A Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol (Vitamin E) Side Chain

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Optically pure (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (16), corresponding to the α-tocopherol side chain, was synthesized by the coupling reaction of a chiral isoprene unit (3*S*)-9 derived from an enzymatically hydrolyzed product (2*S*,3*S*)-2 and a ten-carbon alkylating reagent (*R*)-13 derived from (*R*)-(+)-pulegone.

Key words α-tocopherol; (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol; sulfone; chiral isoprene unit

α-Tocopherol, a potent antioxidant and radical scavenger in chemical and biological systems, has potential clinical and nutritional applications in human health. Therefore, attempts have been made to develop an efficient and stereocontrolled synthesis of the natural form of α-tocopherol.[2] The reported approaches have been based on the coupling of chroman and side-chain moieties. Our strategy for the synthesis of the side-chain moiety corresponding to (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**16**) was based on the use of a chiral isoprene unit A in which the phenylsulfonyl group represents a reactive function capable of coupling with a ten-carbon synthon such as (*R*)-β-citronellol.

In the previous paper,[3] an enantioselective hydrolysis of the (±)-*syn*-β-acetoxy-α-methyl propionate (**1**) using the lipase "Amano A" from *Asperigillus niger* gave an alcohol (2*S*,3*S*)-**2** ($[\alpha]_D^{23}$ −16.4° (*c*=4.7, $CHCl_3$), 51% yield) in high optical purity (94% enantiomeric excess (ee)), along with the unchanged acetate (2*R*,3*R*)-**1** ($[\alpha]_D^{23}$ +47.3° (*c*=4.6, $CHCl_3$) corresponding to >99% ee, 48% yield). Synthesis of optically active fungicides, oudemansins A, B and X, from (2*R*,3*R*)-**1** has already been achieved by us.[3] In this paper, we wish to describe the application of (2*S*,3*S*)-**2** to the synthesis of (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**16**) *via* the chiral isoprene unit A according to the above-mentioned strategy.

First, to increase the optical purity of (2*S*,3*S*)-**2**, we conducted acetylation of (2*S*,3*S*)-**2** followed by crystallization to afford an optically pure acetate (2*S*,3*S*)-**1** ($[\alpha]_D^{22}$ −47.9° (*c*=1.0, $CHCl_3$)) in 70% overall yield. The optical purity of (2*S*,3*S*)-**1** was confirmed by high-performance liquid chromatography (HPLC). $LiAlH_4$ reduction of (2*S*,3*S*)-**1** provided a 1,3-diol (2*S*,3*S*)-**3** ($[\alpha]_D^{25}$ −56.8° (*c*=1.24, $CHCl_3$), 84% yield), which was subjected to hydrogenolysis in the presence of 20% $Pd(OH)_2$–C and a trace amount of 60% perchloric acid to give an alcohol (2*S*)-**4** ($[\alpha]_D^{23}$ −8.1° (*c*=0.64, $CHCl_3$)) in 88% yield. Reaction of (2*S*)-**4** with *N*-bromosuccinimide (NBS) and triphenylphosphine (Ph_3P) afforded a bromide (2*S*)-**5** (89% yield), which was treated with benzenesulfinate ($PhSO_2Na \cdot 2H_2O$) to yield a phenylsulfone (2*S*)-**6** ($[\alpha]_D^{26}$ +12.2° (*c*=1.1, $CHCl_3$)) in 74% yield. Ozonolysis of (2*S*)-**6** followed by oxidative treatment with 30% H_2O_2 gave the carboxylic acid, which was treated with diazomethane (CH_2N_2) to provide the corresponding methyl ester (3*S*)-**7** ($[\alpha]_D^{25}$ −5.02° (*c*=0.9, $CHCl_3$)) in 70% overall yield. In order to differentiate the functional groups of (*S*)-**7**, the ester group of (3*S*)-**7** was reduced with $LiBH_4$ to afford an alcohol (3*S*)-**8** ($[\alpha]_D^{26}$ +5.01° (*c*=1.67, $CHCl_3$)) in 86% yield. Protection of the hydroxyl group of (3*S*)-**8** by treatment with dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) gave a tetrahydropyranyl ether (*S*)-**9** (99% yield), corresponding to the chiral isoprene unit A.

