New Syntheses of the Rice Moth and Stink Bug Pheromones by Employing (2R, 6S)-7-Acetoxy-2,6-dimethyl-1-heptanol as a Building Block†

Yoshihide Nakamura†† and Kenji Mori†††

Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-8601, Japan

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(2R, 6R, 10R)-6,10,14-Trimethyl-2-pentadecanol, the female pheromone of the rice moth (Corcyra cephalonica), and methyl (2R, 6R, 10R)-2,6,10-trimethyltridecanoate, the male pheromone of the stink bug (Euschistus heros) were synthesized by employing (2R, 6S)-7-acetoxy-2,6-dimethyl-1-heptanol as the common chiral building block.

Key words: Corcyra cephalonica; Euschistus heros; pheromone; rice moth; stink bug

There are many aliphatic insect pheromones and terpenoids which possess syn-oriented methyl groups at the 1,5-positions of their carbon chains. (2R, 6R, 10R)-6,10,14-Trimethyl-2-pentadecanol (1, Scheme 1), the pheromone of the female rice moth (Corcyra cephalonica), and methyl (2R, 6R, 10R)-2,6,10-trimethyltridecanoate (2), the pheromone of the male stink bug (Euschistus heros), belong to that group of pheromones. Previously, both 1 and 2 have been synthesized by utilizing three chiral building blocks to construct their carbon skeletons with three stereogenic centers. Such stepwise and linear synthetic approaches are unfortunately inefficient. If one can obtain meso-2,6-dimethyl-1,7-heptanediol (A) and desymmetrize it to give a (2R, 6S)-monooacetate (B), meso-A and chiral B will serve as useful building blocks in organic synthesis to enable one to construct the two stereogenic centers with syn-1,5-dimethyl groups. In 1996, Chénervat and Desjardins achieved the lipase-catalyzed asymmetric acetylation of A to give B. We have recently employed A and B to efficiently synthesize pheromones with two or three methyl branchings such as pine sawfly (Microdiprion pallipes) pheromone components C and D, pheromone component E of the spring hemlock looper (Lambdina athisaria), and secretions F and G of the locust (Schistocerca gregaria). In continuation of this project to demonstrate the usefulness of building blocks A and B in pheromone synthesis, we now report new syntheses of rice moth pheromone 1 and stink bug pheromone 2 starting from B.

In 1991, four stereoisomers of rice moth pheromone 1 were synthesized and bioassayed. The results indicated (2R, 6R, 10R)-1 to be as active as the natural pheromone, while (2S, 6S, 10S)-1 was inactive. We envisaged, as shown in Scheme 1, that (2R, 6R, 10R)-1 could be efficiently prepared by connecting two minor building blocks to the central building block derived from B. Scheme 2 summarizes the new synthesis of (2R, 6R, 10R)-1 based on this idea. The right-hand part of the target molecule originated from commercially available ethyl (R)-3-hydroxybutanoate (3, 100% ee) which was converted to known iodide 4. Chiral building block B (95% ee) was converted to known tosylate 5, whose chain was elongated by treating with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate to give 6. Removal of the tert-butyldiphenylsilyl (TBDPS) group of 6 yielded free alcohol 7. The corresponding tosylate gave phenylsulfone 9 via iodide 8. Alkylation of the anion derived from 9 with iodide 4 furnished 10, which was reduced with sodium amalgam to give 11. Final deprotection of its tert-butyldimethylsilyl (TBS)-protected hydroxy group afforded the rice moth pheromone, (2R, 6R, 10R)-1. The overall yield of 1 was 45% based on B (11 steps). In our 1991 synthesis, (2R, 6R, 10R)-1 was obtained in a 29% overall yield (12 steps) starting from (R)-citronellol.

Immediately after the identification of methyl 2,6,10-trimethyltridecanoate (2) as a male-specific volatile from stink bugs, we carried out its synthesis, first as a stereoisomeric mixture and then as eight individual stereoisomers including (2R, 6R, 10R)-2. Borges et al. have confirmed the attractiveness of the stereoisomeric mixture of 2 to females of the neotropical brown stink bug (Euschistus heros) by a laboratory bioassay. In a field bioassay, although the result was not so clear, 2 was shown to attract not...
only *E. heros*, but also its hymenopteran egg parasite such as *Telenomus podisi*. It is therefore evident that 2 acts both as a pheromone and a kairomone.

Our retrosynthetic analysis of (2R, 6R, 10R)-2 shown in Scheme 1 brought about its new synthesis from B shown in Scheme 3. The starting material for the right-hand part of the target molecule was commercially available (R)-3-tert-butyloxycarbonyl-2-methylpropanoic acid (12, 100% ee) which was reduced with a borane-dimethyl sulfide complex to give 13. After protecting the hydroxy group of 13 as a TBS ether, resulting 14 was reduced with diisobutylaluminum hydride to afford alcohol 15. Corresponding iodide 16 was prepared in the conventional manner via the tosylate of 15. The rest of the molecule was constructed from known tosylate [5] which was prepared from B (95% ee). Treatment of 5 with ethylmagnesium bromide in the presence of dilithium tetrachlorocuprate [10] yielded 17. Subsequent removal of the TBDPS protective group of 17 furnished alcohol 18, from which corresponding iodide 19 was prepared under the conventional conditions. Iodide 19 was then treated with sodium phenylsulfinate to give phenylsulfone 20.

