Stereoselective Preparation of *Syn* α-Hydroxy-*β*-amino Ester Units via Regioselective Opening of α,*β*-Epoxy Esters: Enantioselective Synthesis of Taxol C-13 Side Chain and Cyclohexylnorstatine

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Received August 3, 1995

A number of important compounds that show interesting pharmacological properties possess α-hydroxy-*β*-amino ester units within their structures. Such moieties are present in several peptide enzyme inhibitors such as bestatin and pepstatin.[1] Taxol, a complex natural product currently considered to be a promising anticancer agent,[2] bears the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine unit (see Figure 1) in its C-13 side chain and this is essential to its antitumor activity.[3]

A further example is seen in the structure of KRI-1314 (see Figure 1), one of the renin inhibitors developed for its promising antihypertensive activity and oral efficacy.[4] Its active site contains the (2*R*,3*S*)-isopropyl-2-hydroxy-3-amino-4-cyclohexyl butyrate subunit (cyclohexylnorstatine), essential for the activity of the drug.

Suitable precursors of *syn* α-hydroxy-*β*-amino esters are the *cis* α-*β*-epoxy esters of type **A** (see Scheme 1) which can be directly opened by nitrogen nucleophiles[5] to the corresponding amino or azido alcohols of type **B**. This direct approach is viable only if the *cis* epoxy esters can be prepared in enantiopure form. However the Sharpless AE usually fails to give more than 80% ee with the corresponding *Z* allylic alcohols.[6] The Jacobsen asymmetric epoxidation[7] of *cis*-unsaturated esters[8] might

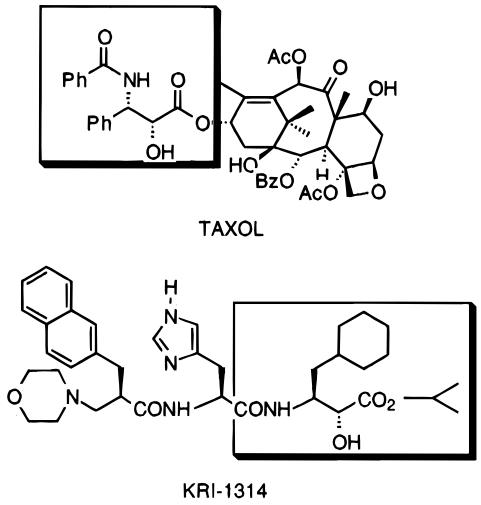
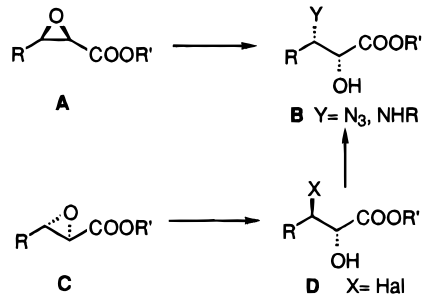


Figure 1.

Scheme 1



be more promising, although the enantioselectivity of the reaction varies depending upon the sterics of the substrates.

On the contrary, *trans* α,*β*-epoxy esters of type **C** are easily obtained in optically enriched form (ee >90%), by Sharpless AE of the *E* allylic alcohols and subsequent oxidation and esterification.[9] Then the oxirane ring could be regio- and stereoselectively opened to an intermediate of type **D** with a first inversion of configuration. If the nucleophile were a good leaving group, then the subsequent reaction with an aminating agent would produce *syn* α-hydroxy-*β*-azido (or amino) esters of type **B**. In order to achieve this, we looked to recent developments in the regioselective opening of α,*β*-epoxy alcohols and derivatives with metal halides.[10] In particular, those methods utilizing Lewis acid promoters (i.e., MgI_2[11] or LiI[12]) appeared to be the most suitable to effect C-3 opening of 2,3-epoxy alcohols and esters.

