Pergamon

Tetrahedron Vol. 50, No. 30, pp. 9181-9188, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00516-8

A Practical New Asymmetric Synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-3-Hydroxyleucine

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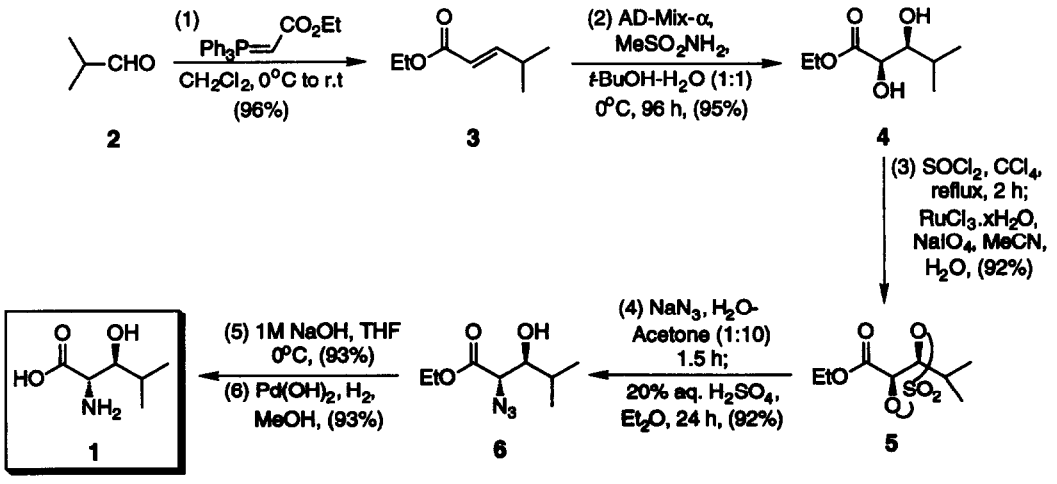
Abstract: A convenient new asymmetric synthesis of both enantiomers of *erythro*-3-hydroxyleucine is described. The key steps involve Sharpless asymmetric dihydroxylation (AD) of α,β-unsaturated ester **3**, cyclic sulphate formation from the resulting diol, S_N2 reaction with sodium azide, deesterification with aqueous sodium hydroxide, and hydrogenolysis. Utilising this route, (2*S*,3*S*)-(+)-3-hydroxyleucine (**1**) was obtained in 97% ee and 67% overall yield; the (2*R*,3*R*)-(-)-enantiomer was isolated in 92% ee and 57% overall yield.

(2*S*,3*S*)-(+)-3-Hydroxyleucine (**1**) is a key constituent of a range of naturally-occurring cyclodepsipeptides that include telomycin,[1] A83586C,[2] azinothricin,[3] citropeptin,[4] variapeptin,[4] L-156,602,[5] and verucopeptin.[6] While a number of elegant asymmetric approaches to **1** have already been described in the literature,[7] we sought to develop an alternative, more convenient, asymmetric synthesis of **1** for our total synthesis programme on the antitumour antibiotic A83586C.[8]

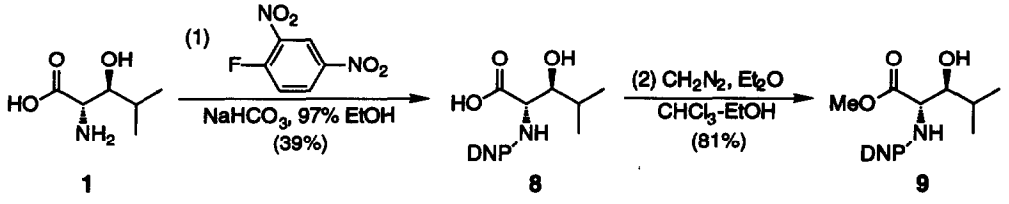
Our new route to **1** is outlined in Scheme 1 and requires only 6 steps. It begins with a Wittig condensation between isobutyraldehyde (**2**) and carboethoxymethylene triphenylphosphorane to afford alkene **3**

