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A Stereoselective Synthesis of the Dihydroxyethylene Dipeptide Isostere, A-82768

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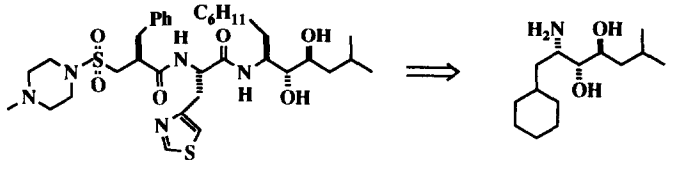
Abstract: A stereocontrolled synthesis of the dihydroxyethylene dipeptide isostere, A-82768, **1** via an *erythro*-selective addition of a Grignard reagent to a *cis* α,β-epoxy aldehyde is described. The resulting *erythro*-epoxy alcohol was converted to the desired 3-amino-1,2-diol in a two step sequence which made use of a regioselective azide addition reaction. Procedures for the resolution of racemic **1** as well as the enantiomeric purification of scalemic **1** are also presented.

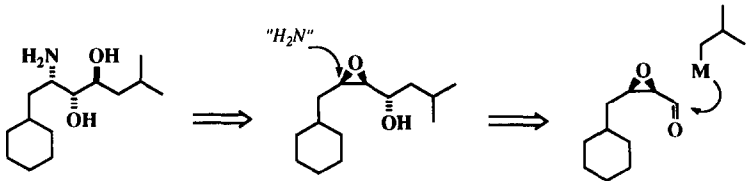


A-72517 A-82768 (1)

As part of a process research project in these laboratories, we required an efficient, stereoselective synthesis of the dihydroxyethylene dipeptide isostere subunit, A-82768 (**1**), of the orally active renin inhibitor A-72517.[2] Although **1** has been the subject of a number of synthetic studies,[3] issues of raw material availablity and cost rendered none of the previous approaches completely satisfactory for our purposes. In response to this need, we developed the following α,β-epoxy aldehyde based preparation of **1** which utilizes commercially available reagents, requires no chromatography, makes no use of protecting groups, and provides highly enantiomerically and diastereomerically enriched (>99%) material.

This paper is dedicated to Dr. James L. Krysan on the occasion of his 60th Birthday.

Scheme 1.

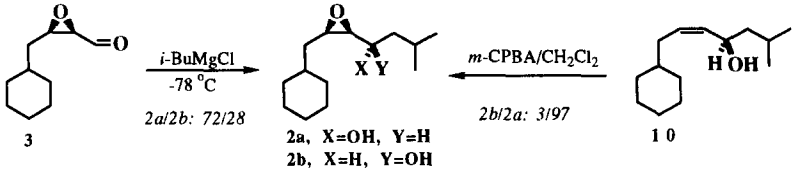


1 2 3

Retrosynthetic analysis of **1** (Scheme 1) led us to consider construction of the (1*S*, 2*R*, 3*S*)-3-amino-1,2-diol framework through the regioselective addition of a nitrogen nucleophile to the *cis*-epoxy alcohol **2**.[4] **2**, in turn, was envisioned to arise from the Felkin-Ahn[5] controlled addition of an isobutyl nucleophile to the corresponding α,β-epoxy aldehyde **3**.[6] The epoxy aldehyde **3** appeared to be readily available in enantio-enriched form starting with inexpensive materials through the application of standard synthetic methodology

The 2,2,6,6-tetramethylpiperidinyloxy free radical (TEMPO)-catalyzed oxidation of 2-cyclohexylethanol **4** served as our point of departure (Scheme 2) and provided the corresponding aldehyde **5** in excellent yield.[7] In a sequence analogous to that recently reported by Piers and co-workers,[8] application of the Corey-Fuchs alkyne synthesis proceeded uneventfully to give the propargylic alcohol **7** in 87% overall yield from **4** on a 1.0 mole scale.[9] **7** was smoothly reduced to the (*Z*)-allylic alcohol **8** in near quantitative yield (>95%) with less than 5% contamination by the (*E*) isomer.

At this point, both racemic and enantioselective epoxidations were examined. The treatment of **8** with magnesium monoperoxypthalate (MMPP)[10] provided racemic **9** in 88% yield while (2*S*, 3*R*)-**9** (59%, unoptimized) was obtained by Sharpless asymmetric epoxidation (A.E.).[11] Oxidation of **9** under modified Parikh-Doering conditions[12, 6d] generated the sensitive α,β-epoxy aldehyde **3** which was used immediately after work-up.

