Total Synthesis of Mucocin

Partha Neogi,[†] Thomas Doundoulakis,[†] Ahmad Yazbak,[†,‡] Santosh C. Sinha,[†,‡] Subhash C. Sinha,*[,†] and Ehud Keinan*[,†,‡,§]

Contribution from the Department of Molecular Biology and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel

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Abstract: The synthesis of the potent antitumor agent, mucocin, **1**, was efficiently achieved in 20 steps from cyclododecatriene, thus confirming the proposed structure of this unusual member of the Annonaceous acetogenins. Demonstrating the power of the "naked" carbon skeleton strategy, all seven asymmetric centers in the key fragment of the molecule were introduced by double AE reaction followed by double AD reaction. Simultaneous two ring closure reactions provided both the THP and THF rings in a single step.

The diverse bioactivities of the Annonaceous acetogenins as antitumor, immunosuppressive, pesticidal, antiprotozoal, antifeedant, anthelmintic, and antimicrobial agents have attracted increasing interest.[1,2] On the basis of the number and relative positioning of the tetrahydrofuran moieties within the molecule, these acetogenins have been classified into three subgroups: the mono-THF, the adjacent bis-THF, and the nonadjacent bis-THF acetogenins.[1] The structure and absolute configuration of many of these acetogenins have been unequivocally confirmed by total synthesis.

Mucocin, **1**,[3] which was recently isolated from leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae), was the first Annonaceous acetogenin reported that bears a hydroxylated tetrahydropyran (THP) ring along with a THF ring, thus representing a new skeletal type in this rapidly growing family of bioactive natural products. Mucocin was found to be quite active in the BST assay[4] (IC_{50} 1.3 μg/mL) and showed selective inhibitory effect against A-549 (lung cancer) and PACA-2 (pancreatic cancer) in a panel of six human solid tumor cell lines.[3] Its selective potency was up to 10000 times that of adriamycin. Interestingly, mucocin was found to be as active as bullatacin in inhibition of oxygen uptake by rat liver mitochondria (LC_{50} 18 and 9 nM/mg protein, respectively).[3] These findings suggest that **1**, like other potent antitumor bis-THF acetogenins, may also block the mitochondrial complex I (NADH−ubiquinone oxidoreductase)[5] and inhibit the plasma membrane NADH oxidase,[6] thus depleting ATP and likely to induce apoptosis.[7]

Structure **1** was proposed for mucocin on the basis of its MS, ^{1}H, ^{13}C and 2D ^{1}H −^{1}H NMR spectral data (relative stereochemistry)[3] and data derived from advanced Mosher ester technology (absolute configuration).[8] Biogenetically, **1** seems to originate from a different pathway than the proposed pathways for known nonadjacent bis-THF Annonaceous acetogenins.[1,3] Therefore, an efficient total synthesis of **1** was required not only for making the compound available for further biological studies, but also for verification of the proposed

* Corresponding author. Phone: (619) 784-8511, Fax: (619) 784-8732, E-Mail: Keinan@scripps.edu or subhash@scripps.edu.
[†] The Scripps Research Institute.
[‡] Technion-Israel Institute of Technology.
[§] Incumbent of the Benno Gitter & Ilana Ben-Ami chair of Biotechnology, Technion.

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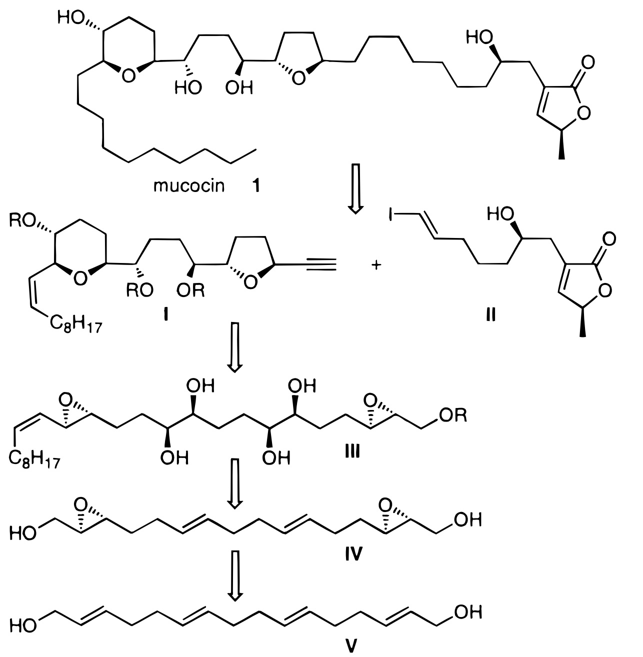
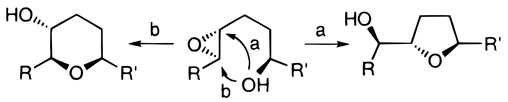
Scheme 1. Retrosynthetic Analysis of Mucocin



structure. Here we report on the first total synthesis of **1**, thus unequivocally confirming its absolute configuration.

