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(21) International Application Number: PCT/US94/12201 (22) International Filing Date: 31 October 1994 (31.10.94) (30) Priority Data: 08/156,498 23 November 1993 (23.11.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/156,498 (CON) Filed on 23 November 1993 (23.11.93) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): NG, John, S. [US/US]; 341 West 30th Place, Chicago, IL 60616 (US). PRZYBYLA, Claire, A. [US/US]; 1373 Walnut Street, Des Plaines, IL 60016 (US). MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US). VASQUEZ, Michael, L. [US/US]; 233 Saratoga Court, Gurnee, IL 60031 (US). GETMAN, Daniel, P. [US/US]; 66 Sunnyhill Court,		Chesterfield, MO 63017 (US). FRESKOS, John, J. [US/US]; 7572 York, Clayton, MO 63105 (US). DECRESCENZO, Gary, A. [US/US]; 536 Schrader Farm Drive, St. Peters, MO 63376 (US). BERTENSHAW, Deborah, E. [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US). HEINTZ, Robert, M. [US/US]; 603 Nancy Place, Ballwin, MO 63021 (US). ZHANG, Suhong [CN/US]; Apartment 309, 9735 Sumac Road, Des Plaines, IL 60016 (US). LIU, Chin [CN/US]; Apartment #BG, 3763 Salem Walk N., Northbrook, IL 60062 (US). LANEMAN, Scott, A. [US/US]; 300 Apollo Court, Vernon Hills, IL 60061 (US). (74) Agents: UNGEMACH, Frank, S. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: METHOD FOR MAKING INTERMEDIATES USEFUL IN SYNTHESIS OF RETROVIRAL PROTEASE INHIBITORS (57) Abstract <p>A synthesis is described for intermediates which are readily amenable to the large scale preparation of hydroxyethylurea-based chiral HIV protease inhibitors. The method includes forming a diastereoselective epoxide of cyanohydrin from a chiral alpha amino aldehyde.</p>		

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**METHOD FOR MAKING INTERMEDIATES USEFUL IN SYNTHESIS
OF RETROVIRAL PROTEASE INHIBITORS**

This application is a continuation in part of Patent Application Serial No. PCT/US93/04804, filed May 20, 1993, which is a continuation in part of Patent Application Serial No. 07/886,558, filed May 20, 1992, which is a continuation in part of PCT/US91/8613, filed November 18, 1991, which is a continuation in part of 07/789,646, filed November 14, 1991, which is a continuation in part of U.S. Patent Application Serial No. 07/615,210, filed November 19, 1990, each of which is co-owned and incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

Synthesis of many HIV protease inhibitors containing a hydroxyethylamine or hydroxyethylurea isostere include the amine opening of a key intermediate chiral epoxide. The synthesis of the key chiral epoxide requires a multi-step synthesis starting from L-phenylalanine and results in a low overall yield. The diastereoselectivity of the reduction step of the intermediate amino chloromethylketone is low and use of explosive diazomethane prevents the scale up of the method to multikilogram productions. The present invention relates to a method of preparing retroviral protease inhibitors and more particularly to a diastereoselective method of forming chiral intermediates for the preparation of urea containing hydroxyethylamine protease inhibitors.

2. Related Art

Roberts et al, Science, 248, 358 (1990),
5 Krohn et al, J. Med. Chem. 344, 3340 (1991) and
Getman, et al, J. Med. Chem., 346, 288 (1993) have
previously reported synthesis of protease inhibitors
containing the hydroxyethylamine or hydroxyethylurea
isostere which include the opening of an epoxide
10 generated in a multi-step synthesis starting from an
amino acid. These methods also contain steps which
include diazomethane and the reduction of an amino
chloromethyl ketone intermediate to an amino alcohol
prior to formation of the epoxide. The overall yield
15 of these syntheses are low and the use of explosive
diazomethane additionally prevents such methods from
being commercially acceptable.

Tinker et al U.S. Patent No. 4,268,688
20 discloses a catalytic process for the asymmetric
hydroformylation to prepare optically active aldehydes
from unsaturated olefins. Similarly, Reetz et al U.S.
Patent No. 4,990,669 discloses the formation of
optically active alpha amino aldehydes through the
25 reduction of alpha amino carboxylic acids or their
esters with lithium aluminum hydride followed by
oxidation of the resulting protected beta amino
alcohol by dimethyl sulfoxide/oxalyl chloride or
chromium trioxide/pyridine. Alternatively, protected
30 alpha amino carboxylic acids or esters thereof can be
reduced with diisobutylaluminum hydride to form the
protected amino aldehydes.

Reetz et al (Tet. Lett., 30, 5425 (1989))
35 disclosed the use of sulfonium and arsonium ylides and
their reactions of protected α -amino aldehydes to form
aminoalkyl epoxides. This method suffers from the use

of highly toxic arsonium compounds or the use of combination of sodium hydride and dimethyl sulfoxide which is extremely hazardous in large scale. (Sodium hydride and DMSO are incompatible: Sax, N.I.,
5 "Dangerous Properties of Industrial Materials", 6th Ed., Van Nostrand Reinhold Co., 1984, p. 433. Violent explosions have been reported on the reaction of sodium hydride and excess DMSO, "Handbook of Reactive Chemical Hazards", 3rd Ed., Butterworths, 1985,
10 p. 295. Matteson et al Synlett., 1991, 631 reported the addition of chloromethylithium or bromomethylithium to racemic aldehydes.

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SUMMARY OF THE INVENTION

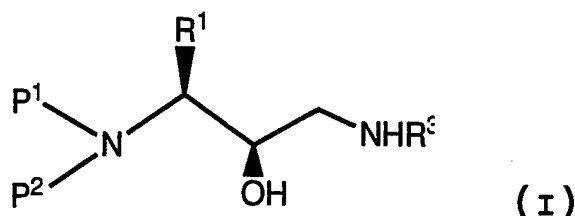
Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), encodes three enzymes, including the well-
20 characterized proteinase belonging to the aspartic proteinase family, the HIV protease. Inhibition of this enzyme is regarded as a promising approach for treating AIDS. One potential strategy for inhibitor design involves the introduction of hydroxyethylene
25 transition-state analogs into inhibitors. Inhibitors adapting the hydroxyethylamine or hydroxyethylurea isostere are found to be highly potent inhibitors of HIV proteases. Despite the potential clinical importance of these compounds, previously there were
30 no satisfactory synthesis which could be readily and safely scaled up to prepare large kilogram quantities of such inhibitors needed for development and clinical studies. This invention provides an efficient synthesis of intermediates which are readily amenable
35 to the large scale preparation of hydroxyethylurea-based chiral HIV protease inhibitors.

Specifically, the method includes preparing a chiral diaminopropanol from a chiral alpha amino aldehyde via a diastereoselective epoxide or a stereospecific cyanohydrin.

5

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method of preparation of HIV protease inhibitor that allows the preparation of commercial quantities of intermediates of the formula



wherein R¹ is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and arylalkyl, which are optionally substituted with a group selected from alkyl, halogen, NO₂, OR⁹ or SR⁹, where R⁹ represents hydrogen or alkyl; and

20

R³ represents hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical. Preferably, R³ represents radicals as

30

defined above which contain no alpha-branching, e.g., as in an isopropyl radical or a t-butyl radical. The preferred radicals are those which contain a -CH₂- moiety between the nitrogen and the remaining portion of the radical. Such preferred groups include, but are not limited to, benzyl, isobutyl, n-butyl, isoamyl, cyclohexylmethyl and the like.

P¹ and P² independently are selected from amine protecting groups, including but not limited to, arylalkyl, substituted arylalkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples of arylalkyl include, but are not limited to benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkenylalkyl radicals containing cycloalkyls of C₆-C₁₀. Suitable acyl groups include carbobenzoyl, t-butoxycarbonyl, isobutoxycarbonyl, benzoyl, substituted benzoyl such as 2-methylbenzoyl, 2,6-dimethylbenzoyl, 2,4,6-trimethylbenzoyl and 2,4,6-triisopropylbenzoyl, 1-naphthoyl, 2-naphthoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P¹ and/or P² protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be

mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

5

Suitable carbamate protecting groups include, but are not limited to, methyl and ethyl carbamate; 9-fluorenylmethyl carbamate; 9-(2-Sulfo)fluorenylmethyl carbamate; 9-(2,7-dibromo)fluorenylmethyl carbamate; 2,7-di-t-butyl-[9-(10,10-dioxo-10,10-tetrahydrothioxanthyl)methyl carbamate; 4-methoxyphenacyl carbamate; 2,2,2-trichloroethyl carbamate; 2-trimethylsilylethyl carbamate; 2-phenylethyl carbamate; 1-(1-adamantyl)-1-methylethyl carbamate; 1,1-dimethyl-2-haloethyl carbamate; 1,1-dimethyl-2,2-dibromoethyl carbamate; 1,1-dimethyl-2,2,2-trichloroethyl carbamate; 1-methyl-1-(4-biphenyl)-ethyl carbamate; 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate; 2-(2'-and 4'-pyridyl)ethyl carbamate; 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate; t-butyl carbamate; 1-adamantyl carbamate; vinyl carbamate; allyl carbamate; 1-isopropylallyl carbamate; cinnamyl carbamate; 4-nitrocinnamyl carbamate; 8-quinolyl carbamate; N-hydroxypiperidinyl carbamate; alkylidithio carbamate; benzyl carbamate; p-methoxybenzyl carbamate; p-nitrobenzyl carbamate; p-bromobenzyl carbamate; p-chlorobenzyl carbamate; 2,4-dichlorobenzyl carbamate; 4-methylsulfinylbenzyl carbamate; 9-anthrylmethyl carbamate; diphenylmethyl carbamate; 2-methylthioethyl carbamate; 2-methylsulfonylethyl carbamate; 2-(p-toluenesulfonyl)ethyl carbamate; [2-(1,3-dithianyl)methyl carbamate; 4-methylthiophenyl-2,4-dimethylthiophenyl, 2-phosphonioethyl carbamate; 2-triphenylphosphonioisopropyl carbamate; 1,1-dimethyl-2-cyanoethyl carbamate; m-chloro-p-acyloxybenzyl carbamate; p-(dihydroxyboryl)benzyl carbamate; 5-benziosoxazolylmethyl carbamate; 2-(trifluoromethyl)-6-chromonylmethyl carbamate; m-

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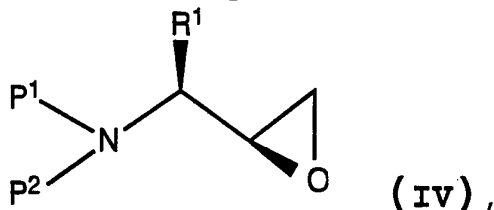
nitrophenyl carbamate; 3,5-dimethoxybenzyl carbamate; o-nitrobenzyl carbamate; 3,4-dimethoxy-6-nitrobenzyl carbamate; phenyl(o-nitrophenyl)methyl carbamate; phenothiazinyl-(10)-carbonyl derivative; N'-p-toluenesulfonylaminocarbonyl derivative; N'-phenylaminothiocarbonyl derivative t-amyl carbamate; S-benzyl thiocarbamate; p-cyanobenzyl carbamate; cyclobutyl carbamate; cyclohexyl carbamate; cyclopentyl carbamate; cyclopropylmethyl carbamate; p-decyloxybenzyl carbamate; 10 diisopropylmethyl carbamate; 2,2-dimethoxycarbonylvinyl carbamate; o-(N,N-dimethylcarboxamido)benzyl carbamate; 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate; 1,1-dimethylpropynyl carbamate; di(2-pyridyl)methyl carbamate; 2-furanylmethyl carbamate; 2-iodoethyl carbamate; isobornyl carbamate; isobutyl carbamate; 15 isonicotinyl carbamate; p-(p'-methoxyphenylazo)benzyl carbamate; 1-methylcyclobutyl carbamate; 1-methylcyclohexyl carbamate; 1-methyl-1-cyclopropylmethyl carbamate; 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate; 1-methyl-1-(p-phenylazophenyl)ethyl carbamate; 20 and 1-methyl-1-phenylethyl carbamate. T. Greene and P. Wuts ("Protective Groups In Organic Synthesis," 2nd Ed., John Wiley & Sons, Inc. (1991)) describe the preparation and cleavage of such carbamate protecting groups.

25
Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 30 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid 35 esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to

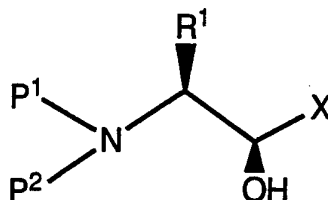
the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyldimethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Preferably P^1 is selected from aralkyl, substituted aralkyl, alkylcarbonyl, aralkylcarbonyl, arylcarbonyl, alkoxycarbonyl and aralkoxycarbonyl, P^2 is selected from aralkyl and substituted aralkyl and R^1 is selected from aralkyl and substituted aralkyl. Alternatively, when P^1 is alkoxycarbonyl or aralkoxycarbonyl, P^2 can be hydrogen. More preferably, P^1 is t-butoxycarbonyl, phenylmethoxycarbonyl or benzyl, P^2 is hydrogen or benzyl and R^1 is benzyl.

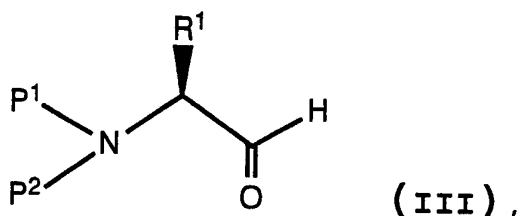
Protected amino epoxides of the formula



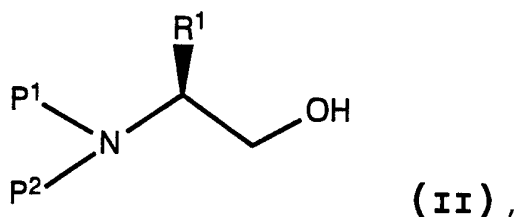
protected amino alpha-hydroxycyanides and acids of the formula



wherein X is -CN, -CH₂NO₂ or -COOH, protected alpha-
5 aminoaldehyde intermediates of the formula



and protected chiral alpha-amino alcohols of the formula
10



wherein P¹, P² and R¹ are as defined above, are also
described herein.

