Enantiopure Preparation of the Two Enantiomers of the Pseudo-C_2-Symmetric *N*,*N*-Dibenzyl-1,2:4,5-diepoxypentan-3-amine

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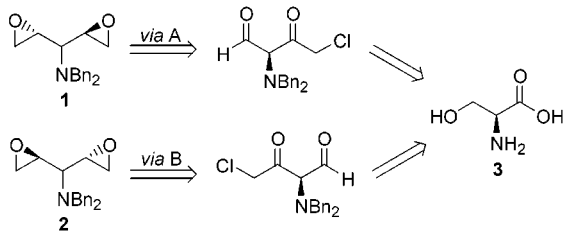
Introduction

The enantioselective synthesis of organic compounds with C_2 symmetry and pseudosymmetry has received much attention due to the applications of these molecules both as chiral ligands,[1] to prepare chiral catalysts,[2] and as a core unit of pseudopeptide HIV protease inhibitors and other bioactive compounds.[3] Among the numerous compounds with C_2 symmetry that have been prepared in recent years,[4] to the best of our knowledge, only an example of symmetrically substituted 3-amino-2,4-diols has been described.[5]

Scheme 1. Retrosynthetic Analysis



Recently, we have reported some synthetic applications of halomethyllithium in the preparation of enantiopure 1-aminoalkyl chloromethyl ketones[6] and aminoepoxides[6b] starting from α-amino esters and α-amino aldehydes, respectively. Furthermore, we have also described some synthetic applications of these α-amino α′-chloro ketones.[6b,7] On the basis of this methodology, we wish to report here an enantiopure preparation of the pseudo-C_2-symmetric (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1** and **2**, respectively (Scheme 1). Retrosynthetic analysis (Scheme 1) suggested that **1** and **2** could be obtained from the same starting product **3**, assuming that the formation of each oxirane ring comes from the sequential addition of two different nucleophiles, hydride and halomethyllithium, to the corresponding to theoretical ester function of the starting compound. Thus, depending on the order of addition, the two oxirane rings of both enantiomers **1** (via A) and **2** (via B) could be obtained. Compounds **1** and **2** could be used to obtain amino diols such as 3-amino-2,4-diols and 1,3,5-triamino-2,4-diols in enantiomerically pure form.[8] In both proposed synthetic routes to the bis-epoxides **1** and **2**, other highly functionalized, enantiopure compounds are obtained.

Results and Discussion

The synthesis of (2*R*,4*R*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine **1** from the methyl *N*,*N*-dibenzylated *O*-protected ester **4**,[9] derived from serine **3**, is depicted in Scheme 2. In the first step, treatment of the protected compound **4** with in situ[10] generated chloromethyllithium

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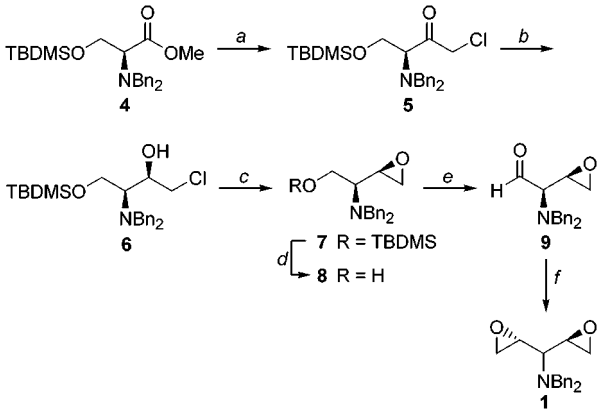
Scheme 2. Synthesis of (2*R*,4*R*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine 1 (via A)[a]



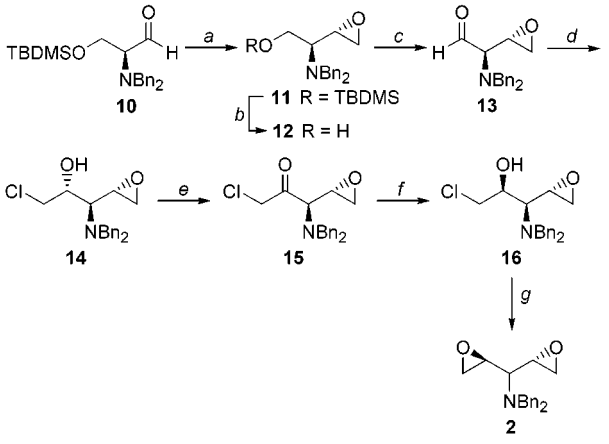
[a] Reagents: (a) [$LiCH_2Cl$], THF, −78 °C, 90%; (b) $LiAlH_4$, THF, −100 °C, 87%; (c) MeLi, THF, −78 °C→rt, 87%; (d) $(NBu_4)F$, THF, 80%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −63 °C, 98%; (f) [$LiCH_2I$], THF, −78 °C→rt, 86%.

