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Invited Paper

Synthesis of Three Acyclic All-*trans*-Tetraterpene Diols, Putative Precursors of Bacterial Lipids

Bertrand CHAPPE,* Hélène MUSIKAS, Dominique MARIE, and Guy OURISSON
Institut de Chimie des Substances Naturelles du CNRS, 91198-Gif-sur-Yvette, France
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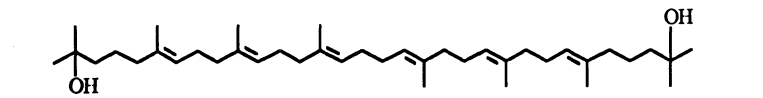
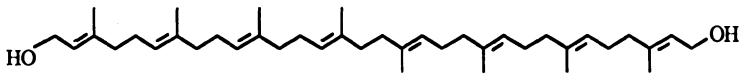
Three acyclic all-*trans*-tetraterpene diols, **A**, **B**, and **C** have been synthesized from geraniol (**1**), by a convergent scheme involving six different C_{10} synthons derived from geraniol, and coupling by known reactions of three different types: substitution of allylic chlorides by carbanions α to sulfones, duplication of allylic alcohols, and Pd(0)-catalyzed coupling of allylic carbonates with doubly stabilized carbanions. **A**, **B**, and **C** represent postulated phylogenetic precursors of known membrane reinforcers, and are the three possible distally dihydroxylated dimers of geranylgeraniol: tail-to-tail, head-to-head, and head-to-tail.

We describe below the syntheses of three acyclic all-*trans*-tetraterpene diols **A**, **B**, and **C**, representing the three possible modes of coupling geranylgeraniol units (**A**: tail-to-tail, **B**: head-to-head, and **C**: head-to-tail). The diols thus obtained are distally dihydroxylated polyterpene chains about 40 Å long, and should therefore be able to form transmembrane inserts in normal biological phospholipid bilayers; they have been postulated[1] to be phylogenetic precursors of bacterial membrane-spanning carotenoids,[2] of the tricyclopolyprenols assumed from their known molecular fossils to be bacterial membrane lipids,[3] and of the known archaebacterial phospholipids.[4] **A**, **B**, and **C** are thus not known *per se* as natural products. We plan, and have begun, to test their membrane properties, either as such or as part of phospholipids or of other highly polar derivatives (phosphates, glucosides, ···), and also to test their effect on some lipid-dependent microorganisms.

The syntheses so far carried out have been limited to the all-trans substances; we plan to complete them later with syntheses of some of their Z-isomers, at least for the head-to-tail diol **C**: biologically important regular polyterpenols are often partially Z.



A



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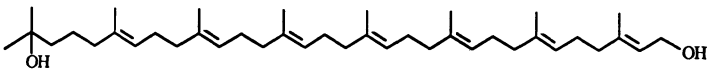


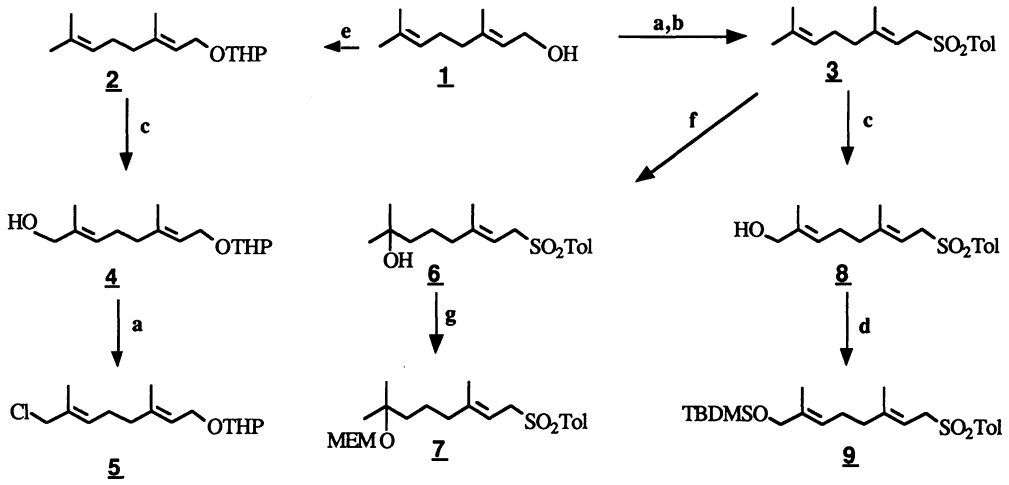
C

Methods and Results

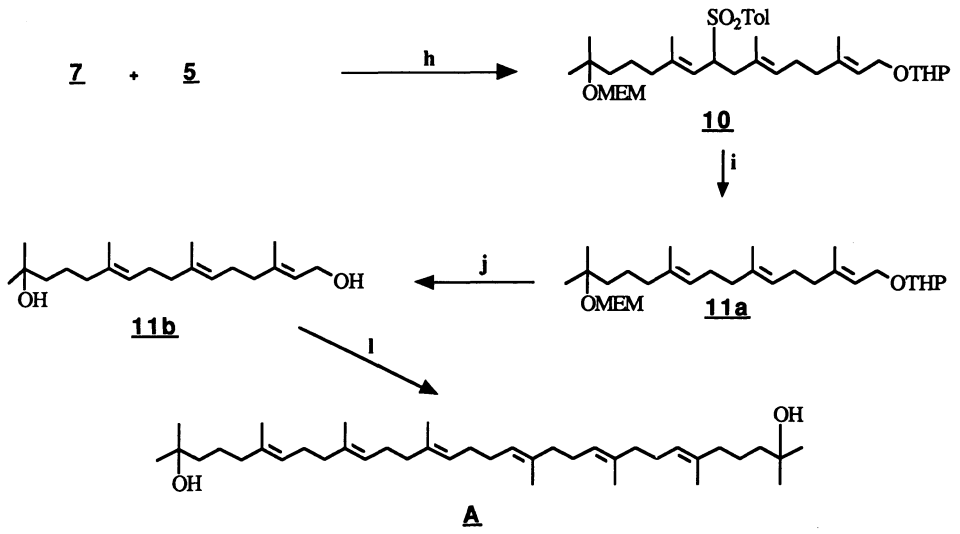
The syntheses of carotenoids have illustrated the various ingenious ways to reach C_{40} by all possible arithmetic combinations of smaller units. We have chosen for our syntheses to start from the readily available geraniol (**1**), which was first modified in three ways to obtain the C_{10} properly functionnalized derivatives **5**, **7**, and **9**; the chloride **5** is the potential source of an allylic carbenium ion on one of the "head" methyl groups, and sulfones **7** and **9** function as potential sources of allylic carbanions on C-1, the "tail" of the geraniol unit, with different hydroxylation patterns at the "head". The practical synthetic problems have revolved around the proper choice of temporary protecting groups and of efficient coupling methods.

