Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Supporting Information

Asymmetric Sommelet–Hauser Rearrangement of *N*-Benzylic Ammonium Salts

Eiji Tayama* and Hiroshi Kimura

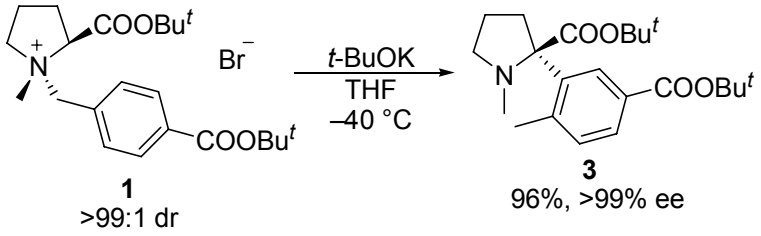
Graduate School of Science and Technology, Niigata University 950-2181, Japan

E-mail: tayama@gs.niigata-u.ac.jp

Experimental details and products characterization

General: Infrared (IR) spectra were recorded on a HITACHI Infrared Spectrometer 270–30. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JMN–Excalibur (^{1}H: 270 MHz, ^{13}C: 68 MHz) and a Varian UNITY plus–500SW (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometers. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel $60F_{254}$) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan). The elemental analyses were recorded on a Yanaco CHN corder, MT–3. Reactions were conducted in appropriate round-bottomed flask with a magnetic stirring bar under an atmosphere of argon. Tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc., Japan as anhydrous solvent. Diethyl ether was distilled from benzophenoneketyl prior to use.

Asymmetric Sommelet–Hauser rearrangement of 1:



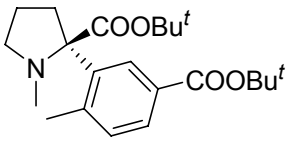
1
>99:1 dr

3
96%, >99% ee

Potassium *tert*-butoxide (43 mg, 0.38 mmol) was added in one portion to a suspension of **1** (125 mg, 0.25 mmol) in THF (2.5 mL) at –40 °C. The mixture was stirred for 6 h at the same temperature under an argon atmosphere. The resulting mixture was quenched with water and the mixture was extracted with

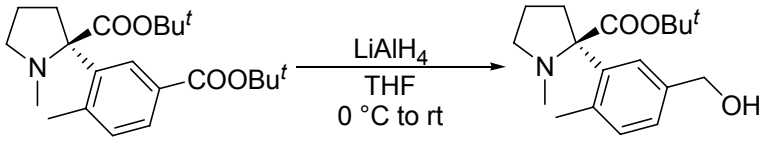
ether. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 30:1 to 10:1 as eluent) to afford **3** (90 mg, 96% yield) as a colorless oil. The enantiomer excess (ee) was determined after conversion to the corresponding amino alcohol **15** by reduction with lithium aluminium hydride.

(2*R*)-2-(5'-*tert*-Butoxycarbonyl-2'-methyl)phenyl-*N*-methylproline *tert*-butyl ester (3): colorless oil;



$[\alpha]^{25}_{589}$ = 110.9 (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.27 (1H, d, *J* = 1.6 Hz, 6'-H), 7.74 (1H, dd, *J* = 7.8, 1.6 Hz, 4'-H), 7.15 (1H, d, *J* = 7.8 Hz, 3'-H), 3.27-3.20 (1H, m, 5-H), 2.94-2.73 (2H, m, 3-H and 5-H), 2.44 (3H, s, CH_3N), 2.27 (3H, s, Ar-CH_3), 1.95-1.61 (3H, m, 3-H and 4-H), 1.59 (9H, s, 5'-COOBu^t), 1.45 (9H, s, 2-COOBu^t); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.8, 166.4, 142.5, 140.7, 130.9, 129.2, 127.4, 126.7, 81.4, 80.4, 73.9, 54.5, 37.4, 36.8, 28.3, 28.2, 22.3, 20.8; IR (film) 3064, 2972, 2932, 2796, 1710, 1608, 1576, 1474, 1454, 1392, 1368, 1304, 1252, 1164, 1126, 1098, 1044, 1002, 920, 892, 844, 792, 764, 736 cm^{-1}; Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.63; H, 8.85; N, 3.68.

Reduction of 3 to amino alcohol 15 for determination of the enantiomer excess by chiral HPLC analysis:

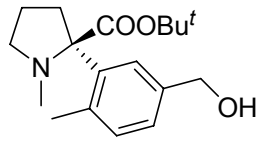


3 **15**
85%

To a suspension of lithium aluminium hydride (34 mg, 0.90 mmol) in THF (0.9 mL) was added a solution of **3** (66.2 mg, 0.176 mmol) in THF (0.9 mL) at 0 °C and the mixture was stirred for 2 h at room temperature under an argon atmosphere. The resulting mixture was cooled at 0 °C and quenched with water (34 μL), 15 wt. % aqueous sodium hydroxide solution (34 μL), and water (102 μL). The mixture was stirred for 1 h at room temperature and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3:1 to 2:1 as eluent) to obtain amino alcohol **15** (46.3 mg, 85% yield) as a colorless oil. The ee was determined to be >99% ee

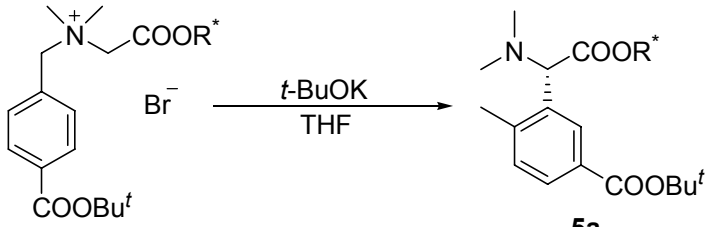
by chiral HPLC analysis [Daicel Chiralcel OJ–H, hexane/ethanol = 90:10, 0.50 mL/min, t_R = 9.4 min for the (*S*)-isomer and 12.5 min for the (*R*)-isomer].

(2*R*)-2-(5'-Hydroxymethyl-2'-methyl)phenyl-*N*-methylproline *tert*-butyl ester (15): colorless oil;

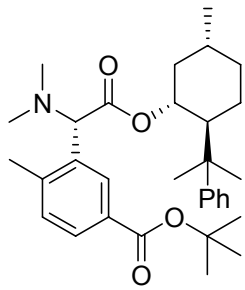


$[\alpha]^{25}_{589}$ = 134.4 (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.60 (1H, d, *J* = 1.4 Hz, 6'-H), 7.16 (1H, dd, *J* = 7.8, 1.4 Hz, 4'-H), 7.12 (1H, d, *J* = 7.8 Hz, 3'-H), 4.66 (2H, d, *J* = 5.4 Hz, 5'-CH_2), 3.27-3.19 (1H, m, 5-H), 2.94-2.74 (2H, m, 3-H and 5-H), 2.42 (3H, s, CH_3N), 2.22 (3H, s, Ar-CH_3), 1.98-1.64 (4H, m, 3-H, 4-H, and OH), 1.46 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.8, 142.3, 137.8, 134.9, 131.3, 125.2, 124.2, 81.4, 74.1, 65.6, 54.5, 37.2, 37.0, 28.3, 22.2, 20.4; IR (film) 3388, 2968, 2928, 2796, 1712, 1454, 1392, 1368, 1248, 1160, 1130, 1098, 1042, 1002, 912, 842, 818, 754 cm^{-1}; Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.50; H, 9.09; N, 4.52.

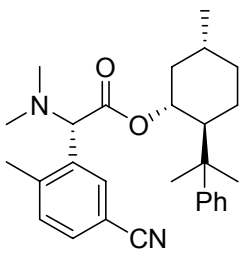
Representative procedure for asymmetric Sommelet–Hauser rearrangement of glycine (–)-8-phenylmenthol ester-derived ammonium salts 4a:



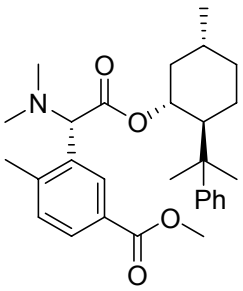
A solution of **4a** (123 mg, 0.209 mmol) in THF (2.1 mL) was cooled to –40 °C and treated with a 1.0 M THF solution of potassium *tert*-butoxide (0.25 mL, 0.25 mmol). The mixture was stirred for 4 h at the same temperature under an argon atmosphere. The resulting mixture was added to stirred ice-cold saturated aqueous ammonium chloride and the mixture was extracted with ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 7:1 to 4:1 as eluent) gave **5a** (101 mg, 95% yield) as a colorless gum.

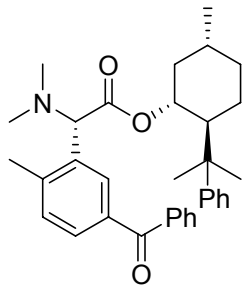
(2*S*)-2-(5'-*tert*-Butoxycarbonyl-2'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (5a): 

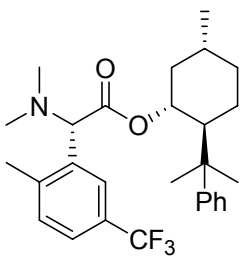
colorless gum; $[\alpha]^{25}_{589}$ = 7.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.77-7.72 (2H, m, Ar-H), 7.34-7.24 (4H, m, Ar-H), 7.22-7.12 (2H, m, Ar-H), 4.83 (1H, ddd, *J* = 10.8, 10.8, 4.2 Hz, COOCH), 3.46 (1H, s, NCHCOO), 2.25 (6H, s, $(CH_3)_2N$), 2.21 (3H, s, Ar-CH_3), 2.00-1.88 (1H, m, 8-Ph-Men-H), 1.73-0.69 (6H, m, 8-Ph-Men-H), 1.56 (9H, s, *t*-Bu), 1.30 (3H, s, 8-Ph-Men-CH_3), 1.17 (3H, s, 8-Ph-Men-CH_3), 0.77 (3H, d, *J* = 6.6 Hz, 8-Ph-Men-CH_3), 0.53 (1H, ddd, *J* = 11.9, 11.9, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.5, 165.7, 152.0, 142.5, 135.2, 130.4, 129.8, 129.4, 128.6, 128.1, 125.4, 125.0, 80.7, 74.5, 68.8, 49.8, 42.5, 40.3, 39.5, 34.5, 31.1, 28.6, 28.2, 26.4, 24.2, 21.7, 19.8; IR (film) 3052, 2952, 2924, 2864, 2776, 1730, 1712, 1610, 1456, 1390, 1368, 1302, 1264, 1204, 1164, 1124, 1092, 1050, 984, 928, 886, 848, 762, 736, 700 cm^{-1}; Anal. Calcd for $C_{32}H_{45}NO_4$: C, 75.70; H, 8.93; N, 2.76. Found: C, 75.86; H, 9.05; N, 2.70.

