# A $C_{10}$ Chiron Applicable to the Synthesis of Archaebacterial Lipids

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The membrane lipids[1] of archaebacteria may be an important factor in the unusual adaptation of such organisms to extremes of temperature, salt concentration, and pH. Among the most common lipids isolated from these prokaryotes are derivatives of two[2] $C_2$-symmetric, *sn*-2,3-bisbiphytanylglycerol tetraethers **1** and **2** (R, R′ = glycoside, phosphate ester, hexitol, etc.[1c]), containing a 72-membered ring with 16 configurationally defined methyl groups Chart 1).

The $C_{40}$ bisbiphytanediol chains (**3**) of lipids **1** and **2**, which are octamers of a common $C_5$ ("isopranyl") unit, have been synthesized by Heathcock,[3] Czeskis,[4] and Kakinuma,[5] who coupled two ($C_{20}$) tetramers (**4**) head to head. In turn, the tetramers were assembled by head to tail coupling of two $C_{10}$ dimers (**5**). This $C_{10}$ unit occurs in a variety of other substances as well: e.g. the ubiquitous phytol[6] side chains of Vitamins E[7] and K,[8] and chlorophyll;[9] lycopadiene produced by the microalga *Botryococcus braunii*;[10] and pheromones of pine sawflies,[11,12] tsetse flies,[12,13] red flour beetles,[12,14] male stink bugs,[12] mountain ash bentwings, and alfalfa blotch leaf miners.[12]

The requirement for a means to obtain sufficient archaebacterial lipid for biomedical study led us to examine new routes to key intermediate **5**. Although the synthesis of **5**[3−5,15,16] and the closely related $C_9$ unit[17−20] have received fair attention, with results ranging from a short synthesis of three steps and 10% yield (ee >95%), to one with a yield of 25%, in 10 steps (racemic), we were prompted to attempt further improvement. The results reported in this Note compare favorably as to length, yield, and optical purity of the final product: five steps, 27% yield, ee >95%.

We have adapted Chenevert's approach,[18] *i.e.* cyclic hydroboration of 2,6-dimethyl-1,6-heptadiene (**8**) and have increased the carbon count to 10 by carbonylation. Asymmetry was induced by enolization of the resulting *meso*-3,7-dimethylcyclooctanone with lithium (+)-bis[(*R*)-(1-phenylethyl)]amine[21] (**11**) which afforded the 3*S*,7*R* enol silyl ether. Ozonolysis/reduction of the silyl enol ether afforded **5a**. We have also developed an efficient, two-step synthesis of diene **8** (Scheme 1).

## Results and Discussion

Cross coupling of 4-bromo-2-methyl-1-butene[22] (**7**) with the Grignard[23] reagent of methallyl chloride in the presence of $Li_2CuCl_4$[24] gave 2,6-dimethyl-1,6-heptadiene (**8**) in 65% yield starting from 3-methyl-3-butenol, a considerable improvement over previous methods.[25]

Cyclic hydroboration/oxidation of diene **8** with thexylborane[26] (Scheme 2) was found by Still[27] (and confirmed by Chenevert[18]) to give a predominately *meso*-diol in 73%[25] (59%[18]) yield (*meso*/*d*,*l* = 15/1). On the other hand, cyclic hydroboration with thexyl borane followed by carbonylation[28] of the crude product produced *meso*-3,7-dimethylcyclooctanone (**10**) as a pure diastereoisomer in 51% yield. GC-MS showed one other component with $M^+$ 154 but of negligible intensity (0−0.2%), and $^{13}C$ NMR showed no peaks consistent with the *d*,*l* diastereoisomer (Scheme 2). It is likely that the Still/Chenevert results were due to the presence of appreciable polymeric borane

