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A stereodivergent approach to *syn*- and *anti*-β-hydroxy-γ-amino acids. Enantioselective synthesis of *N*-Boc-statine and *N*-Boc-3-epistatine mediated by sulfoxides

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Abstract—Asymmetric syntheses of the *syn*- and *anti*-stereoisomers of *N*-Boc statine, based on the stereodivergent reduction of a single sulfoxide **5**, derived from *N*-Boc-L-leucine, are reported.

1. Introduction

Recently, β-hydroxy-γ-amino acids have received considerable attention, notably those acting as key components of peptidomimetic protease inhibitors.[1] In particular statine **1**, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, a nonproteinogenic amino acid is an essential component of the naturally occurring pepstatin, which acts as an inhibitor of aspartic acid proteases such as renin, pepsin and cathepsin D.[2] The low selectivity of pepstatin provided impetus for the development of more specific synthetic analogs such as the widely used cyclohexylstatine **2**, in which the isobutyl moiety of statine has been substituted by a cyclohexylmethyl group.[3] Interestingly, the *syn* (*threo*) relative configuration of the amino and hydroxyl groups in statine is essential for this bioactivity. However, several examples of the corresponding diastereomeric *anti* (*erythro*) series are also of natural occurrence. Thus, for example, isostatine **3**[4] is a component of didemnins, a family of cyclodepsipeptides which exhibits a broad spectrum of biological activities, and (3*R*,4*S*)-3-hydroxy-4-methylamino-5-phenylpentanoic acid **4** is an amino acid constituent of hapalosin[5] (Fig. 1).

A large number of syntheses of statine and its derivatives have been reported.[6] Although satisfactory degrees of stereocontrol have been achieved, multistep procedures are typically required and the number of general and unified routes to the four stereoisomers of statine is small.[7] Recently, we have demonstrated that the DIBAH and DIBAH/$ZnBr_2$ reductions of *N*-Boc γ-amino-β-keto sulfoxides, derived from readily available amino acid methyl ester hydrochlorides, produce diastereoisomeric β-hydroxy sulfoxides, this being a general stereodivergent procedure to prepare (R_1,S_2)- and (S_1,S_2)-2-amino alcohols, where the desired configuration at the hydroxylic carbon can be obtained by choosing a suitable reducing system.[8] Herein, we report a unique approach to the *syn*- and *anti*-stereoisomers of *N*-Boc statine, based on the stereodivergent reduction of a single β-keto sulfoxide **5**, derived from *N*-Boc-L-leucine methyl ester. Since *N*-Boc-D-leucine is also commercially available, the synthesis of the four stereoisomers of statine could be performed using this methodology.

2. Results and discussion

The overall synthetic sequence is depicted in Scheme 1. The starting diastereomerically pure (3*S*,*R*s)-*N*-(*tert*-butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfinyl]-2-hexanone **5** was obtained following a

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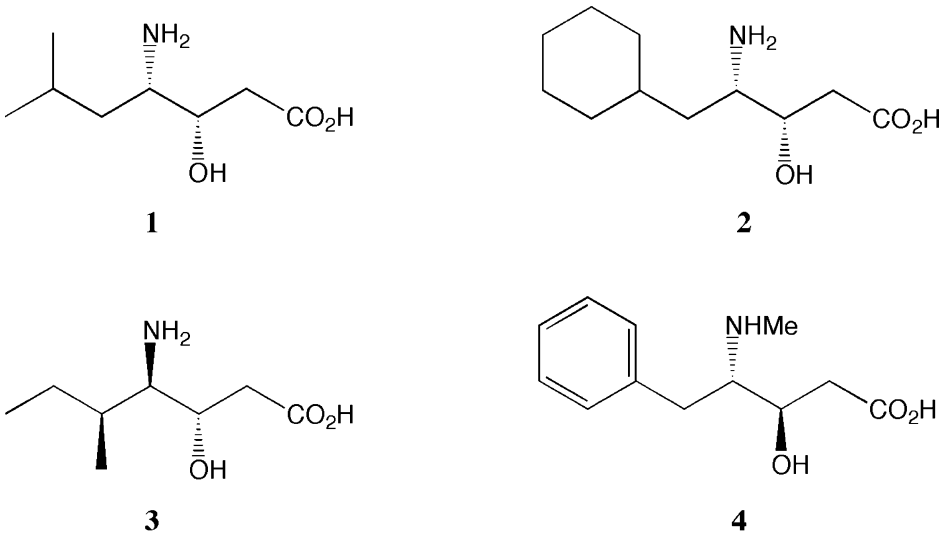


Figure 1.