Scheme 1



as a single isomer in 96% yield. The ^{1}H NMR spectrum of **3** indicated that it had (*E*)-olefin geometry since there was a large coupling constant (J = 15.7 Hz) between the vinylic protons at δ 6.90 and δ 5.72. Sharpless asymmetric dihydroxylation[9] of alkene **3** with AD-mix-α in the presence of methanesulphonamide proceeded smoothly to give diol **4** in 95% yield, as expected from the Sharpless face-selection rule. The structure of **4** was apparent from its ^{1}H NMR spectrum, there being a doublet at δ 4.24 (J = 1.7 Hz) for H-2, and a double-doublet at δ 3.47 (J = 1.7 and 8.7 Hz) attributable to H-3. Diol **4** was converted to its 2,3-cyclic sulphite by heating with thionyl chloride in carbon tetrachloride at reflux for 2 hours.[10] Without isolation, the crude sulphite was oxidised to the 2,3-cyclic sulphate by addition of catalytic ruthenium (III) chloride and excess sodium periodate, along with acetonitrile and water.[10] Compound **5** was obtained as a crystalline, air-stable, solid in 92% yield. It readily underwent nucleophilic displacement α- to the carbonyl group, when treated with sodium azide in aqueous acetone,[10] to produce α-azido ester **6** in 92% yield. The IR spectrum of **6** confirmed that nucleophilic substitution had been successful since there was now a strong absorption at 2111 cm^{-1} due to the azido group, a broad absorption of medium intensity at 3494 cm^{-1} due to the hydroxyl group, and a characteristic ester C=O stretching absorption at 1739 cm^{-1}. Hydrolysis of the ester was accomplished with 1M aqueous sodium hydroxide in THF at 0°C; the crystalline α-azido acid **7** was isolated in 93% yield. Hydrogenation of **7** proceeded readily in methanol at atmospheric pressure using Pearlman's catalyst (20% Palladium Hydroxide on carbon),[11] to afford (*2S,3S*)-(+)-3-hydroxyleucine (**1**)[1] in 93% yield. The ee of **1** was determined (Scheme 2) after it was converted to **9** by sequential treatment with 2,4-dinitrofluorobenzene and diazomethane. The enantiomeric purity of **9** was shown to be 97% by HPLC comparison with (*2,3-RS*)-3-(2,4-dinitrophenyl)-3-hydroxyleucine methyl ester on a CHIRALCEL OD™ high-performance analytical column.

Scheme 2



When AD-mix-β replaced AD-mix-α in the above reaction sequence, (*2R,3R*)-3-hydroxyleucine was obtained in 92% ee and 57% overall yield.

Experimental Section

Materials and Methods. AD-mixes-α and β™ were used as supplied by the Aldrich Chemical Company. Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}), and visualised with 10% phosphomolybdic acid in 96% EtOH. Flash column chromatography was carried out with Sorbsil C60 40/60A (230-400 mesh) silica gel. Melting points were determined on a Reichert micro hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. IR spectra were recorded on a Nicolet 205 FT IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian AX-400 (400 MHz) spectrometer. High-resolution mass spectra were measured by

the ULIRS Mass Spectrometry Service Centre at the London School of Pharmacy on a VG 70-70 or VG-ZAB instrument with a Finnigan Incos II data system. Microanalyses were performed by the Microanalytical Laboratory of University College London. High pressure liquid chromatography (HPLC) was performed on a Gilson analytical chromatograph equipped with Gilson 303 and 305 pump systems, a Gilson 811b dynamic mixer, a Gilson 805s manometric module, and a Gilson 115 u.v. absorbance detector set at 254 nm. A CHIRALCEL OD™ (25 cm x 4.6 mm I.D.) column was employed for ee determination.

Ethyl 3-[isopropyl]propenoate 3. To a stirred solution of carboethoxymethylene triphenylphosphorane (58.4 g, 167.6 mmol) in dry CH_2Cl_2 (168 mL) at 0°C was added dropwise over 1 min isobutyraldehyde **2** (17.4 mL, 191.6 mmol). After 5 min, the reaction was warmed to room temperature and stirred for 24 h. The solvent was removed *in vacuo* at 28°C, and pentane added to precipitate triphenylphosphine oxide. The solid was filtered off and the filtrate concentrated *in vacuo*. This procedure was repeated until virtually all the triphenylphosphine oxide had been removed and the crude alkene **3** (22.9 g, 96%) was obtained as a yellow oil that was sufficiently pure for the next step. An analytical sample of **3** was prepared by high vacuum Kugelrohr distillation: b.p. 60°C at 0.2 mm Hg; IR (neat film) ν 2966 (s), 2937 (m), 2873 (m), 1721 (s), 1654 (m), 1467 (m), 1368 (m), 1301 (s), 1267 (s), 1192 (s), 1167 (s), 1134 (m), 1039 (m), 986 (m), 864 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, J = 15.7, 6.7 Hz, 1H), 5.72 (dd, J = 15.7, 1.5 Hz, 1H), 4.14 (q, J = 7.3 Hz, 2H), 2.41 (m, 1H), 1.24 (t, J = 7.3 Hz, 3H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 155.4, 118.5, 60.1, 30.9, 21.2, 14.2; HRMS (CI, NH_3) for $C_8H_{15}O_2$ $(M+H)^+$ calcd 143.1072, found 143.1069.

