A Catalytic Asymmetric Synthesis of Cyclohexylnorstatine

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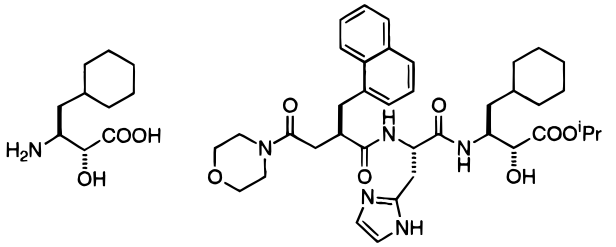
Introduction

The isopropyl ester of cyclohexylnorstatine (**1**) is the C-terminal residue of KRI 1314 (**2**), a tripeptide with potent renin inhibitory activity.[1] Other bioactive small peptides also contain this α-hydroxy β-amino acid substructure.[2]



1 **2**

Several preparations of **1** in homochiral or scalemic forms have been reported in recent years. However, they either use chiral natural products as starting materials, and involve in all cases a large number of steps,[3] or employ stoichiometric amounts of expensive chiral auxiliaries and/or chiral promoters.[4] A catalytic asymmetric synthesis of **1**, which could be of high interest for the potential large scale production of the compound, is still lacking.

We have previously reported that *anti*-3-amino 1,2-diols, readily available in high enantiomeric purity through the use of a catalytic Sharpless epoxidation[5] as the sole source of chirality, are convenient starting materials for the enantioselective synthesis of α-amino acids,[6] β-amino acids,[7] and model α-hydroxy β-amino acids.[8] We wish to disclose in the present paper the enantioselective synthesis of cyclohexylnorstatine in a fully protected form by application of this general methodology.

Results and Discussion

Our synthetic strategy is outlined in Scheme 1.

(*E*)-4-Cyclohexyl-2-buten-1-ol (**4**),[9] the substrate for Sharpless epoxidation, was prepared in the present instance by Swern oxidation of commercial 2-cyclohexylethanol (**3**), followed by highly stereoselective Wittig reaction with ethyl triphenylphosphoranylacetate and reduction with DIBALH (Scheme 2). This procedure is amenable to multigram scale and takes place with a 87−88% overall yield. The allyl alcohol **4** was then submitted to a Sharpless epoxidation[5d] in the presence of catalytic amounts of D-(−)-diisopropyl tartrate (7.5%) and titanium tetraisopropoxide (5%). Conducting the reaction at −20 °C for 24 h, (2*R*,3*R*)-4-cyclohexyl-2,3-epoxy-1-butanol (**5**) could be isolated in 87% yield. The enantiomeric excess of the so prepared **5** is 90% according to ^{1}H NMR analysis of its diastereomeric Mosher esters.

A regioselective ring opening of **5**, performed with a nitrogen nucleophile, should lead to our key intermediate (see Scheme 1), already possessing a 3-amino 1,2-diol functionality array and that can be converted to the ultimate target by simple stereochemical manipulation and adjustment of oxidation level.

According to previous experience in our laboratories, we initially performed the ring opening process with benzhydrylamine in the presence of titanium tetraisoproxide[10] (Scheme 3). The C-3/C-2 selectivity was 88/12 and, after chromatographic separation of the regioisomers, the desired 3-benzhydrylamino derivative **6** was isolated in 61% yield. The benzhydrylamino group was subsequently changed to the more convenient Boc-amino by hydrogenolysis over Pearlman's catalyst in the presence of Boc_2O. A 85% yield of the *N*-Boc-3-amino 1,2-diol **8** was obtained in this way. This intermediate has also been prepared through the following alternative procedure: Treatment of **5** with titanium diazidodiisopropoxide[11] induces a completely regioselective nucleophilic ring opening, the 3-azido 1,2-diol **7** being isolated in 99% yield. The hydrogenolysis of **7** over 10% Pd−C in the presence of Boc_2O then affords **8** in 97% yield. Whereas this last sequence is clearly superior at the laboratory scale, the ring opening with benzhydrylamine (which avoids the use of potentially risky azides) can be preferable when work at a larger scale is considered.

(1) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1678−1680.

(2) (a) Dhanoa, D. S.; Parsons, W. H.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1992**, *33*, 1725−1728. (b) Yang, L.; Weber, A. E.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1993**, *34*, 7035−7038.

