Synthesis of (+)- and (−)-Statine via Chiral Sulfoxide Chemistry

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Statine ([3*S*,4*S*]-4-amino-3-hydroxy-6-methylheptanoic acid) is a nonproteinogenic amino acid contained in microbial aspartyl protease inhibitors such as Pepstatin.[1] A number of syntheses of the four stereoisomers of statine has been reported.[2] Extremely effective and highly stereoselective are the approaches of Rich (1988) with the modification of Reetz (1989),[3] Noyori (1988),[4] Terashima (1990),[5] and Gennari (1995).[6] Most of the conceivable retrosynthetic pathways to statine have been explored, spanning from the following: (a) the dominating asymmetric C_2-C_3 bond forming reaction (see Figure 1 for atom numbering) of *N*-protected leucinal with acetate enolate equivalents;[7] (b) the stereoselective reduction of leucine derived β-ketoesters;[8] (c) manipulation of other substrates derived from the chiral pool, such as sugars, or suitably functionalized lactams, oxazolidin-2-ones and related compounds;[9] (d) asymmetric ring opening reactions of epoxides having statine or statine-like carbon frameworks.[10,11] However, a route based on a stereoselective C_3-C_4 bond forming reaction between an imine derived from (3-methyl)butanal and a chiral equivalent of (3-hydroxy)propanoate 3-carbanion has not been reported yet (Figure 1).[12] Recently, we have demonstrated that α-lithium alkyl sulfoxides can be used as chiral α-hydroxyalkyl carbanion equivalents with nonenolizable imines for the asymmetric synthesis of β-amino alcohols.[13] This strategy takes advantage of a synergistic combination of two methodologies recently developed in our laboratories: (1) the chiral sulfoxide stereocontrolled

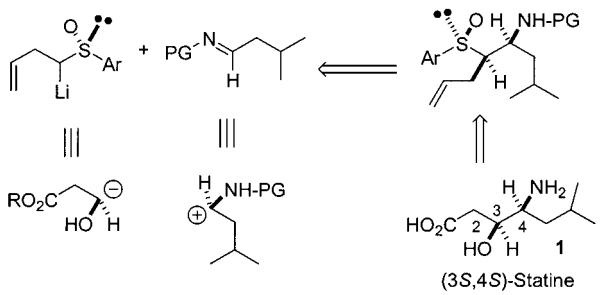

Figure 1. Retrosynthetic Scheme.

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(12) This might be due to the fact that synthetic equivalents of chiral α-hydroxy carbanions are not yet a well established tool in asymmetric organic synthesis, and only a relatively little number of such equivalents has hitherto found some practical use. See for example: (a) Fernández-Megía, E.; Ley, S. V. *Synlett* **2000**, 455−458 and the list of references therein. (b) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392−2398. (c) Deiters, A.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2105−2107. (d) Heimbach, D. K.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **2000**, 950−954 and references therein.

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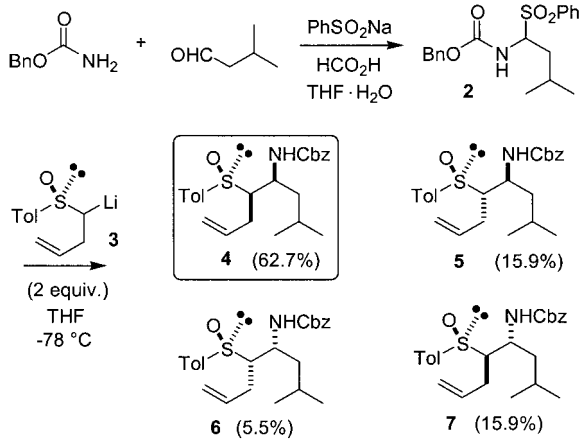
additions of carbon nucleophiles to imines derived from aryl or fluoroalkyl aldehydes and ketones,[14] and (2) the ≪nonoxidative≫ Pummerer reaction (NOPR),[15] that allows for a one-pot S_N2-type displacement of the sulfinyl auxiliary by a hydroxyl from the intermediate *β*-sulfinylamines. The use of *N*-PMP imines for the C−C bond forming step proved to be extremely rewarding in terms of yields, stereocontrol and easy cleavage. However, essential to an efficient outcome of the NOPR is a neighboring group participation by the *β*-amino group, which must be protected as monoamide (NHCOR) or monocarbamate (NHCOOR), whereas the PMP group gives rise to a totally different outcome.[16] For this reason, cleavage of the PMP group followed by *N*-acylation or *N*-alcoxycarbonylation were necessary prior to performing the NOPR.