The protecting groups used have been chosen to permit selective removals; they include THP (tetrahydropyranyl), MEM (2-methoxyethoxymethoxy) and tBDMS (*t*-butyldimethylsilyl) ethers. The coupling methods involve base-catalyzed reaction of allylic chlorides with allylic sulfones, reductive dimerization of allylic alcohols with Ti(III), and Pd(0)-catalyzed reaction of allylic carbonates with allylic carbanions

Dedicated respectfully and with admiration to Professor Edgar Lederer, on the occasion of his approaching 80th birthday (G.O.).



Scheme 1. a: TsCl, DMAP, TEA/CH_2Cl_2; b: *p*-$MeC_6H_4SO_2Na$/DMF; c: SeO_2, TBHP/CH_2Cl_2; d: tBDMSCl, DIPEA/DMF; e: DHP, PPTS/CH_2Cl_2; f: $(AcO)_2Hg$, NaOH, $NaBH_4$/THF, H_2O; g: MEMCl, DIPEA/CH_2Cl_2.



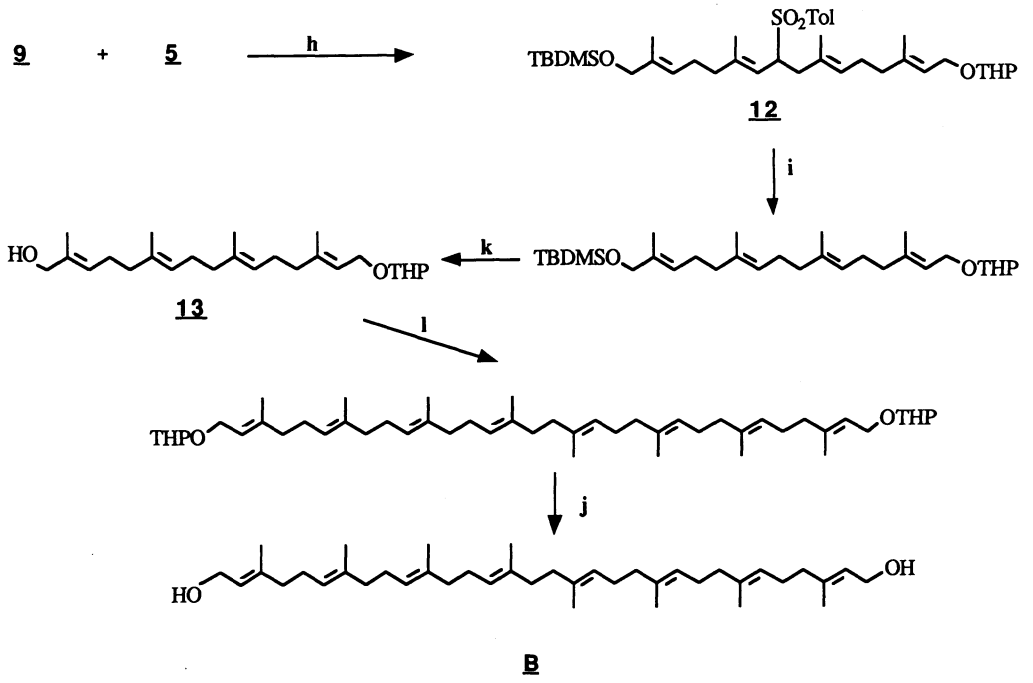
Scheme 2. h: *n*-BuLi/THF; i: Na/Hg, Na_2HPO_4/MeOH; j: TsOH/EtOH; l: $TiCl_3$, *n*-BuLi/Dimethoxyethane.

(in this case, with additional stabilization of the carbanion by a methoxycarbonyl group geminated with the sulfone).

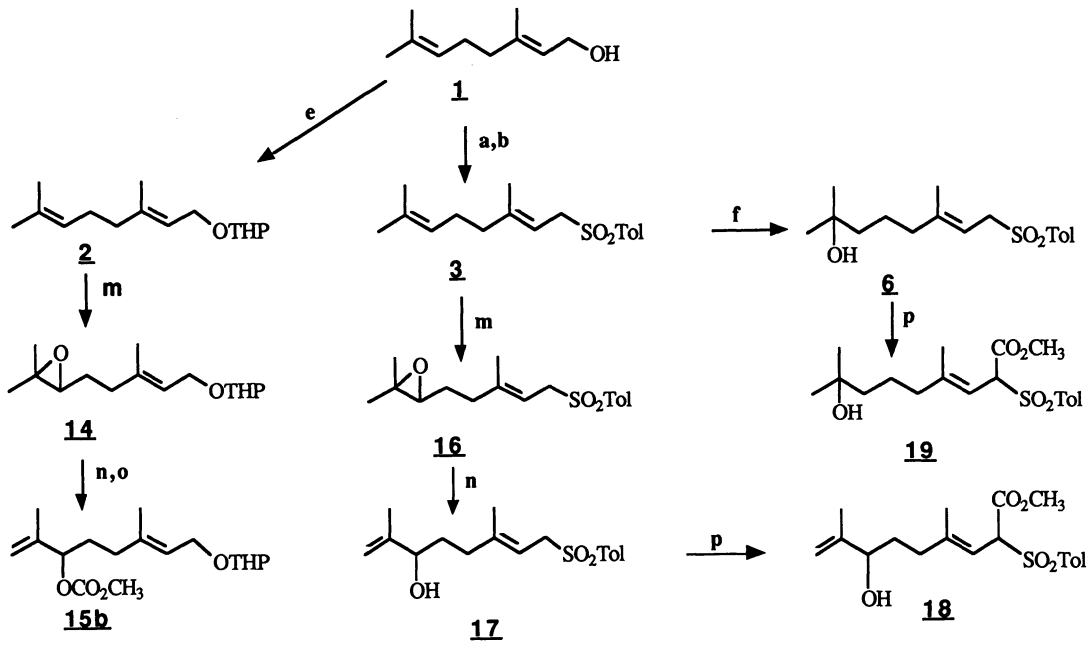
Chloride **5** was obtained by reaction of the THP-protected hydroxygeraniol **4** by reaction with tosyl chloride and triethylamine/4-dimethylaminopyridine.[5] The allylic oxidation of geranyl-THP ether **2** was efficiently achieved with *t*-butyl hydroperoxide with selenium dioxide as a catalyst;[6] this method is known to oxidize selectively the (E)-methyl group. Geraniol (**1**) itself gave, by the same chlorination method, geranyl chloride which was directly transformed into the *p*-tolyl sulfone **3** by reaction with sodium *p*-toluenesulfinate in DMF.[7] Geranyl *p*-tolylsulfone (**3**) was converted into the alcohols **6** and **8**, respectively by Brown's mercuration-reduction sequence,[8] and by the SeO_2-catalyzed allylic oxidation already mentioned.