(3) (a) Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 3031−3034. (b) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175−4178. (c) Inokuchi, T.; Tanigawa, S.; Kanazaki, M.; Torii, S. *Synlett* **1991**, 707−708. (d) Dugger, R. W.; Ralbowsky, J. L.; Bryant, D.; Commander, J.; Massett, S. S.; Sage, N. A.; Selvidio, J. R. *Tetrahedron Lett.* **1992**, *33*, 6763−6766. (e) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W. *J. Med. Chem.* **1993**, *36*, 2431−2447.

(4) (a) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853−1868. (b) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett* **1992**, *33*, 5737−5740. (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785−2792.

(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 193−246. (c) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 247−308. (d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (e) Sharpless, K. B.; Wooddard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823−1836. (f) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589−604.

(6) (a) Poch, M.; Alcón, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781−7784. (b) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthetic Commun.* **1994**, *24*, 1231−1238.

(7) Alcón, M.; Canas, M.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1994**, *35*, 1589−1592.

(8) (a) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2329−2342. (b) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1996**, *7*, 243−262.

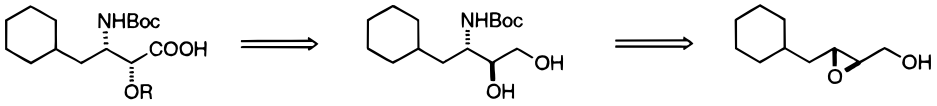
(9) Huyser, E.; Munson, L. R. *J. Org. Chem.* **1965**, *30*, 1436−1439.

(10) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A., *Tetrahedron Lett.* **1991**, *32*, 6931−6934.

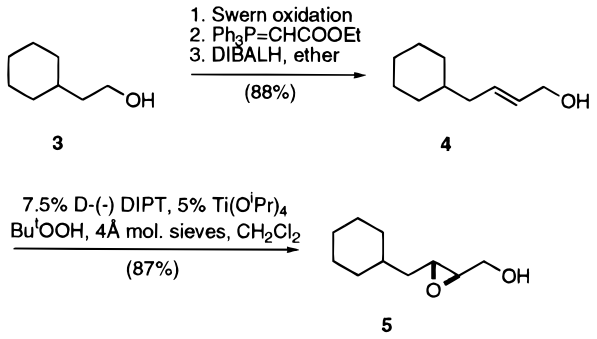
(11) M. Caron, P. R. Carlier, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 5185−5187.

S0022-3263(96)00351-9 CCC: $12.00

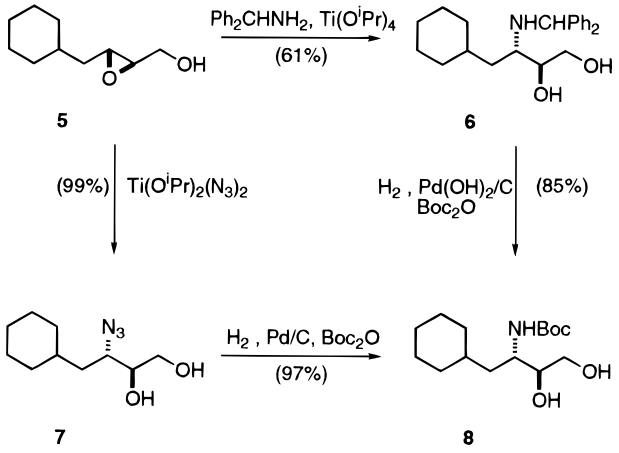
Scheme 1



Scheme 2



Scheme 3



The *N*-Boc amino diol **8** is a highly crystalline solid which offers good opportunity for enantioenrichment. Thus, a single crystallization from ether/hexane at this stage allows improvement of the enantiomeric excess up to 94%, as indicated by chiral HPLC analysis of the final product in the sequence (see below). Besides the work described here, **8** has also shown to be a convenient precursor of both *anti* and *syn* aminoalkyl epoxides,[12] which are valuable intermediates for the synthesis of hydroxyethylene dipeptide isosteres.

Conversion of **8** into our target, protected cyclohexylnorstatine, requires only inversion at C-2 and oxidation of the primary hydroxy group. However, these operations are not straightforward, and attention must be paid to the implementation of orthogonal protection schemes for the different functions along the sequence.

