups with 2*R*,7*R*-

configurations rather than methyl or combinations thereof, as indicated in the generic structure 1.¹¹

Very recently, two synthesis routes to CGP-60536B, an analogue of 1 (where R_1 = 2,2-dimethylpropionamide, R_2, R_3 = dialkoxy; R_4, R_5 = isopropyl), representing original efforts at ex.Ciba-Geigy in Basel¹² and the U.K.,¹³ respectively, were published. Both groups utilized a convergent approach where a derivative of 2*R*-isopropyl-4*R*-hydroxymethylbutyrolactone, obtained by auxiliary-mediated asymmetric alkylation¹⁴ of appropriate amide enolates, was a key chiron. Despite the need for chromatographic separation of mixtures of diastereomers, it was possible to develop viable routes to the target structure. The source of nitrogen in the β -hydroxy amino alcohol portion of 1 was azide ion, introduced via an S_N2 -type inversion of a suitably protected diol intermediate. A third synthesis was based on nitron chemistry, and led to the target compound as a minor diastereomer.¹⁵ A synthesis of *N*-substituted 2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoylamides has been reported in the recent patent literature.¹⁶

We report herein a full account of our efforts toward the development of stereocontrolled synthesis routes aimed at the generic structure 1, while allowing flexibility for variations in the aromatic substituents and the nature of the amide moiety. In considering various practical approaches, we chose to capitalize on a synthesis plan that utilizes readily available *N*-containing chiral templates as starting materials, thus avoiding the potential hazards of azide reagents. Added to this daunting task was the desire to combine practicality with innovation, even if the project was an academically based endeavor.¹⁷

(8) (a) Göschke, R.; Cohen, N. C.; Wood, J. M.; Maibbaum, J. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2735. (b) Göschke, R.; Maibbaum, J. K.; Schilling, W.; Stutz, S.; Rigollier, P.; Yamaguchi, Y.; Cohen, N. C.; Herold, P. U.S. Patent 5,654,445, Aug 5, 1997.

(9) Lefker, B. A.; Hada, W. A.; Right, A. S.; Martin, W. H.; Stock, I. A.; Schulte, G. K.; Pandit, J.; Danley, D. E.; Ammirati, M. J.; Sneedon, S. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2623.

(10) (a) Plummer, M. S.; Shahripour, A.; Kaltenbronn, J. S.; Lunney, E. A.; Steinbaugh, B. A.; Hamby, J. M.; Hamilton, H. W.; Sawyer, T. K.; Humblet, C.; Doherty, A. M.; Taylor, M. D.; Hingorani, G.; Batley, B. L.; Rapundalo, S. T. *J. Med. Chem.* **1995**, *38*, 2893. (b) Plummer, M. S.; Hamby, J. M.; Hingorani, G.; Batley, B. L.; Rapundalo, S. T. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2119.

(11) Rahuel, J.; Rasetti, V.; Maibbaum, J.; Rüegger, H.; Göschke, R.; Cohen, N. C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Grütter, M. G. *Chem. Biol.* **2001**, *7*, 493.

(12) Rüegger, H.; Stutz, S.; Göschke, R.; Spindler, F.; Maibbaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085.

(13) Sandham, d. A.; Taylor, R. J.; Carey, J. S.; Fässler, A. *Tetrahedron Lett.* **2000**, *41*, 10091.

(14) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(15) Dondoni, A.; DeLathauwer, G.; Perrone, D. *Tetrahedron Lett.* **2001**, *42*, 4819.

(16) Herold, P.; Stutz, S.; Indolese, A. WO 109083, Feb 8, 2001.

(17) For a previous approach, see: Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1696.

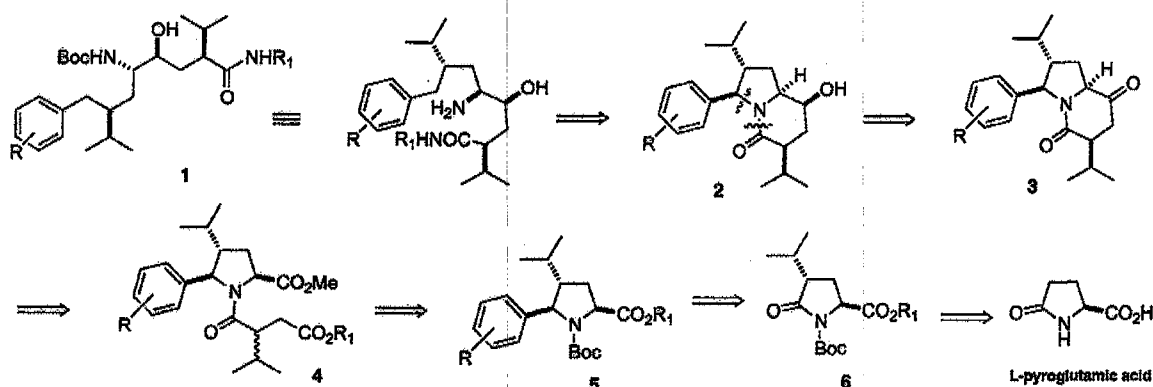


Figure 2.

The retrosynthetic analysis of an 8-aryl-2*R*-isopropyl-3*S*-hydroxy-4*S*-amino-6*S*-isopropyloctanoic acid amide representing the prototypical structure of 1 ($R_2 \approx H$, p -methoxy; $R_3 = H$; $R_4, R_5 = \text{isopropyl}$) is shown in Figure 2. Inspection of the generic backbone structure of 1 with the required substituents reveals that it may be derived from 2 by two logical disconnections, involving cleavage of the lactam and the hydrogenolysis of the *N*-benzyl bond in the pyrrolidine motif (Figure 2). The alcohol 2 may, in turn, be obtained by a simple diastereoselective reduction of ketolactam 3, originating from an intramolecular Dieckmann cyclization reaction between the two ester moieties of 4. To simplify the process, our original plan called for the utilization of a racemic 2-isopropyl succinate side chain as in 4, with the hope that the correct stereochemistry could be attained by equilibration of the unwanted isomer en route to the intended target 3. Amide 4 would be obtained from the pyrrolidine 5, itself synthesized from pyrrolidinone 6 via the diastereoselective addition of aryl cuprates¹⁸ to an intermediate iminium ion precursor.¹⁹ Finally, pyrrolidinone 6 would be prepared from the readily available L-pyrogutamic acid²⁰ by a stereocontrolled introduction of the isopropyl group. The synthesis plan shown in Figure 2 presented a number of practical advantages, in addition to being innovative in design.

The principle of using conformational constraint to control stereochemistry, as well as to avoid protective group manipulations, is particularly noteworthy in this strategy. It is also of heuristic interest to point out the value of visual imagery in synthesis planning.²¹ Depicting the familiar acyclic representation of the target structure 1 as one whose backbone overlaps better *visually* with the bicyclic lactam 2 reveals a strategy that may not have been so obvious otherwise. Once assembled as 2, it would

suffice to cleave two bonds, thereby unveiling the intended acyclic target structure 1. Attractive as this Dali-esque synthetic plan appeared to be,²² it was imperative to test its feasibility, particularly as related to stereochemistry issues and overall efficacy.

Results

The first task in this synthesis was the introduction of the 2*R*-isopropyl group in a suitably protected L-pyrogutamic acid. Unlike many examples of lactam enolate alkylations with reactive halides such as methyl, benzyl, or allyl in a pyrogutamic ester motif,²³ the introduction of an isopropyl group has few precedents.²⁴ In fact, the treatment of the lithium, potassium, or magnesium enolates of *N*-Boc-L-pyrogutamic acid methyl ester 7 (Scheme 1) with isopropyl iodide failed to give any of the desired 4-isopropylated lactam. We were successful in adding acetone to the lithium enolate of 7 to give 8 in 85% yield as a 5:1 mixture of *anti*- and *syn*-isomers, respectively, with no evidence of racemization of the ester.²⁵ The diastereoselectivity of the acetone addition reaction could be raised to >10:1 in favor of the desired *anti*-isomer by using the bulkier benzylhydrol ester to direct the approach of the electrophile. It was decided to proceed with the methyl ester and to separate diastereomers further downstream. Moreover, we surmised that the methyl ester would be a better intermediate in the intended intramolecular Dieckmann condensation. Thus, protection of the tertiary alcohol of the 5:1

(22) For fascinating examples of concealed imagery in Salvador Dali's work, see, for example: (a) Slave Market with Visible Bust of Voltaire, 1940, Dali Museum, St. Petersburg, FL. (b) Gala Looking at the Mediterranean Sea-Concealed Portrait of Lincoln, 1976, Minami Museum, Tokyo.

(23) See, for example: (a) Ezquerro, J.; Pedregal, C.; Yruetagoena, B.; Rubio, A.; Carreno, M. C.; Escribano, A.; Ruano, J. L. G. *J. Org. Chem.* **1995**, *60*, 2925. (b) Brena-Valle, L. J.; Sanchez, R. C.; Cruz-Almanza, R. *Tetrahedron Lett.* **1996**, *37*, 1019. (c) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emmet, E. A.; Schleif, W. A.; Quintero, J. C.; Liu, J. H.; Chen, I.-W.; Holloway, H. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3445. (d) Maldaner, A.; Pilli, R. A. *Tetrahedron* **1999**, *55*, 13321. (e) Charrier, J.-D.; Duffy, J. E.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1998**, *39*, 2199.

(24) For lactone enolates, see: Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020. For lactam enolates, see: Meyers, A. L.; Wallace, R. H.; Harre, M.; Garland, R. *J. Org. Chem.* **1990**, *55*, 3137.

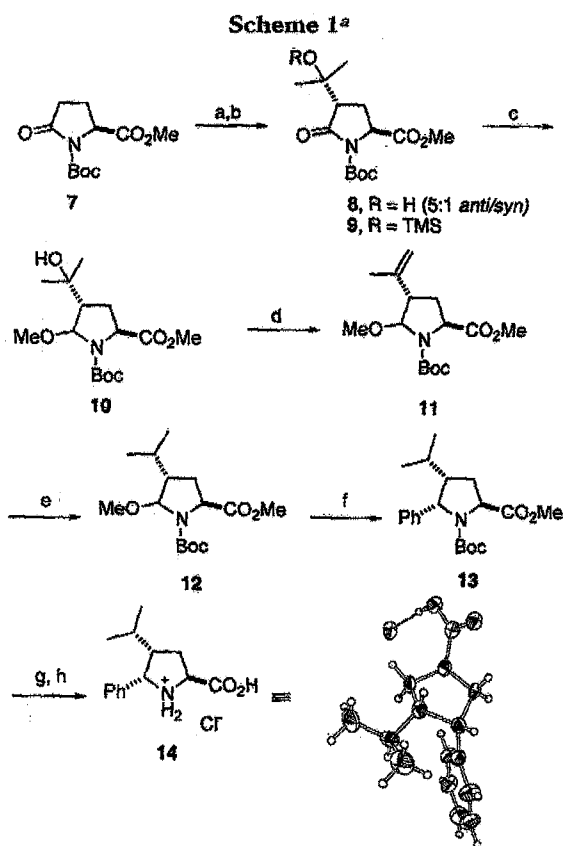
(25) For examples of aldol reactions with lactam enolates, see: (a) Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920. (b) Dikshit, D. K.; Bajpai, S. N. *Tetrahedron Lett.* **1995**, *36*, 3231. (c) Escribano, A.; Ezquerro, J.; Pedregal, C.; Rubio, A.; Yruetagoena, B.; Baker, S. R.; Wright, R. A.; Johnson, B. G.; Schoep, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 765.

(18) (a) Kemp, D. S.; Renold, P.; McClure, K. F. *J. Org. Chem.* **1995**, *60*, 454. (b) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1990**, *44*, 707. (c) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron* **1991**, *47*, 573. (d) Thanning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1992**, *46*, 194. (e) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1994**, *48*, 367. (f) Zietlow, A.; Streckan, E. *J. Org. Chem.* **1994**, *59*, 5658. (g) Cellmène, C.; Dhiman, H.; Le Bail, M.; Lhomme, G. *Tetrahedron Lett.* **1994**, *35*, 6105. (h) Collado, I.; Pedregal, C.; Ezquerro, J. *J. Org. Chem.* **1995**, *60*, 5011.

(19) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.5, p 1047.

(20) For a review, see: Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245.

(21) Hanessian, S.; Franco, J.; Larouche, B. *Pure Appl. Chem.* **1990**, *62*, 1887.



