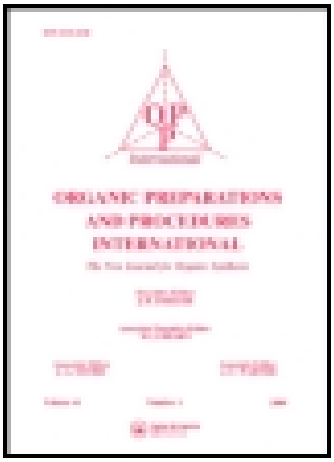

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A CONVENIENT AND EFFICIENT ASYMMETRIC SYNTHESIS OF (S)-α-ARYLTHIOMETHYL-α-HYDROXYBUTYRIC ACID ESTERS

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A CONVENIENT AND EFFICIENT ASYMMETRIC SYNTHESIS OF (S)-α-ARYLTHIOMETHYL-α-HYDROXYBUTYRIC ACID ESTERS

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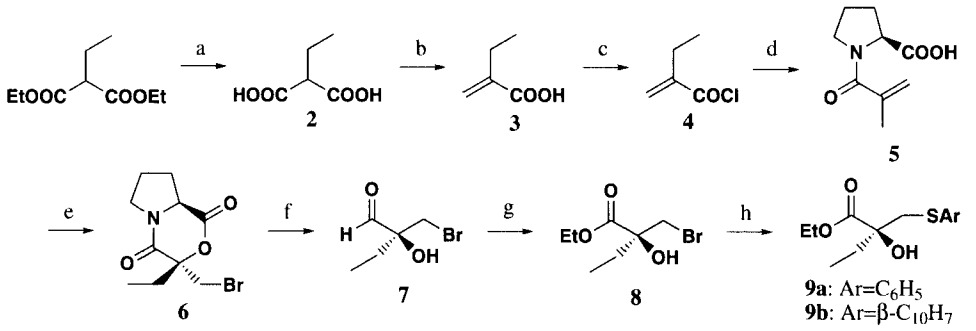
As a part of our continuing exploration of new synthetic approaches to 20(S)-camptothecins,[1] we envisioned the possiblility of developing a total asymmetric total synthesis of 20(S)-camptothecins employing (S)-α-arylthiomethyl-α-hydroxybutyric acid esters (**9a,b**) as key chiral building blocks for the construction of E-ring unit of 20(S)-camptothecins. Herein, we describe a convenient asymmetric preparation of **9a,b** starting from commercially available diethyl ethylmalonate.

The synthetic route to **9a-b** is depicted in *Scheme 1*. Ethylmalonic acid (**2**), obtained by base hydrolysis of diethyl ethylmalonate, was subjected to a Mannich reaction[2] with diethylamine and paraformaldehyde to produce 2-methylenebutyric acid (**3**) in 90% yield. 2-Methylenebutyryl chloride (**4**) was obtained in 55% yield along with 30% of 2-chloro-2-methylbutyryl chloride as an undesired by-product in the chlorination of **3**, according to the reported



a) 2 N aq. NaOH, reflux 3 h, 95%; b) Et_2NH, 5-10°C, then $(HCHO)_n$, reflux , 90%; c) $SOCl_2$, 50°C, 5 h, 82%; d) (S)-proline, 2 N aq. NaOH, $(CH_3)_2CO$, 0-5°C, 0.5 h, then r. t., 3 h, 74%; e) NBS, DMF, r. t., 24 h, 80%; f) 35% aq. H_2SO_4, reflux 8 h, 77%; g) EtOH, conc. H_2SO_4(cat.), reflux 12 h, 92%; h) NaH, PhSH (or $C_{10}H_7SH$), THF, r.t., 28 h, 91% (or 93%)

Scheme 1

procedure.[3] After several attempts, it was found that the yield of **4** could be increased to 82% if the HCl gas formed in the course of chlorination was efficiently removed by bubbling nitrogen through the reaction mixture. Condensation of **4** with (S)-proline as a chiral auxiliary in aqueous acetone at 0-5°C *via* a Schottenn-Baumann reaction[4] afforded (S)-prolineamide **5**. Bromolactonization of **5** with NBS in anhydrous DMF at room temperature gave the bromo-

lactone **6** in 80% yield. Acid hydrolysis of **6** in boiling conc. HCl smoothly afforded the bromohydrin acid **7**, accompanied by 15% of the chlorohydrin acid by-product. However, **7** was obtained as the sole product (in 75% and 77% yields respectively) when compound **6** was heated at reflux in 40% aq. HBr or 35% aq. H_2SO_4. Finally, esterification of **7** with EtOH under acidic conditions, followed conversion to the thioethers with thiophenol or thionaphthol provided the desired (S)-α-arylthiomethyl-α-hydroxybutyric acid esters (**9a,b**) in yield of 91% and 93%, respectively. The absolute S configuration of **9a,b** was assigned on the basis of their chemical correlation with (S)-bromolactone **6** which was established by X-ray single crystal structure.[5]