As illustrated in our retrosynthetic analysis (Scheme 1), **1** may be constructed from two key building blocks, **I** and **II**. While the fragment **II** is relatively easy to synthesize considering a number of well documented precedents, construction of the main fragment, **I**, which contains both THP and THF rings with seven asymmetric carbon atoms, represents a nontrivial synthetic challenge. In fact, previous attempts to synthesize mucocin have focused on the preparation of the hydroxylated THP ring.[9] Our synthetic design was based on a key step in which two ring closure reactions lead from the linear intermediate **III** to the bicyclic intermediate **I**. According to the Baldwin rules, the formation of a six-membered ring via a 6-endo hydroxy epoxide opening (route b, Scheme 2) is disfavored in comparison with the alternative formation of a five-membered ring via a 5-exo ring closure (route a).[10] Therefore, in our synthetic design we have incorporated an unsaturated substituent (R = alkenyl) to revert the regioselectivity and promote formation of a THP ring rather than the THF product.[11]

Scheme 2



Our synthetic approach to **III** was based on the "naked" carbon skeleton strategy, i.e., selective placement of the oxygen functions onto a naked, unsaturated carbon skeleton.[12,13] For that purpose we planned to use the Sharpless asymmetric dihydroxylation (AD)[14] and asymmetric epoxidation (AE)[15] reactions. Thus, one may envision the synthesis of **III** in two major steps starting with the "naked" carbon skeleton, **V**. First, the AE reaction is used to epoxidize the two allylic double bonds, affording **IV**, and then the AD reaction is used to dihydroxylate the remaining two double bonds, producing the fully oxidized intermediate **III**.

Our synthesis of **1** (Scheme 3) starts with *trans*,*trans*,*trans*-1,5,9-cyclododecatriene as a convenient source of a 12-carbon skeleton.[16] Selective dihydroxylation of one of the three double bonds was achieved using NMO and catalytic amounts of osmium tetraoxide. The resultant diol was oxidatively cleaved with sodium metaperiodate to produce dialdehyde **2**. Wittig olefination of the latter afforded the bis-enoate **3** which was reduced with DIBAL-H to provide the desired "naked" carbon skeleton intermediate, **4**. Double AE reaction with the bis-allylic alcohol, **4**, in the presence of (−)-diethyl tartrate followed by chromatographic purification and recrystallization afforded the C_2 symmetric diepoxide **5** in 98% ee. Desymmetrization of **5** was achieved by monosilation with TBDMSCl to give silyl ether **6**. Oxidation of the unprotected alcohol in **6** with SO_3−pyridine produced aldehyde **7**. The Wittig reaction of aldehyde **7** with triphenylnonylphosphorane produced the (*Z*) alkene **8** which contained the required unsaturation next to the epoxide function (vide supra). We took advantage of the known higher reactivity of (*E*) disubstituted alkenes relative to (*Z*) alkenes in the AD reaction,[16] which, added to the steric hindrance of the latter double bond, could enable selective dihydroxylation of the former in the presence of the latter. Indeed, asymmetric dihydroxylation of **8** using AD-mix-α selectively oxidized the two trans double bonds in the molecule, affording the tetrahydroxylated intermediate **9**, and keeping the (*Z*) double bond intact. This reaction set the stage for the key step in the entire synthetic strategy, i.e., double ring closure of the diepoxytetrol intermediate **9** to produce the nonadjacent THP−THF ring system, **10a**, with the required stereochemistry. Thus, treatment of **9** with a catalytic amount of TsOH for 1 h produced **10a** in high yield. Treatment of **10a** with TsOH for an additional period of 16 h at room-temperature hydrolyzed the silyl ether to give pentol **10b**. The latter was reacted with 2,2-dimethoxypropane and TsOH, affording the bis-acetonide **11**. The less stable, seven-membered ring acetonide was selectively hydrolyzed in aqueous TsOH at 0 °C to produce triol **12a**. The latter was fully protected by reaction with MEM-Cl to give **12b**. Cleavage of the acetonide function with aqueous acetic acid followed by oxidative cleavage of the resultant 1,2-diol with sodium metaperiodate yielded aldehyde **14**. The latter was transformed to the dibromide **15**,[17] which, upon treatment with 2 equiv of n-BuLi at −78 °C, produced the terminal alkyne **16** in 50% yield, along with the *trans*-alkene monobromide (20%), thus completing the crucial fragment of the target molecule. Generation of an alkyne from a dibromoalkene is usually a high-yielding process;[17,18] however, the low yield in this case can be attributed due to the instability of the produced alkyne. In fact, when the same reaction was left till all the produced monobromide was consumed, the alkyne **16** was obtained in only 25% yield.