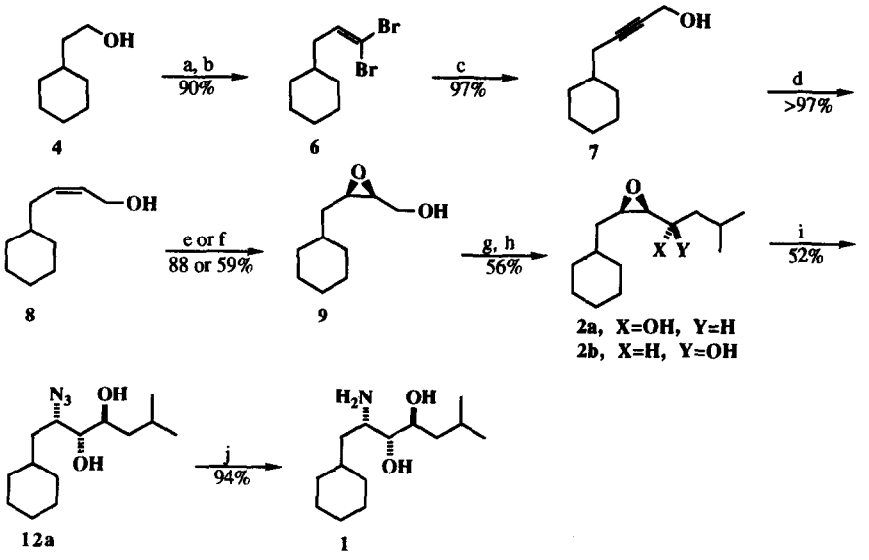


3 **2a**, X=OH, Y=H; **2b**, X=H, Y=OH 1 0 (1)

Treatment of **3** with *i*-butylmagnesium chloride at –78°C effected the crucial *i*-butyl addition and led to a 72/28 mixture of diastereomeric epoxy alcohols in moderate (60-65% for two steps) yield based on epoxy alcohol **9**. The major diastereomer was assigned the desired *erythro* stereochemistry based upon ^{1}H NMR and gas chromatographic (GC) comparison of the crude reaction mixtures to the authentic *threo* isomer **2b**, obtained by *m*-chloro-peroxybenzoic acid oxidation of the corresponding (*Z*)-allylic alcohol **10**.[13] This stereochemistry was subsequently

confirmed by conversion of **2a** to **1**. The Felkin-Ahn controlled, *erythro* selective nature of the Grignard addition was consistent with literature precedent as was the level of diastereocontrol.[6d]

Scheme 2.



Reagents and Conditions: (a) TEMPO, NaBr, 5% NaOCl, aq. $NaHCO_3/CH_2Cl_2$, 5°C. (b) Ph_3P, CBr_4, CH_2Cl_2, room temperature (c) *i. n-BuLi*, 4:1 THF/hexane, 0°C; *ii.* $(CHO)_n$, 0°C to room temperature. (d) H_2 (5 psi), 5% $Pd/BaSO_4$, hexane, room temperature. (e) MMPP, 9:1 MeOH/H_2O, room temperature. (f) Ti(O-*i*-Pr)4, (*R*, *R*)-DIPT, *t*-BuOOH, 4A M.S., CH_2Cl_2, –20°C. (g) Pyr-SO_3, Et_3N, 5:1 CH_2Cl_2/DMSO, 0°C. (h) *i*-BuMgCl, 2:1 Et_2O/THF, –78°C to 0°C. (i) NaN_3, NH_4Cl, 8:1 MeOH/H_2O, reflux. (j) H_2 (20 psi), 5% Pd/C, MeOH, room temperature.

Curiously, allowing the reaction mixture to warm to 0°C led to an improved 82/18 ratio of diastereomers in a slightly reduced yield of 56% (eq. 2). This initially surprising observation was apparently the result of a selective, magnesium halide-mediated (*vide infra*) conversion of the undesired *threo* isomer **2b** to a compound tentatively assigned as a chlorohydrin of **2b** (**11**).[14] Since the highly insoluble **11** could be readily removed from the oily mixture of **2a,b** by filtration of an ethyl acetate/heptane solution of the crude product, a partial diastereomeric enrichment was easily accomplished and the conversion of **9** to **2a,b** was routinely performed in this manner.

