



Industria y Comercio

S U P E R I N T E N D E N C I A

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

06-109669

54. TÍTULO Síntesis de compuestos de éster y ácido bórico

51. CLASIFICACIÓN INTERNACIONAL C07F5/02

71. SOLICITANTE Millenium Pharmaceuticals, Inc.

DOMICILIO Cambridge, Massachusetts, Estados Unidos

74. APODERADO Luis Patiño Leyva

22. BOGOTÁ, D. C., 27 de Octubre de 2006

S.S.

Industria y Comercio
SUPERINTENDENCIA

Rad. CS-109369-00000-0000

Rec 2008 10 27 17:14 CS Dep 2020 NULCHLACIO

Tra 11 PATENTEIN

1 vs 1/11 FASE NACIONAL

Art 411 PRESENTACION

Folios 2/5

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

30-10-06

①

SOLICITUD DE :



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

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Nacionalidad o Domicilio: Cambridge, Massachussets
Estados Unidos

Lugar de Constitución: Estados Unidos

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Fax:

E-mail:

IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

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Dirección Cra. 11ª No. 94-76 - Of. 308

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Fax: 6163976

E-mail:

IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual

Número 2.930.616 TP 2698

④

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Dirección: 115 Liberty Street,

Nacionalidad o Domicilio: Newton, MA 18940, Estados Unidos

⑤

PCT (86)

Solicitud Internacional No. PCT/US2005/009774
WO 2005/097809 A2

Fecha: Marzo 24 de 2005

Publicación Internacional No. WO 2005/097809 A3

Fecha Octubre 28 de 2004

⑥

Título (54) SÍNTESIS DE COMPUESTOS DE ÉSTER Y ÁCIDO BÓRICO.

⑦

Clasificación Internacional (51) C07F 5/02

⑧

PRIORIDAD:

SI



NO



(33) País de Origen

Estados Unidos

(32) Fecha

Marzo 30 de 2004

(31) Numero de Solicitud

60/557,535

⑨

Comprobante de pago No. 06 - 82,120

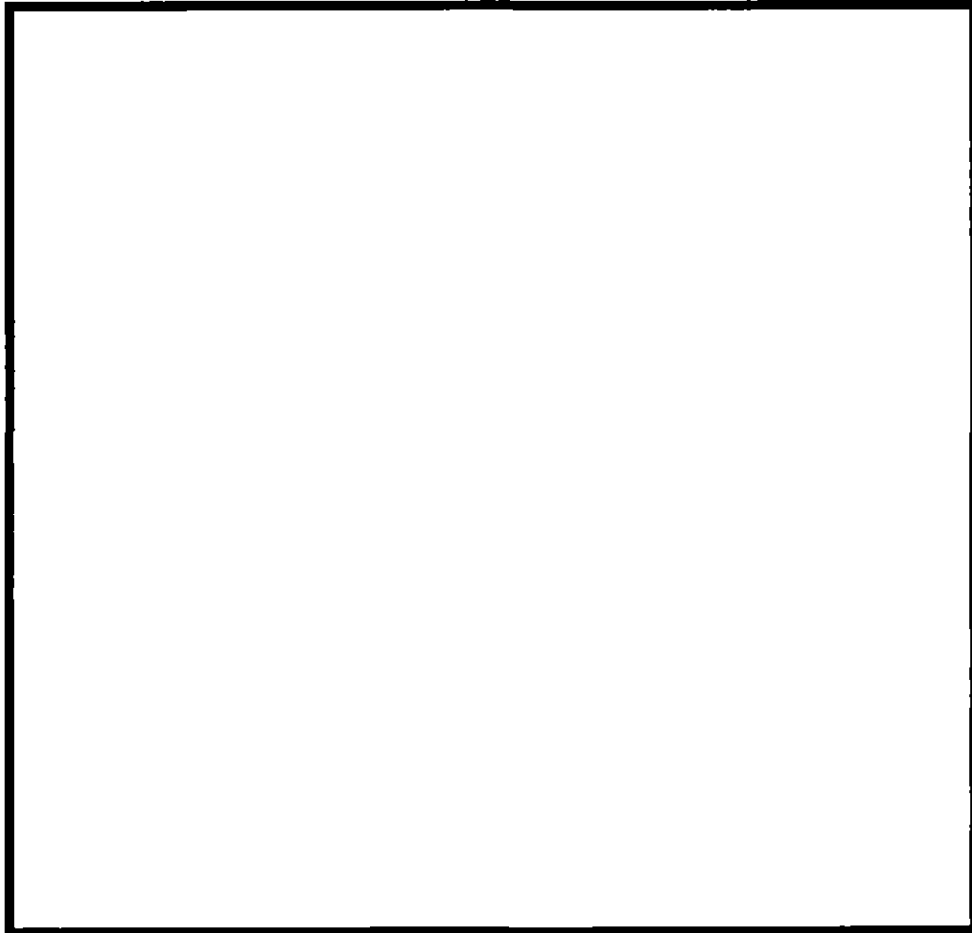
Fecha Octubre 24 de 2006

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros Reporte de Búsqueda Internacional.

(11) FIGURA CARACTERISTICA



(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA:

C.C. 2.930.616 Bogotá T.P. 2698

Instrucciones para el diligenciamiento del presente formulario , ver reverso de esta página.

Continuación nombre, dirección y domicilio de inventores:

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GOMEZ Jean-Marc	Amcis AG, Haupstrasse 159-173	CH-4416 Bubendorf, China
GEISER Achim	CarboGen Laboratories (Neuland) AG, Neulandweg 5,	CH-5502 Hunzenschwil, China
HETT Robert	CarboGen Laboratories (Neuland) AG, Neulandweg 5,	CH-5502 Hunzenschwil China
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MUNK Stephen	Ash Stevens Inc.,	18655 Krause Street, Riverview, MI 48192 Estados Unidos
LO Young	Chemicals, Inc., North Normando Drive, P.O. Box 1658,	Petersburg, VA 23805- 93-82 Estados Unidos
CHUI Fang-Ting	Boehringer Ingelheim Chemicals, Inc.,	2820 North Normandy Drive, P.O. Box 1658, Petersburg, VA 23805- 9382 Estados Unidos
KULKARNI Vithalanand, R.,	Boehringer Ingelheim Chemicals, Inc., 2820 North Normandy Drive, P.O. Box 1658,	Petersburg, VA 23805- 9382 Estados Unidos

Otros anexos que se acompañan a la solicitud.

Copia formulario PCT/RO/101 correspondiente a la presentación de la solicitud internacional.

Copia formulario PCT/IB/304 correspondiente a la notificación relativa al envío o transmisión del documento de prioridad.

Copia formulario PCT/IB/311 concerniente a la notificación de transmisión de copia de la solicitud internacional como se publicó o republicó.

Copia formulario PCT/ISA/220 referente a la notificación de transmisión del reporte de búsqueda internacional y la opinión escrita de la autoridad de búsqueda internacional, o declaración.

Copia formulario PCT/ISA/237 correspondiente a la opinión escrita de la Autoridad de Búsqueda Internacional.

Copia de antecedentes de la invención.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

Rad. 08-109869-00000-0000
Fec 2003-10-27 17:14:00 Dep 2020 NUECREACIONES
Tra 11 PATENTILYII
Eve 378 FAMIL NACIONAL
Art 411 PRESENTACION Fecha 27/10

RECIBO OFICIAL DE CAJA : 06 - 82,120
FECHA : OCTUBRE 24 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMANN 8	CONSIGNACION	BANCO POPULAR	050-00110-6	48143655	23/10/2006	926,000.00
GUSTAVO HOLLMANN 6	CONSIGNACION	BANCO POPULAR	050-00110-6	50105007	24/10/2006	970,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
	TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

Ref. 58994

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



Apostille

(Convention de La Haye du 5 octobre 1961)

- 1. *District of Columbia*
United States of America

ALBERT L. THEMES

- 2. This public document has been signed by _____
NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA
- 3. acting in the capacity of _____

- 4. bears the seal/stamp of _____
ALBERT L. THEMES, NOTARY PUBLIC IN AND FOR THE
DISTRICT OF COLUMBIA

CERTIFIED

- 5. at Washington, D.C.
12TH

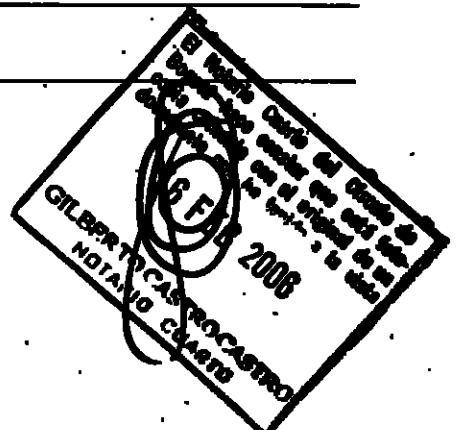
DECEMBER 2005

- 6. the _____ day of _____

- 7. by *Secretary of the District of Columbia*

- 8. No. 149773

- 9. Seal/Stamp



- 10. Signature

Patricia Elwood
Patricia Elwood (Interim)

G. HOLLMANN RESTREPO
ABOGADOS LTDAG. HOLLMANN RESTREPO
ABOGADOS LTDA

6

The undersigned, acting on behalf of and representing of **MILLENNIUM PHARMACEUTICALS, INC.**, domiciled in Cambridge, Massachusetts, Estados Unidos, hereby appoint(s) **LUIS PATIÑO LEYVA** and/or **GUSTAVO HOLLMANN RESTREPO** and/or, domiciled in Bogotá D.C., Republic of Colombia, as our true and legal attorney with the necessary powers:

1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial engravings and names, trademarks, slogans, health licenses, copyrights and domain names as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial engravings and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remedies on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in on this 6th day of December, 2005
Cambridge, MA, U.S.A.

Millennium Pharmaceuticals, Inc.

BY: Ian R. Silverman
Ian R. Silverman, Associate General Counsel

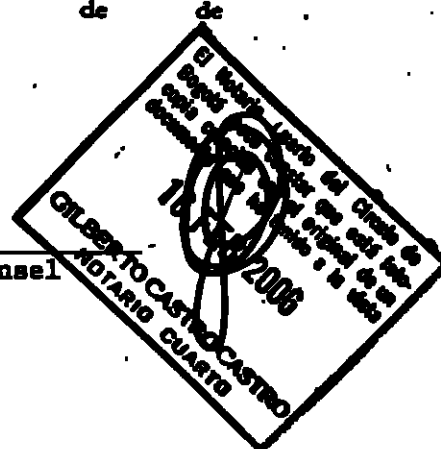
Yo (nosotros) obrando en nombre propio y representación de, con domicilio en nombre(amos) a **LUIS PATIÑO LEYVA y/o GUSTAVO HOLLMANN RESTREPO**, con domicilio en Bogotá D.C., República de Colombia; apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de marcas comerciales, depósito de nombres y enseñanzas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus trasposos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; el ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistirse a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en el de de



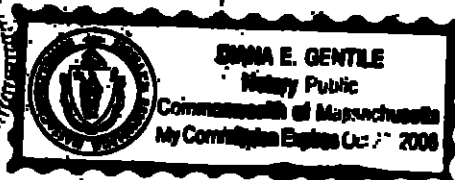
CERTIFICATION COMPANIES

The undersigned Diana E. Gentile certifies: that the preceding signature(s) reading Jan R. Silveira is (are) authentic; that the signer(s) at present fill(s) the position of Assistant General of Millenium Pharmaceuticals, Inc., that he. (they) is (are) empowered to grant this power, and that said company exists, accomplishes its social object and is organized in Cambridge, MA in accordance with the Laws of Delaware.

All the foregoing facts are known to me due to my having examined the respective documents to which I attest.

Signed in Cambridge, MA on this 6th day of December of 2005

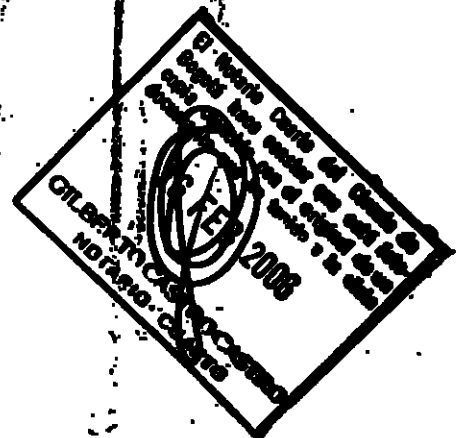
Diana E. Gentile



CERTIFICACIÓN SOCIEDADES

El (la) infrascripto(a) _____ certifica: que la(s) firma(s) que antecede(n) y dice(n) _____ es (son) auténtica(s); que el (los) signatario(s) desempeña(n) actualmente el cargo(s) de _____ de _____; que tiene(n) facultad para otorgar este poder; y que dicha compañía existe, cumple su objeto social y está organizada en _____ conforma a las Leyes de _____ Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en _____ el _____ de _____ de _____



El Notario Público de la Provincia de
 Pinar del Río, en virtud de la
 copia certificada que se le ha
 presentado, declara que el
 documento que se le ha
 presentado es el original.
 C. M. L. B. 2008
 NOTARIO CASTRO CASTRO
 NOTARIO CUARTO

My Commission Expires
 Notary Public
 MARIA E. GENTILE
 Notary Public
 Commission Expires 2008



I HEREBY CERTIFY THAT THIS
 IS THE ORIGINAL DOCUMENT

SAMI SWANER R. 2008

Subscribed and sworn to before me, in my presence, this
 8 day of Dec 2008, a Notary Public
 in and for the State of Florida
 Notary Public
 My commission expires 6/14 2009

ALBERT L. THEMES
 NOTARY PUBLIC DISTRICT OF COLUMBIA
 My Commission Expires 12/14/2008

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

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(71) Applicant (for all designated States except US): MIL-
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(72) Inventors; and

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AMMOSCATO, Vince [CA/US]; Ash Stevens, Inc.,
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(US). CHUI, Fung-Ting [US/US]; Boehringer Ingelheim

Chemicals, Inc., 2820 North Normandy Drive, P.O. Box
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icals, Inc., 2820 North Normandy Drive, P.O. Box 1658,
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(74) Agents: KLUNDER, Janke, M. et al.; Millennium Phar-
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02139 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
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TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW.

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

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS

(57) Abstract: The invention relates to the synthesis of boronic ester and acid compounds. More particularly, the invention provides improved synthetic processes for the large-scale production of boronic ester and acid compounds, including the peptide boronic acid proteasome inhibitor bortezomib.

WO 2005/097809 A2

SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS

(Attorney Docket No. MPI04-044P1R WO M)

BACKGROUND OF THE INVENTION**Field of the Invention**

[001] This invention relates to the synthesis of boronic ester and acid compounds. More particularly, the invention relates to large-scale synthetic processes for the preparation of boronic ester and acid compounds by Lewis acid promoted rearrangement of boron "ate" complexes.

Background of the Invention

[002] Boronic acid and ester compounds display a variety of pharmaceutically useful biological activities. Shenvi *et al.*, U.S. Pat. No. 4,499,082 (1985), discloses that peptide boronic acids are inhibitors of certain proteolytic enzymes. Kettner and Shenvi, U.S. Pat. No. 5,187,157 (1993), U.S. Pat. No. 5,242,904 (1993), and U.S. Pat. No. 5,250,720 (1993), describe a class of peptide boronic acids that inhibit trypsin-like proteases. Kleeman *et al.*, U.S. Pat. No. 5,169,841 (1992), discloses *N*-terminally modified peptide boronic acids that inhibit the action of renin. Kinder *et al.*, U.S. Pat. No. 5,106,948 (1992), discloses that certain tripeptide boronic acid compounds inhibit the growth of cancer cells.

[003] More recently, boronic acid and ester compounds have displayed particular promise as inhibitors of the proteasome, a multicatalytic protease responsible for the majority of intracellular protein turnover. Ciechanover, *Cell*, 79: 13-21 (1994), discloses that the proteasome is the proteolytic component of the ubiquitin-proteasome pathway, in which proteins are targeted for degradation by conjugation to multiple molecules of ubiquitin. Ciechanover also discloses that the ubiquitin-proteasome pathway plays a key role in a variety of important physiological processes.

[004] Adams *et al.*, U.S. Patent No. 5,780,454 (1998), U.S. Patent No. 6,066,730 (2000), U.S. Patent No. 6,083,903 (2000), U.S. Patent No. 6,297,217 (2001), U.S. Patent No. 6,548,668, and U.S. Patent No. 6,617,317 (2003), hereby incorporated by reference in their entirety, describe peptide boronic ester and acid compounds useful as proteasome inhibitors. The references also describe the use of boronic ester and acid compounds to reduce the rate of muscle protein degradation, to reduce the activity of NF- κ B in a cell, to reduce the rate of degradation of p53 protein in a cell, to inhibit cyclin degradation in a cell, to inhibit the growth of a cancer cell, to inhibit antigen presentation in a cell, to inhibit NF- κ B dependent cell adhesion, and to inhibit HIV replication.

[005] Albanell and Adams, *Drugs of the Future* 27: 1079-1092 (2002), discloses that one such peptide boronic acid proteasome inhibitor, bortezomib (N-2-pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid), shows significant antitumor activity in human tumor xenograft models and is undergoing clinical evaluation. Richardson *et al.*, *New Engl. J. Med.*, 348:2609 (2003), reports the results of a Phase 2 study of bortezomib, showing its effectiveness in treating relapsed and refractory multiple myeloma.

[006] Studies of boronic acid protease inhibitors have been greatly advanced by the development of chemistry for the preparation of functionalized boronic acid compounds, particularly alpha-halo- and alpha-aminoboronic acids. Matteson and Majumdar, *J. Am. Chem. Soc.*, 102:7590 (1980), discloses a method for preparing alpha-chloroboronic esters by homologation of boronic esters, and Matteson and Ray, *J. Am. Chem. Soc.*, 102:7591 (1980), reports that chiral control of the homologation reaction can be achieved by the use of pinanediol boronic esters. The preparation of alpha-aminoboronic acid and ester compounds from the corresponding alpha-chloroboronic esters has also been reported (Matteson *et al.*, *J. Am. Chem. Soc.*, 103:5241 (1981); Shenvi, U.S. Patent No. 4,537,773 (1985)).

[007] Matteson and Sadhu, U.S. Patent No. 4,525,309 (1985), describes an improved procedure for the homologation of boronic esters by rearrangement of the intermediate boron "ate" complex in the presence of a Lewis acid catalyst. The Lewis acid is reported to promote the rearrangement reaction and to minimize epimerization at the alpha-carbon atom. Rigorous exclusion of water and careful control of Lewis acid stoichiometry are required for optimum results, however. These features render the reaction difficult to perform successfully on a production scale, and limit the availability of pharmaceutically important boronic ester and acid compounds, such as bortezomib. Thus, there remains a need in the art for improved methods for the large-scale production of boronic ester and acid compounds.

DESCRIPTION OF THE INVENTION

[008] The present invention provides improved synthetic processes for the large-scale production of boronic ester and acid compounds. These processes offer increased yield and purity, increased throughput, and greater ease of handling as compared to prior art methods. Notably, the processes described herein are suitable for batch production on a large, multi-kilogram scale that is limited only by the size of the available manufacturing capabilities. The processes of the invention are particularly advantageous for the synthesis of chiral boronic ester and acid compounds, including alpha-aminoboronic ester and acid compounds. Regardless of scale, the desired products are produced with very high chemical and stereochemical purity.

[009] The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention relates. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

[010] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10%.

[011] The term "comprises" is used herein to mean "includes, but is not limited to."

[012] The term "aliphatic", as used herein, means a straight-chain, branched or cyclic C_{1-12} hydrocarbon which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl. In various embodiments, the aliphatic group has 1-12, 1-8, 1-6, or 1-4 carbons.

[013] The terms "alkyl", "alkenyl", and "alkynyl", used alone or as part of a larger moiety, refer to a straight and branched chain aliphatic group having from 1 to 12 carbon atoms, which is optionally substituted with one, two or three substituents. For purposes of the present invention, the term "alkyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule is a saturated carbon atom. However, an alkyl group may include unsaturation at other carbon atoms. Thus, alkyl groups include, without limitation, methyl, ethyl, propyl, allyl, propargyl, butyl, pentyl, and hexyl.

[014] For purposes of the present invention, the term "alkenyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon double bond. Alkenyl groups include, without limitation, vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For purposes of the present invention, the term "alkynyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon triple bond. Alkynyl groups include, without limitation, ethynyl, 1-propynyl, 1-butyne, 1-pentyne, and 1-hexynyl.

[015] The terms "cycloalkyl", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, means a saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 members, wherein the aliphatic ring system is optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloalkyl has 3-6 carbons. The terms "cycloalkyl", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

[016] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an alkyl, alkenyl or alkoxy group, as the case may be, substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. Unless otherwise indicated, the terms "alkyl", "alkenyl", and "alkoxy" include haloalkyl, haloalkenyl and haloalkoxy groups, including, in particular, those with 1-5 fluorine atoms.

[017] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to a C_{6-14} aromatic moiety comprising one to three aromatic rings, which are optionally substituted. Preferably, the aryl group is a C_{6-10} aryl group. Aryl groups include, without limitation, phenyl, naphthyl, and anthracenyl. The term "aryl", as used herein, also includes groups in which an aromatic ring is fused to

one or more non-aromatic rings, such as indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring. The term "aryl" may be used interchangeably with the term "aryl ring".

[018] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C_{1-10} aryl(C_{1-6})alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[019] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, *e.g.*, heteroaralkyl, or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms selected from the group consisting of N, O, and S. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, and phenazinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more nonaromatic rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[3,4-d]pyrimidinyl. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[020] As used herein, the terms "heterocycle", "heterocyclyl", or "heterocyclic radical" refer to a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur heteroatoms are optionally oxidized and the nitrogen atoms are optionally quaternized. The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure, and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation,

tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, and morpholinyl. The terms "heterocycle", "heterocyclyl", and "heterocyclic radical", as used herein, also include groups in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as indolinyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocyclalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[021] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having one or multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[022] The term "substituted", as used herein, means that one or more hydrogen atoms of the designated moiety are replaced, provided that the substitution results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for the synthetic processes of the invention. The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[023] An aryl (including the aryl moiety in aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including the heteroaryl moiety in heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Examples of suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group include -halo, -NO₂, -CN, -R*, -OR*, -SR*, -N(R*)₂, -NR*C(O)R*, -NR*C(O)N(R*)₂, -NR*CO₂R*, -O-CO₂R*, -O-C(O)R*, -CO₂R*, -C(O)R*, -C(O)N(R*)₂, -OC(O)N(R*)₂, -S(O)₂R*, -SO₂N(R*)₂, -S(O)R*, and -NR*SO₂N(R*)₂. Each R* independently is selected from the group consisting of R*, -C(O)R*, -CO₂R*, and -SO₂R*, or two R* on the same nitrogen atom, taken together with the nitrogen atom, form a 5-8 membered aromatic or non-aromatic ring having, in addition to the nitrogen, 0-2 ring heteroatoms selected from N, O, and S. Each R* independently is hydrogen or an optionally

substituted aliphatic, aryl, heteroaryl, or heterocyclyl group. Each R^o independently is an optionally substituted aliphatic or aryl group.

[024] An aliphatic group also may be substituted with one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring include, without limitation, those listed above for the unsaturated carbon of an aryl or heteroaryl group.

[025] The present inventors have discovered that the requirement for scrupulously dry equipment, solvents, and reagents that characterized previously described procedures for the Lewis acid promoted rearrangement of boron "ate" complexes can be obviated by use of an ether solvent that has low miscibility with water. Remarkably, use of such a solvent permits the reaction to be run on a multi-kilogram scale without deterioration in yield or purity. In essence, the scale of the reaction is limited only by the size of the available manufacturing capabilities.

[026] In one aspect, therefore, the invention provides a large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S.

[027] The process comprises the steps:

(a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation; and

each of R¹ to R³ is as defined above; and

(b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

[028] The previously reported processes for Lewis acid promoted rearrangement of boron "ate" complexes employ tetrahydrofuran, an ether solvent that is fully miscible with water. Failure to employ rigorously dried equipment, solvents, and reagents in these processes results in a dramatic reduction in the diastereomeric ratio. The hygroscopic Lewis acids, in particular, typically must be flame-dried immediately prior to use in the reaction. Although techniques for running moisture-sensitive reactions are familiar to those of skill in the art and are routinely practiced on a laboratory scale, such reactions are costly and difficult to scale up.

[029] Moreover, attempted scale-up of the prior art process frequently results in a further deterioration in diastereomeric ratio during workup and isolation of the product boronic ester compound. Matteson and Erdlik, *Organometallics*, 2:1083 (1983), reports that exposure of alpha-haloboronic ester products to free halide ion results in epimerization at the alpha-carbon center. Without wishing to be bound by theory, the present inventors believe that epimerization is particularly problematic during reaction work-up and/or subsequent steps. For example, epimerization is believed to occur during concentration of the reaction mixture to remove the tetrahydrofuran solvent and exchange it for a water-immiscible solvent. Failure to completely remove the tetrahydrofuran also negatively impacts diastereomeric ratio during the subsequent aqueous washes. Exposure of the

product to halide ion during these steps is difficult to avoid, particularly when the reaction is performed on a large scale.

[030] The present inventors have discovered that the rearrangement of boron "ate" complexes is advantageously performed in an ether solvent that has low miscibility with water. Use of such solvents obviates the need for solvent exchange prior to the aqueous washes, and the organic-soluble product is effectively shielded from aqueous halide ion during the washes, even if performed on a large scale. Preferably, the solubility of water in the ether solvent is less than about 5% w/w, more preferably less than about 2% w/w. In various embodiments, ether solvent that has low miscibility with water constitutes at least about 70%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% v/v of the reaction mixture.

[031] The ether solvent preferably is one that is suitable for routine use in large-scale production. As used herein, the term "large-scale" refers to a reaction that utilizes at least about five moles of at least one starting material. Preferably, a large-scale process utilizes at least about 10, 20, 50, or 100 moles of at least one starting material.

[032] For purposes of the invention, the term "ether" refers to any of a class of chemical compounds characterized in having an oxygen atom attached to two carbon atoms. An "ether solvent" is an ether compound that exists in liquid form at the desired reaction temperature and is capable of dissolving the starting material(s) and/or product(s) of the reaction. Non-limiting examples of ether solvents suitable for use in the process of the invention include *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, and isopropyl ether.

[033] In one embodiment, the reaction mixture further comprises a coordinating co-solvent. In another embodiment, the ether solvent that has low miscibility with water is sufficiently coordinating that a coordinating co-solvent is not necessary. For purposes of the invention, the terms "coordinating co-solvent" and "coordinating solvent" refer to a solvent that is capable of coordinating the Lewis acid and solvating the ionic components of the reaction. Hindered ether solvents, such as *tert*-butyl methyl ether, are poorly coordinating and preferably are used with a coordinating co-solvent. Nonlimiting examples of coordinating co-solvents suitable for use in the practice of the invention include tetrahydrofuran, dioxane, water, and mixtures thereof.

[034] In some embodiments, the reaction mixture comprises at least about 5% or at least about 10% v/v of a coordinating co-solvent. Preferably, the amount of a water-miscible

coordinating co-solvent present in the reaction mixture is not so great as to interfere with phase separation during the reaction or workup. In various embodiments, the coordinating co-solvent constitutes no more than about 20%, about 15%, or about 10% v/v of the reaction mixture.

[035] As used herein, the term "nucleofugic" refers to any group that is capable of undergoing nucleophilic displacement under the rearrangement conditions of the present process. Such nucleofugic groups are known in the art. Preferably, the nucleofugic group is a halogen, more preferably chloro or bromo. In the course of the rearrangement reaction converting the boron "ate" complex of formula (II) into the boronic ester compound of formula (I), the nucleofugic group Y is released as Y⁻. By way of example, when Y is chloro, chloride ion is released in step (b).

[036] The variable M⁺ is any cationic counterion for the negatively charged tetravalent boron atom in the boron "ate" complex of formula (II). In some preferred embodiments, M⁺ is selected from the group consisting of Li⁺, Na⁺, and K⁺. One of skill in the art will recognize that the salt M⁺Y⁻ is formed as a byproduct in the rearrangement reaction of step (b).

[037] The variable R¹ preferably is a group with good migratory aptitude. In some embodiments, R¹ is C₁₋₄ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₄ aliphatic), any of which groups is optionally substituted. In certain embodiments, R¹ is C₁₋₄ aliphatic, particularly isobutyl.

[038] The variable R² preferably is hydrogen, a nucleofugic group, or an optionally substituted C₁₋₄ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₄ aliphatic) group. The variable R³ preferably is a nucleofugic group or an optionally substituted C₁₋₄ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₄ aliphatic) group. One of skill in the art will recognize that functional substituents may be present on any of R¹, R², or R³, provided that the functional substituent does not interfere with the formation of the boron "ate" complex of formula (II).

[039] One embodiment of the invention relates to a process for preparing a boronic ester compound of formula (I), wherein R³ is a nucleofugic group. Such compounds are useful as intermediates for the synthesis of alpha-substituted boronic ester and acid compounds, including alpha-aminoboronic ester and acid compounds, as described below. In certain preferred embodiments, R² is a nucleofugic group and R³ is hydrogen.

[040] The variables R⁴ and R⁵ can be the same or different. In some embodiments, R⁴ and R⁵ are directly linked, so that R⁴ and R⁵, taken together with the intervening oxygen

and boron atoms, form an optionally substituted 5- to 10-membered ring, which can have 0-2 additional ring heteroatoms selected from N, O, or S. In some embodiments, the ring is a 5- or 6-membered ring, preferably a 5-membered ring.

[041] The present invention is particularly advantageous for the Lewis acid promoted rearrangement of boron "ate" complexes of formula (II), wherein R^4 and R^5 are directly linked and together are a chiral moiety. One embodiment of the invention relates to the rearrangement of such chiral boron "ate" complexes to provide a boronic ester compound of formula (I) wherein the carbon atom bearing R^1 , R^2 , and R^3 is a chiral center. The rearrangement reaction preferably proceeds with a high degree of stereodirection by the R^4 - R^5 chiral moiety to provide the boronic ester compound of formula (I) having a diastereomeric ratio at the carbon atom bearing R^1 , R^2 , and R^3 of at least about 96:4 relative to a chiral center in the R^4 - R^5 chiral moiety. Preferably, the diastereomeric ratio is at least about 97:3.

[042] The terms "stereoisomer", "enantiomer", "diastereomer", "epimer", and "chiral center", are used herein in accordance with the meaning each is given in ordinary usage by those of ordinary skill in the art. Thus, stereoisomers are compounds that have the same atomic connectivity, but differ in the spatial arrangement of the atoms. Enantiomers are stereoisomers that have a mirror image relationship, that is, the stereochemical configuration at all corresponding chiral centers is opposite. Diastereomers are stereoisomers having more than one chiral center, which differ from one another in that the stereochemical configuration of at least one, but not all, of the corresponding chiral centers is opposite. Epimers are diastereomers that differ in stereochemical configuration at only one chiral center.

[043] As used herein, the term "diastereomeric ratio" refers to the ratio between diastereomers which differ in the stereochemical configuration at one chiral center, relative to a second chiral center in the same molecule. By way of example, a chemical structure with two chiral centers provides four possible stereoisomers: R^*R , R^*S , S^*R , and S^*S , wherein the asterisk denotes the corresponding chiral center in each stereoisomer. The diastereomeric ratio for such a mixture of stereoisomers is the ratio of one diastereomer and its enantiomer to the other diastereomer and its enantiomer = $(R^*R + S^*S) : (R^*S + S^*R)$.

[044] One of ordinary skill in the art will recognize that additional stereoisomers are possible when the molecule has more than two chiral centers. For purposes of the present invention, the term "diastereomeric ratio" has identical meaning in reference to

compounds with multiple chiral centers as it does in reference to compounds having two chiral centers. Thus, the term "diastereomeric ratio" refers to the ratio of all compounds having R^*R or S^*S configuration at the specified chiral centers to all compounds having R^*S or S^*R configuration at the specified chiral centers. For convenience, this ratio is referred to herein as the diastereomeric ratio at the asterisked carbon, relative to the second specified chiral center.

[045] The diastereomeric ratio can be measured by any analytical method suitable for distinguishing between diastereomeric compounds having different relative stereochemical configurations at the specified chiral centers. Such methods include, without limitation, nuclear magnetic resonance (NMR), gas chromatography (GC), and high performance liquid chromatography (HPLC) methods.

[046] As discussed above, one embodiment of the invention is directed to processes that provide a boronic ester compound of formula (I) having a diastereomeric ratio at the carbon atom bearing R^1 , R^2 , and R^3 of at least about 96:4 relative to a chiral center in the R^4 - R^5 chiral moiety. One of skill in the art will recognize that the R^4 - R^5 chiral moiety may itself contain more than one chiral center. When R^4 - R^5 does have more than one chiral center, it preferably has high diastereomeric purity, and the diastereomeric ratio at the carbon atom bearing R^1 , R^2 , and R^3 can be measured relative to any one of the chiral centers in R^4 - R^5 .

[047] In the processes of the invention, the R^4 - R^5 chiral moiety preferably has a high level of enantiomeric purity. For purposes of the invention, the term "enantiomeric purity" is used to mean "enantiomeric excess", which is the amount by which the major enantiomer is in excess of the minor enantiomer, expressed as a percentage of the total. Preferably, the R^4 - R^5 chiral moiety has an enantiomeric purity of at least about 98%, more preferably at least about 99%, still more preferably at least about 99.5%, and most preferably at least about 99.9%.

[048] When the R^4 - R^5 chiral moiety has very high enantiomeric purity, the diastereomeric ratio at the carbon atom bearing R^1 , R^2 , R^3 approximates the epimeric ratio at that center, *i.e.*, diastereomeric ratio $\equiv (R^*R) : (S^*R)$ or $(R^*S) : (S^*S) \equiv (R^*) : (S^*)$. As used herein, the term "epimeric ratio" refers to the ratio of product having one absolute stereochemical configuration at a given chiral center to product having the opposite absolute stereochemical configuration at the corresponding chiral center. Preferably, the products have identical stereochemical configuration at all other corresponding chiral centers. In one embodiment, therefore, the invention relates to the rearrangement of a chiral boron "ate"

complex of formula (II) to provide a boronic ester compound of formula (I) wherein the epimeric ratio at the carbon atom bearing R¹, R², and R³ is at least about 96:4, more preferably at least about 97:3.

[049] Lewis acids suitable for use in the practice of the invention are those capable of complexing with the nucleofugic group to facilitate its displacement upon migration of R¹. Preferably, the Lewis acid is additionally capable of coordinating with an oxygen atom attached to boron. Nonlimiting examples of suitable Lewis acids include zinc bromide, zinc chloride, ferric bromide, and ferric chloride. In certain preferred embodiments, the Lewis acid is zinc chloride.

[050] The contacting step preferably is performed at low temperature, but may be performed at ambient or elevated temperature. The selection of an appropriate reaction temperature will depend largely on the Lewis acid employed, as well as the migratory aptitude of the R¹ moiety. One skilled in the art will be able to select a suitable temperature in view of the reaction conditions being used.

[051] In some embodiments, the contacting step is performed at a reaction temperature of at least about -100 °C, -78 °C, or -60 °C. In some embodiments, the contacting step is performed at a reaction temperature that is no greater than about 80 °C, 40 °C, or 30 °C. Any range encompassing these high and low temperatures are included within the scope of the invention. Preferably, the contacting step is performed at a reaction temperature in the range of about -100 °C to about 80 °C, about -70 °C to about 40 °C, about -60 °C to about 30 °C, or about -50 °C to about 30 °C. In certain preferred embodiments, the contacting step is begun at low temperature, preferably in the range of about -70 °C to about -30 °C, and then the reaction mixture is allowed to warm, preferably to ambient temperature.

[052] Surprisingly, the process of the present invention requires no special precautions to avoid the presence of water during the rearrangement reaction itself. In some embodiments, moist Lewis acid is employed, with minimal deterioration in diastereomeric ratio. When used in reference to the Lewis acid, the term "moist" means that the water content of the Lewis acid is greater than about 100, 200, 500, or 1,000 ppm. Remarkably, the Lewis acid even can be added to the reaction mixture in the form of an aqueous solution without deleterious impact on diastereomeric ratio.

[053] In some embodiments, therefore, the process of the invention comprises the steps:

- (a) providing a solution comprising a boron "ate" complex of formula (II) and

- (i) a coordinating ether solvent that has low miscibility with water; or
 - (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and
- (b) adding to the solution of step (a) a Lewis acid solution comprising water and a Lewis acid.

[054] In some other embodiments, the Lewis acid solution comprises tetrahydrofuran and a Lewis acid.

[055] Thus, unlike the prior art process, the process of the invention is readily amenable to large-scale production. In various embodiments, at least about 5, 10, 20, 50, 100, 500, or 1000 moles of boron "ate" complex of formula (II) is contacted with a Lewis acid under conditions that afford the boronic ester compound of formula (I). The invention further provides a composition comprising a boronic ester compound of formula (I), as described herein, and an ether solvent that has low miscibility with water. The composition preferably comprises at least about 5, 10, 20, 50, 100, 500, or 1000 moles of the boronic ester compound of formula (I). In certain embodiments, R⁴ and R⁵ together are a chiral moiety, and the compound of formula (I) present in the composition has a diastereomeric ratio of at least about 96:4 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety.

[056] Workup of the reaction preferably comprises washing the reaction mixture with an aqueous solution and concentrating the washed reaction mixture by removal of solvents to afford a residue comprising the boronic ester compound of formula (I). Preferably, the residue comprises at least about 5, 10, 20, 50, 100, 500, or 1000 moles of the boronic ester compound of formula (I). In those embodiments wherein R⁴-R⁵ is a chiral moiety, the boronic ester compound of formula (I) present in the residue preferably has a diastereomeric ratio of at least about 96:4 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety. More preferably, the diastereomeric ratio is at least about 97:3.

[057] The boron "ate" complex of formula (II) can be prepared by any known method, but preferably is prepared by reaction of a boronic ester of formula (III):



with a reagent of formula (IV):



wherein each of M^+ , Y, and R^1 to R^3 are as defined above for the boron "ate" complex of formula (II). In some embodiments, the reaction is performed at a reaction temperature of at least about -100°C , -78°C , or -60°C . In some embodiments, the reaction is performed at a reaction temperature no greater than about 0°C , -20°C , or -40°C . Any range encompassing these high and low temperatures are included within the scope of the invention. The reaction preferably is performed at a reaction temperature in the range of about -100°C to about 0°C , about -78°C to about -20°C , or about -60°C to about -40°C . In some embodiments, the boron "ate" complex of formula (II) is prepared in a solution comprising an ether solvent having low miscibility with water, and the reaction mixture is directly treated with a Lewis acid to effect rearrangement to the boron ester compound of formula (I).

[058] In some embodiments, the reagent of formula (IV) is formed *in situ*. Such embodiments include the steps:

(i) providing a solution comprising a boronic ester of formula (III), as defined above, and a compound of formula (V):



wherein R^2 and R^3 are as defined above for the reagent of formula (IV); and

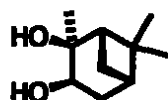
(ii) treating the solution with a strong, sterically hindered base to form the boron "ate" complex of formula (II).

[059] In some embodiments, the sterically hindered base is an alkali metal dialkylamide bases of formula $\text{M}^2\text{N}(\text{R}^4)_2$, where M^2 is Li, Na, or K, and each R^4 , independently is a branched or cyclic C_{3-4} aliphatic. *In situ* formation of the reagent of formula (IV) is especially advantageous in those embodiments wherein Y is a nucleofugic group, due to the instability of the reagent of formula (IV).

[060] The boronic ester of formula (III) can be prepared by any known method, but typically is prepared by esterification of the corresponding boronic acid compound, e.g., by methods described in Brown *et al.*, *Organometallics*, 2: 1311-1316 (1983). Cyclic boronic esters of formula (III) preferably are prepared by:

- (a) providing a solution comprising:
 - (i) a boronic acid compound of formula $R^1-B(OH)_2$;
 - (ii) a compound of formula $HO-R^4-R^5-OH$, wherein R^4 and R^5 , taken together, are an optionally substituted linking chain comprising 2-5 carbon atoms and 0-2 heteroatoms selected from the group consisting of O, N, and S; and
 - (iii) an organic solvent that forms an azeotrope with water; and
- (b) heating the solution at reflux with azeotropic removal of water.

[061] As used in reference to R^4 and R^5 , the term "linking chain" refers to the shortest linear chain of atoms connecting the oxygen atoms to which R^4 and R^5 are attached. The linking chain optionally is substituted at any chain atom, and one or more chain atoms also may form part of a ring system that is spiro to, fused to, or bridging the linear linking chain. By way of example, but not limitation, in some embodiments, the compound of formula $HO-R^4-R^5-OH$ is pinanediol, having the structure:



In such embodiments, the linking chain R^4-R^5 comprises two carbon atoms, which together form one side of the bicyclo[3.1.1]heptane ring system, and one of which additionally is substituted with a methyl group.

[062] In some embodiments, the compound of formula $HO-R^4-R^5-OH$ is a chiral diol, preferably one having high diastereomeric and enantiomeric purity. One of skill in the art will appreciate that in such embodiment, the compound of formula $HO-R^4-R^5-OH$ is employed as a chiral auxiliary to direct the stereochemical configuration at the carbon bearing R^1 , R^2 , and R^3 . Chiral diols useful as chiral auxiliaries in organic synthesis are well-known in the art. Nonlimiting examples include 2,3-butanediol, preferably (2R,3R)-(-)-2,3-butanediol or (2S,3S)-(+)-2,3-butanediol; pinanediol, preferably (1R,2R,3R,5S)-(-)-pinanediol or (1S,2S,3S,5R)-(+)-pinanediol; 1,2-cyclopentanediol, preferably (1S,2S)-(+)-*trans*-1,2-cyclopentanediol or (1R,2R)-(-)-*trans*-1,2-cyclopentanediol; 2,5-hexanediol, preferably (2S,5S)-2,5-hexanediol or (2R,5R)-2,5-hexanediol; 1,2-dicyclohexyl-1,2-ethanediol, preferably (1R,2R)-1,2-dicyclohexyl-1,2-ethanediol or (1S,2S)-1,2-dicyclohexyl-1,2-ethanediol; hydrobenzoin, preferably (S,S)-(-)-hydrobenzoin or (R,R)-(+)-hydrobenzoin; 2,4-pentanediol, preferably (R,R)-(-)-2,4-pentanediol or (S,S)-(+)-2,4-pentanediol; erythronic γ -lactone,

preferably D-erythronic γ -lactone. Carbohydrates, *e.g.* a 1,2,5,6-symmetrically protected mannitol, also may be used as chiral diols.

[063] Nonlimiting examples of organic solvents suitable for use in the esterification reaction include acetonitrile, toluene, hexane, heptane, and mixtures thereof. In some embodiments, the organic solvent is an ether solvent, preferably an ether solvent that has low miscibility with water. In certain preferred embodiments, the esterification reaction is performed in an ether solvent that has low miscibility with water, and the product solution comprising the boronic ester of formula (III) is used directly in the next step, without isolation of the boronic ester.

[064] As noted above, the process of the present invention for the first time permits workup of large-scale reactions without significant deterioration in diastereomeric ratio. In another aspect, therefore, the invention provides a composition comprising at least about 5, 10, 20, 50, 100, 500, or 1000 moles of a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered chiral ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, preferably at least about 97:3, relative to a chiral center in the R^4 - R^5 chiral moiety.

[065] Preferred values for R^1 to R^5 are as described above. Preferably, solvents constitute less than about 30% w/w, 20% w/w, 10% w/w, or 5% w/w of the composition according to this aspect of the invention. In some embodiments, the boronic ester

compound of formula (I) constitutes at least about 70% w/w, 80% w/w, 90% w/w, or 95% w/w of the composition.

[066] One embodiment relates to the composition described above, wherein at least one of the following features is present:

- (a) R^3 is chloro;
- (b) the boronic ester compound (I) is



- (c) R^3 is hydrogen; and
- (d) R^1 is C_{1-4} aliphatic.

[067] All of the boronic ester compound of formula (I) present in the composition may be produced in a single batch run. For purposes of the invention, the term "batch run" refers to execution of a synthetic process, wherein each step of the process is performed only once. Preferably, the boronic ester compound of formula (I) present in the composition is prepared in a single batch run of the process according to the first aspect of the invention. One of ordinary skill in the art will appreciate that preparation of a given quantity of product by a single batch run of a large-scale process is more efficient and provides a more homogeneous product than preparation of the same quantity of product by repeated execution of a small-scale process.

[068] The boronic ester compounds of formula (I) wherein R^3 is a nucleofugic group are useful as intermediates for the synthesis of alpha-aminoboronic ester compounds. In another aspect, therefore, the invention provides a large-scale process for preparing an alpha-aminoboronic ester, preferably by a process comprising the steps:

- (a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M^+ is a cation;

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen;

R^3 is a nucleofugic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

(b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I):



where each of R^1 to R^5 is as defined above, said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and

(c) treating the boronic ester compound of formula (I) with a reagent of formula $M^+-N(G)_2$, where M^+ is an alkali metal and each G individually or together is an amino group protecting group to form a byproduct of formula M^+-R^3 and a compound of formula (VIII):



wherein each G and R^1 to R^5 are as defined above; and

(d) removing the G groups to form a compound of formula (VII):



or an acid addition salt thereof.

[069] In some embodiments, in step (c), the boronic ester compound of formula (I) is treated with a reagent of formula $M^1-N(Si(R^4))_3$, where M^1 is an alkali metal and each R^4 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted.

[070] Reaction of the boronic ester compound of formula (I) with the reagent of formula $M^1-N(G)_2$ preferably is conducted at a reaction temperature in the range of about -100 °C to about 50 °C, preferably about -50 °C to about 25 °C, and more preferably about -30 °C to about 0 °C. In some embodiments, R^3 is halo, preferably chloro, and M^1 is Li. To facilitate isolation of the product of formula (VIII), the reaction mixture preferably comprises an organic solvent in which the byproduct M^1-R^3 has low solubility. Nonlimiting examples of suitable organic solvents include methylcyclohexane, cyclohexane, heptane, hexane, and toluene. In some embodiments, step (c) further comprises filtering the reaction mixture to remove M^1-R^3 and provide a filtrate comprising the compound of formula (VIII). Preferably, the filtrate is used directly in step (d).

[071] In those embodiments wherein the reaction mixture comprises an organic solvent in which the byproduct M^1-R^3 has low solubility, the reaction mixture may additionally comprise a solvent in which the byproduct M^1-R^3 has high solubility. In such cases, the solvent in which the byproduct M^1-R^3 has high solubility preferably is removed prior to filtration of the reaction mixture. By way of example, in some embodiments, a reagent of formula $M^1-N(Si(R^4))_3$ is added to the reaction mixture as a solution comprising tetrahydrofuran. In such embodiments, step (c) preferably further comprises removing the tetrahydrofuran before filtering the reaction mixture.

[072] Those of skill in the art are aware of various methods that can be used to remove the protecting groups G in the compound of formula (VIII), including, *e.g.*, aqueous hydrolysis or treatment with acid. The product alpha-aminoboronic ester of formula (VII) has low stability and preferably is immediately derivatized (Matteson *et al.*, *J. Am. Chem. Soc.*, 103:5241 (1981)) or is isolated as an acid addition salt. In some embodiments, step (d) comprises treating the compound of formula (VIII) with an acid and isolating the compound of formula (VII) as the acid addition salt. In certain preferred embodiments, the acid is trifluoroacetic acid, and the compound of formula (VII) is isolated as the trifluoroacetic acid addition salt.

[073] ... As discussed above, the processes of the invention are particularly well-suited for preparing alpha-aminoboronic ester compounds of formula (VII), wherein the

alpha carbon is a chiral center. Thus, one embodiment of the invention relates to a large-scale process for preparing an alpha-aminoboronic ester compound of formula (VIIa) or (VIIb):



or an acid addition salt thereof, wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted chiral cyclic boronic ester;

said process comprising:

(a) providing a boron "ate" complex of formula (IIa) or (IIb):



where

Y is a nucleofugic group;

M^+ is a cation;

R^1 is hydrogen;

R^2 is a nucleofugic group; and

R^4 and R^5 are as defined above;

(b) contacting the boron "ate" complex of formula (IIa) or (IIb) with a Lewis acid under conditions that afford a boronic ester compound of formula (Ia) or (Ib):

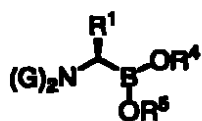


where each of R^1 to R^5 is as defined above, said contacting step being conducted in a reaction mixture comprising:

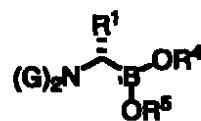
(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and

(c) treating the boronic ester compound of formula (Ia) or (Ib) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and G is an amino group protecting moiety, to form a compound of formula (VIIIa) or (VIIIb):



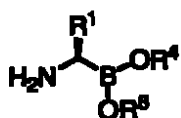
(VIIIa)



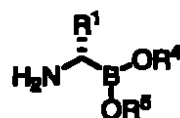
(VIIIb)

wherein each G and R^1 to R^5 are as defined above; and

(d) removing the G groups to form a compound of formula (VIIa) or (VIIb):



(VIIa)

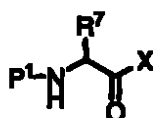


(VIIb)

or an acid addition salt thereof.

[074] Preferred values for Y, M^1 , R^1 to R^5 , and G are as described above. The compound of formula (VIIa) or (VIIb) preferably has a diastereomeric ratio at the alpha-carbon of at least about 96:4, more preferably at least about 97:3, relative to a chiral center in the R^4 - R^5 chiral moiety.

[075] The alpha-aminoboronic ester compounds of formula (VII) are useful synthetic intermediates for the preparation of peptidyl boronic ester compounds. In some embodiments, therefore, the process according to this aspect of the invention further comprises coupling the compound of formula (VII) with a compound of formula (IX):



(IX)

wherein:

P^1 is an amino group blocking moiety;

R^7 is selected from the group consisting of hydrogen, C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or C_{1-6} aliphatic- R^8 ; and

R^4 is selected from the group consisting of alkoxy, alkylthio, optionally substituted aryl, heteroaryl, and heterocyclyl groups, and optionally protected amino, hydroxy, and guanidino groups; and

X is OH or a leaving group;

to form a compound of formula (X):



wherein each of P^1 , R^1 , R^4 , R^5 , and R^7 is as defined above.

[076] The leaving group X is any group capable of nucleophilic displacement by the alpha-amino group of the compound of formula (VII). In some embodiments, the moiety $C(O)-X$ is an activated ester, such as an *O*-(*N*-hydroxysuccinimide) ester. In some embodiments, an activated ester is generated *in situ* by contacting a compound of formula (IX), wherein X is OH, with a peptide coupling reagent. Examples of suitable peptide coupling reagents include, without limitation, carbodiimide reagents, *e.g.*, dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC); phosphonium reagents, *e.g.*, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent); and uronium reagents, *e.g.*, *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU).

[077] Those of skill in the art also are aware of procedures that permit the direct coupling of silyl protected amines, without a prior deprotection step. In such procedures, the silyl groups are removed *in situ* under the coupling reaction conditions. In some embodiments of the present invention, therefore, a compound of formula (VIII) is contacted with a compound of formula (IX) under conditions that remove the $(R^6)_3Si$ groups *in situ* and form a compound of formula (X).

[078] For purposes of the invention, the term "amino-group blocking moiety" refers to any group used to derivatize an amino group, especially an *N*-terminal amino group of a peptide or amino acid. The term "amino-group blocking moiety" includes, but is not limited to, protecting groups that are commonly employed in organic synthesis, especially peptide synthesis. See, for example, Gross and Mienhoffer, eds., *The Peptides*, Vol. 3, Academic Press, New York, 1981, pp. 3-88; Green and Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley and Sons, Inc., New York, 1999. Unless otherwise specified, however, it is not

necessary for an amino-group blocking moiety to be readily cleavable. Amino-group blocking moieties include, *e.g.*, alkyl, acyl, alkoxycarbonyl, aminocarbonyl, and sulfonyl moieties. In some embodiments, the amino-group blocking moiety is an acyl moiety derived from an amino acid or peptide, or a derivative or analog thereof.

[079] As used herein, the term "amino acid" includes both naturally occurring and unnatural amino acids. For purposes of the invention, a "derivative" of an amino acid or peptide is one in which a functional group, *e.g.*, a hydroxy, amino, carboxy, or guanidino group at the *N*-terminus or on a side chain, is modified with a blocking group. As used herein, an "analog" of an amino acid or peptide is one which includes a modified backbone or side chain. The term "peptide analog" is intended to include peptides wherein one or more stereocenters are inverted and one or more peptide bonds are replaced with a peptide isostere.

[080] In some embodiments, P^1 is a cleavable protecting group. Examples of cleavable protecting groups include, without limitation, acyl protecting groups, *e.g.*, formyl, acetyl (Ac), succinyl (Suc), or methoxysuccinyl (MeOSuc), and urethane protecting groups, *e.g.*, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), or fluorenylmethoxycarbonyl (Fmoc).

[081] In some such embodiments, the process according to this aspect of the invention further comprises the steps:

- (f) removing the protecting group P^1 to form a compound of formula (XI):



or an acid addition salt thereof, wherein each of R^1 , R^4 , R^5 , and R^7 is as defined above; and

- (g) coupling the compound of formula (XI) with a reagent of formula P^2-X , wherein P^2 is any amino group blocking moiety, as described above, and X is a leaving group, to form a compound of formula (XII):

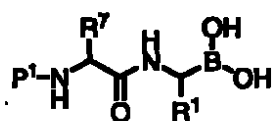


wherein each of P^2 , R^1 , R^4 , R^5 , and R^7 are as defined above. One of skill in the art will recognize that in those embodiments wherein P^1 is an acyl group, including, *e.g.*, an acyl

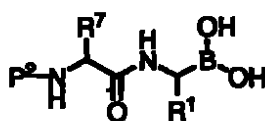
moiety derived from an amino acid or peptide, or an analog or derivative thereof, the leaving group X may be generated *in situ*, as discussed above for the compound of formula (IX).

[082] In each of the compounds (X) and (XII), the boronic acid moiety is protected as a boronic ester. If desired, the boronic acid moiety can be deprotected by any method known in the art. Preferably, the boronic acid moiety is deprotected by transesterification in a biphasic mixture. More preferably, the boronic acid deprotecting step comprises the steps:

- (i) providing a biphasic mixture comprising the boronic ester compound of formula (X) or (XII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₆ hydrocarbon solvent, and aqueous mineral acid;
- (ii) stirring the biphasic mixture to afford the corresponding deprotected boronic acid compound of formula (Xa) or (XIII):



(Xa)



(XIII);

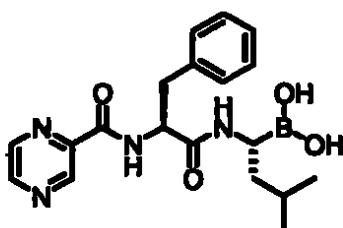
- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (Xa), (XIII), or a boronic acid anhydride thereof, into an organic solvent.

[083] The organic boronic acid acceptor in step (i) preferably is an aliphatic, aryl, or ar(aliphatic)boronic acid. In some embodiments, the boronic acid acceptor is selected from the group consisting of phenylboronic acid, benzylboronic acid, butylboronic acid, pentylboronic acid, hexylboronic acid, and cyclohexylboronic acid. In certain embodiments, the boronic acid acceptor is isobutylboronic acid. In some embodiments, the boronic acid acceptor is selected so that the boronic ester compound of formula (III) is formed as a byproduct of the deprotection reaction. The boronic ester compound of formula (III) can then be used in another batch run of the process described above. In such embodiments, the moiety R⁴-R⁵ is effectively recycled, which may be particularly advantageous if R⁴-R⁵ is an expensive chiral moiety.

[084] To enhance the purity of the product, the aqueous layer containing the compound of formula (Xa) or (XIII) preferably is washed to remove neutral organic impurities prior to the extracting step (iv). In such embodiments, step (iii) preferably comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6.

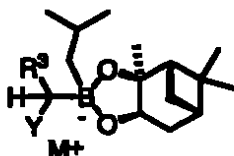
[065] In some embodiments, the invention relates to an improved process for manufacturing the proteasome inhibitor bortezomib. Thus, in one embodiment, the invention provides a large-scale process for forming a compound of formula (XIV):



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

- (a) providing a boron "ate" complex of formula (XV):



(XV)

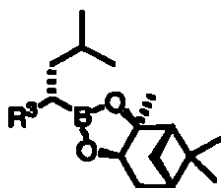
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M^+ is an alkali metal;

- (b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



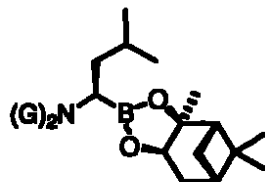
(XVI)

said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or

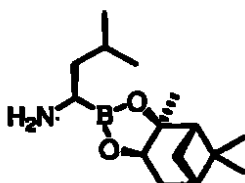
(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and each G individually or together is an amino group protecting group, to form a compound of formula (XVII):



(XVII)

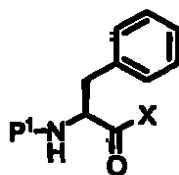
(d) removing the G groups to form a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XIX);



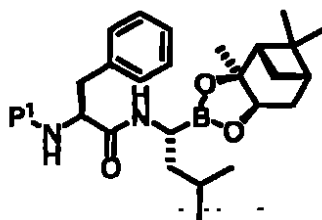
(XIX)

wherein:

P^1 is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

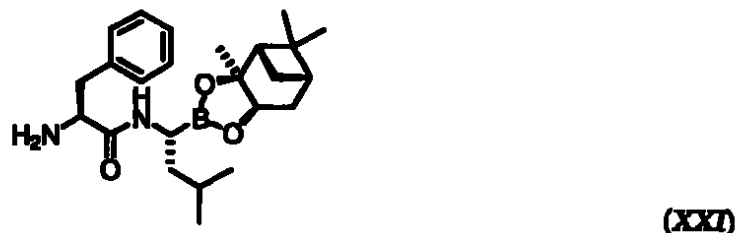
to form a compound of formula (XX):



(XX)

wherein P^1 is as defined above;

- (f) removing the protecting group P¹ to form a compound of formula (XXI):

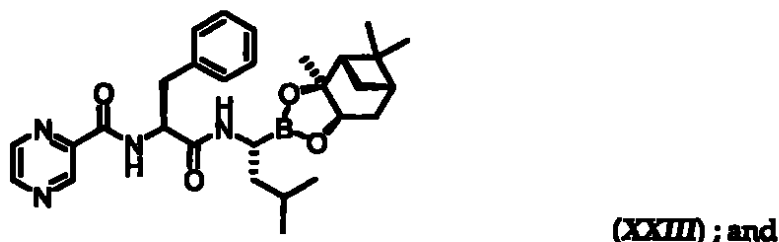


or an acid addition salt thereof;

- (g) coupling the compound of formula (XXI) with a reagent of formula (XXII)



wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



- (h) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

[086] In some embodiments, the process is characterized by at least one of the following features (1)–(5). In certain preferred embodiments, the process is characterized by all five features (1)–(5) below.