An alkylating reagent (3*R*)-**13** corresponding to a ten-carbon species was derived from (*R*)-(+)-pulegone. Namely, optically pure (*R*)-(+)-citronellic acid **10** ($[\alpha]_D^{25}$ +8.7° (*c*=1.19, $CHCl_3$) corresponding to >99% ee) obtained from (*R*)-(+)-pulegone by the reported method[4] was reduced with $LiAlH_4$ to give (*R*)-(+)-β-citronellol **11** ($[\alpha]_D^{24}$ +4.3° (*c*=1.1, $CHCl_3$)) in 80% yield. Hydrogenation of (*R*)-**11** gave an alcohol (*R*)-**12** ($[\alpha]_D^{24}$ +3.9° (*c*=0.7,

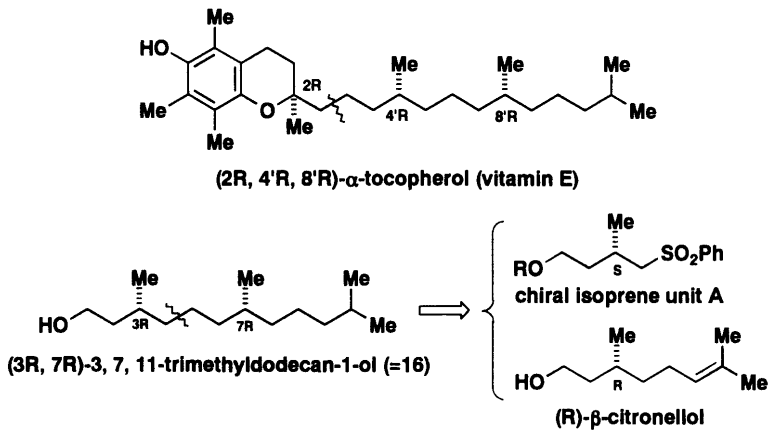

Chart 1

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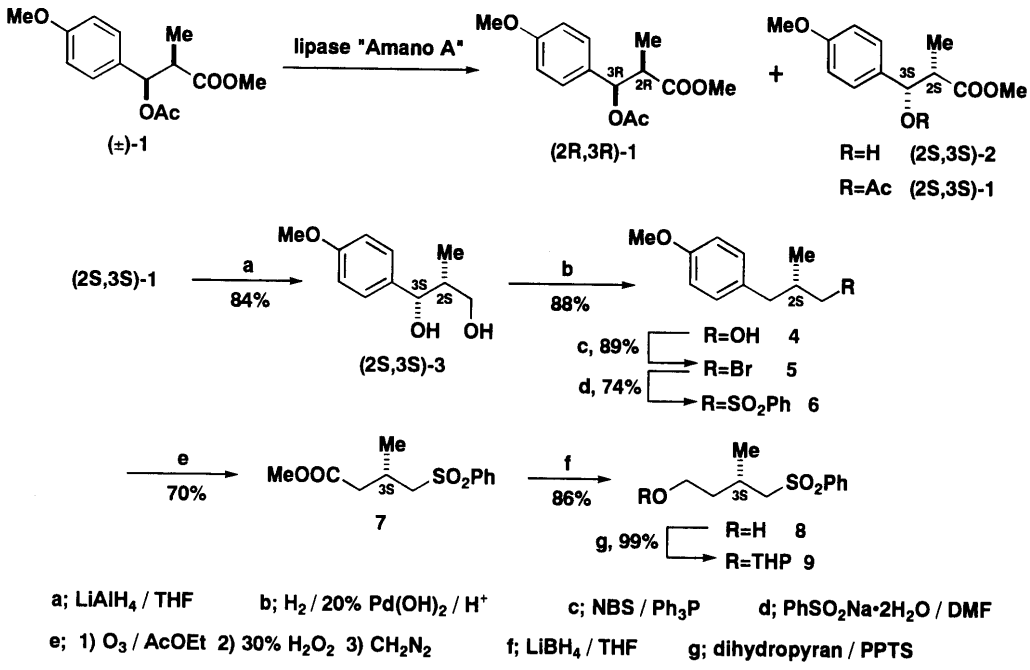