With **2** in hand, we turned to regioselective introduction of a suitable ammonia synthon to the C.3 position of the epoxide. As literature precedent suggested,[15] this was easily executed by reacting **2** with a mixture of sodium azide and ammonium chloride in refluxing methanol/water (8/1). Under these conditions, a 65% yield of two diastereomeric azido-diols **12a,b** was obtained;

no evidence of C.2 azides could be found by ^{1}H NMR or GC-MS. The desired (2*S*, 3*R*, 4*S*) (*vide infra*) epimer **12a** was obtained diastereomerically pure (>95% by ^{1}H NMR) by crystallization from hot heptane (2 crops, 80% of theory, 52% yield of single diastereomer based on **2a,b**).

Completion of the synthesis was achieved by catalytic reduction of the azide to amino-diol **1** (94%),[16] obtained as a diastereomerically pure (>98% by HPLC, GC and ^{1}H NMR) white crystalline solid following crystallization from ethanol/water. In the non-racemic series, a somewhat disappointing enantiomeric excess (ee) of only 70% was obtained for **1** (based upon chiral HPLC analysis). Since (*Z*)-allylic alcohols are not ideal substrates for the Sharpless A.E.,[17] this result was not completely unexpected. Fortunately, formation of a tartrate salt of either racemic or enantiomerically enriched **1** followed by crystallization from acetone efficently (>95% recovery) provided either enantiomer with an ee of >99 % by chiral HPLC assay.

In conclusion, we have developed a stereocontrolled synthesis of **1** which makes no use of either chiral pool synthons or protecting groups and which employs commercially available reagents and materials. The route is reasonably short (10 steps, including resolution) and efficient (13% overall yield via Sharpless A.E. and 10% via resolution) and has been executed on a multi-gram scale. Also, the conceptual features of this synthesis could easily be adapted to other substitution patterns about the central amino-diol framework and, consequently, this strategy should represent a general entry into this important class of molecules.

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EXPERIMENTAL

General. All reactions were carried out under a nitrogen atmosphere in heat-gun dried glassware. Solvents and reagents were obtained from commercial sources and were used as received. Reaction temperatures refer to the temperature of the bath. Gas chromatograms were recorded on a Hewlet Packard HP 5890 instrument equipped with an Alltech AT-1 column. Determinations of enantiomeric purity based on chiral HPLC were made on a Spectra Physics SP8800 instrument using a Regis Pirkle Covalent D-2-napthylalanine column. ^{1}H and ^{13}C NMR were recorded on a GE QE300 spectrometer at 300 MHz and 74.8 MHz, respectively, and were referenced to internal TMS (0.00 ppm). **5**,[8,18] **6**,[8] **7**[19] and **8**[20] are literature compounds and displayed consistent spectral data.

3-Cyclohexyl-1,1-dibromo-1-propene (6). A 3 L 3 neck round bottom flask equipped with a mechanical stirring mechanism, a thermometer, and a 500 mL pressure equalizing addition funnel was charged with 2-cyclohexylethanol **4** (128.2 g, 1.0 mol, 1.0 equiv), dichloromethane (650 mL) and TEMPO (0.63 g, 0.004 mol, 0.004 equiv). The mixture was treated with an aqueous (50 mL) solution of sodium bromide (5.2 g, 0.05 mol, 0.05 equiv) and cooled to –5°C. While the biphasic mixture was vigorously stirred, a sodium bicarbonate (70g) buffered solution of 5% bleach (1.5 L) was added at such a rate as to maintain the internal temperature below 5°C. The resulting mixture was stirred for 30 min at which time gas chromatographic (GC) analysis indicated complete consumption of starting material. The reaction was quenched with 20% sodium thiosulfate (250 mL), stirred for 30 min, and separated. The aqueous layer was extracted with dichloromethane (500 mL) and the combined organic fractions were washed with 10% sodium thiosulfate (250 mL), 10% citric acid (250 mL), and brine (250 mL). The resulting solution was dried (sodium sulfate) and filtered to give a rose colored solution of 2-cyclohexylethanal (**5**): GC retention time: 4.16 min, 40°C-100°C/10°C/min; ^{1}H NMR ($CDCl_3$) δ 9.68 (1H, t, J = 3.0 Hz), 2.21 (2H, dd, J = 3.0, 7.5 Hz), 1.8 (1H, m), 1.6 (6H, m), 1.4-1.05 (2H, m), 1.0-0.85 (1H, m); ^{13}C NMR ($CDCl_3$) δ 202.95, 51.33, 33.16, 32.16, 25.99. IR (neat) 2920, 2845, 1745, 1720, 1445, 1150, 790 cm^{-1}; EI MS *m/z* 126 (M^+), 108, 82 (100), 67, 55, 53, 41.