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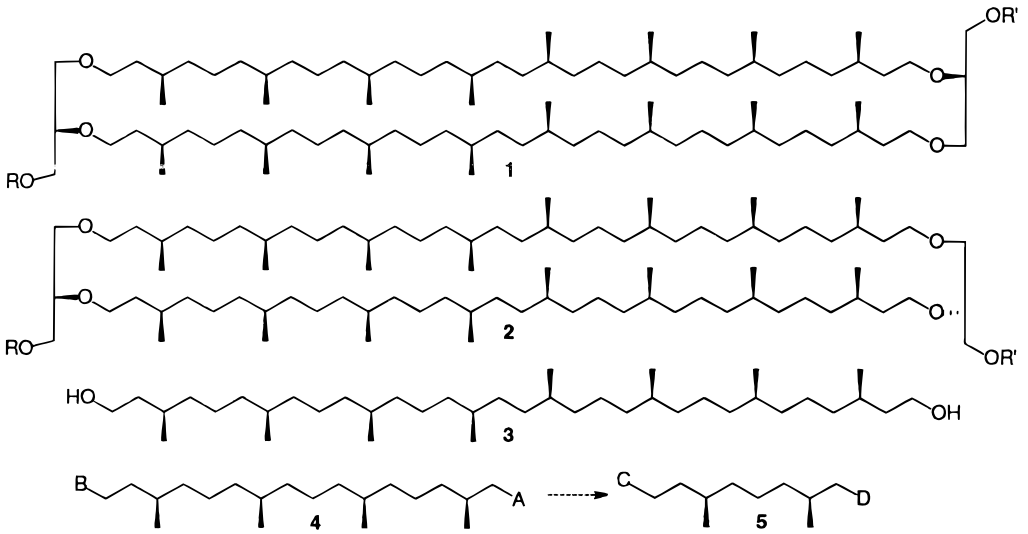
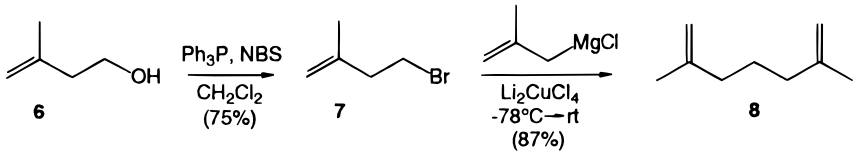
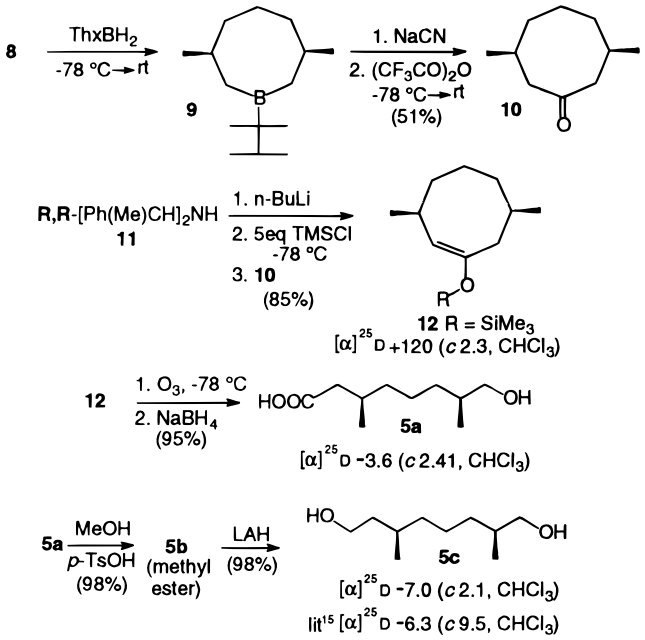
**Chart 1**




**Scheme 1**




**Scheme 2**




besides the desired (cyclic) borocane **9**, and oxidation of this mixture gave the *meso*/*d*,*l* diol products actually isolated. Carbonylation, on the other hand, could have proceeded only from the borocane intermediate, which resulted from a highly stereoselective cyclic hydroboration as Still had predicted. We are presently trying to find ways to minimize the polymeric byproduct of the hydroboration step.

The key step, asymmetric enolization, using the lithium salt of (+)-bis[(*R*)-(1-phenylethyl)]amine (**11**) proceeded remarkably well.[21] The corresponding enol trimethylsilyl ether **12** was produced in 85% yield by internal quenching of the enolate with excess trimethylsilyl chloride.

