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Enzymatic Synthesis of (2*E*,4*E*)-(6*R*,10*R*)-4,6,10,12-Tetramethyl-2,4-Tridecadien-7-one, the Sex Pheromone of *Matsucoccus matsumurae* Japanese Pine Bast Scale

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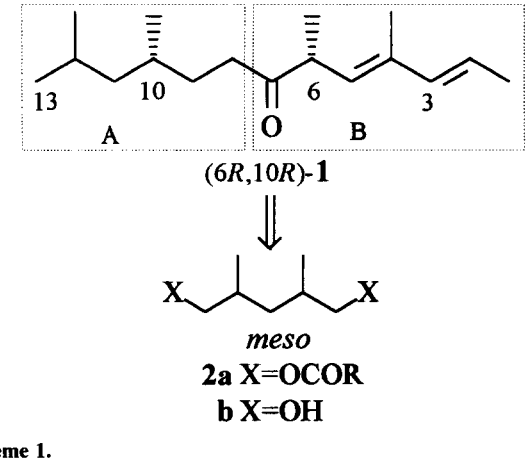
Abstract—The sex pheromone of *Matsucoccus matsumurae* Japanese pine bast scale (2*E*,4*E*)-(6*R*,10*R*)-4,6,10,12-tetramethyl-2,4-tridecadien-7-one (**1**) was synthesized with stereocontrol from (2*R*,4*S*)-5-acetoxy-2,4-dimethyl-pentanol (**3**), which in turn was prepared by lipase-catalyzed transesterification of *meso*-2,4-dimethyl-1,5-propanediol (**2**). Copyright © 1996 Elsevier Science Ltd

Introduction

Since the structure elucidation of the sex pheromone of the Japanese pine bast scale *M. matsumurae* in 1989 by Lanier et al.,[1] several total syntheses of the title compound **1** have been reported.[2] The absolute configuration of **1** was later on determined as (6*R*,10*R*) on the basis of the laboratory bioassay and field tests performed.[3] All of the reported synthetic methods shared the same strategy. That is, the optically active natural products were used to establish one of the two chiral centers of **1**, then some types of the asymmetric reaction were adopted to introduce the absolute configuration of another chiral center. In this article we wish to report a new approach relying on a different synthetic strategy, where both chiral centers of **1** are stereocontrolled via manipulation of a bifunctional building block (**3**), obtained by the lipase-catalyzed transacetylation of *meso*-**2** (Scheme 1).



Scheme 1.

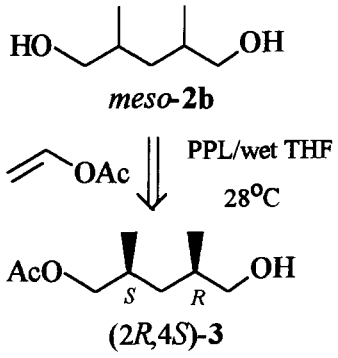
Results and Discussion

Compound **1** has a pseudosymmetrical structure, consisting of two parts with the similar carbon skeleton, i.e. A and B fragments. These two fragments bear the structurally similar 7-C synthon (from C-9 to C-13 and C-3 to C-7, respectively), which in turn could be easily generated from the lipase-catalyzed transacetylation or hydrolysis reaction of *meso*-**2**.

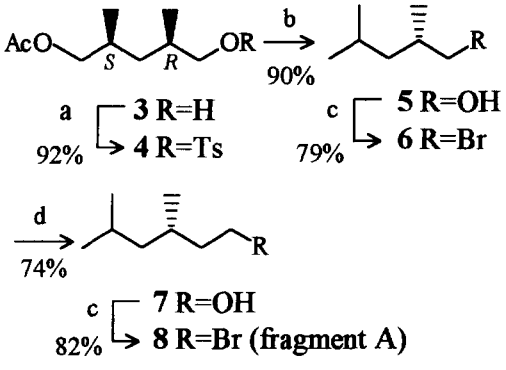
Several articles have been reported on the lipase-catalyzed hydrolysis reaction of the analogues of compound **2a**.[4] Unfortunately, we found that in our hands it is not always convenient to achieve the expected high ee of the hydrolyzed compound according to the reported procedures. This led us to turn to the lipase-catalyzed acyl transformation of the *meso*-diol (**2b**). Finally, a better procedure was found in which the crude porcine pancreatic lipase was used to effect the enantioselective acyl transfer of *meso*-diol† (**2b**) with vinyl acetate in wet THF. The monoacetate (**3**) was thus obtained in 50% yield (98% ee), together with 20% of the diacetylated side product[6] (Scheme 2).

Thus, the tosylate (**4**) derived from **3** (92% yield), was converted into **5** (90%) by routine $LiAlH_4$ reduction. Bromination of **5** gave **6** in satisfactory yield (79%).[7] Treatment of the organomagnesium reagent derived from **6** with formaldehyde afforded alcohol (**7**), which was subjected to the bromination again to give **8** (fragment A) in a total yield of 39.7% over five steps from **3**‡ (Scheme 3).