(2R,3S)-(-)-Ethyl 2,3-dihydroxy-3-[isopropyl]propionate 4. A mixture of AD-mix-α (225.6 g), methanesulphonamide (15.3 g, 161.0 mmol), and *tert*-butanol-water (1:1, 1.61 L) was stirred vigorously at room temperature for 5 min. The reaction mixture was then cooled to 0°C and α,β-unsaturated ester **3** (22.9 g, 161.1 mmol) was added via a Pasteur pipette. After stirring at 0°C for 96 h, Na_2SO_3 (241.6 g) was added, and stirring continued at room temperature for 1 h. The mixture was diluted with ethyl acetate (500 mL) and transferred to a separatory funnel. The organic layer was removed and the aqueous phase extracted with ethyl acetate (2 x 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude product by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) afforded diol **4** (27.0 g, 95%) as a colourless oil; $[\alpha]_D$ -1.85° (*c* 2, CH_2Cl_2); IR (neat film) ν 3452 (br m), 2963 (m), 1738 (s), 1476 (w), 1398 (w), 1370 (w), 1268 (m), 1215 (m), 1142 (s), 1094 (m), 1049 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (q, J = 7.2 Hz, 2H) superimposed on 4.24 (d, J =1.7 Hz, 1H), 3.47 (dd, J = 8.7, 1.7 Hz, 1H), 2.80-1.60 (very br s, 2H), 1.84 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 77.9, 71.4, 61.9, 30.9, 19.0, 18.9, 14.0; HRMS (CI, NH_3) for $C_8H_{17}O_4$ $(M+H)^+$ calcd 177.1127, found 177.1128.

Utilising exactly the same procedure with AD-mix-β, alkene **3** (7.0 g) furnished 8.2 g (95%) of the corresponding (2S,3R)-diol as a colourless oil, $[\alpha]_D$ +2.7° (*c* 2, CH_2Cl_2).

The 2,3-cyclic sulphate (5) of (*2R,3S*)-(-)-ethyl 2,3-dihydroxy-3-[isopropyl]propionate 4. To a 1 L, two-necked, round-bottomed flask fitted with a reflux condenser (topped with a $CaCl_2$ drying tube connected to an HCl trap containing KOH flakes) and a rubber septum, was added diol (-)-**4** (27.0 g, 153.3 mmol) and CCl_4 (155 mL). Thionyl chloride (13.5 mL) was added dropwise over 1 min and the resulting solution heated at reflux for 2 h. The reaction mixture was then cooled to 0°C and MeCN (155 mL) added. $RuCl_3.xH_2O$ (24.7 mg, 0.094 mmol) and $NaIO_4$ (49.5 g, 231.4 mmol) were added followed by H_2O (232 mL). The resulting orange mixture was stirred at room temperature for 2 h, poured into ether (600 mL), and the two phases separated. The aqueous layer was then extracted with ether (2 x 600 mL). The combined ether layers were washed successively with water (2 x 300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL). After drying over $MgSO_4$, the solution was filtered and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (10:1 then 8:1 hexane/ethyl acetate) to give **5** (33.6 g, 92%) as a white solid: m.p. 64-66°C; $[\alpha]_D$ -52.5° (*c* 2, CH_2Cl_2); IR (KBr) *v* 2978 (m), 1770 (s), 1747 (s), 1471 (m), 1397 (s), 1301 (m), 1211 (s), 1065 (m), 1029 (m), 983 (s), 920 (m), 838 (m), 793 (m), 657 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, *J* = 6.5 Hz, 1H), 4.76 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.324 (q, *J* = 7.2 Hz, 1H), 4.321 (q, *J* = 7.1 Hz, 1H), 2.19 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 88.1, 77.9, 63.3, 31.1, 17.7, 16.8, 13.9; HRMS (CI, NH_3) for $C_8H_{18}NO_6S$ $(M+NH_4)^+$ calcd 256.0855, found 256.0854. Anal. Calcd for $C_8H_{14}O_6S$: C, 40.33; H, 5.92. Found: C, 40.24; H, 5.86.

