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ISOTACTIC POLYMETHOXY-1-ALKENES FROM THE TERRESTRIAL BLUE-GREEN ALGA *Scytonema ocellatum*: STRUCTURE AND SYNTHESIS

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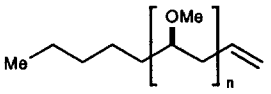
Abstract: Novel isotactic polymethoxy-1-alkenes 2-5 were isolated from the tolytoxin-producing blue-green alga *Scytonema ocellatum*. The gross structures and relative configurations were determined by NMR and mass spectral analysis. Synthesis of optically active 2-4 in a stereocontrolled manner established their absolute configurations.

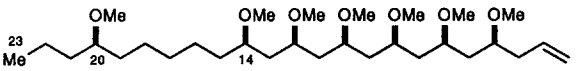
Isotactic polymethoxy-1-alkenes having the general formula 1, where n=5, 6, 8, 9 and 10, have been found in three species of terrestrial, tolytoxin-producing blue-green algae belonging to the family Scytonemataceae, viz. *Tolypothrix conglutinata* var. *colorata* Ghose,[2] *Scytonema mirabile* (Dillwyn) Bornet[3] and *S. burmanicum* Skuja.[3] Tolytoxin-producing *S. ocellatum* Lyngbye ex Bornet & Flahault (strain FF-66-3) elaborates different isotactic polymethoxy-1-alkenes (2-5). We describe here the isolation and structure elucidation of 2-5 and the synthesis of 2-4.

Structure Determination

The gross structures and relative stereochemistry of 2-5 were determined by mass and NMR spectral analyses using previously described methodology.[2,3] The FAB mass spectrum of the major polymethoxy-1-alkene (3) showed a MH^+ ion at m/z 533 and its ^1H NMR spectrum indicated the presence of eight methoxyl groups with a 6H singlet at 3.278 ppm and six 3H singlets at 3.257, 3.255, 3.235, 3.217, 3.195, and 3.172 ppm, strongly suggesting that 3 had the elemental composition $C_{33}H_{66}O_8$. The formula was confirmed and a gross structure proposed on the basis of COSY, HMQC, and HMBC experiments coupled with an INADEQUATE experiment on the 82% ^{13}C-enriched compound. The structures of the C-1 to C-8 and C-14 to C-25 segments were easily deduced from the INADEQUATE spectrum. The INADEQUATE experiment also showed strong connectivities for the repeating CH_2-$CHOCH_3$ unit, but the length of the C-8 to C-14 fragment had to be deduced on the basis of the integration of the oxy-



1 n= 5, 6, 8, 9, 10



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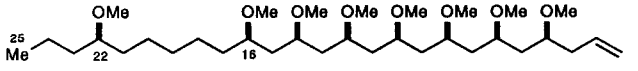

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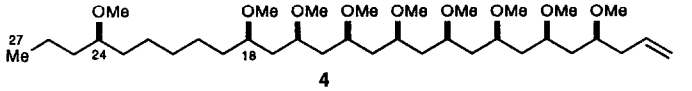

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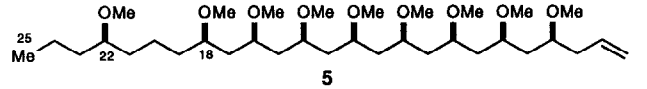


5

methine and methoxyl proton NMR signals (eight oxymethines and eight methoxyls). As for the polymethoxy-1-alkenes of structure 1, the protons on the methylenes between the methoxymethines, viz. C-5, C-7, C-9, C-11, C-13, and C-15, were found to be magnetically nonequivalent, indicating that the methoxyl groups were all on the same side of the carbon chain. The stereochemistry of the methoxyl group on C-22 was proposed from biogenesis. Compound 3 was therefore isotactic 4,6,8,10,12,14,16,22-octamethoxy-1-pentacosene.

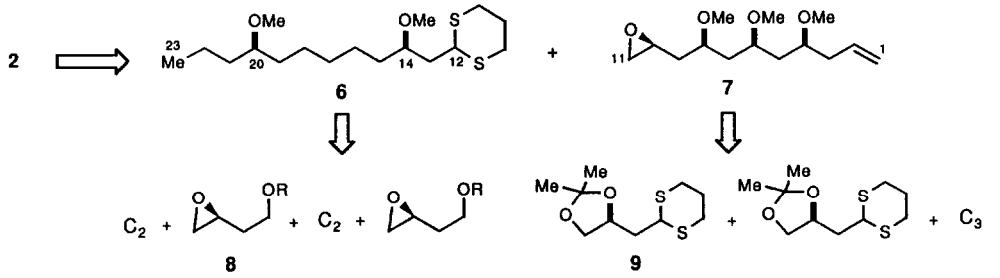
Comparison of the proton and carbon NMR spectra of compounds 2-4 revealed that 2 was a lower homolog and 4 was a higher homolog of 3. Compound 2 had the elemental formula $C_{30}H_{60}O_7$, since its FAB mass spectrum showed a MH^+ ion at m/z 533 and its ^1H NMR spectrum exhibited seven methoxyl signals at 3.275, 3.259, 3.255, 3.237, 3.219, 3.195, and 3.174 ppm. Compound 4, however, had the composition $C_{36}H_{72}O_9$, because its FABMS MH^+ ion was at m/z 649 and its ^1H NMR spectrum revealed the presence of nine methoxyl groups with a 6H singlet at 3.284 ppm and seven 3H singlets at 3.287, 3.260, 3.259, 3.239, 3.219, 3.197, and 3.173 ppm. Using the same arguments presented above for the structure of 3, compounds 2 and 4 were found to be isotactic 4,6,8,10,12,14,20-heptamethoxy-1-tricosene and 4,6,8,10,12,14,16,18,24-nonamethoxy-1-heptacosene, respectively.

Compound 5, which showed a MH^+ ion at m/z 621 in its FAB mass spectrum and eight methoxyl signals (for nine methoxyl groups) at 3.284 (6H), 3.281, 3.260, 3.252, 3.235, 3.218, 3.195, and 3.172 ppm in its ^1H NMR spectrum, had the composition $C_{34}H_{68}O_9$. Compound 5, however, showed a ^{13}C NMR spectrum that was quite different from those of compounds 2, 3, and 4. Only five methylene signals could be observed between 37 and 18 ppm instead of the seven signals for compounds 2-4. The integration of the signals in the aliphatic region of the NMR spectrum of 5 was different from that measured in the spectra of com-

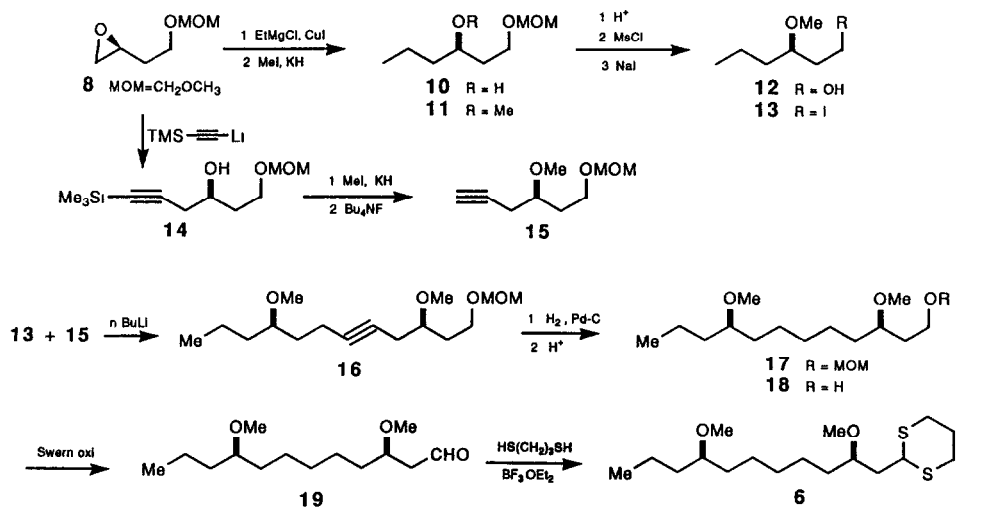
pounds 2-4. These data, especially the changes in ^{13}C chemical shift, suggested that compound 5 differed from compound 3 in having a methoxyl group on C-18. Compound 5 was therefore isotactic 4,6,8,10,12,14,16,18,22-nonamethoxy-1-pentacosene.