†The enantiomeric excess was determined by ^1H NMR and GC (chiral column) analysis of the corresponding Mosher's ester of **3**.
‡Recently compound **7** was also prepared from (*S*)-citronellol in 57% yield over nine steps (Scheme 6). All the physical data were identical with those of **7** prepared from **3**.



Scheme 2.



Scheme 3. Reagents and conditions: (a) *p*-TsCl, pyridine; (b) $LiAlH_4/Et_2O$, reflux; (c) Ph_3P, CBr_4/CH_2Cl_2; (d) i. CH_3I, Mg/Et_2O, reflux; ii. $(HCHO)_n$, reflux.

Synthesis of fragment B (Scheme 4) also started with **3**. The hydroxyl group of **3** was protected as the *tert*-butyldiphenylsilyl ether (**9**) (98%). Hydrolysis of **9** under basic condition followed by the treatment of Jones oxidation afforded the crude acid, which without purification was treated with CH_2N_2 to give the methyl ester (**11**). Compound **11** was subjected to phenylselenenylation (LDA and PhSeBr) and oxidative elimination of the phenylselenenyl moiety offered the alkene **12** and **13** (**12**:**13** 1:5) in 85% yield. The undesired **12** could be converted quantitatively to **13** at reflux temperature in anhydrous ethanol in the presence of catalytic $RhCl_3$. Treatment of the α,β-unsaturated ester (**13**) with the lithium derivative of the phosphine oxide $Ph_2P(O)Et$ afforded the diastereoisomers of α′-Ph_2PO enones (**14**), which were then subjected to the regioselective 1,2-reduction according to the Luche conditions[8] ($NaBH_4$, $CeCl_3$, MeOH, −78 °C) to furnish the product **15** with good selectivity (*threo*:*erythro* 4:1). The *erythro* isomer of **15** could be removed by flash column chromatography. Upon treatment of **15** with NaH in DMF at 40 °C and followed by removal of the silyl protecting group **16** was obtained, which composed the carbon skeleton of the C-1–C-7 fragment of **1** (fragment B).

The coupling of the two fragments was effected as follows (Scheme 5). Swern oxidation[9] of **16** afforded the crude aldehyde, which was subjected to a copper-promoted coupling reaction with an organomagnesium reagent derived from optically active bromide (**8**) (fragment A) to give the alcohol **17** in 55% yield. Oxidation of **17** under the Swern oxidation condition[9] gave (6*R*,10*R*)-**1** in the yield 92%. The total yield of **1** was 21.5% over 12 steps (based on fragment B).

In summary, we have achieved a convergent and stereoselective synthesis of (6*R*,10*R*)-**1**. Notable points of our synthesis include the control of both chiral centers of **1** by a two-directional chain synthesis from the building block **3**, which in turn was readily prepared by the lipase-catalyzed transacetylation of *meso*-**2**.

Experimental

General

^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker AMX-300 spectrometer. Capillary GC analyses were performed on an HP 5890 instrument equipped with chiral column (CYDEX-B, 50 m × 0.32 mm). MS were obtained with HP-5989A model mass spectrometer with electron impact source. HRMS spectra were obtained with Finnigan Mat 4201 model mass spectrometer. IR spectra were determined on an IR-440 spectrometer. Optical rotations were measured at 20 °C with a Perkin–Elmer 241 polarimeter.

All reactions were conducted under dry N_2, using glassware dried at ca. 125 °C. Ether and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and DMF were distilled from CaH_2; methanol and ethanol were distilled from Mg turnings; pyridine was distilled from NaOH. Most other solvents and reagents were dried over 4 Å molecular sieves before use. Removal of solvents was accomplished on a rotary evaporator at reduced pressure.

