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A Practical Synthesis of an HIV Protease Inhibitor Intermediate - Diastereoselective Epoxide Formation from Chiral α-Aminoaldehydes

John S. Ng*, Claire A. Przybyla, Chin Liu, Joe C. Yen, Frank W. Muellner and Cara L. Weyker

Chemical Sciences Department, Research and Development, Searle,
Skokie, Illinois 60077

Abstract: A practical and efficient synthesis of an HIV protease inhibitor intermediate has been developed based on the diastereoselective epoxide formation from a chiral α-aminoaldehyde and an *in situ* generated halomethyllithium reagent.

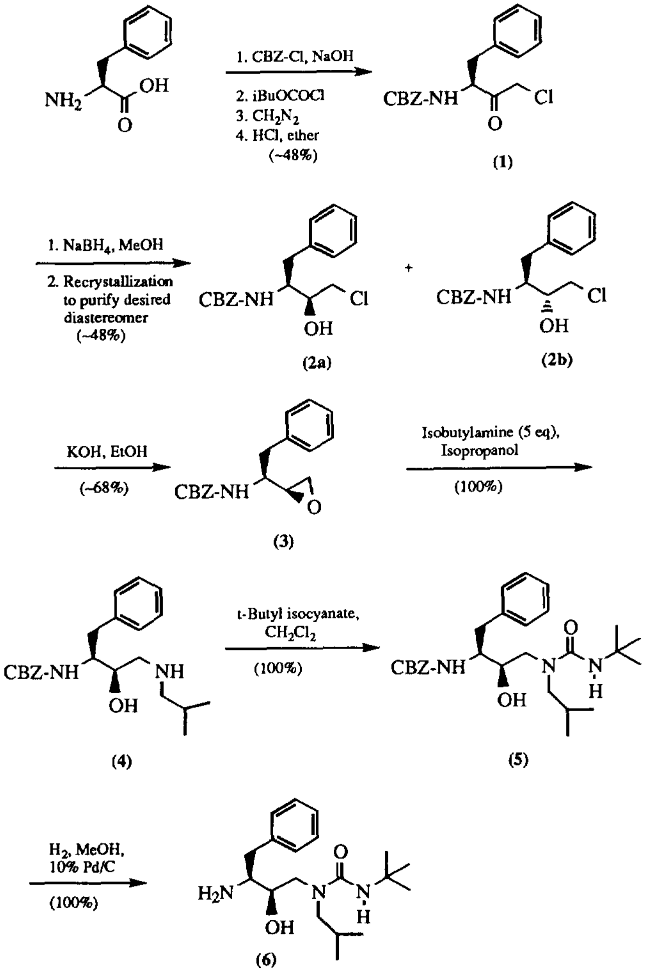
INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1), the etiologic agent of acquired immunodeficiency syndrome (AIDS), encodes for a specific aspartyl proteinase (HIV protease)[1]. Inhibition of this enzyme is regarded as a promising approach for the treatment of AIDS[2]. Compounds incorporating hydroxyethylamine or hydroxyethylurea isosteres, as transition-state analogues, have been found to be highly potent inhibitors of HIV proteases.[3] Due to the potential clinical importance of these compounds, many syntheses of intermediates leading to these types of compounds have been reported[4]; however, none of these methods would be readily amenable for the preparation of kilogram quantities of material. In this paper, we describe an efficient synthesis of a hydroxyethylurea intermediate used in the preparation of a HIV protease inhibitor, which is suitable for large scale production.

