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Synthesis and Absolute Configuration of an Isotactic Nonamethoxy-1-pentacosene from the Blue-Green Alga *Scytonema ocellatum*

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Abstract: Synthesis of the novel isotactic nonamethoy-1-pentacosene (**3**) isolated from the terrestrial blue-green alga *Scytonema ocellatum* was accomplished in a stereocontrolled manner and the absolute configuration was established.

The terrestrial tolytoxin-producing blue-green algae belonging to the family Scytonemataceae produce novel isotactic polymethoxy-1-alkenes. Isotactic polymethoxy-1-alkenes having the general formula **1**, where n=5, 6, 8, 9, and 10 have been isolated from *Tolypothrix conglutinata* var. *colorata* Ghose,[1] *Scytonema mirabile* (Dillwyn) Bornet [2] and *S. burmanicum* Skuja.[2] Another tolytoxin-producing alga *S. ocellatum* Lyngbye ex Bornet & Flahault (strain FF-66-3) produces different polymethoxy-1-alkenes **2** (n=6,7,8) and **3**.[3] Spectroscopic assignment of the absolute stereochemistry of these polyol derivatives was not possible because the hydroxyl groups of these polyol derivatives are permethylated. Therefore, synthetic approach plays an essential role in their stereochemical elucidations. The absolute stereochemistries of **1** (n=5,6,8,9) and **2** (n=6,7,8) have been determined by synthesis using a new strategy developed in our laboratory.[2-4] Other syntheses of **1** (n=8,9 and 10) have also been reported recently.[5]

Among the polymethoxy-1-alkenes isolated so far, 4,6,8,10,12,14,16,18,22-nonamethoxy-1-pentacosene (**3**) was distinguished from the homologs **2** in having an additional methoxy group. The gross structure and relative stereochemistry of **3** were determined by mass and NMR spectral analyses, and the absolute stereochemistry was assigned based on the optical rotation ($[\alpha]_D$ +11.2°),[3] although the $[\alpha]_D$ value was rather large compared with those of the **2**-type homologs. We had noted that optical rotation of isotactic polymethoxyalkenes decreased with the increasing number of methoxy group as shown in Table I. This cast doubt on the structure of **3** and prompted us to confirm the proposed stereochemistry by synthesis. In this paper, we report the synthesis and absolute configuration of nonamethoxy-1-pentacosene **3**.

Our synthetic plan was to construct the linear backbone from an optically active epoxide **4** and an alkylated dithiane **5**. Further simplification of the fragment **5** was somewhat obvious. In the interest of convergence, the decision was made to dissect **5** at the C_{19-20} bond to provide

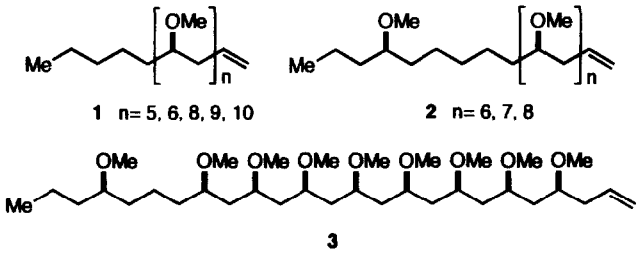
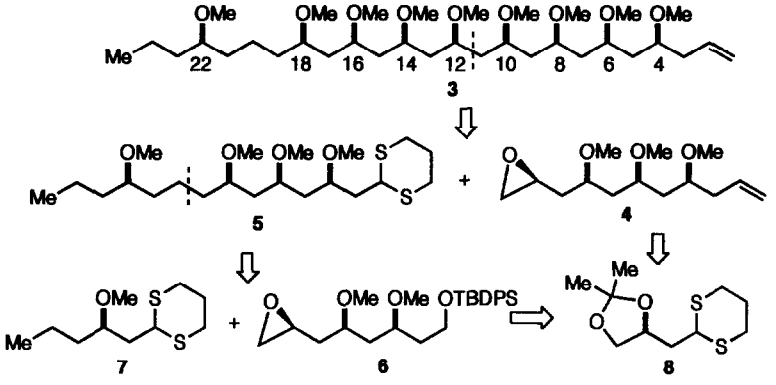


Table I. Optical Rotations of Polymethoxy-1-alkenes **1** and **2**

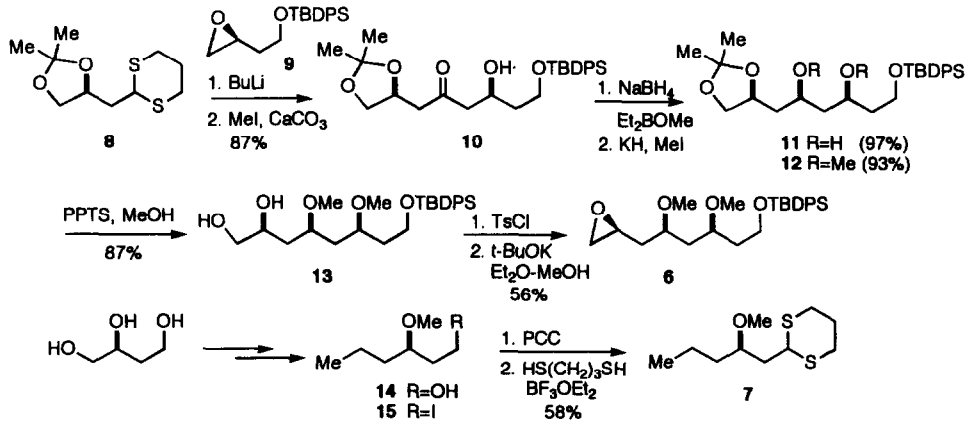
compound	n	$[\alpha]_D$ ($CHCl_3$)	compound	n	$[\alpha]_D$ ($CHCl_3$)
	5	+ 7.39°		6	+ 8.89°
1	6	+ 6.23°	**2**	7	+ 5.78°
	8	+ 5.44°		8	+ 4.47°
	9	+ 4.73°			