MgI_2[11a] was first applied to the regio- and stereoselective opening of 2,3-epoxy esters. Unfortunately, in our hands this reagent did not give good results with known[13]

(1) See numerous references in a recent review on *β*-amino acids: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.

(2) Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1. Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. Bormann, S. *Chem. Eng. News* **1991**, *69* (35), 11; **1992**, *70* (41), 30. Potier, P.; Guènard, D.; Guèritte-Voegelein, F. *Acc. Chem. Res.* **1993**, *26*, 160. Lavelle, F.; Guèritte-Voegelein, F.; Guènard, D. *Bull. Cancer* **1993**, *80*, 326. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, Suffness, L. M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, pp 305−314. Nicolaou, K. C.; Dai, W-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(3) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. Rowinsky, E. K.; Cazenave, L. A.; Nonehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. Mathew, A. E.; Mejillano, M. R.; Nath, J. P.; Himes, R. H.; Stella, V. J. *J. Med. Chem.* **1992**, *35*, 145.

(4) Iizuka, K.; Kamijo, T.; Harada, H.; Ahakane, K.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707.

(5) For amine opening, see: (a) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. For azide opening, see: (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.

(6) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(7) For a complete overview of the reaction, see: Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers, Inc.: New York, 1993; p 159.

(8) One of the most successful application of the Jacobsen epoxidation on unsaturated *cis* esters has led to a simple and direct synthesis of the taxol C-13 side chain: Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.

(9) Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 4683 and references therein.

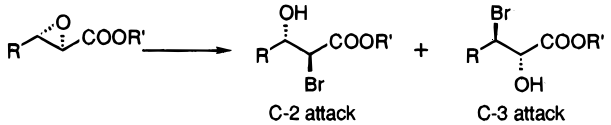
(10) See review: Bonini, C.; Righi, G. *Synthesis* **1994**, 225.

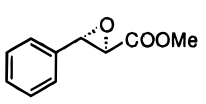
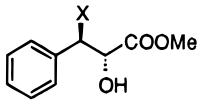
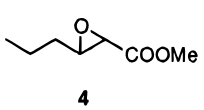
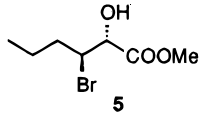
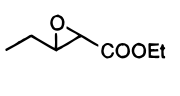
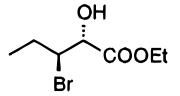
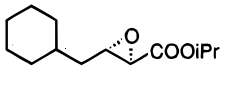
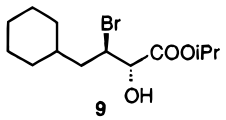
(11) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *38*, 4435. (b) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206. Bonini, C.; Righi, G. *Tetrahedron* **1992**, *48*, 1531.

(12) (a) Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* **1992**, *22*, 1863. (b) Federici, C.; Righi, G.; Rossi, L.; Bonini, C.; Chiummientu, L.; Funicello, M. *Tetrahedron Lett.* **1994**, *35*, 797. These papers reported the use of LiI with Amberlyst 15 in the regioselective C-3 oxirane opening of 2,3-epoxy alcohols and derivatives. The application of the reported conditions on 2,3-epoxy esters did not give consistent results. More interestingly, the use of NaI and NaBr in acetone afforded 2-halo-3-hydroxy esters: Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401.

S0022-3263(95)01441-1 CCC: $12.00

Table 1. Regioselective C-3 Opening of α,β-Epoxy Esters with $MgBr_2$ Etherate



α–β-Epoxy Ester	Main Bromohydrin	C-3/C-2 ratio[a,b]
 1[c]	 2[d] X= I 3 X= Br	80:20 >99:1
 4	 5	97:3
 6	 7	>99:1
 8[c]	 9	>99:1

