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Syntheses of (*R*)- and (*S*)-3-Methylheptanoic Acids

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Starting from chiral methyl molecules **3** and **4**, both derived from (*R*)-4-methyl-*δ*-valerolactone, we have accomplished the synthesis of (*R*) and (*S*)-3-methylheptanoic acids. Our methods are amendable to the syntheses of a wide variety of chiral 3-methyl alkanoic acids.

Keywords pheromones, chiral pool, natural products, total synthesis, (*R*)-4-methyl-*δ*-valerolactone

Introduction

Optically active 3-methyl substituted carboxylic acids are an important class of structural units in natural products and building blocks in organic synthesis, therefore, have received significant attention from research community and resulted in a variety of successful strategies. For instance, as illustrated in Figure 1, (*S*)-3-methylheptanoic acid (**1**) is a synthetic unit used in the syntheses of PGI_2 (prostacyclin I_2) analogues such as pimilprost and ronoprost, while its enantiomer, (*R*)-3-methylheptanoic acid (**2**) is a constituent of the abdominal sex-attracting secretion of male *Kheper nigroaeneus* dung beetle.[1] Both **1** and **2** have been synthesized for many times.[1b,2]

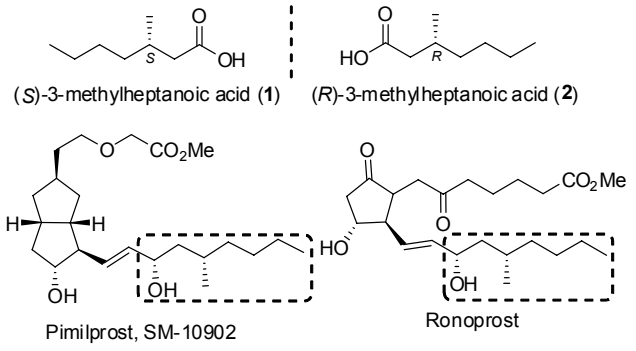

Figure 1 The structures of (*S*)- and (*R*)-3-methylheptanoic acid.

Typical synthetic methods required the use of chiral auxiliaries and/or sensitive organometallic reagents at low temperatures, hence, although efficient, were of limited value for large-scale production. Although Chiu and co-workers from Pfizer have developed a practical approach for chiral **1** by functional group manipulation of optically active citronellol,[2j] the expensiveness of citronellol made the search of its alternatives appealing. Herein, we reported the syntheses of (*S*)-**1** and (*R*)-**2** from two new chiral pool molecules we recently developed.

Experimental

Methyl (*S*)-4-methyloctanoate (6)

At ambient temperature, under argon, to a solution of methyl (*R*)-5-bromo-4-methylpentanoate (**3**, 2.03 g, 10 mmol) and *N*-methylpyrrolidinone (NMP, 3.8 mL, 40 mmol) in anhydous THF (25 mL) was added Li_2CuCl_4 (1.5 mol•L^{-1} in THF, 0.66 mL, 1 mmol), then *n*-PrMgBr (freshly prepared by refluxing *n*-PrBr with Mg in THF, 24 mmol, 20 mL) dropwise. Stirring was continued for 4 h and the reaction mixture was quenched with an aqueous NH_4Cl solution. After decantation, the aqueous layer was extracted with ether and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE/EA: 200/1 then 100/1) gave **6** (1.51 g, 8.8 mmol, 90%) as colorless oil. $[\alpha]_D^{24}$ +1.1 (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.67 (s, 3H), 2.33−2.30 (m, 2H), 1.73−1.08 (m, 9H), 0.91−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 174.6, 51.4, 40.6, 36.3, 32.4, 31.9, 31.9, 29.2, 22.9, 19.3, 14.1; IR (KBr) *v*: 2959, 2930, 2874, 2862, 1744, 1460, 1437, 1380, 1261, 1172, 1111, 1020, 807 cm^{-1}; ESIMS *m/z*: 173 ($[M+H]^+$), 195 ($[M+Na]^+$); HRMS calcd for $C_{10}H_{20}O_2$172.1463, found 172.1463.