The solution of **5** was charged directly into a 5L 3 neck flask equipped with a nitrogen inlet, thermometer, and a pressure equalizing addition funnel. The solution was treated with triphenylphosphine (655 g, 2.5 mol, 2.5 equiv) and placed in a 15°C water bath. A dichloromethane (630 mL) solution of carbon tetrabromide (414 g, 1.25 mol, 1.25 equiv) was added at a rate which maintained the internal temperature below 30°C. The mixture was stirred for 30 min after addition at which time no starting material was detected by GC analysis. The solvent was removed *in vacuo* and the resulting orange residue was carefully treated with methanol (1.8L) and water (200 mL). This solution was then extracted with heptane (1 x 1L, 1 x 800 mL). The combined hydrocarbon extracts were washed with 10% water/90% dimethylformamide (2 x 500 mL) and water (600 mL) before being dried (sodium sulfate) and concentrated to give **6** as a clear, colorless oil (255 g, 90%): GC retention time: 7.40 min, 50°C-250°C/20°C/min; ^{1}H NMR ($CDCl_3$) δ 6.41 (1H, t, J = 9.0, 7.5 Hz), 2.02 (2H, t, J = 7.5 Hz), 1.80-1.50 (6H, m), 1.40 (1H, m), 1.3-1.1 (2H, m), 1.0-0.8 (2H, m); ^{13}C NMR ($CDCl_3$) δ 137.79, 88.66, 40.58, 37.18, 32.93, 26.28, 26.15; IR (neat) 2950, 2860, 1520, 760 cm^{-1}; EI MS *m/z* 282 (M^+), 212, 199, 119, 96, 83 (100), 55, 41.

4-Cyclohexyl-1-hydroxy-2-butyne (7). A 5L 3 neck round bottom flask equipped with a nitrogen inlet, a mechanical stirrer, a thermometer and a 1L sidearm equalizing addition funnel was charged with dibromoalkene **6** (250.0 g, 0.89 mol, 1.0 equiv) and dry tetrahydrofuran (2.75 L). The solution was cooled to –10°C with an ice/salt bath and treated with 2.5 M solution of *n*-butyllithium in hexane (709 mL, 1.78 mol, 2.0 equiv) at a rate which maintained the internal temperature below 0°C. After 30 min, solid *para*-formaldehye (66.6 g, 2.22 mol, 2.5 equiv) was added at once as a solid. The slurry was allowed to warm to room temperature and stir for 15 h. GC analysis showed no remaining starting material and the reaction was quenched by slow addition of 10% aqueous ammonium chloride (1 L). After stirring for 30 min, the biphasic system was concentrated in vacuo and the residue was extracted with ethyl acetate (2.5 L). The organic extract was washed with 10% aqueous citric acid (1 L) and brine (1 L) before being dried with sodium sulfate and concentrated to give **7** as a brown oil (132.4 g, 97%): GC retention time: 6.45 min, 50°C-250°C/20°C/min; ^{1}H NMR ($CDCl_3$) δ 4.28 (2H, t, J = 3.0, 2.4 Hz), 2.12 (2H, dt, J = 6.0, 2.4, 1.5 Hz), 1.8-1.6 (6H, m), 1.45 (1H, m), 1.35-1.1 (2H, m). 1.05-0.85 (2H, m): ^{13}C NMR

($CDCl_3$) δ 85.52, 79.11, 51.42, 37.22, 32.66, 26.53, 26.20, 26.07; IR (neat) 3360, 2920, 2840, 2280, 2220, 1500, 1030 cm^{-1}; CI MS (NH_4^+) *m/z* 170 ($M+NH_4^+$), 152, 108, 81.

