Pheromone Synthesis, CXCVIII[+]

Synthesis of (1*S*,2*S*,6*S*,10*R*)- and (1*S*,2*R*,6*R*,10*R*)-1,2,6,10-Tetramethyldodecyl Propanoate, the Components of the Sex Pheromone of the Pine Sawfly, *Microdiprion pallipes*

Yoshihide Nakamura[a,b] and Kenji Mori*[a]

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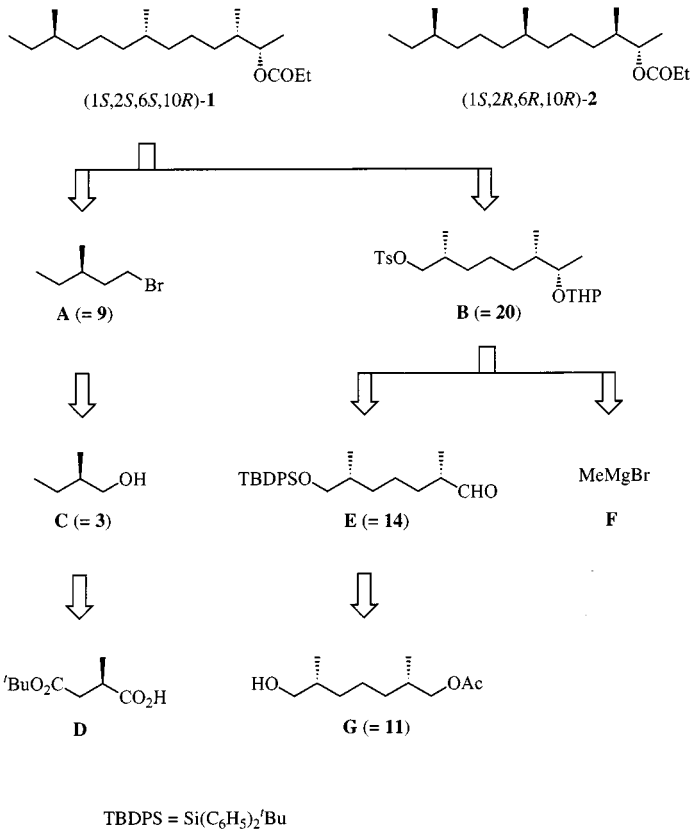
(1*S*,2*S*,6*S*,10*R*)- and (1*S*,2*R*,6*R*,10*R*)-1,2,6,10-tetramethyldodecyl propanoate (**1** and **2**), the components of the pheromone of *Microdiprion pallipes*, were synthesized from two chiral and nonracemic building blocks, (*R*)-3-*tert*-butoxycarbonyl-2-methylpropanoic acid (**D**) and (2*R*,6*S*)-7-acetoxy-2,6-dimethyl-1-heptanol (**G**), by employing lipase-catalyzed kinetic resolution in a later step.

Pine sawflies, which are classified into more than 120 species, are serious pests on pines in the northern part of the world.[1] The minor pine sawfly, *Microdiprion pallipes*, occurs in Northern Europe and Asia. In 1998 its female-produced sex pheromone was identified as 1,2,6,10-tetramethyldodecyl propanoate by Bergström et al.[2] Synthesis and field experiments of its stereoisomers by Larsson et al. revealed that (1*S*,2*S*,6*S*,10*R*)-**1** and (1*S*,2*R*,6*R*,10*R*)-**2** catch male *M. pallipes*.[3]

There are numerous reports on the synthesis of pine sawfly pheromones including our own enantioselective synthesis in 1979.[4] The recorded syntheses of pine sawfly pheromones were previously reviewed twice.[5][6] Even after 1990, the activity in this area of synthesis still continues, reflecting the ecological importance of clarifying the chemical communication system of the pine sawflies.[1,7–10] We report herein the synthesis of **1** and **2** based on the use of enzymatic systems in enantioselective transformations.[11]

Scheme 1 shows the retrosynthetic analysis of (1*S*,2*S*,6*S*,10*R*)-**1**. The target molecule **1** can be dissected between C-7 and C-8 to give the building blocks **A** and **B**. The bromide **A** can be prepared from the known compound **C**,[12] which can be derived from **D**. The half ester **D** is an industrial building block manufactured biochemically by Mitsubishi Rayon Co.[13] Another building block **B** is obtainable from **E** and **F**, the former of which can be derived from the known monoacetate **G**.[14] Synthesis of **2** is also possible by starting from the same building blocks **D**, **G** and **F**.



Scheme 1. Structures of the components **1** and **2** of the sex pheromone of *Microdiprion pallipes* and the retrosynthetic analysis of **1**

Preparation of the building block **A** (= **9**) was executed in a conventional manner as summarized in Scheme 2. Treatment of (*R*)-2-methyl-1-butanol (**3**) with tosyl chloride in pyridine yielded the tosylate **4**, whose tosyloxy group was displaced by a cyanide anion to furnish the nitrile **5**. Acid hydrolysis of **5** gave the acid **6**, which was reduced with lithium aluminum hydride to afford the alcohol **7**. The alcohol was then converted into the corresponding bromide **9** via the tosylate **8**. The overall yield of **9** was 60% based on **3** (6 steps).

Scheme 3 shows the synthesis of the pheromone component **1** starting from the key building block (2*R*,6*S*)-7-acetoxy-2,6-dimethyl-1-heptanol **11** (= **G**). At the time the syn-

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[a] Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1–3, Shinjuku-ku, Tokyo 162–8601, Japan
Fax: (internat.) +81–3/3235–2214
[b] Research fellow on leave from Fuji Chemical Industries, Ltd. (1998–2000).

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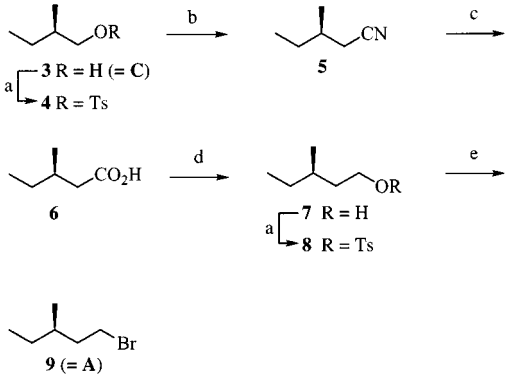
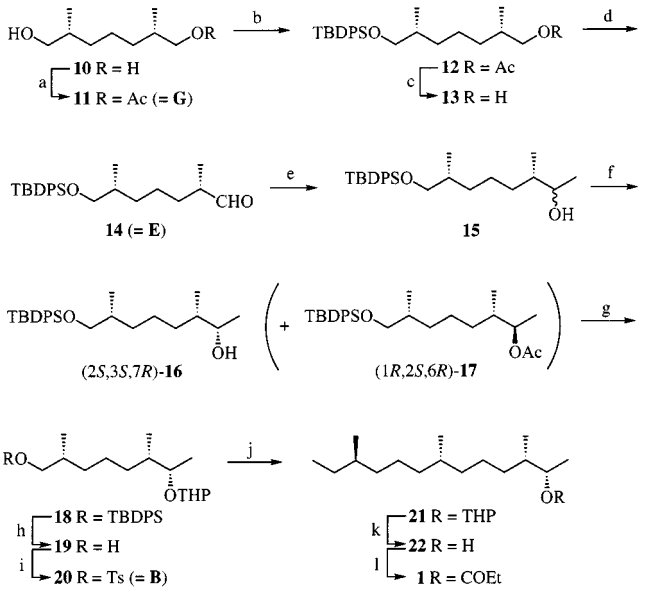


Scheme 2. Synthesis of the building block **A** (= **9**); reagents: (a) *p*-TsCl, C_5H_5N (99%); (b) NaCN, DMSO (83%); (c) H_2SO_4, H_2O (96%); (d) $LiAlH_4$, Et_2O (93%); (e)LiBr, DMF (82%).

thesis of this building block **11** was reported by Chênevert and Desjardins,[14] we were independently working on the preparation of (2*R*,6*S*)-2,6-dimethylheptanedioic acid by using an enzymatic reaction. Our results, however, were less satisfactory than the reported synthesis,[15][16] and we therefore followed the Canadian method[14] to obtain **11**.