The ring was opened by ozonolysis/reduction,[29] and the resulting acid **5a** was converted in turn to the hydroxy ester **5b** and diol **5c**. Chiral shift reagent, Eu(hfc)$_3$,[21b,30] induced separation of the $^1$H NMR position of diastereoisomeric methoxyl groups of optically active hydroxy ester **5b** by 20 Hz. Integrated intensities of the two peaks indicated an ee of 96−98%. (The proton spectrum of the enol silyl ether was unaffected by the shift reagent.) In addition, the optical rotation of diol **5c** was the same sign and of greater magnitude than that reported by Gramatica[15b] for diol **5c** prepared from (*R*)-citronellol and shown to have an ee >95%. Had cyclooctanone **10** been the *trans*-dimethyl diastereoisomer, the product enolate, and thus subsequent products, would have perforce been racemic. Consequently, hydroxy acid **5a** is determined to be (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoic acid, and the absolute configuration of acid enol silyl ether **12** produced with the *R*,*R* base is 3*S*,7*R*, with an ee of 98%. The high ee obtained is consistent with the transition state model proposed by Majewski,[21b] and the distinct differences in the environments of the α and α′ protons of cyclooctanone **10** in stable conformations.[31]

## Conclusions

In conclusion, we have fashioned an improved synthesis of diene **9** and have used it in a sequence involving (1) cyclic hydroboration/carbonylation, followed by (2) asymmetric enolization and (3) ozonization of the derived enol silyl ether **12**, to produce $C_{10}$ chiron **5a** in five steps, with an ee of 98%, applicable to the synthesis of archaebacterial lipids and other natural products containing the $C_{10}$ diisopranyl unit.

## Experimental Section

**General.** All air-sensitive reactions were carried out under argon or nitrogen. Diethyl ether and THF were distilled under

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nitrogen from sodium and benzophenone. $CH_2Cl_2$ was distilled from $CaH_2$. All amines were distilled from $CaH_2$. Trimethylsilyl chloride was distilled from $CaH_2$ and used immediately. IR spectra of solutions in $CCl_4$ or $CDCl_3$ were recorded in $cm^{-1}$. Gas chromatographic analyses were performed on a 1 m 2% OV-1 column. GC-MS spectra were performed using a fused silica capillary column. TLC was carried out on silica gel. Flash[32] column chromatography was performed on silica gel 60 (230−400 mesh ASTM). $^1H$ and $^{13}C$ NMR spectra were recorded for $CDCl_3$ solutions using a Bruker DPX 400 spectrometer, and chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Distillations were performed with either a column packed with glass helices or on an annular Teflon spinning band column. Elemental analyses were performed by Galbraith Laboratories, Inc, Knoxville, TN.

**4-Bromo-2-methyl-1-butene[22] (7).** The method of Bose was used.[33] To a mixture of 3-methyl-3-butene-1-ol (**6**) (50.5 mL, 0.500 mol), triphenylphosphine (144 g, 0.550 mol), and dry $CH_2Cl_2$ (100 mL) cooled in an ice bath was added *N*-bromosuccinimide (97.9 g, 0.550 mol) in several portions with vigorous stirring. Stirring was continued for 3 h at room temperature. Then, hexane (300 mL) was added to the flask, and the mixture was filtered through a short silica gel pad, which was washed with hexane (200 mL). The solvents were removed by distillation at 1 atm, and the residue was distilled under reduced pressure to yield 55.9 g (75%) of 4-bromo-2-bromo-1-butene (**8**), bp 63−65 °C/90 mmHg (lit.[22a] bp 40 °C, 40 mmHg), and GC-MS showed a single peak. IR 3080.7, 1649.7, 1450.2, 897.6; $^1H$ NMR 1.75 (s, 3H), 2.58 (t, $J$ = 7.4 Hz, 2H), 3.48 (t, $J$ = 7.3 Hz, 2H), 4.78, 4.86 (s,s, 2H); $^{13}C$ NMR 21.94, 30.80, 40.90, 112.68, 142.4; mass spectrum *m/e* (% relative intensity) 150 ($M^+$, $^{81}Br$, 13), 148 ($M^+$, $^{79}Br$, 14), 135 (0.4), 133 (0.5), 95 (2.3), 93 (2.5), 82 (1.3), 80 (1.3), 70 (5.5), 69 (100), 68 (9.1), 67 (16), 55 (20), 53 (21), 41 (81), 39 (46), 27 (22).

