Enzymatic Desymmetrization of *meso*-2,6-Dimethyl-1,7-heptanediol. Enantioselective Formal Synthesis of the Vitamin E Side Chain and the Insect Pheromone Tribolure

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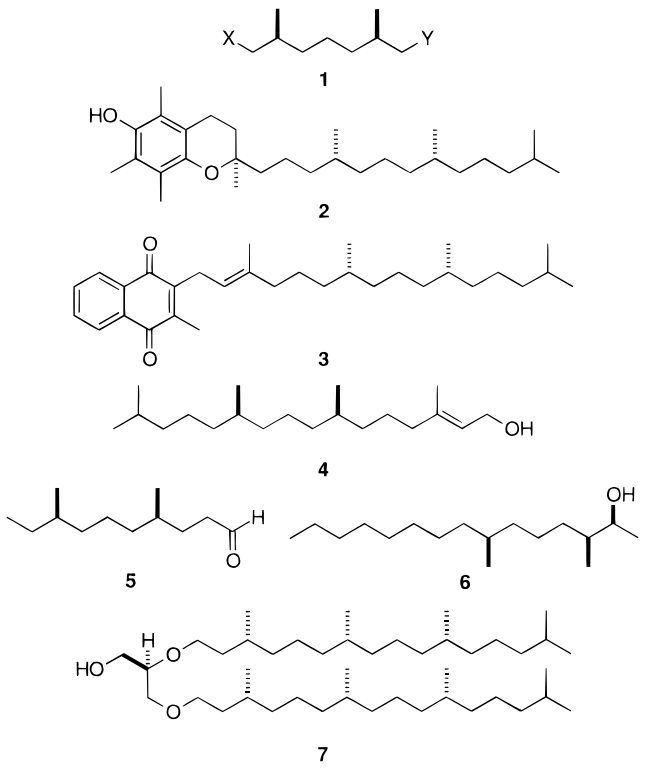
The chiral *syn*-1,5-dimethylalkyl subunit is found in many natural products with significant biological activities. Enzymatic esterification of *meso*-2,6-dimethyl-1,7-heptanediol with isopropenyl acetate in the presence of *Pseudomonas cepacia* lipase in organic medium provided the chiral nonracemic monoester in high enantiomeric excess (ee = 95%). This chiral building block was used in the formal syntheses of vitamin E side chain and the insect pheromone tribolure.

Introduction

The chiral *syn*-1,5-dimethylalkyl subunit **1** is found in many natural products such as vitamin E[1] (**2**), vitamin K[2] (**3**), phytol[3] (**4**) (the side chain of chlorophyll), and phytene-1,2-diol[4] (a novel diterpene from *Artemisia annua*) (Chart 1). This structural element is also found in several insect pheromones[5] such as **5** and **6**, in some marine natural products,[6] and in membrane lipids (e.g., **7**) of archaebacteria,[7] a type of microorganisms living under extreme conditions such as high temperature, high salt concentration, low pH, or absence of oxygen. We report here the enzymatic desymmetrization of *meso*-2,6-dimethyl-1,7-heptanediol and the use of the corresponding enantiomerically enriched monoester in the synthesis of vitamin E side chain and the insect pheromone tribolure.

Chart 1



Results and Discussion

meso-2,6-Dimethyl-1,7-heptanediol (**9**) was prepared by hydroboration of 2,6-dimethylhepta-1,6-diene (**8**) with thexyl borane according to the method reported by Still *et al.*[8] This reaction proceeds by formation of a borocycle and gives the meso diol **9** with high 1,5-asymmetric induction (meso:racemic ~15:1).[8] However, the separation of the minor racemic fraction cannot be achieved by standard chromatography.