- (1) In the boron "ate" complex of formula (XV), R³ and Y both are chloro.

- (2) The coupling step (e) comprises the steps:

(i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;

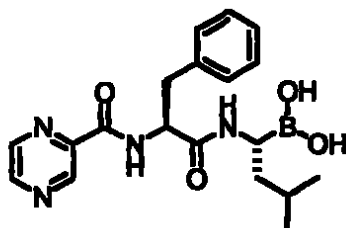
(ii) performing a solvent-exchange to replace dichloromethane with ethyl acetate; and

- (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) The protecting group removing step (f) comprises the steps:
- (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt.
- (4) The coupling step (g) comprises the steps:
- (i) coupling the compound of formula (XXI) with 2-pyrazinecarboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (5) The boronic acid deprotecting step (h) comprises the steps:
- (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₆₋₁₀ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

[087] Preferably, step (h)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

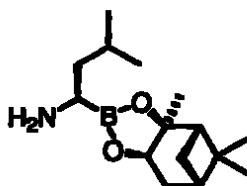
[068] In another embodiment, the invention relates to a large-scale process for forming a compound of formula (XIV)



(XIV)

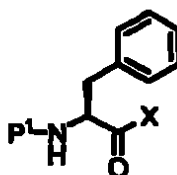
or a boronic acid anhydride thereof, comprising the steps:

(aa) coupling a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof, with a compound of formula (XIX):



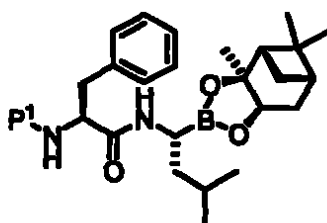
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

to form a compound of formula (XX):



(XX)

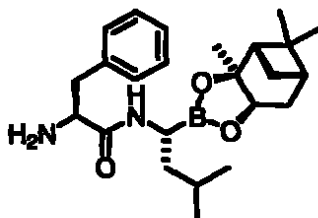
wherein P¹ is as defined above, said coupling step (aa) comprising the steps:

(i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-

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tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;

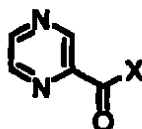
- (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution;
- (bb) removing the protecting group P¹ to form a compound of formula (XXI):



(XXI)

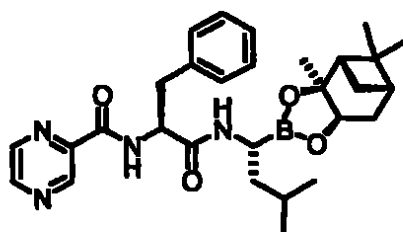
or an acid addition salt thereof, said protecting group removing step (bb) comprising the steps:

- (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt;
- (cc) coupling the compound of formula (XXI) with a reagent of formula (XXII)



(XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(XXIII),

said coupling step (cc) comprising the steps:

- (i) coupling the compound of formula (XXI) with 2-pyrazinecarboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;

- (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
- (iii) performing an aqueous wash of the ethyl acetate solution; and
- (dd) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof, said deprotecting step (dd) comprising the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₄₋₆ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

[089] Preferably, step (dd)(iii) comprises the steps:

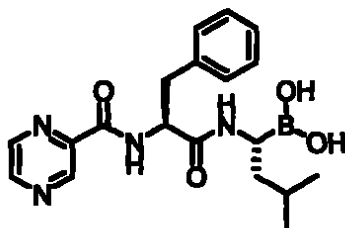
- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

[090] The efficiency of the processes described above is further enhanced by telescoping steps, for example, by carrying a reaction mixture or worked-up product solution from one reaction directly into the following reaction, without isolation of the intermediate product. For example, in some embodiments, step (e)(iii) or (aa)(iii) affords an ethyl acetate solution comprising a compound of formula (XX), and the ethyl acetate solution is directly subjected in step (f) or (bb) to conditions effective to remove the protecting group P¹. In some such embodiments, the protecting group P¹ is an acid-labile protecting group, for example, *tert*-butoxycarbonyl (Boc), and the ethyl acetate solution from step (e)(iii) or (aa)(iii) is treated with acid. In certain preferred embodiments, the ethyl acetate solution from step (e)(iii) or (aa)(iii) is dried azeotropically and then treated with gaseous HCl.

[091] When the deprotecting step (f) or (bb) is performed under anhydrous conditions, as described above, the product of formula (XXI) can be isolated by crystallization from the reaction mixture as its HCl addition salt. Crystallization of the product salt is promoted by addition of a hydrocarbon solvent such as *n*-heptane. In some embodiments, the reaction mixture is partially concentrated prior to addition of the hydrocarbon solvent. The present inventors have discovered that crystallization of the compound of formula (XXI) in this manner efficiently removes any tripeptide impurity that may have formed during the coupling step (e) or (aa). Such impurities are difficult to remove at later stages in the synthesis.

[092] Further telescoping of the process is possible by carrying the product mixture from the coupling step (g) or (cc) directly into the boronic acid moiety deprotecting step (h) or (dd). Preferably, the organic solvent from the coupling reaction is first replaced with ethyl acetate in order to facilitate aqueous washes. A second solvent exchange into a hydrocarbon solvent then permits the product solution from step (g) or (cc) to be used directly in the biphasic boronic acid deprotecting step (h) or (dd), without isolation of the compound of formula (XXIII).

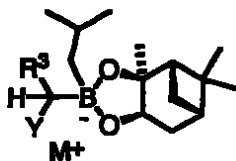
[093] Alternatively, a more convergent approach may be adopted for the synthesis of the compound of formula (XIV). Thus, in yet another embodiment, the invention provides a large-scale process for forming a compound of formula (XIV)



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

- (a) providing a boron "ate" complex of formula (XV):



(XV)

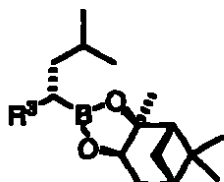
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M⁺ is an alkali metal;

(b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



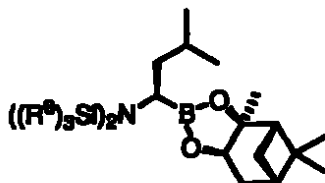
(XVI)

said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

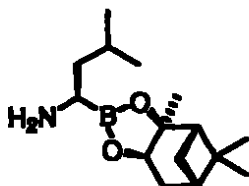
(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula M⁺-N(Si(R⁶)₃)₂, where M⁺ is an alkali metal and each R⁶ independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a compound of formula (XVII):



(XVII)

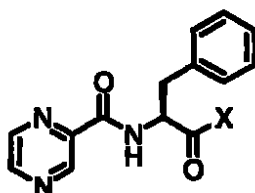
(d) removing the (R⁶)₃Si groups to form a compound of formula (XVIII):



(XVIII)

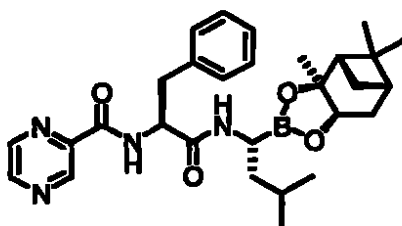
or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XLXa):



(XIXa)

wherein X is OH or a leaving group, to form a compound of formula (XXIII):



(XXIII); and

(f') deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

[094] In some embodiments, the process is characterized by at least one of the following features (1)-(3). In certain preferred embodiments, the process is characterized by all three features (1)-(3) below.

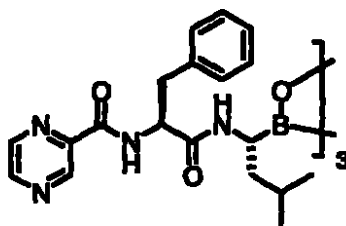
- (1) In the boron "ate" complex of formula (XV), R³ and Y both are chloro.
- (2) The coupling step (e') comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XIXa) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) The boronic acid deprotecting step (f') comprises the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₁₋₄ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);

- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

[095] Preferably, step (f)(iii) comprises the steps:

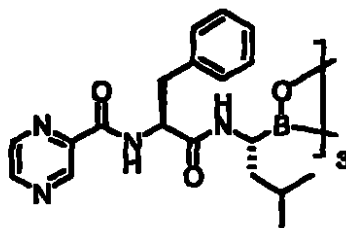
- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

[096] In step (h)(iv), (dd)(iv), or (f)(iv) of the processes described above, the compound of formula (XIV), or a boronic acid anhydride thereof, preferably is extracted into ethyl acetate and crystallized by addition of hexane or heptane. In some embodiments, the process further comprises isolation of a boronic acid anhydride of the compound of formula (XIV), preferably a trimeric boronic acid anhydride of formula (XXIV):



(XXIV)

[097] The processes of the invention permit the large-scale manufacture of bortezomib of very high chemical and stereochemical purity. Prior art processes were limited in scale and afforded product of lower overall purity. In yet another aspect, therefore, the invention provides a composition comprising at least one kilogram of a compound of formula (XXIV):



(XXIV)

The compound of formula (XXIV) preferably is prepared according to the process described above, and preferably constitutes at least 99% w/w of the composition according to this aspect of the invention.

EXAMPLES

Abbreviations

BOC	<i>tert</i> -butoxycarbonyl
D.I	de-ionized
DMF	<i>N,N</i> -dimethylformamide
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	Hours
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
LOD	loss on drying
min	Minutes
MTBE	<i>t</i> -butyl methyl ether
RP-HPLC	reverse phase high performance liquid chromatography
RPM	revolutions per minute
TBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
THF	tetrahydrofuran

Example 1: (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate Manufacturing Process

(1S)-(S)-Pinanediol 1-chloro-3-methylbutane-1-boronate

1. (S)-Pinanediol-2-methylpropane-1-boronate (12.0 kg, 50.8 moles) was charged to a reaction vessel maintained under a nitrogen atmosphere.

2. *tert*-Butyl methyl ether (53 kg) and dichloromethane (22.5 kg) were charged and the resultant mixture was cooled to -57 °C with stirring.
3. Diisopropylamine, (6.7 kg) was charged to another reaction vessel maintained under a nitrogen atmosphere.
4. *tert*-Butyl methyl ether (27 kg) was charged to the diisopropylamine and the resultant mixture was cooled to -10 °C with stirring.
5. *n*-Hexyllithium in hexane (33.2 weight% solution) (17.6 kg) was added to the diisopropylamine mixture over a period of 57 minutes, while the reaction temperature was maintained at -10 °C to -7 °C.
6. This mixture (LDA-mixture) was stirred for 33 minutes at -9 °C to -7 °C before it was used.
7. Zinc chloride, (12.1 kg) was charged to a third reaction vessel maintained under a nitrogen atmosphere.
8. *tert*-Butyl methyl ether (16 kg) was charged to the zinc chloride and the resultant mixture was warmed to 30 °C with stirring.
9. Tetrahydrofuran (53 kg) was added to the zinc chloride suspension over a period of 18 minutes, while the reaction temperature was maintained at 35 °C to 40 °C.
10. This mixture (ZnCl₂-mixture) was stirred for 4 hours and 28 minutes at 38 °C to 39 °C until it was used.
11. The LDA-mixture (from # 3 - 6) was added over a period of 60 minutes to the reaction vessel containing (*S*)-pinanediol-2-methylpropane-1-boronate, while the reaction temperature was maintained at -60 °C to -55 °C.
12. A *tert*-butyl methyl ether rinse (10 kg) was used to complete the addition.
13. The reaction mixture was stirred for an additional 20 minutes at -59 °C to -55 °C.
14. The reaction mixture was warmed to -50 °C over a period of 11 minutes.
15. The ZnCl₂-mixture (from # 7 - 10) was added over a period of 48 minutes to the reaction vessel containing (*S*)-pinanediol-2-methylpropane-1-boronate and the LDA-mixture, while the reaction temperature was maintained at -50 °C to -45 °C.
16. A *tert*-butyl methyl ether rinse (10 kg) was used to complete the addition.

17. The reaction mixture was stirred for an additional 30 minutes at -45 °C to -40 °C and then warmed to 10 °C over a period of 81 minutes.
18. A 10% sulfuric acid solution (72 kg) was added over a period of 40 minutes to the reaction vessel, while the reaction temperature was maintained at 10 °C to 21 °C.
19. The reaction mixture was stirred for 16 minutes at ambient temperature, before the aqueous phase was separated.
20. The organic phase was washed successively with deionized (D.I.) water (32 kg), and 10% sodium chloride solution (26.7 kg), each wash involved vigorous stirring for 15 to 17 minutes at ambient temperature.
21. The reaction mixture was concentrated under reduced pressure ($p_{\text{mm}} = 81$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C, providing a residue which was dissolved in methylcyclohexane (56 kg).
22. The reaction mixture was refluxed (in a Dean-Stark type condenser for water separation) under reduced pressure ($p_{\text{mm}} = 67$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C for 2 hours and 7 minutes, until no more water was separated.
23. About 35 L of the solvents were distilled off under reduced pressure ($p_{\text{mm}} = 81$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C.
24. The resultant dry methylcyclohexane mixture containing (1S)-(S)-pinanediol 1-chloro-3-methylbutane-1-boronate was cooled to 14 °C.

(1R)-(S)-Pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate

1. Lithium bis(trimethylsilyl)amide in tetrahydrofuran (19.4 weight% solution), (41.8 kg) was charged to a reaction vessel maintained under a nitrogen atmosphere and cooled to -19 °C with stirring.
2. The methylcyclohexane mixture containing (1S)-(S)-pinanediol 1-chloro-3-methylbutane-1-boronate was added over a period of 55 minutes, while the reaction temperature was maintained at -19 °C to -13 °C.
3. A methylcyclohexane rinse (5 kg) was used to complete the addition.
4. The reaction mixture was stirred for an additional 65 minutes at -13 °C to -12 °C and then warmed to 25 °C over a period of 25 minutes.

5. A suspension of Celite (2.5 kg) in methylcyclohexane (22 kg) was added to the reaction mixture.
6. The reaction mixture was concentrated under reduced pressure ($p_{\text{min}} = 25$ mbar), maintaining an external (jacket/bath) temperature of 45 °C to 50 °C, providing a residue which was dissolved in methylcyclohexane (36 kg).
7. A sample was then removed for in-process testing for tetrahydrofuran content by GC.
8. The tetrahydrofuran assay was 0.58%.
9. The solids were removed by filtration, the filtrate was filtered through a plug of Silica Gel (2.0 kg).
10. Both filter units were washed with isopropyl ether (30 kg).
11. The resultant methylcyclohexane/isopropyl ether mixture containing (1R)-(S)-pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate was stored in a container at ambient temperature until it was used in the next step.

(1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate

1. Trifluoroacetic acid, (12 kg) was charged to another reaction vessel maintained under a nitrogen atmosphere.
2. Isopropyl ether (78 kg) was charged to the trifluoroacetic acid and the resultant mixture was cooled to -10 °C with stirring.
3. The methylcyclohexane/isopropyl ether mixture containing (1R)-(S)-pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate was added over a period of 53 minutes causing product precipitation, while the reaction temperature was maintained at -10 °C to -5 °C.
4. An isopropyl ether rinse (5 kg) was used to complete the addition.
5. The reaction mixture was stirred for an additional 8 hours and 20 minutes at -9 °C to -7 °C.
6. The solid was collected by filtration, washed with isopropyl ether (70 kg) in two portions, and dried under reduced pressure ($p_{\text{min}} = 56$ mbar) at 41 °C to 42 °C for 2 hours and 15 minutes.

7. The solid was stirred with D.I. water (60 kg) for 24 minutes at ambient temperature, before the D.I. water was removed by filtration.
8. The solid was washed with D.I. water (12 kg).
9. The solid was then dried under vacuum (pmin = 4 mbar) at 40 °C to 44 °C for 9 hours and 22 minutes, after that time the loss on drying was 0.51%, which meets the ≤ 1% requirement.
10. The intermediate, (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude, was then packaged into single polyethylene bags in polypropylene drums and labeled. The yield was 72%.

Recrystallization of (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude

1. (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude, (13 kg) was charged to a reaction vessel maintained under a nitrogen atmosphere.
2. Trifluoroacetic acid (31 kg) was charged to the reaction vessel and the resultant mixture was cooled to 4 °C with stirring.
3. Once all of the solid was dissolved leaving a slightly turbid mixture, isopropyl ether (29 kg) was added over a period of 57 minutes, while the reaction temperature was maintained at 2 °C to 3 °C.
4. After complete addition the mixture was filtered through a filter into a receiving vessel maintained under a nitrogen atmosphere.
5. Reactor and filter were rinsed with a mixture of trifluoroacetic acid (3.8 kg) and isopropyl ether (5 kg). The rinse was added to the filtrate.
6. Isopropyl ether (126 kg) was added over a period of 15 minutes causing product precipitation, while the reaction temperature was maintained at 16 °C to 18 °C.
7. The mixture was stirred at 16 °C to 18 °C for 15 min, then cooled to -5 °C over a period of 67 minutes, and stirred at -3 °C to -5 °C under a nitrogen atmosphere for 89 minutes.
8. The solid was then isolated by filtration, washed with isopropyl ether (48 kg) in two portions, and dried under vacuum (pmin = 2 mbar) at 34 °C to 40 °C for 2 hours and 55 minutes after that time the loss on drying was 0.32%, which meets the ≤ 0.5% requirement.

9. The product, (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, was then packaged into double polyethylene bags in fiber drums and labeled. The yield was 86%.

**Example 2: N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride
Manufacturing Process**

(1S,2S,3R,5S)-Pinanediol N-BOC-L-phenylalanine-L-leucine boronate

1. In a fume hood, a three-necked glass reaction flask equipped with a Claisen head temperature recorder and a mechanical stirrer was flushed with nitrogen.
2. (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate (2.0 kg), was charged to the flask.
3. BOC-L-phenylalanine (1.398 kg) was charged to the flask.
4. 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, TBTU (1.864 kg) was charged to the flask.
5. Dichloromethane (15.8 L) was charged to the flask.
6. The stirring motor was adjusted to provide stirring at 260 KPM.
7. Using an ice/water cooling bath, the reaction mixture was cooled to 1.0 °C, maintaining a nitrogen atmosphere.
8. N,N-Diisopropylethylamine (2.778 L) was charged to a glass flask and transferred to the reaction mixture over a period of 117 minutes using a peristaltic pump maintaining a reaction temperature range of 0.7 °C – 2.1 °C. The overall addition rate was 23.7 mL/min.
9. A dichloromethane (0.2 L) rinse of the flask into the reaction mixture was used to complete the addition.
10. The reaction mixture was stirred for an additional 35 minutes. The temperature at the start of the stir time was 1.8 °C, and 2.5 °C at the end.
11. A sample was then removed for in-process testing by reverse phase high performance liquid chromatography (RP-HPLC). The percent conversion was determined to be 99.3%.
12. The reaction mixture was transferred in approximately two equal halves to two rotary evaporator flasks. The reaction mixture was concentrated under reduced

- pressure using a rotary evaporator, maintaining an external bath temperature of 29-30 °C.
13. Ethyl acetate (4.0 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks.
 14. The mixtures in each flask were again concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 29-30 °C.
 15. The residues in each rotary evaporator flask were then transferred back to the reaction flask using ethyl acetate (13.34 L).
 16. In a glass flask equipped with a stirrer, a 1% aqueous phosphoric acid solution was prepared by mixing D.I. water (13.18 L) and phosphoric acid (0.160 kg).
 17. In a glass flask equipped with a stirrer, a 2% aqueous potassium carbonate solution (12.0 L) was prepared by mixing D.I. water (11.76 L) and potassium carbonate (0.24 kg).
 18. In a glass flask equipped with a stirrer, a 10% aqueous sodium chloride solution (13.34 L) was prepared by mixing D.I. water (13.34 L) and sodium chloride (1.334 kg).
 19. D.I. water (13.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 380 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred under vacuum to a suitable flask and discarded.
 20. Again, D.I. water (13.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 385 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred under vacuum to a suitable flask and discarded.
 21. The 1% phosphoric acid solution prepared in Step 16 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 365 RPM for 7 minutes. The layers were allowed to separate and the acidic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
 22. The 2% potassium carbonate solution prepared in Step 17 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 367 RPM for 7 minutes. The layers were allowed to separate and the basic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.

23. The 10% sodium chloride solution prepared in Step 18 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 373 RPM for 6 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
24. The ethyl acetate solution was transferred to a rotary evaporator flask and concentrated under reduced pressure using a rotary evaporator, maintaining a bath temperature of 29-30 °C, to provide a residue.
25. The residue was then redissolved in ethyl acetate (4.68 L).
26. The solution was concentrated under vacuum using a rotary evaporator, maintaining a bath temperature of 29-30 °C, to provide a residue once more.
27. Again, the residue was then redissolved in ethyl acetate (4.68 L) and two samples taken for determination of water content by Karl Fisher titration. The water content of two samples was determined as 0.216 % and 0.207 %.
28. Using a further quantity of ethyl acetate (12.66 L), the mixture was transferred from the rotary evaporator flask to a dry reaction flask equipped with a temperature recorder, a mechanical stirrer, and a fritted gas dispersion tube, and purged with nitrogen.

(1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt

1. The ethyl acetate solution containing (1S,2S,3R,5S)-pinanediol N-BOC-L-phenylalanine-L-leucine boronate was cooled using an ice/water cooling bath to -0.9 °C.
2. Hydrogen chloride (1.115 kg) gas was bubbled into the reaction mixture over a period of 1.48 hours. The temperature at the start of the addition was -0.9 °C, and 6.8 °C at the end.
3. The reaction was then allowed to warm to 14.4 °C over 50 minutes, while maintaining a nitrogen atmosphere.
4. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 68.9 % (area %).
5. The reaction was stirred for 35 minutes. The temperature at the start was 14 °C, and 14.8 °C at the end.

6. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 94.7% (area %).
7. The reaction was stirred for approximately a further 50 minutes, maintaining a temperature of $10^{\circ}\text{C} \pm 5^{\circ}\text{C}$.
8. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 97.3%.
9. The reaction was stirred for approximately a further 50 minutes, maintaining a temperature of $10^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The final temperature was 14.6°C .
10. A sample was removed for in-process testing by RP-HPLC. The total reaction time after addition of hydrogen chloride gas was four (4) hours.
11. The percent conversion was 99%.
12. A slurry was observed.
13. n-Heptane (8.8 L) was charged to the reaction mixture.
14. The slurry was stirred for 2 hours. The temperature at the start of the stir time was 12.7°C , and 15.3°C at the end.
15. The solid was isolated by filtration on a Buchner funnel lined with a polypropylene felt filter pad.
16. The solid was washed with n-heptane (4.68 L).
17. In a hood, the solid was transferred to three drying trays at not more than 1" deep and air-dried for 1 hour.
18. The solid was then dried at $\leq 35^{\circ}\text{C}$ under a vacuum of 27" of Hg for 16 hours 28 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.
19. The solid was sampled from each drying tray to determine the % Loss on Drying. The LOD was determined to be 0 %, 0.02 %, and 0.02 % on the three samples taken.
20. (1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt was then packaged into double poly bags in fiber drums and labeled, and sampled.
21. The isolated yield was 1.87 kg, 79.1%. The intermediate was stored at $2-8^{\circ}\text{C}$ until used in further manufacturing.

(1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate

1. In a fume hood a three-necked glass reaction flask equipped with a Claisen head, temperature recorder and a mechanical stirrer was flushed with nitrogen.
2. (1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt (1.85 kg) was charged to the flask.
3. 2-Pyrazinecarboxylic acid (0.564 kg) was charged to the flask.
4. 2-(H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, TBTU (1.460 kg) was charged to the flask.
5. Dichloromethane (18.13 L) was charged to the flask.
6. The stirring motor was adjusted to provide stirring at 272 RPM.
7. Using a cooling bath, the reaction mixture was cooled to -1.2 °C.
8. N,N-Diisopropylethylamine (1.865 kg) was charged to a glass flask and transferred to the reaction over a period of 50 minutes using a peristaltic pump maintaining a reaction temperature range of -1.2 °C to 2.8 °C.
9. A dichloromethane rinse (0.37 L) of the flask into the reaction mixture was used to complete the addition.
10. The reaction mixture was allowed to warm and stirred for an additional 81 minutes.
11. The temperature at the start of the stir time was 15 °C, and 24.9 °C at the end.
12. A sample was then removed for in-process testing by RP-HPLC. The percent conversion was determined to be 99.9%.
13. The reaction mixture was transferred in approximately two equal halves to two rotary evaporator flasks. The reaction mixture was concentrated under reduced pressure using two rotary evaporators, maintaining an external bath temperature of 33-34 °C.
14. Ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks.
15. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 33-34 °C.
16. The residues in each rotary evaporator flask were then transferred back to the reaction flask using ethyl acetate (12.95 L).

17. In a glass flask equipped with a stirrer, a 1% aqueous phosphoric acid solution (12.34 L) was prepared by mixing D.I. water (12.19 L) and phosphoric acid (0.148 kg).
18. In a glass flask equipped with a stirrer, a 2% aqueous potassium carbonate solution (12.34 L) was prepared by mixing D.I. water (12.09 L) and potassium carbonate (0.247 kg).
19. In a glass flask equipped with a stirrer, a 10% aqueous sodium chloride solution (12.34 L) was prepared by mixing D.I. water (12.34 L) and sodium chloride (1.234 kg).
20. D.I. water (12.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 382 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
21. Again, D.I. water (12.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 398 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
22. The 1% phosphoric acid solution prepared in Step 17 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 364 RPM for 8 minutes. The layers were allowed to separate and the acidic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
23. The 2% potassium carbonate solution prepared in Step 18 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 367 RPM for 8 minutes. The layers were allowed to separate and the basic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
24. The 10% sodium chloride solution prepared in Step 19 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 374 RPM for 8 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
25. The ethyl acetate solution was transferred under vacuum in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 34 °C.
26. n-Heptane (14.8 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then

concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 34 °C.

N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude

1. In a glass flask equipped with a stirrer, a 1N solution of hydrochloric acid (22.2 L) was prepared by mixing D.I. water (20.36 L) and hydrochloric acid (1.84 kg).
2. In a glass flask equipped with a stirrer, a 2N sodium hydroxide solution (12.03 L) was prepared by mixing D.I. water (12.03 L) and sodium hydroxide (0.962 kg).
3. The residues containing (1S,2S,3R,5S)-pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate in each rotary evaporator flask were then transferred to a three-necked glass reaction flask equipped with a temperature recorder and a mechanical stirrer, using n-heptane (14.8 L) and methanol (14.8 L).
4. The stirring motor was adjusted to provide stirring at 284 RPM.
5. 2-Methylpropaneboronic acid (0.672 kg) was charged to the flask.
6. 1N hydrochloric acid prepared in Step 1 (11.2 L) was charged to the flask.
7. The stirring motor was adjusted to provide stirring at 326 RPM.
8. The reaction mixture was stirred for 16.38 hours. The start batch temperature was 28.6 °C, and the end batch temperature was 21.6 °C.
9. A sample was then removed for in-process testing by RP-HPLC.
10. The percent conversion was determined to be 100%.
11. Stirring was stopped and the biphasic mixture allowed to separate.
12. The n-heptane layer (upper layer) was transferred to a suitable flask and discarded.
13. n-Heptane (5.37 L) was charged to the reaction flask and the mixture stirred at 381 RPM for 6 minutes. The layers were allowed to separate and the n-heptane phase (upper layer) was transferred to a suitable flask and discarded.
14. Again, n-heptane (5.37 L) was charged to the reaction flask and the mixture stirred at 340 RPM for 6 minutes. The layers were allowed to separate and the n-heptane phase (upper layer) was transferred to a suitable flask and discarded.
15. The aqueous methanol solution was transferred in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a

rotary evaporator, maintaining an external bath temperature of 33-34 °C. 15 L of methanol were collected.

16. Dichloromethane (5.37 L) was used to transfer the residue from the rotary evaporator flasks back into the reaction flask.
17. 2N sodium hydroxide (11.2 L) prepared in Step 2 was charged to the flask.
18. The dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
19. Dichloromethane (5.37 L) was charged to the flask and the mixture stirred at 374 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
20. Again, dichloromethane, (5.37 L) was charged to the flask and the mixture stirred at 368 RPM for 8 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
21. Dichloromethane (5.37 L) was charged to the flask.
22. 1N hydrochloric acid (10.7 L) was charged to the flask with stirring. The pH of the aqueous phase was determined to be 6.
23. Stirring was discontinued and the phases allowed to separate.
24. The dichloromethane phase (lower layer) was transferred under vacuum to a glass receiving flask.
25. Dichloromethane (5.37 L) was charged to the flask and the mixture stirred at 330 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to the glass receiving flask.
26. Again, dichloromethane, (5.37 L) was charged to the flask and the mixture stirred at 335 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to the glass receiving flask.
27. The dichloromethane extracts were combined and transferred in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 33-34 °C.

28. Ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 45-46 °C.
29. Again, ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 45-46 °C, until approximately 10% of the original volume remained.
30. n-Heptane (10.2 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks, and the slurry stirred under a nitrogen atmosphere for 2.67 hours at 22-23 °C.
31. The solid was isolated by filtration on a Buchner funnel, lined with a polypropylene felt filter pad.
32. The solid was washed with n-heptane (2.96 L).
33. In a hood, the solid was transferred to four drying trays and air-dried for 1.25 hours.
34. The solid was then dried at 36 - 50 °C under a vacuum of 27" of Hg for 18 hours 27 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.
35. The solid was sampled from each tray to determine the % Loss on Drying (LOD). The LOD was determined to be 0.38%, 0.62%, 0.71%, and 0.63% on the four samples taken.
36. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude was packaged into two 5L, HDPE, tamper-proof wide-mouth bottles and labeled.
37. The isolated yield was 1.314 kg, 83%.

Recrystallization of N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude

1. In a hood a glass reaction flask equipped with a mechanical stirrer, a reflux condenser and a temperature recorder was flushed with nitrogen.
2. Ethyl acetate (21 L) was charged to the flask.

3. The ethyl acetate was heated to 66.8 °C under a nitrogen atmosphere, using a hot water/steam bath.
4. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude (1.311 kg) was slowly charged to the reaction flask. Charging occurred over a period of 3 minutes.
5. The mixture was stirred for 1 minute until all the solid had dissolved. The temperature of the solution was 64 °C.
6. The heat source was removed and the mixture was slowly cooled to 60 °C using a cold bath.
7. The hot ethyl acetate solution was transferred into a receiving flask via poly tubing and a polypropylene in-line filter capsule using a peristaltic pump.
8. The mixture was allowed to cool to 27.2 °C, and allowed to stand under a nitrogen atmosphere without stirring, for 17.75 hours. The final temperature was recorded as 20.5 °C.
9. The mixture was cooled using an ice/water bath with stirring for 2.33 hours. The temperature at the start of the stir time was 3.8 °C, and -2.8 °C at the end.
10. The solid was isolated by filtration on a Buchner funnel lined with a polypropylene felt filter pad. The filtrate was collected in a collection flask.
11. The solid was washed with ethyl acetate (2.62 L), cooled to 4.7 °C.
12. In a hood, the solid was transferred to two drying trays.
13. The solid was then dried at 51-65 °C under a vacuum of 27" of Hg for 19 hours 10 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.
14. The solid was sampled to determine the % Loss on Drying (LOD). The LOD was determined to be 0.65 % and 0.62 % on the two samples taken.
15. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride was packaged into four 1L, Type 3, Amber Wide-Mouth Bottles with Teflon-Lined Caps and labeled.
16. The isolated yield was 1.132 kg, 86.3%.
17. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride was stored at -25 to -15 °C.

**Example 3: N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride
Convergent Synthesis**

(1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate

[098] A solution of (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate (13.97 g) and N-hydroxysuccinimide (6.23 g) of in 66 mL of DMF was cooled to -5 °C, followed by the addition of dicyclohexylcarbodiimide (10.83 g). The resulting suspension was stirred for one hour at a temperature of -5 to 0 °C. To a solution of N-(2-pyrazinecarbonyl)-L-phenylalanine (19.52 g; prepared by coupling the preformed succinimide ester of pyrazinecarboxylic acid with L-phenylalanine in dioxane-water) in 62 mL of DMF was added N-methylmorpholine (5.7 mL) at a temperature of 0 °C, and the resulting solution was added to the suspension. The suspension was adjusted to pH 7 by the addition of another 5.7 mL of N-methylmorpholine and stirred overnight, raising the temperature slowly to 21 °C. After filtration, the filtercake was washed twice with MTBE and the combined filtrates were diluted with 950 mL of MTBE. The organic layer was washed with 20% aqueous citric acid (3 × 150 mL), 20% aqueous NaHCO₃ (3 × 150 mL), and brine (2×). The organic layer was dried over Na₂SO₄, filtered, and concentrated, yielding 25.5 g (95.5 %) of the title compound as a foam. As indicated by tic this material contained some minor impurities, including approximately 2% of cyclohexyl urea.

N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride

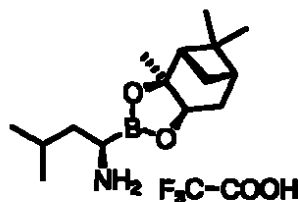
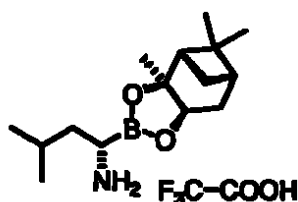
[099] A solution of (1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate (25.2 g) in 207 mL of MeOH and 190 mL of hexane was cooled to 15 °C, and 109.4 mL of 1N HCl were added in portions, keeping the temperature between 15 and 25 °C. 2-Methylpropaneboronic acid (8.67 g) was then added under vigorous stirring, and the stirring of the biphasic mixture was continued over night. After separation of the two phases, the lower layer was extracted once with 75 mL of hexane. The lower layer was then concentrated in vacuo until it became cloudy, followed by the addition of 109.4 mL of 2N NaOH and 100 mL of Et₂O. The two phases were separated the lower layer was extracted with Et₂O (4 × 100 mL each), and then brought to pH 6.0 by the addition of 109 mL of 1N HCl. After extraction with 100 mL of ethyl acetate, the lower layer was adjusted to pH 6.0 with 1N HCl and extracted one more time with 75 mL of ethyl acetate. The combined ethyl acetate layers were washed with semi-saturated brine (2 × 25 mL) and brine (2 × 25 mL), dried over Na₂SO₄, filtered, and concentrated to afford 15.3 g (81.8 %) of crude N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride as a foam. The

crude material was dissolved in 150 mL of ethyl acetate and concentrated in vacuo to a suspension, followed by the addition of 150 mL of MTBE. The suspension was stored between 2 and 8 °C over night, filtered, washed twice with MTBE, and dried under high vacuum, yielding 10.69 g (57.2 %) of N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride as a white solid.

Example 4: Measurement of Diastereomeric Ratio of (1R)-(1S,2S,3R,5S)-Pinaradiol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate

[0100] The diastereomeric purity of (1R)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate (compound 1) was determined by non-chiral gas chromatography (GC).

Chemicals:	Acetonitrile (p.a. Bruker or equivalent) Tetradecane (internal standard) (Fluka puriss. or equivalent) Trifluoroacetic anhydride (TFAA) (p.a. Merck or equivalent)
Instrument:	Trace-GC 2000 system or equivalent
Mobile phase:	H ₂
Solvent A (with internal standard)	Approximately 300 mg of tetradecane were weighed with an accuracy of 0.1 mg into a 100-mL volumetric flask. 1.5 mL of TFAA were added and the flask was brought to volume with acetonitrile.
Sample Preparation:	About 150 mg of the sample were exactly weighed (within 0.1 mg) into a 10-mL volumetric flask. The flask was brought to volume with Solvent A. The solution was stored for 15 minutes before injection.
GC Parameters:	
Column:	Rtx-200; 105m x 0.25 mm i.d. x 0.25 µm film
Mobile phase:	H ₂
Temp. program:	130 °C (0.5 min); 0.5 °C/min to 200 °C (0 min); 30 °C/min to 300 °C (2 min)
Flow:	0.9 mL/min (const. flow)
Injector temperature:	250 °C
Detector temperature:	250 °C (FID)
Split:	1: 50
Injection volume:	1 µL

Substances**Compound 1****(1R)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate****Compound 2****(1S)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate****Stability of the solution**

[0101] A stock solution of compound 1 was prepared by weighing 150.13 mg of compound 1 into a 10-mL volumetric flask and bringing it to volume with Solvent A. Stability of this solution was tested at ambient temperature over 48 hours. The stock solution was filled in 6 separate GC vials. Injections onto the GC system were carried out from these vials after 0, 12, 24, 48, and 72 hours (double injection out of each vial). The area% of compound 1 and compound 2 were determined. No changes in area% were observed, indicating that the solution is stable over 72 hours at ambient temperature.

Specificity

[0102] Approximately 150 mg of a sample comprising compound 1 and compound 2 were dissolved in Solvent A and injected to the GC chromatographic system. The peak for compound 1 was well separated from the peak for compound 2. Peak purity check by GC-MS showed no other components co-eluting with compound 1 or compound 2.

Limit of Detection

[0103] The limit of detection (LOD) was defined to be that concentration where the signal of compound 1 showed a signal to noise ratio of at least 3:1. A previous blank measurement was carried out to show that no other peaks interfered. The signal to noise ratio was calculated by the equation:

$$S / N = \frac{H(\text{signal})}{H(\text{baseline})}$$

S/N = signal to noise ratio

H(signal) = height of signal for compound 1 [mm]

H(baseline) = height of signal baseline [mm]

[0104] A sample concentration of 0.05% of the standard test sample concentration was injected and showed a signal to noise ratio of 4.3. Therefore, the limit of detection is 0.0075 mg/mL.

Limit of Quantitation

[0105] The limit of quantitation (LOQ) was defined to be that concentration where the signal of compound 1 showed a signal to noise ratio of at least 10:1. Signal to noise ratio was calculated as described above. A sample concentration of 0.1% of the standard sample concentration was injected and showed a signal to noise ratio of 10.1. Therefore, the limit of quantitation is 0.015 mg/mL.

Example 5: Purity Assay for N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride

[0106] The purity of N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride (compound 3) was assayed by reverse phase HPLC.

Reagents: Water, HPLC grade
Acetonitrile, HPLC grade
Formic acid, ACS grade, ≥ 98% pure
3% Hydrogen peroxide, ACS grade or equivalent

Instrument

High performance liquid chromatograph

Autosampler capable of delivering 20- μ L injections and maintaining a temperature of 5 °C

Pump capable of gradient delivery at 1.0 mL/min

UV detector capable of monitoring effluent at 270 nm

Column

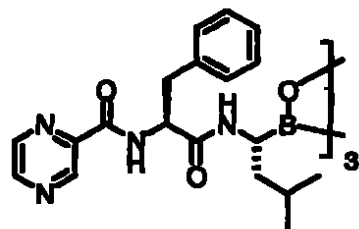
Symmetry C18 chromatographic column, 250 mm $\times$ 4.6 mm ID, 5- μ m, Waters, cat# WAT054275.

Sample Preparation: Approximately 50 mg of compound 3 were accurately weighed into a 50-mL volumetric flask. Mobile Phase B (5 mL) was added and the mixture was sonicated to dissolve compound 3 (approximately 30-60 seconds). The solution was allowed to reach room temperature, diluted to volume with Mobile Phase A, and mixed well. Each sample was prepared in duplicate and was stable for 7 days when stored at 2-8 °C protected from light.

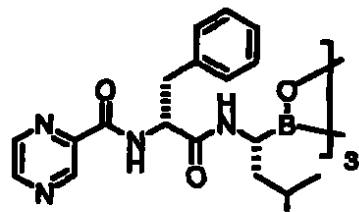
HPLC Parameters:			
<i>Mobile phase A:</i>	Acetonitrile/water/formic acid, 30:70:0.1 (v/v/v), degassed		
<i>Mobile phase B:</i>	Acetonitrile/water/formic acid, 80:20:0.1 (v/v/v), degassed		
<i>Flow rate:</i>	1.0 mL/min		
<i>Detector:</i>	UV at 270 nm		
<i>Injection Volume:</i>	20 µL		
<i>Column Temp:</i>	Ambient		
<i>Sample Tray Temp:</i>	5 °C		
<i>Gradient Program:</i>	<u>Time</u>	<u>%A</u>	<u>%B</u>
	0	100	0
	15	100	0
	30	0	100
	45	0	100
	47	100	0
	55	100	0

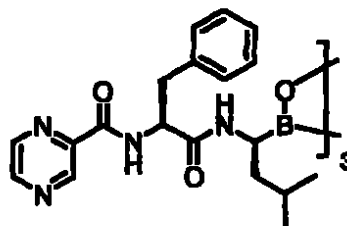
Substances

Compound 3 *N*-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride



Compound 4 *N*-(2-Pyrazinecarbonyl)-L-phenylalanine-D-leucine boronic anhydride



Compound 5**N-(2-Pyrazinecarbonyl)-L-phenylalanine-D-leucine boronic anhydride**

[0107] The retention time of compound 3 was typically between 10 and 14 minutes when using an HPLC system with a 1.3 minute dwell volume. Compounds 4 and 5 co-eluted at longer retention time, with a resolution of ≥ 2.0 .

[0108] The relative retention of compound 3 in a sample chromatogram to that in the standard chromatogram was calculated according to the following equation:

$$R_r = \frac{t_{\text{sam}}}{t_{\text{std}}}$$

Where:

- R_r = relative retention
 t_{sam} = retention time of compound 3 peak in the sample chromatogram, minutes
 t_{std} = retention time of the drug substance peak in the closest preceding standard chromatogram, minutes

[0109] Assay results were calculated for each sample according to the following equation:

$$\% \text{assay} = \frac{A_{\text{sam}}}{A_{\text{std}}} \times \frac{W_{\text{std}} \times P}{W_{\text{sam}}} \times \frac{1}{\left(\frac{100 - M}{100} \right)} \times 100$$

Where:

- A_{sam} = peak area response of compound 3 in the sample preparation
 A_{std} = mean peak area response of compound 3 in the working standard preparation
 W_{std} = weight of the standard, mg
 P = assigned purity of the standard (decimal format)
 W_{sam} = weight of the sample, mg
 M = moisture content of the sample, %

100 = conversion to percent

[0110] Relative retention and impurity levels in each sample were calculated according to the following equations:

$$R_r = \frac{t_r}{t_{r_3}}$$

Where:

- R_r = relative retention
- t_r = retention time of the individual impurity
- t_{r₃} = retention time of the compound 3 peak

$$\%I_i = \frac{A_i \times W_{std} \times P \times DF \times RF_i}{A_{std, 1\%} \times W_{sam}} \times 100$$

Where:

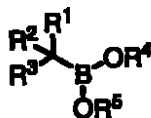
- I_i = individual impurity
- A_i = peak area response of individual impurity in the sample preparation
- A_{std, 1%} = average peak area response of compound 3 in the 1% standard preparation
- W_{std} = weight of the standard, mg
- W_{sam} = weight of sample, mg
- P = assigned purity of the standard (decimal format)
- DF = dilution factor, 1/100
- RF_i = relative response factor of individual impurity
- 100 = conversion to percentage factor

[0111] When assayed by this method, N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucineboronic anhydride from Example 2 showed total impurities of less than 1%.

[0112] While the foregoing invention has been described in some detail for purposes of clarity and understanding, these particular embodiments are to be considered as illustrative and not restrictive. It will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention and appended claims.

WHAT IS CLAIMED IS:

1. A large-scale process for preparing a boronic ester compound of formula (I):



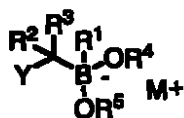
(I)

wherein:

- R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;
 R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;
 R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and
 each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

- (a) providing a boron "ate" complex of formula (II):



(II)

where

- Y is a nucleofugic group;
 M^+ is a cation; and
 each of R^1 to R^5 is as defined above; and

- (b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

2. The process of claim 1, wherein the reaction mixture comprises a coordinating co-solvent.

3. The process of claim 2, wherein the coordinating co-solvent is selected from the group consisting of tetrahydrofuran, dioxane, water, and mixtures thereof.

4. The process of claim 3, wherein the coordinating co-solvent constitutes no more than about 20% v/v of the reaction mixture.

5. The process of claim 3, wherein the coordinating co-solvent constitutes no more than about 15% v/v of the reaction mixture.

6. The process of claim 1, wherein the solubility of water in the ether solvent that has low miscibility with water is less than about 2% w/w.

7. The process of claim 6, wherein the ether solvent that has low miscibility with water is selected from the group consisting of *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, isopropyl ether, and mixtures thereof.

8. The process of claim 7, wherein the ether solvent that has low miscibility with water constitutes at least about 70% v/v of the reaction mixture.

9. The process of claim 1, wherein at least about 5 moles of the boron "ate" complex of formula (II) are provided in step (a).

10. The process of claim 1, wherein at least about 20 moles of the boron "ate" complex of formula (II) are provided in step (a).

11. The process of claim 1, wherein at least about 50 moles of the boron "ate" complex of formula (II) are provided in step (a).

12. The process of claim 1, wherein at least about 100 moles of the boron "ate" complex of formula (II) are provided in step (a).

13. The process of claim 1, wherein the Lewis acid is selected from the group consisting of zinc chloride, zinc bromide, ferric chloride, and ferric bromide.
14. The process of claim 13, wherein the Lewis acid is moist.
15. The process of claim 13, wherein in step (a) the boron "ate" complex of formula (II) is provided in a solution comprising an ether solvent that has low miscibility with water, and the contacting step (b) comprises the steps:
- (i) providing a solution comprising a Lewis acid and tetrahydrofuran; and
 - (ii) adding the Lewis acid solution to the solution of the boron "ate" complex of formula (II) from step (a).
16. The process of claim 13, wherein in step (a) the boron "ate" complex of formula (II) is provided in a solution comprising an ether solvent that has low miscibility with water, and the contacting step (b) comprises the steps:
- (i) providing a solution comprising a Lewis acid and water; and
 - (ii) adding the Lewis acid solution to the solution of the boron "ate" complex of formula (II) from step (a).
17. The process of claim 1, wherein Y is a halogen.
18. The process of claim 1, wherein Y is chloro.
19. The process of claim 1, wherein R¹ is C₁₋₄ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₄ aliphatic).
20. The process of claim 1, wherein M⁺ is selected from the group consisting of Li⁺, Na⁺, and K⁺.
21. The process of claim 1, wherein R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5-membered ring.
22. The process of claim 21, wherein R⁴ and R⁵ together are a chiral moiety.

23. The process of claim 22, wherein the boron "ate" complex of formula (II) is:



24. The process of claim 22, wherein step (b) provides the boronic ester compound of formula (I) wherein the carbon atom bearing R^1 , R^2 , and R^3 is a chiral center having a diastereomeric ratio of at least about 96:4 relative to a chiral center in the R^4 - R^5 chiral moiety.

25. The process of claim 22, wherein step (b) provides the boronic ester compound of formula (I) wherein the carbon atom bearing R^1 , R^2 , and R^3 is a chiral center having a diastereomeric ratio of at least about 97:3 relative to a chiral center in the R^4 - R^5 chiral moiety

26. The process of claim 22, characterized by at least one of the following features:

- (a) the contacting step (b) is conducted in a reaction mixture comprising *tert*-butyl methyl ether;
- (b) the Lewis acid is zinc chloride;
- (c) at least about 5 moles of the boronic ester of formula (II) are provided in step (a);
- (d) the contacting step (b) is performed at a reaction temperature in the range of about -60 °C to about -30 °C;
- (e) the Lewis acid is moist;
- (f) Y is chloro;
- (g) R^3 is chloro;
- (h) R^4 is hydrogen; and
- (i) R^1 is C_{1-6} aliphatic.

27. The process of claim 26, characterized by at least two of the features (a)-(h).

28. The process of claim 26, characterized by at least three of the features (a)-(h).
29. The process of claim 26, characterized by all eight of the features (a)-(h).
30. The process of claim 24, further comprising:
- (c) washing the reaction mixture with an aqueous solution; and
 - (d) concentrating the washed reaction mixture by removal of solvents to afford a residue comprising the boronic ester compound of formula (I).
31. The process of claim 26, wherein the residue comprises at least about five moles of the boronic ester compound of formula (I).
32. The process of claim 31, wherein the boronic ester compound of formula (I) present in the residue has a diastereomeric ratio of at least about 96:4 at the carbon atom bearing R^1 , R^2 , and R^3 , relative to a chiral center in the R^4 - R^5 chiral moiety.
33. The process of claim 31, wherein the boronic ester compound of formula (I) present in the residue has a diastereomeric ratio of at least about 97:3 at the carbon atom bearing R^1 , R^2 , and R^3 , relative to a chiral center in the R^4 - R^5 chiral moiety.
34. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



wherein:

- R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;
- R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;
- R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and
- each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms,

form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S.

35. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, relative to a chiral center in the R^4 - R^5 chiral moiety.

36. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having an epimeric ratio of at least about 96:4.

37. The composition of any one of claims 34-36, wherein the solubility of water in the ether solvent is less than about 2% w/w.

38. The composition of any one of claims 34-36, wherein the ether solvent is selected from the group consisting of *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, isopropyl ether, and mixtures thereof.

39. The composition of any one of claims 34-36, wherein R^1 is C_{1-4} aliphatic, C_{6-10} aryl, or $(C_{1-10}$ aryl)(C_{1-4} aliphatic).

40. The composition of any one of claims 34-36, characterized by at least one of the following features:

- (a) R^3 is chloro;
- (b) R^3 is hydrogen; and
- (c) R^1 is C_{1-4} aliphatic

41. The composition of any one of claims 34-36, wherein R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5-membered ring.

42. The composition of any one of claims 34-36, wherein the compound of formula (I) is



43. A composition comprising at least about ten moles of a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered chiral ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, relative to a chiral center in the R^4 - R^5 chiral moiety; and

wherein the boronic ester compound of formula (I) constitutes at least about 70% w/w of the composition.

44. The composition of claim 36 comprising at least about 20 moles of the boronic ester compound of formula (I).

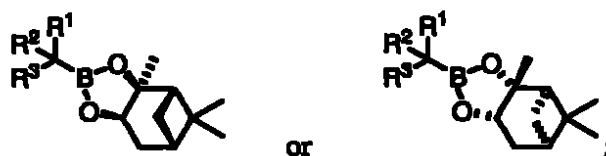
45. The composition of claim 36, wherein the carbon atom to which R^1 , R^2 , and R^3 are attached has a diastereomeric ratio of at least about 97:3, relative to a chiral center in the R^4 - R^5 chiral moiety.

46. The composition of claim 36, wherein all of the boronic ester compound of formula (I) present in the composition is produced in a single batch run.

47. The composition of claim 36, wherein all of the boronic ester compound of formula (I) present in the composition is produced in a single batch run of the process according to claim 1.

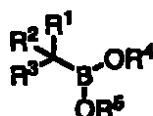
48. The composition of claim 36, wherein at least one of the following features is present:

- (a) R^3 is chloro;
- (b) the boronic ester compound of formula (I) is:



- (c) R^2 is hydrogen; and
- (d) R^1 is C_{1-4} aliphatic.

49. A large-scale process for preparing a boronic ester compound of formula (I):



(I)

wherein:

- R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;
- R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;
- R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and
- each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic ester of formula (III):



wherein R^1 , R^4 , and R^5 are as defined above; and

(ii) an ether solvent that has low miscibility with water;

(b) treating the solution with a reagent of formula (IV):



to form a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M^+ is a cation; and

each of R^1 to R^5 are as defined above; and

(c) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

50. A large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic ester of formula (III):



wherein R^1 , R^4 , and R^5 are as defined above;

(ii) a compound of formula (V):



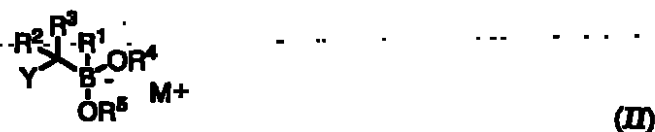
where Y is a nucleofugic group, and R^2 and R^3 are as defined above; and

(iii) a solvent comprising:

(aa) a coordinating ether solvent that has low miscibility with water; or

(bb) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(b) treating the solution of step (a) with a strong, sterically hindered base to form a boron "ate" complex of formula (II):



where M^+ is a cation derived from the base, and each of Y and R^1 to R^3 are as defined above;
and

(c) contacting the boron "ate" complex of formula (II) with a Lewis acid in a solution comprising an ether solvent that has low miscibility with water to form the boronic ester compound of formula (I).

51. A large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together, form an optionally substituted linking chain comprising 2-5 carbon atoms and 0-2 heteroatoms selected from the group consisting of O, N, and S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic acid compound of formula (VI):

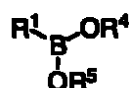


wherein R^1 is as defined above;

(ii) a compound of formula $HO-R^4-R^5-OH$, wherein R^4 and R^5 are as defined above; and

(iii) an organic solvent that forms an azeotrope with water;

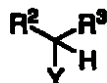
(b) heating the solution of step (a) at reflux, with azeotropic removal of water, to form a boronic ester of formula (III):



(III)

wherein R^1 , R^4 , and R^5 are as defined above;

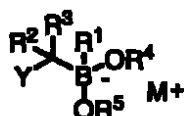
- (c) providing a solution comprising:
- (i) the boronic ester of formula (III);
 - (ii) a compound of formula (V):



(V)

wherein Y is a nucleofugic group, and R^2 and R^3 are as defined above; and

- (iii) a solvent comprising:
 - (aa) a coordinating ether solvent that has low miscibility with water; or
 - (bb) an ether solvent that has low miscibility with water and a coordinating co-solvent;
- (d) treating the solution from step (c) with a strong, sterically hindered base to form a boron "ate" complex of formula (II):



(II)

where M^+ is a cation derived from the base, and each of Y and R^1 to R^5 are as defined above; and

- (e) contacting the boron "ate" complex of formula (II) with a Lewis acid in a solution comprising an ether solvent that has low miscibility with water to form the boronic ester compound of formula (I).

52. The process of claim 50 or 51, wherein the sterically hindered base is an alkali metal dialkylamide base of formula $M^+N(R^6)_2$, wherein M^+ is selected from the group consisting of Li, Na, and K, and each R^6 , independently, is a branched or cyclic C_{2-6} aliphatic.

53. The process of claim 51, wherein the organic solvent in step (a) is selected from the group consisting of acetonitrile, toluene, hexane, heptane, and mixtures thereof.

54. The process of claim 51, wherein the organic solvent in step (a) is an ether solvent that has low miscibility with water.

55. The process of claim 54, wherein the solutions in steps (a) and (c) each comprise the same ether solvent.

56. The process of claim 55, wherein step (b) provides a product solution comprising the boronic ester of formula (III), and the product solution from step (b) is used in step (c) without isolation of the boronic ester of formula (III).

57. A large-scale process for preparing an aminoboronic ester compound of formula (VII):



or an acid addition salt thereof, wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M^+ is a cation;

R^2 is hydrogen;

R^3 is a nucleofugic group; and

each of R^1 , R^4 , and R^5 are as defined above;

(b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I):



where each of R^1 to R^5 is as defined above, said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(c) treating the boronic ester compound of formula (I) with a reagent of formula $M^1-N(Si(R^6)_3)_x$, where M^1 is an alkali metal and each R^6 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a byproduct of formula M^1-R^3 and a compound of formula (VIII):



wherein each G and R^1 to R^5 are as defined above; and

(d) removing the G groups to form a compound of formula (VII):



or an acid addition salt thereof.

58. The process of claim 57, wherein the reaction mixture in step (c) comprises an organic solvent in which the byproduct M^1-R^3 has low solubility.

59. The process of claim 58, wherein M^1 is Li and R^3 is Cl.

60. The process of claim 59, wherein the reaction mixture in step (c) comprises an organic solvent selected from the group consisting of methylcyclohexane, cyclohexane, heptane, hexane, toluene, and mixtures thereof.

61. The process of claim 57, wherein the reaction in step (c) is conducted at a reaction temperature in the range of about -100 °C to about 50 °C.

62. The process of claim 61, wherein the reaction temperature is in the range of about -50 °C to about 25 °C.

63. The process of claim 61, wherein the reaction temperature is in the range of about -30 °C to about 0 °C.

64. The process of claim 57, wherein step (d) comprises treating the compound of formula (VIII) with an acid and isolating the compound of formula (VII) as the acid addition salt.