^a Reagents and conditions: (a) LiHMDS, -78°C , THF, then acetone, 85%; (b) TMSCl, imidazole, DCM, 70%; (c) DIBAL, -78°C , THF, then MeOH, pTSA, 95%; (d) MsCl, DMAP, Et₃N, 72%; separation of minor *syn*-isomer; (e) H₂, Pd/C, EtOAc, NaHCO₃, 82%; (f) PhMgBr, CuBr-Me₂S, BF₃·OEt₂, THF, 89%; (g) LiOH, THF/H₂O; (h) HCl, dioxane, 80% (two steps).

mixture of diastereomers **8** as a TMS ether afforded **9**, which was reduced with DIBAL-H to give the corresponding mixture of hemiaminals. Subsequent treatment with acidic methanol afforded the methoxy analogue **10** in high overall yield. Mesylation of **10**, followed by base-catalyzed elimination, proceeded regioselectively to give the alkene **11** exclusively, which could be separated from the minor *syn*-2-propenyl isomer by chromatography. Hydrogenation over Pd/C in the presence of sodium carbonate gave the desired *O*-methyl hemiaminal **12** in excellent yield. An alternative synthesis of **12** in our laboratory relied on a radical-induced deoxygenation^{26,27} of the half methyloxalate ester of **8**.²⁸ Thus, we had successfully introduced an isopropyl group with the desired regio- and enriched stereochemistry in six high-yielding steps starting from the readily available **7**. The next task was to explore methods for the introduction of an aryl group following the synthesis plan outlined in Figure 1. We focused on introducing phenyl and *p*-methoxyphenyl groups as prototypes, and further exploring chemistry toward the elaboration of the generic structure **1**. Thus, treatment of **12** with 4 equiv of a mixture of phenylmagnesium bromide, copper bromide-

dimethyl sulfide complex, and boron trifluoride diethyl etherate¹⁸ⁱ resulted in the formation of an adduct, **13**, in 89% yield (Scheme 1). Deprotection of the *N*-Boc and ester groups afforded a crystalline proline analogue, **14**, whose structure was ascertained by single-crystal X-ray crystallography. Contrary to expectations based solely on steric effects, the phenyl group had been introduced from a trajectory of attack on the intermediate iminium ion that was *opposite* the ester group and *syn* to the isopropyl group. The coordination of the ester group with the excess organometallic reagent, coupled with a possible conformational change as a result of such a steric encumbrance, may explain the observed result. It is of interest that the steric effect imposed by the 4-isopropyl group is counterbalanced by the bulk of the coordinated ester in directing the attack on the iminium ion. The formation of *anti*-adducts in the reaction of *N*-Boc iminium ions derived from *L*-pyroglutamic esters with organocopper reagents has been rationalized on the basis of complexation with the ester, resulting in a shielding of the *syn*-face.^{18c,d,h} This tendency also overrides the 1,2-induction of a C-4 substituent,^{18h} as observed in the case of **13**. However, exceptions to this stereochemical course of *anti*-addition can be found.^{18a}

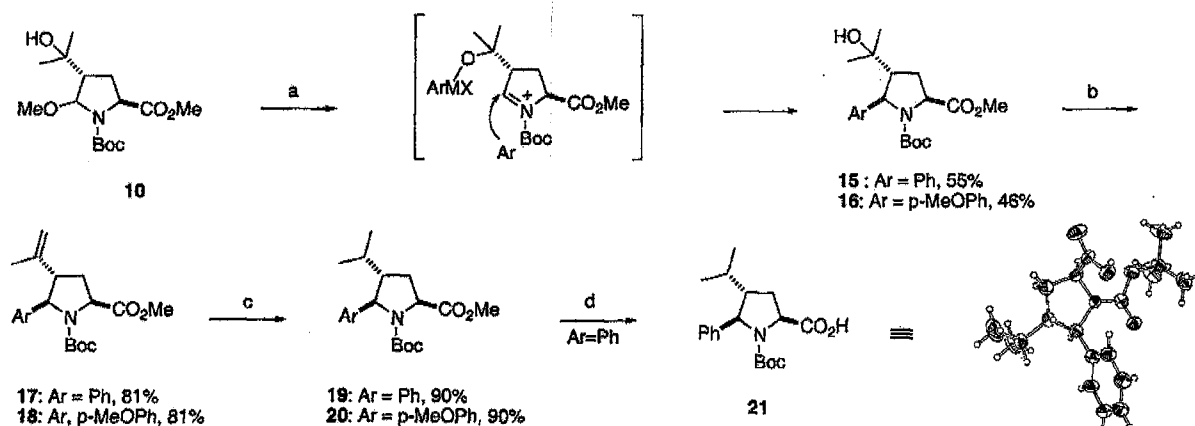
In an alternative approach, we opted to introduce the phenyl group prior to deoxygenation of the tertiary alcohol (Scheme 2). In this strategy one would expect the nucleophile to approach the iminium ion from the side opposite the bulky metal alkoxide organic complex, provided excess reagent was used. Thus, treatment of **10** with 5 equiv of the phenylmagnesiumcuprate reagent gave the corresponding adduct **15** in 55% yield as a 5:1 mixture of diastereomers. Reaction of the alcohol with mesyl chloride, triethylamine, and DMAP gave the corresponding alkene **17**, which could be separated from the minor *syn*-isomer by column chromatography. Catalytic hydrogenation afforded **19** as a single isomer in high overall yield. There was no evidence of any product arising from ring opening by hydrogenolysis. Hydrolysis of the ester with lithium hydroxide gave the acid **21**, which after X-ray analysis showed that the phenyl group had, in fact, added to the iminium ion in an *anti* fashion to the alkoxy isopropyl group. The same sequences were performed in the *p*-methoxyphenyl series to give **16**, which was further transformed to **20** as described for the phenyl analogue (Scheme 2). With both 4,5-*syn*-proline **14** and 4,5-*anti*-prolines **19** and **20**, available in enantiopure form, we turned to the introduction of the second isopropyl group and to test the prospects of a Dieckmann cyclization.²⁹ It was interesting that a cursory literature search for carrying out the synthesis of substituted indolizidinones such as **3** (Figure 2) by a Dieckmann cyclization showed no precedents,³⁰ which heightened our interest to pursue this strategy. The more directly accessible 4,5-*anti*-proline analogue **19** was investigated. Removal of the Boc group, and converting the resulting product to the monobenzyloxycarbonyl 2-isopropylsuccinamide **22** proceeded smoothly to give a 1:1 mixture of diastereomers (Scheme 3).

Subsequent treatment with KHMDS at -50°C gave a bicyclic product, **23**, which after hydrogenolysis and decarboxylation was converted to **24**. Isolated as a single isomer in only 30% yield. Numerous attempts at improving the yield by variations of bases proved futile. Having reached this stage in our planned sequence, we decided to continue the synthesis despite this apparent setback.

(26) Dolan, S. C.; MacMillan, J. J. *Chem. Soc., Chem. Commun.* **1983**, 1588. See also ref 4h.

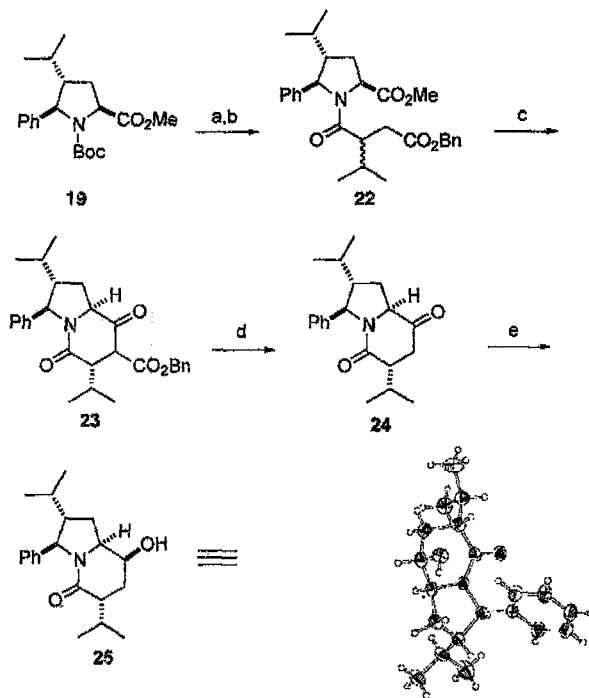
(27) Hanessian, S.; Abad-Grillo, T.; McNaughton-Smith, G. *Tetrahedron* **1997**, 53, 6281.

(28) Hanessian, S.; McNaughton Smith, G. Unpublished results.

Scheme 2^a

^a Reagents and conditions: (a) PhMgBr (or p-MeOC₆H₄Li, CuBr-Me₂S, BF₃·OEt₂, THF; (b) MsCl, DMAP, Et₃N; (c) H₂, 10% Pd/C, EtOAc; (d) LiOH, MeOH, H₂O, 95%.

Reduction of the carbonyl group in **24** with L-Selectride gave the corresponding alcohol whose structure and absolute stereochemistry were definitively shown to be **25** on the basis of a single-crystal X-ray analysis. Except for an important stereochemical caveat revealed in the opposite orientation of the new isopropyl group, we had indeed succeeded in elaborating the entire carbon skeleton and required functionalities in **1**. Each chemical step leading to the bicyclic product **25** had proceeded with excellent stereoselectivity, thus validating to a large measure our original synthetic plan (Figure 2). Attempts to epimerize the 2*S*-isopropyl-bearing carbon using a variety of conditions³¹ resulted in the recovery of starting material with no trace of the desired epimer. A simple rationalization of the results is illustrated in Scheme 4. On the basis of the presence of equal proportions of amides **22a** and **22b**, it is clear why isomer **23**, possibly arising from a hypothetical chairlike conformation in the *pro-S*-isomer **22a** with a predisposed pseudoequatorial isopropyl group, is the observed product. An analogous

Scheme 3^a

^a Reagents and conditions: (a) TFA, toluene, 95%; (b) BOPCl, Pr₂NEt, HO₂CCH(CHMe)₂CH₂CO₂Bn, 85%; (c) KHMDS, THF, -50 °C; (d) H₂, Pd/C, 30% (two steps); (e) L-Selectride, THF, -78 °C, 60%.

pathway from the enolate formed from the desired *pro-R*-isomer **22b** would be unfavorable (Scheme 4).

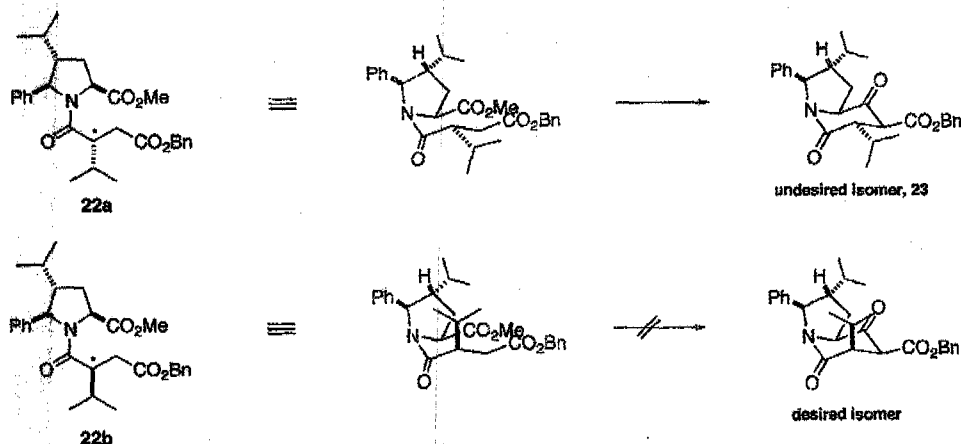
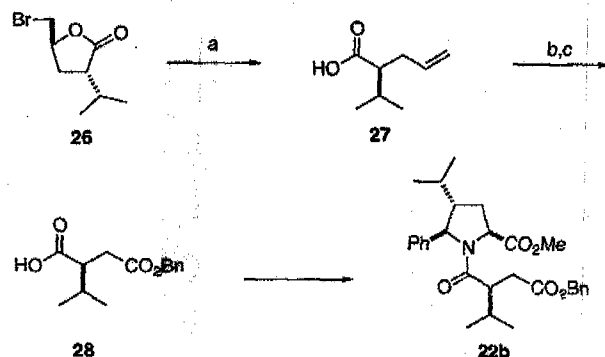
Considering the modest 30% yield in the Dieckmann cyclization, and excluding the possibility of equilibration between the two isomers via the corresponding enolate prior to cyclization, we assumed that the ester enolate of the *pro-R*-isomer **22b** must follow a different course during the reaction, leading to unidentified products. To lend credence to this supposition, we prepared **22b** independently, and subjected it to a Dieckmann cyclization under the same conditions as for the mixture (Scheme 5). A complex mixture of unidentifiable products was obtained with no trace of the expected bicyclic lactam **23**.