Synthesis and Absolute Stereochemistry

To confirm the proposed relative stereochemistry and establish the absolute configuration of polymethoxy-1-alkene 2 by synthesis, we devised a plan to construct the entire carbon chain from two segments 6 and 7. Segment 6 could be disassembled into two pairs of C_2 and C_4 units. Right segment 7 was prepared by a convergent method for 1,3-polyol synthesis using 9,[4] a C_4 unit which was used as a key intermediate in the synthesis of 1 (n=5, 6, and 9).[3] Syntheses of polymethoxy-1-alkenes 3 and 4 could be achieved by homologation of 2 using Brown's asymmetric allylation procedure.[5]

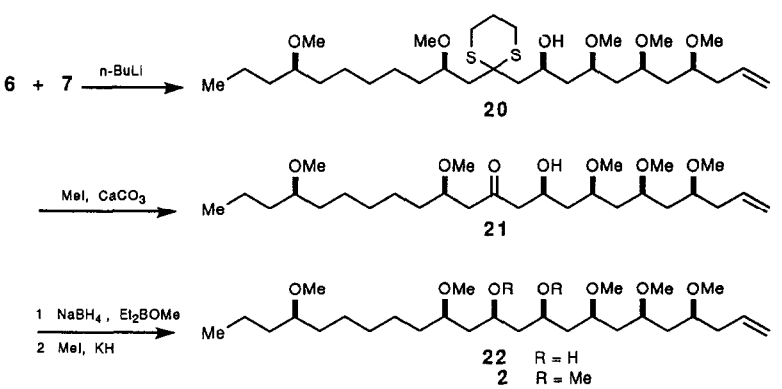


Treatment of optically active epoxide 8, prepared from (S)-butane-1,2,4-triol in five steps, with ethylmagnesium chloride in the presence of a catalytic amount of cuprous iodide gave 10 which was then methylated to 11 in 85% yield. Removal of the methoxymethyl group resulted in alcohol 12 which was converted to iodide 13 via the mesylate in



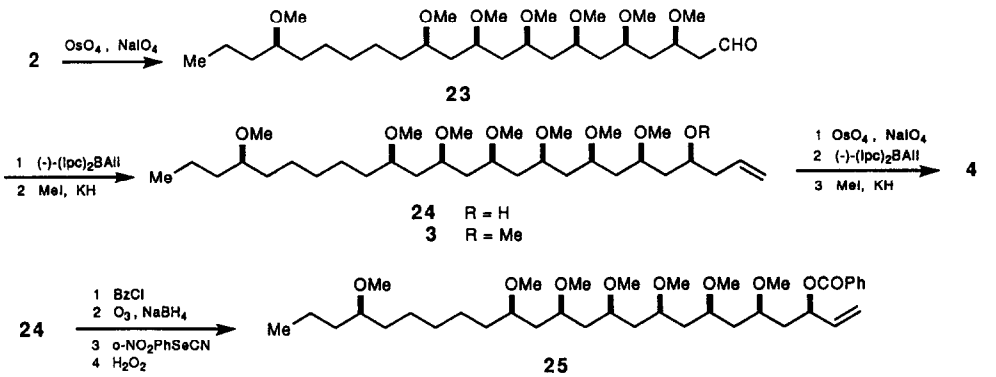
81% overall yield. Epoxide 8 was also reacted with lithium trimethylsilylacetylide[6] to yield acetylenic alcohol 14 (73%), a compound corresponding to the C_{12}-C_{17} fragment of 6. Methylation of the hydroxyl group and removal of trimethylsilyl group gave 15 in 86% yield. Coupling of iodide 13 with lithium acetylide, prepared from 15 by treatment with n-butyllithium in THF-HMPA, afforded 16 (78%). Catalytic hydrogenation of the triple bond in 16 followed by acid treatment of 17 gave dimethoxy alcohol 18 (79% in two steps), which was converted to aldehyde 19 by Swern oxidation[7] in 96% yield. Dithioacetalization of 19 with 1,3-propanedithiol in the presence of boron trifluoride etherate afforded the left segment 6 in 58% yield.

Connection of the last bond to 2 was achieved by coupling epoxide 7[3] and the anion generated from dithiane 6 with n-butyllithium in THF to give bisalkylated dithiane 20 in 64% yield. Removal of the dithioacetal group with methyl iodide and calcium carbonate[8] in aqueous acetonitrile at room temperature gave hydroxyketone 21 (85%). Reduction of 21 to the desired diol 22 was accomplished using a 1,3-syn-stereoselective reduction with sodium borohydride-diethylmethoxyborane,[9] resulting in a 95:5 mixture of separable diastereoisomers as determined from the ^1H NMR spectrum in benzene-d_6 which showed resolved methoxyl signals for the diastereoisomers. The desired syn-diol 22 was isolated in 92% yield by flash chromatography. Finally, methylation of 22 with methyl iodide and KH in THF afforded heptamethoxy-1-tricosene (2), $[\alpha]_D^{25}$ +6.47° ($CHCl_3$), in 89% yield. Natural 2 had a specific rotation of +8.89° ($CHCl_3$) and ^1H and ^{13}C NMR, IR, and mass spectra that were identical with those of synthetic 2. The absolute configuration of 2 was therefore concluded to be 4S, 6S, 8S, 10R, 12R, 14R, 20R.



Asymmetric allylation is one of the useful methods for the preparation of 1,3-polyols.[10] Brown's allyl $(Ipc)_2$borane reagent,[5] which provided the necessary asymmetric induction and flexibility in constructing the requisite stereoisomers, was chosen for the synthesis of higher homologs 3 and 4 from 2. Heptamethoxy-1-tricosene (2) was initially transformed to aldehyde 23 (94%) by OsO_4-$NaIO_4$ oxidation[11] in aqueous dioxane. Reaction of 23 with the allyl reagent derived from (-)-$(Ipc)_2BOMe$ and allylmagnesium bromide in

toluene at -78℃ resulted in a 83% yield of a mixture of homoallylic alcohols with 88:12 selectivity.[12] Careful chromatographic separation of the mixture using spherical silica gel (30-50 μm) afforded pure 24 in 50% yield. Stereochemistry of the newly formed asymmetric center was determined by a CD study of an appropriate degradation product.[13] Homoallylic alcohol 24 was transformed to allylic benzoate 25 (58% overall yield) by the following series of reactions; 1) benzoylation of 24, 2) ozonolysis followed by sodium borohydride reduction, 3) selenylation with o-nitrophenylselenocyanide and oxidative elimination by H_2O_2. The CD spectrum of allylic benzoate 25 exhibited a negative Cotton effect at 226 nm ($\Delta\varepsilon$ -3.19) which correlated to the 2R configuration for 25 and, hence, the 4S configuration for 24.



Methylation of the hydroxyl group of 24 with methyl iodide and KH gave optically active octamethoxy-1-pentacosene (3), $[\alpha]_D^{25}$ +5.02° ($CHCl_3$). Synthetic 3 exhibited identical chromatographic and spectroscopic data as natural 3 with $[\alpha]_D^{25}$ +5.78° ($CHCl_3$). Thus, the 4S, 6S, 8S, 10R, 12R, 14R, 16R, 22R absolute stereochemistry was assigned for octamethoxy-1-pentacosene (3).

Nonamethoxy-1-heptacosene (4) was also synthesized from 3 by the same route for the preparation of 3 from 2; 1) OsO_4-$NaIO_4$ oxidation (78%), 2) asymmetric allylation (95%, β : α=86:14) and separation of the major isomer using spherical silica gel (67% isolated yield), and 3) methylation with methyl iodide and KH (89%). The ^1H and ^{13}C NMR spectra and specific rotations of synthetic and natural 4 were identical; the $[\alpha]_D$ values of synthetic and natural 4 were found to be +4.36° ($CHCl_3$) and +4.47 ° ($CHCl_3$), respectively. Compound 4 was therefore (4S, 6S, 8S, 10S, 12R, 14R, 16R, 18R, 24R)-nonamethoxy-1-heptacosene.

Isotactic 4, 6, 8, 10, 12, 14, 16, 18, 22-nonamethoxy-1-pentacosene presumably has the relative and absolute stereochemistry depicted by 5, since all of the polymethoxy-1-alkenes isolated so far from the family Scytonemataceae[2, 3] have the same stereochemistry.

Experimental Section

Spectral Analysis. NMR spectra were determined on a GN-OMEGA instrument operating at 500 MHz for proton and 125 MHz for carbon-13 and on JEOL JNM-GX 400 and 270 instruments operating at 400 MHz and 270 MHz for proton, respectively. Proton chemical shifts are referenced in benzene-d_6 to the residual benzene signal (7.15 ppm) and in chloroform-d to TMS (0 ppm); ^{13}C chemical shifts are referenced in benzene-d_6 to the solvent signal (128 ppm). Homonuclear ^1H connectivities were determined by using the COSY experiment. Heteronuclear ^1H-^{13}C connectivities were determined by heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond connectivity (HMBC) experiments.[14,15] IR spectra were measured on a Hitachi 215 spectrometer. Mass spectra were determined in the FAB mode, using glycerol as the matrix, with a VG Analytical 70 SE instrument and in the CI mode with a Shimadzu GCMS QP-1000 instrument. Optical rotations were determined on a JASCO DIP-370 digital polarimeter.