In conclusion, we have developed an efficient asymmetric synthesis of (S)-α-arylthiomethyl-α-hydroxybutyric acid esters (**9a,b**) in eight steps in 27% overall yield. The mild conditions, simple work-up procedures and the elimination of chromatographic separation make this procedure suitable for the large-scale preparation of the (S)-α-arylthiomethyl-α-hydroxyalkanic acid esters. The total synthesis of 20(S)-CPTs, utilizing **9a,b** as key chiral intermediates is in progress.

EXPERIMENTAL SECTION

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. IR spectra were recorded on an Avvatar 360 FT-IR instrument. NMR spectra were recorded on Bruker DMX500 (500MHz) and MSL400 (125MHz) instruments using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. GC-MS spectra were recorded on Finnigan Voyager instrument. Mass spectra (MS) were recorded on MAT95 and for the electronic impacts (EI) at 70 eV. Elemental analyses were performed on a Carlo-Erba 1006 elemental analyzer. Specific rotations were measured with a WZZ-2S digital automatic polarimeter.

Ethylmalonic Acid (2).- A mixture of diethyl ethylmalonate (47 g, 0.25 mol) and 2 N aq. NaOH (313 mL) was heated at reflux with stirring for 2 h, cooled and then extracted with petroleum ether (60-90°C) (100 mL x 2). The aqueous layer was adjusted to pH 1 with conc. HCl, and extracted with EtOAc (100 mL x 3). The combined organic extracts were washed successively with H_2O (100 mL x 2) and brine (100 mL x 2) and dried over Na_2SO_4. Concentration of the solvent under reduced pressure gave compound **2** (31.3 g, 95%) as colorless needles, mp. 112.5-114°C, *lit.*[6] 114°C.

2-Methylenebutyric Acid (3).- To a solution of **2** (33 g, 0.25 mol) in EtOAc (330 mL) was added dropwise diethylamine (26.1 mL, 0.25 mol) at 5-10°C, followed by paraformaldehyde (12 g, 0.375 mol). The reaction mixture was stirred under reflux for 2 h, then cooled to r.t. Water (80 mL) was then added to the reaction mixture, and adjusted to pH 1 with conc. HCl. The organic phase was washed successively with H_2O (50 mL x 2) and brine (50 mL x 2) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave compound **3** (22.5 g, 90%) as a pale yellow oil, purity ≥ 98.5% (GC-MS analysis), which was used directly in the

next step. *lit.*[7] bp. 76.5-83°C/12mmHg.

^{1}H NMR ($CDCl_3$): δ 6.30, 5.65 (s, 2H), 2.34 (q, 2H, J = 7.3 Hz,), 1.11 (t, 3H, J = 7.4 Hz); GC-MS (m/z): 100 (M^+, 63), 85 (40), 72 (15), 55 (100), 45 (25), 41 (20).

2-Methylenebutyryl Chloride (4).- Freshly redistilled $SOCl_2$ (34 mL, 0.24 mol) was added dropwise to 2-methylenebutyric acid (**3**) (20 g, 0.2 mol) at r.t., and nitrogen was simultaneously bubbled into the reaction mixture in order to drive out HCl gas evolved. The reaction mixture was stirred at 50°C for 5 h, then distilled under reduced pressure to yield **4** (20 g, 85%) as a colorless oil, bp. 60-62°C/150 mmHg, purity ≥ 94% (GC-MS analysis), *lit.*[3] 105-107°C/760 mmHg.

GC-MS (m/z): 90 (M^+-28, 3), 83 (100), 55 (95).

