Pheromone Synthesis, CCI[+]

Synthesis of (3*S*,7*S*)- and (3*S*,7*S*,15*S*)- Stereoisomers of 3,7-Dimethyl-2-heptacosanone and 3,7,15-Trimethyl-2-heptacosanone, the Ketones Identified from the Locust *Schistocerca gregaria*

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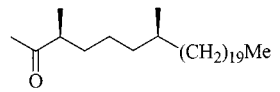
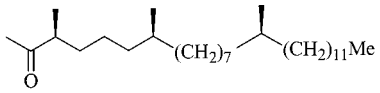
The (3*S*,7*S*) and (3*S*,7*S*,15*S*) stereoisomers of 3,7-dimethyl-2-heptacosanone (**1**) and 3,7,15-trimethyl-2-heptacosanone (**2**), the ketones identified from the locust *Schistocerca gregaria*, were synthesized by employing (2*R*,6*S*)-7-acetoxy-2,6-dimethyl-1-heptanol (**4**) as the starting material.

Introduction

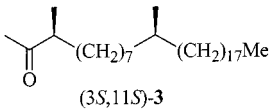
Locust (*Schistocerca gregaria*) is a notorious migratory grasshopper often stripping the areas passed of all vegetation. Very recently Francke and co-workers[1] identified from locust two new ketones, 3,7-dimethyl-2-heptacosanone (**1**, Scheme 1) and 3,7,15-trimethyl-2-heptacosanone (**2**). A similar aliphatic ketone had previously been isolated from the female German cockroach (*Blattella germanica*) as the sex pheromone; its structure was confirmed by synthetic means as (3*S*,11*S*)-3,11-dimethyl-2-nonacosanone (**3**).[2] Although the stereochemistry and biological function of **1** and **2** have not yet been clarified, we became interested in synthesizing them to demonstrate the usefulness of the building block (2*R*,6*S*)-**4**,[3] which was recently employed by us for the synthesis of the pine sawfly pheromone.[4] Because locusts and cockroaches are closely related taxonomically, we decided to synthesize (3*S*,7*S*)-**1** and (3*S*,7*S*,15*S*)-**2**, which share the same *S*-configuration at their stereogenic centers with that of the German cockroach pheromone (3*S*,11*S*)-**3**. Our synthetic strategy was to utilize the nine-carbon building block **4** for the construction of the (3*S*,7*S*) chiral centers in **1** and **2**.



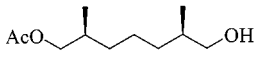
(3*S*,7*S*)-**1**



(3*S*,7*S*,15*S*)-**2**



(3*S*,11*S*)-**3**



(2*R*,6*S*)-**4**

Scheme 1. Structures of the locust ketones (**1** and **2**) and related compounds

Scheme 2 summarizes the synthesis of (3*S*,7*S*)-**1**. Protection of the free hydroxy group of **4** as its *tert*-butyldiphenylsilyl (TBDPS) ether gave **5**, the acetyl group of which was removed to give the mono-TBDPS protected diol **6**. This was oxidized under Dess–Martin conditions[5] to afford the aldehyde **7**.[4] Treatment of **7** with methylmagnesium bromide furnished **8**. Protection of the newly generated secondary hydroxy group of **8** as its tetrahydropyranyl (THP) ether provided **9**. Removal of the TBDPS protective group of **9** yielded **10**, which was tosylated to give **11**. The (2*R*,6*S*,7*S*) isomers of **8**–**11** were previously synthesized in the course of our work on the pine sawfly pheromone.[4] In the present case, we employed the diastereomeric mixture of **8**–**11** at C-7, because in the final products **1** and **2** that position was to be oxidized to give a carbonyl group. Chain-extension of **11** was performed by the method of Fouquet and Schlosser,[6] yielding **12**. After deprotection of the THP group of **12**, the resulting alcohol **13** was oxidized to give (3*S*,7*S*)-**1** as crystals. The overall yield of **1** was 38% based on **4** (10 steps).

The synthesis of (3*S*,7*S*,15*S*)-**2** is summarized in Scheme 3. Initially, (*S*)-7-methylnonadecyl bromide (**24**) had to be provided as the partner of the coupling reaction with **11**, and the commercially available methyl (*S*)-3-hy-