RESULTS AND DISCUSSION

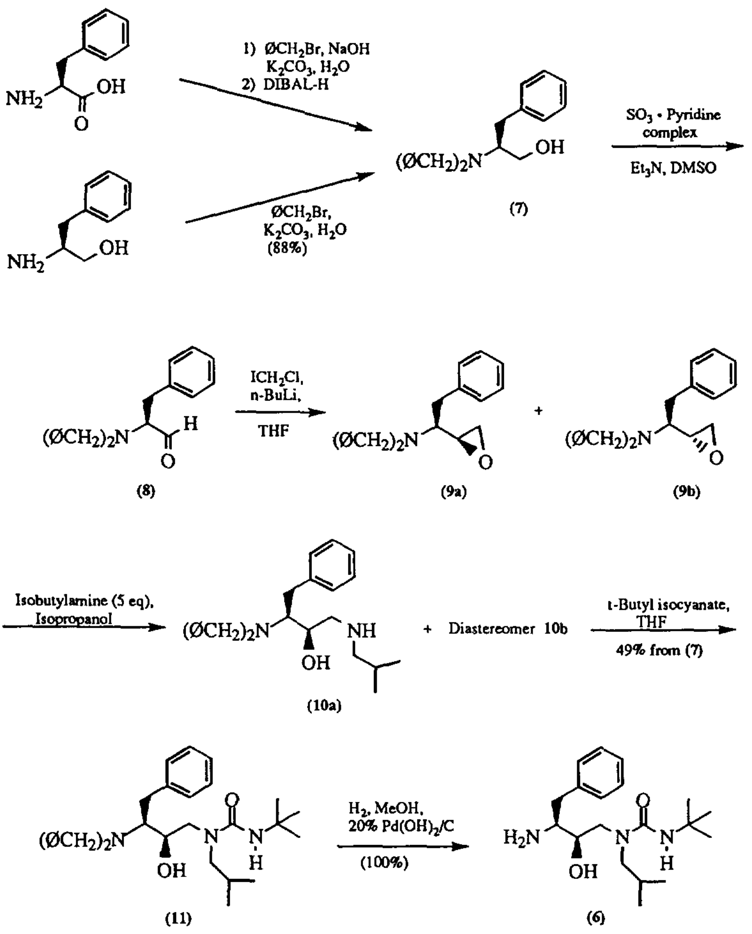
The previously reported synthesis[3a], shown in Scheme I, was used to prepare initial supplies of the hydroxyethylurea intermediate (6) required for the synthesis of a compound cited for development as a potential HIV protease inhibitor. The key protected epoxide (3) was prepared from a six-step synthesis starting from L-phenylalanine.[5] The use of diazomethane, the low levels of diastereoselectivity in the sodium borohydride reduction (~50% d.e.) and low overall yield (~16%) made the scale up of this synthesis impractical.

Scheme I



In order to circumvent these problems, we developed an alternate synthesis of the hydroxyethylurea intermediate (**6**), which was based on a synthetic equivalent of epoxide (**3**), namely, chiral N, N, α-S-tris(phenylmethyl)-2S-oxiranemethanamine (**9a**), shown in Scheme II.

Scheme II



Starting from L-phenylalanine, the aldehyde (**8**) was synthesized in three steps by a modified Reetz procedure.[6] First, N,N-bis(phenylmethyl)-L-phenylalanine, phenylmethyl ester was prepared from L-phenylalanine using benzyl bromide under aqueous conditions. The ester was then reduced with diisobutylaluminum hydride (DIBAL-H) in toluene. The substitution of DIBAL-H for lithium aluminum hydride, as used by Reetz, provided a safer method for the reduction of the benzyl ester. The quench of the reaction mixture with aqueous acid gave a white solid from which the alcohol (**7**) was isolated after treatment with aqueous base and extraction with toluene. After one recrystallization, chemically (>99%) and optically pure (>99.5% ee) alcohol (**7**) was obtained in 65% yield. Alternatively, alcohol (**7**) could be obtained in one step in 88% yield by the benzylation of 2-amino-3-phenyl-1-propanol (L-phenylalaninol)[7] using benzylbromide under aqueous conditions. The oxidation of alcohol (**7**) to aldehyde (**8**) was also modified from the Reetz procedure to allow for safe operation during scaleup. Instead of the standard Swern procedure[8] using oxalyl chloride and DMSO in methylene chloride at low temperatures (-78 °C), the sulfur trioxide-pyridine/DMSO modification[9], which could be conveniently performed at room temperature, was employed resulting in an excellent yield (100% crude product) of the desired analytically pure aldehyde (**8**). These modifications eliminated the need for kilogram scale chromatography and made the large scale operation much less hazardous to perform.