**2,6-Dimethyl-1,6-heptadiene (8).**[25] Kochi's coupling method was employed.[23,24] The Grignard reagent prepared from 3-chloro-2-methyl-1-propene (59.2 mL, 0.60 mol) in dry THF (200 mL) was siphoned into a 1-L three-necked flask which contained 4-bromo-2-bromo-1-butene (**7**) (44.8 g, 0.30 mol), $Li_2CuCl_4$ (30 mL of 0.1 M solution in THF, 3.00 mmol), and dry THF (200 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C and then for 6 h at 0 °C and 18 h at room temperature. Then, saturated NaCl (100 mL) was added, and the resulting mixture was filtered through a short pad of Celite 545, which was washed with ether (150 mL). The aqueous layer was separated and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine and dried, and the solvent was removed by distillation at 1 atm. The residue was distilled to yield 32.43 g (87%) of 2,6-dimethyl-1,6-heptadiene (**8**), bp 135−136 °C (lit.[25a] bp 138−139 °C) and GC-MS showed a single peak. IR 3073.4, 1649.3, 1648.8; $^1H$ NMR 1.57 (p, $J$ = 7.6 Hz, 2H), 1.72 (s, 6H), 2.00 (t, $J$ = 7.7 Hz, 4H), 4.68, 4.71 (s,s, 4H); $^{13}C$ NMR 22.41, 25.56, 37.38, 109.83, 145.94; mass spectrum *m/e* (% relative intensity) 124 ($M^+$, 2), 109 (24), 96 (14), 81 (20), 68 (100), 57 (12), 53 (18), 41 (61).

***cis*-3,7-Dimethylcyclooctanone (10).** An oven dried, three-neck flask was fitted with an L-shaped solid-addition tube, an injection septum, a magnetic stirring bar, and a vacuum/nitrogen inlet. Into the sidearm was placed dry, finely divided sodium cyanide (1.08 g, 22.0 mmol).[28b] The apparatus was then evacuated and filled with nitrogen, which was maintained at a positive pressure until the oxidation step was complete. Tetrahydrofuran (200 mL) and borane−THF (22.0 mL of 1.0 M, 22.0 mmol) were introduced, and the temperature was lowered to −25 °C. By syringe, 2,3-dimethylbut-2-ene (2.62 mL, 22.0 mmol) was slowly added to the stirred solution. Stirring was continued for 2 h at 0 °C, and then the temperature was lowered to −78 °C and 2,6-dimethyl-1,6-heptadiene (**8**, 2.48 g, 20.0 mmol) was added during 15 min. The cooling bath was removed after addition of the diene, and the mixture was allowed to warm to room temperature and stirred for 20 h.

The solid addition sidearm was then rotated so that the sodium cyanide was introduced. The mixture was stirred for 2 h, during which time most of the sodium cyanide dissolved. The mixture was cooled to −78 °C, trifluoroacetic anhydride[28b] (3.38 mL, 24.0 mmol) was added dropwise with vigorous stirring, and the mixture was allowed to warm to room temperature during 1 h. The flask was cooled to 0 °C, and aqueous NaOH (15 mL, 3 M) followed by 30% $H_2O_2$ (28 mL) were added. This mixture was stirred for 3 h at room temperature and 20 min at 50 °C. The solution was then saturated with sodium chloride, and the organic phase was separated, washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and filtered. The solvent was distilled at 1 atm, and the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 40/1) and then distilled to yield 1.58 g (51%) of *cis*-3,7-dimethylcyclooctanone (**10**), bp 63.5−64.0 °C/1.5 mmHg. GC-MS showed a single peak. IR 1696.4; $^1H$ NMR 0.99 (d, $J$ = 6.4 Hz, 6H), 1.23−1.37 (m, 3H), 1.40−1.54 (m, 1H), 1.60−1.75 (m, 2H), 2.15−2.22 (m, 4H), 2.53 (q, $J$ = 18.0 Hz, 8.7 Hz, 2H); $^{13}C$ NMR 22.44, 22.63, 32.49, 36.42, 50.45, 215.3; mass spectrum *m/e* (% relative intensity) 154 ($M^+$, 12), 139 (14), 125 (11), 121 (9), 112 (45), 98 (17), 84 (15), 81 (9), 69 (100), 55 (52), 41 (60), 39 (29), 27 (16). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.51; H, 11.72.

