Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 2, pp. 435-442, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00026-2

A Practical Synthesis of 3(*S*)-Methyl-Heptanoic Acid from (*S*)-Citronellol†

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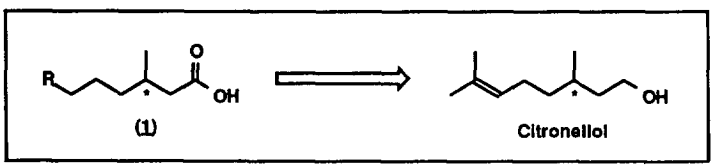
Abstract: Chiral 3-methyl-heptanoic acid is readily accessible by functional group manipulation of optically active citronellol. In principle, this approach is general and could be applied to the synthesis of chiral 3-methyl-alkanoic acids seven carbon atoms in length and longer.

The synthesis of optically active 3-alkyl substituted carboxylic acids has received significant attention from a number of research groups, resulting in a variety of successful strategies.[2] Although some of these methods are quite efficient, they are of limited value for large-scale production since they require the use of chiral auxiliaries[3] (some of which require significant synthetic effort) and/or sensitive organometallic reagents at low temperatures.[4] Faced with the task of supplying a large quantity of optically pure 3-methyl-heptanoic acid (1, R=Me) for the synthesis of one of our drug candidates, a more acceptable approach was sought.

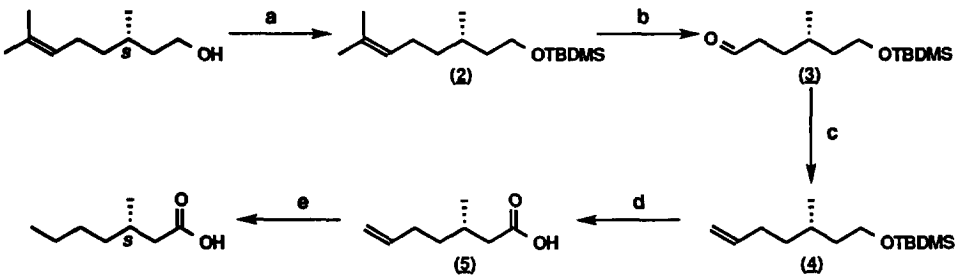


(1) Citronellol

In the search for an alternative route, it quickly became apparent that commercially available chiral citronellol[5] presented an excellent synthetic opportunity for several reasons, not the least of which was its inherent chirality. This feature, along with the conveniently located olefin and primary hydroxyl group, made (*S*)-citronellol particularly well-suited for the task at hand (Scheme 1).[6] In fact, this turned out to be the case. After first protecting the hydroxyl group of (*S*)-citronellol as its *t*-butyldimethylsilyl (TBDMS) ether (2),[7] ozonolysis of the olefinic double bond proceeded smoothly to give the aldehyde (3). Standard Wittig

† In memory of Dr. C. W. (Bill) Murtiashaw, a fine chemist and respected colleague.

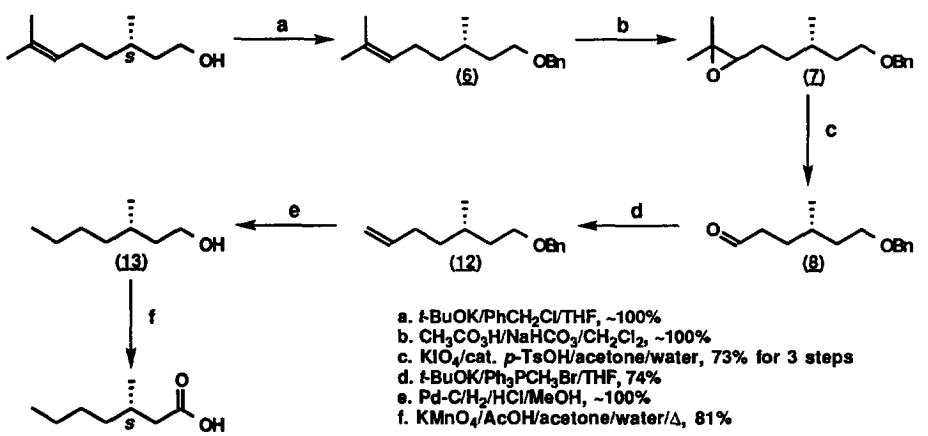
homologation[8] (Ph_3PCH_3Br/*n*-BuLi) of the aldehyde (3) provided a means for extension of the alkyl chain to furnish the alkene (4). Subsequent treatment of (4) with Jones reagent[9] resulted in concomitant desilylation and oxidation to give the carboxylic acid (5). Finally, hydrogenation (Pd-C/H_2) of the olefinic double bond gave the desired 3(*S*)-methyl-heptanoic acid in high overall yield (61%) and optical purity (>96%).[10]