(S)-1-(2-Methylenebutyryl)pyrrolidine-2-carboxylic Acid (5).- To a stirred solution of (S)-proline (20.7 g, 0.18 mol) in 2 N aq. NaOH (110 mL) and acetone (110 mL) was added dropwise **4** (31.8 g, 0.27 mol) in acetone (110 mL) at 0-5°C. 2 N aq. NaOH was simultaneously added dropwise so that the pH of the reaction mixture solution was kept within 10-11. After stirring at r. t. for 4 h, the acetone was removed under reduced pressure. EtOAc (110 mL) was added into the residual solution. The aqueous layer was acidified to pH 2 with conc. HCl and extracted with EtOAc (100 mL x 3). The combined organic layer was washed successively with H_2O (100 mL x 2) and brine (100 mL x 2) and dried over Na_2SO_4. The solvent was concentrated under reduced pressure to provide compound **5** (26 g, 74%) as a white solid, mp. 103.4-104.8°C.

^{1}H NMR ($CDCl_3$): δ 5.23, 5.13 (s, 2H), 4.25 (dd, 1H, J = 4.5, 8.6 Hz), 3.51 (m, 2H), 2.21 (q, 2H, J = 7.4Hz), 2.21, 1.84 (m, 4H), 0.98 (t, 3H, J = 7.4Hz). MS (m/z): 197 (M^+, 5), 182 (4), 152 (34), 138 (58), 83 (100), 70 (17), 55 (69), 41 (16), 39 (14).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.10; H, 7.75; N, 7.18

(3S, 9S)-3-Bromomethyl-3-ethyl-1, 4-dioxotetrahydropyrrolo[2, 1-*c*][1, 4]oxazine (6).- To a stirred solution of **5** (19.7 g, 0.1 mol) in anhydrous DMF (300 mL) was added *N*-bromosuccimide (35.6 g, 0.2 mol) in portions at r.t. under a nitrogen. The reaction mixture was stirred for 24 h, and then evaporated to dryness under reduced pressure. The residue was dissolved with EtOAc (300 mL) and washed successively with 5% aq. $NaHCO_3$ (80 mL x 2) and H_2O (100 mL x 3) and brine (100 mL x 2) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave compound **6** (22 g, 80%) as a white solid, mp. 103.8-105.5°C; $[\alpha]_D^{25}$ = –134.7°C (*c* 1.022, $CHCl_3$).

IR (KBr, cm^{-1}): 3040, 2979, 1754, 1664, 1488, 1350, 1162, 1036, 969, 648. ^{1}H NMR (DMSO-d_6): δ 4.51 (dd, 1H, J = 6.3, 10.2 Hz), 3.89, 3.63 (d, 2H, J = 11.1 Hz), 3.74, 3.60 (m, 2H), 2.50, 2.10 (m, 2H), 2.20, 1.83 (m, 2H), 2.00 (m, 2H), 0.93 (t, 3H, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 166.73, 163.78, 100.00, 58.10, 45.11, 38.01, 31.31, 30.05, 21.53, 8.33. MS (m/z): 277 (M^++2, 4), 275 (M^+, 4), 168 (100), 152 (43), 83 (52), 70 (60).

Anal. Calcd for $C_{10}H_{14}BrNO_3$: C, 43.50; H, 5.11; N, 5.07. Found: C, 43.67; H, 5.30; N, 5.25

(S)-2-Bromomethyl-2-hydroxybutyric Acid (7).- A mixture of **6** (13.8 g, 50 mmol) and 35% aq. H_2SO_4 (110 mL) was refluxed with stirring for 8 h, and cooled to r. t.. Water (200 mL) was then added to the reaction mixture, and extracted with EtOAc (80 mL x 3). The combined organic phase was washed with sat. aq. $NaHCO_3$ (50 mL x 4). The combined alkaline extracts were acidified to pH 2 with 6 N aq. HCl, then extracted with EtOAc (50 mL x3). The combined organic extracts were washed with H_2O (50 mL x 2) and brine (50 mL x 2) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield compound **7** (7.6 g, 77%) as white needles, mp. 98.9-99.7°C; $[\alpha]_D^{25} = -31.8°C$ (*c* 1.118, MeOH).

^1H NMR ($CDCl_3$): δ 3.75, 3.54 (d, 2H, *J* = 10.4Hz), 1.95, 1.85 (m, 2H), 1.01 (t, 3H, *J* = 7.4Hz). ^{13}C NMR ($CDCl_3$): δ 178.30, 100.03, 39.05, 30.62, 8.31. MS (m/z): 198 (M^++2, 3), 196 (M^+, 3), 151(90), 153 (90), 103 (62), 57 (68), 43 (100).