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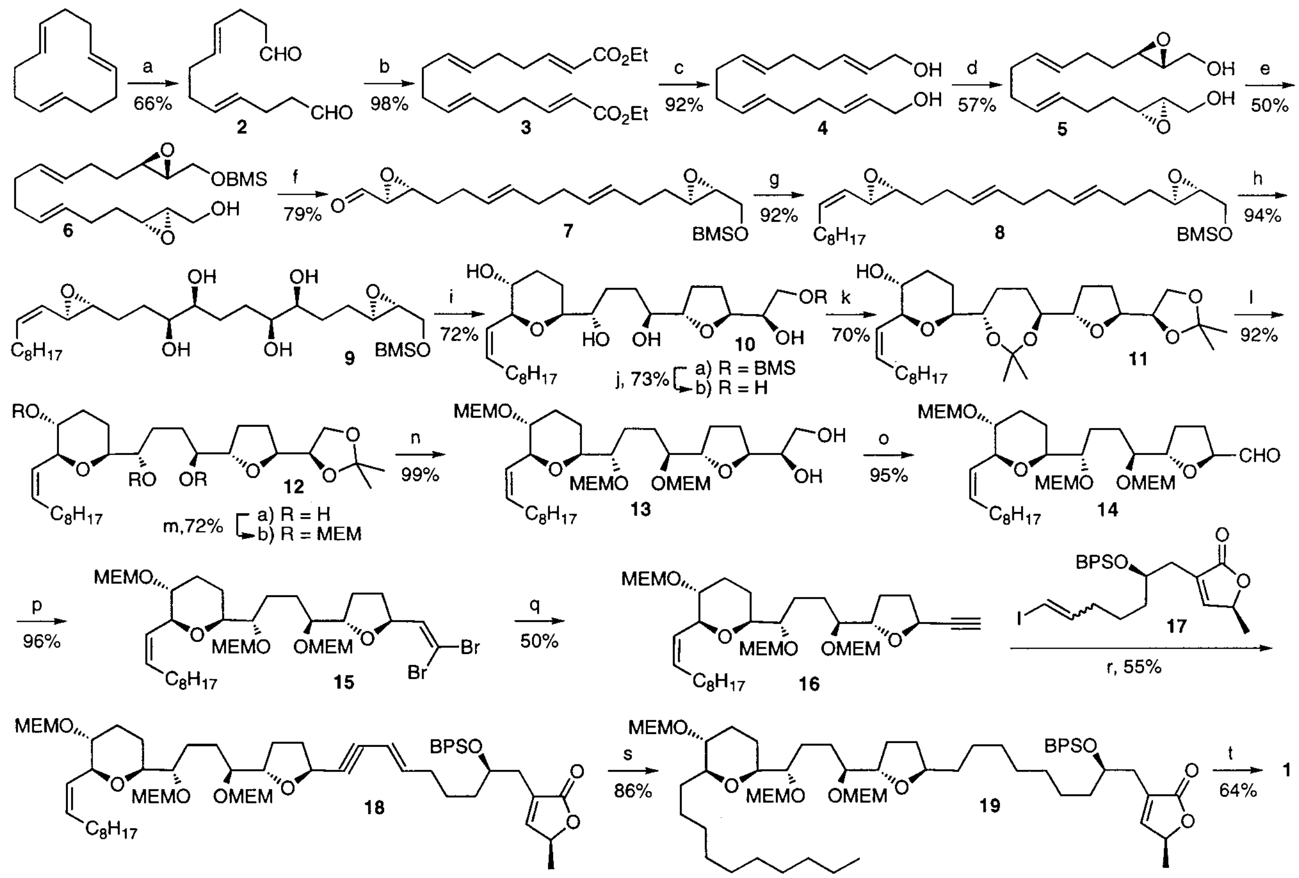
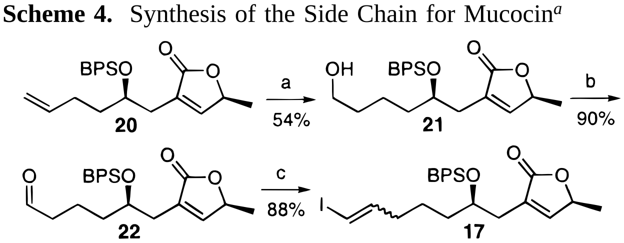
Scheme 3. Total Synthesis of Mucocin[a]