a. TBDMS-Cl/imidazole/DMF, ~100%; b. O_3/CH_2Cl_2/MeOH/$NaHCO_3$/-78 °C, then Me_2S, ~100%;
c. *n*-BuLi/Ph_3PCH_3Br/THF, ~100%; d. H_2CrO_4/acetone/water, 70%; e. Pd-C/H_2/EtOAc, 88%

Scheme 1

The above sequence (Scheme 1), while short and requiring no sensitive or costly reagents, nevertheless caused some concerns for large scale preparation. In particular, restricted in-house ozone generation capacity[11] as well as concerns about the safety of handling the ozonide intermediate led us to consider alternative methodology for the cleavage of the olefinic double bond, and a different sequence was developed (Scheme 2).

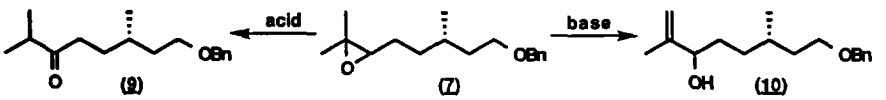


a. *t*-BuOK/$PhCH_2Cl$/THF, ~100%
b. CH_3CO_3H/$NaHCO_3$/CH_2Cl_2, ~100%
c. KIO_4/cat. *p*-TsOH/acetone/water, 73% for 3 steps
d. *t*-BuOK/Ph_3PCH_3Br/THF, 74%
e. Pd-C/H_2/HCl/MeOH, ~100%
f. $KMnO_4$/AcOH/acetone/water/Δ, 81%

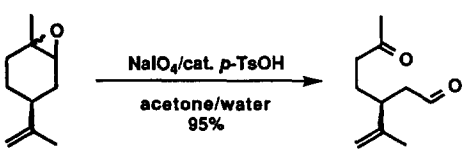
Scheme 2

Hydroxyl protection of (*S*)-citronellol (*t*-BuOK/$PhCH_2Cl$) as its benzyl ether was uneventful to provide (6) in high yield. Epoxidation of (6) was cleanly effected using peroxyacetic acid to produce the epoxide (7).[12] The oxidative cleavage of epoxide (7), although a process well documented in the literature, was not

straightforward for this particular substrate. On treatment with periodic acid (H_5IO_6),[13] 15-20% of the ketone (9) was obtained in addition to the desired aldehyde (8), presumably *via* an acid-catalyzed rearrangement. The rearrangement of epoxides (particularly highly substituted ones) under both acidic[14] and basic[15] conditions is well-known. In this system, apparently HIO_4 and/or HIO_3 are able to promote a significant amount of this rearrangement. Basic conditions were also problematic. If strong caustic was used in the workup of the epoxidation, the formation of the allylic alcohol (10) was observed.