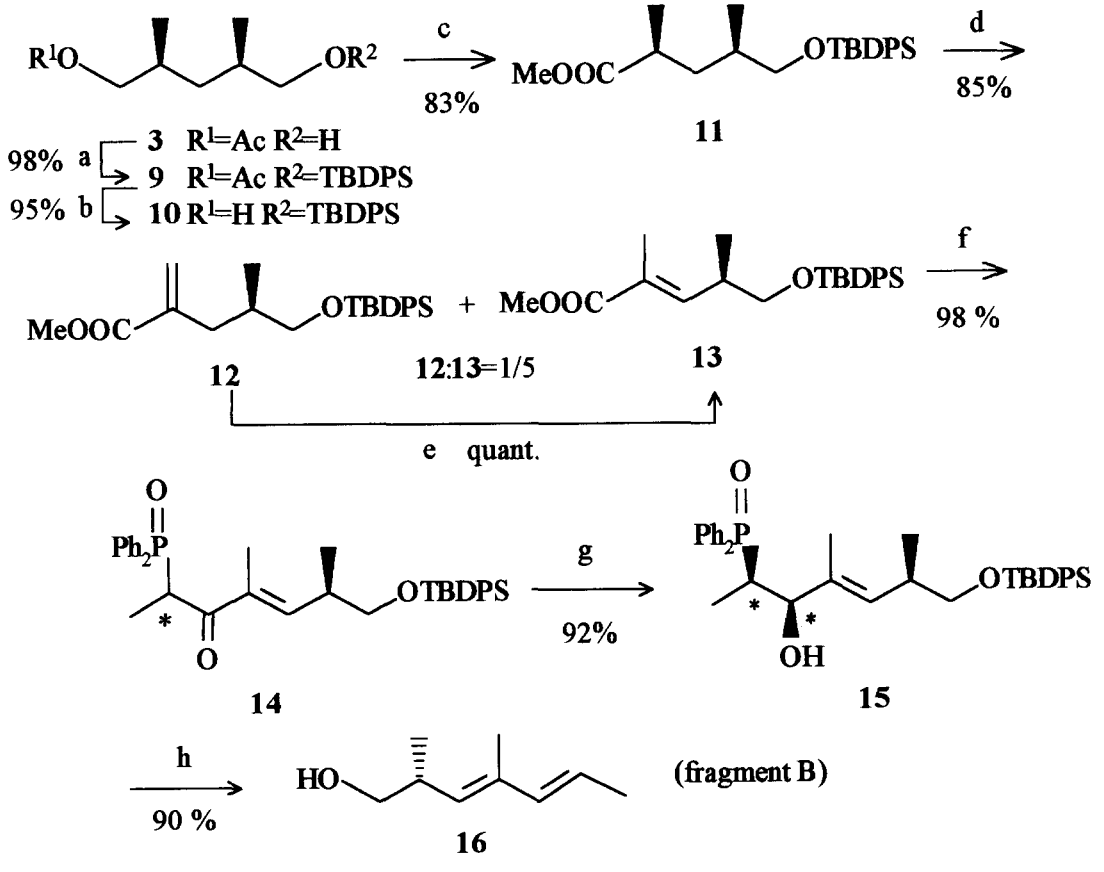
Analytical TLC was performed using 2 cm × 5 cm plates coated with 0.25 mm thick F_{254} silica gel. Preparative TLC was performed using 20 × 20 cm plates coated with 0.25 or 0.50 mm thick F_{254} silica gel. Flash chromatography was performed by using Kieselgel 60 (200–300 mesh). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4 or phosphomolybdic acid, or by staining with iodine vapor. Unless noted otherwise, all compounds purified by chromatography are sufficiently pure (>95% by ^1H NMR analysis) for use directly in subsequent preparative reactions.

(2*R*,4*S*)-5-Acetoxy-2,4-dimethylpentan-1-ol (3). To a solution of **2b** (120 mg, 0.90 mmol) in anhydrous THF (4 mL) were added H_2O (5 μL), PPL (350 mg) and vinyl acetate (0.8 mL, 0.75 g, 8.72 mmol). The mixture was stirred at 28 °C for 8 h before being filtered and concentrated. Flash chromatography gave 62 mg of **3** as a colorless oil. $[\alpha]_D^{20}$ +10.4° (*c* 1.2, $CHCl_3$); lit.

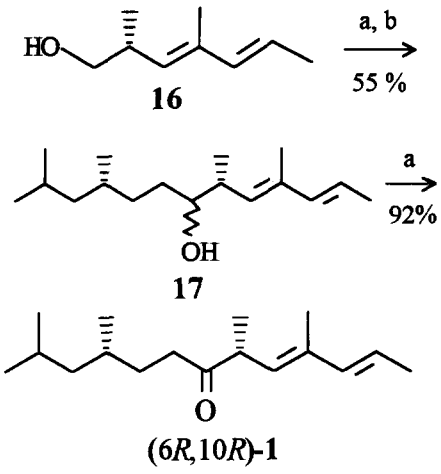
$[\alpha]_D$ +11.7° (*c* 1.9, $CHCl_3$),[4d] lit. the enantiomer of **3** $[\alpha]_D^{25}$ −9.5° (89.7% ee).[4a] ν_{max}: 3350, 2950, 1725 cm^{-1}. δ_H: 3.60 (4H, m), 1.98 (3H, s), 1.85–1.35 (4H, m), 0.91 (3H, d, *J* = 6.4 Hz), 0.87 (3H, d, *J* = 6.4 Hz) ppm. *m/z* (%): 175 (M+1, 1.9), 84 ($C_6H_{12}^+$, 42.9), 59 (CH_3COO^+, 40.0), 56 ($C_4H_8^+$, 100.0). (*R*)-MTPA ester of **3**:[5b] (+)-MTPA chloride was prepared by refluxing (*R*)-(+)-MTPA (10 mg, 0.05 mmol) in $(COCl)_2$ (0.2 mL, 1.1 mmol) for 2 h before the excess $(COCl)_2$ was removed under reduced pressure. Then to a solution of **3** (4 mg, 0.02 mmol) in pyridine (20 μL) was added (+)-MTPA chloride (9 μL, 0.04 mmol) and the solution was allowed to stand at room temperature for 5 h. H_2O (1 mL) and CH_2Cl_2 (1 mL) were added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL). The combined extracts were concentrated in vacuo. The residue was subjected to preparative TLC, affording 7 mg of the (*R*)-MTPA ester of **3** (70%). δ_H: 7.51 (2H, m), 7.40 (3H, m), 4.23 (1H, dd, *J* = 10.8, 5.3 Hz), 4.05 (1H, dd, *J* = 10.7, 6.2 Hz), 3.90 (1H, dd, *J* = 10.8, 5.7 Hz), 3.80 (1H, dd, *J* = 10.8, 6.3 Hz), 3.55 (3H, s), 2.01 (3H, s), 1.90–1.35 (4H, m), 0.94 (3H, d, *J* = 6.7 Hz), 0.93 (3H, d, *J* = 6.7 Hz) ppm. t_R = 21.69 min. The (*R*)-MTPA ester of the enantiomer of **3**, t_R = 22.58 min. GC conditions: the temperature was programmed from 150 °C (maintained for 1 min) to 220 °C, increasing at a rate of 5 °C/min.