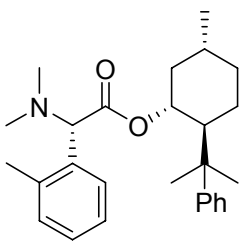
(2*S*)-2-(5'-Cyano-2'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (5b): 

white solid; mp 128–130 °C; $[\alpha]^{25}_{589}$ = –7.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.61 (1H, d, *J* = 1.6 Hz, Ar-H), 7.40 (1H, dd, *J* = 7.8, 1.6 Hz, Ar-H), 7.36-7.25 (4H, m, Ar-H), 7.23-7.15 (2H, m, Ar-H), 4.77 (1H, ddd, *J* = 10.8, 10.8, 4.3 Hz, COOCH), 3.34 (1H, s, NCHCOO), 2.20 (6H, s, $(CH_3)_2N$), 2.19 (3H, s, Ar-CH_3), 2.03-1.92 (1H, m, 8-Ph-Men-H), 1.79-1.68 (1H, m, 8-Ph-Men-H), 1.67-1.56 (1H, m, 8-Ph-Men-H), 1.54-0.70 (4H, m, 8-Ph-Men-H), 1.29 (3H, s, 8-Ph-Men-CH_3), 1.17 (3H, s, 8-Ph-Men-CH_3), 0.77 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.47 (1H, ddd, *J* = 11.6, 11.6, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 169.9, 152.1, 143.0, 136.9, 132.0, 131.1, 131.0, 128.1, 125.4, 125.0, 118.7, 110.0, 75.1, 69.0, 49.9, 43.0, 40.3, 39.4, 34.4, 31.0, 28.8, 26.3, 23.8, 21.6, 20.0; IR (film) 3052, 2952, 2920, 2864, 2776, 2224, 1734, 1602, 1494, 1456, 1368, 1344, 1314, 1258, 1202, 1172, 1152, 1094, 1050, 984, 912, 824, 768, 700 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.48. Found: C, 77.57; H, 8.53; N, 6.36.

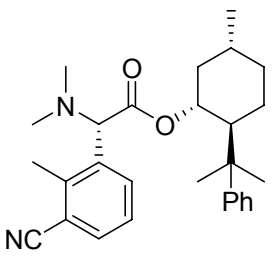
(2*S*)-2-(Dimethylamino)-2-(5'-methoxycarbonyl-2'-methylphenyl)acetic acid (–)-8-phenylmenthol ester (5c): 
colorless crystals; mp 109–110 °C; $[\alpha]^{25}_{589}$ = 2.3 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.88 (1H, d, *J* = 1.6 Hz, Ar-H), 7.82 (1H, dd, *J* = 8.1, 1.6 Hz, Ar-H), 7.35-7.25 (4H, m, Ar-H), 7.23-7.14 (2H, m, Ar-H), 4.81 (1H, ddd, *J* = 10.5, 10.5, 4.1 Hz, COOCH), 3.86 (3H, s, $COOCH_3$), 3.43 (1H, s, NCHCOO), 2.24 (6H, s, $(CH_3)_2N$), 2.20 (3H, s, Ar-CH_3), 2.01-1.89 (1H, m, 8-Ph-Men-H), 1.74-1.65 (1H, m, 8-Ph-Men-H), 1.63-0.99 (4H, m, 8-Ph-Men-H), 1.31 (3H, s, 8-Ph-Men-CH_3), 1.18 (3H, s, 8-Ph-Men-CH_3), 0.85-0.68 (1H, m, 8-Ph-Men-H), 0.74 (3H, d, *J* = 6.5 Hz, 8-Ph-Men-CH_3), 0.49 (1H, ddd, *J* = 11.9, 11.9, 10.5 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.6, 167.0, 152.0, 142.9, 135.6, 130.6, 129.4, 128.8, 128.1, 128.0, 125.4, 125.0, 74.6, 69.1, 51.8, 49.9, 42.8, 40.3, 39.5, 34.4, 31.0, 28.6, 26.4, 24.2, 21.6, 19.9; IR (film) 3052, 2948, 2864, 2772, 1724, 1612, 1494, 1436, 1368, 1298, 1258, 1202, 1172, 1122, 1092, 1052, 982, 922, 884, 840, 760, 736, 700 cm^{-1}; Anal. Calcd for $C_{29}H_{39}NO_4$: C, 74.81; H, 8.44; N, 3.01. Found: C, 74.70; H, 8.44; N, 3.01.

(2*S*)-2-(5'-Benzoyl-2'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (5d): 
colorless gum; $[\alpha]^{25}_{589}$ = –5.8 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.72-7.70 (2H, m, Ar-H), 7.65-7.60 (2H, m, Ar-H), 7.59-7.52 (1H, m, Ar-H), 7.48-7.40 (2H, m, Ar-H), 7.33-7.12 (6H, m, Ar-H), 4.77 (1H, ddd, *J* = 10.8, 10.8, 4.3 Hz, COOCH), 3.43 (1H, s, NCHCOO), 2.24 (3H, s, Ar-CH_3), 2.21 (6H, s, $(CH_3)_2N$), 2.02-1.90 (1H, m, 8-Ph-Men-H), 1.76-0.68 (6H, m, 8-Ph-Men-H), 1.30 (3H, s, 8-Ph-Men-CH_3), 1.17 (3H, s, 8-Ph-Men-CH_3), 0.74 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.50 (1H, ddd, *J* = 11.9, 11.9, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 196.3, 170.4, 152.0, 142.4, 137.8, 135.6, 135.2, 132.3, 130.7, 130.3, 129.9, 129.1, 128.2, 128.1, 125.5, 125.0, 74.8, 69.4, 49.9, 43.0, 40.3, 39.5, 34.4, 31.0, 28.6, 26.4, 24.2, 21.7. 20.0; IR (film) 3052, 2952, 2924, 2864, 2772, 1730, 1656, 1600, 1496, 1446, 1370, 1316, 1264, 1204, 1170, 1152, 1094, 1050, 984, 892, 840, 768, 738, 702 cm^{-1}; Anal. Calcd for $C_{34}H_{41}NO_3$: C, 79.81; H, 8.08; N, 2.74. Found: C, 79.51; H, 8.26; N, 2.64.

(2*S*)-2-(Dimethylamino)-2-(2'-methyl-5'-trifluoromethylphenyl)acetic acid (–)-8-phenylmenthol ester (5e):  white solid; mp 78–80 °C; $[\alpha]^{25}_{589}$ = 44.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.48 (1H, s, Ar-H), 7.43-7.15 (7H, m, Ar-H), 4.80 (1H, ddd, *J* = 10.8, 10.8, 4.3 Hz, COOCH), 3.42 (1H, s, NCHCOO), 2.24 (6H, s, $(CH_3)_2N$), 2.20 (3H, s, Ar-CH_3), 2.00-1.88 (1H, m, 8-Ph-Men-H), 1.77-1.66 (1H, m, 8-Ph-Men-H), 1.64-0.70 (5H, m, 8-Ph-Men-H), 1.28 (3H, s, 8-Ph-Men-CH_3), 1.17 (3H, s, 8-Ph-Men-CH_3), 0.74 (3H, d, *J* = 6.5 Hz, 8-Ph-Men-CH_3), 0.46 (1H, ddd, *J* = 11.6, 11.6, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.3, 152.1, 141.5, 136.1, 130.7, 128.1, 125.5 (q, *J* = 26 Hz), 125.4, 125.2 (q, *J* = 4 Hz), 124.9, 124.2 (q, *J* = 4 Hz), 120.1 (d, *J* = 270 Hz), 74.7, 68.9, 49.9, 42.7, 40.2, 39.4, 34.4, 31.0, 28.7, 26.3, 23.9, 21.5, 19.6; IR (film) 3052, 2952, 2924, 2868, 2776, 1732, 1620, 1600, 1496, 1456, 1368, 1330, 1288, 1266, 1204, 1164, 1124, 1080, 1050, 984, 920, 828, 768, 740, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{36}F_3NO_2$: C, 70.71; H, 7.63; N, 2.95. Found: C, 70.72; H, 7.74; N, 2.76.

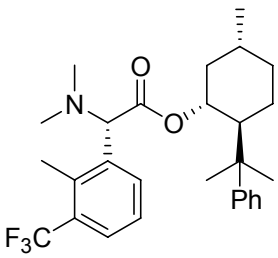
(2*S*)-2-(Dimethylamino)-2-(2'-methylphenyl)acetic acid (–)-8-phenylmenthol ester (5f):  white solid; mp 88–90 °C; $[\alpha]^{25}_{589}$ = 64.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35-7.24 (5H, m, Ar-H), 7.22-7.15 (1H, m, Ar-H), 7.14-7.05 (3H, m, Ar-H), 4.77 (1H, ddd, *J* = 10.8, 10.8, 4.3 Hz, COOCH), 3.46 (1H, s, NCHCOO), 2.22 (6H, s, $(CH_3)_2N$), 2.15 (3H, s, Ar-CH_3), 2.00-1.88 (1H, m, 8-Ph-Men-H), 1.70-0.67 (6H, m, 8-Ph-Men-H), 1.32 (3H, s, 8-Ph-Men-CH_3), 1.19 (3H, s, 8-Ph-Men-CH_3), 0.72 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.47 (1H, ddd, *J* = 11.9, 11.9, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 171.1, 151.9, 137.1, 135.1, 130.3, 128.1, 128.0, 127.5, 125.9, 125.5, 125.0, 74.5, 69.3, 50.0, 43.1, 40.2, 39.5, 34.5, 31.0, 28.1, 26.5, 24.8, 21.6, 19.8; IR (film) 3048, 3020, 2948, 2864, 2784, 1720, 1598, 1496, 1456, 1440, 1388, 1364, 1346, 1268, 1212, 1172, 1092, 1058, 1046, 988, 934, 812, 762, 702 cm^{-1}; Anal. Calcd for $C_{27}H_{37}NO_2$: C, 79.56; H, 9.15; N, 3.44. Found: C, 79.27; H, 9.24; N, 3.46.