fragments 6 and 7. Each of these fragments 4 and 6 contained the common theme of alternating methoxy-bearing stereocenters characteristic of an acetate-derived sequence, and could be prepared by replication strategy using a four-carbon chiral building block 8. Fragment 4 had been a common intermediate in our synthesis of polymethoxy-1-alkenes of the 1 and 2 types.[2]

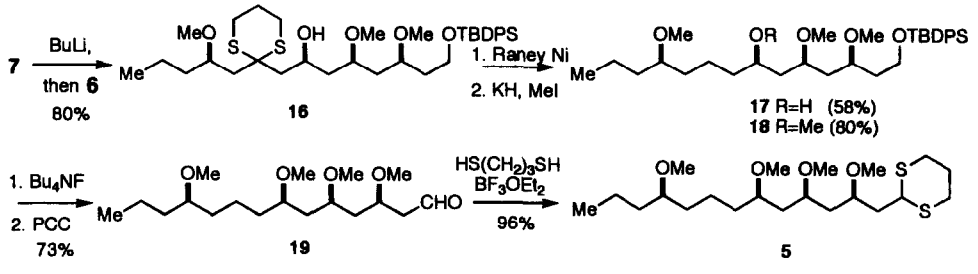


Synthesis of the fragment **6** started with the coupling reaction of the anion generated from the chiral dithiane **8** and the chiral epoxide **9**, both prepared from (*S*)-butane-1,2,4-triol 1,2-acetonide (99% ee),[4] to yield a bisalkylated dithiane in 98% yield. Deprotection of the dithioketal group with methyl iodide-calcium carbonate in aqueous acetonitrile[6] gave β-hydroxy ketone **10** in 89% yield. Reduction of the ketone with our original method using lithium aluminum hydride-lithium iodide[7] gave **11** in good yield with high *syn*-selectivity (*syn*:*anti*=95:5). The diastereoselectivity of the reduction was determined by the intensity of the ^{1}H-NMR signals of one of the corresponding acetonide methyl groups in benzene-d_6 (*syn*, 1.35ppm; *anti*, 1.42ppm). A better result was obtained by the reduction with diethylmethoxyborane-sodium borohydride

according to the procedure of Prasad and co-workers[8] to afford a 97:3 selectivity, from which **11** was isolated in 97% yield. Methylation of **11** with potassium hydride and methyl iodide in THF afforded **12** which was deprotected with pyridinium *p*-toluenesulfonate in methanol to give an 87% yield of **13**. Conversion of diol **13** into epoxide **6** was achieved in 56% overall yield by routine synthetic operation, *viz.*, tosylation and cyclization by base. After attempts to couple **6** with the Grignard reagent prepared from **15**[3] in the presence of CuI or the corresponding cuprate reagent failed, giving mainly the iodohydrin of **6**, the decision was made to employ the dithiane derivative **7** which was easily obtained from **14**[3] by oxidation and dithioacetalization.

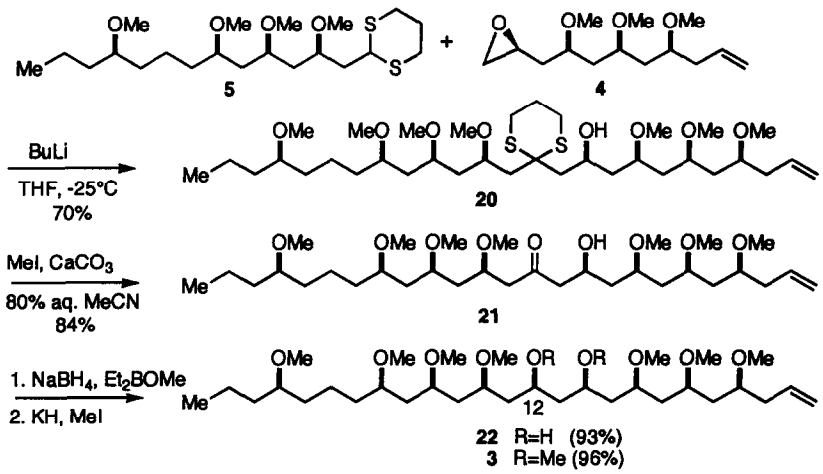


Deprotonation of **7** with butyllithium at -25°C for 2 h followed by addition of epoxide **6** gave the adduct **16** in 80% yield. Treatment with Raney nickel led to smooth desulfurization and methylation of the remaining hydroxyl group provided the $C_{12\text{-}25}$ fragment **18** in 46% overall yield. There now remained the task of oxidizing this intermediate to the desired left fragment **5**. This was achieved without incident by sequential desilylation, treatment with pyridinium chlorochromate, and dithioacetalization with 1,3-propanedithiol.