**[((3*S*,7*R*)-3,7-Dimethylcycloocten-1-yl)oxy]trimethylsilane (12).** To a cold (−78 °C), 100 mL, flame-dried, three-necked flask which contained (+)-bis[(*R*)-(1-phenylethyl)]amine[21] (**11**) (Fluka, 1.46 g, 6.50 mmol) in dry THF (65 mL) was added dropwise a solution of *n*-butyllithium in hexane (6.25 mmol, 2.50 mL of 2.5 M). After 5 min, the cooling bath was removed, and the temperature was allowed to warm to room temperature during 35 min and then again lowered to −78 °C. Freshly distilled TMSCl (3.17 mL, 25.0 mmol) in THF (6 mL) was added dropwise. The cold mixture was stirred for 8 min, and then *cis*-3,7-dimethylcyclooctanone (**10**) (0.770 g, 5.00 mmol) in THF (15 mL) was added dropwise during 40 min. The resulting solution was stirred at −78 °C for 3 h, and then $Et_3N$ (9 mL) was added. The solution was allowed to warm to room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added, and the solvents were removed under vacuum. The residue was extracted with pentane (3 × 50 mL), and the combined extracts were washed with 0.1 M aqueous citric acid (2 × 50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product which was purified by flash chromatography ($SiO_2$, pentane) to yield 0.96 g (85%) of enol silyl ether **12** (0.96 g, 85%) as a colorless oil. GC-MS showed a single peak.

$[\alpha]^{25}_D$ +120 (*c* 2.32, $CHCl_3$); IR 1656.0, 1252.0, 847.4; $^1H$ NMR 0.13 (s, 9H), 0.95 (d, $J$ = 5.0 Hz, 3H), 0.97 (d, $J$ = 4.8 Hz, 3H), 1.08−1.18 (m, 1H), 1.20−1.40 (m, 2H), 1.52−1.62 (m, 2H), 1.70−1.80 (m, 2H), 1.88−1.98 (m, 1H), 2.2−2.3 (m, 1H), 2.60 (q, $J$ = 14.0 Hz, 4.9 Hz, 1H), 4.45 (d, $J$ = 7.6 Hz, 1H); $^{13}C$ NMR 0.41, 21.63, 23.59, 24.81, 32.08, 33.79, 34.28, 37.18, 39.82, 113.44, 150.06; mass spectrum *m/e* (% relative intensity) 226 ($M^+$, 15), 211 (28.6), 197 (9.2), 184 (23.4), 183 (63.9), 169 (15.3), 157 (93.2), 144 (12.9), 130 (14.5), 121 (6.2), 115 (13.8), 99 (3.8), 93 (5.5), 75 (47), 73 (100), 55 (12.0), 45 (17.5), 39 (6.9). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.58; H, 11.32.

***rac*-[(3,7-Dimethylcycloocten-1-yl)oxy]trimethylsilane (12).** Corey's method was employed.[34] To a cold (−78 °C), 25-mL, flame-dried, three-necked flask which contained diisopropylamine (0.14 mL, 1.1 mmol) in dry THF (2 mL) was added *n*-butylithium (1.1 mmol, 0.44 mL of 2.5 M solution in hexane) by syringe. After addition of *n*-butyllithium was complete, the mixture was stirred for 10 min at −78 °C. Freshly distilled TMSCl (0.89 mL, 7.0 mmol) in THF (2 mL) was added dropwise, followed by *cis*-3,7-dimethylcyclooctanone (**10**) (0.154 g, 1.0 mmol) in THF (2 mL). The resulting solution was stirred at −78 °C for 20 min, and while still at −78 °C $Et_3N$ (2 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added. The mixture was allowed to warm to room temperature, and the solvents were removed under reduced pressure. The residue was extracted with ether (3 × 10 mL), and the combined ether extracts were washed with 0.1 M aqueous citric acid (2 × 10 mL) and water (10 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give the crude product which was purified by flash chromatography ($SiO_2$, pentane) to yield 0.20 g (88%) of racemic [(3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane (**12**). GC-MS showed a single peak. IR 1655.0, 1251.9; $^1H$ NMR 0.13 (s, 9H), 0.95 (d, $J$ = 5.0 Hz, 3H), 0.97 (d, $J$ = 4.8 Hz, 3H),

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1.08−1.18 (m, 1H), 1.20−1.40 (m, 2H), 1.52−1.62 (m, 2H), 1.70−1.80 (m, 2H), 1.88−1.98 (m, 1H), 2.2−2.3 (m, 1H), 2.60 (q, $J$ = 14.0 Hz, 4.9 Hz, 1H), 4.45 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR 0.41, 21.63, 23.59, 24.81, 32.08, 33.79, 34.28, 37.18, 39.82, 113.44, 150.06; mass spectrum *m/e* (% relative intensity) 226 ($M^+$, 15), 211 (27), 197 (9), 184 (23), 183 (64), 169 (15), 157 (93), 144 (13), 130 (15), 121 (6), 115 (14), 99 (4), 93 (6), 75 (47), 73 (100), 55 (12), 45 (18), 39 (7).