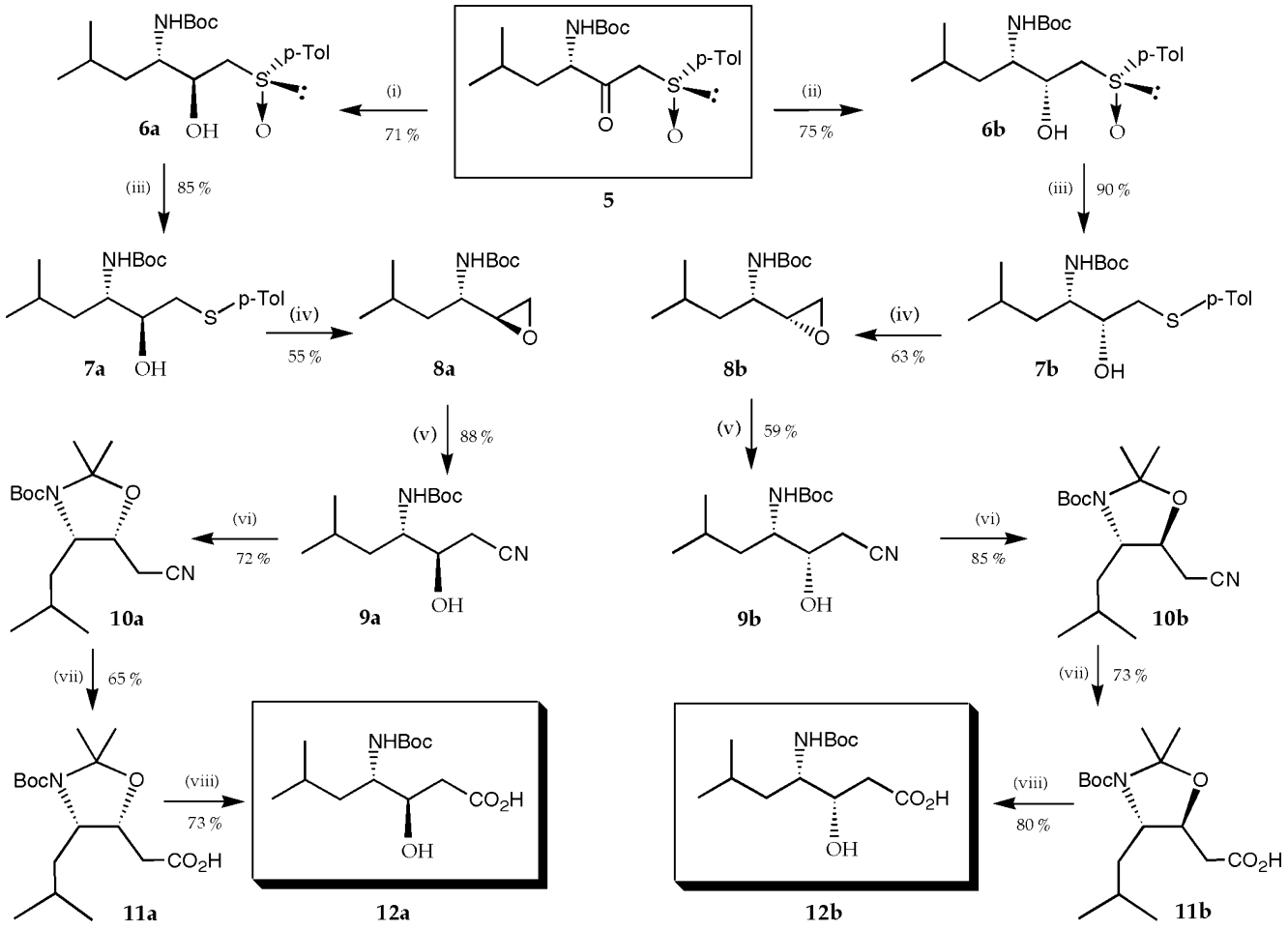
previously described synthetic route.[9] The reduction of β-keto sulfoxide **5** with DIBAH at −78°C gave the β-hydroxy sulfoxide **6a** with high stereoselectivity (*de* 90%).[8] An excess of the reducing agent was necessary to achieve complete transformation of the starting product in high yields. The β-hydroxy sulfoxide was purified by column chromatography to produce diastereoisomerically pure product (*de* >97%) in 71% yield. The synthesis of the β-hydroxy sulfoxide **6b**, with the opposite configuration at the hydroxylic carbon, was accomplished by reduction of the β-keto sulfoxide **5** with DIBAH/$ZnBr_2$.[8] Similarly, the reduction proceeded with high stereoselectivity (*de* 85%). Diastereoisomerically pure **6b** (*de* >97%) was obtained, in 75% yield, by crystallization of the crude product. Configurational assignment of the resulting diastereoisomers was deduced from the ^{1}H NMR spectra taking into account the well-known behavior of diastereoisomeric β-sulfinyl carbinols,[10] which agrees with the predictions made on the basis of the stereochemical model proposed to explain the DIBAH reduction of β-keto sulfoxides.[11]