(*S*)-4-Methyl-1,1-diphenyloctan-1-ol (7)

To a suspension of Mg (322 mg, 13.4 mmol) in THF (15 mL) was added a solution of bromobenzene (1.4 mL, 13.3 mmol) in THF (5 mL) dropwise, at ambient tem-

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perature, under argon. The mixture was allowed to stir for 30 min, then added a solution of **6** (990 mg, 5.76 mmol) in THF (5 mL), and stirred for 6 h before being quenched with 1.2 mol•L^{-1} HCl. The mixture was extracted with EtOAc for three times and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (PE/EA: 200/1) provided **7** (1.43 g, 4.8 mmol, 84%) as colorless oil. $[\alpha]_D^{24}$ +3.8 (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.43−7.19 (m, 10H), 2.37−2.18 (m, 2H), 2.13(s, 1H), 1.44−1.06 (m, 9H), 0.88−0.84 (m, 6H); IR (KBr) *v*: 3480, 3062, 3026, 2956, 2928, 1494, 1448, 1378, 699 cm^{-1}; EIMS (70 eV) *m/z* (%): 183 ([Ph_2COH]$^+$, 100), 278 ([M−H_2O]$^+$, 1). Anal. calcd for $C_{21}H_{28}O$: C 85.05, H 9.52; found 85.25, H 9.50.

(*S*)-(4-Methyloct-1-ene-1,1-diyl)dibenzene (8)

Compound **7** (2.865 g, 9.7 mmol) was treated with TMSCl (0.55 mL, 4.3 mmol) in CH_2Cl_2 (100 mL) at ambient temperature for 6 h. The reaction mixture was concentrated and purified on silica gel (eluted with pentane) to give **8** (2.76 g, 9.7 mmol, 99%) as colorless liquid. $[\alpha]_D^{23}$ +21.6 (*c* 1.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.38−7.15 (m, 10H), 6.11 (t, *J*=7.5 Hz, 1H), 2.17−1.90 (m, 2H), 1.35−1.05 (m, 7H), 0.89−0.84 (m, 6H); IR (KBr) *v*: 3081, 3058, 3024, 2957, 2927, 2872, 2859, 1599, 1495, 1459, 1444, 1377, 769, 758, 700 cm^{-1}; EIMS *m/z* (%): 193 ([Ph_2CCHCH_2]$^+$, 100), 278 (M$^+$, 16). Anal. calcd for $C_{21}H_{26}$: C 90.59, H 9.41; found C 90.76, H 9.47.

(*S*)-3-Methylheptanoic acid (1)

Method 1: To a solution of **8** (301 mg, 1.08 mmol) in *tert*-butanol (70 mL) was added a solution of $NaIO_4$ (1.38 g, 6.4 mmol) and $KMnO_4$ (57 mg, 0.36 mmol) in water (200 mL). The pH value of the reaction solution was adjusted with 5% aqueous K_2CO_3 solution to 8−9 and the mixture was allowed to stir at ambient temperature for 6 h and acidified to pH 1−2 with 1.2 mol•L^{-1} HCl. The mixture was extracted with EtOAc for three times and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel (PE/EA: 100/1) provided **1** (131 mg, 0.91 mmol, 84%) as colorless liquid.

Method 2: A solution of **8** (176 mg, 0.63 mml) in EtOAc (10 mL) was treated with ozone for 30 min at 0 ℃ and 30% H_2O_2 (10 mL) and 1.2 mol•L^{-1} HCl (10 mL) for 8 h at ambient temperature. The mixture was extracted with ether for three times and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel (PE/EA: 100/1) provided **1** (83 mg, 0.58 mmol, 91%) as colorless liquid. $[\alpha]_D^{25}$ –4.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.48 (s, 1H), 2.36 (dd, *J*=15.0, 6.0 Hz, 1H), 2.14 (dd, *J*=14.7, 5.1 Hz, 1H), 2.01−1.90 (m, 1H), 1.38−1.17 (m, 6H), 0.97 (d, *J*=6.6 Hz, 3H), 0.89 (t, *J*=6.6 Hz, 3H); IR (KBr) *v*: 2960, 2875, 2671, 1710, 1460, 1413, 1382, 1289, 937, 714 cm^{-1}; ESIMS *m/z*: 143.0 ([M−H]$^-$).