The C_{10} sulfone **7** has next been converted with butyllithium into its carbanion, which reacted with the chloride **5** to give the C_{20} sulfone **10**; this was desulfonated by mild reduction with sodium amalgam in methanol, in the presence of disodium hydrogenphosphate.[9] After acid-catalyzed deprotection, the allylic alcohol **11b** was reductively duplicated with titanium trichloride and butyllithium,[10] to give the first C_{40} diol wanted, the tail-to-tail tetraterpenediol **A**.

The second goal, the head-to-head diol **B**, was similarly obtained, by identical reactions, from the same chloride **5** and the other sulfone **9**. In this case, the use of a tBDMS-ether permitted the selective deprotection with tetrabutylammonium fluoride (TBAF) of the silyl ether,[11] to unmask one only of the two allylic groups of the C_{20} chain, before the allylic



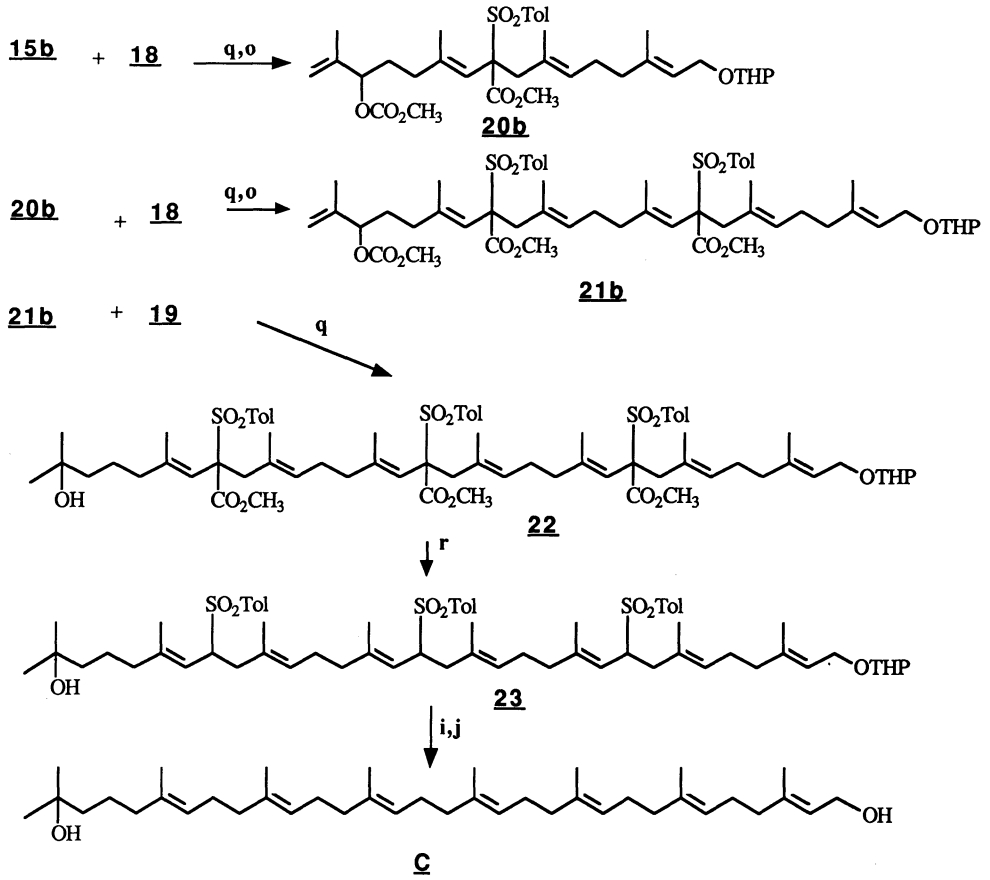
Scheme 3. h: *n*-BuLi/THF; i: Na/Hg, Na_2HPO_4/MeOH; j: TsOH/EtOH; k: TBAF/THF; l: $TiCl_3$, *n*-BuLi/Dimethoxyethane.



Scheme 4. a: TsCl, DMAP, TEA/CH_2Cl_2; b: *p*-$MeC_6H_4SO_2Na$/DMF; f: $(AcO)_2Hg$, NaOH, $NaBH_4$/THF, H_2O; m: mCPBA/CH_2Cl_2; n: $(C_3H_7O)_3Al$/*i*-PrOH/Tol; o: $ClCO_2Me$, Py/Tol; p: Me_2CO_3, *t*-BuOK/DMF.

alcohol **13** was coupled as before.

The third tetraterpene diol, **C**, has a regular head-to-tail polyprenyl chain. It was synthesized by iteration, according to a C_{10}–C_{20}–C_{30}–C_{40} sequence. The coupling reaction used was that developed by Keynan.[12] This required first the construction of the new C_{10} building blocks **15b**, **18**, and **19**; the known isomerization of epoxides into allylic alcohols with aluminium isopropoxide[13] paved the way for condensation, with the help of Pd(0) as its triphenylphosphine tetracoordinated complex, of the corresponding allylic carbonate. The demethoxycarbonylation was



Scheme 5. i: Na/Hg, Na_2HPO_4/MeOH; j: TsOH/EtOH; o: $ClCO_2Me$, Py/Tol; q: $(Ph_3P)_4Pd/Et_2O$; r: PATP, $CsCO_3$/DMF.

achieved with 4-aminothiophenol (PATP) and cesium carbonate, and the removal of the sulfone residues as above with sodium amalgam.

The convergent nature of this synthesis has made it possible to obtain sufficient amounts for the physical studies, which will be reported later.

Experimental

General Methods: NMR spectra were recorded in deuterochloroform with tetramethylsilane as internal standard on Bruker 80, 200 or 400 MHz spectrometers and are expressed as δ. Mass spectra: Kratos MS-80 or MS-9 spectrometers; expressed as m/z. Infrared spectra: chloroform solutions, Perkin-Elmer 297 spectrophotometer; date in agreement with the structures, available on request. Elemental analyses were carried out in the microanalytical laboratory of ICSN by Mlle C. Muller. Thin-layer chromatography (TLC): on Merck silica gel 60-F254 glass plates. Column chromatography: on Chromatogel 60ACC, 70—230 mesh or (for flash chromatography) 230—400 mesh silica gel. All solvents were freshly distilled; tetrahydrofuran (THF) was dried by distillation over sodium-benzophenone, ether by distillation over lithium aluminium hydride, *N,N*-dimethylformamide (DMF) by distillation over calcium hydride, methylene chloride by distillation over calcium chloride. All the substances obtained are oils, which gave however in general good analytical results after purification by flash chromatography monitored by TLC.

General Treatment of Ether Extracts: The usual treatment of ether extracts was to wash them successively with water, if necessary with dilute acid or alkali and again with water, and with saturated brine; they were then dried over anhydrous sodium sulfate and evaporated in vacuo.