Culture Conditions. An epidaphic form of Scytonema ocellatum Lyngbye ex Bornet & Flahault was isolated from an algal sample collected at South Pasture Pond, Shawanee, Illinois (strain FF-66-3). A clonal culture was prepared by repeated subculture on solidified media and grown in 20 L glass bottles containing a modified inorganic medium, designated A_3M_7, as previously described for Hapalosiphon fontinalis.[16] Prior to autoclaving, the pH of the medium was adjusted to 7.0 with sodium hydroxide. Cultures were illuminated continuously at an incident intensity of 300 μeinstein $m^{-2}s^{-1}$ from banks of cool-white fluorescent tubes, aerated at a rate of 1 L/min with a mixture of 0.5% CO_2 in air and maintained at an incubation temperature of 24 ± 1 °C. The alga was harvested by filtration after 30 days and freeze-dried. Typical yields of lyophilized cells averaged 0.374 g/L.

Uniformly ^{13}C, ^{15}N enriched S. ocellatum strain FF-66-3 was prepared using a previously described procedure.[3] After 33 days, the 8 L culture was harvested and the alga collected by filtration and freeze-dried to give 1.62 g of lyophilized material.

Isolation. Freeze-dried alga (50 g) was extracted with 3×1 L portions of 7:3 EtOH/water solution (24 h for each). The total extract (9.4 g) was flash chromatographed on a RP-18 column (80 mL, YMC-GEL, ODS 120A). The chromatogram was developed with 300 mL of each of the following solvents: 3:2, 1:1, 1:3, and 1:9 H_2O/MeOH mixtures, MeOH, MeCN, and EtOAc. Seven fractions (300 mL) were collected. The fourth and fifth fractions from the RP-18 column (1.4 g) were combined and rechromatographed on a silica gel (30 mL, EM Science Kieselgel 60, 230-400 mesh) flash column (2.5 ×10 cm) using a gradient of 7:3 hexane/EtOAc to 100% EtOAc (100 mL fractions collected). 4,6,8,10,12,14,20-Heptamethoxy-1-tricosene (2, 20 mg) was eluted from the column with 7:3 hexane/EtOAc, 4,6,8,10,12,14,16,22-octamethoxy-1-pentacosene (3, 200 mg) with 6:4 hexane/EtOAc, 4,6,8,10,12,14,16,18,24-nonamethoxy-1-heptacosene (4, 75 mg) with 55:45 hexane/EtOAc, and 4,6,8,10,12,14,16,18,22-nonamethoxy-1-pentacosene (5, 120 mg) with 1:1 hexane/EtOAc.

The uniformly ^{13}C, ^{15}N-enriched alga (1.62 g) was treated in the same way to give 248

mg of crude extract and 8.0 mg of 82% ^{13}C-enriched 3.

The compounds had the following R_f values on silica gel (Kieselgel 60 F_{254}) plates using 3:2 EtOAc/hexane: 2, 0.46; 3, 0.41; 4, 0.34; 5 0.26. The spots were visualized with 1% ceric sulfate/10% H_2SO_4. The R_f values for 3 and 4 were comparable with those for polymethoxy-1-alkenes of general structure 1 where n=8 and 9, respectively.

4,6,8,10,12,14,20-Heptamethoxy-1-tricosene (2): $[\alpha]_D^{25}$ +8.89° (c=0.12, $CHCl_3$); FAB mass spectrum m/z 533 ($C_{30}H_{60}O_7$, MH^+); ^1H NMR (500 MHz, benzene-d_6) δ 5.09 (ddt, J=17.1, 2.5, and 1.2 Hz, H-1Z), 5.07 (br d, J=10.0, 2.0 and 1.2 Hz, H-1E), 5.90 (ddt, J=17.1, 10.0 and 7.0 Hz, H-2), 2.30 (dddd, J=1.2, 2.5, 5.4 and 7.0Hz, H-3 and H-3'), 3.37 (m, H-4), 3.18 (s, OMe on C-4), 1.70 (m, H-5), 1.98 (m, H-5'), 3.61 (m, H-6), 3.22 (s, OMe on C-6), 1.77 (m, H-7), 2.00 (m, H-7'), 3.65 (m, H-8), 3.26 (s, OMe on C-8), 1.85 (m, H-9), 2.05 (m, H-9'), 3.65 (m, H-10), 3.28 (s, OMe on C-10), 1.85 (m, H-11), 2.05 (m, H-11'), 3.65 (m, H-12), 3.26 (s, OMe on C-12), 1.74 (m, H-13), 2.03 (m, H-13'), 3.37 (m, H-14), 3.24 (s, OMe on C-14), 1.62 (m, H-15 and H-15'), 1.42 (m, H-16 and H-16'), 1.41 (m, H-17), 1.49 (m, H-18), 1.49 (m, H-19), 3.07 (tt, J=7.3 and 6.8 Hz, H-20), 3.20 (s, OMe on C-20), 1.43 (m, H-21), 1.54 (m, H-21'), 1.43 (m, H-22 and H-22'), 0.92 (t, J=6.9 Hz, H_3-23); ^{13}C NMR (125 MHz, benzene-d_6) δ (multiplicity, carbon position) 117.02 (t, C-1), 135.25 (d, C-2), 38.24 (t, C-3), 77.59 (d, C-4), 56.16 (q, OMe on C-4), 38.02 (t, C-5), 75.62 (d, C-6), 55.93 (q, OMe on C-6), 38.59 (t, C-7), 75.71 (d, C-8), 56.00 (q, OMe on C-8), 38.62 (t, C-9), 75.72 (d, C-10), 56.00 (q, OMe on C-10), 38.62 (t, C-11), 75.80 (d, C-12), 56.00 (q, OMe on C-12), 38.34 (t, C-13), 78.12 (t, C-14), 56.09 (q, OMe on C-14), 34.00 (t, C-15), 25.73 (t, C-16), 30.61 (t, C-17), 25.46 (t, C-18), 33.89 (t, C-19), 80.74 (d, C-20), 56.21 (q, OMe on C-20), 36.16 (t, C-21), 18.88 (t, C-22), 14.54 (q, C-23).

4,6,8,10,12,14,16,22-Octamethoxy-1-pentacosene (3): $[\alpha]_D^{25}$ +5.78° (c=0.90, $CHCl_3$); FAB mass spectrum m/z 591 ($C_{33}H_{66}O_8$, MH^+); ^1H NMR (500 MHz, benzene-d_6) δ 5.11 (ddt, J=17.1, 2.5 and 1.2 Hz, H-1Z), 5.08 (br d, J=10.0, 2.0 and 1.2 Hz, H-1E), 5.90 (ddt, J=17.1, 10.0, and 7.0 Hz, H-2), 2.31 (dddd, J=1.2, 2.5, 5.4 and 7.0 Hz, H-3 and H-3'), 3.38 (m, H-4), 3.17 (s, OMe on C-4), 1.67 (m, H-5), 1.96 (m, H-5'), 3.59 (m, H-6), 3.22 (s, OMe on C-6), 1.75 (m, H-7), 1.98 (m, H-7'), 3.65 (m, H-8), 3.26 (s, OMe on C-8), 1.82 (m, H-9), 2.03 (m, H-9'), 3.65 (m, H-10), 3.28 (s, OMe on C-10), 1.82 (m, H-11), 2.03 (m, H-11'), 3.65 (m, H-12), 3.28 (s, OMe on C-12), 1.82 (m, H-13), 2.03 (m, H-13'), 3.64 (m, H-14), 3.26 (s, OMe on C-14), 1.69 (m, H-15), 2.01 (m, H-15'), 3.38 (m, H-16 and H-16'), 3.24 (s, OMe on C-16), 1.60 (m, H-17 and H-17'), 1.40 (m, H-18 and H-18'), 1.39 (m, H-19 and H-19'), 1.47 (m, H-20 and H-20'), 1.47 (m, H-21), 1.55 (m, H-21'), 3.07 (tt, J=7.3 and 6.9 Hz, H-22), 3.20 (s, OMe on C-22), 1.41 (m, H-23), 1.52 (m, H-23'), 1.41 (m, H-24 and H-24'), 0.92 (t, J=6.9 Hz, H_3-25); ^{13}C NMR (125 MHz, benzene-d_6) δ (multiplicity, carbon position) 117.01 (t, C-1), 135.28 (d, C-2), 38.25 (t, C-3), 77.62 (d, C-4), 56.19 (q, OMe on C-4), 38.05 (t, C-5), 75.65 (d, C-6), 55.96 (q, OMe on C-6), 38.59 (t, C-7), 75.74 (d, C-8), 56.02 (q, OMe on C-8), 38.65 (t, C-9), 75.74 (d, C-10), 56.02 (q, OMe on C-10), 38.65 (t, C-11), 75.74 (d, C-12), 56.02 (q, OMe on C-12), 38.65 (t, C-13), 75.83 (d, C-14), 56.07 (q, OMe on C-14), 38.36 (t, C-15), 78.15 (d, C-16), 56.12 (q, OMe on C-16), 34.03 (t, C-