4-Methoxyphenyl (*S*)-3-methylheptanoate (9)

A solution of 4-methoxyphenol (24 mg, 0.19 mmol), **1** (23 mg, 0.16 mmol), DCC (48 mg, 0.23 mmol) and DMAP (11 mg, 0.1 mmol) was stirred at ambient temperature for 10 h and filtered. The filtrate was washed with aqueous KOH solution, water, aqueous HOAc solution and water, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel afforded **9** (33 mg, 83% yield, 91.0% *ee*). HPLC (chiral) Chiralpakic AD-H (4.6 cm×250 cm) at 23 ℃, λ=220 nm, hexane/2-propanol 90/10, retention times 7.48 min (*S*), 7.87 min (*R*) at 0.70 mL/min flow rate. $[\alpha]_D^{22}$ –2.1 (*c* 0.95, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 7.01−6.88 (m, 4H), 3.81 (s, 3H), 2.54 (dd, *J*=14.7, 6.0 Hz, 1H), 2.34 (dd, *J*=14.7, 8.1 Hz, 1H), 2.14−2.03 (m, 1H), 1.46−1.24 (m, 6H), 1.04 (d, *J*=6.9 Hz, 3H), 0.92 (t, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.2, 157.1, 144.2, 122.3, 114.4, 55.6, 41.8, 36.4, 30.5, 29.1, 22.8, 19.7, 14.0; IR (KBr) *v*: 2959, 2932, 2874, 2860, 1758, 1507, 1467, 1443, 1380, 1298, 1249, 1197, 1147, 1103, 1036, 838 cm^{-1}; ESIMS *m/z*: 251.2 ([M+H]$^+$), 273.2 ([M+Na]$^+$); HRMS-ESI [M+H]$^+$ calcd for $C_{15}H_{23}O_3$ 251.1642; found 251.1637.

(*R*)-5-(Methoxymethoxy)-4-methylpentanal (10)

Ester **4** (1.05 g, 5.5 mmol) in anhydrous ether (70 mL) was treated with $LiAlH_4$ (209 mg, 5.5 mmol) at 0 ℃ for 5 h. The reaction mixture was quenched with Na_2SO_4•10H_2O, filtered and washed with ether. The filtrate was concentrated and subjected to flash column chromatography on silica gel (PE/EA: 5/1) to provide (*R*)-5-(methoxymethoxy)-4-methylpentan-1-ol (860 mg, 5.3 mmol, 96%) as colorless oil. $[\alpha]_D^{23}$ +4.4 (*c* 1.02, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 4.61 (s, 2H), 3.64 (t, *J*=6.6 Hz, 2H), 3.41−3.29 (m, 5H), 1.80−1.44 (m, 4H), 1.25−1.13 (m, 1H), 0.94 (d, *J*=6.9 Hz, 3H); IR (KBr) *v*: 3415, 2936, 2880, 2827, 2772, 1465, 1388, 1216, 1151, 1112, 1048, 963, 921 cm^{-1}; ESIMS *m/z*: 163.2 ([M+H]$^+$). Anal. calcd for $C_8H_{18}O_3$: C 59.23, H 11.18; found C 59.45, H 11.37.

To a solution of oxalyl chloride (8 mL, 93 mmol) in CH_2Cl_2 (230 mL) cooled at −78 ℃ was added dropwise a solution of dimethylsulfoxide (DMSO 13.5 mL, 190 mmol) in CH_2Cl_2 (20 mL). After 30 min, a solution of (*R*)-5-(methoxymethoxy)-4-methylpentan-1-ol (10.0 g, 62 mmol) in CH_2Cl_2 (30 mL) was added. The reaction mixture was then stirred for 60 min at −78 ℃ and triethylamine (43 mL, 300 mmol) was added in one portion. After 10 min at −78 ℃, the mixture was allowed to warm to room temperature, stirred for 3 h, and quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 and the com-