In this paper we present the following: (1) an extension of our stereoselective NOPR-based methodology to enolizable imines, (2) an improvement consisting in the use of *N*-Cbz imines for the C−C bond forming step, that allows for a direct use of the NOPR without the need of intermediate *N*-deprotection/reprotections, and (3) an application of this chemistry to the stereocontrolled synthesis of both enantiomers of statine, even in selectively protected forms suitable for peptide chemistry.

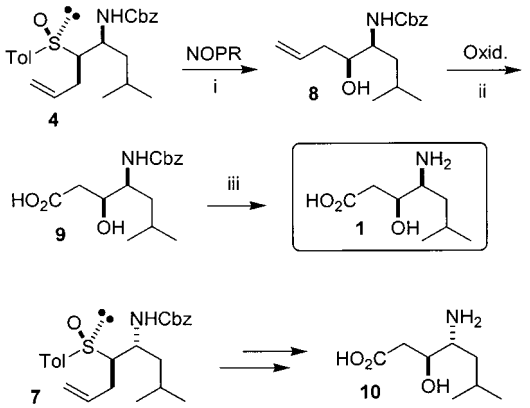
Results and Discussion

To accomplish the first step of our synthetic plan (C−C bond forming) we needed to achieve addition of enantiomerically pure α-lithium 3-butenyl *p*-tolylsulfoxide to an imine derived from 3-methyl butanal. However this goal appeared rather challenging, because it was already known from previous work by Pyne et al. that additions of α-lithium sulfoxides to enolizable *N*-aryl and *N*-alkyl imines are poorly synthetically useful, due to competitive enolization/polymerization side-processes involving the imine.[17] To overcome this trouble we envisioned the use of an activated imine having a *N*-electron-withdrawing group, which was expected to be much more reactive toward the nucleophile. The use of *N*-acyl and *N*-tosyl imines was immediately discarded, due to the difficulties connected with the hydrolysis of the resulting amides and sulfonamides. Next, we considered the possibility to use a *N*-sulfinyl-imine.[18] In fact, Ellman et al. reported that enolizable *tert*-butylsulfinyl imines give rise to highly stereoselective reactions with enolates,[19] while García Ruano et al. described the stereoselective additions of lithiated alkyl sulfoxides to benzaldehyde-derived *p*-tolylsulfinimines.[20] However, the latter authors showed that the NOPR cannot be performed directly on the resulting sulfinamides, because *N*-desulfinylation occurs. As a consequence, the sulfinamides must be hydrolyzed and reprotected as NHCOOR derivatives prior to performing the NOPR process, leading to a two-steps lengthening of the synthesis. For the reasons above, the use of a *N*-alkoxycarbonyl imine appeared as the optimal choice. Mecozzi and Petrini have recently published the preparation of stable and easy-to-handle precursors (α-amidoalkyl sulfones) of a wide range of enolizable *N*-alkoxycarbonyl imines,[21] from which the latter can be generated in situ by action of an excess of the carbon nucleophile, or by an extra-amount of base such as *n*-BuLi. The α-amidoalkyl sulfone **2** (Scheme 1) derived from 3-methyl-butanal was therefore reacted with 2 equiv of α-lithium sulfoxide (*S*)-**3**. Although we did not try to optimize the stereoselectivity of the reaction, the result was satisfactory. In fact, a mixture of the four diastereomeric sulfoxides (−)-**4**−**7** formed in excellent overall yield, with good stereocontrol in favor of the major diastereomer (−)-**4**, having the correct stereochemistry to provide the natural statine (−)-**1** through NOPR chemistry (see below).[22] The excess of protonated (*S*)-**3** was recovered