(2*R*,4*S*)-5-Acetoxy-2,4-dimethylpentyl tosylate (4). *p*-TsCl (500 mg, 2.63 mmol) was added to a stirred and ice-cooled solution of **3** (250 mg, 1.44 mmol) in dry pyridine (3 mL). The mixture was stirred at room temperature for 1.5 h before it was diluted with ether (40 mL) and washed successively with water, saturated $CuSO_4$ aq and brine. The ethereal solution was dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography of the crude product provided 435 mg of **4** (92%). $[\alpha]_D$ −3.2° (*c* 1.2, $CHCl_3$). ν_{max}: 2900, 1725, 1595, 1460, 1355, 1230, 1190, 1170, 1090, 1025, 955, 810, 790 cm^{-1}. δ_H: 7.75 (2H, m), 7.35 (2H, m), 3.84 (3H, m), 2.48 (3H, s), 2.02 (3H, s), 1.90–1.35 (4H, m), 0.92 (3H, d, *J* = 6.4 Hz), 0.90 (3H, d, *J* = 6.4 Hz) ppm. *m/z* (%): 329 (M+1, 0.6), 328 (M, 1.1), 155 ($CH_3PhSO_2^+$, 68.3), 97 ($C_7H_{13}^+$, 100.0), 91 (CH_3Ph^+, 75.9), 83 ($C_6H_{11}^+$, 40.3), 55 ($C_4H_9^+$, 43.0), 43 (CH_3CO^+, 64.8).

(*S*)-2,4-Dimethylpentan-1-ol (5). A solution of **4** (490 mg, 1.49 mmol) in dry ether (2 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in dry ether (10 mL). The mixture was heated and refluxed for 5 h before H_2O (0.5 mL) was added at 0 °C. The mixture was filtered and ether was removed by distillation. Chromatography of the crude product gave 155 mg of **5** (90%). $[\alpha]_D$ −4.1° (*c* 4.0, $CHCl_3$), lit. −3.9° (*c* 3.3, $CHCl_3$)[4c]. ν_{max}: 3460, 2950 cm^{-1}. δ_H: 3.45 (2H, m), 1.40 (1H, br s),



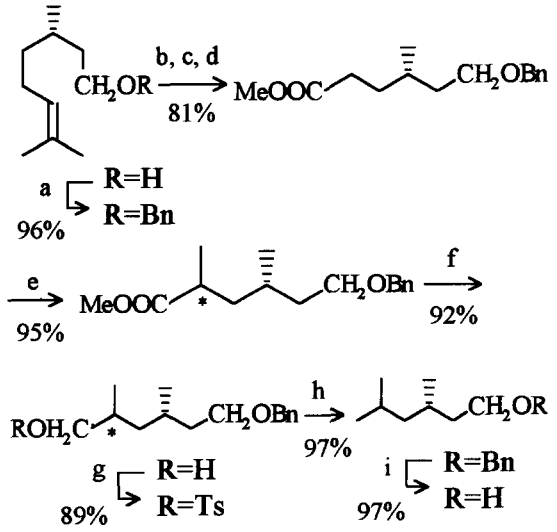
Scheme 4. Reagents and conditions: (a) TBDPS-Cl, imidazole/DMF; (b) K_2CO_3/MeOH, 40 °C; (c) i. Jones oxidation, 0 °C; ii. CH_2N_2/Et_2O, 0 °C; (d) i. $^iPr_2NH$, ^nBuLi/THF, 0 °C; ii. PhSeBr, −78 °C; iii. H_2O_2, pyridine/CH_2Cl_2; (e) $RhCl_3 \cdot 3H_2O$/EtOH, reflux; (f) $Ph_2P(O)CH_2CH_3$, ^nBuLi, −78 °C; (g) $NaBH_4$, $CeCl_3$/EtOH, −78 °C; (h) NaH/DMF, 40 °C.