Anal. Calcd for $C_5H_9BrO_3$: C, 30.48; H, 4.60. Found: C, 30.60; H, 4.55.

(S)-Ethyl 2-Bromomethyl-2-hydroxybutanoate (8).- A mixture of **7** (39.4 g, 0.2 mol), anhydrous EtOH (800 mL), and conc. H_2SO_4 (1 mL) was refluxed for 12 h, and cooled to r.t. After removal of EtOH under reduced pressure, the residue was diluted with H_2O (300 mL) and extracted with Et_2O (80 mL x 3). The combined organic phase was washed with 10% aq. $NaHCO_3$ (50 mL x 2) and H_2O (50 mL x 2), then dried over $MgSO_4$. The solvent was concentrated under reduced pressure to give compound **8** (41.4 g, 92%) as a pale-yellow oil, purity ≥ 97% (GC-MS analysis). $[\alpha]_D^{20} = +6.16°C$ (*c* 2.11, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 4.30 (m, 2H), 3.48, 3.67 (d, 2H, *J* = 10.3 Hz), 3.51-3.43 (br s, 1H), 1.85, 1.74 (m, 2H), 1.33(t, 3H, *J* = 7.13 Hz), 0.93(t, 3H, *J* = 7.4Hz). MS (m/z): 226 (M^++2, 7), 224 (M^+, 7), 197(5), 195 (5), 153 (100), 151 (99), 131 (38), 71 (27), 57(60), 43 (87).

Anal. Calcd for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.50; H, 5.70

(S)-Ethyl α-Phenylthiomethyl-α-hydroxybutanoate (9a).- To a solution of thiophenol (9.6 mL, 9.34 mmol) in the anhydrous THF (20 mL) was added 60% NaH (0.4 g, 9.78 mmol) under nitrogen, and stirred for 3 h. Then, a solution of **8** (2.0 g, 8.89 mmol) in anhydrous THF (20 mL) was added dropwise, and the stirring was continued for another 28 h. Ice water (60 mL) was added to the reaction mixture, and extracted with Et_2O (30 mL x 3). The combined organic phase was washed with 1N aq. NaOH (30 mL x 2) and H_2O (50 mL x 3) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by chromatography [PE (60-90°C) /CH_2Cl_2, 9/1, *V/V*] to give compound **9a** (2.14g, 91%) as a colorless oil. $[\alpha]_D^{20} = -20.28°C$ (*c* 2.16, $CHCl_3$).

^1H NMR ($CDCl_3$): δ 7.43-7.13 (m, 5H), 4.10, 3.9 (m, 2H), 3.35, 3.22 (d, 2H, *J* = 13.6 Hz), 3.37-3.2 (br s, 1H), 1.87-1.70 (m, 2H), 1.17 (t, 3H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 7.4Hz). MS (m/z): 254 (M^+, 22), 236 (15), 181(18), 123 (100), 109 (16), 71 (19), 57 (45), 45 (18).

Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; S, 12.61. Found: C, 61.50; H, 7.02; S, 12.80

(S)-Ethyl α-(2-Naphthylthiomethyl)-α-hydroxybutanoate (9b).- To a solution of β-thionaphthol (1.5 g, 9.34 mmol) in the anhydrous THF (20 mL) was added 60% NaH (0.4 g, 9.78

mmol) under nitrogen, and stirred for 3 h. Then, a solution of **8** (2.0 g, 8.89 mmol) in anhydrous THF (20 mL) was added dropwise, and the reaction mixture was worked up as described for **9a** to give **9b** (2.51 g, 93%) as a colorless oil. $[\alpha]_D^{20} = -19.94°C$ (*c* 1.99, $CHCl_3$).
^1H NMR ($CDCl_3$): δ 7.85 (s, 1H), 7.77-7.72 (m, 3H), 7.5-7.4 (m, 3H), 4.04, 3.8 (m, 2H), 3.43, 3.31 (d, 2H, *J* = 13.6 Hz), 1.86, 1.76 (m, 2H), 1.09 (t, 3H, *J* = 7.1 Hz), 0.9 (t, 3H, *J* = 7.4 Hz).
MS (m/z): 304 (M^+, 32), 286 (4), 231(7), 173 (100), 159 (18), 129 (16), 115 (37), 57 (27).
Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 66.90; H, 6.55; S, 10.38

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