65. The process of claim 64, wherein the acid is trifluoroacetic acid.

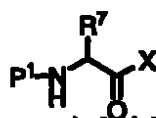
66. The process of claim 57, wherein step (c) further comprises filtering the reaction mixture to provide a filtrate comprising the compound of formula (VIII).

67. The process of claim 66, wherein in step (c), the reagent of formula $M^1-N(Si(R^4)_2)_2$ is added to the reaction mixture as a solution comprising tetrahydrofuran, and step (c) further comprises removing the tetrahydrofuran before filtering the reaction mixture.

68. The process of claim 66, wherein the filtrate is used directly in step (d).

69. The process of claim 57, further comprising the step:

(e) coupling the compound of formula (VII) with a compound of formula (IX):



-(IX)

wherein:

P^1 is an amino group blocking moiety;

R^7 is selected from the group consisting of hydrogen, C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or C_{1-6} aliphatic- R^8 ; and

R^8 is selected from the group consisting of alkoxy, alkylthio, optionally substituted aryl, heteroaryl, and heterocyclyl groups, and optionally protected amino, hydroxy, and guanidino groups; and

X is OH or a leaving group;

to form a compound of formula (X):



wherein each of P^1 , R^1 , R^4 , R^5 , and R^7 is as defined above.

70. The process of claim 69, wherein P^1 is a cleavable protecting group.

71. The process of claim 70, further comprising the steps:

(f) cleaving the protecting group P^1 to form a compound of formula (XI):



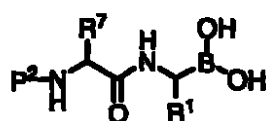
or an acid addition salt thereof, wherein each of R^1 , R^4 , R^5 , and R^7 is as defined above;

(g) coupling the compound of formula (XI) with a reagent of formula P^2 -X, wherein P^2 is an amino group blocking moiety and X is a leaving group, to form a compound of formula (XII):



wherein each of P^2 , R^1 , R^4 , R^5 , and R^7 are as defined above; and

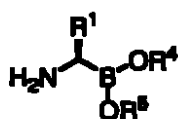
(h) deprotecting the boronic acid moiety to form a compound of formula (XIII):



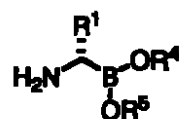
(XIII)

or a boronic acid anhydride thereof, wherein each of P^1 , R^1 , and R^7 are as defined above.

72. A large-scale process for preparing an aminoboronic ester compound of formula (VIIa) or (VIIb):



(VIIa)



(VIIb)

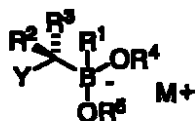
or an acid addition salt thereof, wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

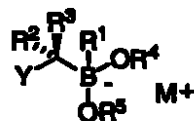
R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted chiral cyclic boronic ester;

said process comprising:

(a) providing a boron "ate" complex of formula (IIa) or (IIb):



(IIa)



(IIb)

where

Y is a nucleofugic group;

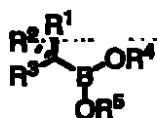
M^+ is a cation;

R^2 is hydrogen;

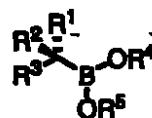
R^3 is a nucleofugic group; and

R^4 and R^5 are as defined above;

(b) contacting the boron "ate" complex of formula (IIa) or (IIb) with a Lewis acid under conditions that afford a boronic ester compound of formula (Ia) or (Ib):



(Ia)



(Ib)

where each of R^1 to R^8 is as defined above, said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;
- (c) treating the boronic ester compound of formula (Ia) or (Ib) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and each G is an amino group protecting moiety, to form a compound of formula (VIIIa) or (VIIIb):



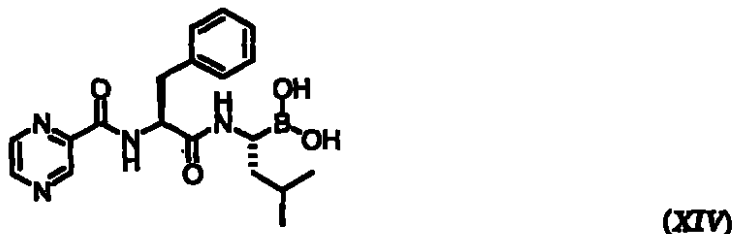
wherein each G and R^1 to R^8 are as defined above; and

- (d) removing the G groups to form a compound of formula (VIIa) or (VIIb):



or an acid addition salt thereof.

73. A large-scale process for forming a compound of formula (XIV):



or a boronic acid anhydride thereof, said process comprising:

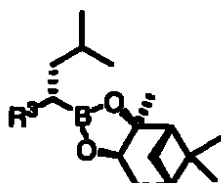
- (a) providing a boron "ate" complex of formula (XV):



wherein:

M^+ is an alkali metal;

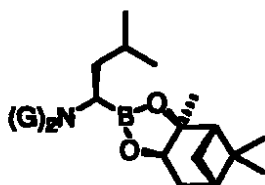
(b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



(XVI)

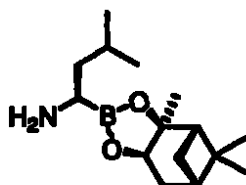
said contacting step being conducted in a reaction mixture comprising an ether solvent that has low miscibility with water;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and each G individually or together is an amino group protecting group, to form a compound of formula (XVII):



(XVII)

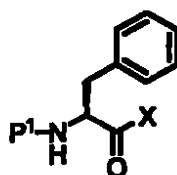
(d) removing the G groups to form a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XIX);



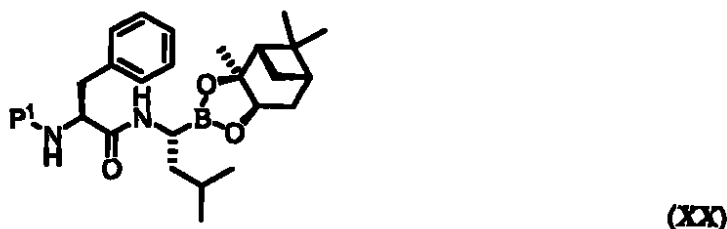
(XIX)

wherein:

P^1 is a cleavable amino group protecting moiety; and

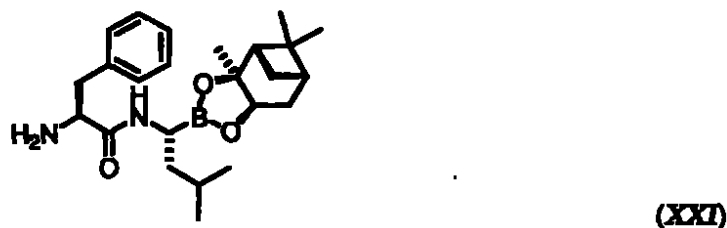
X is OH or a leaving group;

to form a compound of formula (XX):



wherein P^1 is as defined above;

(f) removing the protecting group P^1 to form a compound of formula (XXI):

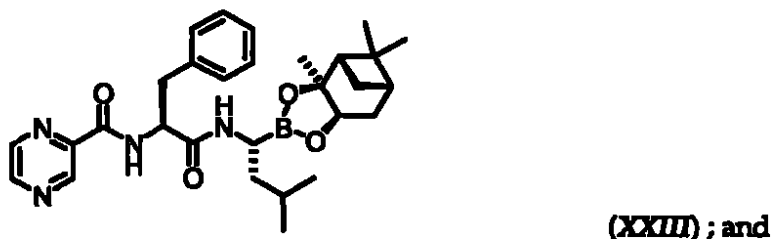


or an acid addition salt thereof;

(g) coupling the compound of formula (XXI) with a reagent of formula (XXII):



wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(h) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

74. The process of claim 73, characterized by at least one of the following features (1)-(5):

- (1) in the boron "ate" complex of formula (XV), R³ and Y both are chloro;
- (2) the coupling step (e) comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) the protecting group removing step (f) comprises the steps:
 - (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt;
- (4) the coupling step (g) comprises the steps:
 - (i) coupling the compound of formula (XXI) with 2-pyrazine-carboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution; and
- (5) the boronic acid deprotecting step (h) comprises the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₄ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and

(iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

75. The process of claim 74, characterized by all five features (1)-(5).

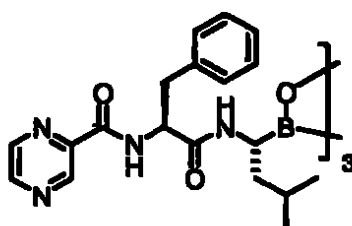
76. The process of claim 74, wherein step (h)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 8.

77. The process of claim 76, wherein in step (h)(iii)(3), the aqueous layer is washed with dichloromethane.

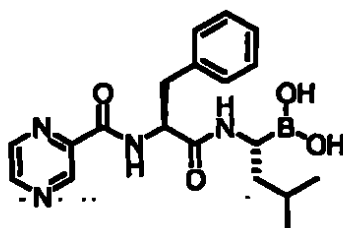
78. The process of claim 76, wherein in step (h)(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

79. The process of claim 78, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):



(XXIV).

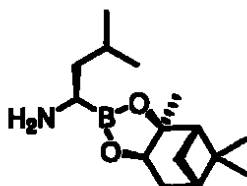
80. A large-scale process for forming a compound of formula (XIV):



(XIV)

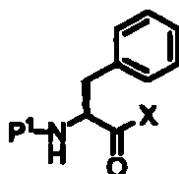
or a boronic acid anhydride thereof, comprising the steps:

(aa) coupling a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof, with a compound of formula (XIX):



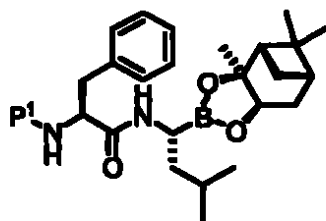
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

to form a compound of formula (XX):



(XX)

wherein P¹ is as defined above, said coupling step (aa) comprising the steps:

(i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;

(ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and

(iii) performing an aqueous wash of the ethyl acetate solution;

(bb) removing the protecting group P¹ to form a compound of formula (XXI):

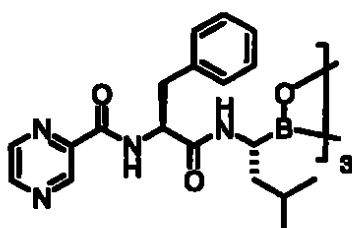
- (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₈ hydrocarbon solvent, and aqueous mineral acid;
- (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

81. The process of claim 80, wherein step (dd)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 8.

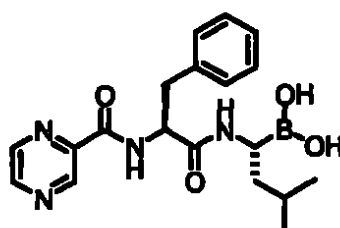
82. The process of claim 81, wherein in step (dd)(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

83. The process of claim 82, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):



(XXIV).

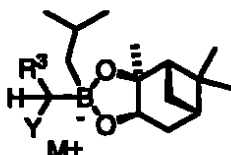
84. A large-scale process for forming a compound of formula (XIV):



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

- (a) providing a boron "ate" complex of formula (XV):



(XV)

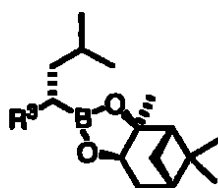
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M^+ is an alkali metal;

- (b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):

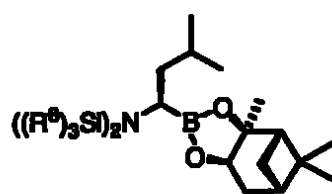


(XVI)

said contacting step being conducted in a reaction mixture comprising:

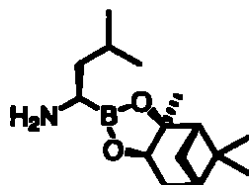
- (i) a coordinating ether solvent that has low miscibility with water; or
(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

- (c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(Si(R^4))_3$, where M^1 is an alkali metal and each R^4 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a compound of formula (XVII):



(XVII)

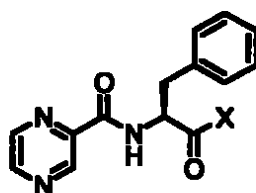
- (d) removing the $(R^6)_3Si$ groups to form a compound of formula (XVIII):



(XVIII)

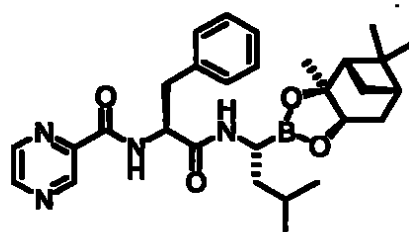
or an acid addition salt thereof;

- (e) coupling the compound of formula (XVIII) with a compound of formula (XIXa):



(XIXa)

wherein X is OH or a leaving group, to form a compound of formula (XXIII):



(XXIII); and

- (f) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

85. The process of claim 84, characterized by at least one of the following features (1)-(3):

- (1) In the boron "ate" complex of formula (XV), R^1 and Y both are chloro.

- (2) The coupling step (e') comprises the steps:

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(i) coupling the compound of formula (XVIII) with a compound of formula (XLXa) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;

(ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and

(iii) performing an aqueous wash of the ethyl acetate solution.

(3) The boronic acid deprotecting step (f') comprises the steps:

(i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₆₋₈ hydrocarbon solvent, and aqueous mineral acid;

(ii) stirring the biphasic mixture to afford the compound of formula (XIV);

(iii) separating the solvent layers; and

(iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

86. The process of claim 85, wherein step (f')(iii) comprises the steps:

(1) separating the solvent layers;

(2) adjusting the aqueous layer to basic pH;

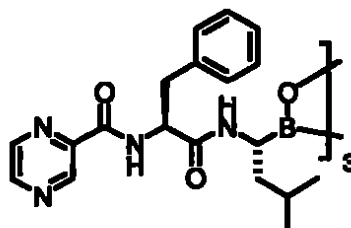
(3) washing the aqueous layer with an organic solvent; and

(4) adjusting the aqueous layer to a pH less than about 8.

87. The process of claim 86, wherein in step (f')(iii)(3), the aqueous layer is washed with dichloromethane.

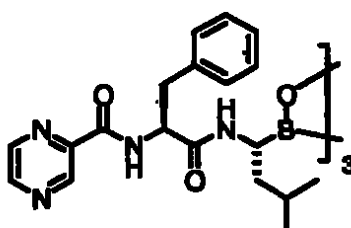
88. The process of claim 86, wherein in step (f')(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

89. The process of claim 88, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):



(XXIV).

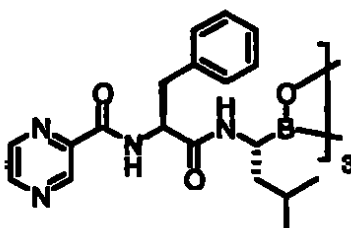
90. A composition comprising at least one kilogram of a compound of formula (XXIV):



(XXIV)

wherein the compound of formula (XXIV) is prepared according to the process of claim 73 or 80.

91. A composition comprising at least one kilogram of a compound of formula (XXIV):



(XXIV)

wherein the compound of formula (XXIV) constitutes at least 99% w/w of the composition.

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NOTIFICATION CONCERNING
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FEB 23 2006

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Millennium Pharmaceuticals, Inc.
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Cambridge, MA 02139
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Date of mailing (day/month/year)

16 February 2006 (16.02.2006)

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Priority date (day/month/year)

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Applicant

MILLENNIUM PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith the following documents:

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No. WOcopy of international application as republished by the International Bureau on 16 February 2006 (16.02.2006) under
No. WO 2005/097809For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48)
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Petersburg, VA 23805-9382 (US).(74) Agents: KLUNDER, Janice, M. et al.; Millennium Phar-
maceuticals, Inc., 40 Landsdowne Street, Cambridge, MA
02139 (US).(81) Designated States (unless otherwise indicated, for every
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AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
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SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
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(88) Date of publication of the international search report:
16 February 2006For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS

(57) Abstract: The invention relates to the synthesis of boronic ester and acid compounds. More particularly, the invention provides improved synthetic processes for the large-scale production of boronic ester and acid compounds, including the peptide boronic acid proteasome inhibitor bortezomib.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009774

A. CLASSIFICATION OF SUBJECT MATTER
C07F5/02 C07F5/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 699 835 B2 (PLAMONDON LOUIS ET AL) 2 March 2004 (2004-03-02) cited in the application	34
A	claims 89-92; examples 2-5	1
X	column 15	90, 91
X	US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application	1, 12, 17-23, 34-36, 40-48, 57-59, 61-68
	examples 1-3, 6-10	
	----- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

9 November 2005

Date of mailing of the international search report

08. 12. 2005

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Authorized officer

Richter, H

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KOLOMEITSEV A A ET AL: "Perfluoroalkyl borates and boronic esters: new promising partners for Suzuki and Petasis reactions" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 45, 3 November 2003 (2003-11-03), pages 8273-8277, XP004463842 ISSN: 0040-4039 Entry 1, 2, 8, 9table 2	1
X	entry 9, table 2	34
A	PERGAMENT I. ET AL.: "Arbuzov Reaction of 1-Iodoborates as a Means of preparing Cl-Bridged Phosphonoborates" TETRAHEDRON LETTERS, vol. 40, 1999, pages 3895-3898, XP004163774 Scheme 1	50-56
Y	PRIESTLEY ET AL: "P1 Phenethyl Peptide Boronic acid Inhibitors of HCV NS3 Protease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, 2002, pages 3199-3202, XP002339235 ISSN: 0960-894X Schemes 1 and 2 + corresponding text page 3200	57-59, 61-68
A	DOU, Q. PING ET AL: "Bortezomib Millennium Pharmaceuticals" IDRUGS , 5(8), 828-834 CODEN: IDRUFN; ISSN: 1369-7056, 2002, XP002351534 page 828 & WO 96/13266 A1 (LEUKOSITE, INC., USA) 9 May 1996 (1996-05-09)	73-89
Y	DATABASE BEILSTEIN 'Online! BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002351537 Database accession no. Reaction ID 8638739 abstract & DUSDON, R. M. ET AL.: BIOORG. MED. CHEM. LETT., vol. 10, no. 14, 2000, pages 1577-1580,	65
Y	DATABASE BEILSTEIN 'Online! BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002351538 Database accession no. Reaction ID 8726664 abstract	57-59, 61-64, 66-68
	-/-	

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56

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2005/009774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& VON MATT, A. ET AL.: BIORG. MED. CHEM., vol. 8, no. 9, 2000, pages 2291-2304, -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009774

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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57

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-48

2. claim: 49

3. claims: 50, partially: 52

4. claims: 51,53-56; partially: 52

5. claims: 57-72

6. claims: 73-79

7. claims: 80-83

8. claims: 84-91

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/009774

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6699835	B2	02-03-2004	US	2002188100 A1	12-12-2002
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			NZ	296717 A	29-11-1999
			PT	788360 T	31-10-2003
			US	5780454 A	14-07-1998

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(54) Título: **SÍNTESIS DE COMPUESTOS DE ÉSTER Y ÁCIDO BÓRICO.**

(57) Resumen: La invención se refiere a la síntesis de compuestos de éster y ácido bórico. Más particularmente, la invención proporciona procesos sintéticos mejorados para la producción a gran escala de compuestos de éster y ácido bórico, incluyendo el inhibidor de proteasoma peptídico de ácido bórico bortezomib.

SÍNTESIS DE COMPUESTOS DE ÉSTER Y ÁCIDO BÓRICO

ANTECEDENTES DE LA INVENCION

Campo de la invención

- 5 Esta invención se refiere a la síntesis de compuestos de éster y ácido bórico. Más particularmente, la invención se refiere a procesos sintéticos a gran escala para la preparación de compuestos de éster y ácido bórico mediante redistribución promovida por ácido de Lewis de complejos boronato.

Antecedente de la invención

- 10 Los compuestos de ácido y éster bórico muestran una diversidad de actividades biológicas útiles. Shenvi *et al.*, Patente de Estados Unidos Nº 4.499.082 (1985), describe que los ácidos bóricos de péptidos son inhibidores de ciertas enzimas proteolíticas. Kettner y Shenvi, Patente de Estados Unidos Nº 5.187.157 (1993), Patente de Estados Unidos Nº 5.242.904 (1993), y
15 Patente de Estados Unidos Nº 5.250.720 (1993), describen una clase de ácidos bóricos de péptidos que inhiben las proteasas de tipo tripsina. Kleeman *et al.*, Patente de Estados Unidos Nº 5.169.841 (1992), describe ácidos bóricos de péptidos modificados de extremo N que inhiben la acción de la renina. Kinder *et al.*, Patente de Estados Unidos Nº 5.106.948 (1992), describe que ciertos
20 compuestos de ácido bórico de tripéptidos inhiben el crecimiento de células cancerígenas.

- Más recientemente, los compuestos de ácido y éster bórico han mostrado ser prometedores como inhibidores del proteasoma, una proteasa multicatalítica responsable de la mayoría de las conversiones de proteínas intracelulares. Ciechanover, *Cell*, 79: 13-21 (1994), describe que el proteasoma
25 es el componente proteolítico de la ruta de ubiquitina-proteasoma, donde las proteínas son el objetivo de la degradación por conjugación con múltiples moléculas de ubiquitina. Ciechanover también describe que la vía de ubiquitina-proteasoma juega un papel clave en una diversidad de procesos fisiológicos
30 importantes.

Adams *et al.*, Patente de Estados Unidos N° 5.780.454 (1998), Patente de Estados Unidos N° 6.066.730 (2000), Patente de Estados Unidos N° 6.083.903 (2000), Patente de Estados Unidos N° 6.297.217 (2001), Patente de Estados Unidos N° 6.548.668 y Patente de Estados Unidos N° 6.617.317 (2003), incorporadas en este documento como referencia en su totalidad, describen compuestos de éster y ácido bórico de péptidos útiles como inhibidores de proteasoma. Las referencias también describen el uso de compuestos de éster y ácido bórico para reducir la velocidad de degradación de las proteínas musculares, para reducir la actividad de NF-κB en una célula, para reducir la velocidad de degradación de la proteína p53 en una célula, para inhibir la degradación de ciclina en una célula, para inhibir el crecimiento de una célula cancerígena, para inhibir la presentación antigénica en una célula, para inhibir la adhesión celular dependiente de NF-κB y para inhibir la replicación del VIH.

Albanell y Adams, *Drugs of the Future* 27: 1079-1092 (2002), describe que uno de tales inhibidores de proteasoma peptídicos de ácido bórico, bortezomib (ácido N-2-pirazina-carbonil-L-fenilalanina-L-leucinabórico), muestra una actividad antitumoral significativa en los modelos de xenoinjerto de tumor humano y está bajo evaluación clínica. Richardson *et al.*, *New Engl. J. Med.*, 348:2609 (2003), informa de los resultados de un estudio de 2 fases del bortezomib, que muestra su eficacia en el tratamiento del mieloma múltiple refractorio y de recaída.

Los estudios de inhibidores de proteasa de ácido bórico han avanzado enormemente mediante el desarrollo de la química para la preparación de compuestos de ácido bórico funcionalizados, particularmente ácidos alfa-halo- y alfa-aminobóricos. Matteson y Majumdar, *J. Am. Chem. Soc.*, 102: 7590 (1980), describe un procedimiento para preparar ésteres alfa-clorobóricos por homologación de ésteres bóricos, y Matteson y Ray, *J. Am. Chem. Soc.*, 102: 7591 (1980), informa de que el control quiral de la reacción de homologación puede alcanzarse mediante el uso de ésteres bóricos de pinanodiol. También se ha informado sobre la preparación de compuestos de ácido y éster alfa-

aminobóricos a partir de ésteres alfa-clorobóricos correspondientes (Matteson *et al.*, *J. Am. Chem. Soc.*, 103: 5241 (1981); Shenvi, Patente de Estados Unidos N° 4.537.773 (1985)).

5 Matteson y Sadhu, Patente de Estados Unidos N° 4.525.309 (1985), describe un procedimiento mejorado para la homologación de ésteres bóricos mediante la redistribución del complejo boronato intermedio en presencia de un catalizador de ácido de Lewis. Se informa del ácido de Lewis para promover la reacción de redistribución y para minimizar la epimerización en el átomo alfa-carbono. Sin embargo, se requieren una exclusión rigurosa del agua y un control cuidadoso de la estequiometría del ácido de Lewis para obtener unos resultados óptimos. Estas características hacen que la reacción sea difícil de realizar de forma satisfactoria en una escala de producción, y limitan la disponibilidad de los compuestos de éster y ácido bórico farmacéuticamente importantes, tales como bortezomib. De esta manera, queda una necesidad en 10 la técnica para métodos mejorados para la producción a gran escala de compuestos de éster y ácido bórico.

DESCRIPCIÓN DE LA INVENCION

La presente invención proporciona procesos sintéticos mejorados para la producción a gran escala de compuestos de éster y ácido bórico. Estos procesos ofrecen un rendimiento y una pureza aumentados, una producción 20 aumentada y una mayor facilidad de manejo en comparación con los métodos anteriores de la técnica. Notablemente, los procesos descritos en este documento son adecuados para la producción en lote a gran escala, a escala multi-kilogramo que se limita sólo por el tamaño de las capacidades de fabricación disponibles. Los procesos de la invención son particularmente ventajosos para la síntesis de compuestos de éster y ácido bórico quirales, incluyendo compuestos de éster y ácido alfa-aminobórico. Sin tener en cuenta la escala, los productos deseados se producen con una pureza química y estereoquímica mucho mayor.

30 Las patentes y la bibliografía específica indicadas en este documento establecen el conocimiento que está disponible para los especialistas en la

técnica. A menos que se defina otra cosa, todos los términos técnicas y científicos usados en este documento tienen el mismo significado que se entiende comúnmente por un especialista en la técnica a la que se refiere esta invención. Aunque pueden usarse métodos y materiales similares o equivalentes a los descritos en este documento en la práctica o ensayo de la presente invención, los métodos y materiales preferidos se describen en este documento. Las patentes, solicitudes y referencias expedidas que se citan en este documento se incorporan como referencia en la misma extensión que si cada una se indicara específica e individualmente como referencia. En el caso de inconsistencias, controlará la presente descripción, incluyendo las definiciones. Además, los materiales, métodos y ejemplos son sólo ilustrativos y no pretenden ser limitantes.

El término "aproximadamente" se usa en este documento para indicar aproximadamente, en la región de, más o menos o alrededor. Cuando se usa el término "aproximadamente" junto con un intervalo numérico, modifica ese intervalo extendiendo los límites superior e inferior de los valores numéricos indicados. En general, el término "aproximadamente" se usa en este documento para modificar un valor numérico por encima y por debajo del valor establecido por una varianza del 10%.

El término "comprende" se usa en este documento para indicar "incluye, pero sin limitación".

El término "alifático", como se usa en este documento, significa un hidrocarburo C_{1-12} de cadena lineal, ramificada o cíclica que está completamente saturado o que contiene una o más unidades de insaturación, pero que no es aromático. Por ejemplo, los grupos alifáticos adecuados incluyen grupos alquilo, alquenilo o alquinilo lineales, ramificados o cíclicos saturados o insaturados e híbridos de los mismos, tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo. En varias realizaciones, el grupo alifático tiene 1-12, 1-8, 1-6, ó 1-4 carbonos.

Los términos "alquilo", "alquenilo" y "alquinilo", usados solos o como parte de un resto mayor, se refieren a un grupo alifático de cadena lineal y

ramificada que tiene de 1 a 12 átomos de carbono, que está opcionalmente sustituido con uno, dos o tres sustituyentes. Para los propósitos de la presente invención, el término "alquilo" se usará cuando el átomo de carbono que une el grupo alifático con el resto de la molécula es un átomo de carbono saturado.

5 Sin embargo, un grupo alquilo puede incluir insaturación en otros átomos de carbono. De esta manera, los grupos alquilo incluyen, sin limitación, metilo, etilo, propilo, alilo, propargilo, butilo, pentilo y hexilo.

Para los propósitos de la presente invención, el término "alquenilo" se usará cuando el átomo de carbono que une el grupo alifático con el resto de la molécula forma parte de un doble enlace carbono-carbono. Los grupos alquenilo incluyen, sin limitación, vinilo, 1-propenilo, 1-butenilo, 1-pentenilo y 1-hexenilo. Para los propósitos de la presente invención, el término "alquinilo" se usará cuando el átomo de carbono que une el grupo alifático con el resto de la molécula forma parte de un triple enlace carbono-carbono. Los grupos alquinilo incluyen, sin limitación, etinilo, 1-propinilo, 1-butinilo, 1-pentinilo y 1-hexinilo.

Los términos "cicloalquilo", "carbociclo", "carbociclilo", "carbociclo" o "carbocíclico", usados solos o como parte de un resto mayor, significan un sistema de anillos alifáticos cíclicos saturados o parcialmente insaturados que tienen de 3 a 14 miembros, donde el sistema de anillos alifáticos está opcionalmente sustituido. Los grupos cicloalquilo incluyen, sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, cicloheptilo, cicloheptenilo, ciclooctilo, ciclooctenilo y ciclooctadienilo. En algunas realizaciones, el cicloalquilo tiene 3-6 carbonos. Los términos "cicloalquilo", "carbociclo", "carbociclilo", "carbociclo" o "carbocíclico" también incluyen anillos alifáticos que se condensan a uno o más anillos aromáticos o no aromáticos, tales como decahidronaftilo o tetrahidronaftilo, donde el radical o punto de unión está en el anillo alifático.

Los términos "haloalquilo", "haloalquenilo" y "haloalcoxi" se refieren a un grupo alquilo, alquenilo o alcoxi, como puede ser el caso, sustituido con uno o más átomos de halógeno. Como se usa en este documento, el término "halógeno" o "halo" significa F, C, Br o I. A menos que se indique otra cosa, los

términos "alquilo", "alquenilo" y "alcoxi" incluyen grupos haloalquilo, haloalquenilo y haloalcoxi, incluyendo, en particular, aquellos con 1-5 átomos de flúor.

Los términos "arilo" y "ar-", usados solos o como parte de un resto mayor, por ejemplo, "aralquilo", "aralcoxi" o "ariloxialquilo", se refieren a un resto aromático C₆₋₁₄ que comprende de uno a tres anillos aromáticos, que están opcionalmente sustituidos. Preferiblemente, el grupo arilo es un grupo arilo C₆₋₁₀. Los grupos arilo incluyen, sin limitación, fenilo, naftilo y antracenilo. El término "arilo", como se usa en este documento, también incluye grupos en los que un anillo aromático se condensa a uno o más anillos no aromáticos, tales como indanilo, fenantridinilo o tetrahidronaftilo, donde el radical o punto de unión está en el anillo aromático. El término "arilo" puede usarse de forma intercambiable con el término "anillo arilo".

Un grupo "aralquilo" o "arilalquilo" comprende un grupo arilo unido covalentemente a un grupo alquilo, cualquiera de los cuales está opcionalmente sustituido. Preferiblemente, el grupo aralquilo es aril(C₁₋₆)alquilo C₆₋₁₀, incluyendo, sin limitación, bencilo, fenetilo y naftilmetilo.

Los términos "heteroarilo" y "heteroar-", usados solos o como parte de un resto mayor, por ejemplo, heteroaralquilo o "heteroaralcoxi", se refieren a grupos que tienen de 5 a 14 átomos en el anillo, preferiblemente 5, 6, 9 ó 10 átomos en el anillo; que tienen 6, 10 o 14 electrones π compartidos en una serie cíclica; y que tienen, además de átomos de carbono, de uno a cuatro heteroátomos seleccionados entre el grupo compuesto por N, O y S. Los grupos heteroarilo incluyen, sin limitación, tienilo, furanilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, indolilo, isoindolilo, benzotienilo, benzofuranilo, dibenzofuranilo, indazolilo, benzimidazolilo, benzotiazolilo, purinilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinoxalinilo, naftiridinilo, pteridinilo, carbazolilo, acridinilo y fenazinilo. Los términos "heteroarilo" y "heteroar-", como se usan en este documento, también incluyen grupos en los que un anillo heteroaromático se

condensa a uno o más anillos no aromáticos, donde el radical o punto de unión está en el anillo heteroaromático. Los ejemplos no limitantes incluyen tetrahydroquinolinilo, tetrahydroisoquinolinilo y pirido[3,4-d]pirimidinilo. El término "heteroarilo" puede usarse de forma intercambiable con el término "anillo heteroarilo" o el término "heteroaromático", incluyendo esos términos anillos que están opcionalmente sustituidos. El término "heteroaralquilo" se refiere a un grupo alquilo sustituido con un heteroarilo, donde las porciones alquilo y heteroarilo están independientemente opcionalmente sustituidas.

Como se usan en este documento, los términos "heterociclo", "heterociclilo" o "radical heterocíclico" se refieren a un resto heterocíclico monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros que está saturado o parcialmente insaturado y que tiene, además de átomos de carbono, uno o más, preferiblemente de uno a cuatro, heteroátomos seleccionados entre el grupo compuesto por N, O y S, donde los heteroátomos nitrógeno y azufre están opcionalmente oxidados y los átomos de nitrógeno están opcionalmente cuaternizados. El anillo heterocíclico puede unirse a su grupo pendiente en cualquier heteroátomo o átomo de carbono que de como resultado una estructura estable y cualquiera de los átomos del anillo puede estar opcionalmente sustituido. Los ejemplos de tales radicales heterocíclicos saturados o parcialmente insaturados incluyen, sin limitación, tetrahydrofuranilo, tetrahydrotienilo, pirrolidinilo, pirrolidonilo, piperidinilo, pirrolinilo, tetrahydroquinolinilo, tetrahydroisoquinolinilo, decahydroquinolinilo, oxazolidinilo, piperazinilo, dioxanilo, dioxolanilo, diazepinilo, oxazepinilo, tiazepinilo y morfolinilo. Los términos "heterociclo", "heterociclilo" y "radical heterocíclico", como se usan en este documento, también incluyen grupos en los que un anillo no aromático que contiene heteroátomos se condensa a uno o más anillos aromáticos o no aromáticos, tales como indolinilo, cromanilo, fenantridinilo o tetrahydroquinolinilo, donde el radical o punto de unión está en el anillo no aromático que contiene heteroátomos. El término "heterociclilalquilo" se refiere a un grupo alquilo sustituido con un heterociclilo, donde las porciones alquilo y heterociclilo están independientemente opcionalmente sustituidas.

Como se usa en este documento, el término "parcialmente insaturado" se refiere a un resto del anillo que incluye al menos un doble o triple enlace entre los átomos del anillo. El término "parcialmente insaturado" pretende abarcar anillos que tienen uno o múltiples sitios de insaturación, pero no pretende incluir restos arilo o heteroarilo, como se ha definido en este documento.

El término "sustituido", como se usa en este documento, significa que se reemplazan uno o más átomos de hidrógeno del resto indicado, con la condición de que la sustitución da como resultado un compuesto químicamente factible o estable. Un compuesto estable o químicamente factible es uno en el que la estructura química no se altera sustancialmente cuando se mantiene a una temperatura de 40°C o menos, en ausencia de humedad u otras condiciones químicamente reactivas, durante al menos una semana, o un compuesto que mantiene su integridad durante el tiempo suficiente para ser útil para los procesos sintéticos de la invención. La frase "uno o más sustituyentes", como se usa en este documento, se refiere a un número de sustituyentes que es de uno al número máximo de sustituyentes posibles basándose en el número de sitios de unión disponibles, con la condición de que se cumplan las condiciones anteriores de estabilidad y factibilidad química.

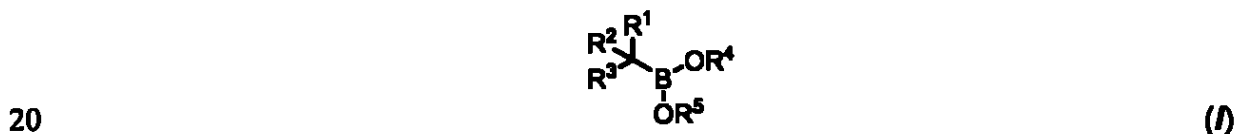
Un grupo arilo "incluyendo el resto arilo de aralquilo, aralcoxi, ariloxialquilo y similares) o heteroarilo (incluyendo el resto heteroarilo en heteroaralquilo y heteroarilalcoxi y similares) puede contener uno o más sustituyentes. Los ejemplos de sustituyentes adecuados en el átomo de carbono insaturado de un grupo arilo o heteroarilo incluyen -halo, -NO₂, -CN, -R*, -OR*, -SR°, -N(R*)₂, -NR*C(O)R*, -NR*C(O)N(R*)₂, -NR*CO₂R°, -O-CO₂R*, -O-C(O)R*, -CO₂R*, -C(O)R*, -C(O)N(R*)₂, -OC(O)N(R*)₂, -S(O)₂R°, -SO₂N(R*)₂, -S(O)R° y -NR*SO₂N(R*)₂. Cada R* se selecciona independientemente entre el grupo compuesto por R*, -C(O)R*, -CO₂R* y -SO₂R* o dos R* en el mismo átomo de nitrógeno, tomados junto con el átomo de nitrógeno, forman un anillo aromático o no aromático de 5-8 miembros que tiene, además del nitrógeno, 0-2 heteroátomos en el anillo seleccionados entre

N, O y S. Cada R* es independientemente hidrógeno o un grupo alifático, arilo, heteroarilo o heterociclilo opcionalmente sustituido. Cada R° es independientemente un grupo alifático o arilo opcionalmente sustituido.

Un grupo alifático también puede estar sustituido con uno o más
 5 sustituyentes. Los ejemplos de sustituyentes adecuados en el carbono saturado de un grupo alifático o de un anillo heterocíclico no aromático incluyen, sin limitación, los listados anteriormente para el carbono insaturado de un grupo arilo o heteroarilo.

Los presentes inventores han descubierto que el requerimiento de
 10 equipamiento escrupulosamente seco, disolventes y reactivos que caracterizan los procedimientos descritos anteriormente para la redistribución promovida por ácido de Lewis de los complejos boron"ato" puede obtenerse mediante el uso de un disolvente de éter que tenga una baja miscibilidad con el agua. De forma remarcada, el uso de tal disolvente permite que la reacción se realice en una
 15 escala multi-kilogramo sin deteriorar el rendimiento o la pureza. En esencia, la escala de la reacción se limita únicamente por el tamaño de las capacidades de fabricación disponibles.

En un aspecto, por lo tanto, los inventores proporcionan un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



en la que:

R¹ es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R² es hidrógeno, un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

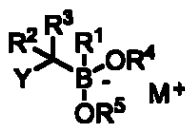
25 R³ es un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

cada uno de R⁴ y R⁵, independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R⁴ y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10

miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S.

El proceso comprende las etapas:

(a) proporcionar un complejo boron"ato" de fórmula (II):



(II)

en la que

Y es un grupo nucleófilo;

M⁺ es un catión; y

cada uno de R¹ a R⁵ es como se ha definido anteriormente; y

10 poner en contacto el complejo boron"ato" de fórmula (II) con un ácido de Lewis en condiciones que produzcan el compuesto de éster bórico de fórmula (I), realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

15 (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación.

Los procesos informados anteriormente para la redistribución de complejos boron"ato" promovida por ácido de Lewis emplean tetrahidrofurano, un disolvente de éter que es totalmente miscible con agua. El fallo al emplear

20 equipamiento, disolventes y reactivos rigurosamente secados en estos procesos da como resultado una reducción drástica en la relación diastereomérica. Los ácidos higroscópicos de Lewis, en particular, típicamente deberían secarse a la llama inmediatamente antes del uso en la reacción.

25 Aunque las técnicas para realizar reacciones sensibles a la humedad son familiares para los especialistas en la técnica y se practican rutinariamente a escala de laboratorio, tales reacciones son costosas y difíciles de escalar.

Además, los intentos de escalar los procesos anteriores de la técnica normalmente dan como resultado un mayor deterioro en la relación

diastereomérica durante el tratamiento y el aislamiento del compuesto de éster bórico producto. Matteson y Erdiik, *Organometallics*, 2: 1083 (1983), informa de que la exposición de productos de éster alfa-halobórico a iones de haluro libre da como resultado la epimerización en el centro alfa-carbono. Sin querer unirse
5 a una teoría, los presentes inventores creen que la epimerización es particularmente problemática durante el tratamiento de reacción y/o etapas posteriores. Por ejemplo, se cree que la epimerización aparece durante la concentración de la mezcla de reacción para retirar el disolvente tetrahidrofurano e intercambiarlo por un disolvente inmiscible en agua. El fallo
10 al retirar completamente el tetrahidrofurano también impacta de forma negativa en la relación diastereomérica durante los lavados acuosos posteriores. La exposición del producto a un ión haluro durante estas etapas es difícil de evitar, particularmente cuando la reacción se realiza a gran escala.

Los presentes inventores han descubierto que la redistribución de los
15 complejos boron"ato" se realiza ventajosamente en un disolvente de éter que tiene baja miscibilidad con el agua. El uso de tales disolventes obvia la necesidad del intercambio de disolvente antes de los lavados acuosos, y el producto soluble orgánico se escuda eficazmente del ión de haluro acuoso durante los lavados, incluso si se realiza a gran escala. Preferiblemente, la
20 solubilidad del agua en el disolvente de éter es menor de aproximadamente 5% p/p, más preferiblemente menor de aproximadamente 2% p/p. En varias realizaciones, el disolvente de éter que tiene baja miscibilidad con el agua constituye al menos aproximadamente 70%; al menos aproximadamente 80%, al menos aproximadamente 85%, al menos aproximadamente 90% o al menos
25 aproximadamente 95% v/v de la mezcla de reacción.

El disolvente de éter es preferiblemente uno que es adecuado para el uso convencional en la producción a gran escala. Como se usa en este documento, el término "gran escala" se refiere a una reacción que utiliza al menos aproximadamente cinco mol de al menos un material de partida.
30 Preferiblemente, un proceso a gran escala utiliza al menos aproximadamente 10, 20, 50 ó 100 mol de al menos un material de partida.

Para los propósitos de la invención, el término "éter" se refiere a cualquiera de una clase de compuestos químicos caracterizados por tener un átomo de oxígeno unido a dos átomos de carbono. Un "disolvente de éter" es un compuesto de éter que está en forma líquida a la temperatura de reacción deseada y que es capaz de disolver el/los material(es) y/o producto(s) de partida de la reacción. Los ejemplos no limitantes de disolventes de éter adecuados para el uso en los procesos de la invención incluyen *terc*-butil metil éter, *terc*-butil etil éter, *terc*-amil metil éter y éter isopropílico.

En una realización, la mezcla de reacción comprende además un co-disolvente de coordinación. En otra realización, el disolvente de éter que tiene baja miscibilidad con el agua es lo suficientemente coordinante para que no sea necesario un co-disolvente de coordinación. Para los propósitos de la invención, los términos "co-disolvente de coordinación" y "disolvente de coordinación" se refieren a un disolvente que es capaz de coordinar el ácido de Lewis y solvatar los componentes iónicos de la reacción. Los disolventes de éter impedidos, tales como *terc*-butil metil éter, son pobremente coordinantes y se usan preferiblemente con un co-disolvente de coordinación. Los ejemplos no limitantes de co-disolventes de coordinación para el uso en la práctica de la invención incluyen tetrahidrofurano, dioxano, agua y mezclas de los mismos.

En algunas realizaciones, la mezcla de reacción comprende al menos aproximadamente 5% o al menos aproximadamente 10% de un co-disolvente de coordinación. Preferiblemente, la cantidad de un co-disolvente de coordinación miscible en agua presente en la mezcla de reacción no es tan grande como para interferir con la separación de las fases durante la reacción o el tratamiento. En varias realizaciones, el co-disolvente de coordinación no constituye más de aproximadamente 20%, aproximadamente 15% o aproximadamente 10% v/v de la mezcla de reacción.

Como se usa en este documento, el término "nucleófugo" se refiere a cualquier grupo que es capaz de experimentar desplazamiento nucleófilo en las condiciones de redistribución del presente proceso. Tales grupos nucleófugos se conocen en la técnica. Preferiblemente, el grupo nucleófugo es un halógeno,

más preferiblemente cloro o bromo. En el transcurso de la reacción de redistribución que convierte el complejo boron"ato" de fórmula (II) en el compuesto de éster bórico de fórmula (I), el grupo nucleófilo Y se libera como Y⁻. A modo de ejemplo, cuando Y es cloro, el ión cloruro se libera en la etapa

5 (b)

La variable M⁺ es cualquier contraión catiónico para el átomo de boro tetravalente cargado de forma negativa en el complejo boron"ato" de fórmula (II). En algunas realizaciones preferidas, M⁺ se selecciona entre el grupo compuesto por Li⁺, Na⁺ y K⁺. Un especialista en la técnica reconocerá que la sal M⁺Y⁻ se forma como un subproducto en la reacción de redistribución de la etapa (b).

La variable R¹ es preferiblemente un grupo con buena aptitud migratoria. En algunas realizaciones, R¹ es alifático C₁₋₆, arilo C₆₋₁₀ o (aril C₆₋₁₀)(alifático C₁₋₆), cualquiera de los cuales está opcionalmente sustituido. En ciertas realizaciones, R¹ es alifático C₁₋₄, particularmente isobutilo.

La variable R² es preferiblemente hidrógeno, un grupo nucleófilo o un grupo alifático C₁₋₆ opcionalmente sustituido, arilo C₆₋₁₀ o (aril C₆₋₁₀)(alifático C₁₋₆). La variable R³ es preferiblemente un grupo nucleófilo o un grupo alifático C₁₋₆ opcionalmente sustituido, arilo C₆₋₁₀ o (aril C₆₋₁₀)(alifático C₁₋₆). Un especialista en la técnica reconocerá que los sustituyentes funcionales pueden estar presentes sobre cualquiera de R¹, R² o R³, con la condición de que el sustituyente funcional no interfiera con la formación del complejo boron"ato" de fórmula (II).

Una realización de la invención se refiere a un proceso para preparar un compuesto de éster bórico de fórmula (I), en el que R³ es un grupo nucleófilo. Tales compuestos son útiles como intermedios para la síntesis de compuestos de éster y ácido bórico alfa-sustituidos, incluyendo compuestos de éster y ácido alfa-aminobórico, como se describe a continuación. En ciertas realizaciones preferidas, R³ es un grupo nucleófilo y R² es hidrógeno.

Las variables R⁴ y R⁵ pueden ser iguales o diferentes. En algunas realizaciones, R⁴ y R⁵ se unen directamente, para que R⁴ y R⁵, tomados junto

con los átomos de oxígeno y boro que intervienen, formen un anillo de 5 a 10 miembros opcionalmente sustituido, que puede tener 0-2 heteroátomos más en el anillo seleccionados entre N, O o S. En algunas realizaciones, el anillo es un anillo de 5 ó 6 miembros, preferiblemente un anillo de 5 miembros.

5 La presente invención es particularmente ventajosa para la redistribución promovida por ácido de Lewis de los complejos boron"ato" de fórmula (II), en la que R^4 y R^5 se unen directamente y juntos son un resto quiral. Una realización de la invención se refiere a la redistribución de tales complejos boron"ato" quirales para proporcionar un compuesto de éster bórico de fórmula (I) en la
10 que el átomo de carbono que tiene R^1 , R^2 y R^3 es un centro quiral. La reacción de redistribución se realiza preferiblemente con un alto calidad de estereodirección por el resto R^4 - R^5 para proporcionar el compuesto de éster bórico de fórmula (I) que tiene una relación diastereomérica en el átomo de carbono que tiene R^1 , R^2 y R^3 de al menos aproximadamente 96:4 en relación
15 al centro quiral en el resto quiral R^4 - R^5 . Preferiblemente, la relación diastereomérica es al menos aproximadamente 97:3.

 Los términos "estereoisómero", "enantiómero", "diastereómero", "epímero" y "centro quiral", se usan en este documento de acuerdo con el significado de que se da para cada uno de ellos en el uso convencional por los
20 especialistas en la técnica. De esta manera, los estereoisómeros son compuestos que tienen la misma conectividad atómica, pero difieren en la organización espacial de los átomos. Los enantiómeros son estereoisómeros que tienen una relación de imagen espejo, esto es, la configuración estereoquímica en todos los centros quirales correspondientes es opuesta. Los
25 diastereómeros son estereoisómeros que tienen más de un centro quiral, que difiere uno de otro en que la configuración estereoquímica de al menos uno, pero no de todos, de los centros quirales correspondientes es opuesta. Los epímeros son diastereómeros que difieren en la configuración estereoquímica sólo en un centro quiral.

30 Como se usa en este documento, el término "relación diastereomérica" se refiere a la relación entre los diastereómeros que difieren en la configuración

estereoquímica en un centro quiral, en relación con un segundo centro quiral en la misma molécula. A modo de ejemplo, una estructura química con los centros quirales proporciona cuatro estereoisómeros posibles: R^*R , R^*S , S^*R y S^*S , donde el asterisco indica el centro quiral correspondiente en cada estereoisómero. La relación diastereomérica para tal mezcla de estereoisómeros es la relación de un diastereómero y su enantiómero con el otro diastereómero y su enantiómero = $(R^*R + S^*S):(R^*S + S^*R)$.

Un especialista en la técnica reconocerá que son posibles otros estereoisómeros cuando la molécula tiene más de dos centros quirales. Para los propósitos de la presente invención, el término "relación diastereomérica" tiene el mismo significado con respecto a los compuestos con múltiples centros quirales que el que tiene con respecto a los compuestos que tienen dos centros quirales. De esta manera, el término "relación diastereomérica" se refiere a la relación de todos los compuestos que tienen configuración R^*R o S^*S en los centros quirales especificados. Por conveniencia, esta relación se denomina en este documento relación diastereomérica en el carbono del asterisco, en relación con el segundo centro quiral especificado.

La relación diastereomérica puede medirse por cualquier método adecuado para distinguir entre compuestos diastereoméricos que tienen diferentes configuraciones estereoquímicas relativas en los centros quirales especificados. Tales métodos incluyen, sin limitación, métodos de resonancia magnética nuclear (RMN), cromatografía de gas (GC) y cromatografía líquida de alta resolución (HPLC).

Como se ha discutido anteriormente, una realización de la invención se refiere a procesos que proporcionan un compuesto de éster bórico de fórmula (I) que tiene una relación diastereomérica en el átomo de carbono que tiene R^1 , R^2 y R^3 de al menos 96:4 en relación con el centro quiral del resto quiral R^4 - R^5 . Un especialista en la técnica reconocerá que el centro quiral R^4 - R^5 puede contener por sí mismo más de un centro quiral. Cuando R^4 - R^5 no tiene más de un centro quiral, preferiblemente tiene gran pureza diastereomérica, y la

relación diastereomérica en el átomo de carbono que tiene R^1 , R^2 y R^3 puede medirse en relación con cualquiera de los centros quirales de R^4 - R^5 .

En los procesos de la invención, el resto quiral R^4 - R^5 tiene preferiblemente un elevado nivel de pureza enantiomérica. Para los propósitos de la invención, el término "pureza enantiomérica" se usa para indicar el "exceso enantiomérico", que es la cantidad mediante la que el enantiómero principal está en exceso del enantiómero menor, expresado como un porcentaje del total. Preferiblemente, el resto quiral R^4 - R^5 tiene una pureza enantiomérica de al menos aproximadamente 98%, más preferiblemente al menos aproximadamente 99%, aún más preferiblemente al menos aproximadamente 99,5%, y más preferiblemente al menos aproximadamente 99,9%.

Cuando los restos quirales R^4 - R^5 tienen una pureza enantiomérica muy elevada, la relación diastereomérica en el átomo de carbono que tiene R^1 , R^2 y R^3 se aproxima a la relación epimérica en ese centro, es decir, relación diastereomérica = $(R^*R):(S^*R)$ o $(R^*S):(S^*S) = (R^*):(S^*)$. Como se usa en este documento, el término "relación epimérica" se refiere a la relación del producto que tiene una configuración estereoquímica absoluta en un centro quiral dado para que el producto tenga la configuración estereoquímica absoluta opuesta en el centro quiral correspondiente. Preferiblemente, los productos tienen una configuración estereoquímica idéntica a todos los otros centros quirales correspondientes. En una realización, por lo tanto, la invención se refiere a la redistribución de un complejo boron"ato" quiral de fórmula (II) para proporcionar un compuesto de éster bórico de fórmula (I) en la que la relación epimérica en el átomo de carbono que tiene R^1 , R^2 y R^3 es al menos aproximadamente 96:4, más preferiblemente al menos aproximadamente 97:3.

Los ácidos de Lewis apropiados para el uso en la práctica de la invención son aquellos capaces de complejarse con el grupo nucleófilo para facilitar su desplazamiento tras la migración de R^1 . Preferiblemente, el ácido de Lewis también es capaz de coordinarse con un átomo de oxígeno unido a boro. Los ejemplos no limitantes de ácidos de Lewis adecuados incluyen bromuro de

cinc, cloruro de cinc, bromuro férrico y cloruro férrico. En ciertas realizaciones preferidas, el ácido de Lewis es cloruro de cinc.

La etapa de contacto se realiza preferiblemente a baja temperatura, pero puede realizarse a temperatura ambiente o elevada. La selección de una temperatura de reacción dependerá enormemente del ácido de Lewis empleado, así como de la aptitud migratoria del resto R¹. Un especialista en la técnica será capaz de seleccionar una temperatura adecuada en vista de las condiciones de reacción que se usen.

En algunas realizaciones, la etapa de contacto se realiza a una temperatura de reacción de al menos aproximadamente -100°C, -78°C o -60°C. En algunas realizaciones, la etapa de contacto se realiza a una temperatura de reacción que no es mayor de aproximadamente 80°C, 40°C o 30°C. Cualquier intervalo que abarque estas temperatura altas y bajas se incluye dentro del alcance de la invención. Preferiblemente, la etapa de contacto se realiza a una temperatura de reacción en el intervalo de aproximadamente -100°C a aproximadamente 80°C, de aproximadamente 70°C a aproximadamente 40°C, de aproximadamente -60°C a aproximadamente 30°C, o de aproximadamente -50°C a aproximadamente 30°C. En ciertas realizaciones preferidas, la etapa de contacto comienza a baja temperatura, preferiblemente en el intervalo de -70°C a aproximadamente -30°C, y después la mezcla de reacción se deja calentar, preferiblemente a temperatura ambiente.

Sorprendentemente, el proceso de la presente invención no requiere precauciones especiales para evitar la presencia del agua durante la reacción de redistribución en sí misma. En algunas realizaciones, se emplea ácido de Lewis húmedo, con deterioro mínimo de la relación diastereomérica. Cuando se usa con respecto al ácido de Lewis, el término "húmedo" significa que el contenido del agua del ácido de Lewis es mayor de aproximadamente 100, 200, 500 o 1.000 ppm. Remarcadamente, el ácido de Lewis puede añadirse a la mezcla de reacción en forma de una solución acuosa sin impacto nocivo en la relación diastereomérica.

En algunas realizaciones, por lo tanto, el proceso de la invención requiere las etapas:

(a) proporcionar una solución que comprende un complejo boron"ato" de fórmula (II) y

5 (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación; y

añadir a la solución de la etapa (a) una solución de ácido de Lewis que
10 comprende el agua y un ácido de Lewis

En otras realizaciones, la solución de ácido de Lewis comprende tetrahidrofurano y un ácido de Lewis.

De esta manera, a diferencia de los procesos anteriores de la técnica, el proceso de la invención es fácilmente flexible a producción a gran escala. En
15 varias realizaciones, se ponen en contacto aproximadamente 5, 10, 20, 50, 100, 500 ó 1000 mol de complejo boron"ato" de fórmula (II) con un ácido de Lewis en condiciones que proporcionan el compuesto de éster bórico de fórmula (I). La invención también proporciona una composición que comprende un compuesto de éster bórico de fórmula (I), como se ha descrito en este
20 documento, y un disolvente de éter que tienen baja miscibilidad con el agua. La composición comprende preferiblemente al menos aproximadamente 5, 10, 20, 50, 100, 500 ó 1000 mol de compuesto de éster bórico de fórmula (I). En ciertas realizaciones, R⁴ y R⁵ juntos son un resto quiral, y el compuesto de fórmula (I) presente en la composición tiene una relación diastereomérica de al
25 menos aproximadamente 96:4 en el átomo de carbono que tiene R¹, R² y R³, en relación con el centro quiral en el resto quiral R⁴-R⁵.

El tratamiento de la reacción comprende preferiblemente el lavado de la mezcla de reacción con una solución acuosa y el concentrado de la mezcla de reacción lavada mediante la retirada de los disolventes para producir un
30 residuo que comprende el compuesto de éster bórico de fórmula (I). Preferiblemente, el residuo comprende al menos aproximadamente 5, 10, 20,

50, 100, 500 ó 1000 mol del compuesto de éster bórico de fórmula (I). En las realizaciones en las que R^4 - R^5 es un resto quiral, el compuesto de éster bórico de fórmula (I) presente en el residuo tiene preferiblemente una relación diastereomérica de al menos 96:4 en el átomo de carbono que tiene R^1 , R^2 y R^3 , en relación al centro quiral en el resto quiral R^4 - R^5 . Más preferiblemente, la relación diastereomérica es de al menos aproximadamente 97:3.

El complejo boron"ato" de fórmula (II) puede prepararse mediante cualquier método conocido, pero preferiblemente se prepara por reacción de un éster bórico de fórmula (III):

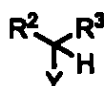
10

con un reactivo de fórmula (IV):

en la que cada uno de M^+ , Y y de R^1 a R^5 son como se han definido para el complejo boron"ato" de fórmula (II). En algunas realizaciones, la reacción se realiza a una temperatura de reacción de al menos aproximadamente -100°C , -78°C o -60°C . En algunas realizaciones, la reacción se realiza a una temperatura de reacción no superior a aproximadamente 0°C , -20°C o -40°C . Cualquier intervalo que abarque estas temperaturas altas y bajas se incluye dentro del alcance de la invención. La reacción se realiza preferiblemente a una temperatura de reacción en el intervalo de aproximadamente -100°C a aproximadamente 0°C , de aproximadamente -78°C a aproximadamente -20°C , o de aproximadamente -60°C a aproximadamente -40°C . En algunas realizaciones, el complejo boron"ato" de fórmula (II) se prepara en una solución que comprende un disolvente de éter que tiene baja miscibilidad con el agua, y la mezcla de reacción se trata directamente con un ácido de Lewis para realizar la redistribución con el compuesto de éster de boro de fórmula (I).