Scheme 3. Synthesis of the pheromone component **1**; reagents: (a) Lipase PS, CH_2=C(Me)OAc, THF (57%); (b) TBDPSCl, imidazole, DMF (96%); (c) K_2CO_3, MeOH (99%); (d) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2 (95%); (e) MeMgBr, THF (88%); (f) Lipase PS, CH_2=CHOAc; then MPLC purification (48%); (g) DHP, *p*-TsOH, Et_2O (90%); (h) Bu_4NF, THF (96%); (i) *p*-TsCl, C_5H_5N (quant.); (j) (*R*)-3-methylpentylmagnesium bromide, Li_2CuCl_4, THF (85%); (k) *p*-TsOH, MeOH (93%); (l) EtCOCl, Et_3N, CH_2Cl_2 (82%)

The *meso* diol **10** was prepared by the known method first developed by Still and Darst.[14,17,18] The diol **10** could be obtained as a 14:1 mixture of *meso* **10** and its (±)-isomer. Attempts to further improve this diastereomeric ratio by recrystallization of the corresponding bis-*p*-nitrobenzoate or bis-3,5-dinitrobenzoate were unsuccessful. Asymmetric acetylation of **10** with excess isopropenyl acetate in the presence of immobilized lipase PS gave (*S*)-acetate **11** (= **G**) in 57% yield with 95% *de* (as determined by its ^{13}C NMR spectrum), $[\alpha]_D^{24}$ = +8.83 ($CHCl_3$) {ref.[14] $[\alpha]_D^{25}$ = +8.8 ($CHCl_3$)}. Its enantiomeric purity was estimated to be 95% *ee* as determined by the reported method.[14] The free hydroxy group of **11** was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether to give **12**, which was treated with potassium carbonate in methanol to remove the acetyl group, to yield **13**. Dess−Martin oxidation[19] of **13** gave the aldehyde **14** (= **E**).

Methylation of **14** was first attempted with dimethylzinc in the presence of chiral catalysts to effect asymmetric synthesis of **16**. However, the negative results of that attempt forced us to employ the conventional Grignard reagent, methylmagnasium bromide **F**. The addition took place in accordance with Cram's rule to give, in 88% yield, a mixture of (2*S*,3*S*,7*R*)-**16** (*syn*-product) and its (2*R*)-isomer (*anti*-product) in a ratio of 2:1. The assignment of the *syn* stereochemistry **16** to the major product was based on a comparison of the ^1H NMR spectra of these two products.[20] The major product showed a three-proton signal in its ^1H NMR spectrum due to C*H*$_3$CH(OH) at δ = 1.14 (d, *J* = 6.4 Hz) and a one-proton signal due to C*H*(OH) at δ = 3.69 (dq, *J* = 3.9, 6.4 Hz), while the minor one showed the corresponding signals at δ = 1.11 (d, *J* = 6.1 Hz), and δ = 3.64 (dq, *J* = 5.8, 6.1 Hz). A similar *syn* alcohol showed signals at δ = 1.16 (d, *J* = 7 Hz) and at δ = 3.70 (dq, *J* = 4, 7 Hz), while the *anti* one exhibited the signals at δ = 1.12 (d, *J* = 7 Hz) and at δ = 3.66 (dq, *J* = 5, 7 Hz).[20]

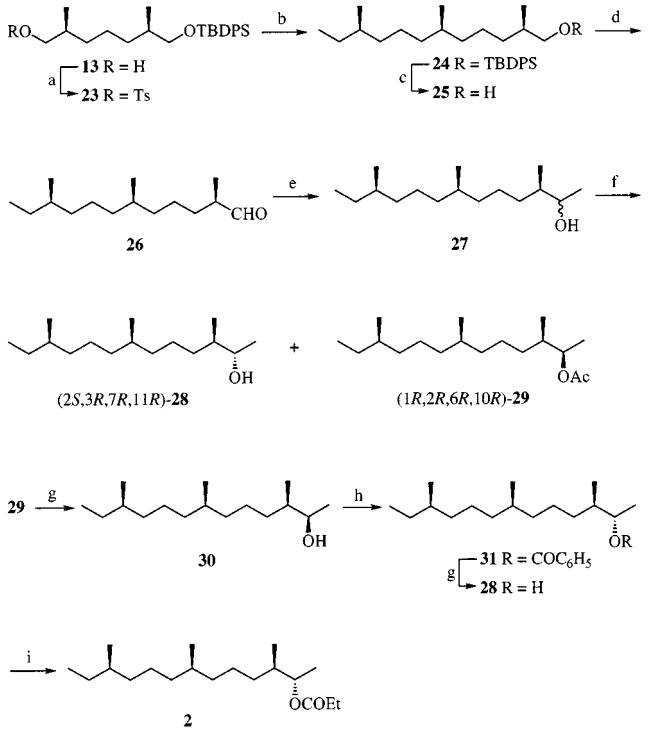
This mixture **15** was acetylated with vinyl acetate in the presence of lipase PS to give the acetate (1*R*,2*S*,6*R*)-**17** of the *anti* product (37%) leaving the *syn* alcohol (2*S*,3*S*,7*R*)-**16** intact in 48% yield. The present result with selective acetylation of the (2*R*) isomer of **15** is in agreement with the result reported by Lundh et al. in the case of the similar alcohol.[10] Because the diastereomeric purity of (2*S*,3*S*,7*R*)-**16** was approximately 93% *de*, the alcohol **16** was further purified by MPLC to give a purer **16** with 97% *de*. The diastereomeric purity of the acetate (1*R*,2*S*,6*R*)-**17** was about 70% *de* as determined by an HPLC analysis of the corresponding alcohol.

Protection of the free hydroxy group at C-2 of **16** as the tetrahydropyranyl (THP) ether gave **18**, whose TBDPS group was subsequently removed to give **19**. The corresponding tosylate **20** was treated with (*R*)-3-methylpentylmagnesium bromide in the presence of dilithium tetrachlorocuprate[21] to give the coupling product **21** in 85% yield. Removal of its THP protective group gave (2*S*,3*S*,7*S*,11*R*)-3,7,11-trimethyl-2-tridecanol **22**, which was acylated with propanoyl chloride to give the final product (1*S*,2*S*,6*S*,10*R*)-**1**, $[\alpha]_D^{23}$ = −12.7 (hexane), in 12% overall yield (12 steps) based on *meso* diol **10**. The ester **1** was 99% chemically pure according to GC analysis, and the stereochemical purities at each stereogenic center was >99% *ee* at C-10, = 95% *ee* at C-6 and C-2 with 95% *de* between them and with 97% *de* between C-1 and C-2. Our sample of **1** thus contains at least 93% of (1*S*,2*S*,6*S*,10*R*)-**1**.

The synthesis of the pheromone component **2** is summarized in Scheme 4. The TBDPS-monoprotected diol **13** was

tosylated, and the resulting tosylate **23** was coupled with (*R*)-3-methylpentylmagnesium bromide under the Schlosser conditions[21] to give **24**. Removal of the TBDPS protective group of **24** was followed by Dess−Martin oxidation[19] of the resulting alcohol **25** to give the aldehyde **26**. Addition of methylmagnesium bromide to **26** furnished **27** as a diastereomeric mixture (*syn*/*anti* = 2.3:1.0). Enzymatic acetylation of **27** with vinyl acetate and lipase PS gave (2*S*,3*R*,7*R*,11*R*)-3,7,11-trimethyl-2-tridecanol (**28**, *syn*-product) in 31% yield. This was further purified by MPLC to give a purer material with 96% *de*. The acetate **29** (*anti* acetate), obtained in 66% yield, was hydrolyzed to **30**, which was subjected to the Mitsunobu inversion[22] to give **31**, affording a further amount of the desired **28** (96% *de*) after hydrolysis. The alcohol **28** was esterified with propanoyl chloride to give the desired product (1*S*,2*R*,6*R*,10*R*)-**2**, $[\alpha]_D^{23}$ = +1.23 (hexane), in 24% overall yield (12 steps) based on *meso* diol **10**. Its chemical purity was 99%, and the stereochemical purities at each stereogenic centers were >99% *ee* at C-10, = 95% e.e. at both C-6 and C-2 with 95% *de* between them, and 96% *de* between C-1 and C-2. Accordingly, our sample of **2** contains at least 92% of (1*S*,2*R*,6*R*,10*R*)-**2**.