(2*Z*)-4-Cyclohexyl-1-hydroxy-2-butene (8). A Parr-shaker hydrogenation apparatus was charged with **7** (40.0 g, 0.263 mol, 1.0 equiv), hexane (400 mL), and 5% $Pd/BaSO_4$ (4.0 g). The mixture was pressurized with hydrogen (5 psi) and the reaction was allowed to proceed for 50 min, during which time 106% of the theoretical amount of hydrogen had been consumed. The solution was filtered through Celite™ and the resulting solution was concentrated to give **8** as a slightly yellow oil (39.8 g, 98%): GC retention time: 6.17 min, 50°C-250°C/20°C/min; ^1H NMR ($CDCl_3$) δ 5.7-5.5 (2H, m), 4.18 (2H, d, *J* = 6.0 Hz), 1.96 (2H, t, *J* = 9.0, 6.0 Hz), 1.75-1.55 (6H, m), 1.35-1.1 (3H, m), 1.0-0.8 (2H, m); ^{13}C ($CDCl_3$) δ 131.76, 128.95, 58.64, 38.04, 35.16, 33.08, 26.48, 26.30; CI MS *m/z* 154 (M^+), 136, 121, 107, 94, 81, 67 (100), 55, 41.

(2*S, 3*R**)-4-Cyclohexyl-2,3-epoxy-1-butanol (9).** A 1L 3-neck equipped with a mechanical stirring mechanism, a nitrogen inlet, and a rubber septum was charged with magnesium monoperoxypthalate (100.0 g, 0.20 mol, 2.5 equiv) and a 9/1 methanol/water solution (550 mL). The stirred solution was treated with a methanol (20 mL) solution of **8** (13.0 g, 0.084 mol, 1.0 equiv). The mixture was stirred at room temperature for 15 h after which time TLC analysis showed no remaining starting material. The mixture was slowly poured into ice-cooled 10% aqueous sodium bisulfite (300 mL) and stirred for 30 min. The aqueous solution was extracted with dichloromethane (2 x 300 mL) and the organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 150 mL) and brine (150 mL). After drying with sodium sulfate, the solution was concentrated to give racemic **9** as a pale yellow oil (12.6 g, 88%): R_f = 0.28, 1/1 EtOAc/Heptane, Ce^{IV}; ^1H NMR ($CDCl_3$) δ 3.78 (1H, dd, *J* = 12.0, 4.5 Hz), 3.66 (1H, dd, *J* = 12.0, 7.5 Hz), 3.10-3.00 (2H, m), 2.80 (1H, broad s), 1.75-1.50 (4H, m), 1.40-1.30 (2H, m), 1.25-1.0 (3H, m), 0.95-0.75 (2H, m); ^{13}C NMR ($CDCl_3$) δ 60.78, 56.80, 55.94, 36.02, 35.19, 33.33, 32.98, 32.54, 26.27, 26.06; IR (neat) 3420, 2920, 2845, 1450, 1040 cm^{-1}; CI MS (NH_4^+) *m/z* 188 (100, $M+NH_4^+$), 170 ($M+NH_4^+-H_2O$), 135, 108, 81, 77; CI HRMS calc'd for $C_{10}H_{19}O_2$: 171.1390; found: 171.1385.

(2*S*, 3*R*)-4-Cyclohexyl-2,3-epoxy-1-butanol (9). A 500 mL 3 neck round bottom flask equipped with a nitrogen inlet, a pressure equalizing addition funnel, and a thermometer was charged with 4A molecular sieves (5.0 g) and titanium(IV) tetrakis(isopropoxide) (2.13 g, 0.0075 mol, 0.15 equiv) and dry dichloromethane (175 mL). The mixture was cooled to –20°C with a dry ice/salt bath (20% $CaCl_2$). (*R*, *R*)-Diisopropyltartrate (1.86 g, 0.0078 mol, 0.16 equiv) was added followed by allylic alcohol **8** (7.7 g, 0.05 mol, 1.0 equiv) in dichloromethane (10 mL). The mixture was stirred for 1 h and then treated with a 4.55 M toluene solution of *tert*-butyl hydroperoxide[21] (22 mL, 0.01 mol, 2.0 equiv) over a 10 min period. The mixture was allowed to stand at –20°C for 50 h at which time no starting material remained by TLC. The reaction mixture was then poured into an ice cold aqueous (150 mL) solution containing ferrous sulfate (49.5 g) and citric acid (16.5 g). After stirring for 30 min, the mixture was filtered through Celite™ to effect separation of the layers. The lower aqueous layer was extracted with diethyl ether (1 x 100 mL and 1 x 50 mL). The combined organic extracts were cooled to 0°C and treated with an aqueous (60 mL) solution containing sodium chloride (5 g) and 50% aqueous sodium hydroxide (60 g). After 1h, the mixture was diluted with water (75 mL) and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 150 mL) and the combined organics were dried (sodium sulfate) and concentrated to give (2*S*, 3*R*)-**9** as a pale yellow oil (5.6 g, 59%).