Alkylation of the carbanion derived from 20 with iodide 16 provided 21 with the whole carbon skeleton of the target molecule. Removal of the phenylsulfonyl group of 21 was achieved by reduction with sodium amalgam to furnish 22. Deprotection of the TBS protective group of 22 afforded alcohol 23, which was oxidized with Jones chromic acid to give carboxylic acid 24. Under the conditions of the Jones oxidation, no epimerization at C-2 took place as already reported by us. 6 Finally, esterification of acid 24 with diazomethane yielded the stink bug pheromone, (2R, 6R, 10R)-2, which showed a single peak by GC analysis. The overall yield of 2 was 46% based on B (13 steps). In our 1994 synthesis, the overall yield of (2R, 6R, 10R)-2 was 25% (16 steps) starting from (R)-citronellol. 8 Hopefully, the present sample of (2R, 6R, 10R)-2, together with the previous samples, 4 will serve to clarify the absolute configuration of the natural pheromone.

In conclusion, both the rice moth and stink bug pheromones, 1 and 2, were efficiently synthesized by employing (2R, 6S)-7-acetoxy-2,6-dimethyl-1-heptanol (B) as the common chiral building block.
Scheme 2. Synthesis of Rice Moth Pheromone 1.
Reagents: (a) Me₂CH(CH₃)₂MgBr, Li₃CoCl₃, THF (91%). (b) (n-Bu)₃NF, THF (94% for 7; 98% for 11). (c) i) TiCl₃, C₅H₇N; ii) NaI, Me₂CO (94%). (d) PhSO₂Na, DMF (89%). (e) n-BuLi, 4, THF, HMPA (84%). (f) Na₂-Hg, EtOH (80%).

Reagents: (a) TBSCI, imidazole, DMF (96%). (b) (n-Bu)₂AlH, CH₂Cl₂ (86%). (c) i) TiCl₃, C₅H₇N; ii) NaI, NaHCO₃, Me₂CO (89% for 16; 94% for 19). (d) EtMgBr, Li₃CoCl₃, THF (91%). (e) (n-Bu)₃NF, THF (97% for 18; 99% for 23). (f) PhSO₂Na, DMF (89%). (g) n-BuLi, 16, THF, HMPA (96%). (h) Na₂-Hg, EtOH (82%). (i) Jones CrO₃, Me₂CO (91%). (j) CH₃N₂, Et₂O (92%).
Experimental

IR: Jasco A-102; 1H-NMR: Jeol JNM-EX 90A (90 MHz) and Jeol JNM-LA500 (500 MHz) with TMS at $\delta = 0.00$ or CHCl$_3$ at $\delta = 7.26$ as an internal standard; 13C-NMR: Jeol JNM-LA500 (125 MHz) with CDCl$_3$ at $\delta = 77.0$ as an internal standard; optical rotation: Jasco DIP-1000; column chromatography: Merck Kieselgel 60 Art 1.07734; TLC: 0.25 mm Merck silica gel plates (60F254). THF was used and distilled from sodium and benzophenone.

(2R, 6R)-1-tert-Butylidenephosphitylxylo-2, 6, 10-trimethylundecane (6). The Grignard reagent was prepared by adding magnesium (790 mg, 32.5 mmol) to an argon-purged flask. The metal was added dropwise a solution of 3-methylbutyl bromide (3.78 g, 25.0 mmol) in dry THF (20 ml), and the mixture was stirred at 40°C for 1 h. The resulting solution was used immediately. Under an argon atmosphere, to a solution of crude tosylate $5^\circ$ (2.79 g, ca. 5.02 mmol) in dry THF (15 ml) were added this Grignard reagent and a solution of (0.5 m, 0.5 ml, 0.25 mmol) of Li$_2$CuCl$_4$ in dry THF at $-78^\circ$C. After stirring at $-78^\circ$C for 1 h, the mixture was warmed slowly to 0°C, and then stirred at 0°C for 24 h. The mixture was quenched with saturated aqueous NH$_4$Cl, 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 (60 g; hexane/ethyl acetate, 500:1) to give 2.08 g (91%) of 6 as a colorless oil; $n_D^{15}$ 1.5064; $[\alpha]_D^{20} + 0.72^\circ$ (c 1.04, CHCl$_3$). IR $\nu_{max}$ (film) cm$^{-1}$: 1590 (m, aromatic), 1110 (s, Si-O). NMR $\delta$H (90 MHz, CDCl$_3$): 0.86 (9H, d, J = 6.2 Hz, 6-, 10-CH$_3$, 11-H$_3$), 0.92 (3H, d, J = 6.4 Hz, 2-CH$_3$), 1.05 (9H, s, tert-Bu), 1.00--1.80 (15H, m, 2-, 6-, 10-H), 3.54 (1H, dd, J = 5.9, 9.6 Hz, 1-H$_3$), 1.10 (9H, m, Ar--H), 7.62--7.73 (4H, m, Ar-H). Anal. Found: C, 79.59; H, 10.63%. Calcd. for C$_{38}$H$_{58}$O: C, 79.58; H, 10.69%.