En algunas realizaciones, el reactivo de fórmula (IV) se forma en situ. Tales realizaciones incluyen las etapas:

(i) proporcionar una solución que comprende un éster bórico de fórmula (III), como se ha definido anteriormente y un compuesto de fórmula (V):



(V)

en la que R^2 y R^3 son como se ha definido anteriormente para el reactivo de fórmula (IV); y

- (ii) tratar la solución con una base fuerte y estéricamente impedida para
5 formar el complejo boron"ato" de fórmula (II).

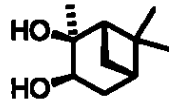
En algunas realizaciones, la base estéricamente impedida es una base de dialquilamida de metal alcalino de fórmula $M^2N(R^*)_2$, en la que M^2 es Li, Na o K y cada R^* , es independientemente un alifático C_{3-8} ramificado o cíclico. La formación en situ de reactivo de fórmula (IV) es especialmente ventajosa en
10 aquellas realizaciones en las que Y es un grupo nucleóforo, debido a la inestabilidad del reactivo de fórmula (IV).

El éster bórico de fórmula (III) puede prepararse mediante cualquier método conocido, pero típicamente se prepara por esterificación del compuesto de ácido bórico correspondiente, es decir, mediante los métodos descritos en
15 Brown *et al.*, *Organometallics*, 2: 1311-1316 (1983). Los ésteres bóricos cíclicos de fórmula (III) se preparan preferiblemente por:

- (a) proporcionando una solución que comprende:
- (i) un compuesto de ácido bórico de fórmula $R^1-B(OH)_2$;
- (ii) un compuesto de fórmula $HO-R^4-R^5-OH$, en la que R^4 y R^5 , tomados
20 juntos, son una cadena de unión opcionalmente sustituida que comprende 2-5 átomos de carbono y 0-2 heteroátomos seleccionados entre el grupo compuesto por O, N y S; y
- (iii) un disolvente orgánico que forma un azeótropo con agua; y
- (b) calentar la solución a reflujo con retirada azeotrópica del agua.

25 Como se usa con respecto a R^4 y R^5 , el término "cadena de unión" se refiere a la cadena de átomos lineal más corta que conecta los átomos de oxígeno a los que están unidos R^4 y R^5 . La cadena de unión está opcionalmente sustituida en cualquier átomo de la cadena, y uno o más átomos de la cadena también puede formar parte de un sistema de anillos que es
30 espiro a, condensado a, o que une la cadena de enlace lineal. A modo de

ejemplo, pero sin limitación, en algunas realizaciones, el compuesto de fórmula $\text{HO-R}^4\text{-R}^5\text{-OH}$ es pinanodiol, que tiene la estructura:



En tales realizaciones, la cadena de unión $\text{R}^4\text{-R}^5$ comprende dos átomos de carbono, que juntos forman un lado del sistema de anillos biciclo[3,1,1]heptano, y uno de los cuales además está sustituido con un grupo metilo.

En algunas realizaciones, el compuesto de fórmula $\text{HO-R}^4\text{-R}^5\text{-OH}$ es un diol quiral, preferiblemente uno que tiene una pureza diastereomérica y enantiomérica elevada. Un especialista en la técnica apreciará que en tal realización, el compuesto de fórmula $\text{HO-R}^4\text{-R}^5\text{-OH}$ se emplea como un auxiliar quiral para dirigir la configuración estereoquímica en el carbono que tiene R^1 , R^2 y R^3 . Los dioles quirales útiles como auxiliares quirales en la síntesis inorgánica se conocen bien en la técnica. Los ejemplos no limitantes incluyen 2,3-butanodiol, preferiblemente (2*R*,3*R*)-(-)-2,3-butanodiol o (2*S*,3*S*)-(+)-2,3-butanodiol; pinanodiol, preferiblemente (1*R*,2*R*,3*R*,5*S*)-(-)-pinanodiol o (1*S*,2*S*,3*S*,5*R*)-(+)-pinanodiol; 1,2-ciclopentanodiol, preferiblemente (1*S*,2*S*)-(+)-*trans*-1,2-ciclopentanodiol o (1*R*,2*R*)-(-)-*trans*-1,2-ciclopentanodiol; 2,5-hexanodiol, preferiblemente (2*S*,5*S*)-2,5-hexanodiol o (2*R*,5*R*)-2,5-hexanodiol; 1,2-diciclohexil-1,2-etanodiol, preferiblemente (1*R*,2*R*)-1,2-diciclohexil-1,2-etanodiol o (1*S*,2*S*)-1,2-diciclohexil-1,2-etanodiol; hidrobencolna, preferiblemente (S,S)-(-)-hidrobencolna o (R,R)-(+)-hidrobencolna; 2,4-pentanodiol, preferiblemente (R,R)-(-)-2,4-pentanodiol o (S,S)-(+)-2,4-pentanodiol; γ -lactona eritrónica, preferiblemente γ -lactona D-eritrónica. También pueden usarse como dioles quirales los carbohidratos, por ejemplo un manitol 1,2,5,6-simétricamente protegido.

Los ejemplos no limitantes de disolventes orgánicos adecuados para el uso en la reacción de esterificación incluyen acetonitrilo, tolueno, hexano, heptano y mezclas de los mismos. En algunas realizaciones, el disolvente orgánico es un disolvente de éter, preferiblemente un disolvente de éter que tiene baja miscibilidad con el agua. En ciertas realizaciones preferidas, la

reacción de esterificación se realiza en un disolvente de éter que tiene baja miscibilidad en agua, y la solución del producto que comprende el éster bórico de fórmula (III) se usa directamente en la siguiente etapa, sin aislamiento del éster bórico.

- 5 Como se ha indicado anteriormente, el proceso de la presente invención para el primer momento permite el tratamiento de reacciones a gran escala sin un deterioro significativo en la relación diastereomérica. En otro aspecto, por lo tanto, la invención proporciona una composición que comprende al menos aproximadamente 5, 10, 20, 50, 100, 500 ó 1000 mol de un compuesto de éster bórico de fórmula (I):
- 10 bórico de fórmula (I):

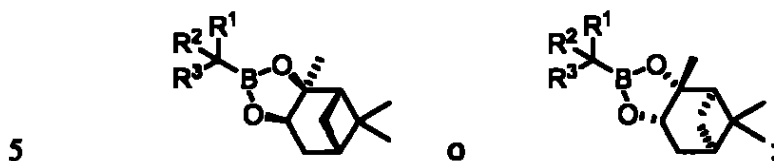
en la que:

- R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;
 R^2 es hidrógeno, un grupo nucleófilo o un grupo alifático, aromático o
15 heteroaromático opcionalmente sustituido;
 R^3 es un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y
 R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo quiral de 5 a 10 miembros opcionalmente sustituido que tienen
20 0-2 heteroátomos más en el anillo seleccionados entre N, O o S;
donde el átomo de carbono al que se unen R^1 , R^2 y R^3 es un centro quiral, que tienen una relación diastereomérica de al menos aproximadamente 96:4, preferiblemente al menos aproximadamente 97:3, con respecto al centro quiral en el resto quiral R^4 - R^5 .

- 25 Los valores preferidos para R^1 a R^3 son como se han descrito anteriormente. Preferiblemente, los disolventes constituyen menos de aproximadamente 30% p/p, 20% p/p, 10% p/p o 5% p/p de la composición de acuerdo con este aspecto de la invención. En algunas realizaciones, el compuesto de éster bórico de fórmula (I) constituye al menos aproximadamente
30 70% p/p, 80% p/p, 90% p/p o 95% p/p de la composición.

Una realización se refiere a la composición descrita anteriormente, en la que está presente al menos una de las siguientes características:

- (a) R^3 es cloro;
- (b) el compuesto de éster bórico (I) es



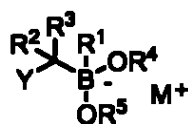
- (c) R^2 es hidrógeno; y
- (d) R^1 es alifático C_{1-4} .

10 Todo el compuesto de éster bórico de fórmula (I) presente en la composición puede producirse en una única realización de lote. Para los propósitos de la invención, el término "realización de lote" se refiere a la ejecución de un proceso sintético, donde cada etapa del proceso se realiza únicamente una vez. Preferiblemente, el compuesto de éster bórico de fórmula (I) presente en la composición se prepara en una única realización de lote del proceso de acuerdo con el primer aspecto de la invención. Un especialista en la

15 técnica apreciará que la preparación de una cantidad dada de producto mediante una única realización de lote de un proceso a gran escala es más eficaz y proporciona un producto más homogéneo que la preparación de la misma cantidad de producto por ejecución repetida de un proceso a pequeña escala.

20 Los compuestos de éster bórico de fórmula (I) en la que R^3 es un grupo nucleófilo son útiles como intermediarios para la síntesis de compuestos de éster alfa-aminobórico. En otro aspecto, por lo tanto, la invención proporciona un proceso a gran escala para preparar un éster alfa-aminobórico, preferiblemente mediante un proceso que comprende las etapas:

- 25 (a) proporcionar un complejo boronato de fórmula (II):



(II)

donde

Y es un grupo nucleófilo;

M⁺ es un catión;

R¹ es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

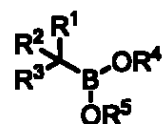
R² es hidrógeno;

5 R³ es un grupo nucleófilo; y

cada uno de R⁴ y R⁵, independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R⁴ y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tienen 0-2 heteroátomos más en el

10 anillo seleccionados entre N, O o S;

(b) poner en contacto el complejo boron"ato" de fórmula (I) con un ácido de Lewis en condiciones que produzcan el compuesto de éster bórico de fórmula (I):



(I)

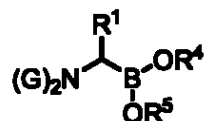
15 en la que cada uno de R¹ a R⁵ es como se ha definido anteriormente, realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

(i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o

20 (ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación; y

(c) tratar el compuesto de éster bórico de fórmula (I) con un reactivo de fórmula M¹-N(G)₂, donde M¹ es un metal alcalino y cada G individualmente o

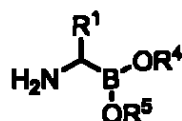
25 juntos son un grupo protector de grupo amino para formar un subproducto de fórmula M¹-R³ y un compuesto de fórmula (VIII):



(VIII)

en la que cada uno de G y R¹ a R⁵ son como se han definido anteriormente; y

(d) retirar los grupos G para formar un compuesto de fórmula (VII):



(VII)

o una sal de adición de ácidos del mismo.

En algunas realizaciones, en la etapa (c), el compuesto de éster bórico
5 fórmula (I) se trata con un reactivo de fórmula $\text{M}^1\text{-N}(\text{Si}(\text{R}^6)_3)_2$ en la que M^1 es un metal alcalino y cada R^6 se selecciona independientemente entre el grupo compuesto por alquilo, aralquilo y arilo, donde la porción arilo o arilo del aralquilo está opcionalmente sustituida.

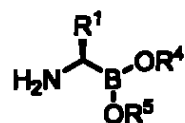
La reacción del compuesto de éster bórico de fórmula (I) con el reactivo
10 de fórmula $\text{M}^1\text{-N}(\text{G})_2$ se realiza preferiblemente a una temperatura de reacción en el intervalo de aproximadamente -100°C a aproximadamente 50°C , preferiblemente de aproximadamente -50°C a aproximadamente 25°C y más preferiblemente de aproximadamente -30°C a aproximadamente 0°C . En algunas realizaciones, R^3 es halo, preferiblemente cloro y M^1 es Li. Para
15 facilitar el aislamiento del producto de fórmula (VIII), la mezcla de reacción preferiblemente comprende un disolvente orgánico en el que el subproducto $\text{M}^1\text{-R}^3$ tiene baja solubilidad. Los ejemplos no limitantes de disolventes orgánicos adecuados incluyen metilciclohexano, ciclohexano, heptano, hexano y tolueno. En algunas realizaciones, la etapa (c) comprende además filtrar la
20 mezcla de reacción para retirar el $\text{M}^1\text{-R}^3$ y proporcionar un filtrado que comprende el compuesto de fórmula (VIII). Preferiblemente, el filtrado se usa directamente en la etapa (d).

En aquellas realizaciones en las que la mezcla de reacción comprende un disolvente orgánico en el que el subproducto $\text{M}^1\text{-R}^3$ tiene baja solubilidad, la
25 mezcla de reacción puede comprender además un disolvente en el que el subproducto $\text{M}^1\text{-R}^3$ tiene una solubilidad elevada. En tales casos, el disolvente en el que el subproducto $\text{M}^1\text{-R}^3$ tiene una solubilidad elevada preferiblemente se retira antes de la filtración de la mezcla de reacción. A modo de ejemplo, en algunas realizaciones, a la mezcla de reacción se le añade un reactivo de

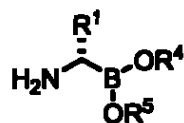
fórmula $M^1-N(Si(R^6)_3)_2$ en forma de una solución que comprende tetrahidrofurano. En tales realizaciones, la etapa (c) preferiblemente comprende además la retirada del tetrahidrofurano antes del filtrado de mezcla de reacción.

Los especialistas en la técnica sabrán que existen varios métodos que pueden usarse para retirar los grupos protectores G en el compuesto (VIII), incluyendo, por ejemplo, hidrólisis acuosa o tratamiento con ácido. El producto éster alfa-aminobórico de fórmula (VII) tiene baja solubilidad y preferiblemente se deriva inmediatamente (Matteson *et al.*, *J. Am. Chem. Soc.*, 103: 5241 (1981)) o se aísla en forma de una sal de adición de ácidos. En algunas realizaciones, la etapa (d) comprende tratar el compuesto de fórmula (VIII) con un ácido y aislar el compuesto de fórmula (VII) en forma de la sal de adición de ácidos. En ciertas realizaciones preferidas, el ácido es ácido trifluoroacético, y el compuesto de fórmula (VII) se aísla en forma de la sal de adición de ácido trifluoroacético.

Como se ha discutido anteriormente, los procesos de la invención son particularmente adecuados para preparar compuestos de éster alfa-aminobórico de fórmula (VII), en la que el carbono alfa es un centro quiral. De esta manera, una realización de la invención se refiere a un proceso a gran escala para preparar un compuesto de éster alfa-aminobórico de fórmula (VIIa) o (VIIb):



(VIIa)



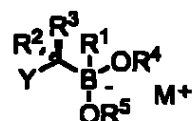
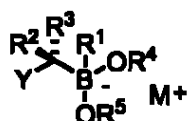
(VIIb)

o una sal de adición de ácidos del mismo, donde:

R¹ es un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

R⁴ y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman un éster bórico cíclico quiral opcionalmente sustituido; comprendiendo dicho proceso:

(a) proporcionar un complejo boron"ato" de fórmula (IIa) o (IIb):



donde

Y es un grupo nucleófilo;

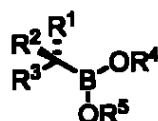
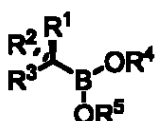
5 M^+ es un catión;

R^2 es hidrógeno;

R^3 es un grupo nucleófilo; y

R^4 y R^5 son como se han definido anteriormente;

10 (b) poner en contacto el complejo boron"ato" de fórmula (IIa) o (IIb) con un ácido de Lewis en condiciones que produzcan un compuesto de éster bórico de fórmula (Ia) o (Ib):

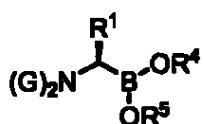


donde cada uno de R^1 a R^5 es como se ha definido anteriormente, realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

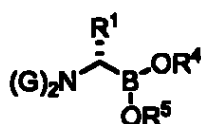
15 (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación; y

20 (c) tratar el compuesto de éster bórico de fórmula (Ia) o (Ib) con un reactivo de fórmula $\text{M}^1\text{-N}(\text{G})_2$, donde M^1 es un metal alcalino y G es un resto protector de grupo amino, para formar un compuesto de fórmula (VIIIa) o (VIIIb):

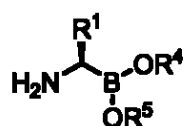


(VIIIb)

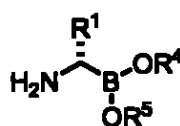


donde cada uno de G y R^1 a R^5 son como se han definido anteriormente; y

25 (d) retirar los grupos G para formar un compuesto de fórmula (VIIa) o (VIIb):



(Vila)

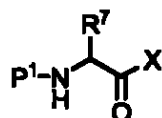


(VIB)

o una sal de adición de ácidos del mismo.

Los valores preferidos para Y, M⁺, R¹ a R⁵ y G son como se han descrito anteriormente. El compuesto de fórmula (VIIa) o (VIIb) preferiblemente tiene una relación diastereomérica en el carbono alfa de al menos aproximadamente 96:4, más preferiblemente al menos aproximadamente 97:3, con respecto al centro quiral en el resto quiral R⁴-R⁵.

Los compuestos de éster alfa-aminobórico de fórmula (VII) son
intermedios sintéticos útiles para la preparación de compuestos de éster
peptidilbórico. En algunas realizaciones, por lo tanto, el proceso de acuerdo
con este aspecto de la invención comprende además acoplar el compuesto de
fórmula (VII) con un compuesto de fórmula (IX):



(X)

15 en la que:

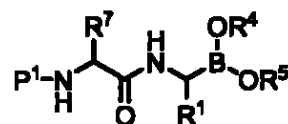
P¹ es un resto bloqueante de grupo amino;

R⁷ se selecciona entre el grupo compuesto por hidrógeno, alifático C₁₋₁₀, arilo C₆₋₁₀ opcionalmente sustituido o alifático C₁₋₅-R⁸; y

**R⁵ se selecciona entre el grupo compuesto por grupos alcoxi, alquiltio, arilo
opcionalmente sustituido, heteroarilo y heterociclilo y grupos amino
opcionalmente protegido, hidroxilo y guanidino; y**

X es OH o un grupo saliente;

para formar un compuesto de fórmula (X):



(X)

25 en la que cada uno de P^1 , R^1 , R^4 , R^5 y R^7 es como se ha definido anteriormente.

El grupo saliente X es cualquier grupo capaz de desplazamiento nucleófilo mediante el grupo alfa-amino del compuesto de fórmula (VII). En algunas realizaciones, el resto $-C(O)-X$ es un éster activado, tal como un éster de O-(N-hidroxisuccinimida). En algunas realizaciones, un éster activado se genera en situ poniendo en contacto un compuesto de fórmula (IX), en la que X es OH, con un reactivo de acoplamiento de péptidos. Los ejemplos de reactivos de acoplamiento de péptidos adecuados incluyen, pero sin limitación, reactivos de carbodiimida, por ejemplo, dicitclohexilcarbodiimida (DCC) o 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC); reactivos de fosfonio, por ejemplo, hexafluorofosfato de benzotriazol-1-iloxitris-(dimetilamino)-fosfonio (reactivo de BOP); y reactivos de uronio, por ejemplo, tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (TBTU).

Los especialistas en la técnica también sabrán que existen procedimientos que permiten el acoplamiento directo de aminas silioprotegidas, sin una etapa de desprotección anterior. En tales procedimientos, los grupos sililo se retiran en situ en condiciones de reacción de acoplamiento. En tales realizaciones de la presente invención, por lo tanto, un compuesto de fórmula (VIII) se pone en contacto con un compuesto de fórmula (IX) en condiciones que retiran los grupos $(R^6)_3Si$ en situ y forman un compuesto de fórmula (X).

Para los propósitos de la invención, el término "resto bloqueante de grupo amino" se refiere a cualquier grupo usado para derivar un grupo amino, especialmente un grupo amino de extremo N de un péptido o aminoácido. El término "resto bloqueante de grupo amino" incluye, pero sin limitación, grupos protectores que se emplean comúnmente en la síntesis orgánica, especialmente síntesis de péptidos. Véase, por ejemplo, Gross y Mienhoffer, eds., *The Peptides*, Vol. 3, Academic Press, New York, 1981, págs. 3-88; Green y Wuts, *Protective Groups in Organic Synthesis*, 3ª edición, John Wiley y Sons, Inc., New York, 1999. A menos que se indique otra cosa, sin embargo, no es necesario para un resto bloqueante de grupo amino que sea fácilmente escindible. Los restos bloqueantes de grupo amino incluyen, por ejemplo, restos alquilo, acilo, alcóxicarbonilo, aminocarbonilo y sulfonilo. En algunas

realizaciones, el resto bloqueante de grupo amino es un resto acilo derivado de un aminoácido o péptido, o un derivado o análogo del mismo.

Como se usa en este documento, el término "aminoácido" incluye aminoácidos que se encuentran en la naturaleza y no naturales. Para los
 5 propósitos de la invención, un "derivado" de un aminoácido o péptido es uno en el que un grupo funcional, por ejemplo, un grupo hidroxilo, amino, carboxi o guanidino en el extremo N o sobre una cadena lateral, se modifica con un grupo bloqueante. Como se usa en este documento, un "análogo" de un aminoácido o péptido es uno que incluye un esqueleto o cadena lateral
 10 modificada. El término "análogo de péptido" pretende incluir péptidos en los que uno o más estereocentros se invierten y uno o más enlaces péptido se reemplazan con un isómero peptídico.

En algunas realizaciones, P¹ es un grupo protector escindible. Los ejemplos de grupos protectores escindibles incluyen, sin limitación, grupos
 15 protectores de acilo, por ejemplo, formilo, acetilo (Ac), succinilo (Suc) o metoxisuccinilo (MeOSuc) y grupos protectores de uretano, por ejemplo, *terc*-butoxicarbonilo (Boc), benciloxicarbonilo (Cbz) o fluorenilmetoxicarbonilo (Fmoc).

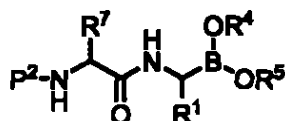
En algunas de esas realizaciones, el proceso de acuerdo con este
 20 aspecto de la invención también comprende las etapas:

(f) retirar el grupo protector P¹ para formar un compuesto de fórmula (XI):



o una sal de adición de ácidos del mismo, en la que cada uno de R¹, R⁴, R⁵ y
 25 R⁷ es como se ha definido anteriormente; y

(g) acoplamiento del compuesto de fórmula (XI) con un reactivo de fórmula P²-X, en la que P² es cualquier resto bloqueante de grupo amino, como se ha descrito anteriormente y X es un grupo saliente, para formar un compuesto de fórmula (XII):

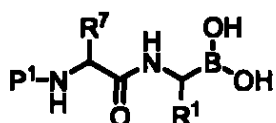


(XII)

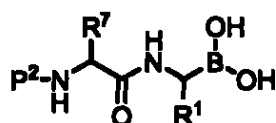
en la que cada uno de P^2 , R^1 , R^4 , R^5 y R^7 son como se han definido anteriormente. Un especialista en la técnica reconocerá que en aquellas realizaciones en las que P^2 es un grupo acilo, incluyendo, por ejemplo, un resto acilo derivado de un aminoácido o péptido o un análogo o un derivado del mismo, el grupo saliente X puede generarse in situ, como se ha discutido anteriormente para el compuesto de fórmula (IX).

En cada uno de los compuestos (X) y (XII), el resto ácido bórico se protege en forma de un éster bórico. Si se desea, el resto de ácido bórico puede desprotegerse mediante cualquier método conocido en la técnica. Preferiblemente, el resto de ácido bórico se desprotege por transesterificación en una mezcla bifásica. Más preferiblemente, la etapa de desprotección del ácido bórico comprende las etapas:

- (i) proporcionar una mezcla bifásica que comprende el compuesto de éster bórico de fórmula (X) o (XII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente de hidrocarburo C_{5-8} y un ácido mineral acuoso;
- (ii) agitar la mezcla bifásica para proporcionar el compuesto de ácido bórico desprotegido correspondiente de fórmula (Xa) o (XIII):



(Xa)



(XIII);

- (iii) separar las fases de disolvente; y
- (iv) extraer el compuesto de fórmula (Xa), (XIII) o un aldehído de ácido bórico del mismo, en un disolvente orgánico.

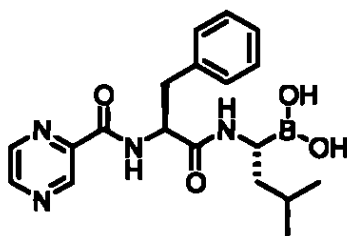
El aceptor orgánico de ácido bórico de la etapa (i) preferiblemente es alifático, arilo o ácido ar(alifático)bórico. En algunas realizaciones, el aceptor de ácido bórico se selecciona entre el grupo compuesto pro ácido fenilbórico, ácido bencilbórico, ácido butilbórico, ácido pentilbórico, ácido hexilbórico y ácido ciclohexilbórico. En ciertas realizaciones, el aceptor de ácido bórico es

ácido isobutilbórico. En algunas realizaciones, el aceptor de ácido bórico se selecciona para que el compuesto de éster bórico de fórmula (III) se forme en forma de un subproducto de la reacción de desprotección. El compuesto de éster bórico de fórmula (III) puede usarse después en otra realización de lote del proceso descrito anteriormente. En tales realizaciones, el resto R⁴-R⁵ se recicla de forma eficaz, lo que puede ser particularmente ventajoso si R⁴-R⁵ es un resto quiral caro.

Para mejorar la pureza del producto, la fase acuosa que contiene el compuesto de fórmula (Xa) o (XIII) preferiblemente se lava para retirar las impurezas orgánicas neutras antes de la etapa de extracción (iv). En tales realizaciones, la etapa (iii) comprende preferiblemente las etapas:

- (1) separar las fases de disolvente;
- (2) ajustar la fase acuosa a pH básico;
- (3) lavar la fase acuosa con un disolvente orgánico; y
- (4) ajustar la fase acuosa a un pH menor de aproximadamente 6.

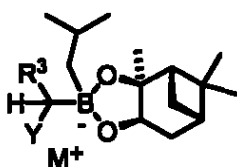
En algunas realizaciones, la invención se refiere a un proceso mejorado para fabricar el inhibidor de proteasoma bortezomib. De esta manera, en una realización, la invención proporciona un proceso a gran escala para formar un compuesto de fórmula (XIV):



(XIV)

o un aldehído de ácido bórico del mismo. El proceso comprende las etapas:

- (a) proporcionar un complejo boron"ato" de fórmula (XV):



(XV)

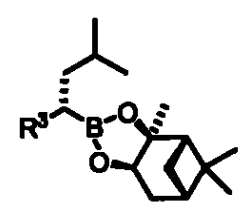
en la que:

- R³ es un grupo nucleófilo;

Y es un grupo nucleófilo; y

M⁺ es un metal alcalino;

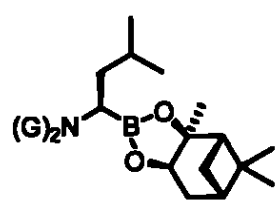
- (b) poner en contacto el complejo boronato de fórmula (XV) con un ácido de Lewis en condiciones que produzcan un compuesto de éster bórico de fórmula (XVI):



(XVI)

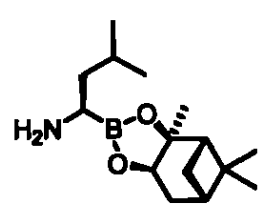
realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

- (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o
- (ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;
- (c) tratar el compuesto de éster bórico de fórmula (XVI) con un reactivo de fórmula M¹-N(G)₂, donde M¹ es un metal alcalino y cada G individualmente o juntos son un grupo protector de grupo amino, para formar un compuesto de fórmula (XVII):



(XVII)

- (d) retirar los grupos G para formar un compuesto de fórmula (XVIII):

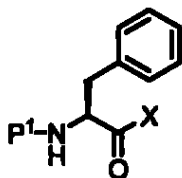


(XVIII)

- o una sal de adición de ácidos del mismo;
- (e) acoplamiento del compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX);

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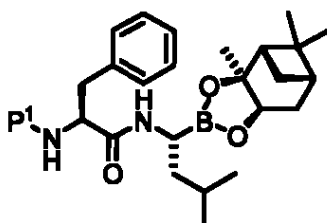
(XIX)

en la que:

P¹ es un resto protector de grupo amino escindible; y

X es OH o un grupo saliente;

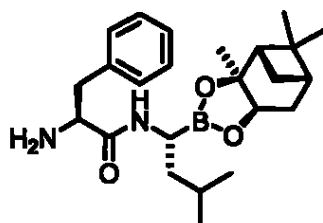
- 5 para formar un compuesto de fórmula (XX):



(XX)

en la que P¹ es como se ha definido anteriormente;

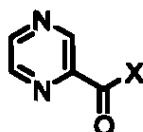
- (f) retirar el grupo protector P¹ para formar un compuesto de fórmula (XXI):



(XXI)

- 10 o una sal de adición de ácidos del mismo;

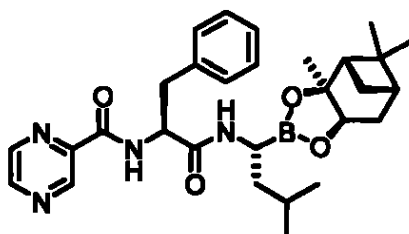
- (g) acoplamiento del compuesto de fórmula (XXI) con un reactivo de fórmula (XXII)



(XXII)

en la que X es a OH o un grupo saliente, para formar un compuesto de fórmula

- 15 (XXIII):



(XXIII); y

(h) desproteger el resto de ácido bórico para formar el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo.

En algunas realizaciones, el proceso se caracteriza por al menos una de las siguientes características (1)-(5). En ciertas realizaciones preferidas, el proceso se caracteriza por las cinco características (1)-(5) mostradas a continuación.

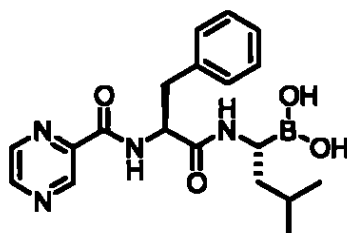
- (1) En el complejo boron"ato" de fórmula (XV), R³ e Y son ambos cloro.
- (2) La etapa de acoplamiento (e) comprende las etapas:
 - 10 (i) acoplamiento del compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX) en la que X es OH en presencia de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;
 - (ii) realizar un intercambio de disolvente para reemplazar el diclorometano por acetato de etilo; y
 - 15 (iii) realizar un lavado acuoso de la solución de acetato de etilo.
- (3) La etapa de retirada del grupo protector (f) comprende las etapas:
 - (i) tratar el compuesto de fórmula (XX) con HCl en acetato de etilo;
 - (ii) añadir heptano a la mezcla de reacción; y
 - 20 (iii) aislar por cristalización el compuesto de fórmula (XXI) en forma de su sal de adición de HCl.
- (4) La etapa de acoplamiento (g) comprende las etapas:
 - (i) acoplamiento del compuesto de fórmula (XXI) con ácido 2-pirazina-carboxílico en presencia de TBTU y una amina terciaria en diclorometano;
 - 25 (ii) realizar un intercambio de disolvente para reemplazar el diclorometano por acetato de etilo; y
 - (iii) realizar un lavado acuoso de la solución de acetato de etilo.

- (5) La etapa de desprotección de ácido bórico (h) comprende las etapas:
- (i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente de hidrocarburo C₅₋₈ y un ácido mineral acuoso;
- 5 (ii) agitar la mezcla bifásica para producir el compuesto de fórmula (XIV);
- (iii) separar las fases de disolvente; y
- (iv) extraer el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo, en un disolvente orgánico.

Preferiblemente, la etapa (h)(iii) comprende las etapas:

- 10 (1) separar las fases de disolvente;
- (2) ajustar la fase acuosa a pH básico;
- (3) lavar la fase acuosa con un disolvente orgánico; y
- (4) ajustar la fase acuosa a un pH menor de aproximadamente 6;

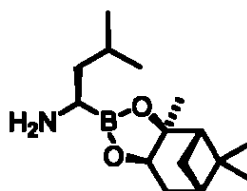
- En otra realización, la invención se refiere a un proceso a gran escala
- 15 para formar un compuesto de fórmula (XIV)



(XIV)

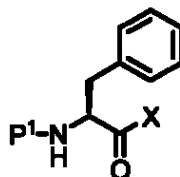
o un aldehído de ácido bórico del mismo, comprendiendo las etapas:

- (aa) acoplar un compuesto de fórmula (XVIII):



(XVIII)

- 20 o una sal de adición de ácidos del mismo, con un compuesto de fórmula (XIX):



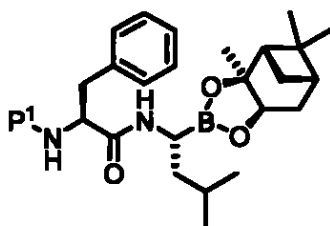
(XIX)

en la que:

P¹ es un resto protector de grupo amino escindible; y

X es OH o un grupo saliente;

para formar un compuesto de fórmula (XX):



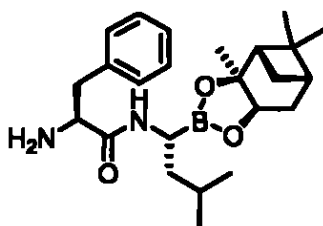
5

(XX)

en la que P¹ es como se ha definido anteriormente, comprendiendo dicha etapa de acoplamiento (aa) las etapas:

- (i) acoplamiento del compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX) en la que X es OH en presencia de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;
- (ii) realizar un intercambio de disolvente para reemplazar el diclorometano por acetato de etilo; y
- (iii) realizar un lavado acuoso de la solución de acetato de etilo;
- (bb) retirar el grupo protector P¹ para formar un compuesto de fórmula (XXI):

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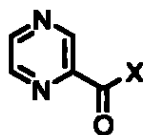


(XXI)

o una sal de adición de ácidos del mismo, comprendiendo dicha etapa de retirada del grupo protector (bb) las etapas:

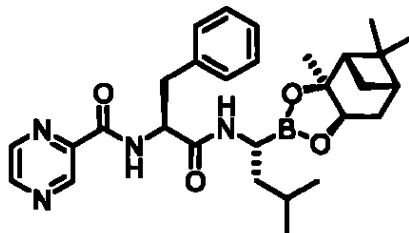
- (i) tratar el compuesto de fórmula (XX) con HCl en acetato de etilo;
- (ii) añadir heptano a la mezcla de reacción; y
- (iii) aislar por cristalización el compuesto de fórmula (XXI) en forma de su sal de adición de HCl;
- (cc) acoplamiento del compuesto de fórmula (XXI) con un reactivo de fórmula (XXII)

20



(XXII)

en la que X es a OH o un grupo saliente, para formar un compuesto de fórmula (XXIII):



(XXIII),

- 5 comprendiendo dicha etapa de acoplamiento (cc) las etapas:
 - (i) acoplamiento del compuesto de fórmula (XXI) con ácido 2-pirazinacarboxílico en presencia de TBTU y una amina terciaria en diclorometano;
 - (ii) realizar un intercambio de disolvente para reemplazar el diclorometano
- 10 por acetato de etilo; y
 - (iii) realizar un lavado acuoso de la solución de acetato de etilo; y
 - (dd) desproteger el resto de ácido bórico para formar el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo, comprendiendo dicha etapa de desprotección (dd) las etapas:
 - 15 (i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente de hidrocarburo C₅₋₆ y un ácido mineral acuoso;
 - (ii) agitar la mezcla bifásica para producir el compuesto de fórmula (XIV);
 - (iii) separar las fases de disolvente; y
 - 20 (iv) extraer el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo, en un disolvente orgánico.

Preferiblemente, la etapa (dd)(iii) comprende las etapas:

- (1) separar las fases de disolvente;
- (2) ajustar la fase acuosa a pH básico;
- 25 (3) lavar la fase acuosa con un disolvente orgánico; y

(4) ajustar la fase acuosa a un pH menor de aproximadamente 6;

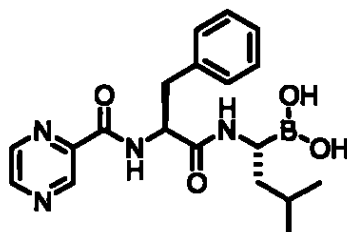
La eficacia de los procesos descritos anteriormente se mejora mediante etapas telescópicas, por ejemplo, llevando la mezcla de reacción o solución de producto tratado de una reacción directamente a la siguiente reacción, sin aislamiento del producto intermedio. Por ejemplo, en algunas realizaciones, la etapa (e)(iii) o (aa)(iii) produce una solución de acetato de etilo que comprende un compuesto de fórmula (XX) y la solución de acetato de etilo se somete directamente en la etapa (f) o (bb) a condiciones eficaces para retirar el grupo protector P¹. En algunas de esas realizaciones, el grupo protector P¹ es un grupo protector inestable al ácido, por ejemplo, *tert*-butoxicarbonilo (Boc) y la solución de acetato de etilo de la etapa (e)(iii) o (aa)(iii) se trata con ácido. En ciertas realizaciones preferidas, la solución de acetato de etilo de la etapa (a)(iii) o (aa)(iii) se seca azeotrópicamente y después se trata con HCl gaseoso.

Cuando la etapa de desprotección (f) o (bb) se realiza en condiciones anhidras, como se ha descrito anteriormente, el producto de fórmula (XXI) puede aislarse por cristalización de la mezcla de reacción en forma de su sal de adición de HCl. La cristalización de la sal producto se promueve por la adición de un disolvente de hidrocarburo tal como *n*-heptano. En algunas realizaciones, la mezcla de reacción se concentra parcialmente antes de la adición del disolvente de hidrocarburo. Los presentes inventores han descubierto que la cristalización del compuesto de fórmula (XXI) de esta manera retira de forma eficaz cualquier impureza de tripéptido que pueda haberse formado durante la etapa de acoplamiento (e) o (aa). Tales impurezas son difíciles de retirar en las últimas etapas de la síntesis.

Es posible abreviar adicionalmente el proceso llevando la mezcla del producto de la etapa de acoplamiento (g) o (cc) directamente a la etapa de desprotección del resto de ácido bórico (g) o (dd). Preferiblemente, el disolvente orgánico de la etapa de acoplamiento se reemplaza primero por acetato de etilo con el fin de facilitar los lavados acuosos. Un segundo intercambio de disolvente en un disolvente de hidrocarburo permite después que la solución del producto de la etapa (g) o (cc) se use directamente en la

etapa de desprotección de ácido bórico bifásico (h) o (dd), sin aislamiento del compuesto de fórmula (XXIII).

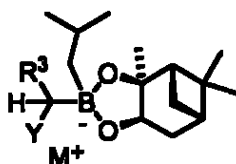
- Como alternativa, puede adoptarse una aproximación más convergente para la síntesis del compuesto de fórmula (XIV). De esta manera, en otra realización, la invención proporciona un proceso a gran escala para formar un compuesto de fórmula (XIV)



(XIV)

o un aldehído de ácido bórico del mismo. El proceso comprende las etapas:

- (a) proporcionar un complejo boron"ato" de fórmula (XV):



10

(XV)

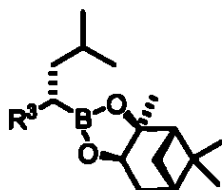
en la que:

R^3 es un grupo nucleófilo;

Y es un grupo nucleófilo; y

M^+ es un metal alcalino;

- 15 (b) poner en contacto el complejo boron"ato" de fórmula (XV) con un ácido de Lewis en condiciones que produzcan un compuesto de éster bórico de fórmula (XVI):



(XVI)

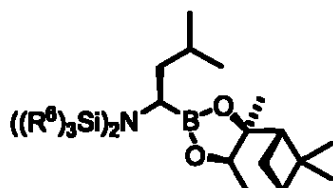
- realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

20

- (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o

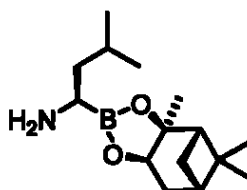
(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;

- (c) tratar el compuesto de éster bórico de fórmula (XVI) con un reactivo de fórmula $M^1-N(Si(R^6)_3)_2$, donde M^1 es un metal alcalino y cada R^6 se selecciona independientemente entre el grupo compuesto por alquilo, aralquilo y arilo, donde el arilo o porción del aralquilo está opcionalmente sustituida, para formar un compuesto de fórmula (XVII):



(XVII)

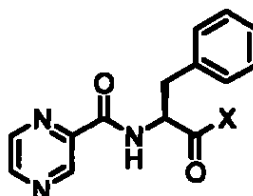
- (d) retirar los grupos $(R^6)_3Si$ para formar un compuesto de fórmula (XVIII):



(XVIII)

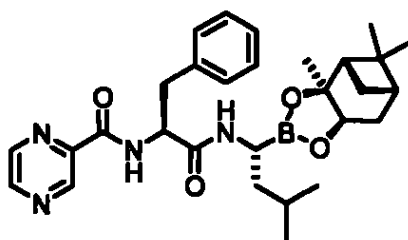
o una sal de adición de ácidos del mismo;

- (e') acoplamiento del compuesto de fórmula (XVIII) con un compuesto de fórmula (XIXa):



(XIXa)

- 15 en la que X es OH o un grupo saliente, para formar un compuesto de fórmula (XXIII):



(XXIII) ; y

(f) desproteger el resto de ácido bórico para formar el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo.

En algunas realizaciones, el proceso se caracteriza por al menos una de las siguientes características (1)-(3). En ciertas realizaciones preferidas, el proceso se caracteriza por las tres características (1)-(3) mostradas a continuación.

(1) En el complejo boronato de fórmula (XV), R³ e Y son ambos cloro.

(2) La etapa de acoplamiento (e') comprende las etapas:

(i) acoplamiento del compuesto de fórmula (XVIII) con un compuesto de fórmula (XIXa) en la que X es OH en presencia de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;

(ii) realizar un intercambio de disolvente para reemplazar el diclorometano por acetato de etilo; y

(iii) realizar un lavado acuoso de la solución de acetato de etilo.

(3) La etapa de desprotección de ácido bórico (f) comprende las etapas:

(i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente de hidrocarburo C₅₋₈ y un ácido mineral acuoso;

(ii) agitar la mezcla bifásica para producir el compuesto de fórmula (XIV);

(iii) separar las fases de disolvente; y

(iv) extraer el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo, en un disolvente orgánico.

Preferiblemente, la etapa (f)(iii) comprende las etapas:

(1) separar las fases de disolvente;

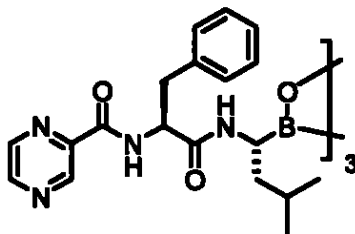
(2) ajustar la fase acuosa a pH básico;

(3) lavar la fase acuosa con un disolvente orgánico; y

(4) ajustar la fase acuosa a un pH menor de aproximadamente 6;

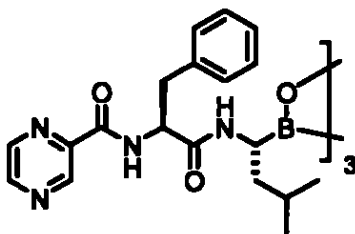
En la etapa (h)(iv), (dd)(iv) o (f)(iv) de los procesos descritos anteriormente, el compuesto de fórmula (XIV) o un aldehído de ácido bórico del mismo, preferiblemente se extrae en acetato de etilo y se cristaliza mediante la adición de hexano o heptano. En algunas realizaciones, el proceso comprende

además el aislamiento del anhídrido de ácido bórico del compuesto de fórmula (XIV), preferiblemente un anhídrido de ácido bórico trimérico de fórmula (XXIV):



(XXIV)

- 5 Los procesos de la invención permiten la fabricación a gran escala de bortezomib de pureza química y estereoquímica muy elevadas. Los procesos anteriores de la técnica limitaban la escala y producían el producto con una pureza total menor. En otro aspecto más, por lo tanto, la invención proporciona una composición que comprende al menos un kilogramo de un compuesto de
- 10 fórmula (XXIV):



(XXIV)

El compuesto de fórmula (XXIV) se prepara preferiblemente de acuerdo con el proceso descrito anteriormente, y preferiblemente constituye al menos 99% p/p de la composición de acuerdo con este aspecto de la invención.

15

EJEMPLOS

Abreviaturas

BOC	<i>tert</i> -butoxicarbonilo
D.I.	desionizado
DMF	<i>N,N</i> -dimetilformamida
GC	cromatografía de gas
GC-MS	cromatografía de gas-espectrometría de masas
h	horas
HDPE	polietileno de alta densidad

HPLC	cromatografía líquida de alta resolución
LDA	diisopropilamida de litio
LOD	perdido en el secado
min	minutos
MTBE	<i>t</i> -butil metil éter
RP-HPLC	cromatografía líquida de alta resolución y de fase inversa
RPM	revoluciones por minuto
TBTU	Tetrafluoroborato de <i>O</i> -benzotriazol-1-il- <i>N,N,N',N'</i> -tetrametiluronio
THF	tetrahidrofurano

Ejemplo 1: Proceso de fabricación de trifluoroacetato-3-metilbutano-1-boronato de (1*R*)-(S)-pinanodiol 1-amonio

(1*S*)-(S)-pinanodiol 1-cloro-3-metilbutano-1-boronato

- 5
- 10
- 15
1. Se cargó 2-metilpropano-1-boronato de (S)-pinanodiol (12,0 kg, 50,8 mol) en un recipiente de reacción mantenido en una atmósfera de nitrógeno.
 2. Se cargaron *terc*-butil metil éter (53 kg) y diclorometano (22,5 kg) y la mezcla resultante se enfrió a -57°C con agitación.
 3. Se cargó diisopropilamina (6,7 kg) en otro recipiente de reacción mantenido en una atmósfera de nitrógeno.
 4. Se cargó *terc*-butil metil éter (27 kg) a la diisopropilamina y la mezcla resultante se enfrió a -10°C con agitación.
 5. Se añadió *n*-hexillitio en hexano (solución al 33,2% en peso) (17,6 kg) a la mezcla de diisopropilamina durante un periodo de 57 minutos, mientras la temperatura de reacción se mantenía de -10°C a -7°C.
 6. Esta mezcla (mezcla LDA) se agitó durante 33 minutos de -9°C a -7°C antes de usarse.
 7. Se cargó cloruro de cinc, (12,1 kg) a un tercer recipiente de reacción mantenido en una atmósfera de nitrógeno.

8. Se cargó *terc*-butil metil éter (16 kg) al cloruro de cinc y la mezcla resultante se calentó a 30°C con agitación.
9. Se añadió tetrahidrofurano (53 kg) a la suspensión de cloruro de cinc durante un periodo de 18 minutos, mientras la temperatura de reacción se mantenía de 35°C a 40°C.
10. Esta mezcla (mezcla de ZnCl_2) se agitó durante 4 horas y 28 minutos de 38°C a 39°C hasta que se usó.
11. La mezcla de LDA (de # 3 - 6) se añadió durante un periodo de 60 minutos al recipiente de reacción que contenía 2-metilpropano-1-boronato de (S)-pinanodiolboronato, mientras la temperatura de reacción se mantenía de -60°C a -55°C.
12. Se usó un aclarado de *terc*-butil metil éter (10 kg) para completar la adición.
13. La mezcla de reacción se agitó durante 20 minutos más de -59°C a -55°C.
14. La mezcla de reacción se calentó a -50°C durante un periodo de 11 minutos.
15. La mezcla de ZnCl_2 (de # 7 - 10) se añadió durante un periodo de 48 minutos al recipiente de reacción que contenía 2-metilpropano-1-boronato de (S)-pinanodiol y la mezcla de LDA, mientras la temperatura de reacción se mantenía de -50°C a -45°C.
16. Se usó un aclarado de *terc*-butil metil éter (10 kg) para completar la adición.
17. La mezcla de reacción se agitó durante 30 minutos más de -45°C a -40°C y después se calentó a 10°C durante un periodo de 81 minutos.
18. Al recipiente de reacción se le añadió una solución al 10% de ácido sulfúrico (72 kg) durante un periodo de 40 minutos, mientras la temperatura de reacción se mantenía de 10°C a 21°C.
19. La mezcla de reacción se agitó durante 16 minutos a temperatura ambiente, antes de separar la fase acuosa.

20. La fase orgánica se lavó sucesivamente con agua desionizada (D.I.) (32 kg), y una solución al 10% de cloruro sódico (26,7 kg), cada lavado implicó agitación vigorosa durante de 15 a 17 minutos a temperatura ambiente.
21. La mezcla de reacción se concentró a presión reducida ($p_{min} = 81$ mbar),
5 manteniendo una temperatura externa (camisa/baño) de 50°C a 55°C, proporcionando un residuo que se disolvió en metilciclohexano (56 kg).
22. La mezcla de reacción se calentó a reflujo (en un condensador de tipo Dean-Stark para la separación del agua) a presión reducida ($p_{min} = 67$ mbar), manteniendo una temperatura externa (camisa/baño) de 50°C a 55°C durante 2
10 horas y 7 minutos, hasta que no se separó más agua.
23. Se retiraron por destilación aproximadamente 35 l de los disolventes a presión reducida ($p_{min} = 81$ mbar), manteniendo una temperatura externa (camisa/baño) de 50°C a 55°C.
24. La mezcla de metilciclohexano seca resultante que contenía 1-cloro-3-
15 metilbutano-1-boronato de (1S)-(S)-pinanodiol se enfrió a 14°C.
- 1-Bis(trimetilsilil)amino-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol
1. Se cargó bis(trimetilsilil)amida de litio en tetrahidrofurano (solución al 19,4% en peso), (41,8 kg) en un recipiente de reacción mantenido en una atmósfera de nitrógeno y se enfrió a -19°C con agitación.
- 20 2. La mezcla de metilciclohexano que contenía 1-cloro-3-metilbutano-1-boronato de (1S)-(S)-pinanodiol se añadió durante un periodo de 55 minutos, mientras la temperatura de reacción se mantenía de -19°C a -13°C.
3. Se usó un aclarado de metilciclohexano (5 kg) para completar la adición.
4. La mezcla de reacción se agitó durante 65 minutos más de -13°C a -
25 12°C y después se calentó a 25°C durante un periodo de 25 minutos.
5. A la mezcla de reacción se le añadió una suspensión de Celite (2,5 kg) en metilciclohexano (22 kg).
6. La mezcla de reacción se concentró a presión reducida ($p_{min} = 25$ mbar), manteniendo una temperatura externa (camisa/baño) de 45°C a 50°C,
30 proporcionando un residuo que se disolvió en metilciclohexano (36 kg).

7. Después, se retiró una muestra para el ensayo en proceso para el contenido de tetrahidrofurano por GC.
8. El ensayo de tetrahidrofurano fue del 0,58%.
9. Los sólidos se retiraron por filtración y el filtrado se filtró a través de un lecho de Gel de Sílice (2,0 kg).
10. Ambas unidades de filtro se lavaron con éter isopropílico (30 kg).
11. La mezcla de metilciclohexano/éter isopropílico resultante que contenía 1-bis(trimetilsilil)amino-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol se almacenó en un contenedor a temperatura ambiente hasta que se usó en la siguiente etapa.
- Trifluoroacetato-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol-1-amonio
1. Se cargó ácido trifluoroacético (12 kg) en otro recipiente de reacción mantenido en una atmósfera de nitrógeno.
2. Se cargó éter isopropílico (78 kg) al ácido trifluoroacético y la mezcla resultante se enfrió a -10°C con agitación.
3. La mezcla de metilciclohexano/éter isopropílico que contenía 1-bis(trimetilsilil)amino-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol se añadió durante un periodo de 53 minutos provocando la precipitación del producto, mientras la temperatura de reacción se mantenía de -10°C a -5°C .
4. Se usó un aclarado de éter isopropílico (5 kg) para completar la adición.
5. La mezcla de reacción se agitó durante 8 horas y 20 minutos más de -9°C a -7°C .
6. El sólido se recogió por filtración, se lavó con éter isopropílico (70 kg) en dos porciones y se secó a presión reducida ($p_{\text{min}} = 56 \text{ mbar}$) de 41°C a 42°C durante 2 horas y 15 minutos.
7. El sólido se agitó con agua D.I. (60 kg) durante 24 minutos a temperatura ambiente, antes de que el agua D.I. se retirase por filtración.
8. El sólido se lavó con agua D. I. (12 kg).
9. Después, el sólido se secó al vacío ($p_{\text{min}} = 4 \text{ mbar}$) de 40°C a 44°C durante 9 horas y 22 minutos, tiempo después del cual la pérdida tras el secado fue del 0,51%, que satisface el requerimiento de $\leq 1\%$.

10. Después, el intermedio, 1-amonio trifluoroacetato-3-metilbutano-1-boronato de (1*R*)-(S)-pinanodiol, bruto, se empaquetó en bolsas unitarias de polietileno en bidones de polipropileno y se marcaron. El rendimiento fue del 72%.

5 Recristalización de 1-amonio trifluoroacetato-3-metilbutano-1-boronato de (1*R*)-(S)-pinanodiol, bruto

1. Se cargó 1-amonio trifluoroacetato-3-metilbutano-1-boronato de (1*R*)-(S)-pinanodiol, bruto, (13 kg) en un recipiente de reacción mantenido en una atmósfera de nitrógeno.
- 10 2. Se cargó ácido trifluoroacético (31 kg) al recipiente de reacción y la mezcla resultante se enfrió a 4°C con agitación.
3. Cuando se disolvió todo el sólido dejando una mezcla ligeramente turbia, se añadió éter isopropílico (29 kg) durante un periodo de 57 minutos, mientras la temperatura de reacción se mantenía de 2°C a 3°C.
- 15 4. Después de que se completara la adición, la mezcla se filtró a través de un filtro en un recipiente de recepción mantenido en una atmósfera de nitrógeno.
5. El reactor y el filtro se aclararon con una mezcla de ácido trifluoroacético (3,8 kg) y éter isopropílico (5 kg). El aclarado se añadió al filtrado.
- 20 6. Se añadió éter isopropílico (126 kg) durante un periodo de 15 minutos provocando la precipitación del producto, mientras la temperatura de reacción se mantenía de 16°C a 18°C.
7. La mezcla se agitó de 16°C a 18°C durante 15 min, después se enfrió a -5°C durante un periodo de 67 minutos y se agitó de -3°C a -5°C en una atmósfera de nitrógeno durante 89 minutos.
- 25 8. Después, el sólido se aisló por filtración, se lavó en dos porciones con éter isopropílico (48 kg) y se secó al vacío ($p_{\min} = 2 \text{ mbar}$) de 34°C a 40°C durante 2 horas y 55 minutos, tiempo después del cual la pérdida tras el secado fue de 0,32%, que satisface el requerimiento de $\leq 0,5\%$.

9. Después, el producto, 1-amonio-trifluoroacetato-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol, se empaquetó en bolsas dobles de polietileno en barriles de fibra y se marcaron. El rendimiento fue del 86%.

Ejemplo 2: Proceso de fabricación de anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico

N-BOC-L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol

1. En una capa fumante, un matraz de reacción de vidrio de tres bocas equipado con un registro de temperatura de cabeza Claisen y un agitador mecánico se lavó abundantemente con nitrógeno.
- 10 2. Se cargó en el matraz 1-amonio-trifluoroacetato-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol (2,0 kg).
3. Se cargó en el matraz BOC-L-fenilalanina (1,398 kg).
4. Se cargó en el matraz tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio, TBTU (1,864 kg).
- 15 5. Se cargó en el matraz diclorometano (15,8 l).
6. El motor resultante se ajustó para proporcionar agitación a 260 RPM.
7. Usando un baño de refrigeración de hielo/agua, la mezcla de reacción se enfrió a 1,0°C, manteniendo una atmósfera de nitrógeno.
8. Se cargó en un matraz de vidrio N,N-diisopropiletilamina (2,778 l) y se
- 20 transfirió a la mezcla de reacción durante un periodo de 117 minutos usando una bomba peristáltica manteniendo una intervalo de la temperatura de reacción de 0,7°C – 2,1°C. La velocidad de adición total fue de 23,7 ml/min.
9. Se usó un aclarado de diclorometano (0,2 l) del matraz en la mezcla de reacción para completar la adición.
- 25 10. La mezcla de reacción se agitó durante 35 minutos más. La temperatura al principio de este tiempo fue de 1,8°C, y de 2,5°C al final.
11. Después, se retiró una muestra para ensayo en proceso por cromatografía líquida de alta resolución y de fase inversa (RP-HPLC). Se determinó que el porcentaje de conversión era 99,3%.
- 30 12. La mezcla de reacción se transfirió en aproximadamente dos partes iguales a dos matraces evaporadores rotatorios. La mezcla de reacción se

concentró a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 29-30°C.

13. Se dividió acetato de etilo (4,0 l) en dos porciones aproximadamente iguales y se cargaron en los dos matraces evaporadores rotatorios.

5 14. Las mezclas de cada matraz se concentraron de nuevo a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 29-30°C.

15. Los residuos de cada matraz evaporador rotatorio se transfirieron después al matraz de reacción usando acetato de etilo (13,34 l).

10 16. En un matraz de vidrio equipado con un agitador, se preparó una solución acuosa al 1% de ácido fosfórico mezclando agua D. I. (13,18 l) y ácido fosfórico (0,180 kg).

17. En un matraz de vidrio equipado con un agitador, se preparó una solución acuosa al 2% de carbonato potásico (12,0 l) mezclando agua D. I. (11,76 l) y carbonato potásico (0,24 kg).

18. En un matraz de vidrio equipado con un agitador, se preparó una solución acuosa al 10% de cloruro sódico (13,34 l) mezclando agua D. I. (13,34 l) y cloruro sódico (1,334 kg).