In conclusion we synthesized both components **1** and **2** of the female-produced sex pheromone of *Microdiprion pallipes* by using enzymatic asymmetric processes.



Scheme 4. Synthesis of the pheromone component **2**; reagents: (a) *p*-TsCl, C_5H_5N (99%); (b) (*R*)-3-methylpentylmagnesium bromide, Li_2CuCl_4, THF (84%); (c) Bu_4NF, THF (99%); (d) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2 (95%); (e) MeMgBr, THF (83%); (f) Lipase PS, CH_2=CHOAc (31% of **28** and 66% of **29**); (g) K_2CO_3, MeOH (92% for **30**; 96% for **28**); (h) $(C_6H_5)_3P$, $C_6H_5CO_2H$, EtO_2CN=NCO_2Et, THF (85%); (i) EtCOCl, Et_3N, CH_2Cl_2 (95%)

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Experimental Section

General: IR: Jasco A-102 and Perkin−Elmer 1640. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA400 (400 MHz) and Jeol JNM-LA500 (500 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). − ^{13}C NMR: Jeol JNM−LA400 (100 MHz) and Jeol JNM-LA500 (126 MHz) (TMS at δ = 0.00 as an internal standard). − Optical rotation: Jasco DIP-1000. − MS: Jeol JMS-SX102A. − Column chromatography: Merck Kieselgel 60 Art 1.07734.

(*R*)-2-Methylbutyl Tosylate (4): To a solution of **3** (4.75 g, 53.9 mmol) in dry pyridine (30 mL) was added *p*-toluenesulfonyl chloride (13.4 g, 70.0 mmol) at 0°C. After stirring at 0°C for 18 h, the mixture was poured onto ice and 1 M hydrochloric acid and extracted with diethyl ether. The organic phase was washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo to give 12.8 g (99%) of crude **4**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}_{max}$ = 1600 cm^{-1} (m, aromatic), 1500 (m), 1360 (s, SO_2), 1180 (s, SO_2), 1120 (m), 970 (m), 815 (s), 665 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.0 Hz, 3 H, 4-H_3), 0.88 (d, *J* = 6.6 Hz, 3 H, 2-CH_3), 1.10−1.90 (m, 3 H, 2-H, 3-H_2), 2.45 (s, 3 H, Ar−CH_3), 3.84 (d, *J* = 5.9 Hz, 1 H, 1-H_a), 3.92 (d, *J* = 5.9 Hz, 1 H, 1-H_b), 7.34 (d, *J* = 8.1 Hz, 2 H, Ar−H), 7.79 (d, *J* = 8.1 Hz, 2 H, Ar−H).

(*R*)-3-Methylpentanenitrile (5): To a solution of **4** (12.7 g, 52.4 mmol) in dry dimethyl sulfoxide (30 mL) was added sodium cyanide (2.52 g, 63.0 mmol) at room temperature. After stirring at room temperature for 14 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water, and brine, dried with $MgSO_4$, and concentrated. The residue was distilled to give 4.22 g (83%) of **5** as a colorless oil; b.p. 84−85°C / 83 Torr. − n_D^{26} = 1.3980. − $[\alpha]_D^{20}$ = −7.68 (*c* = 1.92, CCl_4) {ref.[23] $[\alpha]_D$ = +7.65 (CCl_4) for the (*S*)-enantiomer}. − IR (film): $\tilde{\nu}_{max}$ = 2220 cm^{-1} (m, CN), 1460 (m, C−H), 1425 (m), 1385 (m, C−H). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.1 Hz, 3 H, 5-H_3), 1.06 (d, *J* = 6.4 Hz, 3 H, 3-CH_3), 1.10−2.00 (m, 3 H, 3-H, 4-H_2), 2.27 (d, *J* = 5.7 Hz, 1 H, 2-H_a), 2.29 (d, *J* = 6.0 Hz, 1 H, 2-H_b).

(*R*)-3-Methylpentanoic Acid (6): To 56 mL of water was added 46.5 mL of concentrated sulfuric acid. When the mixture was cooled to about 50°C, **5** (4.40 g, 45.3 mmol) was added, and the mixture was stirred and refluxed for 6 h. The mixture was then poured into water and extracted with diethyl ether. The organic phase was washed with water, and brine, dried with $MgSO_4$, and concentrated in vacuo to give 5.04 g (96%) of crude **6**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}_{max}$ = 3300−2550 cm^{-1} (br. s, O−H), 1710 (s, C=O), 1410 (m), 1290 (m), 940 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, 5-H_3), 0.97 (d, *J* = 6.4 Hz, 3 H, 3-CH_3), 1.30, (m, 2 H, 4-H_2), 1.89, (m, 1 H, 3-H), 2.21 (d, *J* = 7.2 Hz, 1 H, 2-H_a), 2.31 (d, *J* = 6.2 Hz, 1 H, 2-H_b).

(*R*)-3-Methyl-1-pentanol (7): To a stirred and ice-cooled suspension of $LiAlH_4$ (4.10 g, 108 mmol) in dry diethyl ether (120 mL) was added a solution of **6** (5.00 g, 430 mmol) in dry diethyl ether (30 mL) at 0°C, and the mixture was stirred at room temperature for 2 h. Then the mixture was quenched with water (4.0 mL), 15% aqueous NaOH (4.0 mL) and water (12 mL) at 0°C. After stirring for 30 min, the suspension was filtered through Celite. The filtrate was dried with $MgSO_4$ and concentrated. The residue was distilled to give 4.07 g (93%) of **7** as a colorless oil; b.p. 148−150°C. − n_D^{26} = 1.4163. − $[\alpha]_D^{22}$ = −8.25 (*c* = 1.07, $CHCl_3$) {ref[24] $[\alpha]_D^{20}$ = −8.2 (*c* = 1, $CHCl_3$)}. − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 1060 (s, C−O), 1030 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3 H, 5-H_3), 0.89 (d, *J* = 6.5 Hz, 3 H, 3-CH_3), 1.00−1.80 (m, 6 H, 3-H, 2, 4-H_2 and OH), 3.66 (t, *J* = 6.5 Hz, 2 H, 1-H_2).

(*R*)-3-Methylpentyl Tosylate (8): To a solution of **7** (3.96 g, 38.8 mmol) in dry pyridine (25 mL) was added *p*-toluenesulfonyl chloride (9.86 g, 51.7 mmol) at 0°C. After stirring at 0°C for 12 h, the mixture was poured onto ice and 1 M hydrochloric acid and extracted with diethyl ether. The organic phase was washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo to give 9.9 g (99%) of crude **8**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}_{max}$ = 1615 cm^{-1} (m, aromatic), 1510 (m), 1370 (s, SO_2), 1190 (s, SO_2), 940 (m), 810 (m), 665 (m, C−S). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.77−0.89 (m, 6 H, 5-H_3, 3-CH_3), 1.00−1.80 (m, 5 H, 3-H, 2,4-H_2), 2.45 (s, 3 H, Ar−CH_3), 4.07 (t, *J* = 6.4 Hz 2 H, 1-H_2), 7.34 (d, *J* = 8.2 Hz, 2 H, Ar−H), 7.80 (d, *J* = 8.2 Hz, 2 H, Ar−H).