(29) For examples of monocyclic nitrogen heterocycles, see: (a) Blake, J.; Willson, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293. (b) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145. (c) Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3521. (d) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209. (e) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3673. (f) Ma, D.; Sun, H. *Tetrahedron Lett.* **1999**, *40*, 3609. For examples of bicyclic and polycyclic nitrogen heterocycles, see: (g) Leonard, N. G.; Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457. (h) Davies, W. A. M.; Pinder, A. R.; Morris, I. G. *Tetrahedron* **1962**, *18*, 405. (i) Holden, R. T.; Raper, R. *J. Chem. Soc.* **1963**, 2545. (j) Beckett, A. H.; Lingard, R. G.; Theobald, A. E. E. *J. Med. Chem.* **1969**, *12*, 563. Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457. (k) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848. (l) Howard, A. S.; Gerrans, G. C.; Meerholtz, C. A. *Tetrahedron Lett.* **1980**, *21*, 1373. (m) Hatamaka, M.; Ishimaru, T. *Tetrahedron Lett.* **1983**, *24*, 4837. (n) Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1990**, *31*, 6317. (o) Neyer, G.; Ugi, I. *Synthesis* **1991**, 743. (p) Bureau, R.; Mortier, J.; Joucla, M. *Tetrahedron* **1992**, *48*, 8947. (q) Liu, R.; Castelles, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069. (r) Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Warkin, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 223. (s) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998. (t) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623. (u) Haudreche, A.; Chassaing, C.; Riche, C.; Langlois, N. *Tetrahedron* **2000**, *56*, 3181.

(30) For the synthesis of indolizidinones and pyrrolizidinones by Dieckmann condensations of proline-derived precursors, see refs 29t and 29k,p, respectively.

(31) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739.

Scheme 4

Scheme 5^a

^a Reagents and conditions: (a) Zn, PrOH, H₂O, 60%; (b) OsO₄/NaIO₄, then Jones oxidation; (c) BnOH, EDC, Et₃N, DCM, 40% (three steps).

This could account for the modest yield of cyclization when the mixture of 2-isopropyl-2*R*- and 2-isopropyl-2*S*-succinates 22a and 22b was used in the Dieckmann reaction, since only the 2*S*-isomer reacted. The synthesis of enantiopure succinate 28 from a known precursor²⁷ is shown in Scheme 5.

At this juncture, we decided to introduce the second isopropyl group later in the sequence, without compromising the original plan shown in Figure 2 (Scheme 6). Removal of the *N*-Boc group in 19 followed by amide formation with succinic acid monobenzyl ester afforded 29. In this case Dieckmann cyclization was best achieved using sodium *tert*-pentoxide as a base. However, the yield of the product 30 after decarboxylation was modest. In the presence of other bases (NaH, KH, LiHMDS) yields were substantially lower. Clearly the possibility of multiple enolate formation sites and different reactivities must be controlling factors in the Dieckmann cyclizations of polysubstituted proline analogues such as 29. Nevertheless, we continued this sequence with the phenyl analogue 30. Reduction with L-Selectride afforded the alcohol 31 as the only detectable isomer (NMR). Treatment with hydrochloric acid in methanol resulted in the hydrolysis of the lactam to afford the corresponding lactone hydrochloride.³² Protection of the pyrrolidine

moiety as the *N*-Boc derivative afforded the lactone 32. Formation of the lithium enolate and treatment with acetone afforded the corresponding adduct 33 as a single isomer. Treatment of 33 with phosphorus pentachloride in dichloromethane,³³ in the absence of base, gave the side chain alkene derivative 34 in excellent yield. Reduction of the double bond, followed by ring opening of the resulting lactone 35 with 2-propylamine in the presence of trimethylaluminum,³⁴ and catalytic hydrogenation afforded the prototypical target 36.

We turned our attention to an alternative route that utilized the disubstituted proline scaffolds prepared from L-pyrroglutamic acid (Scheme 7). The reaction of the *p*-methoxyphenyl derivative 20 with the lithium salt of dimethyl methylphosphonate³⁵ gave the corresponding phosphonate in 88% yield. Horner–Emmons–Wadsworth reaction in the presence of LiCl³⁶ with methyl glyoxal gave the unsaturated ester 38 as a mixture of *cis*- and *trans*-isomers in 68% yield. Hydrogenation of the double bond and subsequent reduction of both the ester and the ketone groups with sodium borohydride in methanol gave the diol 39 in 88% yield as a single diastereoisomer, as ascertained by ¹H NMR. Selective oxidation of the primary alcohol with TEMPO and iodo-benzene diacetate³⁷ gave the corresponding lactone 40 in 75% yield. We were now poised to introduce the isopropyl group via the corresponding lithium enolate as in the phenyl series (Scheme 6). Thus, treatment of 40 with LiHMDS, followed by addition of acetone, gave the aldol product 41 as a single isomer in 87% yield. Treatment of 41 with phosphorus pentachloride³³ at –60 °C in dichloromethane in the absence of added base gave the desired alkene 42 in 80% yield, whose structure and absolute configuration were ascertained by X-ray crystallographic analysis. The remaining steps followed closely the chemistry already described in Scheme 6. In this series, we opened the lactone ring with 1-butylamine^{8,38} in the presence of trimethylaluminum³⁴ to afford the amide 43 in 75% yield.

(32) Rehders, F.; Hoppe, D. *Synthesis* 1992, 859.

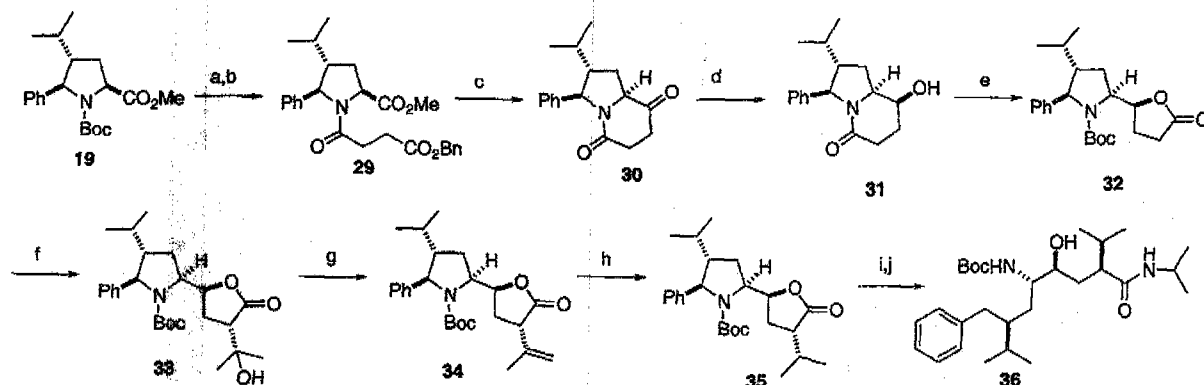
(34) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* 1981, 22, 2815.

(35) Chakravarty, P. K.; Combs, P.; Rorh, A.; Greenlee, W. J. *Tetrahedron Lett.* 1981, 23, 611.

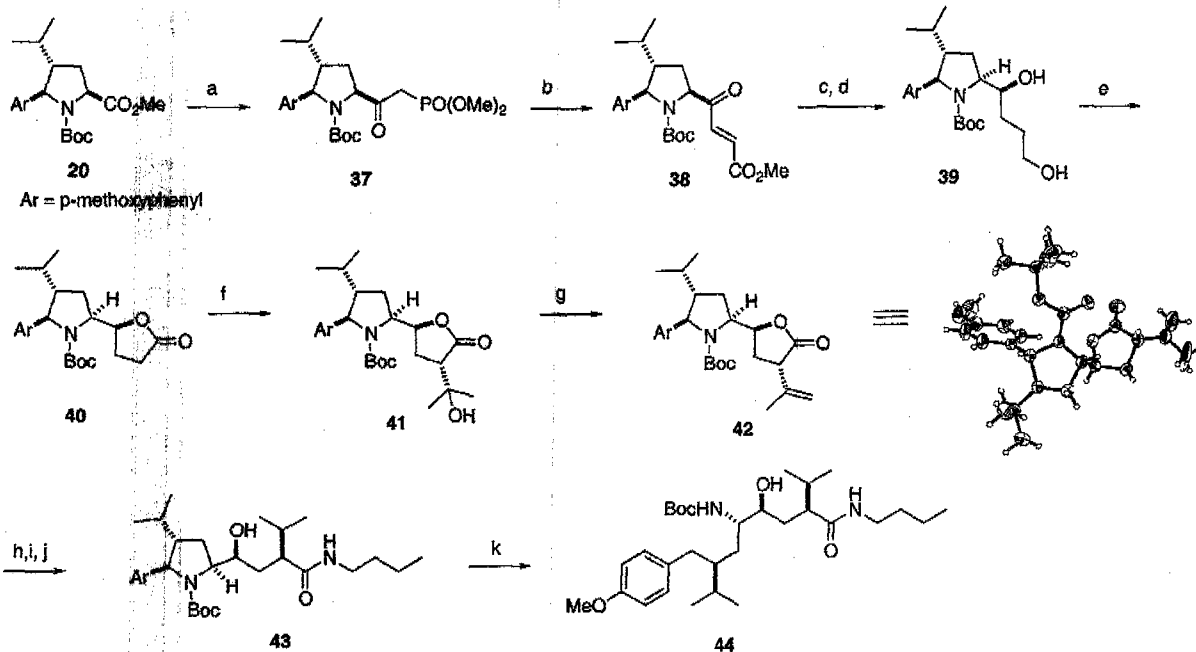
(36) Blanchette, M. A.; Choy, W.; Davis, J. T.; Esserfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* 1984, 25, 2183.

(37) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* 1997, 62, 6974.

(32) For a related acid-catalyzed lactam to lactone transformation, see: Plata, D. J.; Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* 1991, 32, 3623.

Scheme 6^a

^a Reagents and conditions: (a) TFA, benzene, quantitative; (b) BOPCl, Et₃N, Pr₂NEt, HO₂C(CH₂)₂CO₂Bn, 85%; (c) sodium *tert*-pentoxide, THF, -20 °C, then H₂, 10% Pd/C, 46%; (d) L-Selectride, -78 °C, THF, 66%; (e) concentrated HCl, MeOH, reflux, then Boc₂O, 60%; (f) LiHMDS, -78 °C, THF, then acetone, 85%; (g) PCl₅, DCM, 80%; (h) H₂, 10% Pd/C, EtOAc, 90%; (i) NH₂CHMe₂, AlMe₃, DCM; (j) H₂, 10% Pd/C, EtOAc, 60 psi, 3 days, 50% (two steps).

Scheme 7^a

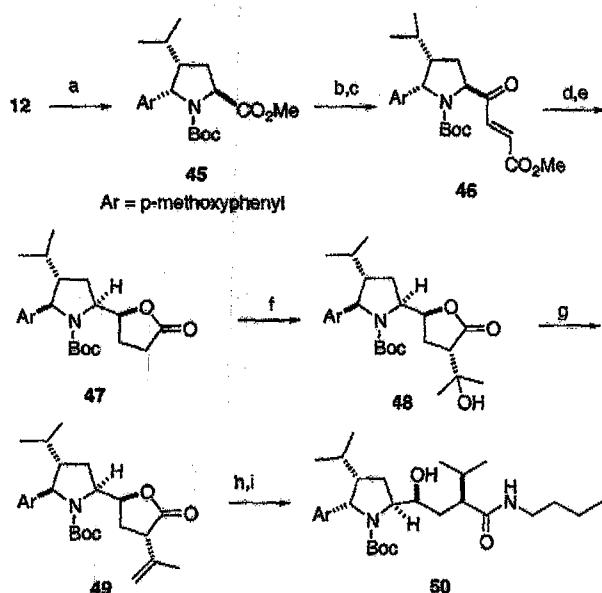
^a Reagents and conditions: (a) MePO(OMe)₂, ⁿBuLi, THF, -78 °C, 88%; (b) CHOCO₂Me, LiCl, MeCN, Pr₂NEt, 68%; (c) H₂, 10% Pd/C, EtOAc, 90%; (d) NaBH₄, MeOH, 88%; (e) TEMPO, DCM, PhI(OAc)₂, 75%; (f) LiHMDS, THF, -78 °C, then acetone, 87%; (g) PCl₅, DCM, -60 °C, 80%; (h) H₂, 10% Pd/C, EtOAc, 90%; (i) ⁿBuNH₂, AlMe₃, DCM, 75%; (k) H₂, 10% Pd/C, MeOH, 3 days, 60%.

Finally, cleavage of the pyrrolidine *N*-benzyl bond with 10% Pd/C under an atmosphere of hydrogen at 60 psi gave the intended prototype **44** in 60% yield. The same sequence was adopted in the case of the *syn*-oriented analogue **45**, prepared essentially as described for the phenyl analogue **13** (Scheme 1). The sequence proceeding through the steps shown in Scheme 8 led to the lactone intermediate **49**, which was transformed to the *n*-butyl amide **50**. Unfortunately, the same conditions that resulted in smooth hydrogenolysis of the pyrrolidine *N*-benzyl bond in **35** and **43** were not successful with **50**. A survey of other catalysts and conditions were tried,

but only unchanged starting material was recovered (10% Pd/C, 10% Pd(OH)₂, Pd black in methanol, at 60 psi for 3 days).