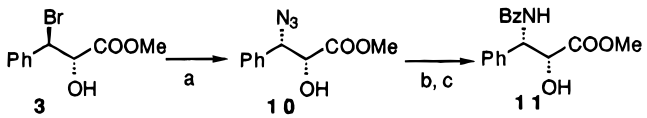
[a]The ratio has been determined by ^{1}H-NMR (200 MHz) analysis of the peracetylated products. [b]Chemical yields of the isolated products are nearly quantitative. [c]Optically active. [d]Obtained with MgI_2.

optically active *trans* methyl cinnamoyl ester **1** (see Table 1). We were utilizing this compound for the synthesis of the taxol C-13 side chain, as recently described in a preliminary communication.[14] The observed regioselectivity (4:1 in favor of C-3 iodohydrin **2**) prompted us to investigate the alternative use of $MgBr_2$ etherate, a commercially available reagent. The results with compound **1** were particularly satisfactory. The reaction could be effected at −60 °C in ether with the quantitative production of bromohydrin ester **3**. This optically enriched bromohydrin was therefore used to complete the synthesis of the taxol side chain.

In order to investigate the scope of this reaction, we have submitted other *trans* α,β-epoxy esters (see Table 1, compounds **4**, **6**, and optically active **8** prepared as described below) to the reaction conditions ($MgBr_2$ etherate, 1.5 equiv in ether). In all cases the regioselectivity[15] and the chemical yields were excellent. Furthermore, with these compounds the reaction can be carried out at room temperature without significant loss of regioselectivity and with very short reaction time.

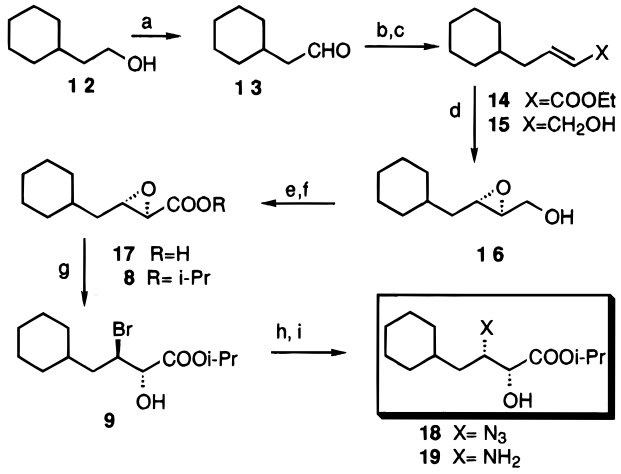
The use of $MgBr_2$ to obtain bromohydrins by oxirane opening offers two principal advantages over MgI_2: the reagent is commercially available and the reaction proceeds with clean inversion of configuration by a presumed SN_2 pathway.[16]

Scheme 2. Enantioselective Synthesis of Taxol Side Chain



a: NaN_3, DMF, 65 °C, 6h, 99%. **b**: BzCl, DMAP, rt, 1h, 90%. **c**: H_2 (50 psi), Pd/C, MeOH, rt, 4 h, then 1h 88%.

Scheme 3. Enantioselective Synthesis of Cyclohexylnorstatine 19



a: PCC, CH_2Cl_2, rt, 3h, 98%; **b**: TEPA, LiOH, THF, 65 °C, 2h, 80%; **c**: DIBAL, $PhCH_3$, 1h, -78 °C, 95%; **d**: L(+)-DET, $Ti(OiPr)_4$, t-BuOOH, CH_2Cl_2, -23 °C,24h, 80%; **e**: $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, rt, 2h, 71.5%; **f**: DCC, i-PrOH, DMPA, CH_2Cl_2, 0 °C, 3h, 70%; **g**: $MgBr_2 \cdot Et_2O$, Et_2O, rt, 2h, 99%; **h**: NaN_3, DMF, 65 °C, 6h, 70%; **I**: H_2, Pd/C, EtOAc, rt, 4h, 80%.