It is interesting to note that the extent of the rearrangement is affected by the nature and concentration of the acid present. For example, treatment of the epoxide (7) with potassium periodate (KIO_4) and a catalytic amount of perchloric acid allowed the isolation of the aldehyde (8) in 90% yield accompanied by only 7% of the ketone (9). In a further improvement, *p*-toluenesulfonic acid was identified as highly effective in promoting the periodate cleavage of the epoxide (7), free of significant rearrangement product. It appears that the epoxide (7) was first hydrolytically converted to the corresponding diol,[16] which was then oxidatively cleaved to provide the aldehyde (8) in high yield.[17] Moreover, these conditions were found to be generally useful, and have been successfully extended to the oxidative cleavage of other substituted epoxides, *e.g.* limonene oxide (11) (95%), stilbene oxide (99%) and 1-methyl-cyclohexene oxide (57%). The reaction is typically carried out with a slight excess of potassium or sodium periodate and a catalytic amount of *p*-toluenesulfonic acid (1g/300mL of solvent, 18mM) in a 1:1 mixture of acetone and water.



(11)

The final three steps of the synthesis proceeded without incident. Wittig homologation (Ph_3PCH_3Br/*t*-BuOK) of the aldehyde (8) gave a high yield of the alkene (12). Subsequent hydrogenation (Pd-C/H_2) of the olefinic double bond was accompanied by removal of the benzyl protecting group.[18] The concluding oxidation of the alcohol (13) was achieved with potassium permanganate[19] instead of Jones reagent, thereby avoiding the issue of chromium contaminated waste streams, to give 3(*S*)-methyl-heptanoic acid of high optical purity (>98:2) as judged by chiral GC assay.[20]

In summary, we have demonstrated a practical synthesis of 3(*S*)-methyl-heptanoic acid.[21] Since the length of the carbon backbone may be easily varied in the Wittig homologation step, a wide variety of chiral (either enantiomer) 3-methyl-alkanoic acids (of seven-carbon in length and longer) is presumably accessible. Improved conditions for the oxidative cleavage of substituted epoxides are also reported.

Experimental

(*S*)-Citronellol-*t*-butyldimethylsilyl ether

To a solution of (*S*)-citronellol (547 g, 3.5 mol) in DMF (547 mL) was added imidazole (262.1 g, 3.85 mol) at room temperature. After cooling to 0 °C, a solution of *t*-butyldimethylsilyl chloride (580.3 g, 3.85 mol) in DMF (1160 mL) was slowly added over a period of 1.25 hrs. The resulting white suspension was stirred an additional 15 min, poured into a mixture of hexanes (500 mL) and ice water (1 L), agitated, and allowed to stand until the phases had separated. The organic layer was washed with cold 0.5M HCl, dried over $MgSO_4$, filtered and concentrated on the rotary evaporator to yield 986.7 g (104.2%)[22] of (2) as a colorless oil.

R_f = 0.41 (3:1 ether/hexanes). IR (neat) 3849, 3807, 3652, 2951, 2924, 2854, 2731, 2022, 1730, 1672, 1638, 1546, 1472, 1463, 1407, 1638, 1546, 1472, 1463, 1407, 1377, 1361, 1256, 1214, 1094, 1036, 1005, 986, 938, 895, 835, 810, 773, 731, 676, 660, 599, 252, 232, 220, 214, 205 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 5.2 (t, 1 H, J = 7.0 Hz), 3.65 (t, 2 H, J = 6.5 Hz), 1.0-2.2 (m, 14 H), 0.8 (s, 12 H), 0.02 (s, 6 H). Mass spec.(70 eV) 271.2 (M+1), 74.9 (base peak).

6-(*t*-Butyldimethylsiloxy)-4(*S*)-methyl-hexan-1-al

A 500-mL flask was charged with the silyl ether (2) (84.6 g, 0.3 mol), CH_2Cl_2 (120 mL), MeOH (81 mL), $NaHCO_3$ (6.3 g), and subjected to a bubbling stream of ozone for 6 hours at -70 °C. The clear, bluish solution was then treated with dimethyl sulfide (26.4 mL, 0.36 mol), allowed to come to room temperature, and continue stirring for 15 hrs or until negative to starch iodide test. After removal of volatiles on a rotary evaporator (keeping the bath temperature <26 °C), the resulting oil was dissolved in EtOAc (150 mL) and washed 3 times with water (300 mL). The organic layer was then dried over $MgSO_4$, concentrated on the rotary evaporator (bath temperature <26°C) and evacuated under high vacuum overnight to give 74.7 g (101.9%)[22] of slightly impure aldehyde (3).