We have reported our strategies for the stereocontrolled synthesis of 2*R*-isopropyl-4*S*-hydroxy-5*S*-amino-7*S*-isopropyl-8-aryloctanoic acid amides representing the generic renin inhibitor structure **1**, starting from the readily available L-pyrroglutamic acid. The resident chirality in this versatile template was efficiently exploited to control the stereochemistry of the 4*R*-isopropyl group and to introduce the 5-aryl group, as well as being the source of the 5-amino group in the target structures (Schemes 1 and 2). The difficulty in achieving lactam enolate alkylations with 2-propyl halides was circumvented by an aldol-type condensation with acetone, followed by

(38) See, for example: (a) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* 1992, 33, 1411. (b) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* 1991, 32, 4503.

Scheme 8^a

^a Reagents and conditions: (a) *p*-MeOC₆H₄Li, CuBr-Me₂S, BF₃·OEt₂, 70%; (b) MePO(OMe)₂, ^tBuLi, THF, -78 °C, 80%; (c) CHOCOMe, LiCl, MeCN, Pr₂NEt, 60%; (d) H₂, 10% Pd/C, EtOAc, 90%; (e) NaBH₄, MeOH, then pTSA, toluene, reflux, 40%; (f) LiHMDS, THF, -78 °C, then acetone, 66%; (g) PCl₅, DCM, -60 °C, 62%; (h) H₂, 10% Pd/C, EtOAc, 95%; (i) ^tBuNH₂, AlMe₃, DCM, 60%.

elimination to a 2-propenyl appendage, and subsequent reduction. Further chemical elaboration of the 4,5-disubstituted proline analogues afforded the enantiopure 8-aryl-7-isopropyl-5-amino-4-hydroxyoctanoic acid skeleton disguised as a pyrrolidinolactone, **40**. Stereocontrolled enolate alkylation with acetone as a 7*S*-isopropyl equivalent, amide formation, and cleavage of the benzylic pyrrolidine bond led to the intended targets exemplified by **36** and **44**. The entire sequence shown in Schemes 1, 2, and 7 adopting the "β-ketophosphonate" route constitutes 18 linear steps starting with *N*-Boc-pyrroglutamic acid methyl ester and proceeds in an overall yield of 2.5%. Several intermediates were crystalline, and purifications were easily accomplished in other cases.

Although the original plan as outlined in Figure 2 could not be realized past the Dieckmann cyclization step, it served as a visual stimulus to devise alternative strategies that were successfully executed. The implementation of these and related strategies to other aryl-substituted congeners of **1**, and variations in the amide portion, should prove useful in further fine-tuning the biological profile of this class of novel inhibitors of renin.

Experimental Section

General Procedures. All commercially available reagents were used without further purification. Solvents were distilled under positive pressure of dry nitrogen before use, THF and ether were distilled from *K*/benzophenone, and CH₂Cl₂ and toluene were distilled from CaCl₂. NMR (¹H, ¹³C, ³¹P) spectra were recorded on 300, 400, and 600 MHz spectrometers in CDCl₃, and DEPT experiments were performed routinely. Low- and high-resolution mass spectra were measured using fast atom bombardment (FAB) or electrospray techniques. Optical rotations were measured at the sodium line at ambient temperature. Flash column chromatography³⁹ was performed

in the usual way using silica gel (40–60 μm). Melting points are uncorrected.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5-oxopyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **8.** To a solution of **7** (15 g, 61.7 mmol) in dry THF (600 mL) at -78 °C was added LiHMDS (62.6 mL, 62.6 mmol, 1 M solution in THF), and the mixture was stirred at -78 °C for 2 h. Dry acetone (17.6 g, 5 equiv, 0.3 mol) was then added, and the mixture was stirred at -78 °C for an additional 4 h. The reaction mixture was quenched with saturated ammonium chloride solution and allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed, and the residual pale yellow oil consisted of a 5:1 mixture of **8** and its 4-epimer, which was used directly without further purification (18.5 g, quantitative): ¹H NMR (300 MHz, CDCl₃) δ 4.56 (dd, 1H, *J* = 2, 9 Hz), 3.77 (s, 3H), 2.79 (dd, 1H, *J* = 9, 12 Hz), 2.10 (m, 2H), 1.48 (s, 9H), 1.24 (s, 3H), 1.22 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 171.4, 148.9, 83.9, 71.0, 56.5, 52.6, 51.1, 27.8, 25.1, 24.9; LRMS (*m/z*) (*M*⁺ + 1) 302.2.

4*R*- and 4*S*-(1-Methyl-1-trimethylsilyloxyethyl)-5-oxopyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **9.** To a solution of **8** (18.5 g, 61.4 mmol) in dry dichloromethane (600 mL) was added imidazole (4.54 g, 2 equiv, 0.13 mol), and the mixture was stirred for 5 min. Chlorotrimethylsilane (6.48 g, 60 mmol) was then added in one portion, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was then filtered, and the filtrate was washed rapidly with distilled water (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to give a yellow oil which was used without further purification (16.04 g, 70%): ¹H NMR (300 MHz, CDCl₃) δ 4.52 (dd, 1H, *J* = 2, 9 Hz), 3.77 (s, 3H), 2.55 (m, 1H), 2.37 (m, 1H), 2.01 (m, 1H), 1.48 (s, 9H), 1.42 (s, 3H), 1.38 (s, 3H), 0.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 172.6, 172.2, 149.0, 83.1, 74.5, 57.0, 52.9, 52.3, 29.8, 27.8, 26.1, 24.4, 2.2; MS (*m/z*) (*M*⁺ + 1) 374.2; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₁₇H₃₁NO₆Si 374.1982, found 374.1999.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5-methoxypyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **10.** To a solution of **9** (16.0 g, 42.9 mmol) in dry THF (400 mL) was added at -78 °C DIBAL-H (80 mL, 80 mmol, 1 M solution in toluene), and the mixture was stirred at that temperature for 2 h. The reaction mixture was quenched with distilled water, and the organic solvents were removed under vacuum. The residue was suspended in 3 M NaOH solution, and the suspension was rapidly washed with ethyl acetate (3 × 150 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to give the hemiaminal (15 g, 40 mmol) as a yellow oil which was dissolved in dry methanol (150 mL), pTSA(cat.) was added, and the mixture was stirred overnight. Solid sodium bicarbonate was added, and the mixture was stirred for 20 min before the solvent was removed under vacuum. The residue was dissolved in ethyl acetate and washed with distilled water. The organic phase was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to give a yellow oil. The oil was dissolved in benzene, and any residual water was removed azeotropically. The oil was then used directly without further purification (11.4 g, 95%): IR (neat) 3516, 2976, 1750, 1710, 1479, 1458, 1438, 1368, 1300, 1203 cm⁻¹.

4*S*-Isopropyl-5*S*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **13.** To a solution of **10** (1.0 g, 3.15 mmol) in DCM (50 mL) were added DMAP (15.4 g, 12.6 mmol), triethylamine (12.7 g, 12.6 mmol), and MsCl (14.4 g, 12.6 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure,

and the crude was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated NaHCO₃, and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure, and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to separate the minor 4*R*-isomer to give **11** as a colorless oil (0.68 g, 72%). To a solution of **11** (600 mg, 2.0 mmol) in ethyl acetate were added solid sodium bicarbonate (large excess) and 10% Pd/C. The reaction mixture was stirred under an atmosphere of hydrogen gas. The solids were removed by filtration, and the solvent was removed to give **12** as a colorless oil, which was used without further purification (500 mg, 82%). To a suspension of copper(II) bromide-dimethyl sulfide complex (1.22 g, 4.4 equiv, 5.95 mmol) in anhydrous ether (5 mL) at -78 °C was added phenylmagnesium bromide (5.95 mL, 4.4 equiv, 5.95 mmol), and the reaction mixture was stirred at -40 °C for 45 min. BF₃·OEt₂ (0.84 mL, 4.4 equiv, 5.95 mmol) was added at -78 °C, and the mixture was stirred for a further 30 min. The amination **12** (0.41 g, 1.36 mmol) was then added, and the reaction mixture was stirred at -78 °C for 1 h and then slowly warmed to room temperature. The reaction mixture was quenched with a 1:1 mixture of NH₄OH/NH₄Cl and extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The mixture was concentrated and purified by column chromatography (1:4 ethyl acetate/hexane) to yield **13** (yield 420 mg, 89%): ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.10 (m, 5H), 4.97 (and rotamer at 5.1) (d, 1H, *J* = 7.19 Hz), 4.68 (and rotamer at 4.58) (d, 1H, *J* = 10 Hz), 3.78 (s, 3H), 2.35–2.20 (m, 2H), 2.10–2.01 (m, 1H), 1.15 (s, 9H), 0.91–0.85 (m, 4H), 0.78–0.72 (m, 3H); HRMS (*m/z*) calcd for C₂₀H₂₅NO₄ 347.2096, found 347.2084.

4*S*-Isopropenyl-5*S*-phenyl-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester, **14.** To a solution of **13** (100 mg, 0.29 mmol) in THF (5 mL) and water (2 mL) was added lithium hydroxide (24 mg, 2 equiv, 0.57 mmol), and the reaction mixture was stirred overnight. The THF was removed under vacuum, and the solution was extracted with diethyl ether and then acidified to pH 1. The aqueous phase was extracted with ethyl acetate, the organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give an oil which was treated with HCl in dioxane overnight. The solvent was removed under reduced pressure to give an oil which was triturated with diethyl ether to **14** as a white solid (76 mg, 80%); mp 162–164 °C dec; ¹H NMR (free amino acid) (300 MHz, CDCl₃) δ 9.4–8.9 (br s, 2H), 7.38–7.25 (m, 5H), 5.18 (d, 1H, *J* = 7 Hz), 4.91 (s, 1H), 2.40–2.05 (m, 3H), 1.26 (m, 1H), 0.8 (dd, 6H, *J* = 4, 6 Hz); ¹³C NMR (free amino acid) (75 MHz, CDCl₃) δ 171.5, 132.7, 129.1, 128.6, 128.7, 65.9, 58.6, 49.6, 32.1, 27.6, 21.6, 21.3; LRMS (*m/z*) (*M*⁺ + 1) 234; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₁₄H₂₀NO₂ 234.1485, found 234.1494.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **15.** Copper(II) bromide-dimethyl sulfide complex (20.4 g, 99.6 mmol) was suspended in dry THF (450 mL), and the mixture was cooled to -40 °C. Phenylmagnesium bromide (99.6 mL, 99.6 mmol, 1 M in THF) was then added slowly at such a rate so as to keep the reaction temperature between -40 and -30 °C. After complete addition of the Grignard reagent, the yellow suspension was stirred at -30 °C for 1 h. The reaction mixture was then cooled to -78 °C whereupon BF₃·OEt₂ (14.04 g, 99 mmol) was added, and the mixture was stirred at this temperature for 30 min. A solution of **10** (7.5 g, 24.8 mmol) in dry THF (60 mL) was then added, and the mixture was allowed to slowly warm to room temperature and then stirred for 1 h. The black suspension was quenched with a 1:1 mixture of aqueous ammonia and ammonium chloride (60 mL), and the THF was removed under vacuum. The residue was dissolved in diethyl ether (100 mL) and washed with ammonium chloride solution. The aqueous phase was extracted with diethyl ether (3 × 100 mL), and the organic extracts were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed, and the dark oil was purified by column chromatography (1:4 ethyl acetate/hexane) to afford **15** (5:1 mixture) as an off-white solid

(4.97 g, 55%); mp 122–124 °C; [α]_D -11.92 (c 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.44 (m, 5H), 6.96 (br, 1H), 5.00 (d, 1H, *J* = 14 Hz), 4.54 (m, 1H), 3.89 (s, 3H), 2.71–2.40 (m, 3H), 1.21 (s, 3H), 0.97 (s, 3H) (free amine); ¹³C NMR (75 MHz, CDCl₃) δ 174.0, 153.1, 144.0, 128.3, 128.0, 126.6, 80.1, 71.4, 63.9, 59.5, 57.9, 52.1, 30.2, 28.1, 27.9, 27.7; LRMS (*m/z*) (*M*⁺ + 1) 364.1; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₀H₂₅NO₅ 364.2130, found 364.2124.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **16.** To a solution of *p*-bromoisole (23.6 g, 0.126 mol) in dry THF (150 mL) at -78 °C was added *n*-butyllithium (63.2 mL, 0.126 mol, 2 M in hexanes), and the reaction mixture was stirred at -78 °C for 20 min. The lithium reagent was added to a stirring suspension of copper(II) bromide-dimethyl sulfide complex (26 g, 0.126 mol) at -78 °C in THF (150 mL), and the resultant black solution was stirred at -78 °C for 1 h. BF₃·OEt₂ (35.8 g, 0.25 mol) was then added in one portion, and the reaction mixture was stirred for a further 30 min. A solution of **10** as described above (8 g, 25.2 mmol) in dry THF (20 mL) was then added, and the reaction mixture was then allowed to slowly warm to room temperature. The black suspension was quenched with a 1:1 mixture of ammonium chloride solution and aqueous ammonia and extracted with ethyl acetate (4 × 30 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the resultant yellow oil was purified by column chromatography (1:4 ethyl acetate/hexane) to give a clear oil consisting of 5:1 mixture of diastereomers (4.56 g, 46%); [α]_D -9.3 (c 1.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, 2H, *J* = 9 Hz), 6.84 (d, 2H, *J* = 8 Hz), 4.90–4.46 (m, 2H), 3.79 (s, 6H), 2.40–2.08 (m, 3H), 1.35–1.10 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 173.8, 158.3, 154.2, 136.6, 113.3, 80.1, 71.2, 63.2, 60.3, 57.8, 55.1, 52.1, 30.1, 28.7, 28.1, 27.9, 27.8; LRMS (*m/z*) (*M*⁺ + 1) 394; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₁H₃₂NO₆ 394.2236, found 394.2229.