The final bond construction was carried out by coupling the lithium salt of the left fragment **5** with the right fragment **4**, which had been prepared previously,[2a] to give **20** in 70% yield. With the carbon backbone in hand, attention was directed toward setting up the hydroxy-directed reduction to establish the final stereocenter at C_{12}. The β-hydroxy ketone **21** was produced in 84% yield by treatment with methyl iodide-calcium carbonate in aqueous acetonitrile. Reduction

of the ketone with sodium borohydride in the presence of diethylmethoxyborane at -78°C proceeded in excellent yield and stereoselectivity (97:3) and the *syn*-diol **22** was isolated in 93% yield after chromatographic separation. The ^{13}C NMR chemical shifts of acetonide methyl groups of the acetonide derivative of **22** confirmed the presence of a *syn*-acetonide ring (30.7 and 19.9 ppm).[9] Finally, methylation of the hydroxyl groups with methyl iodide and potassium hydride in THF afforded optically active synthetic 4,6,8,10,12,14,16,18,22-nonamethoxy-1-pentacosene (**3**), $[\alpha]_D$+5.42° (c=0.5, $CHCl_3$). The 400MHz ^1H and 100MHz ^{13}C NMR spectra in benzene-d_6 and TLC mobility of synthetic **3** were identical with those of natural **3** ($[\alpha]_D$+11.2°, (c=0.38, $CHCl_3$)) except for optical rotation.



The accuracy of the optical rotation determination of natural **3** was unlikely to improve considering the results listed in Table I. Then, we decided to purify a sample (4.5 mg) of natural material. After repeated flash chromatography, 3.0 mg of the purified **3** was obtained. The optical rotation of the purified sample was +5.12° (c=0.25, $CHCl_3$), virtually identical to that of the synthetic material. Thus, the absolute configuration of **3** was determined to be 4*S*,6*S*,8*S*,10*S*,12*R*,14*R*,16*R*,18*R*,22*R*. It is worthwhile to note that the ^1H NMR spectra of **3** and the stereoisomer of **3** having (12*S*)-configuration, prepared from the minor isomer of the reduction products of **21**, were characterized by rather pronounced differences in the chemical shifts of their nine methoxy groups as illustrated in Figure 1. This allowed an unequivocal identification of the synthetic and natural samples.

In conclusion, the synthesis of (+)-nonamethoxy-1-pentacosene **3** was achieved by using the dithiane-epoxide coupling reactions and the relative and absolute configurations of **3** were rigorously established.

Experimental Section

General. NMR spectra were determined on JEOL JNM-GX 400 and GX-270 spectrometers. IR spectra were recorded on a JASCO IR-810. Mass spectra, including high resolution mass measurements, were determined in either the EI or FAB mode with a JEOL HX-110 instrument.

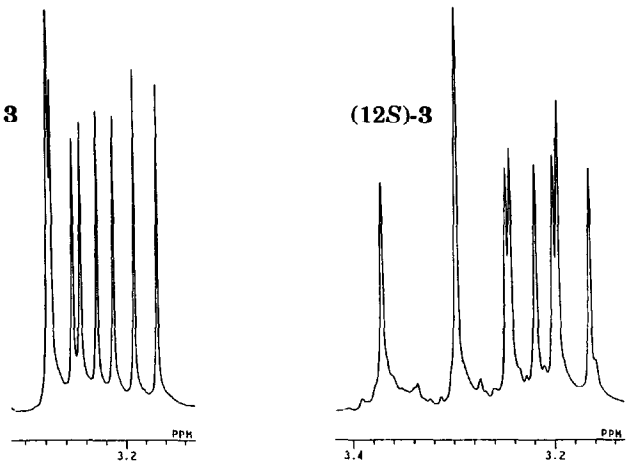


Figure 1. Methoxy group region of ^{1}H NMR (400MHz, C_6D_6) spectra of **3** and (12*S*)-**3**.

Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Analytical thin-layer chromatography was performed on E. Merck silica gel 60F plates (0.25 mm). Flash chromatography was carried out with the use of E. Merck silica gel 60 (230-400 mesh). The term "dried" refers to the drying of an organic solution over $MgSO_4$.

(2*S*,6*S*)-8-(*O*-*tert*-Butyldiphenylsilyl)-1,2-(*O*-isopropylidene)-octan-4-one-1,2,6,8-tetrol (10). A stirred solution of **8** (3.38 g, 14.4 mmol) in 40 ml of tetrahydrofuran (THF) under argon was treated with 1.6M *n*-BuLi in hexane (9.0 ml, 14.4 mmol) at -40°C. The solution was stirred at -30°C for 2 h and then a solution of **9** (3.40 g, 10.4 mmol) in 10 ml of THF was added. The reaction vessel was closed under positive pressure of argon and stored at -20°C for 20 h. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and evaporated. The residue was purified by flash chromatography (20% EtOAc/hexane) to give 6.20 g (98%) of the adduct as a colorless oil. $[\alpha]_D^{22}$ +12.76° (c=0.7, $CHCl_3$). IR (neat): 3470, 1585, 1423, 1375, 1365, 1108, 820, 735, 700 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.06 (9H, s) 1.33 (3H, s), 1.36 (3H, s), 1.76 (2H, m), 1.93 (1H, m), 2.01 (1H, m), 2.11 (1H, dd, *J*=15.2, 1.7Hz), 2.24 (1H, dd, *J*=14.9, 4.6Hz), 2.32 (1H, dd, *J*=14.9, 6.4Hz), 2.33 (1H, dd, *J*=15.2, 8.5Hz), 2.74-3.01 (4H, m), 3.47 (1H, d, *J*=2.2Hz, OH), 3.55 (1H, t, *J*=8.0Hz), 3.85 (2H, t, *J*=6.1Hz), 4.14 (1H, dd, *J*=8.0, 5.9Hz), 4.26 (1H, m), 4.42 (1H, m), 7.37-7.45 (6H, m), 7.67-7.70 (4H, m). FABMS *m/z*: 561 (MH^+).