bined organic extracts were washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Distillation of the residue under reduced pressure afforded aldehyde **10** (7.98 g, 50 mmol, 81%, 75 ℃/1 mm Hg) as a colorless oil. $[\alpha]_D^{24}$ +2.9 (*c* 1.42, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 9.76 (t, J=1.8 Hz, 1H), 4.59 (s, 2H), 3.36−3.34 (m, 5H), 2.53−2.38 (m, 2H), 1.85−1.69 (m, 2H), 1.54−1.41 (m, 1H), 0.93 (d, J=6.9 Hz, 3H); IR (KBr) *v*: 3448, 2955, 2933, 2877, 1715, 1460, 1389, 1229, 1188, 1125, 1049, 987, 924 cm^{-1}; ESIMS *m/z*: 178.2 ($[M+H_2O]^+$). Anal. calcd for $C_8H_{16}O_3$: C 59.97, H 10.07; found C 59.95, H 9.93.

(*R*)-6-(Methoxymethoxy)-5-methylhex-1-ene (11)

To a suspension of methyltriphenylphosponium iodide (27.0 g, 66.8 mmol) in dry THF (160 mL) at 0 ℃ under argon was added *n*-BuLi (24 mL of 2.5 mol•L^{-1} solution in hexanes, 60 mmol). The mixture was stirred for 20 min, and a solution of the aldehyde (7.92 g, 50 mmol) in THF (20 mL) was added over 30 min. The resulting reaction mixture was stirred for 5 h, quenched by addition of aqueous ammonium chloride, and the mixture was diluted with ether. The phases were separated, and the aqueous phase extracted with ether twice. The organic phases were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel (PE/EA: 200/1) to afford alkene **11** (6.738 g, 43 mmol, 86%) as colorless oil. $[\alpha]_D^{23}$ +0.3 (*c* 1.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.89−5.75 (m, 1H), 5.06−4.93 (m, 2H), 4.62 (s, 2H), 3.43−3.30 (m, 5H), 2.20−1.99 (m, 2H), 1.81−1.70 (m, 1H), 1.60−1.49 (m, 1H), 1.29−1.17 (m, 1H), 0.95 (d, J=9.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 300 MHz) δ: 139.0, 114.3, 96.6, 73.1, 55.1, 32.9, 32.8, 31.2, 17.0; IR (KBr) *v*: 3079, 2930, 2884, 2824, 2770, 1642, 1465, 1441, 1387, 1217, 1153, 1112, 1049, 918 cm^{-1}; EIMS *m/z* (%): 97 ($[M–MeOMe]^+$, 4). Anal. calcd for $C_9H1_{18}O_2$: C 68.31, H 11.47; found C 68.11, H 11.44.

(*R*)-2-Methylhexan-1-ol (12)

The alkene **11** (140 mg, 0.89 mmol), 5% Pd/C (29 mg), and MeOH (10 mL) were combined, and the reaction vessel was evacuated and back-filled with hydrogen (1 atm). The reaction mixture was stirred under hydrogen for 12 h and then filtered over a plug of silica gel topped with Celite (MeOH eluent). To the filtrate was added concentrated HCl (0.1 mL) and the resulting solution was heated to reflux for 3 h and cooled. After being neutrilized with saturated $NaHCO_3$, washed with brine, the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford **12** (85 mg, 0.73 mmol, 83%) as colorless oil.[3] $[\alpha]_D^{22}$ +10.8 (*c* 1.73, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 300Mz) δ: 3.50 (dd, J=15.9, 5.7 Hz, 1H), 3.42 (dd, J=10.2, 6.6 Hz, 1H), 1.66−1.58 (m, 1H), 1.46−1.06 (m, 6H), 0.92 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.9 Hz, 3H); IR (KBr) *v*: 3300, 2959, 2929, 2875, 1467, 1380, 1256, 1039, 982, 798, 667 cm^{-1}; ESIMS *m/z*: 139.1 ($[M+Na]^+$).