(*R*)-3-Methylpentyl Bromide (9): To a solution of **8** (9.90 g, 38.6 mmol) in dry DMF (18 mL) was added lithium bromide (5.03 g, 57.9 mmol) at room temperature. After stirring at room temperature for 5 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated. The residue was distilled to give 5.20 g (82%) of **9** as a colorless oil; B.p. 139−141°C. − n_D^{24} = 1.4439. − $[\alpha]_D^{20}$ = −20.5 (*c* = 1.76, ether) {ref.[25] n_D^{23} = 1.4436, $[\alpha]_D^{22}$ = −19.9 (*c* = 1.72, ether)}. − IR (film): $\tilde{\nu}_{max}$ = 2980 cm^{-1} (s, C−H), 2950 (s, C−H), 2890 (s, C−H), 1465 (m, C−H), 1380 (m, C−H), 1255 (m), 1210 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, 5-H_3), 0.89 (d, *J* = 5.9 Hz, 3 H, 3-CH_3), 1.05−2.00 (m, 5 H, 3-H, 2, 4-H_2), 3.43 (t, *J* = 6.6 Hz, 2 H, 1-H_2).

(2*R*,6*S*)-7-Acetoxy-2,6-dimethyl-1-heptanol (11): Immobilization of Lipase PS: Lipase PS (Amano, 3.0 g) was mixed thoroughly with Hyflo Super Cell® (10.0 g). Then, 0.1 M potassium phosphate buffer (pH 7, 10 mL) was added. The mixture was shaken vigorously and dried in vacuo. To a solution of **10** (5.30 g, 33.1 mmol) in dry THF (350 mL) was added immobilized lipase PS (2.20 g) and dry isopropenyl acetate (6 mL). The reaction mixture was stirred at 0°C and monitored by TLC (3 days). The solid was filtered off and washed with THF, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (140 g, hexane/ethyl acetate, 20:1 to 10:1) to give 3.8 g (57%) of mono ester **11** as a colorless oil along with diacetate (2.1 g, 26%) and diol (0.7 g, 13%); n_D^{24} = 1.4426. − $[\alpha]_D^{24}$ = +8.8 (*c* = 0.98, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3420 cm^{-1} (s, O−H), 1735 (s, C=O), 1240 (s, CO_2), 1030 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.6 Hz, 6 H, 2-, 6-CH_3), 1.00−2.00 (m, 9 H, 2-, 6-H, 3 to 5-H_2 and OH), 2.04 (3 H, s, $COCH_3$), 3.44 (d, *J* = 5.9 Hz, 1 H, 1-H_a), 3.46 (d, *J* = 5.7 Hz, 1 H, 1-H_b), 3.81 (dd, *J* = 6.4, 10.6 Hz, 1 H, 7-H_a), 3.97 (dd, *J* = 6.1, 10.6 Hz, 1 H, 7-H_b). The *syn*/*anti* ratio was calculated from ^{13}C NMR spectrum of the free alcohol [^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.3 (*syn* isomer, signal height = 40.9), 33.4 (*anti* isomer, signal height = 1.0). The diastereomeric purity of (2*R*,6*S*)-**11** was 95.1% *de* These data are in good agreement with those in ref.[14]

(2*S*,6*R*)-1-Acetoxy-7-*tert*-butyldiphenylsilyloxy-2,6-dimethylheptane (12): To a solution of **11** (3.10 g, 15.3 mmol) under an atmosphere of argon in dry DMF (28 mL) was added TBDPSCl (5.00 g, 18.2 mmol) and imidazole (3.60 g, 52.9 mmol) at room temperature. After stirring at room temperature for 4 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/ethyl acetate, 50:1) to give 6.44 g (96%) of **12** as a colorless oil; n_D^{20} = 1.5175. − $[\alpha]_D^{20}$ = +1.7 (*c* = 0.99, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (s, C=O), 1590 (w, aromatic), 1240 (s, CO_2), 1115 (s, Si−O), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.90, 0.91 (d, *J* = 6.4 Hz, 6 H, 2-, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.00−1.80 (m, 8 H, 2-, 6-H and 3 to 5-H_2), 2.04 (s, 3 H, $COCH_3$), 3.41 (dd, *J* = 6.1, 9.7 Hz, 1 H, 7-H_a), 3.53 (dd, *J* = 6.1, 9.7 Hz, 1 H, 7-H_b), 3.83 (dd, *J* = 6.6, 10.6 Hz, 1 H, 1-H_a), 3.94 (dd, *J* = 5.9, 10.6 Hz, 1 H, 1-H_b), 7.37 (m, 6 H, Ar−H), 7.68 (m, 4 H, Ar−H). − $C_{27}H_{40}O_3Si$ (440.7): calcd. C 73.59, H 9.15; found C 73.24, H 9.04.

(2*S*,6*R*)-7-*tert*-Butyldiphenylsilyloxy-2,6-dimethyl-1-heptanol (13): To a solution of **12** (6.30 g, 14.3 mmol) in MeOH (150 mL) was added K_2CO_3 (4.09 g, 21.4 mmol) at room temperature. After stirring at room temperature for 5 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (40 g, hexane/ethyl acetate, 20:1) to give 5.67 g (99%) of **13** as a colorless oil; n_D^{25} = 1.5170. − $[\alpha]_D^{23}$ = −3.02 (*c* = 1.10, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 1590 (w, aromatic), 1115 (s, Si−O), 1040 (m), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89, 0.91 (d, *J* = 6.4 Hz, 6 H, 2-, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.10−1.80 (m, 9 H, 2-, 6-H, 3 to 5-H_2 and OH), 3.45 (m, 4 H, 1-, 7-H_2), 7.37 (m, 6 H, Ar−H), 7.68 (m, 4 H, Ar−H). − $C_{25}H_{38}O_2Si$ (398.7): calcd. C 75.32, H 9.61; found C 75.60, H 9.64.

(2*S*,6*R*)-7-*tert*-Butyldiphenylsilyloxy-2,6-dimethylheptanal (14): To a solution of Dess−Martin periodinane (5.29 g, 12.5 mmol) under an atmosphere of argon in dry CH_2Cl_2 (90 mL) was added pyridine (5.04 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **13** (3.10 g, 7.78 mmol) in dry CH_2Cl_2 (25 mL) was then added dropwise at room temperature. After stirring at room temperature for 1 h, the mixture was diluted with CH_2Cl_2 and quenched by adding solutions of saturated aqueous sodium hydrogen cabonate (30 mL) and saturated aqueous sodium thiosulfate (30 mL). The resulting mixture was stirred for 10 min and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (60 g, hexane/ethyl acetate, 40:1) to give 2.94 g (95%) of **14** as a colorless oil; n_D^{26} = 1.5240. − $[\alpha]_D^{20}$ = +12.3 (*c* = 1.00, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 2710 cm^{-1} (w, CHO), 1725 (s, C=O), 1590 (w, aromatic), 1110 (s, Si−O), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.08 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 1.15−1.80 (m, 7 H, 6-H and 3 to 5-H_2), 2.31 (m, 1 H, 2-H), 3.47 (d, *J* = 5.7 Hz, 2 H, 7-H_2), 7.34 (m, 6 H, Ar−H), 7.66 (m, 4 H, Ar−H), 9.61 (d, *J* = 2.0 Hz, 1 H, CHO). − $C_{25}H_{36}O_2Si$ (396.7): calcd. C 75.70, H 9.15; found C 75.97, H 9.04.

(2*S*/*R*,3*S*,7*R*)-8-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-2-octanol (15): To a solution of **14** (2.74 g, 6.91 mmol) under an atmosphere of argon in dry THF (60 mL) was added dropwise MeMgBr (0.93 M in THF, 15 mL, 14.0 mmol) at −78°C. After stirring at this temperature for 1 h, the mixture was warmed to 0°C. It was then quenched with aqueous 1 M HCl, and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/ethyl acetate, 20:1) to give 2.50 g (88%) of **15** as a colorless oil; $n_D^{26} = 1.5249$. − IR (film): $\tilde{\nu}_{max} = 3380\ cm^{-1}$ (m, O−H), 1590 (w, aromatic), 1110 (s, Si−O), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.91 (d, *J* = 6.4 Hz, 3 H, 3-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.12, 1.14 (d, *J* = 6.4 Hz, 3 H, 1-H_3), 1.00−1.80 (m, 9 H, 3-,7-H, 4 to 6-H_2 and OH), 3.48 (d, *J* = 6.8 Hz, 2 H, 8-H_2), 3.65 (m, 1 H, 2-H), 7.38 (m, 6 H, Ar−H), 7.68 (m, 4 H, Ar−H). − HPLC [column: pegasil, 4.6 mm × 25 cm; solvent: hexane/THF, 9/1, flow rate: 0.4 mL/min; detection: 254 nm], t_R = 21.0 min [(2*S*,3*S*)-**15**, 66.4%], 21.5 [(2*R*,3*S*)-**15**, 33.6%]. The diastereomer ratio of (2*S*,3*S*)-**15**/(2*R*,3*S*)-**15** was 2.0/1.0.

