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TETRAHEDRON

Synthesis of Tricyclopolyprenols *via* a Radical Addition and a Stereoselective Elimination. Part II: (Z)-Tricyclopentaprenol, (*E,E*)- and (*Z,Z*)-Tricyclohexaprenol, (*Z,Z,Z*)-Tricycloheptaprenol

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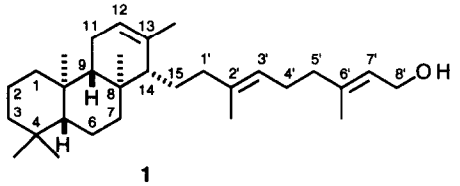
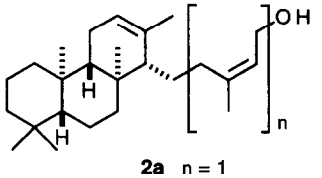
Abstract: Four tricyclopolyprenols have been synthesised by addition of the isocopalenyl radical either to a 2-methylene-3-hydroxy alkenenitrile (in the case of (*E,E*)-tricyclohexaprenol) or to a methyl 2-methylene-3-hydroxy alkenoate (in the case of the three (*Z*)-tricyclopolyprenols). Elaboration of the newly introduced side chains includes a stereoselective elimination reaction and the reduction of the electron withdrawing groups (-CN or -CO_2Me) into a methyl. © 1997 Elsevier Science Ltd. All rights reserved.

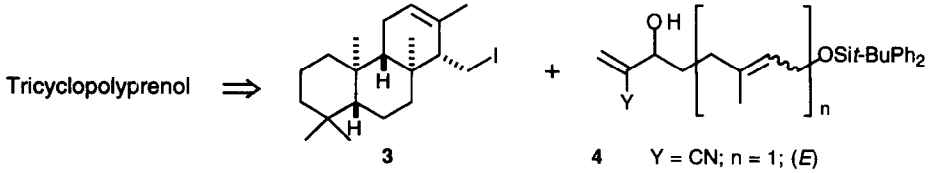
The preceding paper describes a number of chemical studies designed to test the feasibility of a new synthesis of tricyclopolyprenols, bearing either an all-*trans* or an all-*cis* side chain. In this article, we utilize this methodology to prepare the hypothetic geoterpane precursors (*E,E*)-tricyclohexaprenol **1**[1a] and (*Z,Z*)-tricyclohexaprenol **2b**.[1b] Since geoterpanes with extended side chains have also been identified,[2] we have also applied our methodology to the synthesis of (*Z,Z,Z*)-tricycloheptaprenol **2c**. Finally, (*Z*)-tricyclopentaprenol **2a**, the synthetic precursor of the sesterterpene *ent*-cheilanthenediol,[3] has also been prepared according to the same lines. The starting materials were on the one hand isocopalenyl iodide **3** and on the other the substituted acrylonitrile **4** in the case of the *ditrans* compound **1** or the substituted methyl acrylates **5a-c** in the case of the all-*cis* compounds **2a-c**. These side chain precursors had first to be prepared as described below.



1



2a n = 1
2b n = 2
2c n = 3



3

4 Y = CN; n = 1; (*E*)
5a-c Y = CO_2Me; n = 0, 1, 2; all-(*Z*)

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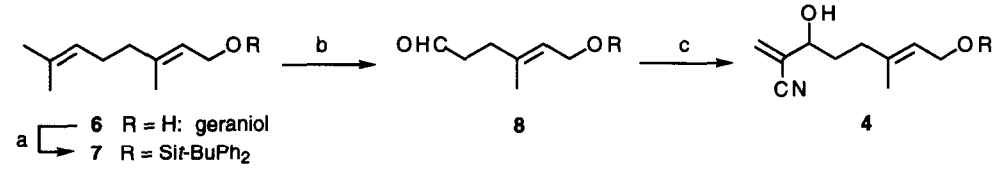
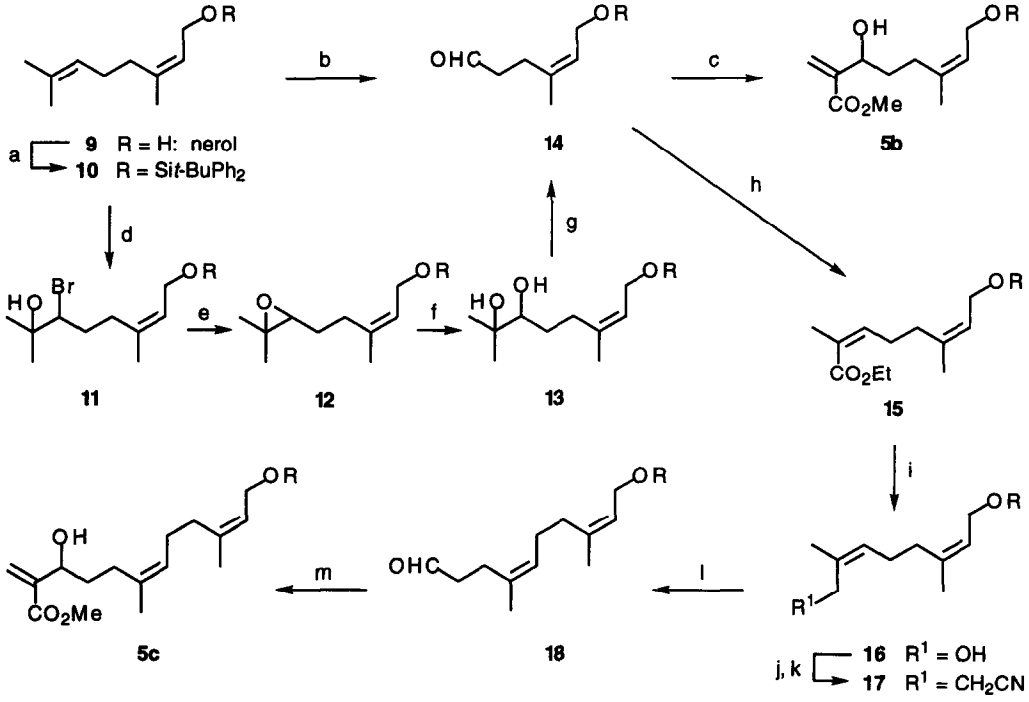
Preparation of the side chain precursors

The synthesis of the compound **1** which has a *ditrans* side chain required first the preparation of the nitrile **4**. This could be achieved by subjection of the aldehyde **8** to a Baylis-Hillman reaction[4] with acrylonitrile. The aldehyde **8** was obtained in 45% yield from geraniol **6** by protection of the hydroxy group followed by ozonolysis (Scheme 1).

Subjection of an appropriate aldehyde to a Baylis-Hillman reaction with methyl acrylate seemed also a good method for the preparation of the α,β-unsaturated esters **5a-c** that we needed for the synthesis of the all-*cis* side chain compounds **2a-c**. The ester **5b** could be prepared from the aldehyde **14** obtained in 44% yield from nerol **9** by protection of the hydroxy

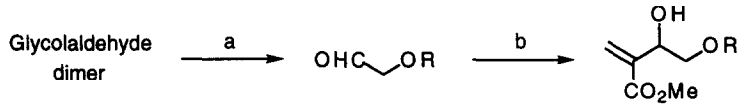


Scheme 1. Reagents: a) *t*-$BuPh_2SiCl$, imidazole, DMF, r. t. (100%); b) O_3, CH_2Cl_2, –78 °C, 1 h; then Me_2S, –78 °C → r. t. (45%), c) acrylonitrile, 1,4-diazabicyclo[2.2.2]octane (DABCO), 17 days (60%).



Scheme 2. Reagents: a) *t*-$BuPh_2SiCl$, imidazole, DMF, r. t. 0.25 h (100% yield); b) O_3, pyridine, CH_2Cl_2, –78 °C, 1 h; then Me_2S, –78 °C → r. t., 2 h (44%); c) methyl acrylate, DABCO, 23 days (44%); d) N-Bromosuccinimide, 1,2-dimethoxyethane (DME)/H_2O 8/2, –5 °C, 3.5 h (89%); e) K_2CO_3, MeOH, r. t., 1 h (93%); f) $HClO_4$, DME/H_2O 9/1, r. t., 5 h (93%); g) $NaIO_4$, H_2SO_4, DME/H_2O 95/5, r. t., 3.5 h, (96%); h) $(CF_3CH_2O)_2P(O)CH(Me)CO_2Et$, $KN(SiMe_3)_2$, 18-crown-6 ether, THF, –78 °C, 1 h (63%); i) DIBAH, toluene, –78 °C, 0.25 h (59%); j) PBr_3, Et_2O, r. t., 1.5 h; k) CH_3CN, Li*N*-Pr_2, THF, –78 °C, 0.3 h (steps j + k = 55%); l) DIBAH, toluene, 0 °C, 5 min, then NH_4Cl (85%); m) methyl acrylate, quinuclidin-3-ol, r. t., 6 days (50%).