A mixture of the adduct (2.06 g, 3.68 mmol), $CaCO_3$ (3.68 g, 3.68 mmol), and MeI (22.9 ml, 368 mmol) in 200 ml of 80% aqueous MeCN was stirred for 24 h at room temperature. The mixture was filtered through a short column of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (25% EtOAc/hexane) to give **10** (1.54 g, 89%) as a colorless oil. $[\alpha]_D^{24}$ +18.33° (c=0.3, $CHCl_3$). IR (neat): 3450, 1705, 1582 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.05 (9H, s), 1.35 (3H, s), 1.41 (3H, s), 1.68 (1H, m), 1.74 (1H, m), 2.59 (1H, dd, *J*=16.6, 4.2Hz), 2.62 (1H, dd, *J*=16.9, 6.8Hz), 2.68 (1H, dd, *J*=16.6,

8.1Hz), 2.92 (1H, dd, *J*=16.9, 6.4Hz), 3.45 (1H, d, *J*=2.9Hz, OH), 3.55 (1H, dd, *J*=8.3, 6.8Hz), 3.84 (2H, m), 4.18 (1H, dd, *J*=8.3, 6.1Hz), 4.35 (1H, m), 4.48 (1H, quintet, *J*=6.6Hz), 7.30-7.47 (6H, m), 7.52-7.68 (4H, m). FABMS *m/z*: 471 (MH^+). HRFABMS *m/z*: calcd for $C_{27}H_{39}O_5Si$, 471.2564; found, 471.2591.

(2*S*,4*S*,6*S*)-8-(*O*-*tert*-Butyldiphenylsilyl)-1,2-(*O*-isopropylidene)-octane-1,2,4,6,8-pentol (11) To a stirred solution of **10** (2.69 g, 5.73 mmol) in THF (64 ml) and MeOH (11.5 ml) at -78°C was added 1M diethylmethoxyborane in THF (6.4 ml, 6.30 mmol). After 20 min, $NaBH_4$ (240 mg, 6.30 mmol) was added and the solution was stirred at -78°C for 2.5 h. The reaction mixture was extracted with EtOAc The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The residue was subjected to azeotropic evaporation with MeOH several times. Flash chromatography (30% EtOAc/hexane) of the residue gave 2.62 g of **11** (97%) as a colorless oil. $[\alpha]_D^{25}$ +6.47° (c=0.34, $CHCl_3$). IR ($CHCl_3$): 3480 cm^{-1}.^{1}H NMR (400MHz, $CDCl_3$) δ: 1.05 (9H, s), 1.37 (3H, s), 1.43 (3H, s), 1.53-1.82 (6H, m), 3.59 (1H, dd, *J*=8.1, 7.6Hz), 3.87 (2H, m), 3.98 (2H, OH), 4.08 (1H, m), 4.12 (1H, dd, *J*=8.1, 6.1Hz), 4.16 (1H, m), 4.30 (1H, m), 7.38-7.46 (6H, m), 7.66-7.69 (4H, m). FABMS *m/z*: 473 (MH^+).

(2*S*,4*S*,6*S*)-8-*tert*-Butyldiphenylsiloxy-4,6-dimethoxy-1,2-(*O*-isopropylidene)-octane-1,2-diol (12) To a stirred solution of **11** (2.62 g, 5.55 mmol) in THF (32 ml) and MeI (3.46 ml, 55.48 mmol) was added excess KH in mineral oil. The suspension was stirred for 50 min and then excess KH was decomposed by careful addition of MeOH. The mixture was extracted with ether and the extract was washed with water and brine, dried, and evaporated. Purification by flash chromatography (20% EtOAc/hexane) gave **12** (2.58 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ +1.67° (c=1.0, $CHCl_3$). IR ($CHCl_3$) : 1430, 1380, 1115, 825, 705 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.05 (9H, s), 1.34 (3H, s), 1.40 (3H, s), 1.51-1.96 (6H, m), 3.275 (3H, s), 3.279 (3H, s), 3.37 (1H, quintet, *J*=5.9Hz), 3.52 (1H, t, *J*=7.8Hz), 3.53 (1H, m), 3.73 (1H, m), 3.80 (1H, m), 4.06 (1H, dd, *J*=8.1, 5.9Hz), 4.21 (1H, quintet, *J*=6.7Hz). 7.35-7.44 (6H, m), 7.65-7.69 (4H, m). FABMS *m/z*: 501 (MH^+). HRFABMS *m/z*: calcd for $C_{29}H_{45}O_5Si$, 501.3034; found, 501.3009.