The synthesis of oxiranes **8** starting from β-sulfinyl alcohols was performed following a synthetic sequence involving reduction of the sulfoxides, methylation of the sulfenyl group and S_Ni of the sulfonium salt by the alkoxide generated by treatment with base.[12] Thus, the reduction of the sulfinyl group of **6a** and **6b** was accomplished by reaction with $TiCl_3$ in EtOH at room temperature to furnish the corresponding β-hydroxy sulfenyl derivatives **7a** and **7b**, respectively. The reaction of sulfenyl derivatives **7a** and **7b** with trimethyl oxonium tetrafluoroborate in anhydrous CH_2Cl_2 followed by aqueous K_2CO_3 (one-pot procedure) afforded the optically active oxiranes **8a** and **8b**. Regioselective oxirane opening was achieved by treatment of **8a** and **8b** with Et_2AlCN in toluene at −78 to −15°C, affording hydroxy nitriles **9a** and **9b** in 88 and 59% yield, respectively.

The hydrolysis of the cyano group of hydroxy nitrile **9a** according to several reported procedures yielded either complex reaction mixtures or the recovery of the starting material. A similar troublesome situation was observed by Moyano and Pericàs in the hydrolysis of (3*R*,4*S*)-4-(*tert*-butoxycarbonylamino)-3-hydroxypentanenitrile.[6b] These authors discovered that this product could be efficiently protected as a *N*-Boc oxazolidine and further transformed into the required carboxylic acid by the use of non hydrolytic conditions (DIBAH reduction followed by $KMnO_4$ oxidation at controlled pH). Following this methodology, the reaction of hydroxy nitriles **9a** and **9b** with an excess of 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene produced, after column chromatography, *cis*-*N*-Boc oxazolidine **10a** (72% yield) and *trans*-*N*-Boc oxazolidine **10b** (85% yield), respectively. The reduction of **10a** and **10b** with DIBAH at −40°C gave the corresponding aldehydes. Although the yields of the crude products were high, these compounds were not very stable and suffered extensive degradation when purified by silica gel chromatography. Therefore, we tried the oxidation step on crude aldehydes, which involved the use of $KMnO_4$ in buffered (pH 4) aqueous *tert*-butyl alcohol.[13] Under these conditions, the protected carboxylic acids **11a** and **11b** were obtained in 65 and 73% yield, respectively.

Finally, acidic hydrolysis of the oxazolidine protecting group proceeded in good yields by treatment of **11a** and **11b** with aqueous AcOH at 70°C producing *N*-Boc-3-epistatine **12a**[7b,14] and *N*-Boc-statine **12b**.[7b,14]

In summary, we have shown that both (3*R*,4*S*)- and (3*S*,4*S*) - 4 - (*tert* - butoxycarbonylamino) - 3 - hydroxy-6-methylheptanoic acids **12a** and **12b** can be easily synthesized in high diastereomeric purity from the readily available β-keto sulfoxide **5** by a sequence involving stereodivergent reduction of **5** with DIBAH or DIBAH/$ZnBr_2$, conversion of the resulting hydroxy sulfoxides **6a** and **6b** to oxiranes **8a** and **8b**, regioselec-



Scheme 1. *Reagents and conditions:* (i) DIBAH, THF, −78°C. (ii) DIBAH/$ZnBr_2$, THF, −78°C. (iii) $TiCl_3$/HCl/EtOH. (iv) 1. Me_3OBF_4/CH_2Cl_2; 2. K_2CO_3/H_2O. (v) Et_2AlCN/toluene; −78→−15°C. (vi) DMP/C_6H_6/Δ. (vii) 1. DIBAH/Et_2O/−40°C; 2. $KMnO_4$/*t*BuOH/pH 4. (viii) AcOH/H_2O/70°C.

tive opening of the epoxide ring by cyanide ion, simultaneous protection of the resulting secondary alcohol and NH carbamate groups, nitrile to carboxyl transformation, and final acid hydrolysis of the oxazolidine protecting group.