Scheme 5. Reagents and conditions: (a) $(COCl)_2$, $DMSO/CH_2Cl_2$, −78 °C, then Et_3N; (b) **8**, Mg/THF, CuI, reflux.

1.60–1.20 (4H, m), 1.05 (3H, d, J = 6.0 Hz), 0.95 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.2 Hz) ppm. *m/z* (%): 116 (M, 1.1), 115 (M−1, 13.0), 97 (M-H_2O, 23.2), 85 ($C_6H_{13}^+$, 47.1), 57 ($C_4H_9^+$, 100.0), 43 ($C_3H_7^+$, 73.5). HRMS: Calcd for $C_7H_{15}O$: 115.1123. Found: 115.1108.

(3*R*)-3,5-Dimethylhexan-1-ol (7). A solution of Ph_3P (270 mg, 1.03 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise via a syringe over a period of 5 min to a well stirred solution of **5** (120 mg, 1.03 mmol) and CBr_4 (500 mg, 1.51 mmol) in dry CH_2Cl_2 (1 mL) at room temperature. After an additional 30 min of stirring, the reaction mixture was treated with *n*-pentane (150 mL) and the resulting precipitate (Ph_3PO) was removed by filtration and washed several times with *n*-pentane. The combined *n*-pentane solutions were washed successively with 5% Na_2CO_3 aq, H_2O and brine, and dried ($MgSO_4$). Upon removal of the solvent, the unreacted



Scheme 6. Reagents and conditions: (a) NaH/THF, BnBr, $^nBu_4NI$; (b) O_3, acetone, −78 °C; (c) Jones oxidation, 0 °C; (d) CH_2N_2/Et_2O, 0 °C; (e) LDA/THF, CH_3I, HMPA, −78 °C; (f) $LiAlH_4/Et_2O$; (g) *p*-TsCl, pyridine; (h) $LiAlH_4/Et_2O$, reflux; (i) H_2, Pd/C, EtOH.

CBr_4 was easily removed by passing the mixture through a short pad of silica gel, elution with *n*-pentane gave 145 mg of crude **6** (79%). The Grignard reagent prepared from Mg (70 mg, 3.0 mmol) and **6** (100 mg, 0.56 mmol) was treated with stoichiometric amounts of powdered and dried paraformaldehyde and allowed to stand for 2 days. The reaction was quenched by addition of ice followed by 2 N HCl (5 mL). The phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined ethereal solution was washed with $NaHSO_3$ aq, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue gave 72 mg of **7** (74%). $[\alpha]_D$ −8.5° (*c* 3.5, $CHCl_3$). ν_{max}: 3460, 2950 cm^{-1}. δ_H: 3.45 (2H, t, J = 6.0 Hz), 1.48 (1H, br s), 1.60–1.20 (6H, m), 1.02 (3H, d, J = 6.0 Hz), 0.94 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.2 Hz) ppm. HRMS: Calcd for $C_8H_{18}O$: 130.1358. Found: 130.1349.

(2*R*,4*S*)-1-(*tert*-Butyldiphenylsilyloxy)-5-acetoxypentane (9). A solution of **3** (500 mg, 2.87 mmol) in dry DMF (5 mL) was treated with imidazole (100 mg, 1.47 mmol) and *tert*-butyldiphenylchlorosilane (0.8 mL, 860 mg, 3.13 mmol). After being vigorously stirred for 4 h at room temperature, the reaction mixture was partitioned between 1:1 hexane:ether (10 mL) and brine (10 mL). The phases were separated and the aqueous layer was extracted with ether:*n*-hexane (1:1, 3 × 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography gave 1.16 g of **9** (98%). $[\alpha]_D$ +7.2° (*c* 0.8, $CHCl_3$). ν_{max}: 3050, 2910, 1725, 1460, 1425, 1230, 1010, 820, 725, 705 cm^{-1}. δ_H: 7.60–7.20 (10H, m), 3.80 (2H, m), 3.40 (2H, m), 1.94 (3H, s), 1.85–1.40 (4H, m), 0.99 (9H, s), 0.93 (3H, d, J = 6.4 Hz), 0.89 (3H, d, J = 6.2 Hz) ppm. *m/z* (%): 355 (M-CMe_3^+, 5.5), 241 ($Ph_2SiOC_3H_7^+$, 65.4), 199 (Ph_2Si^+OH, 100.0), 181 (Ph_2Si^+, 55.9), 97 ($C_7H_{13}^+$, 39.8), 55 ($C_4H_7^+$, 30.1).