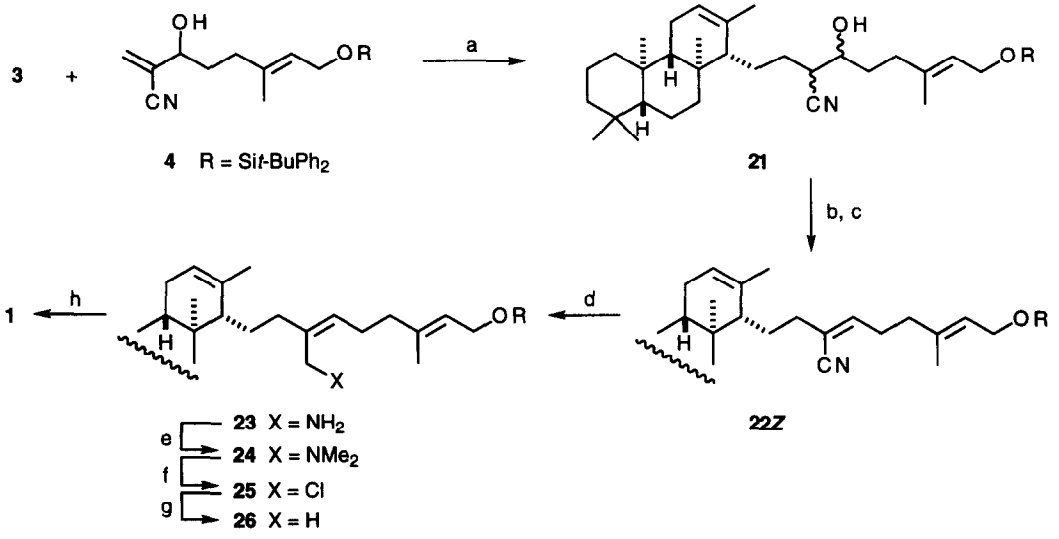
group and ozonolysis. But since **14** was also the starting material for the prenylogous aldehyde **18**, multigram amounts of **14** were prepared in 74% yield from the protected nerol **10**, *via* the epoxide **12**, by a classic four step sequence (Scheme 2).[5] Transformation of the aldehyde **14** into the (*Z*)-α,β-unsaturated ester **15** by a Horner-Wadsworth-Emmons reaction with one of Still's phosphonates[6] followed by reduction with diisobutylaluminium hydride (DIBAH) gave the alcohol **16** which, after conversion into the corresponding bromide, substitution with lithioacetonitrile,[7] reduction with DIBAH and hydrolysis, furnished the aldehyde **18**. The latter when treated with methyl acrylate and quinuclidin-3-ol gave the substituted acrylate **5c**. The α,β-unsaturated ester **5a** was obtained from the protected hydroxyacetaldehyde **20** prepared from 2,5-dihydroxy-1,4-dioxane, the commercial glycolaldehyde dimer[3b,8] (Scheme 3).



20 R = Si*t*-BuPh$_2$ **5a**

Scheme 3. Reagents: a) i) NEt_3, CH_2Cl_2, r. t., 2 min.; ii) *t*-$BuPh_2SiCl$, 4-(dimethylamino)pyridine (DMAP), r. t., 1 day; b) methyl acrylate, quinuclidin-3-ol, 1 month; (steps a + b: 30%).

Synthesis of the tricyclopolyprenols



4 R = Si*t*-BuPh$_2$ **21** **22Z**

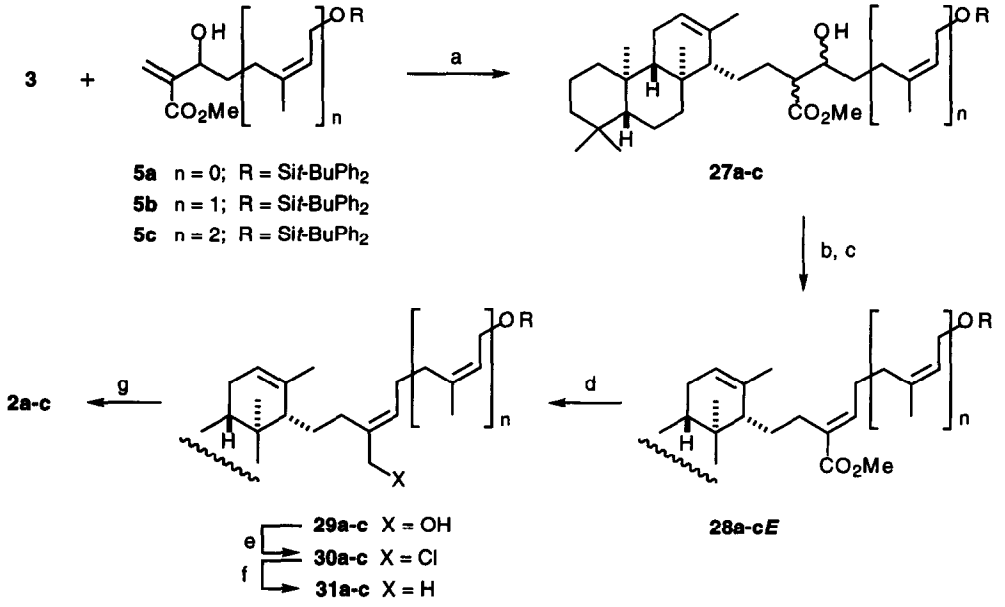
23 X = NH_2
24 X = NMe_2
25 X = Cl
26 X = H

Scheme 4. Reagents: a) *n*-Bu_3SnH, Et_2O, hν (300 W tungsten lamp), 8 h (40% yield); b) Ac_2O, DMAP, toluene, 20 °C, 0.5 h; c) DBU, toluene, reflux, 5 days (steps b + c: 62%; **22Z/22E** = 81/19; unreacted **21**: 22%); then chromatographic separation of the *E* and *Z* nitriles; d) AlH_3, Et_2O, 0 °C → r. t., 2 h; e) $(CH_2O)_n$, MeOH, reflux, 1.5 h; then $NaBH_3CN$, r. t., 1 h; f) $ClCO_2Et$, K_2CO_3, toluene, 0 °C, 1 h; then r. t., 1 day; g) $LiBHEt_3$, THF, r. t., 0.25 h (d - g: 42%); h) *n*-Bu_4NF, THF, r. t., 8 h (81%).

We were then ready to undertake the synthesis of (*E,E*)-tricyclohexaprenol. Addition of the isocopalenyl radical, prepared from the isocopalenyl iodide **3**,[10] to the α,β-unsaturated nitrile **4** gave a mixture of four diastereomeric hydroxy nitriles **21** which, after acetylation and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene, led to a

81/19 *trans/cis* mixture of the α,β-unsaturated nitriles **22**.[9] After chromatographic separation, the *trans* isomer **22Z** was transformed into the (*E,E*)-tricyclohexaprenol **1** *via* the dimethylamine **24** and the chloride **25** as described in Scheme 4.[10]

The (*Z,Z*)-tricyclohexaprenol **2b** was also within close reach. Addition of the isocopalenyl radical to the methyl acrylate **5b** gave a mixture of four diastereomeric hydroxy esters **27b** which, after mesylation and treatment with DBU, furnished a 91/9 *cis/trans* mixture of the α,β-unsaturated esters **28b**.[11] After chromatographic separation, the *cis* isomer was reduced into (*Z,Z*)-tricyclohexaprenol **2b** via the alcohol **29b** and the chloride **30b**. (*Z*)-Tricyclopentaprenol **2a** and (*Z,Z,Z*)-tricycloheptaprenol **2c** were subsequently prepared according to the same lines (Scheme 5).[10]



Scheme 5. Reagents: a) *n*-Bu_3SnH, EtO_2, hν (300 W tungsten lamp), 5-11 h (**27a** : 49%; **b:** 48%; **c**: 35%); b) MsCl, NEt_3, CH_2Cl_2, 0 °C, 0.25 h; c) DBU, toluene, reflux, 4 h (steps b + c: **28a**: 86%, *E/Z* = 77/23; **b**: 91%, *E/Z* = 91/9; **c**: 79%, *E/Z* = 92/8)[11]; then chromatographic separation of the *E* and *Z* esters†; d) DIBAH, toluene, –78 °C, 0.5 h (**29a**: 83%; **b**: 85%; **c**: 84%); e) CCl_4, PPh_3, reflux, 3 days; f) $LiBHEt_3$, THF, r. t., 1 h (e + f: **31a**: 95%; **b**: 77%; **c**: 71%); g) *n*-Bu_4NF, THF, r. t., 7 h (**2a**: 100%; **b**: 92%; **c**: 74%).

† Except for the esters **28a** where it was difficult and was performed after reduction into **29a**.

The membrane reinforcing properties of the tricyclopolyprenols **1**, **2b** and **2c** were assessed on dimyristoylphosphatidylcholine-d_{27} bilayers by means of ^{2}H-NMR.[12]

EXPERIMENTAL SECTION

For a description of the general techniques, see the preceding paper.