(2*R, 3*R**)-4-Cyclohexyl-2,3-epoxybutanal (3).** A 1L 3 neck round bottom flask equipped with a nitrogen inlet, a thermometer, and a rubber septum was charged with epoxy-alcohol **9** (16.3 g, 0.096 mol, 1.0 equiv), triethylamine (38.4 g, 0.384 mol, 4.0 equiv) and a 5/1 solution of dichloromethane and dimethylsulfoxide (500 mL). The solution was cooled to an internal temperature of 0°C with a –10°C ice/salt bath and treated with solid pyridine-sulfur trioxide complex (38.2 g, 0.24 mol, 2.5 eq) in three portions over a 20 min period. The solution was stirred for 2 h at 0°C at which time TLC indicated consumption of starting material. The mixture was poured into 10% aqueous citric acid (300 mL) and stirred for 10 min. The layers were separated and the organic phase was washed with an additional portion of 10% aqueous citric acid (300 mL), 10% aqueous sodium bicarbonate (300 mL), and brine (300 mL) before being dried (magnesium sulfate)[22] and concentrated to give **3** as an unstable yellow oil which was used immediately: R_f = 0.75, 1/1 EtOAc/Heptane, Ce^{IV}; ^1H NMR ($CDCl_3$) δ 9.45 (1H, d, *J* = 6.0 Hz), 3.31 (2H, m), 1.85-1.60 (7H, m), 1.55 (1H, m), 1.40-1.10 (3H, m), 1.00-0.80 (2H,m); ^{13}C NMR ($CDCl_3$) δ 199.30, 58.01, 57.71, 36.21, 35.40, 33.29, 32.90, 26.19, 26.06, 26.01.

(2*R, 3*R**, 4*S**)- and (2*R**, 3*R**, 4*R**)-1-Cyclohexyl-2,3-epoxy-4-hydroxy-6-methylheptane (2a,b).** A 1L 3 neck round bottom flask equipped with a nitrogen inlet, mechanical stirring apparatus, and a pressure equalizing addition funnel was charged with a 2.0 M tetrahydrofuran solution of *i*-butylmagnesium chloride (96.0 mL, 0.192 mol, 2.0 equiv) and cooled to –78°C. A tetrahydrofuran (50 mL) solution of crude **3** was added to the solution in a dropwise fashion over a 30 min period. After the addition was complete, the resulting suspension was stirred for 2.5 h at –78°C and warmed to 0°C. After 45 min at 0°C, no starting material remained and the mixture was diluted with tetrahydrofuran (150 mL) and slowly poured into 10% ammonium chloride (250 mL) containing ice (approximately 30 g). After stirring 15 min, the mixture was extracted with ethyl acetate (2 x 300 mL). The combined extracts were washed with 10% citric acid (200 mL) and brine (200 mL) before being dried (sodium sulfate) and concentrated to a thick oil contaminated with solid **11** [^1H NMR ($CDCl_3$) δ 4.28 (1H,dt, *J* = 10.5, 5.0, 4.5 Hz), 3.79 (1H, m), 3.37 (1H, t, *J* = 6.0, 4.5 Hz), 1.95-1.50 (11H, m), 1.40-1.10 (7H, m), 0.97 (3H, d, *J* = 4.5 Hz), 0.93 (3H, d, *J* =4.5 Hz); EI MS *m/z* 264 (M+2, ^{37}Cl isotopomer), 262 (M+, ^{35}Cl isotopomer), 186 (100)] The oil was taken up in ethyl acetate (50 mL) and treated with heptane (100 mL). After 1 hr, the resulting solids were removed by filtration and the remaining liquors were concentrated to give an 82/18 mixture of **2a/b** as a pale yellow oil (12.1 g, 56% based on **9**): **2a**, R_f = 0.48; **2b**, R_f = 0.43, 1/1 EtOAc/Heptane, Ce^{IV}; GC retention time: 5.98 min, **2b**; 6.04 min, **2a**; 50°C-250°C/20°C/min; ^1H NMR ($CDCl_3$) δ 3.50 (1H, overlapping ddd, *J* = 9.0, 7.5, 4.5 Hz, **2a**), 3.48 (1H, overlapping ddd, *J* = 9.0, 9.0, 6.0 Hz, **2b**), 3.12 (1H, dt, *J* = 9.0, 8.0, 4.0, Hz, **2b**), 3.04 (1H, dt, *J* = 7.5, 4.5, 4.5 Hz, **2a**), 2.86 (1H, dd, *J* = 8.0, 4.0 Hz, **2b**), 2.83 (1H, dd, *J* = 7.5, 4.5 Hz, **2a**), 1.85-1.10 (14H, m), 0.89 (6H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 69.59, 58.84, 56.01, 36.34, 35.26, 34.13, 33.51, 33.29, 33.24, 28.11, 26.36, 26.19, 22.58, 22.48; IR (neat) 3400, 3155, 2920, 2845, 1465, 1445, 1360, 1385 cm^{-1}; CI MS (NH_4^+) *m/z* 244 ($M+NH_4^+$), 226 ($M+NH_4^+-H_2O$), 186 (100), 170, 135, 95, 78, 71; CI HRMS calc'd for $C_{14}H_{26}O_2$: 227.2023; found: 227.2011.