**8-Hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoic Acid (5a).** Heathcock's method was employed.[29] [((3*S*,7*R*)-3,7-Dimethylcycloocten-1-yl)oxy]trimethylsilane (**12**) (0.800 g, 3.54 mmol) in methanol (20 mL) and $CH_2Cl_2$ (20 mL) was treated with excess $O_3$ at −78 °C until the solution turned blue. After purging with nitrogen, the cold solution was reduced with excess sodium borohydride (1.34 g, 35.4 mmol), allowed to warm to room temperature, and stirred overnight. After the solvent was evaporated on a rotary evaporator, the residue was stirred with HCl (20 mL, 10%) and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated to give the crude product, which was purified by flash chromatography ($SiO_2$, hexane/acetone, 1:1) to yield 0.632 g (95%) of 8-hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoic acid (**5a**): $[\alpha]^{25}_D$ −3.6 (*c* 2.42, $CHCl_3$). IR 3625.9, 2800−3400(br), 1707.6, 1030.2; $^1$H NMR 0.92 (d, $J$ = 6.8 Hz, 3H), 0.97 (d, $J$ = 6.7 Hz, 3H), 1.02−1.48 (m, 7H), 1.62 (m, 1H), 1.96 (m, 1H), 2.16 (q, $J$ = 15.0 Hz, 8.0 Hz, 1H), 2.34 (q, $J$ = 15.0 Hz, 6.1 Hz, 1H), 3.47 (m, 2H), 5.0−6.5 (s,br, 1H); $^{13}$C NMR 16.57, 19.78, 24.21, 30.13, 33.12, 35.65, 36.87, 41.45, 68.25, 178.85; mass spectrum *m/e* (% relative intensity) 159(3), 158(25), 152(1), 139(3), 129(2), 115(8), 111(8), 110(13), 101(8), 97(22), 95(9), 87(100), 83(10), 81(9), 69(51), 55(57), 45(16), 41(44), 31(20), 28(22), 18(19). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.76; H, 10.88.

**Methyl 8-Hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoate (5b).** A mixture of 8-hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoic acid (**5a**) (0.632 g, 3.36 mmol), methanol (50 mL), and *p*-toluenesulfonic acid (20 mg) was refluxed for 24 h. The solvent was evaporated under reduced pressure, and the residue was extracted with ether (3 × 30 mL), washed with saturated aqueous $NaHCO_3$ (40 mL) and brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to yield crude product which was purified by flash chromatography ($SiO_2$, hexane/EtOAc, 6:1) to yield 0.665 g (98%) of methyl 8-hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoate (**5b**) as a colorless oil. GC-MS showed a single peak.

Addition of 6.5 mg of chiral shift reagent tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) ($Eu(hfc)_3$) to 3.7 mg of the racemic hydroxy ester **5b** in 0.7 mL of $CDCl_3$ gave rise to two diastereomeric complexes. The methyl group ($\delta$ 3.67, s, $COOCH_3$) was split into a doublet ($\delta$ 4.16, 4.11) with a 1:1 ratio and base line separation.

When $Eu(hfc)_3$ was similarly added to optically active hydroxy ester **5b**, the methyl group ($\delta$ 3.67, s) was split into a doublet ($\delta$ 4.15, 4.10) with a 99:1 ratio (ee = 98%). $[\alpha]^{25}_D$ −3.91 (*c* 15.0, $CHCl_3$). IR 3640.6, 3638.5, 1740.4, 1028.2; $^1$H NMR 0.93 (t, $J$ = 7.0 Hz, 6H), 1.05−1.45 (m, 7H), 1.55−1.65 (m, 1H), 1.90−2.00 (m, 1H), 2.21 (q, $J$ = 14.7 Hz, 8.1 Hz, 1H), 2.31 (q, $J$ = 14.7 Hz, 6.1 Hz, 1H), 3.38−3.53 (m, 2H), 3.67 (s, 3H); $^{13}$C NMR 16.58, 19.80, 24.25, 30.32, 33.18, 35.71, 36.95, 41.62, 51.40, 68.29, 173.81; mass spectrum *m/e* (% relative intensity) 172 (36), 157 (4), 152 (4), 139 (5), 129 (9), 128 (4), 115 (8), 112 (5), 111 (12), 110 (16), 109 (8), 101 (100), 97 (17), 87 (7), 81 (7), 74 (36), 69 (44), 59 (17), 55 (30), 43 (12), 41 (18). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 64.93; H, 11.23.