With optically active **3** on hand, we completed[13] the synthesis of the taxol C-13 side chain[17] (see Scheme 2) following previously described procedures[17g] (see data in Experimental Section related to the compounds **3**, **10**, and **11**).

The same strategy has also been applied to the synthesis of cyclohexylnorstatine (see Scheme 3), which has been the target of other synthetic approaches.[18]

The synthetic sequence is outlined in Scheme 3, starting with commercially available alcohol **12**. Quantitative oxidation to known aldehyde **13**[18c] is followed by

(13) Hiang, D.-F. Huang, L. *Tetrahedron* **1990**, *46*, 3135.
(14) Bonini, C.; Righi, G. *J. Chem. Soc., Chem. Commun.* **1994**, 2767.
(15) The regioisomeric ratio can be easily determined on the mixture of the peracetylated products. In the ^{1}H-NMR spectra the acetyl group in C-3 position (β to the carboxyl group) always resonates at 2.01−2.03 ppm; on the contrary the acetyl group in C-2 position resonates downfield at 2.16−2.18 ppm.
(16) In some instances we observed an enhanced reactivity of the iodo derivatives toward nucleophilic substitution with azide ion. However reduced optical yields were also obtained with these compounds. This may arise from an interfering SN_1-like pathway or from "self-displacement" by adventitious iodide ion. The lower reactivity of the bromo alcohol results in longer reaction times but in a complete, stereoselective displacement of the bromine by azide ion: Bonini, C.; Righi, G., unpublished results.
(17) For some of the most recent taxol C-13 side chain syntheses, see: (a) Denis, J. N.; Greene, A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 46. (b) Honig, H.; Seufer-Wasserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841. (c) Denis, J. N.; Carrea, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (d) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinge, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (e) Denis, J. N.; Carrea; A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939. (f) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375. (g) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287. (h) Koskinen, Ari, M. P.; Karvinen, E. K.; Siirila, J. P. *J. Chem. Soc., Chem. Commun.* **1994**, 21. (i) Kearnes, J.; Kayser, M. M. *Tetrahedron Lett.* **1994**, *35*, 2845. (j) Wang, Z.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104. (k) Dondoni, A.; Parroni, D.; Semola, T. *Synthesis* **1995**, 187.

standard two-carbon homologation to unsaturated ester **14**. Chemoselective reduction with DIBAL to allylic alcohol **15**, followed by AE, leads to epoxy alcohol **16** in >92% ee. The oxidation of compound **16** with $RuCl_3$[9] to acid **17** and subsequent esterification produces *trans* epoxy ester **8**. Both $MgBr_2$-mediated opening to bromohydrin **9** and then azide substitution to produce compound **18** proceed smoothly and with complete inversion of stereochemistry in each step. The final hydrogenation of **18** leads to the target compound **19** which shows spectroscopic data identical to those of the same compound prepared by another route.[18c] All steps in the reaction sequence proceed in good to high yield, making our synthetic approach competitive with the one already published.

In conclusion a highly regio- and stereoselective sequence from *trans* α,*β*-epoxy esters is now available for the preparation of *syn* α-hydroxy-*β*-amino esters.

Experimental Section

General. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and 50.3 MHz, respectively. The enantiomeric excesses of the chiral compounds were measured by ^{1}H-NMR analysis with Eu(hfc)$_3$ or via Mosher derivatives prepared by standard procedures. Reactions were monitored by TLC using Merck silica gel 60 F-254 plates with UV indicator or/and visualized with phosphomolybdic acid (10% solution in EtOH). All the organic layers were dried over Na_2SO_4 before concentration in vacuo. Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. All solvents were purified before use with standard drying procedures, unless otherwise specified. Elemental analyses for C, H, and N are in agreement with the theoretical data, except for compounds containing halogens, where combustion analysis could not be performed.

Preparation of the Starting Epoxy Esters. Epoxy esters **1**[13] and **4**[19] are known compounds. Epoxy ester **6** was prepared according to ref 19; for epoxy ester **8** see below.