(2R, 6R)-2, 6, 10-Trimethyl-1-undecane (7). Under an argon atmosphere, to a solution of 6 (1.96 g, 4.33 mmol) in dry THF (25 ml) was added an (n-Bu)$_3$NF [a 1.0 m solution in dry THF (6.5 ml, 6.5 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 successively washed with saturated aqueous NaHCO$_3$ and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g; hexane/ethyl acetate, 100:1) to give 0.87 g (94%) of 7 as a colorless oil; $n_D^{15}$ 1.4429; $[\alpha]_D^{20} + 10.1^\circ$ (c 1.00, methanol) [ref. 3 $n_D^{15}$ 1.4417; $[\alpha]_D^{20} + 10.6^\circ$ (c 0.995, methanol)]. IR $\nu_{max}$ (film) cm$^{-1}$: 3350 (s, O-H), 1035 (s, C-O). NMR $\delta$H (90 MHz, CDCl$_3$): 0.86 (9H, d, J = 6.2 Hz, 6-, 10-CH$_3$, 11-H$_3$), 0.92 (3H, d, J = 6.6 Hz, 2-CH$_3$), 1.00--1.80 (16H, m, 2-, 6-, 10-H, 3--5, 7--9-H$_2$), 3.39 (1H, dd, J = 6.0, 10.5 Hz, 1-H$_3$), 3.54 (1H, dd, J = 5.7, 10.5 Hz, 1-H$_3$). This compound was used in the next step without further purification.

(2R, 6R)-2, 6, 10-Trimethylundecyl iodide (8). i) To a solution of 7 (0.78 g, 3.4 mmol) in dry pyridine (8 ml) was added p-toluenesulfonyl chloride (0.84 g, 4.4 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 diethyl ether. The organic phase was successively washed with saturated aqueous CuSO$_4$ water, saturated aqueous NaHCO$_3$ and brine, dried with MgSO$_4$, and concentrated in vacuo to give 1.37 g (quant.) of the crude tosylate of 7 as a colorless oil. This was employed in the next step without further purification. ii) To a solution of this tosylate (1.37 g, ca. 3.40 mmol) in dry acetone (18 ml) was added sodium iodide (0.84 g, 5.6 mmol) at room temperature. After stirring for 4 h under reflux, the mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethyl ether. The organic phase was successively washed with 10% aqueous sodium thiosulfate, water and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g; hexane/ethyl acetate, 300:1) to give 1.04 g (94%) of 8 as a colorless oil; $n_D^{15}$ 1.4819; $[\alpha]_D^{20} - 2.90^\circ$ (c 1.06, hexane). IR $\nu_{max}$ (film) cm$^{-1}$: 1195 (s, CH$_3$I). NMR $\delta$H (90 MHz, CDCl$_3$): 0.86 (9H, d, J = 6.4 Hz, 6-, 10-CH$_3$, 11-H$_3$), 0.97 (3H, d, J = 5.7 Hz, 3H, 2-CH$_3$), 1.00--1.80 (15H, m, 2-, 6-, 10-H, 3--5, 7--9-H$_2$), 3.13 (1H, dd, J = 5.0, 9.4 Hz, 1-H$_3$), 3.26 (1H, dd, J = 4.6, 9.4 Hz, 1-H$_3$). Anal. Found: C, 51.72; H, 9.18%. Calcd. for C$_{39}$H$_{62}$I: C, 51.85; H, 9.01%.

(2R, 6R)-2, 6, 10-Trimethyl-1-phenylsulfonylundecane (9). To a stirred solution of 8 (540 mg, 1.66 mmol) in dry DMF (5 ml) was added sodium benzenesulfinate dihydrate (0.5 g, 2.5 mmol). After stirring for 12 h at room temperature, the mixture was diluted with water and extracted with diethyl ether. The organic phase was successively 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, 100:1) to give 497 mg (89%) of 9 as a colorless oil; $n_D^{15}$ 1.4942; $[\alpha]_D^{20} - 1.88^\circ$ (c 1.12, CHCl$_3$) [ref. 3 $n_D^{15}$ 1.4896. $[\alpha]_D^{20} - 1.9^\circ$ (c 1.00, CHCl$_3$)]. IR $\nu_{max}$ (film) cm$^{-1}$: 1590 (w, aromatic), 1310 (s, SO$_2$), 1150 (s, SO$_2$). NMR $\delta$H (90 MHz, CDCl$_3$): 0.86 (9H, d, J = 6.2 Hz, 6-, 10-CH$_3$, 11-H$_3$), 1.06 (3H, d, J = 6.4 Hz, 2-CH$_3$), 1.00--1.80 (14H, m, 6-, 10-H, 3--5, 7--9-H$_2$), 2.08 (1H, m, 2-H), 2.89 (1H, dd, J = 7.4, 14.0 Hz, 1-H$_3$), 3.11 (1H, dd, J = 5.0, 14.0 Hz, 1-H$_3$), 7.44--7.74 (3H, m, Ar--H).
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7.87–8.00 (2H, m, Ar–H). This compound was used in the next step without further purification.