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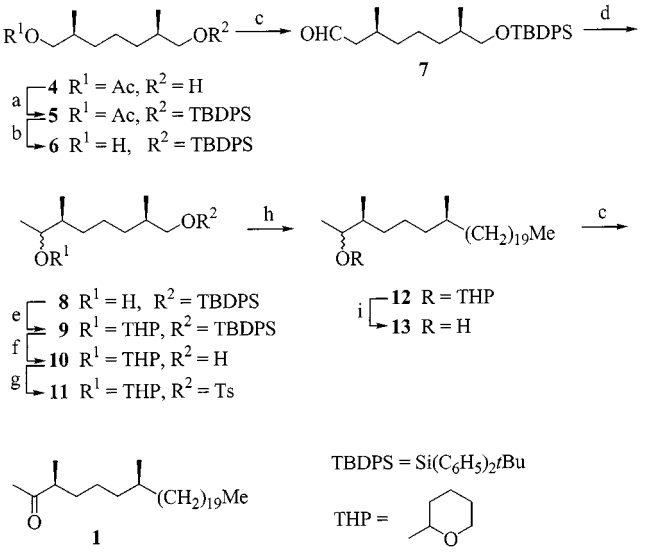
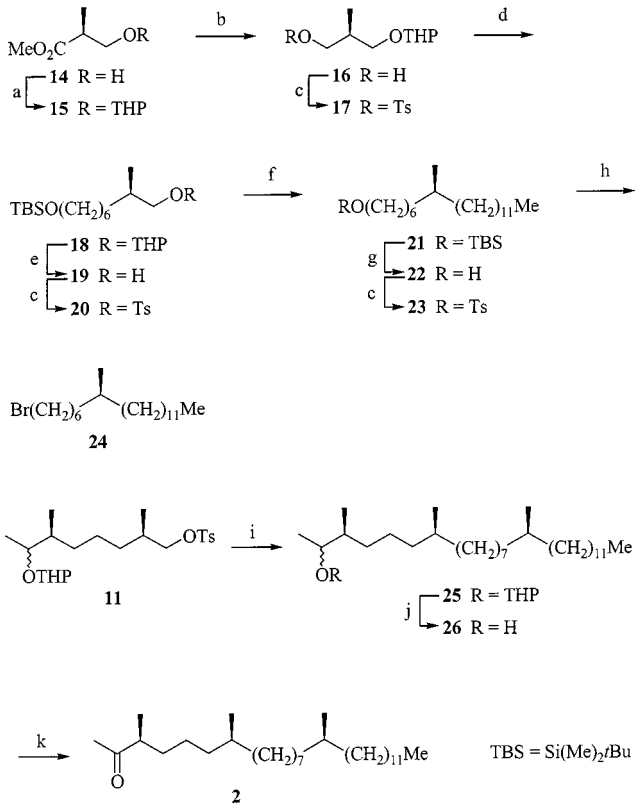


Scheme 2. Synthesis of (3*S*,7*S*)-**1**; reagents: (a) TBDPSCl, imidazole, DMF (96%); (b) K_2CO_3, MeOH (99%); (c) Dess–Martin periodinane, C_5H_5N, CH_2Cl_2 (95% for **7**; 90% for **1**); (d) MeMgBr, THF (88%); (e) DHP, *p*TsOH, Et_2O (98%); (f) Bu_4NF, THF (99%); (g) *p*TsCl, C_5H_5N (quant.); (h) $Me(CH_2)_{18}MgBr$, Li_2CuCl_4, THF (62%); (i) *p*TsOH, 90% EtOH (89%)



Scheme 3. Synthesis of (3*S*,7*S*,15*S*)-**2**; reagents: (a) DHP, *p*TsOH, Et_2O (99%); (b) $LiAlH_4$, Et_2O (94%); (c) *p*TsCl, C_5H_5N (quant.); (d) $TBSO(CH_2)_5MgBr$, Li_2CuCl_4, THF (64%); (e) $MgBr_2$, Et_2O (93%); (f) $Me(CH_2)_{10}MgBr$, Li_2CuCl_4, THF (90%); (g) Bu_4NF, THF (94%); (h) LiBr, Me_2CO (88%); (i) **24**, Mg, Li_2CuCl_4, THF (63%); (j) *p*TsOH, 90%EtOH (94%); (k) Dess–Martin periodinane, C_5H_5N, CH_2Cl_2 (94%)

droxy-2-methylpropanoate (**14**) was selected as the starting material. Reduction of the corresponding THP ether **15** with lithium aluminum hydride yielded **16**, which was tosylated to give (*S*)-**17**. The (*R*) isomer of **17** is a known compound.[7] The Schlosser coupling[6] of **17** with 5-*tert*-butyldimethylsilyl (TBS) oxypentylmagnesium bromide took place smoothly to give **18**. Removal of the THP protective group gave **19**. The corresponding tosylate **20** was coupled with undecylmagnesium bromide to give **21**, the TBS group of which was removed to afford (*S*)-7-methyl-1-nonadecanol (**22**). This was converted into the bromide **24** via the tosylate **23**. The Schlosser coupling[6] of the Grignard reagent prepared from **24** with **11** furnished **25**. Removal of the THP protective group of **25** was followed by the Dess–Martin oxidation[5] of the alcohol **26** to give (3*S*,7*S*,15*S*)-**2** as an oil. The overall yield of **2** was 23% based on **14** (13 steps) or 43% based on **4** (10 steps). Mass spectral comparison of the ketones **1** and **2** with the locust ketones proved their identity.