15

As utilized herein, the term "amino epoxide" alone or in combination, means an amino-substituted alkyl epoxide wherein the amino group can be a primary, or secondary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, alkenyl, alkoxy carbonyl, aralkoxy carbonyl, cycloalkenyl, silyl, cycloalkylalkenyl radicals and the like and the epoxide can be alpha to the amine. The term "amino aldehyde" alone or in combination, means an amino-substituted alkyl aldehyde wherein the amino group can be a primary, or secondary amino group containing substituents selected
20
25

from hydrogen, and alkyl, aryl, aralkyl, alkenyl, aralkoxycarbonyl, alkoxy carbonyl, cycloalkenyl, silyl, cycloalkylalkenyl radicals and the like and the aldehyde can be alpha to the amine. The term "alkyl", alone or in
5 combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10, preferably from 1 to about 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl,
10 iso-amyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to about 18 carbon atoms preferably from 2 to about 8 carbon atoms.
15 Examples of suitable alkenyl radicals include ethenyl, propenyl, allyl, 1,4-butadienyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include
20 methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkenyl", alone or in combination, means an alkyl radical which contains from about 3 to about 8 carbon atoms and is cyclic and which contains at least
25 one double bond in the ring which is non-aromatic in character. The term "alkynyl", alone or in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and containing from 2 to about 10 carbon atoms. Examples of alkynyl radicals include
30 ethynyl, propynyl, (propargyl), butynyl and the like. The term "cycloalkenylalkyl" means cycloalkenyl radical as defined above which is attached to an alkyl radical, the cyclic portion containing from 3 to about 8, preferably from 3 to about 6, carbon atoms. Examples of
35 such cycloalkenyl radicals include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, dihydrophenyl and the like. The term "cycloalkyl", alone or in

combination, means an alkyl radical which contains from about 3 to about 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing
5 from about 3 to about 8, preferably from about 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two
10 or three rings wherein such rings may be attached together in a pendent manner or may be fused. Examples of "aryl" include phenyl or naphthyl radical either of which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino,
15 nitro and the like, as well as p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom
20 is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. Examples of substituted aralkyl include 3,5-dimethoxybenzyl bromide, 3,4-dimethoxybenzyl bromide, 2,4-dimethoxybenzyl bromide, 3,4,5-trimethoxybenzyl bromide, 4-nitrobenzyl iodide,
25 2,6-dichlorobenzyl bromide, 1,4-bis(chloromethyl)benzene, 1,2-bis(bromomethyl)benzene, 1,3-bis(chloromethyl)-benzene, 4-chlorobenzyl chloride, 3-chlorobenzyl chloride, 1,2-bis(chloromethyl)benzene,
6-chloropiperonyl chloride, 2-chlorobenzyl chloride,
30 4-chloro-2-nitrobenzyl chloride, 2-chloro-6-fluorobenzyl chloride, 1,2-bis(chloromethyl)-4,5-dimethylbenzene, 3,6-bis(chloromethyl)durene, 9,10-bis(chloromethyl)anthracene, 2,5-bis(chloromethyl)-p-xylene, 2,5-bis(chloromethyl)-1,4-dimethoxybenzene,
35 2,4-bis(chloromethyl)anisole, 4,6-(dichloromethyl)-m-xylene, 2,4-bis(chloromethyl)mesitylene, 4-(bromomethyl)-3,5-dichlorobenzophenone, n-(alpha-chloro-o-tolyl)-

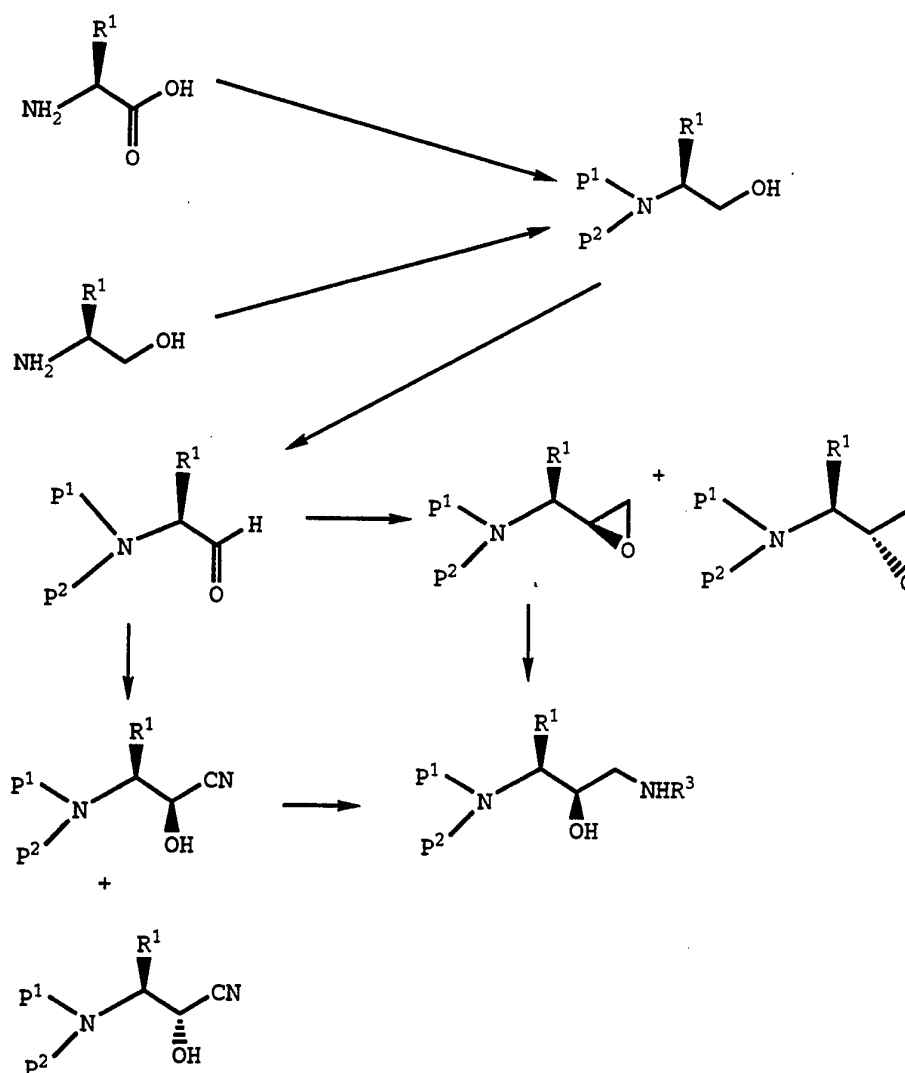
- benzylamine hydrochloride, 3-(chloromethyl)benzoyl
chloride, 2-chloro-4-chloromethyltoluene,
3,4-dichlorobenzyl bromide, 6-chloro-8-chloromethylbenzo-
1,3-dioxan, 4-(2,6-dichlorobenzylsulphonyl)benzylbromide,
5 5-(4-chloromethylphenyl)-3-(4-chlorophenyl)-1,2,4-
oxadiazole, 5-(3-chloromethylphenyl)-3-(4-chlorophenyl)-
1,2,4-oxadiazole, 4-(chloromethyl)benzoyl chloride,
di(chloromethyl)toluene, 4-chloro-3-nitrobenzyl chloride,
1-(dimethylchlorosilyl)-2-(p,m-chloromethylphenyl)ethane,
10 1-(dimethylchlorosilyl)-2-(p,m-chloromethylphenyl)ethane,
3-chloro-4-methoxybenzyl chloride, 2,6-bis(chloromethyl)-
4-methylphenol, 2,6-bis(chloromethyl)-p-tolyl acetate,
4-bromobenzyl bromide, p-bromobenzoyl bromide, alpha
alpha'-dibromo-m-xylene, 3-bromobenzyl bromide,
15 2-bromobenzyl bromide, 1,8-bis(bromomethyl)naphthalene,
o-xylylene dibromide, p-xylylene dibromide,
2,2'-bis(bromomethyl)-1,1'-biphenyl, alpha,alpha'-
dibromo-2,5-dimethoxy-p-xylene, benzyl chloride, benzyl
bromide, 4,5-bis(bromomethyl)phenanthrene,
20 3-(bromomethyl)benzyltriphenylphosphonium bromide,
4-(bromomethyl)benzyltriphenylphosphonium bromide,
2-(bromomethyl)benzyltriphenylphosphonium bromide,
1-(2-bromoethyl)-2-(bromomethyl)-4-nitrobenzene,
2-bromo-5-fluorobenzylbromide, 2,6-bis(bromomethyl)
25 fluorobenzene, o-bromomethylbenzoyl bromide,
p-bromomethyl benzoyl bromide, 1-bromo-2-
(bromomethyl)naphthalene, 2-bromo-5-methoxybenzyl
bromide, 2,4-dichlorobenzyl chloride, 3,4-dichlorobenzyl
chloride, 2,6-dichlorobenzyl chloride, 2,3-dichlorobenzyl
30 chloride, 2,5-dichlorobenzyl chloride,
methyldichlorosilyl(chloromethylphenyl)ethane,
methyldichlorosilyl(chloromethylphenyl)ethane,
methyldichlorosilyl(chloromethylphenyl)ethane,
3,5-dichlorobenzyl chloride, 3,5-dibromo-2-hydroxybenzyl
35 bromide, 3,5-dibromobenzyl bromide,
p-(chloromethyl)phenyltrichlorosilane,

1-trichlorosilyl-2-(p,m-chloromethylphenyl)ethane,
1-trichlorosilyl-2-(p,m-chloromethylphenyl)ethane,
1,2,4,5-tetrakis(bromomethyl)benzene. The term
aralkoxycarbonyl means an aralkoxyl group attached to a
5 carbonyl. Carbobenzoxy is an example of
aralkoxycarbonyl. The term "heterocyclic ring system"
means a saturated or partially unsaturated monocyclic,
bicyclic or tricyclic heterocycle which contains one or
more hetero atoms as ring atoms, selected from nitrogen,
10 oxygen, silicon and sulphur, which is optionally
substituted on one or more carbon atoms by halogen,
alkyl, alkoxy, oxo, and the like, and/or on a secondary
nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl,
alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen
15 atom (i.e. = N-) by oxido and which is attached via a
carbon atom. The heteroaryl portion of a heteroaryl,
heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group
or the like is an aromatic monocyclic, bicyclic, or
tricyclic heterocycle which contains the hetero atoms and
20 is optionally substituted as defined above with respect
to the definition of aryl. Examples of such heterocyclic
groups are pyrrolidinyl, piperidinyl, piperazinyl,
morpholinyl, thiamorpholinyl, pyrrolyl, phthalimide,
succinimide, maleimide, and the like. Also included are
25 heterocycles containing two silicon atoms simultaneously
attached to the nitrogen and joined by carbon atoms. The
term "alkylamino" alone or in combination, means an
amino-substituted alkyl group wherein the amino group can
be a primary, or secondary amino group containing
30 substituents selected from hydrogen, and alkyl, aryl,
aralkyl, cycloalkyl, cycloalkylalkyl radicals and the
like. The term "halogen" means fluorine, chlorine,
bromine or iodine. The term dihaloalkyl means two
halogen atoms, the same or different, substituted on the
35 same carbon atom. The term "oxidizing agent" includes a
single agent or a mixture of oxidizing reagents.
Examples of mixtures of oxidizing reagents include sulfur

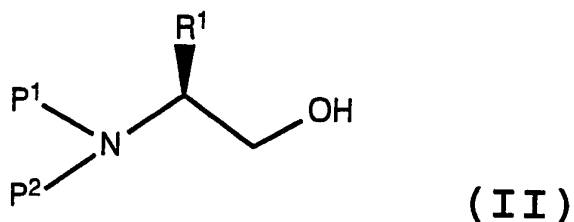
- trioxide-pyridine/dimethylsulfoxide, oxalyl
chloride/dimethyl sulfoxide, acetyl chloride/dimethyl
sulfoxide, acetyl anhydride/dimethyl sulfoxide,
trifluoroacetyl chloride/dimethyl sulfoxide,
5 toluenesulfonyl bromide/dimethyl sulfoxide, phosphorous
pentachloride/dimethyl sulfoxide and
isobutylchloroformate/dimethyl sulfoxide.

- A general Scheme for the preparation of
10 amino epoxides, useful as intermediates in the
synthesis of HIV protease inhibitors is shown in
Scheme 1 below.

Scheme I



The economical and safe large scale method of preparation of protease inhibitors of the present invention can alternatively utilize amino acids or amino alcohols to form N,N-protected alpha aminoalcohol of the formula



wherein P¹, P² and R¹ are described above.

Whether the compounds of Formula II are formed from amino acids or aminoalcohols, such compounds have the amine protected with groups p¹ and p² as previously identified. The nitrogen atom can be alkylated such as by the addition of suitable alkylating agents in an appropriate solvent in the presence of base.

Alternate bases used in alkylation include sodium hydroxide, sodium bicarbonate, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, cesium hydroxide, magnesium hydroxide, calcium hydroxide or calcium oxide, or tertiary amine bases such as triethyl amine, diisopropylethylamine, N-methylpiperidine, pyridine, dimethylaminopyridine and azabicyclononane. Reactions can be homogenous or heterogenous. Suitable solvents are water and protic solvents or solvents miscible with water, such as methanol, ethanol, isopropyl alcohol, tetrahydrofuran and the like, with or without added water. Dipolar aprotic solvents may also be used with or without added protic solvents including water. Examples of dipolar aprotic solvents include

acetonitrile, dimethylformamide, dimethyl acetamide, acetamide, tetramethyl urea and its cyclic analog, dimethylsulfoxide, N-methylpyrrolidone, sulfolane, nitromethane and the like. Reaction temperature can
5 range between about -20° to 100°C with the preferred temperature of about 25-85°C. The reaction may be carried out under an inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive
10 pressure. The most preferred alkylating agents are benzyl bromide or benzyl chloride or monosubstituted aralkyl halides or polysubstituted aralkyl halides. Sulfate or sulfonate esters are also suitable reagents to provide the corresponding benzyl analogs and they
15 can be preformed from the corresponding benzyl alcohol or formed in situ by methods well known to those skilled in the art. Trityl, benzhydryl, substituted trityl and substituted benzhydryl groups, independently, are also effective amine protecting
20 groups [P¹, P²] as are allyl and substituted allyl groups. Their halide derivatives can also be prepared from the corresponding alcohols by methods well known to those skilled in the art such as treatment with thionyl chloride or bromide or with phosphorus tri- or
25 pentachloride, bromide or iodide or the corresponding phosphoryl trihalide. Examples of groups that can be substituted on the aryl ring include alkyl, alkoxy, hydroxy, nitro, halo and alkylene, amino, mono- and dialkyl amino and acyl amino, acyl and water
30 solubilizing groups such as phosphonium salts and ammonium salts. The aryl ring can be derived from, for example, benzene, naphthalene, indane, anthracene, 9-(9-phenyl fluorenyl, durene, phenanthrene and the like. In addition, 1,2-bis (substituted alkylene)
35 aryl halides or sulfonate esters can be used to form a nitrogen containing aryl or non-aromatic heterocyclic derivative [with P¹ and P²] or bis-heterocycles.