Bearing this idea in mind, the primary hydroxy group in **8** was selectively protected by reaction with TBDMS-Cl/imidazole in DMF to afford the secondary alcohol **9** in 83% yield (Scheme 4). Inversion at C-2 under Mitsunobu conditions using *p*-nitrobenzoic acid as the nucleophile[13] took place very cleanly to afford the diastereomerically pure *syn* derivative **10** in 89% yield. At this point, it seemed desirable to convert the *p*-nitrobenzoate to a less labile function. To this end, **10** was first submitted to reduction with DIBALH in CH_2Cl_2 which led in good yield to the secondary alcohol **11** without any alteration in stereochemical purity. Treatment of **11** with a tenfold excess of ethyl vinyl ether and a catalytic amount of PPTS provided in 83% yield the 1-ethoxyethyl derivative **12**, as a *ca.* 1:1 mixture of epimers at the acetal moiety.

To complete the synthesis, the primary hydroxyl group was selectively deprotected by treatment with tetrabutylammonium fluoride in THF, and the resulting primary alcohol **13** (89% yield) was oxidized with the $RuCl_3/NaIO_4$ system[14] to the fully protected cyclohexylnorstatine derivative **14** in 86% yield. To facilitate chiral HPLC analysis, crude **14** was transformed into the known hydroxy ester **15**[3e] by treatment with ethyl orthoacetate and subsequent acidic workup. The spectroscopic data of **15** turned out to be fully coincident with those reported in the literature. The enantiomeric excess of **15** was 94%, as determined by chiral HPLC with a Chiralcel OD-R column.

In summary, we have developed an efficient approach to the bioactive stereoisomer of cyclohexylnorstatine from (*E*)-4-cyclohexyl-2-buten-1-ol. The synthesis involves nine steps and can be accomplished in 28% overall yield. The source of enantioselectivity in the sequence is a catalytic Sharpless epoxidation. According to that, both enantiomeric series of the target α-hydroxy-*β*-amino acid are equally available (by simply selecting the enantiomeric series of the tartrate ester employed in the epoxidation). If required, the *anti* diastereomers could also be prepared (with even greater efficiency) by this methodology, by simply supressing the C-2 inversion sequence.[8] Further applications of this flexible approach to α-hydroxy *β*-amino acids are in progress in our laboratories and will be reported in due course.

Experimental Section

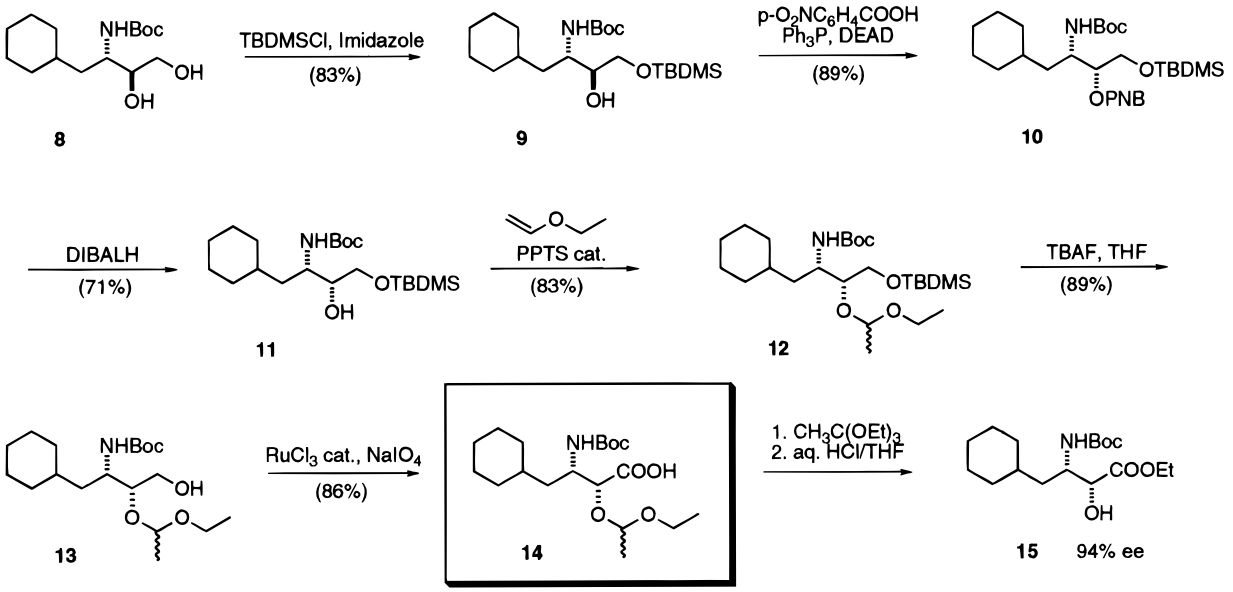
General. Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. The ^1H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ unless specified otherwise. *J* values are given in Hz. The ^{13}C NMR spectra were recorded at 50.3 or 75.4 MHz in $CDCl_3$ unless specified otherwise. Signal multiplicities were established by DEPT experiments. In all cases, chemical shifts are in ppm downfield of TMS. Mass spectra were recorded at 70 eV ionizing voltage; ammonia was used for chemical ionization (CI). Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". 2-Cyclohexylethanol (99%) was purchased from Aldrich. THF and diethyl ether were distilled from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2, and triethylamine from KOH. All reactions were performed in oven-dried glassware under a N_2 atmosphere. Reaction progress was followed by TLC (Merck DC-Alufolien Kieselgel 60 F254). Chromatographic separations were carried out using Et_3N pretreated (2.5% v/v) SiO_2 (70−230 mesh), eluting with hexane/ethyl acetate mixtures of increasing polarity. HPLC analyses were performed with Nucleosil 120 C18 or Chiralcel OD-R columns.