at −78 °C (from chloroiodomethane and methyllithium) gave, after hydrolysis, the corresponding chlorinated amino ketone **5** in 90% yield. Reduction of **5** with $LiAlH_4$ at −100 °C afforded the chlorohydrin **6** in 87% yield. Epoxidation of **6** was achieved by lithiation of the hydroxyl group by using methyllithium (87% yield), the diastereoisomeric excess (de) of **7** being >95%. Deprotection of hydroxyl group of **7** with $(NBu_4)F$ and subsequent careful oxidation, under Swern conditions, led to the corresponding amino aldehyde **9** (98% yield from **7**). The final product **1** was obtained in 86% yield and 95% de by iodomethylation of **9** with in situ generated iodomethyllithium at −78 °C (from diiodomethane and methyllithium). The epoxidation of the obtained lithium alcoholate took place spontaneously in these reaction conditions, affording the C_2-pseudosymmetrical bis-epoxide **1**.

On the basis of our earlier studies which examined the nonchelation controlled reduction of chiral α-dibenzylamino α′-chloro ketones and the addition of iodomethyllithium to α-aminoaldehydes,[6b] the absolute configuration of amino diepoxide **1** is believed to be (2*R*,4*R*).[11]

The synthesis of (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine **2** is depicted in Scheme 3. Transformation of α-amino aldehyde **10**[11a] into the amino epoxide **11** by using in situ generated iodomethyllithium at −78 °C (from diiodomethane and methyllithium) was accomplished in 86% yield and with high diastereoselectivity (de = 95%). Desilylation of **11** was achieved by using $(NBu_4)F$, followed by Swern oxidation afforded aldehyde **13**, which was chloromethylated by treatment with in situ generated chlomethyllithium (from chloroiodomethane and methyllithium) affording the corresponding chlorohydrin **14** in 85% yield (from **12**). To obtain the required configuration at the second oxirane ring, **14** was successively oxidized, (Swern oxidation) to the chloroketone **15** (98% yield), and reduced with $LiAlH_4$ at −100 °C (95% yield) affording the appropriate chlorohydrin **16**, which when treated with sodium hydride produced the expected (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine **2** (96% yield and 95% de).

Scheme 3. Synthesis of (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine 2 (via B)[a]



[a] Reagents: (a) [$LiCH_2I$], THF, −78 °C→rt, 86%; (b) $(NBu_4)F$, THF, 97%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −63 °C, 98%; (d) [$LiCH_2Cl$], THF, −78 °C, 85%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −63 °C, 98%; (f) $LiAlH_4$, THF, −100 °C, 95%; (g) NaH, CH_2Cl_2, rt, 96%.

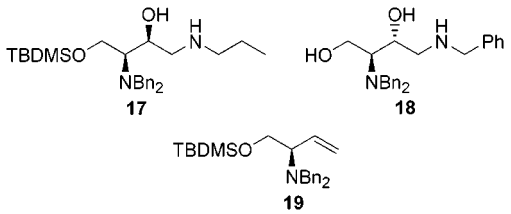


Figure 1. Some synthetic applications of intermediate compounds.

Since all the intermediate compounds (**4**−**9** and **11**−**16**) were obtained with a high degree of purity, except for the products **8** and **12** from the deprotection step, they could be used without further purification. This has allowed the isolation of the bis-epoxides **1** and **2** in high yield.

Synthesis of **1** and **2** proceeded with no detectable racemization. The enantiomeric purity of diepoxides **1** and **2** was determined by chiral HPLC (Chiralcel OD-RH) analysis, showing in both cases an enantiomeric excess (ee) >98%. To exclude the possibility of coelution of both enantiomers, a mixture of **1** and **2** was prepared and analyzed by HPLC.