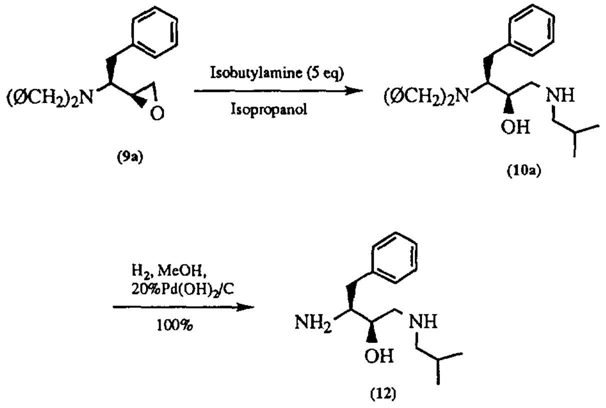
The key step in the synthesis shown in Scheme II, involved the reaction of chloromethylithium or bromomethylithium with the aldehyde (**8**) to form the required epoxide (**9a**). Previously, Reetz successfully prepared this epoxide from the reaction of the aldehyde with a sulfonium or sulfoxonium ylide[10], however, our attempts to use this procedure resulted in significant racemization (10-80%). Although the reaction of halomethyllithium reagents with aldehydes had been previously reported by Matteson[11], the addition of such species to chiral α-amino aldehydes to form α-aminoepoxides had not been investigated.[12] We found that the reaction of chloromethylithium or bromomethylithium with (**8**) did produce the *erythro* epoxide (**9a**) with good diastereoselectivity, similar to the results reported by Reetz which involved the addition of other nucleophiles to the same aldehyde.[6] In this reaction, the halomethyllithium reagent was generated by the addition of n-butyllithium to a cold (-78 to -30 °C) THF solution of either chloroiodomethane, bromochloromethane or dibromomethane in the presence of aldehyde (**8**). It is necessary to have the aldehyde present because of the instability of the halomethyllithium reagent. Also, several additions of the dihalomethane and n-butyllithium reagents are required to maximize the conversion of aldehyde to the epoxide. Chlorohydrin products could be isolated from the reaction of aldehyde (**8**) with chloromethyllithium if the reaction mixture was quenched at low temperatures.[13] Epoxides (**9a and 9b**) were produced in an 85:15 ratio from the reaction of aldehyde (**8**) with chloromethyllithium after warming to room temperature or from the reaction of the aldehyde with bromomethyllithium at colder temperatures.[14] The *erythro* epoxide (**9a**) could be isloated by chromatography as an oil in a 65% yield, however, it was found the crude product could be used directly without purification.[15]

The crude epoxide mixture was treated with isobutylamine in isopropanol at 80 °C for 1.5

hours to give the crude diastereomeric amine mixture (**10a**+**10b**) in a good yield (95% by quantitative HPLC analysis). Reaction of the crude amine with t-butyl isocyanate in methylene chloride, THF or ethyl acetate at room temperature for 10-30 minutes provided a diastereomeric mixture of ureas in 94% yield by quantitative HPLC analysis. The desired diastereomer (**11**) was purified by one recrystallization of the crude product from ethyl acetate/heptane in an overall yield of 52% from (**7**). Hydogenation using Pearlman's catalyst (20% palladium hydroxide on carbon) in methanol resulted in a quantitative yield of the amino hydroxyethylurea intermediate (**6**), which was shown by NMR and HPLC analyses to be identical to the compound previously prepared according to the route depicted in Scheme I. This method was used to prepare intermediate (**6**) which was then used successfully to synthesize potent HIV protease inhibitors containing the hydroxyethylurea moiety according to a recently published procedure.[3a]

In order to ensure that the HIV protease inhibitors prepared by this method were of high enantiomeric purity, we developed four HPLC methods to analyze for the enantiomeric excess of various key intermediates. Enantiomers of intermediate (**7**) were resolved on a Astec Cyclobond I SP HPLC column and the enantiomers of intermediates (**8**) and (**9**) were separated on a Regis (S,S)-Whelk-O 1 HPLC column. Intermediate (**10a**) was converted to the diaminoalcohol (**12**) by debenzylation as shown in Scheme III and the product was analyzed using a Daicel Chiral Crown Pak CR(+) column. In all cases, the intermediates from the synthesis described were determined to be of high optical purity (>99.5% ee).

Scheme III



The synthesis described here was successfully scaled up to the multikilogram level. Several advantages of this route over other syntheses for the large scale preparation of compounds containing the hydroxyethylamine moiety are as follows: (1) the elimination of the use of extremely hazardous reagents, such as diazomethane, (2) no purifications by chromatography are required (3) the use of inexpensive and readily available starting materials and (4) the route is short and efficient.