(2*S*,3*S*,7*R*)-8-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-2-octanol (16): To a solution of **15** (1.94 g, 4.70 mmol) in dry vinyl acetate (40 mL) was added immobilized lipase PS (0.50 g). The reaction mixture was stirred at 0°C, and was monitored by TLC (3 days). The solid was then filtered off, washed with THF and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel (40 g, hexane/ethyl acetate, 50:1 to 20:1) to give 1.16 g (60%) of **16** and 0.78 g (37%) of **17**. The compound **16** was purified by preparative MPLC (silica gel 50 g, hexane/ethyl acetate, 50:1) to give 0.93 g(48% from **15**) of **16** as a colorless oil; $n_D^{26} = 1.5258$. − $[\alpha]_D^{20} = -6.54$ (*c* = 1.00, $CHCl_3$). − IR (film): $\tilde{\nu}_{max} = 3380\ cm^{-1}$ (m, O−H), 1590 (w, aromatic), 1110 (s, Si−O), 705 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.92 (d, *J* = 6.4 Hz, 3 H, 3-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.14 (d, *J* = 6.4 Hz, 3 H, 1-H_3), 1.10−1.70 (m, 9 H, 3-, 7-H, 4 to 6-H_2 and OH), 3.44 (dd, *J* = 6.3, 9.7 Hz, 1 H, 8-H_a), 3.51 (dd, *J* = 5.8, 9.7 Hz, 1 H, 8-H_b), 3.69 (dq, *J* = 3.9, 6.4 Hz, 1 H, 2-H), 7.39 (m, 6 H, Ar−H), 7.66 (m, 4 H, Ar−H). − $C_{26}H_{40}O_2Si$ (412.7): calcd. C 75.67, H 9.77; found C 75.33, H 9.57. − HPLC [under the same conditions as for the analysis of **15**]: t_R = 21.0 min [(2*S*,3*S*)-**16**, 98.5%], 21.5 [(2*R*,3*S*)-**16**, 1.5%]. The diastereomeric purity of (2*S*,3*S*)-**16** was 97.0% *de*.

(1*R*,2*S*,6*R*)-7-*tert*-Butyldiphenylsilyloxy-1,2,6-trimethylheptyl Acetate (17): a colorless oil. − $n_D^{21} = 1.5129$. − IR (film): $\tilde{\nu}_{max}$ = 1740 cm^{-1} (s, C=O), 1590 (w, aromatic), 1250 (s, C−O), 1110 (s, Si−O), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 0.91 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.12 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 1.00−1.80 (m, 8 H, 2-, 6-H, 3 to 5-H_2), 2.02 (s, 3 H, $COCH_3$), 3.46 (d, *J* = 5.8 Hz, 2 H, 7-H_2), 4.78 (m, 1 H, 1-H), 7.38 (m, 6 H, Ar−H), 7.67 (m, 4 H, Ar−H). − $C_{28}H_{42}O_3Si$ (454.7): calcd. C 73.96, H 9.31; found C 74.14, H 9.10. The diastereomeric purity of **17** was analyzed after the deacetylation of **17**; HPLC [under the same conditions as for the analysis of **15**]: t_R = 21.0 min [deacetylated compound of (1*S*,2*S*)-**17**, 15.2%], 21.5 [deacetylated compound of (1*R*,2*S*)-**17**, 84.8%]. The diastereomeric purity of (1*R*,2*S*)-**17** was 69.6% *de*.

(2*R*,6*S*,7*S*)-1-*tert*-Butyldiphenylsilyloxy-7-tetrahydropyranyloxy-2,6-dimethyloctane (18): To a solution of **16** (0.47 g, 1.14 mmol) in dry diethyl ether (7 mL) was added 3,4-dihydro-2H-pyran (DHP, 0.15 mL, 1.66 mmol) and *p*-toluenesulfonic acid monohydrate (0.01 g) at room temperature. After stirring for 4 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic phase was washed with brine, dried with K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 100:1) to give 506 mg (90%) of **18** as a colorless oil; $n_D^{26} = 1.5181$. − $[\alpha]_D^{21} = +8.2$ (*c* = 0.99, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1590 cm^{-1} (w, aromatic), 1200 (m, C−O), 1115 (s, Si−O), 705 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.91 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.16 (d, *J* = 6.4 Hz, 3 H, 8-H_3), 1.10−1.90 (m, 14 H, 2-, 6-H, 3 to 5-H_2 and 3′ to 5′-H_2), 3.30− 4.00 (m, 5 H, 7-H, 1-H_2 and 6′-H_2), 4.63 (br, 1 H, 2′-H), 7.38 (m, 6 H, Ar−H), 7.68 (m, 4 H, Ar−H). − $C_{31}H_{48}O_3Si$ (496.8): calcd. C 74.95, H 9.74; found C 75.20, H 9.61.

(2*R*,6*S*,7*S*)-7-Tetrahydropranyloxy-2,6-dimethyl-1-octanol (19): To a solution of **18** (462 mg, 0.93 mmol) in dry THF (5 mL) was added Bu_4NF (1.0 M solution in dry THF, 1.4 mL, 1.40 mmol) at room temperature. After stirring at this temperature for 12 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 30:1) to give 231 mg (96%) of **19** as a colorless oil; $n_D^{26} = 1.4512$. − $[\alpha]_D^{19} = +8.27$ (*c* = 1.00, hexane). − IR (film): $\tilde{\nu}_{max}$ = 3420 cm^{-1} (s, O−H), 1200 (m, C−O), 1110 (m) 1040 (s, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.92 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.05, 1.16 (d, *J* = 6.4 Hz, 3 H, 8-H_3), 1.00−1.90 (m, 15 H, 2-, 6-H, 3 to 5-H_2, 3′ to 5′-H_2 and OH), 3.30−4.00 (m, 5 H, 7-H, 1-, 6′-H_2), 4.63 (br, 1 H, 2′-H). − $C_{15}H_{30}O_3$ (258.4): calcd. C 69.72, H 11.70; found C 69.49, H 11.44.

(2*R*,6*S*,7*S*)-7-Tetrahydropranyloxy-2,6-dimethyloctyl Tosylate (20): To a solution of **19** (139 mg, 0.54 mmol) in dry pyridine (2 mL) was added *p*-toluenesulfonyl chloride (154 mg, 0.81 mmol) at 0°C. After stirring at this temperature for 15 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and brine, dried with K_2CO_3, and concentrated in vacuo to give 223 mg (quant.) of crude **20**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}_{max}$ = 1600 cm^{-1} (m, aromatic), 1360 (m, SO_2), 1190 (m), 1180 (s, SO_2), 1025 (m, C−O). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.88 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.03, 1.14 (d, *J* = 6.4 Hz, 3 H, 8-H_3), 1.10−2.00 (m, 14 H, 2-, 6-H, 3 to 5-H_2, 3′ to 5′-H_2), 2.45 (s, 3 H, Ar−CH_3), 3.20−4.00 (m, 3 H, 7-H and 6′-H_2), 3.85 (dd, *J* = 2.1, 6.0 Hz, 2 H, 1-H_2), 4.63 (br, 1 H, 2′-H), 7.34 (d, *J* = 8.2 Hz, 2 H, Ar−H), 7.79 (d, *J* = 8.2 Hz, 2 H, Ar−H).