General Procedure for Removal of *p*-Tolylsulfonyl Groups: To a mixture of sulfone (1 mol) and disodium hydrogenphosphate (4 mol) in anhydrous methanol, was added at 0 °C an excess of freshly prepared 6% sodium amalgam. Stirring was continued at 0 °C until the starting material had disappeared (TLC), and excess amalgam was destroyed with cold water. The ether extract of the reaction mixture was treated as usual and chromatographed on silica gel.

General Procedure for Terminal Allylic Oxidation: To a solution of selenium dioxide (0.03 mol) in methylene chloride, was added 70% *t*-butyl hydroperoxide (3 mol). The mixture was stirred at 25 °C for 30 min, then the substrate (1 mol) was introduced as a solution in methylene chloride, and stirring was continued for 20 h at 25 °C. Toluene was added, and the solvents were removed in a rotatory evaporator in vacuo. The residue was extracted three times with ether. The ether extract was treated as usual. The residue was dissolved in ethanol and treated with sodium borohydride at 0 °C for 1 h. Cold water was added, the

reaction mixture was extracted with ether, and the ether extract was treated as usual. Flash chromatography was used to isolate the allylic alcohol.

Geranyl Tetrahydropyranyl Ether (2). To a solution of geraniol (**1**) (15.4 g, 0.1 mol) in dry methylene chloride, were added dihydropyran (12.6 g, 0.15 mol) and *p*-toluenesulfonic acid (2.5 g, 0.01 mol). The mixture was stirred for 3 h at room temperature, and evaporated in vacuo. The ether extract of the residue was treated as usual. Filtration on silica gel gave the ether **2** (23.7 g, 99.5%). R_f=0.95 (hexane/ether 1/1). ^{1}H NMR: 5.39 (t, 1H), 5.10 (m, 1H), 4.65 (s, 1H), 4.31 (m, 2H), 3.60 (m, 2H), 2.08 (m, 4H), 1.73 (s, 6H), 1.60 (s, 9H); MS 238 (M^+), 137 (M^+—OTHP). Found: C, 75.4; H, 10.8; O, 13.5%. Calcd for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92; O, 13.45%.

Geranyl *p*-Tolyl Sulfone (3). To a stirred solution of geraniol (**1**) (15.6 g, 0.101 mol) in dry methylene chloride (30 ml), were added at room temperature under an argon atmosphere 4-(dimethylamino)pyridine (DMAP, 7.15 g, 0.06 mol), *p*-toluenesulfonyl chloride (23.2 g, 0.12 mol) and triethylamine (14.09 ml, 0.1 mol). Stirring was maintained during 3 h, and methylene chloride was removed in vacuo. The ether extract of the residue was first washed with 10% $CuSO_4$, then with 10% $NaHCO_3$, and finally treated as usual, and purified by flash chromatography to give geranyl chloride (17.03 g, 97%), characterized by its ^{1}H NMR and mass spectra (*m/z* 172—174 M^+). R_f=0.96 (hexane/ether 1/1). Geranyl chloride (3.8 g, 22 mmol) in dry DMF (50 ml) was treated overnight at 25 °C with sodium *p*-toluenesulfinate (4.3 g, 24 mmol) under nitrogen. After evaporation of the solvent, addition of water and extraction with ether, the extract was treated as usual, and purified by flash chromatography (hexane/ether 1/1) to give geranyl *p*-tolyl sulfone (**3**) (5.6 g, 86%) as a colorless oil, apparently crystallizable at low temperature, but which we could not further purify (cf. analysis below). R_f 0.97 (ether). ^{1}H NMR 7.62 (d, 2H), 7.13 (d, 2H), 5.07 (m, 2H), 3.77 (m, 2H), 2.35 (s, 3H), 2.00 (d, 4H), 1.73 (s, 3H), 1.63 (s, 3H), 1.40 (s, 3H). MS 292 (M^+), 137 (M^+—$TolSO_2$). Found: C, 70.2; H, 8.5; S, 10.6%. Calcd for $C_{17}H_{24}O_2S$: C, 69.22; H, 8.5; S, 10.96%.

(2*E*,6*E*)-1-(Tetrahydro-2-pyranyloxy)-3,7-dimethyl-2,6-octadien-8-ol (4). Geranyl tetrahydropyranyl ether (**2**) (4.05 g, 17 mmol) was oxidized with *t*-BuOOH/SeO_2 according to the general procedure. After purification by flash chromatography on silica gel (hexane/ether 1/1), the mono THP-ether **4** was obtained (2.46 g, 57%). R_f 0.17 (hexane/ether 1/1). ^{1}H NMR 5.25 (m, 2H), 4.52 (s, 1H), 4.15—3.70 (m, 6H), 2.83 (s, 1H), 2.08 (m, 4H), 1.63 (m, 12H). MS 254 (M^+), 236 (M^+—H_2O), 153 (M^+—OTHP). Found: C, 70.6; H, 10.2; O, 19.2%. Calcd for $C_{15}H_{26}O_3$: C, 70.87; H, 10.24; O, 18.90%.

(2*E*,6*E*)-8-Chloro-1-(tetrahydro-2-pyranyloxy)-3,7-dimethyl-2,6-octadiene (5). To a solution of the mono THP-ether **4** (4.2 g, 16 mmol) in dry methylene chloride (40 ml) were added sequentially under nitrogen at 25 °C 4-(dimethylamino)pyridine (1.21 g, 10 mmol), tosyl chloride (3.8 g, 20 mmol) and triethylamine (2.22 ml, 16 mmol). The reaction mixture was stirred for 3 h, and methylene chloride was removed was removed in vacuo. The residue, diluted with water, was extracted 4 times with ether, with gentle magnetic stirring. Purification on silica gel afforded 4.55 g of pure chloride **5** (95%) as a colorless oil which could not be obtained analytically pure. R_f 0.97 (hexane/ether 1/1). ^{1}H NMR 5.27 (m, 2H), 4.50 (s, 1H), 4.15—3.70 (m, 6H), 2.08 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.67—1.57 (m, 6H). MS 274—272 (M^+), 236 (M^+—HCl).

(2*E*)-1-(*p*-Tolylsulfonyl)-3,7-dimethyl-2-octen-7-ol (6). To a magnetically stirred solution of sulfone **3** (3.1 g, 10.6 mmol) in THF (40 ml) and water (10 ml), was added with ice cooling mercuric acetate (3.38 g, 10.6 mmol). After 2 h, the reaction was completed by addition of 3 M sodium hydroxide (10 ml) and 0.5 M sodium borohydride in 3 M sodium hydroxide (10 ml). Stirring was continued for 30 min. The reaction mixture was saturated with potassium carbonate and extracted with ether. The extract was treated as usual, evaporated and purified on silica gel to give the hydroxy sulfone **6** (2.95 g, 89%). R_f 0.50 (ether). ^{1}H NMR 7.71 (d, 2H), 7.29 (d, 2H), 5.16 (t, 1H), 3.76 (d, 2H), 2.44 (s, 3H), 2.08 (m, 2H), 1.37 (s, 3H), 1.52—1.30 (m, 5H), 1.22 (s, 6H). MS 310 (M^+), 292 (M^+—H_2O). Found: C, 65.7; H, 8.7; O, 15.6; S, 10.05%. Calcd for $C_{17}H_{26}O_3S$: C,65.80; H, 8.38; O, 15.48; S, 10.32%.