CONCLUSION

Diastereoselective epoxide formation, from N,N-dibenzyl protected chiral α-amino-aldehydes and *in situ* generated halomethyllithium reagents, has been demonstrated to be an effective method for the large scale production of a hydroxyethylurea intermediate used for the preparation HIV protease inhibitors.

EXPERIMENTAL SECTION

Electron impact and chemical ionization mass spectra were obtained using a Finnigan-MAT 8430 mass spectrometer, a Finnigan-MAT SS300 data system, and a desorption probe at a source temperature of 170 °C. Ammonia was used as the CI reagent gas. The proton and carbon-13 NMR spectra were recorded on a GE QE-300 or a Varian VXR400 spectrometer with Me_4Si-d_{12} as an internal standard. Infrared (IR) spectra were recorded using a Perkin Elmer Model 681 spectrophotometer and $CHCl_3$ solutions. Elemental analyses were determined with a Control Equipment Corporation 240XA analyzer. Differential scanning calorimetry (DSC) thermograms were obtained using a DuPont Model 9900 thermal analysis system. Solvents and reagents were obtained from commercial sources and were not further purified unless specified. Gas chromatography was performed on a Hewlett Packard 5890 gas chromatograph equipped with a methyl silicone column (15m x 0.25 x 0.25 μm film thickness). Optical rotations were measured on a Perkin Elmer 241 polarimeter with a path length of 1 dm. Concentrations were given in g/mL. Purchased raw materials were of reagent grade and used without purification. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. Merck Silica Gel 60 was used in the chromatographic purification of all specified products.

βS-2-[Bis(phenylmethyl)amino]benzenepropanol (7)

METHOD 1

Step 1: Benzylation of L-Phenylalanine

A solution of L-phenylalanine (50.0 g, 0.302 mol), 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. The mixture was stirred at 97 °C for 30 minutes. 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. Analytical tlc (10% ethyl acetate/hexane, silica gel) showed the major component (Rf=0.32) to be the desired tribenzylated compound, N, N-bis(phenylmethyl)-L-phenylalanine, phenylmethyl ester. The product can be purified by column chromatography (silica gel, 15% ethyl acetate/hexanes), however, the crude product was usually used directly in the next step without further purification. ^{1}H NMR spectrum was in agreement with published literature.[6] ^{1}H NMR ($CDCl_3$) δ 3.00 and 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: βS-2-[Bis(phenylmethyl)amino]benzenepropanol (7) from the diisobutylaluminium hydride (DIBAL-H) reduction of N, N-bis(phenylmethyl)-L-phenylalanine, phenylmethyl ester : N, N-bis(phenylmethyl)-L-phenylalanine, phenylmethyl ester (0.302 mol), from Step 1 was dissolved in toluene (750 mL) and cooled to -55 °C. A 1.5 M solution of DIBAL-H in toluene (443.9 mL, 0.666 mol) was added at a rate to maintain the temperature between -55 to -50 °C. The mixture was stirred for 20 minutes 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 precipitated solid was filtered off and washed with toluene. The solid was suspended in a mixture of toluene (400 mL) and water (100 mL), cooled to 5 °C and treated with 2.5 N NaOH (186 mL). The mixture was stirred at room temperature until the 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 (75 mL) were added to the residue upon which the desired alcohol precipitated. The solid was filtered and washed with 50 mL hexane to give 34.9 g of product as the first crop. A second crop of product (5.6 g) was isolated by refiltering the mother liquor. Recrystallization of the two combined crops from ethyl acetate (20 mL) and hexane (30 mL) gave 40 g of βS-2-[Bis(phenylmethyl)amino]benzenepropanol (7), 40% yield from L-phenylalanine. An additional 7 g (7%) of product was obtained by recrystallyzation of the concentrated mother liquor. TLC (10% ethyl acetate/hexane, silica gel) : Rf = 0.23; mp 71.5-73.0 °C; ^{1}H 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); $[\alpha]_D^{25}$ +42.4 (c 1.45, CH_2Cl_2); DSC 77.67°C; Anal. Calcd. for $C_{23}H_{25}ON$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.43; H, 7.59; N, 4.22. HPLC analysis on chiral stationary phase, Astec 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 ml/min, detection with UV detector at 230nm and a temperature of 0 °C. Retention time of **(7)**: 11.25 min., retention time of enantiomer of **(7)**: 12.5 min.