[a] Key: (a) i. OsO_4, acetone−H_2O, rt, 24 h. (ii) $NaIO_4$, CH_2Cl_2−acetone, H_2O, 0 °C to rt, 2 h. (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 15 min. (c) DIBAL-H, THF, −78 °C, 90 min. (d) $Ti(OiPr)_4$, (−)-DET, TBHP, powdered molecular sieves 4 Å, −20 °C, 16 h. (e) TBDMSCl, imidazole, DMF, rt, 16 h. (f) SO_3−pyridine, DMSO, TEA, CH_2Cl_2, 0 °C to rt, 3 h. (g) $C_9H_{19}PPh_3Br$, $KN(SiMe_3)_2$, THF, 2 h, −78 °C then HMPA and aldehyde **7** in THF, −78 °C to rt, 16 h. (h) AD-mix-α, $MeSO_2NH_2$, OsO_4, *tert*-butanol−H_2O (1:1), 0 °C, 16 h. (i) TsOH, CH_2Cl_2, 0 °C, 6 h. (j) TsOH, CH_2Cl_2−MeOH, rt, 16 h. (k) DMP, acetone, *p*-TsOH, rt, 2 h. (l) TsOH, MeOH−H_2O, 0 °C, 30 min. (m) MEM−Cl, diisopropylethyl amine, CH_2Cl_2, 0 °C to rt, 16 h. (n) AcOH−H_2O, 30 °C, 4 h. (o) $NaIO_4$, CH_2Cl_2−acetone, H_2O, 0 °C to rt, 2 h. (p) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 15 min. (q) *n*-BuLi, THF, −78 to −10 °C, 2 h. (r) **17**, TEA, $(PPh_3)_2PdCl_2$, CuI, rt, 16 h. (s) $(PPh_3)_3RhCl$, benzene−EtOH, rt, 48 h. (t) 5% CH_3COCl in MeOH, CH_2Cl_2, rt, 16 h.

Scheme 4. Synthesis of the Side Chain for Mucocin[a]



[a] Key: (a) 9-BBN, THF, 0 °C, 1 h. (b) PCC, CH_2Cl_2, rt, 1.5 h. (c) CHI_3, $CrCl_2$, THF, 0 °C, 4 h.

Synthesis of the substituted butenolide fragment, **17**, was carried out using well precedented chemistry (Scheme 4). Thus, oxidative hydroboration of alkene **20**[19] produced alcohol **21**, which was then oxidized with PCC to produce aldehyde **22**. Finally, olefination with iodoform and chromium dichloride afforded the desired vinyl iodide **17** in the form of a 4:1 mixture of the (*E*):(*Z*) isomers.[20]

With both fragments **16** and **17** at hand, we turned to the final steps of the synthesis. Although both $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ were found to be useful cross-coupling catalysts, Pd(II) was found to be more effective than the Pd(0) catalyst, affording enyne **18** in 55% yield. Homogeneous catalytic hydrogenation using Wilkinson's catalyst produced **19** in high yield, keeping the butenolide function intact. Finally, acid-catalyzed deprotection of all four protecting groups in **19** afforded **1**, which was found to be identical (MS, ^{1}H and ^{13}C NMR, $[\alpha]_D$) with the naturally occurring mucocin.[5]

In conclusion, the synthesis of **1** was efficiently achieved in 20 steps from cyclododecatriene, using the "naked" carbon skeleton strategy. All seven asymmetric centers in the key fragment of the molecule were introduced by double AE reaction followed by double AD reaction. Double ring closure reactions provided both THF and THP rings in a single step.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB−VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Negative mass spectra were obtained with Sciex API 100. Optical rotations were measured in a 1-dm (1.3 mL) cell using an Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230−

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400 mesh, Art. 9385) under pressure. THF was dried and distilled over sodium ketyl. AD-mix-α (no.39,275-8) was purchased from Aldrich.