(2R, 5RS, 6R, 10R)-2-tert-Butyldimethylsilyloxy-6,10,14-trimethyl-5-phenylsulfonylpentadecane (10). Under an argon atmosphere, to a stirred and cooled solution of 9 (435 mg, 1.28 mmol) in dry THF (10 mL) and dry hexamethyldisiloxane triethyl chloride (3 mL) was added dropwise a solution of n-butyllithium in hexane (1.50 M, 1.03 mL, 1.54 mmol) at −78°C. After this addition, the mixture was kept at −30°C for 1 h and again cooled to −78°C. A solution of 4 (484 mg, 1.54 mmol) in dry THF (3 mL) was then added dropwise to the mixture at −78°C while stirring. The mixture was stirred at ambient temperature for 12 h, poured into ice and saturated aqueous NH$_4$Cl, and extracted with diethyl ether. The organic phase was successively 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, 150:1) to give 563 mg (84%) of 10 as a colorless oil. IR $\nu_{\text{max}}$ (film) cm$^{-1}$: 1590 (w, aromatic), 1305 (s, SO$_2$), 1250 (s, Si–CH$_3$), 1150 (s, SO$_3$). NMR $\delta$$_H$ (90 MHz, CDCl$_3$): 0.01 (6H, s, Si–CH$_3$), 0.85 (9H, s, tert-Bu), 0.86 (9H, d, J = 6.2 Hz, 10-, 14-CH$_3$, 15-H$_3$), 0.99 (3H, d, J = 6.8 Hz, 6-CH$_3$), 1.06 (3H, d, J = 6.0 Hz, 1-H$_3$), 1.00–2.40 (19H, m, 6-, 10-, 14-H, 3-, 4-, 7–9, 11–13-H$_2$), 2.87 (1H, m, 5-H$_3$), 3.73 (1H, m, 2-H), 7.47–7.66 (3H, m, Ar–H), 7.83–7.94 (2H, m, Ar–H). This compound was used in the next step without further purification.

(2R, 6R, 10R)-2-tert-Butyldimethylsilyloxy-6,10,14-trimethylpentadecane (11). Under an argon atmosphere, a solution of 10 (160 mg, 0.305 mmol) in dry ethanol (10 mL) was added dropwise to 5% sodium amalgam (5.8 g; 0.29 g of sodium, 13 mmol) at 0°C. The mixture was stirred vigorously at room temperature for 22 h. It was then filtered through Celite, and the filter cake was washed several times with diethyl ether. The combined filtrate and washings were concentrated in vacuo to give crude 11. This crude material contained a few percent of olefinic compounds that had been formed by elimination of the phenylsulfonyl group from 10. Crude 11 was dissolved in hexane (5 mL), and m-CPBA (70%, 25 mg, 0.10 mmol) was added at 0°C. The mixture was stirred at room temperature for 4 h, saturated aqueous sodium thiosulfate and saturated aqueous NaHCO$_3$ were added, and the mixture was extracted with hexane. The organic phase was successively washed with water and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (10 g; hexane/ethyl acetate, 1000:1) to give 93 mg (80%) of 11 as a colorless oil; $n$$_D^2$ 1.4417; [a]$_D^2$ +7.32 (c 1.02, CHCl$_3$). IR $\nu_{\text{max}}$ (film) cm$^{-1}$: 1460 (s, C–H), 1375 (m, C–H), 1250 (s, Si–CH$_3$), 1130 (m, Si–O). NMR $\delta$$_H$ (500 MHz, CDCl$_3$): 0.05 (6H, s, Si–CH$_3$), 0.84, 0.85, 0.87 (total 12H, each d, J = 6.7, 6.7, 6.7 Hz, 6-, 10-, 14-CH$_3$, 15-H$_3$), 0.89 (9H, s, tert-Bu), 1.11 (3H, d, J = 6.1 Hz, 1-H$_3$), 1.00–1.57 (21H, m, 6-, 10-, 14-CH, 3–5, 7–9, 11–13-H$_3$), 3.77 (1H, sextet like, J = 5.9 Hz, 2-H). NMR $\delta$C (125 MHz, CDCl$_3$): −4.7, −4.4, 18.1, 19.7, 19.8, 22.6, 22.7, 23.3, 23.9, 24.5, 24.8, 25.9, 28.0, 32.78, 32.80, 37.1, 37.3, 37.4, 37.5, 39.4, 40.1. HRMS m/z (M$^+$): calcd. for C$_{24}$H$_{36}$OSi: 384.3787; found, 384.3775. Anal. Found: C, 75.64; H, 13.74%. Calcd. for C$_{24}$H$_{36}$OSi: C, 74.92; H, 13.62%.

(2R, 6R, 10R)-6,10,14-Trimethyl-2-pentadecan-1-ol (12). Under an argon atmosphere, to a solution of 11 (68 mg, 0.18 mmol) in dry THF (2 mL) was added (n-Bu)NF [a 1.0 mol solution in dry THF (0.25 mL, 0.25 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 successively 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, 100:1) to give 47 mg (98%) of 12 as a colorless oil; $n$$_D^2$ 1.4489; [a]$_D^2$ +6.33 (c 1.10, n-pentane) [ref. 3 $n$$_D^2$ 1.4497; [a]$_D^2$ +6.4° (c 1.07, n-pentane)]. IR $\nu_{\text{max}}$ (film) cm$^{-1}$: 3350 (s, O–H), 1460 (s, C–H), 1380 (m, C–H), 1120 (w), 940 (w), 740 (w). NMR $\delta$C (500 MHz, CDCl$_3$): 0.84, 0.86, 0.89 (total 12H, each d, J = 6.4, 6.4, 6.4 Hz, 6–4, 14-CH$_3$, 15-H$_3$), 1.19 (3H, d, J = 6.1 Hz, 1-H$_3$), 1.02–1.56 (22H, m, 6–10, 14-H, 3–5, 7–9, 11–13-H$_2$, OCH), 3.80 (1H, t, J = 5.4, 6.1 Hz, 2-H). NMR $\delta$C (125 MHz, CDCl$_3$): 19.67, 19.73, 22.6, 22.7, 23.2, 23.5, 24.4, 24.8, 28.0, 32.75, 32.78, 37.0, 37.28, 37.35, 37.42, 39.4, 39.7, 68.2. Anal. Found: C, 79.68; H, 14.44%. Calcd. for C$_{18}$H$_{32}$O: C, 79.93; H, 14.16%. GC [DB-5 column (0.25 mm × 30 m), 100 to 270°C, +8.0°C/min; He carrier gas at a 110 kPa pressure]: $t$$_R$ = 17.1 min (I, 99.1%).