(2*S, 3*R**, 4*S**)-2-Azido-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (11a).** A 250 mL round bottom flask equipped with a reflux condensor was charged with **2a,b** (6.1 g, 0.027 mol, 1.0 equiv) and a 8/1 methanol/water solution (108 mL). The solution was treated with sodium azide (8.6 g, 0.13 mol, 4.9 equiv) and ammonium chloride (3.1 g, 0.058 mol, 2.2 equiv) and placed behind a blast shield. The solution was brought to a gentle reflux and stirred for 15 h. TLC analysis indicated complete consumption of starting material and the solution was allowed to cool before being diluted with water (50 mL). The aqueous mixture was extracted with

ethyl acetate (2 x 100 mL) and the extracts were washed with sodium bicarbonate (75 mL) and brine (75 mL). After drying (sodium sulfate), the solution was concentrated to give **11a,b** as a pale brown oil (4.6 g, 64%). The crude mixture of diastereomeric azido-diols was dissolved in hot heptane (25 mL) and allowed to cool to room temperature and then placed in a –20°C freezer overnight. Filtration of the resulting mixture provided **11a** (>95% d.e. by ^{1}H NMR) as a white crystalline solid (2.2 g). A second crop (0.8 g) was obtained after concentration and redissolution of the mother liquors; total yield of **11a** was 3.0 g (80% of theoretical recovery based upon crude yield of **11a,b**): mp 97-98°C; R_f = 0.85, 1/1 EtOAc/Heptane, Ce^{IV}; ^{1}H NMR δ ($CDCl_3$) 3.87-3.61 (2H, overlapping broad multiplets), 3.41-3.33 (1H, m), 2.3 (1H, broad d, *J* = 7.5 Hz), 1.98 (1H, broad d, *J* = 7.5 Hz), 1.80-1.60 (10H, m), 1.5-1.1 (6H, m), 0.97 (3H, d, *J* = 8.0 Hz), 0.94 (3H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 76.00, 70.87, 59.84, 42.16, 37.99, 34.26, 33.58, 32.93, 26.41, 26.17, 26.04, 24.49, 23.86, 21.56; IR ($CHCl_3$) 3620, 3580, 2975, 2920, 2845, 2100, 1465, 1450, 1385, 1370, 1260, 1210, 1060 cm^{-1}; CI MS (NH_4^+) *m/z* 287 ($M+NH_4^+$), 242, 173, 156, 143, 134, 126 (100), 77; CI HRMS calc'd for $C_{14}H_{28}N_3O_2$: 270.2184; found: 270.2182.