Chart 2

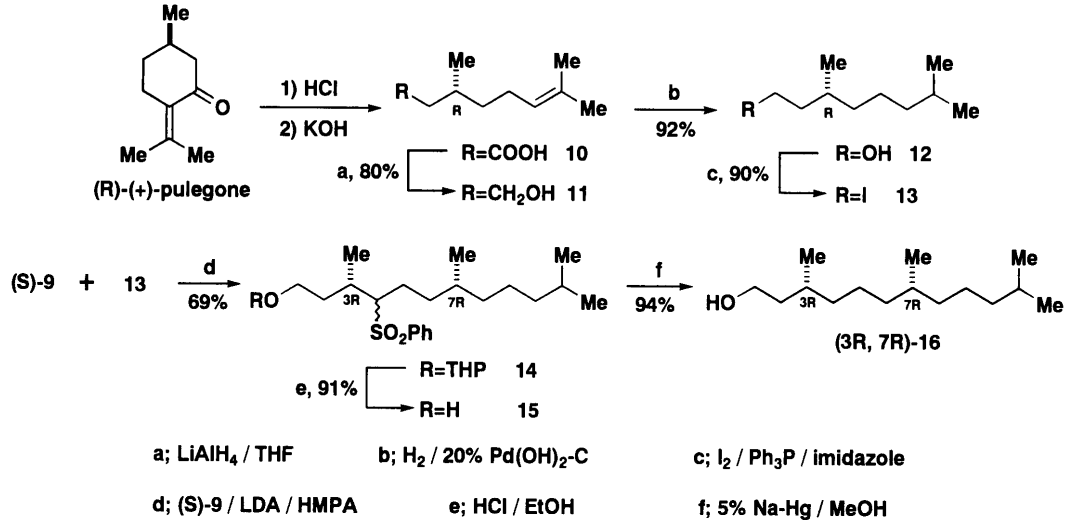

Chart 3

$CHCl_3$), 92% yield), which was treated with iodine (I_2) and Ph_3P in the presence of imidazole to provide the desired iodide (*R*)-**13** ($[\alpha]_D^{28}$ $-10.8°$ ($c=1.08$, $CHCl_3$)) in 90% yield. An anion of (*S*)-**9** generated by treatment with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) was subjected to alkylation with the iodide (*R*)-**3** to give a coupling product **15** in 69% yield. Removal of the tetrahydropyranyl (THP) group of **14** by treatment with a trace amount of concentrated HCl in EtOH gave an alcohol **15** in 91% yield, and this was treated with sodium amalgam (5% Na–Hg) to yield the desired alcohol (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**16**) in 94% yield. Physical constants of (3*R*,7*R*)-**16** ($[\alpha]_D^{27}$ $+3.44°$ ($c=0.99$, $CHCl_3$)) were identical with those ($[\alpha]_D^{18}$ $+3.49°$ ($c=0.98$, $CHCl_3$)) of the reported (3*R*,7*R*)-**16**.[2)]

In conclusion, optically pure (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**16**), corresponding to the α-tocopherol side chain, was synthesized by the coupling reaction of a chiral isoprene unit (3*S*)-**9** derived from an enzymatic hydrolysis product (2*S*,3*S*)-**2** and a ten-carbon alkylating reagent (*R*)-**13** derived from (*R*)-(+)-pulegone.