Scheme 1



Scheme 2[a]



[a] Key: (i) (a) TFAA, *sym*-collidine, MeCN; (b) $NaBH_4$, THF/H_2O (76%). (ii) $KMnO_4$, H_2SO_4 (48%). (iii) (a) $Pd(OH)_2-C/H_2$; (b) DOWEX-50W (57%).

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(16) In our previous works on the NOPR we almost invariably used COOR as protecting group for the *β*-nitrogen, because unlike amides (NHCOR), carbamates can be transformed into primary amines under very mild conditions.

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(22) Diastereoselectivity was measured by HPLC analysis (see Experimental Section).

by FC in nearly quantitative yield. It is worth noting that the reaction portrayed in Scheme 1 took place with opposite diastereofacial selectivity in comparison with that involving α-lithium **3** and the *N*-PMP-imine of trifluoroacetaldehyde.[23] Although the good observed stereocontrol suggests that a chelated transition state might be responsible for the preferential formation of (−)-**4**, the current little knowledge of this new kind of C−C bond forming reactions involving lithium sulfoxides and *N*-acyl imines does not allow for drawing a reliable mechanistic hypothesis.

To our satisfaction, the NOPR occurred effectively on a stereochemically pure sample of (−)-**4** providing the *syn*-*β*-amino-alcohol **8** in good yield and diastereocontrol > 98:2, with clean stereoinversion at carbon. For preparative purposes, given the difficulties connected with the separation of pure (−)-**4** from (−)-**5** by FC, the NOPR was routinely performed on mixtures of (−)-**4** and (−)-**5**, from which pure **8** was isolated in ca. 75% yield by FC. Next, **8** was submitted to oxidative demolition with $KMnO_4$, that delivered (3*S*,4*S*)-**9**, which is a selectively protected *N*-Cbz statine very useful for incorporation into peptide sequences. Hydrogenolysis of the *N*-Cbz group afforded the target natural statine (−)-(3*S*,4*S*)-**1**, whose ^{1}H NMR spectrum (500 MHz) and $[\alpha]^{20}_D$ were identical to those of a commercial sample (see Supporting Information).

The same sequence was repeated on both (−)-**7** and (+)-**4**, prepared from **2** and lithiated (*R*)-**3**, affording respectively (+)−(3*S*,4*R*)-statine in 34% overall yield, and (+)−(3*R*,4*R*)-statine.

Unambiguous absolute stereochemical assignment of **4**−**7** was achieved combining X-ray diffraction of a single crystal of (+)-**7** (see Supporting Information), with chemical correlation. In fact, deoxygenation of **4**−**7** (Me_3SiCl/NaI)[24] to the corresponding sulfides revealed an enantiomeric relationship between those deriving from the couples **4**/**6** and **5**/**7**, allowing us to assess the absolute configurations at the carbon stereocenters.

In conclusion, we have developed a conceptually new and synthetically efficient route to both enantiomers of natural statine, exploiting an α-lithiated alkylsulfoxide as a chiral α-hydroxyalkyl carbanion equivalent. This demonstrates that the methodology based on the NOPR has general scope and can be successfully extended to enolizable imines, which were previously considered as "difficult" substrates.