(12) Castejón, P.; Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1995**, *36*, 3019−3022.

(13) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(14) Carlsen, P. H. J.; Katsuki, T.; Martín, V. S.; Sharpless, K .B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

Scheme 4



(*E*)-4-Cyclohexyl-2-buten-1-ol (4). (a) To a stirred solution of oxalyl chloride (8.16 mL. 93.6 mmol) in CH_2Cl_2 (170 mL) at −78 °C was added DMSO (14.63 g, 187 mmol) in CH_2Cl_2 (42 mL) *via* cannula. After stirring for 10 min, commercial 2-cyclohexylethanol (10.0 g, 78.0 mmol) in CH_2Cl_2 (70 mL) was added *via* cannula. After a further 30 min period, triethylamine (39.46 g, 390 mmol) was slowly added and stirring was continued for 2 h. Following aqueous workup, CH_2Cl_2 extraction, drying with Na_2SO_4, and solvent evaporation, cyclohexylacetaldehyde (9.7 g, 77.0 mmol), pure enough for the continuation of the synthesis, was obtained. (b) To the crude aldehyde (7.5 g, 59.4 mmol) in dichloromethane (80 mL), ethyl triphenylphosphoranylacetate (24.84 g, 71.3 mmol) in dichloromethane (90 mL) was added, and the mixture was refluxed for 24 h. The solvent was then evaporated and the residue extracted with petroleum ether. Evaporation and column chromatography allowed the isolation of ethyl (*E*)-4-cyclohexyl-2-butenoate (10.39 g, 52.93 mmol), and of a small amount (0.29 g) of the corresponding (*Z*) isomer. (c) To a stirred solution of the stereochemically pure (*E*) ester (9.0 g, 45.85 mmol) in diethyl ether (60 mL) at −78 °C, 20% DIBALH in hexanes (115 mL, 115 mmol) was added *via* cannula. After 30 min of stirring, methanol (100 mL) was added. Precipitated aluminum oxide was separated by filtration and washed with CH_2Cl_2. This solution was washed with saturated brine, dried ($MgSO_4$), and evaporated to an oily residue which was purified by column chromatography to afford 6.77 g (87% overall yield) of **4** as a colorless liquid: ^{1}H NMR (200 MHz) δ 0.8−1.8 (m, 11H), 1.92 (m, 2H). 2.60 (bs, 1H), 4.06 (m, 2H), 5.62 (m, 2H); ^{13}C NMR (50 MHz) δ 26.2 (CH_2), 26.4 (CH_2), 32.9 (CH_2), 37.7 (CH), 40.1 (CH_2), 63.4 (CH_2), 129.9 (CH), 131.5 (CH).