Experimental

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-300 instrument. NMR spectra were measured on a JEOL EX 4000 instrument. Spectra were taken for 5—10% (w/v) solutions in $CDCl_3$ with Me_4Si as an internal reference (s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br; broad). High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D 300 or JEOL JMS-DX 303 spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. The HPLC system was composed of two SSC instruments (an ultraviolet (UV) detector 3000B and a flow system 3100). All organic solvent extracts were washed with saturated brine and dried over anhydrous magnesium sulfate ($MgSO_4$). All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl (2*S*,3*S*)-3-Acetoxy-3-(4-methoxyphenyl)-2-methylpropanoate (1) A mixture of (2*S*,3*S*)-**2** (94% ee, 5.428 g), Ac_2O (10 ml) and pyridine (6 ml) was stirred for 4 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with saturated aqueous $NaHCO_3$ and saturated brine, then dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (150 g) to provide (2*S*,3*S*)-**1** as a homogeneous oil from the *n*-hexane–ethyl acetate (9 : 1) eluate. Crystallization of (2*S*,3*S*)-**1** from *n*-hexane gave colorless needles (4.511 g, 70% yield). (2*S*,3*S*)-**1**: mp 58.5—59.5 °C. $[\alpha]_D^{22}$ −47.9° (c = 1.00, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.77; H, 6.87. IR (CCl_4): 1744 cm^{-1}. NMR δ: 1.23 (3H, d, J = 6.8 Hz, 2-Me), 2.08 (3H, s, 3-OAc), 2.94 (1H, dq, J = 6.8, 7.6 Hz, 2-H), 3.56 (3H, s, COOMe), 3.79 (3H, s, 4-OMe), 5.97 (1H, d, J = 7.6 Hz, 3-H), 6.85 and 7.24 (each 2H, d, J = 8 Hz, aromatic-H).

(2*S*,3*S*)-3-(4-Methoxyphenyl)-2-methylpropane-1,3-diol (3) A solution of (2*S*,3*S*)-**1** (3.902 g) in tetrahydrofuran (THF, 20 ml) was added to a suspension of $LiAlH_4$ (0.84 g) in THF (20 ml) at 0 °C with stirring, and stirring was continued for 15 min at the same temperature. Then H_2O (1 ml) was added and the mixture was diluted with ethyl acetate and filtered with the aid of Celite. The filtrate was dried over $MgSO_4$ and evaporated to give a residue, which was crystallized from *n*-hexane–ethyl acetate to afford (−)-**3** as colorless needles (2.424 g, 84% yield). (−)-**3**: mp 88—90 °C. $[\alpha]_D^{25}$ −56.8° (c = 1.24, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.24; H, 8.21. IR (Nujol): 3305 cm^{-1}. NMR δ: 0.82 (3H, d, J = 7.3 Hz, 2-Me), 1.84 (1H, s, OH), 1.97—2.08 (1H, m, 2-H), 2.85 (1H, br s, OH), 3.24 (1H, br s, OH), 3.60 (2H, d, J = 4.9 Hz, 1-H_2), 3.79 (3H, s, 4-OMe), 4.84 (1H, br s, 3-H), 6.87 and 7.23 (each 2H, d, J = 8.3 Hz, aromatic-H).

(2*S*)-3-(4-Methoxyphenyl)-2-methylpropanol (4) A solution of (2*S*,3*S*)-**3** (2.063 g) in ethyl acetate (24 ml) was hydrogenated at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (0.4 g) and 60% perchloric acid (2 drops). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was washed with saturated aqueous $NaHCO_3$ and saturated brine, then dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (60 g) to provide (2*S*)-**4** as a homogeneous oil (1.661 g, 88% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (2*S*)-**4**: MS m/z: 180 (M^+). $[\alpha]_D^{23}$ −8.1° (c = 0.64, $CHCl_3$). IR (neat): 3379 cm^{-1}. NMR δ: 0.89 (3H, d, J = 6.8 Hz, 2-Me), 1.90 (1H, m, 2-H), 1.97 (1H, br s, OH), 2.35 (1H, dd, J = 8.3, 13.7 Hz, 3-H), 2.68 (1H, dd, J = 6.4, 13.7 Hz, 3-H), 3.43 (1H, dd, J = 6.4, 10.7 Hz, 1-H), 3.50 (1H, dd, J = 6.4, 10.7 Hz, 1-H), 3.77 (3H, s, 4-OMe), 6.82 and 7.07 (each 2H, d, J = 8.3 Hz, aromatic-H).