In conclusion (3*S*,7*S*)-**1** and (3*S*,7*S*,15*S*)-**2** were synthesized, and showed mass spectra identical with those of the natural locust ketones. As for the absolute configuration of the natural ketones, it remains undetermined due to the lack of suitable analytical methods to clarify it. Even GC analysis on a chiral stationary phase does not solve the problem at present.[8]

Experimental Section

General: IR: Jasco A-102. – ^{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) ($CDCl_3$ at δ = 77.0 as an internal standard). – Optical rotation: Jasco DIP-1000. – MS: Jeol JMS-SX102A. – M.p.: Yanaco MP-S3. – Column chromatography: Merck Kieselgel 60 Art 1.07734. – TLC: 0.25 mm Merck silica gel plates (60F-254).

(2*S*/*R*,3*S*,7*R*)-8-*tert*-Butyldiphenylsilyloxy-3,7-dimethyl-2-octanol (8): To a solution of **7**[4] (2.74 g, 6.91 mmol) in dry THF (60 mL) under argon 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 **8** as a colorless oil; n_D^{26} = 1.5249. – $[\alpha]_D^{23}$ = –7.7 (*c* = 0.99, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (m, O–H), 1590 (w, aromatic), 1110 (s, Si–O), 705 (s). – ^{1}H 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 (each d, *J* = 6.4 Hz, total 3 H, 1-H_3), 1.00–1.80 (m, 9 H, 3-, 7-H, 4–6-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). – $C_{26}H_{40}O_2Si$ (412.7): calcd. C 75.67, H 9.77; found C 75.55 H 9.85. – 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*)-**8**, 66.4%], 21.5 [(2*R*,3*S*)-**8**, 33.6%]. The diastereomer ratio of (2*S*,3*S*)-**8**/(2*R*,3*S*)-**8** was 2:1.

(2*R*,6*S*,7*R*/*S*)-1-*tert*-Butyldiphenylsilyloxy-2,6-dimethyl-7-tetrahydropyranyloxyoctane (9): To a solution of **8** (0.44 g, 1.07 mmol) in dry diethyl ether (7 mL) was added 3,4-dihydro-2*H*-pyran (DHP, 0.15 mL, 1.66 mmol) and *p*-toluenesulfonic acid monohydrate (0.03 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 (10 g, hexane/ethyl acetate, 200:1) to give 520 mg (98%) of **9** as a colorless oil; n_D^{26} = 1.5165. – $[\alpha]_D^{21}$ = +2.62 (*c* = 1.02, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1590 cm^{-1} (w, aromatic), 1250 (m, *t*Bu), 1200 (m, C–O), 1115 (s, Si–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.92 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.00–1.90 (m, 17 H, 2-, 6-H, 3–5-H_2, 3′–5′-H_2 and 8-H_3), 3.30–4.10 (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). This was employed in the next step without further purification.

(2*R*,6*S*,7*R*/*S*)-2,6-Dimethyl-7-tetrahydropyranyloxy-1-octanol (10): To a solution of **9** (520 mg, 1.05 mmol) in dry THF (5 mL) was added Bu_4NF (1.0 M solution in dry THF, 1.3 mL, 1.3 mmol) at room temperature. After stirring at room temperature for 2 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 (15 g, hexane/ethyl acetate, 20:1) to give 270 mg (99%) of **10** as a colorless oil; n_D^{26} = 1.4596. – $[\alpha]_D^{26}$ = +3.63 (*c* = 1.05, hexane). – IR (film): $\tilde{\nu}$ = 3420 cm^{-1} (s, O–H), 1200 (m, C–O), 1110 (m) 1040 (s, C–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.90 (d, *J* = 6.4 Hz, 3 H, 6-CH_3), 1.00–1.90 (m, 18 H, 2-, 6-H, 3–5-H_2, 3′–5′-H_2, 8-H_3 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 11.74; found C 69.81, H 11.71.