(2*S, 3*R**, 4*S**)-2-Amino-3,4-dihydroxy-6-methylheptane (1).** A par-shaker hydrogenation apparatus was charged with **11a** (1.6 g, 0.006 mol, 1.0 equiv), 5% Pd/C (1.0 g), and methanol (23 mL). The system was pressurized with hydrogen (20 psi) and the reaction was allowed to proceed for 23 h at room temperature. The catalyst was removed by filtration through Celite™ and the solvent was removed under vacuum to give crude **1** as an off-white foam. The crude residue was recrystallized from 3/2 ethanol/water to give pure **1** as a white crystalline solid (1.35 g, 94%): ^{1}H NMR ($CDCl_3$) δ 3.81 (1H, d of t, *J* = 10.5, 4.5, 3.0 Hz), 3.37 (1H, dd, *J* = 4.5, 3.0 Hz), 3.08 (1H, m), 2.60 (4H, broad s), 1.8-1.6 (6H, m), 1.48 (1H, m), 1.35 (4H, m), 1.15 (5H, m), 0.97 (3H, d, *J* = 7.5 Hz), 0.93 (3H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 74.54, 73.25, 48.39, 43.52, 43.20, 34.08, 34.01, 33.00, 26.54, 26.32, 26.19, 24.80, 23.63, 22.00; IR ($CDCl_3$) 3590, 2950, 2920, 2840, 2240, 1600, 1575, 1460, 1445 cm^{-1}; CI MS (NH_4^+) *m/z* 244 ($M+H^+$, 100), 208, 173, 156, 126; CI HRMS calc'd for $C_{14}H_{30}NO_2$: 244.2273; found: 244.2277. In the scalemic series, HPLC analysis showed a single diastereomer (>98%) and chiral HPLC analysis showed an ee of 70%.

(2*S*, 3*R*, 4*S*)-2-Amino-3,4-dihydroxy-6-methylheptane (1). Resolution of *Rac*-1. A 125 mL Erlenmeyer flask was charged with rac-1 (2.5 g, 0.010 mol, 1.0 equiv), (*S*, *S*)-tartaric acid (1.2 g, 0.08 mol, 0.8 equiv), and acetone (25 mL). The mixture deposited a white crystalline solid after approximately 2 h but was stirred overnight to ensure complete precipitation. The suspension was filtered and the resulting solid was washed with acetone (25 mL). The solid was dissolved in an ethyl acetate (100 mL)/water (50 mL) partition and the pH was adjusted to 11 with 10% aqueous sodium carbonate. The aqueous layer was removed and washed with additional ethyl acetate (100 mL). The combined organics were washed with brine, dried (sodium sulfate), and concentrated to give *ent*-**1** (1.1 g, 88% of theoretical) which was >99% ee by chiral HPLC analysis: mp 109-111°C; $[\alpha]^{25}_D$ = +28.9 (*c* 2, EtOH).

The acetone filtrate was concentrated to a thick residue, partitioned between ethyl acetate (100 mL)/water (50 mL) and basified to pH 11 with 10% aqueous sodium carbonate. The aqueous layer was removed and washed with additional ethyl acetate (100 mL). The combined organics were washed with brine, dried (sodium sulfate), and concentrated to give **1** (1.2 g, 96% of theoretical) which was >99% ee by chiral HPLC analysis. mp 110-111°C; $[\alpha]^{25}_D$ = –29.0 (*c* 2, EtOH); authentic sample,[23] $[\alpha]^{25}_D$ = –28.9 (*c* = 1, EtOH).

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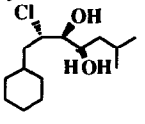
14. (a) Proposed structure for chloro-hydrin **11**:



(b) *Threo*-2,3-epoxy alcohols have been shown to undergo nucleophilic opening much faster than the corresponding *erythro*-2,3-epoxy alcohols, *c.f.* Kirshenbaum, K.S.; Sharpless, K.B. *Chem. Lett.* **1987**, 11.

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22. Intial attempts at the addition of *i*-BuMgCl to **3** were complicated by incomplete reaction. This was later found to be due to the facile hydration of **3** to its corresponding hemiacetal. Drying the dichloromethane solution of **3** with magnesium sulfate instead of sodium sulfate solved the problem.
23. Authentic samples of **1** were prepared by a slightly modified version of the route initially described by Luly, et. al.[15]

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