(2*S*,4*S*,6*S*)-8-*tert*-Butyldiphenylsiloxy-4,6-dimethoxyoctane-1,2-diol (13) A solution of **12** (2.58 g, 5.152 mmol) and pyridinium *p*-toluenesulfonate (50 mg, 0.199 mmol) in MeOH (100 ml) was heated at 50°C for 5 h. After addition of triethylamine (0.5 ml) the solution was concentrated. The residue was purified by flash chromatography (70% EtOAc/hexane) to give **13** (2.06 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ +20.61° (c=1.0, $CHCl_3$). IR ($CHCl_3$): 3450, 1480, 1425, 1110, 820, 700 cm^{-1}. ^{1}H NMR (270MHz, $CDCl_3$) δ: 1.05 (9H, s), 1.54 (1H, m), 1.62-1.82 (4H, m), 1.86 (1H, m), 3.27 (3H, s), 3.33 (3H, s), 3.47 (1H, dd, *J*=11.1, 6.1Hz), 3.49 (1H, m), 3.59 (1H, m), 3.60 (1H, dd, *J*=11.1, 8.7Hz), 3.74 (1H, m), 3.76 (1H, m), 3.90 (1H, m), 7.35-7.46 (6H, m), 7.64-7.68 (4H, m). FABMS *m/z*: 461 (MH^+).

(2*S*,4*S*,6*S*)-1,2-Epoxy-8-*tert*-butyldiphenylsiloxy-4,6-dimethoxyoctane (6) To a stirred solution of **13** (2.26 g, 4.92 mmol) in pyridine (15 ml) at 0°C was added *p*-toluenesulfonyl chloride (2.81 g, 14.76 mmol). The mixture was stirred at 0°C for 2 h and extracted with EtOAc. The extract was washed with water and brine, dried, and evaporated. The residual pyridine was azeotropically removed with heptane (3x50 ml). Purification of the residual oil by flash chromatography (30% EtOAc/hexane) provided the tosylate (2.00 g, 66%).

To a stirred solution of the tosylate obtained above in ether (58 ml) and MeOH (12 ml) at 0°C was added potassium *t*-butoxide (726 mg, 6.79 mmol) . The mixture was stirred for 30 min and extracted with ether. The extract was washed with water and brine, dried, and evaporated. The oily residue was purified by flash chromatography (18% EtOAc/hexane) to give **6** (1.22 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ -10.22° (c=0.86, $CHCl_3$). IR ($CHCl_3$): 1470, 1425, 1110, 820, 703 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ:1.05 (9H, s), 1.60 (1H, dt, *J*=14.2, 5.7Hz), 1.68-1.84 (4H, m), 1.89 (1H, dt, *J*=14.2, 5.8Hz), 2.48 (1H, dd, *J*=5.1, 2.9Hz), 2.76 (1H, dd, *J*=5.1, 3.9Hz), 3.01 (1H, m), 3.28 (3H, s), 3.32 (3H, s), 3.45 (1H, quintet, *J*=6.2Hz), 3.56 (1H, quintet, *J*=5.7Hz), 3.57 (1H, m), 3.81 (1H, m), 7.35-7.44 (6H, m), 7.65-7.69 (4H, m). FABMS *m/z*: 443 (MH^+). HRFABMS *m/z*: calcd for $C_{26}H_{39}O_4Si$, 443.2615; found, 443.2633.

2-[(2*R*)-2-Methoxypentyl]-1,3-dithiane (7) To a stirred suspension of pyridinium chlorochromate (PCC)(3.69 g, 17.12 mmol) in dichloromethane (20 ml) was added a solution of **14** (1.13 g, 8.56 mmol) in dichloromethane (20 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ether , filtered through a short column of Florisil, and evaporated to give an aldehyde (1.10g) of purity suitable for use in the following reaction.

1,3-Propanedithiol (1.27 ml, 12.7 mmol) and 5 drops of borontrifluoride etherate was added to a solution of the crude aldehyde in dichloromethane (50 ml) at 0°C and the mixture was stirred at room temperature for 14 h. 2,2-Dimethoxypropane (6 ml) was added to the mixture and, after an additional 1 h, triethylamine (1 ml) was added. The reaction mixture was concentrated *in vacuo* and the resulting residue was flash chromatographed (3%-7% EtOAc/hexane) to afford **7** (1.89 g, 58%) as a colorless oil after distillation (Kugelrohr, 210°C, 6 mmHg). $[\alpha]_D^{25}$ -12.89° (c=0.29, $CHCl_3$). IR ($CHCl_3$): 1460, 1420, 1275, 1035, 1090, 905 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ: 0.93 (3H, t, *J*=7.3Hz), 1.33-1.58 (4H, m), 1.76-1.94 (3H, m), 2.13 (1H, m), 2.80-2.96 (4H, m), 3.36 (3H, s), 3.48 (1H, m), 4.20 (1H, dd, *J*=9.2, 5.4Hz). Anal. calcd for $C_{10}H_{20}OS_2$: C, 54.52; H, 9.16. Found: C, 54.11; H, 9.13.