(*E*,*E*)-Dodeca-4,8-diene-1,12-dial, 2. OsO_4 (0.2 M, 2.3 mL, 0.46 mmol) and 4-methylmorpholine N-oxide (NMO) (50% aqueous, 38.4 mL, 185.2 mmol) were added to a solution of (*trans*,*trans*,*trans*)-1,5,9-cyclododecatriene (15.0 g, 92.6 mmol) in CH_2Cl_2 (500 mL), and the reaction mixture was stirred at room temperature for 24 h. Solid was filtered, washed with water, and dried under vacuum to afford diol (12.9 g, 71%) which was taken to next step without further purification. ^{1}H NMR: 5.11 (m, 4H), 3.74 (q, J = 6.5 Hz, 2H), 2.14 (m, 4H), 2.06 (m, 2H), 1.99 (m, 2H), 1.68 (m, 4H), 1.54 (d, J = 6.9 Hz, 2H); ^{13}C NMR: 132.2, 130.6, 68.6, 32.1, 31.8, 28.9; HRMS: found 219.1357 ($C_{12}H_{20}O_2Na$ = 219.1361, MNa^+).

Sodium metaperiodate (17.12 g, 80 mmol) was added to a solution of above-mentioned diol (7.58 g, 40 mmol) in CH_2Cl_2 (275 mL) and acetone (25 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 4:1) to **2** (7.2 g, 93%) in the form of a colorless oil. ^{1}H NMR: 9.70 (t, J = 1.8 Hz, 2H), 5.38 (m, 4H), 2.44 (m, 4H), 2.30 (m, 4H) and 1.98 (m, 4H); ^{13}C NMR: 202.4, 131.1, 128.3, 43.4, 32.2, 25.0.

(*E*,*E*,*E*,*E*)-Diethyl -hexadeca-2,6,10,14-tetraendioate, 3. Triethyl phosphonoacetate (14.8 g, 66 mmol) was added to a suspension of NaH (60% in mineral oil, 2.64 g, 66 mmol) in THF at 0 °C, and the mixture was stirred for 15 min. A solution of aldehyde **3** (5.1 g, 26.3 mmol) in THF (20 mL) was added, and the mixture was stirred for 15 min at 0 °C. The mixture was quenched with saturated aqueous NH_4Cl solution and diluted with water (60 mL), and the mixture was extracted with hexanes−Et_2O (1:1, 3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 9:1) to yield **3** (8.6 g, 98%) in the form of a colorless oil. ^{1}H NMR: 6.92 (dt, J = 15.6, 6.7 Hz, 2H), 5.79 (dt, J = 15.6, 1.5 Hz, 2H), 5.39 (m, 4H), 4.16 (q, J = 5.6 Hz, 4H), 2.22 (q, J = 6.8 Hz, 4H), 2.11 (q, J = 5.3 Hz, 4H), 2.01 (m, 4H), 1.25 (t, J = 5.6 Hz, 6H); ^{13}C NMR: 166.7, 148.6, 131.0, 128 0.9, 121.6, 60.1, 32.5, 32.1, 30.9, 29.7, 14.3; HRMS: found 335.2228 ($C_{20}H_{31}O_4$ = 335.2222, MH^+).

(*E*,*E*,*E*,*E*)-Hexadeca-2,6,10,14-tetraene-1,16-diol, 4. DIBAL-H (1 M in toluene, 127.2 mL, 127.2 mmol) was added dropwise to a solution of **4** (8.5 g, 25.4 mmol) in THF (80 mL) at −78 °C. The mixture was stirred at the same temperature for 1.5 h and then quenched by slow addition of saturated aqueous NH_4Cl solution (35 mL) followed by Celite (35 g). The mixture was diluted with Et_2O, warmed slowly to room temperature, and stirred till all aluminum precipitated. Solid was filtered and washed with Et_2O (3 × 50 mL), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2−MeOH, 49:1) to give the **4** (5.8 g, 92.0%) in the form of a white solid, mp 98−100 °C; ^{1}H NMR: 5.64 (m, 4H), 5.34 (m, 4H), 4.29 (d, J = 5.0 Hz, 4H), 2.11−2.06 (m, 12H), 1.83 (br s, 2H); ^{13}C NMR: 132.8, 130.3, 129.6, 129.1, 63.8, 32.6, 32.2, 32.1; HRMS: found 273.1834 ($C_{16}H_{26}O_2Na$ = 273.1830, MNa^+).