3. Experimental

3.1. General methods

All moisture sensitive reactions were carried out in flame dried glassware under an argon atmosphere and monitored by TLC. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were determined in a Culatti melting point apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) using a Jasco DIP-360 polarimeter (concentration in g/100 mL). The IR spectra were recorded in a Nicolet-5SX spectrophotometer. The NMR spectra were determined in $CDCl_3$ solutions at 200 (or 300) and 50.3 (or 75.5) MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. The diastereoisomeric excesses were determined by 300 MHz ^1H NMR spectroscopy. Mass spectra were measured at 70 eV and 190°C. All described compounds were over 97% pure by NMR analysis.

3.1.1. (2*S*,3*S*,*R*s)-*N*-(*tert*-Butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfinyl]-2-hexanol, 6a. To a solution of β-keto sulfoxide **5**[9] (1.14 g, 3.1 mmol, 1 equiv.) in anhydrous THF (20 mL) at −78°C a solution of DIBAH in toluene (1.5 M, 15.5 mmol, 5 equiv.) was added dropwise. The reaction mixture was stirred for 10 min at −78°C and the excess of DIBAH was decomposed by adding 20 mL of MeOH. The solvents were removed under vacuum, the residue was treated with 25 mL of 5% HCl and extracted with Et_2O (2×50 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4) and evaporated. The crude product (1.2 g, *de* 90%) was purified by flash chromatography (hexane–ethyl acetate, 20:80), to produce 1.0 g (71%) of **6a** as a white solid, mp 95°C (CH_2Cl_2–hexane); $[\alpha]_D$ +105.0 (*c* 1.0, $CHCl_3$) *de* >97%; IR ($CHCl_3$) ν_{max}: 3610, 3439, 2961, 1706, 1596, 1499, 1368, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, 3H, *J* 6.6), 0.91 (d, 3H, *J* 6.6), 1.32–1.36 (m, 2H), 1.40 (s, 9H), 1.60 (m, 1H), 2.42 (s, 3H), 2.71 (dd, 1H, *J* 1.8 and 13.5), 3.00 (dd, 1H, *J* 10.2 and 13.5), 3.66 (broad m, 1H), 4.06 (broad m,

1H), 4.51 (broad d, 1H, *J* 8.7), 7.34 and 7.52 (AA'BB' system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 23.6, 24.7, 28.3, 39.2, 53.2, 59.6, 69.9, 79.7, 124.0, 130.1, 139.9, 141.5, 156.1; EIMS *m*/*z* 369 (5%, M^+), 296 (15), 268 (10), 186 (55), 183 (58), 174 (79), 139 (85), 130 (100), 86 (85), 57 (48); HRMS (EI): $C_{19}H_{31}NO_4S$ requires 369.1974. Found: 369.1980.

3.1.2. (2*R*,3*S*,*R*s)-*N*-(*tert*-Butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfinyl]-2-hexanol, 6b. A solution of β-keto sulfoxide **5**[9] (2.8 g, 7.63 mmol, 1 equiv.) in anhydrous THF (5 mL) was added to a cooled solution of $ZnBr_2$ (0.946 g, 7.63 mmol, 1 equiv.) in 15 mL of THF at 0°C and the resulting mixture was stirred at this temperature for 1.5 h. Then the solution was cooled at −78°C and a 1.5 M solution of DIBAH in toluene (15 mmol, 1.97 equiv.) was added dropwise. The reaction mixture was stirred for 1 h at −78°C and the excess DIBAH was decomposed by adding 20 mL of MeOH. Once the solution reached room temperature, the volatiles were removed under vacuum, the residue was treated with 25 mL of 5% HCl and extracted with Et_2O (2×50 mL). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The crude product (2.5 g, *de* 85%) was purified by crystallization from CH_2Cl_2/hexane to give 2.11 g (75%) of **6b** as white crystals, mp 115°C; $[\alpha]_D$ +111.5 (*c* 1.0, $CHCl_3$) *de* >97%; IR ($CHCl_3$) ν_{max}: 3440, 2961, 1703, 1499, 1367, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (d, 6H, *J* 6.3), 1.20–1.70 (broad m, 3H), 1.37 (s, 9H), 2.41 (s, 3H), 2.87 (dd, 1H, *J* 3.6 and 13.5), 2.96 (dd, 1H, *J* 8.7 and 13.5), 3.75 (m, 2H, partially interchangeable with D_2O), 4.29 (m, 1H), 4.51 (broad d, 1H, *J* 9.6), 7.31 and 7.52 (AA'BB' system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 22.2, 23.0, 24.7, 28.3, 41.3, 52.7, 60.7, 70.3, 79.2, 123.9, 130.0, 140.4, 141.9, 156.1; EIMS *m*/*z* 369 (4%, M^+), 296 (10), 268 (9), 186 (40), 174 (100), 139 (53), 130 (84), 86 (90), 57 (82); HRMS (EI): $C_{19}H_{31}NO_4S$ requires 369.1974. Found: 369.1978.