(2*S*,3*S*,7*S*,11*R*)-2-Tetrahydropranyloxy-3,7,11-trimethyltridecane (21): Preparation of the Grignard reagent. Magnesium (102 mg, 4.20 mmol) was added to an argon-purged flask. To the metal was added, dropwise, a solution of bromide **9** (426 mg, 2.80 mmol) in dry THF (3 mL), and the mixture was stirred at 45°C for 1 h. The resulting solution was used immediately. To a solution of **20** (223 mg, 0.54 mmol) in dry THF (2 mL) under an atmosphere of argon was added the Grignard reagent solution and a solution (0.1 M, 1 mL, 0.1 mmol) of Li_2CuCl_4 in THF at −78°C. After stirring at this temperature for 1 h, the mixture was warmed slowly to 0°C, and stirred at 0°C for 24 h. The mixture was quenched with saturated aqueous NH_4Cl, and extracted with diethyl ether. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (5 g, hexane/ethyl acetate, 1000:1 to 100:1) to give 150 mg (85%) of **21** as a colorless oil; $n_D^{26} = 1.4509$. − $[\alpha]_D^{23} = -10.4$ (*c* = 0.98, hexane). − IR (film): $\tilde{\nu}_{max}$ = 1200 cm^{-1} (m, C−O), 1130 (m), 1075 (m), 1020 (s, C−O). − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d,

J = 6.8 Hz, 6 H, 7-, 11-CH_3), 0.86 (t, J = 7.1 Hz, 3 H, 13-H_3), 0.92 (d, J = 6.8 Hz, 3 H, 3-CH_3), 1.03, 1.17 (d, J = 6.4 Hz, 3 H, 1-H_3), 1.00−1.85 (m, 23 H, 3-, 7-, 11-H and 4 to 6-, 8 to 10-, 12-, 3′ to 5′-H_2), 3.48 (m, 1 H, 6′-H_a), 3.59, 3.65 (m, 1 H, 2-H), 3.90 (m, 1 H, 6′-H_b), 4.55−4.75 (br, 1 H, 2′-H). − $C_{21}H_{42}O_2$ (326.6): calcd. C 77.24, H 12.96; found C 76.82, H 13.09.

(2*S*,3*S*,7*S*,11*R*)-3,7,11-Trimethyl-2-tridecanol (22): To a solution of **21** (150 mg, 0.46 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid monohydrate (5.0 mg, 0.03 mmol) and the mixture was stirred for 3 h under reflux. After neutralization with K_2CO_3, the mixture was poured into brine and extracted with diethyl ether. The organic phase was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (3 g, hexane/ethyl acetate, 50:1) to give 104 mg (93%) of **22** as a colorless oil; n_D^{24} = 1.4495. − $[\alpha]_D^{23}$ = −20.0 (c = 1.02, hexane). − IR (film): $\tilde{\nu}_{max}$ = 3360 cm^{-1} (s, O−H), 1150 (w), 1110 (w), 1000 (w), 930 (w). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.3 Hz, 3 H, 11-CH_3), 0.85 (d, J = 6.3 Hz, 3 H, 7-CH_3), 0.86 (t, J = 7.3 Hz, 3 H, 13-H_3), 0.89 (d, J = 6.8 Hz, 3 H, 3-CH_3), 1.16 (d, J = 6.3 Hz, 3 H, 1-H_3), 1.00−1.50 (m, 18 H, 3-, 7-, 11-H, 4 to 6-, 8 to 10-, 12-H_2 and OH), 3.71 (dq, J = 4.1, 6.3 Hz, 1 H, 2-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 14.2, 19.2, 19.8, 20.3, 24.5, 24.8, 29.6, 32.8, 33.0, 34.4, 36.9, 37.3, 37.5, 39.8, 71.4. − $C_{16}H_{34}O$ (242.5): calcd. C 79.27, H 14.14; found C 79.09, H 13.75.

(1*S*,2*S*,6*S*,10*R*)-1,2,6,10-Tetramethyldodecyl Propanoate (1): To a solution of **22** (88.0 mg, 0.36 mmol) in dry CH_2Cl_2 (3 mL) was added propanoyl chloride (42.8 mg, 0.46 mmol) and Et_3N (0.10 mL, 0.75 mmol) at room temperature. After stirring at room temperature for 10 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with aqueous 1 M HCl, water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (3 g, hexane/ethyl acetate, 500:1) to give 89 mg (82%) of **1** as a colorless oil; n_D^{26} = 1.4391. − $[\alpha]_D^{23}$ = −12.7 (c = 1.02, hexane). − IR (film): $\tilde{\nu}_{max}$ = 2950 cm^{-1} (s, C−H), 2880 (m, C−H), 1740 (m, C=O), 1465 (m, C−H), 1375 (m, C−H), 1270 (m), 1200 (s, C−O), 1130 (w), 1085 (m), 1010 (m), 920 (w), 870 (w), 810 (w), 740 (w). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.4 Hz, 6 H, 6-, 10-CH_3), 0.86 (t, J = 7.3 Hz, 3 H, 12-H_3), 0.90 (d, J = 7.0 Hz, 3 H, 2-CH_3), 1.14 (t, J = 7.6 Hz, 3 H, 3′-H_3), 1.16 (d, J = 6.4 Hz, 3 H, 1-CH_3), 1.00−1.50 (m, 16 H, 6-, 10-H, 3 to 5-, 7 to 9-, 11-H_2), 1.58 (m, 1 H, 2-H), 2.30 (q, J = 7.6 Hz, 2 H, 2′-H_2), 4.85 (dq, J = 4.8, 6.4 Hz, 1 H, 1-H). − ^{13}C NMR (126 MHz, $CDCl_3$): δ = 9.3, 11.4, 14.8, 17.0, 19.2, 19.7, 24.5, 24.6, 28.0, 29.6, 32.7, 32.9, 34.4, 37.0, 37.3, 37.4, 37.7, 73.8, 174.2. − EI MS: m/z (%) = 297 (3) [$(M - 1)^+$], 283 (13) [$(M - CH_3)^+$], 269 (3) [$(M - C_2H_5)^+$], 254 (3), 224 (22), 140 (15), 125 (19), 101 (48), 86 (42), 70 (24), 57 (100) [$C_2H_5(CH_3)CH^+$ or $(C_2H_5C{=}O)^+$], 43 (15). − $C_{19}H_{38}O_2$ (298.5): calcd. C 76.45, H 12.83; found C 76.51, H 12.82. − GC [column: TC-wax 0.53 mm × 15 m, 80 + 2.0°C/min; carrier gas: He, pressure 110 kPa]: t_R = 16.5 min [(**1**, 98.9%].

(2*S*,6*R*)-7-*tert*-Butyldiphenylsilyloxy-2,6-dimethylheptyl tosylate (23): To a solution of **13** (1.50 g, 3.76 mmol) in dry pyridine (15 mL) was added *p*-toluenesulfonyl chloride (9.26 g, 4.86 mmol) at 0°C. After stirring at 0°C for 14 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo to give 2.06 g (99%) of crude **23**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}_{max}$ = 1600 cm^{-1} (m, aromatic), 1360 (m, SO_2), 1180 (m, SO_2), 1050 (s, Si−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.6 Hz, 6 H, 2-, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.10−1.80 (m, 8 H, 2-, 6-H, 3 to 5-H_2), 2.43 (s, 3 H, Ar-CH_3), 3.44 (d, J = 5.5 Hz, 2 H, 7-H_2), 3.82 (d, J = 6.4 Hz, 1 H, 2-H_a), 3.84 (d, J = 5.9 Hz, 1 H, 2-H_b), 7.25−7.83 (m, 14 H, Ar−H).