R_f = 0.45 (2:1 hexanes/ether). IR (neat) 3706, 3411, 2947, 2925, 2852, 2722, 2466, 2023, 1723, 1462, 1390, 1361, 1248, 1081, 1005, 937, 894, 833, 663, 266, 213 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 9.75 (t, 1 H, J = 2 Hz), 3.61 (m, 2 H), 2.41 (m, 2 H), 1.20-1.71 (m, 5 H), 0.88 (s, 12 H), 0.06 (s, 6 H). ^{13}C-NMR ($CDCl_3$) δ 202.81, 61.04, 41.65, 39.51, 29.16, 28.94, 25.93, 19.34, 18.29. Exact mass calculated for $C_{13}H_{29}O_2Si$ (M+1) = 245.1936, high res. mass spec. 245.1947.

7-(*t*-Butyldimethylsiloxy)-5(*S*)-methyl-hept-1-ene

To a cooled (0° C) suspension of methyltriphenylphosphonium bromide (1249.7 g, 3.5 mol) in THF (3125 mL) was added a 2.5M solution of *n*-buLi in hexanes (1343.3 mL, 3.36 mol) over a period of 1 hr and 23 min. The resulting red suspension was then treated with a solution of aldehyde (3) (684.1 g, 2.8 mol) in THF (500 mL) over a period of 50 min. After 40 min, water (7.3 L) and EtOAc (4.4 L) were rapidly added and the mixture was transferred to a separatory funnel. Following separation of the phases, the organic layer was washed twice with water (5 L), and the aqueous layers were extracted once with EtOAc (2 L). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a pasty beige oil. Trituration with hexanes (250 mL) removed the majority of the triphenylphosphine oxide, leaving, after filtration and removal of solvent, 754 g (111%)[22] of the slightly impure alkene (4) as an amber oil.

R_f = 0.70 (1:1 ether/hexanes). IR (neat) 3408, 2945, 2923, 2853, 1723, 1640, 1462, 1382, 1361, 1250, 1081, 1003, 910, 892, 832, 765, 715, 662, 236, 214 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 5.80 (m, 1 H), 4.94 (m, 2 H), 3.62 (m, 2 H), 2.04 (m, 2 H), 1.57 (m, 2 H), 1.13-1.47 (m, 4 H), 0.89 (s, 12 H), 0.03 (s, 6 H). ^{13}C-NMR ($CDCl_3$) δ 139.13, 114.06, 61.33, 39.85, 36.31, 31.28, 29.02, 25.95, 19.53, 18.30. Exact mass calculated for $C_{14}H_{31}OSi$ (M+1) = 243.2136, high res. mass spec. 243.1818.

3(*S*)-Methyl-hept-6-enoic acid

To a cooled (0 °C) solution of the silyl ether (4) (48.4 g, 0.2 mol) in acetone (195 mL) and water (19.5 mL) was added a 2.87M solution of Jones reagent (150 mL) over a period of 1 hr and 39 min. After an additional 10 min, the addition of 2-propanol (35 mL) provided a green suspension which was concentrated on the rotary evaporator and diluted with water (250 mL), creating a clear, dark, aqueous solution that was extracted 3 times with isopropyl ether (IPE). The combined organic layers were backwashed once with 1N H_2SO_4 and then extracted with 2M NaOH (3 x 80 mL). The aqueous layers were acidified with the slow addition of conc. HCl (50 mL) to pH ~ 1-2, extracted with IPE (3 x 150 mL) and the organic layers were dried over $MgSO_4$. Filtration and evaporation of the solvent provided the carboxylic acid (5) as a light yellow oil (21.6 g, 76.2%).
IR (neat) 3237, 3195, 3073, 3034, 2963, 2918, 2873, 2738, 2706, 2683, 1709, 1642, 1455, 1410, 1381, 1299, 1254, 1224, 1186, 994, 908, 765, 687, 630, 554, 480, 277, 256, 249, 240, 231, 214 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 11.1 (s, 1 H), 5.5-6.3 (m, 1 H), 4.8-5.3 (m, 2 H), 1.2-2.8 (m, 10 H), 0.98 (d, 3 H, J = 6.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 179.07, 138.43, 114.56, 41.39, 35.69, 31.07, 29.62, 19.44. Exact mass calculated for $C_8H_{14}O_2$ = 142.0990, high res. mass spec. 142.0920.