Experimental Section

General Procedure. For full general experimental information see ref 25. Reactions with dry solvents were carried out under N_2 atmosphere. Coupling constants (*J*) are reported in Hertz. Sulfoxide (*S*)-**3** was prepared according to the literature procedure.[26]

Synthesis of [2-(4-Methyl-phenyl)sulfinyl-1-isobutyl-pent-4-enyl]-carbamic acid benzyl esters (4−7). A solution of (*S*)-1-(but-3-ene-1-sulfinyl)-4-methyl-benzene (2.15 g, 11.08 mmol) in dry THF (10 mL) was added dropwise to a solution of freshly prepared LDA (13.3 mmol) in the same solvent (27 mL) cooled at − 60 °C. The resulting yellow solution of **3** was cooled to − 70 °C and, after 10 min, a solution of (1-benzenesulfonyl-isobutyl)-carbamic acid benzyl ester (**2**) (2.0 g, 5.54 mmol) in dry THF (10 mL) was added dropwise at the same temperature. After 20 min the reaction was complete, as shown by TLC monitoring (*n*-Hex/AcOEt 7:3). A saturated NH_4Cl solution was added, the mixture was diluted with water, warmed to room temperature and extracted with AcOEt (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. HPLC analysis (with both achiral and chiral columns) showed the following diastereomers ratio: (1*S*,2*R*,S_S)-**4**/(1*S*,2*S*,S_S)-**5**/(1*R*,2*S*,S_S)-**6**/(1*R*,2*R*,S_S)-**7** = 62.7/15.9/5.5/15.9. LiChrosorb Si 60 (5 μm), 4 mm, *n*-Hex/AcOEt = 4:1, 1 mL/min., t_R 6.22 min (**7**), t_R 7.83 min (**6**), t_R 8.60 min (**5** + **4**). Chiracel OD, 4.6 mm,, *n*-Hex/*iso*-PrOH = 95:5, 0.8 mL/min., t_R 12.18 min (**7**), t_R 13.50 min (**6** + **5**), t_R 14.48 min (**4**).

The crude was purified by FC (*n*-Hex/AcOEt 4:1 to 7:3) affording: pure **7** (360 mg, 15.4%). The resulting mixture of **4**, **5**, and **6** was submitted to a further FC in toluene/AcOEt 9:1 affording pure (1*R*,2*S*,S_S)-**6** (123 mg, 5.3%), and a mixture of **4** and **5** (1.53 g, 60.8% and 15.4% respectively). The four diastereomers were isolated in 97% overall yield.

(1*S*,2*R*,S_S)-**4**: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.855 (3H, d, *J* = 6.7), 0.91 (3H, d, *J* = 6.2), 1.49−1.57 (1H, m), 1.59−1.70 (2H, m), 2.30−2.50 (2H, m), 2.39 (3H, s), 2.90−2.95 (1H, m), 4.05−4.15 (1H, m), 4.95−5.20 (4H, m), 5.55−5.67 (1H, m), 7.25−7.30 (2H, m), 7.30−7.45 (7H, m); ^{13}C NMR (63 MHz, $CDCl_3$) *δ* 155.7, 141.0, 139.6, 136.6, 134.3, 129.8, 128.6, 128.1, 124.4, 118.0, 68.7, 66.9, 50.1, 39.3, 26.1, 25.1, 23.5, 21.3, 21.3. (1*S*,2*S*,S_S)-**5**: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.79 (3H, d, *J* = 5.9), 0.860 (3H, d, *J* = 6.7), 1.49−1.57 (2H, m), 1.59−1.70 (1H, m), 2.405 (3H, s), 2.85−2.90 (1H, m), 4.15−4.25 (1H, m), 4.95−5.20 (4H, m), 5.67−5.79 (1H, m), 7.25−7.30 (2H, m), 7.30−7.45 (7H, m); ^{13}C NMR (63 MHz, $CDCl_3$) *δ* 156.2, 141.6, 139.6, 136.7, 136.4, 130.1, 128.5, 127.9, 125.2, 118.7, 66.9, 66.7, 50.5, 44.7, 31.4, 25.0, 22.7, 21.5, 21.4. Mixture of **4** and **5**: FT-IR (film) (cm^{-1}) 3290, 3035, 2957, 2870, 1715, 1531; MS (DIS EI, 70 eV) *m*/*z* (%) 414 (MH^+, 35), 274 (18), 230 (10), 182 (8).