(2*S*,4*R*)-2,4-Dimethyl-5-(*tert*-butyldiphenylsilyloxy)-1-pentanol (10). A mixture of **9** (800 mg, 1.94 mmol) and K_2CO_3 (500 mg, 3.62 mmol) in MeOH (10 mL) and water (1 mL) ws stirred at 40 °C for 2 h. Then H_2O (10 mL) and ether (10 mL) were added to the mixture at room temperature. The phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography of the residue afforded 680 mg of **10** (95%). $[\alpha]_D$ +0.2° (*c* 2.4, $CHCl_3$). ν_{max}: 3400, 2910, 1460, 1425, 1010, 820, 725, 705 cm^{-1}. δ_H: 7.70–7.30 (10H, m), 3.50 (4H, m), 1.80–1.40 (4H, m), 1.05 (9H, s), 0.92 (3H, d, J = 6.0 Hz), 0.89 (3H, d, J = 6.0 Hz) ppm. *m/z* (%): 313 (M-CMe_3^+, 3.2), 199 (Ph_2Si^+OH, 100.0), 97 ($C_7H_{13}^+$, 48.1), 55 ($C_3H_7^+$, 31.5).

(2*R*,4*S*)-2,4-Dimethyl-1-(*tert*-butyldiphenylsilyloxy)pentanoic acid, methyl ester (11). With cooling (0 °C bath) and stirring, Jones reagent (2 mL, 2.58 M, 5.16 mmol) was added dropwise to a solution of **10** (800 mg, 2.16 mmol) in acetone (10 mL). The mixture was

stirred for 30 min before being quenched by the addition of 2-propanol (1 mL) and then filtered through a fritted glass funnel. The filtrate was concentrated on a rotary evaporator to remove most of the acetone. H_2O (10 mL) was added and then the solution was extracted with ether (3 × 10 mL). The combined extracts were extracted with 2 N NaOH (3 × 30 mL). The combined aqueous extracts were adjusted to pH 2 using 1 N HCl and extracted with additional ether (3 × 30 mL). The ethereal extracts were washed with brine (3 × 30 mL) and concentrated in vacuo to provide the crude acid.

To a solution of NaOH (2 g, 50 mmol) in H_2O (10 mL) and ether (30 mL), *N*-methyl-*N*-nitrosourea (500 mg, 4.85 mmol) was added slowly at 0 °C and the mixture was stirred vigorously for 5 min. The resulting yellow CH_2N_2 ethereal solution was added to the crude acid (prepared above) in ether (10 mL) at 0 °C and stirred for 30 min. The solution was concentrated in vacuo and the residue was chromatographed to give 730 mg of **11** (85%). $[\alpha]_D$ +11.5° (*c* 0.7, $CHCl_3$). ν_{max}: 2910, 1725, 1460, 1425, 1360, 1010, 820, 725, 705 cm^{-1}, δ_H: 7.70–7.30 (10H, m), 3.65 (3H, s), 3.40 (2H, m), 2.52 (1H, m), 1.90–1.60 (3H, m), 1.12 (3H, d, *J* = 6.9 Hz), 1.05 (9H, s), 0.90 (3H, d, *J* = 6.7 Hz) ppm. *m/z* (%): 367 (M-MeO$^+$, 7.1), 341 (M-Me_3^+, 72.8), 213 [$Ph_2Si(H)OCH_2^+$, 100.0], 199 (Ph_2SiOH^+, 20.4), 183 (Ph_2SiH^+, 34.0). HRMS: Calcd for (M-CMe_3^+) $C_{20}H_{25}O_3Si$: 341.1573. Found: 341.1607.

(2*E*,4*S*)-2,4-Dimethyl-5-(*tert*-butyldiphenylsilyloxy)-2-pentenoic acid, methyl ester (13). A solution of **11** (800 mg, 2.01 mmol) in anhydrous THF (1 mL) was added slowly to an LDA solution [prepared from diisopropylamine (0.5 mL, 3.96 mmol) and *n*-BuLi (1.6 M, 2 mL, 3.2 mmol)] at −78 °C. The stirring was continued for 1 h before PhSeBr [prepared from $(PhSe)_2$ (624 mg, 2.0 mmol) and dry Br_2 (0.10 mL, 310 mg, 1.94 mmol)] in anhydrous THF (2 mL) was added. After another hour of stirring at −78 °C, the temperature was gradually raised to 0 °C. H_2O (5 mL) was added and after 5 min of standing the phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL), concentrated in vacuo and chromatographed to provide the intermediate, which was then dissolved in CH_2Cl_2 (10 mL). Then pyridine (0.05 mL) and H_2O_2 (30%, 0.5 mL, 4.41 mmol) were added and the resulting mixture was stirred vigorosly at room temperature for 2 h. Then the solution was diluted with CH_2Cl_2 (30 mL) and washed successively with 5% sodium thiosulfate aq, satd $CuSO_4$ sq and brine. The CH_2Cl_2 solution was dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography of the crude product gave 135 mg of **12**, 541 mg of **13**, with the ratio **12**:**13** 1:5. Compound **12** (135 mg, 0.34 mmol) was converted to **13** quantitatively by dissolving **12** in anhydrous ethanol (5 mL) and treated with $RhCl_3 \cdot 3H_2O$ (5 mg, 0.02 mmol) at reflux for 5 h. The total yield of **13** was 85%. $[\alpha]_D$ +5.7° (*c* 0.7, $CHCl_3$). ν_{max}: 2950, 1725, 1425, 1050, 825, 725, 705 cm^{-1}. δ_H: 7.70–7.30 (10H, m), 6.57 (1H, dd, *J* = 9.9, 1.4 Hz), 3.73 (3H, s), 3.40 (2H, m), 2.60 (1H, m), 1.81 (3H, d, *J* = 1.4 Hz), 1.05 (9H, s), 0.94 (3H, d, *J* = 6.6 Hz) ppm. *m/z* (%): 339 (M-CMe_3^+, 41.32), 213 [$Ph_2Si(OH)CH_2^+$, 100.00], 183 (Ph_2Si^+H, 21.16). HRMS: Calcd for $C_{20}H_{23}O_3Si$: 339.1416. Found: 339.1431.