(2*E*)-1-(*p*-Tolylsulfonyl)-7-(2-methoxyethoxymethoxy)-3,7-dimethyl-2-octene (7). To a stirred solution of the hydroxy sulfone **6** (2.8 g, 9 mmol) in dry methylene chloride (30 ml), were added at 25 °C *N,N*-diisopropylethylamine (DIPEA, 2.4 ml, 13.9 mmol) and MEM-chloride (1.6 ml, 14 mmol). Stirring was continued for 4 h (disappearance of the starting material, TLC), water and ether were added and the ether extract was treated as usual. Purification on silica gel afforded the MEM-ether **7** (3.45 g, 96%). R_f 0.72 (ether). ^{1}H NMR: 7.65 (d, 2H), 7.23 (d, 2H), 5.13 (m, 1H), 4.72 (s, 2H), 3.78 (d, 2H), 3.73—3.42 (m, 4H), 3.30 (s, 3H), 2.43 (s, 3H), 2.08—1.83 (m, 2H), 1.48—1.31 (m, 4H), 1.37 (s, 3H), 1.22 (s, 6H). MS 398 (M^+), 367 (M^+—31). Found: C, 63.0; H, 8.5; S, 7.74%. Calcd for $C_{21}H_{34}O_5S$: C, 63.31; H, 8.54; S, 8.04%.

(2*E*,6*E*)-1-(*p*-Tolylsulfonyl)-3,7-dimethyl-2,6-octadien-8-ol (8). Sulfone **3** (2.52 g, 8.6 mmol) was oxidized with *t*-BuOOH/SeO_2 in methylene chloride according to the general procedure, which afforded the hydroxy sulfone **8** (1.75 g, 66%). R_f 0.54 (ether). ^{1}H NMR 7.72 (d, 2H), 7.29 (d, 2H), 5.25 (m, 2H), 4.00 (s, 2H), 3.83 (d, 2H), 2.45 (s, 3H), 2.08 (m, 4H), 1.66 (s, 4H), 1.42 (s, 3H). MS 308 (M^+), 153 (M^+—$TolSO_2$). Found: C, 66.3; H, 7.8; O, 15.5; S, 10.2%. Calcd for $C_{17}H_{24}O_3S$: C, 66.23; H, 7.79; O, 15.58; S 10.39%.

(2*E*,6*E*)-1-(*p*-Tolylsulfonyl)-8-(*t*-butyldimethylsilyloxy)-3,7-dimethyl-2,6-octadiene (9). A stirred mixture of the hydroxy sulfone **8** (4.21 g, 13.6 mmol), *N,N*-diisopropylethylamine (3.56 ml, 20.5 mmol) and disodium hydrogenphosphate (7.75 g, 54.6 mmole) in dry DMF was treated at 25 °C with *t*-butyldimethylsilyl chloride (2.46 g, 16.4 mmol). Stirring was continued for 3 h at room temperature, water and ether were added and the ether extract was teated as usual. After evaporation in vacuo and flash chromatography on silica gel, the TBDMS-ether **9** was obtained (5.55 g, 96%). ^{1}H NMR 7.70 (d, 2H), 7.25 (d, 2H), 5.25 (m, 2H), 3.98 (s, 2H), 3.75 (d, 2H), 2.42 (s, 3H), 2.07 (m, 4H), 1.57 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H). MS (CI, NH_3) 423 (M^++1), 291 (M^++1—*t*-BuDMSiOH). Found: C, 65.5; H, 8.75%. Calcd for $C_{23}H_{38}O_3SiS$: C, 65.40; H, 9.00%.

(2*E*,6*E*,10*E*)-1-(Tetrahydro-2-pyranyloxy)-9-(*p*-tolylsulfonyl)-15-(2-methoxyethoxymethoxy)-3,7,11,15-tetramethyl-2,6,10-hexadecatriene (10). To a stirred solution of the MEM-sulfone **7** (3.35 g, 8.42 mmol) in dry THF (40 ml) and HMPA (10 ml), was added at −78 °C, under nitrogen, a solution of

n-BuLi (6.6 ml, 9.25 mmol). After 2h, was added at −78 °C, over 1 h a solution of the THP-chloride **5** (2.52 g, 9.25 mmol) in dry THF (8 ml) and HMPA (2 ml). The mixture was stirred overnight and worked up as usual. The crude product, after flash chromatography (ether/hexane 1/1) gave the triene **10** (3.2 g, 58%). R_f 0.3 (ether/hexane 1/1). ^{1}H NMR 7.70 (d, 2H), 7.26 (d, 2H), 5.57—4.98 (m, 3H), 4.78 (s, 2H), 4.58 (s, 1H), 4.37—3.78 (m, 5H), 3.78—3.45 (m, 4H), 3.38 (s, 3H), 2.43 (s, 3H), 2.32—1.78 (m, 8H), 1.75—1.46 (m, 6H), 1.67 (s, 9H), 1.46—1.32 (m, 4H), 1.22 (s, 6H). MS 634 (M^+), 603 (M^+-31). Found; C, 68.3; H, 9.0; O, 17.8; S, 4.8%. Calcd for $C_{36}H_{58}O_7S$: C, 68.14; H, 9.15; O, 17.67; S, 5.04%.

(2*E*,6*E*,10*E*)-1-(Tetrahydro-2-pyranyloxy)-15-(2-methoxyethoxymethoxy)-3,7,11,15-tetramethyl-2,6,10-hexadecatriene (11a). Elimination of the *p*-tolylsulfonyl group of the preceding product **10** (3.1 g, 4.9 mmol) was carried out according to the general procedure to give the THP-MEM-protected triene **11a** (2.12 g, 90%). R_f 0.55 (hexane/ether 1/1). ^{1}H NMR 5.47—4.95 (m, 3H), 4.78 (s, 2H), 4.58 (s, 1H), 4.37—3.80 (m, 4H), 3.80—3.46 (m, 4H), 3.38 (s, 3H), 2.22—1.80 (m, 10H), 1.75—1.55 (m, 15H), 1.55—1.38 (m, 4H), 1.22 (s, 6H). MS 480 (M^+), 404 ($M^+-HOCH_2CH_2OCH_3$), 374 ($M^+-HOMEM$). Found: C, 72.7; H, 11.0; O, 16.4%. Calce for $C_{29}H_{52}O_5$: C, 72.50; H, 10.83; O, 16.67%.