(*E*,*E*,2*R*,3*R*,14*R*,15*R*)-2,3:14,15-Dioxido-hexadeca-6,10-diene-1,16-diol, 5. D-(−)-Diethyl tartrate (1.73 g, 8.4 mmol) and Ti(*iso*-OPr)$_4$ (2.4 g, 8.4 mmol) was added sequentially to a mixture of alcohol **4** (5.2 g, 21 mmol) and 4 Å dry molecular sieves powder (5.2 g) in dry CH_2Cl_2 (100 mL) at −20 °C, and the mixture was stirred at the same temperature for 30 min. *tert*-BuOOH (5.2 M in isooctane, 21 mL, 109.2 mmol) was added, and the solution was stirred at −20 °C for 16 h. Aqueous NaOH (3 M, 20 mL) was added to the reaction mixture, allowed to warm to room temperature over 1 h, and then filtered through a bed of Celite, and the bed was washed with ethyl acetate (3 × 50 mL). The combined organic layer was dried over $MgSO_4$, and the crude product was purified by column chromatography (silica gel, CH_2Cl_2−MeOH, 19:1) to give **5** (3.34 g, 57.0%) in the form of a white solid after crystallization from Et_2O, mp 105−107 °C; $[\alpha]_D$: +40 (c = 1.1, $CHCl_3$); ^{1}H NMR: 5.44 (m, 4H), 3.88 (ddd, J = 12.6, 4.9, 2.6 Hz, 2H) 3.63 (ddd, J = 12.6, 6.7, 4.3 Hz, 2H), 2.96 (td, J = 5.8, 2.4 Hz, 2H), 2.92 (dt, J = 4.3, 2.5 Hz, 2H), 2.13 (m, 4H), 2.05 (m, 4H), 1.78 (dd, J = 7.4, 5.6 Hz, 2H), 1.62 (td, J = 7.4, 5.8 Hz, 4H); ^{13}C NMR: 130.7, 129.1, 61.6, 58.5, 55.5, 32.4, 31.5, 28.9; HRMS: found 305.1724 ($C_{16}H_{26}O_4Na$ = 305.1729, MNa^+).

(*E*,*E*,2*R*,3*R*,14*R*,15*R*)-16-(*tert*-Butyldimethylsilyloxy)-2,3:14,15-dioxido-hexadeca-6,10-dien-1-ol, 6. Imidazole (0.53, 7.84 mmol) and TBDMSCl (0.83 g, 5.53 mmol) were added sequentially to a stirred solution of **6** (1.3 g, 4.61 mmol) in dry DMF (10 mL). After being stirred at room temperature for 16 h, the mixture was poured into water and extracted with ether (3 × 25 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 4:1) to yield **6** (0.62 g, 38%, 50% based on 25% recovered starting material and di-TBDMS derivative, 455 mg, 35%), $[\alpha]_D$: +21 (c = 1.3, $CHCl_3$); ^{1}H NMR: 5.40 (m, 4H), 3.85 (m, 1H), 3.76 (m, 1H), 3.61 (m, 2H), 2.93 (m, 1H), 2.90 (m, 1H), 2.81 (m, 2H), 2.11 (m, 4H), 2.01 (br s, 4H), 1.59 (m, 4H), 1.21 (br d, J = 7.6 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: 130.7, 130.5, 129.2, 129.1, 63.5, 61.6, 58.8, 58.5, 55.8, 55.5, 32.5, 31.7, 31.5, 28.9, 26.4, 25.9, 18.3, −5.3, −5.4; HRMS: found 419.2788 ($C_{22}H_{40}O_4SiNa$ = 419.2594, MNa^+).

(*E*,*E*,2*R*,3*R*,14*R*,15*R*)-16-(*tert*-Butyldimethylsilyloxy)-2,3:14,15-dioxido-hexadeca-6,10-dien-1-al, 7. SO_3−pyridine complex (1.77 g, 11.1 mmol) was added to a stirred solution of **7** (2.2 g, 5.5 mmol), Et_3N (4.64 mL, 33.3 mmol), and dry DMSO (1.57 mL, 22.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 3 h (0 °C−rt). Water (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, hexanes−EtOAc, 19:1) afforded **7** (1.73 g, 79%) in the form of a colorless oil. ^{1}H NMR: 8.99 (d, J = 5.2 Hz, 1H), 5.41 (m, 4H), 3.76 (dd, J = 11.6, 3.2 Hz, 1H), 3.62 (dd, J = 11.6, 4.4 Hz, 1H), 3.21(dt, J = 5.6, 2.0 Hz, 1H), 3.11 (dd, J = 6.0, 1.2 Hz, 1H), 2.82 (m, 2H), 2.13 (m, 4H), 2.02 (br s, 4H), 1.69 (m, 2H), 1.59 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: 198.3, 131.5, 130.4, 129.3, 128.2, 63.5, 59.2, 58.7, 56.3, 55.8, 32.4, 31.7, 31.1, 29.0, 28.8, 25.8, −5.3, −5.4; MS: 395 (MH^+).