(2*S*)-2-(3'-Cyano-2'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (7a):



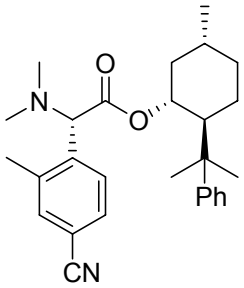
colorless crystals; mp 81–83 °C; $[\alpha]^{25}_{589}$ = 109.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.55-7.48 (2H, m, Ar-H), 7.37-7.18 (6H, m, Ar-H), 4.76 (1H, ddd, *J* = 10.8, 10.8, 4.1 Hz, COOCH), 3.36 (1H, s, NCHCOO), 2.30 (3H, s, Ar-CH_3), 2.20 (6H, s, $(CH_3)_2$N), 2.04-1.93 (1H, m, 8-Ph-Men-H), 1.82-1.72 (1H, m, 8-Ph-Men-H), 1.67-0.71 (5H, m, 8-Ph-Men-H), 1.30 (3H, s, 8-Ph-Men-CH_3), 1.17 (3H, s, 8-Ph-Men-CH_3), 0.75 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.44 (1H, ddd, *J* = 11.9, 11.9, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.0, 152.1, 140.9, 136.9, 132.5, 132.1, 128.1, 126.3, 125.4, 124.9, 118.4, 113.7, 74.9, 68.7, 49.8, 42.8, 40.1, 39.3, 34.3, 31.0, 29.2, 26.2, 23.4, 21.6, 17.7; IR (film) 3052, 2952, 2924, 2864, 2772, 2220, 1734, 1598, 1456, 1368, 1344, 1312, 1266, 1204, 1168, 1046, 982, 898, 844, 790, 766, 738, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.48. Found: C, 77.46; H, 8.66; N, 6.20.

(2*S*)-2-(Dimethylamino)-2-(2'-methyl-3'-trifluoromethylphenyl)acetic acid (–)-8-phenylmenthol ester (7b):



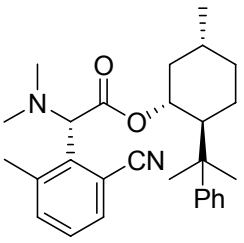
colorless crystals; mp 46–48 °C; $[\alpha]^{23}_{589}$ = 56.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.55-7.47 (2H, m, Ar-H), 7.37-7.16 (6H, m, Ar-H), 4.78 (1H, ddd, *J* = 10.8, 10.8, 4.1 Hz, COOCH), 3.50 (1H, s, NCHCOO), 2.22 (9H, s, $(CH_3)_2$N and Ar-CH_3), 2.04-1.92 (1H, m, 8-Ph-Men-H), 1.77-1.67 (1H, m, 8-Ph-Men-H), 1.65-1.55 (1H, m, 8-Ph-Men-H), 1.51-0.70 (5H, m, 8-Ph-Men-H), 1.30 (3H, s, 8-Ph-Men-CH_3), 1.18 (3H, s, 8-Ph-Men-CH_3), 0.74 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.47 (1H, ddd, *J* = 11.3, 11.3, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.6, 152.0, 137.4, 136.2 (q, *J* = 2 Hz), 131.7 (d, *J* = 1 Hz), 129.4 (q, *J* = 29 Hz), 128.1, 125.5, 125.43, 125.35 (q, *J* = 6 Hz), 125.0, 124.5 (d, *J* = 272 Hz), 74.8, 68.6, 49.9, 42.8, 40.2, 39.4, 34.4, 31.0, 28.8, 26.3, 23.9, 21.6, 15.0 (q, *J* = 3 Hz); IR (film) 3048, 2952, 2920, 2864, 2772, 1732, 1598, 1456, 1368, 1316, 1266, 1204, 1168, 1124, 1054, 1024, 984, 894, 792, 766, 740, 700 cm^{-1}; Anal. Calcd for $C_{28}H_{36}F_3NO_2$: C, 70.71; H, 7.63; N, 2.95. Found: C, 70.90; H, 7.65; N, 2.96.

(2*S*)-2-(4'-Cyano-2'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (10a):

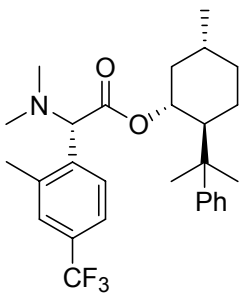


colorless crystals; mp 134–136 °C; $[\alpha]^{25}_{589}$ = 59.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.64 (1H, s, Ar-H), 7.61 (1H, d, *J* = 8.0 Hz, Ar-H), 7.34-7.28 (5H, m, Ar-H), 7.19 (1H, t, *J* = 6.8 Hz, Ar-H), 4.63 (1H, ddd, *J* = 10.6, 10.6, 4.0 Hz, COOCH), 3.37 (1H, s, NCHCOO), 2.12 (6H, s, $(CH_3)_2$N), 2.11 (3H, s, Ar-CH_3), 2.00 (1H, ddd, *J* = 11.3, 11.3, 3.0 Hz, 8-Ph-Men-H), 1.70-1.64 (1H, m, 8-Ph-Men-H), 1.59-1.52 (1H, m, 8-Ph-Men-H), 1.41-1.32 (2H, m, 8-Ph-Men-H), 1.24 (3H, s, 8-Ph-Men-CH_3), 1.15-1.04 (1H, m, 8-Ph-Men-H), 1.11 (3H, s, 8-Ph-Men-CH_3), 0.87-0.76 (1H, m, 8-Ph-Men-H), 0.72 (3H, d, *J* = 6.5 Hz, 8-Ph-Men-CH_3), 0.47 (1H, ddd, *J* = 12.0, 12.0, 10.6 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 169.9, 152.1, 140.7, 138.6, 133.7, 129.6, 128.8, 128.1, 125.4, 124.9, 118.7, 111.3, 75.0, 69.0, 49.9, 42.9, 40.1, 39.3, 34.4, 31.0, 28.9, 26.3, 23.7, 21.6, 19.5; IR (film) 3052, 2952, 2864, 2780, 2224, 1728, 1602, 1496, 1450, 1368, 1346, 1266, 1208, 1172, 1096, 1052, 982, 966, 892, 832, 764, 740, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.48. Found: C, 77.45; H, 8.50; N, 6.19.

(2*S*)-2-(2'-Cyano-6'-methylphenyl)-2-(dimethylamino)acetic acid (–)-8-phenylmenthol ester (11a):

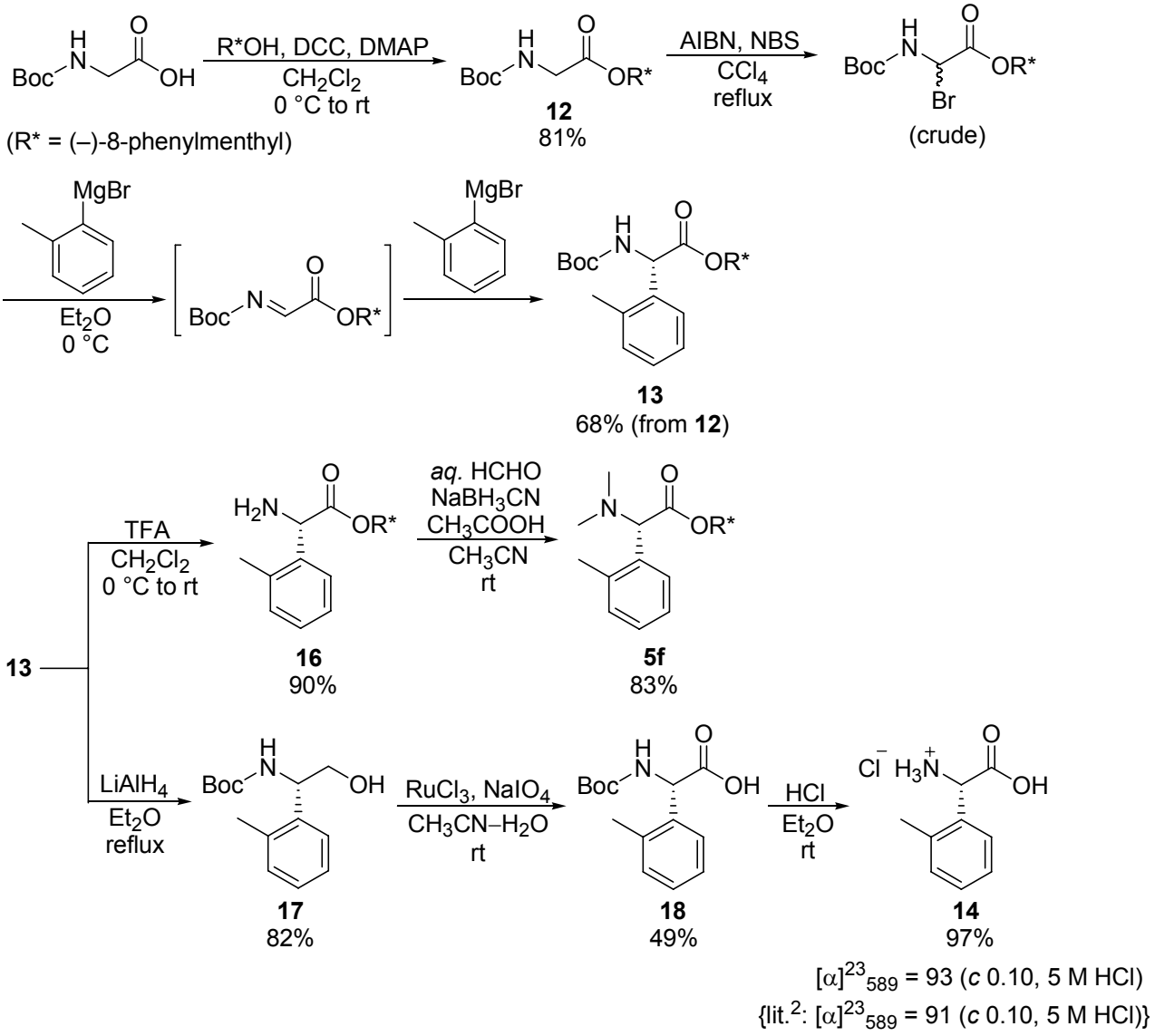


pale yellow gum; $[\alpha]^{25}_{589}$ = 44.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.54 (1H, d, *J* = 7.6 Hz, Ar-H), 7.38-7.23 (6H, m, Ar-H), 7.22-7.13 (1H, m, Ar-H), 4.84 (1H, ddd, *J* = 10.5, 10.5, 4.3 Hz, COOCH), 4.12 (1H, s, NCHCOO), 2.45 (3H, s, Ar-CH_3), 2.26 (6H, s, $(CH_3)_2$N), 1.88-1.76 (1H, m, 8-Ph-Men-H), 1.53-0.54 (6H, m, 8-Ph-Men-H), 1.35 (3H, s, 8-Ph-Men-CH_3), 1.26 (3H, s, 8-Ph-Men-CH_3), 0.71 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.48 (1H, ddd, *J* = 11.9, 11.9, 10.5 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 168.4, 150.5, 139.8, 137.9, 135.7, 131.8, 128.11, 128.09, 125.6, 125.4, 118.4, 114.7, 75.2, 72.4, 50.2, 43.9, 40.7, 40.0, 34.2, 31.0, 28.6, 26.9, 25.2, 21.6, 19.8; IR (film) 3052, 2952, 2920, 2864, 2772, 2220, 1740, 1600, 1462, 1370, 1322, 1266, 1208, 1174, 1150, 1094, 1056, 980, 890, 836, 788, 764, 736, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.48. Found: C, 77.88; H, 8.64; N, 6.18.