tert-Butyl (R)-4-tert-butyldimethylsilyloxy-3-methylbutanoate (14). To a solution of 13 (17.4 g, 0.10 mol) in dry DMP (150 mL) was added tert-butyldimethylsilyl chloride (18.1 g, 0.12 mol) and imidazole (23.8 g, 0.35 mol) at room temperature. After stirring for 3 h at room temperature, the mixture was diluted with water and extracted with diethyl ether. The organic phase was successively washed with saturated aqueous NaHCO$_3$ and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was distilled to give 27.5 g (96%) of 14 as a colorless oil; bp 89–91°C at 1.0 torr; $n$$_D^2$ 1.4269; [a]$_D^2$ +4.39° (c 1.10, CHCl$_3$). IR $\nu_{\text{max}}$ (film) cm$^{-1}$: 1730 (s, C = O), 1260 (s, Si–CH$_3$), 1160 (s, C–O), 1110 (m, Si–O). NMR $\delta$H (90 MHz, CDCl$_3$): 0.03 (6H, s, Si–CH$_3$), 0.89 (9H, s, tert-Bu), 0.93 (3H, d, J = 6.4 Hz, Ar–H).
(R)-4-tert-Butyldimethylsilyloxy-3-methyl-1-butanol (15). Under an argon atmosphere, to a stirred and cooled solution of 14 (8.3 g, 29 mmol) in dry CH₂Cl₂ (70 ml) was added dropwise a solution of disobutylaluminum hydride in hexane (0.95 m, 67 ml, 64 mmol) at −78°C. After stirring at −78°C for 1 h, the mixture was added saturated aqueous potassium hydroxide (−tartarate hydrate), and the mixture was warmed to room temperature. Water and diethyl ether were then added to the mixture, and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine, dried with MgSO₄, and concentrated in vacuo. The residue was distilled to give 5.5 g (86%) of 15 as a colorless oil, bp 73–74°C at 0.99 torr; nD₀ 1.4341; [α]D₂ + 8.0° (c 1.05, CHCl₃) [ref. 15 nD₀ 1.4372; [α]D₂ + 8.0° (c 1.07, CHCl₃)]. IR νmax (film cm⁻¹): 3350 (s, O=H), 1255 (s, Si-CH₃), 1110 (m, Si-O), 1050 (m, C-O). NMR δH (90 MHz, CDCl₃): 0.04 (6H, s, Si-CH₃), 0.90 (3H, d, J=7.1 Hz, 3-CH₃), 0.91 (9H, s, tert-Bu), 1.48–1.90 (4H, m, 3-H, 2-H₂, OH), 3.41 (1H, dd, J=6.0, 10.1 Hz, 4-H), 3.57 (1H, dd, J=4.8, 10.1 Hz, 4-H), 3.67 (2H, m, 1-H). This compound was used in the next step without further purification.

(R)-4-tert-Butyldimethylsilyloxy-3-methylbutyl iodide (16). i) To a solution of 15 (1.82 g, 8.33 mmol) in dry pyridine (15 ml) was added p-toluene sulfonyl chloride (2.16 g, 11.3 mmol) at 0°C. After stirring at 0°C for 12 h, the mixture was poured into ice and water, and extracted with diethyl ether. The organic phase was successively washed with saturated aqueous CuSO₄, water, saturated aqueous NaHCO₃ and brine, dried with MgSO₄, and concentrated in vacuo to give 3.25 g (quant.) of the crude tosylate of 15. This was employed in the next step without further purification. ii) To a solution of this tosylate (3.25 g) in dry acetonitrile (40 ml) were added sodium iodide (1.96 g, 13.1 mmol) and NaHCO₃ (3.70 g, 44.1 mmol) at room temperature. After stirring for 3 h under reflux, the mixture was concentrated in vacuo. The residue was distilled with water and extracted with diethyl ether. The organic phase was successively washed with 10% aqueous sodium thiosulfate, water and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane) to give 2.45 g (89%) of 16 as a colorless oil; nD₀ 1.4702; [α]D +10.6° (c 1.11, CHCl₃) [ref. 15 nD₀ 1.4753; [α]D +10.7° (c 0.92, CHCl₃)]. IR νmax (film cm⁻¹): 1255 (s, Si-CH₃), 1190 (m, CH₂), 1110 (m, Si-O). NMR δH (90 MHz, CDCl₃): 0.04 (6H, s, Si-CH₃), 0.88 (3H, d, J=7.2 Hz, 3-CH₃), 0.89 (9H, s, tert-Bu), 1.51–2.14 (3H, m, 3-H, 2-H₂), 3.24 (2H, m, 1-H₂), 3.45 (2H, d, J=5.3 Hz, 4-H₂). Anal. Found: C, 39.99; H, 7.38%. Calcd. for C₁₁H₁₃OSi: C, 40.24; H, 7.68%.