(2*S*)-1-Bromo-3-(4-methoxyphenyl)-2-methylpropane (5) NBS (1.7 g) and Ph_3P (2.5 g) were added to a solution of (2*S*)-**4** (1.453 g) in CH_2Cl_2 (100 ml) under ice-water cooling. The mixture was stirred for 90 min at room temperature, then diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (40 g) to provide (2*S*)-**5** as a homogeneous oil (1.74 g, 89% yield) from the *n*-hexane–ethyl acetate (29 : 1) eluate. (2*S*)-**5**: IR (neat): 1612, 835 cm^{-1}. NMR δ: 1.03 (3H, d, J = 6.4 Hz, 2-Me), 1.99—2.10 (1H, m, 2-H), 2.50 (1H, dd, J = 7.3, 13.7 Hz, 3-H), 2.69 (1H, dd, J = 7.3, 13.7 Hz, 3-H), 3.29 (1H, dd, J = 5.6, 9.8 Hz, 1-H), 3.37 (1H, dd, J = 4.9, 9.8 Hz, 1-H), 3.79 (3H, s, 4-OMe), 6.83 and 7.10 (each 2H, d, J = 9 Hz, aromatic-H).

(2*S*)-3-(4-Methoxyphenyl)-1-phenylsulfonyl-2-methylpropane (6) A mixture of (2*S*)-**5** (1.162 g) and sodium benzenesulfinate (1.19 g) in dimethylformamide (DMF, 30 ml) was heated at 100 °C for 2 h with stirring, then diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave a crude residue, which was chromatographed on silica gel (30 g) to afford (2*S*)-**6** as a homogeneous oil (1.069 g, 74% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (2*S*)-**6**: MS (FAB) m/z: 305 ($M^+ + 1$). $[\alpha]_D^{26}$ +12.2° (c = 1.1, $CHCl_3$). IR (neat): 1320, 1150 cm^{-1}. NMR δ: 1.08 (3H, d, J = 6.8 Hz, 2-Me), 2.23—2.35 (1H, m, 2-H), 2.53 (1H, dd, J = 7.1, 14 Hz, 3-H), 2.61 (1H, dd, J = 7.1, 14 Hz, 3-H), 2.89 (1H, dd, J = 7.8, 14.2 Hz, 1-H), 3.11 (1H, dd, J = 4.9, 14.2 Hz, 1-H), 3.78 (3H, s, 4-OMe), 6.77 and 6.94 (each 2H, d, J = 8.3 Hz, aromatic-H).

Methyl (3*S*)-3-Methyl-4-phenylsulfonylbutanoate (7) Ozone was passed through a solution of (2*S*)-**6** (1.002 g) in ethyl acetate (50 ml) at room temperature for 2 h, then 30% aqueous H_2O_2 (5 ml) was added to the ozonolyzed product. The reaction mixture was stirred for 10 min at room temperature, then diluted with H_2O and extracted with ether. The organic solution was dried over $MgSO_4$. Removal of the solvent gave a residue, which was treated with CH_2N_2 in ether to provide an oily product. This was subjected to chromatographic separation on silica gel (15 g) to give (3*S*)-**7** as a homogeneous oil (587 mg, 70% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (3*S*)-**7**: MS (FAB) m/z: 257 ($M^+ + 1$). $[\alpha]_D^{25}$ −5.02° (c = 0.9, $CHCl_3$). IR (neat): 1732 cm^{-1}. NMR δ: 1.14 (3H, d, J = 7.0 Hz, 3-Me), 2.38 (1H, dd, J = 6.2, 14.8 Hz, 2-H or 4-H), 2.58 (1H, dd, J = 5.9, 14.8 Hz, 2-H or 4-H), 3.04 (1H, dd, J = 6.6, 14.1 Hz, 2-H or 4-H), 3.29 (1H, dd, J = 5.9, 14.1 Hz, 2-H or 4-H), 3.64 (3H, s, COOMe), 7.58 (2H, t, aromatic-H), 7.67 (1H, tt, J = 1.3, 7.3 Hz, aromatic-H), 7.92 (2H, d, J = 7.3 Hz, aromatic-H).