(1*R*,2*S*,S_S)-**6**: $[\alpha]_D^{20}$ −147.5 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.94 (3H, m), 0.97 (3H, d, *J* = 6.7), 1.48−1.58 (1H, m), 1.72−1.83 (1H, m), 1.85−2.00 (2H, m), 2.02−2.14 (1H, m), 2.43 (3H, s), 2.97−3.04 (1H, m), 4.27−4.35 (1H, m), 4.97−5.12 (2H, m), 5.09 (1H, d, *J* = 9.1), 5.13 (1H, d, *J* = 9.1), 5.43−5.51 (1H, m), 6.20−6.30 (1H, m), 7.30 (2H, d, *J* = 8.3), 7.32−7.39 (m, 5H), 7.59 (2H, d, *J* = 8.3); ^{13}C NMR (63 MHz, $CDCl_3$) *δ* 156.1, 142.8, 139.5, 136.9, 133.1, 130.1, 128.4, 127.9, 126.1, 118.6, 68.9, 66.5, 50.5, 39.2, 30.4, 25.0, 23.7, 21.54, 21.51; FT-IR (film) (cm^{-1}) 3299, 3034, 2956, 2870, 1719, 1509, 1227; MS (DIS EI 70 eV) *m*/*z* (%) 414 (MH^+, 35), 274 (18), 230 (10), 182 (8), 140 (18), 139 (9), 91 (100).

(1*R*,2*R*,S_S)-**7**: mp 120−121 °C (diisopropyl ether); $[\alpha]_D^{20}$ −136.6 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.01 (3H, d, *J* = 6.6), 1.04 (3H, d, *J* = 6.4), 1.72−1.83 (2H, m), 1.93−2.00 (1H, m), 2.06−2.13 (1H, m), 2.39−2.46 (1H, m), 2.44 (3H, s), 2.60 (1H, ddd, *J* = 9.2, 4.0, 3.9), 4.28−4.35 (1H, m), 4.88 (1H, d, *J* = 17.1), 4.95 (1H, d, *J* = 9.9), 5.10 (2H, br s), 5.45−5.55 (1H, m), 5.86 (1H, d, *J* = 9.21), 7.28−7.40 (9H, m); ^{13}C NMR (63 MHz, $CDCl_3$) *δ* 156.2, 141.3, 137.9, 136.8, 134.1, 130.0, 128.4, 127.9, 124.3, 118.3, 66.6, 65.4, 50.2, 43.4, 26.1, 25.1, 22.7, 22.4, 21.4; FT-IR microscopy (solid) (cm^{-1}) 3240, 3062, 2957, 2867, 1711, 1552; MS (DIS EI 70 eV) *m*/*z* (%) 414 (MH^+, 1), 413 (M^+, 8), 274 (10), 230 (8), 216 (2), 182 (5), 139 (18), 91 (100).

Starting from (*R*)-**3**, (1*S*,2*S*,R_S)-**7** was obtained and submitted to X-ray diffraction (see Supporting Info); R_f 0.35; mp 120−121 °C (diisopropyl ether); $[\alpha]_D^{20}$ + 135.6 (c 1.1, $CHCl_3$); FT-IR, ^{1}H and ^{13}C NMR ($CDCl_3$), MS (EI) data were overimposable to those of the already described enantiomer.

Synthesis of (2-Hydroxy-1-isobutyl-pent-4-enyl)-carbamic acid benzyl ester (8). *Sym*-collidine (1.35 mL, 10.0 mmol) was added to a cooled (−10 °C) solution of a mixture (ca. 4:1) of **4** and **5** (3.36 mmol, 1.40 g) in acetonitrile (80 mL). Trifluoroacetic anhydride (16.8 mmol, 3.30 mL) was added dropwise and the reaction was monitored by TLC (*n*-Hex/AcOEt 7:3). After 10 min the starting compound was consumed. Water was added, the organics were extracted with AcOEt (3 × 50 mL), combined,

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dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. The residue was dissolved in a THF/H_2O 4:1 mixture (70 mL), cooled to 0 °C (water/ice bath), and $NaBH_4$ was added portionwise up to pH 7−8. After 5 min, a saturated NH_4Cl solution was added, followed by a 1N HCl solution until pH 1−2 was reached, then the reaction mixture was diluted with water, the organics were extracted with AcOEt (3 × 50 mL), combined, dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. The residue was purified by FC (*n*-Hex/AcOEt 9:1 to 4:1) to give (1*S*,2*S*)-**8** (740 mg, 76%).