**(2*S*,6*R*)-2,6-Dimethyl-1,8-octanediol (5c).** To $LiAlH_4$ (0.100 g, 2.50 mmol) in dry ether (10 mL) was added methyl 8-hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoate (**5b**) (50.0 mg, 0.250 mmol) in dry ether (10 mL) during a period of 7 min. The resulting mixture was stirred for 4 h and then cooled to 0 °C, and a mixture of ether (4 mL) and methanol (4 mL) was added dropwise, followed by HCl (10 mL, 1 M). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic phases were washed with saturated $NaHCO_3$ and brine and dried. The solvent was evaporated under reduced pressure to crude product which was purified by flash chromatography ($SiO_2$, hexane/EtOAc, 2:1) to yield 42.6 mg (98%) of diol **5c** as a colorless oil. GC-MS showed a single peak. $[\alpha]^{25}_D$ −7.0 (*c* 2.1, $CHCl_3$); lit.[15b] $[\alpha]^{25}_D$ −6.3 (*c* 9.5, $CHCl_3$). IR 3639.0, 3628.3, 1028.7; $^1$H NMR 0.91 (t, $J$ = 7.0 Hz, 6H), 1.04−1.48 (m, 9H), 1.55−1.70 (m, 3H), 3.42 (q, $J$ = 10.5 Hz, 5.9 Hz, 1H), 3.51 (q, $J$ = 10.4 Hz, 6.5 Hz, 1H), 3.65−3.75 (m, 2H); $^{13}$C NMR 16.62, 19.68, 24.25, 29.45, 33.35, 35.76, 37.38, 39.89, 61.21, 68.33; mass spectrum *m/e* (% relative intensity) 144 (0.1), 137 (0.3), 126 (5), 123 (7),112 (2), 109 (15), 99 (7), 97 (7), 81 (46), 70 (38), 69 (82), 56 (36), 55 (100), 43 (39), 41 (73), 39 (18), 31 (56). Anal. Calcd for $C_{10}H_{22}O_2$: C, 68.92; H, 12.72. Found: C, 68.63, H; 12.40.

***rac*-Methyl 8-Hydroxy-3,7-dimethyloctanoate (5b).** Racemic [(3,7-dimethylcycloocten-1-yl)oxy]trimethylsilane (**12**) (0.200 g, 0.880 mmol) in methanol (5 mL) and $CH_2Cl_2$ (5 mL) was ozonized as above[29] (the ozonide was reduced with 0.400 g of sodium borohydride, 10.6 mmol). Workup gave crude racemic 8-hydroxyl-3,7-dimethyloctanoic acid. Without further purification, this acid was dissolved in methanol (15 mL), and *p*-toluenesulfonic acid (8 mg) was added. The resulting solution was heated to reflux for 15 h. The solvent was evaporated under reduced pressure, and the residue was extracted into ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (40 mL) and brine and dried. The solvent was evaporated under reduced pressure to crude product which was purified by flash chromatography ($SiO_2$, hexane/EtOAc, 6:1) to yield 0.16 g (90%) of **5b**. IR 3640.0, 1739.9, 1197.0, 1166.9, 1028.9; $^1$H NMR 0.93 (t, $J$ = 7.0 Hz, 6H), 1.05−1.45 (m, 7H), 1.55−1.65 (m, 1H), 1.90−2.00 (m, 1H), 2.21 (q, $J$ = 14.7 Hz, 8.1 Hz, 1H), 2.31 (q, $J$ = 14.7 Hz, 6.1 Hz, 1H), 3.38−3.53 (m, 2H), 3.67 (s, 3H); $^{13}$C NMR 16.58, 19.80, 24.25, 30.32, 33.18, 35.71, 36.95, 41.62, 51.40, 68.29, 173.8; mass spectrum *m/e* (% relative intensity) 172 (36), 157 (4), 152 (4), 139 (5), 129 (9), 128 (4), 115 (8), 112 (5), 111 (12), 110 (16), 109 (8), 101 (100), 97 (17), 87 (7), 81 (7), 74 (36), 69 (44), 59 (17), 55 (30), 43 (12), 41 (18).

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