(2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-2,6,10-hexadecatriene-1,15-diol (11b). The THP-MEM ether **11a** (1.3 g, 2.7 mmol) was treated with *p*-toluenesulfonic acid in ethanol at 55 °C for 3 h. The solvent was removed in vacuo and water was added. The rection mixture was taken in ether and treated as usual. Flash chromatography afforded the diol **11b** (0.3 g) and two partially deprotected products, which were treated again with *p*-TsOH in the same conditions, to give 0.218 g more of the diol **11b**. Total yield 0.518 g (62%). ^{1}H NMR 5.52—4.95 (m, 3H), 4.11 (d, 2H), 2.63 (s, 1H), 2.26—1.83 (m, 10H), 1.68 (s)+1.60 (s)+1 OH (10H), 1.52—1.28 (m, 4H), 1.21 (s, 6H). MS (CI, NH_3): 291 (MH^+-H_2O), 273 (MH^+-2H_2O). Found: C, 78.1; H, 11.5; O, 10.6%. Calcd. for $C_{20}H_{36}O_2$: C, 77.92; H, 11.69; O, 10.39%.

(6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,)-2,6,10,14,19,23,27,31-Octamethyl-6,10,14,18,22,26-dotriacontahexaene-2,31-diol (A). To a stirred solution of titanium trichloride (75 mg, 0.49 mmol) in dry 1,2-dimethoxyethane (2 ml), was added at −78 °C *n*-BuLi (1.1 ml, 1.40 mmol). After 5 min, alcohol **11b** (300 mg, 0.97 mmol) was added, and the reaction mixture was warmed to room temperature and retained for 15 min before addition of water and ether. The ether extract was treated as usual and silica gel chromatography gave the desired diol **A** (100 mg, 35%). ^{1}H NMR 5.25—4.91 (m, 6H), 2.60 (s, 2H), 2.17—1.87 (m, 24H), 1.62 (m, 18H), 1.47—1.31 (m, 8H), 1.22 (s, 12H). MS 582 (M^+), 564 (M^+-H_2O), 546 (M^+-2H_2O). Found: C, 82.1; H, 11.9%. Calcd for $C_{40}H_{70}O_2$: C, 82.47; H, 12.02%.

(2*E*,6*E*,10*E*,14*E*)-1-(*t*-Butyldimethylsilyloxy)-8-(*p*-tolylsulfonyl)-16-(tetrahydro-2-pyranyloxy)-2,6,10,14-tetramethyl-2,6,10,14-hexadecatetraene (12). The allylic cross-coupling reaction between the sulfone **9** (5.55 g, 13.15 mmol) and the chloride **5** (4.29 g, 15.77 mmol) was carried out in the same manner as for the synthesis of **10** from **5** and **7**. Yield: 6.85 g (72%). ^{1}H NMR 7.65 (d, 2H), 7.23 (d, 2H), 5.37—4.75 (m, 4H), 4.58 (s, 1H), 4.18—3.30 (m, 5H), 3.98 (s, 2H), 2.43 (s, 3H), 2.00—1.91 (m, 10H), 1.64 (s, 3H), 1.58 (s, 3H), 1.64—1.48 (m, 6H), 1.23 (s, 6H), 0.90 (s, 9H) 0.08 (s, 6H). MS 658 (M^+), 573 (M^+-THP), 557 (M^+-OTHP). Found: C, 69.2; H, 9.6; S, 4.9%. Calcd for $C_{38}H_{62}O_5SSi$: C, 69.30; H, 9.42; S, 4.86%.

(2*E*,6*E*,10*E*,14*E*)-16-(Tetrahydro-2-pyranyloxy)-2,6,10,14-tetramethyl-2,6,10,14-hexadecatetraen-1-ol (13). The TBDMS-THP ether **12** (3.07 g, 4.66 mmol) was treated with sodium amalgam according to the general procedure for sulfone removal. The reaction mixture was purified on silica gel and afforded the desulfonated product (2.05 g, 87%; R_f=0.9 in hexane/ether 7/3).

This product (1.84 g, 3.65 mmol) was treated for 3 h at 25 °C with N $(n\text{-Bu})_4$NF in THF (10.7 ml, 3 equiv). The solvent was removed and the crude product, obtained from the ether extract in the usual way, was purified on sillica gel (hexane/ehter 7/3), to give the THP-monoprotected diol **13** (1.14 g, 81%). ^{1}H NMR 5.47—4.91 (m, 4H), 4.60 (s, 1H), 4.23—3.30 (m, 6H), 2.33—1.92 (m, 12H), 1.78—1.42 (m, 19H). MS (CI, NH_3) 408 ($M+NH_4^+$), 373 (MH^+-H_2O). Found: C, 76.75; H, 10.75; O, 12.3%. Calcd for $C_{25}H_{42}O_3$: C, 76.92; H, 10.77; O, 12.31%.

(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*)-3,7,11,18,22,26,30-Octamethyl-2,6,10,14,18,22,26,30-dotriacontaoctaene-1,32-diol (B). The allylic coupling of the THP-monoprotected diol **13** (1 g, 2.56 mol) to give diol **B** was carried out with the same procedure as for the conversion of **11b** into **A**. The crude product was purified on silica gel (hexane/ether 7/3) to give the C_{40}-bis-THP-ether (0.22 g, 23%). This (0.18 g) was treated with *p*-TsOH in ethanol at 55 °C for 3 h. The solvent was evaporated in vacuo, the residue was extracted 4 time with ether and purified on silica gel (hexane/ether 1/1) to give the C_{40}-diol **B** (97 mg, 70%). ^{1}H NMR 5.55—4.98 (m, 8H), 4.72 (s, 2H), 4.17 (d, 4H), 2.32—1.91 (m, 28H), 1.70 (s, 12H), 1.62 (s, 12H). MS (CI, NH_3) 596 (MNH_4^+), 561 (MH^+-H_2O), 543 (MH^+-2H_2O). Found: C, 82.8; H, 11.6; O, 5.6%. Calcd for $C_{40}H_{66}O_2$: C, 83.04; H, 11.41; O, 5.53%.

(2*E*)-6,7-Epoxy-1-(tetrahydro-2-pyranyloxy)-3,7-dimethyl-2-octene (14). To a stirred solution of the THP-ether **2** (15 g, 63 mmol) in methylene chloride (100 ml), was added at 0 °C a solution of *m*-chloroperbenzoic acid (12 g) in the same solvent (100 ml). After 1 h, the reaction mixture was washed with a saturated solution of sodium hydrogencarbonate, water and brine, and was dried over sodium sulfate. The crude product was chromatographed on silica gel to give the epoxide **14** (12.3 g, 77%). R_f=0.83 (hexane/ether 1/1). ^{1}H NMR 5.30 (t, 1H), 4.52 (s, 1H), 4.30—3.23 (m, 4H), 2.60 (t, 1H), 2.11 (m, 2H), 1.62 (s, 3H), 1.96—1.30 (m, 8H), 1.22 (s, 3H), 1.18 (s, 3H). MS 254 (M^+), 169 (M^+-THP), 153 (M^+-OTHP). Found: C, 71.0; H, 10.15; O, 19.1%. Calcd for $C_{15}H_{26}O_3$: C, 70.87; H, 10.23; O, 18.90%.