(2*R*,6*S*,7*R*/*S*)-2,6-Dimethyl-7-tetrahydropyranyloxyoctyl Tosylate (11): To a solution of **10** (233 mg, 0.90 mmol) in dry pyridine (4 mL) was added *p*-toluenesulfonyl chloride (259 mg, 1.36 mmol) at 0 °C. After stirring at this temperature for 10 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 373 mg (quant.) of crude **11**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (m, aromatic), 1360 (m, SO_2), 1200 (m, C–O), 1190 (s, SO_2), 1180 (s, SO_2), 1025 (m, C–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 6 H, 2-, 6-CH_3), 0.90–2.00 (m, 17 H, 2-, 6-H, 3–5-H_2, 3′–5′-H_2 and 8-CH_3), 2.45 (s, 3 H, Ar-CH_3), 3.20–4.10 (m, 3 H, 7-H and 6′-H_2), 3.84 (dd, *J* = 2.0, 5.9 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*R*/*S*,3*S*,7*S*)-3,7-Dimethyl-2-tetrahydropyranyloxyheptacosane (12): Preparation of the Grignard reagent. Magnesium (66 mg, 2.7 mmol) was added to an argon-purged flask. To the metal was added dropwise a solution of $Me(CH_2)_{18}Br$ (556 mg, 1.60 mmol) in dry THF (8 mL), and the mixture was stirred for 2 h under reflux. The resulting solution was used immediately. Under argon, to a solution of **11** (125 mg, 0.303 mmol) in dry THF (3 mL) was added the Grignard reagent solution and a solution (0.1 M, 0.1 mL, 0.01 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 for a further 48 h. The mixture was quenched with saturated aqueous NH_4Cl, 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 (12 g, hexane/ethyl acetate, 300:1) to give 95 mg (62%) of **12** as a colorless oil; n_D^{25} = 1.4511. – $[\alpha]_D^{22}$ = –1.1 (*c* = 0.97, hexane). – IR (film): $\tilde{\nu}$ = 1200 cm^{-1} (m, C–O), 1120 (m), 1080 (m), 1025 (s, C–O). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.92 (m, 9 H, 3-, 7-CH_3 and 27-H_3), 1.02, 1.05, 1.13, 1.17 (each d, *J* = 6.3 Hz, total 3 H, 1-H_3), 1.00–1.72 (m, 51 H, 4–6-, 8–26-, 3′–5′-H_2 and 7-H), 1.82 (m, 1 H, 3-H), 3.48 (m, 1 H, 6′-H_a), 3.56–3.66 (m, 1 H, 2-H), 3.91 (m, 1 H, 6′-H_b), 4.60, 4.70 (each br, total 1 H, 2′-H). – $C_{34}H_{68}O_2$ (508.9): calcd. C 80.24, H 13.47; found C 80.67, H 13.11.

(2*R*/*S*,3*S*,7*S*)-3,7-Dimethyl-2-heptacosanol (13): To a solution of **12** (95 mg, 0.19 mmol) in 90%EtOH (5 mL) was added *p*-toluenesulfonic acid monohydrate (5.0 mg, 0.03 mmol) and the mixture was stirred for 4 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, 100:1) to give 71 mg (89%) of **13**. This was recrystallized from pentane as white powder; m.p. 51.0–52.5 °C – $[\alpha]_D^{23}$ = –2.77 (*c* = 1.01, hexane). – IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (s, O–H), 2820 (vs), 1460 (s), 1375 (s). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.6 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 6.7 Hz, 3 H, 27-H_3), 0.89 (d, *J* = 6.6 Hz, 3 H, 3-CH_3), 1.12, 1.15 (each d, *J* = 6.3 Hz, total 3 H, 1-H_3), 1.00–1.67 (m, 47 H, 3-, 7-H, 4–6-, 8–26-H_2 and OH), 3.63–3.74 (m, 1 H, 2-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.09, 14.14, 19.8, 20.3, 22.7, 24.7, 27.0, 29.3, 29.6, 29.66, 29.69, 30.0, 31.9, 32.7, 33.0, 37.0, 37.3, 39.8, 71.3. – $C_{29}H_{60}O$ (424.8): calcd. C 82.00, H 14.24; found C 81.82, H 14.60.

(3*S*,7*S*)-3,7-Dimethyl-2-heptacosanone (1): To a solution of Dess–Martin periodinane (55 mg, 0.13 mmol) in dry CH_2Cl_2 (3 mL) under argon was added pyridine (0.10 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **13** (37 mg, 0.087 mmol) in dry CH_2Cl_2 (2 mL) was then added dropwise at room temperature. After stirring for 2 h, the mixture was diluted with Et_2O and quenched by adding solutions of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous sodium thiosulfate (3 mL). The resulting mixture was stirred for 10 min, and extracted with Et_2O. 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 (3 g, hexane/ethyl acetate, 500:1) to give 33 mg (90%) of **1**. This was recrystallized from EtOH to give crystalline **1** as colorless needles; m.p. 39.0–40.0 °C – $[\alpha]_D^{24}$ = +4.4 (*c* = 0.75, hexane). – IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1} (s), 2860 (s), 1710 (s, C=O), 1465 (s), 1360 (s), 1180 (w), 1160 (w), 960 (w), 725 (m). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.7 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 7.0 Hz, 3 H, 27-H_3), 1.08 (d, *J* = 7.0 Hz, 3 H, 3-CH_3), 1.04–1.37 (m, 44 H, 4–6-, 8–26-H_2), 1.63 (m, 1 H, 7-H), 2.13 (s, 3 H, 1-H_3), 2.50 (sextet like, *J* = 6.8 Hz, 1 H, 3-H). – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1, 16.2, 19.6, 22.7, 24.7, 27.1, 28.0, 29.4, 29.65, 29.70, 30.0, 31.9, 32.6, 33.6, 37.0, 37.1, 47.3, 213.0. – EI MS (as measured by Prof. Dr. W. Francke); *m*/*z* (%): 422 (19) [M^+], 404 (1) [$(M - H_2O)^+$], 375 (1), 348 (2), 141 (6), 123 (5), 111 (4), 97 (2), 85 (8), 72 (100), 57 (11), 43 (12). – HRMS ($C_{29}H_{58}O$): calcd. 422.4488; found 422.4503. – $C_{29}H_{58}O$ (422.8): calcd. C 82.39, H 13.83; found C 82.17, H 14.12. – GC [column: TC-wax 0.53 mm × 15 m, 170 to 200 °C, +10.0 °C/min; carrier gas: He, pressure 110 kPa]: t_R = 12.9 min [**1**, 97.9%].