Cycloalkylenealkyl or substituted cycloalkylene radicals containing 6-10 carbon atoms and alkylene radicals constitute additional acceptable class of substituents on nitrogen prepared as outlined above
5 including, for example, cyclohexylenemethylene.

Compounds of Formula II can also be prepared by reductive alkylation by, for example, compounds and intermediates formed from the addition of an aldehyde
10 with the amine and a reducing agent, reduction of a Schiff Base, carbinolamine or enamine or reduction of an acylated amine derivative. Reducing agents include metals [platinum, palladium, palladium hydroxide, palladium on carbon, platinum oxide, rhodium and the
15 like] with hydrogen gas or hydrogen transfer molecules such as cyclohexene or cyclohexadiene or hydride agents such as lithium aluminumhydride, sodium borohydride, lithium borohydride, sodium cyanoborohydride, diisobutylaluminum hydride or
20 lithium tri-tert-butoxyaluminum hydride.

Additives such as sodium or potassium bromide, sodium or potassium iodide can catalyze or accelerate the rate of amine alkylation, especially
25 when benzyl chloride was used as the nitrogen alkylating agent.

Phase transfer catalysis wherein the amine to be protected and the nitrogen alkylating agent are
30 reacted with base in a solvent mixture in the presence of a phase transfer reagent, catalyst or promoter. The mixture can consist of, for example, toluene, benzene, ethylene dichloride, cyclohexane, methylene chloride or the like with water or a aqueous solution of an organic
35 water miscible solvent such as THF. Examples of phase transfer catalysts or reagents include tetrabutylammonium chloride or iodide or bromide, tetrabutylammonium

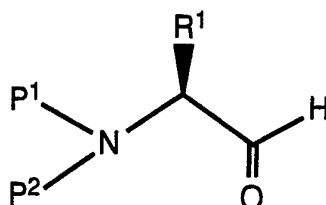
hydroxide, tri-butyloctylammonium chloride, dodecyltrihexylammonium hydroxide, methyltrihexylammonium chloride and the like.

5 A preferred method of forming substituted amines involves the aqueous addition of about 3 moles of organic halide to the amino acid or about 2 moles to the aminoalcohol. In a more preferred method of forming a protected amino alcohol, about 2 moles of
10 benzylhalide in a basic aqueous solution is utilized. In an even more preferred method, the alkylation occurs at 50°C to 80°C with potassium carbonate in water, ethanol/water or denatured ethanol/water. In a more preferred method of forming a protected amino
15 acid ester, about 3 moles of benzylhalide is added to a solution containing the amino acid.

 The protected amino acid ester is additionally reduced to the protected amino alcohol in
20 an organic solvent. Preferred reducing agents include lithium aluminiumhydride, lithium borohydride, sodium borohydride, borane, lithium tri-tert-butoxyaluminum hydride, borane•THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H)
25 in toluene. These reduction conditions provide an alternative to a lithium aluminum hydride reduction.

 Purification by chromatography is possible. In the preferred purification method the alpha amino
30 alcohol can be purified by an acid quench of the reaction, such as with hydrochloric acid, and the resulting salt can be filtered off as a solid and the amino alcohol can be liberated such as by acid/base extraction.

The protected alpha amino alcohol is oxidized to form a chiral amino aldehyde of the formula



Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydrothiaphene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutylchloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

The reaction may be carried out under an inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide, acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding N-monosubstituted [either P^1 or $P^2 = H$] or N,N-disubstituted aldehyde.

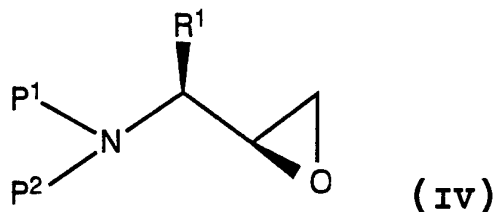
In addition, hydride reduction of an amide or ester derivative of the corresponding alkyl, benzyl or cycloalkenyl nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenylalanine derivative can be carried out to provide a compound of Formula III. Hydride transfer is an additional method of aldehyde synthesis under conditions where aldehyde condensations are avoided, cf, Oppenauer Oxidation.

The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester

derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from about 5°C to about 25°C. Two
5 additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde
10 is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a
15 protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund
20 Reduction).

An important aspect of the present invention is a reaction involving the addition of chloromethylithium or bromomethylithium to the α -amino aldehyde. Although
25 addition of chloromethylithium or bromomethylithium to aldehydes is known, the addition of such species to racemic or chiral amino aldehydes to form aminoepoxides of the formula



30

is novel. The addition of chloromethylithium or bromomethylithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethylithium

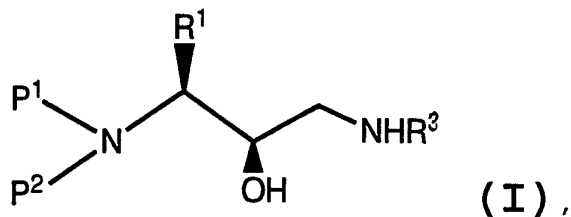
or bromomethylithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloriodomethane, bromochloromethane, dibromomethane, diiodomethane, bromofluoromethane and the like. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometallic reagents such as methylolithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, phenyl sodium and the like. The reaction can be carried out at temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precursor species followed by their treatment with base to form the analogous anion. Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl chloride or the like, in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

The desired epoxides form, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare HIV protease inhibitors.

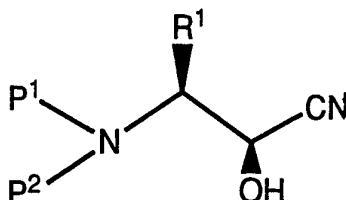
The epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, with R^3NH_2 to form the amino alcohol of Formula I



wherein R^3 is as defined above.

The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. In some cases, R^3NH_2 can be used as the solvent, such as isobutylamine.

Alternatively, the protected amino aldehyde of Formula III can also be reacted with a cyanide salt, such as sodium cyanide or potassium cyanide to form a chiral cyanohydrin of the formula

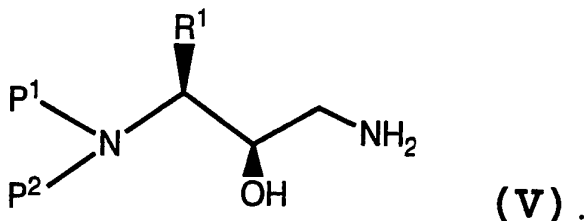


Preferably, a reaction rate enhancer, such as sodium bisulfite, is used to enhance the rate of cyanohydrin formation. Alternatively, trimethylsilylnitrile can be used to form a trimethylsilyloxycyano intermediate, which can be readily hydrolyzed to the cyanohydrin.

The reaction can be carried out at temperatures of between about -5°C to 5°C but preferably between about 0°C to 5°C. The desired cyanohydrins form, using sodium cyanide and sodium bisulfite, diastereoselectively in

ratio amounts of at least about an 88:12 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product.

- 5 The cyano group can be reduced to the amine of Formula V



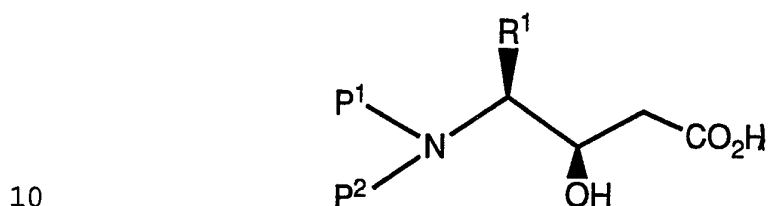
- The reduction can be accomplished using a variety of reducing reagents, such as hydride transfer, metal reductions and catalytic hydrogenation which are well known to those skilled in the art. Examples of hydride reagents with and without heavy metal(s) or heavy metal salts as adjunct reagents include, for example, lithium aluminum hydride, lithium tri-tert-butoxyaluminum hydride, lithium trimethoxy-aluminum hydride, aluminum hydride, diborane (or borane), borane/THF, borane/dimethyl sulfide, borane/pyridine, sodium borohydride, lithium borohydride, sodium borohydride/cobalt salts, sodium borohydride/Raney-nickel, sodium borohydride/acetic acid and the like. Solvents for the reaction include, for the more reactive hydrides, THF, diethyl ether, dimethoxy ethane, diglyme, toluene, heptane, cyclohexane, methyl tert-butyl ether and the like. Solvents or solvent mixtures for reductions using reagents such as sodium borohydride, in addition to the non-protic solvents listed above, can include ethanol, n-butanol, tert-butyl alcohol, ethylene glycol and the like. Metal reductions include, for example, sodium and ethanol. Reaction temperatures can vary between solvent reflux and -20°C. An inert atmosphere such as nitrogen or argon is usually preferred especially where the possibility of flammable gas or solvent production/evolution is possible. Catalytic

hydrogenation (metal catalyst plus hydrogen gas) can be carried out in the same solvents as above with metals or metal salts such as nickel, palladium chloride, platinum, rhodium, platinum oxide or palladium on carbon or other catalysts known to those skilled in the art. These catalysts can also be modified with, for example, phosphine ligands, sulfur or sulfur containing compounds or amines such as quinoline. Hydrogenations can be carried out at atmospheric pressure or at elevated pressures to about 1500 psi at temperatures between 0° to about 250°C. The most preferred reducing reagent is diborane-tetrahydrofuran, preferably at room temperature under an atmosphere of nitrogen and atmospheric pressure.

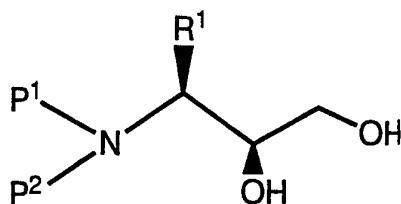
The amine of Formula V can then be reacted with R^3L , wherein L is a leaving group selected from halo, tosylate, and the like, and R^3 represents alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, and heteroaralkyl. Alternatively, the primary amino group of Formula V can be reductively alkylated with an aldehyde to introduce the R^3 group. For example, when R^3 is an isobutyl group, treatment of Formula V with isobutyraldehyde under reductive amination conditions affords the desired Formula I. Similarly, when R^3 is an isoamyl group, treatment of Formula V with isovaleraldehyde under reductive amination conditions affords the desired Formula I. Other aldehydes can be used to introduce various R^3 groups. Reductive amination can be performed using a variety of reaction conditions well-known to those skilled in the art. For example, the reductive amination of Formula V with an aldehyde can be carried out with a reducing agent such as sodium cyanoborohydride or sodium borohydride in a suitable solvent, such as methanol, ethanol, tetrahydrofuran and the like. Alternatively, the reductive amination can be carried out using hydrogen in the presence of a catalyst

such as palladium or platinum, palladium on carbon or platinum on carbon, or various other metal catalysts known to those skilled in the art, in a suitable solvent such as methanol, ethanol, tetrahydrofuran, ethyl acetate, toluene and the like.

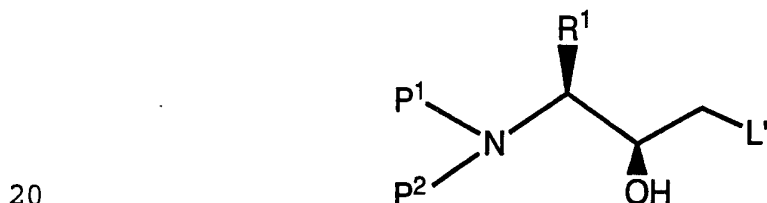
Alternatively, the amine of Formula I can be prepared by reduction of the protected amino acid of formula



(commercially available from Nippon Kayaku, Japan) to the corresponding alcohol of formula



The reduction can be accomplished using a variety of reducing reagents and conditions. A preferred reducing reagent is diborane-tetrahydrofuran. The alcohol is then converted into a leaving group (L') by tosylation, mesylation or conversion into a halo group, such as chloro or bromo:



Finally, the leaving group (L') is reacted with R^3NH_2 as described above to form amino alcohol of Formula I. Alternatively, base treatment of the alcohol can result in the formation of the amino epoxide of Formula IV.

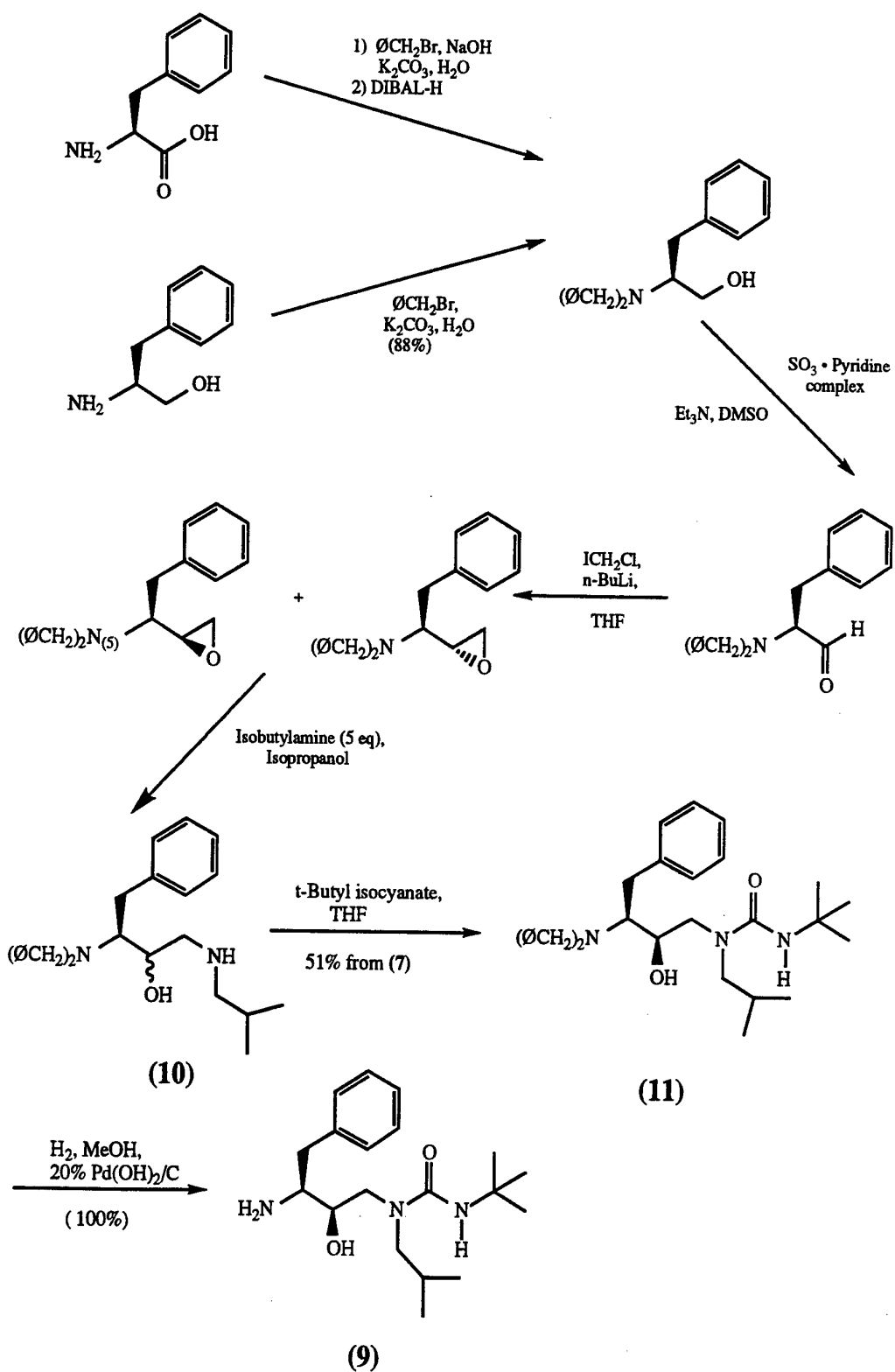
The above preparation of amino alcohol of Formula I is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivalents of camphor sulfonic acid, citric acid, camphoric acid, 2-methoxyphenylacetic acid and the like can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled in the art.