(2*S*)-2-(Dimethylamino)-2-(2'-methyl-4'-trifluoromethylphenyl)acetic acid (–)-8-phenylmenthol ester (10b): 

colorless crystals; mp 48–50 °C; $[\alpha]^{23}_{589}$ = 51.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 7.53 (1H, d, *J* = 8.0 Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.22-7.17 (5H, m, Ar-H), 7.10-7.04 (1H, m, Ar-H), 4.89 (1H, ddd, *J* = 10.8, 10.8, 4.0 Hz, COOCH), 3.56 (1H, s, NCHCOO), 2.26 (6H, s, $(CH_3)_2N$), 2.08 (3H, s, Ar-CH_3), 1.82 (1H, ddd, *J* = 13.0, 10.8, 3.5 Hz, 8-Ph-Men-H), 1.67 (1H, ddd, *J* = 11.9, 6.2, 4.0 Hz, 8-Ph-Men-H), 1.48 (1H, ddd, *J* = 13.0, 6.6, 3.5 Hz, 8-Ph-Men-H), 1.33-1.25 (1H, m, 8-Ph-Men-H), 1.28 (3H, s, 8-Ph-Men-CH_3), 1.12-1.00 (1H, m, 8-Ph-Men-H), 1.07 (3H, s, 8-Ph-Men-CH_3), 0.79 (1H, ddd, *J* = 13.0, 13.0, 3.5 Hz, 8-Ph-Men-H), 0.61-0.43 (2H, m, 8-Ph-Men-H), 0.57 (3H, d, *J* = 6.5 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.4, 152.0, 139.1 (q, *J* = 1 Hz), 138.0, 129.6 (q, *J* = 32 Hz), 128.5, 128.1, 127.0 (q, *J* = 4 Hz), 125.4, 125.0, 124.1 (d, *J* = 270 Hz), 122.7 (q, *J* = 4 Hz), 74.9, 69.0, 49.9, 42.9, 40.2, 39.4, 34.4, 31.0, 28.7, 26.4, 24.1, 21.6, 19.7; IR (film) 2952, 2864, 2772, 1736, 1446, 1412, 1368, 1332, 1272, 1216, 1200, 1162, 1124, 1084, 1052, 984, 882, 836, 770, 740, 700 cm^{-1}; Anal. Calcd for $C_{28}H_{36}F_3NO_2$: C, 70.71; H, 7.63; N, 2.95. Found: C, 70.96; H, 7.80; N, 3.09.

Determination of the absolute configurations of 5



The *S*-configuration of **5f** was determined by ^{1}H NMR comparison of the (*S*)-authentic sample which prepared from (*S*)-*N*-Boc-(2-methylphenyl)glycine (–)-8-phenylmenthol ester (**13**). Other configurations of **5a**–**5e** were determined by the analogy with **5f**. The compound **13** was prepared by diastereoselective addition of 2-methylphenylmagnesium bromide to *N*-Boc-iminoacetate of (–)-8-phenylmenthol.[1] The absolute configration of **13** was determined after conversion to (2-methylphenyl)glycine hydrochloride (**14**). The assignment was confirmed by comparison of the sign of the specific rotation of $[\alpha]^{23}_{589} = 93$ with that of the known (*S*)-(2-methylphenyl)glycine [(*S*)-**14**][2] {$[\alpha]^{23}_{589} = 91$ (*c* 0.10, 5 M HCl)}.

(2*S*)-2-Amino-*N*-*tert*-butoxycarbonyl-2-(2'-methylphenyl)acetic acid (–)-8-phenylmenthol ester (13): (Step 1) To a mixture of Boc-glycine (84 mg, 0.48 mmol), (–)-8-phenylmenthol[3] (94 mg, 0.40 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (10 mg, 0.09 mmol) in dichloromethane (1 mL) was added a solution of *N*,*N*-dicyclohexylcarbodiimide (DCC) (99 mg, 0.48 mmol) in dichloromethane (1 mL) at 0 °C. The mixture was stirred for 1.5 h at 0 °C and for 12 h at room temperature. The resulting mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 7:1 to 5:1 as eluent) to afford *N*-Boc-glycine (–)-8-phenylmenthol ester (**12**) (152 mg, 81% yield) as a colorless gum.

(Step 2) A mixture of **12** (273 mg, 0.70 mmol), *N*-bromosuccinimide (NBS) (125 mg, 0.70 mmol), 2,2'-azobis(2-methylpropionitrile) (AIBN) (6 mg, 0.04 mmol) in carbon tetrachloride (1.4 mL) was refluxed for 15 min. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was dissolved in ether (1.4 mL). The solution was added to a ca. 1 M solution of 2-methylphenylmagnesium bromide diethyl ether solution (2.1 mL, 2.1 mmol, prepared from magnesium turnings and *o*-bromotoluene) at 0 °C. After stirring for 5 min, the mixture was quenched with saturated aqueous ammonium chloride and extracted with ether. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 15:1 to 8:1 as eluent) to give **13** (227 mg, 68% yield) as a white solid.

13: white solid; mp 42–44 °C; $[\alpha]^{25}_{589}$ = 30.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz, 77:23 mixture of rotamers) δ 7.35-7.00 (9H, m, Ar-H), 5.49 (1H, d, *J* = 6.8 Hz, NCHCOO), 4.83 (1H, ddd, *J* = 10.8, 10.8, 4.2 Hz, COOCH), 4.63 (0.77H, d, *J* = 6.8 Hz, NH), 4.24 (0.23H, br, NH), 2.24 (2.31H, s, Ar-CH_3), 2.10 (0.69H, s, Ar-CH_3), 2.02-0.67 (7H, m, 8-Ph-Men-H), 1.44 (9H, s, *t*-Bu), 1.34 (3H, s, 8-Ph-Men-CH_3), 1.23 (3H, s, 8-Ph-Men-CH_3), 0.74 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3), 0.56 (1H, ddd, *J* = 11.6, 11.6, 10.8 Hz, 8-Ph-Men-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 170.8, 154.4, 151.2, 136.5, 136.2, 130.5, 128.0, 127.7, 126.1, 126.0, 125.5, 125.4, 79.5, 75.4, 53.9, 50.5, 40.5, 39.5, 34.3, 31.1, 28.5, 28.3, 26.3, 24.2, 21.6, 19.5; IR (film) 3444, 2960, 2920, 1716, 1600, 1494, 1390, 1366, 1308, 1266, 1206, 1170, 1092, 1050, 1028,

988, 762, 736, 700 cm^{-1}; Anal. Calcd for $C_{30}H_{41}NO_4$: C, 75.12; H, 8.62; N, 2.92. Found: C, 75.33; H, 8.79; N, 3.03.

Preparation of the authentic sample 5f from 13

(Step 1) A solution of **13** (200 mg, 0.42 mmol) in dichloromethane (0.42 mL) was treated with trifluoroacetic acid (0.21 mL) at 0 °C. The mixture was stirred for 6 h at 0 °C and 2 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was treated with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ether and the combined extracts were washed with brine. The ethereal solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (dichloromethane/methanol = 20:1 as eluent) gave (2*S*)-(2-methylphenyl)glycine (–)-8-phenylmenthol ester (**16**) (144 mg, 90% yield) as a yellow oil.

(Step 2) To a mixture of **16** (144 mg, 0.38 mmol), 37 wt. % aqueous formaldehyde solution (0.27 mL), and sodium cyanoborohydride (69 mg, 1.1 mmol) in acetonitrile (2 mL) was added acetic acid (0.8 mL) slowly over 30 min at room temperature. The mixture was stirred for 3 h at the same temperature and treated with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ether and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 15:1 to 5:1 as eluent) to give **5f** (128 mg, 83% yield) as a white solid.

Preparation of (2-methylphenyl)glycine hydrochloride (14) from 13 for determination of absolute configration

(Step 1) A solution of **13** (114 mg, 0.24 mmol) in diethyl ether (2.4 mL) was added to a suspention of lithium aluminium hydride (14 mg, 0.36 mmol) in diethyl ether (2.4 mL) at 0 °C under an argon atomosphere. The mixture was refluxed for 30 min and the ractant was quenched with water at 0 °C. The mixture was treated with 1 M aqueous potassium hydrogensulfate solution and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. The residue was purified by

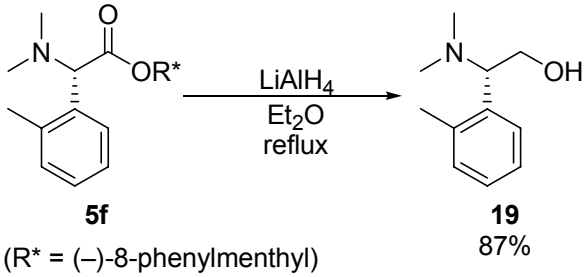
chromatography on silica gel (dichloromethane/methanol = 50:1 to 20:1 as eluent) to obtain *N*-Boc-amino alcohol **17** (49.5 mg, 82% yield) as colorless crystals.

(Step 2) A mixture of **17** (16 mg, 0.064 mmol), ruthenium (III) chloride hydrate (40% Ru, 1 mg, 0.004 mmol), and sodium periodate (56 mg, 0.26 mmol) in acetonitrile (0.38 mL) and water (0.26 mL) was stirred for 2.5 h at room temperature. The resulting mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chlomatography on silica gel (dichloromethane/methanol = 6:1 to 4:1 as eluent) gave *N*-Boc-(2-methylphenyl)glycine (**18**) (8.4 mg, 49% yield) as a colorless gum.

(Step 3) **18** (13 mg, 0.049 mmol) was treated with a 2 M diethyl ether solution of hydrogen chloride (2.5 mL, 5 mmol) for 24 h at room temperature. The resulting mixture was filtered and the filtracts were washed with dichloromethane. The filtracts were dissolved in methanol and the solution was concentrated to give (*S*)-(2-methylphenyl)glycine hydrochloride [(*S*)-**14**] (9.6 mg, 97% yield) as a white solid.

(*S*)-(2-Methylphenyl)glycine hydrochloride [(*S*)-14]: white solid; $[\alpha]^{25}_{589}$ = 93 (*c* 0.10, 5 M *aq*. HCl)[2]; ^{1}H NMR [D_2O, 270 MHz, tetramethylsilane (TMS) was used as an external standard (δ = 0)] δ 6.75-6.65 (4H, m, Ar-H), 4.67 (1H, s, NCHCOO), 1.79 (3H, s, Ar-CH_3); ^{13}C NMR [D_2O, 68 MHz, TMS was used as an external standard (δ = 0)] δ 171.8, 137.4, 131.4, 130.7, 130.1, 127.1, 126.9, 53.3, 18.4; IR (KBr) 3416, 3016, 1744, 1606, 1512, 1462, 1404, 1346, 1208, 1176, 1128, 1050, 890, 802, 760, 726 cm^{-1}.