(3*E*,2*R*)-2,4-Dimethyl-1-(*tert*-butyldiphenylsilyloxy)-6-diphenylphosphineoxido-3-hepten-5-one (14). With cooling (−78 °C) and stirring, ^{n}BuLi (1.6 M, 0.6 mL, 0.96 mmol) was added dropwise to a mixture of ethyldiphenylphosphineoxide (250 mg, 1.10 mmol) in anhydrous THF (4 mL). The stirring was continued at −78 °C for 30 min before a solution of **13** (300 mg, 0.76 mmol) in anhydrous THF (1 mL) was introduced. After another hour of stirring at −78 °C, the temperature was gradually raised to 0 °C, the temperature was gradually raised to 0 °C. Then H_2O (5 mL) was added and after 5 min of standing the phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL) and dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography of the crude product gave 442 mg of **14** (98%). ν_{max}: 2950, 1680, 1425, 1130, 1050, 825, 725, 705 cm^{-1}. δ_H: 7.95–7.25 (20H, m), 6.47 (1H, m), 4.40 (1H, m), 3.40 (2H, m), 2.20 (2H, m), 1.52 (3H, d, *J* = 6.8 Hz), 1.25 (3H, s), 1.05 (9H, s), 0.99 (3H, d, *J* = 6.7 Hz) ppm. *m/z* (%): 595 (M+1, 0.2), 537 (M-Me_3^+, 100.0), 259 [M-Me_3C-P(O)Ph_2-Ph, 19.1], 201 [P(O)Ph_2, 81.0], 199 (Ph_2SiOH^+, 39.1), 77 ($C_6H_5^+$, 26.1), 69 ($C_5H_9^+$, 20.1), 55 ($C_4H_7^+$, 17.8). HRMS: Calcd for (M-Me_3C^+) $C_{33}H_{34}O_3PSi$ = 537.2015. Found: 537.2131.

(3*E*,2*R*,5*S,6*S**)-2,4-Dimethyl-1-(*tert*-butyldiphenylsilyloxy)-6-diphenylphosphineoxido-3-hepten-5-ol (15).** To a solution of **14** (90 mg, 0.15 mmol) in anhydrous ethanol (2 mL) was added $CeCl_3 \cdot 7H_2O$ (57 mg, 0.15 mmol) and the mixture was then cooled to −78 °C. $NaBH_4$ (25 mg, 0.66 mmol) was added and stirring was continued for another 30 min. Then 1 N HCl (2 mL) was added slowly and the temperature was gradually raised to 0 °C. The solution was extracted with ether (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL), concentrated in vacuo and chromatographed to provide 67 mg of the *threo* diastereomer **15** and 16 mg of the *erythro* diastereomer. The *erythro* isomer could be recycled as **14** via Swern oxidation: to a solution of $(COCl)_2$ (0.1 mL, 70 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added a solution of DMSO (0.06 mL, 70 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The stirring was continued for 10 min and then the *erythro* isomer (16 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added at −78 °C. After 10 min, Et_3N (0.2 mL) was added and the temperature was gradually raised to 0 °C, then H_2O (5 mL) was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (3 × 10 mL), concentrated in vacuo and chromatographed to provide 14 mg of **14** (90%). ν_{max}: 3400, 2950, 1425, 1130, 1050, 825, 725, 705 cm^{-1}.

δ_H: 7.90–7.30 (20H, m), 5.05 (1H, m), 4.10 (1H, m), 3.40 (2H, m), 2.20 (2H, m), 1.60 (1H, s), 1.51 (3H, d, J = 6.8 Hz), 1.25 (3H, s), 1.03 (9H, s), 0.94 (3H, d, J = 6.6 Hz) ppm. *m/z* (%): 539 ($M-Me_3^+$, 4.1), 230 [$CH_3CH^+P(O)Ph_2$, 25.7], 201 [$P(O)Ph_2$, 100.0], 199 (Ph_2SiOH^+, 36.4), 77 ($C_6H_5^+$, 20.8), 69 ($C_5H_9^+$, 20.9). HRMS: Calcd for ($M-Me_3C^+$) $C_{33}H_{36}O_3PSi$: 539.2171. Found: 539.2169.