The 2,3-cyclic sulphate from (*2S,3R*)-(+)-ethyl 2,3-dihydroxy-3-[isopropyl]propionate was obtained in 81% yield by an identical procedure; it had $[\alpha]_D$ +55.8° (*c* 2, CH_2Cl_2) and m.p. 61.5-63°C. Anal. Calcd for $C_8H_{14}O_6S$: C, 40.33; H, 5.92. Found: C, 39.91; H, 5.73.

(*2S,3S*)-(-)-Ethyl 2-azido-3-isopropyl-3-hydroxypropionate 6. To a solution of cyclic sulphate (-)-**5** (33.6 g, 141.0 mmol) in (10:1) acetone:water (280 mL) at room temperature was added NaN_3 (18.3 g, 281.5 mmol). The reaction mixture was stirred for 1.5 h and the solvent removed *in vacuo*. The solid residue was treated with 20% aqueous H_2SO_4 (697 mL) and ether (697 mL) and vigorously stirred at room temperature for 24 h. The ether layer was separated and the aqueous fraction further extracted with Et_2O (3 x 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (18:1 then 16:1 hexane/ethyl acetate) to afford **6** (26.1 g, 92%) as a colourless oil; $[\alpha]_D$ -36.7° (*c* 2, CH_2Cl_2); IR (neat film) *v* 3494 (br m), 2967 (m), 2111 (s), 1739 (s), 1469 (w), 1373 (m), 1257 (m), 1192 (s), 1024 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (q, *J* = 7.2 Hz, 2H), 3.87 (d, *J* = 6.5 Hz, 1H), 3.64 (apparent q, *J* = 6.0 Hz, 1H), 2.46 (d, *J* = 6.0 Hz, 1H), 1.89 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 76.3, 63.7, 62.1, 30.1, 19.3, 16.5, 14.1; HRMS (CI, NH_3) for $C_8H_{16}N_3O_3$ $(M+H)^+$ calcd 202.1191, found 202.1190.

When this procedure was applied to the 2,3-cyclic sulphate derived from (*2S,3R*)-(+)-ethyl 2,3-dihydroxy-3-[isopropyl]propionate (2.8 g), ethyl (*2R,3R*)-(+)-2-azido-3-isopropyl-3-hydroxypropionate (2.04 g, 86%) was obtained with $[\alpha]_D$ +39.8° (*c* 2, CH_2Cl_2).

(2*S*,3*S*)-(-)-2-Azido-3-isopropyl-3-hydroxypropionic acid 7. To a solution of α-azido ester (-)-**6** (5.0 g, 24.9 mmol) in THF (28 mL) at 0°C was added NaOH (1M in H_2O, 25 mL). The reaction mixture was stirred at 0°C for 75 min and then diluted with ether (50 mL). The organic layer was separated and the aqueous phase extracted with ether (50 mL). The aqueous layer was then cooled to 0°C, acidified to pH 2 by dropwise addition of conc. HCl, and extracted with ethyl acetate (5 x 250 mL). The combined ethyl acetate extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (5:1 hexane/ethyl acetate) to furnish **7** (4.0 g, 93%) as white crystals; m.p. 61-65°C; $[\alpha]_D$ -33.7° (*c* 2, CH_2Cl_2); IR (KBr) *v* 3600-3000 (very br m), 2969 (s), 2929 (br m), 2115 (s), 1725 (s), 1469 (w), 1384 (w), 1257 (br m), 1131 (w), 1061 (w), 1012 (w), 789 (s), 773 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.7-6.0 (br s, 2H), 4.00 (d, *J* = 6.4 Hz, 1H), 3.71 (dd, *J* = 6.0 Hz, 1H), 2.01 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 76.8, 63.7, 30.0, 19.2, 16.6; HRMS (FAB MNOBA matrix) for $C_6H_{11}N_3O_3Na$ $(M+Na)^+$ calcd. 196.0698, found, 196.0699. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found: C, 41.86; H, 6.13; N, 24.13.

Application of the above procedure to ethyl (2*R*,3*R*)-(+)-2-azido-3-isopropyl-3-hydroxypropionate (3.51 g) led to (2*R*,3*R*)-(+)-2-azido-3-isopropyl-3-hydroxypropionic acid (2.92 g, 97%) with $[\alpha]_D$ +43.8° (*c* 2, CH_2Cl_2) and m.p. 62-66°C. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found: C, 42.00; H, 6.24; N, 24.30.