It is noteworthy that all the carbon atoms of all the intermediate compounds (**3**−**16**) in the two synthetic routes described are functionalized. These functional groups have very different reactivities, and consequently they could be transformed selectively into other compounds. For this reason these compounds could be used as chiral building blocks in the synthesis of enantiopure compounds. To illustrate this potential, amino epoxides **7** and **12** were treated with propylamine and benzylamine, respectively, affording the corresponding diamino compounds **17** (60% yield) and **18** (66% yield) (see Figure 1) with total regioselectivity (300 MHz ^1H NMR), the ring opening being at the less substituted primary carbon. Likewise, **10** was successively treated with in situ gener-

(11) (a) The stereochemistry of **1** is also based upon the study of the addition of organometallics compounds to dibenzylated α-amino aldehydes: Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

ated chloromethyllithium and lithium powder affording the corresponding allylamine **19** (65% yield, based on the aldehyde **10**) in enantiomeric pure form (see Figure 1).[12]

In conclusion, the results reported here represent a synthetic route for the preparation of (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1** and **2**, in enantiomerically pure form, and with good yield. This synthetic route is simple, and the starting material (serine) is easily available. Moreover, other enantiopure highly functionalized compounds have been prepared, and we have shown some synthetic applications of these compounds.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 or 200 MHz. ^{13}C NMR spectra were recorded at 75 or 50 MHz. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$. Only the molecular ions and/or base peaks in MS are given. Optical rotations were measured in $CHCl_3$. The enantiomeric purity was determined by chiral HPLC analysis using a Chiralcel OD-RH (0.46 × 15 cm, Daicel) column. Analytical TLC was conducted in precoated silica gel 60 F-254 on aluminum sheets; compounds were visualized with UV light or iodine. Flash chromatography was carried out on Merck silica gel 60 (230−400 mesh).

DMSO was distilled from CaH_2 and stored over activated 4 Å molecular sieves. Methyl α-amino *O*-protected ester **4** and α-aminoaldehyde **10** were prepared according to literature procedures.[9,11a] All reactions were conducted in oven-dried glassware under dry nitrogen. All solvents were purified before using. THF was distilled from sodium in a recycling still using benzophenone ketyl as indicator; dichloromethane was distilled from P_2O_5.

(−)-(3*S*)-3-(Dibenzylamino)-4-[(*tert*-butyldimethylsilanyl)oxy]-1-chlorobutan-2-one (5). To a −78 °C stirred solution of the methyl α-amino *O*-protected ester **4** (1.29 g, 3.1 mmol) and chloroidomethane (0.45 mL, 6.2 mmol) in dry THF (15 mL) was added methyllithium (4.1 mL of 1.5 M solution in diethyl ether, 6.2 mmol) dropwise over 5 min. After stirring the mixture at −78 °C for 30 min, it was treated with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo, yielding the chloromethyl ketone **5** as a yellowish solid. The crude ketone **5** was reduced without further purification: R_f = 0.46 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D = -56.1$ (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.29 (10 H, m), 4.27 (2 H, AB syst., *J* = 16.2), 4.10 (2 H, dd, *J* = 6.3, 2.0), 3.85 (2 × 2 H, AB syst., *J* = 13.7), 3.67 (1 H, t, *J* = 6.3), 0.95 (9 H, s), 0.14 (3 H, s), 0.12 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5 (C), 138.8 (C), 128.7, 128.3 and 127.2 (3 × CH), 65.2 (CH), 59.9 (CH_2), 55.0 (CH_2), 48.2 (CH_2), 25.7 (CH_3), 17.9 (C), −5.7 (CH_3), −5.8 (CH_3); IR (neat) 1730; MS, *m*/*z* 382.2 ($M^+ - CH_2Cl$, <1), 354.2 (49), 190.0 (31), 147.0 (40), 91.0 (100), 75.0 (55). HRMS Calcd for $C_{24}H_{32}NO_2Si$ ($M - CH_2Cl$)$^+$: 382.2202. Found: 382.2200.