***t*-Butyldiphenylsilyl geranyl ether 7.** Imidazole (5.64 g, 83.0 mmol) and *t*-butyldiphenylsilyl chloride (13.8 ml, 53.2 mmol) were added to a solution of geraniol **6** (5.82 g, 37.8 mmol) in dimethylformamide (DMF) (60 ml). The mixture was stirred for 15 min at room temperature and then poured into vigorously stirred

hexane (100 ml). The two phases were partitioned, and the DMF phase was extracted another time with hexane (100 ml). The combined hexane phases were then washed with brine, dried, concentrated, and chromatographed on a silica gel column (eluent: hexane/ether 99/1, then hexane/ether 9/1) to give the silyl ether **7** (14.82 g, 37.7 mmol, 100%) as a colourless oil. IR: 3076, 2934, 1668, 1112, 1060 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.06 (s, 9 H), 1.45 (s, 3 H), 1.62 (s, 3 H), 1.70 (s, 3 H), 1.95-2.13 (m, 4 H), 4.24 (br d, J = 6.2 Hz, 2 H), 5.11 (br t, J = 6.0 Hz, 1 H), 5.40 (br t, J = 6.2 Hz, 1 H), 7.33-7.48 (m, 6 H), 7.65-7.76 (m, 4 H). Anal. Calcd for $C_{26}H_{36}OSi$: C, 79.53; H, 9.24. Found C, 79.5; H, 9.4.

(*E*)-6-[(*t*-Butyldiphenylsilyl)oxy]-4-methylhex-4-enal 8. Ozone was passed through a solution of the silyl ether **7** (4.00 g, 10.2 mmol) and pyridine (1.0 ml, 12.4 mmol) in methylene chloride (26 ml) at –78 °C. After 1 h, dimethyl sulfide (4 ml) was added and the reaction medium was allowed to warm to room temperature. Rotary evaporation (bleach trap) left a brown compound which was dissolved in methylene chloride (5 ml). Addition of water (50 ml) and of a few drops of 10% aqueous HCl gave a slurry which was extracted with pentane, washed with brine and dried. Concentration and chromatography on a silica gel column (hexane/ether 95/5) afforded unreacted silyl ether **7** (1.30 g, 3.3 mmol) and the aldehyde **8** (1.68 g, 4.6 mmol, 45%) as a colourless oil. IR: 3076, 2936, 2714, 1728, 1112, 1072 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.04 (s, 9 H), 1.45 (br s, 3 H), 2.29 (m, 2 H), 2.50 (m, 2 H), 4.22 (m, 2 H), 5.38 (tq, J = 6.2, 1.2 Hz, 1 H), 7.33-7.48 (m, 6 H), 7.62-7.74 (m, 4 H), 9.76 (t, J = 1.7 Hz, 1 H).

***t*-Butyldiphenylsilyl neryl ether 10.** The same procedure as for the ether **7** allowed the transformation of the nerol **9** (1.80 g; 11.7 mmol) into the silyl ether **10** (4.60 g; 11.7 mmol; 100%) as a colourless oil. IR: 3078, 2934, 1666, 1112, 1060 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.51 (br s, 3 H), 1.61 (br s, 3 H), 1.71 (d, J = 1.2 Hz, 3 H), 1.82-2.04 (m, 4 H), 4.19 (dd, J = 6.4, 1.0 Hz, 2 H), 4.94-5.05 (m, 1 H), 5.40 (br t, J = 6.5 Hz, 1 H), 7.33-7.45 (m, 6 H), 7.66-7.74 (m, 4 H). Anal. Calcd. for $C_{26}H_{36}OSi$: C, 79.53; H, 9.24. Found C, 79.5; H, 9.2.

(*Z*)-1-[(*t*-Butyldiphenylsilyl)oxy]-3,7-dimethyl-6,7-epoxyoct-2-ene 12. N-Bromosuccinimide (5.00 g, 28.1 mmol) was added slowly to a solution of the silyl ether **10** (10.00 g, 25.4 mmol) in 8/2 DME/water (510 ml) at –5 °C. The mixture was stirred for 3.5 h and then diluted with ethyl acetate (200 ml). The aqueous phase was extracted with hexane (100 ml) and methylene chloride (20 ml). The combined organic phases were then washed with brine and dried. Concentration and column chromatography (hexane/ether 95/5) afforded the bromohydrine **11** (11.10 g, 22.6 mmol, 89%) as a yellow oil. IR: 3616, 3570, 3072, 3016, 2932, 1668, 1110, 1058 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.27 (s, 3 H), 1.29 (s, 3 H), 1.70 (d, J = 1.2 Hz, 3 H), 3.84 (dd, J = 11.0, 2.1 Hz, 1 H), 4.24 (br d, J = 6.6 Hz, 2 H), 5.47 (br t, J = 6.6 Hz, 1 H), 7.32-7.47 (m, 6 H), 7.65-7.75 (m, 4 H). Solid potassium carbonate (3.00 g, 21.7 mmol) was slowly added to a stirred solution of the bromohydrine **11** (10.50 g, 21.4 mmol) in methanol (215 ml) and the mixture was allowed to react for 1 h at room temperature. The methanol was then removed in vacuo and the residue dissolved in hexane (400 ml) and water (400 ml). After extraction of the aqueous phase with hexane, the combined organic phases were washed with brine and dried. Concentration afforded pure epoxyde **12** (8.10 g, 19.8 mmol, 93%). IR: 3072, 2998, 2932, 1664, 1112, 1070 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.16 (s, 3 H), 1.22 (s, 3 H), 1.72 (br s, 3 H), 1.94-2.06 (m, 2 H), 2.57 (t, J = 6.4 Hz, 1 H), 4.20 (d, J = 6.4 Hz, 2 H), 5.44 (t, J = 6.4 Hz, 1 H), 7.32-7.47 (m, 6 H), 7.65-7.73 (m, 4 H).

(*Z*)-6-[(*t*-Butyldiphenylsilyl)oxy]-4-methylhex-4-enal 14. ***Method A: from silyl ether 10.*** The same procedure as for the aldehyde **8** allowed the transformation of the silyl ether **10** (1.80 g, 4.6 mmol) into the aldehyde **14** (0.73 g, 2.0 mmol, 44%). Unreacted silyl ether **10** was also recovered (0.63 g, 1.6 mmol). ***Method B: from epoxyde 12.*** 70% Aqueous perchloric acid (0.6 ml) was added at room temperature to a solution of the epoxide **12** (8.00 g, 19.6 mmol) in 9/1 DME/water (400 ml) and the mixture was allowed to react for 5 h. It was then diluted with ethyl acetate (100 ml), hexane (100 ml) and methylene chloride (20 ml). The organic phase was washed with saturated $NaHCO_3$ and brine, and dried. Concentration and column chromatography (hexane/ether 6/4) afforded the diol **13** (7.80 g, 18.3 mmol, 93%). IR: 3576, 3452, 3072, 3018, 2932, 1470, 1664, 1110 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.13 (s, 3 H), 1.17 (s, 3 H), 1.72 (br s, 3 H), 1.91-2.07 (m, 1 H), 2.34-2.51 (m, 1 H), 3.26-3.36 (m, 1 H), 4.06 (dd, J = 11.7, 6.7 Hz, 1 H), 4.32 (dd, J = 11.7, 8.3 Hz, 1 H), 5.43 (br t, J = 7.2 Hz, 1 H), 7.36-7.47 (m, 6 H), 7.66-7.77 (m, 4 H). A solution of concentrated sulfuric acid (1.1 ml, 21.6 mmol) and of sodium metaperiodate (4.62 g, 21.6

mmol) in water (40 ml) was slowly added at room temperature to a solution of the diol **13** (7.70 g, 18.0 mmol) in 95/5 DME/water (300 ml). The mixture was stirred for 3.5 h and then diluted with hexane (200 ml) and methylene chloride (20 ml). The organic phase was washed with saturated $NaHCO_3$ and brine, and dried. Concentration and column chromatography (hexane/ethyl acetate 9/1) afforded the aldehyde **14** (6.31 g, 17.2 mmol, 96%) as a colourless oil. IR: 3076, 2936, 2814, 2714, 1728, 1664, 1112, 1066 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.69 (d, J = 1.2 Hz, 3 H), 2.12-2.23 (m, 2 H), 2.31-2.43 (m, 2 H), 4.20 (dd, J = 6.5, 1.1 Hz, 2 H), 5.44 (t, J = 6.5 Hz, 1 H), 7.32-7.48 (m, 6 H), 7.64-7.73 (m, 4 H), 9.65 (t, J = 1.5 Hz, 1 H). Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found C, 75.4; H, 8.1.

Ethyl (2Z,6Z)-8-[(*t*-butyldiphenylsilyl)oxy]-2,6-dimethylocta-2,6-dienoate 15. 0.5 M Potassium bis(trimethylsilyl)amide in THF (2.3 ml, 1.15 mmol) was slowly added to a cold (0 °C) solution of $(CF_3CH_2O)_2P(O)CH(Me)CO_2Et$ (400 mg, 1.16 mmol) and of dry 18-crown-6 ether (611 mg, 2.31 mmol) in THF (6 ml). After 10 min, the mixture was cooled to –78 °C and a solution of the aldehyde **14** (400 mg, 1.09 mmol) in THF (1 ml) was added. After 1 h, the reaction medium was quenched with aqueous NH_4Cl (5 ml) and extracted with ether. The combined organic phases were dried, concentrated and chromatographed on a silica gel column (hexane/ether 95/5) to give unreacted aldehyde **14** (150 mg, 0.41 mmol) and the ester **15**[13] (311 mg, 0.69 mmol, 63%) as a colourless oil. IR: 3072, 2930, 1714, 1670, 1648, 1210, 1176, 1110 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.05 (s, 9 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.71 (d, J = 1.2 Hz, 3 H), 1.82 (d, J = 1.3 Hz, 3 H), 1.97 (t, J = 7.6 Hz, 2 H), 2.45 (br q, J = 7.4 Hz, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.20 (br d, J = 6.3 Hz, 2 H), 5.42 (t, J = 6.3 Hz, 1 H), 5.76 (tq, J = 7.4, 1.3 Hz, 1 H), 7.34-7.47 (m, 6 H), 7.64-7.75 (m, 4 H). Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found C, 74.4; H, 8.3.