(2R, 6R)-1-tert-Butylidenephylsilyloxy-2,6-dimethyl-1,3-dioxolane (17). The Grignard reagent was prepared by adding magnesium (0.77 g, 32 mmol) to an argon-purged flask. To the mixture was added dropwise a solution of ethyl bromide (2.86 g, 26.3 mmol) in dry THF (20 ml), and the mixture was stirred at room temperature for 1 h. The resulting solution was used immediately. Under an argon atmosphere, to a solution of crude tosylate 5° (2.95 g, ca. 5.22 mmol) in dry THF (15 ml) were added this Grignard reagent and a solution (0.5 m, 0.5 ml, 0.25 mmol) of Li₂CuCl₂ in dry THF at −78°C. After stirring at −78°C for 1 h, the mixture was warmed slowly to 0°C, and then stirred at 0°C for 20 h. The mixture was quenched with saturated aqueous NH₄Cl, and extracted with diethyl ether. The organic phase was washed with brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (60 g, hexane/ethyl acetate, 500:1) to give 1.96 g (91%) of 17 as a colorless oil; nD₀ 1.5151; [α]D +0.37° (c 1.00, CHCl₃). IR νmax (film cm⁻¹): 1590 (w, aromatic), 1110 (s, Si-O). NMR δH (90 MHz, CDCl₃): 0.84 (3H, d, J=7.5 Hz, 6-CH₃), 0.88 (3H, t, J=7.1 Hz, 9-H₂), 0.92 (3H, d, J=6.8 Hz, 2-CH₂), 1.06 (9H, s, tert-Bu), 1.00–1.80 (12H, m, 2-, 6-H, 3–5, 7–8-H₂), 3.42 (1H, dd, J=5.7, 9.8 Hz, 1-H), 3.57 (1H, dd, J=5.7, 9.8 Hz, 1-H), 7.35–7.42 (6H, m, Ar-H), 7.63–7.73 (4H, m, Ar-H). Anal. Found: C, 79.23; H, 10.42%. Calcd. for C₂₇H₄₆O₃Si: C, 78.96; H, 10.31%.

(2R, 6R)-2,6-Dimethylnonan-1-ol (18). Under an argon atmosphere, to a solution of 17 (1.90 g, 4.63 mmol) in dry THF (24 ml) was added (n-Bu)₂NF [a 1.0 m solution in dry THF (6.9 ml, 6.9 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 successively washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 100:1) to give 0.77 g (97%) of 18 as a colorless oil; nD₀ 1.4450; [α]D +37.3° (c 1.11, CHCl₃). IR νmax (film cm⁻¹): 3350 (s, O-H), 1040 (s, C-O). NMR δH (90 MHz, CDCl₃): 0.84 (3H, d, J=6.2 Hz, 6-CH₃), 0.88 (3H, t, J=6.4 Hz, 9-H₂), 0.92 (3H, d, J=6.6 Hz, 2-CH₂), 1.00–1.80 (13H, m, 2-, 6-H, 3–5, 7–8-H₂, OH), 3.39 (1H, dd, J=6.0, 10.6 Hz, 1-H), 3.54 (1H, dd, J=5.6, 10.6 Hz, 1-H). Anal. Found: C, 76.64; H, 14.08%. Calcd. for C₁₅H₂₄O: C, 76.68; H, 14.04%.

(2R, 6R)-2,6-Dimethylnonyl iodide (19). i) To a solution of 18 (0.66 g, 3.8 mmol) in dry pyridine (8 ml)
was added p-toluenesulfonyl chloride (0.94 g, 4.9 mmol) at 0°C. After stirring at 0°C for 11 h, the mixture was poured into ice and water, and extracted with diethyl ether. The organic phase was successively washed with saturated aqueous CuSO₄ water, saturated aqueous NaHCO₃ and brine, dried with MgSO₄, and concentrated in vacuo to give 1.25 g (quant.) of the crude tosylate of 18. This was employed in the next step without further purification.

ii) To a solution of this tosylate (1.25 g) in dry acetone (17 ml) was added sodium iodide (0.86 g, 5.7 mmol) at room temperature. After stirring for 5 h under reflux, the mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethyl ether. The organic phase was successively washed with 10% aqueous sodium thiosulfate, water and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane) to give 1.02 g (94%) of 19 as a colorless oil; nD²⁰ 1.4837; [α]D⁻⁻⁰ 4.70° (c 1.00, CHCl₃). IR νmax (film) cm⁻¹: 1200 (s, CH=I). NMR δH (90 MHz, CDCl₃): 0.85 (3H, d, J = 5.7 Hz, 6-CH₃), 0.88 (3H, t, J = 5.7 Hz, 9-H₂), 0.97 (3H, d, J = 5.9 Hz, 2-CH₃), 1.00-1.60 (12H, m, 2-, 6-H, 3-, 5-, 7-, 8-H₂), 3.12 (1H, dd, J = 5.3, 8.3 Hz, 1-H₂), 3.28 (1H, dd, J = 4.4, 8.3 Hz, 1-H₁). Anal. Found: C, 46.98; H, 8.21%. Calcd for C₁₇H₃₁O₂C: C, 46.82; H, 8.21%.