(3*S*,5*S*,7*S*,11*R*)-1-*tert*-Butyldiphenylsiloxy-3,5,11-trimethoxy-9-(trimethylenedithio)-tetradecan-7-ol (16) The title compound was prepared in the same way as described for the coupling reaction of **8** and **9** using **7** (728 mg, 3.31 mmol) and **6** (1.22 g, 2.76 mmol). Flash chromatographic purification (16%-20% EtOAc/hexane) afforded **16** (1.47 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ -4.36° (c=1.0, $CHCl_3$). IR ($CHCl_3$): 3450, 1425, 1220, 1110, 1095, 700 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ: 0.94 (3H, t, *J*=7.1Hz), 1.05 (9H, s), 1.26-1.61 (6H, m), 1.72-1.89 (4H, m), 1.92-2.08 (4H, m), 2.16 (1H, dd, *J*=15.1, 7.4Hz), 2.32 (1H, dd, *J*=15.1, 8.1Hz), 2.69-3.06 (4H, m), 3.26 (3H, s), 3.29 (3H, s), 3.32 (3H, s), 3.52 (3H, m), 3.76 (2H, m), 3.81 (1H, s, OH), 4.12 (1H, m), 7.35-7.44 (6H, m), 7.64-7.69 (4H, m). FABMS *m/z*: 663 (MH^+). HRFABMS *m/z*: calcd for $C_{36}H_{59}O_5S_2Si$, 663.3570; found, 663.3597.

(3*S*,5*R*,7*R*,11*R*)-1-*tert*-Butyldiphenylsiloxy-3,5,9,11-trimethoxytetradecan-7-ol (18) To a solution of **16** (1,43 g, 2.16 mmol) in anhydrous ethanol (50 ml) was added W-4 Raney nickel (6 g wet weight) and the mixture was refluxed with stirring for 6.5 h. The mixture was cooled to room temperature, then filtered through a short pad of Celite, and concentrated under reduced pressure. The oily residue was purified by flash chromatography (30% EtOAc/hexane) to give **17** (701 mg, 58%) as a colorless oil. $[\alpha]_D^{25}$ +18.76° (c=0.83, $CHCl_3$). IR ($CHCl_3$): 3450, 1460, 1425,

1220, 1110, 1085, 700 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ: 0.90 (3H, t, *J*=7.4Hz), 1.05 (9H, s), 1.28-1.88 (16H, m), 3.15 (1H, m), 3.27 (3H, s), 3.31 (3H, s), 3.33 (3H, s), 3.49 (1H, m), 3.57 (1H, m), 3.63-3.82 (4H, m), 7.35-7.45 (6H, m), 7.64-7.68 (4H, m).

The procedure for **12** was employed with **17** obtained above and purification by flash chromatography (7% acetone/hexane) gave **18** (578 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ -5.96° (c=0.75, $CHCl_3$). IR ($CHCl_3$): 1460, 1425, 1380, 1110, 1085, 820, 700 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.3Hz), 1.20 (9H, s), 1.33-1.68 (12H, m), 1.88 (2H, m), 1.98 (2H, m), 3.08 (1H, m), 3.192 (3H, s), 3.195 (3H, s), 3.202 (3H, s), 3.207 (3H, s), 3.37 (1H, m), 3.56 (1H, quintet, *J*=6.1Hz), 3.68 (1H, quintet, J=5.7Hz), 3.88 (1H, m), 3.98 (1H, m), 7.15-7.25 (6H, m), 7.80-7.83 (4H, m). FABMS *m/z*: 573 (MH^+).

(3*R*,5*R*,7*R*,11*R*)-3,5,7,11-Tetramethoxytetradecanal (19) To a stirred solution of **18** (578 mg, 1.01 mmol) in THF (10 ml) was added a solution of 1M tetrabutylammonium fluoride in THF (2.1 ml, 2.1 mmol) and the mixture was stirred at room temperature for 14 h. After evaporation of the solvent, the residue was purified by flash chromatography (95% EtOAc/hexane) to give 332 mg (88%) of the alcohol. $[\alpha]_D^{25}$ -47.1° (c=0.26, $CHCl_3$). IR ($CHCl_3$): 3450, 1480, 1380, 1085, 900 cm^{-1}. ^1H NMR (270MHz, C_6D_6) δ: 0.91 (3H, t, *J*=6.7Hz), 1.32-1.66 (12H, m), 1.73 (2H, m), 1.94 (2H, m), 3.05 (1H, m), 3.13 (3H, s), 3.15 (3H, s), 3.17 (3H, s), 3.19 (3H, s), 3.30 (1H, m), 3.52 (2H, m), 3.71 (2H, m).

The procedure for the oxidation of **14** with PCC was employed with the alcohol obtained above (323 mg, 0.967 mmol) and purification by flash chromatography (40-60% EtOAc/hexane) afforded **19** (265 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ -26.4° (c=0.54, $CHCl_3$). IR ($CHCl_3$): 1725, 1460, 1380, 1085 cm^{-1}. ^1H NMR (270MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.1Hz), 1.32-1.65 (12H, m), 1.88 (2H, m), 2.30 (2H, m), 3.06 (3H, s), 3.07 (1H, m), 3.10 (3H, s), 3.17 (3H, s), 3.19 (3H, s), 3.25 (1H, m), 3.45 (1H, m), 3.75 (1H, quintet, *J*=5.9Hz), 9.55 (1H, t, *J*=2.3Hz). FABMS *m/z*: 333 (MH^+).