METHOD 2

Preparation of βS-2-[bis(phenylmethyl)amino]benzenepropanol **(7)** from the N, N-dibenzylation of 2-amino-3-phenyl-1-propanol (L-phenylalaninol): L-Phenylalaninol (176.6 g, 1.168 mol) was added to a solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65 °C. A solution of benzyl bromide (400 g, 2.339 mol) in ethanol (305 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 mixture was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic salts. The product was isolated by filtration and washed with water until the pH was 7. The crude product was air-dried overnight to give a white 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 βS-2-[Bis(phenylmethyl)amino]-benzenepropanol **(7)**, mp 71.5-73.0 °C. This compound was identical to that prepared by method 1.

αS-[Bis(phenylmethyl)amino]benzenepropanaldehyde (8)

βS-2-[Bis(phenylmethyl)amino]benzenepropanol **(7)** (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 maintain the temperature between 8-17 °C (addition time - 1.0 h). The solution was stirred at ambient temperature for 1.5 h at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled in an ice/water bath and quenched by the addition of 1.6 L of cold water (10-15 °C) over 45 minutes. The dimethyl sulfide by-product was removed by sparging the quenched reaction mixture with nitrogen and scrubbing the off gas with 5% bleach solution. The product solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), brine (2.2 L), dried over $MgSO_4$ (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 αS-[Bis-(phenylmethyl)amino]-benzenepropanaldehyde **(8)** as a pale yellow oil (99.9%). The crude product was used directly in the next step **without** purification. The analytical data of the compound were consistent with the published literature[6]. $[\alpha]_D^{25} = -92.9$ ° (c 1.87, CH_2Cl_2); ^1H

NMR (100 MHz, $CDCl_3$) 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) $C_{23}H_{24}NO$ 330.450, found: 330.1836. Anal. Calcd. for $C_{23}H_{23}ON$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase: Regis (S,S)-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)**: 8.75 min., retention time of enantiomer of **(8)**: 10.62 min.

N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine (9a) and N,N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine (9b)

A solution of αS-[Bis-(phenylmethyl)amino]benzenepropanaldehyde **(8)** (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35 °C in a stainless steel reactor. 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. After the addition, the mixture was stirred at -30 to -35 °C for 10 minutes. Additional chloroiodomethane and n-butyllithium were added many times in small portions in the same manner to maximize the conversion of the aldehyde to the epoxide. The specific additions were as follows: 2 additions of 17 ml (0.22 mol) of chloroiodomethane and 110 ml (0.18 mol) of n-butyllithium; 6 additions of 8.5 ml (0.11mol) of chloroiodomethane and 55ml (0.09 mol) n-butyllithium; and one addition of 8.5 ml (0.11 mol) of chloroiodomethane and 37 ml (0.06 mol) of n-butyllithium. After the final addition of the reagents, the mixture was stirred at -30 to -35 °C for 10 minutes and then the external cooling was stopped. The mixture warmed to ambient temperature over 4 hours. TLC analysis of the reaction mixture (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was complete. The reaction mixture was cooled to 10 °C and quenched by the addition of 1.4 L of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1.2 L of water), at a rate which kept the temperature below 23 °C. After the addition was complete, the mixture was stirred for 10 minutes and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 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 oily residue was dried at 70 °C *in vacuo* (0.8 bar) for 1 h to give 222.8 g (>100% yield) of crude product. Quantitative HPLC analysis of the crude product indicated ~ 85 % yield of the mixture of the two epoxide diastereomers **(9a)** and **(9b)**. Due to the relative instability of the product on silica gel, the crude product was used directly in the next step without purification. The diastereomeric ratio of the crude mixture was determined by proton NMR to be: **(9a)/(9b)**: 86:14. The minor and major epoxide diastereomers were also characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), Rf = 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:

N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine (9a)

^{1}H 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 (100 MHz,CDCl$_3$) δ 139.6, 129.5, 128.4, 128.1, 128.1, 126.8, 126.0, 60.3, 54.2, 52.1, 46.0, 33.8; HRMS calcd for $C_{24}H_{26}NO$ (M+1) 344.477, found 344.2003.

N, N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine (9b)

^{1}H NMR (300 MHz, CDCl3) 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 analysis on chiral stationary phase: Regis (S,S)-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 210 nm. Retention time of **(9a)**: 9.38 min., retention time of enantiomer **(9b)**: 13.75 min.