4*S*-Isopropenyl-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **17.** To a solution of **15** (3.2 g, 8.77 mmol) in dry dichloromethane (240 mL) were added dry triethylamine (3.56 g, 4 equiv, 35.2 mmol) and DMAP (4.3 g, 4 equiv, 35.2 mmol), and the mixture was stirred for 5 min at 0 °C. Methanesulfonyl chloride (4.01 g, 4 equiv, 35.2 mmol) was slowly added, and the deep red solution was allowed to stir at room temperature overnight. The reaction mixture was quenched by the addition of ammonium chloride solution (20 mL) and ethyl acetate (100 mL). The organic phase was separated, and the aqueous phase was washed with ethyl acetate (3 × 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under vacuum, and the crude red oil was purified by column chromatography (1:9 ethyl acetate/hexane) to give **17** as a colorless oil which solidified on standing (2.16 g, 81%); mp 46–48 °C; [α]_D -36.4 (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.53–7.17 (m, 5H), 4.8 (br, 1H), 4.67 (br, 1H), 4.3 (dd, 2H, *J* = 9, 20 Hz), 3.84 (s, 3H), 3.76 (d, 1H, *J* = 3 Hz), 2.94 (m, 1H), 2.15 (m, 2H), 1.75–1.09 (br m, 11H); ¹³C NMR (75 MHz, CDCl₃) δ 173.5, 143.0, 127.8, 127.6, 126.6, 125.9, 113.0, 80.3, 66.4, 59.1, 54.9, 52.1, 33.4, 28.1, 27.8, 20.2; MS (*m/z*) (*M*⁺ + 1) 346; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₀H₂₃NO₄ 346.2013, found 346.2018.

4*S*-Isopropenyl-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, **18.** To a solution of **16** (3.1 g, 7.9 mmol) in dry dichloromethane (200 mL) were added dry triethylamine (3.19 g, 4 equiv, 31.6 mmol) and DMAP (3.86 g, 4 equiv, 31.6 mmol), and the mixture was stirred for 5 min at 0 °C. Methanesulfonyl chloride (3.6 g, 4 equiv, 31.6 mmol) was then slowly added, and the deep red solution was allowed to stir at room temperature overnight. The reaction mixture was quenched by the addition of ammonium chloride solution (20 mL) and ethyl acetate (100 mL), and the organic phase was separated and processed as described for **17** to give a red oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give **18** as a colorless oil (2.40 g, 81%); [α]_D -12.55 (c 1,

CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, 2H, *J* = 8 Hz), 6.74 (d, 2H, *J* = 7 Hz), 4.72–4.35 (m, 3H), 3.70 (s, 4H), 3.66 (s, 3H), 2.05 (m, 2H), 1.29 (m, 4H), 1.45–1.02 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 158.3, 141.8, 135.1, 128.1, 127.6, 113.0, 79.7, 65.7, 60.0, 58.9, 54.8, 33.2, 28.0, 20.7, 13.9; LRMS (*m/z*) (*M*⁺ + 1) 376; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₁H₃₀NO₅ 376.2126, found 376.2124.

4*S*-Isopropyl-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 19. To a solution of 17 (2.46 g, 7.13 mmol) in ethyl acetate (100 mL) was added 10% Pd/C (150 mg), and the mixture was reduced under an atmosphere of hydrogen at 40 psi for 24 h. The catalyst was filtered, and the solvent was removed under reduced pressure to give a colorless oil which solidified on standing and was used without further purification (2.23 g, 90%); mp 48–50 °C; [α]_D²⁰ –31.6 (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.29 (m, 5H), 4.6 (br, 1H), 4.36 (m, 1H), 3.82 (dd, 1H, *J* = 4, 9 Hz), 3.72 (s, 3H), 2.1–2.0 (m, 3H), 1.6 (m, 1H), 1.39 (s, 3H), 1.09 (s, 6H), 0.85 (d, 3H, *J* = 7 Hz), 0.70 (d, 3H, *J* = 6 Hz) (free amine); ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 143.9, 128.2, 127.9, 126.9, 126.6, 126.2, 80.3, 65.9, 59.1, 53.7, 52.1, 29.6, 28.1, 27.8, 26.9, 21.7, 17.6; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₀H₃₀NO₄ 348.2168, found 348.2175.

4*S*-Isopropyl-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 20. To a solution of 18 (2.3 g, 6.1 mmol) in ethyl acetate (100 mL) was added 10% Pd/C (200 mg), and the mixture was reduced under an atmosphere of hydrogen at 40 psi for 24 h. The catalyst was filtered, and the solvent was removed under reduced pressure to give 20 as a colorless oil which was used without further purification (2.08 mg, 90%); [α]_D²⁰ –22.9 (c 0.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, 2H, *J* = 9 Hz), 6.85 (d, 2H, *J* = 8 Hz), 4.61–4.30 (m, 2H), 3.80 (s, 6H), 2.13–1.94 (m, 3H), 1.70–1.60 (m, 1H), 1.37 (s, 3H), 1.11 (s, 6H), 1.0–0.73 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 158.3, 154.3, 135.9, 128.1, 113.1, 79.6, 65.4, 59.9, 51.9, 29.6, 27.8, 21.6, 17.7.

4*S*-Isopropyl-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester, 21. To a solution of 19 (100 mg, 0.29 mmol) in 10:1 MeOH/water (5 mL) was added lithium hydroxide (1.5 equiv, 0.44 mmol), and the reaction mixture was stirred at room temperature overnight. Methanol was removed under reduced pressure, and the aqueous phase was extracted with diethyl ether (2 × 10 mL), acidified to pH 1, and then extracted with diethyl ether. The solvent was removed under reduced pressure to give a white solid (91.7 mg, 95%); mp > 200 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.28 (m, 5H), 4.51 (d, 1H, *J* = 8 Hz), 4.33 (d, 1H, *J* = 7 Hz), 2.43 (m, 1H), 2.16 (m, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 1.1 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 177.0, 142.9, 128.2, 127.0, 126.8, 66.4, 60.2, 53.7, 27.8, 21.6, 17.8; LRMS (*m/z*) (*M*⁺ + 1) 334; HRMS (*m/z*) calcd for C₁₉H₂₈NO₄ 334.2025, found 334.2018.

1-(2-Benzoyloxycarbonylmethyl-3-*R,S*-methylbutyryl)-4*S*-isopropyl-5*R*-phenylpyrrolidine-2*S*-carboxylic Acid Methyl Ester, 22. To a solution of 2-isopropylsuccinic acid monobenzyl ester (405 mg, 2 equiv, 1.62 mmol) in dry dichloromethane (4 mL) at 0 °C was added BOPCl (411 mg, 2 equiv, 1.62 mmol), and the reaction mixture was stirred at 0 °C for 2 h. A solution of the free amine of 19, obtained by treatment with TFA (200 mg, 0.81 mmol), and diisopropylethylamine (627 mg, 6 equiv, 4.86 mmol) in dry dichloromethane (5 mL) was then added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and then washed sequentially with dilute hydrochloric acid (15 mL), sodium bicarbonate solution (15 mL), and brine (15 mL). The organic layer was dried over sodium sulfate and then filtered, and the solvent was removed under vacuum to give a brown oil. Purification by column chromatography (1:2 diethyl ether/hexane) gave 22 (1:1 mixture of diastereomers) as a colorless oil (330 mg, 85%); ¹H NMR (300 MHz, CDCl₃) δ 7.66–7.17 (m, 10H), 5.15–4.81 (m, 3H), 4.64–4.56 (m, 1H), 3.85–3.52 (m, 3H), 2.87–2.74 (m, 1H), 2.64–2.56 (m, 1H), 2.49–2.24 (m, 2H), 2.17–1.92 (m, 3H), 1.68–1.60 (m, 2H), 1.50–1.43 (m, 1H), 1.06–0.29 (multiple dd, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 173.2, 172.9, 143.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2,

127.1, 126.5, 66.2, 59.4, 55.6, 52.0, 45.2, 44.2, 33.3, 31.7, 29.7, 28.7, 28.2, 21.6, 20.8, 20.6, 18.9, 17.9, 14.0; LRMS (*m/z*) (*M*⁺ + 1) 480; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₉H₃₈NO₅ 480.2762 found 480.2750.

2*S*,6*R*-Diisopropyl-3*R*-phenylhexahydroindolizine-5,8-dione, 24. To a solution of 22 (275 mg, 0.57 mmol) in dry THF (50 mL) at –78 °C was added KHMDS (4.56 mL, 2.28 mmol, 0.5M in toluene), and the reaction mixture was allowed to warm to –50 °C and stirred at that temperature for 3 h. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 30 mL), the combined organic phases were dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure to give 23 as a crude oil. The oil was dissolved immediately in methanol (5 mL), 10% Pd/C was added, and the mixture was stirred under an atmosphere of hydrogen gas for 3 h. The catalyst was removed by passage through a pad of Celite, and the solvent was removed. Purification of the resultant oil by column chromatography (1:4 ethyl acetate/hexane) gave 24 as a colorless oil (54 mg, 30%, two steps); [α]_D²⁰ –25.8 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.05 (m, 5H), 5.30 (s, 1H), 4.29–4.10 (m, 1H), 2.86–2.74 (m, 2H), 2.43–2.38 (m, 1H), 2.25–2.05 (m, 2H), 1.93–1.87 (m, 1H), 1.83–1.72 (m, 1H), 1.71–1.67 (m, 1H), 1.10 (t, 3H, *J* = 6 Hz), 0.99 (t, 3H, *J* = 6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.4, 142.4, 128.5, 128.3, 124.1, 64.6, 63.8, 52.3, 49.6, 39.2, 30.1, 29.6, 28.3, 28.0, 22.6, 21.2, 20.8, 20.8, 20.1; LRMS (*m/z*) (*M*⁺ + 1) 313.

8*S*-Hydroxy-2*S*,6*R*-diisopropyl-3*R*-phenylhexahydroindolizine-5-one, 25. To a solution of 24 (54 mg, 0.173 mmol) in dry THF (2 mL) was added 1-Selectride (0.21 mL, 0.21 mmol, 1 M solution in THF), and the reaction mixture was stirred at –78 °C. After 2 h, the reaction was quenched by the addition of saturated ammonium chloride solution, and the mixture was warmed to room temperature. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed under vacuum to give a clear oil. Purification by column chromatography (1:3 ethyl acetate/hexane) gave 25 as a white solid (33 mg, 60%); mp > 180 °C; [α]_D²⁰ +4.0 (c 0.3, CHCl₃); IR (CHCl₃) 3684, 3620, 3019, 1658, 1602, 1522, 1476, 1423, 1046, 928 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.11 (m, 5H), 4.91 (br s, 1H), 4.18 (br s, 1H), 3.68 (dd, 2H, *J* = 5, 12 Hz), 2.58–2.53 (m, 2H), 2.26–2.18 (dt, 1H, *J* = 6, 12 Hz), 2.06–2.0 (m, 1H), 1.77–1.65 (m, 4H), 1.13 (d, 3H, *J* = 6 Hz), 0.96 (d, 3H, *J* = 6 Hz), 0.90 (d, 3H, *J* = 7 Hz), 0.84 (d, 3H, *J* = 7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.5, 144.2, 128.1, 126.0, 125.3, 64.9, 64.3, 60.9, 52.8, 42.0, 30.1, 29.6, 27.8, 27.6, 21.3, 20.5, 19.8, 17.3; LRMS (*m/z*) (*M*⁺ + 1) 316; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₀H₃₀NO₂ 316.2291, found 316.2276.

2*S*-Isopropylpent-4-enoic Acid, 27. To a solution of 26 (500 mg, 2.26 mmol) in a 2-propanol/water mixture (10:1, 50 mL) was added zinc metal (8.81 g, 135.6 mmol, 60 equiv), and the mixture was heated to reflux for 5 h. The reaction mixture was cooled, and the 2-propanol was removed under vacuum. The aqueous phase was acidified to pH 1 and extracted with ethyl acetate. The organic fractions were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give 27 as a dark oil which was purified by column chromatography (ethyl acetate) to give a colorless oil (193 mg, 60%); ¹H NMR (400 MHz, CDCl₃) δ 5.70 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 2.19 (m, 2H), 2.38 (m, 1H), 2.15 (m, 1H), 1.01 (d, 6H).