(2*R*,6*R*,10*R*)-1-*tert*-Butyldiphenylsilyloxy-2,6,10-trimethyldodecane (24): Preparation of the Grignard reagent. Magnesium (0.47 g, 19.3 mmol) was added to an argon-purged flask. To the metal was added, dropwise, a solution of bromide **9** (2.46 g, 14.9 mmol) in dry THF (12 mL), and the mixture was stirred at 45 °C for 1 h. The resulting solution was used immediately. To a solution of **23** (2.06 g, 3.72 mmol) in dry THF (10 mL) under an atmosphere of argon was added the Grignard reagent solution and a solution of Li_2CuCl_4 (0.1 M, 3.7 mL, 0.37 mmol) in dry THF at −78°C. After stirring at this temperature for 1 h, the mixture was warmed slowly to 0°C, and stirred at 0°C for 24 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic phase was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 1000:1 to 100:1) to give 1.40 g (84%) of **24** as a colorless oil; n_D^{25} = 1.5088. − $[\alpha]_D^{23}$ = −2.2 (c = 0.99, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1590 cm^{-1} (m, aromatic), 1120 (s, Si−O), 830 (m), 730 (m), 705 (s). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.4 Hz, 3 H, 10-CH_3), 0.84 (d, J = 6.4 Hz, 3 H, 6-CH_3), 0.86 (t, J = 7.0 Hz, 3 H, 12-H_3), 0.92 (d, J = 6.7 Hz, 3 H, 2-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.05−1.50 (m, 16 H, 6-, 10-H, 3 to 5-, 7 to 9-,11-H_2), 1.64 (m, 1 H, 2-H), 3.44 (dd, J = 6.7, 9.8 Hz, 1 H, 1-H_a), 3.51 (dd, J = 5.6, 9.8 Hz, 1 H, 1-H_b), 7.40 (m, 6 H, Ar−H), 7.76 (d, J = 6.4 Hz, 4 H, Ar−H). − $C_{31}H_{50}OSi$ (466.8): calcd. C 79.76, H 10.80; found C 80.12, H 10.66.

(2*R*,6*R*,10*R*)-2,6,10-Trimethyl-1-dodecanol (25): To a solution of **24** (1.40 g, 3.13 mmol) in dry THF (10 mL) was added Bu_4NF (1.0 M solution in dry THF, 4.7 mL, 4.70 mmol) at room temperature. After stirring at room temperature for 4 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with K_2CO_3 and concentrated in vacuo. The residue was chromatographed on silica gel (40 g, hexane/ethyl acetate, 40:1) to give 0.71 g (99%) of **25** as a colorless oil; n_D^{25} = 1.4513. − $[\alpha]_D^{23}$ = +0.83 (c = 0.99, $CDCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3340 cm^{-1} (m, O−H), 2930 (s, C−H), 1135 (m), 1030 (s). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.4 Hz, 3 H, 10-CH_3), 0.85 (d, J = 6.4 Hz, 3 H, 6-CH_3), 0.86 (t, J = 6.9 Hz, 3 H, 12-H_3), 0.92 (d, J = 6.7 Hz, 3 H, 2-CH_3), 1.00−1.45 (m, 17 H, 6-, 10-H, 3 to 5-, 7 to 9-, 11-H_2 and OH), 1.61 (m, 1 H, 2-H), 3.42 (dd, J = 6.7, 10.5 Hz, 1 H, 1-H_a), 3.51 (dd, J = 5.6, 10.5 Hz, 1 H, 1-H_b). − $C_{15}H_{32}O$ (228.4): calcd. C 78.87, H 14.12; found C 78.45, H 14.01.

(2*R*,6*R*,10*R*)-2,6,10-Trimethyldodecanal (26): To a solution of Dess−Martin periodinane (0.95 g, 22.5 mmol) under an atmosphere of argon in dry CH_2Cl_2 (15 mL) was added pyridine (0.9 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **25** (0.35 g, 15.3 mmol) in dry CH_2Cl_2 (5 mL) was then added dropwise at room temperature. After stirring at room temperature for 1 h, the mixture was diluted with CH_2Cl_2, quenched by adding a solution of saturated aqueous sodium hydrogen cabonate (8 mL) and saturated aqueous sodium thiosulfate (8 mL). The resulting mixture was stirred for 10 min, and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 100:1) to give 329 mg (95%) of **26** as a colorless oil; n_D^{25} = 1.4391. − $[\alpha]_D^{22}$ = −19.2 (c = 1.10, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 2720 cm^{-1} (m, CHO), 1730 (s, C=O), 1240 (m), 930 (w). − ^{1}H NMR

(90 MHz, $CDCl_3$): δ = 0.81−0.97 (m, 9 H, 6-, 10-CH_3, 12-H_3), 1.09 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 1.00−1.80 (m, 16 H, 6-, 10-H, 3 to 5-, 7 to 9-, 11-H_2), 2.32 (m, 1 H, 2-H), 9.61 (d, *J* = 2.0 Hz, 1 H, CHO). − HRMS [$C_{15}H_{30}OSi$]: calcd. 266.2297; found 266.2286. − No correct combustion analytical data could be obtained due to the instability of **26**.

(2*S*/*R*,3*R*,7*R*,11*R*)-3,7,11-Trimethyl-2-tridecanol (27): To a solution of **26** (300 mg, 1.33 mmol) under an atmosphere of argon in dry THF (12 mL) was added, dropwise, MeMgBr (0.93 M in THF, 2.8 mL, 2.60 mmol) at −78°C. After stirring at this temperature for 1 h, the mixture was warmed to 0°C. The mixture was then quenched with aqueous 1 M HCl, and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (15 g, hexane/ethyl acetate, 50:1) to give 267 mg (83%) of **27** as a colorless oil; n_D^{25} = 1.4504. − IR (film): $\tilde{\nu}_{max}$ = 3370 cm^{-1} (s, O−H), 1110 (w), 930(w). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (m, 12 H, 3-, 7-, 11-CH_3 and 13-H_3), 1.13, 1.15 (3 H, d, *J* = 6.1 Hz, *anti*-1-H_3 and *J* = 6.4 Hz, *syn*-1-H_3), 1.00−1.60 (m, 18 H, 3-, 7-, 11-H, 4 to 6-, 8 to 10-, 12-H_2 and OH), 3.66, 3.71 (m, 1 H, *syn*-2-H and *anti*-2-H). − GC [column: Chirasil-DEX®-CB, 0.25 mm × 25 m, 150 + 0.2°C/min; carrier gas: He, pressure 110 kPa]: t_R = 29.5 min [(2*R*,3*R*)-**27**, 69.8%], 30.0 min [(2*S*,3*R*)-**27**, 30.2%]. The diastereomer ratio of (2*R*,3*R*)-**27**/(2*S*,3*R*)-**27** was 2.3/1.0.

(2*S*,3*R*,7*R*,11*R*)-3,7,11-Trimethyl-2-tridecanol (28): To a solution of **27** (240 mg, 0.99 mmol) in dry vinyl acetate (8 mL) was added immobilized lipase PS (60.0 mg). The reaction mixture was stirred at 0°C, and was monitored by TLC (3 days). The solid was filtered off and washed with THF, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (12 g, hexane/ethyl acetate, 100:1 to 50:1) to give 88 mg (31%) of **28** and 187 mg (66%) of **29**. The compound **28** was purified by preparative MPLC (silica gel 10 g, hexane/ethyl acetate, 50:1) to give 67 mg (24% from **27**) of **28** as a colorless oil; n_D^{25} = 1.4517. − $[\alpha]_D^{20}$ = +10.5 (c = 0.99, hexane). − IR (film): $\tilde{\nu}_{max}$ = 3360 cm^{-1} (m, O−H), 1100 (m), 1065 (w), 1000 (w), 930 (w). − ^1H NMR (500 MHz, $CDCl_3$): *δ* = 0.84 (d, *J* = 6.1 Hz, 3 H, 11-CH_3), 0.85 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.86 (t, *J* = 6.4 Hz, 3 H, 13-H_3), 0.88 (d, *J* = 6.7 Hz, 3 H, 3-CH_3), 1.13 (d, *J* = 6.4 Hz, 3 H, 1-H_3), 1.10−1.60 (m, 18 H, 3-, 7-, 11-H, 4 to 6-, 8 to 10-, 12-H_2 and OH), 3.66 (dq, *J* = 4.9, 6.4 Hz, 1 H, 2-H). − ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.4, 14.6, 19.27, 19.34, 19.8, 24.5, 24.7, 29.5, 32.8, 32.9, 34.4, 37.0, 37.36, 37.39, 40.1, 71.8. − $C_{16}H_{34}O$ (242.5): calcd. C 79.27, H 14.14; found C 78.88, H 14.42. − GC [under the same conditions as for the analysis of **27**]: t_R = 29.5 min [(2*R*,3*R*)-**28**, 2.1%], 30.0 min [(2*S*,3*R*)-**28**, 97.9%]. The diastereomeric purity of (2*S*,3*R*)-**28** was 95.8% *de*.