19. Se cargó en el matraz de reacción agua D. I. (13,34 l) que contenía la solución de acetato de etilo y la mezcla se agitó a 380 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió al vacío a un matraz adecuado y se desechó.

20. De nuevo, se cargó agua D. I. (13,34 l) en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 385 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió al vacío a un matraz adecuado y se desechó.

21. La solución al 1% de ácido fosfórico preparada en la Etapa 16 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 365 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa ácida (capa del fondo) se transfirió a un matraz adecuado y se desechó.

22. La solución al 2% de carbonato potásico preparada en la Etapa 17 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 367 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa básica (capa del fondo) se transfirió a un matraz adecuado y se desechó.
5
 23. La solución al 10% de cloruro sódico preparada en la Etapa 18 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 373 RPM durante 6 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió a un matraz adecuado y se desechó.
10
 24. La solución de acetato de etilo se transfirió a un matraz evaporador rotatorio y se concentró a presión reducida usando un evaporador rotatorio, manteniendo una temperatura del baño de 29-30°C, para proporcionar un residuo.
 - 15 25. Después, el residuo se disolvió de nuevo en acetato de etilo (4,68 l).
 26. La solución se concentró al vacío usando un evaporador rotatorio, manteniendo una temperatura del baño de 29-30°C, para proporcionar de nuevo un residuo.
 27. De nuevo, el residuo se redisolvió después en acetato de etilo (4,68 l) y se tomaron muestras para la determinación del contenido del agua por titulación de Karl Fisher. El contenido del agua de las dos muestras se determinó como 0,216% y 0,207%.
20
 28. Usando una cantidad más de acetato de etilo (12,66 l), la mezcla se transfirió del matraz evaporador rotatorio a un matraz de reacción seco equipado con un registro de temperatura, un agitador mecánico y un tubo de dispersión de gas vitrificado, y se purgó con nitrógeno.
25
- L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol, sal HCl
1. La solución de acetato de etilo que contenía N-BOC-L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol se enfrió usando un baño de refrigeración de hielo/agua a -0,9°C.
30

2. Se burbujeó gas cloruro de hidrógeno (1,115 kg) en la mezcla de reacción durante un periodo de 1,48 horas. La temperatura al principio de la adición fue de $-0,9^{\circ}\text{C}$, y de $6,8^{\circ}\text{C}$ al final.
3. Después, la reacción se dejó calentar a $14,4^{\circ}\text{C}$ durante 50 minutos, mientras se mantenía una atmósfera de nitrógeno.
4. Se retiró una muestra para el ensayo en proceso por RP-HPLC. El porcentaje de conversión fue de 68,9% (% de área).
5. La reacción se agitó durante 35 minutos. La temperatura al principio fue de 14°C y de $14,8^{\circ}\text{C}$ al final.
- 10 6. Se retiró una muestra para el ensayo en proceso por RP-HPLC. El porcentaje de conversión fue de 94,7% (% de área).
7. La reacción se agitó durante aproximadamente 50 minutos más, manteniendo una temperatura de $10^{\circ}\text{C} \pm 5^{\circ}\text{C}$.
8. Se retiró una muestra para el ensayo en proceso por RP-HPLC. El porcentaje de conversión fue de 97,3%.
- 15 9. La reacción se agitó durante aproximadamente 50 minutos más, manteniendo una temperatura de $10^{\circ}\text{C} \pm 5^{\circ}\text{C}$. La temperatura final fue de $14,6^{\circ}\text{C}$.
10. Se retiró una muestra para el ensayo en proceso por RP-HPLC. El tiempo de reacción total después de la adición de gas cloruro de hidrógeno fue de cuatro (4) horas.
- 20 11. El porcentaje de conversión fue de 99%.
12. Se observó una suspensión.
13. Se cargó n-heptano (8,8 l) en la mezcla de reacción.
- 25 14. La suspensión se agitó durante 2 horas. La temperatura al principio del tiempo de agitación fue de $12,7^{\circ}\text{C}$, y de $15,3^{\circ}\text{C}$ al final.
15. El sólido se aisló por filtración sobre un embudo Buchner revestido con una capa de papel filtro de polipropileno.
16. El sólido se lavó con n-heptano (4,68 l).
- 30 17. En una tapa, el sólido se transfirió a tres bandejas secantes de no más de 1" de profundidad y se secó al aire durante 1 hora.

18. Después, el sólido se secó a $\leq 35^{\circ}\text{C}$ a un vacío de 27" de Hg durante 16 horas y 28 minutos en un horno de vacío equipado con un calibre de vacío y registro de temperatura.
19. El sólido se muestreó de cada bandeja secante para determinar el % de pérdida tras el secado. Se determinó que el LOD era de 0%, 0,02%, y 0,02% para las tres muestras tomadas.
20. Después, se empaquetó L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-Pinanodiol, sal HCl en bolsas poli dobles en bidones de fibra y se marcaron y se muestrearon.
- 10 21. El rendimiento aislado fue de 1,87 kg, 79,1%. El intermedio se almacenó a $2-8^{\circ}\text{C}$ hasta que se usó en la fabricación adicional.
- N-(2-Pirazinacarbonil)-L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol
1. En una capa fumante se lavó abundantemente con nitrógeno un matraz de reacción de vidrio de tres bocas equipado con una cabeza Claisen, registro de temperatura y un agitador mecánico.
- 15 2. Se cargó L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol, sal HCl (1,85 kg) en el matraz.
3. Se cargó ácido 2-pirazinacarboxílico (0,564 kg) en el matraz.
- 20 4. Se cargó tetrafluorofosfato de 2-(H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio tetrafluoroborato, TBTU (1,460 kg) en el matraz.
5. Se cargó diclorometano (18,13 l) en el matraz.
6. El motor de agitación se ajustó para proporcionar agitación a 272 RPM.
7. Usando un baño de refrigeración, la mezcla de reacción se enfrió a -
- 25 $1,2^{\circ}\text{C}$.
8. Se cargó N,N-diisopropiletilamina (1,865 kg) en un matraz de vidrio y se transfirió a la reacción durante un período de 50 minutos usando una bomba peristáltica manteniendo un intervalo de temperatura de reacción de $-1,2^{\circ}\text{C}$ a $2,8^{\circ}\text{C}$.
- 30 9. Se usó un aclarado de diclorometano (0,37 l) del matraz en la mezcla de reacción para completar la adición.

10. La mezcla de reacción se dejó calentar y se agito durante 81 minutos más.
11. La temperatura al principio del tiempo de agitación fue de 15°C, y de 24,9°C al final.
- 5 12. Después, se retiró una muestra para el ensayo en proceso por RP-HPLC. Se determinó que el porcentaje de conversión era 99,9%.
13. La mezcla de reacción se transfirió en aproximadamente dos mitades iguales a dos matraces evaporadores rotatorios. La mezcla de reacción se concentró a presión reducida usando dos evaporadores rotatorios,
- 10 manteniendo una temperatura externa del baño de 33-34°C.
14. Se dividió acetato de etilo (12,95 l) en dos porciones aproximadamente iguales y se cargó en los dos matraces evaporadores rotatorios.
15. Después, las mezclas de cada matraz se concentraron a presión reducida usando un evaporador rotatorio, manteniendo una temperatura
- 15 externa del baño de 33-34°C.
16. Después, los residuos de cada matraz evaporador rotatorio se transfirieron al matraz de reacción usando acetato de etilo (12,95 l).
17. En un matraz de vidrio equipado con un agitador, se preparó una solución acuosa al 1% de ácido fosfórico (12,34 l) mezclando agua D. I. (12,19
- 20 l) y ácido fosfórico (0,148 kg).
18. En un matraz de vidrio equipado con un agitador, se preparó una solución acuosa al 2% de carbonato potásico (12,34 l) mezclando agua D. I. (12,09 l) y carbonato potásico (0,247 kg).
19. En un matraz de vidrio equipado con un agitador, se preparó una
- 25 solución acuosa al 10% de cloruro sódico (12,34 l) mezclando agua D. I. (12,34 l) y cloruro sódico (1,234 kg).
20. agua D. I. (12,34 l) se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 382 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió a
- 30 un matraz adecuado y se desechó.

21. De nuevo, se cargó agua D. I. (12,34 l) en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 398 RPM durante 7 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió a un matraz adecuado y se desechó.
- 5 22. La solución al 1% de ácido fosfórico preparada en la Etapa 17 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 364 RPM durante 8 minutos. Las fases se dejaron separar y la fase acuosa ácida (capa del fondo) se transfirió a un matraz adecuado y se desechó.
- 10 23. La solución al 2% de carbonato potásico preparada en la Etapa 18 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 367 RPM durante 8 minutos. Las fases se dejaron separar y la fase acuosa básica (capa del fondo) se transfirió a un matraz adecuado y se desechó.
- 15 24. La solución al 10% de cloruro sódico preparada en la Etapa 19 se cargó en el matraz de reacción que contenía la solución de acetato de etilo y la mezcla se agitó a 374 RPM durante 8 minutos. Las fases se dejaron separar y la fase acuosa (capa del fondo) se transfirió a un matraz adecuado y se desechó.
- 20 25. La solución de acetato de etilo se transfirió al vacío en aproximadamente dos mitades iguales a los dos matraces evaporadores rotatorios y se concentró a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 34°C.
- 25 26. Se dividió n-heptano (14,8 l) en dos porciones aproximadamente iguales y se cargó en los dos matraces evaporadores rotatorios. Después, las mezclas de cada matraz se concentraron a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 34°C.
- Anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico, bruto
1. En un matraz de vidrio equipado con un agitador, se preparó una
- 30 solución 1 N de ácido clorhídrico (22,2 l) mezclando agua D. I. (20,36 l) y ácido clorhídrico (1,84 kg).

2. En un matraz de vidrio equipado con un agitador, se preparó una solución 2 N de hidróxido sódico (12,03 l) mezclando agua D. l. (12,03 l) e hidróxido sódico (0,962 kg).
3. Después, los residuos que contenían N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol en cada matraz evaporador rotatorio se transfirieron a un matraz de reacción de vidrio de tres bocas equipado con un registro de temperatura y un agitador mecánico, usando n-heptano (14,8 l) y metanol (14,8 l).
4. El motor de agitación se ajustó para proporcionar agitación a 284 RPM.
- 10 5. Se cargó ácido 2-metilpropanobórico (0,672 kg) en el matraz.
6. Se cargó ácido clorhídrico 1 N preparado en la Etapa 1 (11,2 l) en el matraz.
7. El motor de agitación se ajustó para proporcionar agitación a 326 RPM.
8. La mezcla de reacción se agitó durante 16,38 horas. La temperatura del lote de partida fue de 28,6°C, y la temperatura final del lote fue de 21,6°C.
- 15 9. Después, se retiró una muestra para el ensayo en proceso por RP-HPLC.
10. Se determinó que el porcentaje de conversión era 100%.
11. La agitación se interrumpió y la mezcla bifásica se dejó separar.
- 20 12. La fase de n-heptano (capa superior) se transfirió a un matraz adecuado y se desechó.
13. Se cargó n-heptano (5,37 l) en el matraz de reacción y la mezcla se agitó a 381 RPM durante 6 minutos. Las fases se dejaron separar y la fase de n-heptano (capa superior) se transfirió a un matraz adecuado y se desechó.
- 25 14. De nuevo, se cargó n-heptano (5,37 l) en el matraz de reacción y la mezcla se agitó a 340 RPM durante 6 minutos. Las fases se dejaron separar y la fase de n-heptano (capa superior) se transfirió a un matraz adecuado y se desechó.
- 30 15. La solución acuosa de metanol se transfirió en aproximadamente dos mitades iguales a los dos matraces evaporadores rotatorios y se concentró a

- presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 33-34°C. Se recogieron 15 l de metanol.
16. Se usó diclorometano (5,37 l) para transferir el residuo de los matraces evaporadores rotatorios al matraz de reacción.
- 5 17. Se cargó hidróxido sódico 2 N (11,2 l) preparado en la Etapa 2 en el matraz.
18. La fase de diclorometano (capa inferior) se transfirió a un matraz adecuado y se desechó.
19. Se cargó diclorometano (5,37 l) en el matraz y la mezcla se agitó a 374
- 10 RPM durante 6 minutos. Las fases se dejaron separar y la fase de diclorometano (capa inferior) se transfirió a un matraz adecuado y se desechó.
20. De nuevo, se cargó diclorometano (5,37 l) en el matraz y la mezcla se agitó a 368 RPM durante 8 minutos. Las fases se dejaron separar y la fase de diclorometano (capa inferior) se transfirió a un matraz adecuado y se desechó.
- 15 21. Se cargó diclorometano (5,37 l) en el matraz.
22. Se cargó ácido clorhídrico 1 N (10,7 l) en el matraz con agitación. Se determinó que el pH de la fase acuosa era 6.
23. La agitación fue discontinua y las fases se dejaron separar.
24. La fase de diclorometano (capa inferior) se transfirió al vacío a un matraz
- 20 receptor de vidrio.
25. Se cargó diclorometano (5,37 l) en el matraz y la mezcla se agitó a 330 RPM durante 6 minutos. Las fases se dejaron separar y la fase de diclorometano (capa inferior) se transfirió a un matraz receptor de vidrio.
26. De nuevo, se cargó diclorometano, (5,37 l) en el matraz y la mezcla se
- 25 agitó a 335 RPM durante 6 minutos. Las fases se dejaron separar y la fase de diclorometano (capa inferior) se transfirió a un matraz receptor de vidrio.
27. Los extractos de diclorometano se combinaron y se transfirieron en aproximadamente dos mitades iguales a los dos matraces evaporadores rotatorios y se concentró a presión reducida usando un evaporador rotatorio,
- 30 manteniendo una temperatura externa del baño de 33-34°C.

28. Se dividió acetato de etilo (12,95 l) en dos porciones aproximadamente iguales y se cargó en los dos matraces evaporadores rotatorios. Después, las mezclas de cada matraz se concentraron a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 45-46°C.
29. De nuevo, se dividió acetato de etilo (12,95 l) en dos porciones aproximadamente iguales y se cargó en los dos matraces evaporadores rotatorios. Después, las mezclas de cada matraz se concentraron a presión reducida usando un evaporador rotatorio, manteniendo una temperatura externa del baño de 45-46°C, hasta que quedó aproximadamente un 10% de del volumen original.
30. Se dividió n-heptano (10,2 l) en dos porciones aproximadamente iguales y se cargó en los dos matraces evaporadores rotatorios, y la suspensión se agitó en una atmósfera de nitrógeno durante 2,67 horas a 22-23°C.
31. El sólido se aisló por filtración en un embudo Buchner, revestido con una capa de papel de filtro de polipropileno.
32. El sólido se lavó con n-heptano (2,96 l).
33. En una tapa, el sólido se transfirió a cuatro bandejas secantes y se secó al aire durante 1,25 horas.
34. Después, el sólido se secó a 36 - 50°C a un vacío de 27" de Hg durante 18 horas y 27 minutos en un homo de vacío equipado con un calibre de vacío y un registro de temperatura.
35. El sólido se muestreó de cada bandeja para determinar el % de pérdida de secado (LOD). Se determinó que el LOD era 0,38%, 0,62%, 0,71%, y 0,63% en las cuatro muestras tomadas.
36. Se empaquetó anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico, bruto, en dos botellas de 5 l, HDPE, sin manipular y de boca ancha y se marcaron.
37. El rendimiento aislado fue de 1,314 kg, 83%.

Recristalización de anhídrido N-(2-Pirazinacarbonil)-L-fenilalanina-L-leucina bórico-anhídrido, bruto

1. En una tapa, se lavó abundantemente con nitrógeno un matraz de reacción de vidrio equipado con un agitador mecánico, un condensador de reflujo y un registro de temperatura.
2. se cargó acetato de etilo (21 l) en el matraz.
3. El acetato de etilo se calentó a 66,8°C en una atmósfera de nitrógeno, usando un baño caliente del agua/vapor.
4. Se cargó lentamente anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico anhídrido, bruto (1,311 kg) en el matraz de reacción. Ocurrió un cambio durante un periodo de 3 minutos.
5. La mezcla se agitó durante 1 minuto hasta que se disolvió todo el sólido. La temperatura de la solución fue de 64°C.
6. La fuente de calor se retiró y la mezcla se enfrió lentamente a 60°C usando un baño frío.
7. La solución de acetato de etilo caliente se transfirió en un matraz receptor mediante múltiples tuberías y una cápsula de filtro en línea de polietileno usando una bomba peristáltica.
8. La mezcla se dejó enfriar a 27,2°C y se dejó en reposo en una atmósfera de nitrógeno sin agitación, durante 17,75 horas. La temperatura final registrada fue de 20,5°C.
9. La mezcla se enfrió usando un baño de hielo/agua con agitación durante 2,33 horas. La temperatura al principio del tiempo de agitación fue de 3,8°C y de -2,8°C al final.
10. El sólido se aisló por filtración en un embudo Buchner revestido con una capa de papel de filtro de polipropileno. El filtrado se recogió en un matraz de recolección.
11. El sólido se lavó con acetato de etilo (2,62 l) y se enfrió a 4,7°C.
12. En una tapa, el sólido se transfirió a dos bandejas secantes.

13. Después, el sólido se secó a 51-65°C a un vacío de 27" de Hg durante 19 horas y 10 minutos en un horno de vacío equipado con un calibre de vacío y un registro de temperatura.
14. El sólido se muestreó para determinar el % de pérdida tras el secado (LOD). Se determinó que el LOD era 0,65% y 0,62% para las dos muestras tomadas.
15. Se empaquetó anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico en cuatro botellas de boca ancha ámbar de 3 l, Tipo 3, con Tapas Revestidas con Teflón y se marcaron.
- 10 16. El rendimiento aislado fue de 1,132 kg, 86,3%.
17. Se almacenó anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico anhídrido de -25 a -15°C.

Ejemplo 3: Síntesis convergente de anhídrido N-(2-Pirazinacarbonil)-L-fenilalanina-L-leucina-bórico

15 N-(2-Pirazinacarbonil)-L-fenilalanina-L-leucina-boronato de (1S,2S,3R,5S)-pinanodiol

- Una solución de 1-amonio-trifluoroacetato-3-metilbutano-1-boronato de (1R)-(S)-pinanodiol (13,97 g) y N-hidroxisuccinimida (6,23 g) en 66 ml de DMF se enfrió a -5°C, seguido de la adición de dicitclohexilcarbodiimida (10,83 g). La
- 20 suspensión resultante se agitó durante una hora a una temperatura de -5 a 0°C. A una solución de N-(2-pirazina-carbonil)-L-fenilalanina (19,52 g; preparada por acoplamiento del éster de succinimida preformado de ácido pirazinacarboxílico con L-fenilalanina en dioxano-agua) en 62 ml de DMF se le añadió N-metilmorfolina (5,7 ml) a una temperatura de 0°C, y la solución
- 25 resultante se añadió a la suspensión. La suspensión se ajustó a pH 7 mediante la adición de 5,7 ml más de N-metilmorfolina y se agitó durante una noche, aumentando lentamente la temperatura a 21°C. Después de la filtración, la torta de filtro se lavó dos veces con MTBE y los filtrados combinados se diluyeron con 950 ml de MTBE. La fase orgánica se lavó con ácido cítrico acuoso al 20%
- 30 (3 x 150 ml), NaHCO₃ acuoso al 20% (3 x 150 ml) y salmuera (2 x). La fase orgánica se secó sobre Na₂SO₄, se filtró y se concentró, produciendo 25,5 g

(95,5%) del compuesto del título en forma de una espuma. Como se indicó por tic, este material contenía algunas impurezas menores, incluyendo aproximadamente 2% de ciclohexilurea.

Anhídrido de N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico

- 5 Una solución de N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-boronoato de (1S,2S,3R,5S)-pinanodiol (25,2 g) en 207 ml de MeOH y 190 ml de hexano se enfrió a 15°C, y se le añadieron en porciones 109,4 ml de HCl 1 N, manteniendo la temperatura entre 15 y 25°C. Después, se añadió ácido 2-metilpropanobórico (8,67 g) con agitación vigorosa, y la agitación de la mezcla
- 10 bifásica se continuó durante una noche. Después de la separación de las dos fases, la fase inferior se extrajo una vez con 75 ml de hexano. Después, la fase inferior se concentró al vacío hasta que se hizo turbia, seguido de la adición de 109,4 ml de NaOH 2 N y 100 ml de Et₂O. Las dos fases se separaron y la fase inferior se extrajo con Et₂O (4 x 100 ml cada vez) y después se llevó a pH 6,0
- 15 mediante la adición de 109 ml de HCl 1 N. Después de la extracción con 100 ml de acetato de etilo, la fase inferior se ajustó a pH 6,0 con HCl 1 N y se extrajo una vez más con 75 ml de acetato de etilo. Las fases de acetato de etilo combinadas se lavaron con salmuera semi-saturada (2 x 25 ml) y salmuera (2 x 25 ml), se secaron sobre Na₂SO₄, se filtraron y se concentraron para producir
- 20 15,3 g (81,8%) de anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico bruto en forma de una espuma. El material bruto se disolvió en 150 ml de acetato de etilo y se concentró al vacío hasta una suspensión, seguido de la adición de 150 ml de MTBE. La suspensión se almacenó entre 2 y 8°C durante una noche, se filtró, se lavó dos veces con MTBE y se secó a alto vacío, produciendo 10,69 g (57,2%) de anhídrido N-(2-pirazina-carbonil)-L-
- 25 fenilalanina-L-leucina-bórico en forma de un sólido blanco.

Ejemplo 4: Medición de la Relación Diastereomérica de 1-amoniotrifluoroacetato-3-metilbutano-1-boronoato de (1R)-(1S,2S,3R,5S)-pinanodiol

La pureza diastereomérica de 1-amoniotrifluoroacetato-3-metilbutano-1-boronato de (1*R*)-(1*S*,2*S*,3*R*,5*S*)-pinanodiol (compuesto 1) se determinó por cromatografía de gas no quiral (GC).

Productos Acetonitrilo (p.a. Bruker o equivalente)

Químicos:

Tetradecano (patrón interno) (Fluka puriss. o equivalente)

Anhídrido trifluoroacético (TFAA) (p.a. Merck o equivalente)

Instrumental: sistema Trace-GC 2000 o equivalente

Fase móvil: H₂

Disolvente A (con patrón interno) Aproximadamente 300 mg de tetradecano se pesaron con una exactitud de 0,1 mg en un matraz volumétrico de 100 ml. Se añadieron 1,5 ml de TFAA y el matraz se llevó a volumen con acetonitrilo.

Preparación de la muestra: Se pesaron de forma exacta aproximadamente 150 mg de la muestra (dentro de 0,1 mg) en un matraz volumétrico de 10 ml. El matraz se llevó a volumen con el Disolvente A. La solución se almacenó durante 15 minutos antes de la inyección.

Parámetros de GC:

Columna: película Rtx-200; 105 m x 0,25 mm d.i. x 0,25 µm

Fase móvil: H₂

Programa de Temp.: 130°C (0,5 min); de 0,5°C/min a 200°C (0 min); de 30°C/min a 300°C (2 min)

Flujo: 0,9 ml/min (flujo const.)

Temperatura del inyector: 250°C

Temperatura del detector: 250°C (FID)

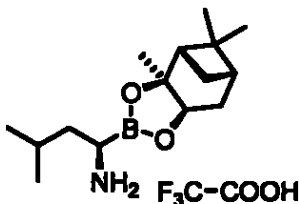
Filtro:

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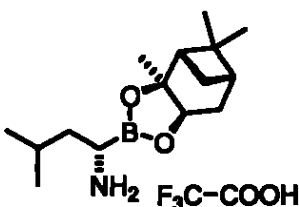
Volumen Inyectable: 1 μ l

Sustancias

Compuesto 1 1-amoniotrifluoroacetato-3-metilbutano-1-boronato de (1R)-(1S,2S,3R,5S)-pinanodiol



Compuesto 2 1-amoniotrifluoroacetato-3-metilbutano-1-boronato de (1S)-(1S,2S,3R,5S)-pinanodiol



Estabilidad de la solución

Se preparó una solución madre del compuesto 1 pesando 150,13 mg del compuesto 1 en un matraz volumétrico de 10 ml y llevándolo a volumen con el Disolvente A. La estabilidad de esta solución se ensayo a temperatura ambiente durante 48 horas. La solución madre se rellenó en 6 viales de GC separados. Las inyecciones en el sistema GC se realizaron desde estos viales después de 0, 12, 24, 48 y 72 horas (doble inyección de cada vial. Se determinó el % de área del compuesto 1 y el compuesto 2. No se observaron cambios en el % de área, indicando que la solución es estable durante 72 horas a temperatura ambiente.

Especificidad

Se disolvieron aproximadamente 150 mg de una muestra que comprendía el compuesto 1 y el compuesto 2 en el Disolvente A y se inyectaron en el sistema cromatográfico GC. El pico para el compuesto 1 se separó bien del pico para el compuesto 2. La comprobación de la pureza del pico por GC-EM mostró que no co-eluían otros componentes con el compuesto 1 o el compuesto 2.

Límite de detección

El límite de detección (LOD) se definió como la concentración en la que la señal del compuesto 1 mostraba una señal a relación de ruido de al menos 3:1. Se realizó una medición en blanco anterior para mostrar que no interferían otros picos. La señal a relación de ruido se calculó mediante la ecuación:

$$S / N = \frac{H(signal)}{H(baseline)}$$

- S/N = señal a relación de ruido
- 10 H (señal) = altura de la señal para el compuesto 1 [mm]
- H (referencia) = altura de la señal de referencia [mm]

Se inyectó una concentración de muestra de 0,05% de la concentración de la muestra de ensayo convencional y mostró una señal de relación de ruido de 4,3. Por lo tanto, el límite de detección es 0,0075 mg/ml.

15 **Límite de cuantificación**

El límite de cuantificación (LOQ) se definió como la concentración en la que la señal del compuesto 1 mostraba una señal de relación de ruido de al menos 10:1. La señal de relación de ruido se calculó como se ha descrito anteriormente. Se inyectó una concentración de muestra de 0,1% de la concentración de muestra convencional y mostró una señal de relación de ruido de 10,1. Por lo tanto, el límite de cuantificación es 0,015 mg/ml.

Ejemplo 5: Ensayo de Pureza para anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico

La pureza de anhídrido N-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico (compuesto 3) se ensayó por HPLC de fase inversa.

- Reactivos:**
- Agua, calidad de HPLC
 - Acetonitrilo, calidad de HPLC
 - Ácido fórmico, calidad de ACS, puro ≥98%
 - Peróxido de hidrógeno al 3%, calidad de ACS o equivalente

11.4
124

Instrumental

Cromatografía líquida de alta resolución Automuestreador capaz de liberar inyecciones de 20 µl y manteniendo una temperatura de 5°C
Bomba capaz de liberar el gradiente a 1,0 ml/min.
Detector UV capaz de controlar las aguas residuales a 270 nm

Columna columna cromatográfica de Symmetry C18, 250 mm x 4,6 mm ID, 5 µm, Waters, N° de cat. WAT054275.

Preparación de la muestra: Se pesaron con exactitud aproximadamente 50 mg del compuesto 3 en un matraz volumétrico de 50 ml. Se añadió Fase Móvil B (5 ml) y la mezcla se sonicó para disolver el compuesto 3 (aproximadamente 30-60 segundos). La solución se dejó alcanzar la temperatura ambiente, se diluyó a volumen con Fase Móvil A y se mezcló bien. Cada muestra se preparó por duplicado y fue estable durante 7 días, cuando se almacenó a 2-8°C protegida de la luz.

Parámetros de HPLC:

Fase móvil A: acetonitrilo/agua/ácido fórmico, 30:70:0,1 (v/v/v), desgasificado

Fase móvil B: acetonitrilo/agua/ácido fórmico, 80:20:0,1 (v/v/v), desgasificado

Caudal: 1,0 ml/min

Detector: UV a 270 nm

Volumen de inyección: 20 µl

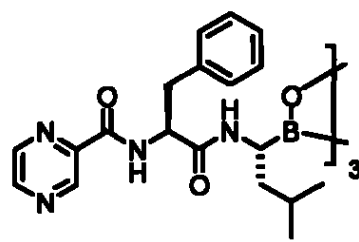
Temp. de columna: ambiente

Temp. de Bandeja de muestra: 5°C

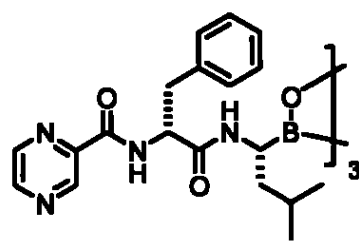
Programa gradiente:	Tiempo	%A	%B
	0	100	0
	15	100	0
	30	0	100
	45	0	100
	47	100	0
	55	100	0

Sustancias

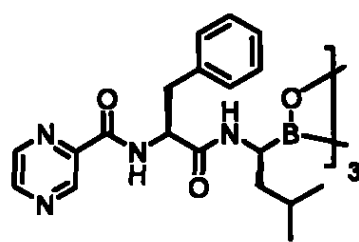
Compuesto 3 Anhídrido *N*-(2-pirazina-carbonil)-L-fenilalanina-L-leucina-bórico anhídrido



Compuesto 4 Anhídrido *N*-(2-pirazina-carbonil)-L-fenilalanina-D-leucina-bórico



Compuesto 5 Anhídrido *N*-(2-pirazina-carbonil)-L-fenilalanina-D-leucina-bórico



El tiempo de reacción del compuesto 3 estuvo típicamente entre 10 y 14 minutos cuando se usó un sistema de HPLC con un volumen de 1,3 minutos.

Los compuestos 4 y 5 co-eluyeron al tiempo de retención más largo, con una resolución de $\geq 2,0$.

La retención relativa del compuesto 3 en un cromatograma de muestra con respecto al cromatograma patrón se calculó de acuerdo con la siguiente ecuación:

5

$$R_r = \frac{t_{mues}}{t_{std}}$$

Donde:

R_r = retención relativa

t_{mues} = tiempo de retención del pico del compuesto 3 en el cromatograma de muestra, minutos

10

t_{std} = tiempo de retención del pico de sustancia fármaco en el cromatograma convencional anterior más próximo, minutos

Los resultados del ensayo se calcularon para cada muestra de acuerdo con la siguiente ecuación:

15

$$\%ensayo = \frac{A_{mues}}{A_{std}} \times \frac{W_{std} \times P}{W_{mues}} \times \frac{1}{\left(\frac{100 - M}{100}\right)} \times 100$$

Donde:

A_{mues} = respuesta de área de pico del compuesto 3 en la preparación de la muestra

A_{std} = respuesta al área de pico principal del compuesto 3 en la preparación de tratamiento estándar

20

W_{std} = peso del patrón, mg

P = pureza asignada del patrón (formato decimal)

W_{mues} = peso de la muestra, mg

M = contenido de humedad de la muestra, %

25

100 = conversión a porcentaje

La retención relativa y los niveles de impureza de cada muestra se calcularon de acuerdo con las siguientes ecuaciones:

HF

127

$$R_r = \frac{t_i}{t_{ds}}$$

Donde:

- R_r = retención relativa
- t_i = tiempo de retención de la impureza individual
- 5 t_{ds} = tiempo de retención del pico del compuesto 3

$$\%I_i = \frac{A_i \times W_{std} \times P \times DF \times RF_i}{A_{std,1\%} \times W_{muestra}} \times 100$$

Donde:

- I_i = impureza individual
- A_i = respuesta al área de pico de la impureza individual en la
- 10 preparación de la muestra
- $A_{std,1\%}$ = respuesta de pico media del compuesto 3 en la preparación convencional al 1%
- W_{std} = peso de patrón, mg
- $W_{muestra}$ = peso de la muestra, mg
- 15 P = pureza asignada del patrón (formato decimal)
- DF = factor de dilución, 1/100
- RF_i = factor de respuesta relativo de la impureza individual
- 100 = conversión al factor de porcentaje

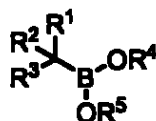
20 Cuando se ensayó mediante este método, el anhídrido *N*-(2-pirazina-carbonil)-*L*-fenilalanina-*L*-leucinabórico del Ejemplo 2 mostró impurezas totales de menos del 1%.

Aunque la invención anterior se ha descrito con detalle para propósitos de claridad y entendimiento, estas realizaciones particulares deben considerarse como ilustrativas y no restrictivas. Un especialista en la técnica apreciará, a partir de una lectura de esta descripción, que pueden hacerse

25 diversos cambios en la forma y detalle sin apartarse del verdadero alcance de la invención y de las reivindicaciones adjuntas.

REIVINDICACIONES

1. 1. Un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



5

(I)

en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

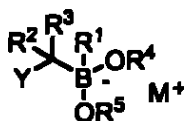
10 R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

15 cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S;

comprendiendo dicho proceso las etapas:

(a) proporcionar un complejo boronato de fórmula (II):



20

(II)

en la que

Y es un grupo nucleóforo;

M^+ es un catión; y

cada uno de R^1 a R^5 es como se ha definido anteriormente; y

25

(b) poner en contacto el complejo boronato de fórmula (II) con un ácido de Lewis en condiciones que produzcan el compuesto de éster bórico de

fórmula (I), realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

- (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o
- 5 (ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación.

2. El proceso de la reivindicación 1, donde la mezcla de reacción comprende un co-disolvente de coordinación.

10

3. El proceso de la reivindicación 2, donde el co-disolvente de coordinación se selecciona entre el grupo compuesto por tetrahidrofurano, dioxano, agua, y mezclas de los mismos.

15 4. El proceso de la reivindicación 0, donde el co-disolvente de coordinación no constituye más de aproximadamente 20% v/v de la mezcla de reacción.

5. El proceso de la reivindicación 0, donde el co-disolvente de coordinación no constituye más de aproximadamente el 15% v/v de la mezcla de reacción.

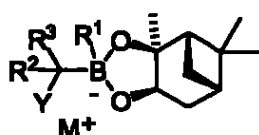
20

6. El proceso de la reivindicación 1, donde la solubilidad del agua en el disolvente de éter que tiene una baja miscibilidad con agua es menor de aproximadamente el 2% p/p.

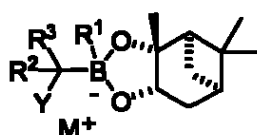
25 7. El proceso de la reivindicación 0, donde el disolvente de éter que tiene una baja miscibilidad con agua se selecciona entre el grupo compuesto por *terc*-butil metil éter, *terc*-butil etil éter, *terc*-amil metil éter, éter isopropílico, y mezclas de los mismos.

8. El proceso de la reivindicación 0, donde el disolvente de éter que tiene una baja miscibilidad con agua constituye al menos aproximadamente el 70% v/v de la mezcla de reacción.
- 5 9. El proceso de la reivindicación 1, donde al menos aproximadamente 5 moles del complejo boron"ato" de fórmula (II) se proporcionan en la etapa (a).
10. El proceso de la reivindicación 1, donde al menos aproximadamente 20 moles del complejo boron"ato" de fórmula (II) se proporcionan en la etapa (a).
- 10 11. El proceso de la reivindicación 1, donde al menos aproximadamente 50 moles del complejo boron"ato" de fórmula (II) se proporcionan en la etapa (a).
- 15 12. El proceso de la reivindicación 1, donde al menos aproximadamente 100 moles del complejo boron"ato" de fórmula (II) se proporcionan en la etapa (a).
- 20 13. El proceso de la reivindicación 1, donde el ácido de Lewis se selecciona entre el grupo compuesto por cloruro de zinc, bromuro de zinc, cloruro férrico, y bromuro férrico.
14. El proceso de la reivindicación 0, donde el ácido de Lewis es húmedo.
15. El proceso de la reivindicación 0, donde en la etapa (a) el complejo boron"ato" de fórmula (II) se proporciona en una solución que comprende un disolvente de éter que tiene una baja miscibilidad con agua, y la etapa de contacto (b) comprende las etapas:
- 25 (i) proporcionar una solución que comprende un ácido de Lewis y tetrahidrofurano; y
- (ii) añadir la solución de ácido de Lewis a la solución del complejo boron"ato" de fórmula (II) de la etapa (a).
- 30

16. El proceso de la reivindicación 0, donde en la etapa (a) el complejo boron"ato" de fórmula (II) se proporciona en una solución que comprende un disolvente de éter que tiene una baja miscibilidad con agua, y la etapa de contacto (b) comprende las etapas:
- 5 (i) proporcionar una solución que comprende un ácido de Lewis y agua; y
- (ii) añadir la solución de ácido de Lewis a la solución del complejo boron"ato" de fórmula (II) de la etapa (a).
- 10 17. El proceso de la reivindicación 1, donde Y es un halógeno.
18. El proceso de la reivindicación 1, donde Y es cloro.
19. El proceso de la reivindicación 1, donde R¹ es alifático C₁₋₈, arilo C₆₋₁₀, o
- 15 (aril C₆₋₁₀)(alifático C₁₋₈).
20. El proceso de la reivindicación 1, donde M⁺ se selecciona entre el grupo compuesto por Li⁺, Na⁺, y K⁺.
- 20 21. El proceso de la reivindicación 1, donde R⁴ y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 miembros opcionalmente sustituido.
22. El proceso de la reivindicación 0, donde R⁴ y R⁵ juntos son un resto
- 25 quiral.
23. El proceso de la reivindicación 0, donde el complejo boron"ato" de fórmula (II) es:



o



24. El proceso de la reivindicación 0, donde la etapa (b) proporciona el compuesto de éster bórico de fórmula (I) donde el átomo de carbono que lleva R^1 , R^2 , y R^3 es un centro quiral que tiene una proporción diastereomérica de al menos aproximadamente 96:4 con respecto a un centro quiral en el resto quiral R^4 - R^5 .

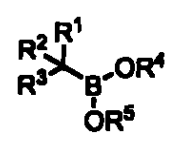
25. El proceso de la reivindicación 0, donde la etapa (b) proporciona el compuesto de éster bórico de fórmula (I) donde el átomo de carbono que lleva R^1 , R^2 , y R^3 es un centro quiral que tiene una proporción diastereomérica de al menos aproximadamente 97:3 con respecto a un centro quiral en el resto quiral R^4 - R^5 .

26. El proceso de la reivindicación 0, caracterizado al menos por una de las siguientes características:

- (a) la etapa de contacto (b) se realiza en una mezcla de reacción que comprende *tert*-butil metil éter;
- (b) el ácido de Lewis es cloruro de zinc;
- (c) al menos aproximadamente 5 moles del éster bórico de fórmula (II) se proporcionan en la etapa (a);
- (d) la etapa de contacto (b) se realiza a una temperatura de reacción en el intervalo de aproximadamente -60°C a aproximadamente -30°C ;
- (e) el ácido de Lewis es húmedo;
- (f) Y es cloro;
- (g) R^3 es cloro;
- (h) R^2 es hidrógeno; y
- (i) R^1 es alifático C_{1-4} .

27. El proceso de la reivindicación 0, caracterizado por al menos dos de las características (a)-(h).

28. El proceso de la reivindicación 0, caracterizado por al menos tres de las características (a)-(h).
29. El proceso de la reivindicación 0, caracterizado por las ocho características (a)-(h) en su totalidad.
30. El proceso de la reivindicación 0, que comprende adicionalmente:
 - (c) lavar la mezcla de reacción con una solución acuosa; y
 - (d) concentrar la mezcla de reacción lavada retirando los disolventes para dar un residuo que comprende el compuesto de éster bórico de fórmula (I).
31. El proceso de la reivindicación 0, donde el residuo comprende al menos aproximadamente cinco moles del compuesto de éster bórico de fórmula (I).
32. El proceso de la reivindicación 0, donde el compuesto de éster bórico de fórmula (I) presente en el residuo tiene una proporción diastereomérica de al menos aproximadamente 96:4 en el átomo de carbono que lleva R¹, R², y R³, con respecto a un centro quiral en el resto quiral R⁴-R⁵.
33. El proceso de la reivindicación 0, donde el compuesto de éster bórico de fórmula (I) presente en el residuo tiene una proporción diastereomérica de al menos aproximadamente 97:3 en el átomo de carbono que lleva R¹, R², y R³, con respecto a un centro quiral en el resto quiral R⁴-R⁵.
34. Una composición que comprende un disolvente de éter que tiene una baja miscibilidad con agua y al menos aproximadamente diez moles de un compuesto de éster bórico de fórmula (I):



(I)

en la que:

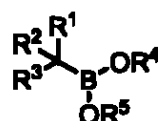
R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S.

35. Una composición que comprende un disolvente de éter que tiene una baja miscibilidad con agua y al menos aproximadamente diez moles de un compuesto de éster bórico de fórmula (I):



(I)

en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

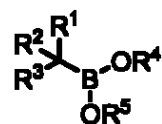
R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S.

donde el átomo de carbono al que están unidos R^1 , R^2 , y R^3 es un centro quiral, que tiene una proporción diastereomérica de al menos aproximadamente 96:4, con respecto a un centro quiral en el resto quiral R^4 - R^5 .

- 5 36. Una composición que comprende un disolvente de éter que tiene una baja miscibilidad con agua y al menos aproximadamente diez moles de un compuesto de éster bórico de fórmula (I):



(I)

en la que:

- 10 R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

- 15 R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

- 20 cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S.

donde el átomo de carbono al que están unidos R^1 , R^2 , y R^3 es un centro quiral, que tiene una proporción epimérica de al menos aproximadamente 96:4,

- 25 37. La composición de una cualquiera de las reivindicaciones 0-0, donde la solubilidad del agua en el disolvente de éter es menor de aproximadamente el 2% p/p.

38. La composición de una cualquiera de las reivindicaciones 0-0, donde el disolvente de éter se selecciona entre el grupo compuesto por *tert*-butil metil

éter, *terc*-butil etil éter, *terc*-amil metil éter, éter isopropílico, y mezclas de los mismos.

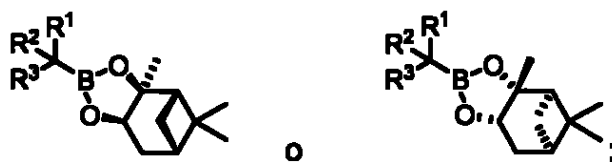
39. La composición de una cualquiera de las reivindicaciones 0-0, donde R¹
5 es alifático C₁₋₈, arilo C₆₋₁₀, o (aril C₆₋₁₀)(alifático C₁₋₈).

40. La composición de una cualquiera de las reivindicaciones 0-0, caracterizada al menos por una de las siguientes características:

- (a) R³ es cloro;
10 (b) R² es hidrógeno; y
(C) R¹ es alifático C₁₋₄

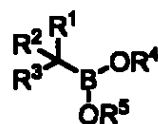
41. La composición de una cualquiera de las reivindicaciones 0-0, donde R⁴
y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman
15 un anillo de 5 miembros opcionalmente sustituido.

42. La composición de una cualquiera de las reivindicaciones 0-0, donde el compuesto de fórmula (I) es



20

43. Una composición que comprende al menos aproximadamente diez moles de un compuesto de éster bórico de fórmula (I):



(I)

en la que:

25 R¹ es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

5 cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S.

10 donde el átomo de carbono al que están unidos R^1 , R^2 , y R^3 es un centro quiral, que tiene una proporción diastereomérica de al menos aproximadamente 96:4, con respecto a un centro quiral en el resto quiral R^4 - R^5 ; y

15 donde el compuesto de éster bórico de fórmula (I) constituye al menos aproximadamente el 70% p/p de la composición.

44. La composición de la reivindicación 0 que comprende al menos aproximadamente 20 moles del compuesto de éster bórico de fórmula (I).

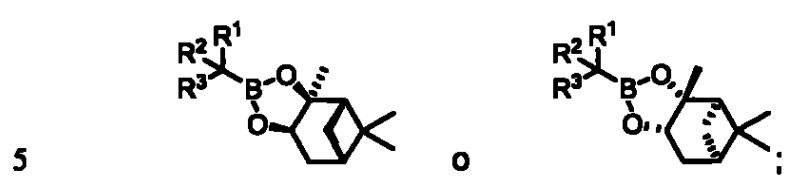
20 45. La composición de la reivindicación 0, donde el átomo de carbono al que están unidos R^1 , R^2 , y R^3 tiene una proporción diastereomérica de al menos aproximadamente 97:3, con respecto a un centro quiral en el resto quiral R^4 - R^5 .

25 46. La composición de la reivindicación 0, donde todo el compuesto de éster bórico de fórmula (I) presente en la composición se produce en un solo lote.

47. La composición de la reivindicación 0, donde todo el compuesto de éster bórico de fórmula (I) presente en la composición se produce en un solo lote del proceso de acuerdo con la reivindicación 1.

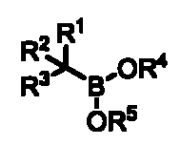
48. La composición de la reivindicación 0, donde hay presente al menos alguna de las siguientes características:

- (a) R^3 es cloro;
- (b) el compuesto de éster bórico de fórmula (I) es:



- (c) R^2 es hidrógeno; y
- (d) R^1 es alifático C_{1-4} .

49. Un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

15 R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

20 cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S;

comprendiendo dicho proceso:

- 25 (a) proporcionar una solución que comprende:
- (i) un éster bórico de fórmula (II):



en la que R¹, R⁴, y R⁵ son como se han definido anteriormente; y

(ii) un disolvente de éter que tiene una baja miscibilidad con agua;

5 (b) tratar la solución con un reactivo de fórmula (IV):



para formar un complejo boron"ato" de fórmula (II):



en la que:

10 Y es un grupo nucleófilo;

M⁺ es un catión; y

cada uno de R¹ a R⁵ es como se han definido anteriormente; y

(c) poner en contacto el complejo boron"ato" de fórmula (II) con un ácido de Lewis en condiciones que dan el compuesto de éster bórico de fórmula (I), realizándose dicha etapa de puesta en contacto en una mezcla de reacción que comprende:

15 (i) un disolvente de coordinación de éter que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación.

50. Un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



25 en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^2 es hidrógeno, un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

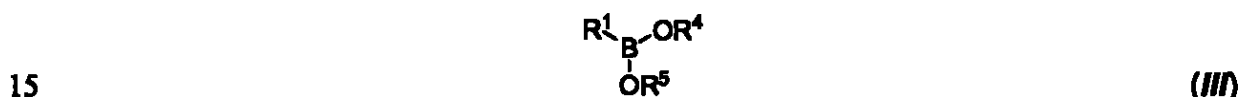
5 R^3 es un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

10 cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S;

comprendiendo dicho proceso:

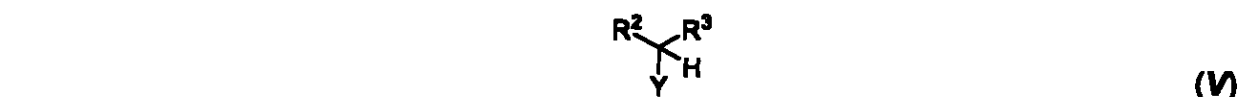
(a) proporcionar una solución que comprende:

(i) un éster bórico de fórmula (III):



donde R^1 , R^4 , y R^5 son como se han definido anteriormente;

(ii) un compuesto de fórmula (V):



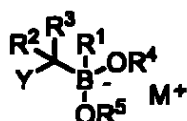
donde Y es un grupo nucleófilo, y R^2 y R^3 son como se han definido anteriormente; y

(iii) un disolvente que comprende:

(aa) un disolvente de coordinación de éter que tiene una baja miscibilidad con agua; o

25 (bb) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;

(b) tratar la solución de la etapa (a) con una base fuerte, con impedimentos estéricos, para formar un complejo boron"ato" de fórmula (II):

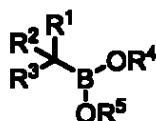


(II)

donde M^+ es un catión derivado de la base, y cada uno de Y y R^1 a R^5 son como se han definido anteriormente; y

- (c) poner en contacto el complejo boron"ato" de fórmula (II) con un ácido de Lewis en una solución que comprende un disolvente de éter que tiene una baja miscibilidad con agua para formar el compuesto de éster bórico de fórmula (I).

51. Un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



(I)

en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

- R^2 es hidrógeno, un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

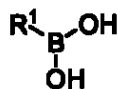
R^3 es un grupo nucleóforo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

- R^4 y R^5 , tomados conjuntamente, forman una cadena de unión opcionalmente sustituida que comprende 2-5 átomos de carbono y 0-2 heteroátomos seleccionados entre el grupo compuesto por O, N, y S;

comprendiendo dicho proceso:

- (a) proporcionar una solución que comprende:

- (i) un compuesto de ácido bórico de fórmula (VI):



(VI)

donde R^1 es como se ha definido anteriormente;

(ii) un compuesto de fórmula $\text{HO-R}^4\text{-R}^5\text{-OH}$, donde R^4 y R^5 son como se han definido anteriormente; y

(iii) un disolvente orgánico que forma un azeótropo con agua;

(b) calentar la solución de la etapa (a) a reflujo, con retirada azeotrópica del agua, para formar un éster bórico de fórmula (III):



donde R^1 , R^4 , y R^5 son como se han definido anteriormente;

(c) proporcionar una solución que comprende:

(i) el éster bórico de fórmula (III);

10 (ii) un compuesto de fórmula (V):



donde Y es un grupo nucleófilo, y R^2 y R^3 son como se han definido anteriormente; y

(iii) un disolvente que comprende:

15 (aa) un disolvente de coordinación de éter que tiene una baja miscibilidad con agua; o

(bb) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;

(d) tratar la solución de la etapa (c) con una base fuerte, con 20 impedimentos estéricos, para formar un complejo boron"ato" de fórmula (II):



donde M^+ es un catión derivado de la base, y cada uno de Y y R^1 a R^5 son como se han definido anteriormente; y

(e) poner en contacto el complejo boron"ato" de fórmula (II) con un 25 ácido de Lewis en una solución que comprende un disolvente de éter que tiene una baja miscibilidad con agua para formar el compuesto de éster bórico de fórmula (I).

52. El proceso de la reivindicación 0 o 0, donde la base con impedimentos estéricos es una base de dialquilamida de metal alcalino de fórmula $M^2N(R^*)_2$, donde M^2 se selecciona entre el grupo compuesto por Li, Na, y K, y cada R^* , independientemente, es un alifático C_{3-6} ramificado o cíclico.

5

53. El proceso de la reivindicación 0, donde el disolvente orgánico en la etapa (a) se selecciona entre el grupo compuesto por acetonitrilo, tolueno, hexano, heptano, y mezclas de los mismos.

10 54. El proceso de la reivindicación 0, donde el disolvente orgánico en la etapa (a) es un disolvente de éter que tiene una baja miscibilidad con agua.

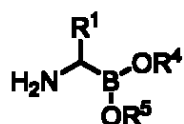
55. El proceso de la reivindicación 0, donde las soluciones en cada una de las etapas (a) y (c) comprenden el mismo disolvente de éter.

15

56. El proceso de la reivindicación 0, donde la etapa (b) proporciona una solución de producto que comprende el éster bórico de fórmula (III), y la solución de producto de la etapa (b) se usa en la etapa (c) sin aislar el éster bórico de fórmula (III).

20

57. Un proceso a gran escala para preparar un compuesto de éster aminobórico de fórmula (VII):



(VII)

o una sal de adición de ácidos del mismo, donde:

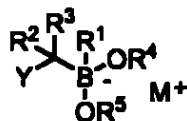
25 en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto

con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S comprendiendo dicho proceso:

- 5 (a) proporcionar un complejo boron"ato" de fórmula (II):



(II)

donde

Y es un grupo nucleófilo;

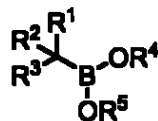
M⁺ es un catión;

10 R² es hidrógeno;

R³ es un grupo nucleófilo; y

cada uno de R¹, R⁴, y R⁵ son como se han definido anteriormente;

- (b) poner en contacto el complejo boron"ato" de fórmula (II) con un ácido de Lewis en condiciones que dan el compuesto de éster bórico de
15 fórmula (I):



(I)

donde cada uno de R¹ a R⁵ es como se ha definido anteriormente, realizándose dicha etapa de puesta en contacto en a mezcla de reacción que comprende:

- (i) un disolvente de coordinación de éter que tiene una baja
20 miscibilidad con agua; o
(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;

- (c) tratar el compuesto de éster bórico de fórmula (I) con un reactivo de fórmula M¹-N(Si(R⁶)₃)₂, donde M¹ es un metal alcalino y cada R⁶
25 independientemente se selecciona entre el grupo compuesto por alquilo, aralquilo, y arilo, donde el arilo o porción arilo del aralquilo está opcionalmente

sustituido, para formar un subproducto de fórmula M^1-R^3 y un compuesto de fórmula (VIII):



en la que cada G y R^1 a R^5 son como se han definido anteriormente; y

- 5 (d) retirar los grupos G para formar un compuesto de fórmula (VII):



o una sal de adición de ácidos del mismo.

- 10 58. El proceso de la reivindicación 0, donde la mezcla de reacción en la etapa (c) comprende un disolvente orgánico en el que el subproducto M^1-R^3 tiene poca solubilidad.

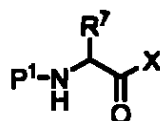
59. El proceso de la reivindicación 0, donde M^1 es Li y R^3 es Cl.

- 15 60. El proceso de la reivindicación 0, donde la mezcla de reacción en la etapa (c) comprende un disolvente orgánico seleccionado entre el grupo compuesto por metilciclohexano, ciclohexano, heptano, hexano, tolueno, y mezclas de los mismos.

- 20 61. El proceso de la reivindicación 0, donde la reacción en la etapa (c) se realiza a una temperatura de reacción en el intervalo de aproximadamente -100°C a aproximadamente 50°C.

- 25 62. El proceso de la reivindicación 0, donde la temperatura de reacción está en el intervalo de aproximadamente -50°C a aproximadamente 25°C.

63. El proceso de la reivindicación 0, donde la temperatura de reacción está en el intervalo de aproximadamente -30°C a aproximadamente 0°C.
64. El proceso de la reivindicación 0, donde la etapa (d) comprende tratar el compuesto de fórmula (VIII) con un ácido y aislar el compuesto de fórmula (VII) en forma de la sal de adición de ácidos.
65. El proceso de la reivindicación 0, donde el ácido es ácido trifluoroacético.
66. El proceso de la reivindicación 0, donde la etapa (c) comprende adicionalmente filtrar la mezcla de reacción para proporcionar un filtrado que comprende el compuesto de fórmula (VIII).
67. El proceso de la reivindicación 0, donde en la etapa (c), el reactivo de fórmula $M^1-N(Si(R^6)_3)_2$ se añade a la mezcla de reacción en forma de una solución que comprende tetrahidrofurano, y la etapa (c) comprende adicionalmente retirar the tetrahidrofurano antes de filtrar la mezcla de reacción.
68. El proceso de la reivindicación 0, donde el filtrado se usa directamente en la etapa (d).
69. El proceso de la reivindicación 0, que comprende adicionalmente la etapa:
- (e) acoplar el compuesto de fórmula (VII) con un compuesto de fórmula (IX):



(IX)

donde:

P^1 es resto que bloquea al grupo amino;

R^7 se selecciona entre el grupo compuesto por hidrógeno, alifático C_{1-10} , arilo C_{6-10} opcionalmente sustituido, o alifático $C_{1-6}-R^6$; y

R^6 se selecciona entre el grupo compuesto por grupos alcoxi, alquiltio, arilo opcionalmente sustituido, heteroarilo, y heterociclilo, y grupos amino, hidroxilo, y guanidino opcionalmente protegidos; y

X es OH o un grupo saliente;

para formar un compuesto de fórmula (X):



donde cada uno de P^1 , R^1 , R^4 , R^5 , y R^7 es como se ha definido anteriormente.

10

70. El proceso de la reivindicación 0, donde P^1 es un grupo protector escindible.

71. El proceso de la reivindicación 0, que comprende adicionalmente las etapas:

15

(f) escindir el grupo protector P^1 para formar un compuesto de fórmula (XI):



o una sal de adición de ácidos del mismo, donde cada uno de R^1 , R^4 , R^5 , y R^7 es como se ha definido anteriormente;

20

(g) acoplar el compuesto de fórmula (XI) con un reactivo de fórmula P^2-X , donde P^2 es un resto que bloquea al grupo amino y X es un grupo saliente, para formar un compuesto de fórmula (XII):



donde cada uno de P^2 , R^1 , R^4 , R^5 , y R^7 son como se han definido anteriormente; y

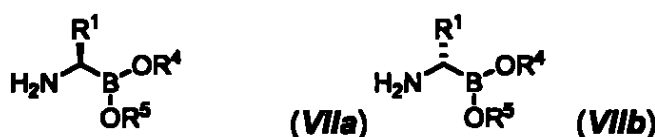
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(h) desproteger el resto ácido bórico para formar un compuesto de fórmula (XIII):



o un anhídrido de ácido bórico del mismo, donde cada uno de P¹, R¹, y R⁷ son como se han definido anteriormente.