3.1.3. (2*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfenyl]-2-hexanol, 7a. To a stirred solution of **6a** (0.5 g, 1.35 mmol, 1 equiv.) in EtOH (10 mL) a 15% wt. solution of $TiCl_3$ (2 equiv.) in 20–30% aqueous HCl was added at room temperature. After 20 min, the solution was cooled in an ice bath, treated with 10 mL of water and 10 mL of 10% $NaHCO_3$ and extracted with Et_2O (3×15 mL). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was crystallized from CH_2Cl_2/hexane, to produce 0.41 g (85%) of **7a** as a white solid, mp 97–99°C; $[\alpha]_D$ −24.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3442, 3014, 2960, 2930, 1706, 1499, 1368, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, 3H, *J* 6.6), 0.92 (d, 3H, *J* 6.6), 1.30–1.40 (m, 2H), 1.43 (s, 9H), 1.64 (m, 1H), 2.32 (s, 3H), 2.84 (dd, 1H, *J* 9.3 and 13.5), 3.08 (dd, 1H, *J* 3.3 and 13.5), 3.62 (broad m, 1H), 3.72 (broad m, 1H), 4.58 (broad d, 1H, *J* 7.2), 7.11 and 7.30 (AA'BB' system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.0, 21.6, 23.7, 24.7, 28.4, 38.9, 39.4, 52.8, 72.8, 79.9, 129.9, 130.9, 131.0, 136.9, 156.1; EIMS *m*/*z* 353 (12%, M^+), 222 (25), 212 (45), 156 (70), 130 (92), 86 (100), 57 (93); HRMS (EI): $C_{19}H_{31}NO_3S$ requires 353.2025. Found: 353.2034.

3.1.4. (2*R*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfenyl]-2-hexanol, 7b. Following the same procedure used for the preparation of **7a**, and starting from 0.50 g (1.35 mmol) of **6b**, 0.432 g (90%) of **7b** were obtained. The product was purified by column chromatography. Colorless oil; $[\alpha]_D$ −30.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3443, 2961, 1705, 1498, 1367, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, 3H, *J* 6.6), 0.89 (d, 3H, *J* 6.6), 1.20–1.35 (m, 2H), 1.43 (s, 9H), 1.50–1.65 (m, 1H), 2.31 (s, 3H), 2.82 (dd, 1H, *J* 9.9 and 14.0), 3.10 (dd, 1H, *J* 4.2 and 14.0), 3.50 (broad m, 1H), 3.66 (broad m, 1H), 4.69 (broad d, 1H, *J* 9.6), 7.10 and 7.29 (AA'BB' system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.0, 22.1, 23.1, 24.8, 28.4, 40.3, 42.0, 51.5, 70.7, 79.3, 129.9, 130.7, 131.1, 137.2, 156.1; EIMS *m*/*z* 353 (6%, M^+), 279 (8), 264 (10), 222 (13), 212 (27), 156 (48), 130 (53), 86 (86), 57 (100).

3.1.5. (*S*)-1-[(*S*)-1-(*tert*-Butoxycarbonylamino)-3-methylbutyl]oxirane, 8a. Trimethyloxonium tetrafluoroborate (2 equiv.) was added to a solution of **7a** (0.5 g, 1.42 mmol) in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1 h and then a solution of K_2CO_3 (1.58 mmol) in 3 mL of water was added. The resulting mixture was vigorously stirred for 24 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate, 8:2) to produce 0.178 g (55%,) of **8a** as a white solid, mp 45–47°C; $[\alpha]_D$ −27.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3443, 2962, 1709, 1500, 1368, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, 3H, *J* 6.6), 0.94 (d, 3H, *J* 6.6), 1.35–1.42 (m, 2H), 1.44 (s, 9H), 1.65–1.80 (m, 1H), 2.75 (d, 2H, *J* 3.8), 2.82–2.86 (m, 1H), 3.50 (broad m, 1H), 4.44 (broad m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 23.3, 24.4, 28.3, 40.8, 46.1, 50.3, 54.5, 79.4, 155.4; EIMS *m*/*z* 229 (not observed, M^+), 186 (23), 130 (47), 86 (55), 72 (34), 57 (100).