17), 25.75 (t, C-18), 30.64 (t, C-19), 25.49 (t, C-20), 33.93 (t, C-21), 80.78 (d, C-22), 56.26 (q, OMe on C-22), 36.19 (t, C-23), 18.93 (t, C-24), 14.59 (q, C-25). Carbon position (proton HMBC correlation) C-1 (H-3 and H-3'), C-2 (H-3 and H-3'), C-3 (H-1, H-1', H-5 and H-5'), C-4 (H-3, H-3' and OMe on C-4), OMe on C-4 (H-4), C-5 (H-3, H-3', H-7 and H-7'), C-6 (H-4, H-5, H-5' and OMe on C-6), OMe on C-6 (H-6), C-7 (H-5, H-5', H-9 and H-9'), C-8 (OMe on C-8), OMe on C-8 (C-8), C-10 (OMe on C-10), OMe on C-10 (H-10), C-12 (OMe on C-12), OMe on C-12 (H-12), C-14 (H-13, H-13', OMe on C-14, H-15 and H-15'), OMe on C-14 (H-14), C-15 (H-13 and H-13'), C-16 (H-14, H-15, H-15' and OMe on C-16), OMe on C-16 (H-16), C-22 (OMe on C-22), OMe on C-22 (H-22), C-23 (H_3-25), C-24 (H_3-25).

4,6,8,10,12,14,16,18,24-Nonanethoxy-1-heptacosene (4): $[\alpha]_D^{25}$ +4.47° (c=0.43, $CHCl_3$); FAB mass spectrum m/z 649 ($C_{36}H_{72}O_9$, MH^+); ^1H NMR (400 MHz, benzene-d_6) δ5.11 (ddt, J=17.1, 2.5 and 1.2 Hz, H-1Z), 5.08 (br d, J=10.0, 2.0 and 1.2 Hz, H-1E), 5.90 (ddt, J=17.1, 10.0 and 7.0 Hz, H-2), 2.31 (dddd, J=1.2, 2.5, 5.4 and 7.0 Hz, H-3 and H-3'), 3.38 (m, H-4), 3.17 (s, OMe on C-4), 1.71 (m, H-5), 1.96 (m, H-5'), 3.59 (m, H-6), 3.22 (s, OMe on C-6), 1.75 (m, H-7), 1.98 (m, H-7'), 3.65 (m, H-8), 3.26 (s, OMe on C-8), 1.82 (m, H-9), 2.03 (m, H-9'), 3.65 (m, H-10), 3.28 (s, OMe on C-10), 1.82 (m, H-11), 2.03 (m, H-11'), 3.65 (m, H-12), 3.29 (s, OMe on C-12), 1.82 (m, H-13), 2.03 (m, H-13'), 3.65 (m, H-14), 3.28 (s, OMe on C-14), 1.82 (m, H-15), 2.03 (m, C-15'), 3.64 (m, H-16), 3.26 (s, OMe on C-16), 1.69 (m, H-17), 2.01 (m, H-17'), 3.38 (m, H-18), 3.24 (s, OMe on C-18), 1.60 (m, C-19 and H-19'), 1.40 (m, H-20 and H-20'), 1.39 (m, H-21 and H-21'), 1.47 (m, H-22 and H-22'), 1.47 (m, H-23), 1.55 (m, H-23'), 3.07 (tt, J=7.3 and 6.9 Hz, H-24), 3.20 (s, OMe on C-24), 1.41 (m, H-25), 1.52 (m, H-25'), 1.41 (m, H-26 and H-26'), 0.92 (t, J=6.9 Hz, H_3-27); ^{13}C NMR (100 MHz, benzene-d_6) δ (multiplicity, carbon position) 117.04 (t, C-1), 135.24 (d, C-2), 38.21 (t, C-3), 77.57 (d, C-4), 56.22 (q, OMe on C-4), 38.02 (t, C-5), 75.60 (d, C-6), 55.93 (q, OMe on C-6), 38.56 (t, C-7), 75.71 (d, C-8), 56.00 (q, OMe on C-8), 38.62 (t, C-9), 75.71 (d, C-10), 56.00 (q, OMe on C-10), 38.62 (t, C-11), 75.71 (d, C-12), 56.00 (q, OMe on C-12), 38.62 (t, C-13), 75.71 (d, C-14), 56.00 (q, OMe on C-14), 38.62 (t, C-15), 75.79 (d, C-16), 56.09 (q, OMe on C-16), 38.34 (t, C-17), 78.11 (d, C-18), 56.15 (q, OMe on C-18), 33.99 (t, C-19), 25.72 (t, C-20), 30.61 (t, C-21), 25.45 (t, C-22), 33.89 (t, C-23), 80.74 (d, C-24), 55.22 (q, OMe on C-24), 36.15 (t, C-25), 18.89 (t, C-26), 14.55 (q, C-27).

4,6,8,10,12,14,16,18,22-Nonamethoxy-1-pentacosene (5): $[\alpha]_D^{25}$ +11.20° (c=0.38, $CHCl_3$); FAB mass spectrum m/z 621 ($C_{34}H_{68}O_9$, MH^+); ^1H NMR (500 MHz, benzene-d_6) δ5.10 (ddt, J=17.1, 2.5 and 1.2 Hz, H-1Z), 5.08 (br d, J=10.0, 2.0 and 1.2 Hz, H-1E), 5.91 (ddt, J=17.1, 10.0 and 7.0 Hz, H-2), 2.31 (dddd, J=1.2, 2.5, 5.4 and 7.0 Hz, H-3 and H-3'), 3.40 (m, H-4), 3.17 (s, OMe on C-4), 1.68 (m, H-5), 1.96 (m, H-5'), 3.61 (m, H-6), 3.22 (s, OMe on C-6), 1.75 (m, H-7), 1.98 (m, H-7'), 3.65 (m, H-8), 3.25 (s, OMe on C-8), 1.83 (m, H-9), 2.03 (m, H-9'), 3.65 (m, H-10), 3.26 (s, OMe on C-10), 1.83 (m, H-11), 2.03 (m, H-11'), 3.65 (m, H-12), 3.28 (s, OMe on C-12), 1.83 (m, H-13), 2.03 (m, H-13'), 3.65 (m, H-14), 3.28 (s, OMe on C-14), 1.83 (m, H-15), 2.03 (m, H-15'), 3.65 (m, H-16), 3.28 (s, OMe on C-16), 1.72 (m, H-17), 2.01 (m, H-17'), 3.38 (m, H-18), 3.23 (s, OMe on C-18), 1.60 (m, H-19

and H-19'), 1.39 (m, H-20 and H-20'), 1.47 (m, H-21 and H-21'), 3.05 (tt, J=7.3 and 6.8 Hz, H-22), 3.20 (s, OMe on C-22), 1.41 (m, H-23), 1.52 (m, H-23'), 1.41 (m, H-24 and H-24'), 0.91 (t, J=6.9 Hz, H_3-25); ^{13}C NMR (125 MHz, benzene-d_6) δ (multiplicity, carbon position) 117.03 (t, C-1), 135.21 (d, C-2), 38.21 (t, C-3), 77.57 (d, C-4), 56.15 (q, OMe on C-4), 38.01 (t, C-5), 75.60 (d, C-6), 56.00 (q, OMe on C-6), 38.59 (t, C-7), 75.72 (d, C-8), 56.00 (q, OMe on C-8), 38.63 (t, C-9), 75.72 (d, C-10), 56.00 (q, OMe on C-10), 38.63 (t, C-11), 75.72 (d, C-12), 56.00 (q, OMe on C-12), 38.63 (t, C-13), 75.72 (d, C-14), 56.00 (q, OMe on C-14), 38.63 (t, C-15), 75.72 (d, C-16), 56.00 (q, OMe on C-16), 38.27 (t, C-17), 78.12 (t, C-18), 56.10 (q, OMe on C-18), 34.21 (t, C-19), 21.19 (t, C-20), 34.21 (t, C-21), 80.77 (d, C-22), 56.24 (q, OMe on C-22), 36.12 (t, C-23), 18.87 (t, C-24), 14.53 (q, C-25).