A further advantage of the present process is that materials can be carried through the above steps without purification of the intermediate products. However, if purification is desired, the intermediates disclosed can be prepared and stored in a pure state.

The practical and efficient synthesis described here has been successfully scaled up to prepare large quantity of intermediates for the preparation of HIV protease inhibitors. It offers several advantages for multikilogram preparations: (1) it does not require the use of hazardous reagents such as diazomethane, (2) it requires no purification by chromatography, (3) it is short and efficient, (4) it utilizes inexpensive and readily available commercial reagents, (5) it produces enantiomerically pure alpha amino epoxides. In particular, the process of the invention produces enantiomerically-pure epoxide as required for the preparation of enantiomerically-pure intermediate for further synthesis of HIV protease inhibitors.

The amino epoxides were prepared utilizing the following procedure as disclosed in Scheme II below.

Scheme II



In Scheme II, there is shown a synthesis for the epoxide, chiral N, N, α -S-tris(phenylmethyl)-2S-

oxiranemethan-amine. The synthesis starts from L-phenylalanine. The aldehyde is prepared in three steps from L-phenylalanine or phenylalinalol. L-Phenylalanine is converted to the N,N-dibenzylamino acid benzyl ester using benzyl bromide under aqueous conditions. The reduction of benzyl ester is carried out using diisobutylaluminum hydride (DIBAL-H) in toluene. Instead of purification by chromatography, the product is purified by an acid (hydrochloric acid) quench of the reaction, the hydrochloride salt is filtered off as a white solid and then liberated by an acid/base extraction. After one recrystallization, chemically and optically pure alcohol is obtained. Alternately, and preferably, the alcohol can be obtained in one step in 88% yield by the benzylation of L-phenylalinalol using benzylbromide under aqueous conditions. The oxidation of alcohol to aldehyde is also modified to allow for more convenient operation during scaleup. Instead of the standard Swern procedures using oxalyl chloride and DMSO in methylene chloride at low temperatures (very exothermic reaction), sulfur trioxide-pyridine/DMSO was employed (Parikh, J., Doering, W., J. Am. Chem. Soc., 89, p. 5505, 1967) which can be conveniently performed at room temperature to give excellent yields of the desired aldehyde with high chemical and enantiomer purity which does not require purification.

An important reaction involves the addition of chloromethylithium or bromomethylithium to the aldehyde. Although addition of chloromethylithium or bromomethylithium to aldehydes has been reported previously, the addition of such species to chiral α -amino aldehydes to form chiral-aminoepoxides is believed to be novel. Now, chloromethylithium or bromomethylithium is generated in-situ from chloriodomethane (or bromochloromethane) or

dibromomethane and n-butyllithium at a temperature in a range from about -78°C to about -10°C in THF in the presence of aldehyde. The desired chlorohydrin or bromohydrin is formed as evidenced by TLC analyses.

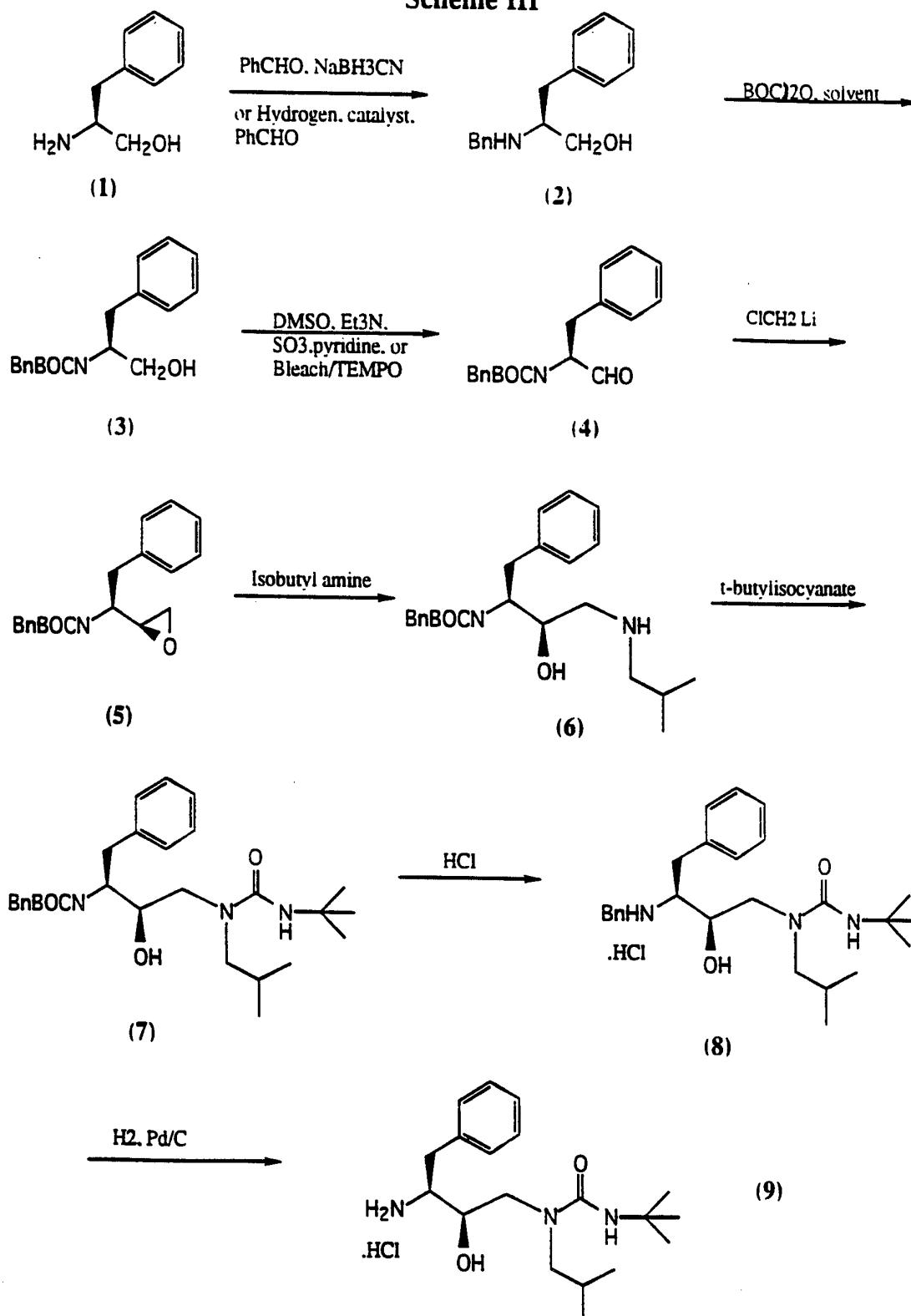
5 After warming to room temperature, the desired epoxide is formed diastereoselectively in a 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically pure product as a colorless oil but it is more conveniently used directly without

10 purification.

Scheme III illustrates the preparation of the aminopropylurea (9) utilizing mixed protected amine of phenylalaninol, where BOC is t-butoxycarbonyl and Bn is

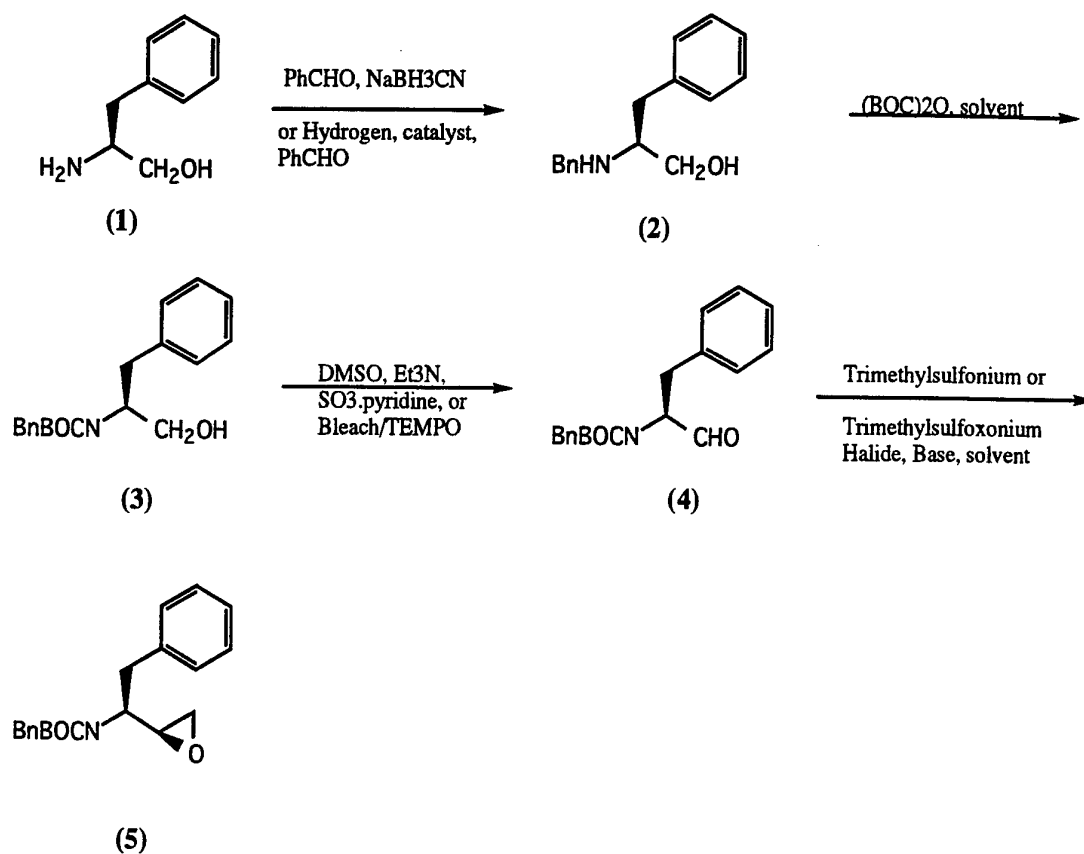
15 benzyl.

Scheme III



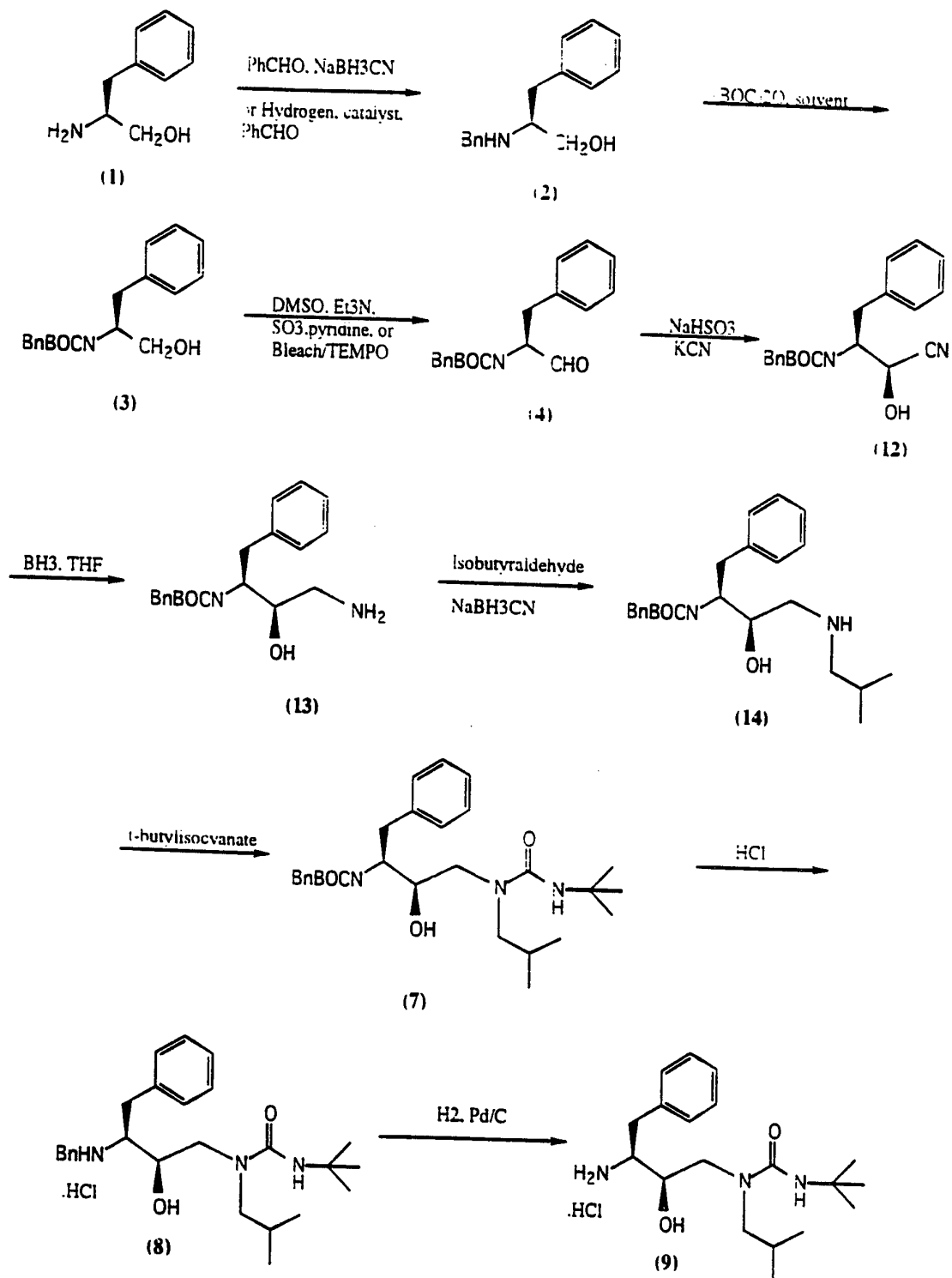
Scheme IV illustrates an alternative preparation of the amino epoxide (5) utilizing a sulfur ylide.