(1*S*,2*S*)-**8**: R_f = 0.35 (*c*-Hex/AcOEt 4:1); $[\alpha]_D^{20}$ − 20.1 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.0), 0.94 (3H, d, J = 6.0), 1.30−1.39 (1H, m), 1.47−1.56 (1H, m), 1.61−1.72 (1H, m), 1.75−1.87 (1H, br signal), 2.14−2.24 (1H, m), 2.28−2.36 (1H, m), 3.59−3.65 (1H, m), 3.69−3.78 (1H, m), 4.89 (1H, br d, J = 9.0), 5.08−5.20 (4H, m), 5.77−5.90 (1H, m), 7.30−7.40 (5H, m);^{13}C NMR (63 MHz, $CDCl_3$) δ 156.7, 136.7, 134.4, 128.5, 128.1, 128.0, 118.4, 72.6, 66.7, 52.7, 42.0, 39.1, 24.8, 23.2, 22.2; FT-IR (film) (cm^{-1}) 3433, 2957, 1698, 1520; MS (DIS EI 70 eV) *m*/*z* (%) 292 (MH^+, 2), 220 (10), 176 (18), 130 (10), 91 (100).

Synthesis of 4-(Carbamic acid benzyl ester)-3-hydroxy-6-methyl-heptanoic acid (9). A quantity of 3 N Aqueous H_2SO_4 (5.0 mL) was added dropwise to a solution of (1*S*,2*S*)-**8** (740 mg, 2.54 mmol) in acetone (40 mL) cooled to 0 °C. Then, an aqueous solution (70 mL) of $KMnO_4$ (2.41 g, 15.26 mmol) was added dropwise at the same temperature. The reaction was quenched after 5 min by portionwise addition of solid Na_2SO_3 until a brown slurry was obtained. A 3N H_2SO_4 solution was then added up to pH 2, the mixture was diluted with water and the organics were extracted with AcOEt (3 × 60 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. The crude was purified by FC ($CHCl_3$/AcOEt/AcOH 7:3:0.1) to give (3*S*,4*S*)-**9** (376 mg, 48%) R_f 0.35; mp 117−118 °C (diisopropyl ether); $[\alpha]_D^{20}$ −33.3 (c 1.0, MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ 0.91 (3H, d, J = 6.0), 0.93 (3H, d, J = 6.0), 1.25−1.38 (1H, m), 1.42−1.55 (1H, m), 1.56−1.71 (1H, m), 2.35 (1H, dd, J = 15.8, 8.6), 2.46 (1H, dd, J = 15.8, 4.4), 3.66−3.78 (1H, m), 3.97−4.05 (1H, m), 5.08 (2H, br s), 6.64 (1H, br d, J = 9.4), 7.25−7.40 (5H, m);^{13}C NMR (63 MHz, $CDCl_3$) δ 175.5, 158.8, 138.4, 129.4, 128.9, 128.6, 71.0, 67.5, 54.3, 41.5, 39.7, 25.9, 23.6, 22.4; FT-IR microscopy (solid) (cm^{-1}) 3484, 3381, 2959, 1725, 1693, 1521; MS (DIS EI 70 eV) *m*/*z* (%) 310 (MH^+, 18), 292 (21), 266 (3), 220 (45), 176 (60).