Removal of (–)-8-phenylmenthol moiety from 5f by reduction with lithium aluminium hydride



5f
(R* = (–)-8-phenylmenthyl)

19
87%

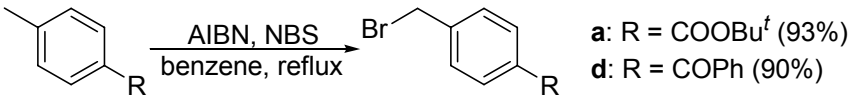
To a suspension of lithium aluminium hydride (20 mg, 0.53 mmol) in diethyl ether (1.8 mL) was added a solution of **5f** (74 mg, 0.18 mmol) in diethyl ether (1.8 mL) at 0 °C and the mixture was refluxed for 6 h under an argon atmosphere. The resulting mixture was quenched with water at 0 °C and extracted with

diethyl ether. The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on pH-controlled (pH = 9.5) silica gel[4] (hexane/ethyl acetate = 4:1 to 1.5:1 as eluent) to obtain (*S*)-2-(dimethylamino)-2-(2-methylphenyl)ethanol [(*S*)-**19**] (28.2 mg, 87% yield) as colorless crystals. The ee was determined to by chiral HPLC analysis [Daicel Chiralpak AD–H, hexane/ethanol/diethylamine = 98:2:0.1, 0.50 mL/min, t_R = 14.4 min for the (*S*)-isomer and 16.3 min for the (*R*)-isomer].

(*S*)-2-(Dimethylamino)-2-(2-methylphenyl)ethanol [(*S*)-19]: 98% ee; colorless crystals; mp 37–39 °C; $[\alpha]^{24}_{589}$ = 41.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.28 (1H, m, Ar-H), 7.22-7.17 (3H, m, Ar-H), 3.87 (1H, dd, *J* = 10.1, 7.3 Hz, 1-H), 3.82 (1H, dd, *J* = 7.3, 4.8 Hz, 2-H), 3.69 (1H, dd, *J* = 10.1, 4.8 Hz, 1-H), 2.39 (3H, s, Ar-CH_3), 2.26 (7H, s, $(CH_3)_2$N and OH); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 137.2, 135.8, 130.8, 127.7, 127.2, 125.8, 65.3, 62.4, 42.4, 20.1; IR (film) 3384, 2944, 2864, 2820, 2772, 1460, 1344, 1262, 1178, 1160, 1098, 1040, 952, 882, 856, 760, 728 cm^{-1}; Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: 73.60; H, 9.60; N, 7.54.

Preparation of Substrates

Preparation of benzylic bromides (20):



20

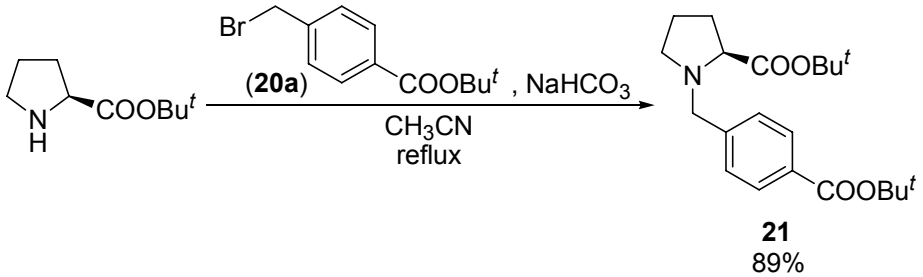
a: R = COOBu^t (93%)
d: R = COPh (90%)

A mixture of 4-substituted toluene (1.0 equiv), *N*-bromosuccinimide (1.1 equiv), and 2,2'-azobis(2-methylpropionitrile) (AIBN) (0.05 equiv) in benzene (0.2 M) was refluxed for 5 h. The resulting mixture was cooled to 0 °C and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 30:1 to 10:1 as eluent) to afford **20**.

***tert*-Butyl 4-(bromomethyl)benzoate (20a):** prepared from *tert*-butyl 4-methylbenzoate[5] in 93% yield; white solid; mp 53–55 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.96 (2H, d, J = 8.4 Hz, Ar-H), 7.43 (2H, d, J = 8.4 Hz, Ar-H), 4.50 (2H, s, CH_2Br), 1.59 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 165.2, 142.1, 132.0, 129.9, 128.8, 81.2, 32.3, 28.1; IR (KBr) 3004, 2976, 2928, 1698, 1612, 1578, 1416, 1364, 1316, 1296, 1254, 1226, 1160, 1118, 1094, 1020, 866, 848, 806, 776, 706 cm^{-1}; Anal. Calcd for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58. Found: C, 52.96; H, 5.44.

4-Benzoyl-1-bromomethylbenzene (20d): prepared from 4-methylbenzophenone in 90% yield; white solid; mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.82-7.71 (4H, m, Ar-H), 7.60 (1H, t, J = 7.3 Hz, Ar-H), 7.53-7.42 (4H, m, Ar-H), 4.53 (2H, s, CH_2Br); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 195.9, 142.0, 137.4, 137.3, 132.5, 130.5, 129.9, 128.9, 128.3, 32.2; IR (KBr) 3052, 3016, 1648, 1606, 1592, 1446, 1412, 1318, 1280, 1226, 1200, 1176, 1150, 1098, 974, 942, 924, 852, 790, 744, 702 cm^{-1}; Anal. Calcd for $C_{14}H_{11}BrO$: C, 61.11; H, 4.03. Found: C, 60.85; H, 4.04.

(2*S*)-*N*-(4'-*tert*-Butoxycarbonylbenzyl)proline *tert*-butyl ester (21):

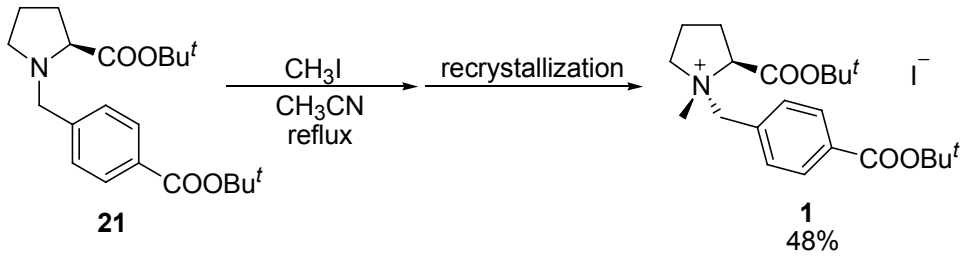


21
89%

A mixture of proline *tert*-butyl ester[6] (0.45 g, 2.6 mmol), sodium hydrogen carbonate (0.66 g, 7.9 mmol) and **20a** (0.78 g, 2.9 mmol) in acetonitrile (13 mL) was refluxed for 3 h. The resulting mixture was concentrated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 15:1 as eluent) to give **21** (0.84 g, 89% yield) as a pale yellow oil.

21: pale yellow oil; $[\alpha]^{25}_{589}$ = –45.6 (*c* 1.00, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.0 Hz, Ar-H), 7.40 (2H, d, *J* = 8.0 Hz, Ar-H), 4.04 (1H, d, *J* = 13.2 Hz, CHAr), 3.55 (1H, d, *J* = 13.2 Hz, CHAr), 3.17 (1H, dd, *J* = 8.6, 6.0 Hz, 2-H), 2.96 (1H, ddd, *J* = 7.8, 7.8, 3.4 Hz, 5-H), 2.42-2.30 (1H, m, 5-H), 2.17-1.68 (4H, m, 3- and 4-H), 1.59 (9H, s, 4'-COOBu^t), 1.46 (9H, s, 2-COOBu^t); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.2, 165.8, 143.9, 130.7, 129.3, 128.6, 80.7, 80.6, 65.7, 58.0, 52.9, 29.1, 28.2, 28.1, 22.9; IR (film) 2972, 2812, 1712, 1612, 1478, 1456, 1414, 1392, 1368, 1292, 1256, 1212, 1164, 1116, 1020, 848, 762, 708 cm^{-1}; Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.87. Found: C, 69.70; H, 8.70; N, 3.83.

(1*S*, 2*S*)-*N*-(4'-*tert*-Butoxycarbonylbenzyl)-*N*-methylproline *tert*-butyl ester (1):

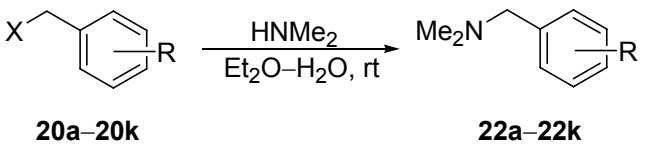


A mixture of **21** (0.49 g, 1.4 mmol) and iodomethane (0.26 mL, 4.2 mmol) in acetonitrile (5.5 mL) was refluxed for 6 h and the resulting mixture was concentrated. Purification of the residue by chromatography on silica gel (dichloromethane/methanol = 30:1 to 10:1 as eluent) gave 87:13 diastereomixture of **1** (0.55 g, 78% yield) as a pale yellow solid. Recrystallization of the solid from hexane/dichloromethane/benzene gave diastereomerically pure **1** (0.34 g, 48% yield) as colorless prisms.

1: colorless prisms; mp 157–159 °C dec; $[\alpha]^{27}_{589}$ = –27.7 (*c* 1.00, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.08 (2H, d, *J* = 8.1 Hz, Ar-H), 7.77 (2H, d, *J* = 8.1 Hz, Ar-H), 5.54 (1H, d, *J* = 12.7 Hz, CHAr), 5.29 (1H, dd, *J* = 9.8, 9.8 Hz, 2-H), 5.20 (1H, d, *J* = 12.7 Hz, CHAr), 4.84 (1H, ddd, *J* = 10.5, 10.5, 10.5 Hz, 5-H), 3.48-3.38 (1H, m, 5-H), 3.09 (3H, s, CH_3N), 2.86-2.68 (1H, m, 3-H or 4-H), 2.50-2.18 (2H, m, 3-H or 4-H), 2.10-1.93 (1H, m, 3-H or 4-H), 1.61 (9H, s, 4'-COOBu^t), 1.55 (9H, s, 2-COOBu^t); ^{13}C NMR (68 MHz,

$CDCl_3$) δ 165.0, 164.5, 134.3, 132.7, 131.6, 130.2, 86.0, 81.9, 72.1, 65.2, 64.1, 44.1, 28.0, 27.9, 24.5, 18.4; IR (KBr) 3012, 2972, 2936, 1714, 1478, 1458, 1412, 1394, 1370, 1314, 1298, 1258, 1166, 1120, 1036, 994, 928, 846, 750, 708 cm^{-1}; Anal. Calcd for $C_{22}H_{34}INO_4$: C, 52.49; H, 6.81; N, 2.78. Found: C, 52.37; H, 6.80; N, 2.79.