72. Un proceso a gran escala para preparar un compuesto de éster aminobórico de fórmula (VIIa) o (VIIb):



o una sal de adición de ácidos del mismo, donde:

R¹ es un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

R⁴ y R⁵, tomados junto con los átomos de oxígeno y boro que intervienen, forman un éster bórico cíclico quiral opcionalmente sustituido;

comprendiendo dicho proceso:

(a) proporcionar un complejo boron"ato" de fórmula (IIa) o (IIb):



donde

Y es un grupo nucleófilo;

M⁺ es un catión;

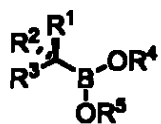
R² es hidrógeno;

R³ es un grupo nucleófilo; y

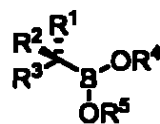
R⁴ y R⁵ son como se han definido anteriormente;

(b) poner en contacto el complejo boron"ato" de fórmula (IIa) o (IIb)

con un ácido de Lewis en condiciones que dan un compuesto de éster bórico de fórmula (Ia) o (Ib):



(Ia)



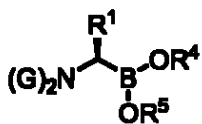
(Ib)

donde cada uno de R^1 a R^5 es como se ha definido anteriormente, realizándose dicha etapa de puesta en contacto en a mezcla de reacción que comprende:

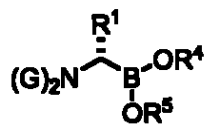
(i) un disolvente de coordinación de éter que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación;

(c) tratar el compuesto de éster bórico de fórmula (Ia) o (Ib) con un reactivo de fórmula $M^1-N(G)_2$, donde M^1 es un metal alcalino y cada G es un resto protector del grupo amino, para formar un compuesto de fórmula (VIIIa) o (VIIIb):



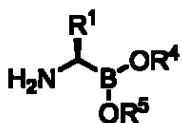
(VIIIa)



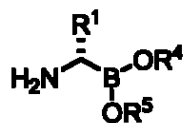
(VIIIb)

donde cada G y R^1 a R^5 son como se han definido anteriormente; y

(d) retirar los grupos G para formar un compuesto de fórmula (VIIa) o (VIIb):



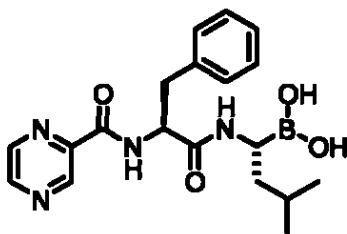
(VIIa)



(VIIb)

o una sal de adición de ácidos del mismo.

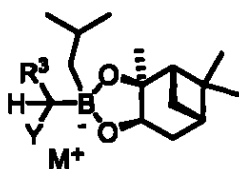
73. Un proceso a gran escala para formar un compuesto de fórmula (XIV):



(XIV)

o un anhídrido de ácido bórico del mismo, comprendiendo dicho proceso:

(a) proporcionar un complejo boron"ato" de fórmula (XV):

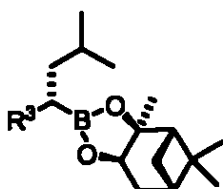


(XV)

donde:

M^+ es un metal alcalino;

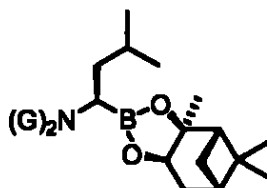
- (b) poner en contacto el complejo boron"ato" de fórmula (XV) con un ácido de Lewis en condiciones que dan un compuesto de éster bórico de fórmula (XVI):



(XVI)

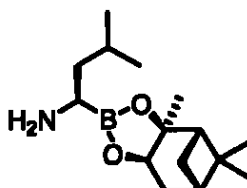
realizándose dicha etapa de puesta en contacto en a mezcla de reacción que comprende un disolvente de éter que tiene una baja miscibilidad con agua;

- (c) tratar el compuesto de éster bórico de fórmula (XVI) con un reactivo de fórmula $M^1-N(G)_2$, donde M^1 es un metal alcalino y cada G individual o conjuntamente es un grupo protector del grupo amino, para formar un compuesto de fórmula (XVII):



(XVII)

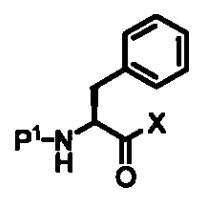
- (d) retirar los grupos G para formar un compuesto de fórmula (XVIII):



(XVIII)

o una sal de adición de ácidos del mismo;

- (e) acoplar el compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX):



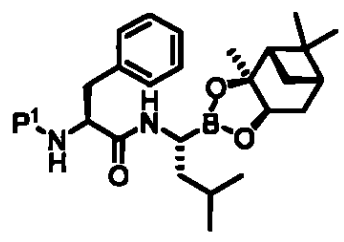
(XIX)

en la que:

P¹ es un resto protector del grupo amino escindible; y

X es OH o un grupo saliente;

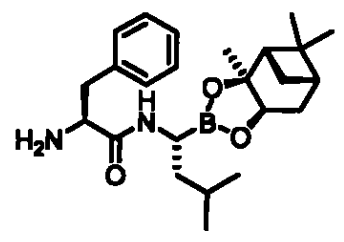
5 para formar un compuesto de fórmula (XX):



(XX)

donde P¹ es como se ha definido anteriormente;

(f) retirar el grupo protector P¹ para formar un compuesto de fórmula (XXI):

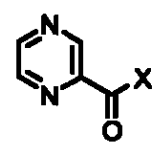


(XXI)

10

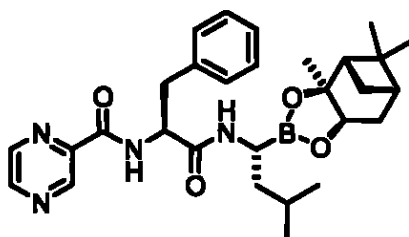
o una sal de adición de ácidos del mismo;

(g) acoplar el compuesto de fórmula (XXI) con un reactivo de fórmula (XXII)



(XXII)

15 donde X es un OH o un grupo saliente, para formar un compuesto de fórmula (XXIII):



(XXIII); y

(h) desproteger el resto ácido bórico para formar el compuesto de fórmula (XIV) o un anhídrido de ácido bórico del mismo.

5 74. El proceso de la reivindicación 0, caracterizado al menos por una de las siguientes características (1)-(5):

(1) en el complejo boron"ato" de fórmula (XV), R^3 y Y son ambos cloro;

(2) la etapa de acoplamiento (e) comprende las etapas:

10 (i) acoplar el compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX) donde X es OH en presencia de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;

(ii) realizar un intercambio de disolvente para sustituir
15 diclorometano con acetato de etilo; y

(iii) realizar un lavado acuoso de la solución de acetato de etilo.

(3) la etapa de retirar el grupo protector (f) comprende las etapas:

(i) tratar el compuesto de fórmula (XX) con HCl en acetato de
etilo;

20 (ii) añadir heptano a la mezcla de reacción; y

(iii) aislar por cristalización el compuesto de fórmula (XXI) en forma de su sal de adición de HCl;

(4) la etapa de acoplamiento (g) comprende las etapas:

25 (i) acoplar el compuesto de fórmula (XXI) con ácido 2-pirazina-carboxílico en presencia de TBTU y una amina terciaria en diclorometano;

(ii) realizar un intercambio de disolvente para sustituir diclorometano con acetato de etilo; y

(iii) realizar un lavado acuoso de la solución de acetato de etilo; y

5 (5) la etapa de desproteger el ácido bórico (h) comprende las etapas:

(i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente hidrocarburo C₅₋₈, y un ácido mineral acuoso;

10 (ii) agitar la mezcla bifásica para dar el compuesto de fórmula (XIV);

(iii) separar las capas de disolvente; y

(iv) extraer el compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, en un disolvente orgánico.

15

75. El proceso de la reivindicación 0, caracterizado por las cinco características (1)-(5) en su totalidad.

20 76. El proceso de la reivindicación 0, donde la etapa (h)(iii) comprende las etapas:

(1) separar las capas de disolvente;

(2) ajustar la capa acuosa a pH básico;

(3) lavar la capa acuosa con un disolvente orgánico; y

(4) ajustar la capa acuosa a un pH menor de aproximadamente 8,

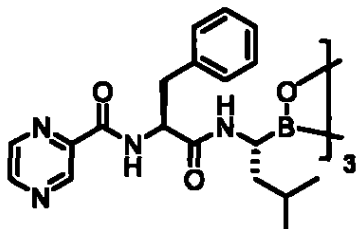
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77. El proceso de la reivindicación 0, donde en la etapa (h)(iii)(3), la capa acuosa se lava con diclorometano.

30 78. El proceso de la reivindicación 0, donde en la etapa (h)(iv), el compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, se extrae en diclorometano, el disolvente se cambia a acetato de etilo, y el compuesto de

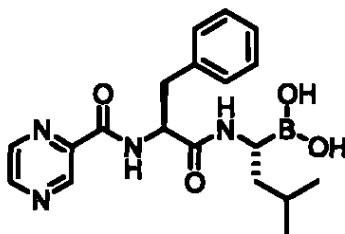
fórmula (XIV), o un anhídrido de ácido bórico del mismo, se cristaliza por adición de hexano o heptano.

79. El proceso de la reivindicación 0, donde la adición de hexano o heptano da como resultado la cristalización de un anhídrido de ácido bórico trimérico cíclico de fórmula (XXIV):



(XXIV).

80. Un proceso a gran escala para formar un compuesto de fórmula (XIV):

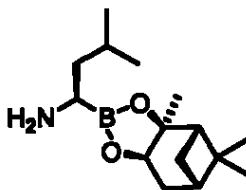


(XIV)

10

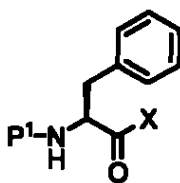
o un anhídrido de ácido bórico del mismo, que comprende las etapas:

- (aa) acoplar un compuesto de fórmula (XVIII):



(XVIII)

o una sal de adición de ácidos del mismo, con un compuesto de fórmula (XIX):



(XIX)

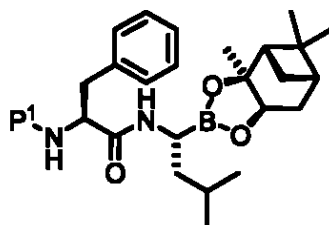
15

en la que:

P¹ es un resto protector del grupo amino escindible; y

X es OH o un grupo saliente;

para formar un compuesto de fórmula (XX):



(XX)

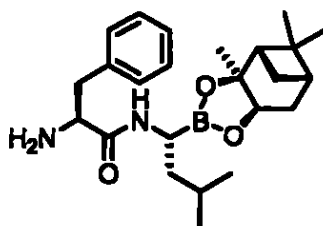
en la que P¹ es como se ha definido anteriormente, comprendiendo dicha etapa (aa) de acoplamiento las etapas:

- 5 (i) acoplar el compuesto de fórmula (XVIII) con un compuesto de fórmula (XIX) donde X es OH en presencia de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;

- 10 (ii) realizar un intercambio de disolvente para sustituir diclorometano con acetato de etilo; y

- (iii) realizar un lavado acuoso de la solución de acetato de etilo;

(bb) retirar el grupo protector P¹ para formar un compuesto de fórmula (XXI):



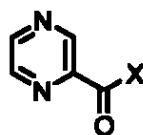
(XXI)

- 15 o una sal de adición de ácidos del mismo, comprendiendo dicha etapa (bb) de retirar el grupo protector las etapas:

- (i) tratar el compuesto de fórmula (XX) con HCl en acetato de etilo;
(ii) añadir heptano a la mezcla de reacción; y
(iii) aislar por cristalización el compuesto de fórmula (XXI) en forma de

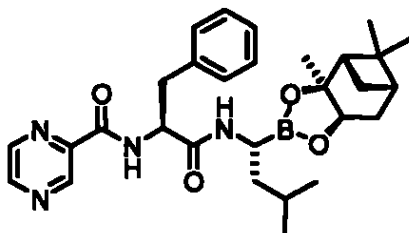
- 20 su sal de adición de HCl;

(cc) acoplar el compuesto de fórmula (XXI) con un reactivo de fórmula (XXII)



(XXII)

donde X es un OH o un grupo saliente, para formar un compuesto de fórmula (XXIII):



(XXIII).

5 comprendiendo dicha etapa (cc) de acoplamiento las etapas:

(i) acoplar el compuesto de fórmula (XXI) con ácido 2-pirazina-carboxílico en presencia de TBTU y una amina terciaria en diclorometano;

10 (ii) realizar un intercambio de disolvente para sustituir diclorometano con acetato de etilo; y

(iii) realizar un lavado acuoso de la solución de acetato de etilo;

y

(dd) desproteger el resto ácido bórico para formar el compuesto de fórmula (XIV) o un anhídrido de ácido bórico del mismo, comprendiendo dicha

15 etapa (dd) de desprotección las etapas:

(i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un alcohol inferior, un disolvente hidrocarburo C₅₋₈, y ácido mineral acuoso;

20 (ii) agitar la mezcla bifásica para dar el compuesto de fórmula (XIV);

(iii) separar las capas de disolvente; y

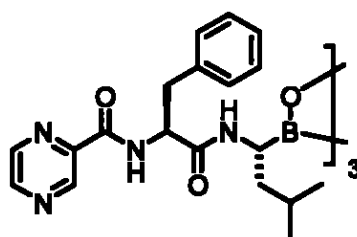
(iv) extraer el compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, en un disolvente orgánico.

81. El proceso de la reivindicación 0, donde la etapa (dd)(iii) comprende las etapas:

- (1) separar las capas de disolvente;
- (2) ajustar la capa acuosa a pH básico;
- 5 (3) lavar la capa acuosa con un disolvente orgánico; y
- (4) ajustar la capa acuosa a un pH menor de aproximadamente 8.

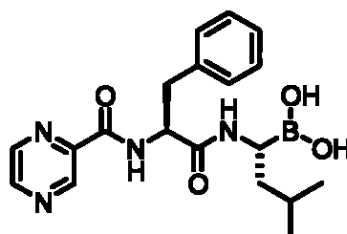
82. El proceso de la reivindicación 0, donde en la etapa (dd)(iv), el compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, se extrae en diclorometano, el disolvente se cambia a acetato de etilo, y el
10 compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, se cristaliza por adición de hexano o heptano.

83. El proceso de la reivindicación 0, donde la adición de hexano o heptano
15 da como resultado la cristalización de un anhídrido de ácido bórico trimérico cíclico de fórmula (XXIV):



(XXIV).

84. Un proceso a gran escala para formar un compuesto de fórmula (XIV):

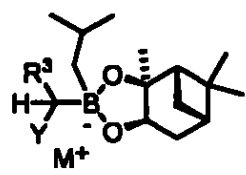


(XIV)

20

o un anhídrido de ácido bórico del mismo. Comprendiendo el proceso las etapas:

- (a) proporcionar un complejo boron"ato" de fórmula (XV):



(XV)

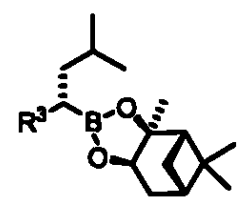
en la que:

R^3 es un grupo nucleófilo;

Y es un grupo nucleófilo; y

5 M^+ es un metal alcalino;

(b) poner en contacto el complejo boronato de fórmula (XV) con un ácido de Lewis en condiciones que dan un compuesto de éster bórico de fórmula (XVI):



(XVI)

10 realizándose dicha etapa de puesta en contacto en una mezcla de reacción que comprende:

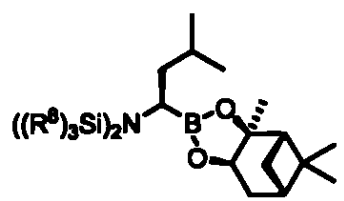
(i) un disolvente de coordinación de éter que tiene una baja miscibilidad con agua; o

(ii) un disolvente de éter que tiene una baja miscibilidad con

15 agua y un co-disolvente de coordinación;

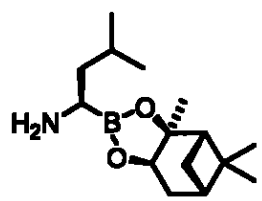
(c) tratar el compuesto de éster bórico de fórmula (XVI) con un reactivo de fórmula $M^1-N(Si(R^6)_3)_2$, donde M^1 es un metal alcalino y cada R^6 se selecciona independientemente entre el grupo compuesto por alquilo, aralquilo, y arilo, donde el arilo o porción arilo del aralquilo está opcionalmente sustituido,

20 para formar un compuesto de fórmula (XVII):



(XVII)

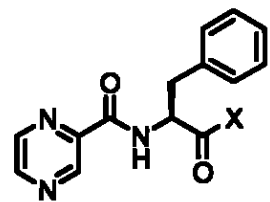
(d) retirar los grupos $(R^8)_3Si$ para formar un compuesto de fórmula (XVIII):



(XVIII)

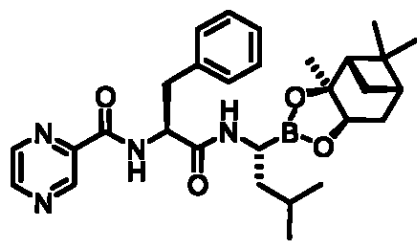
o una sal de adición de ácidos del mismo;

5 (e') acoplar el compuesto de fórmula (XVIII) con un compuesto de fórmula (XIXa):



(XIXa)

en la que X es OH o un grupo saliente, para formar un compuesto de fórmula (XXIII):



(XXIII) ; y

10

(f') desproteger el resto ácido bórico para formar el compuesto de fórmula (XIV) o un anhídrido de ácido bórico del mismo.

85. El proceso de la reivindicación 0, caracterizado al menos por una de las siguientes características (1)-(3):

15

(1) En el complejo boron"ato" de fórmula (XV), R^3 y Y son ambos cloro.

(2) La etapa de acoplamiento (e') comprende las etapas:

20

(i) acoplar el compuesto de fórmula (XVIII) con un compuesto de fórmula (XIXa) donde X es OH en presencia de tetrafluoroborato de

2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU) y una amina terciaria en diclorometano;

(ii) realizar un intercambio de disolvente para sustituir diclorometano con acetato de etilo; y

5 (iii) realizar un lavado acuoso de la solución de acetato de etilo.

(3) Comprendiendo la etapa de desproteger el ácido bórico (f) las etapas:

(i) proporcionar una mezcla bifásica que comprende el compuesto de fórmula (XXIII), un aceptor orgánico de ácido bórico, un
10 alcohol inferior, un disolvente hidrocarburo C₅₋₈, y ácido mineral acuoso;

(ii) agitar la mezcla bifásica para dar el compuesto de fórmula (XIV);

(iii) separar las capas de disolvente; y

(iv) extraer el compuesto de fórmula (XIV), o un anhídrido de ácido
15 bórico del mismo, en un disolvente orgánico.

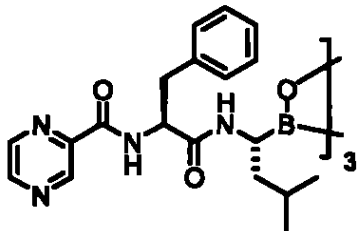
86. El proceso de la reivindicación 0, donde la etapa (f)(iii) comprende las etapas:

- 20 (1) separar las capas de disolvente;
- (2) ajustar la capa acuosa a pH básico;
- (3) lavar la capa acuosa con un disolvente orgánico; y
- (4) ajustar la capa acuosa a un pH menor de aproximadamente 8.

87. El proceso de la reivindicación 0, donde en la etapa (f)(iii)(3), la capa
25 acuosa se lava con diclorometano.

88. El proceso de la reivindicación 0, donde en la etapa (f)(iv), el compuesto de fórmula (XIV), o un anhídrido de ácido bórico del mismo, se extrae en diclorometano, el disolvente se cambia a acetato de etilo, y el compuesto de
30 fórmula (XIV), o un anhídrido de ácido bórico del mismo, se cristaliza por adición de hexano o heptano.

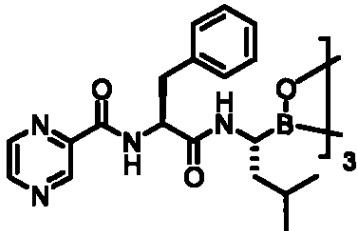
89. El proceso de la reivindicación 0, donde la adición de hexano o heptano da como resultado la cristalización de un anhídrido de ácido bórico trimérico cíclico de fórmula (XXIV):



5

(XXIV).

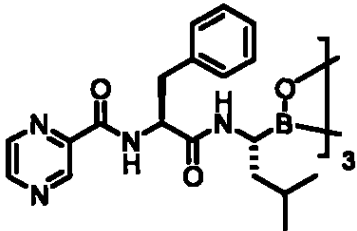
90. Una composición que comprende al menos un kilogramo de un compuesto de fórmula (XXIV):



(XXIV)

10 donde el compuesto de fórmula (XXIV) se prepara de acuerdo con el proceso de la reivindicación 0 o 0.

91. Una composición que comprende al menos un kilogramo de un compuesto de fórmula (XXIV):



15

(XXIV)

donde el compuesto de fórmula (XXIV) constituye al menos el 99% p/p de la composición.

752
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RESUMEN DE LA DESCRIPCIÓN

La invención se refiere a la síntesis de compuestos de éster y ácido bórico. Más particularmente, la invención proporciona procesos sintéticos
5 mejorados para la producción a gran escala de compuestos de éster y ácido bórico, incluyendo el inhibidor de proteasoma peptídico de ácido bórico bortezomib.

SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

[001] This invention relates to the synthesis of boronic ester and acid compounds. More particularly, the invention relates to large-scale synthetic processes for the preparation of boronic ester and acid compounds by Lewis acid promoted rearrangement of boron "ate" complexes.

Background of the Invention

[002] Boronic acid and ester compounds display a variety of pharmaceutically useful biological activities. Shenvi *et al.*, U.S. Pat. No. 4,499,082 (1985), discloses that peptide boronic acids are inhibitors of certain proteolytic enzymes. Kettner and Shenvi, U.S. Pat. No. 5,187,157 (1993), U.S. Pat. No. 5,242,904 (1993), and U.S. Pat. No. 5,250,720 (1993), describe a class of peptide boronic acids that inhibit trypsin-like proteases. Kleeman *et al.*, U.S. Pat. No. 5,169,841 (1992), discloses *N*-terminally modified peptide boronic acids that inhibit the action of renin. Kinder *et al.*, U.S. Pat. No. 5,106,948 (1992), discloses that certain tripeptide boronic acid compounds inhibit the growth of cancer cells.

[003] More recently, boronic acid and ester compounds have displayed particular promise as inhibitors of the proteasome, a multicatalytic protease responsible for the majority of intracellular protein turnover. Ciechanover, *Cell*, 79: 13-21 (1994), discloses that the proteasome is the proteolytic component of the ubiquitin-proteasome pathway, in which proteins are targeted for degradation by conjugation to multiple molecules of ubiquitin. Ciechanover also discloses that the ubiquitin-proteasome pathway plays a key role in a variety of important physiological processes.

[004] Adams *et al.*, U.S. Patent No. 5,780,454 (1998), U.S. Patent No. 6,066,730 (2000), U.S. Patent No. 6,083,903 (2000), U.S. Patent No. 6,297,217 (2001), U.S. Patent No. 6,548,668,

and U.S. Patent No. 6,617,317 (2003), hereby incorporated by reference in their entirety, describe peptide boronic ester and acid compounds useful as proteasome inhibitors. The references also describe the use of boronic ester and acid compounds to reduce the rate of muscle protein degradation, to reduce the activity of NF- κ B in a cell, to reduce the rate of degradation of p53 protein in a cell, to inhibit cyclin degradation in a cell, to inhibit the growth of a cancer cell, to inhibit antigen presentation in a cell, to inhibit NF- κ B dependent cell adhesion, and to inhibit HIV replication.

[005] Albanell and Adams, *Drugs of the Future* 27: 1079-1092 (2002), discloses that one such peptide boronic acid proteasome inhibitor, bortezomib (N-2-pyrazinecarbonyl-L-phenylalanine-L-leucineboronic acid), shows significant antitumor activity in human tumor xenograft models and is undergoing clinical evaluation. Richardson *et al.*, *New Engl. J. Med.*, 348:2609 (2003), reports the results of a Phase 2 study of bortezomib, showing its effectiveness in treating relapsed and refractory multiple myeloma.

[006] Studies of boronic acid protease inhibitors have been greatly advanced by the development of chemistry for the preparation of functionalized boronic acid compounds, particularly alpha-halo- and alpha-aminoboronic acids. Matteson and Majumdar, *J. Am. Chem. Soc.*, 102:7590 (1980), discloses a method for preparing alpha-chloroboronic esters by homologation of boronic esters, and Matteson and Ray, *J. Am. Chem. Soc.*, 102:7591 (1980), reports that chiral control of the homologation reaction can be achieved by the use of pinanediol boronic esters. The preparation of alpha-aminoboronic acid and ester compounds from the corresponding alpha-chloroboronic esters has also been reported (Matteson *et al.*, *J. Am. Chem. Soc.*, 103:5241 (1981); Shenvi, U.S. Patent No. 4,537,773 (1985)).

[007] Matteson and Sadhu, U.S. Patent No. 4,525,309 (1985), describes an improved procedure for the homologation of boronic esters by rearrangement of the intermediate boron "ate" complex in the presence of a Lewis acid catalyst. The Lewis acid is reported to promote the rearrangement reaction and to minimize epimerization at the alpha-carbon atom. Rigorous exclusion of water and careful control of Lewis acid stoichiometry are required for optimum results, however. These features render the reaction difficult to perform successfully on a production scale, and limit the availability of pharmaceutically important boronic ester and acid compounds, such as bortezomib. Thus, there remains a need in the art for improved methods for the large-scale production of boronic ester and acid compounds.

DESCRIPTION OF THE INVENTION

[008] The present invention provides improved synthetic processes for the large-scale production of boronic ester and acid compounds. These processes offer increased yield and purity, increased throughput, and greater ease of handling as compared to prior art methods. Notably, the processes described herein are suitable for batch production on a large, multi-kilogram scale that is limited only by the size of the available manufacturing capabilities. The processes of the invention are particularly advantageous for the synthesis of chiral boronic ester and acid compounds, including alpha-aminoboronic ester and acid compounds. Regardless of scale, the desired products are produced with very high chemical and stereochemical purity.

[009] The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention relates. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

[010] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10%.

[011] The term "comprises" is used herein to mean "includes, but is not limited to."

[012] The term "aliphatic", as used herein, means a straight-chain, branched or cyclic C₁₋₁₂ hydrocarbon which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and

hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl. In various embodiments, the aliphatic group has 1-12, 1-8, 1-6, or 1-4 carbons.

[013] The terms "alkyl", "alkenyl", and "alkynyl", used alone or as part of a larger moiety, refer to a straight and branched chain aliphatic group having from 1 to 12 carbon atoms, which is optionally substituted with one, two or three substituents. For purposes of the present invention, the term "alkyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule is a saturated carbon atom. However, an alkyl group may include unsaturation at other carbon atoms. Thus, alkyl groups include, without limitation, methyl, ethyl, propyl, allyl, propargyl, butyl, pentyl, and hexyl.

[014] For purposes of the present invention, the term "alkenyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon double bond. Alkenyl groups include, without limitation, vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For purposes of the present invention, the term "alkynyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon triple bond. Alkynyl groups include, without limitation, ethynyl, 1-propynyl, 1-butyne, 1-pentyne, and 1-hexynyl.

[015] The terms "cycloalkyl", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, means a saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 members, wherein the aliphatic ring system is optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloalkyl has 3-6 carbons. The terms "cycloalkyl", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

[016] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an alkyl, alkenyl or alkoxy group, as the case may be, substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. Unless otherwise indicated, the terms "alkyl", "alkenyl", and "alkoxy" include haloalkyl, haloalkenyl and haloalkoxy groups, including, in particular, those with 1-5 fluorine atoms.

[017] The terms "aryl" and "ar-", used alone or as part of a larger moiety, *e.g.*, "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to a C₆₋₁₄ aromatic moiety comprising one to three aromatic rings, which are optionally substituted. Preferably, the aryl group is a C₆₋₁₀ aryl group. Aryl groups include, without limitation, phenyl, naphthyl, and anthracenyl. The term "aryl", as used herein, also includes groups in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring. The term "aryl" may be used interchangeably with the term "aryl ring".

[018] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C₆₋₁₀ aryl(C₁₋₄)alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[019] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, *e.g.*, heteroaralkyl, or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms selected from the group consisting of N, O, and S. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, and phenazinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more nonaromatic rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[3,4-d]pyrimidinyl. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[020] As used herein, the terms "heterocycle", "heterocyclyl", or "heterocyclic radical" refer to a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition

to carbon atoms, one or more, preferably one to four, heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur heteroatoms are optionally oxidized and the nitrogen atoms are optionally quaternized. The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure, and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, and morpholinyl. The terms "heterocycle", "heterocyclyl", and "heterocyclic radical", as used herein, also include groups in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as indolinyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocyclalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[021] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having one or multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[022] The term "substituted", as used herein, means that one or more hydrogen atoms of the designated moiety are replaced, provided that the substitution results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for the synthetic processes of the invention. The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[023] An aryl (including the aryl moiety in aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including the heteroaryl moiety in heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Examples of suitable substituents

on the unsaturated carbon atom of an aryl or heteroaryl group include -halo, -NO₂, -CN, -R*, -OR*, -SR°, -N(R*)₂, -NR*⁺C(O)R*, -NR*⁺C(O)N(R*)₂, -NR*⁺CO₂R°, -O-CO₂R*, -O-C(O)R*, -CO₂R*, -C(O)R*, -C(O)N(R*)₂, -OC(O)N(R*)₂, -S(O)₂R°, -SO₂N(R*)₂, -S(O)R°, and -NR*⁺SO₂N(R*)₂. Each R* independently is selected from the group consisting of R*, -C(O)R*, -CO₂R*, and -SO₂R*, or two R* on the same nitrogen atom, taken together with the nitrogen atom, form a 5-8 membered aromatic or non-aromatic ring having, in addition to the nitrogen, 0-2 ring heteroatoms selected from N, O, and S. Each R* independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group. Each R° independently is an optionally substituted aliphatic or aryl group.

[024] An aliphatic group also may be substituted with one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring include, without limitation, those listed above for the unsaturated carbon of an aryl or heteroaryl group.

[025] The present inventors have discovered that the requirement for scrupulously dry equipment, solvents, and reagents that characterized previously described procedures for the Lewis acid promoted rearrangement of boron "ate" complexes can be obviated by use of an ether solvent that has low miscibility with water. Remarkably, use of such a solvent permits the reaction to be run on a multi-kilogram scale without deterioration in yield or purity. In essence, the scale of the reaction is limited only by the size of the available manufacturing capabilities.

[026] In one aspect, therefore, the invention provides a large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S.

[027] The process comprises the steps:

(a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation: and

each of R^1 to R^5 is as defined above; and

(b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

[028] The previously reported processes for Lewis acid promoted rearrangement of boron "ate" complexes employ tetrahydrofuran, an ether solvent that is fully miscible with water. Failure to employ rigorously dried equipment, solvents, and reagents in these processes results in a dramatic reduction in the diastereomeric ratio. The hygroscopic Lewis acids, in particular, typically must be flame-dried immediately prior to use in the reaction. Although techniques for running moisture-sensitive reactions are familiar to those of skill in the art and are routinely practiced on a laboratory scale, such reactions are costly and difficult to scale up.

[029] Moreover, attempted scale-up of the prior art process frequently results in a further deterioration in diastereomeric ratio during workup and isolation of the product boronic ester compound. Matteson and Erdiik, *Organometallics*, 2:1083 (1983), reports that

exposure of alpha-haloboronic ester products to free halide ion results in epimerization at the alpha-carbon center. Without wishing to be bound by theory, the present inventors believe that epimerization is particularly problematic during reaction work-up and/or subsequent steps. For example, epimerization is believed to occur during concentration of the reaction mixture to remove the tetrahydrofuran solvent and exchange it for a water-immiscible solvent. Failure to completely remove the tetrahydrofuran also negatively impacts diastereomeric ratio during the subsequent aqueous washes. Exposure of the product to halide ion during these steps is difficult to avoid, particularly when the reaction is performed on a large scale.

[030] The present inventors have discovered that the rearrangement of boron "ate" complexes is advantageously performed in an ether solvent that has low miscibility with water. Use of such solvents obviates the need for solvent exchange prior to the aqueous washes, and the organic-soluble product is effectively shielded from aqueous halide ion during the washes, even if performed on a large scale. Preferably, the solubility of water in the ether solvent is less than about 5% w/w, more preferably less than about 2% w/w. In various embodiments, ether solvent that has low miscibility with water constitutes at least about 70%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% v/v of the reaction mixture.

[031] The ether solvent preferably is one that is suitable for routine use in large-scale production. As used herein, the term "large-scale" refers to a reaction that utilizes at least about five moles of at least one starting material. Preferably, a large-scale process utilizes at least about 10, 20, 50, or 100 moles of at least one starting material.

[032] For purposes of the invention, the term "ether" refers to any of a class of chemical compounds characterized in having an oxygen atom attached to two carbon atoms. An "ether solvent" is an ether compound that exists in liquid form at the desired reaction temperature and is capable of dissolving the starting material(s) and/or product(s) of the reaction. Non-limiting examples of ether solvents suitable for use in the process of the invention include *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, and isopropyl ether.

[033] In one embodiment, the reaction mixture further comprises a coordinating co-solvent. In another embodiment, the ether solvent that has low miscibility with water is sufficiently coordinating that a coordinating co-solvent is not necessary. For purposes of the invention, the terms "coordinating co-solvent" and "coordinating solvent" refer to a solvent

that is capable of coordinating the Lewis acid and solvating the ionic components of the reaction. Hindered ether solvents, such as *tert*-butyl methyl ether, are poorly coordinating and preferably are used with a coordinating co-solvent. Nonlimiting examples of coordinating co-solvents suitable for use in the practice of the invention include tetrahydrofuran, dioxane, water, and mixtures thereof.

[034] In some embodiments, the reaction mixture comprises at least about 5% or at least about 10% v/v of a coordinating co-solvent. Preferably, the amount of a water-miscible coordinating co-solvent present in the reaction mixture is not so great as to interfere with phase separation during the reaction or workup. In various embodiments, the coordinating co-solvent constitutes no more than about 20%, about 15%, or about 10% v/v of the reaction mixture.

[035] As used herein, the term "nucleofugic" refers to any group that is capable of undergoing nucleophilic displacement under the rearrangement conditions of the present process. Such nucleofugic groups are known in the art. Preferably, the nucleofugic group is a halogen, more preferably chloro or bromo. In the course of the rearrangement reaction converting the boron "ate" complex of formula (II) into the boronic ester compound of formula (I), the nucleofugic group Y is released as Y⁻. By way of example, when Y is chloro, chloride ion is released in step (b).

[036] The variable M⁺ is any cationic counterion for the negatively charged tetravalent boron atom in the boron "ate" complex of formula (II). In some preferred embodiments, M⁺ is selected from the group consisting of Li⁺, Na⁺, and K⁺. One of skill in the art will recognize that the salt M⁺Y⁻ is formed as a byproduct in the rearrangement reaction of step (b).

[037] The variable R¹ preferably is a group with good migratory aptitude. In some embodiments, R¹ is C₁₋₈ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₆ aliphatic), any of which groups is optionally substituted. In certain embodiments, R¹ is C₁₋₄ aliphatic, particularly isobutyl.

[038] The variable R² preferably is hydrogen, a nucleofugic group, or an optionally substituted C₁₋₈ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₆ aliphatic) group. The variable R³ preferably is a nucleofugic group or an optionally substituted C₁₋₈ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₆ aliphatic) group. One of skill in the art will recognize that functional substituents may be present on any of R¹, R², or R³, provided that the functional substituent does not interfere with the formation of the boron "ate" complex of formula (II).

[039] One embodiment of the invention relates to a process for preparing a boronic ester compound of formula (I), wherein R³ is a nucleofugic group. Such compounds are useful as intermediates for the synthesis of alpha-substituted boronic ester and acid compounds, including alpha-aminoboronic ester and acid compounds, as described below. In certain preferred embodiments, R³ is a nucleofugic group and R² is hydrogen.

[040] The variables R⁴ and R⁵ can be the same or different. In some embodiments, R⁴ and R⁵ are directly linked, so that R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring, which can have 0-2 additional ring heteroatoms selected from N, O, or S. In some embodiments, the ring is a 5- or 6-membered ring, preferably a 5-membered ring.

[041] The present invention is particularly advantageous for the Lewis acid promoted rearrangement of boron "ate" complexes of formula (II), wherein R⁴ and R⁵ are directly linked and together are a chiral moiety. One embodiment of the invention relates to the rearrangement of such chiral boron "ate" complexes to provide a boronic ester compound of formula (I) wherein the carbon atom bearing R¹, R², and R³ is a chiral center. The rearrangement reaction preferably proceeds with a high degree of stereodirection by the R⁴-R⁵ chiral moiety to provide the boronic ester compound of formula (I) having a diastereomeric ratio at the carbon atom bearing R¹, R², and R³ of at least about 96:4 relative to a chiral center in the R⁴-R⁵ chiral moiety. Preferably, the diastereomeric ratio is at least about 97:3.

[042] The terms "stereoisomer", "enantiomer", "diastereomer", "epimer", and "chiral center", are used herein in accordance with the meaning each is given in ordinary usage by those of ordinary skill in the art. Thus, stereoisomers are compounds that have the same atomic connectivity, but differ in the spatial arrangement of the atoms. Enantiomers are stereoisomers that have a mirror image relationship, that is, the stereochemical configuration at all corresponding chiral centers is opposite. Diastereomers are stereoisomers having more than one chiral center, which differ from one another in that the stereochemical configuration of at least one, but not all, of the corresponding chiral centers is opposite. Epimers are diastereomers that differ in stereochemical configuration at only one chiral center.

[043] As used herein, the term "diastereomeric ratio" refers to the ratio between diastereomers which differ in the stereochemical configuration at one chiral center, relative to a second chiral center in the same molecule. By way of example, a chemical structure

with two chiral centers provides four possible stereoisomers: R^*R , R^*S , S^*R , and S^*S , wherein the asterisk denotes the corresponding chiral center in each stereoisomer. The diastereomeric ratio for such a mixture of stereoisomers is the ratio of one diastereomer and its enantiomer to the other diastereomer and its enantiomer = $(R^*R + S^*S) : (R^*S + S^*R)$.

[044] One of ordinary skill in the art will recognize that additional stereoisomers are possible when the molecule has more than two chiral centers. For purposes of the present invention, the term "diastereomeric ratio" has identical meaning in reference to compounds with multiple chiral centers as it does in reference to compounds having two chiral centers. Thus, the term "diastereomeric ratio" refers to the ratio of all compounds having R^*R or S^*S configuration at the specified chiral centers to all compounds having R^*S or S^*R configuration at the specified chiral centers. For convenience, this ratio is referred to herein as the diastereomeric ratio at the asterisked carbon, relative to the second specified chiral center.

[045] The diastereomeric ratio can be measured by any analytical method suitable for distinguishing between diastereomeric compounds having different relative stereochemical configurations at the specified chiral centers. Such methods include, without limitation, nuclear magnetic resonance (NMR), gas chromatography (GC), and high performance liquid chromatography (HPLC) methods.

[046] As discussed above, one embodiment of the invention is directed to processes that provide a boronic ester compound of formula (I) having a diastereomeric ratio at the carbon atom bearing R^1 , R^2 , and R^3 of at least about 96:4 relative to a chiral center in the R^4 - R^5 chiral moiety. One of skill in the art will recognize that the R^4 - R^5 chiral moiety may itself contain more than one chiral center. When R^4 - R^5 does have more than one chiral center, it preferably has high diastereomeric purity, and the diastereomeric ratio at the carbon atom bearing R^1 , R^2 , and R^3 can be measured relative to any one of the chiral centers in R^4 - R^5 .

[047] In the processes of the invention, the R^4 - R^5 chiral moiety preferably has a high level of enantiomeric purity. For purposes of the invention, the term "enantiomeric purity" is used to mean "enantiomeric excess", which is the amount by which the major enantiomer is in excess of the minor enantiomer, expressed as a percentage of the total. Preferably, the R^4 - R^5 chiral moiety has an enantiomeric purity of at least about 98%, more preferably at least about 99%, still more preferably at least about 99.5%, and most preferably at least about 99.9%.

[048] When the R⁴-R⁵ chiral moiety has very high enantiomeric purity, the diastereomeric ratio at the carbon atom bearing R¹, R², R³ approximates the epimeric ratio at that center, *i.e.*, diastereomeric ratio $\equiv (R^*R) : (S^*R)$ or $(R^*S) : (S^*S) \equiv (R^*) : (S^*)$. As used herein, the term "epimeric ratio" refers to the ratio of product having one absolute stereochemical configuration at a given chiral center to product having the opposite absolute stereochemical configuration at the corresponding chiral center. Preferably, the products have identical stereochemical configuration at all other corresponding chiral centers. In one embodiment, therefore, the invention relates to the rearrangement of a chiral boron "ate" complex of formula (II) to provide a boronic ester compound of formula (I) wherein the epimeric ratio at the carbon atom bearing R¹, R², and R³ is at least about 96:4, more preferably at least about 97:3.

[049] Lewis acids suitable for use in the practice of the invention are those capable of complexing with the nucleofugic group to facilitate its displacement upon migration of R¹. Preferably, the Lewis acid is additionally capable of coordinating with an oxygen atom attached to boron. Nonlimiting examples of suitable Lewis acids include zinc bromide, zinc chloride, ferric bromide, and ferric chloride. In certain preferred embodiments, the Lewis acid is zinc chloride.

[050] The contacting step preferably is performed at low temperature, but may be performed at ambient or elevated temperature. The selection of an appropriate reaction temperature will depend largely on the Lewis acid employed, as well as the migratory aptitude of the R¹ moiety. One skilled in the art will be able to select a suitable temperature in view of the reaction conditions being used.

[051] In some embodiments, the contacting step is performed at a reaction temperature of at least about -100 °C, -78 °C, or -60 °C. In some embodiments, the contacting step is performed at a reaction temperature that is no greater than about 80 °C, 40 °C, or 30 °C. Any range encompassing these high and low temperatures are included within the scope of the invention. Preferably, the contacting step is performed at a reaction temperature in the range of about -100 °C to about 80 °C, about -70 °C to about 40 °C, about -60 °C to about 30 °C, or about -50 °C to about 30 °C. In certain preferred embodiments, the contacting step is begun at low temperature, preferably in the range of about -70 °C to about -30 °C, and then the reaction mixture is allowed to warm, preferably to ambient temperature.

[052] Surprisingly, the process of the present invention requires no special precautions to avoid the presence of water during the rearrangement reaction itself. In some

embodiments, moist Lewis acid is employed, with minimal deterioration in diastereomeric ratio. When used in reference to the Lewis acid, the term "moist" means that the water content of the Lewis acid is greater than about 100, 200, 500, or 1,000 ppm. Remarkably, the Lewis acid even can be added to the reaction mixture in the form of an aqueous solution without deleterious impact on diastereomeric ratio.

[053] In some embodiments, therefore, the process of the invention comprises the steps:

- (a) providing a solution comprising a boron "ate" complex of formula (II) and
 - (i) a coordinating ether solvent that has low miscibility with water; or
 - (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and
- (b) adding to the solution of step (a) a Lewis acid solution comprising water and a Lewis acid.

[054] In some other embodiments, the Lewis acid solution comprises tetrahydrofuran and a Lewis acid.

[055] Thus, unlike the prior art process, the process of the invention is readily amenable to large-scale production. In various embodiments, at least about 5, 10, 20, 50, 100, 500, or 1000 moles of boron "ate" complex of formula (II) is contacted with a Lewis acid under conditions that afford the boronic ester compound of formula (I). The invention further provides a composition comprising a boronic ester compound of formula (I), as described herein, and an ether solvent that has low miscibility with water. The composition preferably comprises at least about 5, 10, 20, 50, 100, 500, or 1000 moles of the boronic ester compound of formula (I). In certain embodiments, R⁴ and R⁵ together are a chiral moiety, and the compound of formula (I) present in the composition has a diastereomeric ratio of at least about 96:4 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety.

[056] Workup of the reaction preferably comprises washing the reaction mixture with an aqueous solution and concentrating the washed reaction mixture by removal of solvents to afford a residue comprising the boronic ester compound of formula (I). Preferably, the residue comprises at least about 5, 10, 20, 50, 100, 500, or 1000 moles of the boronic ester compound of formula (I). In those embodiments wherein R⁴-R⁵ is a chiral moiety, the boronic ester compound of formula (I) present in the residue preferably has a

diastereomeric ratio of at least about 96:4 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety. More preferably, the diastereomeric ratio is at least about 97:3.

[057] The boron "ate" complex of formula (II) can be prepared by any known method, but preferably is prepared by reaction of a boronic ester of formula (III):



with a reagent of formula (IV):



wherein each of M⁺, Y, and R¹ to R⁵ are as defined above for the boron "ate" complex of formula (II). In some embodiments, the reaction is performed at a reaction temperature of at least about -100 °C, -78 °C, or -60 °C. In some embodiments, the reaction is performed at a reaction temperature no greater than about 0 °C, -20 °C, or -40 °C. Any range encompassing these high and low temperatures are included within the scope of the invention. The reaction preferably is performed at a reaction temperature in the range of about -100 °C to about 0 °C, about -78 °C to about -20 °C, or about -60 °C to about -40 °C. In some embodiments, the boron "ate" complex of formula (II) is prepared in a solution comprising an ether solvent having low miscibility with water, and the reaction mixture is directly treated with a Lewis acid to effect rearrangement to the boron ester compound of formula (I).

[058] In some embodiments, the reagent of formula (IV) is formed *in situ*. Such embodiments include the steps:

(i) providing a solution comprising a boronic ester of formula (III), as defined above, and a compound of formula (V):



wherein R² and R³ are as defined above for the reagent of formula (IV); and

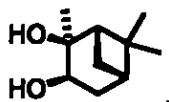
(ii) treating the solution with a strong, sterically hindered base to form the boron "ate" complex of formula (II).

[059] In some embodiments, the sterically hindered base is an alkali metal dialkylamide bases of formula $M^2N(R^*)_2$, where M^2 is Li, Na, or K, and each R^* , independently is a branched or cyclic C_{3-6} aliphatic. *In situ* formation of the reagent of formula (IV) is especially advantageous in those embodiments wherein Y is a nucleofugic group, due to the instability of the reagent of formula (IV).

[060] The boronic ester of formula (III) can be prepared by any known method, but typically is prepared by esterification of the corresponding boronic acid compound, e.g., by methods described in Brown *et al.*, *Organometallics*, 2: 1311-1316 (1983). Cyclic boronic esters of formula (III) preferably are prepared by:

- (a) providing a solution comprising:
 - (i) a boronic acid compound of formula $R^1-B(OH)_2$;
 - (ii) a compound of formula $HO-R^4-R^5-OH$, wherein R^4 and R^5 , taken together, are an optionally substituted linking chain comprising 2-5 carbon atoms and 0-2 heteroatoms selected from the group consisting of O, N, and S; and
 - (iii) an organic solvent that forms an azeotrope with water; and
- (b) heating the solution at reflux with azeotropic removal of water.

[061] As used in reference to R^4 and R^5 , the term "linking chain" refers to the shortest linear chain of atoms connecting the oxygen atoms to which R^4 and R^5 are attached. The linking chain optionally is substituted at any chain atom, and one or more chain atoms also may form part of a ring system that is spiro to, fused to, or bridging the linear linking chain. By way of example, but not limitation, in some embodiments, the compound of formula $HO-R^4-R^5-OH$ is pinanediol, having the structure:



In such embodiments, the linking chain R^4-R^5 comprises two carbon atoms, which together form one side of the bicyclo[3.1.1]heptane ring system, and one of which additionally is substituted with a methyl group.

[062] In some embodiments, the compound of formula $HO-R^4-R^5-OH$ is a chiral diol, preferably one having high diastereomeric and enantiomeric purity. One of skill in the art will appreciate that in such embodiment, the compound of formula $HO-R^4-R^5-OH$ is

employed as a chiral auxiliary to direct the stereochemical configuration at the carbon bearing R¹, R², and R³. Chiral diols useful as chiral auxiliaries in organic synthesis are well-known in the art. Nonlimiting examples include 2,3-butanediol, preferably (2*R*,3*R*)-(-)-2,3-butanediol or (2*S*,3*S*)-(+)-2,3-butanediol; pinanediol, preferably (1*R*,2*R*,3*R*,5*S*)-(-)-pinanediol or (1*S*,2*S*,3*S*,5*R*)-(+)-pinanediol; 1,2-cyclopentanediol, preferably (1*S*,2*S*)-(+)-*trans*-1,2-cyclopentanediol or (1*R*,2*R*)-(-)-*trans*-1,2-cyclopentanediol; 2,5-hexanediol, preferably (2*S*,5*S*)-2,5-hexanediol or (2*R*,5*R*)-2,5-hexanediol; 1,2-dicyclohexyl-1,2-ethanediol, preferably (1*R*,2*R*)-1,2-dicyclohexyl-1,2-ethanediol or (1*S*,2*S*)-1,2-dicyclohexyl-1,2-ethanediol; hydrobenzoin, preferably (*S*,*S*)-(-)-hydrobenzoin or (*R*,*R*)-(+)-hydrobenzoin; 2,4-pentanediol, preferably (*R*,*R*)-(-)-2,4-pentanediol or (*S*,*S*)-(+)-2,4-pentanediol; erythronic γ -lactone, preferably D-erythronic γ -lactone. Carbohydrates, *e.g.* a 1,2,5,6-symmetrically protected mannitol, also may be used as chiral diols.

[063] Nonlimiting examples of organic solvents suitable for use in the esterification reaction include acetonitrile, toluene, hexane, heptane, and mixtures thereof. In some embodiments, the organic solvent is an ether solvent, preferably an ether solvent that has low miscibility with water. In certain preferred embodiments, the esterification reaction is performed in an ether solvent that has low miscibility with water, and the product solution comprising the boronic ester of formula (III) is used directly in the next step, without isolation of the boronic ester.

[064] As noted above, the process of the present invention for the first time permits workup of large-scale reactions without significant deterioration in diastereomeric ratio. In another aspect, therefore, the invention provides a composition comprising at least about 5, 10, 20, 50, 100, 500, or 1000 moles of a boronic ester compound of formula (I):



wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered chiral ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, preferably at least about 97:3, relative to a chiral center in the R^4 - R^5 chiral moiety.

[065] Preferred values for R^1 to R^3 are as described above. Preferably, solvents constitute less than about 30% w/w, 20% w/w, 10% w/w, or 5% w/w of the composition according to this aspect of the invention. In some embodiments, the boronic ester compound of formula (I) constitutes at least about 70% w/w, 80% w/w, 90% w/w, or 95% w/w of the composition.

[066] One embodiment relates to the composition described above, wherein at least one of the following features is present:

- (a) R^3 is chloro;
- (b) the boronic ester compound (I) is



- (c) R^2 is hydrogen; and
- (d) R^1 is C_{1-4} aliphatic.

[067] All of the boronic ester compound of formula (I) present in the composition may be produced in a single batch run. For purposes of the invention, the term "batch run" refers to execution of a synthetic process, wherein each step of the process is performed only once. Preferably, the boronic ester compound of formula (I) present in the composition is prepared in a single batch run of the process according to the first aspect of the invention. One of ordinary skill in the art will appreciate that preparation of a given quantity of product by a single batch run of a large-scale process is more efficient and provides a more

homogeneous product than preparation of the same quantity of product by repeated execution of a small-scale process.

[068] The boronic ester compounds of formula (I) wherein R³ is a nucleofugic group are useful as intermediates for the synthesis of alpha-aminoboronic ester compounds. In another aspect, therefore, the invention provides a large-scale process for preparing an alpha-aminoboronic ester, preferably by a process comprising the steps:

- (a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation;

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen;

R³ is a nucleofugic group; and

each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

- (b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I):



where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and

(c) treating the boronic ester compound of formula (I) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and each G individually or together is an amino group protecting group to form a byproduct of formula M^1-R^3 and a compound of formula (VIII):



wherein each G and R^1 to R^5 are as defined above; and

(d) removing the G groups to form a compound of formula (VII):



or an acid addition salt thereof.

[069] In some embodiments, in step (c), the boronic ester compound of formula (I) is treated with a reagent of formula $M^1-N(Si(R^6)_3)_2$ where M^1 is an alkali metal and each R^6 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted.

[070] Reaction of the boronic ester compound of formula (I) with the reagent of formula $M^1-N(G)_2$ preferably is conducted at a reaction temperature in the range of about -100°C to about 50°C , preferably about -50°C to about 25°C , and more preferably about -30°C to about 0°C . In some embodiments, R^3 is halo, preferably chloro, and M^1 is Li. To facilitate isolation of the product of formula (VIII), the reaction mixture preferably comprises an organic solvent in which the byproduct M^1-R^3 has low solubility. Nonlimiting examples of suitable organic solvents include methylcyclohexane, cyclohexane, heptane, hexane, and toluene. In some embodiments, step (c) further comprises filtering the reaction mixture to remove M^1-R^3 and provide a filtrate comprising the compound of formula (VIII). Preferably, the filtrate is used directly in step (d).

[071] In those embodiments wherein the reaction mixture comprises an organic solvent in which the byproduct M^1-R^3 has low solubility, the reaction mixture may additionally comprise a solvent in which the byproduct M^1-R^3 has high solubility. In such cases, the solvent in which the byproduct M^1-R^3 has high solubility preferably is removed prior to filtration of the reaction mixture. By way of example, in some embodiments, a reagent of formula $M^1-N(Si(R^6)_3)_2$ is added to the reaction mixture as a solution comprising

tetrahydrofuran. In such embodiments, step (c) preferably further comprises removing the tetrahydrofuran before filtering the reaction mixture.

[072] Those of skill in the art are aware of various methods that can be used to remove the protecting groups G in the compound of formula (VIII), including, *e.g.*, aqueous hydrolysis or treatment with acid. The product alpha-aminoboronic ester of formula (VII) has low stability and preferably is immediately derivatized (Matteson *et al.*, *J. Am. Chem. Soc.*, 103:5241 (1981)) or is isolated as an acid addition salt. In some embodiments, step (d) comprises treating the compound of formula (VIII) with an acid and isolating the compound of formula (VII) as the acid addition salt. In certain preferred embodiments, the acid is trifluoroacetic acid, and the compound of formula (VII) is isolated as the trifluoroacetic acid addition salt.

[073] As discussed above, the processes of the invention are particularly well-suited for preparing alpha-aminoboronic ester compounds of formula (VII), wherein the alpha carbon is a chiral center. Thus, one embodiment of the invention relates to a large-scale process for preparing an alpha-aminoboronic ester compound of formula (VIIa) or (VIIb):



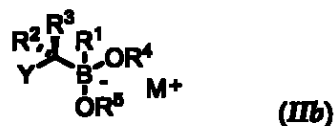
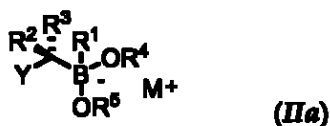
or an acid addition salt thereof, wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted chiral cyclic boronic ester;

said process comprising:

(a) providing a boron "ate" complex of formula (IIa) or (IIb):



where

Y is a nucleofugic group;

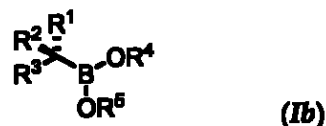
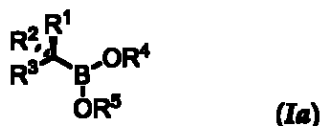
M⁺ is a cation;

R² is hydrogen;

R³ is a nucleofugic group; and

R⁴ and R⁵ are as defined above;

(b) contacting the boron "ate" complex of formula (IIa) or (IIb) with a Lewis acid under conditions that afford a boronic ester compound of formula (Ia) or (Ib):

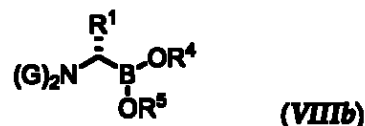
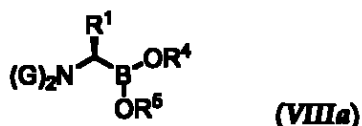


where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent; and

(c) treating the boronic ester compound of formula (Ia) or (Ib) with a reagent of formula M¹-N(G)₂, where M¹ is an alkali metal and G is an amino group protecting moiety, to form a compound of formula (VIIIa) or (VIIIb):



wherein each G and R¹ to R⁵ are as defined above; and

(d) removing the G groups to form a compound of formula (VIIa) or (VIIb):



or an acid addition salt thereof.

[074] Preferred values for Y, M⁺, R¹ to R⁵, and G are as described above. The compound of formula (VIIa) or (VIIb) preferably has a diastereomeric ratio at the alpha-carbon of at least about 96:4, more preferably at least about 97:3, relative to a chiral center in the R⁴-R⁵ chiral moiety.

[075] The alpha-aminoboronic ester compounds of formula (VII) are useful synthetic intermediates for the preparation of peptidyl boronic ester compounds. In some embodiments, therefore, the process according to this aspect of the invention further comprises coupling the compound of formula (VII) with a compound of formula (IX):



wherein:

P¹ is an amino group blocking moiety;

R⁷ is selected from the group consisting of hydrogen, C₁₋₁₀aliphatic, optionally substituted C₆₋₁₀aryl, or C₁₋₆aliphatic-R⁸; and

R⁸ is selected from the group consisting of alkoxy, alkylthio, optionally substituted aryl, heteroaryl, and heterocyclyl groups, and optionally protected amino, hydroxy, and guanidino groups; and

X is OH or a leaving group;

to form a compound of formula (X):



wherein each of P¹, R¹, R⁴, R⁵, and R⁷ is as defined above.

[076] The leaving group X is any group capable of nucleophilic displacement by the alpha-amino group of the compound of formula (VII). In some embodiments, the moiety -C(O)-X is an activated ester, such as an O-(N-hydroxysuccinimide) ester. In some embodiments, an activated ester is generated *in situ* by contacting a compound of formula (IX), wherein X is OH, with a peptide coupling reagent. Examples of suitable peptide coupling reagents include, without limitation, carbodiimide reagents, *e.g.*, dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC); phosphonium reagents, *e.g.*, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent); and uronium reagents, *e.g.*, O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU).

[077] Those of skill in the art also are aware of procedures that permit the direct coupling of silyl protected amines, without a prior deprotection step. In such procedures, the silyl groups are removed *in situ* under the coupling reaction conditions. In some embodiments of the present invention, therefore, a compound of formula (VIII) is contacted with a compound of formula (IX) under conditions that remove the (R⁶)₃Si groups *in situ* and form a compound of formula (X).