Scheme IV



The aminopropylurea (9) was also prepared utilizing the procedure as disclosed in Scheme V below.

Scheme V

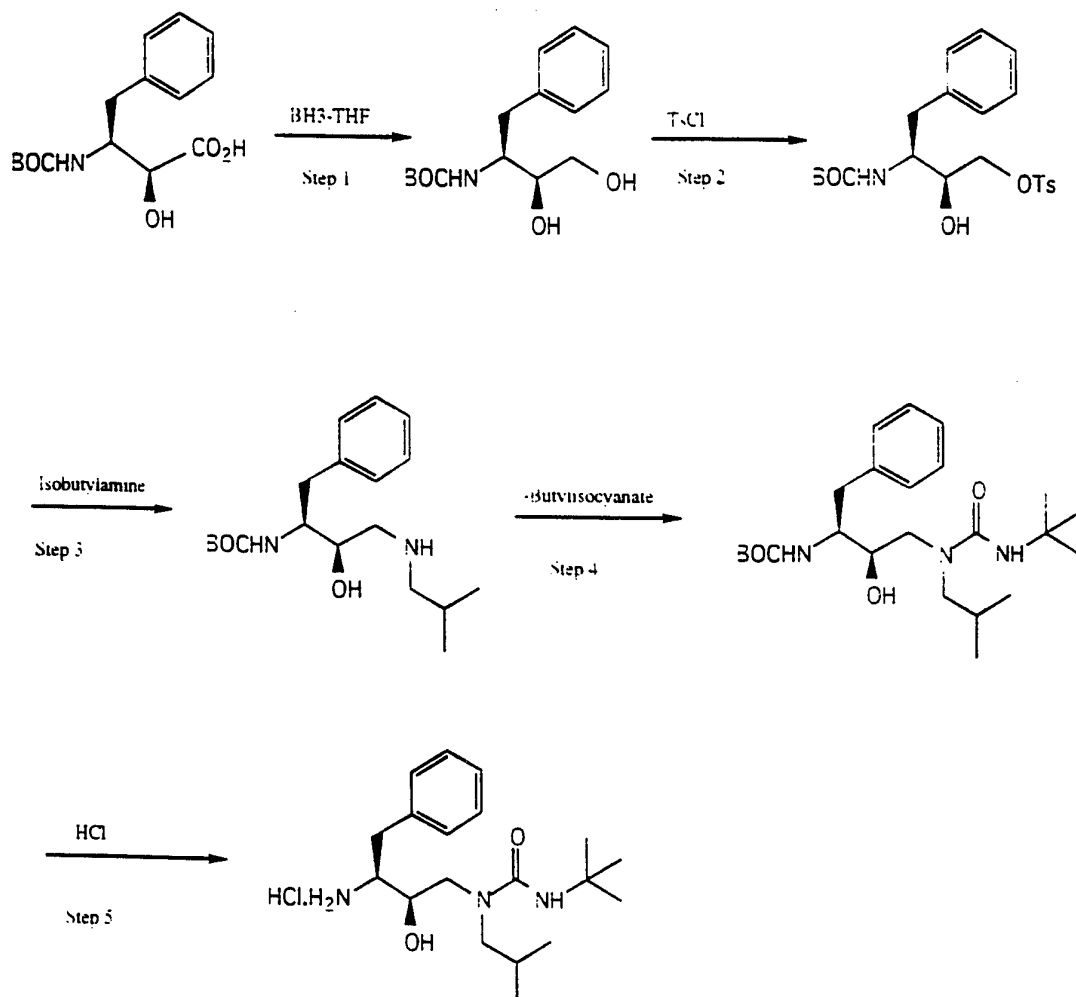


In Scheme V a mixed protected amine of phenylalaninal, where BOC is t-butoxycarbonyl and Bn is benzyl, was reacted with potassium cyanide to form the desired stereoisomeric cyanohydrin (12) in high yield. In
5 additional to the stereospecificity of the cyanohydrin reaction, this process has the added advantage of being easier and less expensive because the temperature of the reactions need not be less than -5°C.

10

The aminourea (9) was also prepared utilizing the procedure as disclosed in Scheme VI below.

Scheme VI



The procedure in Scheme VI required only one protecting group, BOC, for the amine of the hydroxyamino acid. This procedure has the advantage of having the desired stereochemistry of the benzyl and hydroxy groups established in the starting material. Thus the chirality does not need to be introduced with the resulting loss of material due to preparation of diastereomers.

EXAMPLE 1

β -2-[Bis(phenylmethyl)amino]benzenepropanol

5 METHOD 1:Step 1: Benzylation of L-Phenylalanine

A solution of L-phenylalanine (50.0 g, 0.302 mol),
10 sodium hydroxide (24.2 g, 0.605 mol) and potassium
carbonate (83.6 g, 0.605 mol) in water (500 mL) was
heated to 97°C. Benzyl bromide (108.5 mL, 0.605 mol)
was then slowly added (addition time - 25 min). The
mixture was stirred at 97°C for 30 minutes under a
15 nitrogen atmosphere. The solution was cooled to room
temperature and extracted with toluene (2 x 250 mL).
The combined organic layers were washed with water and
brine, dried over magnesium sulfate, filtered and
concentrated to an oil. The identity of the product
20 was confirmed as follows. Analytical TLC (10% ethyl
acetate/hexane, silica gel) showed major component at
R_f value = 0.32 to be the desired tribenzylated
compound, N,N-bis(phenylmethyl)-L-phenylalanine
phenylmethyl ester. This compound can be purified by
25 column chromatography (silica gel, 15% ethyl
acetate/hexanes). Usually the product is pure enough
to be used directly in the next step without further
purification. ¹H NMR spectrum was in agreement with
published literature. ¹H NMR (CDCl₃) δ , 3.00 and
30 3.14 (ABX-system, 2H, J_{AB}=14.1 Hz, J_{AX}=7.3 Hz and
J_{BX}= 5.9 Hz), 3.54 and 3.92 (AB-System, 4 H, J_{AB}=13.9
Hz), 3.71 (t, 1H, J=7.6 Hz), 5.11 and 5.23 (AB-System,
2H, J_{AB}=12.3 Hz), and 7.18 (m, 20 H). EIMS: m/z 434
(M-1).

Step 2: β S-2-[Bis(phenylmethyl)amino]benzenepropanol from the DIBAL Reduction of N,N-bis(phenylmethyl)-L-Phenylalanine phenylmethyl ester

- 5 The benzylated phenylalanine phenylmethyl ester (0.302 mol) from the previous reaction was dissolved in toluene (750 mL) and cooled to -55°C. A 1.5 M solution of DIBAL in toluene (443.9 mL, 0.666 mol) was added at a rate to maintain the temperature between
- 10 -55 to -50°C (addition time - 1 hr). The mixture was stirred for 20 minutes under a nitrogen atmosphere and then quenched at -55°C by the slow addition of methanol (37 ml). The cold solution was then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The
- 15 precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture of toluene (400 mL) and water (100 ml). The mixture was cooled to 5°C and treated with 2.5 N NaOH (186 mL) and then stirred at room
- 20 temperature until solid dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 mL (89 g). Ethyl acetate (25 mL) and hexane (25 mL) were added to
- 25 the residue upon which the desired alcohol product began to crystallize. After 30 min, an additional 50 mL hexane were added to promote further crystallization. The solid was filtered off and washed with 50 mL hexane to give 34.9 g of first crop
- 30 product. A second crop of product (5.6 g) was isolated by refiltering the mother liquor. The two crops were combined and recrystallized from ethyl acetate (20 mL) and hexane (30 mL) to give 40 g of β S-2-[Bis(phenyl-methyl)amino]benzenepropanol, 40%
- 35 yield from L-phenylalanine. An additional 7 g (7%) of product can be obtained from recrystallization of the concentrated mother liquor. TLC of product R_f = 0.23

(10% ethyl acetate/hexane, silica gel); ^1H NMR (CDCl_3)
 δ 2.44 (m, 1H), 3.09 (m, 2H), 3.33 (m, 1H), 3.48 and
3.92 (AB-System, 4H, J_{AB} = 13.3 Hz), 3.52 (m, 1H) and
7.23 (m, 15H); $[\alpha]_{\text{D}25}$ +42.4 (c 1.45, CH_2Cl_2); DSC
5 77.67°C; Anal. Calcd. for $\text{C}_{23}\text{H}_{25}\text{ON}$: C, 83.34; H, 7.60;
N, 4.23. Found: C, 83.43; H, 7.59; N, 4.22. HPLC on
chiral stationary phase: Cyclobond I SP column (250 x
4.6 mm I.D.), mobile phase: methanol/triethyl ammonium
acetate buffer pH 4.2 (58:42, v/v), flow-rate of 0.5
10 ml/min, detection with detector at 230nm and a temper-
ature of 0°C. Retention time: 11.25 min., retention
time of the desired product enantiomer: 12.5 min.

METHOD 2:

15

Preparation of β S-2-[Bis(phenylmethyl)amino]benzene-
propanol from the N,N-Dibenzylation of
L-Phenylalaninol:

20 L-phenylalaninol (176.6 g, 1.168 mol) was added to a
stirred solution of potassium carbonate (484.6 g,
3.506 mol) in 710 mL of water. The mixture was heated
to 65°C under a nitrogen atmosphere. A solution of
benzyl bromide (400 g, 2.339 mol) in 3A ethanol (305
25 mL) was added at a rate that maintained the
temperature between 60-68°C. The biphasic solution
was stirred at 65°C for 55 min and then allowed to
cool to 10°C with vigorous stirring. The oily product
solidified into small granules. The product was
30 diluted with 2.0 L of tap water and stirred for 5
minutes to dissolve the inorganic by products. The
product was isolated by filtration under reduced
pressure and washed with water until the pH is 7. The
crude product obtained was air dried overnight to give
35 a semi-dry solid (407 g) which was recrystallized from
1.1 L of ethyl acetate/heptane (1:10 by volume). The
product was isolated by filtration (at -8°C), washed

with 1.6 L of cold (-10°C) ethyl acetate/heptane (1:10 by volume) and air-dried to give 339 g (88% yield) of β S-2-[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-73.0°C. More product can be
5 obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described in Method 1.

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EXAMPLE 2

α S-[Bis(phenylmethyl)amino]benzenepropanaldehyde

METHOD 1:

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β S-2-[Bis(phenylmethyl)amino]benzene-propanol (200 g, 0.604 mol) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to 12°C and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to
20 maintain the temperature between 8-17°C (addition time - 1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TLC
25 analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled with ice water and quenched with 1.6 L of cold water (10-15°C) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L),
30 and brine (2.2 L), dried over MgSO₄ (280 g) and filtered. The solvent was removed on a rotary evaporator at 35-40°C and then dried under vacuum to give 198.8 g of α S-[Bis-(phenylmethyl)amino]-benzenepropanaldehyde as a pale yellow oil (99.9%).
35 The crude product obtained was pure enough to be used directly in the next step without purification. The analytical data of the compound were consistent with

the published literature. $[\alpha]_{D25} = -92.9^\circ$ (c 1.87, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ , 2.94 and 3.15 (ABX-System, 2H, J_{AB}= 13.9 Hz, J_{AX}= 7.3 Hz and J_{BX} = 6.2 Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}= 13.7 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for (M+1) C₂₃H₂₄NO 330.450, found: 330.1836. Anal. Calcd. for C₂₃H₂₃ON: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase: (S,S) Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enantiomer 10.62 min.

METHOD 2:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of BS-2-[bis(phenylmethyl)amino]benzene-propanol (0.074 mol) in 100 ml of dichloromethane (addition time ~20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes under a nitrogen atmosphere. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt.

The filtrate was concentrated to give α S-[bis(phenylmethyl)amino]benzenepropanaldehyde. The aldehyde was carried on to the next step without purification.

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METHOD 3:

To a mixture of 1.0 g (3.0 mmol) of β S-2-[bis(phenylmethyl)amino]benzenepropanol 0.531 g (4.53 mmol) of N-methyl morpholine, 2.27 g of molecular sieves(4A) and 9.1 mL of acetonitrile was added 53 mg (0.15 mmol) of tetrapropylammonium perruthenate (TPAP). The mixture was stirred for 40 minutes at room temperature and concentrated under reduced pressure. The residue was suspended in 15 mL of ethyl acetate, filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a product containing approximately 50% of α S-2-[bis(phenylmethyl)amino]benzene propanaldehyde as a pale yellow oil.

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METHOD 4:

To a solution of 1.0 g (3.02 mmol) of β S-2-[bis(phenylmethyl)amino]benzenepropanol in 9.0 mL of toluene was added 4.69 mg (0.03 mmol) of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), 0.32g (3.11 mmol) of sodium bromide, 9.0 mL of ethyl acetate and 1.5 mL of water. The mixture was cooled to 0 °C and an aqueous solution of 2.87 mL of 5% household bleach containing 0.735 g (8.75 mmol) of sodium bicarbonate and 8.53 mL of water was added slowly over 25 minutes. The mixture was stirred at 0 °C for 60 minutes. Two more additions (1.44 mL each) of bleach was added followed by stirring for 10 minutes. The two phase mixture was allowed to separate. The aqueous layer was extracted twice with

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20 mL of ethyl acetate. The combined organic layer was washed with 4.0 mL of a solution containing 25 mg of potassium iodide and water (4.0 mL), 20 mL of 10% aqueous sodium thiosulfate solution and then brine solution. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 1.34g of crude oil containing a small amount of the desired product aldehyde, α S-[bis(phenylmethyl)amino]benzenepropanaldehyde.