(3*E*,5*E*,2*S*)-2,4-Dimethyl-3-,5-heptadien-1-ol (16). A solution of **15** (40 mg, 0.07 mmol) in dry DMF (4 mL) was added to a suspension of NaH (30 mg, 60%, 0.75 mmol) in dry DMF (7 mL). The mixture was stirred at 40 °C for 2 h and then cooled with an ice bath. Then H_2O (5 mL) was added slowly. The phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography of the crude product gave 8.5 mg of **16** (90%). $[\alpha]_D$ +29.0° (*c* 0.1, $CHCl_3$). ν_{max}: 3400, 3040, 2950, 1620, 1080, 1010, 965 cm^{-1}. δ_H: 6.09 (1H, d, J = 15.3 Hz), 5.65 (1H, dq, J = 15.3, 6.6 Hz), 5.10 (1H, br d, J = 9.5 Hz), 3.45 (2H, m), 2.70 (1H, m), 1.79 (3H, d, J = 6.5 Hz), 1.77 (3H, s), 0.97 (3H, d, J = 6.7 Hz) ppm. *m/z* (%): 140 (M, 5.1), 122 ($M-H_2O$, 3.2), 95 ($C_7H_{11}^+$, 100.0), 69 (C_5H9^+, 28.3), 43 ($C_3H_7^+$, 54.2). HRMS: Calcd for $C_9H_{16}O$: 140.1201. Found: 140.1232.

(2*E*,4*E*,6*R*,10*R*)-4,6,10,12-Tetramethyl-2,4-tridecadien-7-ol (17). Compound **8** was obtained in 82% yield under the same conditions as described for preparing **6**. Compound **16** (10 mg, 0.07 mmol) was oxidized under the Swern conditions as indicated previously [$(COCl)_2$ (0.2 mL, 145 mg, 1.14 mmol), DMSO (0.1 mL, 110 mg, 1.41 mmol), Et_3N (0.2 mL)] into the corresponding crude aldehyde before being added to the Grignard reagent [prepared from **8** (30 mg, 0.15 mmol), Mg (24 mg, 1 mmol) and CuI (30 mg, 0.15 mmol)]. The mixture was refluxed for 30 min and saturated aqueous NH_4Cl (3 mL) was added. The phases were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography of the crude product gave 9 mg of **17** (55%). ν_{max}: 3400, 3040, 2950, 1620, 1470, 1050, 965 cm^{-1}. δ_H: 5.98 (1H, d, J = 15.3 Hz), 5.50 (1H, dq, J = 15.3, 6.4 Hz), 5.18 (1H, d, J = 9.8 Hz), 3.30 (1H, m), 2.40 (1H, ddq, J = 9.8, 6.4, 6.4 Hz), 1.74 (3H, d, J = 6.4 Hz), 1.65 (3H, d, J = 1.0 Hz), 1.70–1.10 (8H, m), 0.98 (3H, d, J = 6.4 Hz), 0.90–0.85 (9H, m) ppm. *m/z* (%): 253 (M + 1, 3.9), 235 ($M-H_2O$, 10.8), 110 ($C_8H_{14}^+$, 68.0), 95 ($C_7H_{11}^+$, 100.0), 69 ($C_5H_9^+$, 31.2), 43 ($C_3H_7^+$, 41.2).

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(2*E*,4*E*,6*R*,10*R*)-4,6,10,12-Tetramethyl-2,4-tridecadien-7-one (1). Compound **17** (6 mg, 0.02 mmol) was treated under the Swern conditions as indicated above [$(COCl)_2$ (0.2 mL, 145 mg, 1.14 mmol), DMSO (0.1 mL, 110 mg, 1.41 mmol) and Et_3N (0.2 mL)] to give 5 mg of **1** (90%). $[\alpha]_D$ −151.5° (*c* 0.25, $CHCl_3$). ν_{max}: 3040, 1710, 1630, 965 cm^{-1}. δ_H (C_6D_6): 6.06 (1H, brd, J = 15.5 Hz), 5.54 (1H, dq, J = 15.5, 6.8 Hz), 5.29 (1H, d, J = 9.9 Hz), 3.36 (1H, dq, J = 9.9, 6.8 Hz), 2.31 (1H, ddd, J = 16.5, 9.3, 6.4 Hz), 2.22 (1H, ddd, J = 16.5, 9.1, 5.2 Hz), 1.72 (3H, brs), 1.65 (3H, brd, J = 7.5 Hz), 1.18 (3H, d, J = 6.8 Hz), 1.75–1.00 (6H, m), 0.90 (3H, d, J = 6.6 Hz), 0.85 (3 H, d, J = 6.6 Hz), 0.80 (3H, d, J = 6.2 Hz) ppm. δ_C (C_6D_6): 210.18, 136.77, 136.24, 130.23, 124.41, 47.58, 47.31, 39.13, 32.04, 30.90, 26.16, 24.11, 23.13, 20.33, 18.86, 17.40, 13.62 ppm. HRMS: Calcd for $C_{17}H_{30}O$: 250.2297. Found: 250.2293.

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