(2*R*,3*R*)-4-Cyclohexyl-2,3-epoxy-1-butanol (5). To a suspension of powdered, freshly activated 4 Å molecular sieves (0.78 g) in dry CH_2Cl_2 (37 mL), cooled at −20 °C, were sequentially added *via* cannula with stirring D-(−)-diisopropyl tartrate (0.45 g, 1.93 mmol) in dry CH_2Cl_2 (11.4 mL), titanium tetraisopropoxide (390 μL, 1.30 mmol), and a solution of **4** (4.0 g, 25.9 mmol) in dry CH_2Cl_2 (11.4 mL). The resulting mixture was stirred for 30 min at −20 °C, and a solution of *tert*-butyl hydroperoxide (TBHP) in isooctane (18.7 mL, 2.78 M, 51.9 mmol) was then added *via* cannula. The reaction mixture was stirred for 24 h at −20 °C and quenched with a cold (0 °C) solution of $FeSO_4 \cdot 7H_2O$ (8.65 g, 31.1 mmol) and tartaric acid (2.33 g, 15.5 mmol) in H_2O (25 mL). After the layers were separated and the aqueous one extracted with dichloromethane (2 × 25 mL), the combined organic extracts were cooled to 0 °C and treated with a cold 30% NaOH solution in saturated brine (2.6 mL) with vigorous stirrring. After 2 h at 0 °C, water (15 mL) was added, the layers were separated, and the aqueous one was extracted with diethyl ether (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to an oily residue, which was purified by column chromatography to afford 3.84 g (87% yield) of **5** as a colorless oil: ^{1}H NMR (200 MHz) δ 0.80−1.80 (m, 13H), 2.15 (bs, 1H), 2.90 (m, 1H), 2.98 (m, 1H), 3.60 (dd, J = 10 Hz, J = 5 Hz, 1H), 3.92 (dd, J = 10 Hz, J = 2 Hz, 1H); ^{13}C NMR (50 MHz) δ 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 32.9 (CH_2), 33.5 (CH_2), 35.6 (CH), 39.2 (CH_2), 54.7 (CH), 58.9 (CH), 61.6 (CH_2); MS(CI) *m/e* 188 (M + 18$^+$, 100%), 205 (M + 35$^+$, 12%); $[\alpha]^{25}_D$ +35.65 (*c* 1.15, $CHCl_3$).

Preparation of the Mosher Ester of 5. The following procedure was used starting from (a) a racemic sample of **5**, prepared by epoxidation of **4** with *m*-CPBA, and (b) the enantioenriched sample of (+)-**5** whose preparation has been described in the preceding experiment: To a solution of **5** (0.030 g, 0.18 mmol) in dry CH_2Cl_2 (0.6 mL) at room temperature, (*N*,*N*-dimethylamino)pyridine (0.022 g), triethylamine (117 μL), and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (35 μL) were sequentially added, and the resulting orange solution was stirred for 60 min, until no starting material could be detected by TLC. The reaction was quenched by addition of 3-(dimethylamino)propylamine, and the solvent was removed under vacuum. Filtration of the residue through a short pad of silicagel afforded 0.060 g (86% yield) of the corresponding Mosher ester: ^{1}H NMR (300 MHz) of the diastereomeric mixture from (±)-**5** δ 0.80−1.80 (m, 13H + 13H), 2.81−2.86 (m, 1H + 1H), 2.87−3.10 (m, 1H + 1H), 3.60 (s, 3H + 3H), 4.23 (dd, J = 12 Hz, J = 5.4 Hz, 1H), 4.24 (dd, J = 12, J = Hz, J = 6 Hz, 1H), 4.54 (dd, J = 12 Hz, J = 3.6 Hz, 1H), 4.57 (dd, J = 12 Hz, J = 3.3 Hz, 1H), 7.4−7.6 (m, 5H + 5H).

The enantiomeric excess of the sample from (+)-**5** was determined by integration and mathematical analysis of the dd signals at 4.54 and 4.57 ppm, which correspond to one of the CH_2O protons of each diastereomer.

(2*S*,3*S*)-3-(Benzhydrylamino)-4-cyclohexyl-1,2-butanediol (6). To a solution of **5** (0.66 g, 3.91 mmol) in dry 1,2-dichloroethane (25 mL) at room temperature were sequentially added benzydrylamine (1.39 g, 7.82 mmol) in 1,2-dichloroethane (25 mL) and $Ti(O^iPr)_4$ (3.48 mL, 11.7 mmol) *via* cannula. The solution was heated under reflux for 24 h and cooled, and a 10% NaOH in saturated brine (7.5 mL) was added, the resulting suspension being stirred at room temperature for an additional period of 12 h. The mixture was filtered through Celite, the organic layer was separated, and the aqueous one was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated *in vacuo*. The crude product was dissolved in ether, and solid CO_2 was added to the solution until a white precipitate appeared. The mixture was filtered through a pad of Celite and the residue thoroughly washed with diethyl ether. Solvent evaporation yielded an oil that was purified by flash chromatography to afford 0.11 g (8% yield) of the unwanted regioisomer, (2*S*,3*S*)-2-(benzhydrylamino)-4-cyclohexyl-1,3-butanediol, and 0.84 g (61% yield) of **6** as a colorless oil that slowly crystallizes

on standing: mp 69−72 °C; ^{1}H NMR (200 MHz) δ 0.6−1.8 (m, 13H), 2.9 (m, 1H), 2.8−3.1 (m, 2H), 3.5−3.9 (m, 3H), 5.0 (s, 1H), 7.1−7.5 (m, 10H); ^{13}C NMR (50 MHz) δ 26.0 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 34.0 (CH), 38.4 (CH_2), 54.5 (CH), 64.0 (CH_2), 64.3 (CH), 71.7 (CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 128.5 (CH), 143.1 (C), 143.7 (C); $[\alpha]^{25}_D$ +5.8 (*c* 1.99, $CHCl_3$). Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 77.89; H, 8.95; N, 3.72.