(*R*)-2-Methylhexyl 4-methylbenzenesulfonate (13)

Alcohol **12** (2.01 g, 17.4 mmol) was treated with TsCl (4.24 g, 22.2 mmol) in dry pyridine (20 mL) at ambient temperature for 36 h. The mixture was poured into cold diluted aqueous HCl solution and extracted with ether for three times. The combined organic layers were washed with a saturated aqueous $CuSO_4$ solution, water, a saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified via flash column chromatography on silica gel (PE/EA: 100/1) to furnish **13** (4.32 g, 16 mmol, 92%) as colorless oil.[1b] $[\alpha]_D^{22}$ –2.7 (*c* 1.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Mz) δ: 7.79 (d, J=8.4 Hz, 2H), 7.35 (d, J=7.8 Hz, 2H), 3.87 (dd, J=9.3, 5.7 Hz, 1H), 3.80 (dd, J=9.0, 6.6 Hz, 1H), 2.45 (s, 3H), 1.82−1.71 (m, 1H), 1.36−1.04 (m, 6H), 0.87 (d, J=6.9 Hz, 3H), 0.85 (d, J=7.2 Hz, 3H); IR (KBr) *v*: 2961, 2932, 1599, 1362, 1189, 1178, 1098, 966, 832, 814, 792, 667, 556 cm^{-1}; ESIMS *m/z*: 293.0 ($[M+Na]^+$); HRMS-ESI $[M+Na]^+$ calcd for $C_{14}H_{22}O_3S$: 293.1182, found 293.1169.

(*R*)-3-Methylheptanenitrile (14)

A solution of **13** (3.704 g, 13.7 mmol) and NaCN (818 mg, 16.7 mmol) in dry DMSO (20 mL) was stirred at 30 ℃ under argon for 36 h, then diluted with water and extracted with ether for three times. The combined organic layers were washed with water, a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified via flash column chromatography on silica gel (PE/EA: 80/1) to afford nitrile **14** (1.69 g, 13.5 mmol, 99%) as colorless oil. $[\alpha]_D^{23}$ –3.1 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.33 (dd, J=16.5, 5.7 Hz, 1H), 2.24 (dd, J=16.5, 6.9 Hz, 1H), 1.90−1.77 (m, 1H), 1.48−1.28 (m, 6H), 1.06 (d, J=6.6 Hz, 3H), 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 118.9, 35.6, 30.4, 29.0, 24.5, 22.6, 19.5, 14.0; IR (KBr) *v*: 2962, 931, 2875, 2861, 2248, 1463, 1427, 1384, 1348 cm^{-1}; EIMS *m/z* (%): 110 ($[M–Me]^+$, 11), 124 ($[M–H]^+$, 2); HRMS-EI $[M–Me]^+$ calcd for $C_7H_{12}N$: 110.0970, found 110.0972.

(*R*)-3-Methylheptanoic acid (2)

A solution of nitrile **14** (199 mg, 1.6 mmol) in H_2SO_4/H_2O (6 mL/6 mL) was stirred at reflux for 6 h and cooled and diluted with water (50 mL). The mixture was extracted with ether for three times and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via flash column chromatography on silica gel (PE/EA: 100/1) afforded acid **2** (209 mg, 1.45 mmol, 91%) as a colorless oil. $[\alpha]_D^{23}$ +4.3 (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.94 (br s, 1H), 2.36 (dd, J=15.0, 6.0 Hz, 1H), 2.14 (dd, J=15.0, 8.1 Hz, 1H), 2.10−1.90 (m, 1H), 1.38−1.16 (m, 6H), 0.97 (d, J=

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6.9 Hz, 3H), 0.89 (t, J=6.3 Hz, 3H); IR (KBr) ν: 2962, 2932, 2878, 1710, 1466, 1412, 1381, 1300, 1229, 939, 812 cm^{-1}; ESIMS *m/z*: 167.2 ($[M+Na]^+$).

4-Methoxyphenyl (*R*)-3-methylheptanoate (15)