2-[(3*R*,5*R*,7*R*,11*R*)-3,5,7,11-Tetramethoxytetradecyl]-1,3-dithiane (5) The procedure for **7** was employed with **19** (265 mg, 0.798 mmol) and purification by flash chromatography (25% EtOAc/hexane) gave **5** (325 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ -5.49° (c=0.36, $CHCl_3$). IR ($CHCl_3$): 1460, 1375, 1085 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.1Hz), 1.33-1.69 (14H, m), 1.97 (2H, m), 2.16 (1H, m), 2.21 (1H, m), 2.31-2.48 (4H, m), 3.08 (1H, m), 3.18 (3H, s), 3.19 (3H, s), 3.20 (3H, s), 3.28 (1H, m), 3.29 (3H, s), 3.52 (1H, m), 3.89 (1H, m), 4.41 (1H, dd, *J*=8.8, 5.4Hz). FABMS *m/z*: 423 (MH^+). HRFABMS *m/z*: calcd for $C_{21}H_{43}O_4S_2$, 423.2600; found, 423.2623.

(4*S*,6*S*,8*S*,10*S*,14*R*,16*R*,18*R*,22*R*)-,4,6,8,14,16,18,22-Heptamethoxy-10-hydroxy-12-(trimetylenedithio)-1-pentacosene (20) The procedure for **16** was employed with **4** (189 mg, 0.734 mmol) and **5** (325 mg, 0.734 mmol) and purification by flash chromatography (60% EtOAc/hexane) gave **20** (346 mg, 70%) as a colorless oil. $[\alpha]_D^{25}$ -10.25° (c=0.28, $CHCl_3$). IR ($CHCl_3$): 3450, 1455, 1380, 1085 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.92 (3H, t, *J*=6.9Hz), 1.33-1.65 (14H, m), 1.74 (3H, m), 1.86-2.15 (6H, m), 2.26-2.61 (8H, m), 2.70 (1H, m), 3.08 (1H, m), 3.17 (1H, m), 3.20 (9H, s, 3xOMe), 3.23 (3H, s), 3.25 (3H, s), 3.28 (3H, s), 3.29 (3H, s), 3.44 (1H, m), 3.58 (1H, m), 3.66 (1H, quintet, *J*=5.6Hz), 3.82 (1H, quintet, *J*=5.9Hz), 3.87 (1H, s, OH), 3.99

(1H, m), 4.51 (1H, m), 5.08 (1H, d, *J*=10.0Hz), 5.12 (1H, d, *J*=17.1Hz), 5.92 (1H, ddt, *J*=17.1, 10.0, 7.1Hz). FABMS *m/z*: 681 (MH^+). HRFABMS *m/z*: calcd for $C_{35}H_{69}O_8S_2$, 681.4430; found, 681.4441.

(4*S*,6*S*,8*S*,10*S*,14*R*,16*R*,18*R*,22*R*)-,4,6,8,14,16,18,22-Heptamethoxy-10-hydroxy-12-oxo-1-pentacosene (21) To a stirred solution of **20** (338 mg, 0.497 mmol) in acetonitrile (20 ml) and water (5 ml) were added $CaCO_3$ (498 mg, 4.97 mmol) and MeI (3.1 ml, 49.7 mmol). The suspension was stirred at room temperature for 18 h, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by flash chromatography (90% EtOAc/hexane) to give **21** (247 mg, 84%) as a colorless oil. $[\alpha]_D^{25}$ +19.40° (c=0.13, $CHCl_3$). IR ($CHCl_3$): 3450, 1705, 1460, 1380, 1090 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.1Hz), 1.33-1.78 (15H, m), 1.80-2.01 (5H, m), 2.25 (2H, t, *J*=6.2Hz), 2.41 (1H, dd, *J*=16.4, 4.2Hz), 2.52 (1H, dd, *J*=15.9, 5.6Hz), 2.61 (1H, dd, *J*=16.4, 8.1Hz), 2.65 (1H, dd, *J*=15.9, 6.6Hz), 3.09 (1H, m), 3.11 (3H, s), 3.15 (3H, s), 3.17 (3H, s), 3.18 (3H, s), 3.19 (3H, s), 3.20 (3H, s), 3.22 (3H, s), 3.32 (2H, m), 3.55 (2H, m), 3.66 (1H, quintet, *J*=6.5Hz), 3.75 (1H, s, OH), 3.99 (1H, quintet, J=6.1Hz), 4.42 (1H, m), 5.07 (1H, d, *J*=10.3Hz), 5.08 (1H, d, *J*=17.1Hz), 5.84 (1H, ddt, *J*=17.1, 10.3, 7.1Hz). FABMS *m/z*: 591(MH^+).

(4*S*,6*S*,8*S*,10*S*,12*R*,14*R*,16*R*,18*R*,22*R*)-,4,6,8,14,16,18,22-Heptamethoxy-10,12-dihydroxy-1-pentacosene (22) The procedure for **11** was employed with **21** (80 mg, 0.136 mmol) and purification by flash chromatography (80%-90% EtOAc/hexane) gave **22** (75 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ +4.03° (c=0.37, $CHCl_3$). IR ($CHCl_3$): 3450, 1460, 1380, 1090 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.1Hz), 1.33-1.83 (18H, m), 1.84-2.04 (6H, m), 2.27 (2H, t, *J*=6.3Hz), 3.08 (1H, m), 3.13 (3H, s), 3.14 (3H, s), 3.16 (3H, s), 3.17 (3H, s), 3.20 (3H, s), 3.21 (6H, s, 2xOMe), 3.35 (2H, m), 3.57 (2H, m), 3.70 (2H, m), 4.13 (2H, m), 4.35 (1H, s, OH), 4.36 (1H, s, OH), 5.08 (1H, d, *J*=10.3Hz), 5.09 (1H, d, *J*=17.3Hz), 5.87 (1H, ddt, *J*=17.3, 10.3, 7.1Hz). FABMS *m/z*: 593 (MH^+).