[078] For purposes of the invention, the term "amino-group blocking moiety" refers to any group used to derivatize an amino group, especially an N-terminal amino group of a peptide or amino acid. The term "amino-group blocking moiety" includes, but is not limited to, protecting groups that are commonly employed in organic synthesis, especially peptide synthesis. See, for example, Gross and Mienhoffer, eds., *The Peptides*, Vol. 3, Academic Press, New York, 1981, pp. 3-88; Green and Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley and Sons, Inc., New York, 1999. Unless otherwise specified, however, it is not necessary for an amino-group blocking moiety to be readily cleavable. Amino-group blocking moieties include, *e.g.*, alkyl, acyl, alkoxycarbonyl, aminocarbonyl, and sulfonyl moieties. In some embodiments, the amino-group blocking moiety is an acyl moiety derived from an amino acid or peptide, or a derivative or analog thereof.

[079] As used herein, the term "amino acid" includes both naturally occurring and unnatural amino acids. For purposes of the invention, a "derivative" of an amino acid or peptide is one in which a functional group, *e.g.*, a hydroxy, amino, carboxy, or guanidino group at the N-terminus or on a side chain, is modified with a blocking group. As used herein, an "analog" of an amino acid or peptide is one which includes a modified backbone or side chain. The term "peptide analog" is intended to include peptides wherein one or more stereocenters are inverted and one or more peptide bonds are replaced with a peptide isostere.

[080] In some embodiments, P¹ is a cleavable protecting group. Examples of cleavable protecting groups include, without limitation, acyl protecting groups, *e.g.*, formyl, acetyl (Ac), succinyl (Suc), or methoxysuccinyl (MeOSuc), and urethane protecting groups, *e.g.*, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), or fluorenylmethoxycarbonyl (Fmoc).

[081] In some such embodiments, the process according to this aspect of the invention further comprises the steps:

- (f) removing the protecting group P¹ to form a compound of formula (XI):



or an acid addition salt thereof, wherein each of R¹, R⁴, R⁵, and R⁷ is as defined above; and

- (g) coupling the compound of formula (XI) with a reagent of formula P²-X, wherein P² is any amino group blocking moiety, as described above, and X is a leaving group, to form a compound of formula (XII):



wherein each of P², R¹, R⁴, R⁵, and R⁷ are as defined above. One of skill in the art will recognize that in those embodiments wherein P² is an acyl group, including, *e.g.*, an acyl moiety derived from an amino acid or peptide, or an analog or derivative thereof, the leaving group X may be generated *in situ*, as discussed above for the compound of formula (IX).

[082] In each of the compounds (X) and (XII), the boronic acid moiety is protected as a boronic ester. If desired, the boronic acid moiety can be deprotected by any method known in the art. Preferably, the boronic acid moiety is deprotected by transesterification in a biphasic mixture. More preferably, the boronic acid deprotecting step comprises the steps:

- (i) providing a biphasic mixture comprising the boronic ester compound of formula (X) or (XII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₈ hydrocarbon solvent, and aqueous mineral acid;
- (ii) stirring the biphasic mixture to afford the corresponding deprotected boronic acid compound of formula (Xa) or (XIII):



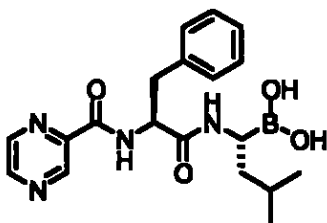
- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (Xa), (XIII), or a boronic acid anhydride thereof, into an organic solvent.

[083] The organic boronic acid acceptor in step (i) preferably is an aliphatic, aryl, or ar(aliphatic)boronic acid. In some embodiments, the boronic acid acceptor is selected from the group consisting of phenylboronic acid, benzylboronic acid, butylboronic acid, pentylboronic acid, hexylboronic acid, and cyclohexylboronic acid. In certain embodiments, the boronic acid acceptor is isobutylboronic acid. In some embodiments, the boronic acid acceptor is selected so that the boronic ester compound of formula (III) is formed as a byproduct of the deprotection reaction. The boronic ester compound of formula (III) can then be used in another batch run of the process described above. In such embodiments, the moiety R^4 - R^5 is effectively recycled, which may be particularly advantageous if R^4 - R^5 is an expensive chiral moiety.

[084] To enhance the purity of the product, the aqueous layer containing the compound of formula (Xa) or (XIII) preferably is washed to remove neutral organic impurities prior to the extracting step (iv). In such embodiments, step (iii) preferably comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6.

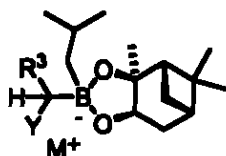
[085] In some embodiments, the invention relates to an improved process for manufacturing the proteasome inhibitor bortezomib. Thus, in one embodiment, the invention provides a large-scale process for forming a compound of formula (XIV):



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

- (a) providing a boron "ate" complex of formula (XV):



(XV)

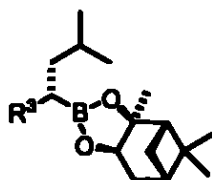
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M^+ is an alkali metal;

(b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



(XVI)

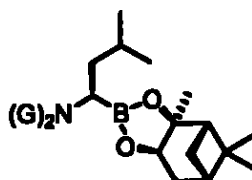
said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a

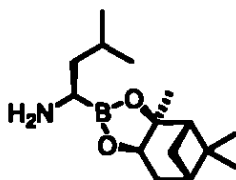
coordinating co-solvent;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(G)_2$, where M^1 is an alkali metal and each G individually or together is an amino group protecting group, to form a compound of formula (XVII):



(XVII)

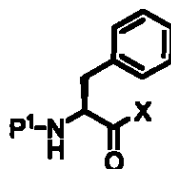
(d) removing the G groups to form a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XIX);



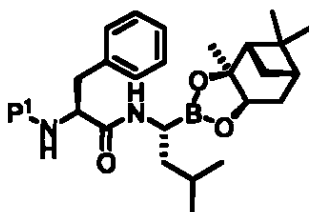
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

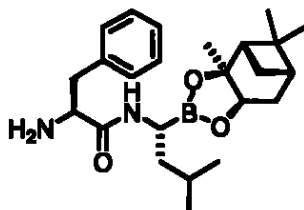
to form a compound of formula (XX):



(XX)

wherein P¹ is as defined above;

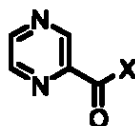
(f) removing the protecting group P¹ to form a compound of formula (XXI):



(XXI)

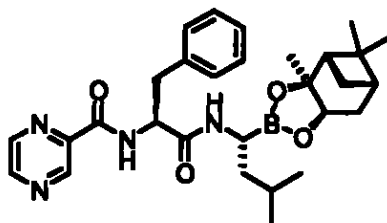
or an acid addition salt thereof;

(g) coupling the compound of formula (XXI) with a reagent of formula (XXII)



(XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(XXIII) ; and

(h) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

[086] In some embodiments, the process is characterized by at least one of the following features (1)-(5). In certain preferred embodiments, the process is characterized by all five features (1)-(5) below.

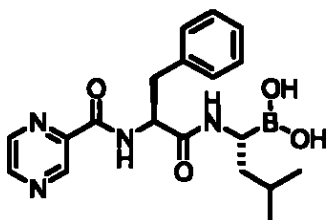
- (1) In the boron "ate" complex of formula (XV), R³ and Y both are chloro.
- (2) The coupling step (e) comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) The protecting group removing step (f) comprises the steps:
 - (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt.
- (4) The coupling step (g) comprises the steps:
 - (i) coupling the compound of formula (XXI) with 2-pyrazinecarboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;

- (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (5) The boronic acid deprotecting step (h) comprises the steps:
- (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₈ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent

[087] Preferably, step (h)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

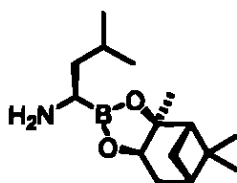
[088] In another embodiment, the invention relates to a large-scale process for forming a compound of formula (XIV)



(XIV)

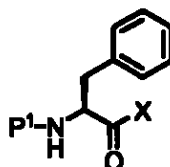
or a boronic acid anhydride thereof, comprising the steps:

- (aa) coupling a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof, with a compound of formula (XIX):



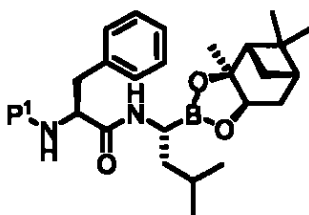
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

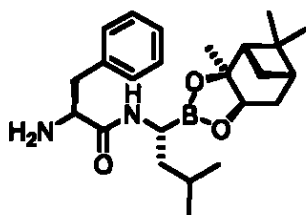
to form a compound of formula (XX):



(XX)

wherein P¹ is as defined above, said coupling step (aa) comprising the steps:

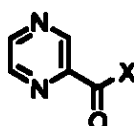
- (i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution;
- (bb) removing the protecting group P¹ to form a compound of formula (XXI):



(XXI)

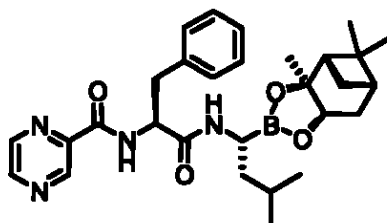
or an acid addition salt thereof, said protecting group removing step (bb) comprising the steps:

- (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt;
- (cc) coupling the compound of formula (XXI) with a reagent of formula (XXII)



(XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(XXIII),

said coupling step (cc) comprising the steps:

- (i) coupling the compound of formula (XXI) with 2-pyrazinecarboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution; and
- (dd) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof, said deprotecting step (dd) comprising the steps:

- (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₃₋₆ hydrocarbon solvent, and aqueous mineral acid;
- (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

[089] Preferably, step (dd)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

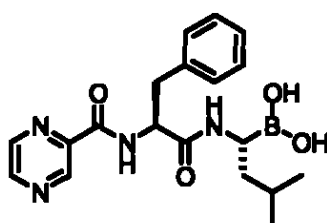
[090] The efficiency of the processes described above is further enhanced by telescoping steps, for example, by carrying a reaction mixture or worked-up product solution from one reaction directly into the following reaction, without isolation of the intermediate product. For example, in some embodiments, step (e)(iii) or (aa)(iii) affords an ethyl acetate solution comprising a compound of formula (XX), and the ethyl acetate solution is directly subjected in step (f) or (bb) to conditions effective to remove the protecting group P¹. In some such embodiments, the protecting group P¹ is an acid-labile protecting group, for example, *tert*-butoxycarbonyl (Boc), and the ethyl acetate solution from step (e)(iii) or (aa)(iii) is treated with acid. In certain preferred embodiments, the ethyl acetate solution from step (e)(iii) or (aa)(iii) is dried azeotropically and then treated with gaseous HCl.

[091] When the deprotecting step (f) or (bb) is performed under anhydrous conditions, as described above, the product of formula (XXI) can be isolated by crystallization from the reaction mixture as its HCl addition salt. Crystallization of the product salt is promoted by addition of a hydrocarbon solvent such as *n*-heptane. In some embodiments, the reaction mixture is partially concentrated prior to addition of the hydrocarbon solvent. The present inventors have discovered that crystallization of the

compound of formula (XXI) in this manner efficiently removes any tripeptide impurity that may have formed during the coupling step (e) or (aa). Such impurities are difficult to remove at later stages in the synthesis.

[092] Further telescoping of the process is possible by carrying the product mixture from the coupling step (g) or (cc) directly into the boronic acid moiety deprotecting step (h) or (dd). Preferably, the organic solvent from the coupling reaction is first replaced with ethyl acetate in order to facilitate aqueous washes. A second solvent exchange into a hydrocarbon solvent then permits the product solution from step (g) or (cc) to be used directly in the biphasic boronic acid deprotecting step (h) or (dd), without isolation of the compound of formula (XXII).

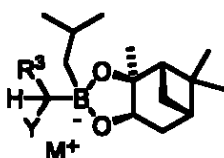
[093] Alternatively, a more convergent approach may be adopted for the synthesis of the compound of formula (XIV). Thus, in yet another embodiment, the invention provides a large-scale process for forming a compound of formula (XIV)



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

- (a) providing a boron "ate" complex of formula (XV):



(XV)

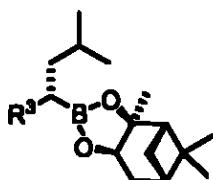
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M^+ is an alkali metal;

- (b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



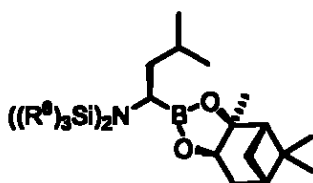
(XVI)

said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a

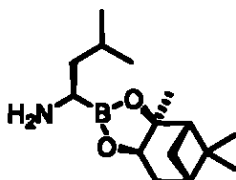
coordinating co-solvent;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(Si(R^6)_3)_2$, where M^1 is an alkali metal and each R^6 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a compound of formula (XVII):



(XVII)

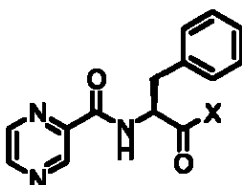
- (d) removing the $(R^6)_3Si$ groups to form a compound of formula (XVIII):



(XVIII)

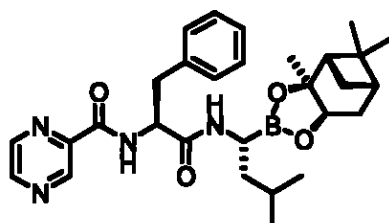
or an acid addition salt thereof;

(e') coupling the compound of formula (XVIII) with a compound of formula (XIXa):



(XIXa)

wherein X is OH or a leaving group, to form a compound of formula (XXIII):



(XXIII) ; and

(F) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

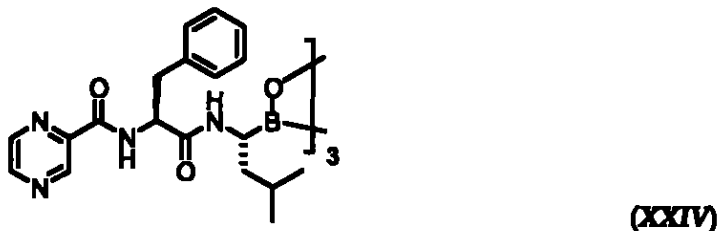
[094] In some embodiments, the process is characterized by at least one of the following features (1)-(3). In certain preferred embodiments, the process is characterized by all three features (1)-(3) below.

- (1) In the boron "ate" complex of formula (XV), R³ and Y both are chloro.
- (2) The coupling step (e') comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XIXa) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) The boronic acid deprotecting step (f') comprises the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₅₋₈ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

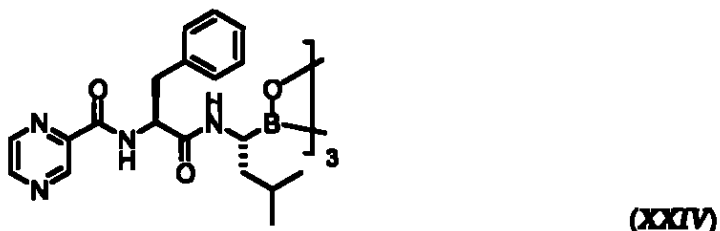
[095] Preferably, step (f')(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 6;

[096] In step (h)(iv), (dd)(iv), or (f)(iv) of the processes described above, the compound of formula (XIV), or a boronic acid anhydride thereof, preferably is extracted into ethyl acetate and crystallized by addition of hexane or heptane. In some embodiments, the process further comprises isolation of a boronic acid anhydride of the compound of formula (XIV), preferably a trimeric boronic acid anhydride of formula (XXIV):



[097] The processes of the invention permit the large-scale manufacture of bortezomib of very high chemical and stereochemical purity. Prior art processes were limited in scale and afforded product of lower overall purity. In yet another aspect, therefore, the invention provides a composition comprising at least one kilogram of a compound of formula (XXIV):



The compound of formula (XXIV) preferably is prepared according to the process described above, and preferably constitutes at least 99% w/w of the composition according to this aspect of the invention.

EXAMPLES

Abbreviations

BOC	<i>tert</i> -butoxycarbonyl
D.I.	de-ionized
DMF	<i>N,N</i> -dimethylformamide
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hours
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
LOD	loss on drying
min	minutes
MTBE	<i>t</i> -butyl methyl ether
RP-HPLC	reverse phase high performance liquid chromatography
RPM	revolutions per minute
TBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
THF	tetrahydrofuran

Example 1: (1*R*)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate Manufacturing Process

(1*S*)-(S)-Pinanediol 1-chloro-3-methylbutane-1-boronate

1. (S)-Pinanediol-2-methylpropane-1-boronate (12.0 kg, 50.8 moles) was charged to a reaction vessel maintained under a nitrogen atmosphere.
2. *tert*-Butyl methyl ether (53 kg) and dichloromethane (22.5 kg) were charged and the resultant mixture was cooled to -57 °C with stirring.

3. Diisopropylamine, (6.7 kg) was charged to another reaction vessel maintained under a nitrogen atmosphere.
4. *tert*-Butyl methyl ether (27 kg) was charged to the diisopropylamine and the resultant mixture was cooled to -10 °C with stirring.
5. *n*-Hexyllithium in hexane (33.2 weight% solution) (17.6 kg) was added to the diisopropylamine mixture over a period of 57 minutes, while the reaction temperature was maintained at -10 °C to -7 °C.
6. This mixture (LDA-mixture) was stirred for 33 minutes at -9 °C to -7 °C before it was used.
7. Zinc chloride, (12.1 kg) was charged to a third reaction vessel maintained under a nitrogen atmosphere.
8. *tert*-Butyl methyl ether (16 kg) was charged to the zinc chloride and the resultant mixture was warmed to 30 °C with stirring.
9. Tetrahydrofuran (53 kg) was added to the zinc chloride suspension over a period of 18 minutes, while the reaction temperature was maintained at 35 °C to 40 °C.
10. This mixture (ZnCl₂-mixture) was stirred for 4 hours and 28 minutes at 38 °C to 39 °C until it was used.
11. The LDA-mixture (from # 3 - 6) was added over a period of 60 minutes to the reaction vessel containing (*S*)-pinanediol-2-methylpropane-1-boronate, while the reaction temperature was maintained at -60 °C to -55 °C.
12. A *tert*-butyl methyl ether rinse (10 kg) was used to complete the addition.
13. The reaction mixture was stirred for an additional 20 minutes at -59 °C to -55 °C.
14. The reaction mixture was warmed to -50 °C over a period of 11 minutes.
15. The ZnCl₂-mixture (from # 7 - 10) was added over a period of 48 minutes to the reaction vessel containing (*S*)-pinanediol-2-methylpropane-1-boronate and the LDA-mixture, while the reaction temperature was maintained at -50 °C to -45 °C.
16. A *tert*-butyl methyl ether rinse (10 kg) was used to complete the addition.
17. The reaction mixture was stirred for an additional 30 minutes at -45 °C to -40 °C and then warmed to 10 °C over a period of 81 minutes.

18. A 10% sulfuric acid solution (72 kg) was added over a period of 40 minutes to the reaction vessel, while the reaction temperature was maintained at 10 °C to 21 °C.
19. The reaction mixture was stirred for 16 minutes at ambient temperature, before the aqueous phase was separated.
20. The organic phase was washed successively with deionized (D.I.) water (32 kg), and 10% sodium chloride solution (26.7 kg), each wash involved vigorous stirring for 15 to 17 minutes at ambient temperature.
21. The reaction mixture was concentrated under reduced pressure ($p_{\min} = 81$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C, providing a residue which was dissolved in methylcyclohexane (56 kg).
22. The reaction mixture was refluxed (in a Dean-Stark type condenser for water separation) under reduced pressure ($p_{\min} = 67$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C for 2 hours and 7 minutes, until no more water was separated.
23. About 35 L of the solvents were distilled off under reduced pressure ($p_{\min} = 81$ mbar), maintaining an external (jacket/bath) temperature of 50 °C to 55 °C.
24. The resultant dry methylcyclohexane mixture containing (1S)-(S)-pinanediol 1-chloro-3-methylbutane-1-boronate was cooled to 14 °C.

(1R)-(S)-Pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate

1. Lithium bis(trimethylsilyl)amide in tetrahydrofuran (19.4 weight% solution), (41.8 kg) was charged to a reaction vessel maintained under a nitrogen atmosphere and cooled to -19 °C with stirring.
2. The methylcyclohexane mixture containing (1S)-(S)-pinanediol 1-chloro-3-methylbutane-1-boronate was added over a period of 55 minutes, while the reaction temperature was maintained at -19 °C to -13 °C.
3. A methylcyclohexane rinse (5 kg) was used to complete the addition.
4. The reaction mixture was stirred for an additional 65 minutes at -13 °C to -12 °C and then warmed to 25 °C over a period of 25 minutes.
5. A suspension of Celite (25 kg) in methylcyclohexane (22 kg) was added to the reaction mixture.

6. The reaction mixture was concentrated under reduced pressure ($p_{\text{mm}} = 25$ mbar), maintaining an external (jacket/bath) temperature of 45 °C to 50 °C, providing a residue which was dissolved in methylcyclohexane (36 kg).
7. A sample was then removed for in-process testing for tetrahydrofuran content by GC.
8. The tetrahydrofuran assay was 0.58%.
9. The solids were removed by filtration, the filtrate was filtered through a plug of Silica Gel (2.0 kg).
10. Both filter units were washed with isopropyl ether (30 kg).
11. The resultant methylcyclohexane/isopropyl ether mixture containing (1R)-(S)-pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate was stored in a container at ambient temperature until it was used in the next step.

(1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate

1. Trifluoroacetic acid, (12 kg) was charged to another reaction vessel maintained under a nitrogen atmosphere.
2. Isopropyl ether (78 kg) was charged to the trifluoroacetic acid and the resultant mixture was cooled to -10 °C with stirring.
3. The methylcyclohexane/isopropyl ether mixture containing (1R)-(S)-pinanediol 1-bis(trimethylsilyl)amino-3-methylbutane-1-boronate was added over a period of 53 minutes causing product precipitation, while the reaction temperature was maintained at -10 °C to -5 °C.
4. An isopropyl ether rinse (5 kg) was used to complete the addition.
5. The reaction mixture was stirred for an additional 8 hours and 20 minutes at -9 °C to -7 °C.
6. The solid was collected by filtration, washed with isopropyl ether (70 kg) in two portions, and dried under reduced pressure ($p_{\text{min}} = 56$ mbar) at 41 °C to 42 °C for 2 hours and 15 minutes.
7. The solid was stirred with D.I. water (60 kg) for 24 minutes at ambient temperature, before the D.I. water was removed by filtration.
8. The solid was washed with D.I. water (12 kg).

9. The solid was then dried under vacuum ($p_{min} = 4$ mbar) at 40 °C to 44 °C for 9 hours and 22 minutes, after that time the loss on drying was 0.51 %, which meets the $\leq 1\%$ requirement.
10. The intermediate, (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude, was then packaged into single polyethylene bags in polypropylene drums and labeled. The yield was 72%.

Recrystallization of (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude

1. (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, crude, (13 kg) was charged to a reaction vessel maintained under a nitrogen atmosphere.
2. Trifluoroacetic acid (31 kg) was charged to the reaction vessel and the resultant mixture was cooled to 4 °C with stirring.
3. Once all of the solid was dissolved leaving a slightly turbid mixture, isopropyl ether (29 kg) was added over a period of 57 minutes, while the reaction temperature was maintained at 2 °C to 3 °C.
4. After complete addition the mixture was filtered through a filter into a receiving vessel maintained under a nitrogen atmosphere.
5. Reactor and filter were rinsed with a mixture of trifluoroacetic acid (3.8 kg) and isopropyl ether (5 kg). The rinse was added to the filtrate.
6. Isopropyl ether (126 kg) was added over a period of 15 minutes causing product precipitation, while the reaction temperature was maintained at 16 °C to 18 °C.
7. The mixture was stirred at 16 °C to 18 °C for 15 min, then cooled to -5 °C over a period of 67 minutes, and stirred at -3 °C to -5 °C under a nitrogen atmosphere for 89 minutes.
8. The solid was then isolated by filtration, washed with isopropyl ether (48 kg) in two portions, and dried under vacuum ($p_{min} = 2$ mbar) at 34 °C to 40 °C for 2 hours and 55 minutes after that time the loss on drying was 0.32%, which meets the $\leq 0.5\%$ requirement.
9. The product, (1R)-(S)-pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate, was then packaged into double polyethylene bags in fiber drums and labeled. The yield was 86%.

**Example 2: N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride
Manufacturing Process****(1S,2S,3R,5S)-Pinanediol N-BOC-L-phenylalanine-L-leucine boronate**

1. In a fume hood, a three-necked glass reaction flask equipped with a Claisen head temperature recorder and a mechanical stirrer was flushed with nitrogen.
2. (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate (2.0 kg), was charged to the flask.
3. BOC-L-phenylalanine (1.398 kg) was charged to the flask.
4. 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, TBTU (1.864 kg) was charged to the flask.
5. Dichloromethane (15.8 L) was charged to the flask.
6. The stirring motor was adjusted to provide stirring at 260 RPM.
7. Using an ice/water cooling bath, the reaction mixture was cooled to 1.0 °C, maintaining a nitrogen atmosphere.
8. N,N-Diisopropylethylamine (2.778 L) was charged to a glass flask and transferred to the reaction mixture over a period of 117 minutes using a peristaltic pump maintaining a reaction temperature range of 0.7 °C – 2.1 °C. The overall addition rate was 23.7 mL/min.
9. A dichloromethane (0.2 L) rinse of the flask into the reaction mixture was used to complete the addition.
10. The reaction mixture was stirred for an additional 35 minutes. The temperature at the start of the stir time was 1.8 °C, and 2.5 °C at the end.
11. A sample was then removed for in-process testing by reverse phase high performance liquid chromatography (RP-HPLC). The percent conversion was determined to be 99.3%.
12. The reaction mixture was transferred in approximately two equal halves to two rotary evaporator flasks. The reaction mixture was concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 29-30 °C.

13. Ethyl acetate (4.0 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks.
14. The mixtures in each flask were again concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 29-30 °C.
15. The residues in each rotary evaporator flask were then transferred back to the reaction flask using ethyl acetate (13.34 L).
16. In a glass flask equipped with a stirrer, a 1% aqueous phosphoric acid solution was prepared by mixing D.I. water (13.18 L) and phosphoric acid (0.160 kg).
17. In a glass flask equipped with a stirrer, a 2% aqueous potassium carbonate solution (12.0 L) was prepared by mixing D.I. water (11.76 L) and potassium carbonate (0.24 kg).
18. In a glass flask equipped with a stirrer, a 10% aqueous sodium chloride solution (13.34 L) was prepared by mixing D.I. water (13.34 L) and sodium chloride (1.334 kg).
19. D.I. water (13.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 380 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred under vacuum to a suitable flask and discarded.
20. Again, D.I. water (13.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 385 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred under vacuum to a suitable flask and discarded.
21. The 1% phosphoric acid solution prepared in Step 16 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 365 RPM for 7 minutes. The layers were allowed to separate and the acidic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
22. The 2% potassium carbonate solution prepared in Step 17 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 367 RPM for 7 minutes. The layers were allowed to separate and the basic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
23. The 10% sodium chloride solution prepared in Step 18 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 373 RPM for 6

minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.

24. The ethyl acetate solution was transferred to a rotary evaporator flask and concentrated under reduced pressure using a rotary evaporator, maintaining a bath temperature of 29-30 °C, to provide a residue.
25. The residue was then redissolved in ethyl acetate (4.68 L).
26. The solution was concentrated under vacuum using a rotary evaporator, maintaining a bath temperature of 29-30 °C, to provide a residue once more.
27. Again, the residue was then redissolved in ethyl acetate (4.68 L) and two samples taken for determination of water content by Karl Fisher titration. The water content of two samples was determined as 0.216 % and 0.207 %.
28. Using a further quantity of ethyl acetate (12.66 L), the mixture was transferred from the rotary evaporator flask to a dry reaction flask equipped with a temperature recorder, a mechanical stirrer, and a fritted gas dispersion tube, and purged with nitrogen.

(1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt

1. The ethyl acetate solution containing (1S,2S,3R,5S)-pinanediol N-BOC-L-phenylalanine-L-leucine boronate was cooled using an ice/water cooling bath to -0.9 °C.
2. Hydrogen chloride (1.115 kg) gas was bubbled into the reaction mixture over a period of 1.48 hours. The temperature at the start of the addition was -0.9 °C, and 6.8 °C at the end.
3. The reaction was then allowed to warm to 14.4 °C over 50 minutes, while maintaining a nitrogen atmosphere.
4. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 68.9 % (area %).
5. The reaction was stirred for 35 minutes. The temperature at the start was 14 °C, and 14.8 °C at the end.
6. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 94.7% (area %).

7. The reaction was stirred for approximately a further 50 minutes, maintaining a temperature of $10\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$.
8. A sample was removed for in-process testing by RP-HPLC. The percent conversion was 97.3%.
9. The reaction was stirred for approximately a further 50 minutes, maintaining a temperature of $10\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$. The final temperature was $14.6\text{ }^{\circ}\text{C}$.
10. A sample was removed for in-process testing by RP-HPLC. The total reaction time after addition of hydrogen chloride gas was four (4) hours.
11. The percent conversion was 99%.
12. A slurry was observed.
13. n-Heptane (8.8 L) was charged to the reaction mixture.
14. The slurry was stirred for 2 hours. The temperature at the start of the stir time was $12.7\text{ }^{\circ}\text{C}$, and $15.3\text{ }^{\circ}\text{C}$ at the end.
15. The solid was isolated by filtration on a Buchner funnel lined with a polypropylene felt filter pad.
16. The solid was washed with n-heptane (4.68 L).
17. In a hood, the solid was transferred to three drying trays at not more than 1" deep and air-dried for 1 hour.
18. The solid was then dried at $\leq 35\text{ }^{\circ}\text{C}$ under a vacuum of 27" of Hg for 16 hours 28 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.
19. The solid was sampled from each drying tray to determine the % Loss on Drying. The LOD was determined to be 0 %, 0.02 %, and 0.02 % on the three samples taken.
20. (1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt was then packaged into double poly bags in fiber drums and labeled, and sampled.
21. The isolated yield was 1.87 kg, 79.1%. The intermediate was stored at $2-8\text{ }^{\circ}\text{C}$ until used in further manufacturing.

(1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate

1. In a fume hood a three-necked glass reaction flask equipped with a Claisen head, temperature recorder and a mechanical stirrer was flushed with nitrogen.
2. (1S,2S,3R,5S)-Pinanediol L-phenylalanine-L-leucine boronate, HCl salt (1.85 kg) was charged to the flask.
3. 2-Pyrazinecarboxylic acid (0.564 kg) was charged to the flask.
4. 2-(H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, TBTU (1.460 kg) was charged to the flask.
5. Dichloromethane (18.13 L) was charged to the flask.
6. The stirring motor was adjusted to provide stirring at 272 RPM.
7. Using a cooling bath, the reaction mixture was cooled to -1.2 °C.
8. N,N-Diisopropylethylamine (1.865 kg) was charged to a glass flask and transferred to the reaction over a period of 50 minutes using a peristaltic pump maintaining a reaction temperature range of -1.2 °C to 2.8 °C.
9. A dichloromethane rinse (0.37 L) of the flask into the reaction mixture was used to complete the addition.
10. The reaction mixture was allowed to warm and stirred for an additional 81 minutes.
11. The temperature at the start of the stir time was 15 °C, and 24.9 °C at the end.
12. A sample was then removed for in-process testing by RP-HPLC. The percent conversion was determined to be 99.9%.
13. The reaction mixture was transferred in approximately two equal halves to two rotary evaporator flasks. The reaction mixture was concentrated under reduced pressure using two rotary evaporators, maintaining an external bath temperature of 33-34 °C.
14. Ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks.
15. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 33-34 °C.

16. The residues in each rotary evaporator flask were then transferred back to the reaction flask using ethyl acetate (12.95 L).
17. In a glass flask equipped with a stirrer, a 1% aqueous phosphoric acid solution (12.34 L) was prepared by mixing D.I. water (12.19 L) and phosphoric acid (0.148 kg).
18. In a glass flask equipped with a stirrer, a 2% aqueous potassium carbonate solution (12.34 L) was prepared by mixing D.I. water (12.09 L) and potassium carbonate (0.247 kg).
19. In a glass flask equipped with a stirrer, a 10% aqueous sodium chloride solution (12.34 L) was prepared by mixing D.I. water (12.34 L) and sodium chloride (1.234 kg).
20. D.I. water (12.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 382 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
21. Again, D.I. water (12.34 L) was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 398 RPM for 7 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
22. The 1% phosphoric acid solution prepared in Step 17 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 364 RPM for 8 minutes. The layers were allowed to separate and the acidic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
23. The 2% potassium carbonate solution prepared in Step 18 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 367 RPM for 8 minutes. The layers were allowed to separate and the basic aqueous phase (bottom layer) was transferred to a suitable flask and discarded.
24. The 10% sodium chloride solution prepared in Step 19 was charged to the reaction flask containing the ethyl acetate solution and the mixture stirred at 374 RPM for 8 minutes. The layers were allowed to separate and the aqueous phase (bottom layer) was transferred to a suitable flask and discarded.

25. The ethyl acetate solution was transferred under vacuum in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 34 °C.
26. n-Heptane (14.8 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 34 °C.

N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude

1. In a glass flask equipped with a stirrer, a 1N solution of hydrochloric acid (22.2 L) was prepared by mixing D.I. water (20.36 L) and hydrochloric acid (1.84 kg).
2. In a glass flask equipped with a stirrer, a 2N sodium hydroxide solution (12.03 L) was prepared by mixing D.I. water (12.03 L) and sodium hydroxide (0.962 kg).
3. The residues containing (1S,2S,3R,5S)-pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate in each rotary evaporator flask were then transferred to a three-necked glass reaction flask equipped with a temperature recorder and a mechanical stirrer, using n-heptane (14.8 L) and methanol (14.8 L).
4. The stirring motor was adjusted to provide stirring at 284 RPM.
5. 2-Methylpropaneboronic acid (0.672 kg) was charged to the flask.
6. 1N hydrochloric acid prepared in Step 1 (11.2 L) was charged to the flask.
7. The stirring motor was adjusted to provide stirring at 326 RPM.
8. The reaction mixture was stirred for 16.38 hours. The start batch temperature was 28.6 °C, and the end batch temperature was 21.6 °C.
9. A sample was then removed for in-process testing by RP-HPLC.
10. The percent conversion was determined to be 100%.
11. Stirring was stopped and the biphasic mixture allowed to separate.
12. The n-heptane layer (upper layer) was transferred to a suitable flask and discarded.
13. n-Heptane (5.37 L) was charged to the reaction flask and the mixture stirred at 381 RPM for 6 minutes. The layers were allowed to separate and the n-heptane phase (upper layer) was transferred to a suitable flask and discarded.

14. Again, n-heptane (5.37 L) was charged to the reaction flask and the mixture stirred at 340 RPM for 6 minutes. The layers were allowed to separate and the n-heptane phase (upper layer) was transferred to a suitable flask and discarded.
15. The aqueous methanol solution was transferred in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 33-34 °C. 15 L of methanol were collected.
16. Dichloromethane (5.37 L) was used to transfer the residue from the rotary evaporator flasks back into the reaction flask.
17. 2N sodium hydroxide (11.2 L) prepared in Step 2 was charged to the flask.
18. The dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
19. Dichloromethane (5.37 L) was charged to the flask and the mixture stirred at 374 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
20. Again, dichloromethane, (5.37 L) was charged to the flask and the mixture stirred at 368 RPM for 8 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to a suitable flask and discarded.
21. Dichloromethane (5.37 L) was charged to the flask.
22. 1N hydrochloric acid (10.7 L) was charged to the flask with stirring. The pH of the aqueous phase was determined to be 6.
23. Stirring was discontinued and the phases allowed to separate.
24. The dichloromethane phase (lower layer) was transferred under vacuum to a glass receiving flask.
25. Dichloromethane (5.37 L) was charged to the flask and the mixture stirred at 330 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to the glass receiving flask.

26. Again, dichloromethane, (5.37 L) was charged to the flask and the mixture stirred at 335 RPM for 6 minutes. The phases were allowed to separate and the dichloromethane layer (lower layer) was transferred to the glass receiving flask.
27. The dichloromethane extracts were combined and transferred in approximately two equal halves to two rotary evaporator flasks and concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 33-34 °C.
28. Ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 45-46 °C.
29. Again, ethyl acetate (12.95 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks. The mixtures in each flask were then concentrated under reduced pressure using a rotary evaporator, maintaining an external bath temperature of 45-46 °C, until approximately 10% of the original volume remained.
30. n-Heptane (10.2 L) was divided into two approximately equal portions and charged to the two rotary evaporator flasks, and the slurry stirred under a nitrogen atmosphere for 2.67 hours at 22-23 °C.
31. The solid was isolated by filtration on a Buchner funnel, lined with a polypropylene felt filter pad.
32. The solid was washed with n-heptane (2.96 L).
33. In a hood, the solid was transferred to four drying trays and air-dried for 1.25 hours.
34. The solid was then dried at 36 - 50 °C under a vacuum of 27" of Hg for 18 hours 27 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.
35. The solid was sampled from each tray to determine the % Loss on Drying (LOD). The LOD was determined to be 0.38%, 0.62%, 0.71%, and 0.63% on the four samples taken.
36. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude was packaged into two 5L, HDPE, tamper-proof wide-mouth bottles and labeled.

37. The isolated yield was 1.314 kg, 83%.

Recrystallization of N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude

1. In a hood a glass reaction flask equipped with a mechanical stirrer, a reflux condenser and a temperature recorder was flushed with nitrogen.
2. Ethyl acetate (21 L) was charged to the flask.
3. The ethyl acetate was heated to 66.8 °C under a nitrogen atmosphere, using a hot water/steam bath.
4. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride, crude (1.311 kg) was slowly charged to the reaction flask. Charging occurred over a period of 3 minutes.
5. The mixture was stirred for 1 minute until all the solid had dissolved. The temperature of the solution was 64 °C.
6. The heat source was removed and the mixture was slowly cooled to 60 °C using a cold bath.
7. The hot ethyl acetate solution was transferred into a receiving flask via poly tubing and a polypropylene in-line filter capsule using a peristaltic pump.
8. The mixture was allowed to cool to 27.2 °C, and allowed to stand under a nitrogen atmosphere without stirring, for 17.75 hours. The final temperature was recorded as 20.5 °C.
9. The mixture was cooled using an ice/water bath with stirring for 2.33 hours. The temperature at the start of the stir time was 3.8 °C, and -2.8 °C at the end.
10. The solid was isolated by filtration on a Buchner funnel lined with a polypropylene felt filter pad. The filtrate was collected in a collection flask.
11. The solid was washed with ethyl acetate (2.62 L), cooled to 4.7 °C.
12. In a hood, the solid was transferred to two drying trays.
13. The solid was then dried at 51-65 °C under a vacuum of 27" of Hg for 19 hours 10 minutes in a vacuum oven equipped with a vacuum gauge and a temperature recorder.

14. The solid was sampled to determine the % Loss on Drying (LOD). The LOD was determined to be 0.65 % and 0.62 % on the two samples taken.
15. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride was packaged into four 1L, Type 3, Amber Wide-Mouth Bottles with Teflon-Lined Caps and labeled.
16. The isolated yield was 1.132 kg, 86.3%.
17. N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride was stored at -25 to -15 °C.

**Example 3: N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride
Convergent Synthesis**

(1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate

[098] A solution of (1R)-(S)-Pinanediol 1-ammonium trifluoroacetate-3-methylbutane-1-boronate (13.97 g) and N-hydroxysuccinimide (6.23 g) of in 66 mL of DMF was cooled to -5 °C, followed by the addition of dicyclohexylcarbodiimide (10.83 g). The resulting suspension was stirred for one hour at a temperature of -5 to 0 °C. To a solution of N-(2-pyrazinecarbonyl)-L-phenylalanine (19.52 g; prepared by coupling the preformed succinimide ester of pyrazinecarboxylic acid with L-phenylalanine in dioxane-water) in 62 mL of DMF was added N-methylmorpholine (5.7 mL) at a temperature of 0 °C, and the resulting solution was added to the suspension. The suspension was adjusted to pH 7 by the addition of another 5.7 mL of N-methylmorpholine and stirred overnight, raising the temperature slowly to 21 °C. After filtration, the filtercake was washed twice with MTBE and the combined filtrates were diluted with 950 mL of MTBE. The organic layer was washed with 20% aqueous citric acid (3 × 150 mL), 20% aqueous NaHCO₃ (3 × 150 mL), and brine (2×). The organic layer was dried over Na₂SO₄, filtered, and concentrated, yielding 25.5 g (95.5 %) of the title compound as a foam. As indicated by tlc this material contained some minor impurities, including approximately 2% of cyclohexyl urea.

N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride

[099] A solution of (1S,2S,3R,5S)-Pinanediol N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate (25.2 g) in 207 mL of MeOH and 190 mL of hexane was cooled to 15 °C, and 109.4 mL of 1N HCl were added in portions, keeping the temperature between 15 and 25 °C. 2-Methylpropaneboronic acid (8.67 g) was then added under

vigorous stirring, and the stirring of the biphasic mixture was continued over night. After separation of the two phases, the lower layer was extracted once with 75 mL of hexane. The lower layer was then concentrated in vacuo until it became cloudy, followed by the addition of 109.4 mL of 2N NaOH and 100 mL of Et₂O. The two phases were separated the lower layer was extracted with Et₂O (4 × 100 mL each), and then brought to pH 6.0 by the addition of 109 mL of 1N HCl. After extraction with 100 mL of ethyl acetate, the lower layer was adjusted to pH 6.0 with 1N HCl and extracted one more time with 75 mL of ethyl acetate. The combined ethyl acetate layers were washed with semi-saturated brine (2 × 25 mL) and brine (2 × 25 mL), dried over Na₂SO₄, filtered, and concentrated to afford 15.3 g (81.8 %) of crude N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride as a foam. The crude material was dissolved in 150 mL of ethyl acetate and concentrated in vacuo to a suspension, followed by the addition of 150 mL of MTBE. The suspension was stored between 2 and 8 °C over night, filtered, washed twice with MTBE, and dried under high vacuum, yielding 10.69 g (57.2 %) of N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride as a white solid.

Example 4: Measurement of Diastereomeric Ratio of (1R)-(1S,2S,3R,5S)-Pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate

[0100] The diastereomeric purity of (1R)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate (compound 1) was determined by non-chiral gas chromatography (GC).

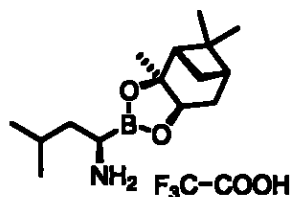
Chemicals:	Acetonitrile (p.a. Bruker or equivalent) Tetradecane (internal standard) (Fluka puriss. or equivalent) Trifluoroacetic anhydride (TFAA) (p.a. Merck or equivalent)
Instrument:	Trace-GC 2000 system or equivalent
<i>Mobile phase:</i>	H ₂
<i>Solvent A (with internal standard)</i>	Approximately 300 mg of tetradecane were weighed with an accuracy of 0.1 mg into a 100-mL volumetric flask. 1.5 mL of TFAA were added and the flask was brought to volume with acetonitrile.
Sample Preparation:	About 150 mg of the sample were exactly weighed (within 0.1 mg) into a 10-mL volumetric flask. The flask was brought to volume with Solvent A. The solution was stored for 15 minutes before injection.

GC Parameters:

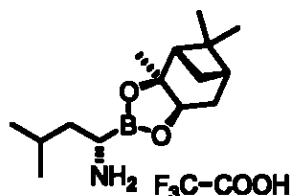
<i>Column:</i>	Rtx-200; 105m × 0.25 mm i.d. × 0.25 µm film
<i>Mobile phase:</i>	H ₂
<i>Temp. program:</i>	130 °C (0.5 min); 0.5 °C/min to 200 °C (0 min); 30 °C/min to 300 °C (2 min)
<i>Flow:</i>	0.9 mL/min (const. flow)
<i>Injector temperature:</i>	250 °C
<i>Detector temperature:</i>	250 °C (FID)
<i>Split:</i>	1: 50
<i>Injection volume:</i>	1 µL

Substances

<i>Compound 1</i>	(1R)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate
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<i>Compound 2</i>	(1S)-(1S,2S,3R,5S)-pinanediol-1-ammoniumtrifluoroacetate-3-methylbutane-1-boronate
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**Stability of the solution**

[0101] A stock solution of compound 1 was prepared by weighing 150.13 mg of compound 1 into a 10-mL volumetric flask and bringing it to volume with Solvent A. Stability of this solution was tested at ambient temperature over 48 hours. The stock solution was filled in 6 separate GC vials. Injections onto the GC system were carried out from these vials after 0, 12, 24, 48, and 72 hours (double injection out of each vial. The area% of compound 1 and compound 2 were determined. No changes in area% were observed, indicating that the solution is stable over 72 hours at ambient temperature.

Specificity

[0102] Approximately 150 mg of a sample comprising compound 1 and compound 2 were dissolved in Solvent A and injected to the GC chromatographic system. The peak for compound 1 was well separated from the peak for compound 2. Peak purity check by GC-MS showed no other components co-eluting with compound 1 or compound 2.

Limit of Detection

[0103] The limit of detection (LOD) was defined to be that concentration where the signal of compound 1 showed a signal to noise ratio of at least 3:1. A previous blank measurement was carried out to show that no other peaks interfered. The signal to noise ratio was calculated by the equation:

$$S / N = \frac{H(\text{signal})}{H(\text{baseline})}$$

S/N = signal to noise ratio

H(signal) = height of signal for compound 1 [mm]

H(baseline) = height of signal baseline [mm]

[0104] A sample concentration of 0.05% of the standard test sample concentration was injected and showed a signal to noise ratio of 4.3. Therefore, the limit of detection is 0.0075 mg/mL.

Limit of Quantitation

[0105] The limit of quantitation (LOQ) was defined to be that concentration where the signal of compound 1 showed a signal to noise ratio of at least 10:1. Signal to noise ratio was calculated as described above. A sample concentration of 0.1% of the standard sample concentration was injected and showed a signal to noise ratio of 10.1. Therefore, the limit of quantitation is 0.015 mg/mL.

Example 5: Purity Assay for N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride

[0106] The purity of N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride (compound 3) was assayed by reverse phase HPLC.

Reagents: Water, HPLC grade
Acetonitrile, HPLC grade

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Formic acid, ACS grade, ≥ 98% pure
3% Hydrogen peroxide, ACS grade or equivalent

Instrument

High performance liquid chromatograph

Autosampler capable of delivering 20-μL injections and maintaining a temperature of 5 °C
Pump capable of gradient delivery at 1.0 mL/min
UV detector capable of monitoring effluent at 270 nm

Column

Symmetry C18 chromatographic column, 250 mm × 4.6 mm ID, 5-μm, Waters, cat# WAT054275.

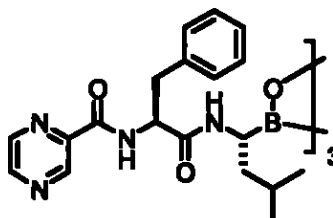
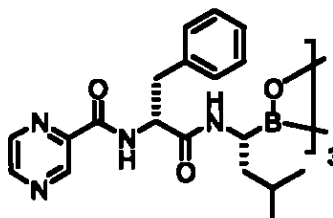
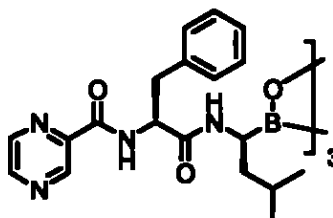
Sample Preparation:

Approximately 50 mg of compound 3 were accurately weighed into a 50-mL volumetric flask. Mobile Phase B (5 mL) was added and the mixture was sonicated to dissolve compound 3 (approximately 30-60 seconds). The solution was allowed to reach room temperature, diluted to volume with Mobile Phase A, and mixed well. Each sample was prepared in duplicate and was stable for 7 days when stored at 2-8 °C protected from light.

HPLC Parameters:

Mobile phase A: acetonitrile/water/formic acid, 30:70:0.1 (v/v/v), degassed
Mobile phase B: acetonitrile/water/formic acid, 80:20:0.1 (v/v/v), degassed
Flow rate: 1.0 mL/min
Detector: UV at 270 nm
Injection Volume: 20 μL
Column Temp: ambient
Sample Tray Temp: 5 °C
Gradient Program:

<u>Time</u>	<u>%A</u>	<u>%B</u>
0	100	0
15	100	0
30	0	100
45	0	100
47	100	0
55	100	0

Substances**Compound 3****N-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride****Compound 4****N-(2-Pyrazinecarbonyl)-L-phenylalanine-D-leucine boronic anhydride****Compound 5****N-(2-Pyrazinecarbonyl)-L-phenylalanine-D-leucine boronic anhydride**

[0107] The retention time of compound 3 was typically between 10 and 14 minutes when using an HPLC system with a 1.3 minute dwell volume. Compounds 4 and 5 co-eluted at longer retention time, with a resolution of ≥ 2.0 .

[0108] The relative retention of compound 3 in a sample chromatogram to that in the standard chromatogram was calculated according to the following equation:

$$R_r = \frac{t_{sam}}{t_{std}}$$

Where:

R_r = relative retention

t_{sam} = retention time of compound 3 peak in the sample chromatogram, minutes

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t_{std} = retention time of the drug substance peak in the closest preceding standard chromatogram, minutes

[0109] Assay results were calculated for each sample according to the following equation:

$$\% assay = \frac{A_{sam}}{A_{std}} \times \frac{W_{std} \times P}{W_{sam}} \times \frac{1}{\left(\frac{100-M}{100}\right)} \times 100$$

Where:

- A_{sam}** = peak area response of compound 3 in the sample preparation
- A_{std}** = mean peak area response of compound 3 in the working standard preparation
- W_{std}** = weight of the standard, mg
- P** = assigned purity of the standard (decimal format)
- W_{sam}** = weight of the sample, mg
- M** = moisture content of the sample, %
- 100** = conversion to percent

[0110] Relative retention and impurity levels in each sample were calculated according to the following equations:

$$R_r = \frac{t_i}{t_{ds}}$$

Where:

- R_r** = relative retention
- t_i** = retention time of the individual impurity
- t_{ds}** = retention time of the compound 3 peak

$$\% I_i = \frac{A_i \times W_{std} \times P \times DF \times RF_i}{A_{std,1\%} \times W_{sam}} \times 100$$

Where:

- I_i** = individual impurity
- A_i** = peak area response of individual impurity in the sample preparation
- A_{std,1%}** = average peak area response of compound 3 in the 1% standard preparation
- W_{std}** = weight of the standard, mg

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W_{sam}	=	weight of sample, mg
P	=	assigned purity of the standard (decimal format)
DF	=	dilution factor, 1/100
RF_i	=	relative response factor of individual impurity
100	=	conversion to percentage factor

[0111] When assayed by this method, N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucineboronic anhydride from Example 2 showed total impurities of less than 1%.

[0112] While the foregoing invention has been described in some detail for purposes of clarity and understanding, these particular embodiments are to be considered as illustrative and not restrictive. It will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention and appended claims.

WHAT IS CLAIMED IS:

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1. A large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

- (a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation; and

each of R¹ to R³ is as defined above; and

- (b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or

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(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

2. The process of claim 1, wherein the reaction mixture comprises a coordinating co-solvent.

3. The process of claim 2, wherein the coordinating co-solvent is selected from the group consisting of tetrahydrofuran, dioxane, water, and mixtures thereof.

4. The process of claim 3, wherein the coordinating co-solvent constitutes no more than about 20% v/v of the reaction mixture.

5. The process of claim 3, wherein the coordinating co-solvent constitutes no more than about 15% v/v of the reaction mixture.

6. The process of claim 1, wherein the solubility of water in the ether solvent that has low miscibility with water is less than about 2% w/w.

7. The process of claim 6, wherein the ether solvent that has low miscibility with water is selected from the group consisting of *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, isopropyl ether, and mixtures thereof.

8. The process of claim 7, wherein the ether solvent that has low miscibility with water constitutes at least about 70% v/v of the reaction mixture.

9. The process of claim 1, wherein at least about 5 moles of the boron "ate" complex of formula (II) are provided in step (a).

10. The process of claim 1, wherein at least about 20 moles of the boron "ate" complex of formula (II) are provided in step (a).

11. The process of claim 1, wherein at least about 50 moles of the boron "ate" complex of formula (II) are provided in step (a).

12. The process of claim 1, wherein at least about 100 moles of the boron "ate" complex of formula (II) are provided in step (a).
13. The process of claim 1, wherein the Lewis acid is selected from the group consisting of zinc chloride, zinc bromide, ferric chloride, and ferric bromide.
14. The process of claim 13, wherein the Lewis acid is moist.
15. The process of claim 13, wherein in step (a) the boron "ate" complex of formula (II) is provided in a solution comprising an ether solvent that has low miscibility with water, and the contacting step (b) comprises the steps:
- (i) providing a solution comprising a Lewis acid and tetrahydrofuran; and
 - (ii) adding the Lewis acid solution to the solution of the boron "ate" complex of formula (II) from step (a).
16. The process of claim 13, wherein in step (a) the boron "ate" complex of formula (II) is provided in a solution comprising an ether solvent that has low miscibility with water, and the contacting step (b) comprises the steps:
- (i) providing a solution comprising a Lewis acid and water; and
 - (ii) adding the Lewis acid solution to the solution of the boron "ate" complex of formula (II) from step (a).
17. The process of claim 1, wherein Y is a halogen.
18. The process of claim 1, wherein Y is chloro.
19. The process of claim 1, wherein R¹ is C₁₋₈ aliphatic, C₆₋₁₀ aryl, or (C₆₋₁₀ aryl)(C₁₋₆ aliphatic).
20. The process of claim 1, wherein M⁺ is selected from the group consisting of Li⁺, Na⁺, and K⁺.

21. The process of claim 1, wherein R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5-membered ring.
22. The process of claim 21, wherein R^4 and R^5 together are a chiral moiety.
23. The process of claim 22, wherein the boron "ate" complex of formula (II) is:



24. The process of claim 22, wherein step (b) provides the boronic ester compound of formula (I) wherein the carbon atom bearing R^1 , R^2 , and R^3 is a chiral center having a diastereomeric ratio of at least about 96:4 relative to a chiral center in the R^4 - R^5 chiral moiety.
25. The process of claim 22, wherein step (b) provides the boronic ester compound of formula (I) wherein the carbon atom bearing R^1 , R^2 , and R^3 is a chiral center having a diastereomeric ratio of at least about 97:3 relative to a chiral center in the R^4 - R^5 chiral moiety.
26. The process of claim 22, characterized by at least one of the following features:
- (a) the contacting step (b) is conducted in a reaction mixture comprising *tert*-butyl methyl ether;
 - (b) the Lewis acid is zinc chloride;
 - (c) at least about 5 moles of the boronic ester of formula (II) are provided in step (a);
 - (d) the contacting step (b) is performed at a reaction temperature in the range of about -60 °C to about -30 °C;
 - (e) the Lewis acid is moist;
 - (f) Y is chloro;
 - (g) R^3 is chloro;

(h) R² is hydrogen; and

(i) R¹ is C₁₋₄ aliphatic.

27. The process of claim 26, characterized by at least two of the features (a)-(h).

28. The process of claim 26, characterized by at least three of the features (a)-(h).

29. The process of claim 26, characterized by all eight of the features (a)-(h).

30. The process of claim 24, further comprising:

(c) washing the reaction mixture with an aqueous solution; and

(d) concentrating the washed reaction mixture by removal of solvents to afford a residue comprising the boronic ester compound of formula (I).

31. The process of claim 26, wherein the residue comprises at least about five moles of the boronic ester compound of formula (I).

32. The process of claim 31, wherein the boronic ester compound of formula (I) present in the residue has a diastereomeric ratio of at least about 96:4 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety.

33. The process of claim 31, wherein the boronic ester compound of formula (I) present in the residue has a diastereomeric ratio of at least about 97:3 at the carbon atom bearing R¹, R², and R³, relative to a chiral center in the R⁴-R⁵ chiral moiety.

34. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



wherein:

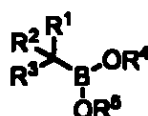
R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S.

35. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



(I)

wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

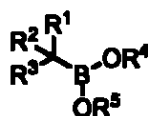
R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, relative to a chiral center in the R^4 - R^5 chiral moiety.

36. A composition comprising an ether solvent that has low miscibility with water and at least about ten moles of a boronic ester compound of formula (I):



(I)

wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic or aromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having an epimeric ratio of at least about 96:4.

37. The composition of any one of claims 34-36, wherein the solubility of water in the ether solvent is less than about 2% w/w.

38. The composition of any one of claims 34-36, wherein the ether solvent is selected from the group consisting of *tert*-butyl methyl ether, *tert*-butyl ethyl ether, *tert*-amyl methyl ether, isopropyl ether, and mixtures thereof.

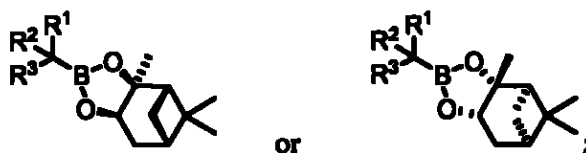
39. The composition of any one of claims 34-36, wherein R^1 is C_{1-8} aliphatic, C_{6-10} aryl, or $(C_{6-10}$ aryl)(C_{1-6} aliphatic).

40. The composition of any one of claims 34-36, characterized by at least one of the following features:

- (a) R^3 is chloro;
- (b) R^2 is hydrogen; and
- (c) R^1 is C_{1-4} aliphatic

41. The composition of any one of claims 34-36, wherein R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5-membered ring.