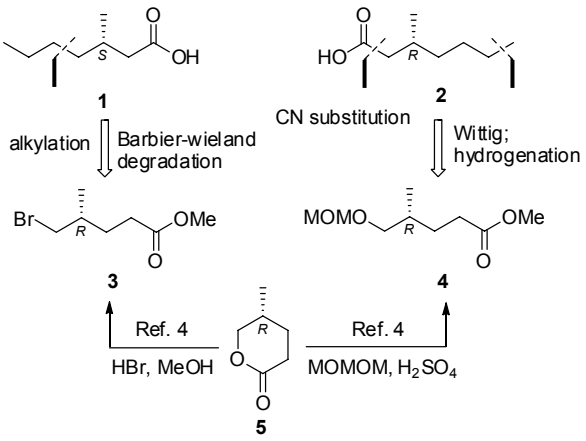
A solution of 4-methoxyphenol (204 mg, 1.65 mmol), **2** (167 mg, 1.16 mmol), DCC (410 mg, 2.0 mmol) and DMAP (83 mg, 0.7 mmol) was stirred at ambient temperature for 10 h and filtered. The filtrate was washed with aqueous KOH solution, water, aqueous HOAc solution and water, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on silica gel afforded **15** (263 mg, 1.05 mmol, 91% yield, 95.6% *ee*). HPLC (chiral) Chiralpakic AD-H (4.6 cm×250 cm) at 23 ℃, λ=220 nm, hexane/2-propanol 90/10, retention times 7.39 min (*S*), 7.95 min (*R*) at 0.70 mL/min flow rate. $[\alpha]_D^{22}$ +2.5 (*c* 1.99, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 300 MHz) δ: 7.01−6.88 (m, 4H), 3.81 (s, 3H), 2.54 (dd, J=14.7, 6.3 Hz, 1H), 2.34 (dd, J=14.7, 7.8 Hz, 1H), 2.14−2.07 (m, 1H), 1.46−1.24 (m, 6H), 1.04 (d, J=6.3 Hz, 3H), 0.92 (t, J=6.6 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ: 172.1, 157.2, 144.3, 122.3, 114.5, 55.6, 41.8, 36.4, 30.5, 29.1, 22.8, 19.8, 14.1; IR (KBr) ν: 2959, 2931, 2874, 2860, 1758, 1507, 1467, 1443, 1380, 1298, 1249, 1197, 1146, 1103, 1036, 838 cm^{-1}; ESIMS *m/z*: 251.2 ($[M+H]^+$), 273.1 ($[M+Na]^+$); HRMS-ESI $[M+H]^+$ calcd for $C_{15}H_{23}O_3$: 251.1642, found 251.1652.

Results and Discussion

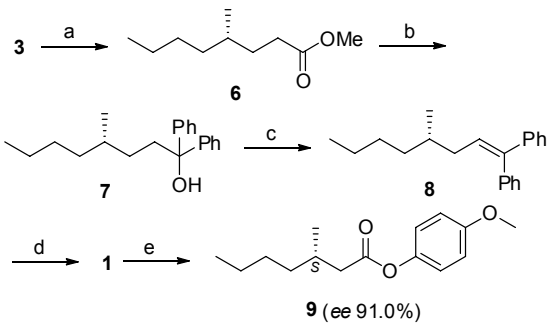
In our synthetic plan, as depicted in Scheme 1, both (*S*)- and (*R*)-3-methylheptanoic acids would obtain their chiral methyl groups from (*R*)-4-methyl-δ-valerolactone **5**, a compound which we obtained from pilot production of pregnenolone and could be conveniently transformed into bromoester **3** and MOM-protected hydroxyl ester **4**.[4] An alkylation at the left side and a one-carbon contraction via Barbier-Wieland degradation[5] at the right side of bromoester **3** would give **1**, while two one-carbon expansions, by a CN substitution and a hydrolysis at the left side and by a Wittig reaction and hydrogenation at the right side, of hydroxylester **4** would provide **2**. All the reactions are routine and scalable.

As in Scheme 2, the synthesis of (*S*)-**1** started with a chemoselective Cu(I)-catalyzed alkylation of propylmagnesium bromide[6] with bromoester **3** to provide ester **6** in excellent yield. Then a Barbier-Wieland degradation was employed to remove the extra one carbon in **6**. By reacting with phenylmagnesium bromide, ester **6** was converted into the alcohol **7**, which underwent dehydration effectively in the presence of catalytic amount of TMSCl in DCM[7] to lead to the diphenyl alkene **8**. Cleavage of the double bond in **8** was achieved by oxidizing with $KMnO_4/NaIO_4$ in *t*-BuOH-H_2O[8] to provide the desired **1** in 84% yield. Oxidation of **8** with ozone in EtOAc followed by treatment of the resulting mixture with 30% H_2O_2/1.2 mol•L^{-1} HCl also gave **1** in better yield. The optical purity of compound **1** (91.0% *ee*) was obtained by its derivative **9**.