βS-[Bis(phenylmethyl)amino]-αR-[[(2-methylpropyl)amino]methyl]-benzenepropanol (10a)

To a solution of the crude epoxides 9a and 9b (388.5 g, 1.13mol) in isopropanol (2.7 L) was added isobutylamine (1.7 kgm, 23.1 mol). The temperature increased from 25 °C to 30 °C during the addition. 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 concentrate was transferred to a 3-L flask and dried *in vacuo* (0.8 mm Hg) for 16 h to give 450 g of a mixture of the desired βs-[Bis(phenylmethyl)amino]-αR-[[(2-methylpropyl)amino]methyl]-benzenepropanol **(10a)** and undesired SS diastereomer **10b** as a crude oil. The crude 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) Rf = 0.28, HPLC analysis: Altex ultrasphere ODS column, 25% triethylamine-/phosphate buffer pH 3/acetonitrile, flow rate 1 mL/min, UV detector; retention time 7.49 min. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (d, 6H, J = 6.64), 1.68 (m, 1H), 2.33 (dd, 1H, J = 11.6, 6.76), 2.41 (dd, 1H, J = 11.6, 6.96), 2.47 (dd, 1H, J = 12.0, 9.26), 2.77 (dd, 1H, J = 12.0, 3.32), 2.86 (m, 1H), 2.98 (dd, 1H, J = 14.2, 5.04), 3.05 (dd, 1H, J = 14.2, 7.95), 3.62 (d, 2H, J = 13.8), 3.69 (d, 2H, J = 13.8), 3.92 (m, 1H), 7.09-7.34 (complex, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.9, 129.6, 128.8, 128.8, 128.2, 128.1, 128.0, 128.1, 126.8, 125.7, 68.7, 62.3 57.3, 54.6, 53.1, 32.6, 28.2, 20.5, 20.5; HRMS calcd for $C_{28}H_{37}N_2O$ (M + 1) 417.616, found 417.2887.

N-[3S-[Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea (11)

A solution of the crude amines **10a** and **10b** (446.0 g, 1.1 mol) in tetrahydrofuran (6 L)[16] was cooled to 8 °C. *Tert* -butyl isocyanate (109.5 g, 1.1 mol) was then added to the solution of the amine from an addition funnel at a rate which maintained the temperature between 10-12 °C. After the addition was complete, the external cooling was stopped and the reaction warmed to 18 °C over 30 min. The solution was concentrated under vacuum at 50 °C. The 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 solution was reduced to 671 mL over 2 h on a rotary evaporator at 50 °C. The concentrate was diluted with 1.6 L of hexane and cooled to 12 °C to crystallize out the desired urea diastereomer. The product was isolated by filtration, washed with 10% ethyl acetate/hexane (1 x 500 mL), hexane (1 x 200 mL) and then dried *in vacuo* (2 mm) at 50 °C for 1 hour to give 248 g of N-[3S-[Bis (phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)-urea (**11**) as an off white solid. 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 (overall yield of **11** from **7**: 49%). Analytical data for the first crop of **11**: Mp 126 °C; $[\alpha]_D^{25}$ = -59.0 ° (c = 1.0, CH_2Cl_2), TLC (silica gel, 25% ethyl acetate/hexane) Rf=0.31 , ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 6.60), 0.92 (d, 3H, J = 6.59), 1.31 (s, 9H), 1.83 (m, 1H), 2.78-2.90 (complex, 3H), 3.00-3.06 (complex, 3H), 3.48 (dd, 1H, J = 14.8, 9.89), 3.65 (d, 2H, J = 14.1), 3.70 (d, 2H, J = 14.1), 3.97 (m, 1H), 4.48 (s, 1H), 4.75 (d, 1H, J = 3.34), 7.10-7.30 (complex, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 141.5, 139.9, 129.7, 128.7, 128.2, 126.9, 125.7, 71.6, 62.5, 56.6, 54.7, 53.9, 50.9, 32.1, 29.5, 28.1, 20.5, 20.3.