Methyl (*S*)-2-Methyl-3-tetrahydropyranyloxypropanoate (15): According to the reported procedure for (*R*)-**15**,[7] compound **14** (21.0 g, 178 mmol) was converted into 35.8 g (99%) of (*S*)-**15** which was isolated as a colorless oil, b.p. 102–105 °C/7 Torr. n_D^{25} = 1.4379. – $[\alpha]_D^{21}$ = +16.5 (*c* = 1.10, Et_2O) {ref[7] $[\alpha]_D^{21}$ = –16.3 (*c* = 1.39, Et_2O) for the (*R*)-enantiomer}. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (S, C=O), 1200 (m, C–O), 1125 (s, C–O), 1040 (s, C–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 3 H, 2-CH_3), 1.30–1.90 (m, 6 H, 3′–5′-H_2), 2.77 (sext-like, *J* = 6.8 Hz, 1 H, 2-H), 3.35–4.01 (m, 4 H, 3-H_2 and 6′-H_2), 3.69 (s, 3 H, CO_2CH_3), 4.61 (br, 1 H, 2′-H).

(*R*)-2-Methyl-3-tetrahydropyranyloxy-1-propanol (16): According to the reported procedure for (*S*)-**16**,[7] compound **15** (34.6 g, 171 mmol) was converted into 27.9 g (94%) of (*R*)-**16** which was isolated as a colorless oil, b.p. 111–113 °C/6 Torr. – n_D^{26} = 1.4547. – $[\alpha]_D^{27}$ = +1.27 (*c* = 1.07, Et_2O) {ref[7] $[\alpha]_D^{21}$ = –1.2 (*c* = 1.47, Et_2O) for the (*S*)-enantiomer}. – IR (film): $\tilde{\nu}$ = 3420 cm^{-1} (s, O–H), 1200 (m, C–O), 1120 (s, C–O), 1030 (s, C–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.20–1.90 (m, 6 H, 3′–5′-H_2), 1.98 (m, 1 H, 2-H), 2.39 (br, 1 H, OH), 3.24–3.98 (m, 6 H, 1-, 3-, 6′-H_2), 4.56 (br, 1 H, 2′-H).

(*S*)-2-Methyl-3-tetrahydropyranyloxypropyl Tosylate (17): According to the reported procedure for (*R*)-**17**,[7] compound **16** (5.00 g, 28.7 mmol) gave 10.5 g (quant.) of crude (*S*)-**17**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (s, aromatic), 1360 (s, SO_2), 1190 (s, SO_2), 1180 (s, SO_2), 1120 (s, C–O), 1030 (s, C–O), 665 (s, C–S). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz 3 H, 2-CH_3), 1.20–1.90 (m, 6 H, 3′–5′-H_2), 2.08 (m, 1 H, 2-H), 2.44 (s, 3 H, Ar-CH_3), 3.09–4.18 (m, 6 H, 1-, 3-, 6′-H_2), 4.34 (br, 1 H, 2′-H), 7.33 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.80 (d, *J* = 8.2 Hz, 2 H, Ar-H).

(*R*)-8-*tert*-Butyldimethylsilyloxy-2-methyl-1-tetrahydropyranyloxyoctane (18): Preparation of the Grignard reagent. Magnesium (2.59 g, 107 mmol) was added to an argon-purged flask. To the metal was added dropwise a solution of 5-*tert*-butyldimethylsilyloxypentyl bromide (20.0 g, 71.1 mmol) in dry THF (70 mL), and the mixture was stirred at 45 °C for 1 h. The resulting solution was used immediately. To a solution of **17** (10.5 g, ca. 28.7 mmol) in dry THF (60 mL) under argon was added the Grignard reagent solution and a solution (0.5 M, 1.2 mL, 0.60 mmol) of Li_2CuCl_4 in dry THF at –78 °C. After stirring at –78 °C for 1 h, the mixture was warmed slowly to 0 °C, and stirred at this temperature for 20 h. The mixture was quenched with saturated aqueous NH_4Cl, 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 (150 g, hexane/ethyl acetate (200:1) to give 6.55 g (64%) of **18** as a colorless oil; n_D^{25} = 1.4494. – $[\alpha]_D^{22}$ = –0.88 (*c* = 1.02, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1255 cm^{-1} (m, *t*Bu), 1200 (m, C–O), 1100 (s, Si–O), 1025 (s, C–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Si–CH_3), 0.89 (s, 9 H, *t*Bu), 0.90, 0.92 (each d, *J* = 6.4 Hz, total 3 H, 2-CH_3), 1.00–1.90 (m, 17 H, 3–7-, 3′–5′-H_2 and 2-H), 3.04–3.93 (m, 6 H, 2-H, 1-, 6-, 6′-H_2), 4.55 (br, 1 H, 2′–H). – $C_{20}H_{42}O_3Si$ (358.6): calcd. C 66.98, H 11.80; found C 67.07, H 11.63.