2*S*-Isopropylsuccinic Acid Monobenzyl Ester, 28. To a solution of 27 (150 mg, 1.06 mmol) in THF/water (9:1, 5 mL) was added sodium metaperiodate (0.45 g, 2.1 mmol), and the reaction mixture was stirred. Osmium tetroxide solution was added (cat.), and the reaction mixture was stirred overnight. The solvent was removed, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated. The crude aldehyde was dissolved in acetone and treated with the Jones reagent at 0 °C. The reaction mixture was quenched

with excess 2-propanol, the solvents were removed, and the crude acid was purified by column chromatography (ethyl acetate) to give 2*S*-isopropylsuccinic acid as a colorless oil. To a solution of the diacid (100 mg, 6.25 mmol) in dichloromethane (5 mL) were added benzyl alcohol (101 mg, 9.35 mmol), Et₃N (94 mg, 9.31 mmol), and EDC (178 mg, 9.3 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and then washed sequentially with dilute HCl (10 mL), NaHCO₃ solution (10 mL), and finally brine solution (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude monoester was purified by column chromatography (1:4 ethyl acetate/hexane) to give **28** as a colorless oil (62.5 mg, 40%): ¹H NMR δ 7.19 (m, 5H), 5.34 (s, 2H), 2.98 (m, 1H), 2.48 (m, 2H), 2.15 (m, 1H), 1.01 (d, 6H).

1-(3-Benzyloxycarbonylpropionyl)-4*S*-isopropyl-5*R*-phenylpyrrolidine-2*S*-carboxylic Acid Methyl Ester, **29.** To a solution of succinic acid monobenzyl ester (2.35 g, 11.3 mmol, 2 equiv) in a mixture of dry dichloromethane and DMF (50 mL, 4:1) was added BOPCl (2.9 g, 11.4 mmol, 2 equiv), and the mixture was stirred at 0 °C for 1 h. A solution of the amine of **19**, obtained by treatment with TFA (1.4 g, 5.7 mmol), in dichloromethane (20 mL) and Hunig's base (4.4 g, 34 mmol, 6 equiv) were then added, and the reaction mixture was stirred at room temperature overnight. The solvents were removed, and the residue was dissolved in ethyl acetate (10 mL). The organic phase was washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and then brine. The organic phase was dried over anhydrous sodium sulfate, and the solvent was then removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **29** as a pale yellow oil (2.2 g, 89%): [α]_D -22.3 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.62–7.18 (m, 10H), 5.10–5.02 (dd, 2H, *J* = 24, 12 Hz), 4.69 (d, 1H, *J* = 13 Hz), 4.63 (t, 1H, *J* = 7 Hz), 3.79 (s, 3H), 2.77–2.69 (m, 1H), 2.52–2.31 (m, 2H), 2.13–1.85 (m, 4H), 1.67 (m, 1H), 0.94 (d, 6H, *J* = 7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 172.5, 171.7, 142.4, 135.9, 128.7, 128.4, 128.1, 127.97, 127.9, 66.2, 66.1, 60.2, 59.4, 55.3, 52.1, 29.4, 29.0, 28.8, 28.7, 27.6, 21.6, 20.9, 18.3, 14.1; LRMS (*m/z*) (*M*⁺ + 1) 438; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₆H₃₂NO₅ 438.2288, found 438.2280.

2*S*-Isopropyl-3*R*-phenylhexahydroindolizine-5,8-dione, **30.** To a solution of **29** (2.0 g, 4.6 mmol) in dry THF (450 mL) at -20 °C was added sodium *tert*-pentoxide (1.5 g, 13.6 mmol), and the reaction mixture was stirred at that temperature until there was no remaining starting material detected by TLC. The reaction mixture was quenched by the addition of saturated ammonium chloride solution, and the THF was then separated. The aqueous phase was extracted with ethyl acetate (3 × 30 mL), the organic extracts were combined and dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. The crude product was dissolved in methanol (50 mL), 10% Pd/C was added, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, the solvent was removed, and the residue was purified by column chromatography (1:1 ethyl acetate/hexane) to give **30** as a yellow oil (570 mg, 46%): [α]_D +15.07 (c 0.7, CHCl₃); IR (neat) 2962, 1732, 1693, 1602, 1429 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.02 (m, 5H), 5.04 (s, 1H), 4.26 (t, 1H, *J* = 8 Hz), 2.75 (m, 4H), 2.18 (m, 2H), 2.0–1.5 (m, 2H), 1.10–0.99 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 207.6, 169.2, 141.9, 130.3, 126.9, 126.1, 124.8, 64.9, 63.6, 34.9, 31.1, 30.8, 26.9, 20.9, 20.1; LRMS (*m/z*) (*M*⁺ + 1) 272; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₁₇H₂₂O₂N 272.1659, found 272.1650.

8*S*-Hydroxy-2*S*-isopropyl-3*R*-phenylhexahydroindolizine-5-one, **31.** To a solution of **30** (451 mg, 1.6 mmol) in dry THF (10 mL) at -78 °C was added *t*-Selectride (2.5 mL, 2.5 mmol, 1 M solution in THF), and the reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched by the addition of saturated ammonium chloride, and the solution was extracted with ethyl acetate (3 × 10 mL) and dichloromethane (3 × 10 mL). The organic extracts were combined and then dried over anhydrous sodium sulfate. The

solvents were removed, and the resultant oil was purified by column chromatography (ethyl acetate) to give **31** as a white solid (300 mg, 66%): mp > 200 °C; [α]_D +6.12 (c 0.8, CHCl₃); IR (CDCl₃) 3428, 2972, 1731, 1635, 1451, 1410, 1373, 1250 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.13 (m, 5H), 4.94 (s, 1H), 4.17 (s, 1H), 3.70 (dd, 1H, *J* = 12, 5 Hz), 2.6–2.5 (m, 1H), 2.35–2.31 (m, 1H), 2.1–1.9 (m, 3H), 1.77 (dd, 1H, *J* = 13, 6 Hz), 1.66 (s, 2H), 1.14 (d, 3H, *J* = 6 Hz), 0.95 (d, 3H, *J* = 8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 143.7, 128.2, 126.2, 64.4, 63.8, 61.3, 53.1, 29.8, 29.2, 27.3, 27.1, 21.4, 20.5; LRMS (*m/z*) (*M*⁺ + 1) 274; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₁₇H₂₂NO₂ 274.1819, found 274.1807.

3*S*-Isopropyl-5*S*-(5-oxotetrahydrofuran-2*S*-yl)-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, **32.** To a solution of **31** (300 mg, 1.1 mmol) in methanol (4 mL) was added concentrated HCl (4 mL), and the reaction mixture was heated to reflux for 3 days. The solvents were removed, the crude lactone was dissolved in dry acetonitrile (5 mL), DMAP (268 mg, 2 equiv, 2.2 mmol), triethylamine (450 mg, 4 equiv, 4.4 mmol), and Boc anhydride (650 mg, 2 equiv, 2.2 mmol) were added, and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude was dissolved in ethyl acetate and then washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was collected and dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil which was purified by column chromatography (1:3 ethyl acetate/hexane) to give **32** as a colorless oil (245 mg, 60%, two steps): [α]_D -27.05 (c 0.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.18 (m, 5H), 4.63–4.61 (m, 1H), 4.40 (s, 1H), 4.21 (m, 1H), 2.59–2.49 (m, 2H), 2.36–2.15 (m, 3H), 1.96–1.88 (m, 1H), 1.77–1.73 (m, 2H), 1.24 (s, 9H), 0.94 (d, 3H, *J* = 7 Hz), 0.82 (d, 3H, *J* = 7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 176.8, 155.9, 143.7, 128.0, 126.6, 82.7, 80.1, 66.5, 59.5, 52.3, 29.5, 28.7, 28.5, 28.3, 28.0, 27.6, 25.4, 21.9, 17.5; LRMS (*m/z*) (*M*⁺ + 1) 374; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₂H₃₂NO₄ 374.2320, found 374.2331.

5*S*-(4*S*-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2*S*-yl)-3*S*-isopropyl-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, **33.** To a solution of **32** (240 mg, 0.63 mmol) in dry THF (8 mL) at -78 °C was added LiHMDS (0.7 mL, 1.15 equiv, 0.7 mmol, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (187 mg, 5 equiv, 3.2 mmol) was then added, and the reaction mixture was quenched by the addition of a saturated ammonium chloride solution and extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **33** as a colorless oil (235 mg, 85%): [α]_D +2.18 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.19 (m, 5H), 4.48 (s, 1H), 4.15 (t, 1H, *J* = 8 Hz), 2.85 (t, 1H, *J* = 10 Hz), 2.27–2.10 (m, 2H), 1.97–1.88 (m, 1H), 1.76–1.67 (s, 2H), 1.31 (s, 17H), 0.94 (d, 3H, *J* = 7 Hz), 0.84 (d, 3H, *J* = 7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 178.3, 143.6, 128.2, 126.7, 126.4, 80.3, 70.9, 59.7, 52.3, 48.9, 29.6, 28.6, 28.4, 29.9, 27.1, 25.4, 21.9, 17.3; LRMS (*m/z*) (*M*⁺ + 1) 432; HRMS (*m/z*) (*M*⁺ + 1) calcd for C₂₅H₃₃NO₅ 432.2750, found 432.2749.

5*S*-(4*S*-Isopropenyl-5-oxotetrahydrofuran-2*S*-yl)-3*S*-isopropyl-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, **34.** To a solution of **33** (100 mg, 0.23 mmol) in dry dichloromethane (4 mL) at -60 °C was added PCl₅ (53 mg, 1.1 equiv, 0.25 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. Purification by column chromatography (1:9 ethyl acetate/hexane) gave **34** as a colorless oil (77 mg, 80%): [α]_D +3.63 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.16 (m, 5H), 5.0 (s, 2H), 4.55 (s, 1H), 4.40 (s, 1H), 4.20 (t, 1H, *J* = 7 Hz), 3.38 (t, 1H, *J* = 8 Hz), 2.40–2.26 (m, 3H), 1.97–1.62 (m, 5H), 1.50–1.0 (s, 9H), 1.0–0.8 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 182.1, 176.3, 143.7, 139.7, 128.1,

126.6, 126.5, 114.3, 80.2, 68.8, 59.4, 52.3, 46.9, 30.9, 30.8, 28.9, 27.9, 27.4, 24.3, 21.9, 21.8, 17.4, 14.0; LRMS (m/z) ($M^+ + 1$) 414; HRMS (m/z) ($M^+ + 1$) calcd for $C_{25}H_{36}NO_4$ 414.2632, found 414.2644.

3S-Isopropyl-5S-(4S-isopropyl-5-oxotetrahydrofuran-2S-yl)-2R-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 35. To a solution of **34** (75 mg, 0.18 mmol) in ethyl acetate (5 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, the solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give **35** as a colorless oil (68 mg, 90%): $[\alpha]_D^{25} +0.74$ (c 0.6, $CHCl_3$); IR (CDCl₃) 2965, 2932, 1777, 1739, 1691, 1650, 1604, 1440, 1369, 1336, 1312 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.15 (m, 5H), 4.95 (s, 1H), 4.62 (s, 1H), 3.93 (t, 1H, $J = 6$ Hz), 2.60 (m, 1H), 2.35–2.24 (m, 4H), 1.96–1.60 (m, 4H), 1.48–1.0 (s, 8H), 1.0–0.8 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 178.4, 160.3, 139.7, 128.1, 125.7, 126.5, 82.8, 70.9, 54.9, 54.2, 51.7, 41.9, 28.6, 25.7, 25.4, 19.5; LRMS (m/z) ($M^+ + 1$) 416; HRMS (m/z) ($M^+ + 1$) calcd for $C_{25}H_{36}NO_4$ 416.2788, found 416.2801.

[1S-(2-Benzyl-3S-methylbutyl)-2S-hydroxy-4S-isopropylcarbamoyl-5-methylhexyl]carbamic Acid *tert*-Butyl Ester, 36. To a solution of isopropylamine (43 mg, 4 equiv, 0.72 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.37 mL, 2 M solution in toluene, 0.74 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was then transferred via cannula to a solution of **35** (75 mg, 0.18 mmol) in dry dichloromethane (2 mL). The reaction mixture was then stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 $\times$ 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then filtered. The solvent was removed to give a dark oil which was used directly in the next step. To a solution of the amide (20 mg, 0.042 mmol) in methanol (3 mL) was added 10% Pd/C (40 mg), and the reaction mixture was stirred under an atmosphere of hydrogen gas at 60 psi for 3 days. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a pink oil. Purification by column chromatography (1:3 ethyl acetate/hexane) gave **36** as a colorless oil (10 mg, 50%): $[\alpha]_D^{25} -15$ (c 0.6, $CHCl_3$); IR (CDCl₃) 3330, 2950, 1697, 1620, 1513, 1359, 1438, 1246, 1041 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.14 (m, 5H), 5.53 (s, 1H), 4.64 (d, 1H, $J = 9$ Hz), 4.11 (m, 1H), 3.53 (d, 9H, $J = 7$ Hz), 3.43 (m, 1H), 2.66 (dd, 1H, $J = 7, 5$ Hz), 2.47 (dd, 1H, $J = 13, 7$ Hz), 2.0–1.83 (m, 3H), 1.76–0.76 (m, 24H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 157.0, 139.4, 128.3, 125.7, 73.0, 70.2, 52.8, 44.1, 41.6, 39.6, 31.6, 30.5, 28.7, 26.4, 23.7, 20.1, 19.1; LRMS (m/z) ($M^+ + 1$) 477; HRMS (m/z) ($M^+ + 1$) calcd for $C_{28}H_{43}N_2O_4$ 477.3686, found 477.3692.