(2*R,3*S**)-Ethyl 2,3-Epoxypentanoate (6).** ^{1}H-NMR: δ 4.03 (2H, q, J = 7.9 Hz), 3.15−2.85 (2H, m), 1.70−1.30 (2H, m), 1.15 (3H, t, J = 7.4 Hz), 0.90 (3H, t, J = 7.8 Hz). ^{13}C-NMR: δ 169.3, 61.1, 59.0, 52.4, 24.1, 13.6, 9.0. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.39; H, 8.36.

General Preparation of 2-Hydroxy-3-bromo Esters: Representative Procedure for the Preparation of (2*R,3*S**)-Methyl 2-Hydroxy-3-bromohexanoate (5).** To a solution of compound **4** (144 mg, 1 mmol) in Et_2O (6 mL) was added $MgBr_2$·Et_2O (193 mg, 1.5 mequiv) was added. The solution was stirred at rt for 2 h and then washed with brine, and the organic layers were evaporated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1), affording pure **5** (220 mg, 98%). ^{1}H-NMR: δ 4.38 (1H, d, J = 3.1 Hz), 4.25−4.12 (1H, m), 3.80 (3H, s), 3.18 (1H, bd, OH, J = 7.3 Hz), 2.05−1.10 (4H, m), 0.90 (3H, t, J = 7.3 Hz). ^{13}C-NMR: δ 171.9, 74.4, 56.6, 52.7, 35.6, 20.7, 13.0.

(2*R,3*S**)-Ethyl 2-Hydroxy-3-bromopentanoate (7).** According to the general procedure with $MgBr_2$, compound **6** (290 mg) afforded pure compound **7** (437 mg, 98%). ^{1}H-NMR: δ 4.45−4.03 (4H, m), 3.20 (1H, bs, OH), 2.07−1.70 (2H, m), 1.23 (3H, t, J = 7.3 Hz), 1.04 (3H, t, J = 7.3 Hz). ^{13}C-NMR: δ 171.5, 74.0, 62.2, 59.0, 27.2, 13.9, 12.3.

(2*R,3*S**)-Methyl 2-Hydroxy-3-iodo-3-phenylpropionate (2).** A solution of MgI_2 in Et_2O (0.5 mequiv) was added to racemic compound **1** (60 mg, 0.33 mmol) under argon at −60 °C. After 2 h, the reaction was quenched with water and the mixture extracted with EtOAc. The organic layers were evaporated in vacuo, affording a crude mixture of regioisomers (100 mg, 98%). ^{1}H-NMR: δ 7.60−7.20 (5H, m), 5.55 (0.2H, d, J = 2.8 Hz), 5.4 (0.8H, d, J = 3.9 Hz), 4.65 (bs, OH) 4,.62 (0.8H, d, J = 3.88 Hz), 4.03 (0.2H, d, J = 2.78 Hz), 3.82 (0.6H, s), 3.70 (2.4H, s), 3.10 (0.2H, bs, OH).

(2*S*,3*R*)-Methyl 2-Hydroxy-3-bromo-3-phenylpropionate (3). According to the general procedure with $MgBr_2$ (with the reaction temperature kept at −60°C), chiral compound **1**[13] (855 mg, 4.8 mmol) afforded pure compound **3** (1.278 g, 98%). $[\alpha]_D$ = −134 ° (*c* 1.1, $CHCl_3$), lit.[17g] $[\alpha]_D$ = −138 ° (*c* 1.5, $CHCl_3$). ^{1}H-NMR: δ 7.50−7.20 (5H, m), 5.24 (1H, d, J = 4.0 Hz), 4.68 (1H, d, J = 4.3 Hz), 3.70 (3H, s), 3.10 (1H, bs, OH).