Initial experiments concerned screening hydrolases (lipases, esterases, proteases) as catalysts in order to determine which enzyme gives the best enantioselectivity for the acylation of **9** or the hydrolysis of the corresponding diacetate. Of the enzymes and conditions studied, the esterification of **9** with isopropenyl acetate (IPA) in the presence of *Pseudomonas cepacia* lipase (PCL) in THF gave the best result and provided the chiral nonracemic monoester **10** (Scheme 1). The enzymatic reaction was performed on the meso/racemic (15:1) mixture. This highly enantioselective lipase-catalyzed reaction can separate all three stereoisomers in a mixture of meso and racemic isomers.[9] PCL favored the *S* stereocenter (vide infra), so the meso (*R*,*S*)-isomer was monoacetylated, the (*S*,*S*)-enantiomer was diacetylated, and the (*R*,*R*)-enantiomer did not react. The monoacetate **10**, the major product, was easily separated from minor contaminants by standard flash chromatography.

This compound was derivatized with several common chiral agents (Mosher's ester, amino acid derivatives), but

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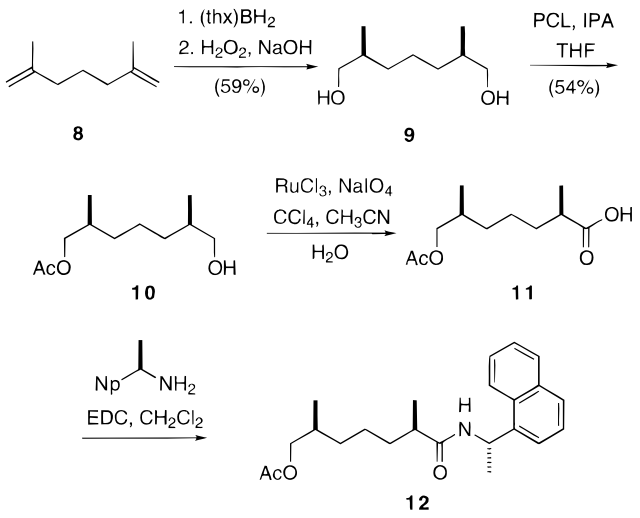
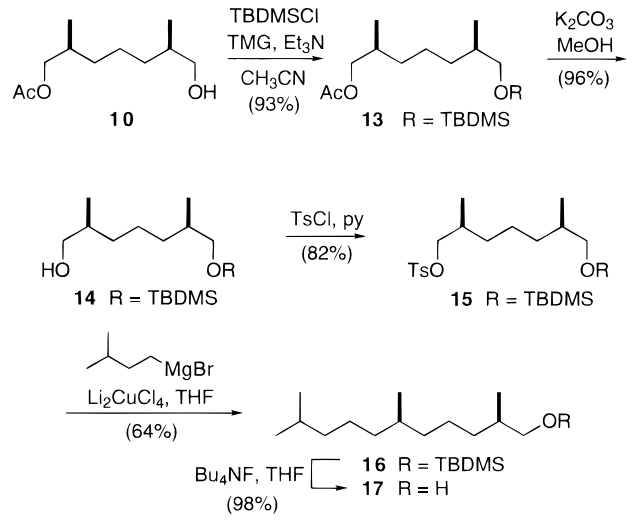
Scheme 1



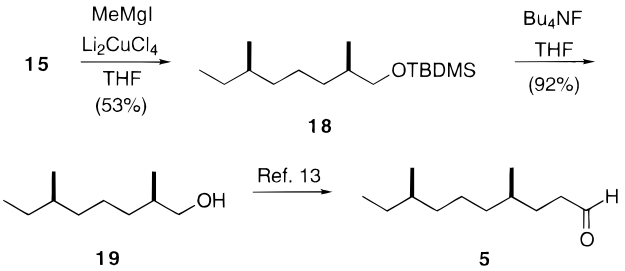
Scheme 2



subsequent NMR or chromatographic analyses failed to give distinct signals for diastereomeric products. As an alternative, alcohol **10** was oxidized to the carboxylic acid **11** by ruthenium tetraoxide−periodate in a CCl_4/H_2O/acetonitrile solvent system,[10] and the latter was derivatized to the amides with (*S*)-(−)-naphthylethylamine. NMR (300 MHz) and HPLC analyses of this derivative (**12**) showed an ee = 95%.