3(*S*)-Methyl-heptanoic acid

A 2-gal autoclave was charged with 5% Pd/C (19.5 g, 50% water wet), EtOAc (1.5 L), and the unsaturated acid (5) (333.4 g, 2.56 mol). After purging with nitrogen followed by H_2, the apparatus was pressurized to 50 psi and agitated for 2 hrs, repressurizing three times along the way. The black suspension was filtered through celite, concentrated and distilled to yield (S)-3-methyl-heptanoic acid as a pale yellow oil (296.3 g, 87%).
b.p. = 76-86 °C @ 0.3 mm of Hg (uncorrected). Optical rotation $[\alpha]_D^{25}$ = -6.41 (*c* = 1 in MeOH); lit.[2a] $[\alpha]_D^{25}$ = -4.18 (neat). IR (neat) 3040, 2958, 2922, 2860, 2660, 1710, 1460, 1410, 1380, 1300, 1228, 1190, 1150, 1100, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 11.6 (s, 1 H), 1.1-2.8 (m, 12 H), 1.0 (d, 3 H, J = 6.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 180.04, 41.63, 36.32, 30.09, 29.07, 22.72, 19.63, 13.98. Exact mass calculated for $C_8H_{16}O_2$ = 144.1146, high res. mass spec. 144.1136.

(*S*)-Citronellol-benzyl ether

A solution of (*S*)-citronellol (1200 g, 7.7 mol) in THF (8.4 L) was treated with potassium *t*-butoxide (1163 g, 10.4 mol) in several portions. After stirring for 1.5 hrs, the resulting homogeneous solution was treated with benzyl chloride (1069 g, 8.4 mol). The mixture was stirred overnight at room temperature for convenience. After distilling off most of the THF, the residue oil was diluted with hexanes (8.4 L), washed with water then brine, and dried over Na_2SO_4. Evaporation of solvent provided the crude benzyl ether (6) as an oil (1985 g, ~100%).[22] An analytical sample was prepared by distillation.
R_f = 0.72 (20:80 EtOAc/hexanes). b.p. = 135-136 °C/1.8 mm Hg (uncorrected). Optical rotation $[\alpha]_D^{25}$ = -1.91 (neat). ^{1}H-NMR ($CDCl_3$) δ 7.37-7.25 (m, 5 H), 5.13-5.07 (m, 1 H), 4.51 (s, 2 H), 3.55-3.47 (m, 2 H), 2.04-1.93 (m, 2 H), 1.69 (bs, 3 H), 1.60 (bs, 3 H), 1.75-1.09 (e, 5 H), 0.89 (d, 3 H, J = 6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 138.75, 131.12, 128.47, 127.52, 124.95, 124.84, 72.95, 68.75, 37.25, 36.78, 29.61, 25.81, 25.53, 19.55, 17.70. GC/MS (retention time 3.47 min) 246 (M^+), 155, 137, 91. Elemental analysis for $C_{17}H_{26}O$ calculated: C 82.87%, H 10.64%; found: C 82.45%, H 10.55%.