(2*R*,3*S*)-Methyl 2-Hydroxy-3-azido-3-phenylpropionate (10). A mixture of compound **3** (1.278 g, 4.7 mmol) and NaN_3 (1.222 g, 18.8 mmol) in DMF (4.7 mL) was stirred at 65 °C for 48 h. The reaction was diluted with EtOAc, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc, 8:2) afforded pure compound **10**[17g] (930 mg, 99%). ^{1}H-NMR: δ 7.70−7.55 (5H, m), 4.86 (1H, d, J = 2.9 Hz), 4.38 (1H, dd, J = 2.9 and 6.6 Hz), 3.84 (3H, s), 3.05 (1H, bs, OH). ^{13}C-NMR: δ 172.5, 135.6, 129.0, 128.9, 127.9, 73.7, 66.9, 52.9.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Methyl Ester (11). Compound **10** (930 mg, 4.6 mmol) treated in CH_2Cl_2 (7 mL) with DMAP (562 mg, 4.6 mmol) and BzCl (0.57 mL, 4.6 mmol) was stirred at rt for 1 h. After standard workup, the crude product was hydrogenated with 10% Pd/C (465 mg) in MeOH (15 mL) under H_2 (50 psi) for 4 h. The solution was then filtered and allowed to stand at 25 °C for 48 h. Concentration under vacuo of the solution and crystallization (2% $CHCl_3$/MeOH) afforded pure compound **11** (1.210 g, 85% from **10**). $[\alpha]_D$ = −47.7° (*c* 1.2, MeOH), lit.[17g] $[\alpha]_D$ = −49° (*c* 1, MeOH). ^{1}H-NMR: δ 7.87−7.70 (5H, m), 7.6−7.13 (8H, m), 7.02 (1H, bd, J = 5 Hz), 5.72 (1H, dd, J = 5 and 1.9 Hz), 4.62 (1H, d, J = 2.0 Hz), 3.81 (3H, s), 2.75 (1H, bs, OH). ^{13}C-NMR: δ 173.6, 167.1, 138.8, 131.9, 128.8, 128.7, 128.0, 127.5, 127.1, 127.0, 73.1, 54.7, 53.1.

2-Cyclohexylethanal (13). To a solution of commercially available compound **12** (2 g, 15.6 mmol) in CH_2Cl_2 (500 mL) was added PCC (5.16 g, 23.8 mmol). After 3 h, Et_2O (150 mL) was added and the solution was allowed to stir for 1 h. After usual workup, the combined organic layers were removed by evaporation in vacuo, affording known **13**[18c] (1.941 g, 98%).^{1}H-NMR: δ 9.63 (1H, s), 2.15 (2H, d, J = 6.5 Hz), 1.97−1.38 (6H, m), 1.32−0.65 (5H, m). ^{13}C-NMR: δ 202.6, 50.9, 32.7, 32.5, 32.1, 25.5.

(2*E*)-Ethyl 4-Cyclohexyl-2-butenoate (14). To a solution of compound **13** (1.941 g, 15.3 mmol) and LiOH (403 mg, 16.8 mmol) in THF (153 mL) was added TEPA (triethyl phosphonoacetate, 3.796 g, 16.8 mmol). The reaction mixture was refluxed for 2 h and then quenched with water (20 mL). The mixture was then extracted with EtOAc (70 mL), and the organic phase was concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 9:1) afforded pure **14** (2.411 g, 80%).^{1}H-NMR: δ 7.00−6.78 (1H, m), 5.73 (1H, dt, J = 15.5 and 1.4 Hz), 4.11 (2H, q, J = 7.1 Hz), 2.15−1.96 (2H, m), 1.84−0.70 (11H, m), 1.12 (3H, t, J = 7.1 Hz). ^{13}C-NMR: δ 166.7, 148.1, 122.2, 59.8, 39.9, 37.0, 32.8, 26.0, 25.9, 13.9. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.49; H, 10.22.