Synthesis of (3*S*,4*S*)-Statine (1). To a solution of (3*S*,4*S*)-**9** (337 mg, 1.09 mmol) in MeOH (15 mL) was added a catalytic amount of $Pd(OH)_2$−C. The slurry was vigorously stirred 3 h at room temperature under H_2 atmosphere, according to TLC reaction monitoring ($CHCl_3$/AcOEt/AcOH 7:3:0.1), then filtered on a Celite pad, washing with MeOH. The solvent was removed in vacuo and the crude purified with acidic DOWEX-50W ion-exchange resin, affording (3*S*,4*S*)-**1** as a white powder (109 mg, 57%): mp 200 °C (dec); $[\alpha]_D^{20}$ −22.7 (c 0.70, H_2O);[27] ^{1}H NMR (400 MHz, CD_3OD) δ 1.08 (3H, d, J = 6.3), 1.10 (3H, d, J = 6.3), 1.60−1.74 (2H, m), 1.80−1.91 (1H,m), 2.58 (1H, dd, J = 15.3, 7.5), 2.71 (1H, dd, J = 15.3, 5.0), 3.41−3.48 (1H, m), 4.18 (1H, ddd, J = 7.5, 5.0, 5.5); ^{13}C NMR (63 MHz, $CDCl_3$) δ 181.4, 70.9, 56.5, 44.0, 41.1, 26.5, 24.7, 23.6; *m*/*z* (EI, %) 158 (MH^+ − H_2O, 38), 157 (M − H_2O, 35), 114 (75), 100 (85).

Synthesis of (3*R*,4*R*)-Statine (ent-1). It was obtained through an identical sequence of reactions from (1*R*,2*S*,R_S)-**4**. $[\alpha]_D^{20}$ + 16.1 (c 0.31, H_2O);[27] the other physical and spectral properties matched those of the enantiomer.

Synthesis of (3*S*,4*R*)-Statine (10). From (1*R*,2*R*,S_S)-**7**, following the same general procedures above-described, (3*S*,4*R*)-**10** was obtained (65 mg, 34% overall yield): mp 195 °C; $[\alpha]_D^{20}$ +19.4 (c 0.5, H_2O);[28] ^{1}H NMR (500 MHz, CD_3OD) δ 0.93 (3H, d, J = 6.6), 0.94 (3H, d, J = 6.6), 1.37−1.42 (2H, m), 1.62−1.73 (1H, m), 2.26 (1H, dd, J = 16.0, 2.5), 2.85 (1H, dd, J = 16.0, 6.7), 3.63 (1H, dt, J = 7.5, 2.0), 4.25 (1H, ddd, J = 6.7, 2.5, 2.0); ^{13}C NMR (63 MHz, $CDCl_3$) δ 180.9, 74.2, 64.4, 44.4, 40.9, 26.8, 24.7, 23.6; FT-IR microscopy (solid) (cm^{-1}) 3262, 2958, 1691, 1468, 1388; MS (DIS EI 70 eV) *m*/*z* (%) 176 (MH^+, 38), 158 (MH^+ − H_2O, 1), 118 (5), 114 (5).

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds (+)- and (−)-**1**, **4**−**10**, ORTEP and crystal data of compound (1*S*,2*S*,R_S)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) A number of different values of optical rotatory powers for **1** and *ent*-**1** have been reported. Some of them, measured in water, are listed below. For (3*S*, 4*S*)-**1**: ref 10a, $[\alpha]_D^{20}$ −20.8 (c 2.3, H_2O); ref 5, $[\alpha]_D^{20}$ −20.4 (c 0.50, H_2O). For (3*R*, 4*R*)-**1**: ref 11b, $[\alpha]_D^{20}$ +18.3 (c 0.43, H_2O); ref 7f, $[\alpha]_D^{20}$ +20 (c 1, H_2O).

(28) Some optical rotatory powers for **10** and *ent*-**10** reported in the literature are listed below. For (3*R*, 4*S*)-**10**: ref 7f, $[\alpha]_D^{20}$ −19 (c 0.73, H_2O). For (3*S*, 4*R*)-**10**: ref 9j, $[\alpha]_D^{20}$ +19.8 (c 0.51, H_2O); ref 7f, $[\alpha]_D^{20}$ +18 (c 0.88, H_2O).