(2R, 6R)-2,6-Dimethyl-1-phenylsulfonylnonane (20). To a stirred solution of 19 (505 mg, 1.79 mmol) in dry DMF (5 ml) was added sodium benzenesulfonate dihydrate (537 mg, 2.68 mmol). After stirring for 15 h at room temperature, the mixture was diluted with water and extracted with diethyl ether. The organic phase was successively washed with water and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 50:1) to give 471 mg (89%) of 20 as a colorless oil; nD²⁰ 1.5011; [α]D⁻⁻⁰ 3.76° (c 1.04, CHCl₃). IR νmax (film) cm⁻¹: 1590 (w, aromatic), 1310 (s, SO₂), 1150 (s, SO₂). NMR δH (90 MHz, CDCl₃): 0.80 (3H, d, J = 5.6 Hz, 6-CH₃), 0.86 (3H, t, J = 5.7 Hz, 9-H₂), 1.07 (3H, d, J = 6.6 Hz, 2-CH₃), 1.00-1.60 (11H, m, 6-H, 3-, 5-, 7-, 8-H₂), 2.08 (1H, m, 2-H), 2.89 (1H, dd, J = 7.2, 14.1 Hz, 1-H₁), 3.12 (1H, dd, J = 5.1, 14.1 Hz, 1-H₂), 7.54-7.68 (3H, m, Ar-H), 7.87-8.98 (2H, m, Ar-H). Anal. Found: C, 68.61; H, 9.54%. Calcd for C₁₇H₂₅O₂C: C, 68.87; H, 9.52%.

(2R, 5RS, 6R, 10R)-1-tert-Butyldimethylsilyloxy-2,6,10-trimethyl-5-phenylsulfonylindranec (21). Under an argon atmosphere, to a stirred and cooled solution of 20 (420 mg, 1.42 mmol) in dry THF (10 ml) and dry hexamethyldisilphoric triamide (3 ml) was added dropwise a solution of n-butyllithium in hexane (1.54 M, 1.09 ml, 1.68 mmol) at −78°C. After this addition, the mixture was kept at −30°C for 1 h and again cooled to −78°C. A solution of 16 (552 mg, 1.68 mmol) in dry THF (3 ml) was then added dropwise to the mixture at −78°C while stirring. The mixture was stirred at ambient temperature for 10 h, poured into ice and saturated aqueous NH₄Cl, and extracted with diethyl ether. The organic phase was successively washed with water and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 100:1) to give 678 mg (96%) of 21 as a colorless oil. IR νmax (film) cm⁻¹: 1590 (w, aromatic), 1310 (s, SO₂), 1260 (s, Si-CH₃), 1150 (s, SO₂). NMR δH (90 MHz, CDCl₃): 0.01 (6H, s, Si-CH₃), 0.75-0.90 (9H, m, 2-, 10-CH₃, 13-H₂), 0.87 (9H, s, tert-Bu), 1.02 (3H, d, J = 6.8 Hz, 6-CH₃), 1.00-2.40 (17H, m, 2-, 6-, 10-H, 3-, 4-, 7-, 9-, 11-, 12-H₂), 2.89 (1H, m, 5-H), 3.32 (2H, d, J = 5.3 Hz, 1-H₁), 7.52-7.61 (3H, m, Ar-H), 7.84-7.95 (2H, m, Ar-H). This compound was used in the next step without further purification.

(2R, 6R, 10R)-1-tert-Butyldimethylsilyloxy-2,6,10-trimethyltridecanone (22). Under an argon atmosphere, a solution of 21 (380 mg, 0.745 mmol) in dry ethanol (25 ml) was added dropwise to 5% sodium amalgam (13.8 g; 0.69 g of sodium, 30 mmol) at 0°C. The mixture was stirred vigorously at room temperature for 36 h. It was then filtered through Celite, and the filter cake was washed several times with diethyl ether. The combined filtrate and washings were concentrated in vacuo to give crude 22. This crude material contained a few percent of olefinic compounds that had been formed by elimination of the phenylsulfonyl group from 21. Crude 22 was dissolved in hexane (10 ml), and m-CPBA (70%, 50 mg, 0.20 mmol) was added at 0°C. The mixture was stirred at room temperature for 4 h. Saturated aqueous sodium thiosulfate and saturated aqueous NaHCO₃ were added to it, and the resulting mixture was extracted with hexane. The organic phase was successively washed with water and brine, dried with MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g, hexane) to give 225 mg (82%) of 22 as a colorless oil; nD²⁰ 1.4406; [α]D⁻⁻⁰ 1.13° (c 1.08, CHCl₃). IR νmax (film) cm⁻¹: 1250 (s, Si-CH₃), 1110 (m, Si-O). NMR δH (90 MHz, CDCl₃): 0.04 (6H, s, Si-CH₃), 0.81-0.92 (12H, m, 2-, 6-, 10-CH₃, 13-H₂), 0.90 (9H, s, tert-Bu), 1.00-1.90 (19H, m, 2- 6-, 10-H, 3-, 5-, 7- 9-, 11-, 12-H₂), 3.32 (1H, dd, J = 6.2, 9.8 Hz, 1-H₁), 3.47 (1H, dd, J = 5.7, 9.8 Hz, 1-H₁). Anal. Found: C, 73.87; H, 13.26%. Calcd for C₂₃H₃₄O₃Si: C, 74.08; H, 13.56%.