(2*S*,3*S*)-3-Azido-4-cyclohexyl-1,2-butanediol (7). To a suspension of titanium diazidodiisopropoxide ($Ti(O^iPr)_2(N_3)_2$) (1.76 g, 7.05 mmol) in dry benzene (30 mL) under argon, heated to 75 °C, a solution of **5** (1 g, 5.87 mmol) in dry benzene (30 mL) was added *via* cannula. The mixture was stirred at 75 °C for 5−10 min and cooled to room temperature, and the solvent was eliminated *in vacuo* . Diethyl ether (115 mL) and 5% H_2SO_4 (45 mL) were added to the residue, and the mixture was stirred for 60 min until both layers were transparent. After phase separation, the aqueous one was extracted with dichloromethane (2 × 30 mL), and the combined organic extracts were dried over $MgSO_4$ and evaporated. A white solid was obtained that was recrystallized from hexanes to afford 1.24 g (99% yield) of **7** as white crystals: mp 47−50 °C, ^{1}H NMR (200 MHz) δ 0.80−1.80 (m, 13H), 2.10 (bs, 1H), 2.68 (bs, 1H), 3.60 (m), 3.71 (m); ^{13}C NMR (50 MHz) δ 26.0 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 32.3 (CH_2), 34.1 (CH_2), 34.4 (CH), 38.2 (CH_2), 62.0 (CH), 63.0 (CH_2), 74.0 (CH); $[\alpha]^{25}_D$ −13.6 (*c* 1.84, $CHCl_3$). Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.32; H, 8.98; N, 19.70. Found: C, 56.44; H, 9.05; N, 19.74.

(2*S*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-4-cyclohexyl-1,2-butanediol (8). (a) From **6:** A solution of **6** (1.06 g, 3 mmol) and Boc_2O (0.85 g, 3.9 mmol) in ethyl acetate (5 mL) was added *via* cannula to a stirred suspension of 20% $Pd(OH)_2/C$ (0.1 g) in ethyl acetate (2 mL) under H_2. The mixture was hydrogenated at atmospheric pressure until no starting material could be observed by TLC, filtered through Celite thoroughly washing with CH_2Cl_2, and evaporated. The oily residue was purified by flash chromatography to afford 0.72 g (85% yield) of **8**: mp 65−68 °C (from diethyl ether/hexanes); ^{1}H NMR (200 MHz) δ 0.8−1.9 (m, 13H), 1.45 (s, 9H), 3.1−3.2 (m, 1H), 3.3−3.4 (m,1H), 3.5−3.8 (m, 4H), 4.5−4.6 (m, 1H); ^{13}C NMR (50 MHz) δ 26.0 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 28.3 (CH_3), 32.1 (CH_2), 34.2 (CH), 38.9 (CH_2), 49.9 (CH), 62.9 (CH_2), 74.9 (CH), 80 (C), 158 (C); $[\alpha]^{25}_D$ −24.4 (*c* 1.59, $CHCl_3$). Anal. Calcd for $C_{15}H_{29}NO_4$: C, 62.74; H, 10.10; N, 4.88. Found: C, 62.86; H,10.19; N, 4.71.

(b) From **7**: A solution of **7** (1.07 g, 5.01 mmol) and Boc_2O (1.42 g, 6.52 mmol) in ethyl acetate (11 mL) was added *via* cannula to a stirred suspension of 10% Pd/C (0.11 g) in ethyl acetate (1.9 mL) under H_2, and the mixture was hydrogenated at atmospheric pressure for 18 h. Workup as in **(a)** afforded 1.40 g (97% yield) of **8**.