Conversion of enantiomerically pure **10** to vitamin E side chain was accomplished by the sequence illustrated in Scheme 2. Monoalcohol **10** was converted into the corresponding *tert*-butyldimethylsilyl ether **13** in high yield by reaction with TBDMSCl in the presence of tetramethylguanidine (TMG) in acetonitrile. Methanolysis of **13** in the presence of K_2CO_3 provided alcohol **14**. Treatment of **14** with *p*-toluenesulfonyl chloride in pyridine led to tosylate **15**. Condensation of tosylate **15** with excess isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate as catalyst in THF produced **16**. Desilylation of **16** with *n*-Bu_4NF in THF resulted in the formation of (2*R*,6*R*)-2,6,10-trimethyl-1-undecanol (**17**), the vitamin E side chain.[11,12] Since the optical rotation and the absolute configuration of **17** are known, the configuration of **10** obtained by enzymatic

Scheme 3



hydrolysis can be correlated with **17** (Scheme 2). This correlation proved that compound **10** has the 2*R*,6*S* configuration and PCL selectively acetylated the *S* stereocenter.

Tosylate **15** was also coupled with methylmagnesium iodide in the presence of dilithium tetrachlorocuprate to give **18** (Scheme 3). Desilylation of **18** provided alcohol **19**. This sequence constitutes a formal synthesis of tribolure **5** since the transformation of **19** into tribolure has been reported.[13] Tribolure, (4*R*,8*R*)-4,8-dimethyldecanal, is the male-produced aggregation pheromone of flour beetles *Tribolium confusum* and *T. castaneum*.[14]

Conclusion

Enzymatic enantiogroup differentiation in meso compounds (also called asymmetrization or desymmetrization) provides enantiomerically pure compounds with multiple stereogenic centers. The enzymatic desymmetrization of *meso*-2,6-dimethyl-1,7-heptanediol provides a versatile chiral building block. Further studies, including the asymmetric synthesis of natural products using **10** as starting material, are in progress in our laboratory.

Experimental Section

Pseudomonas cepacia lipase (formerly called *P. fluorescens*) was purchased from Amano (lipase PS30). Melting points are

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uncorrected. NMR spectra were recorded at 300 MHz (^{1}H), 75.44 MHz (^{13}C), and 282.23 MHz (^{19}F).

Enzymatic Esterification of *meso*-2,6-Dimethyl-1,7-heptanediol (9). Preparation of (2*R*,6*S*)-7-Acetoxy-2,6-dimethyl-1-heptanol (10). To a solution of diol **9** (0.663 g, 4.14 mmol) and isopropenyl acetate (1.2 mL, 10.9 mmol) in anhydrous THF was added *P. cepacia* lipase (300 mg). The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC (53 h). The enzyme was filtered and washed with THF, and the solvent was concentrated in vacuo. Flash chromatography (ether−petroleum ether, 55:45) afforded monoester **10** (451 mg, 54%) along with diacetate (326 mg, 32%) and diol (31 mg, 5%): $[\alpha]_D^{25}$ +8.8 (*c* 1.47, $CHCl_3$); IR (neat) 3100−3650, 2820−2980, 1735, 1460, 1240, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.89 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.02−1.46 (m, 6H), 1.56 (s, 1H), 1.58 (m, 1H), 1.76 (m, 1H), 2.03 (s, 3H), 3.39 (dd, J_1 = 6.4 Hz, J_2 = 10.5 Hz, 1H), 3.49 (dd, J_1 = 5.9 Hz, J_2 = 10.5 Hz, 1H), 3.82 (dd, J_1 = 6.9 Hz, J_2 = 10.6 Hz, 1H), 3.98 (dd, J_1 = 5.9 Hz, J_2 = 10.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 16.42, 16.73, 20.76, 23.99, 32.32, 33.15, 33.47, 35.52, 68.00, 69.23, 171.16. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.57; H, 10.71.