(4*S*,6*S*,8*S*,10*S*,12*R*,14*R*,16*R*,18*R*,22*R*)-,4,6,8,10,12,14,16,18,22-Nonamethoxy-1-pentacosene (3) The procedure for **12** was employed with **22** (27.2 mg, 0.0459 mmol) and purification by flash chromatography (60% EtOAc/hexane) gave **3** (27.4 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ +5.42° (c=0.50, $CHCl_3$). IR ($CHCl_3$): 1460, 1380, 1090 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=7.1Hz), 1.32-1.64 (10H, m), 1.64-1.75 (3H, m), 1.75-1.88 (4H, m), 1.93-2.11 (7H, m), 2.30 (2H, t, *J*=6.2Hz), 3.08 (1H, m), 3.17 (3H, s), 3.19 (3H, s), 3.21 (3H, s), 3.23 (3H, s), 3.24 (3H, s), 3.25 (3H, s), 3.27 (3H, s), 3.28 (6H, s, 2xOMe), 3.39 (2H, m), 3.56-3.70 (6H, m), 5.08 (1H, br d, *J*=10.2Hz), 5.10 (1H, br d, *J*=17.1Hz), 5.91 (1H, ddt, *J*=17.1, 10.2, 7.1Hz). ^{13}C NMR (100MHz, C_6D_6) δ: 14.52, 18.86, 21.18, 34.18, 34.21, 36.11, 38.01, 38.20, 38.27, 38.55, 38.60 (three carbons), 55.91, 55.99 (five carbons), 56.09, 56.15, 56.25, 75.59, 75.69 (five carbons), 77.56, 78.11, 80.74, 117.02, 135.23. FABMS *m/z*: 621 (MH^+).

(12*S*)-Isomer of 3 To a stirred solution of **21** (30 mg, 0.051 mmol) in MeOH was added $NaBH_4$ (9 mg, 0.236 mmol) and the mixture was stirred at room temperature for 10 min. The mixture was extracted with EtOAc and the extract was washed with water and brine, dried, and evaporated. The residue was purified by preparative TLC (4% MeOH/EtOAc) to give the *syn*-diol **22** (21.0 mg, 70%) and the *anti*-diol (5.1 mg, 17%). *Anti*-diol:$[\alpha]_D^{25}$ +18.31° (c=0.43, $CHCl_3$). IR

($CHCl_3$): 3450, 1460, 1380, 1090 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=6.8Hz), 1.32-1.80 (17H, m), 1.84-2.11 (7H, m), 2.24 (2H, t, *J*=5.9Hz), 3.09 (3H, s), 3.13 (6H, s, 2xOMe), 3.19 (3H, s), 3.20 (3H, s), 3.22 (3H, s), 3.23 (3H, s), 3.34 (1H, m), 3.49 (1H, m), 3.56 (1H, m), 3.63 (1H, m), 3.81 (1H, m), 4.34 (1H, m), 4.52 (1H, m), 5.06 (1H, d, *J*=10.5Hz), 5.08 (1H, d, *J*=17.1Hz), 5.84 (1H, ddt, *J*=17.1, 10.5, 7.1Hz).

The *anti*-diol (5.0 mg) was *O*-methylated in the same way as described for **12** and the product was purified by flash chromatography (80% EtOAc/hexane) to give the (12*S*)-isomer of **3** (4.6 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ +5.56° (c=0.38, $CHCl_3$). IR ($CHCl_3$): 1460, 1380, 1090 cm^{-1}. ^1H NMR (400MHz, C_6D_6) δ: 0.91 (3H, t, *J*=6.8Hz), 1.32-1.85 (17H, m), 1.86-2.10 (7H, m), 2.30 (2H, t, *J*=5.6Hz), 3.08 (1H, m), 3.17 (3H, s), 3.196 (3H, s), 3.200 (3H, s), 3.22 (3H, s), 3.243 (3H, s), 3.247 (3H, s), 3.28 (1H, m), 3.30 (6H, s, 2xOMe), 3.36 (1H, m), 3.37 (3H, s), 3.61 (3H, m), 3.72 (2H, m), 3.84 (1H, m), 5.09 (1H, d, *J*=10.0Hz), 5.10 (1H, d, *J*=17.1Hz), 5.90 (1H, ddt, *J*=17.1, 10.0, 7.1Hz). ^{13}C NMR (100MHz, C_6D_6) δ: 14.52, 18.87, 21.24, 34.17, 34.26, 36.12, 38.01, 38.20, 38.39, 38.59, 38.82, 38.85, 40.91, 40.95, 55.91, 56.06, 56.09 (two carbons), 56.15 (three carbons), 56.25, 56.70, 75.59, 75.65, 75.69 (two carbons), 75.73, 75.78, 77.54, 78.11, 80.74, 117.02, 135.24. FABMS *m/z*: 621 (MH^+)

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