(2*S*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-4-cyclohexyl-2-butanol (9). To a solution of **8** (0.33 g, 1.14 mmol) in dimethylformamide (5.5 mL) at room temperature were added TBDMS-Cl (0.22 g, 1.48 mmol) and imidazole (0.17 g, 2.5 mmol), and the progress of the reaction was monitored by TLC. After 48 h, diethyl ether (30 mL) was added and the mixture washed with saturated NH_4Cl solution (20 mL). The organic layer was separated and dried over $MgSO_4$, and the solvents were evaporated *in vacuo*. The crude product was purified by chromatography yielding 0.38 g (83% yield) of **9** as a colorless oil: ^{1}H NMR (200 MHz) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.1−2 (m, 13H), 1.44 (s, 9H), 2.8 (m, 1H), 3.5−3.9 (m, 4H), 4.8−4.9 (m, 1H); ^{13}C NMR (50 MHz) δ −5.5 (CH_3), 18.0 (C), 25.8 (CH_3), 26.1 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 28.3 (CH_3), 32.5 (CH_2), 34.1 (CH_2), 34.2 (CH), 38.7 (CH_2), 50.8 (CH), 64.4 (CH_2), 73.5 (CH), 80 (C), 156 (C); MS(CI) *m/e* 170 (100%), 126 (90%); $[\alpha]^{25}_D$ −17.6 (*c* = 2.00, $CHCl_3$).

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-4-cyclohexyl-2-[(*p*-nitrobenzoyl)oxy]butane (10). To a solution of **9** (0.27 g, 0.68 mmol) in benzene (13 mL) at room temperature were added PPh_3 (0.86 g, 3.3 mmol), *p*-nitrobenzoic acid (0.49 g, 2.9 mmol), and diethyl azodicarboxylate (0.52 mL, 3.3 mmol), and the mixture was stirred at room temperature for 12 h. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to afford 0.33 g (89% yield) of **10** as a colorless oil: ^{1}H NMR (200 MHz) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.8−2 (m, 13H), 0.83 (s, 9H), 1.38 (s, 9H), 3.7−3.9 (m, 2H), 4.1−4.6 (m, 2H), 5.1−5.3 (m,1H), 8.2 (d, 2H), 8.3 (d, 2H); ^{13}C NMR (50 MHz) δ −5.5 (CH_3), 19 (C), 25.6 (CH_3), 26.1 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.2 (CH_3), 32.5 (CH_2), 33.7 (CH_2), 33.9 (CH), 39.7 (CH_2), 48.1 (CH), 62.2 (CH_2), 77.8 (CH), 123.5 (CH), 130.8 (CH), 138 (C), 150 (C), 155 (C), 164 (C); $[\alpha]^{25}_D$ −11.4 (*c* = 2.42, $CHCl_3$). Anal. Calcd for $C_{28}H_{46}N_2O_7Si$: C, 61.06; H, 8.42; N, 5.09. Found: C, 61.16; H,8.54; N, 4.95.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-4-cyclohexyl-2-butanol (11). To a solution of **10** (0.3 g, 0.54 mmol) in CH_2Cl_2 (4.5 mL) at −20 °C was added DIBALH (2.2 mL, 2.17 mmol, 20% in hexanes) and the mixture stirred at −20 °C, the progress of the reaction being monitored by TLC. After 2 h, methanol (3 mL) was added and the solution treated with water (15 mL); phases were then separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by flash chromatography to afford 0.15 g (71% yield) of **11** as a colorless oil: ^{1}H NMR (200 MHz,) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.1−2 (m, 13H), 1.44 (s, 9H), 2.7 (m, 1H), 3.4−3.8 (m, 4H)., 4.7−4.8 (m, 1H); ^{13}C NMR (50 MHz) δ −5.5 (CH_3), −5.4 (CH_3), 19 (C), 25.8 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.3 (CH_3), 32.8 (CH_2), 33.7 (CH_2), 34.1 (CH), 40.3 (CH_2), 48.3 (CH), 64.9 (CH_2), 73.4 (CH), 156 (C); $[\alpha]^{25}_D$ −23.8 (*c* = 1.85, $CHCl_3$).

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-4-cyclohexyl-2-(1-ethoxyethoxy)butane (12). To a solution of **11** (0.16 g, 0.4 mmol) in CH_2Cl_2 (2 mL) at room temperature were added ethyl vinyl ether (0.4 mL, 4 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate, and the mixture was stirred until no starting product could be detected by TLC. The solution was then treated with water; phases were separated and the organic one was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated, yielding an oil that was purified by flash chromatography to give 0.16 g (83% yield) of **12** (1:1 mixture of diastereomers at the 1-ethoxyethoxy group), as an oil: ^{1}H NMR (200 MHz) δ 0.06 (s, 6H), 0.9 (s, 9H), 0.9−2 (m, 13H), 1.2 (t, *J* = 7.1 Hz, 3H), 1.3 (m, 3H), 1.43 (s, 9H), 3.3 −4 (m, 6H), 4.6 (m, 1H), 4.7−5 (m, 1H); ^{13}C NMR (50 MHz) δ −5.4, 15.5, 19, 20.9, 26.1, 26.3, 26.6, 26.8, 28.6, 33.2, 33.3, 33.8, 34.1, 34.3, 34.4, 39.5, 40,2, 48.4, 48.6, 61.3, 61.3, 62.9, 63.9, 77.9, 78.1, 100.2, 101.3; MS(CI) *m/e* 170 (100%), 126 (76%).