Preparation of *N*,*N*-dimethylbenzylic amines (22):

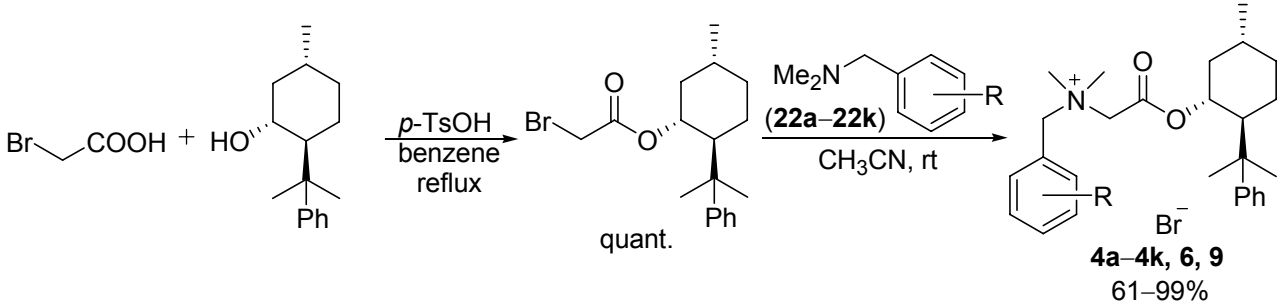


20a–**20k** **22a**–**22k**

a: R = 4-COOBu^t, X = Br (87%)
b: R = 4-CN, X = Br (97%)
c: R = 4-COOMe, X = Br (75%)
d: R = 4-COPh, X = Br (84%)
e: R = 4-CF_3, X = Br (85%)
f: R = 4-H, X = Cl (75%)
g: R = 4-OMe, X = Cl (94%)
h: R = 2-CN, X = Br (98%)
i: R = 2-CF_3, X = Br (90%)
j: R = 3-CN, X = Br (99%)
k: R = 3-CF_3, X = Br (84%)

To a solution of benzylic bromides or chlorides **20a**–**20k** (1.0 equiv) in ether (1 M) was added a solution of 50 wt. % aqueous dimethylamine solution (5 equiv) at room temperature. After stirring for 4–12 h at the same temperature, the resulting mixture was transferred in separatory funnel. The organic phase was separated and the organic phase was extracted with 10 wt. % aqueous citric acid solution. The aqueous phases were treated with 15 wt. % aqueous sodium hydroxide solution. The mixture was extracted with ether and the combined organic extracts were washed with brine. The solution was dried over sodium sulfate and concentrated to obtain *N*,*N*-dimethylbenzylic amines **22a**–**22k** (75–99% yield). The crude products of **22a**–**22k** were used in next step without further purification.

Preparation of *N*-benzylic-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium bromide (4), (6), (9):



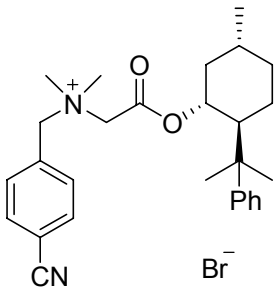
4a–**4k, 6, 9**
61–99%

(1st step) A round-bottomed flask was equipped with a Dean–Stark trap and a reflux condenser. The flask was charged with bromoacetic acid (2.0 equiv), (–)-8-phenylmenthol (1.0 equiv), *p*-toluenesulfonic acid monohydrate (0.05–0.10 equiv), and benzene (0.5 M). The mixture was refluxed for 16 h. The resulting mixture was cooled to room temperature and the solution was washed with saturated aqueous sodium hydrogen carbonate and water. The organic layer was dried over sodium sulfate. Evaporation of the solvent gave bromoacetic acid (–)-8-phenylmenthol ester in quantative yield. The crude product was used in next step without purification.

(2nd step) A solution of bromoacetic acid (–)-8-phenyl menthol ester (1.1 equiv) and **22a**–**22k** (1.0 equiv) in acetonitrile (0.2 M) was stirred for 2–4 days at room temperature. The resulting mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 30:1 to 10:1 as eluent) to obtain quaternary ammonium salt **4a**–**4k**, **6**, or **9**.

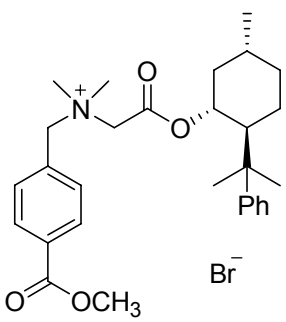
***N*-(4'-*tert*-Butoxycarbonylbenzyl)-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl] ammonium bromide (4a):** 95% yield; white solid; mp 104–106 °C; $[\alpha]^{25}_{589}$ = 32.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.08 (2H, d, *J* = 8.2 Hz, Ar-H), 7.65 (2H, d, *J* = 8.2 Hz, Ar-H), 7.26 (2H, d, *J* = 7.0 Hz, Ar-H), 7.16 (2H, t, *J* = 7.0 Hz, Ar-H), 6.86 (1H, t, *J* = 7.0 Hz, Ar-H), 5.31 (1H, d, *J* = 12.6 Hz, NCHAr), 5.12 (1H, d, *J* = 12.6 Hz, NCHAr), 4.92 (1H, ddd, *J* = 10.8, 10.8, 4.7 Hz, COOCH), 4.17 (1H, d, *J* = 16.6 Hz, NCHCOO), 3.43 (3H, s, CH_3N), 3.27 (3H, s, CH_3N), 2.42 (1H, d, *J* = 16.6 Hz, NCHCOO), 2.21-2.10 (1H, m, 8-Ph-Men-H), 2.05-1.95 (1H, m, 8-Ph-Men-H), 1.88-1.71 (2H, m, 8-Ph-Men-H), 1.62 (9H, s, *t*-Bu), 1.62-1.40 (1H, m, 8-Ph-Men-H), 1.32-0.98 (3H, m, 8-Ph-Men-H), 1.28 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.93 (3H, d, *J* = 6.6 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 164.6, 163.4, 151.8, 134.4, 133.3, 130.8, 130.1, 128.0, 125.3, 125.0, 81.9, 76.8, 67.4, 59.6, 50.5, 50.0, 49.2, 41.2, 39.3, 34.0, 31.2, 30.7, 28.1, 25.9, 21.8, 21.6; IR (film) 2960, 2924, 1736, 1714, 1476, 1456, 1418, 1392, 1370, 1296, 1264, 1248, 1216, 1166, 1120, 1030, 1022, 990, 848, 736, 702 cm^{-1}; Anal. Calcd for $C_{32}H_{46}BrNO_4$: C, 65.30; H, 7.88; N, 2.38. Found: C, 65.10; H, 7.97; N, 2.37.

***N*,*N*-Dimethyl-*N*-(4'-metoxycarbonylbenzyl)-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]**



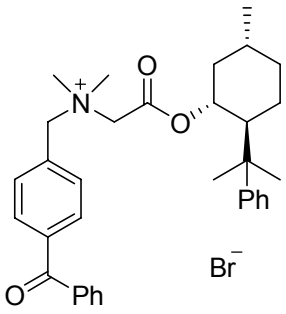
ammonium bromide (4b): 99% yield; white solid; mp 165–167 °C; $[\alpha]^{25}_{589}$ = 36.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.10 (2H, d, *J* = 8.2 Hz, Ar-H), 7.70 (2H, d, *J* = 8.2 Hz, Ar-H), 7.21 (2H, d, *J* = 7.3 Hz, Ar-H), 7.09 (2H, t, *J* = 7.3 Hz, Ar-H), 6.72 (1H, t, *J* = 7.3 Hz, Ar-H), 5.39 (1H, d, *J* = 12.6 Hz, NCHAr), 5.25 (1H, d, *J* = 12.6 Hz, NCHAr), 4.90 (1H, ddd, *J* = 10.5, 10.5, 4.4 Hz, COOCH), 4.14 (1H, d, *J* = 16.7 Hz, NCHCOO), 3.97 (3H, s, $COOCH_3$), 3.50 (3H, s, CH_3N), 3.32 (3H, s, CH_3N), 2.55 (1H, d, *J* = 16.7 Hz, NCHCOO), 2.19-2.05 (1H, m, 8-Ph-Men-H), 2.02-1.92 (1H, m, 8-Ph-Men-H), 1.87-1.68 (2H, m, 8-Ph-Men-H), 1.56-1.38 (1H, m, 8-Ph-Men-H), 1.30-0.86 (3H, m, 8-Ph-Men-H), 1.26 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.91 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 166.0, 163.3, 151.8, 133.6, 132.5, 131.4, 130.2, 128.0, 125.3, 125.0, 76.8, 67.3, 59.6, 52.5, 50.6, 50.0, 49.3, 41.3, 39.3, 34.1, 31.3, 30.8, 25.9, 21.6, 21.6; IR (film) 2952, 2920, 1726, 1614, 1436, 1418, 1280, 1246, 1202, 1112, 1030, 990, 970, 944, 906, 868, 840, 768, 758, 734, 702 cm^{-1}; Anal. Calcd for $C_{29}H_{40}BrNO_4$: C, 63.73; H, 7.38; N, 2.56. Found: C, 63.54; H, 7.30; N, 2.65.

***N*-(4'-Cyanobenzyl)-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium**

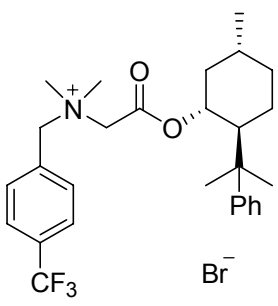


bromide (4c): 92% yield; white solid; mp 180–182 °C; $[\alpha]^{25}_{589}$ = 40.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.83 (2H, d, *J* = 8.4 Hz, Ar-H), 7.78 (2H, d, *J* = 8.4 Hz, Ar-H), 7.25 (2H, d, *J* = 7.0 Hz, Ar-H), 7.14 (2H, t, *J* = 7.0 Hz, Ar-H), 6.81 (1H, t, *J* = 7.0 Hz, Ar-H), 5.47 (1H, d, *J* = 12.3 Hz, NCHAr), 5.29 (1H, d, *J* = 12.3 Hz, NCHAr), 4.92 (1H, ddd, *J* = 10.8, 10.8, 4.6 Hz, COOCH), 4.16 (1H, d, *J* = 17.0 Hz, NCHCOO), 3.45 (3H, s, CH_3N), 3.28 (3H, s, CH_3N), 2.43 (1H, d, *J* = 17.0 Hz, NCHCOO), 2.21-2.09 (1H, m, 8-Ph-Men-H), 2.07-1.96 (1H, m, 8-Ph-Men-H), 1.86-1.71 (2H, m, 8-Ph-Men-H), 1.55-1.41 (1H, m, 8-Ph-Men-H), 1.32-0.88 (3H, m, 8-Ph-Men-H), 1.27 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.92 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.2, 151.9, 134.3, 132.8, 131.8, 128.0, 125.4, 124.8, 117.5, 115.0, 77.0, 66.7, 59.7, 50.6, 50.1, 49.2, 41.3, 39.3, 34.0, 31.3, 30.9, 25.9, 21.62, 21.56; IR (film) 2956, 2920, 2228, 1736, 1598, 1456, 1402, 1246, 1216, 1130,

1092, 1030, 988, 862, 830, 770, 732, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{37}BrN_2O_2$: C, 65.49; H, 7.26; N, 5.46. Found: C, 65.22; H, 7.23; N, 5.42.