(2*S*,3*S*)-(+)-3-Hydroxyleucine 1. To a solution of (-)-α-azido acid **7** (21.2 g, 122.5 mmol) in MeOH (79 mL) was added 20% $Pd(OH)_2$ on carbon (6.0 g). The reaction flask was purged with H_2 gas and vigorously stirred at room temperature and atmospheric pressure for 48 h. The reaction mixture was then filtered and the filter pad exhaustively washed with distilled water and ethanol (N.B. This washing is very important as **1** crystallises from the reaction mixture as the reaction proceeds). The filtrate was concentrated *in vacuo* and **1** (16.8 g, 93%) was obtained as white crystals; m.p. 219-221°C {Lit. m.p. 220-223°C,[6b] 219-224°C,[6c] and 219-222°C[6d]}; $[\alpha]_D$ +27.1° (*c* 2, H_2O) {Lit.[1] for (2*S*,3*S*)-(+)-3-hydroxyleucine $[\alpha]_D$ +22.0° (*c* 1, H_2O)}; IR (KBr) *v* 3447 (br m), 3082 (br s), 2962 (s) 2587 (m), 2502 (m), 2432 (m), 2088 (w), 1657 (s), 1626 (s), 1571 (s), 1476 (m), 1422 (s), 1349 (s), 1324 (s), 1054 (m), 1012 (s), 553 (s) cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.91 (d, *J* = 2.5 Hz, 1H), 3.52 (dd, *J* = 9.2, 2.5 Hz, 1H), 1.93 (m, 1H), 0.97 (two d partially superimposed, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O) δ 174.3, 78.7, 59.7, 32.8, 21.1; HRMS (FAB, glycerol matrix) for $C_6H_{14}NO_3$ $(M+H)^+$ calcd 148.0974, found 148.0986. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.78; H, 9.09; N, 9.24.

Application of the above procedure to (2*R*,3*R*)-(+)-2-azido-3-isopropyl-3-hydroxypropionic acid (2.9 g) led to isolation of (2*R*,3*R*)-(-)-3-hydroxyleucine (2.3 g, 93%) with $[\alpha]_D$ -19.7° (*c* 2, H_2O) {Lit.[6e] $[\alpha]_D$ -22.0° (*c* 0.96, H_2O)} and m.p. 220-222°C (Lit.[6e] m.p. 225-228°C).

(2*S*,3*S*)-(-)-2-(2,4-Dinitrophenyl)-3-hydroxyleucine 8. To a stirred suspension of (+)-**1** (495 mg, 3.37 mmol) and $NaHCO_3$ (3.17 g, 37.7 mmol) in 97% EtOH (35 mL) was added 2,4-dinitrofluorobenzene (5.9 mL, 47.0 mmol). The reaction mixture was stirred at room temperature for 5 h, poured into water (20 mL) and extracted with ether (3 x 30 mL). The aqueous layer, containing the product, was then acidified to pH 2 with

10% aqueous HCl and extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (35:1 CH_2Cl_2/MeOH). This furnished **8** as a yellow crystalline solid (0.41 g, 39%); m.p. 170-174.5°C (Lit.[1] m.p. 173-174°C); $[\alpha]_D$ -19.2° (*c* 1, MeOH); IR (KBr) *v* 3449 (s), 3318 (s), 3114 (s), 3079 (s), 2875 (m), 1760 (s), 1625 (s), 1582 (s), 1538 (m), 1522 (s), 1411 (s), 1331 (s), 1318 (s), 1289 (s), 1257 (s), 1234 (s), 1216 (s), 1150 (s), 1125 (s), 1060 (m), 1039 (s), 922 (m), 828 (m), 777 (m), 747 (m), 725 (m), 664 (m), 555 (w), 520 (w) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.95 (d, *J* = 2.7 Hz, 1H), 8.20 (dd, *J* = 9.5, 2.7 Hz, 1H), 6.96 (d, *J* = 9.7 Hz, 1H), 4.58 (d, *J* = 3.4 Hz, 1H), 3.50 (dd, *J* = 8.9, 3.4 Hz, 1H), 1.93 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.2, 148.6, 137.6, 131.2, 124.7, 116.1, 78.6, 59.8, 32.4, 19.7; HRMS (FAB MNOBA matrix) for $C_{12}H_{16}N_3O_7$ $(M+H)^+$ calcd 314.0988, found 314.0980. Anal. calcd for $C_{12}H_{15}N_3O_7$: C, 46.01; H, 4.83; N, 13.41. Found: C, 45.65, H, 4.80; N, 13.00.