(2*E*)-4-Cyclohexyl-2-buten-1-ol (15). To a cooled solution (−78 °C) of compound **14** (2.411 g, 12.24 mmol) in toluene (160 mL) under argon was added DIBAL (16.3 mL of a 1.5 M solution in toluene, 24.28 mmol) slowly. After 1 h the reaction was quenched with saturated NH_4Cl and the mixture was extracted with Et_2O; the organic layer was then dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 7:3) afforded **15** (1.79 g, 95%). ^{1}H-NMR: δ 5.75−5.42 (2H, m), 4.20 (2H, d, J = 4.1 Hz), 2.22 (1H, bs, OH), 1.88 (2H, t, J = 6.3 Hz), 1.80−1.40 (5H, m), 1.38−1.00 (4H, m), 0.99−0.67 (2H, m). ^{13}C-NMR: δ 131.7, 130.1, 63.4, 40.0, 37.6, 32.9, 26.3, 26.1, 13.9. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.94; H, 11.71.

(2*S*,3*S*)-2,3-Epoxy-4-cyclohexylbutan-1-ol (16). To a 250 mL round bottom flask under argon were added $Ti(OiPr)_4$ (3.297 g, 11.6 mmol) and L-(+)-DET (2.628 g, 12.76 mmol) in CH_2Cl_2 (116 mL) at −23 °C. The solution was allowed to stir for 5 min; then compound **15** (1.79 g, 11.6 mmol) and successively TBHP (7.75 mL of a 3 M solution in isooctane, 23.2 mmol) were added. After 24 h tartaric acid (29 mL of a 10% aqueous solution) was

(18) For recent syntheses of norstatine analogs, see: (a) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kobata, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707. (b) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737. (c) Kobayashi, Y.; Takemoto, Y.; Kamjio, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (d) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785.

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added and the solution was stirred at −23 °C. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 1 h until the aqueous layer became clear. After separation of the aqueous layer, the organic layer was washed once with water, dried over Na_2SO_4, and concentrated. This oil was diluted with Et_2O (87 mL) and cooled in a ice bath, and then NaOH (34 mL of 1 N solution in brine) was added; the two-phase mixture was stirred at 0 °C for 0.5 h, and then the ether phase was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc, 7:3) afforded pure **16** (1.577 g, 80%). $[\alpha]_D = -7.43°$ (c 0.88, $CHCl_3$). ^{1}H-NMR: δ 3.83 (1H, dd, J = 12.6 and 2.5 Hz), 3.50 (1H, dd, J = 12.6 and 4.6 Hz), 2.99−2.67 (2H, m), 2.6 (1H, bs, OH), 1.95−0.70 (13H, m). ^{13}C-NMR: δ 61.6, 58.7, 54.6, 39.2, 35.5, 33.4, 32.9, 26.1, 26.0, 25.9. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.48; H, 10.69.

(2*R*,3*S*)-2,3-Epoxy-4-cyclohexylbutanoic Acid (17). To a vigorously stirred mixture of compound **16** (1.577 g, 9.28 mmol) were added $NaIO_4$ (5.96 g, 27.84 mmol) in CCl_4 (18.5 mL), CH_3CN (18.5 mL), H_2O (27.8 mL), and $RuCl_3 \cdot H_2O$ (46 mg, 0.2 mmol). The mixture was stirred at 20 °C for 2 h; then the acidic material was carefully extracted at 0 °C into ether, which was dried briefly over Na_2SO_4. The residue obtained after evaporation of the solvents was purified by flash chromatography (hexane/ether, 9:1) to afford **17** (1.22 g, 71.5%). ^{1}H-NMR: δ 10.83 (1H, bs, OH), 3.18 (2H, m), 2.06−0.70 (13 H, m). ^{13}C-NMR: δ 175.0, 57.7, 39.0, 35.4, 33.2, 32.7, 26.0, 25.9, 25.8.