(*R*)-8-*tert*-Butyldimethylsilyloxy-2-methyl-1-octanol (19): To a solution of **18** (4.98 g, 13.9 mmol) in dry Et_2O (150 mL) was added anhydrous $MgBr_2$ (7.67 g, 41.7 mmol) at room temperature. After stirring for 4 h, the mixture was 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. The residue was chromatographed on silica gel (150 g, hexane/ethyl acetate, 20:1) to give 3.55 g (93%) of **19** as a colorless oil; n_D^{26} = 1.4462. – $[\alpha]_D^{22}$ = +6.83 (*c* = 1.00, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3350 cm^{-1} (m, O–H), 1255 (m, *t*Bu), 1100 (s, Si–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Si–CH_3), 0.89 (s, 9 H, *t*Bu), 0.91 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 1.00–1.80 (m, 12 H, 2-H, 3–7-H_2 and OH), 3.39 (dd, *J* = 6.1, 10.3 Hz, 1 H, 1-H_a), 3.53 (dd, *J* = 5.7, 10.3 Hz, 1 H, 1-H_b), 3.60 (t, *J* = 6.2 Hz, 2 H, 8-H_2). – $C_{15}H_{34}O_2Si$ (274.5): calcd. C 65.63, H 12.48; found C 65.19, H 12.56.

(*R*)-8-*tert*-Butyldimethylsilyloxy-2-methyloctyl Tosylate (20): To a solution of **19** (3.00 g, 10.9 mmol) in dry pyridine (20 mL) was added *p*-toluenesulfonyl chloride (3.03 g, 15.9 mmol) at 0 °C. After stirring at 0 °C for 12 h, the mixture was poured into ice and water, and extracted with CH_2Cl_2. 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 4.75 g (quant.) of crude **20**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (s, aromatic), 1360 (s, SO_2), 1250 (m, *t*Bu), 1190 (s, SO_2), 1180 (s, SO_2), 1100 (s, Si–O), 665 (s, C–S). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Si–CH_3), 0.87 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.89 (s, 9 H, *t*Bu), 1.00–1.90 (m, 11 H, 2-H and 3–7-H_2), 2.45 (s, 3 H, Ar-CH_3), 3.58 (t, *J* = 6.2 Hz, 2 H, 8-H_2), 3.77 (dd, *J* = 6.2 Hz, *J* = 9.3 Hz, 1 H, 1-H_a), 3.90 (dd, *J* = 5.9 Hz, *J* = 9.3 Hz, 1 H, 1-H_b), 7.34 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.79 (d, *J* = 8.2 Hz, 2 H, Ar-H).

(*S*)-1-*tert*-Butyldimethylsilyloxy-7-methylnonadecane (21): Preparation of the Grignard reagent. Magnesium (1.59 g, 65.4 mmol) was added to an argon-purged flask. To the metal was added dropwise a solution of undecyl bromide (10.3 g, 43.8 mmol) in dry THF (80 mL), and the mixture was stirred at 45 °C for 1 h. The resulting solution was used immediately. To a solution of **20** (4.75 g, 10.9 mmol) in dry THF (50 mL) under argon was added the Grignard reagent solution and a solution (0.5 M, 0.6 mL, 0.30 mmol) of Li_2CuCl_4 in dry THF at –78 °C. After stirring at –78 °C for 1 h, the mixture was warmed slowly to 0 °C, and stirred 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 (100 g, hexane) to give 4.34 g (96%) of **21** as a colorless oil; n_D^{25} = 1.4474. – $[\alpha]_D^{26}$ = –0.53 (*c* = 1.47, hexane). – IR (film): $\tilde{\nu}$ = 1255 cm^{-1}, (m, *t*Bu), 1105 (s, Si–O), 835 (s), 775 (s). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Si–CH_3), 0.84 (d, *J* = 6.3 Hz, 3 H, 7-CH_3), 0.87 (t, *J* = 6.6 Hz, 3 H, 19-H_3), 0.90 (s, 9 H, *t*Bu), 1.00–1.70 (m, 33 H, 2–6-, 8–18-H_2 and 7-H), 3.60 (t, *J* = 6.3 Hz, 2 H, 1-H_2). – $C_{26}H_{56}OSi$ (412.8): calcd. C 75.65, H 13.67; found C 75.51, H 13.45.