Determination of the Enantiomeric Composition of (2*R*,6*S*)-7-Acetoxy-2,6-dimethyl-1-heptanol (10). Alcohol **10** (20 mg, 0.10 mmol) was dissolved into a mixture of acetonitrile (0.2 mL), CCl_4 (0.2 mL) and water (0.3 mL). $RuCl_3$ (1 mg, 0.005 mmol) and $NaIO_4$ (90 mg, 0.42 mmol) were successively added. The mixture was stirred for 3 h at room temperature. The mixture was poured into ether, and the acid was extracted with saturated aqueous $NaHCO_3$. The aqueous phase was acidified to pH 2, and the acid was taken with ether. This organic phase was dried ($MgSO_4$) and concentrated in vacuo. The yield of **11** was quantitative; ^{1}H NMR ($CDCl_3$) 0.90 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H) 1.1−1.8 (m, 7H), 2.04 (s, 3H), 2.44 (m, 1H), 3.88 (m, 2H); ^{13}C NMR ($CDCl_3$) 16.72, 16.89, 20.91, 24.38, 32.33, 33.61, 39.26, 69.39, 171.31, 182.72.

Acid **11** (20 mg, 0.09 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (22 mg, 0.11 mmol), and DMAP (2 mg, 0.02 mmol) were dissolved into CH_2Cl_2 (2 mL). (*S*)-(-)-1-(1-Naphthyl)ethylamine (19 mg, 0.11 mmol) was added, and the solution was stirred at room temperature for 16 h. The solution was poured into ether, and the organic phase was washed with aqueous 1 M HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The diastereomeric ratio of **12** was determined by proton NMR spectroscopy (0.74 and 0.87 ppm, two doublets, CH_3) and by HPLC (column Supelcosil LC-SI; eluant ether/hexane, 35/65, 1.2 mL/min; detection UV at 225 nm; retention times 7.2 and 9.0 min).

(2*S*,6*R*)-1-Acetoxy-7-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethylheptane (13). To a solution of alcohol **10** (432 mg, 2.13 mmol), triethylamine (0.36 mL, 2.6 mmol), and tetramethylguanidine (53 μL, 0.44 mmol) in anhydrous acetonitrile (3.2 mL) was added TBDMSCl (360 mg, 2.4 mmol). The solution was stirred at room temperature under a dry N_2 atmosphere for 1 h. The solution was poured into ether (150 mL), and the organic layer was washed with aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (ether−petroleum ether, 3:97) provided **13** (626 mg, 93%): $[\alpha]_D^{25}$ +1.5 (*c* 1.06, $CHCl_3$); IR (neat) 2950, 2920, 2850, 1740, 1460, 1240, 1090, 830, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.01 (s, 6H), 0.84 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.90 (d, J = 6.5 Hz, 3H), 1.00−1.42 (m, 6H), 1.55 (m, 1H), 1.75 (m, 1H), 2.02 (s, 3H), 3.34 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 3.41 (dd, J_1 = 9.6 Hz, J_2 = 5.9 Hz, 1H), 3.82 (dd, J_1 = 10.6 Hz, J_2 = 6.9 Hz, 1H), 3.93 (dd, J_1 = 10.6 Hz, J_2 = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) −5.54, 16.59, 16.73, 18.17, 20.74, 24.03, 25.78, 32.34, 33.19, 33.54, 35.53, 68.12, 69.26, 170.99. Anal. Calcd for $C_{17}H_{36}OSi$: C, 64.50; H, 11.46. Found: C, 64.67; H, 11.23.