Scheme 1 Retrosynthetic analysis of **1** and **2**



Scheme 2 Synthesis of (*S*)-methylheptanoic acid (**1**)



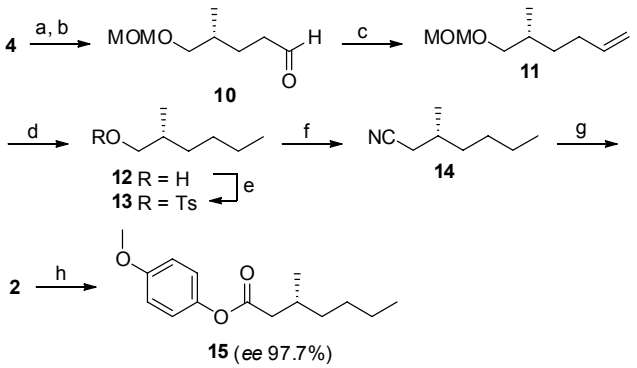
Reagents and conditions: (a) *n*-PrMgBr, Li_2CuCl_4, NMP, THF, r.t., 4 h, 90%; (b) PhMgBr, THF, r.t., 6 h, 84%; (c) TMSCl, CH_2Cl_2, r.t., 6 h, 99%; (d) $NaIO_4$, $KMnO_4$, *t*-BuOH-H_2O, pH 8−9, r.t., 6 h, 84% or O_3, EtOAc, 0 ℃, 30 min, then 30% H_2O_2, 1.2 mol•L^{-1} HCl, r.t., 8 h, 91%; (e) 4-methoxyphenol, DCC, DMAP, CH_2Cl_2, r.t., 10 h, 83%, 91.0% *ee*.

The synthesis of the (*R*)-enantiomer **2** from ester **4** is shown in Scheme 3. Starting from the right side, reduction with $LiAlH_4$ followed by Swern oxidation, allowed to convert ester **4** into aldehyde **10**, which underwent Wittig olefination smoothly to provide alkene **11** in high yield. Hydrogenation of the double bond and removal of the MOM ether in **11** gave alcohol **12** whose newly exposed hydroxyl was employed to expand one carbon. From **12**, a three-step sequence involving sulfonylation (TsCl in pyridine), cyano substitution (NaCN in DMSO) and hydrolysis of nitrile (reflux in sulfuric acid/water) gave the desired (*R*)-methylheptanoic acid **2** over three steps in 83% yield. The enantiomer excess of **2** was measured by its derivative **15** to be 95.6%.

Conclusions

We have accomplished the synthesis of (*S*)-3-methylheptanoic acid **1** from bromoester **3** in four steps with an overall yield of 68% and the synthesis of (*R*)-3-methylheptanoic acid **2** from ester **4** in seven steps with an overall yield of 46%. Since in the alkylation and

Scheme 3 Synthesis of (*R*)-methylheptanoic acid (**2**)



Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0 ℃, 5 h, 96%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, –78 ℃, 2.5 h, Et_3N, r.t., 3 h, 81%; (c) Ph_3PMeI, *n*-BuLi, THF, 0 ℃, 20 min, r.t., 5 h, 86%; (d) 5% Pd/C, H_2, MeOH, r.t., 12 h; then HCl, MeOH, reflux, 3 h, 83%; (e) TsCl, pyridine, 0 ℃, 36 h, 92%; (f) NaCN, DMSO, 30 ℃, 36 h, 99%; (g) H_2SO_4, H_2O, reflux, 6 h, 91%; (e) 4-methoxyphenol, DCC, DMAP, CH_2Cl_2, r.t., 10 h, 91%, 95.6% *ee*.

the Wittig olefination steps the length of the carbon backbone may be easily varied, a wide variety of chiral 3-methyl alkanoic acids (both/either enantiomer) are presumably accessible. Syntheses of other natural products containing chiral methyl unit are ongoing in this laboratory.

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