(3R)-3-Methoxy-1-(0-methoxymethyl)-1-hexanol (11): To a stirred mixture of 8 (4.61 g, 34.9 mmol) and CuI (330 mg, 1.75 mmol) in dry ether (100 mL) at 0 ℃ under argon was added 2M ethylmagnesium chloride in THF (22.7 mL, 45.4 mmol). After stirring for 30 mim, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated to give 5.17 g (91%) of 10 as a pale yellow oil. The oil was dissolved in THF (50 mL) and MeI (20 mL). Excess KH in mineral oil was added to the stirred solution at 0 ℃ and the reaction mixture was stirred for 1 h. Excess KH was decomposed by careful addition of water. The THF was evaporated, the residue was extracted with ether, and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residual oil was distilled in vacuo to give 4.71 g (84%) of 11 as a colorless oil: bp 51℃ (4 mmHg); $[\alpha]_D^{25}$ -12.06 ° (c=0.85, $CHCl_3$); IR ($CHCl_3$) 2925, 1460, 1145, 1085, 1030, 910 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.1 Hz, H-6), 1.30-1.54 (4H, m, H-4 and H-5), 1.75 (2H, q, J=6.4 Hz, H-2), 3.32 (1H, m, H-3), 3.34 (3H, s, OMe), 3.37 (3H, s, OMe), 3.61 (2H, t, J=7.1 Hz, H-1), 4.62 (2H, s, OCH_2O). Anal. Calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.21; H, 11.65.

(3R)-1-Iodo-3-mthoxyhexane (13): A solution of 11 (4.70 g) in MeOH (40 mL) was treated with 5% HCl-MeOH (3 mL) and the solution was heated at 50 ℃ for 6 h. After evaporation of the solvent the residual oil was distilled in vacuo to give 3.46 g (98%) of 12 as a colorless oil: bp 70℃ (10 mmHg); $[\alpha]_D^{25}$ -40.34 ° (c=0.35, $CHCl_3$).

To a stirred solution of 12 (3.10 g, 23.48 mmol) in CH_2Cl_2 (20 mL) at -20℃ were added successively Et_3N (9.8 mL, 70.45 mmol) and methanesulfonyl chloride (2.18 mL, 28.17 mmol). After 40 min, 10 mL of saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and evaporated to give a mesylate. A mixture of the mesylate and NaI (25 g) in acetone (60 mL) was refluxed for 1.5 h. After evaporation of the solvent, the residue was extracted with ether. The extract was washed with water, aqueous $Na_2S_2O_3$, and brine, dried ($MgSO_4$), and evaporated. The residual oil was distilled in vacuo to give 4.68 g (83%, two steps) of 13 as a colorless oil: bp 52 ℃ (6 mmHg); $[\alpha]_D^{25}$ -30.74 ° (c=0.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-6), 1.30-1.56 (6H, m, H-2, H-4 and H-5), 1.97 (2H, t, J= 7.1 Hz, H-1), 3.28 (1H, m, H-3), 3.37 (3H, s, OMe). Anal. Calcd for $C_7H_{15}OI$: C, 34.71; H, 6.25.

Found: C, 34.68; H, 6.31.

(3R)-1-(O-Methoxymethyl)-6-trimethylsilyl-5-hexyn-1,3-diol (14): To a stirred solution of trimethylsilylacetylene (1.96 g, 20 mmol) in dry THF (40 mL) at -78℃ under argon was added 1.5 M n-BuLi in hexane (13.3 mL, 20 mmol) and the solution was stirred for 10 min. BF_3OEt_2 (2.84 g, 20 mmol) was added to the solution. After 15 min, a solution of 8 (2.11 g, 16 mmol) in dry THF (20 ml) was added, and stirring was continued at -78 ℃ for 30 min. The reaction mixture was quenched with Et_3N (10 mL) and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (1:4 EtOAc/hexane) to give 2.68 g (73%) of 14 as a colorless oil: bp (Kugelrohr distillation) 132 ° (5 mmHg); $[\alpha]_D^{25}$-3.60 ° (c=0.86, $CHCl_3$); IR (neat) 3450, 2950, 2170, 1250, 1140, 1105, 1040, 940cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $SiMe_3$), 1.82 (1H, m, H-2), 1.91 (1H, m, H-2'), 2.45 (2H, d, J=6.1 Hz, H-4), 2.73 (1H, br, OH), 3.37 (3H, s, OMe), 3.74 (2H, m, H-1), 3.95 (1H, m, H-3), 4.63 (2H, s, OCH_2O). Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.36; H, 9.63. Found: C, 57.18; H, 9.84.

(3R)-3-Methoxy-1-(O-methoxymethy)-5-hexyn-1-ol (15): To a stirred solution of 14 (4.53 g, 19.7 mmol) and MeI (12 mL, 197 mmol) in dry THF (45 mL) at 0℃ was added in portions excess KH in mineral oil until hydrogen evolution ceased. After 30 min the excess KH was decomposed by careful addition of water, and the mixture was extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (5:95 EtOAc/hexane) gave 3.63 g (76%) of a methyl ether and 0.5 g (15 %) of 15. The methyl ether (3.6 g) was dissolved in dry THF (60 mL) and 1M Bu_4NF in THF (28 mL) was added. The solution was stirred at room temperature for 2 h. After evaporation of THF the residue was extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. The residual oil and 15 obtained above were combined and distilled in vacuo to give 2.89 g (86%, two steps) of 15 as a colorless oil: bp 84℃ (7 mmHg); $[\alpha]_D^{25}$-39.22° (c=0.23, $CHCl_3$); IR ($CHCl_3$) 3300, 2920, 2100, 1145, 1100, 1035, 910 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.90 (2H, m, H-2), 2.01 (1H, t, J=2.4 Hz, H-6), 2.46 (2H, dd, J=5.7 and 2.7 Hz, H-4), 3.37 (3H, s, OMe), 3.40 (3H, s, OMe), 3.50 (1H, ddt, J= 7.7, 5.4 and 5.0 Hz, H-3), 3.64 (2H, m, H-1), 4.62 (2H, s, OCH_2O). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.45; H, 9.58.

(3R,9R)-3,9-Dimethoxy-1-(O-methoxymethyl)-5-dodecyn-1-ol (16): To a stirred solution of 15 (2.75 g, 16.0 mmol) in dry THF (40 mL) at -78℃ under argon was added 1.6 M BuLi in hexane (11 mL, 17.6 mmol) and the solution was stirred for 50 min. The solution was warmed to -50 ℃, and HMPA (20 mL) and 13 (4.2 g, 17.6 mmol) in dry THF (5 mL) were added. The reaction mixture was stirred at -50 ℃ for 2 h and then warmed to 0 ℃. After quenching with aqueous NH_4Cl, the mixture was extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (15:85 EtOAc/hexane) gave 3.57 g (78%) of 16 as a colorless oil: bp (Kugelrohr distillation) 140 ℃ (5 mmHg); $[\alpha]_D^{25}$-40.35° (c=0.75, $CHCl_3$); IR ($CHCl_3$) 1460, 1375, 1230, 1145, 1100, 1035, 910 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-12), 1.28-1.56

(4H, m, H-10 and H-11), 1.66 (2H, m, H-8), 1.82 (1H, m, H-2), 1.95 (1H, m, H-2'), 2.23 (2H, m, H-7), 2.42 (2H, m, H-4), 3.26 (1H, quint, J=5.7 Hz, H-9), 3.33 (3H, s, OMe), 3.37 (3H, s, OMe), 3.39 (3H, s, OMe), 3.44 (1H, m, H-3), 3.64 (2H, m, H-1), 4.62 (2H, s, OCH_2O). Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.09; H, 10.56. Found; C, 67.21; H, 10.69.

(3R,9R)-3,9-Dimethoxy-1-(O-methoxymethyl)-1-dodecanol (17): To a solution of 16 (3.70 g) in EtOAc (40 mL) was added 10% Pd-C (400 mg) and the suspension was stirred under hydrogen for 20 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated. The oily residue was distilled bulb-to-bulb to give 3.70 g (99%) of 17 as a colorless oil: bp(Kugelrohr distillation) 136 ℃ (5 mmHg); $[\alpha]_D^{25}$ -7.69° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 2930, 1460, 1370, 1145, 1085, 1035, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.1 Hz, H-12), 1.26-1.56 (14H), 1.72 (1H, dd, J=13.5 and 6.6 Hz, H-2), 1.77 (1H, dd, J=13.5 and 6.3 Hz, H-2'), 3.13 (1H, quint, J=5.1 Hz, H-9), 3.30 (1H, quint, J=6.1 Hz, H-3), 3.32 (3H, s, OMe), 3.34 (3H, s, OMe), 3.37 (3H, s, OMe), 3.61 (2H, m, H-1). Anal. Calcd for $C_{16}H_{34}O_4$: C, 66.16; H, 11.80. Found: C, 65.93; H, 11.95.