***N*-(4'-Benzoylbenzyl)-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium bromide, monohydrate (4d):** 

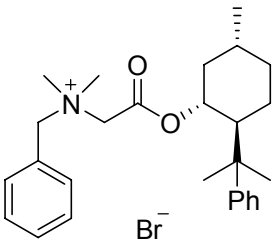
90% yield; white solid; mp 114–117 °C; $[\alpha]^{25}_{589}$ = 38.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.91-7.73 (6H, m, Ar-H), 7.65 (1H, t, *J* = 7.3 Hz, Ar-H), 7.52 (2H, t, *J* = 7.3 Hz, Ar-H), 7.30-7.22 (2H, m, Ar-H), 7.18 (2H, t, *J* = 7.3 Hz, Ar-H), 6.87 (1H, t, *J* = 7.3 Hz, Ar-H), 5.42 (1H, d, *J* = 12.4 Hz, NCHAr), 5.24 (1H, d, *J* = 12.4 Hz, NCHAr), 4.93 (1H, ddd, *J* = 10.5, 10.5, 4.5 Hz, COOCH), 4.15 (1H, d, *J* = 17.0 Hz, NCHCOO), 3.47 (3H, s, CH_3N), 3.32 (3H, s, CH_3N), 2.46 (1H, d, *J* = 17.0 Hz, NCHCOO), 2.23-2.09 (1H, m, 8-Ph-Men-H), 2.07-1.95 (1H, m, 8-Ph-Men-H), 1.90-1.70 (2H, m, 8-Ph-Men-H), 1.56-1.40 (1H, m, 8-Ph-Men-H), 1.33-0.84 (3H, m, 8-Ph-Men-H), 1.28 (3H, s, 8-Ph-Men-CH_3), 1.15 (3H, s, 8-Ph-Men-CH_3), 0.92 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 195.6, 163.4, 151.7, 139.8, 136.4, 133.5, 133.1, 130.7, 130.4, 130.0, 128.5, 127.9, 125.3, 125.0, 76.8, 67.2, 59.5, 50.6, 50.0, 49.2, 41.2, 39.2, 34.0, 31.2, 30.7, 25.9, 21.7, 21.6; IR (film) 3416, 3020, 2952, 2920, 1736, 1660, 1596, 1446, 1416, 1316, 1276, 1246, 1204, 1146, 1130, 1030, 990, 940, 926, 862, 770, 734, 702 cm^{-1}; Anal. Calcd for $C_{34}H_{44}BrNO_4$: C, 66.88; H, 7.26; N, 2.29. Found: C, 67.18; H, 7.41; N, 2.10.

***N*,*N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*-(4'-trifluoromethylbenzyl) ammonium bromide (4e):** 

98% yield; white solid; mp 106–108 °C; $[\alpha]^{25}_{589}$ = 21.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.81 (2H, d, *J* = 8.0 Hz, Ar-H), 7.71 (2H, d, *J* = 8.0 Hz, Ar-H), 7.19 (2H, d, *J* = 7.6 Hz, Ar-H), 7.05 (2H, t, *J* = 7.6 Hz, Ar-H), 6.64 (1H, t, *J* = 7.6 Hz, Ar-H), 5.46 (1H, d, *J* = 12.6 Hz, NCHAr), 5.31 (1H, d, *J* = 12.6 Hz, NCHAr), 4.90 (1H, ddd, *J* = 10.8, 10.8, 4.5 Hz, COOCH), 4.19 (1H, d, *J* = 16.9 Hz, NCHCOO), 3.51 (3H, s, CH_3N), 3.31 (3H, s, CH_3N), 2.52 (1H, d, *J* = 16.9 Hz, NCHCOO), 2.16-2.04 (1H, m, 8-Ph-Men-H), 2.03-1.92 (1H, m, 8-Ph-Men-H), 1.92-1.66 (2H, m, 8-Ph-Men-H), 1.53-1.38 (1H, m, 8-Ph-Men-H), 1.33-0.80 (3H, m, 8-Ph-Men-H), 1.25 (3H, s, 8-Ph-Men-CH_3),

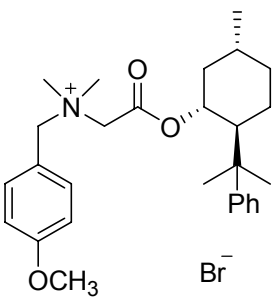
1.12 (3H, s, 8-Ph-Men-CH_3), 0.91 (3H, d, J = 6.2 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.3, 151.8, 134.0, 132.9 (q, J = 33 Hz), 130.8, 127.9, 126.1 (q, J = 3 Hz), 125.3, 124.8, 123.4 (d, J = 272 Hz), 76.8, 67.1, 59.4, 50.6, 49.8, 49.2, 41.3, 39.2, 34.0, 31.2, 30.9, 25.9, 21.6, 21.5; IR (film) 3012, 2956, 2924, 1736, 1622, 1598, 1456, 1422, 1326, 1246, 1204, 1170, 1130, 1068, 1030, 1020, 988, 862, 830, 768, 734, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{37}BrF_3NO_2$: C, 60.43; H, 6.70; N, 2.52. Found: C, 60.15; H, 6.87; N, 2.51.

***N*-Benzyl-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium bromide (4f):** 98%



yield; white solid; mp 196–198 °C; $[\alpha]^{25}_{589}$ = 25.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.64-7.42 (5H, m, Ar-H), 7.20 (2H, d, J = 7.3 H, Ar-H), 7.07 (2H, t, J = 7.3 Hz, Ar-H), 6.69 (1H, t, J = 7.3 Hz, Ar-H), 5.26 (1H, d, J = 12.4 Hz, NCHAr), 5.12 (1H, d, J = 12.4 Hz, NCHAr), 4.89 (1H, ddd, J = 10.8, 10.8, 4.3 Hz, COOCH), 4.20 (1H, d, J = 17.0 Hz, NCHCOO), 3.50 (3H, s, CH_3N), 3.32 (3H, s, CH_3N), 2.63 (1H, d, J = 17.0 Hz, NCHCOO), 2.18-2.03 (1H, m, 8-Ph-Men-H), 2.00-1.89 (1H, m, 8-Ph-Men-H), 1.87-1.78 (1H, m, 8-Ph-Men-H), 1.77-1.66 (1H, m, 8-Ph-Men-H), 1.53-1.36 (1H, m, 8-Ph-Men-H), 1.30-0.82 (3H, m, 8-Ph-Men-H), 1.26 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.90 (3H, d, J = 6.5 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.5, 151.5, 133.3, 130.7, 129.1, 127.8, 126.8, 125.1, 124.9, 76.5, 68.2, 59.1, 50.4, 49.5, 49.2, 41.1, 39.1, 33.9, 31.1, 30.4, 25.8, 21.8, 21.5; IR (KBr) 2996, 2960, 2924, 2868, 1734, 1600, 1494, 1458, 1390, 1246, 1216, 1200, 1132, 1088, 1028, 974, 948, 920, 906, 868, 770, 758, 724, 708 cm^{-1}; Anal. Calcd for $C_{27}H_{38}BrNO_2$: C, 66.38; H, 7.84; N, 2.87. Found: C, 66.65; H, 7.83; N, 2.80.

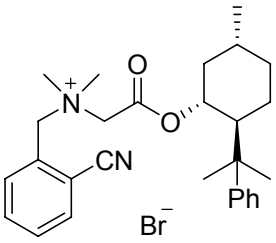
***N*,*N*-Dimethyl-*N*-(4'-methoxybenzyl)-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium**



bromide, 0.5 hydrate (4g): 98% yield; white solid; mp 83–85 °C; $[\alpha]^{25}_{589}$ = 31.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.48 (2H, d, J = 8.5 Hz, Ar-H), 7.29-7.20 (2H, m, Ar-H), 7.15 (2H, t, J = 7.4 Hz, Ar-H), 6.97 (2H, d, J = 8.5 Hz, Ar-H), 6.86 (1H, t, J = 7.4 Hz, Ar-H), 5.12 (1H, d, J = 12.4 Hz, NCHAr), 4.96 (1H,

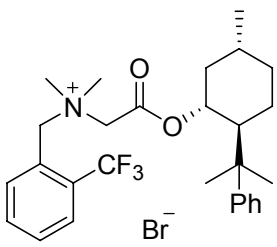
d, J = 12.4 Hz, NCHAr), 4.96-4.83 (1H, m, COOCH), 4.12 (1H, d, J = 16.9 Hz, NCHCOO), 3.86 (3H, s, OCH_3), 3.40 (3H, s, CH_3N), 3.24 (3H, s, CH_3N), 2.47 (1H, d, J = 16.9 Hz, NCHCOO), 2.20-2.07 (1H, m, 8-Ph-Men-H), 2.03-1.92 (1H, m, 8-Ph-Men-H), 1.88-1.64 (2H, m, 8-Ph-Men-H), 1.54-1.39 (1H, m, 8-Ph-Men-H), 1.31-0.84 (3H, m, 8-Ph-Men-H), 1.27 (3H, s, 8-Ph-Men-CH_3), 1.15 (3H, s, 8-Ph-Men-CH_3), 0.92 (3H, d, J = 6.5 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.5, 161.3, 151.4, 134.7, 127.8, 125.1, 124.8, 118.5, 114.4, 76.4, 68.0, 58.9, 55.3, 50.0, 49.2, 49.1, 41.0, 39.1, 33.9, 31.0, 30.2, 25.8, 21.9, 21.4; IR (film) 3392, 2956, 2920, 1736, 1612, 1516, 1460, 1400, 1254, 1218, 1182, 1130, 1092, 1032, 988, 944, 906, 860, 846, 828, 770, 732, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{41}BrNO_{3.5}$: C, 63.75; H, 7.83; N, 2.66. Found: C, 63.89; H, 7.87; N, 2.63.