(6*E*,10*E*,16*Z*,2*R*,3*R*,14*R*,15*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3:14,15-dioxido-pentadodeca-6,10,16-triene, 8. KN(SiMe$_3$)$_2$ (0.5 M in toluene, 7.1 mL, 3.55 mmol) was added to a stirred solution of n-C_9H_{19}-PPh_3Br (1.37 g, 3.55 mmol) in dry THF (70 mL) at −78 °C, and the mixture was stirred at the same temperature for 2 h. HMPA (1.23 mL, 7.1 mmol) and aldehyde **8** (1.40 g, 3.55 mmol) in THF (10 mL) were added dropwise, and the mixture was stirred for 16 h at −78 °C−rt. Saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O (3 × 70 mL). The combined organic layer was washed with brine and dried over $MgSO_4$, and solvents were removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 19:1) to yield **9** (1.65, 92%) in the form of a colorless oil, $[\alpha]_D$: +7.0 (c = 1.10, $CHCl_3$); ^{1}H NMR: 5.66 (dt, J = 11.0, 8.0 Hz, 1H), 5.40 (m, 4H), 5.00 (ddt, J = 11.6, 7.4, 1.5 Hz, 1H), 3.76 (dd, J = 11.6, 3.2 Hz, 1H), 3.64 (dd, J = 11.7, 4.5 Hz, 1H), 3.33 (dd, J = 8.9, 1.5 Hz, 1H), 2.82 (m, 3H), 2.14 (m, 6H), 2.00 (br s, 4H), 1.60 (m, 4H), 1.37 (m, 2H), 1.23 (br s, 10H), 0.88 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: 136.6, 130.6, 129.2, 126.9, 63.6, 59.7, 58.8, 55.8, 54.5, 32.5, 32.1, 31.9, 31.7, 29.6, 29.4, 29.3, 29.2, 29.0, 28.9, 27.7, 25.9, 22.6, 14.1, −5.3, −5.4; MS: 505 (MH^+).