(+)-(2*R*,3*S*)-3-(Dibenzylamino)-4-[(*tert*-butyldimethylsilanyl)oxy]-1-chlorobutan-2-ol (6). To a −100 °C stirred solution of the ketone **5** (1 mmol) in dry THF (5 mL) was added $LiAlH_4$ (0.3 mL of 1.0 M solution in THF, 0.3 mmol). The resulting solution was stirred for 6 h at the same temperature and added to water. The mixture was filtered through a pad of Celite, and the filtrate was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude amino alcohol **6** was used without further purification. The crude product was chromatographed on silica gel (3/1 hexane/ethyl acetate) to provide pure amino alcohol **6**, as a colorless oil, to determinate the optical rotation: R_f = 0.30 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D = +36.0$ (*c* 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.25 (10 H, m), 4.28 (1 H, s), 4.01−3.92 (3 H, m), 3.83 (2 × 2 H, AB syst., *J* = 13.4), 3.71 (1 H, dd, *J* = 11.7, 2.8), 3.50 (1 H, dd, *J* = 11.7, 5.7), 2.92−2.86 (1 H, m) 0.98 (9 H, s), 0.17 (3 H, s), 0.15 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (C), 128.8, 128.3, and 127.1 (3 × CH), 67.9 (CH), 60.6 (CH), 58.9 (CH_2), 54.4 (CH_2), 47.3 (CH_2), 25.6 (CH_3), 17.8 (C), −5.7 (CH_3), −5.8 (CH_3); IR (neat) 3426 (br); MS, *m*/*z* 418.1 ($M^+ - CH_3$, <1), 354.1 (100), 288.0 (33), 91.0 (92). HRMS Calcd for $C_{23}H_{31}ClNO_2Si$ ($M - CH_3$)$^+$: 418.1969. Found: 418.1971.

(+)-(2*R*)-2-{1′(*S*)-(Dibenzylamino)-2′-[(*tert*-butyldimethylsilanyl)oxy]ethyl}oxirane (7). To a −78 °C stirred solution of the amino alcohol **6** (1.16 g, 2.7 mmol) in dry THF (10 mL) was added methyllithium (2.7 mL of 1.5 M solution in diethyl ether, 4.05 mmol). After stirring at 25 °C for 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude epoxide **7** was examined by ^{1}H NMR to give a de >95% and used without further purification. The crude product was chromatographed on silica gel (50/1 hexane/triethylamine) to provide pure epoxide **7**, as a pale yellow oil, to determinate the optical rotation: R_f = 0.41 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D = +13.6$ (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.24 (10 H, m), 3.94 (4 H, s), 3.83−3.81 (2 H, m), 3.23 (1 H, ddd, *J* = 7.0, 4.4, 3.9), 2.77 (1 H, dd, *J* = 5.3, 4.4), 2.67−2.60 (2 H, m), 0.92 (9 H, s), 0.06 (3 H, s), 0.04 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.1 (C), 128.9, 128.3, and 127.0 (3 × CH), 62.5 (CH_2), 60.7 (CH), 55.3 (CH_2), 51.5 (CH), 44.5 (CH_2), 25.7 (CH_3), 17.9 (C), −5.7 (CH_3), −5.8 (CH_3); IR (neat) 3084, 3028. Anal. Calcd for $C_{24}H_{35}NO_2Si$: C, 72.49; H, 8.87; N, 3.52. Found: C, 72.05; H, 8.71; N, 3.48.

(−)-(2*R*)-2-[1′(*S*)-(Dibenzylamino)-2′-hydroxyethyl]oxirane (8). The *tert*-butyldimethylsilyl ether **7** (1 mmol) in THF (10 mL) was stirred with $(Bu_4N)F$ (3 mL of 1 M solution in THF, 3 mmol) at room temperature for 48 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Removal of the solvent followed by purification by flash column chromatography over silica gel (1/1 hexane/ethyl acetate) provided pure compound **8** as a yellowish oil: R_f = 0.20 (hexane/ethyl acetate 3/1); $[\alpha]^{22}_D = -23.1$ (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.29 (10 H, m), 3.93 (2 × 2 H, AB syst., *J* = 13.1), 3.67 (1 H, dd, *J* = 10.5, 10.0), 3.49 (1 H, dd, *J* = 10.5, 5.7), 3.16 (1 H, ddd, *J* = 6.7, 4.1, 2.6), 3.04 (1 H, s), 2.78 (1 H, dd, *J* = 4.8, 4.1), 2.66 (1 H, ddd, *J* = 7.4, 5.4, 2.0), 2.49 (1 H, dd, *J* = 4.8, 2.6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.7 (C), 128.8, 128.2, and 127.0 (3 × CH), 60.9 (CH), 58.1 (CH_2), 54.0 (CH_2), 49.3 (CH), 43.5 (CH_2); IR (neat) 3427 (br); MS, *m*/*z* 283.1 (M^+, 5), 252.1 (18), 181.1 (8), 91.0 (100). HRMS Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1573.