5S-[2-(Dimethoxyphosphoryl)acetyl]-4S-isopropyl-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 37. To a solution of dimethyl methylphosphonate (2.98 g, 6 equiv, 24.0 mmol) in dry THF (50 mL) at -78°C was added *n*-butyllithium (10.56 mL, 6.6 equiv, 26.4 mmol, 2.5 M in hexane), and the mixture was stirred for 30 min at -78°C . A solution of **20** (1.5 g, 4.0 mmol) in THF (50 mL) was added, and the reaction mixture was stirred for 3 h at -78°C . The reaction mixture was quenched with saturated ammonium chloride solution and then extracted with ethyl acetate (3 $\times$ 30 mL). The organic phases were combined, dried over anhydrous sodium sulfate solution, and filtered. The solvent was removed to give a colorless oil which was purified by column chromatography (1:1 ethyl acetate/hexane) to give **37** as a colorless oil (1.64 g, 88%): $[\alpha]_D^{25} -106.3$ (c 0.8, $CHCl_3$); IR (CDCl₃) 2959, 1726, 1687, 1613, 1514, 1463, 1392, 1366, 1248, 1178, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, 2H, $J = 8$ Hz), 6.83 (d, 2H, $J = 8$ Hz), 4.60–4.30 (m, 2H), 3.32–3.78 (2s, 9H), 3.60–3.2 (m, 2H), 2.16–1.94 (m, 3H), 1.63 (m, 1H), 1.37–1.30 (m, 3H), 1.11 (s, 6H), 0.92–0.79 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 201.6, 158.3, 154.7, 135.8, 128.2, 127.6, 113.2, 80.1, 65.6, 55.1, 53.5, 52.9, 39.4, 38.1, 27.9, 21.6,

18.1; LRMS (m/z) ($M^+ + 1$) 470; HRMS (m/z) ($M^+ + 1$) calcd for $C_{26}H_{36}NNaO_7P$ 492.2140, found 492.2127.

4S-Isopropyl-5S-(3-methoxycarbonylacryloyl)-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 38. To a solution of the β -ketophosphonate (1.5 g, 3.2 mmol) in dry acetonitrile (75 mL) were added LiCl (536 mg, 4 equiv, 12.8 mmol), $CHOC_2Me$ (1.12 g, 4 equiv, 12.8 mmol), and Hunig's base (1.65 g, 4 equiv, 12.8 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a dark oil which was purified by column chromatography (1:4 ethyl acetate/hexane) to give **38** as a yellow oil (935 mg, 68%): $[\alpha]_D^{25} -33$ (c 0.8, $CHCl_3$); IR (CDCl₃) 2960, 1731, 1693, 1613, 1513, 1392, 1304, 1247, 1175, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.26 (m, 3H), 6.86–6.83 (m, 3H), 4.76–4.32 (m, 2H), 3.78 (s, 6H), 2.0 (s, 3H), 1.60 (s, 1H), 1.33–0.70 (m, 15H); ¹³C NMR (75 MHz, CDCl₃) δ 198.0, 165.6, 158.4, 154.6, 137.1, 136.7, 131.2, 128.2, 127.5, 113.2, 80.1, 65.5, 64.6, 55.1, 53.5, 52.2, 28.1, 27.9, 21.7, 17.8; LRMS (m/z) ($M^+ + 1$) 432; HRMS (m/z) ($M^+ + 1$) calcd for $C_{24}H_{34}NO_6$ 432.2400, found 432.2386.

5S-(1,4S-Dihydroxybutyl)-4S-isopropyl-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 39. To a solution of **38** (900 mg, 2.1 mmol) in ethyl acetate (40 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, and the solvent was removed under reduced pressure to give a colorless oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (813 mg, 90%): $[\alpha]_D^{25} -29.89$ (c 0.8, $CHCl_3$); LRMS (m/z) ($M^+ + 1$) 434; HRMS (m/z) ($M^+ + 1$) calcd for $C_{24}H_{36}NO_6$ 434.2556, found 434.2542. To a solution of the above compound (750 mg, 1.73 mmol) in methanol (40 mL) was added sodium borohydride (excess), and the reaction was stirred until no remaining starting material was observed by TLC. The reaction mixture was quenched with saturated ammonium chloride solution, and the solvent was removed under reduced pressure. The crude was dissolved in ethyl acetate and washed with water. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a colorless oil which was purified by column chromatography (ethyl acetate) to give **39** as a colorless oil (620 mg, 88%): $[\alpha]_D^{25} -37.88$ (c 0.9, $CHCl_3$); ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, 2H, $J = 8$ Hz), 6.82 (d, 2H, $J = 8$ Hz), 4.37 (d, 1H, $J = 8$ Hz), 3.91 (t, 1H, $J = 9$ Hz), 3.77 (s, 3H), 3.68 (m, 3H), 1.82 (m, 1H), 1.80–1.61 (m, 8H), 1.13 (s, 9H), 0.89 (d, 3H, $J = 7$ Hz), 0.82 (d, 3H, $J = 9$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ 158.3, 135.9, 127.5, 113.4, 80.8, 75.9, 65.6, 63.3, 62.8, 60.2, 55.1, 52.8, 32.9, 29.1, 28.9, 27.9, 27.5, 21.7, 17.9, 14.0; LRMS (m/z) ($M^+ + 1$) 408; HRMS (m/z) ($M^+ + 1$) calcd for $C_{24}H_{36}NO_6$ 408.2742, found 408.2750.

4S-Isopropyl-2R-(4-methoxyphenyl)-5S-(5-oxotetrahydrofuran-2S-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 40. To a solution of **39** (510 mg, 1.25 mmol) in dichloromethane (12 mL) were added TEMPO (19 mg) and iodobenzene diacetate (807 mg, 2 equiv, 2.5 mmol), and the reaction mixture was stirred for 6 h. The reaction mixture was quenched with sodium thiosulfate solution and then extracted with dichloromethane (3 $\times$ 30 mL). The organic phases were combined, then dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a dark oil which was purified by column chromatography (1:2 ethyl acetate/hexane) to give **40** as a colorless oil (379 mg, 75%): $[\alpha]_D^{25} -8.53$ (c 0.8, $CHCl_3$); IR (CDCl₃) 2961, 1778, 1691, 1613, 1513, 1389, 1366, 1247, 1173, 111, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, 2H, $J = 9$ Hz), 6.83 (d, 2H, $J = 9$ Hz), 4.59 (m, 1H), 4.30 (s, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 2.52 (m, 2H), 2.34–2.20 (m, 3H), 2.04–1.70 (m, 3H), 1.25 (s, 9H), 0.92 (d, 3H, $J = 7$ Hz), 0.80 (d, 3H, $J = 7$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ 177.0, 158.2, 135.7, 127.9, 113.4, 80.1, 66.2, 59.6, 55.4, 53.4, 52.3, 29.1, 28.5, 28.0, 26.0, 25.4, 21.8, 17.8;

LRMS (m/z) ($M^+ + 1$) 404; HRMS (m/z) ($M^+ + 1$) calcd for $C_{25}H_{34}NO_5$ 404.2427, found 404.2437.

5S-[4S-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2S-yl]-4S-isopropyl-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 41. To a solution of 40 (300 mg, 0.74 mmol) in dry THF (10 mL) at -78°C was added LiHMDS (0.82 mL, 1.1 equiv, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (215 mg, 5 equiv, 3.7 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and then extracted with ethyl acetate (3×10 mL). The combined extracts were dried over anhydrous sodium sulfate, and then the solvent was removed to give 41 as a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave the product as a colorless oil (299 mg, 87%): $[\alpha]_D^{25} +3.06$ (c 0.8, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, 2H, $J = 9$ Hz), 6.84 (d, 2H, $J = 8$ Hz), 4.61–4.1 (m, 2H), 3.79 (s, 3H), 2.83 (t, 1H, $J = 10$ Hz), 2.40–2.1 (m, 2H), 1.91 (m, 1H), 1.66 (s, 2H), 1.31 (m, 17H), 0.93 (d, 3H, $J = 6$ Hz), 0.82 (d, 3H, $J = 7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 178.4, 158.3, 135.6, 127.6, 113.5, 80.2, 70.9, 59.7, 55.1, 52.2, 51.0, 48.9, 29.1, 28.9, 28.3, 28.0, 27.5, 25.4, 21.9, 17.5; LRMS (m/z) ($M^+ + 1$) 462; HRMS (m/z) ($M^+ + 1$) calcd for $C_{26}H_{40}NO_6$ 462.2845, found 462.2855.

5S-(4S-Isopropenyl-5-oxotetrahydrofuran-2S-yl)-4S-isopropyl-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 42. To a solution of 41 (150 mg, 0.33 mmol) in dry dichloromethane (6 mL) at -60°C was added PCl_5 (74 mg, 1.1 equiv, 0.36 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. Purification by column chromatography (1:9 ethyl acetate/hexane) gave 42 as a white solid (115 mg, 80%): $[\alpha]_D^{25} +5$ (c 1, CHCl_3); IR (CDCl_3) 2967, 1781, 1752, 1686, 1613, 1513, 1457, 1387, 1290, 1247, 1172, 1148 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, 2H, $J = 8$ Hz), 6.82 (d, 2H, $J = 9$ Hz), 4.99 (s, 1H), 4.92 (s, 1H), 4.53 (s, 1H), 4.35 (s, 1H), 4.15 (t, 1H, $J = 7$ Hz), 3.76 (s, 3H), 3.34 (t, 1H, $J = 8$ Hz), 2.33–2.24 (m, 3H), 2.02–1.71 (m, 6H), 1.23 (s, 9H), 0.90 (d, 3H, $J = 7$ Hz), 0.79 (d, 3H, $J = 6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 176.4, 158.3, 139.7, 127.8, 113.4, 80.1, 66.1, 59.6, 55.1, 52.2, 46.9, 30.9, 29.3, 28.0, 27.8, 21.8, 17.7; LRMS (m/z) ($M^+ + 1$) 444; HRMS (m/z) ($M^+ + 1$) calcd for $C_{26}H_{38}NO_5$ 444.2736, found 444.2750.

5S-(3-Butylcarbamoyl-1S-hydroxy-4S-methylpentyl)-3S-isopropyl-2R-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 43. To a solution of 42 (100 mg, 0.26 mmol) in ethyl acetate (7 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, then the solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (90 mg, 90%): $[\alpha]_D^{25} +2.4$ (c 0.8, CHCl_3); LRMS (m/z) ($M^+ + 1$) 446; HRMS (m/z) ($M^+ + 1$) calcd for $C_{26}H_{38}NO_5$ 446.2910, found 444.2906. To a solution of *n*-butylamine (52.6 mg, 4 equiv, 0.72 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.36 mL, 2 M solution in toluene, 0.71 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was then transferred via cannula to a solution of the above compound (80 mg, 0.18 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered, and the solvent was removed. The residue was purified by column chromatography (1:3 ethyl acetate/hexane) to give 43 as a colorless oil (70 mg, 75%): $[\alpha]_D^{25} -31.9$ (c 0.8, CHCl_3); IR (CDCl_3) 3322, 2959, 1740, 1651, 1538, 1514, 1464, 1401, 1367, 1289, 1247, 1175, 1153 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.15 (d, 2H, $J = 8$ Hz), 6.81 (d, 2H, $J = 8$ Hz), 5.89 (s, 1H), 4.36 (d,

1H, $J = 8$ Hz), 3.87 (t, 1H, $J = 8$ Hz), 3.79 (s, 3H), 3.51 (t, 1H, $J = 10$ Hz), 3.34–3.20 (m, 2H), 2.24 (m, 1H), 2.17–1.62 (m, 6H), 1.51 (m, 2H), 1.41–1.15 (m, 14H), 1.0–0.73 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.1, 158.2, 136.2, 127.6, 113.3, 80.7, 73.7, 69.5, 63.9, 55.1, 52.8, 50.5, 38.8, 36.6, 31.7, 30.2, 28.8, 27.8, 27.8, 21.6, 21.2, 21.1, 20.1, 19.9, 18.1, 13.6; LRMS (m/z) ($M^+ + 1$) 518; HRMS (m/z) ($M^+ + 1$) calcd for $C_{30}H_{50}N_2O_5$ 519.3806, found 519.3798.