8-Benzyloxy-2,6(*S*)-dimethyl-2-epoxy-octane

1908 g of the alkene (6) was divided into two equal portions and subjected to epoxidation in two separate 22-L flasks. A solution of the alkene (6) (954 g, 3.9 mol) in CH_2Cl_2 (9.5 L) was cooled in a cold water bath and treated with solid $NaHCO_3$ (705 g, 8.4 mol). A solution of 32% peroxyacetic acid in acetic acid (998 g, 4.2 mol) was added dropwise over 1.5 hrs, and the mixture was stirred for 1.5 hrs. The reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with hexanes. The extract was slurried with KBB Darco for 30 min to quench any unreacted peroxyacetic acid, filtered and dried over Na_2SO_4. Removal of solvent

provided the epoxide (7) as an oil (combined crude yield 2182 g, ~100%),[22] which was used directly for the next reaction.
R_f = 0.53 (20:80 EtOAc/hexanes). ^{1}H-NMR ($CDCl_3$) δ 7.39-7.25 (m, 5 H), 4.50 (s, 2 H), 3.53-3.48 (m, 2 H), 2.69 (t, 1 H, J = 6.0 Hz), 1.75-1.47 (m, 5 H), 1.28 (d, 6 H, J = 11.5 Hz), 0.91 (d, 3 H, J = 6.5 Hz). GC/MS (retention time 4.00 min) 262 (M^+), 171, 153, 107, 91.

6-Benzyloxy-4(*S*)-methyl-hexan-1-al
2168 g of the crude epoxide (7) was divided into two equal portions and subjected to oxidative cleavage in two separate 22-L flasks. A solution of the epoxide (7) (1084 g, ~3.9 mol) in acetone (8.7 L) was treated sequentially with potassium periodate (1068 g, 4.6 mol), water (8.7 L) and a catalytic amount of *p*-TsOH·H_2O (66 g, 0.35 mol). The reaction mixture was stirred at ambient temperature overnight for convenience. The precipitated solids were filtered off, the filtrate was diluted with hexanes, washed with water and concentrated to provide the crude aldehyde (8) as an oil. The aldehyde was purified *via* its bisulfite addition complex as followed: the aldehyde was taken into hexanes and extracted with aqueous solution of $NaHSO_3$. After separation, the aqueous layer was washed with more hexanes. The aqueous layer was neutralized with aqueous Na_2CO_3 and the aldehyde was extracted into hexanes. The extract was treated with KBB Darco, dried over Na_2SO_4 and concentrated to furnish the aldehyde (8) as an oil (combined yield 1237 g, 73% over 3 steps from (*S*)-citronellol). An analytical sample was prepared by column chromatography.
R_f = 0.47 (20:80 EtOAc/hexanes). Optical rotation $[\alpha]_D^{25}$ = -0.96 (neat). IR (thin film) 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 9.76 (t, 1 H, J = 1.8 Hz), 7.39-7.25 (m, 5 H), 4.50 (s, 2 H), 3.55-3.44 (m, 2 H), 2.49-2.36 (m, 2 H), 1.75-1.58 (m, 3 H), 1.53-1.38 (m, 2 H), 0.90 (d, 3 H, J = 6.4 Hz). ^{13}C-NMR ($CDCl_3$) δ 202.64, 138.36, 128.36, 127.62, 127.54, 72.97, 68.28, 41.60, 36.47, 29.55, 28.88, 19.33. GC/MS (retention time 2.96 min) 220 (M^+), 129, 107, 91. Elemental analysis for $C_{14}H_{20}O_2$ calculated: C 76.33%, H 9.15%; found: C 74.36%, H 8.84%.