When this experiment was carried out with (*2R,3R*)-(-)-3-hydroxyleucine (550 mg), (*2R,3R*)-(+)-2-(2,4-dinitrophenyl)-3-hydroxyleucine (0.43 g, 37%) was obtained with $[\alpha]_D$ +18.7° (*c* 1, MeOH) and m.p. 172.5-174°C; HRMS (FAB MNOBA matrix) for $C_{12}H_{16}N_3O_7$ $(M+H)^+$ calcd 314.0988, found 314.0982.

(*2S,3S*)-(-)-2-(2,4-Dinitrophenyl)-3-hydroxyleucine methyl ester 9. A solution of (-)-**8** (130 mg, 0.42 mmol) in $CHCl_3$ (4.4 mL) and EtOH (10 drops) was treated with an ethereal solution of diazomethane at 0°C until TLC (4:1 $CHCl_3$:MeOH) indicated that no starting material remained. A stream of nitrogen gas was then bubbled through the solution for 10 min to remove excess diazomethane, and the solvent removed *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (3:1 then 1:1 hexane:ether) to afford **9** (110 mg, 81% yield) as a yellow crystalline solid; m.p. 121-122.5°C; $[\alpha]_D$ -24.3° (*c* 1, MeOH); IR (KBr) *v* 3506 (s), 3313 (s), 3106 (w), 3077 (w), 2965 (m), 2874 (w), 1744 (s), 1629 (s), 1619 (s), 1587 (s), 1539 (w), 1508 (m), 1420 (m), 1325 (s), 1283 (s), 1253 (s), 1230 (s), 1152 (m), 1058 (s), 921 (s), 830 (m), 747 (m), 727 (m), 673 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, *J* = 7.6 Hz, 1H), 9.12 (d, *J* = 2.6 Hz, 1H), 8.26 (dd, *J* = 9.5, 2.6 Hz, 1H), 6.91 (d, *J* = 9.5 Hz, 1H), 4.45 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.80 (s, 3H), 3.67 (m, 1H), 2.42 (br d, *J* = 7.9 Hz, 1H), 1.80 (m, 1H), 1.06 (2 partially superimposed d, *J* = 6.7, 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 147.0, 136.9, 131.3, 130.5, 124.3, 114.1, 77.7, 58.1, 53.0, 31.4, 19.1, 18.5; HRMS (FAB, MNOBA matrix) for $C_{13}H_{18}N_3O_7$ $(M+H)^+$ calcd 328.1145, found 328.1142. Anal. calcd for $C_{13}H_{17}N_3O_7$: C, 47.70; H, 5.24; N, 12.84. Found: C, 47.62, H, 5.19; N, 12.54. HPLC analysis using a CHIRALCEL OD column and 3:1 hexane/isopropanol as eluant indicated that **9** had 97% ee.

When (*2R,3R*)-(+)-2-(2,4-dinitrophenyl)-3-hydroxyleucine (159 mg) was treated with ethereal diazomethane, (*2R,3R*)-(+)-2-(2,4-dinitrophenyl)-3-hydroxyleucine methyl ester (117 mg, 70%) was obtained with $[\alpha]_D$ +27.1° (*c* 0.8, MeOH), and m.p. 121-123°C; HRMS (FAB, MNOBA matrix) for $C_{13}H_{18}N_3O_7$ $(M+H)^+$ calcd 328.1145, found 328.1140. Anal. calcd for $C_{13}H_{17}N_3O_7$: C, 47.70; H, 5.24; N, 12.84. Found: C, 47.71, H, 5.16; N, 12.66. HPLC analysis of this material with a CHIRALCEL OD column and 3:1 hexane/isopropanol as eluant indicated it had 92% ee.

Acknowledgements: We are very grateful to the SERC for support of this investigation through grant no. GR/G/43102. We also thank Rohm & Haas (Philadelphia) and Pfizer (Sandwich) for additional generous financial support. VMD is the recipient of an SERC EARMARKED studentship. We thank the ULIRS Mass Spectrometry Service at the London School of Pharmacy for obtaining high resolution mass spectra.

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(*Received in UK* 10 *May* 1994; *revised* 8 *June* 1994; *accepted* 10 *June* 1994)