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METHOD 5:

Following the same procedures as described in Example 2 (Method 1) except 3.0 equivalents of sulfur trioxide pyridine complex was used and α S-[bis(phenylmethyl)amino]benzenepropanaldehyde was isolated in comparable yields.

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EXAMPLE 3

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N,N, α S-Tris(phenylmethyl)-2S-oxiranemethanamine

METHOD 1:

25 A solution of α S-[Bis(phenylmethyl)amino]benzene-propanaldehyde (191.7 g, 0.58 mol) and chloriodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C.

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35 After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional

chloriodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at $< -25^{\circ}\text{C}$. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional

5 chloriodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at $< -25^{\circ}\text{C}$. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloriodomethane (8.5 mL, 0.11 mol)

10 was added, followed by n-butyllithium (37 mL, 0.059 mol) at $< -25^{\circ}\text{C}$. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours

15 when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL

20 of water), keeping the temperature below 23°C . The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran

25 layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C . The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was $>100\%$.)

30 Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor

35 and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), $R_f = 0.29$ & 0.32 , respectively. An

analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:

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N,N, α S-Tris(phenylmethyl)-2S-oxiranemethanamine

^1H NMR (400 MHz, CDCl_3) δ 2.49 and 2.51 (AB-System, 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} = 10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB} = 14.00), 7.21 (m, 15H); ^{13}C NMR (400 MHz, CDCl_3) δ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for $\text{C}_{24}\text{H}_{26}\text{NO}$ (M+1) 344.477, found 344.2003.

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N,N, α S-Tris(phenylmethyl)-2R-oxiranemethanamine

^1H NMR (300 MHz, CDCl_3) δ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H). HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of (8): 9.38 min., retention time of enantiomer of (4): 13.75 min.

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METHOD 2:

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A solution of the crude aldehyde 0.074 mol and chloriodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C , under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloriodomethane (1.6 ml, 0.022 mol) was

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added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloriodomethane (0.70 ml, 0.010 mol) and
5 n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The
10 tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The
15 product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

20 METHOD 3:

A solution of α S-[Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in
25 tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in
30 hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional
35 bromochloromethane (14 mL) was added, followed by n-butyllithium (102 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10

minutes. This was repeated once. (2) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

METHOD 4:

Following the same procedures as described in Example 3 (Method 3) except the reaction temperatures were at -20 °C. The resulting N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was a diastereomeric mixture of lesser purity than that of Method 3.

METHOD 5:

Following the same procedures as described in Example 3 (Method 3) except the reaction temperatures were at -70--78 °C. The resulting N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was a diastereomeric mixture, which was used directly in the subsequent steps without purification.

10 METHOD 6:

Following the same procedures as described in Example 3 (Method 3) except a continuous addition of bromochloromethane and n-butyllithium was used at -30 to -35 °C. After the reaction and work up procedures as described in Example 3 (Method 3), the desired N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was isolated in comparable yields and purities.

20 METHOD 7:

Following the same procedures as described in Example 3 (Method 2) except dibromomethane was used instead of chloriodomethane. After the reaction and work up procedures as described in Example 3 (Method 2), the desired N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was isolated.

EXAMPLE 4

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3S-[N,N-Bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

To a solution of crude N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine (388.5 g, 1.13mol) from Example 3 in isopropanol (2.7 L) (or ethyl acetate) was added isobutylamine (1.7 kgm, 23.1

mol) over 2 min. The temperature increased from 25 °C to 30 °C. The solution was heated to 82 °C and stirred at this temperature for 1.5 h. The warm solution was concentrated under reduced pressure at 65 °C. The brown oil residue was transferred to a 3-L flask and dried in vacuo (0.8 mm Hg) for 16 h to give 450 g of 3S-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a crude oil. The product was used directly in the next step without purification. An analytical sample of the desired major diastereomeric product was obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane). Tlc analysis: silica gel, 40% ethyl acetate/hexane; R_f = 0.28; HPLC analysis: ultrasphere ODS column, 25% triethylamine-/phosphate buffer pH 3/acetonitrile, flow rate 1 mL/min, UV detector; retention time 7.49 min.; HRMS calcd for C₂₈H₃₇N₂O (M + 1) 417.616, found 417.2887.

20

An analytical sample of the minor diastereomeric product, 3S-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2S-ol was also obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane).

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EXAMPLE 5

30 3S-[N,N-Bis(phenylmethyl)amino]-1-(3-methylbutyl)amino-4-phenylbutan-2R-ol

Example 4 was followed using isoamylamine instead of isobutylamine to prepare 3S-[N,N-Bis(phenylmethyl)amino]-1-(3-methylbutyl)amino-4-phenylbutan-2R-ol and 3S-[N,N-Bis(phenylmethyl)amino]-1-(3-methylbutyl)amino-4-phenylbutan-2S-ol in

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comparable yields to that of Example 4. The crude amine was used in the next step without further purification.

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EXAMPLE 6

N-[3S-[N,N-Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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A solution of the crude 3S-[N,N-Bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol (446.0 g, 1.1 mol) from Example 4 in tetrahydrofuran (6 L) (or ethyl acetate) was cooled to 15 8 °C. t-Butyl isocyanate (109.5 g, 1.1 mol) was then added to the solution of the amine from an addition funnel at a rate that maintained the temperature between 10-12 °C (addition time was about 10 min). The external cooling was stopped and the reaction was 20 warmed to 18 °C after 30 min. The solution was transferred directly from the reactor to a rotary evaporator flask (10 L) through a teflon tube using vacuum and then concentrated. The flask was heated in a 50 °C water bath during the 2 h required for the 25 distillation of the solvent. The brown residue was dissolved in ethyl acetate (3 L), washed with 5% aq citric acid solution (1 x 1.2 L), water (2 x 500 mL), brine (1 x 400 mL), dried over magnesium sulfate (200 g) and filtered. The volume of product solution was 30 reduced to 671 mL over 2 h on a rotary evaporator at 50 °C. The concentrate was stirred and diluted with 1.6 L of hexane. The mixture was cooled to 12 °C and stirred for 15 hours. The product crystals were isolated by filtration, washed with 10% ethyl acetate/hexane (1 x 35 500 mL), hexane (1 x 200 mL) and dried in vacuo (2 mm) at 50 °C for 1 hour to give 248 g of N-[3S-[N,N-bis-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-

dimethylethyl)-N-(2-methylpropyl)-urea. The mother liquor and washes were combined and concentrated on a rotary evaporator to give 270 g of a brown oil. This material was dissolved in ethyl acetate (140 mL) at 50 °C and diluted with hexane (280 mL) and seeded with crystals of the first crop product (20 mg). The mixture was cooled in an ice bath and stirred for 1 h. The solid was isolated by filtration, washed with 10% ethyl acetate/hexane (1 x 200 mL) and dried in vacuo (2 mm) at 50 °C for 1 h to give 55.7 g of 11 as the second crop (49% overall yield). Mp 126 °C; $[\alpha]_{D25} = -59.0^\circ$ (c = 1.0, CH₂Cl₂), TLC: R_f 0.31 (silica gel, 25% ethyl acetate/hexane).

An analytical sample of the minor diastereomer, N-[3S-[N,N-bis(phenylmethyl)amino]-2S-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea was isolated by silica-gel chromatography (10-15% ethyl acetate/hexane) in an earlier experiment and characterized.

EXAMPLE 7

N-[3S-[N,N-Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea

The crude product from Example 5 was reacted with t-butyldisocyanate following the method of Example 6 to prepare N-[3S-[N,N-Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea and N-[3S-[N,N-Bis(phenylmethyl)amino]-2S-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea in comparable yields to that of Example 6.

EXAMPLE 8

N-[3S-Amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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N-[3S-[N,N-Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea (125.77 g, 0.244 mol) from Example 6 was dissolved in ethanol (1.5 L) (or methanol) and 20% palladium hydroxide on carbon (18.87 g) (or 4% palladium on carbon) was added to the solution under nitrogen. The mixture was stirred at ambient temperature under a hydrogen atmosphere at 60 psi for approximately 8 h. The catalyst was removed by filtration and the filtrate was concentrated to give 85 g of N-[3S-Amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a colorless oil.

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EXAMPLE 9

N-[3S-Amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea

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N-[3S-[N,N-Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea from Example 7 was hydrogenated following the method of Example 8 to prepare N-[3S-Amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea in comparable yields to Example 8.

30

EXAMPLE 10

N-benzyl-L-phenylalaninol

5 METHOD 1:

L-Phenylalaninol (89.51 g, 0.592 moles) was dissolved in 375 mL of methanol under inert atmosphere, 35.52 g (0.592 moles) of glacial acetic acid and 50 mL of methanol was added followed by a solution of 62.83 g (0.592 moles) of benzaldehyde in 100 mL of methanol. The mixture was cooled to approximately 15 °C and a solution of 134.6 g (2.14 moles) of sodium cyanoborohydride in 700 mL of methanol was added in approximately 40 minutes, keeping the temperature between 15 °C and 25 °C. The mixture was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and partitioned between 1 L of 2M ammonium hydroxide solution and 2 L of ether. The ether layer was washed with 1 L of 1M ammonium hydroxide solution, twice with 500 mL water, 500 mL of brine and dried over magnesium sulfate for 1 hour. The ether layer was filtered, concentrated under reduced pressure and the crude solid product was recrystallized from 110 mL of ethyl acetate and 1.3 L of hexane to give 115 g (81% yield) of N-benzyl-L-phenylalaninol as a white solid.

METHOD 2:

30 L-Phenylalaninol (5 g, 33 mmols) and 3.59 g (33.83 mmols) of benzaldehyde were dissolved in 55 mL of 3A ethanol under inert atmosphere in a Parr shaker and the mixture was warmed to 60 °C for 2.7 hours. The mixture was cooled to approximately 25 °C and 0.99 g of 5% platinum on carbon was added and the mixture was hydrogenated at 60 psi of hydrogen and 40 °C for 10 hours. The catalyst was filtered off, the product was

concentrated under reduced pressure and the crude solid product was recrystallized from 150 mL of heptane to give 3.83 g(48 % yield) of N-benzyl-L-phenylalaninol as a white solid.

5

EXAMPLE 11

N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninol

10 N-benzyl-L-phenylalaninol (2.9 g, 12 mmols)
from Example 10 was dissolved in 3 mL of triethylamine
and 27 mL of methanol and 5.25 g(24.1 mmols) of di-
tert-butyl dicarbonate was added. The mixture was
warmed to 60 °C for 35 minutes and concentrated under
15 reduced pressure. The residue was dissolved in 150 mL
of ethyl acetate and washed twice with 10 mL of cold(0-
5 °C), dilute hydrochloric acid (pH 2.5 to 3), 15 mL of
water, 10 mL of brine, dried over magnesium sulfate,
filtered and concentrated under reduced pressure. The
20 crude product oil was purified by silica gel
chromatography (ethyl acetate: hexane, 12:3 as eluting
solvent) to give 3.98 g (97% yield) of colorless oil.

EXAMPLE 12

25

N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninol

METHOD 1:

30 To a solution of 0.32 g(0.94 mmols) of N-(t-
Butoxycarbonyl)-N-benzyl-L-phenylalaninol from Example 11
in 2.8 mL of toluene was added 2.4 mg (0.015 mmols) of
2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
(TEMPO), 0.1g (0.97 mmols) of sodium bromide, 2.8 mL of
35 ethyl acetate and 0.34 mL of water. The mixture was
cooled to 0 °C and an aqueous solution of 4.2 mL of 5%
household bleach containing 0.23 g (3.0 mL, 2.738 mmols)
of sodium bicarbonate was added slowly over 30 minutes.

The mixture was stirred at 0 °C for 10 minutes. Three more additions (0.4 mL each) of bleach was added followed by stirring for 10 minutes after each addition to consume all the starting material. The two phase mixture was
5 allowed to separate. The aqueous layer was extracted twice with 8 mL of toluene. The combined organic layer was washed with 1.25 mL of a solution containing 0.075 g of potassium iodide, sodium bisulfate(0.125 g) and
10 water(1.1 mL), 1.25 mL of 10% aqueous sodium thiosulfate solution, 1.25 mL of pH 7 phosphate buffer and 1.5 mL of brine solution. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 0.32 g (100% yield) of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninal.

15

METHOD 2:

To a solution of 2.38 g(6.98 mmoles) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninol from Example
20 11 in 3.8 mL (27.2 mmoles) of triethylamine at 10 °C was added a solution of 4.33 g (27.2 mmoles) of sulfur trioxide pyridine complex in 17 mL of dimethyl sulfoxide. The mixture was warmed to room temperature and stirred for one hour. Water (16 mL) was added and
25 the mixture was extracted with 20 mL of ethyl acetate. The organic layer was washed with 20 mL of 5% citric acid, 20 mL of water, 20 mL of brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give 2.37 g(100%
30 yield) of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninal.

EXAMPLE 13

N, α S-Bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine

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METHOD 1:

A solution of 2.5 g (7.37 mmoles) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal from Example 12
10 and 0.72 mL of chloriodomethane in 35 mL of THF was cooled to -78 °C. A 4.64 mL of a solution of n-butyllithium (1.6 M in hexane, 7.42 mmoles) was added slowly, keeping the temperature below -70 °C. The mixture was stirred for 10 minutes between -70 to -75 °C.
15 Two additional portions of 0.22 mL of chloriodomethane and 1.4 mL of n-butyllithium was added sequentially and the mixture was stirred for 10 minutes between -70 to -75 °C after each addition. Four additional portions of 0.11 mL of chloriodomethane and 0.7 mL of n-butyllithium was
20 added sequentially and the mixture was stirred for 10 minutes between -70 to -75 °C after each addition. The mixture was warmed to room temperature for 3.5 hours. The product was quenched at below 5 °C with 24 mL of ice-cold water. The biphasic layers were separated and the
25 aqueous layer was extracted twice with 30 mL of ethyl acetate. The combined organic layers was washed three times with 10 mL water, then with 10 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2.8 g of a yellow crude oil. This crude
30 oil (>100% yield) is a mixture of the diastereomeric epoxides N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine. The crude mixture is used directly in the next step without purification.

35

METHOD 2:

To a suspension of 2.92 g (13.28 mmol) of trimethylsulfoxonium iodide in 45 mL of acetonitrile was added 1.49 g (13.28 mmol) of potassium t-butoxide. A solution of 3.0 g (8.85 mmol) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal from Example 12 in 18 mL of acetonitrile was added and the mixture was stirred at room temperature for one hour. The mixture was diluted with 150 mL of water and extracted twice with 200 mL of ethyl acetate. The organic layers were combined and washed with 100 mL water, 50 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 3.0 g of a yellow crude oil. The crude product was purified by silica gel chromatography (ethyl acetate/hexane: 1: 8 as eluting solvent) to give 1.02 g (32.7% yield) of a mixture of the two diastereomers N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine.