(2*S*, 3*R*)-2-(Dibenzylamino)-3,4-epoxybutanal (9). A solution of dry DMSO (0.50 mL, 7.04 mmol) in dry CH_2Cl_2 (2.8 mL) was added dropwise to a −63 °C solution of oxalyl chloride (0.31 mL, 3.52 mmol) in dry CH_2Cl_2 (2.8 mL) over 10 min. The mixture was stirred at the same temperature for 5 min, and a solution of the epoxyalcohol **8** (3.2 mmol) in dry CH_2Cl_2 (23 mL) was added within 10 min. The reaction was stirred for an additional 20 min and then treated dropwise with triethylamine (1.4 mL, 16 mmol) in CH_2Cl_2 (5 mL) over 15 min. The mixture was stirred for another 30 min. Water was then added, and the aqueous layer was reextracted with additional CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with saturated NaCl solution (50 mL), and dried over Na_2SO_4. The solvents were removed in vacuo, yielding the α-aminoaldehyde **9** as an orange oil, which were used without further purification. Due to instability of the epoxyaldehyde **9**, it was characterized by NMR spectroscopy: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.60 (1 H, s), 7.45−7.24 (10 H, m), 3.92 (4 H s), 3.34 (1 H, ddd, *J* = 7.4, 4.3, 2.6), 2.97 (1 H, d, *J* = 7.4), 2.89 (1 H, dd, *J* = 4.6, 4.3), 2.48 (1 H, dd, *J* = 4.6, 2.6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 201.2 (C), 138.4 (C), 128.8, 128.2 and 127.2 (3 × CH), 69.4 (CH), 55.6 (CH_2), 48.3 (CH), 43.8 (CH_2).

(−)-(2*R*,4*R*)-*N*,*N*-Dibenzyl-1,2:4,5-diepoxypentan-3-amine (1). To a −78 °C stirred solution of α-aminoaldehyde **9** (3.2 mmol) and diidomethane (0.77 mL, 9.6 mL) in dry THF (10 mL) was added methyllithium (6.4 mL of 1.5 M solution in diethyl ether, 9.6 mmol) dropwise over 5 min. After stirring the mixure at −78 °C for 30 min, it was allowed to warm to room temperature. Stirring was continued for 1 h, and then the

(12) The enantiomeric purity of the allylamines prepared by using this methodology was determined by chiral HPLC (Chiralcel OD-H) analysis: Concellón, J. M.; Baragaña, B.; Riego, E. *Tetrahedron Lett.* **2000**, *41*, 4361.

reaction was hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude bis-epoxide **1** was examined by ^1H NMR to give a de = 95%. The crude product was chromatographed on silica gel, which was saturated with triethylamine (3/1 hexane/ethyl acetate) to provide pure bis-epoxide **1** as a yellowish oil: $R_f = 0.35$ (hexane/ethyl acetate 5/1); $[\alpha]^{22}_D = -2.9$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.22 (10 H, m), 3.96 (2 × 2 H, AB syst., $J = 13.7$), 3.31−3.26 (1 H, m), 3.14−3.10 (1 H, m), 2.78 (1 H, dd, $J = 5.1, 4.3$), 2.71 (1 H, dd, $J = 4.8, 4.0$), 2.53 (1 H, dd, $J = 5.1, 2.8$), 2.48 (1 H, dd, $J = 5.1, 2.8$), 2.27 (1 H, dd, $J = 7.7, 5.4$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5 (C), 128.5, 128.0, and 126.8 (3 × CH), 62.0 (CH), 55.3 (CH_2), 51.9 (CH), 50.0 (CH), 45.2 (CH_2), 43.8 (CH_2); IR (neat) 3064, 3029; MS, *m*/*z* 295.1 (M^+, <1), 252.1 (83), 91.0 (100). HRMS Calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1577. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.29; H, 7.10; N, 4.68. Chiral HPLC analysis ee >98% (Chiralcel OD-RH, UV detector 210 nm, 0.5 mL/min, 65/35 acetonitrile/water, t_R 17.6 min).