(3R,9R)-3,9-Dimethoxy-1-dodecanol (18): A solution of 17 (3.70 g) in 35% HCl (5 mL) and MeOH (80 mL) was heated at 60 ℃ for 5 h. The solvents were evaporated and the residue was purified by flash chromatography (2:3 EtOAc/hexane) to give 2.52 g (80%) of 18 as a colorless oil: bp(Kugelrohr distillation) 155 ℃ (4 mmHg); $[\alpha]_D^{25}$-22.08° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 3470, 2930, 1460, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-12), 1.30-1.56 (14H), 1.68-1.82 (2H, m, H-2), 2.59 (1H, br, OH), 3.13 (1H, quint, J= 5.4 Hz, H-9), 3.32 (3H, s, OMe), 3.36 (3H, s, OMe), 3.40 (1H, m, H-3), 3.77 (2H, m, H-1). Anal. Calcd for $C_{14}H_{30}O_3$: C, 68.24; H, 12.27. Found: C, 68.07; H, 12.49.

(3R,9R)-3,9-Dimethoxy-1-dodecanal (19): To a stirred solution of oxalyl chloride (1.33 mL, 15.24 mmol) in CH_2Cl_2 (25 mL) at -60℃ under argon was added DMSO (1.30 mL, 18.29 mmol), and the mixture was stirred for 15 min. A solution of 18 (2.50 g, 10.16 mmol) in CH_2Cl_2 (10 mL) was added to the mixture. After 15 min, Et_3N (7.08 mL, 50.81 mmol) was added. The reaction mixture was warmed to 0 ℃ gradually and then extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (1:4 EtOAc/hexane) gave 2.37 g (96%) of 19 as a colorless oil: $[\alpha]_D^{25}$ -5.77° (c=0.62, $CHCl_3$): IR ($CHCl_3$) 2930, 1720, 1460, 1375, 1245, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-12), 1.25-1.64 (14H, CH_2), 2.52 (1H, ddd, J=16.5, 5.1 and 1.8 Hz, H-2), 2.61 (1H, ddd, J=16.5, 7.3 and 2.6 Hz, H-2'), 3.13 (1H, quint, J=5.5 Hz, H-9), 3.32 (3H, s, OMe), 3.35 (3H, s, OMe), 3.71 (1H, quint, J=5.1 Hz, H-3), 9.81 (1H, t, J=2.2 Hz, H-1). CIMS (isobutane) m/z 245 (MH^+), 213 (MH^+-MeOH).

2-[(2R,8R)-2,8-Dimethoxyundecyl]-1,3-dithiane (6): To a stirred solution of 19 (2.37 g, 9.7 mmol) in CH_2Cl_2 (60 mL) at 0℃ were added 1,3-propanedithiol (2.9 mL, 29.1 mmol) and BF_3OEt_2 (0.1 mL), and the solution was stirred at room temperature for 17 h. 2,2-Dimethoxypropane (10 mL) was added and stirring was continued for 1 h. After addition of Et_3N (1 mL) the solvents were evaporated, and the residue was purified by flash chromatography

(7:93 EtOAc/hexane) to give 1.87 g (58%) of 6 as a colorless oil: bp(Kugelrohr distillation) 165 ℃ (4 mmHg); $[\alpha]_D^{25}$ -6.88° (c=0.83, $CHCl_3$); IR ($CHCl_3$) 2930, 1460, 1420, 1365, 1085, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-11'), 1.26-1.58 (14H), 1.80(1H, ddd, J=14.5, 9.0 and 4.1 Hz, H-1'), 1.88 (1H, m, H-5), 1.90 (1H, ddd, J=14.5, 8.1 and 5.1 Hz, H-1'), 2.12 (1H, m, H-5), 2.80-2.96 (4H, H-4 and H-6), 3.13 (1H, qiunt, J=5.4 Hz, H-8'), 3.32 (3H, s, OMe), 3.35 (3H, s, OMe), 3.47 (1H, m, H-2'), 4.20 (1H, dd, J=9.0 and 5.1 Hz, H-1); EIMS m/z 334 (M^+), 302 (M^+-MeOH), 287 (M^+-MeOH-Me), 270 (M^+-2MeOH). Anal. Calcd for $C_{17}H_{34}O_2S_2$: C, 61.64; H, 10.25. Found: C, 61.37; H, 10.41.

(4S, 6S, 8S, 10S, 14R, 20R)-4, 6, 8, 14, 20-Pentamethoxy-12-(trimethylenedithio)-1-tricosen-10-ol (20): To a stirred solution of 6 (804 mg, 2.41 mmol) in dry THF (25 mL) at -40℃ under argon were added successively 1.6 M n-BuLi in hexane (2.25 mL, 3.62 mmol) and TMEDA (0.55 mL, 3.62 mmol). The mixture was stirred at -30 ℃ for 2 h and then cooled to -40 ℃ whereupon a solution of 7 (537 mg, 2.08 mmol) in dry THF (3 mL) was added. The reaction vessel was closed under a positive pressure of argon and stored at -20℃ for 42 h. The reaction mixture was quenched with aqueous NH_4Cl and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (3:7 EtOAc/hexane) gave 797 mg (64%) of 20 as a colorless oil: $[\alpha]_D^{25}$ +5.81° (c=0.83, $CHCl_3$); IR ($CHCl_3$) 3470, 2950, 1460, 1220, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.1 Hz, H-23), 1.30-1.98 (20H), 2.04 (2H, dd, J=15.1 and 7.3 Hz, H-11 and H-13), 2.15 (1H, dd, J=15.1 and 7.6 Hz, H-11' or H-13'), 2.33 (2H, br t, J=7.1 Hz, H-3), 2.33 (1H, dd, J=15.1 and 6.1 Hz, H-13' or H-11'), 2.30-3.04 (4H, SCH_2x2), 3.14 (1H quint, J=5.4 Hz, H-20), 3.28 (3H, s, OMe), 3.30 (3H, s, OMe), 3.32 (3H, s, OMe), 3.33 (3H, s, OMe), 3.34 (3H, s, OMe), 3.37 (1H, m, CHOMe), 3.43 (1H, quint, J=6.1 Hz, CHOMe), 3.52 (1H, quint, J=4.9 Hz, CHOMe), 3.54 (1H, quint, J=6.3 Hz, CHOMe), 3.78 (1H, s, OH), 4.12 (1H, m, H-10), 5.08 (1H, br d, J=10.0 Hz, H-1E), 5.09 (1H, br d, J=17.1 Hz, H-1Z), 5.83 (1H, ddt, J=17.1, 10.0 and 7.1 Hz, H-2); CIMS (isobutane) m/z 593 (MH^+), 575 (MH^+-H_2O), 561 (MH^+-MeOH), 533 (MH^+-H_2O-MeOH), 529 (MH^+-2MeOH), 501 (MH^+-H_2O-2MeOH), 497 (MH^+-3MeOH), 479 (MH^+-H_2O-3MeOH).

(4S, 6S, 8S, 10S, 14R, 20R)-12-Oxo-4, 6, 8, 14, 20-pentamethoxy-1-tricosen-10-ol (21):

To a stirred solution of 20 (775 mg, 1.54 mmol) in 80% aqueous MeCN (80 mL) were added $CaCO_3$ (1.54 g, 15.4 mmol) and MeI (9.6 mL, 154 mmol). The suspension was stirred at room temperature for 15 h, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by flash chromatography (55:45 EtOAc/hexane) to give 556 mg (85%) of 21 as a colorless oil: $[\alpha]_D^{25}$ +30.58 ° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 3450, 2950, 1705, 1640, 1480, 1385, 1220, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.1 Hz, H-23), 1.30-1.85 (20H), 2.31 (2H, br t, J=6.3 Hz, H-3), 2.48 (1H, dd, J=15.6 and 4.6 Hz, H-11), 2.56 (1H, dd, J=16.6 and 4.1 Hz, H-13), 2.67 (1H, dd, J=16.6 and 8.1 Hz, H-13'), 2.71 (1H, dd, J=15.6 and 7.6 Hz, H-11'), 3.13 (1H, quint, J=5.4 Hz, H-20), 3.29 (3H, s, OMe), 3.31 (6H, s, OMex2), 3.33 (6H, s, OMex2), 3.36 (1H, m, CHOMe), 3.40 (1H, m, CHOMe), 3.58 (1H, m, CHOMe), 3.69 (1H, m, CHOMe), 3.74 (1H, s, OH), 4.24 (1H, m, H-10), 5.09 (1H, br d, J=10.3 Hz, H-1E), 5.10 (1H, br d, J=17.1 Hz, H-1Z), 5.81 (1H, ddt,

J=17.1, 10.3 and 7.1 Hz, H-2); CIMS (isobutane) m/z 503 (MH^+), 471 (MH^+-MeOH), 453 (MH^+-H_2O-MeOH), 421 (MH^+-H_2O-2MeOH), 389 (MH^+-H_2O-3MeOH), 357 (MH^+-H_2O-4MeOH).