2R-Isopropyl-4S-hydroxy-5S-*N*-butoxycarbonylamino-7S-isopropyl-8-*p*-methoxyphenyloctanoic Acid *N*-Butylamide, 44. To a solution of 43 (30 mg, 0.058 mmol) in methanol (3 mL) was added 10% Pd/C (50 mg), and the reaction mixture was stirred under an atmosphere of hydrogen gas at 60 psi for 3 days. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a colored oil which was purified by column chromatography (1:2 ethyl acetate/hexane) to give 44 as a colorless oil (18 mg, 60%): $[\alpha]_D^{25} +17.2$ (c 0.7, CHCl_3); IR (CDCl_3) 3333, 2958, 1693, 1633, 1513, 1455, 1366, 1246, 1175, 1044 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.09 (d, 2H, $J = 9$ Hz), 6.79 (d, 2H, $J = 8$ Hz), 5.85 (s, 1H), 4.66 (d, 1H, $J = 10$ Hz), 3.77 (s, 3H), 3.52–3.17 (m, 4H), 2.61 (m, 1H), 2.38 (m, 1H), 2.05–1.90 (m, 2H), 1.60 (m, 4H), 1.5 (s, 9H), 1.08–0.71 (m, 22H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.5, 156.6, 133.6, 129.9, 113.4, 79.1, 71.0, 55.1, 53.7, 51.3, 42.4, 39.6, 34.6, 32.2, 31.8, 31.6, 29.6, 29.2, 28.3, 27.9, 22.6, 21.1, 20.4, 20.0, 16.6, 14.0, 13.6, 12.1; LRMS (m/z) ($M^+ + 1$) 521; HRMS (m/z) ($M^+ + 1$) calcd for $C_{30}H_{50}N_2O_5$ 521.3941, found 521.3954.

4S-Isopropyl-5S-(4-methoxyphenyl)pyrrolidine-1,2S-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester, 45. To a solution of *p*-bromoanisole (18.7 g, 5 equiv, 0.1 mol) in dry THF (150 mL) at -78°C was added *n*-butyllithium (44 mL, 0.11 mmol, 2.5 M in hexanes), and the reaction mixture was stirred at -78°C for 1 h. The lithium reagent was then added to a stirring solution of copper(II) bromide–dimethyl sulfide complex (20.5 g, 5 equiv, 0.1 mol) at -78°C , and the resultant black solution was stirred at -78°C for 1 h. $\text{BF}_3 \cdot \text{OEt}_2$ (28.4 g, 10 equiv, 0.2 mol) was added in one portion, and the reaction mixture was stirred for a further 30 min. A solution of the aminal 12 (6 g, 20.0 mmol) in dry THF (20 mL) was added, and the reaction mixture was allowed to slowly warm to room temperature (black suspension). The mixture was quenched with a 1:1 mixture of ammonium chloride solution and aqueous ammonium hydroxide and extracted with ethyl acetate (4×50 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the resultant yellow oil was purified by column chromatography (1:4 ethyl acetate/hexane) to give 45 as a clear oil (5.29 g, 70%): IR (neat) 3019, 2976, 1746, 1686, 1612, 1586, 1512, 1395, 1368, 1298, 1215, 1178, 1160, 1036, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.09–6.77 (m, 4H), 4.90 (d, 1H, $J = 7$ Hz), 4.63 (d, 1H, $J = 9$ Hz), 3.77 (s, 3H), 3.71 (s, 3H), 2.22–2.0 (m, 4H), 1.33–1.15 (s, 9H), 0.84–0.7 (t, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.8, 158.4, 152.9, 133.2, 128.7, 115.8, 113.1, 79.9, 63.8, 59.3, 55.9, 52.2, 49.9, 31.9, 27.9, 27.6, 21.7, 20.9; LRMS (m/z) (M^+) 377; HRMS (m/z) (M^+) calcd for $C_{21}H_{31}NO_5$ 377.2210, found 377.2202.

4S-Isopropyl-5S-(3-methoxycarbonylacryloyl)-2S-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 46. To a solution of dimethyl methylphosphonate (3.9 g, 6 equiv, 31.9 mmol) in dry THF (80 mL) at -78°C was added *n*-butyllithium (13.6 mL, 6.4 equiv, 34.1 mmol, 2.5 M solution in hexanes), and the mixture was stirred for 30 min at -78°C . A solution of 45 (2 g, 5.31 mmol) was then added, and the reaction mixture was stirred for 3 h at -78°C . The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3×30 mL). The organic phases were combined, dried over anhydrous sodium sulfate solution, and then filtered. The solvent was removed to give a colorless oil (1.99 g, 80%) which was used immediately in the next step. To a solution of the β -ketophosphonate (1.94 g, 4.14 mmol) in dry acetonitrile (10 mL) were added LiCl (670 mg, 5 equiv, 20.7 mmol), methyl glyoxalate (1.82 g, 5 equiv, 20.7 mmol), and Hunig's base (2.67 g, 5 equiv,

21 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a brown oil which was purified by column chromatography (1:4 ethyl acetate/hexane) to give **46** as a yellow oil (1.0 g, 60%): $[\alpha]_D^{25}$ -4.76 (c 0.6, CHCl₃); IR (CHCl₃) 2959, 1730, 1693, 1611, 1521, 1394, 1247, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, 1H, *J* = 16 Hz), 7.04 (d, 1H, *J* = 8 Hz), 6.85–6.79 (m, 4H), 4.93 (m, 2H), 3.77 (m, 6H), 2.24–1.91 (m, 4H), 1.25–1.14 (s, 9H), 0.82 (t, 3H, *J* = 6 Hz), 0.68 (t, 3H, *J* = 6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 197.8, 165.7, 158.5, 136.3, 133.0, 131.6, 128.7, 113.1, 79.9, 64.3, 63.9, 55.4, 52.2, 49.7, 30.6, 27.9, 27.6, 21.6, 20.9; LRMS (*m/z*) (*M*⁺ + 1) 432; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₄H₃₄NO₆ 432.2386, found 432.2396.

4S-Isopropyl-2S-(4-methoxyphenyl)-5S-(5-oxotetrahydrofuran-2S-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 47. To a solution of **46** (1 g, 2.32 mmol) in ethyl acetate (15 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, and the filtrate was processed as usual to give a colorless oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give the saturated ketoester as a colorless oil (904 mg, 90%): $[\alpha]_D^{25}$ -5.8 (c 0.5, CHCl₃); LRMS (*m/z*) (*M*⁺ + 1) 434; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₄H₃₄NO₆ 434.2542, found 434.2551. To a solution of the above compound (500 mg, 1.15 mmol) in methanol (20 mL) was added sodium borohydride (excess), and the reaction was stirred at 0 °C until there was no remaining starting material (observed by TLC). The reaction mixture was quenched by the addition of a solution of ammonium chloride, and the solvents were removed. The mixture was triturated with diethyl ether, and the solvent was removed under reduced pressure to give a dark oil. The oil was dissolved in toluene (5 mL), pTSA(cat.) was added, and the mixture was heated to reflux for 5 h. The toluene was removed, and the crude was purified by column chromatography (ethyl acetate) to give **47** as a colorless oil (186 mg, 40%): $[\alpha]_D^{25}$ -16 (c 0.7, CHCl₃); IR (CDCl₃) 2929, 1780, 1693, 1611, 1513, 1462, 1365, 1250, 1178, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.01 (d, 2H, *J* = 8 Hz), 6.74 (d, 2H, *J* = 8 Hz), 4.93 (m, 1H), 4.62 (s, 1H), 4.04 (m, 1H), 3.73 (s, 3H), 2.48–2.20 (m, 5H), 2.06–1.70 (m, 3H), 1.31 (s, 9H), 1.01 (d, 3H, *J* = 8 Hz), 0.92 (d, 3H, *J* = 8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 172.8, 159.2, 159.1, 131.6, 129.3, 113.4, 83.8, 68.2, 56.0, 54.9, 51.0, 41.9, 35.8, 25.4, 25.4, 20.1, 17.8; LRMS (*m/z*) (*M*⁺ + 1) 404; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₂H₃₄NO₅ 404.2427, found 404.2448.

5S-[4S-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2S-yl]-3S-isopropyl-2S-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 48. To a solution of **47** (150 mg, 0.037 mmol) in dry THF (4 mL) at -78 °C was added LiHMDS (0.41 mL, 1.1 equiv, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (107 mg, 5 equiv, 0.18 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **48** as a colorless oil (113 mg, 66%): $[\alpha]_D^{25}$ -6.5 (c 1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, 2H, *J* = 8 Hz), 6.81 (d, 2H, *J* = 9 Hz), 4.78 (d, 1H, *J* = 7 Hz), 4.60 (m, 1H), 4.41 (m, 1H), 3.78 (m, 3H), 2.75 (m, 2H), 2.40–1.70 (m, 3H), 1.34–1.17 (2s, 9H), 1.05 (s, 9H), 0.90–0.75 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 183.1, 162.6, 160.1, 138.1, 132.7, 117.3, 85.4, 83.8, 75.2, 70.0, 63.4, 59.4, 54.2, 53.3, 35.8, 32.4,

32.1, 31.7, 29.3, 25.9, 25.4; LRMS (*m/z*) (*M*⁺ + 1) 462; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₆H₄₀NO₆ 462.2864, found 462.2855.

5S-(4S-Isopropenyl-5-oxotetrahydrofuran-2S-yl)-4S-isopropyl-2S-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 49. To a solution of **48** (100 mg, 0.22 mmol) in dry dichloromethane (2 mL) at -60 °C was added PCl₅ (50 mg, 1.1 equiv, 0.24 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give **49** as a colorless oil (59 mg, 62%): $[\alpha]_D^{25}$ -65 (c 1, CHCl₃); IR (CDCl₃) 2692, 1776, 1693, 1651, 1513, 1456, 1456, 1366, 1298, 1271, 1249, 1179, 1112 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.99 (d, 2H, *J* = 9 Hz), 6.80 (d, 2H, *J* = 9 Hz), 5.0–4.5 (m, 5H), 3.77 (s, 3H), 3.32 (t, 1H, *J* = 8 Hz), 2.63 (m, 1H), 2.32–2.26 (m, 3H), 2.09–1.65 (m, 5H), 1.04 (s, 9H), 0.98–0.75 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 176.3, 158.4, 155.7, 140.0, 133.9, 128.5, 114.3, 133.1, 81.0, 79.5, 65.7, 58.7, 55.1, 50.0, 47.1, 31.2, 30.5, 28.2, 27.7, 21.6, 21.1, 20.3; LRMS (*m/z*) (*M*⁺ + 1) 444; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₆H₃₈NO₅ 444.2741, found 444.2750.

5S-(3-Butylcarbamoyl-1S-hydroxy-4S-methylpentyl)-4S-isopropyl-2S-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 50. To a solution of **49** (50 mg, 0.11 mmol) in ethyl acetate (3 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (48 mg, 95%): $[\alpha]_D^{25}$ -28.8 (c 1, CHCl₃); LRMS (*m/z*) (*M*⁺ + 1) 446; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₂₆H₃₈NO₅ 446.2914, found 446.2906. To a solution of *n*-butylamine (26 mg, 4 equiv, 0.36 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.18 mL, 2 M solution in toluene, 0.36 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was transferred via cannula to a solution of the lactone (40 mg, 0.09 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride, and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed to give a dark oil which was purified by column chromatography (1:3 ethyl acetate/hexane) to give **50** as a colorless oil (28 mg, 60%): $[\alpha]_D^{25}$ -30.1 (c 0.9, CHCl₃); IR (CDCl₃) 3307, 2958, 1660, 1513, 1464, 1394, 1366, 1248, 1178, 1113 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, 2H, *J* = 8 Hz), 6.81 (d, 2H, *J* = 9 Hz), 5.91 (m, 1H), 4.76 (d, 1H, *J* = 7 Hz), 4.11 (t, 1H, *J* = 9 Hz), 3.79 (s, 3H), 3.35 (t, 1H, *J* = 11 Hz), 3.30–3.19 (m, 2H), 2.19–1.20 (m, 17H), 1.08 (s, 9H), 0.95–0.71 (m, 22H); ¹³C NMR (75 MHz, CDCl₃) δ 175.1, 158.3, 133.6, 128.4, 113.4, 80.2, 74.7, 65.0, 63.3, 55.1, 49.7, 38.7, 36.8, 31.7, 30.3, 30.3, 27.8, 27.6, 21.8, 21.1, 21.0, 20.0, 13.7; LRMS (*m/z*) (*M*⁺ + 1) 519; HRMS (*m/z*) (*M*⁺ + 1) calcd. for C₃₀H₅₁N₂O₅ 519.3800, found 519.3798.

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Supporting Information Available: Selected ¹H and ¹³C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.