(2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-4-cyclohexyl-2-(1-ethoxyethoxy)-1-butanol (13). To a solution of **12** (0.16 g, 0.33 mmol) in tetrahydrofuran (3 mL) was added tetrabutylammonuim fluoride (0.6 mL, 0.66 mmol, 1.1M in THF). The mixture was stirred at room temperature and the progress of the reaction monitored by TLC. After 10 min, the solution was treated with water (10 mL), phases were separated, and the organic one was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography to give 0.11 g (89% yield) of **13** (1:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR (200 MHz) δ 0.8−2 (m, 13H), 1.1−1.4 (m, 6H), 1.44 (s, 9H), 3.4−4 (m, 7H), 4.5−4.8 (m, 2H); ^{13}C NMR (50 MHz) δ 15.1, 20.2, 20.6, 26.1, 26.3, 26.5,28.3, 32.7, 33.7, 33.8, 34.1, 39.4, 39.7, 47.4, 48.0, 61.0, 61.2, 61.9 , 62.3, 76.3, 81.5, 99.3, 102.0. Anal. Calcd for $C_{19}H_{37}NO_5$: C, 63.48; H, 10.37; N, 3.90. Found: C, 63.32; H,10.39; N, 3.85.

(2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-4-cyclohexyl-2-(1-ethoxyethoxy)butanoic Acid (14). To a solution of **13** (0.07 g, 0.20 mmol) in 1.55 mL of a mixture of $CH_3CN/CCl_4/H_2O$ (1/1/1.5) were added $NaHCO_3$ (0.12 g, 1.4 mmol), $NaIO_4$ (0.25 g, 1.17 mmol), and $RuCl_3$ (catalytic amount), and the reaction mixture was stirred at room temperature for 48 h. When no starting material could be detected by TLC, water (15 mL) and diethyl ether (15 mL) were added; the organic layer was separated and the aqueous one washed with ether (15 mL), acidified with phosphate buffer (pH = 5.6), and extracted with ether (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield **14** (0.07 g, 86% yield) as an oil: ^{1}H NMR (200 MHz) δ 0.8−2.0 (m, 19H), 1.43 (s, 9H), 3.4−3.7 (m, 2H), 4.0−4.3 (m, 2H), 4.7−5.1 (m, 2H).

Derivatization of 14 into the Known Hydroxy Ester 15.[3e] Crude **14** (0.07 g, 0.18 mmol) was treated with ethyl orthoacetate (0.1 mL, 0.55 mmol) in toluene (0.22 mL), and the mixture was heated under reflux for 24 h. Following aqueous workup, drying, and evaporation, the ethyl ester of **14** (0.06 g) was transformed into the known ethyl (2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-

cyclohexyl-2-hydroxybutanoate (**15**) by treatment with a mixture of THF (30 mL) and 0.65 M HCl (2.3 mL) for 5 h. To isolate **15**, the mixture was washed with saturated $NaHCO_3$ and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated *in vacuo*. The oily residue was purified by flash chromatography to afford **15** as a colorless oil. ^{1}H NMR (200 MHz) δ 0.8−2 (m, 15H), 1.4 (s, 9H), 3.1 (m, 1H), 4.0−4.4 (m, 4H), 4.6 (m, 1H); ^{13}C NMR (75.4 MHz) δ 14.1 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.2 (CH_3), 32.9 (CH_2), 33.5 (CH_2), 34.2 (CH), 39.9 (CH_2); 50.2 (CH), 62.2 (CH_2), 72.4 (CH), 79.3 (C), 155.2 (C), 173.9 (C). Conditions for Chiral HPLC analysis: Chiralcel OD-R column, 30% MeOH/0.5 M $NaClO_4$, 0.5 mL/min. (2*S*,3*R*) Stereoisomer [minor]: 22.6 min; (2*R*,3*S*) stereoisomer [major]: 27.7 min.

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