(*S*)-7-Methyl-1-nonadecanol (22): To a solution of **21** (4.13 g, 10.0 mmol) in dry THF (40 mL) was added Bu_4NF (1.0 M solution in dry THF, 15.0 mL, 1.50 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 (70 g, hexane/ethyl acetate, 25:1) to give 2.81 g (94%) of **22**; n_D^{25} = 1.4535. – $[\alpha]_D^{23}$ = –0.67 (*c* = 0.99, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (s, O–H), 1465 (s), 1380 (m), 1060 (s), 725 (m). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.3 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 6.6 Hz, 3 H, 19-H_3), 1.00–1.70 (m, 34 H, 2–6-, 8–18-H_2, 2-H and OH), 3.64 (t, *J* = 6.4 Hz, 2 H, 1-H_2). – $C_{20}H_{42}O$ (298.6): calcd. C 80.46, H 14.18; found C 80.32, H 14.43.

(*S*)-7-Methylnonadecyl Tosylate (23): To a solution of **22** (2.00 g, 7.00 mmol) in dry pyridine (20 mL) and dry CH_2Cl_2 (40 mL) was

added *p*-toluenesulfonyl chloride (2.17 g, 11.4 mmol) at 0 °C. After stirring at 0 °C for 10 h, the mixture was poured into ice and 1 M hydrochloric acid and extracted with CH_2Cl_2. 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 3.18 g (quant.) of crude **23**. This was employed in the next step without further purification; IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (s, aromatic), 1365 (s, SO_2), 1190 (s, SO_2), 1180 (s, SO_2), 665 (s, C–S). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.78–0.91 (m, 6 H, 7-CH_3 and 19-H_3), 1.00–1.80 (m, 33 H, 2–6-, 8–18-H_2 and 2-H), 2.45 (s, 3 H, Ar-CH_3), 4.02 (t, *J* = 6.4 Hz, 2 H, 1-H_2), 7.33 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.83 (d, *J* = 8.2 Hz, 2 H, Ar-H).

(*S*)-7-Methylnonadecyl Bromide (24): To a solution of **23** (3.18 g, 7.0 mmol) in dry acetone (50 mL) was added lithium bromide (0.99 g, 11.4 mmol) at room temperature. After stirring for 6 h under reflux, the mixture was concentrated in vacuo. The residue 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, 100:1) to give 2.23 g (88%) of **24** as a colorless oil; n_D^{26} = 1.4630. – $[\alpha]_D^{26}$ = –0.62 (*c* = 1.02, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (s, C–H), 2850 (s, C–H), 1465 (m, C–H), 1375 (m, C–H), 1255 (m), 725 (m). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 6.9 Hz, 3 H, 19-H_3), 1.05–1.46 (m, 31 H, 7-H, 3–6-, 8–18-H_2), 1.85 (quint-like, *J* = 7.2 Hz, 2 H, 2-H_2), 3.41 (t, *J* = 6.9 Hz, 2 H, 1-H_2); – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1, 19.7, 22.7, 26.9, 27.1, 28.2, 29.1 29.4, 29.65, 29.70, 29.73, 30.0, 31.9, 32.7, 32.9, 34.0, 36.9, 37.1. – $C_{20}H_{41}Br$ (361.44): calcd. C 66.46, H 11.43; found C 66.59, H 11.68.

(2*R*/*S*,3*S*,7*S*,15*S*)-3,7,15-Trimethyl-2-tetrahydropyranyloxyheptacosane (25): Preparation of the Grignard reagent. Magnesium (131 mg, 5.39 mmol) was added to an argon-purged flask. To the metal was added dropwise a solution of bromide **24** (1.30 g, 3.60 mmol) in dry THF (10 mL), and the mixture was stirred for 2 h under reflux. The resulting solution was used immediately. To a solution of **11** (300 mg, 0.73 mmol) in dry THF (5 mL) under argon was added the Grignard reagent solution and a solution (0.1 M, 0.2 mL, 0.02 mmol) of Li_2CuCl_4 in THF at –78 °C. After stirring at –78 °C for 1 h, the mixture was warmed slowly to 0 °C, and stirred 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 K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (30 g, hexane/ethyl acetate, 300:1) to give 239 mg (63%) of **25** as a colorless oil; n_D^{26} = 1.4613. – $[\alpha]_D^{23}$ = –3.53 (*c* = 1.00, hexane). – IR (film): $\tilde{\nu}$ = 1205 cm^{-1} (m, C–O), 1120 (m), 1080 (m), 1020 (s, C–O). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.92 (m, 12 H, 3-, 7-, 15-CH_3 and 27-H_3), 1.02, 1.05, 1.13, 1.17 (each d, *J* = 6.4 Hz, total 3 H, 1-H_3), 1.00–1.75 (m, 50 H, 7-, 15-H and 4–6-, 8–14-, 16–26-, 3′–5′-H_2), 1.82 (m, 1 H, 3-H), 3.48 (m, 1 H, 6′-H_a), 3.56–3.67 (m, 1 H, 2-H), 3.91 (m, 1 H, 6′-H_b), 4.60, 4.70 (each br, total 1 H, 2′-H). – $C_{35}H_{70}O_2$ (522.9): calcd. C 80.39, H 13.49; found C 80.33, H 13.66.