(3*S*)-3-Methyl-4-phenylsulfonylbutanol (8) A solution of (3*S*)-**7** (120 mg) in THF (2 ml) was added to a suspension of $LiBH_4$ (10 mg) in THF (5 ml) at 0 °C. The mixture was stirred for 12 h at room temperature, then diluted with H_2O and extracted with ethyl acetate. The organic solution was dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (3 g) to provide (3*S*)-**8** as a homogeneous oil (92 mg, 86% yield) from the *n*-hexane–ethyl acetate (2 : 1) eluate. (3*S*)-**8**: $[\alpha]_D^{26}$ +5.01° (c = 1.67, $CHCl_3$). IR (neat): 3519 cm^{-1}. NMR δ: 1.09 (3H, d, J = 7 Hz, 3-Me), 1.55—2.37 (3H, m, 3-H and 2-H_2), 2.99 (1H, dd, J = 7, 14.2 Hz, 4-H), 3.23 (1H, dd, J = 5.3, 14.2 Hz, 4-H), 3.64 (1H, dt, J = 6.2, 11.1 Hz, 1-H), 3.70 (1H, dt, J = 6.2, 11.1 Hz, 1-H), 7.55—7.93 (5H, m, aromatic-H).

(3*S*)-3-Methyl-4-phenylsulfonylbutyltetrahydropyranyl Ether (9) A mixture of (3*S*)-**8** (229 mg), 3,4-dihydropyran (210 mg), and PPTS (30 mg) in CH_2Cl_2 (10 ml) was stirred for 12 h at room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (10 g) to provide (3*S*)-**9** as a homogeneous oil (312 mg, 99% yield) from the *n*-hexane–ethyl acetate (4 : 1) eluate. (3*S*)-**9**: IR (neat): 1306, 1147 cm^{-1}. NMR δ: 1.13 (3H, d, J = 6.8 Hz, 3-Me), 1.51—1.75 (8H, m), 2.23—2.31 (1H, m), 2.97 (1H, dd, J = 7.8, 14.2 Hz), 3.21—3.49 (3H, m), 3.70—3.81 (2H, m), 4.49—4.51 (1H, m), 7.54—7.92 (5H, m, aromatic-H).

(*R*)-β-Citronellol (11) A solution of (*R*)-**10** ($[\alpha]_D^{25}$ +8.7° (c = 1.19, $CHCl_3$) corresponding to >99% ee, 2.049 g) in THF (10 ml) was added to a suspension of $LiAlH_4$ (0.46 g) in THF (10 ml) at 0 °C with stirring, and the reaction mixture was stirred for 15 min at the same temperature. H_2O (1 ml) was added, and the whole was diluted with ethyl acetate, then filtered with the aid of Celite. The filtrate was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (65 g) to provide (*R*)-**11** as a homogeneous oil (1.503 g, 80% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (*R*)-**11**: $[\alpha]_D^{24}$ +4.3° (c = 1.1, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.75; H, 12.92. NMR δ: 0.90 (3H, d, J = 6.8 Hz, 3-Me), 1.60 and 1.68 (each 3H, s, olefinic-Me), 1.83 (1H, br s), 3.61—3.72 (2H, m, 1-H_2), 5.08—5.12 (1H, m, 6-H).