7-Benzyloxy-5(*S*)-methyl-hept-1-ene
A suspension of methyltriphenylphosphonium bromide (2067 g, 5.8 mol) in THF (12 L) was cooled in an ice-acetone bath under N_2, and treated with potassium *t*-butoxide (620 g, 5.5 mol). The resulting yellow mixture was stirred for 1.5 hrs. The aldehyde (8) (1159 g, 5.3 mol) was added slowly as a solution in THF (6 L) over 2 hrs, with the reaction temperature maintained between -5 and 0 °C. The reaction mixture was stirred for 1.5 hrs, and then concentrated to ~2 L in volume. Hexanes (8 L) was added, and the mixture was concentrated to displaced the residual THF. The white solids (triphenylphosphine oxide) were filtered off, and the filtrate was concentrated to afford the alkene (12) as an oil (857 g, 74%). An analytical sample was prepared by column chromatography.
R_f = 0.70 (20:80 EtOAc/hexanes). Optical rotation $[\alpha]_D^{25}$ = -1.18 (*c* = 41.6 in $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 7.48-7.30 (m, 5 H), 5.96-5.81 (m, 1 H), 5.09 (dd, 1 H, J = 1.5 & 17.2 Hz), 5.02 (dd, 1 H, J = 1.1 & 10.1 Hz), 4.57 (s, 2 H), 3.67-3.52 (m, 2 H), 2.25-2.04 (m, 2 H), 1.82-1.64 (m, 2 H), 1.58-1.45 (m, 2 H), 1.36-1.27 (m, 1 H), 0.98 (d, 3 H, J = 6.4 Hz). ^{13}C-NMR ($CDCl_3$) δ 139.30, 139.07, 138.73, 128.47, 127.55, 114.19, 72.95, 68.66, 36.74, 36.31, 31.31, 29.49, 19.61. GC/MS (retention time 2.41 min) 175, 161, 143, 127, 109, 91. Elemental analysis for $C_{15}H_{22}O$ calculated: C 82.52%, H 10.16%; found: C 82.75%, H 10.17%.

3(*S*)-Methyl-heptan-1-ol
A mixture of the alkene (12) (835 g, 3.8 mol), wet 5% palladium on carbon (100 g) catalyst, and conc. HCl (84 mL) in methanol (42 L) was stirred under H_2 (50 psi) overnight. The palladium catalyst was filtered off, and the filtrate was concentrated to provide the alcohol (13) as an oil (512 g, ~100%).[22] An analytical sample was prepared by column chromatography.

R_f = 0.52 (20:80 EtOAc/hexanes). Optical rotation $[\alpha]_D^{25}$ = -1.59 (*c* = 21.2 in $CHCl_3$). IR (thin film) 3332.7 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 3.63-3.52 (m, 2 H), 2.74 (bs, 1 H), 1.59-1.02 (e, 9 H), 0.91-0.73 (m, 6 H). ^{13}C-NMR ($CDCl_3$) δ 60.84, 39.82, 36.82, 29.45, 29.15, 22.93, 19.64, 13.99. GC/MS (retention time 0.59 min) 112, 97, 84, 70, 55. Elemental analysis for $C_8H_{18}O$ calculated: C 73.78%, H 13.93%; found: C 73.77%, H 13.59%.

3(*S*)-Methyl-heptanoic acid

473 g of the alcohol (**13**) was divided into two equal portions and subjected to permanganate oxidation in two separate 22-L flasks. A solution of the alcohol (**13**) (236.5 g, 1.8 mol) in acetone (3. 3 L) and acetic acid (655 mL) was treated with a solution of $KMnO_4$ (373 g, 2.4 mol) in water (6.7 L) over 2 hrs. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2 (4.7 L), and the pH was adjusted to 4 with conc. HCl (~180 mL). Solid $NaHSO_3$ (~368 g) was added until the brown color of the mixture was completely discharged to colorless. The mixture was further adjusted to pH 3 with conc. HCl, and extracted with CH_2Cl_2. The extract was concentrated to an oil, which was diluted with toluene and further concentrated to remove any residual acetic acid. 3(*S*)-Methyl-heptanoic acid was obtained as an oil (417 g, 81%).

R_f = 0.47 (80:20 EtOAc/hexanes). b.p. = 78-80 °C/0.7 mm Hg (uncorrected). Both ^{1}H-NMR and ^{13}C-NMR are identical to spectra of authentic sample. Chiral GC assays[20] indicate an optical purity of >98:2.