42. The composition of any one of claims 34-36, wherein the compound of formula (I) is



43. A composition comprising at least about ten moles of a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered chiral ring having 0-2 additional ring heteroatoms selected from N, O, or S;

wherein the carbon atom to which R^1 , R^2 , and R^3 are attached is a chiral center, having a diastereomeric ratio of at least about 96:4, relative to a chiral center in the R^4 - R^5 chiral moiety; and

wherein the boronic ester compound of formula (I) constitutes at least about 70% w/w of the composition.

44. The composition of claim 36 comprising at least about 20 moles of the boronic ester compound of formula (I).

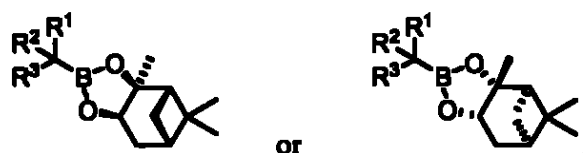
45. The composition of claim 36, wherein the carbon atom to which R¹, R², and R³ are attached has a diastereomeric ratio of at least about 97:3, relative to a chiral center in the R⁴-R⁵ chiral moiety.

46. The composition of claim 36, wherein all of the boronic ester compound of formula (I) present in the composition is produced in a single batch run.

47. The composition of claim 36, wherein all of the boronic ester compound of formula (I) present in the composition is produced in a single batch run of the process according to claim 1.

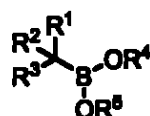
48. The composition of claim 36, wherein at least one of the following features is present:

- (a) R³ is chloro;
- (b) the boronic ester compound of formula (I) is:



- (c) R² is hydrogen; and
- (d) R¹ is C₁₋₄ aliphatic.

49. A large-scale process for preparing a boronic ester compound of formula (I):



(I)

wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic ester of formula (III):



wherein R¹, R⁴, and R⁵ are as defined above; and

(ii) an ether solvent that has low miscibility with water;

(b) treating the solution with a reagent of formula (IV):



to form a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation; and

each of R¹ to R⁵ are as defined above; and

(c) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent.

50. A large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic ester of formula (III):



wherein R^1 , R^4 , and R^5 are as defined above;

(ii) a compound of formula (V):



where Y is a nucleofugic group, and R^2 and R^3 are as defined above; and

(iii) a solvent comprising:

(aa) a coordinating ether solvent that has low miscibility with water; or

(bb) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(b) treating the solution of step (a) with a strong, sterically hindered base to form a boron "ate" complex of formula (II):



where M^+ is a cation derived from the base, and each of Y and R^1 to R^5 are as defined above; and

(c) contacting the boron "ate" complex of formula (II) with a Lewis acid in a solution comprising an ether solvent that has low miscibility with water to form the boronic ester compound of formula (I).

51. A large-scale process for preparing a boronic ester compound of formula (I):



wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

R^4 and R^5 , taken together, form an optionally substituted linking chain comprising 2-5 carbon atoms and 0-2 heteroatoms selected from the group consisting of O, N, and S;

said process comprising:

(a) providing a solution comprising:

(i) a boronic acid compound of formula (VI):



wherein R^1 is as defined above;

- (ii) a compound of formula $\text{HO-R}^4\text{-R}^5\text{-OH}$, wherein R^4 and R^5 are as defined above; and
- (iii) an organic solvent that forms an azeotrope with water;
- (b) heating the solution of step (a) at reflux, with azeotropic removal of water, to form a boronic ester of formula (III):



wherein R^1 , R^4 , and R^5 are as defined above;

- (c) providing a solution comprising:
 - (i) the boronic ester of formula (III);
 - (ii) a compound of formula (V):



wherein Y is a nucleofugic group, and R^2 and R^3 are as defined above; and

- (iii) a solvent comprising:
 - (aa) a coordinating ether solvent that has low miscibility with water; or
 - (bb) an ether solvent that has low miscibility with water and a coordinating co-solvent;
- (d) treating the solution from step (c) with a strong, sterically hindered base to form a boron "ate" complex of formula (II):



where M^+ is a cation derived from the base, and each of Y and R^1 to R^5 are as defined above; and

- (e) contacting the boron "ate" complex of formula (II) with a Lewis acid in a solution comprising an ether solvent that has low miscibility with water to form the boronic ester compound of formula (I).

52. The process of claim 50 or 51, wherein the sterically hindered base is an alkali metal dialkylamide base of formula $M^2N(R^4)_2$, wherein M^2 is selected from the group consisting of Li, Na, and K, and each R^4 , independently, is a branched or cyclic C_{3-6} aliphatic.

53. The process of claim 51, wherein the organic solvent in step (a) is selected from the group consisting of acetonitrile, toluene, hexane, heptane, and mixtures thereof.

54. The process of claim 51, wherein the organic solvent in step (a) is an ether solvent that has low miscibility with water.

55. The process of claim 54, wherein the solutions in steps (a) and (c) each comprise the same ether solvent.

56. The process of claim 55, wherein step (b) provides a product solution comprising the boronic ester of formula (III), and the product solution from step (b) is used in step (c) without isolation of the boronic ester of formula (III).

57. A large-scale process for preparing an aminoboronic ester compound of formula (VII):



or an acid addition salt thereof, wherein:

R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S;

said process comprising:

(a) providing a boron "ate" complex of formula (II):



where

Y is a nucleofugic group;

M⁺ is a cation;

R² is hydrogen;

R³ is a nucleofugic group; and

each of R¹, R⁴, and R⁵ are as defined above;

(b) contacting the boron "ate" complex of formula (II) with a Lewis acid under conditions that afford the boronic ester compound of formula (I):



where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(c) treating the boronic ester compound of formula (I) with a reagent of formula M¹-N(Si(R⁶)₃)₂, where M¹ is an alkali metal and each R⁶ independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a byproduct of formula M¹-R³ and a compound of formula (VIII):



wherein each G and R¹ to R⁵ are as defined above; and

(d) removing the G groups to form a compound of formula (VII):



or an acid addition salt thereof.

58. The process of claim 57, wherein the reaction mixture in step (c) comprises an organic solvent in which the byproduct M^1-R^3 has low solubility.

59. The process of claim 58, wherein M^1 is Li and R^3 is Cl.

60. The process of claim 59, wherein the reaction mixture in step (c) comprises an organic solvent selected from the group consisting of methylcyclohexane, cyclohexane, heptane, hexane, toluene, and mixtures thereof.

61. The process of claim 57, wherein the reaction in step (c) is conducted at a reaction temperature in the range of about $-100\text{ }^{\circ}\text{C}$ to about $50\text{ }^{\circ}\text{C}$.

62. The process of claim 61, wherein the reaction temperature is in the range of about $-50\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$.

63. The process of claim 61, wherein the reaction temperature is in the range of about $-30\text{ }^{\circ}\text{C}$ to about $0\text{ }^{\circ}\text{C}$.

64. The process of claim 57, wherein step (d) comprises treating the compound of formula (VIII) with an acid and isolating the compound of formula (VII) as the acid addition salt.

65. The process of claim 64, wherein the acid is trifluoroacetic acid.

66. The process of claim 57, wherein step (c) further comprises filtering the reaction mixture to provide a filtrate comprising the compound of formula (VIII).

67. The process of claim 66, wherein in step (c), the reagent of formula $M^1-N(Si(R^6)_3)_2$ is added to the reaction mixture as a solution comprising tetrahydrofuran, and step (c) further comprises removing the tetrahydrofuran before filtering the reaction mixture.

68. The process of claim 66, wherein the filtrate is used directly in step (d).

69. The process of claim 57, further comprising the step:

(e) coupling the compound of formula (VII) with a compound of formula (IX):



wherein:

P¹ is an amino group blocking moiety;

R⁷ is selected from the group consisting of hydrogen, C₁₋₁₀aliphatic, optionally substituted C₆₋₁₀aryl, or C₁₋₆aliphatic-R⁸; and

R⁸ is selected from the group consisting of alkoxy, alkylthio, optionally substituted aryl, heteroaryl, and heterocyclyl groups, and optionally protected amino, hydroxy, and guanidino groups; and

X is OH or a leaving group;

to form a compound of formula (X):



wherein each of P¹, R¹, R⁴, R⁵, and R⁷ is as defined above.

70. The process of claim 69, wherein P¹ is a cleavable protecting group.

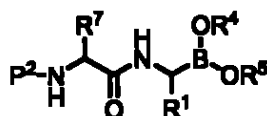
71. The process of claim 70, further comprising the steps:

(f) cleaving the protecting group P¹ to form a compound of formula (XI):



or an acid addition salt thereof, wherein each of R¹, R⁴, R⁵, and R⁷ is as defined above;

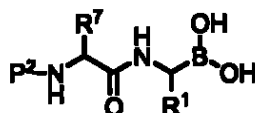
(g) coupling the compound of formula (XI) with a reagent of formula P²-X, wherein P² is an amino group blocking moiety and X is a leaving group, to form a compound of formula (XII):



(XII)

wherein each of P², R¹, R⁴, R⁵, and R⁷ are as defined above; and

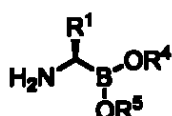
(h) deprotecting the boronic acid moiety to form a compound of formula (XIII):



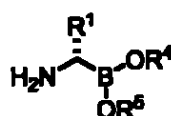
(XIII)

or a boronic acid anhydride thereof, wherein each of P¹, R¹, and R⁷ are as defined above.

72. A large-scale process for preparing an aminoboronic ester compound of formula (VIIa) or (VIIb):



(VIIa)



(VIIb)

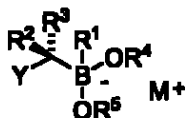
or an acid addition salt thereof, wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and

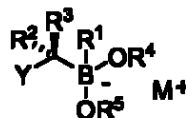
R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted chiral cyclic boronic ester;

said process comprising:

(a) providing a boron "ate" complex of formula (IIa) or (IIb):



(IIa)



(IIb)

where

Y is a nucleofugic group;

M⁺ is a cation;

R² is hydrogen;

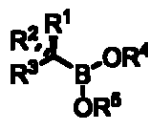
R³ is a nucleofugic group; and

R⁴ and R⁵ are as defined above;

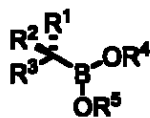
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(b) contacting the boron "ate" complex of formula (IIa) or (IIb) with a Lewis acid under conditions that afford a boronic ester compound of formula (Ia) or (Ib):



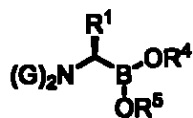
(Ia)



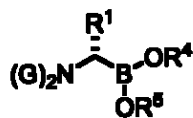
(Ib)

where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;
- (c) treating the boronic ester compound of formula (Ia) or (Ib) with a reagent of formula M¹-N(G)₂, where M¹ is an alkali metal and each G is an amino group protecting moiety, to form a compound of formula (VIIIa) or (VIIIb):



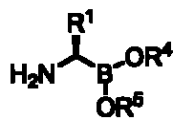
(VIIIa)



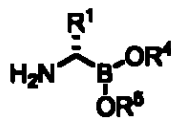
(VIIIb)

wherein each G and R¹ to R⁵ are as defined above; and

- (d) removing the G groups to form a compound of formula (VIIa) or (VIIb):



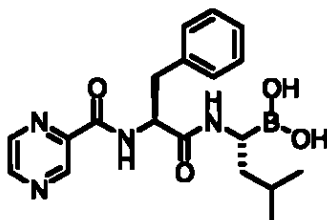
(VIIa)



(VIIb)

or an acid addition salt thereof.

73. A large-scale process for forming a compound of formula (XIV):



(XIV)

or a boronic acid anhydride thereof, said process comprising:

- (a) providing a boron "ate" complex of formula (XV):



wherein:

M⁺ is an alkali metal;

- (b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):

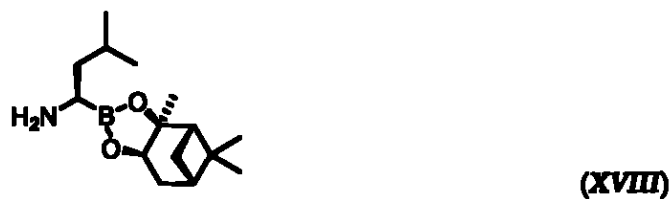


said contacting step being conducted in a reaction mixture comprising an ether solvent that has low miscibility with water;

- (c) treating the boronic ester compound of formula (XVI) with a reagent of formula M¹-N(G)₂, where M¹ is an alkali metal and each G individually or together is an amino group protecting group, to form a compound of formula (XVII):

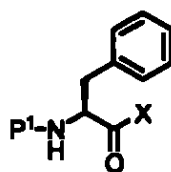


- (d) removing the G groups to form a compound of formula (XVIII):



or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XIX);



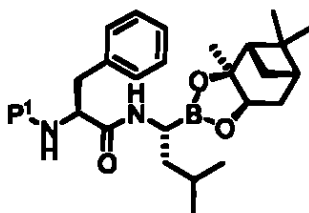
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

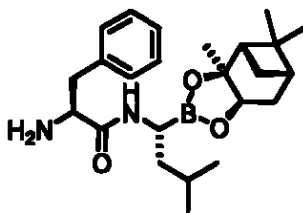
to form a compound of formula (XX):



(XX)

wherein P¹ is as defined above;

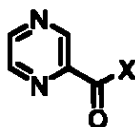
(f) removing the protecting group P¹ to form a compound of formula (XXI):



(XXI)

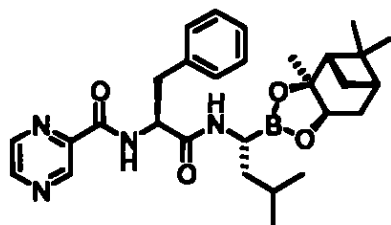
or an acid addition salt thereof;

(g) coupling the compound of formula (XXI) with a reagent of formula (XXII)



(XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(XXIII) ; and

(h) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

74. The process of claim 73, characterized by at least one of the following features (1)-(5):

- (1) in the boron "ate" complex of formula (XV), R³ and Y both are chloro;
- (2) the coupling step (e) comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) the protecting group removing step (f) comprises the steps:
 - (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt;
- (4) the coupling step (g) comprises the steps:
 - (i) coupling the compound of formula (XXI) with 2-pyrazine-carboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;

- (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
- (iii) performing an aqueous wash of the ethyl acetate solution; and
- (5) the boronic acid deprotecting step (h) comprises the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₅₋₈ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

75. The process of claim 74, characterized by all five features (1)-(5).

76. The process of claim 74, wherein step (h)(iii) comprises the steps:

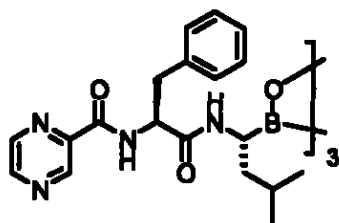
- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 8.

77. The process of claim 76, wherein in step (h)(iii)(3), the aqueous layer is washed with dichloromethane.

78. The process of claim 76, wherein in step (h)(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

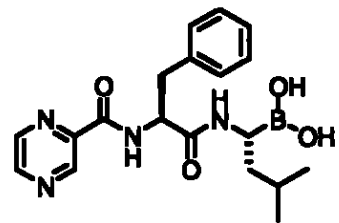
79. The process of claim 78, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):

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246



(XXIV).

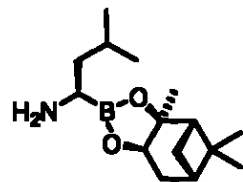
80. A large-scale process for forming a compound of formula (XIV):



(XIV)

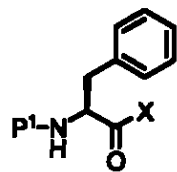
or a boronic acid anhydride thereof, comprising the steps:

(aa) coupling a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof, with a compound of formula (XIX):



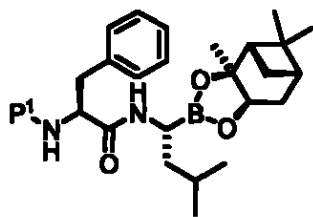
(XIX)

wherein:

P¹ is a cleavable amino group protecting moiety; and

X is OH or a leaving group;

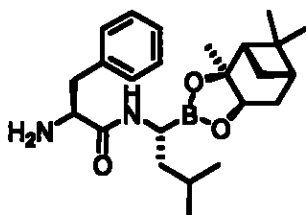
to form a compound of formula (XX):



(XX)

wherein P¹ is as defined above, said coupling step (aa) comprising the steps:

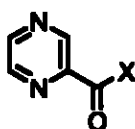
- (i) coupling the compound of formula (XVIII) with a compound of formula (XIX) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution;
- (bb) removing the protecting group P¹ to form a compound of formula (XXI):



(XXI)

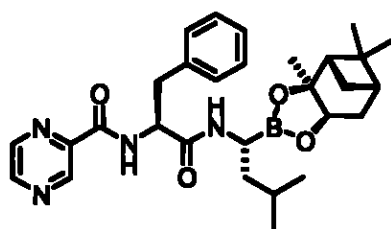
or an acid addition salt thereof, said protecting group removing step (bb) comprising the steps:

- (i) treating the compound of formula (XX) with HCl in ethyl acetate;
 - (ii) adding heptane to the reaction mixture; and
 - (iii) isolating by crystallization the compound of formula (XXI) as its HCl addition salt;
- (cc) coupling the compound of formula (XXI) with a reagent of formula (XXII)



(XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII):



(XXIII),

said coupling step (cc) comprising the steps:

- (i) coupling the compound of formula (XXI) with 2-pyrazinecarboxylic acid in the presence of TBTU and a tertiary amine in dichloromethane;
- (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
- (iii) performing an aqueous wash of the ethyl acetate solution; and
- (dd) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof, said deprotecting step (dd) comprising the steps:

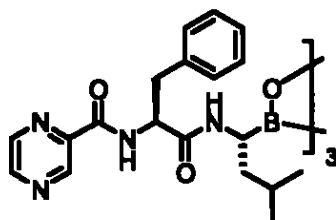
- (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₅₋₈ hydrocarbon solvent, and aqueous mineral acid;
- (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
- (iii) separating the solvent layers; and
- (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

81. The process of claim 80, wherein step (dd)(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 8.

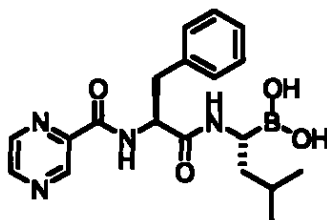
82. The process of claim 81, wherein in step (dd)(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

83. The process of claim 82, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):



(XXIV).

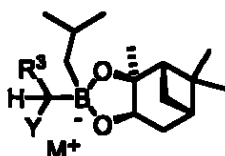
84. A large-scale process for forming a compound of formula (XIV):



(XIV)

or a boronic acid anhydride thereof. The process comprises the steps:

(a) providing a boron "ate" complex of formula (XV):



(XV)

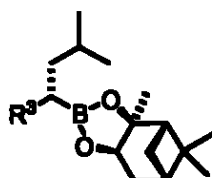
wherein:

R^3 is a nucleofugic group;

Y is a nucleofugic group; and

M^+ is an alkali metal;

(b) contacting the boron "ate" complex of formula (XV) with a Lewis acid under conditions that afford a boronic ester compound of formula (XVI):



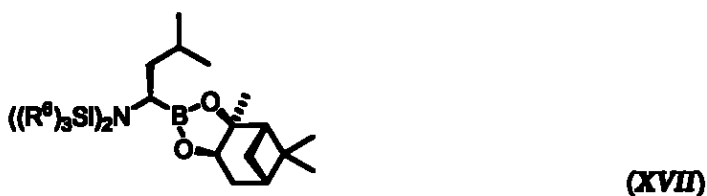
(XVI)

said contacting step being conducted in a reaction mixture comprising:

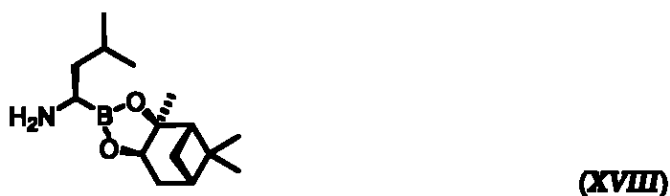
(i) a coordinating ether solvent that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent;

(c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^1-N(Si(R^6)_3)_2$, where M^1 is an alkali metal and each R^6 independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a compound of formula (XVII):



(d) removing the $(R^6)_3Si$ groups to form a compound of formula (XVIII):

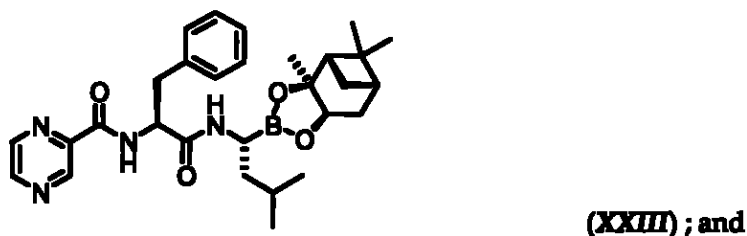


or an acid addition salt thereof;

(e) coupling the compound of formula (XVIII) with a compound of formula (XIXa):



wherein X is OH or a leaving group, to form a compound of formula (XXIII):



(f) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

85. The process of claim 84, characterized by at least one of the following features (1)-(3):

- (1) In the boron "ate" complex of formula (XV), R³ and Y both are chloro.
- (2) The coupling step (e') comprises the steps:
 - (i) coupling the compound of formula (XVIII) with a compound of formula (XXIXa) wherein X is OH in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and a tertiary amine in dichloromethane;
 - (ii) performing a solvent exchange to replace dichloromethane with ethyl acetate; and
 - (iii) performing an aqueous wash of the ethyl acetate solution.
- (3) The boronic acid deprotecting step (f') comprises the steps:
 - (i) providing a biphasic mixture comprising the compound of formula (XXIII), an organic boronic acid acceptor, a lower alkanol, a C₅₋₈ hydrocarbon solvent, and aqueous mineral acid;
 - (ii) stirring the biphasic mixture to afford the compound of formula (XIV);
 - (iii) separating the solvent layers; and
 - (iv) extracting the compound of formula (XIV), or a boronic acid anhydride thereof, into an organic solvent.

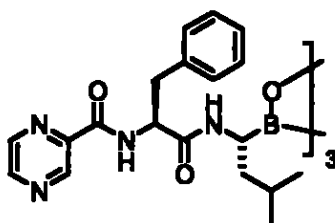
86. The process of claim 85, wherein step (f')(iii) comprises the steps:

- (1) separating the solvent layers;
- (2) adjusting the aqueous layer to basic pH;
- (3) washing the aqueous layer with an organic solvent; and
- (4) adjusting the aqueous layer to a pH less than about 8.

87. The process of claim 86, wherein in step (f')(iii)(3), the aqueous layer is washed with dichloromethane.

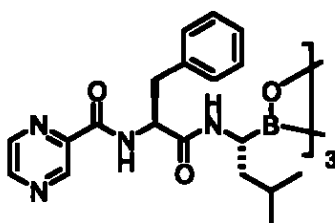
88. The process of claim 86, wherein in step (f)(iv), the compound of formula (XIV), or a boronic acid anhydride thereof, is extracted into dichloromethane, the solvent is exchanged to ethyl acetate, and the compound of formula (XIV), or a boronic acid anhydride thereof, is crystallized by addition of hexane or heptane.

89. The process of claim 88, wherein addition of hexane or heptane results in crystallization of a cyclic trimeric boronic acid anhydride of formula (XXIV):



(XXIV).

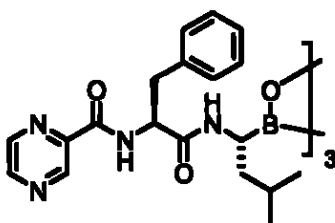
90. A composition comprising at least one kilogram of a compound of formula (XXIV):



(XXIV)

wherein the compound of formula (XXIV) is prepared according to the process of claim 73 or 80.

91. A composition comprising at least one kilogram of a compound of formula (XXIV):



(XXIV)

wherein the compound of formula (XXIV) constitutes at least 99% w/w of the composition.

ABSTRACT OF THE DISCLOSURE

[0113] *The invention relates to the synthesis of boronic ester and acid compounds. More particularly, the invention provides improved synthetic processes for the large-scale production of boronic ester and acid compounds, including the peptide boronic acid proteasome inhibitor bortezomib.*

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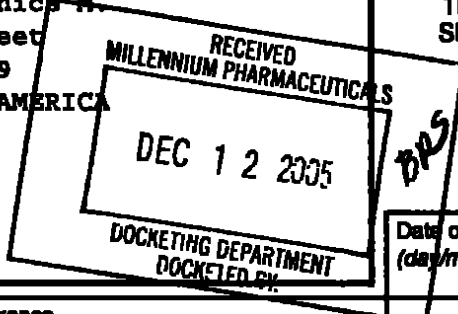
From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

MILLENNIUM PHARMACEUTICALS, INC.
Attn. Klunder, Janice M.
40 Landsdowne Street
Cambridge MA 02139
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION



(PCT Rule 44.1)

Date of mailing
(day/month/year)

08. 12. 2005

Applicant's or agent's file reference

MPI04-044

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2005/009774

International filing date
(day/month/year)

24/03/2005

Applicant

MILLENNIUM PHARMACEUTICALS, INC.

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 6818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stefan Brell

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 26 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

- A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequences if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequences with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MPI04-044	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2005/009774	International filing date (day/month/year) 24/03/2005	(Earliest) Priority Date (day/month/year) 30/03/2004
Applicant MILLENNIUM PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☒ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2005/009774

A. CLASSIFICATION OF SUBJECT MATTER

C07F5/02

C07F5/04

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 699 835 B2 (PLAMONDON LOUIS ET AL) 2 March 2004 (2004-03-02) cited in the application	34
A	claims 89-92; examples 2-5	1
X	column 15	90,91
X	US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application	1,12, 17-23, 34-36, 40-48, 57-59, 61-68
	examples 1-3,6-10	
	----- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

9 November 2005

Date of mailing of the international search report

08.12.2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Richter, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KOLOMEITSEV A A ET AL: "Perfluoroalkyl borates and boronic esters: new promising partners for Suzuki and Petasis reactions" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 45, 3 November 2003 (2003-11-03), pages 8273-8277, XP004463842 ISSN: 0040-4039 Entry 1, 2, 8, 9table 2	1
X	entry 9, table 2	34
A	PERGAMENT I. ET AL.: "Arbuzov Reaction of 1-Iodoborates as a Means of preparing C1-Bridged Phosphonoborates" TETRAHEDRON LETTERS, vol. 40, 1999, pages 3895-3898, XP004163774 Scheme 1	50-56
Y	PRIESTLEY ET AL: "P1 Phenethyl Peptide Boronic acid Inhibitors of HCV NS3 Protease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, 2002, pages 3199-3202, XP002339235 ISSN: 0960-894X Schemes 1 and 2 + corresponding text page 3200	57-59, 61-68
A	DOU, Q. PING ET AL: "Bortezomib Millennium Pharmaceuticals" IDRUGS , 5(8), 828-834 CODEN: IDRUFN; ISSN: 1369-7056, 2002, XP002351534 page 828 & WO 96/13266 A1 (LEUKOSITE, INC., USA) 9 May 1996 (1996-05-09)	73-89
Y	DATABASE BEILSTEIN 'Online! BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002351537 Database accession no. Reaction ID 8638739 abstract & DUSDON, R. M. ET AL.: BIOORG. MED. CHEM. LETT., vol. 10, no. 14, 2000, pages 1577-1580,	65
Y	DATABASE BEILSTEIN 'Online! BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002351538 Database accession no. Reaction ID 8726664 abstract -/-	57-59, 61-64, 66-68

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/009774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& VON MATT, A. ET AL.: BIORG. MED. CHEM., vol. 8, no. 9, 2000, pages 2291-2304,	260

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009774

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

- 1. claims: 1-48

- 2. claim: 49

- 3. claims: 50, partially: 52

- 4. claims: 51,53-56; partially: 52

- 5. claims: 57-72

- 6. claims: 73-79

- 7. claims: 80-83

- 8. claims: 84-91

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US2005/009774

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6699835	B2	02-03-2004	US 2002188100 A1	12-12-2002
			US 2004138411 A1	15-07-2004
US 4525309	A	25-06-1985	NONE	
WO 9613266	A1	09-05-1996	AT 241631 T	15-06-2003
			AU 710564 B2	23-09-1999
			AU 4139896 A	23-05-1996
			CA 2203936 A1	09-05-1996
			CN 1168633 A	24-12-1997
			CY 2484 A	03-06-2005
			DE 69530936 D1	03-07-2003
			DE 69530936 T2	26-02-2004
			DK 788360 T3	22-09-2003
			EP 0788360 A1	13-08-1997
			ES 2199257 T3	16-02-2004
			FI 971746 A	06-06-1997
			HK 1002059 A1	05-09-2003
			IL 115790 A	01-12-2002
			JP 10510245 T	06-10-1998
			LU 91083 A9	09-08-2004
			NL 300151 I1	02-08-2004
			NO 971929 A	12-06-1997
			NZ 296717 A	29-11-1999
			PT 788360 T	31-10-2003
			US 5780454 A	14-07-1998

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From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2005/009774International filing date (day/month/year)
24.03.2005Priority date (day/month/year)
30.03.2004International Patent Classification (IPC) or both national classification and IPC
C07F5/02, C07F5/04Applicant
MILLENNIUM PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 apmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Richter, H

Telephone No. +49 89 2399-8539



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009774

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Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009774

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-12,14-16,24,25, 57-59, 50-89
	No: Claims	1,13,17,23,26-28,30,49
Inventive step (IS)	Yes: Claims	9-12,29,31-33, 50-56, 60, 69-89
	No: Claims	2-8,14-16,24,25,34-48, 57-59, 61-68, 90, 91
Industrial applicability (IA)	Yes: Claims	1-91
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV.

The separate inventions/groups of inventions are:

- I: claims 1-48,
- II: claim 49
- III: claim 50, partially: 52
- IV: claims 51, 53-56; partially: 52
- V: claims 57-72
- VI: claims 73-79
- VII: claims 80-83
- VIII: claims 84-91

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The statement of claims contains the following independent process claims which relate to the following processes:

- Claim 1: (II) → (I)
- Claim 49: (III) + (IV) → (II) → (I)
- Claim 50: (III) + (V) → (II) → (I)
- Claim 51: (IV) → (III); (III) + (V) → (II) → (I)
- Claim 57: (II) → (I) → (VIII) → (VII)
- Claim 72: (IIa or IIb) → (Ia or Ib) → (VIIIa or VIIIb) → (VIIa or VIIb)
- Claim 73: (XV) → (XVI) → (XVII) → (XIII); (XVIII) + (XIX) → (XX) → (XXI);
(XXI) + (XXII) → (XXIII) → (XIV)
- Claim 80: (XVII) + (XIX) → (XX) → (XXI); (XXI) + (XXII) → XXIII → (XIV)
- Claim 84: (XV) + (XVI) → (XVII) → (XVIII); (XVIII) + (XIXa) → (XXIII) → (XIV)

The present application suffers under a-priori non-unity because there is no connection by a common chemical key substance between the 3 groups of independent claims group A: 1,49,50,51,57

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group B: 72 group C: 73, 80, 84.

For instance the amino boronic esters (VII), (VIIb) and (XIV) have a different structure. The present application also suffers under a-posteriori non-unity because some of the final compounds to be prepared by the processes according to the claims and falling within the formulas (XIV) and (XXIV) are already known in the prior art, see in the document US-A-6699835 (=D1), the compound shown at column 18 and example 3 (starting at column 18): N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine Boroxine and N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid and examples 4 to 5 (Bortezomib). Compounds of formula (I) which are used as intermediates for the preparation of amino boronic esters (see claim 57) as well as compounds of formula II are known from US-A-4525309 (= D2). D2 describes processes for preparing a Li boronate complex (formulas II, IIa or IIb) as intermediate and rearranging this intermediate to yield compound (I); see examples 1-3 and 6-10. A salt of formula II is also mentioned in Tetrahedron Letters 44 (2003), page 8275, entry 9.

Boronic esters as well as aminoboronic esters (protected and unprotected) falling within formulas (I), (VII), (VIIb), (VIII) and (VIIIb) are disclosed in Priestley et al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 3199-3202 (=D4); page 3200, left hand column, Scheme 1 (for compounds of formula (I), see also D4, tables 1 and 2). Consequently, the compositions according to claims 34-36, 40-48, 90 and 91 lack inventive step because neither the reference to the preparation process nor the purity of a compound nor its amount in a composition can serve as a factor for limitation or inventive merit.

Hence, there is not a new or inventive product or intermediate which can link the various preparation processes according to independent claims 1, 49, 50, 51, 57, 72, 73, 80, and 84 together as required by the PCT Guidelines (as from 25/03/04), page 77, part 10.12.

Part 10.13 does not apply because the feature "large-scale process" is a relative term as explained in Guidelines 5.34. This unclear term, thus, cannot connect the process and the products and intermediates together.

Hence, neither the products either claimed (claims 90 and 91) or not or the known intermediates of formulas (I), (II), (IIa), (IIb) nor the feature "large-scale process" can serve as special technical feature in the sense of Rule 13 PCT, linking the different subjects

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together.

As there is no other technical feature, that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.

Re Item V.

Invention I

1. Reference is made to the following documents:

D1: US 6 699 835 B2 (PLAMONDON LOUIS ET AL) 2 March 2004 (2004-03-02)

D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: Tetrahedron Letters 44 (2003), pages 8273-8277

D4: Priestley et al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 3199-3202

2. Document D2 (see also paragraph [007] of the present application) describes processes for preparing a Li boronate complex as intermediate and rearranging this intermediate in the presence of a Lewis catalyst; see examples 1-3 and 6-10. The solvent being inter alia ether (example 1). Large-scale process cannot be accepted as distinguishing feature for the reason set out under item IV. See claims 9-12 and 34 in contrast to claim 1. Hence, claims 1,13, 17-23,26,27,28,30 lack novelty over D2

2.1

CLAIMS 2-12, 14-16, 24,25

No effect (and hence no inventive step) can be seen on account of the additional features according to these claims when dependent on present claim 1. Once this claim is correctly limited from D2 by inclusion of e. g. one of claims 9-12, 31-33 this view may be reconsidered.

2.2

INDEPENDENT CLAIM 34

In view of the above document D2, the subject-matter of independent claim 34 can not be considered inventive (Article 33(3) PCT) for the following reasons: Compounds of formula (I) are known from D2 and D4; see item IV, above. The preparation of a composition according to claim 34 by use of a known compound (I) can be done without inventive action.

2.3

INDEPENDENT CLAIMS 35 and 36

In view of the above document D2, the subject-matter of independent claims 35 and 36 can not be considered inventive (Article 33(3) PCT) for the following reasons:
Means for the enrichment of diastereomers and epimers are well known to the skilled person.

2.4

DEPENDENT CLAIMS 37-42

In view of the above document D2, the subject-matter of dependent claims 37-42 can not be considered inventive (Article 33(3) PCT) for the following reasons: see item 2.2, above.

2.5

INDEPENDENT CLAIM 43, DEPENDENT CLAIMS 44-48

In view of the above document D2, the subject-matter of independent claim 43 can not be considered inventive (Article 33(3) PCT) for the following reasons : see items 2.2 and 2.3, above.

Remark in respect of claims 46 and 47: process features cannot be considered as a limiting factor for products.

Re Item VIII.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/009774

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relative terms such as "large-scale process", or functional terms such as "low miscibility with water" in claims 1, 15, 16, 34 are not acceptable under Art. 6 and, therefore, have to be ignored. Also the "abouts" before ranges should be removed.

Invention II

Re Item V.

1. Reference is made to the following document:

D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

2. Document D2 describes processes for preparing a Li boronate complex as intermediate and rearranging this intermediate in the presence of a Lewis catalyst; see examples 1-3 and 6-10. The solvent being inter alia ether (example 1). The features "large-scale process" and "low miscibility with water" cannot be accepted as distinguishing features for the reason set out under item IV or VIII. Hence, claim 49 lacks novelty over D2.

Re Item VIII.

relative terms such as "large-scale process", or functional terms such as "low miscibility with water" in claim 49 are not acceptable under Art. 6 and, therefore, have to be ignored.

Inventions III and IV

Re Item V.

1. Reference is made to the following document:

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D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

2. Document D2 describes processes for preparing a Li boronate complex as intermediate and rearranging this intermediate in the presence of a Lewis catalyst; see examples 1-3 and 6-10. The solvent being inter alia ether (example 1). The strong base chloromethane lithium is prepared in situ and boronic ester in ether is added thereto.

From this prior art the process according to claim 50 is distinguished in that an ether solution of boronic ester (III) and a compound of formula (V) are treated with a strong hindered base to form complex (II) i. e. the sequence of the reaction is changed over the prior art according to D2. Furthermore, the process according to claim 50 uses sterically hindered base rather than n-BuLi as according to D2, example 1. Hence, novelty and inventive step can be acknowledged for claims 50-56.

Invention V

1. Reference is made to the following documents:

D1: US 6 699 835 B2 (PLAMONDON LOUIS ET AL) 2 March 2004 (2004-03-02)

D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: Tetrahedron Letters 44 (2003), pages 8273-8277

D4: Priestley et al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 3199-3202

D5: Beilstein Reaction ID 8638739

D6: Beilstein Reaction ID 8726664

2. Document D2 (see also paragraph [007] of the present application) describes processes for preparing a Li boronate complex as intermediate and rearranging this intermediate in the presence of a Lewis catalyst; see examples 1-3 and 6-10. The solvent being inter alia ether (example 1). The features "large-scale process" and "low miscibility with water" cannot be accepted as distinguishing features for the reason set out under item IV or VIII. Hence, D2 discloses the reaction steps (a) and (b) from (II) to (I). Steps (c) and (d) are

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known from D4; see D4, Schemes 1, 2, reactions b, c and corresponding text in D4 (acidolysis in HCl/dioxane). Hence, claims 57-59, 61-64, 66, 67, 68 are obvious over D2/D4.

D6 (acidolysis in HCl/dioxane) is similar to D4.

Acidolysis with trifluoroacetic acid is described in D5 (step (c)). Hence, claim 65 is considered obvious over D2/D5 because the removal of G groups is within the expertise of the skilled person.

Re Item VIII.

relative terms such as "large-scale process", or functional terms such as "low miscibility with water", low solubility" in claims 57 are not acceptable under Art. 6 and, therefore, have to be ignored.

Art. 6: No definition of "G" in claim 57;

Inventions VI and VII

1. Reference is made to the following documents:

D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: Tetrahedron Letters 44 (2003), pages 8273-8277

D4: Priestley et al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 3199-3202

D5: Beilstein Reaction ID 8638739

D6: Beilstein Reaction ID 8726664

D7: DOU, Q. PING ET AL; IDRUGS , 5(8), 828-834 CODEN: IDRUFN; ISSN: 1369-7056

2. The process for the preparation of Bortezomib according to claims 73 or 80 is entirely different from what is disclosed in document D7. D2 to D6 aim at the preparation of compounds different from Bortezomib. Hence, inventions VI and VII are novel and

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inventive.

Invention VIII

1. Reference is made to the following documents:

D1: US 6 699 835 B2 (PLAMONDON LOUIS ET AL) 2 March 2004 (2004-03-02)

D2: US 4 525 309 A (MATTESON ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: Tetrahedron Letters 44 (2003), pages 8273-8277

D4: Priestley et al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 3199-3202

D5: Beilstein Reaction ID 8638739

D6: Beilstein Reaction ID 8726664

D7: DOU, Q. PING ET AL; IDRUGS , 5(8), 828-834 CODEN: IDRUFN; ISSN: 1369-7056

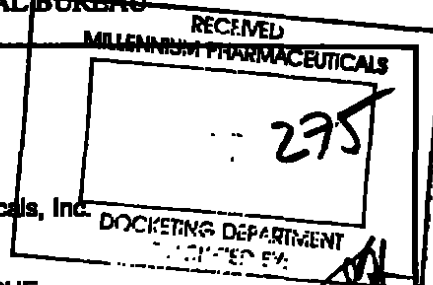
2. The process for the preparation of Bortezomib according to claim 84 is entirely different from what is disclosed in document D7. D2 to D6 aim at the preparation of compounds different from Bortezomib. Hence, claims 84 - 89 are novel and inventive.

3. Compound (XXIV) is shown in D1, column 15. The additional feature (1 kg) of claims 90 and 91 do not provide for inventive excess over D1.
Hence, these claims lack inventive merit.

PCTNOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
APPLICATION AS PUBLISHED OR REPUBLISHED

From the INTERNATIONAL BUREAU

To:

KLUNDER, Janice, M.
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)
20 October 2005 (20.10.2005)Applicant's or agent's file reference
MPI04-044**IMPORTANT NOTICE**International application No.
PCT/US2005/009774International filing date (day/month/year)
24 March 2005 (24.03.2005)Priority date (day/month/year)
30 March 2004 (30.03.2004)

Applicant

MILLENNIUM PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith the following documents:

- ☒ copy of the international application as published by the International Bureau on 20 October 2005 (20.10.2005) under No. WO 2005/097809
- ☐ copy of international application as republished by the International Bureau on under No. WO
- For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (as the case may be) on the front page of the attached document.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.+41 22 740 14 35

Authorized officer

Ellen Moyse

Facsimile No.+41 22 338 89 75

**TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE**

Date	24 March 2005
International Application No.	
Attorney Docket No.	MPI04-044

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I. Certification under 37 CFR 1.10 (If applicable)

EV621834868US
Express Mail Mailing Number

24 March 2005
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.


Signature of Person Mailing Correspondence

Sean Hunziker
Typed or Printed Name of Person Mailing Correspondence

II. ☒ New International Application

TITLE	SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS
-------	---

Earliest priority date (Day/Month/Year)
30 March 2004

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
 B. ☐ There is no prior U.S. application relating to this invention.
 C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RQ/101 (Request) and this listing does not constitute a claim for priority)

application no.	60/557,535	filed on	30 March 2004
application no.		filed on	
application no.		filed on	

application no.		filed on	
application no.		filed on	

- E. ☒ The present international application ☒ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C above. The additional subject matter is found on pages throughout and ☒ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. ☐ A response to an Invitation from the ROUS. The following document(s) is(are) enclosed:

- A. ☐ A Request for an Extension of Time to File a Response
 B. ☐ A Power of Attorney (General or Regular)
 C. ☐ Replacement pages:
 D. ☐ Submission of Priority Documents
 E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RQ/101 annex

IV. ☐ A Request for Rectification under PCT Rule 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☒ Other (please specify): PCT Request Form (7 pages-in duplicate), PCT Fee Calculation Sheet (1 page), 60 pages of Specification (pp. 1-60), 30 pages of Claims (pp. 61-90), 1 page of Abstract (p. 91); General Power of Attorney for Millennium Pharmaceuticals, Inc. by Scott Brown (1 page)

The person
signing this
form is the:

☐ Applicant	Janice M. KLUNDER
☒ Attorney/Agent (Reg. No.) 41,121	Typed name of signer
☐ Common Representative	
	Signature

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PCT REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only	
International Application No.	
International Filing Date	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) MP104-044	

Box No. I		TITLE OF INVENTION	
SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS			
Box No. II		APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) MILLENNIUM PHARMACEUTICALS, INC. 40 Landsdowne Street Cambridge, Massachusetts 02139 United States of America		Telephone No. (617) 679-7000	
		Facsimile No. (617) 551-8820	
		Applicant's Registration No. with the Office	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
Box No. III		FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) PICKERSGILL, I. Fraser 15 Sylvester Lane Hampstead, New Hampshire 03841 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)	
		Applicant's Registration No. with the Office	
		State (that is, country) of nationality: UK	
State (that is, country) of residence: US			
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.			
Box No. IV		AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:		☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country) KLUNDER, Janice M. MILLENNIUM PHARMACEUTICALS, INC. 40 Landsdowne Street Cambridge, Massachusetts 02139 United States of America		Telephone No.: (617) 551-3669	
		Facsimile No.: (617) 551-8820	
		Applicant's Registration No. with the Office 41,121	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.			

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BISHOP, John 878 Townsend Road Groton, Massachusetts 01450 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KOELLNER, Christoph AMCIS AG Hauptstrasse 159-173 CH-4416 Bubendorf Switzerland		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) GOMEZ, Jean-Marc AMCIS AG Hauptstrasse 159-173 CH-4416 Bubendorf Switzerland		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) GEISER, Achim CarboGen Laboratories (Neuland) AG Neulandweg 5 CH-5502 Hunzenschwil Switzerland		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.			

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) HETT, Robert CarboGen Laboratories (Neuland) AG Neulandweg 5 CH-5502 Hunzenschwil Switzerland		279 This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: CH		State (that is, country) of residence: CH	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) AMMOSCATO, Vince Ash Stevens, Inc. 18655 Krause Street Riverview, Michigan 48192 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) MUNK, Stephen Ash Stevens, Inc. 18655 Krause Street Riverview, Michigan 48192 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) LO, Young Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, Virginia 23805-9382 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.			

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Chui, Fang-Ting Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, Virginia 23805-9382 United States of America	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: US State: (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KULKARNI, Vithalanand R. Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, Virginia 23805-9382 United States of America	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: US State: (that is, country) of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: State: (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: State: (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's Registration No. with the Office	
State (that is, country) of nationality: State: (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V

DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection
 ☐ KR Republic of Korea is not designated for any kind of national protection
 ☐ RU Russian federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

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Box No. VI

PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: * regional Office	international application: receiving Office
item (1) 30 March 2004 (30.03.2004)	60/557,535	US		

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☒ all items
 ☐ item (1)
 ☐ item (2)
 ☐ item (3)
 ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII

INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)	Number	Country (or regional Office)
-----------------------	--------	------------------------------

Box No. VIII

DECLARATIONS

The following declarations are contained in Boxes Nos. VIII(i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

☐ Box No. VIII(i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII(ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII(iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII(iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII(v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Supplemental Box

CONTINUATION of Box No. IV (AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE)

282

BROWN, Scott A., Reg. No. 32,724
SILVERMAN, Ian Robert, Reg. No. 37,443
SILVERI, Jean M., Reg. No. 39,030
SHAIR, Karoline K. M., Reg. No. 44,332
SCHRAY, Kerri Pollard, Reg. No. 47,066
SIOUSSAT, Tracy M., Reg. No. 50,609

All of MILLENNIUM PHARMACEUTICALS, INC., 40 Landsdowne Street, Cambridge, MA, 02139, United States of America

273

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets) : 7

description (including sequence listing part and/or tables related thereto) : 58

Claims : 30

Abstract : 1

Drawings : 0

Sub-total number of sheets : 89

sequence listing : :

tables related thereto : :

(for book, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)

Total number of sheets : 96

(b) ☐ only in computer readable form (Section 801(a)(i))(i) ☐ sequence listing(ii) ☐ tables related thereto(c) ☐ also in computer readable form (Section 801(a)(ii))(i) ☐ sequence listing(ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the

☐ sequence listing.....☐ tables related thereto.....

(additional copies to be indicated under item 9(ii), and/or 10(ii), in right column)

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☒ fee calculation sheet : 1
2. ☐ original separate power of attorney : :
3. ☐ original general power of attorney : :
4. ☒ copies of general powers of attorney (4 pgs); reference number, if any : 1
5. ☐ statement explaining lack of signature : :
6. ☐ priority document(s) identified in Box No. VI as item(s): : :
7. ☐ translation of international application into (language) : :
8. ☐ separate indications concerning deposited microorganism or other biological material : :
9. ☐ sequence listing in computer readable form (indicate type and number of carriers) : :
- (i) ☐ Copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : :
- (ii) ☐ Together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in the left column : :
- (iii) ☐ Tables in computer readable form related to sequence listing (indicate type and number of carriers) : :
10. ☐ copy submitted for the purposes of international search under Section 802 (b-quarter) only (and not as part of the international application) (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter) : :
- (i) ☐ Together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : :
- (ii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : :
- (iii) ☐ other (specify) : 2
11. ☒ Transmittal Letter/Postcard

Figure of the drawings which should accompany the abstract: none

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


 Janice M. KLUNDER, Registration No. 41,121
 Agent for Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent):
ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:☐ received☐ not received:**For International Bureau use only**

Date of receipt of the record copy by the International Bureau:

Form PCT/RO/101 (last sheet) (January 2004)

See Notes to the request form

PCT FEE CALCULATION SHEET Annex to the Request		For receiving Office use only International application No. _____	
Applicant's or agent's file reference MPID4-044		Date stamp of the receiving Office _____	
Applicant MILLENNIUM PHARMACEUTICALS, INC. et al.			
CALCULATION OF PRESCRIBED FEES 1. TRANSMITTAL FEE [USD 300 (T)] 2. SEARCH FEE [1920 (S)] International search to be carried out by <u>ISA/EP</u> <i>(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)</i> 3. INTERNATIONAL FEE Where items (b) and/or (c) of Box No. IX apply, enter Sub-Total number of Sheets _____ Where items (b) and (c) of Box No. IX do not apply, enter Total number of Sheets <u>96</u> [1] First 30 sheets [1134 (i1)] [2] <u>66</u> x <u>12</u> = <u>792</u> (i2) number of sheets fee per sheet in excess of 30 [3] additional components (only if sequence listing and/or tables related thereto are filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii). 400 x _____ = _____ (i3) Add amounts entered at i1, i2 and i3 and enter total at 1. [1926 (I)] <i>(Applicants from certain States are entitled to a reduction of 75% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the international filing fee.)</i> 4. FEE FOR PRIORITY DOCUMENT (if applicable) [20 (P)] 5. TOTAL FEES PAYABLE TOTAL [4166] Add amounts entered at T, S, I and P, and enter total in the Total box			
MODE OF PAYMENT ☒ Authorization to charge deposit account (see below) ☐ cheque ☐ postal money order ☐ bank draft ☐ cash ☐ revenue stamps ☐ coupons ☐ other (specify): _____			
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(this mode of payment may not be available at all receiving Offices)</i> ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any over payment in the total fees indicated above. ☒ Authorization to charge the fee for the priority document. Receiving Office: <u>RO/US</u> Deposit Account No.: <u>301668</u> Date: <u>March 24, 2005</u> Name: <u>Jessica M. KLINDER, Reg. No. 41121</u> Signature: <u>Jessica M. Klinder</u>			

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RECEIVED
MILLENNIUM PHARMACEUTICALS
JUL 5 2005
PCT
DOCKETING DEPARTMENT
DOCKETED BY

PATENT COOPERATION TREATY

PCT/US2005/009774

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

To:

KLUNDER, Janice, M.
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139
ETATS-UNIS D'AMERIQUE

285

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 23 June 2005 (23.06.2005)	
Applicant's or agent's file reference MPI04-044	IMPORTANT NOTIFICATION
International application No. PCT/US2005/009774	International filing date (day/month/year) 24 March 2005 (24.03.2005)
International publication date (day/month/year)	Priority date (day/month/year) 30 March 2004 (30.03.2004)
Applicant MILLENNIUM PHARMACEUTICALS, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 March 2004 (30.03.2004)	60/557,535	US	26 May 2005 (26.05.2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer A. ZOLTANSKI (Fax : 338 89 75) Facsimile No. (41-22) 338.89.75 Telephone No. +41 22 338 8608
---	--

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

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PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable 

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

SECRETARÍA DE INDUSTRIA Y COMERCIO
Rad: 06-109669- -0000-0000
Rec: 2006 10 27 17:14:03 Dep: 2020 NUECRACIONES
Tra: 11 PATENTEN
Eva: 379 FASE NACIONAL
Act: 11 PRESENTACION Folios: 2/5

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

287
30-10-06

①

SOLICITUD DE :



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

SOLICITANTE
(71)

Nombre: MILLENUM PHARMACEUTICALS, INC.

Dirección: 40 Landsdowne Street,
Cambridge, MA 02139 Estados Unidos

Nacionalidad o Domicilio: Cambridge, Massachussets
Estados Unidos

Lugar de Constitución: Estados Unidos

Teléfono:

Fax:

E-mail:

IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: LUIS PATIÑO LEYVA

Dirección Cra. 11ª No. 94-76 - Of. 308

Teléfono: 6161948

Fax: 6163976

E-mail:

IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual

Número 2.930.616 TP 2698

④

INVENTOR (ES)
(72)

Nombre: PICKERSGILL I., Fraser

Dirección: 115 Liberty Street,

Nacionalidad o Domicilio: Newton, MA 18940, Estados Unidos

⑤ PCT (86)

Solicitud Internacional No. PCT/US2005/009774

Fecha: Marzo 24 de 2005

WO 2005/097809 A2

Publicación Internacional No. WO 2005/097809 A3

Fecha Octubre 28 de 2004

⑥

Título (54) SÍNTESIS DE COMPUESTOS DE ÉSTER Y ÁCIDO BÓRICO.

⑦

Clasificación Internacional (51) C07F 5/02

⑧

PRÍORIDAD:

(33) País de Origen

(32) Fecha

(31) Numero de Solicitud

SI



NO



Estados Unidos

Marzo 30 de 2004

60/557,535

⑨

Comprobante de pago No. 06 - 82,120

Fecha Octubre 24 de 2006

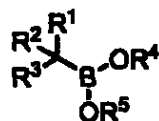
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

Continuación nombre, dirección y domicilio de inventores:

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
BISHOP John	878 Townsend Road,	Groton, MA 01450, Estados Unidos
KOELLNER Christoph	Amcis AG, Haupstrasse 159-173	CH-4416 Bubendorf, China
GOMEZ Jean-Marc	Amcis AG, Haupstrasse 159-173	CH-4416 Bubendorf, China
GEISER Achim	CarboGen Laboratories (Neuland) AG, Neulandweg 5,	CH-5502 Hunzenschwil, China
HETT Robert	CarboGen Laboratories (Neuland) AG, Neulandweg 5,	CH-5502 Hunzenschwil China
AMMOSCATO Vince	Ash Stevens, Inc.,	18655 Krause Street, Riverview, MI 48192 Estados Unidos
MUNK Stephen	Ash Stevens Inc.,	18655 Krause Street, Riverview, MI 48192 Estados Unidos
LO Young	Chemicals, Inc., North Normando Drive, P.O. Box 1658,	Petersburg, VA 23805- 93-82 Estados Unidos
CHUI Fang-Ting	Boehringer Ingelheim Chemicals, Inc.,	2820 North Normandy Drive, P.O. Box 1658, Petersburg, VA 23805- 9382 Estados Unidos
KULKARNI Vithalanand, R.,	Boehringer Ingelheim Chemicals, Inc., 2820 North Normandy Drive, P.O. Box 1658,	Petersburg, VA 23805- 9382 Estados Unidos

REIVINDICACIONES

1. Un proceso a gran escala para preparar un compuesto de éster bórico de fórmula (I):



(I)

en la que:

R^1 es un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

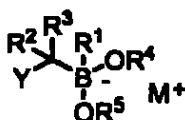
R^2 es hidrógeno, un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido;

R^3 es un grupo nucleófilo o un grupo alifático, aromático o heteroaromático opcionalmente sustituido; y

cada uno de R^4 y R^5 , independientemente, es un grupo alifático, aromático o heteroaromático opcionalmente sustituido o R^4 y R^5 , tomados junto con los átomos de oxígeno y boro que intervienen, forman un anillo de 5 a 10 miembros opcionalmente sustituido que tiene 0-2 heteroátomos más en el anillo seleccionados entre N, O o S;

comprendiendo dicho proceso las etapas:

- (a) proporcionar un complejo boron"ato" de fórmula (II):



(II)

en la que

Y es un grupo nucleófilo;

M^+ es un catión; y

cada uno de R^1 a R^5 es como se ha definido anteriormente; y

- (b) poner en contacto el complejo boron"ato" de fórmula (II) con un ácido de Lewis en condiciones que produzcan el compuesto de éster bórico de

fórmula (I), realizándose dicha etapa de contacto en una mezcla de reacción que comprende:

- (i) un disolvente de éter de coordinación que tiene una baja miscibilidad con agua; o
- (ii) un disolvente de éter que tiene una baja miscibilidad con agua y un co-disolvente de coordinación.

2. El proceso de la reivindicación 1, donde la mezcla de reacción comprende un co-disolvente de coordinación.

3. El proceso de la reivindicación 2, donde el co-disolvente de coordinación se selecciona entre el grupo compuesto por tetrahidrofurano, dioxano, agua, y mezclas de los mismos.

4. El proceso de la reivindicación 0, donde el co-disolvente de coordinación no constituye más de aproximadamente 20% v/v de la mezcla de reacción.

5. El proceso de la reivindicación 0, donde el co-disolvente de coordinación no constituye más de aproximadamente el 15% v/v de la mezcla de reacción.

6. El proceso de la reivindicación 1, donde la solubilidad del agua en el disolvente de éter que tiene una baja miscibilidad con agua es menor de aproximadamente el 2% p/p.

7. El proceso de la reivindicación 0, donde el disolvente de éter que tiene una baja miscibilidad con agua se selecciona entre el grupo compuesto por *terc*-butil metil éter, *terc*-butil etil éter, *terc*-amil metil éter, éter isopropílico, y mezclas de los mismos.

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
MILLENNIUM PHARMACEUTICALS, INC

REFERENCIA	Radicación No.	6 109669
	Solicitud internacional	PCT/US2005/009774
	Fecha inicio fase nacional	30/10/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14710

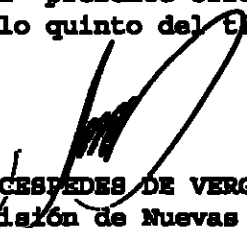
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. Debe aclarar la fecha de publicación internacional, por cuanto el petitorio presentado en fase nacional difiere del presentado en fase internacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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


ALIX CARMONA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior, requerimiento fue notificado por fijación en lista de fecha 22 DIC. 2006 aalvarado