(2Z,6Z)-8-[(*t*-Butyldiphenylsilyl)oxy]-2,6-dimethylocta-2,6-dien-1-ol 16. 1.0 M DIBAH in THF (6.0 ml, 6.0 mmol) was added to a cold (–78 °C) solution of the ester **15** (280 mg, 0.62 mmol) in toluene (10 ml) and the mixture was stirred for 15 min. The reaction was then quenched with aqueous NH_4Cl (10 ml) and 10% HCl (3 ml) and extracted with ether. The combined organic phases were washed with water, dried, and concentrated. Column chromatography (hexane/ether 8/2) gave unreacted ester **15** (48 mg, 0.11 mmol) and the alcohol **16** (149 mg, 0.36 mmol, 59%) as a colourless oil. IR: 3622, 3072, 3018, 2934, 1675, 1110, 1058, 1004 cm^{-1}. ^1H-NMR (200 MHz) δ: 1.04 (s, 9 H), 1.71 (br s, 6 H), 1.85-2.12 (m, 4 H), 3.98 (s, 2 H), 4.16 (br d, J = 6.5 Hz, 2 H), 5.15 (t, J = 7.4 Hz, 1 H), 5.43 (t, J = 6.5 Hz, 1 H), 7.34-7.50 (m, 6 H), 7.66-7.76 (m, 4 H). Anal. Calcd for $C_{26}H_{36}O_2Si$: C, 76.42; H, 8.88. Found C, 76.5; H, 8.7.

(4Z,8Z)-10-[(*t*-Butyldiphenylsilyl)oxy]-4,8-dimethyldeca-4,8-dienenitrile 17. In the dark, phosphorus tribromide (0.33 ml, 0.94 g, 3.5 mmol) was added to a solution of the alcohol **16** (3.65 g, 8.9 mmol) in ether (100 ml) and the mixture was stirred at room temperature for 1.5 h. It was then diluted with ether, washed sequentially with water, with aqueous $NaHCO_3$ and with water, dried, and concentrated to give the crude corresponding bromide (4.20 g). 0.2 M Lithium diisopropylamide in THF (81.0 ml, 16.2 mmol) was slowly added to a cold (–78 °C) solution of the bromide obtained above and of acetonitrile (0.63 ml, 0.49 g, 12.1 mmol) in THF (80 ml) and the mixture was stirred for 20 min at –78 °C. It was then quenched with 0.1% HCl and extracted with ether. The combined organic phases were washed with water, dried, and concentrated. Column chromatography (hexane/ether 95/5) gave the nitrile **17** (2.14 g, 4.9 mmol, 55%) as a colourless oil. IR: 3075, 2934, 2247, 1668, 1111, 1063 cm^{-1}. ^1H-NMR δ: 1.04 (s, 9 H), 1.63 (d, J = 1.3 Hz, 3 H), 1.71 (d, J = 1.3 Hz, 3 H), 1.85-2.07 (m, 4 H), 2.27 (br s, 4 H), 4.17 (dd, J = 6.5, 1.1 Hz, 2 H), 5.16 (br t, J = 6.5 Hz, 1 H), 5.42 (td, J = 6.5, 1.3 Hz, 1 H), 7.33-7.50 (m, 6 H), 7.62-7.74 (m, 4 H). Anal. Calcd for $C_{28}H_{37}NOSi$: C, 77.90; H, 8.64; N, 3.25. Found C, 77.7; H, 8.7; N, 3.2.

(4Z,8Z)-10-[(*t*-Butyldiphenylsilyl)oxy]-4,8-dimethyldeca-4,8-dienal 18. 1.0 M DIBAH in toluene (5.0 ml, 5.0 mmol) was added to a cold (0 °C) solution of the nitrile **17** (2.05 g, 4.7 mmol) in toluene (60 ml). After 5 min, the reaction was quenched with aqueous NH_4Cl (50 ml), extracted with ether and the combined organic phases were washed with water and dried. Concentration and column chromatography (hexane-ether 9/1) gave the aldehyde **18** (1.75 g, 4.0 mmol, 85%) as a colourless oil. IR: 3074, 2936, 2817, 2716, 1728, 1671, 1110, 1060 cm^{-1}. ^1H-NMR δ: 1.05 (s, 9 H), 1.60 (d, J = 1.0 Hz, 3 H), 1.71 (d, J = 1.2 Hz, 3 H), 1.82-2.06 (m, 4 H), 2.19-2.30 (m, 2 H), 2.35-2.45 (m, 2 H), 4.18 (dd, J = 6.4, 1.0 Hz, 2 H), 5.05 (t, J = 6.4 Hz, 1 H), 5.42 (t, J = 6.4 Hz, 1 H), 7.34-7.48 (m, 6 H), 7.65-7.77 (m, 4 H), 9.69 (t, J = 1.7 Hz, 1 H). Anal. Calcd for $C_{28}H_{37}NOSi$: C, 77.37; H, 8.81. Found C, 77.1; H, 8.9.

[(*t*-Butyldiphenylsilyl)oxy]acetaldehyde 20. Triethylamine (0.80 ml, 5.8 mmol) was added to a suspension of 2,5-dihydroxy-1,4-dioxane **19** (0.29 g, 2.4 mmol) in methylene chloride (15 ml). After 2 min the mixture became homogeneous and DMAP (0.12 g, 1.0 mmol) and *t*-butyldiphenylsilyl chloride (1.4 ml, 5.5 mmol) were added. The mixture was stirred for 1 day at room temperature, diluted with methylene chloride, washed with water, aqueous NH_4Cl, and brine, dried and concentrated. Column chromatography (hexane/ether 8/2) gave 1.10 g of aldehyde **20** mixed with a silicon containing contaminant. IR: 1738 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.11 (s, 9 H), 4.22 (d, *J* = 0.8 Hz, 2 H), 7.32-7.54 (m, 6 H), 7.60-7.75 (m, 4 H), 9.73 (t, *J* = 0.8 Hz, 1 H). ^{13}C-NMR (50 MHz) δ: 19.2, 26.7, 70.0, 127.9, 130.0, 132.5, 135.5, 201.5. MS-MS (CI, isobutane) m/z: 299.0 (M+1).

(*E*)-8-[(*t*-Butyldiphenylsilyl)oxy]-3-hydroxy-6-methyl-2-methyleneoct-6-enenitrile 4. The aldehyde **8** (130 mg, 0.35 mmol), acrylonitrile (38 µl, 0.58 mmol) and DABCO (5 mg, 0.04 mmol) were stirred for 17 days at room temperature. The excess acrylonitrile was then removed in vacuo, and the residue was dissolved in ether, washed with 10% aqueous HCl and water, and dried. Concentration and column chromatography (pentane/distilled ether 8/2) gave unreacted aldehyde **8** (25 mg, 0.068 mmol) and the nitrile **4** (90 mg, 0.21 mmol, 60%) as a colourless oil. IR: 3618, 3512, 3072, 3020, 2932, 2226, 1666, 1618, 1110, 1064, 942 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.04 (s, 9 H), 1.46 (s, 3 H), 1.64-1.94 (m, 2 H), 2.09 (t, *J* = 7.4 Hz, 2 H), 4.18 and 4.22 (m and d, *J* = 6.2 Hz, 3 H), 5.41 (t, *J* = 6.2 Hz, 1 H), 5.98 (d, *J* = 1.1 Hz, 2 H), 7.30-7.50 (m, 6 H), 7.60-7.75 (m, 4 H). Anal. Calcd for $C_{26}H_{33}NO_2Si$: C, 74.42; H, 7.93; N 3.34. Found C, 73.9; H, 8.2; N, 3.3.

Methyl 4-[(*t*-butyldiphenylsilyl)oxy]-3-hydroxy-2-methylenebutanoate 5a. The aldehyde **20** (1.10 g, slightly impure), methyl acrylate (0.36 ml, 4.0 mmol) and quinuclidin-3-ol (51 mg, 0.40 mmol) were stirred for 1 month at room temperature. Evaporation in vacuo and column chromatography (hexane, then hexane/ether 8/2) gave the hydroxy ester **5a** (280 mg, 0.73 mmol, 30% from **19**) as a colourless oil. IR: 3575, 3074, 3054, 2936, 1720, 1628, 1300, 1194, 1160, 1106, 956 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.07 (s, 9 H), 3.08 (d, *J* = 5.5 Hz, 1 H), 3.60 (dd, *J* = 10.1, 6.3 Hz, 1 H), 3.68 (s, 3 H), 3.91 (dd, *J* = 10.1, 4.1 Hz, 1 H), 4.64 (br q, J_{app} = 5.1 Hz, 1 H), 6.00 (t, *J* = 1.4 Hz, 1 H), 6.36 (br s, 1 H), 7.30-7.47 (m, 6 H), 7.57-7.72 (m, 4 H). ^{13}C-NMR (50 MHz) δ: 19.2, 26.8, 51.7, 67.1, 71.0, 126.7, 127.7 129.8, 133.0, 135.5, 139.1, 166.3. Anal. Calcd. for $C_{22}H_{28}O_4Si$: C, 68.72; H, 7.34. Found C, 68.7; H, 7.5.