***N*-(2'-Cyanobenzyl)-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium**



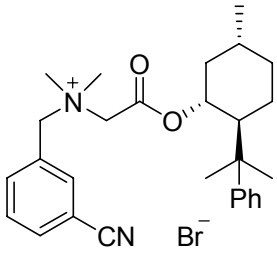
bromide, monohydrate (6a): 84% yield; white solid; mp 164–167 °C; $[\alpha]^{25}_{589}$ = 11.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.40 (1H, d, J = 7.6 Hz, Ar-H), 7.90-7.78 (2H, m, Ar-H), 7.73 (1H, t, J = 7.6 Hz, Ar-H), 7.34-7.19 (4H, m, Ar-H), 6.88 (1H, t, J = 6.8 Hz, Ar-H), 5.52 (1H, d, J = 12.6 Hz, NCHAr), 5.11 (1H, d, J = 12.6 Hz, NCHAr), 4.95 (1H, ddd, J = 10.5, 10.5, 4.6 Hz, COOCH), 4.80 (1H, d, J = 17.0 Hz, NCHCOO), 3.49 (3H, s, CH_3N), 3.20 (3H, s, CH_3N), 2.32-2.15 (1H, m, 8-Ph-Men-H), 2.27 (1H, d, J = 17.0 Hz, NCHCOO), 2.12-2.00 (1H, m, 8-Ph-Men-H), 1.91-1.70 (2H, m, 8-Ph-Men-H), 1.54-1.40 (1H, m 8-Ph-Men-H), 1.35-0.86 (3H, m, 8-Ph-Men-H), 1.29 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.93 (3H, d, J = 6.8 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 162.9, 152.1, 136.3, 134.0, 133.7, 131.6, 129.5, 128.1, 125.3, 124.8, 117.3, 115.6, 76.6, 65.2, 60.7, 49.8, 49.7, 49.0, 41.1, 39.2, 33.9, 31.2, 31.1, 25.7, 21.4, 20.9; IR (film) 3416, 2952, 2920, 2224, 1734, 1596, 1480, 1448, 1402, 1266, 1216, 1130, 1092, 1030, 996, 912, 844, 768, 732, 704 cm^{-1}; Anal. Calcd for $C_{28}H_{39}BrN_2O_3$: C, 63.27; H, 7.40; N, 5.27. Found: C, 63.50; H, 7.49; N, 4.99.

***N*,*N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*-(2'-trifluoromethylbenzyl)-**



ammonium bromide, monohydrate (6b): 61% yield; white solid; mp 72–74 °C; $[\alpha]^{23}_{589}$ = 15.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.21 (1H, d, *J* = 7.0 Hz, Ar-H), 7.85 (1H, dd, *J* = 7.0, 1.4 Hz, Ar-H), 7.80-7.66 (2H, m, Ar-H), 7.40-7.20 (4H, m, Ar-H), 6.94 (1H, t, *J* = 7.0 Hz, Ar-H), 5.42 (1H, d, *J* = 13.2 Hz, NCHAr), 5.16 (1H, d, *J* = 13.2 Hz, NCHAr), 4.93 (1H, ddd, *J* = 10.8, 10.8, 4.3 Hz, COOCH), 4.69 (1H, d, *J* = 16.9 Hz, NCHCOO), 3.44 (3H, s, CH_3N), 3.20 (3H, s, CH_3N), 2.45 (1H, d, *J* = 16.9 Hz, NCHCOO), 2.26-2.10 (1H, m, 8-Ph-Men-H), 2.10-1.95 (1H, m, 8-Ph-Men-H), 1.91-1.70 (2H, m, 8-Ph-Men-H), 1.60-1.38 (1H, m, 8-Ph-Men-H), 1.35-0.84 (3H, m, 8-Ph-Men-H), 1.29 (3H, s, 8-Ph-Men-CH_3), 1.15 (3H, s, 8-Ph-Men-CH_3), 0.92 (3H, d, *J* = 6.2 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.1, 152.2, 137.4, 132.8, 131.4, 131.0 (q, *J* = 29 Hz), 128.1, 127.7 (q, *J* = 6 Hz), 125.3, 124.8, 124.2 (d, *J* = 1 Hz), 123.7 (d, *J* = 273 Hz), 76.6, 64.1 (q, *J* = 2 Hz), 61.2, 50.0, 49.0, 45.2, 41.1, 39.2, 34.0, 31.22, 31.16, 25.7, 21.5, 21.0; IR (film) 3428, 2952, 2920, 2768, 1736, 1600, 1484, 1454, 1402, 1310, 1274, 1210, 1174, 1124, 1064, 1042, 996, 912, 774, 734, 702 cm^{-1}; Anal. Calcd for $C_{28}H_{39}BrF_3NO_3$: C, 58.54; H, 6.84; N, 2.44. Found: C, 58.67; H, 6.72; N, 2.54.

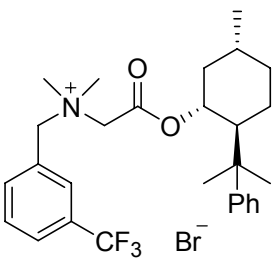
***N*-(3'-Cyanobenzyl)-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium**



bromide, monohydrate (9a): 99% yield; white solid; mp 102–105 °C; $[\alpha]^{25}_{589}$ = 29.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.15 (1H, d, *J* = 7.8 Hz, Ar-H), 7.85 (1H, d, *J* = 7.8 Hz, Ar-H), 7.76 (1H, s, Ar-H), 7.67 (1H, t, *J* = 7.8 Hz, Ar-H), 7.30-7.22 (2H, m, Ar-H), 7.20-7.10 (2H, m, Ar-H), 6.80 (1H, t, *J* = 6.8 Hz, Ar-H), 5.45 (1H, d, *J* = 12.6 Hz, NCHAr), 5.29 (1H, d, *J* = 12.6 Hz, NCHAr), 4.94 (1H, ddd, *J* = 10.5, 10.5, 4.3 Hz, COOCH), 4.06 (1H, d, *J* = 17.0 Hz, NCHCOO), 3.47 (3H, s, CH_3N), 3.30 (3H, s, CH_3N), 2.36 (1H, d, *J* = 17.0 Hz, NCHCOO), 2.23-2.10 (1H, m, 8-Ph-Men-H), 2.09-1.97 (1H, m, 8-Ph-Men-H), 1.89-1.71 (2H, m, 8-Ph-Men-H), 1.56-1.41 (1H, m, 8-Ph-Men-H), 1.34-0.85 (3H, m, 8-Ph-Men-H), 1.29 (3H, s, 8-Ph-Men-CH_3), 1.14 (3H, s, 8-Ph-Men-CH_3), 0.93 (3H, d, *J* = 6.3 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.2, 151.9, 138.3, 136.3, 134.2, 130.4, 128,8, 127.9, 125.3, 124.8, 117.5, 113.5,

76.8, 66.4, 59.3, 50.7, 49.9, 49.2, 41.2, 39.2, 34.0, 31.2, 30.9, 25.9, 21.6, 21.5; IR (film) 3420, 3015, 2952, 2920, 2228, 1736, 1598, 1478, 1456, 1400, 1246, 1204, 1130, 1092, 1032, 992, 912, 866, 812, 770, 732, 704 cm^{-1}; Anal. Calcd for $C_{28}H_{39}BrN_2O_3$: C, 63.27; H, 7.40; N, 5.27. Found: C, 63.35; H, 7.43; N, 4.97.

***N*,*N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*-(3'-trifluoromethylbenzyl)-**



ammonium bromide, monohydrate (9b): 99% yield; white solid; mp 110–113 °C; $[\alpha]^{24}_{589}$ = 25.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.05 (1H, d, *J* = 7.6 Hz, Ar-H), 7.81 (1H, d, *J* = 7.6 Hz, Ar-H), 7.75 (1H, s, Ar-H), 7.65 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 7.21 (2H, d, *J* = 7.6 Hz, Ar-H), 7.08 (2H, t, *J* = 7.6 Hz, Ar-H), 6.65 (1H, t, *J* = 7.6 Hz, Ar-H), 5.43 (1H, d, *J* = 12.7 Hz, NCHAr), 5.34 (1H, d, *J* = 12.7 Hz, NCHAr), 4.92 (1H, ddd, *J* = 10.6, 10.6, 4.6 Hz, COOCH), 4.11 (1H, d, *J* = 16.9 Hz, NCHCOO), 3.56 (3H, s, CH_3N), 3.34 (3H, s, CH_3N), 2.53 (1H, d, *J* = 16.9 Hz, NCHCOO), 2.18-1.92 (2H, m, 8-Ph-Men-H), 1.88-1.68 (2H, m, 8-Ph-Men-H), 1.56-1.38 (1H, m, 8-Ph-Men-H), 1.35-0.82 (3H, m, 8-Ph-Men-H), 1.26 (3H, s, 8-Ph-Men-CH_3), 1.13 (3H, s, 8-Ph-Men-CH_3), 0.91 (3H, d, *J* = 6.5 Hz, 8-Ph-Men-CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 163.3, 151.8, 137.4, 131.6 (q, *J* = 33 Hz), 130.1, 129.4 (q, *J* = 4 Hz), 128.1, 127.8, 127.7 (q, *J* = 3 Hz), 125.3, 124.8, 123.4 (d, *J* = 271 Hz), 76.7, 66.8, 59.1, 50.8, 49.9, 49.2, 41.2, 39.2, 34.0, 31.2, 30.8, 25.9, 21.54, 21.49; IR (film) 3432, 3012, 2956, 2920, 1736, 1454, 1400, 1330, 1246, 1206, 1168, 1128, 1078, 1030, 990, 918, 864, 814, 770, 734, 704 cm^{-1}; Anal. Calcd for $C_{28}H_{39}BrF_3NO_3$: C, 58.54; H, 6.84; N, 2.44. Found: C, 58.77; H, 7.13; N, 2.24.

References

(1) P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, J. -P. Obrecht, *Tetrahedron Lett.* **1988**, *29*, 1265-1268.

(2) C. Mellin-Morlière, D. J. Aitken, S. D. Bull, S. G. Davies, H. -P. Husson, *Tetrahedron Asymmetry* **2001**, *12*, 149-155.

(3) O. Ort, *Org. Syn.* **1987**, *65*, 203-210.

(4) Commercially available from Fuji Silysia Chemical Ltd., Japan (Chromatorex NH–DM1020).

(5) G. P. Crowther, E. M. Kaiser, R. A. Woodruff, C. R. Hauser, *Org. Syn.* **1971**, *51*, 96-99.

(6) G. W. Anderson, F. M. Callahan, *J. Am. Chem. Soc.* **1960**, *82*, 3359-3363.