An analytical sample of the undesired minor diastereomer, N-[3S-[bis(phenylmethyl)-amino]-2S-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethylethyl)-N-(2-methylpropyl)urea was isolated by silica-gel chromatography (10-15% ethyl acetate/hexane) in an earlier experiment and characterized. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, 6H, J = 6.59), 1.26 (s, 9H), 1.69 (m, 1H), 2.68-2.79 (complex, 3H), 2.82-2.91 (complex, 2H), 3.16 (dd, 1H, J =13.7, 5.67), 3.32 (dd, 1H, J = 15.3, 8.34), 3.41 (d, 2H, J = 13.2), 3.64 (m, 1H), 3.99 (d, 2H, J = 13.2), 5.10 (br s, 1H), 5.26 (br s, 1H), 7.20-7.35 (complex, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 139.9, 138.9, 129.2, 129.1, 128.7, 128.6, 128.4, 127.2, 126.3, 71.7, 61.7, 55.8, 54.2, 53.8, 50.2, 32.1, 29.4, 27.6, 20.2, 20.0; HRMS calcd for $C_{33}H_{46}N_3O_2$ (M+1) 516.749, found 516.3591.

N-(3S-Amino)-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methyl-propyl)urea (6)

N-[3S-[Bis(phenylmethyl)amino]-2R-hydroxy-4-phenylbutyl]-N'-(1,1-dimethylethyl)-N-(2-methylpropyl)urea **11** (125.77 g, 0.244 mol) was dissolved in ethanol (1.5 L) and 20% palladium hydroxide on carbon (18.87 g) was added to the solution under nitrogen. The mixture was stirred at ambient temp under a hydrogen atmosphere at 60 psi for 8 h. The cataylst 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-methyl-propyl)urea (**6**) as a colorless oil. The proton and carbon NMR spectra of this material were in agreement with the spectra of a reference standard prepared from the chloromethylketone in Scheme I. ^{1}H NMR (400 MHz, CD_3OD) δ 0.87 (d, 3H, J = 6.61), 0.88 (d,3H, J = 6.61), 1.31 (s, 9H), 1.93 (m, 1H), 2.59 (dd, 1H, J = 13.6, 8.79), 2.95-3.06 (complex, 3H), 3.15 (dd, 1H, J = 14.3, 7.99), 3.30-3.42 (complex, 2H), 3.67 (m, 1H), 7.20-7.33 (complex, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.0, 139.0, 130.3, 129.6, 127.5, 74.8, 57.2, 56.2, 52.1, 39.2, 29.7, 28.5, 20.5, 20.3.

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REFERENCES AND FOOTNOTES

1. Ratner, L.; Haseltine, W.; Patarca, R.; Livak, K.J.; Starcich, B; Josephs, S. F.; Doran, E. R.; Rafalski, J. A.; Whitehorn, E. A.; Baumister, K.; Ivanoff, L.; Petteway, Jr. S. R.; Pearson, M.L.; Lautenberger, J. A.; Papas, T. S.; Ghrayeb, J.; Chang, N.T.; Gallo, R.

C.; Wong-Stahl, F. Complete nucleotide Sequence of the AIDS virus, HTLV-III. *Nature*, **1985**, *313*, 277.

2. Huff, J. R., *J. Med. Chem.*, 1991, *34*, 2305 and references cited therein.

3. (a) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M.L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R.A. *J. Med. Chem*, **1993**, *346*, 288; (b) Krohn, A.; Redshaw, S.; Ritchie, J. C.; Graves, B. J.; Hatada, M. H. *J. Med. Chem*, **1991**, *34*, 3340; (c) Roberts, N. A.; Martin, J. A.; Kinnchington, D.; Broadhurst, A. V.; Craig, C.; Duncan, I.B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.;Redshaw, S.; Ritchie, A.J.; Taylor, D. L.; Thomas, G. J.; Machlin, P. J. *Science*, **1990**, *248*, 358.