(2*R*,3*S*)-Isopropyl 2,3-Epoxy-4-cyclohexylbutanoate (8). To an ice bath cooled solution of **17** (1.220 g, 6.63 mmol) in CH_2Cl_2 (9.28 mL) and iPrOH (2.13 mL, 27.8 mmol) was added DCC (2.167 g, 10.2 mmol) under stirring. After 5 min the solution was allowed at rt for 3 h; then it was filtered, washed with HCl (2 mL of 0.5 N solution) and then with saturated $NaHCO_3$, and filtered again. The organic phase was concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc, 9:1), affording pure **8** (1.053 g, 70%). ^{1}H-NMR: δ 5.15−4.95 (1H, m), 3.20−3.02 (2H, m), 1.85−0.75 (13H, m), 1.22 (6H, d, J = 6.2 Hz). ^{13}C-NMR: δ 169.1, 69.0, 57.0, 53.2, 39.0, 35.5, 33.2, 32.7, 26.0, 25.9, 25.8, 21.5, 21.4. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.8. Found: C, 68.90; H, 10.1.

(2*S*,3*R*)-Isopropyl 2-Hydroxy-3-bromo-4-cyclohexylbutanoate (9). According to the general procedure with $MgBr_2$, compound **8** (1.053 g, 4.64 mmol) gave pure compound **9** (1.40 g, 98%). ^{1}H-NMR: δ 5.23−5.02 (1H, m), 4.45−4.22 (2H, m), 3.20 (1H, bs, OH), 2.02−0.60 (13H, m), 1.22 (6H, d, J = 6.6 Hz). ^{13}C-NMR: δ 170.8, 74.4, 70.4, 54.5, 40.7, 35.0, 33.6, 31.5, 26.2, 25.9, 25.7, 21.6, 21.5.

(2*R*,3*S*)-Isopropyl 2-Hydroxy-3-azido-4-cyclohexylbutanoate (18). A mixture of **9** (1.40 g, 4.54 mmol) and NaN_3 (1.18 g, 18.16 mmol) in DMF (4.54 mL) was stirred at 65 °C for 6 h. The mixture was then diluted with EtOAc, washed with water, and concentrated in vacuo. Flash chromatography (hexanes/ether, 7:3) afforded pure **18** (856 mg, 70%). ^{1}H-NMR: δ 5.26−5.04 (1H, m), 4.09 (1H, dd, J = 5.5 and 2.4 Hz), 3.62−3.48 (1H, m), 3.07 (1H, d, OH, J = 5.4 Hz), 1.90−0.72 (13H, m), 1.23 (6H, d, J = 6.5 Hz). ^{13}C-NMR: δ 172.5; 73.2; 70.5; 60.5; 37.1; 34.2; 33.3; 32.7; 26.2; 26.0; 25.9; 21.5.

(2*R*,3*S*)-Isopropyl 2-Hydroxy-3-amino-4-cyclohexylbutanoate (19). A mixture of **18** (856 mg, 3.17 mmol) was hydrogenated with 10% Pd/C (85.6 mg) in EtOAc (8.6 mL) under H_2 for 4 h; then the solution was filtered and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 1:1) afforded pure compound **19** (618 mg, 80%). $[\alpha]_D = -21.8°$ (*c* 0.32, $CHCl_3$), lit.[18c] $[\alpha]_D = -22°$ (*c* 1.18, $CHCl_3$). ^{1}H-NMR: δ 5.2−5.02 (1H, m), 3.95 (1H, d, J = 2.6 Hz), 3.18−3.09 (1H, m), 1.85−0.72 (16H, m), 1.25 (6H, d, J = 6.5 Hz). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.09; H, 10.39; N, 5.78.

Acknowledgment. This work was partially supported by a 40% MURST grant and by CNR Progetto Finalizzato “Chimica Fine e Secondaria”.

Supporting Information Available: ^{1}H- and ^{13}C-NMR spectra (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951441H