(1*R*,2*R*,6*R*,10*R*)-1,2,6,10-Tetramethyldodecyl Acetate (29): Colorless oil; − n_D^{25} = 1.4378. − $[\alpha]_D^{22}$ = +0.88 (*c* = 1.00, hexane). − IR (film): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (m, C=O), 1250 (s, C−O), 1020 (w), 950 (w). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.81−0.92 (m, 12 H, 2-, 6-, 10-CH_3, 12-H_3), 1.16 (d, *J* = 6.5 Hz, 3 H, 1-CH_3), 1.10−1.70 (m, 17 H, 2-, 6-, 10-H and 3 to 5-, 7 to 9-, 11-H_2), 2.03 (3 H, s, $COCH_3$), 4.88 (dq, *J* = 4.5, 6.5 Hz, 1 H, 1-H). − $C_{18}H_{36}O_2$ (284.5): calcd. C 76.00, H 12.76; found C 75.62, H 13.03.

(2*R*,3*R*,7*R*,11*R*)-3,7,11-Trimethyl-2-tridecanol (30): To a solution of **29** (181 mg, 0.64 mmol) in MeOH (8 mL) was added K_2CO_3 (177 mg, 1.28 mmol) at room temperature. After stirring at room temperature for 17 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 50:1) to give 142 mg (92%) of **30** as a colorless oil; n_D^{25} = 1.4450. − $[\alpha]_D^{23}$ = +5.7 (c = 0.98, hexane). − IR (film): $\tilde{\nu}_{max}$ = 3370 cm^{-1} (m, O−H), 1100 (w), 1065 (w), 1000 (w), 930 (w). − ^1H NMR (500 MHz, $CDCl_3$): *δ* = 0.84 (d, *J* = 6.1 Hz, 3 H, 11-CH_3), 0.85 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.85 (t, *J* = 6.4 Hz, 3 H, 13-H_3), 0.89 (d, *J* = 6.7 Hz, 3 H, 3-CH_3), 1.15 (d, *J* = 6.4 Hz, 3 H, 1-H_3), 1.00−1.70 (m, 18 H, 3-, 7-, 11-H, 4 to 6-, 8 to 10-, 12-H_2 and OH), 3.71 (dq, *J* = 4.0, 6.4 Hz, 1 H, 2-H). − ^{13}C NMR (126 MHz, $CDCl_3$): *δ* = 11.4, 14.2, 19.3, 19.8, 20.3, 24.5, 24.8, 29.5, 32.8, 33.0, 34.4, 37.0, 37.4, 39.8, 71.4. − $C_{16}H_{34}O$ (242.5): calcd. C 79.27, H 14.14; found C 79.10, H 13.77. − GC [under the same conditions as for the analysis of **27**]: t_R = 29.5 min [(2*R*,3*R*)-**30**, 97.9%], 30.0 min [(2*S*,3*R*)-**30**, 2.1%]. The diastereomeric purity of (2*R*,3*R*)-**30** was 95.8% *de*

Mitsunobu Inversion of 30: a) (1*S*,2*R*,6*R*,10*R*)-1,2,6,10-Tetramethyldodecyl Benzoate (31): To a solution of **30** (123 mg, 0.51 mmol) in dry THF (10 mL) was added $P(C_6H_5)_3$ (400 mg, 1.52 mmol), benzoic acid (186 mg, 1.52 mmol) and diethyl azodicarboxylate (40% toluene solution, 0.66 mL, 1.52 mmol) at room temperature. After stirring at this temperature for 2 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. To the residue was added hexane (3 mL) and the mixture was tritulated. The solid was filtered off and washed with hexane, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (7 g, hexane/ethyl acetate, 200:1) to give 150 mg (85%) of **30** as a colorless oil; n_D^{26} = 1.4821. − $[\alpha]_D^{19}$ = +27.7 (*c* = 0.99, hexane). − IR (film): $\tilde{\nu}_{max}$ = 1720 cm^{-1} (s, C=O), 1600 (w, aromatic), 1275 (s, C−O), 1165 (m), 1110 (m), 1030 (m), 715 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.70−1.10 (m, 12 H, 2-, 6-, 10-CH_3 and 12-H_3), 1.27 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 1.10−2.00 (m, 17 H, 2-, 6-, 10-H and 3 to 5-, 7 to 9-, 11-H_2), 5.08 (dq, *J* = 5.2, 6.4 Hz, 1 H, 1-H), 7.55 (m, 3 H, Ar−H), 8.05 (m, 2 H, Ar−H). − $C_{23}H_{38}O_2$ (346.6): calcd. C 79.71, H 11.05; found C 79.79, H 10.89. − **b**) To a solution of **31** (150 mg, 0.43 mmol) in MeOH (15 mL) was added K_2CO_3 (150 mg, 1.09 mmol) at room temperature. After stirring at 60°C for 4 h, the mixture was treated with water and extracted with diethyl ether. The organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (5 g, hexane/ethyl acetate, 200:1) to give 99 mg (96%) of **28** as a colorless oil. Its IR and ^1H NMR spectra were identical to those of the authentic **28**. − GC [under the same conditions as for the analysis of **27**]: t_R = 29.5 min [(2*R*,3*R*)-**28**, 1.9%], 30.0 min [(2*S*,3*R*)-**28**, 98.1%]. The diastereomeric purity of (2*S*,3*R*)-**28** was 96.2% *de*.

(1*S*,2*R*,6*R*,10*R*)-1,2,6,10-Tetramethyldodecyl Propanoate (2): To a solution of **28** (53.0 mg, 0.22 mmol) in dry CH_2Cl_2 (2 mL) was added propanoyl chloride (30.5 mg, 0.33 mmol) and Et_3N (0.06 mL, 0.44 mmol) at room temperature. After stirring at room temperature for 12 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with aqueous 1 M HCl, water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (2 g, hexane/ethyl acetate, 500:1) to give 62.0 mg (95%) of **2** as a colorless oil; n_D^{24} = 1.4412. − $[\alpha]_D^{23}$ = +1.2 (*c* = 0.98, hexane). − IR (film): $\tilde{\nu}_{max}$ = 2930 (s, C−H), 2870 (m, C−H), 1735 (s, C=O), 1465 (m, C−H), 1375 (m, C−H), 1270 (m), 1190 (s, C−O), 1105 (w), 1080 (m), 1030(m), 920 (w), 860 (w), 805 (w), 735(w). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.4 Hz, 6 H, 6-, 10-CH_3), 0.86 (t, *J* = 6.4 Hz, 3 H, 12-H_3), 0.88 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 1.13 (d, *J* = 6.4 Hz, 3 H, 1-CH_3), 1.14 (t, *J* =

7.6 Hz, 3 H, 3′-H_3), 1.00−1.45 (m, 16 H, 6-, 10-H, 3 to 5-, 7 to 9-, 11-H_2), 1.65 (m, 1 H, 2-H), 2.30 (q, J = 6.2 Hz, 2 H, 2′-H), 4.82 (dq, J = 5.5, 6.4 Hz, 1 H, 1-H). − ^{13}C NMR (126 MHz, $CDCl_3$): δ = 9.3, 11.4, 14.6, 15.9, 19.3, 19.8, 24.48, 24.54, 28.0, 29.5, 32.8, 33.0, 34.4, 37.0, 37.32, 37.34, 74.1, 174.1. − EI MS: *m*/*z* (%) = 297 (2) [$(M - 1)^+$], 283 (8) [$(M - CH_3)^+$], 269 (6) [$(M - C_2H_5)^+$], 254 (5), 224 (29), 140 (17), 125 (22), 101 (51), 86 (47), 70 (24), 57 (100) [$C_2H_5(CH_3)CH^+$ or $(C_2H_5C{=}O)^+$], 43 (15). − $C_{19}H_{38}O_2$ (298.5): calcd. C 76.45, H 12.83; found C 76.18, H 12.97. − GC [column: TC-wax 0.53 mm × 15 m, 80 + 2.0°C/min; carrier gas: He, pressure 110 kPa]: t_R = 16.5 min [**2**, 98.7%].

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