Methyl (*Z*)-8-[(*t*-butyldiphenylsilyl)oxy]-3-hydroxy-6-methyl-2-methyleneoct-6-enoate 5b. Same procedure as for **4**. Treatment of the aldehyde **14** (500 mg, 1.36 mmol) with methyl acrylate (0.18 ml, 2.0 mmol) and DABCO (16 mg, 0.14 mmol) for 23 days at room temperature gave unreacted aldehyde **15** (100 mg, 0.27 mmol) and the hydroxy ester **5b** (270 mg, 0.60 mmol, 44%) as a colourless oil. IR: 3614, 3538, 3076, 3022, 2936, 1718, 1664, 1628, 1296, 1194, 1146, 1108, 956 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.04 (s, 9 H), 1.45-1.85 (m, 2 H), 1.74 (d, *J* = 0.8 Hz, 3 H), 1.88-2.04 (m, 1 H), 2.15-2.33 (m, 1 H), 3.74 (s, 3 H), 4.13 (dd, *J* = 12.2, 6.4 Hz, 1 H), 4.27 and 4.31 (dd, *J* = 12.2, 7.3 Hz, and m, 2 H), 5.43 (br t, J_{app} = 6.7 Hz, 1 H), 5.80 (t, *J* = 1.0 Hz, 1 H), 6.19 (br s, 1 H), 7.32-7.49 (m, 6 H), 7.64-7.76 (m, 4 H). Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.64; H, 8.02. Found C, 71.7; H, 8.3.

Methyl (6*Z*,10*Z*)-12-[(*t*-butyldiphenylsilyl)oxy]-6,10-dimethyl-3-hydroxy-2-methylenedodeca-6,10-dienoate 5c. Same procedure as for **4**. Treatment of the aldehyde **18** (1.38 g, 3.2 mmol) with methyl acrylate (0.40 ml, 0.38 g, 4.4 mmol) and quinuclidin-3-ol (51 mg, 0.4 mmol) for 6 days at room temperature gave unreacted aldehyde **18** (0.63 g, 1.5 mmol) and the hydroxy ester **5c** (0.84 g, 1.6 mmol, 50%) as a colourless oil. IR: 3622, 3550, 2932, 1718, 1666, 1628, 1294, 1194, 1150, 1108, 956 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.04 (s, 9 H), 1.61 (d, *J* = 1.1 Hz, 3 H), 1.70 (d, *J* = 1.3 Hz, 3 H), 1.83-2.18 (m, 6 H), 2.44 (d, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 4.19 (dd, *J* = 6.5, 0.8 Hz, 2 H), 4.31 (m, 1 H), 5.03 (t, *J* = 6.2 Hz, 1 H), 5.39 (t, *J* = 6.5 Hz, 1 H), 5.76 (br s, 1 H), 6.20 (br s, 1 H), 7.31-7.48 (m, 6 H), 7.62-7.76 (m, 4 H). Anal. Calcd for $C_{32}H_{44}O_4Si$: C, 73.80; H, 8.52. Found C, 73.8; H, 8.4.

(6'*E*) - 1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-3'-hydroxy-6'-methyloct-6'-ene-2'-carbonitriles 21. A solution of the iodide **3** (50 mg, 0.13 mmol) and of the α,β-unsaturated nitrile **4** (370 mg, 0.88 mmol) in ether (2 ml) was irradiated with a 300 W tungsten lamp for 8 h as a solution of tributyltin hydride (80 µl, 0.29 mmol) in ether (0.5 ml) was added (syringe pump). Then the solution was

treated with aqueous KF (5 ml) for 12 h. The so-formed solid tin compounds were removed by filtration and the filtrate was concentrated in vacuo. Ether was then added and the solution was dried and concentrated. Column chromatography (hexane/ether 8/2) gave unreacted α,β-unsaturated nitrile **4** (300 mg, 0.71 mmol) and the hydroxy nitriles **21** (35 mg, 0.05 mmol, 40%). IR: 3622, 3584, 3072, 2932, 2240, 1668, 1110, 1066 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.74, 0.82, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.47 (br s, 3 H), 1.66 and 1.70 (2 br s), 2.59 (m, 1 H), 3.66 (m, 1 H), 4.21 (d, J = 6.2 Hz, 2 H), 5.39 and 5.45 (m and br t, J = 6.0 Hz, 2 H), 7.32-7.49 (m, 6 H), 7.63-7.75 (m, 4 H). MS m/z: 636 (15), 199 (100), 192 (18), 181 (7), 177 (24). HRMS: Calcd. for $C_{42}H_{58}NO_2Si$ [M–*t*-Bu] 636.424. Found 636.424.

(6'*E*) - 1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-6'-methylocta-2',6'-diene-2'-carbonitriles 22. Acetic anhydride (20 μl, 0.21 mmol) and DMAP (5 mg, 0.04 mmol) were added at room temperature to a solution of the hydroxy nitriles **21** (35 mg, 0.050 mmol) in toluene (10 ml) and the mixture was stirred for 1 h. It was then diluted with ether, washed with water and brine, and dried. Concentration in vacuo gave crude acetoxy nitriles (39 mg) which were dissolved in toluene (10 ml). After addition of DBU (300 μl, 2.0 mmol), the solution was refluxed for 6 days; then it was diluted with ether, washed with 10% HCl and with brine, dried and concentrated to give a 81/19 mixture of the α,β-unsaturated nitriles **22*Z*/22*E***.[9] Column chromatography (hexane/ether 200/1) allowed the separation of the α,β-unsaturated nitriles **22*Z*** (17 mg, 0.025 mmol, 50%) and **22*E*** (4 mg, 0.006 mmol, 12%) and of unreacted hydroxy nitriles **21** (8 mg, 0.011 mmol). Nitrile **22*Z*** (more mobile isomer) IR: 3072, 2932, 2216, 1668, 1110, 1058 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.72, 0.81, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.47 (br s, 3 H), 1.67 (br s, 3 H), 1.79-2.19 (m, 6 H), 2.31-2.54 (m, 3 H), 4.21 (d, J = 6.4 Hz, 2 H), 5.39 (m, 2 H), 6.09 (t, J = 7.4 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.60-7.75 (m, 4 H). MS m/z: 618 (59), 530 (5), 402 (4), 346 (20), 199 (100), 192 (3), 177 (4), 135 (6). HRMS: Calcd. for $C_{42}H_{56}NOSi$ [M–*t*-Bu] 618.413. Found 618.413. Nitrile **22*E*** (less mobile isomer) ^{1}H-NMR (200 MHz) δ: 0.73, 0.81, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.43 (br s, 3 H), 1.71 (br s, 3 H), 4.21 (d, J = 6.4 Hz, 2 H), 5.39 (m, 2 H), 6.29 (t, J = 7.4 Hz, 1 H), 7,32-7.48 (m, 6 H), 7.61-7.75 (m, 4 H).

(2'*Z*,6'*E*) - 1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-6',N,N-trimethylocta-2',6'-diene-2'-methanamine 24. 50 mM Aluminium hydride in ether (1.0 ml, 0.050 mmol) was added to a cold solution (0 °C) of the α,β-unsaturated nitrile **22*Z*** (12 mg, 0.018 mmol) in ether (2.0 ml). After 1 h at 0 °C and 1 h at room temperature, ether and water were added. The aqueous phase was extracted with ether, and the combined organic phases were washed with aqueous sodium potassium tartrate, 10% aqueous HCl, aqueous $NaHCO_3$, and brine, dried and concentrated in vacuo to give the crude amine **23** (13 mg). ^{1}H-NMR (200 MHz) δ: 0.72, 0.81, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 3.24 (m, 2 H), 4.21 (d, J = 6.6 Hz, 2 H), 5.18 (t, J = 6.7 Hz, 1 H), 5.37 (m, 2 H), 7.30-7.46 (m, 6 H), 7.58-7.77 (m, 4 H). Paraformaldehyde (9 mg, 0.300 mmol) was added to a solution of the crude amine **23** (13 mg) in methanol (5.0 ml) and the mixture was refluxed for 1.5 h. It was then allowed to cool to room temperature and was treated with sodium cyanoborohydride (13 mg, 0.200 mmol) for 1 h. After quenching with water (10 ml), the methanol was removed in vacuo and the aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried, and concentrated to give the crude dimethylamine **24** (11 mg).^{1}H-NMR (200 MHz) δ: 0.72, 0.82, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 2.19 (s, 6 H), 2.85 (br s, 2 H), 4.22 (d, J = 6.7 Hz, 2 H), 5.28-5.48 (m, 3 H), 7.34-7.46 (m, 6 H), 7.62-7.77 (m, 4 H).