4. (a) Albeck, A.; Persky, R. *Tetrahedron*, 1994, 50, 6333. (b) Barluenga, J.; Baragana, B.; Alonso, A.; Concellon, J.M. *J. Chem. Soc., Chem. Commun.*, **1994**, 969. (c) Barrish, J.C.; Gordon, E.; Alam, M.; Lin, P.F.; Bisacchi, G.S.; Chen, P.; Cheng, P.T.; Fritz,A.; Greytok, J.A.; Hermsmeier, M.A.; Humphreys, W.G.; Lis, K.A.; Marella, M.A.; Merchant, Z.; Mitt, T.; Morrison, R.A,; Obermeier, M.T.; Pluscec, J.; Skoog, M.; Slusarchyk, W.A.; Spergel, S.H.; Stevenson, J.M.; Sun, C.; Sundeen, J.E.; Taunk, P.; Tino, J.A.; Warrack, B.A.; Colonno, R.J.; Zahler, R. *J. Am. Chem. Soc.* **1994**, *37*, 1758. (d) Gurjar, M.K.; Devi,N.R. Tetrahedron: Asymmetry, 1994, 5, 755. (e) Parkes, K.E.B.; Bushnell, D.J.; Crackett, P.H.; Dunsdon, S.J.; Freeman, A.C.; Gunn, M.P.; Hopkins, R.A.; Lambert, R.W.; Martin, J.A.; Merrett, J.H.; Redshaw, S.; Spurden, W.C.; Thomas, G.J. *J. Org. Chem.*, 1994, *59*, 3656. (f) Pegorier, L.; Petit, Y.; Larcheveque, M. J. Chem. Soc., Chem. Commun., 1994, 633. (g) Sasai, H.; Kim, W.S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett*, 1994, *35*, 6123. (h) Shum, W.P.; Chen, J.; Cannarsa, M.J.; *Chirality*, 1994, *6*, 681. (i) Bennett, F.; Girijavallabhan, V.M.; Patel, N. *J. Chem. Soc., Chem Commun.*, 1993, 737 (j) Thompson, W.J.; Ghosh, A.K.; Holloway, M.K.; Lee, H.Y.; Munson, P.M.; Schwering, J.E.; Wai, J.; Darke, P.L.; Zugay, J.; Emini, E.A.; Schleif, W.A.; Huff, J.R.; Anderson, P.S. *J. Am. Chem. Soc.*, 1993, *115*, 801. (k) Askin, D.; Wallace, M.A.; Vacca, J.P.; Reamer, R.A.; Volante, R.P.; Shinkai, I. *J. Org. Chem.*, **1992**, 2771 (l) Ghosh, A.K.; McKee, S.P.; Lee, H.Y.; Thompson, W.J. *J. Chem. Soc., Chem Commun.*, **1992**, 273. (m) Luly, J.R.; Dellaria, J.F.; Plattner, J.J.; Soderquist, J.L.; Yi,N. *J. Org. Chem.*, **1987**, *52*, 1487. (n) Evans, B.E.; Rittle, K.E.; Homnick, C.F.; Springer, J.P.; Hirshfield, J.; Veber, D.F. *J. Org. Chem.*, 1985, *50*, 4615.

5. The chloromethylketone intermediate (1) can be purchased from BACHEM at \$1200-1600/kg on a contracted basis, however, this high cost could make the use of this starting material on large scale synthesis cost-prohibitive.

6. (a) Reetz, M.T., Drewes, M. W and Schmitz, A., *Angew Chem.*,**1987**, *99*, 1186; *Angew Chem.. Int. Ed. Engl.*,**1987**, *26*, 1141; (b) Drewes, M. W., PhD Thesis, der Phillipps-Universitat Marburg/Lahn, **1988**.

7. L-Phenylalaninol can be purchased from many bulk suppliers such as Newport Synthesis Ireland Ltd, Nutrasweet Company (US) or Degussa (Germany) in multikilogram quantities.

8. Swern, D., *J. Org. Chem.*, **1978**, *43*, 2480.

9. Parikh, J., Doering, W., *J. Am. Chem. Soc.*, **1967**, *89*, 5505.

10. Reetz, M.T., Drewes, M. W., Harms and W. Reif *Tetrahedron Lett*, **1988**, *29*, 3295.

11. Matteson, D.S., Michnick, T.J., *SYNLETT.*, **1991**, 631 and the references therein.

12. The first preparation of chiral functionalised ketones and epoxides was reported during the preparation of this manuscript. Barleunga, J.; Baragana, B.; Alonso, A.; Concellon, J. . *J. Chem. Soc., Chem. Comm.*, 1994, 969.

13. Structures were confirmed by NMR analysis of reaction products after purification by chromatography.

14. The diastereomeric ratio was determined by both proton NMR and HPLC analyses.

15. The yields of the mixture of epoxides (9a + 9b) in the crude reaction mixture were assayed to be approximately 85 % by quantititative HPLC analysis. The yields of the isolated epoxides might be lower due decompositon during chromatography.

16. Methylene chloride or ethyl acetate can be substituted for tetrahydrofuran.

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