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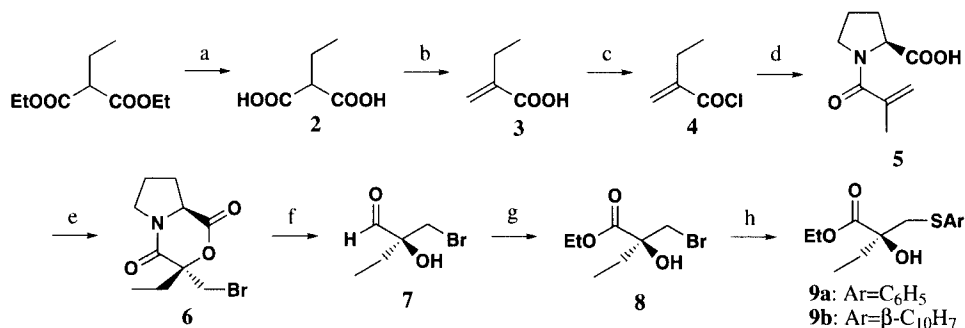
**A CONVENIENT AND EFFICIENT ASYMMETRIC SYNTHESIS
OF (S)- α -ARYLTHIOMETHYL- α -HYDROXYBUTYRIC ACID ESTERS**

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As a part of our continuing exploration of new synthetic approaches to 20(S)-camptothecins,¹ we envisioned the possibility 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 reaction² 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) Et₂NH, 5-10°C, then (HCHO)_n, reflux, 90%; c) SOCl₂, 50°C, 5 h, 82%; d) (S)-proline, 2 N aq. NaOH, (CH₃)₂CO, 0-5°C, 0.5 h, then r. t., 3 h, 74%; e) NBS, DMF, r. t., 24 h, 80%; f) 35% aq. H₂SO₄, reflux 8 h, 77%; g) EtOH, conc. H₂SO₄(cat.), reflux 12 h, 92%; h) NaH, PhSH (or C₁₀H₇SH), 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 Schotten-Baumann reaction⁴ 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. H₂SO₄. 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 H₂O (100 mL x 2) and brine (100 mL x 2) and dried over Na₂SO₄. 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 H₂O (50 mL x 2) and brine (50 mL x 2) and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure gave compound **3** (22.5 g, 90%) as a pale yellow oil, purity \geq 98.5% (GC-MS analysis), which was used directly in the

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

¹H NMR (CDCl₃): 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 SOCl₂ (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 H₂O (100 mL x 2) and brine (100 mL x 2) and dried over Na₂SO₄. The solvent was concentrated under reduced pressure to provide compound 5 (26 g, 74%) as a white solid, mp. 103.4-104.8°C.

¹H NMR (CDCl₃): 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 C₁₀H₁₅NO₃: 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*-bromosuccinimide (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. NaHCO₃ (80 mL x 2) and H₂O (100 mL x 3) and brine (100 mL x 2) and dried over MgSO₄. Evaporation of the solvent *in vacuo* gave compound 6 (22 g, 80%) as a white solid, mp. 103.8-105.5°C; [α]_D²⁵ = -134.7°C (*c* 1.022, CHCl₃).

IR (KBr, cm⁻¹): 3040, 2979, 1754, 1664, 1488, 1350, 1162, 1036, 969, 648. ¹H NMR (DMSO-d₆): 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). ¹³C NMR (CDCl₃): 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 C₁₀H₁₄BrNO₃: 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 x 3). 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; $[\alpha]_{\text{D}}^{25} = -31.8^\circ\text{C}$ (*c* 1.118, MeOH).

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

Anal. Calcd for $\text{C}_5\text{H}_9\text{BrO}_3$: 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 $\geq 97\%$ (GC-MS analysis). $[\alpha]_{\text{D}}^{20} = +6.16^\circ\text{C}$ (*c* 2.11, CHCl_3).

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

Anal. Calcd for $\text{C}_7\text{H}_{13}\text{BrO}_3$: 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. $[\alpha]_{\text{D}}^{20} = -20.28^\circ\text{C}$ (*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, $J = 13.6\text{ Hz}$), 3.37-3.2 (br s, 1H), 1.87-1.70 (m, 2H), 1.17 (t, 3H, $J = 7.4\text{ Hz}$), 0.88 (t, 3H, $J = 7.4\text{Hz}$). MS (*m/z*): 254 (M^+ , 22), 236 (15), 181(18), 123 (100), 109 (16), 71 (19), 57 (45), 45 (18).

Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{S}$: 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. $[\alpha]_D^{20} = -19.94^\circ\text{C}$ (c 1.99, CHCl_3).

$^1\text{H NMR}$ (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 $\text{C}_{17}\text{H}_{20}\text{O}_3\text{S}$: C, 67.08; H, 6.62; S, 10.53. Found: C, 66.90; H, 6.55; S, 10.38

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