(2*R*/*S*,3*S*,7*S*,15*S*)-3,7,15-Trimethyl-2-heptacosanol (26): To a solution of **25** (150 mg, 0.29 mmol) in 90% EtOH (15 mL) was added *p*-toluenesulfonic acid monohydrate (10.0 mg, 0.06 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 (4 g, hexane/ethyl acetate, 100:1) to give 119 mg (94%) of **26** as a colorless oil; n_D^{26} = 1.4599. – $[\alpha]_D^{23}$ = –6.74 (*c* = 1.00, hexane). – IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (s, O–H), 2820 (vs), 1460 (s), 1375 (s). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.4 Hz, 3 H, 15-CH_3), 0.84 (d, *J* = 6.2 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 7.2 Hz, 3 H, 27-H_3), 0.89 (d, *J* = 7.0 Hz, 3 H, 3-CH_3), 1.12, 1.15 (each d, *J* = 6.4 Hz, total 3 H, 1-H_3), 1.00–1.50 (m, 46 H, 3-, 7-, 15-H, 4–6-, 8–14-, 16–26-H_2 and OH), 3.64–3.74 (m, 1 H, 2-H). – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1, 14.2, 19.3, 19.7, 19.8, 20.3, 22.7, 24.7 24.8, 27.1, 29.4, 29.65, 29.73, 29.8, 30.0, 31.9, 32.7, 32.9, 33.0, 37.0, 37.1, 37.4, 39.8, 40.1, 71.4. – $C_{30}H_{62}O$ (438.8): calcd. C 82.11, H 14.24; found C 82.16, H 13.96.

(3*S*,7*S*,15*S*)-3,7,15-Trimethyl-2-heptacosanone (2): Under argon, to a solution of Dess–Martin periodinane (108 mg, 0.256 mmol) in dry CH_2Cl_2 (5 mL) was added pyridine (0.10 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **26** (75 mg, 0.171 mmol) in dry CH_2Cl_2 (3 mL) was then added dropwise at room temperature. After stirring for 1 h, the mixture was diluted with Et_2O and quenched by adding solutions of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous sodium thiosulfate (10 mL). The resulting mixture was stirred for 10 min and then extracted with Et_2O. 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 (3 g, hexane/ethyl acetate, 500:1) to give 70 mg (94%) of **2** as a colorless oil; n_D^{26} = 1.4542. – $[\alpha]_D^{25}$ = +5.91 (*c* = 1.01, hexane). – IR (film): $\tilde{\nu}$ = 2930 cm^{-1} (s), 2860 (s), 1715 (s, C=O), 1460 (s), 1375 (m), 1355 (m), 1165 (w), 1140 (w), 950 (w), 720 (m). – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.4 Hz, 3 H, 15-CH_3), 0.84 (d, *J* = 6.4 Hz, 3 H, 7-CH_3), 0.88 (t, *J* = 7.0 Hz, 3 H, 27-H_3), 1.08 (d, *J* = 7.0 Hz, 3 H, 3-CH_3), 1.04–1.35 (m, 43 H, 4–6-, 8–14-, 16–26-H_2 and 15-H), 1.63 (m, 1 H, 7-H), 2.13 (s, 3 H, 1-H_3), 2.50 (sext-like, *J* = 6.8 Hz, 1 H, 3-H). – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1, 16.2, 19.63, 19.71, 22.7, 24.7, 27.06, 27.08, 28.0, 29.3 29.6, 29.70, 29.72, 29.8, 30.01, 30.03, 31.9, 32.62, 32.74, 33.3, 37.0, 37.06, 37.10, 47.2, 213.0. – EI MS (as measured by Prof. Dr. W. Francke); *m*/*z* (%): 436 (30) [M^+], 418 (4) [$(M - H_2O)^+$], 389 (2), 362 (5), 151 (1), 141 (8), 123 (7), 111 (7), 97 (3), 85 (8), 72 (100), 57 (13), 43 (12). – HRMS [$C_{30}H_{60}O$]: calcd. 436.4644; found 436.4655. – $C_{30}H_{60}O$ (436.8): calcd. C 82.49, H 13.85; found C 82.27, H 13.76. – GC [column: TC-wax 0.53 mm × 15 m, 170 to 200 °C, +10.0 °C/min; carrier gas: He, pressure 110 kPa]: t_R = 12.9 min [**2**, 97.6%].

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