(2*E*)-1-(Tetrahydro-2-pyranyloxy)-3,7-dimethyl-2,7-octadien-6-ol (15a). To a solution of the epoxide **14** (12.3 g, 48.4 mmol) in dry toluene (100 ml), was added a solution of aluminium isopropoxide in 2-propanol. The mixture was heated under reflux for 24 h, cooled, washed with N HCl (50 ml), water and brine, and dried over sodium sulfate. Flash chromatography (hexane/ether 1/1) on silica gel gave the allylic alcohol **15a** (10.7 g, 87%). R_f=0.45 (hexane/ether 1/1). ^{1}H NMR 5.31 (t, 1H), 4.85 (s, 1H), 4.76 (s, 1H), 4.52 (s, 1H), 4.32—3.26 (m, 5H), 2.35—1.87 (m, 2H), 1.87—1.35 (m, 3H+s, 6H at 1.68). MS 254 (M^+), 236 (M^+-H_2O), 170 (M^+-THP), 153 (M^+-OTHP). Found: C, 71.15; H, 10.1; O, 18.7%. Calcd for $C_{15}H_{26}O_3$: C, 70.87; H, 10.24; O, 18.90%.

(2*E*)-6-(Methoxycarbonyloxy)-1-(tetrahydro-2-pyranyloxy)-3,7-dimethyl-2,7-octadiene (15b). To a stirred solution of the alcohol **15a** (4.2 g, 16.5 mmol) in dry toluene (40 ml), were added at 25 °C, over 1 h, dry pyridine (2 ml) and methyl chloroformate (2 ml). Stirring was maintained for 12 h. The reaction mixture was washed with a dilute solution of ammonium chloride, water, a solution of copper sulfate, water and saturated brine, dried over sodium sulfate, evaporated and purified by chromatography over silica gel to give the mixed carbonate **15b** (5.06 g, 98%). ^{1}H NMR 5.31 (t, 1H), 4.97 (s, 1H), 4.88 (s, 1H), 4.58 (s, 1H), 4.37—3.31 (m, 5H), 3.75 (s, 3H), 2.20—1.42 (m, 10H), 1.73 (s, 3H), 1.67 (s, 3H). MS (CI, NH_3) 313 (MH^+), 237 (MH^+-HOCO_2Me), 211 ($MH^+-HOTHP$). Found: C, 65.4; H, 9.04; O, 25.45%. Calcd for $C_{17}H_{28}O_5$: C, 65.38; H, 8.97; O, 25.64%.

(2*E*)-6,7-Epoxy-1-(*p*-tolylsulfonyl)-3,7-dimethyl-2-octene (16) Epoxidation of sulfone **3** (6 g, 19.5 mmol) was carried out in the same manner as for the THP-ether **2** to give epoxide **16** (4.73 g, 75%). R_f=0.30 (hexane/ether 1/1). ^{1}H NMR 7.72 (d, 2H), 7.30 (d, 2H), 5.22 (t, 1H), 3.78 (d, 2H), 2.67 (t, 1H), 2.44 (s, 3H), 2.30—1.83 (m, 2H), 1.72—1.47 (m, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H). MS 308 (M^+), 153 ($M^+-TolSO_2$), 135 ($M^+-TolSO_2-H_2O$).

(2*E*)-6-Hydroxy-1-(*p*-tolylsulfonyl)-3,7-dimethyl-2,7-octadiene (17). Isomerization of **16** was achieved in the same way as for **14** to afford sulfone **17** (1.8 g, 84%), identical with the known product.[12] R_f=0.30 (hexane/ether 1/1). ^{1}H NMR 7.73 (d, 2H), 7.32 (d, 2H), 5.21 (t, 1H), 4.49 (s, 1H), 4.85 (s, 1H), 3.99 (t, 1H), 3.79 (d, 2H), 2.43 (s, 3H), 2.11—1.95 (m, 2H), 1.71 (s, 4H), 1.66—1.48 (m, 2H), 1.35 (s, 3H). MS 308 (M^+), 153 ($M^+-TolSO_2$), 135 ($M^+-TolSO_2-H_2O$).

Methyl (3*E*)-7-Hydroxy-2-(*p*-tolylsulfonyl)-4,8-dimethyl-3,8-nonadienoate (18). This was prepared in 72% yield according to published procedures.[12] ^{1}H NMR 7.70 (d, 2H), 7.30 (d, 2H), 5.28 (d, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 4.73 (d, 1H), 3.97 (t, 1H), 3.73 (s, 3H), 2.43 (s, 3H), 2.25—1.95 (m, 2H), 1.82—1.50 (m, 3H), 1.71 (s, 3H), 1.55 (s, 3H). MS (CI, NH_3) 349 (MH^+-H_2O), 309 ($MH^+-C_2H_2O_2H$).

Methyl (3*E*)-8-Hydroxy-2-(*p*-tolylsulfonyl)-4,8-dimethyl-3-nonenoate (19) Tertiary alcohol **6** (2 g, 6.5 mmol) was treated in the same manner as allylic alcohol **17** to give the sulfone carboxylate **19** (1.7 g, 65%). ^{1}H NMR 7.69 (d, 2H), 7.28 (d, 2H), 5.25 (d, 1H), 4.75 (d, 1H), 3.70 (s, 3H), 2.44 (s, 3H), 2.25—1.91 (m, 2H), 1.82 (s, 1H), 1.55 (s, 3H), 1.50—1.30 (m, 4H), 1.22 (s, 6H). MS (CI, NH_3) 351 (MH^+-H_2O), 293 ($MH^+-H_2O-C_2H_2O_2$), 197 ($MH^+-H_2O-C_7H_6O_2S$), 195 ($MH^+-H_2O-C_7H_8O_2S$). Found: C, 61.7; H, 7.5; O, 21.9; S, 8.7%. Calcd for $C_{19}H_{28}SO_5$: C, 61.96; H, 7.60; O, 21.74; S, 8.70%.