3.1.6. (*R*)-1-[(*S*)-1-(*tert*-Butoxycarbonylamino)-3-methylbutyl]oxirane, 8b. Following the same procedure used for the preparation of **8a**, and starting from 0.40 g (1.13 mmol) of **7b**, 0.164 g (63%) of **8b** were obtained. The product was purified by column chromatography (hexane–ethyl acetate, 8:2). Colorless oil; $[\alpha]_D$ −43.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3440, 2961, 1708, 1503, 1368, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (d, 6H, *J* 6.6), 1.35–1.55 (m, 2H), 1.43 (s, 9H), 1.65–1.80 (m, 1H), 2.60 (broad m, 1H), 2.73 (t, 1H, *J* 4.6), 2.98 (broad m, 1H), 3.97 (broad m, 1H), 4.29 (broad m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 23.0, 24.7, 28.3, 42.3, 44.4, 47.2, 53.9, 79.4, 155.6; EIMS *m*/*z* 230 (3%, M^++1), 186 (28), 172 (25), 130 (57), 116 (17), 86 (63), 72 (65), 57 (100).

3.1.7. (3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanenitrile, 9a. A solution of **8a** (0.285 g, 1.24 mmol, 1 equiv.) in 2 mL of toluene was dropwise added to a solution of Et_2AlCN (2.4 mmol, 1.93 equiv.) in 5 mL of toluene cooled at −78°C. The resulting solution was warmed at −15°C and stirred at this

temperature for 1 h. Then, 10 mL of a solution of concentrated HCl and MeOH (8:2) were added and the resulting mixture was vigorously stirred at −15°C for 1 h. The mixture was treated with 10 mL of water and extracted with Et_2O (3×15 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The residue was crystallized from CH_2Cl_2/hexane, to produce 0.28 g (88%) of **9a** as a white solid, mp 95–97°C; $[\alpha]_D$ −34.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3591, 3440, 2962, 2252, 1752, 1703, 1690, 1501, 1370, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (d, 3H, *J* 6.6), 0.95 (d, 3H, *J* 6.6), 1.32–1.42 (m, 2H), 1.45 (s, 9H), 1.68 (m, 1H), 2.53 (m, 2H), 3.75 (broad m, 1H), 3.90 (broad m, 1H), 4.25 (m, 1H, interchangeable with D_2O), 4.66 (broad d, 1H, *J* 6.3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 21.9, 23.3, 24.9, 28.3, 39.3, 53.7, 71.3, 80.6, 118.0, 157.1; EIMS *m*/*z* 256 (2%, M^+), 186 (28), 130 (82), 86 (95), 57 (100); HRMS (EI): $C_{13}H_{24}N_2O_3$ requires 256.1787. Found: 256.1782.

3.1.8. (3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanenitrile, 9b. Following the same procedure used for the preparation of **9a**, and starting from 0.15 g (0.65 mmol) of **8b**, 0.098 g (59%) of **9b** were obtained. The product was purified by column chromatography. Colorless oil; $[\alpha]_D$ −35.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3616, 3441, 2961, 2253, 1704, 1505, 1469, 1392, 1369, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, 3H, *J* 6.6), 0.95 (d, 3H, *J* 6.6), 1.30–1.80 (m, 3H), 1.45 (s, 9H), 2.57 (m, 2H), 3.23 (broad s, 1H, interchangeable with D_2O), 3.62 (broad m, 1H), 3.94 (broad m, 1H), 4.67 (broad m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.9, 23.0, 23.5, 24.7, 28.2, 40.8, 52.3, 69.6, 79.9, 118.2, 156.4; EIMS *m*/*z* 256 (1%, M^+), 186 (24), 183 (13), 130 (70), 86 (92), 57 (100).