(2'*E*,6'*E*)-1'-(Isocopal-12-en-15-yl)-2',6'-dimethylocta-2',6'-dien-8'-yl *t*-butyldiphenylsilyl ether 26. The crude dimethylamine **24** (11 mg) in toluene (2.0 ml) was added slowly to a cold solution (0 °C) of ethyl chloroformate (96 μl, 1.00 mmol) and of potassium carbonate (10 mg, 0.072 mmol) in toluene (0.5 ml). The mixture was stirred at room temperature for 24 h, diluted with ether, washed with water, dried, and concentrated to give the crude chloride **25** (9 mg). ^{1}H-NMR (200 MHz) δ: 0.72, 0.82, 0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 4.08 (m, 2 H), 4.22 (d, J = 6.4 Hz, 2 H), 5.30-5.45 (m, 3 H), 7.32-7.45 (m, 6 H), 7.60-7.75 (m, 4 H). 1 M Lithium triethylborohydride in THF (2.0 ml, 2.0 mmol) was added to a solution of the crude chloride **25** (9 mg) in THF (2.5 ml). This mixture was stirred for 15 min at room temperature; then it was diluted with ether and quenched with water. The aqueous phase was extracted with ether and the combined organic phases were dried, concentrated, and chromatographed on a silica gel column (hexane/ether 98/2) to afford the silyl ether **26** (5 mg, 0.0075 mmol, 42% from nitrile **22*Z***). ^{1}H-NMR (200 MHz) δ: 0.72, 0.82,

0.85, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.61 (br s), 1.69 (br s, 3 H), 4.22 (d, J = 6.8 Hz, 2 H), 5.11 (m, 1 H), 5.32-5.44 (m, 2 H), 7.32-7.44 (m, 6 H), 7.62-7.74 (m, 4 H).

(*E*,*E*)-Tricyclohexaprenol [(2'*E*,6'*E*)-1'-(Isocopal-12-en-15-yl)-2',6'-dimethylocta-2',6'-dien-8'-ol] 1. 1 M Tetrabutylammonium fluoride in THF (20 µl, 0.020 mmol) was added to a solution of the silyl ether **26** (5.0 mg, 0.0075 mmol) in THF (3.0 ml). This mixture was stirred for 8 h at room temperature, was quenched with water, extracted with ether and dried. Concentration and chromatography on a silica gel column (hexane/ether 8/2) afforded tricyclohexaprenol **1** (2.6 mg, 0.0061 mmol, 81%). IR: 3622, 1666, 1460, 1384, 1000. ^{1}H-NMR (400 MHz) δ: 0.72, 0.82, 0.86, 0.87 (4 s, 12 H), 1.62 (s, 3 H), 1.69 (s, 6 H), 1.80-2.26 (m, 9 H), 4.15 (d, J = 6.6 Hz, 2 H), 5.11 (t, J = 6.3 Hz, 1 H), 5.36 (br s, 1 H), 5.43 (t, J = 6.9 Hz, 1 H). This compound was identical (200 MHz ^{1}H-NMR, IR, GC of the TMS ether) with the compound **1** obtained earlier by one of us.[14]

Methyl 1'-(Isocopal-12-en-15-yl)-4'-[(*t*-butyldiphenylsilyl)oxy]-3'-hydroxybutane-2'-carboxylates 27a. A solution of the iodide **3** (25 mg, 0.062 mmol) and of the α,β-unsaturated ester **5a** (140 mg, 0.364 mmol) in ether (2 ml) was irradiated with a 300 W tungsten lamp for 5 h as a solution of tributyltin hydride (30 µl, 0.110 mmol) in ether (0.5 ml) was added (syringe pump). Then the solution was treated for 2 h with aqueous KF and the so-formed solid tin compound was removed by filtration. The filtrate was diluted with ether, dried, concentrated in vacuo, and chromatographed on a silica gel column (hexane/ether 9/1) to give unreacted **5a** (127 mg, 0.330 mmol) and a mixture of four diastereomeric hydroxy esters **27a** (20 mg, 0.030 mmol, 49%). IR: 3570, 2934, 1734, 1200, 1162, 1113 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.68, 0.69, 0.81, 0.85, and 0.86 (5 s, 12 H), 1.06 (s, 9 H), 1.63 (br s, 3 H), 1.82-1.98 (m, 3 H), 2.55-2.98 (m, 2 H), 3.57-3.72 (m, 2 H), 3.60, 3.61, and 3.69 (3 s, 3 H), 3.87 (m, 1 H), 5.35 (m, 1 H), 7.33-7.50 (m, 6 H), 7.60-7.70 (m, 4 H). MS m/z: 601 (23), 581 (13), 570 (5), 566 (6), 524 (100), 331 (15), 259 (32), 241 (42), 199 (54), 177 (46). HRMS: Calcd. for $C_{38}H_{53}O_4Si$ [M–*t*-Bu] 601.371. Found 601.373.

Methyl (6'Z)-1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-3'-hydroxy-6'-methyloct-6'-ene-2'-carboxylates 27b. Same procedure as for compounds **27a**. Iodide **3** (100 mg, 0.25 mmol) and α,β-unsaturated ester **5b** (1200 mg, 2.65 mmol) in ether (5 ml); tributyltin hydride (0.11 ml, 0.41 mmol) in ether (0.4 ml). Addition over 2 h. Irradiation for 11 h. Column chromatography gave unreacted **5b** (1070 mg, 2.36 mmol) and a mixture of the hydroxy esters **27b** (84 mg, 0.12 mmol, 48%). IR: 3490, 2934, 1732, 1154, 1112 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.69, 0.81, 0.85, and 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.63 (br s, 3 H), 1.69 (br s, 3 H), 1.78-2.05 (m, 5 H), 2.25-2.45 (m, 2 H), 3.55-3.70 (m, 1 H), 3.65, 3.66, 3.67, and 3.69 (4 s, 3 H), 4.00-4.38 (m, 2 H), 5.35 (m, 1 H), 5.41 (t, J = 6.8 Hz, 1 H), 7.32-7.45 (m, 6 H), 7.62-7.75 (m, 4 H). MS m/z: 669 (1), 590 (1), 309 (4), 257 (2), 231 (14), 199 (100), 191 (5), 177 (8). HRMS: Calcd. for $C_{43}H_{61}O_4Si$ [M–*t*-Bu] 669.434. Found 669.433.

Methyl (6'Z,10'Z)-1'-(Isocopal-12-en-15-yl)-12'-[(*t*-butyldiphenylsilyl)oxy]-6',10'-dimethyl-3'-hydroxydodeca-6',10'-diene-2'-carboxylates 27c. Same procedure as for compounds **27a**. Iodide **3** (81 mg, 0.20 mmol) and α,β-unsaturated ester **5c** (960 mg, 1.84 mmol) in ether (5 ml); tributyltin hydride (0.11 ml, 0.41 mmol) in ether (0.5 ml). Addition and irradiation over 6 h. Column chromatography gave unreacted **5c** (877 mg, 1.68 mmol) and a mixture of the hydroxy esters **27c** (56 mg, 0.070 mmol, 35%). IR: 3655, 2933, 1735, 1193, 1158, 1110 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.70, 0.81, 0.85, and 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.60, 1.65, and 1.70 (3 br s, 9 H), 1.80-2.15 (m, 9 H), 2.20-2.45 (m, 2 H), 3.63-3.76 (m, 1 H), 3.67, 3.68 and 3.70 (3 s, 3 H), 4.18 (d, J = 6.4 Hz, 2 H), 5.01 (m, 1 H), 5.35 and 5.39 (m and t, J = 6.4 Hz, 2 H), 7.34-7.44 (m, 6 H), 7.65-7.73 (m, 4 H). MS m/z: 737 (1), 659 (1), 522 (1), 377 (1), 283 (4), 259 (3), 199 (100), 191 (13), 177 (12). HRMS: Calcd. for $C_{48}H_{69}O_4Si$ [M–*t*-Bu] 737.496. Found 737.498.

Methyl (2'*E*)-1'-(Isocopal-12-en-15-yl)-4'-[(*t*-butyldiphenylsilyl)oxy]but-2'-ene-2'-carboxylate 28a*E*. Triethylamine (105 µl, 0.75 mmol) and methanesulfonyl chloride (53 µl, 0.68 mmol) were added to a cold (0 °C) solution of the hydroxy esters **27a** (18 mg, 0.027 mmol) in methylene chloride (5 ml). After 15 min, the mixture was washed with 10% aqueous HCl, aqueous $NaHCO_3$, and brine, and was dried. Concentration gave the crude mesyloxy esters (25 mg) which were dissolved in toluene (5 ml). After addition of DBU (41 µl, 0.27 mmol) the solution was refluxed for 4 h, diluted with ether, washed with

0.1% aqueousHCl and with brine, and dried. Concentration and filtration on silica gel (hexane/ether 9/1) gave a 77/23 mixture of the α,β-unsaturated esters **28a*E*/28a*Z***[11] (15 mg, 0.023 mmol, 86%). Since separation of these compounds by column chromatography was difficult, they were used as an E/Z mixture in the next step. A small sample of pure **28a*E*** (less mobile isomer) could however be obtained for characterisation. IR: 3070, 2934, 1716, 1242, 1194, 1110 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.60, 0.81, 0.84, 0.86 (4 s, 12 H), 1.06 (s, 9 H), 1.58 (br s, 3 H), 1.70 (m, 1 H), 1.75-1.98 (m, 3 H), 2.31 (td, *J* = 12.5, 4.9 Hz, 1 H), 3.76 (s, 3 H), 4.37 (dd, *J* = 5.8, 1.9 Hz, 2 H), 5.31 (m, 1 H), 6.89 (t, *J* = 5.8 Hz, 1 H), 7.36-7.47 (m, 6 H), 7.64-7.70 (m, 4 H). ^{13}C-NMR (100 MHz) δ: 14.2, 15.5, 18.6, 18.8, 19.1, 21.7, 22.8, 26.6, 26.8, 30.0, 33.1, 33.5, 36.9, 37.2, 39.8, 40.3 41.9, 51.8, 55.0, 55.4, 56.2, 61.2, 122.0, 127.8, 129.8, 132.3, 133.2, 134.8, 135.5, 141.4, 167.9.