(2*S*,6*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1-heptanol (14). A suspension of acetate **13** (625 mg, 1.97 mmol) and K_2CO_3 (1.090 g, 7.89 mmol) in MeOH (10 mL) was stirred at room temperature for 1 h. The mixture was treated with water and extracted with ether. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (ether−petroleum ether, 3:7) afforded alcohol **14** (521 mg, 96%): $[\alpha]_D^{25}$ −3.6 (*c* 1.13, $CHCl_3$); lit.[11g] $[\alpha]_D^{30}$ −3.65 (*c* 3.45, $CHCl_3$); IR (neat) 3100−3550, 2950, 2920, 2850, 1460, 1250, 1090, 830, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.03 (s, 6H), 0.86 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.91 (d, J = 6.9 Hz, 3H), 1.01−1.43 (m, 6H), 1.59 (m, 2H), 3.32−3.54 (m, 4H); ^{13}C NMR ($CDCl_3$) −5.35, 16.61, 16.79, 18.38, 24.36, 25.96, 33.50, 35.76, 68.38.

(2*S*,6*R*)-1-(Tosyloxy)-7-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethylheptane (15). Alcohol **14** (518 mg, 1.88 mmol), *p*-toluenesulfonyl chloride (532 mg, 2.79 mmol), and DMAP (61 mg) were dissolved in dry pyridine (20 mL). The solution was stirred at room temperature under a dry atmosphere for 48 h. The solution was poured into ether, and the organic layer was washed with aqueous 1 N HCl, saturated $NaHCO_3$, and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (ether−petroleum ether, 5:95) provided **15** as an oil (661 mg, 82%): $[\alpha]_D$ +3.8 (*c* 1.19, $CHCl_3$); lit.[11g] $[\alpha]_D^{25}$ +3.84 (*c* 3.31, $CHCl_3$); IR (neat) 2950, 2920, 2840, 1590, 1460, 1360, 1185, 1170, 1090, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.02 (s, 6H), 0.81 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.94−1.30 (m, 6H), 1.50 (m, 1H), 1.76 (m, 1H), 2.44 (s, 3H), 3.32 (dd, J_1 = 6.4 Hz, J_2 = 9.7 Hz, 1H), 3.39 (dd, J_1 = 6.0 Hz, J_2 = 9.7 Hz, 1H), 3.79 (dd, J_1 = 6.6 Hz, J_2 = 9.2 Hz, 1H), 3.87 (dd, J_1 = 5.9 Hz, J_2 = 9.2 Hz, 1H), 7.33 (m, 2H), 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) −5.51, 16.32, 16.54, 18.19, 21.46, 23.82, 25.81, 32.64, 32.86, 33.05, 35.49, 68.11, 74.95, 127.75, 129.63, 133.14, 144.43.

(2*R*,6*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,6,10-trimethylundecane (16). To a solution of tosylate **15** (192 mg, 0.45 mmol) in anhydrous THF (0.7 mL) at −78 °C under a dry atmosphere were added dropwise a solution of isoamylmagnesium bromide (0.6 M in THF, 1.6 mL) and then a solution of Li_2CuCl_4 (0.1 M in THF, 32 μL). The mixture was stirred at −78 °C for 20 min and at room temperature for 24 h. The mixture was poured into an aqueous saturated NH_4Cl solution. The aqueous phase was extracted several times with petroleum ether, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (petroleum ether) provided **16** as an oil (94 mg, 64%) and the starting material (49 mg, 25%). **16**: $[\alpha]_D^{25}$ +2.0 (*c* 1.24, $CHCl_3$); lit.[11g] $[\alpha]_D^{26}$ +2.13 (*c* 2.76, $CHCl_3$); IR (neat) 2950, 2920, 2850, 1460, 1250, 1090, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.04 (s, 6H), 0.83−0.89 (m, 12H), 0.89 (s, 9H), 1.00−1.60 (m, 15H), 3.34 (dd, J_1 = 6.6 Hz, J_2 = 9.8 Hz, 1H), 3.45 (dd, J_1 = 5.8 Hz, J_2 = 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) −5.50, 16.67, 18.21, 19.59, 22.47, 22.56, 24.28, 24.64, 25.82, 27.84, 32.60, 33.40, 35.65, 37.14, 37.29, 39.24, 68.28.