3.1.9. (4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-4-isobutyl-2,2-dimethyl-1,3-oxazolidine, 10a. A mixture of **9a** (0.2 g, 0.78 mmol, 1 equiv.), 2,2-dimethoxypropane (7.8 mmol, 10 equiv.), *p*-toluenesulfonic acid monohydrate (0.02 mmol) in dry benzene (5 mL) was refluxed for 1 h. The mixture was diluted with Et_2O (10 mL), washed with saturated $NaHCO_3$, dried and concentrated under vacuum. The residue (0.25 g) was purified by column chromatography (hexane–ethyl acetate, 8:2) to give 0.166 g (72%) of **10a** as a colorless oil; $[\alpha]_D$ −2.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 2961, 2929, 2871, 2258, 1688, 1467, 1456, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.97 (d, 3H, *J* 6.6), 0.98 (d, 3H, *J* 6.6), 1.25–1.40 (m, 2H), 1.40–1.55 (m, 1H), 1.48 (s, 9H), 1.53 (s, 3H), 1.55 (s, 3H), 2.57 (dd, 1H, *J* 7.2 and 16.4), 2.67 (dd, 1H, *J* 6.9 and 16.4), 4.04 (broad m, 1H), 4.28 (td, 1H, *J* 4.8 and 6.9); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.6, 21.3, 21.9*, 22.8, 23.3*, 23.8, 24.7*, 24.9, 25.7*, 28.3*, 28.5, 39.3, 41.9*, 56.7, 72.2, 80.3, 93.8, 116.6, 151.4 (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group); EIMS *m*/*z* 296 (1%, M^+), 281 (8), 225 (20), 181 (45), 152 (50), 85 (100), 57 (90); HRMS (EI): $C_{16}H_{28}N_2O_3$ requires 296.2100. Found: 296.2106.

3.1.10. (4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-4-isobutyl-2,2-dimethyl-1,3-oxazolidine, 10b. Following the same procedure used for the preparation of **10a**, and starting from 0.09 g (0.35 mmol) of **9b**, 0.088 g (85%) of **10b** were obtained. The product was purified by column chromatography. Colorless oil; $[\alpha]_D$ +14.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 2962, 2934, 2873, 2254, 1692, 1467, 1391 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.96 (d, 3H, *J* 6.3), 0.98 (d, 3H, *J* 6.3), 1.40–1.80 (broad m, 3H), 1.48 (s, 9H), 1.52 (s, 3H), 1.62 (s, 3H), 2.64 (d, 2H, *J* 6.6), 3.84 (broad m, 1H), 4.16 (td, 1H, *J* 2.1 and 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 23.9, 24.6, 25.7, 28.5, 42.5*, 60.7, 76.0*, 80.5, 95.0*, 116.6, 151.5 (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); EIMS *m*/*z* 296 (1%, M^+), 281 (18), 225 (32), 181 (100), 57 (88).

3.1.11. (4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-5-carboxymethyl-4-isobutyl-2,2-dimethyl-1,3-oxazolidine, 11a. To a cooled solution (−40°C) of **10a** (0.1 g, 0.34 mmol) in dry Et_2O (3 mL) a 1.5 M solution of DIBAH in toluene (0.4 mL, 0.6 mmol) was added. The mixture was stirred at −40°C for 1 h, at −20°C for another 1 h period, treated with EtOAc (3 mL) and then allowed to reach room temperature. After addition of a saturated sodium potassium tartrate solution (3 mL), the reaction mixture was vigorously stirred for 2 h. The mixture was diluted with EtOAc (5 mL), the organic phase was separated, washed with brine, dried and concentrated under vacuum to give 0.077 g (76%) of the corresponding crude aldehyde as a colorless oil. Without further purification, to this crude product, vigorously stirred with 2-methyl-2-propanol (2 mL) and 5% NaH_2PO_4 (2 mL), 1.5 mL (1.5 mmol) of a 1 M solution of $KMnO_4$ was added. After 15 min, the excess of $KMnO_4$ was decomposed by adding a 10% Na_2SO_3 solution, the mixture was cooled at 0°C and acidified with 10% HCl until pH 4–5. The reaction mixture was extracted with Et_2O (3×10 mL) and the combined extracts were washed with 10% $NaHCO_3$. The washing liqueurs were newly acidified (pH 4–5) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine, dried and evaporated. The residue was crystallized from CH_2Cl_2/hexane to produce 0.07 g (85%) of **11a** as a white solid, mp 95–97°C; $[\alpha]_D$ −6.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3500–2500, 2960, 2932, 1713, 1686, 1454, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, 3H, *J* 6.6), 0.95 (d, 3H, *J* 6.6), 1.20–1.40 (m, 2H), 1.48 (s, 9H), 1.54 (broad s, 7H), 2.62 (dd, 1H, *J* 6.6 and 16.5), 2.64–2.73 (broad m, 1H), 4.00 (broad m, 1H), 4.43 (td, 1H, *J* 4.8 and 6.9); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.7*, 23.6*, 24.9, 25.1*, 27.2*, 28.5, 34.3, 39.6*, 56.7, 72.6, 80.0, 92.9*, 151.9*, 175.8 (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); EIMS *m*/*z* 316 (1%, M^++1), 300 (12), 244 (40), 200 (43), 158 (18), 57 (100).