(4S,6S,8S,10R,12R,14R,20R)-4,6,8,14,20-Pentamethoxy-1-tricosen-10,12-diol (22): To a stirred solution of 21 (548 mg, 1.09 mmol) in dry THF (12 mL) and dry MeOH (3 mL) at -70℃ was added 1M diethylmethoxyborane in THF (2.2 mL, 2.2 mmol). After 15 min, $NaBH_4$ (82 mg, 2.17 mmol) was added and the solution was stirred at -70℃ for 1.5 h. The reaction mixture was quenched with acetic acid (1 mL) and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was subjected to azeotropic distillation several times with MeOH. The diastereoisomeric ratio was found to be 95:5 by ^1H NMR (400 MHz, benzene-d_6) analysis. Flash chromatography (2:3 EtOAc/hexane) gave 509 mg (92%) of 22 as a colorless oil: $[\alpha]_D^{25}$ +16.6° (c=0.86, $CHCl_3$); IR ($CHCl_3$) 3450, 2940, 1460, 1200, 1085, 920 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.1 Hz, H-23), 1.30-2.00 (24H), 2.27 (2H, t, J=5.8 Hz, H-3), 3.07 (3H, s, OMe), 3.08 (1H, m, H-20), 3.15 (6H, s, OMex2), 3.18 (3H, s, OMe), 3.20 (3H, s, OMe), 3.35 (2H, m, CHOMex2), 3.56 (1H, quint, J=5.6 Hz, CHOMe), 3.70 (1H, quint, J=6.1 Hz, CHOMe), 4.08 (1H, br t, J=9.3 Hz, H-10 or H-12), 4.16 (1H, br t, J=9.0 Hz, H-12 or H-10), 4.33 (2H, br, OHx2), 5.08 (1H, br d, J=10.2 Hz, H-1E), 5.09 (1H, br d, J=17.1 Hz, H-1Z), 5.87 (1H, ddt, J=17.1, 10.2 and 7.1 Hz, H-2); FAB mass spectrum m/z 504 (MH^+).

(4S,6S,8S,10R,12R,14R,20R)-4,6,8,10,12,14,20-Heptamethoxy-1-tricosene (2): To a stirred solution of 22 (501 mg, 0.94 mmol) in dry THF (10 mL) at 0℃ were added successively MeI (0.36 mL, 5.65 mmol) and excess KH in mineral oil. The suspension was stirred for 30 min and then excess KH was decomposed by careful addition of water. The mixture was extracted with EtOAc and the extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (3:7 EtOAc/hexane) gave 471 mg (89%) of 2: $[\alpha]_D^{25}$ +6.47° (c=0.34, $CHCl_3$). The spectroscopic data and R_f value on silica gel TLC were identical with those of natural 2.

(3R,5R,7R,9R,11R,13R,19R)-3,5,7,9,11,13,19-Heptamethoxydocosanal (23): To a stirred solution of 2 (189 mg, 0.36 mmol) in dioxane (15 mL) and H_2O (5 mL) was added OsO_4 (5 mg). After 30 min, $NaIO_4$ (228 mg, 1.06 mmol) was added to the solution. The reaction mixture was stirred for 2.5 h and then extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography (7:3 EtOAc/hexane) gave 177 mg (94%) of 23 as a colorless oil: $[\alpha]_D^{25}$ -22.6° (c=0.46, $CHCl_3$); IR ($CHCl_3$) 2940, 1720, 1460, 1380, 1200, 1085 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.0 Hz, H-22), 1.32-2.08 (24H), 2.27 (1H, ddd, J=16.5, 5.5 and 1.8 Hz, H-2), 2.35 (1H, ddd, J=16.5, 6.2 and 2.2 Hz, H-2'), 3.06 (1H, m, H-19), 3.08(3H, s, OMe), 3.14 (3H, s, OMe), 3.20 (3H, s, OMe), 3.23 (3H, s, OMe), 3.23 (3H, s, OMe), 3.24 (3H, s, OMe), 3.26 (3H, s, OMe), 3.37 (1H, quint, J=5.1 Hz, CHOMe), 3.51 (1H, quint, J=5.5 Hz, CHOMe), 3.60 (1H, quint, J=5.5 Hz, CHOMe), 3.63 (2H, quint, J=6.5 Hz, CHOMex2), 3.76 (1H, quint, J=5.8 Hz, CHOMe), 9.54 (1H, dd, J=2.2 and 1.8 Hz, H-1); FAB mass spectrum m/z 535 (MH^+).

(4S, 6S, 8S, 10R, 12R, 14R, 16R, 22R)-6, 8, 10, 12, 14, 16, 22-Heptamethoxy-1-pentacosen-4-ol (24):

To a stirred solution of (-)-diisopinocampheylmethoxyborane (190 mg, 0.60 mmol) in dry toluene (2 mL) at -78 ℃ under argon was added 1.0 M allylmagnesium bromide in THF (0.6 mL, 0.6 mmol). The reaction mixture was stirred at -78 ℃ for 15 min and then at room temperature for 1 h. After cooling at -78℃ a solution of 23 (160 mg, 0.30 mmol) in dry toluene (1 mL) was added and stirring was continued for 30 min. The reaction mixture was warmed to 0 ℃ and refluxed for 3 h after addition of Et_2O (5.0 mL), 3N NaOH (1.0 mL), and 30% H_2O_2 (2.0 mL). The reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography (EtOAc) gave 143 mg (83%) of a mixture of diasteroisomers in a ratio of 88:12 by ^1H NMR (400 MHz, benzene-d_6) analysis. Purification of the products by chromatography (15:85 acetone/hexane) using spherical silica gel (30-50 μm) gave pure 24 (103 mg) as a colorless oil: $[\alpha]_D^{25}$ +4.30° (c=0.88, $CHCl_3$); IR ($CHCl_3$) 3460, 2930, 1460, 1375, 1230, 1090 cm^{-1}; ^1H NMR (270 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.1 Hz, H-25), 1.30-2.08 (26H), 2.28 (2H, m, H-3), 3.07 (1H, m, H-22), 3.12 (3H, s, OMe), 3.20 (6H, s, OMex2), 3.22 (3H, s, OMe), 3.24 (6H, s, OMex2), 3.25 (3H, s, OMe), 3.37 (1H, m, C<u>H</u>OMe), 3.61 (5H, m, C<u>H</u>OMex5), 3.86 (1H, m, H-4), 5.06 (1H, br d, J=10.1 Hz, H-1E), 5.08 (1H, br d, J=17.1 Hz, H-1Z), 5.95 (1H, ddt, J=17.1, 10.1, 7.1 Hz, H-2); FAB mass spectrum m/z 577 (MH^+).

(4S, 6S, 8S, 10R, 12R, 14R, 16R, 22R)-4, 6, 8, 10, 12, 14, 16, 22-Octamethoxy-1-pentacosene (3):

To a stirred solution of 24 (102 mg, 0.177 mmol) in dry THF (4.0 mL) at 0℃ were added successively MeI (0.5 mL, 8.03 mmol) and excess KH in mineral oil. After stirring for 1.5 h the reaction mixture was quenched with water and extracted with EtOAc. The extract was washed with aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography (2:3 EtOAc/hexane) of the residue gave 95 mg (90%) of 3 as a colorless oil: $[\alpha]_D^{25}$ +5.02° (c=0.63, $CHCl_3$). The spectroscopic data and R_f value on silica gel TLC were identical with those of natural 3.