(2*E*,6*E*,10*E*)-9-Methoxycarbonyl-14-methoxycarbonyloxy-1-(tetrahydro-2-pyranyloxy)-9-(*p*-tolylsulfonyl)-3,7,11,15-tetramethyl-2,6,10,15-hexadecatetraene (20b). To a mixture of the THP-ether **15b** (1.45 g, 4.1 mmol) and the allylic alcohol **18** (1.70 g, 4.65 mmol) in dry THF (6 ml), was added at 25 °C 0.268g of tetrakis(triphenylphosphine)palladium(0). After 2 h, ether and water were added, the ether extract was washed with N sodium cyanide, and treated as usual. The crude product was dissolved in dry toluene (20 ml); pyridine (0.5 ml, 6.5 mmol) and methyl chloroformate (0.5 ml, 6.5 mmol) were added. Stirring was continued overnight, and the mixture was washed with dilute ammonium chloride, water, dilute copper sulfate, water, and saturated brine, then dried over sodium sulfate, evaporated and chromatographed (hexane/ether 1/1) to give product **20b** (1.9 g, 62%). R_f=0.45 (hexane/ether 1/1). ^{1}H NMR 7.72 (d, 2H), 7.30 (d, 2H), 5.35 (s, 1H), 5.31 (t, 1H), 5.15 (m, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.61 (s, 1H), 4.11 (m, 2H), 3.88 (t, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.51 (m, 2H), 3.10 (d, 1H), 2.90 (d, 1H), 2.44 (s, 3H), 2.17—1.95 (m, 6H), 1.83—1.53 (m, 8H, incl. 1.73 s, 1.65 s, 1.57 s), 1.48 (s, 3H). MS (CI, NH_3) 661 (MH^+), 559 ($MH^+-HOTHP$), 505 ($MH^+-C_7H_8O_2S$), 483 $MH^+-HOTHP-HOCO_2Me$), 403 ($MH^+-HOTHP-C_7H_8O_2S$). Found: C, 65.3; H, 8.0; O, 21.9; S, 4.9%. Calcd for $C_{36}H_{52}O_9S$: C, 65.45; H, 7.88; O, 21.82; S, 4.85%.

(2*E*,6*E*,10*E*,14*E*,18*E*)-1-(Tetrahydro-2-pyranyloxy)-9-17-bis(methoxycarbonyl)-22-methoxycarbonyloxy-9,17-bis(*p*-tolylsulfonyl)-3,7,11,15,19,23-hexamethyl-2,6,10,14,18,23-tetracosahexaene (21b). The Pd(0)-catalyzed coupling between the allylic carbonate **20b** (1.7 g, 2.6 mmol) and the allylic alcohol **18** (1.1 g, 3.0 mmol) was run as above to give the expected product **21b** (1.6 g, 61%) and starting materials. R_f=0.26 (hexane/ether 3/7). ^{1}H NMR 7.69 (d, 4H), 7.28 (d, 4H), 5.31 (m, 2H), 5.25—5.06 (m, 3H), 4.95 (s, 2H), 4.61 (s, 1H), 4.41—3.90 (m, 3H), 3.78 (s, 3H), 3.68 (s, 6H), 3.52 (m, 2H), 3.20—2.90 (m, 4H), 2.44 (s, 6H), 2.20—1.92 (m, 10H), 1.82—1.52 (m, 23H, incl. s 1.75, 1.65, 1.60), 1.49 (s, 3H). MS (FAB, NaCl) 1031 (MNa^+), 907 ($MH^+-HOTHP$), 853 ($MH^+-TolSO_2$), 751 ($MH^+-TolSO_2-HOTHP$), 675 ($MH^+-TolSO_2-HOTHP-MeOCOOH$) Found: C, 65.6; H, 7.6; O, 20.7; S, 6.6%. Calcd for $C_{55}H_{76}O_{13}S_2$: C, 65.47; H, 7.54; O, 20.63; S, 6.35%.

(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-31-Hydroxy-1-(tetrahydro-2-pyranyloxy)-9,17,25-tris(methoxycarbonyl)-9,17,25-tris(*p*-tolylsulfonyl)-3,7,11,15,19,23,27,31-octamethyl-2,6,10,14,18,22,26-dotriacontaheptaene (22). The same Pd(0)-catalyzed coupling was achieved between substrates **19** (1 g, 2.7 mmol) and **21b** (1.5 g, 1.5 mmol) to give the expected product **22** (1.7 g, 88%). ^{1}H NMR 7.73 (d, 6H), 7.30 (d, 6H), 5.37—5.08 (m, 7H), 4.62 (s, 1H), 4.27—3.41 (m, 4H), 3.68 (s, 9H), 3.25—2.66 (m, 6H), 2.44 (s, 9H), 2.15—1.82 (m, 14H), 1.70—1.25 (m, 32H, incl. s 1.64, 1.60, 1.58, 1.56, 1.46, 1.25), 1.22 (s, 6H). MS (FAB, NaCl) 1323 (MNa^+), 1167 (MNa^+-HSO_2Tol), 1013 ($MNa^+-HSO_2Tol-TolSO_2$). Found: C, 66.2; H, 7.6; O, 18.5; S 7.35%. Calcd for $C_{72}H_{100}O_{15}S_3$: C, 66.46; H, 7.69; O, 18.64; S, 7.38%.

(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-31-Hydroxy-1-(tetrahydro-2-pyranyloxy)-9,17,25-tris(*p*-tolylsulfonyl)-3,7,11,15,19,23,27,31-octamethyldotriaconta-2,6,10,14,18,22,26-heptaene (23). To a solution of the above tricarboxylate **22** (400 mg, 0.3 mmol) in dry DMF (10 ml), were added *p*-aminothiophenol (230 mg, 1.85 mmol) and cesium carbonate (100 mg). The mixture was stirred at 85 °C for 3 h, poured into water and extracted with ether. The usual treatment gave, after purification on silica gel the decarboxylated product **23** (203 mg, 60%). ^{1}H NMR 7.73 (m, 6H), 7.31 (d, 6H), 5.43—4.86 (m, 7H), 4.60 (s, 1H), 4.36—3.46 (m, 7H), 2.46 (s, 9H), 2.11—1.78 (m, 20H), 1.63—1.43 (m, 6H), 1.43—1.30 (m, 4H), 1.65 (s, 4H), 1.51 (s, 9H), 1.25 (s, 9H), 1.21 (s, 6H). MS (FAB, NaCl) 1149 (MNa^+), 993 (MNa^+-HSO_2Tol). Found: C,70.15; H, 8.4; O, 12.8; S, 8.3%. Calcd for $C_{66}H_{94}O_9S_3$: C, 70.34; H, 8.35; O, 12.79; S, 8.52%.

(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-3,7,11,15,19,23,27,31-Octamethyl-2,6,10,14,18,22,26-dotriacontaheptaene-1,31-diol (C). Desulfonation of the preceding substance **23** (200 mg, 1.18 mmol) by the general procedure gave the THP-ether of diol **C**, which was prepared irectly by treatment with

a trace of *p*-TsOH in ethanol at 55 °C for 3 h, to give after purification the desired product **C** (60 mg, 58%). ^{1}H NMR 5.58—4.92 (m, 7H), 4.18 (d, 2H), 3.05—2.92 (m, 2H), 2.54—1.83 (m, 24H), 1.67—1.65 (m, 21H), 1.51—1.33 (m, 6H), 1.24 (s, 6H). MS (CI, NH_3) 598 (MNH_4^+), 563 (MH^+-H_2O), 545 (MH^+-2H_2O). Found: C, 82.7; H, 11.9; O, 5.75%. Calcd for $C_{40}H_{68}O_2$: C, 82.75; H, 11.72; O, 5.52%.

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