References and Notes

1. Deceased 25th October, 1995.
2. (a) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266-6267; (b) Mukaiyama, T.; Takeda, T.; Fujimoto, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368-3372; (c) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886-2888; (d) Mukaiyama, T.; Iwasawa, N. *Chemistry Lett.*. **1981**, 913-916; (e) Mori, K.; Sugai, T. *Synthesis* **1982**, 752-753; (f) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004-5005; (g) Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051-6054; (h) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212-215; (i) Whittaker, M. *Chem. Ind.* **1986**, 463-464; (j) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769-5775; (k) Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81-87; (l) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369-372; (m) Soai, K.; Machida, H.; Yokota, N. *J. Chem. Soc., Perkin Trans. I* **1987**, 1909-1914; (n) Fang, C.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1990**, *31*, 4751-4754; (o) Bergdahl, M.; Nilsson, M.; Olsson, T.; Stern, K. *Tetrahedron* **1991**, *47*, 9692-9702; (p) Tsuruta, T.; Arai, K.; Obara, Y.; Miyaji, K. *Japanese Patent* JP-03-95138, 19th Apr., **1991**; (q) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018-1028; (r) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516-2518; (s) Chiu, C. K.-F. *Tetrahedron: Asymmetry* **1995**, *6*, 881-884; and references cited therein.
3. For syntheses require chiral auxiliaries, see references in 2: (a), (b), (c), (d), (f), (g), (h), (i), (l), (m), (n), (o), (p), (q).
4. For syntheses require organometallic reagents at low temperatures, see references in 2: (a), (c), (e), (h), (n), (o), (p), (q), (r).
5. The commercial naturally derived citronellol is of the (*S*)-configuration and only ~60% ee. The optically pure enantiomers are synthetically derived and manufactured by Takasago International Inc. (available in research quantity from Aldrich). For a report of the chemistry, see (a) Tani, K.; Yamagata, T.;

Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208-5217; (b) Takaya, H.; Ohta, T.; Inoue, S-I., Tokunaga, M.; Kitamura, M.; Noyori, R. *Org. Syn.* **1993**, *72*, 74-85.

6. (a) At the conclusion of our work, a similar synthesis based on citronellol appeared in the patent literature: Ohno, K.; Hiroshi, N.; Ishikawa, M.; Matsumoto, K.; Nishio, S. *U. S. Patent* US-4,564,620, 14th Jan., **1986**; (b) For a recent synthesis utilizing the chiral 3-methyl group of citronellol, see Kefalas, P.; Ragoussis, N. *Synthesis* **1995**, 644-646.
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10. Enantiomeric excesses were measured by (1) optical rotation, (2) coupling with an optically pure peptide and subsequent high field NMR analysis, and (3) coupling of the acid with D-phenylglycinol followed by HPLC analysis.
11. Our research ozone generator is capable of processing 0.3 mol of substrate in an 8-hour period.
12. Based on data from ^{1}H-NMR and GC, the epoxide (7) appeared to be a single diastereomer but it was not vigorously verified. Nevertheless, the absolute relative stereochemistry of the epoxide is of no consequence to the synthesis.
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16. The formation of the diol intermediate was observed on tlc as a polar component at the expense of the epoxide, and was subsequently converted to the aldehyde (8).
17. The crude aldehyde (8), although normally of good quality, was purified *via* its bisulfite addition product. Fieser, L; Fieser, M. *Reagents for Organic Synthesis* **1967**, *1*, 1047-1049.
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20. Chiral GC assays (Column: Chiraldex-GTA (Astec), 30 m) were conducted on the methyl ester derivative prepared by heating the 3-methyl-heptanoic acid in methanol with 0.5N HCl at 60 °C for 30 min. prior to injection. The GC assays were kindly provided by Mr. D. A. Cole of Analytical R&D, Pfizer Inc. Central Research, Groton.
21. All novel compounds were fully characterized by high field NMR, IR, MS and elemental analysis/high resolution MS.
22. The greater than quantitative yield obtained is due to residual solvent, which is often difficult to remove completely in bulk preparation. Analytical samples were prepared by evacuation under high vacuum to purge residual solvent.

(*Received in USA* 16 *November* 1995)