(4S, 6S, 8S, 10S, 12R, 14R, 16R, 18R, 24R)-4, 6, 8, 10, 12, 14, 16, 18, 24-Nonamethoxy-1-heptacosene (4):

1) OsO_4-$NaIO_4$ Oxidation of 3. The procedure for 23 was employed with 3 (84 mg, 0.148 mmol) and purification by flash chromatography (85:15 EtOAc/hexane) gave 66 mg (78%) of (3R, 5R, 7R, 9R, 11R, 13R, 15R, 21R)-3, 5, 7, 9, 11, 13, 15, 21-octamethoxytetracosanal: $[\alpha]_D^{25}$ -22.0° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 2930, 1720, 1460, 1375, 1200, 1085 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.2 Hz, H-24), 1.30-2.19 (26H), 2.28 (1H, ddd, J=16.1, 5.1 and 1.8 Hz, H-2), 2.35 (1H, ddd, J=16.1, 6.6 and 2.2 Hz, H-2'), 3.08 (3H, s, OMe), 3.08 (1H, m, H-21), 3.15 (3H, s, OMe), 3.19 (3H, s, OMe), 3.23 (6H, s, OMex2), 3.25 (3H, s, OMe), 3.26 (3H, s, OMe), 3.27 (3H, s, OMe), 3.38 (1H, quint, J=5.1 Hz, C<u>H</u>OMe), 3.51 (1H, quint, J=5.9 Hz, C<u>H</u>OMe), 3.58 (1H, quint, J=5.9 Hz, C<u>H</u>OMe), 3.64 (3H, quint, J=6.2 Hz, C<u>H</u>OMex3), 3.76 (1H, quint, J=5.9 Hz, C<u>H</u>OMe), 9.54 (1H, t, J=2.2 Hz, H-1); FAB mass spectrum m/z 593 (MH^+).

2) Allylation. The procedure for 24 was employed with the aldehyde (63 mg, 0.107 mmol) obtained above, and purification by flash chromatography (1:4 acetone/hexane) gave 64 mg (95%) of a mixture of diasteroisomers in a ratio of 86:14 by ^1H NMR (400 MHz, benzene-d_6)

analysis. Purification by chromatography (17:83 acetone/hexane) using spherical silica gel (30-50 μm) gave 45 mg of pure (4S, 6S, 8S, 10S, 12R, 14R, 16R, 18R, 24R)-6, 8, 10, 12, 14, 16, 18, 24-octamethoxy-1-heptacosen-4-ol: $[\alpha]_D^{25}$ -32.9° (c=0.78, $CHCl_3$); IR ($CHCl_3$) 3450, 2930, 1460, 1375, 1200, 1080, 920 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.2 Hz, H-27), 1.32-2.08 (28H), 2.25 (1H, dt, J=14.1 and 6.6 Hz, H-3), 2.30 (dt, J=14.1 and 6.8 Hz, H-3'), 3.07 (1H, quint, J=5.6 Hz, H-24), 3.12 (3H, s, OMe), 3.19 (3H, s, OMe), 3.20 (3H, s, OMe), 3.23(3H, s, OMe), 3.24 (3H, s, OMe), 3.25 (3H, s, OMe), 3.26 (3H, s, OMe), 3.27 (3H, s, OMe), 3.37 (1H, quint, J=5.4 Hz, CHOMe), 3.56 (1H, quint, J=5.8 Hz, CHOMe), 3.62 (4H, m, CHOMex4), 3.86 (1H, m, H-4), 5.07 (1H, br d, J=10.2 Hz, H-1E), 5.09 (1H, br d, J=17.1 Hz, H-1Z), 5.95 (1H, ddt, J=17.1, 10.2 and 7.1 Hz, H-2). CIMS (NH_3) m/z 634 (MH^+).

3) O-Methylation. The procedure for 3 was employed with the alcohol (9.3 mg, 0.015 mmol) obtained above, and purification by flash chromatography (7:3 EtOAc/hexane) gave 8.5 mg (89%) of 4 as a colorless oil: $[\alpha]_D^{25}$ +4.36° (c=0.71, $CHCl_3$). The spectroscopic data and R_f value on silica gel TLC were identical with those of natural 4.

(3R, 5R, 7R, 9R, 11R, 13R, 15R, 21R)-3-Benzoyloxy-5, 7, 9, 11, 13, 15, 21-heptamethoxy-1-tetracosene (25): 1) Benzoylation. To a stirred solution of 24 (10.7 mg, 0.019 mmol) in pyridine (0.5 mL) was added benzoyl chloride (22 μL, 0.186 mmol), and the mixture was stirred at room temperature for 15 h. After addition of MeOH (0.1 mL), the reaction mixture was diluted with Et_2O/hexane (1:1) (10 mL), filtered, and concentrated in vacuo. Flash chromatography (35:65 EtOAc/hexane) of the residue gave 11.2 mg (89%) of (4S, 6S, 8S, 10R, 12R, 14R, 16R, 22R)-4-benzoyloxy-6, 8, 10, 12, 14, 16, 22-heptamethoxy-1-pentacosene: $[\alpha]_D^{25}$ +3.95° (c=0.93, $CHCl_3$); FAB mass spectrum m/z 681 (MH^+), 649 (MH^+-MeOH).

2) Ozonolysis. A solution of the benzoate (11.2 mg, 0.017 mmol) obtained above in MeOH (5 mL) was cooled to -78℃ and saturated with ozone. Excess ozone was removed by bubbling nitrogen into the solution and then $NaBH_4$ (29 mg, 0.74 mmol) was added to the solution. The reaction mixture was warmed to room temperature, acidified to pH 5, and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (9:1 EtOAc/hexane) gave 8.6 mg (76%) of (3S, 5S, 7S, 9R, 11R, 13R, 15R, 21R)-3-benzoyloxy-5, 7, 9, 11, 13, 15, 21-heptamethoxy-1-tetracosanol: $[\alpha]_D^{25}$ -5.91° (c=0.72, $CHCl_3$); IR ($CHCl_3$) 3450, 2950, 1710, 1460, 1285, 1100 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.1 Hz, H-24), 1.33-2.18 (28H), 3.07 (1H, quint, J=5.3 Hz, H-21), 3.17 (3H, s, OMe), 3.19 (6H, s, OMex2), 3.23 (6H, s, OMex2), 3.24 (3H, s, OMe), 3.25 (3H, s, OMe), 3.38 (1H, quint, J=6.0 Hz, H-15), 3.55 (2H, m, H-1), 3.61 (5H, m, CHOMe x5), 5.71 (1H, m, H-3), 7.05-7.16 (3H, Ar-H), 8.16 (2H, dd, J=8.6 and 1.7 Hz, Ar-H); FAB mass spectrum m/z 685 (MH^+), 653 (MH^+-MeOH).

3) Preparation of 25. To a stirred solution of the alcohol (7.3 mg, 0.011 mmol) obtained above in dry THF (0.2 mL) were added o-nitrophenyl selenocyanate (6.8 mg, 0.03 mmol) and tributylphosphine (7.5 μL, 0.03 mmol) and the reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was purified by flash chromatography (1:1 EtOAc/hexane) to give 9.0 mg (97%) of a selenide.

The selenide (9.0 mg, 0.01 mmol) was dissolved in THF (0.2 mL) and 30% H_2O_2 (10 μL, 0.098 mmol) was added, and the solution was stirred at room temperature for 13 h. After

evaporation of the solvent the residue was purified by flash chromatography (2:3 EtOAc/hexane) to give 6.1 mg (88%) of 25 as a colorless oil: $[\alpha]_D^{25}$ -16.2° (c=0.49, $CHCl_3$); UV (MeOH) λ_{max} 229 nm (ε 12800); CD (MeOH) 226 nm ($\Delta\varepsilon$ -3.19); IR ($CHCl_3$) 2930, 1710, 1600, 1450, 1275, 1100 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.92 (3H, t, J=7.1 Hz, H-24), 1.32-2.24 (26H), 3.07 (1H, m, H-21), 3.18 (3H, s, OMe), 3.19 (3H, s, OMe), 3.20 (3H, s, OMe), 3.22 (3H, s, OMe), 3.23 (3H, s, OMe), 3.24 (3H, s, OMe), 3.25 (3H, s, OMe), 3.38 (1H, quint, J=5.4 Hz, H-15), 3.61 (5H, m, CHOMex5), 5.07 (1H, d, J=10.5 Hz, H-1E), 5.37 (1H, d, J=17.1 Hz, H-1Z), 5.90 (1H, ddd, J=17.1, 10.5 and 6.6 Hz, H-2), 6.02 (1H, q, J=6.6 Hz, H-3), 7.03-7.16 (3H, Ar-H), 8.02 (2H, dd, J=8.6 and 1.7 Hz, Ar-H). FAB mass spectrum m/z 667 (MH^+), 635 (MH^+-MeOH), 545 (MH^+-C_6H_5COOH).

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