(+)-(2*S*)-2-{1′(*S*)-(Dibenzylamino)-2′-[(*tert*-butyldimethylsilanyl)oxy]ethyl}oxirane (11). This product was prepared following the procedure to obtain **1**, but starting from **10** instead of **9**, and the epoxide **11** was isolated as a pale yellow oil. The crude epoxide **11** was examined by ^1H NMR to give a de = 95%: $R_f = 0.48$ (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D = +16.6$ (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.26 (10 H, m), 3.98−3.85 (6 H, m), 3.21−3.17 (1 H, m), 2.80 (1 H, dd $J = 5.3, 4.3$), 2.71−2.65 (1 H, m), 2.60 (1 H, dd, $J = 5.3, 2.7$), 1.02 (9 H, s), 0.16 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (C), 128.3, 127.9, and 126.6 (3 × CH), 60.8 (CH_2), 60.2 (CH), 55.0 (CH_2), 50.7 (CH), 45.7 (CH_2), 25.7 (CH_3), 17.9 (C), −5.7 (CH_3), −5.8 (CH_3); IR (neat) 3062, 3028; MS, *m*/*z* 397.2 (M^+, <1), 354.2 (10), 252.1 (100), 91.0 (89). HRMS Calcd for $C_{24}H_{35}NO_2Si$: 397.2437. Found: 397.2442.

(−)-(2*S*)-2-[1′(*S*)-(Dibenzylamino)-2′-hydroxiethyl]oxirane (12). This product was prepared following the procedure to synthesize **8**, but starting from **11**. The amino epoxide **12** was isolated as a yellowish oil: $R_f = 0.23$ (hexane/ethyl acetate 3/1); $[\alpha]^{22}_D = -43.8$ (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.26 (10 H, m), 3.89 (2 × 2 H, AB syst., $J = 13.6$), 3.79−3.69 (1 H, m), 3.63 (1 H, dd, $J = 11.0, 5.1$), 3.18 (1 H, ddd, $J = 5.4, 4.9, 2.6$), 2.86 (1 H, dd, $J = 4.9, 4.6$), 2.86−2.76 (1 H, m), 2.61 (1 H, dd, $J = 4.6, 2.6$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.8 (C), 128.6, 128.4, and 127.2 (3 × CH), 59.5 (CH), 58.2 (CH_2), 54.2 (CH_2), 49.0 (CH), 45.1 (CH_2); IR (neat) 3425 (br). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.98; H, 7.59; N, 4.81.

(2*S*, 3*S*)-2-(Dibenzylamino)-3,4-epoxybutanal (13). This product was prepared following the procedure to prepare **9**, but starting from **12**, and isolated as an orange oil. Due to instability of the epoxyaldehyde **13**, it was characterized by NMR spectroscopy: ^1H NMR ($CDCl_3$, 200 MHz) δ 9.79 (1 H, s), 7.48−7.27 (10 H, m), 3.99 (2 × 2 H, AB syst., $J = 13.8$), 3.32 (1 H, ddd, $J = 5.4, 3.8, 2.8$), 3.17 (1 H, d, $J = 5.4$), 2.88 (1 H, dd, $J = 4.9, 3.8$), 2.66 (1 H, dd, $J = 4.9, 2.8$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200. 9 (C), 138.3 (C), 128.3, 128.2, and 127.2 (3 × CH), 67.5 (CH), 55.2 (CH_2), 48.1 (CH), 44.5 (CH_2).

(2*R*, 3*S*, 4*S*)-3-(Dibenzylamino)-1-chloro-4,5-epoxypentan-2-ol (14). This product was prepared following the procedure to obtain **5**, but starting from **13**. The crude chlorohydrin **14** was used without further purification: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44−7.18 (10 H, m), 4.24−4.19 (1 H, m), 3.84 (2 × 2 H, AB syst., $J = 14.0$), 3.81−3.75 (2 H, m), 3.36 (1 H, ddd, $J = 7.4, 4.4, 2.8$), 2.88 (1 H, dd, $J = 5.1, 4.4$), 2.68 (1 H, dd, $J = 5.1, 2.8$), 2.44 (1 H, dd, $J = 7.4, 6.0$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8 (C), 128.4, 128.2, and 127.0 (3 × CH), 71.4 (CH), 61.2 (CH), 55.1 (CH_2), 48.9 (CH), 48.6 (CH_2), 45.5 (CH_2).