3.1.12. (4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-5-carboxymethyl-4-isobutyl-2,2-dimethyl-1,3-oxazolidine, 11b. To a cooled solution (−40°C) of **10b** (0.07 g, 0.23 mmol) in dry Et_2O (3 mL) a 1.5 M solution of DIBAH in toluene (1 mL, 1.5 mmol) was added. The mixture was stirred at −40°C for 15 min, treated with EtOAc (3

mL) and then allowed to reach room temperature. The work-up under conditions above described for **11a** afforded 0.06 g (86%) of the corresponding crude aldehyde as a colorless oil. Without further purification, this crude product was submitted to the oxidation conditions previously used for the preparation of **11a** to produce 0.054 g (85%) of **11b** as a white solid, mp 130–132°C; $[\alpha]_D$ −2.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3500–2500, 2961, 2931, 1708, 1691, 1393 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (d, 3H, *J* 6.0), 0.93 (d, 3H, *J* 6.0), 1.40–1.65 (broad m, 3H), 1.48 (s, 9H), 1.51 (s, 3H), 1.60 (s, 3H), 2.55–2.75 (m, 2H), 4.00 (broad m, 1H), 4.32 (t, 1H, *J* 6.4); EIMS *m*/*z* 315 (not observed, M^+), 300 (8), 244 (33), 200 (25), 158 (13), 86 (12), 57 (100).

3.1.13. (3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanoic acid, 12a. A mixture of **11a** (0.05 g, 0.16 mmol) and 1 mL of 85% AcOH was heated at 70°C for 40 min. After cooling at room temperature, the mixture was diluted with EtOAc (5 mL) and washed with 10% $NaHCO_3$ (2×5 mL). The aqueous phase was acidified to pH 4–5 with 10% HCl and extracted with Et_2O (3×5 mL). The combined ethereal extracts were washed with brine, dried (Na_2SO_4) and evaporated under vacuum. The solid residue was recrystallized from CH_2Cl_2/hexane to give 0.032 g (73%) of **12a** as a white solid, mp 132–135°C (lit.[7b] 132–134°C; lit.[14] 135–136°C; $[\alpha]_D$ −26.5 (*c* 0.31, MeOH) (lit.[14] −27.6 (*c* 0.31, MeOH); IR ($CHCl_3$) ν_{max}: 3725, 3696, 3603, 3439, 2962, 1745, 1707, 1602, 1501, 1369, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, 3H, *J* 6.6), 0.94 (d, 3H, *J* 6.6), 1.28–1.35 (m, 2H), 1.45 (s, 9H), 1.60–1.74 (broad m, 1H), 2.49 (broad d, 2H, *J* 5.9), 3.71 (broad m, 1H), 4.01 (broad m, 1H), 4.67 (broad d, 1H, *J* 7.7), 4.90 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 23.5, 24.6, 28.3, 37.2, 38.8, 53.0, 71.3, 80.0, 156.6, 175.8; EIMS *m*/*z* 275 (not observed, M^+), 256 (2), 202 (10), 186 (30), 130 (92), 86 (100), 57 (98). Anal. calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09. Found: C, 56.66; H, 9.19; N, 5.01%.

3.1.14. (3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanoic acid, 12b. Following the same procedure used for the preparation of **12a**, and starting from 0.05 g (0.16 mmol) of **11a**, 0.035 g (80%) of **12b** were obtained. White solid, mp 115–117°C (lit.[7b] 115–116°C; lit.[14] 117–118°C; $[\alpha]_D$ −38.1 (*c* 0.31, MeOH) (lit.[14] −39.6 (*c* 0.31, MeOH); IR ($CHCl_3$) ν_{max}: 3725, 3694, 3604, 3440, 2961, 1745, 1707, 1602, 1501, 1369, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (d, 3H, *J* 6.3), 0.93 (d, 3H, *J* 6.3), 1.25–1.35 (m, 2H), 1.46 (s, 9H), 1.65–1.75 (m, 1H), 2.54 (broad m, 2H), 3.64 (broad m, 1H), 4.01 (broad s, 1H), 4.86 (d, 1H, *J* 9.0), 5.64 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 23.1, 24.7, 28.3, 39.8, 41.3, 52.1, 69.7, 79.6, 156.4, 177.7; EIMS *m*/*z* 275 (not observed, M^+), 256 (5), 202 (3), 186 (14), 130 (34), 86 (63), 57 (100). Anal. calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09. Found: C, 56.86; H, 9.35; N, 5.16%.

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