(2R, 6R, 10R)-2,6,10-Trimethyl-1-tridecanol (23). Under an argon atmosphere, to a solution of 22 (160 mg, 0.449 mmol) in dry THF (3 ml) was added (n-Bu)₂NF [a 1.0 m solution in dry THF (0.68 ml, 0.68 mmol)] at room temperature. After stirring at room temperature for 3 h, the mixture was poured into
water and extracted with diethyl ether. The organic phase was successively washed with saturated aqueous NaHCO3 and brine, dried with MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (8 g; hexane/ethyl acetate, 100:1) to give 108 mg (99%) of 23 as a colorless oil; \( n_D^20 = 1.4490; [\alpha]_D^20 + 7.59^0 \) (c 1.10, methanol) [ref. 4 \( n_D^20 = 1.4527; [\alpha]_D^20 + 7.56^0 \) (c 1.71, methanol)]. IR \( \nu_{max} \) (film) cm\(^{-1}\): 3330 (s, O-H), 1030 (s, C-O). NMR \( \delta_H \) (90 MHz, CDCl3): 0.84 (6H, d, \( J = 6.2 \) Hz, 6-10-CH3), 0.88 (3H, t, \( J = 6.5 \) Hz, 13-H3), 0.92 (3H, d, \( J = 6.8 \) Hz, 2-CH3), 1.00-1.80 (20H, m, 2-6, 10-H, 3-5, 7-9, 11-, 12-H2, OH), 3.39 (1H, dd, \( J = 6.0, 10.4 \) Hz, 1-H3), 3.54 (1H, dd, \( J = 5.7, 10.4 \) Hz, 1-H3). This compound was used in the next step without further purification.

(2R, 6R, 10R)-2,6,10-Trimethyltridecanoic acid (24). To a stirred and ice-cooled solution of 23 (50 mg, 0.21 mmol) in acetone (1.5 ml) was added dropwise Jones' reagent (0.16 ml, 2.67 m, 0.43 mmol) until the mixture turned red-brown. After stirring at 0º C for 1 h, the mixture was added dropwise 2-propanol (0.1 ml) to destroy any excess CrO3. The mixture was poured into brine and extracted with diethyl ether. The organic phase was successively washed with water and brine, dried with MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (3 g, chloroform/methanol, 100:1) to give 48 mg (91%) of 24 as a colorless oil; \( n_D^20 = 1.4489; [\alpha]_D^20 - 13.0^0 \) (c 1.02, CHCl3) [ref. 4 \( n_D^20 = 1.4526; [\alpha]_D^20 - 13.2^0 \) (c 0.805, CHCl3)]. IR \( \nu_{max} \) (film) cm\(^{-1}\): 3000 (m, br., COO-H), 1710 (s, C=O), 1240 (m, C=O), 940 (m, COO-H). NMR \( \delta_H \) (90 MHz, CDCl3): 0.84 (6H, d, \( J = 5.7 \) Hz, 6-10-CH3), 0.87 (3H, t, \( J = 6.0 \) Hz, 13-H3), 1.18 (3H, d, \( J = 6.8 \) Hz, 2-CH3), 1.00-1.90 (19H, m, 6-, 10-H, 3-5, 7-9, 11-, 12-H2, CO2H), 2.50 (1H, m, 2-H). This compound was used in the next step without further purification.

Methyl (2R, 6R, 10R)-2,6,10-trimethyltridecanoate (2). To a stirred and ice-cooled solution of 24 (36 mg, 0.14 mmol) in dry diethyl ether (2 ml) was added dropwise a solution of diazomethane in diethyl ether (1.0 ml, 0.5 m, 0.5 mmol) until the mixture turned yellow. After stirring at 0º C for 1 h, the excess diazomethane was destroyed by adding acetic acid until the mixture turned colorless. The mixture was poured into water and extracted with diethyl ether. The organic phase was successively washed with saturated aqueous NaHCO3 and brine, dried with MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (2 g, pentane) to give 35 mg (92%) of 2 as a colorless oil; \( n_D^20 = 1.4390; [\alpha]_D^20 - 20.4^0 \) (c 1.02, diethyl ether) [ref. 4 \( n_D^20 = 1.4399; [\alpha]_D^20 - 20.7^0 \) (c 1.12, diethyl ether)]. IR \( \nu_{max} \) (film) cm\(^{-1}\): 1740 (s, C=O), 1460 (s, C-H), 1200 (m, C-O), 1170 (m, C-O). NMR \( \delta_H \) (500 MHz, CDCl3): 0.835, 0.883 (total 6H, each d, \( J = 6.7, 6.4 \) Hz, 6-, 10-CH3), 0.88 (3H, t, \( J = 7.2 \) Hz, 13-H3), 1.14 (3H, d, \( J = 7.0 \) Hz, 2-CH3), 1.02-1.41 (17H, m, 10-H, 3-5, 7-9, 11-, 12-H2), 1.64 (1H, m, 6-H), 2.44 (1H, sextet, \( J = 7.0 \) Hz, 2-H), 3.67 (3H, s, CO2CH3). NMR \( \delta_C \) (125 MHz, CDCl3): 14.4, 17.1, 19.64, 19.70, 20.1, 24.4, 24.7, 32.5, 32.6, 34.2, 36.8, 37.38, 37.40, 39.4, 39.5, 51.4, 177.1. Anal. Found: C, 75.28; H, 12.89 %. Calcd. for C17H32O2 C, 75.50; H, 12.67 %. GC [DB-5 column (0.25 mm x 30 m), 100 to 250º C, +5.0 ºC/min; He carrier gas at a 110 kPa pressure: \( t_R = 15.0 \) min (2, 99.4%).

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