Methyl (2'*E*,6'*Z*)-1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-6'-methylocta-2',6'-diene-2'-carboxylate 28b*E*. Same procedure as for **28a*E***. The hydroxy esters **27b** (9 mg, 0.012 mmol) gave a chromatographed 91/9 mixture of the α,β-unsaturated esters **28b*E*/28b*Z***[11] (8 mg, 0.011 mmol, 91%). Another column chromatography (hexane/ether 95/5) allowed the obtention of pure ester **28b*E***: (7 mg; less mobile isomer) IR: 3070, 2935, 1712, 1166, 1112 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.66, 0.81, 0.85, 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.71 (d, *J* = 1.2 Hz, 3 H), 1.73 (m, 3 H), 1.80-2.28 (m, 8 H), 2.44 (td, *J* = 12.5, 5.0 Hz, 1 H), 3.68 (s, 3 H), 4.19 (dd, *J* = 6.5, 1.0 Hz, 2 H), 5.35 (m, 1 H), 5.44 (t, *J* = 6.5 Hz, 1 H), 6.59 (t, *J* = 7.3 Hz, 1 H), 7.32-7.48 (m, 6 H), 7.63-7.72 (m, 4 H). MS m/z: 651 (25), 379 (19), 348 (5), 272 (23), 257 (13), 213 (22), 199 (100), 197 (9), 191 (7), 177 (11). HRMS: Calcd. for $C_{43}H_{59}O_3Si$ [M–*t*-Bu] 651.423. Found 651.425.

Methyl (2'*E*,6'*Z*,10'*Z*)-1'-(Isocopal-12-en-15-yl)-12'-[(*t*-butyldiphenylsilyl)oxy]-6',10'-dimethyldodeca-2',6',10'-triene-2'-carboxylate 28c*E*. Same procedure as for **28a*E***. The hydroxy esters **27c** (77 mg, 0.097 mmol) gave a chromatographed 92/8 mixture of the α,β-unsaturated esters **28c*E*/28c*Z***[11] (60 mg, 0.077 mmol, 79%). Column chromatography (hexane/ether 95/5) allowed the obtention of pure ester **28c*E***: (37 mg; less mobile isomer) IR: 3070, 2933, 1712, 1265, 1195, 1111 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.68, 0.81, 0.85, 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.62 (br s, 3 H), 1.69 (d, *J* = 1.1 Hz, 3 H), 1.76 (br s, 3 H), 1.80-2.30 (m, 12 H), 2.49 (td, *J* = 12.2, 5.2 Hz, 1 H), 3.71 (s, 3 H), 4.18 (br d, *J* = 6.4 Hz, 2 H), 5.03 (m, 1 H), 5.36 and 5.39 (m and br t, *J* = 6.8 Hz, 2 H), 6.68 (t, *J* = 7.0 Hz, 1 H), 7.34-7.46 (m, 6 H), 7.64-7.74 (m, 4 H). MS m/z: 719 (35), 521 (2), 503 (6), 447 (18), 415 (2), 264 (6), 258 (15), 213 (14), 199 (100), 197 (12), 177 (10). HRMS: Calcd. for $C_{48}H_{67}O_3Si$ [M–*t*-Bu] 719.486. Found 719.487.

[1'-(Isocopal-12-en-15-yl)-4'-[(*t*-butyldiphenylsilyl)oxy]but-2'-en-2'-yl]methanols 29a. 1 M DIBAH in toluene (130 µl, 0.130 mmol) was added to a cold (–78 °C) solution of the esters **28a** (26 mg, 0.041 mmol, 85/15 E/Z mixture) in toluene (2 ml). After 30 min, the mixture was quenched with aqueous NH_4Cl and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. Column chromatography (hexane/ether 8/2) gave a 85/15 mixture (determined by ^{1}H-NMR) of the alcohols **29a*E*** and **29a*Z*** (21 mg, 0.034 mmol, 83%). Another column chromatography (hexane/ether 9/1) allowed the separation of the two alcohols. Alcohol **29a*E*** (18 mg, 0.029 mmol, 71%; less mobile isomer) IR: 3621, 3080, 2934, 1109, 1060, 1002 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.62, 0.81, 0.84, 0.86 (4 s, 12 H), 1.05 (s, 9 H), 1.56 (br s, 3 H), 1.69-1.92 (m, 4 H), 2.07 (td, *J* = 12.4, 5.5 Hz, 1 H), 4.03 (d, *J* = 6.0 Hz, 2 H), 4.28 (d, *J* = 6.2 Hz, 2 H), 5.32 (m, 1 H), 5.63 (t, *J* = 6.2 Hz, 1 H), 7.32-7.50 (m, 6 H), 7.64-7.76 (m, 4 H). ^{13}C-NMR (100 MHz) δ: 14.2, 15.4, 18.5, 18.7, 19.1, 21.7, 21.9, 22.8, 26.4, 26.8, 31.1, 33.1, 33.5, 36.8, 37.2, 39.8, 40.4, 41.9, 55.0, 55.6, 56.2, 60.7, 66.6, 122.2, 125.3, 127.6, 129.6, 133.8, 134.6, 135.6, 141.1. MS m/z: 612 (2), 581 (4), 555 (3), 537 (2), 341 (11), 339 (13), 272 (33), 257 (7), 199 (100). HRMS: Calcd. for $C_{37}H_{51}O_2Si$ [M–*t*-Bu] 555.366. Found 555.366. Alcohol **29a*Z*** (3 mg, 0.005 mmol, 12%; more mobile isomer): ^{1}H-NMR (200 MHz) δ: 0.73, 0.82, 0.84, 0.87 (4 s, 12 H), 1.05 (s, 9 H), 1.69 (s, 3 H), 1.82-2.12 (m, 4 H), 2.22-2.45 (m, 1 H), 3.97 (d, *J* = 4.8 Hz, 2 H), 4.26 (d, *J* = 6.5 Hz, 2 H), 5.37 (m, 1 H), 5.51 (t, *J* = 6.5 Hz, 1 H), 7.32-7.50 (m, 6 H), 7.62-7.75 (m, 4 H).

(2'*E*,6'*Z*) - [1'-(Isocopal-12-en-15-yl)-8'-[(*t*-butyldiphenylsilyl)oxy]-6'-methylocta-2',6'-dien-2'-yl]methanol 29b. Same procedure as for **29a**.The ester **28b*E*** (20 mg, 0.028 mmol) gave the alcohol **29b** (16 mg, 0.024 mmol, 85%). IR: 3625, 3080, 2935, 1110, 1053, 1002 cm^{-1}. ^{1}H-NMR δ: 0.68, 0.81, 0.85, 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.70 and 1.71 (2 s, 6 H), 1.80-2.30 (m, 9 H), 3.97 (br s, 2 H),

4.18 (dd, J = 6.4, 1.0 Hz, 2 H), 5.26 (t, J = 7.0 Hz, 1 H), 5.36 and 5.39 (m and t, J = 6.4 Hz, 2 H), 7.33-7.45 (m, 6 H), 7.63-7.75 (m, 4 H).

(2'*E*,6'*Z*,10'*Z*)-[1'-(Isocopal-12-en-15-yl)-12'-[(*t*-butyldiphenylsilyl)oxy]-6',10'-dimethyldodeca-2',6',10'-trien-2'-yl]methanol 29c. Same procedure as for **29a**. The ester **28c*E*** (34 mg, 0.044 mmol) gave the alcohol **29c** (28 mg, 0.037 mmol, 84%). IR: 3620, 3080, 2932, 1108, 1058, 1000 cm^{-1}. ^{1}H-NMR δ: 0.70, 0.82, 0.86, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.62 (s, 3 H), 1.70 (d, J = 1.1 Hz, 3 H), 1.73 (br s, 3 H), 1.80-2.18 (m, 12 H), 2.27 (td, J = 12.3, 5.5 Hz, 1 H), 4.02 (d, J = 5.3 Hz, 2 H), 4.19 (d, J = 6.4 Hz, 2 H), 5.01 (m, 1 H), 5.36 (m, 3 H), 7.32-7.47 (m, 6 H), 7.62-7.75 (m, 4 H). MS m/z: 748 (0.2), 730 (0.3), 691 (0.3), 492 (0.6), 475 (3), 272 (4), 259 (6), 257 (6), 199 (100). HRMS: Calcd. for $C_{51}H_{76}O_2Si$ 748.561. Found 748.562. Calcd. for $C_{51}H_{74}OSi$ [M–H_2O] 730.551. Found 730.552.