(2*R*,6*R*)-2,6,10-Trimethyl-1-undecanol (17). A solution of compound **16** (89 mg, 0.27 mmol) and *tetra*-*n*-butylammonium fluoride (114 mg, 0.55 mmol) in THF (3 mL) was stirred at room temperature for 24 h. Ether was added (100 mL), and the organic phase was washed with brine. The aqueous layer was extracted with petroleum ether. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (ether−petroleum ether, 1:4) yielded **17**[11] (57 mg, 98%): $[\alpha]_D^{25}$ +7.9 (*c* 1.15, hexane; lit.[11k] $[\alpha]_D^{25}$ +7.67 (*c* 1.02, hexane); lit.[11g] $[\alpha]_D^{25}$ +8.6 (*c* 2.07, hexane); IR (neat) 3060−3580, 2950, 2920, 2860, 1410, 1375, 1360, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.80−0.84 (m, 9H), 0.88 (d, J = 6.6 Hz, 3H), 1.01−1.51 (m, 14H), 1.57 (m, 1H), 3.38 (dd, J_1 = 6.6 Hz, J_2 = 10.4 Hz, 1H), 3.47 (dd, J_1 = 5.7 Hz, J_2 = 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 16.49, 19.57, 22.46, 22.55, 24.27, 24.63, 27.82, 32.61, 33.36, 35.67, 37.12, 37.23, 39.22, 68.23.

(2*R*,6*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyloctane (18). To a solution of tosylate **15** (222 mg, 0.52 mmol) in anhydrous THF (2.0 mL) at −78 °C under a dry atmosphere was added dropwise a solution of methylmagnesium iodide in ether (0.40 mL, 3.0 M) and then a solution of Li_2CuCl_4 (0.1 M in THF, 37 μL). The mixture was stirred at −78 °C for 30 min and at room temperature for 20 h. The mixture was poured into an aqueous saturated NH_4Cl solution. The aqueous phase was extracted several times with pentane, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (petroleum ether) provided **18** as an oil (75 mg, 53%): $[\alpha]_D^{25}$ −2.1 (*c* 1.52, $CHCl_3$); IR (neat)

2950, 2920, 2850, 1455, 1250, 1090, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) 0.04 (s, 6H), 0.84−0.88 (m, 9H), 0.90 (s, 9H), 0.98−1.40 (m, 9H), 1.57 (m, 1H), 3.35 (dd, $J_1 = 6.6$ Hz, $J_2 = 9.6$ Hz, 1H), 3.45 (dd, $J_1 = 5.8$ Hz, $J_2 = 9.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) −5.51, 11.22, 16.66, 18.20, 19.09, 24.58, 25.81, 29.31, 33.40, 34.25, 35.65, 36.82, 68.27. Anal. Calcd for $C_{16}H_{36}OSi$: C, 70.51; H, 13.31. Found: C, 70.24; H, 13.67.

(2*R*,6*R*)-2,6-Dimethyl-1-octanol (19). A solution of compound **18** (69 mg, 0.25 mmol), and tetra-*n*-butylammonium fluoride (137 mg, 0.52 mmol) in THF (1.0 mL) was stirred at room temperature for 20 h. The solution was diluted with pentane−ether (4/1, 100 mL) and washed with brine. The aqueous layer was extracted with pentane−ether and the organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (ether−petroleum ether, 1/3) afforded **19** as an oil (37 mg, 92%): $[\alpha]_D^{25}$ +6.0 (*c* 1.15, $CHCl_3$); lit.[13] $[\alpha]_D^{25}$ +6.9 (*c* 5.0, $CHCl_3$); IR (neat) 3100−3500, 2950, 2920, 2860, 1460, 1370, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) 0.84−0.93 (m, 9H), 1.03−1.40 (m, 9H), 1.62 (m, 1H), 3.41 (dd, $J_1 = 6.6$ Hz, $J_2 = 10.4$ Hz, 1H), 3.51 (dd, $J_1 = 5.8$ Hz, $J_2 = 10.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) 11.21, 16.48, 19.08, 24.28, 29.28, 33.35, 34.23, 35.66, 36.75, 68.24.

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