(+)-(3*S*, 4*S*)-3-(Dibenzylamino)-1-chloro-4,5-epoxypentan-2-one (15). This product was prepared by oxidation of **14** following the procedure to prepare **9**, and isolated as an orange oil: $R_f = 0.36$ (hexane/ethyl acetate 5/1); $[\alpha]^{22}_D = +36.4$ (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.27 (10 H, m), 4.34 (2 H, AB syst., $J = 16.4$) 3.87 (2 × 2 H, AB syst., $J = 14.0$), 3.37 (1 H, ddd, $J = 8.3, 3.5, 2.6$), 3.03 (1 H, d, $J = 8.3$), 2.96 (1 H, dd, $J = 5.2, 3.5$), 2.62 (1 H, dd, $J = 5.2, 2.6$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.3 (C), 138.0 (C), 128.5, 128.4, and 127.5 (3 × CH), 67.5 (CH), 55.3 (CH_2), 47.5 (CH_2), 47.4 (CH), 46.6 (CH_2); IR (neat) 1736. Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.05; H, 6.14; N, 4.30. HRMS Calcd for $C_{19}H_{20}NO_2Cl$: 329.1182. Found: 329.1187.

(−)-(2*S*,3*S*,4*S*)-3-(Dibenzylamino)-1-chloro-4,5-epoxypentan-2-ol (16). This product was prepared following the procedure to obtain **6**, but starting from **15**, and isolated as a yellowish oil: $R_f = 0.35$ (hexane/ethyl acetate 3/1); $[\alpha]^{22}_D = -2.4$ (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.28 (10 H, m), 4.17−4.03 (1 H, m), 3.89 (2 × 2 H, AB syst., $J = 13.3$), 3.91−3.79 (2 H, m), 3.54 (1 H, dd, $J = 11.3, 6.7$), 3.13 (1 H, ddd, $J = 6.7, 3.8, 2.8$), 2.99 (1 H, dd, $J = 4.9, 3.8$), 2.73 (1 H, dd, $J = 4.9, 2.8$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9 (C), 128.5, 128.4, and 127.3 (3 × CH), 70.2 (CH), 61.5 (CH), 54.6 (CH_2), 47.9 (CH), 47.5 (CH_2), 46.1 (CH_2); IR (neat) 3356 (br). HRMS Calcd for $C_{19}H_{22}NO_2Cl$: 331.1339. Found: 331.1312.

(+)-(2*S*,4*S*)-*N*,*N*-Dibenzyl-1,2:4,5-diepoxypentan-3-amine (2). To a stirred solution of the amino alcohol **16** (0.33 g, 1 mmol) in CH_2Cl_2 (5 mL) was added NaH (0.24 g, 10 mmol). After stirring at room temperaure for 1 h, the reaction was carefully quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude bis-epoxide **2** was examined by ^1H NMR to give a de = 95%. The product was chromatographed on silica gel, which was saturated with triethylamine, (3/1 hexane/ethyl acetate) to provide pure bis-epoxide **2** as a yellowish oil: $[\alpha]^{22}_D = +3.2$ (*c* 0.73, $CHCl_3$). Chiral HPLC analysis ee >98% (Chiralcel OD-RH, UV detector 210 nm, 0.5 mL/min, 65/35 acetonitrile/water, t_R 13.2 min).

General Procedure for Ring Opening of the Amino Epoxides 7 and 12. To a solution of the corresponding amino epoxide **7** or **12** (0.5 mmol) and $LiClO_4$ (0.05 g, 0.5 mmol) in acetonitrile (1 mL) was added the corresponding amine (0.6 mmol), and the reaction mixture was stirred at room temperature. The reaction was followed by TLC. Then, water was added and the mixture was extracted with diethyl ether (3 × 5 mL). Removal of the solvents followed by purification by flash column chromatography over silica gel (1/1 hexane/ethyl acetate) provided pure compounds **17** and **18**, as pale yellow oils.