(2'*Z*)-1'-(Isocopal-12-en-15-yl)-2'-methylbut-2'-en-4'-yl *t*-butyldiphenylsilyl ether 31a. A solution of the alcohol **29a** (*E* isomer; 33 mg, 0.053 mmol) and of triphenylphosphine (53 mg, 0.20 mmol) in carbon tetrachloride (4 ml) was refluxed for 3 days. Then the mixture was diluted with methylene chloride, washed with water, and dried. Concentration in vacuo gave the crude chloride **30** (90 mg) which was dissolved in THF (5 ml) and treated at room temperature with 1 M lithium triethylborohydride in THF (5.0 ml, 5.0 mmol) for 1 h. This mixture was then quenched with water, extracted with ether, and dried. Concentration and column chromatography (hexane) gave the silyl ether **31a** (30 mg, 0.050 mmol, 95% overal yield). IR: 3060, 2935, 1109, 1062 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.64, 0.81, 0.84, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.57 (br s, 3 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.77-2.10 (m, 5 H), 4.18 (d, J = 6.5 Hz, 2 H), 5.32 (m, 1 H), 5.39 (td, J = 6.5, 1.2 Hz, 1 H), 7.30-7.50 (m, 6 H), 7.65-7.75 (m, 4 H). ^{13}C-NMR (50 MHz) δ: 14.2, 15.5, 18.6, 18.8, 19.2, 21.7, 21.9, 22.8, 23.6, 25.7, 26.9, 33.1, 33.5, 35.0, 36.8, 37.2, 39.8, 40.4, 42.0, 55.0, 55.4, 56.2, 60.9, 122.0, 124.5, 127.6, 129.5, 134.0, 134.9, 135.6, 138.3. MS m/z: 596.3 (0.1%, M), 539.3 (2, M–*t*-Bu), 339.3 (2), 272.3 (13), 267.2 (9), 199.1 (100).

(2'*Z*,6'*Z*)-1'-(Isocopal-12-en-15-yl)-2',6'-dimethylocta-2',6'-dien-8'-yl *t*-butyldiphenylsilyl ether 31b. Same procedure as for **31a**. The alcohol **29b** (12 mg, 0.017 mmol) gave the compound **31b** (9 mg, 0.013 mmol, 77%). ^{1}H-NMR (200 MHz) δ: 0.68, 0.81, 0.85, 0.86 (4 s, 12 H), 1.04 (s, 9 H), 1.62 (br s, 3 H), 1.69 (br s, 6 H), 1.80-2.24 (m, 9 H), 4.19 (dd, J = 6.4, 1.0 Hz, 2 H), 4.96 (t, J = 6.6 Hz, 1 H), 5.35 and 5.39 (m and t, J = 6.4 Hz, 2 H), 7.32-7.44 (m, 6 H), 7.63-7.73 (m, 4 H).

(2'*Z*,6'*Z*,10'*Z*)-1'-(Isocopal-12-en-15-yl)-2',6',10'-trimethyldodeca-2',6',10'-trien-12'-yl *t*-butyldiphenylsilyl ether 31c. Same procedure as for **31a**. The alcohol **29c** (26 mg, 0.035 mmol) gave the compound **31c** (18 mg, 0.025 mmol, 71%). IR: 3072, 2960, 1110, 1058 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.71, 0.82, 0.86, 0.87 (4 s, 12 H), 1.04 (s, 9 H), 1.61 (d, J = 1.1 Hz, 3 H), 1.67, 1.70, and 1.72 (br s, m, and m, 9 H), 1.80-2.24 (m, 13 H), 4.19 (dd, J = 6.4, 1.0 Hz, 2 H), 4.99 and 5.05 (t, J = 6.7 Hz, and m, 2 H), 5.36 and 5.39 (m and t, J = 6.4 Hz, 2 H), 7.32-7.48 (m, 6 H), 7.62-7.76 (m, 4 H).

(*Z*)-Tricyclopentaprenol [(2'*Z*)-1'-(Isocopal-12-en-15-yl)-2'-methylbut-2'-en-4'-ol] 2a. 1 M Tetrabutylammonium fluoride in THF (30 µl, 0.030 mmol) was added to a solution of the silyl ether **31a** (6.0 mg, 0.010 mmol) in THF (2 ml). This mixture was stirred for 7 h at room temperature, was quenched with water, extracted with ether, dried, and concentrated in vacuo. Silica gel column chromatography (hexane/ether 8/2), and reverse-phase column chromatography (LiChroprep RP-18, 40-63 µm, Merck; acetonitrile/methylene chloride 6/4) to remove the *t*-butyldiphenylsilanol, gave the alcohol **2a** (3.6 mg, 0.010 mmol, 100%). ^{1}H-NMR (400 MHz) δ: 0.71 (s, 3 H), 0.79 (m, 1 H), 0.82, 0.87, and 0.87 (3 s, 9 H), 1.05-1.16 (m, 4 H), 1.19-1.42 (m, 3 H), 1.73 (br s, 3 H), 1.77 (d, J = 1.1 Hz, 3 H), 1.90 (m, 2 H) 1.94 (dt, J = 12.8, 3.2 Hz, 1 H), 2.03 (ddd, J = 12.6, 11.2, 5.9 Hz, 1 H), 2.22 (td, J = 12.6, 5.1 Hz, 1 H), 4.14 (m, 2 H), 5.38 and 5.41 (m and t, J = 6.9 Hz, 2 H). ^{13}C-NMR (100 MHz) δ: 14.3, 15.5, 18.6, 18.8, 21.7, 22.0, 22.8, 23.6, 26.1, 33.2, 33.5, 34.9, 36.9, 37.2, 39.9, 40.6, 41.9, 55.1, 55.6, 56.3, 59.3, 122.3, 123.8, 134.6, 140.9. MS m/z: 358 (4), 343 (2), 340 (1), 325 (3), 272 (80), 259 (23), 190 (100), 177 (71). HRMS: Calcd. for $C_{25}H_{42}O$ 358.324. Found 358.326.

(*Z*,*Z*)-Tricyclohexaprenol [(2'*Z*,6'*Z*)-1'-(Isocopal-12-en-15-yl)-2',6'-dimethylocta-2',6'-dien-8'-ol] 2b. Same procedure as for **2a**. The silyl ether **31b** (9.0 mg, 0.013 mmol) gave the alcohol **2b** (5.0 mg, 0.012 mmol, 92%). ^{1}H-NMR (400 MHz) δ: 0.72 (s, 3 H), 0.79 (m, 1 H), 0.82, 0.87, and 0.87 (3 s,

9 H), 1.05-1.17 (m, 4 H), 1.71, 1.73, and 1.75 (3 s, 9 H), 1.85-2.02 (m, 4 H), 2.05-2.20 (m, 5 H), 4.10 (m, 2 H), 5.09 (m, 1 H), 5.37 (m, 1 H), 5.45 (t, J = 7.1 Hz, 1 H). This compound was identical (200 MHz ^{1}H-NMR, IR, GC of the TMS ether) with the compound **2b** obtained earlier by one of us.[15]

(Z,Z,Z)-Tricycloheptaprenol [(2'Z,6'Z,10'Z)-1'-(Isocopal-12-en-15-yl)-2',6',10'-trimethyldodeca-2',6',10'-trien-12'-ol] 2c. Same procedure as for **2a**. The silyl ether **31c** (8.0 mg, 0.011 mmol) gave the alcohol **2c** (4.0 mg, 0.0081 mmol, 74%). IR: 3684, 3624, 2960, 996 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 0.72 (s, 3 H), 0.79 (m, 1 H), 0.82, 0.86, and 0.87 (3 s, 9 H), 1.05-1.17 (m, 4 H), 1.69, 1.71, 1.74, and 1.75 (4 br s, 12 H), 1.85-2.22 (m, 13 H), 4.10 (m, 2 H), 5.11 (m, 2 H), 5.37 (m, 1 H), 5.45 (t, J = 7.1 Hz, 1 H). MS m/z: 494 (3), 476 (8), 461 (2), 272 (100), 190 (29). HRMS: Calcd. for $C_{35}H_{56}$ [M–H_2O] 476.438. Found 476.439.

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9. Determined by 200 MHz ^{1}H-NMR on the H-3' triplet which was at δ 6.09 for **22*Z*** and at δ 6.29 for **22*E***
10. See also the preceding paper.
11. Determined by 200 MHz ^{1}H-NMR on the H-3' triplet which was at δ 6.89 for **28a*E*** and at δ 6.16 for **28a*Z***, at δ 6.59 for **28b*E*** and at δ 5.73 for **28b*Z***, at δ 6.68 for **28c*E*** and at δ 5.82 for **28c*Z***. The -CO_2Me singlet was at δ 3.60 for **28a*Z***, at δ 3.66 for **28b*Z***, and at δ 3.69 for **28c*Z***.
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13. Reaction of the aldehyde **14** with the sodium salt of triethyl 2-phosphonopropionate gave the (2*E*,6*Z*) isomer of **15** as the major product. ^{1}H-NMR (200 MHz): δ 1.04 (s, 9 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.71 (d, J = 1.2 Hz, 3 H), 1.74 (d, J = 1.2 Hz, 3 H), 1.91-2.03 (m, 2 H), 2.06-2.21 (m, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.18 (d, J = 6.3 Hz, 2 H), 5.43 (br t, J = 6.3 Hz, 1 H), 6.61 (br t, J = 7.3 Hz, 1 H), 7.32-7.44 (m, 6 H), 7.63-7.72 (m, 4 H). Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found C, 74.4; H, 8.6.
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