(3*R*)-3,7-Dimethyloctanol (12) A solution of (3*R*)-**11** (488 mg) in ethyl acetate (10 ml) was hydrogenated at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (0.4 g). After hydrogen absorption had ceased, the catalyst was filtered off. The filtrate was evaporated to give a crude residue, which was chromatographed on silica gel (15 g) to give (3*R*)-**12** as a homogeneous oil (453 mg, 92% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (3*R*)-**12**: $[\alpha]_D^{24}$ +3.9° (c = 0.7, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.49; H, 14.42. IR (neat): 3338 cm^{-1}. NMR δ: 0.85—0.90 (9H, m), 1.10—1.71 (11H, m), 3.62—3.72 (2H, m, 1-H_2).

(3*R*)-3,7-Dimethyloctyl Iodide (13) Ph_3P (1.25 g) and imidazole (422 mg) were added to a solution of (3*R*)-**12** (376 mg) in ether (3 ml) and acetonitrile (CH_3CN, 3 ml) with stirring. Iodine (786 mg) was added to the above reaction mixture in an atmosphere of argon under ice-water cooling, and the whole was stirred for 30 min at 0 °C and then for 50 min at room temperature. It was diluted with *n*-hexane and washed with saturated aqueous sodium thiosulfate, saturated aqueous copper(II) sulfate and saturated brine. The organic layer was dried over $MgSO_4$, and evaporated to give a crude residue, which was chromatographed on silica gel (25 g) to afford (3*R*)-**13** as a homogeneous oil (576 mg, 90% yield) from the *n*-hexane eluate. (3*R*)-**13**: $[\alpha]_D^{28}$ −10.8° (c = 1.08, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{21}I$: C, 44.79; H, 7.89. Found: C, 44.83; H, 8.03. NMR δ: 0.86—0.88 (9H, m), 1.10—1.92 (10H, m), 3.13—3.28 (2H, m, 1-H_2).

(3*R*,7*R*)-3,7,11-Trimethyldodecan-1-ol (16) i) *n*-Butyllithium (1.6 M in

hexane, 2.5 ml) was added to a stirred solution of diisopropylamine (0.5 ml) in THF (2 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min at the same temperature. The resulting LDA–THF solution (1 ml) was added to a solution of (3*R*)-**9** (93 mg) in THF (2 ml) at −78 °C and then HMPA (0.1 ml) was added. The whole was stirred for 30 min at −78 °C, then a solution of (3*R*)-**13** (97 mg) in THF (2 ml) was added at the same temperature. The reaction mixture was stirred for 1 h at −78 °C and for 30 min at 0 °C, then diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (3 g) to afford **14** as a homogeneous oil (94 mg, 69% yield) from the *n*-hexane–ethyl acetate (20 : 1) eluate. ii) A mixture of **14** (207 mg) and concentrated HCl (2 drops) in EtOH (2 ml) was stirred for 3 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (8 g) to afford **15** as a homogeneous oil (153 mg, 91% yield) from the *n*-hexane–ethyl acetate (3 : 1) eluate. iii) 5% Na–Hg (3.02 g) was added to a solution of **15** (112 mg) in MeOH (5 ml) and the mixture was refluxed for 2 h with stirring, then diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (3 g) to provide **16** as a homogeneous oil (65 mg, 94% yield) from the *n*-hexane–ethyl acetate (9 : 1) eluate. (3*R*,7*R*)-**16**: *Anal.* Calcd for $C_{15}H_{32}O$: C, 78.95; H, 14.04. Found: C, 79.41; H, 14.47. *Anal.* HRMS (EI) Calcd for $C_{15}H_{32}O$ ($M^+ - 1$; *m/z*): 227.2367. Found: 227.2379. $[\alpha]_D^{27}$ +3.44° (*c* = 0.99, $CHCl_3$). IR (neat): 3336 cm^{-1}. NMR δ: 0.84—0.90 (12H, m), 3.63—3.70 (2H, m).

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