(+)-(2*S*,3*S*)-3-(Dibenzylamino)-4-[(*tert*-butyldimethylsilanyl)oxi]-1-propylaminobutan-2-ol (17). $R_f = 0.20$ (ethyl acetate); $[\alpha]^{22}_D = +13.3$ (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.26 (10 H, m), 3.95−3.83 (3 H, m), 3.87 (2 × 2 H, AB syst., $J = 13.5$), 2.83−2.46 (2 H, m), 2.62−2.46 (3 H, m), 1.55−1.43 (2 H, m), 1.02 (9 H, s), 0.92 (3 H, t, $J = 7.2$), 0.18 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.2 (C), 129.1, 128.3, and 127.0 (3 × CH), 66.7 (CH), 61.5 (CH), 59.8 (CH_2), 54.5 (CH_2), 53.0 (CH_2), 51.5 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.0 (C), 11.6 (CH_3), −5.6 (CH_3), −5.7 (CH_3); IR (neat) 3364 (br). HRMS Calcd for $C_{27}H_{44}Si\,N_2O_2$: 456.3172. Found: 456.3153.

(−)-(2*S*,3*R*)-2-(Dibenzylamino)-4-benzylaminobutan-1,3-diol (18). $R_f = 0.14$ (ethyl acetate); $[\alpha]^{22}_D = -6.6$ (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.26 (15 H, m), 4.02−3.94 (2 H, m), 3.91 (1 H, dd, $J = 11.4, 6.3$), 3.72 (2 H, s), 3.71 (2 × 2 H, AB syst., $J = 13.7$), 2.88 (1 H, dd, $J = 12.2, 3.7$), 2.66−2.56 (2 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4 (C), 139.2 (C), 128.7, 128.3, 128.2, 128.1, 127.1, and 126.9 (6 × CH), 69.0 (CH), 60.5 (CH), 58.9 (CH_2), 54.5 (CH_2), 53.4 (CH_2), 52.1 (CH_2); IR (neat) 3368 (br). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.71; H, 7.82; N, 7.15. HRMS Calcd for $C_{25}H_{30}N_2O_2$: 390.2307. Found: 390.2231.

(+)-(*S*)-*N*,*N*-Dibenzyl-1-[(*tert*-butyldimethylsilanyl)oxy]-but-3-en-2-amine (19). To a −78 °C stirred solution of the α-amino aldehyde **10** (0.39 g, 1.02 mmol) and chloroidomethane (0.22 mL, 3.06 mmol) in dry THF (5 mL) was added methyllithium (2.0 mL of 1.5M solution in diethyl ether, 3.06 mmol) dropwise over 5 min. After stirring at −78 °C for 30 min, lithium powder (0.07 g, 10.2 mmol) was added and the reaction mixture was stirred at for 8 h −40 °C. The reaction was hydrolyzed with ice, and after the usual workup, crude allylamine **19** was obtained. Flash column chromatography over silica gel (20/1 hexane/ethyl acetate) provided pure allylamine **19** as a pale yellow oil: $R_f = 0.29$ (hexane/ethyl acetate 20/1); $[\alpha]^{22}_D = +5.5$ (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.26 (10 H, m), 5.95 (1 H, ddd, $J = 17.4, 10.5, 6.5$), 5.38 (1 H, d, $J = 10.5$), 5.26 (1 H, d, $J = 17.4$), 3.83 (2 H, dd, $J = 10.4, 6.5$), 3.77 (2 × 2 H, AB syst., $J = 14.3$), 3.32 (1 H, q, $J = 6.5$), 0.97 (9 H, s), 0.09

(6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.4 (C), 134.7, 128.4, 127.9, and 127.9 (4 × CH), 118.2 (CH_2), 64.3 (CH_2), 61.9 (CH), 54.3 (CH_2), 25.8 (CH_3), 18.1 (C), −5.5 (CH_3), −5.6 (CH_3); IR (neat) 1603. Anal. Calcd for $C_{24}H_{35}NO$: C, 75.53; H, 9.24; N, 3.67. Found: C, 75.71; H, 9.26; N, 3.65.

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Supporting Information Available: Copies of ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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