METHOD 3:

To a suspension of 0.90 g (4.42 mmol) of trimethylsulfonium iodide in 18 mL of acetonitrile was added 0.495 g (4.42 mmol) of potassium t-butoxide. A solution of 1.0 g (2.95 mmol) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal from Example 12 in 7 mL of acetonitrile was added and the mixture was stirred at room temperature for one hour. The mixture was diluted with 80 mL of water and extracted twice with 80 mL of ethyl acetate. The organic layers were combined and washed with 100 mL water, 30 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1.04 g of a yellow crude oil. The crude product was a mixture

of the two diastereomers N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine.

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EXAMPLE 14

3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

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To a solution of 500 mg (1.42 mmoles) of the crude epoxide from Example 13 in 0.98 mL of isopropanol was added 0.71 mL (7.14 mmoles) of isobutylamine. The mixture was warmed to reflux at 85 °C to 90 °C for 1.5 hours. The mixture was concentrated under reduced pressure and the product oil was purified by silica gel chromatography (chloroform:methanol, 100:6 as eluting solvents) to give 330 mg of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a colorless oil (54.5% yield). 3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2S-ol was also isolated. When purified N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine was used as starting material, 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol was isolated after purification by chromatography in an 86% yield.

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25
30EXAMPLE 15

N-[3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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To a solution of 309 mg (0.7265 mmoles) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-

5 methylpropyl)amino-4-phenylbutan-2R-ol from Example 14 in 5 mL of THF was added 0.174 mL (1.5 mmoles) of t-butylisocyanate. The mixture was stirred at room temperature for 1.5 hours. The product was concentrated under reduced pressure to give 350 mg (92% yield) of a white solid crude product. The crude product was purified by silica gel chromatography (ethyl acetate/hexane: 1: 4 as eluting solvents) to give 324 mg of N-[3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a white solid (85.3% yield).

EXAMPLE 16

15 3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-2S-hydroxy-4-phenylbutyronitrile

A solution of 7.0 g (20.65 mmoles) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal from Example 12 in 125 mL of THF was cooled to -5 °C. A solution of 12.96 g of sodium bisulfite in 68 mL of water was added over 40 minutes, keeping the temperature below 5 °C. The mixture was stirred for 3 hours at 0 to 5 °C. An additional 1.4 g of sodium bisulfite was added and the mixture was stirred for another two hours. Sodium cyanide (3.3 g, 82.56 mmoles) was added to the bisulfite product at 0 to 5 °C and the mixture was stirred at room temperature for 16 hours. The biphasic mixture was extracted with 150 mL of ethyl acetate. The aqueous layer was extracted twice each with 100 mL of ethyl acetate. The combined organic layers was washed twice with 30 mL water, twice with 25 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 7.5 g (100 % crude yield of both diastereomers) of crude oil. The crude oil was purified by silica gel chromatography (ethyl acetate: hexane, 1: 4 as eluting solvents) to give 5.725 g (76%

yield) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-2S-hydroxy-4-phenylbutyronitrile as the major later eluting diastereomer and 0.73 g (9.6% yield) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyronitrile as the minor diastereomer. The combined yields of both isomers of cyanohydrins is 85.6% yield.

EXAMPLE 17

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3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-1-amino-4-phenylbutan-2R-ol

To a solution of 205.5 mg (0.56 mmol) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-2S-hydroxy-4-phenylbutyronitrile from Example 16 in 4 mL of THF was added 2.4 mL of a solution of borane in THF (1.0 M, 4 mmol). The mixture was stirred at room temperature for 30 minutes. An additional 1.4 mL of borane in THF was added and the mixture was stirred for another 30 minutes. The mixture was cooled to 0 °C and 2.0 mL of cold (0-5 °C) water was added slowly. The mixture was warmed to room temperature and stirred for 30 minutes. The product was extracted twice with 30 mL of ethyl acetate. The organic layers were combined and washed with 4 mL water, 4 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 200 mg of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-amino-4-phenylbutan-2R-ol as a white solid (96.4% yield).

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EXAMPLE 18

3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

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To a solution of 2.41 g (6.522 mmol) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-amino-4-

phenylbutan-2R-ol from Example 17 in 40 mL of methanol was added 0.592 mL (6.522 mmoles) of isobutyraldehyde and 0.373 mL (6.522 mmoles) of acetic acid. The mixture was stirred for 10 minutes. Sodium
5 cyanoborohydride (1.639 g, 26 mmoles) was added and the mixture was stirred for 16 hours at room temperature. The product mixture was concentrated under reduced pressure and partitioned between 150 mL of ethyl acetate and 50 mL of 1.5M ammonium hydroxide. The organic
10 layer was washed twice with 20 mL water, twice with 20 mL brine, dried over sodium sulfate, filtered and concentrated to an yellow oil. The crude product was purified by silica gel chromatography (chloroform: methanol, 100: 6 as eluting solvents) to give 2.326 g
15 of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a colorless oil (88.8% yield).

EXAMPLE 19

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N-[3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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To a solution of 309 mg(0.7265 mmoles) of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol from Example 18 in 5 mL of THF was added 0.174 mL(1.5 mmoles) of t-butylisocyanate. The mixture was stirred at room
30 temperature for 1.5 hours. The product was concentrated under reduced pressure to give 350 mg (92% yield) of a white solid crude product. The crude product was purified by silica gel chromatography (ethyl acetate/hexane: 1: 4 as eluting solvents) to
35 give 324 mg of N-[3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-

(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a white solid (85.3% yield).

EXAMPLE 20

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N-[3S-[N-(Phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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To a solution of 210 mg (0.4 mmoles) of N-[3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea from Example 19 in 5.0 mL of THF was added 5 mL of 4N hydrochloric acid. The mixture was stirred at room temperature for two hours. The solvents were removed under reduced pressure to give 200 mg (100%) of N-[3S-[N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a white solid.

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EXAMPLE 21

N-[3S-Amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

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To a solution of 200 mg (0.433 mmoles) of N-[3S-[N-(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea from Example 20 in 7 mL of 3A ethanol was added 0.05 g of 20% palladium on carbon. The mixture was hydrogenated at 40 °C for 1.8 hours at 5 psi followed by hydrogenation at 60 psi at room temperature for 22 hours. The catalyst was filtered and the solvent and by-product were removed under reduced pressure to give 150 mg (93.4% yield) of N-[3S-amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a white solid.

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EXAMPLE 22

3S-(N-t-Butoxycarbonyl)amino-4-phenylbutan-1,2R-diol

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To a solution of 1 g (3.39 mmoles) of 2S-(N-t-butoxycarbonyl)amino-1S-hydroxy-3-phenylbutanoic acid (commercially available from Nippon Kayaku, Japan) in 50 mL of THF at 0 °C was added 50 mL of borane-THF complex (liquid, 1.0 M in THF), keeping the temperatures below 5 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The mixture was cooled to 0 °C and 20 mL of water was added slowly to destroy the excess BH₃ and to quench the product mixture, keeping the temperature below 12 °C. The quenched mixture was stirred for 20 minutes and concentrated under reduced pressure. The product mixture was extracted three times with 60 mL of ethyl acetate. The organic layers were combined and washed with 20 mL of water, 25 mL of saturated sodium chloride solution and concentrated under reduced pressure to give 1.1 g of crude oil. The crude product was purified by silica gel chromatography (chloroform/methanol, 10:6 as eluting solvents) to give 900 mg (94.4% yield) of 3S-(N-t-butoxycarbonyl)amino-4-phenylbutan-1,2R-diol as a white solid.

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EXAMPLE 23

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3S-(N-t-Butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl Toluenesulfonate

To a solution of 744.8 mg (2.65 mmoles) of 3S-(N-t-butoxycarbonyl)amino-4-phenylbutan-1,2R-diol from Example 22 in 13 mL of pyridine at 0 °C was added 914 mg of toluenesulfonyl chloride in one portion. The

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mixture was stirred at 0 °C to 5 °C for 5 hours. A mixture of 6.5 mL of ethyl acetate and 15 mL of 5% aqueous sodium bicarbonate solution was added to the reaction mixture and stirred for 5 minutes. The product mixture was extracted three times with 50 mL of ethyl acetate. The organic layers were combined and washed with 15 mL of water, 10 mL of saturated sodium chloride solution and concentrated under reduced pressure to give about 1.1 g of a yellow chunky solid. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 1:3 as eluting solvents) to give 850 mg (74% yield) of 3S-(N-t-butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl toluenesulfonate as a white solid.

EXAMPLE 24

3S-[N-(t-Butoxycarbonyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

To a solution of 90 mg (0.207 mmoles) of 3S-(N-t-butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl toluenesulfonate from Example 23 in 0.143 mL of isopropanol and 0.5 mL of toluene was added 0.103 mL (1.034 mmoles) of isobutylamine. The mixture was warmed to 80 to 85 °C and stirred for 1.5 hours. The product mixture was concentrated under reduced pressure at 40 to 50 °C and purified by silica gel chromatography (chloroform/methanol, 10:1 as eluting solvents) to give 54.9 mg (76.8% yield) of 3S-[N-(t-butoxycarbonyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a white solid.

EXAMPLE 25

N-[3S-[N-(t-Butoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

To a solution of 0.1732 g (0.516 mmoles) of 3S-[N-(t-butoxycarbonyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol from Example 24 in 5 mL of ethyl acetate at 0 °C was added 1.62 mL (12.77 mmoles) of t-butylisocyanate and the mixture was stirred for one hour. The product was concentrated under reduced pressure and purified by silica gel chromatography (chloroform/methanol, 100:1.5 as eluting solvents) to give 96 mg (42.9 % yield) of N-[3S-[N-(t-butoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea as a white solid.

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EXAMPLE 26

N-[3S-amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea

To a solution of 10 mg (0.023 mmoles) of N-[3S-[N-(t-butoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea from Example 27 in 1 mL of methanol at 0 °C was added 1.05 mL of a 4M hydrogen chloride in methanol and the mixture was stirred at room temperature for 45 minutes. The product was concentrated under reduced pressure. The residue was dissolved 5 mL of methanol and concentrated under reduced pressure. This operation was repeated three times to remove water from the product, after which 8.09 mg (95.2% yield) of N-[3S-amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-

methylpropyl)urea hydrochloride salt was obtained as a white solid.

EXAMPLE 27

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3S-(N,N-Dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether

10 To a solution of 24.33 g (73.86 mmol) of 2S-(N,N-dibenzyl)amino-3-phenylpropanal in 740 mL of anhydrous methylene chloride at -20 C under a nitrogen atmosphere, was added 11.8 mL (8.8 g, 88.6 mmol) of trimethylsilyl cyanide, then 19.96 g (88.6 mmol) of anhydrous zinc bromide. After 4 hours at -15 C, and 18
15 hours at room temperature, the solvent was removed under reduced pressure, ethyl acetate was added, washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 31.3 g of a brown oil, which was identified as a 95:5 mixture of 3S-(N,N-
20 dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether, m/e=429(M+H) and 3S-(N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether, respectively.

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EXAMPLE 28

3S-(N,N-Dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile

30 A solution of 10.4 g (24.3 mmol) of the crude 95:5 mixture of 3S-(N,N-dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether, and 3S-(N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether from Example 27 in 40 mL of methanol, was added to 220 mL of 1N hydrochloric acid
35 with vigorous stirring. The resulting solid was collected, dissolved in ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried over anhydrous

magnesium sulfate, filtered and concentrated to afford 8.04 g of crude product. This was recrystallized from ethyl acetate and hexane to afford pure 3S-(N,N-dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile,
5 m/e=357 (M+H).

EXAMPLE 29

3S-(N,N-Dibenzyl)amino-2R-hydroxy-4-phenylbutylamine
10

METHOD 1:

A solution of 20.3 g (47.3 mmol) of the crude 95:5 mixture of 3S-(N,N-dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether, and 3S-
15 (N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether from Example 28 in 20 mL of anhydrous diethyl ether, was added to 71 mL (71 mmol) of a 1M solution of lithium aluminum hydride in diethyl
20 ether at reflux. After the addition, the reaction was refluxed for 1 hour, cooled to 0C, and quenched by the careful addition of 2.7 mL of water, 2.7 mL of 15% aqueous sodium hydroxide, and 8.1 mL of water. The resulting solids were removed by filtration and the
25 filtrate washed with water, brine, dried over magnesium sulfate, filtered and concentrated to afford 13.8 g of crude material, which was recrystallized from tetrahydrofuran and isooctane to afford 10.6 g of 3S-
(N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutylamine, mp
30 46-49 C, m/e=361 (M+H), which was contaminated by approximately 2% of 3S-(N,N-dibenzyl)amino-2S-hydroxy-4-phenylbutylamine.

METHOD 2:

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To 15.6 mL (60.4 mmol) of 70% sodium bis(methoxyethoxy)aluminum hydride in toluene, was

added 15mL of anhydrous toluene, and then after cooling to 0C, a solution of 20.0g (46 mmol) of the crude 95:5 mixture of 3S-(N,N-dibenzyl)amino-2S-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether, and 3S-
5 (N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutyronitrile, O-trimethylsilyl ether from Example 28 in 10 mL of anhydrous toluene, at a rate so as to maintain the temperature below 15°C. After 2.5 hours at room temperature, the reaction was quenched by the careful
10 addition of 200 mL of 5% aqueous sodium hydroxide. The solution was diluted with ethyl acetate, washed with 5% sodium hydroxide, sodium tartrate solution, brine, dried over magnesium sulfate, filtered and concentrated to afford 16.6 g of crude product, which was assayed by
15 HPLC and shown to contain 87% of 3S-(N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutylamine.

EXAMPLE 30

20 N-[3S-(N,N-Dibenzyl)amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea

Step 1: To a solution of 1.0 g (2.77 mmol) of 3S-(N,N-dibenzyl)amino-2R-hydroxy-4-phenylbutylamine from
25 Example 29 in 4.6 mL of ethanol, was added 0.3 mL (0.24g, 2.77 mmol) of isovaleraldehyde. After 1 hour at room temperature, the ethanol was removed under reduced pressure, 4 mL of ethyl acetate was added and the solution purged with nitrogen. To the solution was
30 added 360 mg of 5% platinum on carbon catalyst, the solution purged with 40 psig of hydrogen and then maintained under 40 psig of hydrogen for 20 hours. The solution was purged with nitrogen, the catalyst removed by filtration and the solvent removed under reduced
35 pressure to afford 473 mg of the crude product.

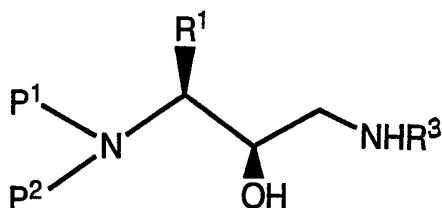
Step 2: The crude product from Step A was directly dissolved in 5.4 mL of ethyl acetate and 109 mg (1.1 mmol) of tertiary-butyl isocyanate was added. After 1 hour at room temperature, the solution was washed with 5% citric acid, brine, dried over magnesium sulfate, filtered and concentrated to afford 470 mg of crude product. The crude product was recrystallized from ethyl acetate and isooctane to afford 160 mg of N-[3S-(N,N-Dibenzyl)amino-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(3-methylbutyl)urea, mp 120.4-121.7°C, m/e=530 (M+H).

From the foregoing detailed description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What Is Claimed Is:

1. A method of preparing an aminoepoxide compound of formula

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wherein P^1 and P^2 independently are selected from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl, alkoxy carbonyl and cycloalkenylalkyl;

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wherein further P^1 and P^2 may be taken together with the nitrogen atom to which they are bonded to form a heterocyclic ring system containing said nitrogen atom as a ring member;

15

wherein R^1 is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl, which are optionally substituted with a group selected from alkyl, halo, NO_2 , OR^9 and SR^9 , wherein R^9 is selected from hydrogen and alkyl;

20

and wherein R^3 represents hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along

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with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

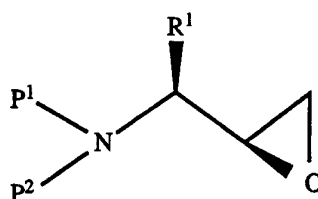
and wherein any of the foregoing groups of P^1 , P^2 , R^1 and R^3 may be substituted at one or more substitutable positions with one or more radicals independently selected from halo, alkyl of C_1 - C_8 , alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

10

said method comprising the steps of forming a protected aminoalcohol, oxidizing said protected aminoalcohol to a chiral protected aminoaldehyde and diastereoselectively forming an aminoepoxide or aminocyanohydrin from said aminoaldehyde with an organometallic methylene-adding reagent in an appropriate solvent.

2. A method of preparing an aminoepoxide compound of Formula I:

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(I)

wherein P^1 and P^2 independently are selected from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl, alkoxycarbonyl and cycloalkenylalkyl;

wherein further P^1 and P^2 may be taken together with the nitrogen atom of Formula I to form a heterocyclic ring system containing said nitrogen atom as a ring member;

30

and wherein R¹ is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl, which are optionally substituted with a group selected from alkyl, halo, NO₂, OR⁹ and SR⁹, wherein R⁹ is selected from
5 hydrogen and alkyl;

and wherein any of the foregoing groups of P¹, P² and R¹ may be substituted at one or more substitutable positions with one or more radicals independently
10 selected from halo, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

said method comprising the steps of forming a
15 protected aminoalcohol, oxidizing said protected aminoalcohol to a chiral protected aminoaldehyde and diastereoselectively forming the aminoepoxide from said aminoaldehyde with an organometallic methylene-adding reagent in an appropriate solvent.

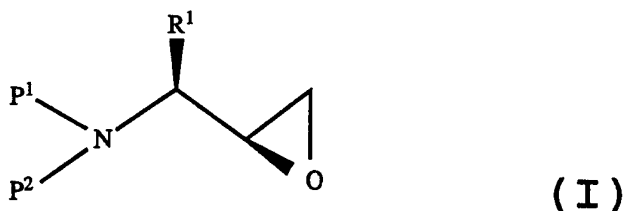
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3. The method of Claim 2 wherein P¹ and P² independently are selected from carbobenzoxy, t-butoxycarbonyl, acetyl, butyryl, benzoyl, isobutyloxycarbonyl, allyl, 1,2-bis(dimethylsilyl)ethane,
25 1,2-bis(dimethylsilyl)benzene, substituted benzoyl, trifluoroacetyl, trichloroacetyl, phthaloyl, benzyl, ortho-methylbenzyl, trityl, 1,2-bis(methylene)benzene, benzhydryl, phenethyl, phenpropyl, phenyl, naphthalenyl, indenyl, anthracenyl, durenyl, 9-(9-phenyl-fluoroenyl)
30 and phenanthrenyl, wherein further P¹ and P² may be taken together to form with the nitrogen atom of Formula I a radical selected from phthalimide, succinimide and maleimide, and wherein any of the foregoing groups of P¹ and P² may be substituted at one or more substitutable
35 positions with one or more radicals independently selected from halo, alkyl of C₁-C₈, alkoxy, hydroxy,

nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof.

4. The method of Claim 2 wherein P^1 and P^2 are
 5 independently selected from aralkyl,
 1-2-bis(methylene)benzene and aralkyl substituted with
 one or more radicals independently selected from halo,
 alkyl of C_1 - C_8 , alkoxy, hydroxy, nitro, alkenyl, amino,
 alkylamino, acylamino and acyl; and wherein R^1 is
 10 aralkyl; or a pharmaceutically-acceptable salt thereof.

5. A diastereoselective and enantioselective
 method of preparing a protected chiral alpha-amino
 epoxide of Formula I:

15



wherein P^1 and P^2 independently are selected
 from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl,
 20 alkoxycarbonyl and cycloalkenylalkyl;

wherein further P^1 and P^2 may be taken together
 with the nitrogen atom of Formula I to form a
 heterocyclic ring system containing said nitrogen atom as
 25 a ring member;

and wherein R^1 is selected from alkyl, aryl,
 cycloalkyl, cycloalkylalkyl and aralkyl, which are
 optionally substituted with a group selected from alkyl,
 30 halo, NO_2 , OR^9 and SR^9 , wherein R^9 is selected from
 hydrogen and alkyl;

and wherein any of the foregoing groups of P^1 , P^2 and R^1 may be substituted at one or more substitutable positions with one or more radicals independently selected from halo, alkyl of C_1 - C_8 , alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

said method comprising treating a protected aminoaldehyde substrate with an organometallic methylene-adding reagent in an appropriate solvent.

6. The method of Claim 5 wherein the organometallic methylene-adding reagent is a halomethylolithium generated in situ.

7. The method of Claim 6 wherein at least an equimolar amount of organometallic methylene-adding reagent is added to the aminoaldehyde.

8. The method of Claim 5 wherein the halomethylolithium is formed through the addition of an organolithium reagent with a dihalomethane.

9. The method of Claim 5 wherein the dihalomethane is selected from bromochloromethane, chloriodomethane, dibromomethane, diiodomethane and bromofluoromethane.

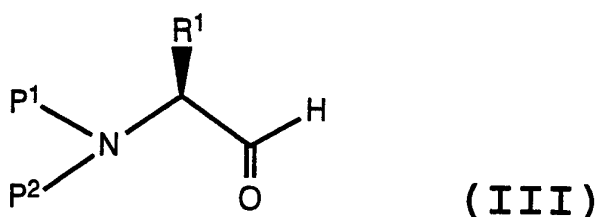
10. The method of Claim 5 wherein the halomethylolithium is added to the amino aldehyde at a temperature in a range of about -80°C to about 0°C .

11. The method of Claim 5 wherein the halomethylolithium is added to the amino aldehyde at a temperature in a range of about -40°C and -15°C .

12. The diastereoselective method of preparing protected chiral alpha-amino epoxides of Claim 5 wherein the amino aldehyde is alpha-S-[bis(phenylmethyl)amino]-benzenepropanaldehyde.

5

13. A method of forming protected alpha-aminoaldehyde of Formula III:



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wherein P¹ and P² independently are selected from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl, alkoxycarbonyl and cycloalkenylalkyl;

15

wherein further P¹ and P² may be taken together with the nitrogen atom of Formula III to form a heterocyclic ring system containing said nitrogen atom as a ring member;

20

and wherein R¹ is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl, which are optionally substituted with a group selected from alkyl, halo, NO₂, OR⁹ and SR⁹, wherein R⁹ is selected from hydrogen and alkyl;

25

and wherein any of the foregoing groups of P¹, P² and R¹ may be substituted at one or more substitutable positions with one or more radicals independently selected from halo, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

30

said method comprising treating at a temperature of about 0°C to about 30°C. a protected aminoalcohol with an oxidizing agent.

5 14. The method of Claim 13 wherein at least an equimolar amount of said oxidizing agent is added to the protected aminoalcohol.

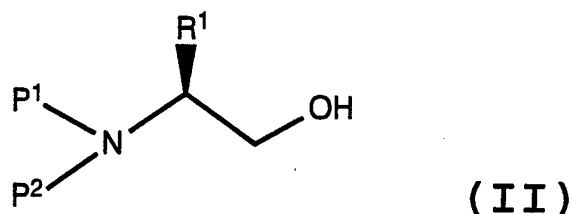
10 15. The method of Claim 13 wherein said oxidizing agent is selected from sulfur trioxide:pyridine complex, acetyl chloride/dimethyl sulfoxide, acetyl anhydride/dimethyl sulfoxide, trifluoroacetyl chloride/dimethyl sulfoxide, toluenesulfonyl bromide/dimethyl sulfoxide, phosphorous
15 pentachloride/dimethyl sulfoxide and isobutylchlorformate/dimethyl sulfoxide.

 16. The method of Claim 13 wherein said oxidizing agent is sulfur trioxide:pyridine complex in an
20 appropriate solvent.

 17. The method of Claim 13 wherein the reaction temperature is between about 15°C and about
25 30°C.

 18. The method of Claim 13 wherein the protected aminoalcohol is [Bis(phenylmethyl)amino]-benzenepropanol.

19. A method of preparing protected chiral alpha-amino alcohol of the formula:



5

wherein P¹ and P² independently are selected from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl, alkoxy carbonyl and cycloalkenylalkyl;

10

wherein further P¹ and P² may be taken together with the nitrogen atom of Formula II to form a heterocyclic ring system containing said nitrogen atom as a ring member;

15

and wherein R¹ is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and arylalkyl, which are optionally substituted at one or more substitutable positions with a group selected from alkyl, halo, NO₂, OR⁹ and SR⁹, wherein R⁹ is selected from hydrogen and

20

alkyl;

and wherein any of the foregoing groups of P¹, P² and R¹ may be substituted with one or more radicals independently selected from halo, alkyl of C₁-C₈, alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

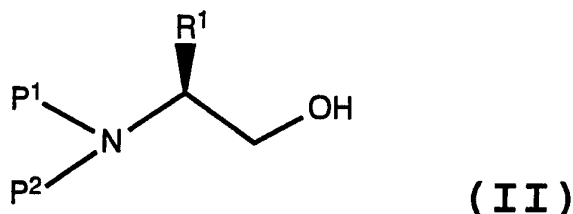
25

said method comprising treating said aminoalcohol with an alkylating agent.

30

20. The method of Claim 19 wherein the aminoalcohol is L-phenylalaninol.

21. A method of preparing protected chiral alpha-amino alcohol of Formula II:



5

wherein P^1 and P^2 independently are selected from acyl, aralkyl, alkenyl, silyl, aralkoxycarbonyl, alkoxycarbonyl and cycloalkenylalkyl;

10

wherein further P^1 and P^2 may be taken together with the nitrogen atom of Formula II to form a heterocyclic ring system containing said nitrogen atom as a ring member;

15

and wherein R^1 is selected from alkyl, aryl, cycloalkyl, cycloalkylalkyl and arylalkyl, which are optionally substituted at one or more substitutable positions with a group selected from alkyl, halo, NO_2 , OR^9 and SR^9 , wherein R^9 is selected from hydrogen and

20

alkyl; and wherein any of the foregoing groups of P^1 , P^2 and R^1 may be substituted one or more radicals independently selected from halo, alkyl of C_1 - C_8 , alkoxy, hydroxy, nitro, alkenyl, amino, alkylamino, acylamino and acyl; or a pharmaceutically-acceptable salt thereof;

25

said method comprising treating an amino acid with an alkylating agent to form a protected amino acid, and forming a protected aminoalcohol by treating said protected amino acid with a reducing agent in a suitable solvent.

30

22. The method of Claim 21 wherein the reducing agent is diisobutylaluminum hydride.

23. The method of Claim 21 wherein said amino
5 acid is L-phenylalanine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/12201

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C215/28 C07C301/02 C07D301/02 C07D303/36 C07C221/00
C07C223/02 C07C269/04 C07C271/20 C07C213/08

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)

IPC 6 C07C C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 288 764 (BAYER) 2 November 1988 cited in the application see claims; examples ---	13-23
X	WO,A,93 13066 (SYNTEX) 8 July 1993 see Reaction Scheme 1a, page 29 line 36-page 30 line 4 ---	13-23
X	ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, vol.26, no.11, November 1987, WEINHEIM DE pages 1141 - 3 M.T. REETZ ET. AL. 'Stereoselective Synthesis of beta-Amino alcohols from Optically Active alpha-Amino Acids.' see whole document --- -/--	13-23

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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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.
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Date of the actual completion of the international search

1 March 1995

Date of mailing of the international search report

15. 03. 95

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/12201

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF ORGANIC CHEMISTRY., vol.50, no.23, 15 November 1985, EASTON US pages 4615 - 24 B.E. EVANS ET. AL. 'A Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres Using Novel, chiral Aminoalkyl Epoxides and gamma-(Aminoalkyl) gamma-Lactones.' see page 4616, Schemes I and II ---	1-12
Y	TETRAHEDRON LETTERS., vol.30, no.40, 1989, OXFORD GB pages 5425 - 8 M. T. REETZ ET. AL. 'Protective Group Tuning in the Stereoselective Conversion of alpha-Amino Aldehydes into Aminoalkyl Epoxides.' see whole document ---	1-12
Y	SYNLETT, no.9, September 1991, STUTTGART DE pages 631 - 2 T. J. MICHNICK ET. AL. '(Bromomethyl)lithium. Efficient in situ Reactions.' see whole document ---	1-12
A	WO,A,92 14703 (I.C.I.) 3 September 1992 see claims; examples -----	1-12

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/12201

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0288764	02-11-88	DE-A- 3711911 JP-A- 63258838 US-A- 4990669	20-10-88 26-10-88 05-02-91
WO-A-9313066	08-07-93	AU-B- 3278293	28-07-93
WO-A-9214703	03-09-92	EP-A- 0636120	01-02-95