(16*Z*,2*R*,3*R*,6*S*,7*S*,10*S*,11*S*,14*R*,15*R*)-1-(*tert*-Butyldimethylsilyloxy)-pentadodec-16-ene-6,7,10,11-tetrol, 9. Compound **8** (0.77 g, 1.52 mmol) was added to a cold (0 °C) solution of AD-mix-α (4.28 g, OsO_4 content 0.4%) and $MeSO_2NH_2$ (0.29 g, 3.0 mmol) in *tert*-BuOH−water (1:1, 30 mL), and the mixture was stirred at this temperature for 16 h. The reaction was quenched by slow addition of $Na_2S_2O_3$ (4.5 g) and stirred at room temperature for 30 min. The mixture was extracted with EtOAc (3 × 30 mL), washed with brine, and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude product (0.82 g, 94%) was used in the next step without further purification, ^{1}H NMR: 5.70 (dt, J = 8.8, 7.6 Hz, 1H), 5.05 (br s, 1 H), 5.01 (br t, $J = 7.6$ Hz, 1H), 3.78 (dd, $J = 9.6$, 2.4 Hz, 1H), 3.66 (m, 1H), 3.80−3.60 (br, 1H), 3.52−3.32 (m, 6H), 3.01 (m, 1H), 2.88 (m, 3H), 2.18 (m, 2H), 2.02−1.20 (m and br s, 24H), 0.88 (s, 9H), 0.86 (t, $J = 6.0$ Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$ + CD_3-OD): 137.2, 126.2, 74.1, 73.9, 73.8, 63.3, 60.5, 58.8, 56.4, 54.6, 43.0, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.4, 28.0, 27.6, 25.7, 22.5, 18.22, 14.0, −5.5; MS: found 705.3144 ($C_{31}H_{60}O_7SiCs$ = 705.3163, MCs^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-1-(*tert*-Butyldimethylsilyloxy)-3,6:11,15-dioxido-pentadodec-16-ene-2,7,10,14-tetrol, 10a. *p*-TsOH (0.025 g, 0.13 mmol) was added to a solution of **9** (0.80 g, 1.39 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 6 h and then washed with saturated aqueous $NaHCO_3$ (3 mL) and brine. The organic layer was dried over $MgSO_4$, the solvent was removed, and the crude product was purified by chromatography (silica gel, CH_2Cl_2-MeOH, 23:2) to yield **10a** (0.57 g, 72%) in the form of a colorless oil, ^{1}H NMR: 5.74 (dt, $J = 11.0$, 7.4 Hz, 1H), 5.32 (br t, $J = 11$ Hz, 1H), 3.85 (m, 2H), 3.78 (q, $J = 7.0$ Hz, 1H), 3.68 (m, 1H), 3.60 (m, 2H), 3.46−3.38 (m, 2H), 3.29−3.20 (m, 2H), 3.04−2.24 (br, 2H), 2.19−1.25 (m, 18H), 1.20 (br s, 10H), 0.87 (s, 9H), 0.85 (t, $J = 6$ Hz, 3H), 0.05 (s, 6H); ^{13}C NMR: 137.1, 127.1, 82.9, 80.2, 79.1, 78.2, 73.9, 73.4, 73.1, 70.1, 64.2, 31.8, 30.8, 29.7, 29.4, 29.3, 29.2, 28.9, 28.6, 28.4, 28.1, 20.0, 26.6, 22.6, 18.3, 14.4, −5.4; MS: 595 (MNa^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-3,6:11,15-Dioxido-pentadodec-16-ene-1,2,7,10,14-pentol, 10b. *p*-TsOH (0.018 g, 0.096 mmol) was added to a stirred solution of **10a** (0.55 g, 0.96 mmol) in CH_2Cl_2 (10 mL) and MeOH (5 mL) at 0 °C, and the mixture was stirred at room temperature for 16 h. Solvent was removed under reduced pressure at room temperature. The crude product, **10b**, was taken to the next step without further purification (0.32 g, 73%), ^{1}H NMR: 5.73 (dt, $J =$ 11.0, 7.4 Hz, 1H), 5.31 (dd, $J = 11.0$, 9.0 Hz, 1H), 3.88 (m, 1H), 3.85 (t, $J = 8.9$ Hz, 1H), 3.79 (q, $J = 7.5$ Hz, 1H), 3.61 (m, 4H), 3.41 (m, 4H), 3.24 (m, 3H), 2.10−1.52 (m, 17H), 1.20 (br s, 12H), 0.81 (t, $J =$ 6.8 Hz, 3H); MS: 481 (MNa^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-1,2:7,10-(Diisopropylidene-dioxy)-3,6:11,15-dioxido-pentadodec-16-en-14-ol, 11. *p*-TsOH (0.10 g, 0.52 mmol) was added to a stirred solution of **10b** (0.52 g, 1.1 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (20 mL), and the mixture was stirred at room temperature for 2 h. The mixture was mixed with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (2 × 10 mL). The organic layer was dried over $MgSO_4$, and solvents were removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 3:1) to yield **11** (0.42 g, 70%) in the form of a colorless oil, $[\alpha]_D$: −47 (c = 1.80, CH_2Cl_2); ^{1}H NMR (300 MHz): 5.72 (m, 1H), 5.36 (br t, $J = 8.4$ Hz, 1H), 4.05 (m, 2H), 3.95 (m, 2H), 3.89 (m, 4H), 3.83 (m, 1H), 3.80 (m, 2H), 2.15−1.64 (m, 6H), 1.69−1.61 (m, 8H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (s, 6H), 1.29−1.23 (br s, 12H), 0.85 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR: 136.4, 127.6, 109.1, 100.3, 81.7, 79.9, 79.5, 78.7, 78.0, 73.9, 72.6, 70.0, 67.6, 31.9, 31.2, 29.6, 29.4, 29.2, 29.1,29.0, 28.3, 28.0, 26.6, 25.9, 25.2, 22.6, 14.0; MS: 561 (MNa^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-1,2-(Isopropylidenedioxy)-3,6:11,15-dioxido-pentadodec-16-ene-7,10,14-triol, 12a. *p*-TsOH (30 mg, 0.16 mmol) was added to a stirred solution of **11** (0.40 g, 0.74 mmol) in MeOH (5 mL) and water (0.5 mL) at 0 °C, and the mixture was stirred for 30 min. The reaction mixture was mixed with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (2 × 10 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2−MeOH, 97:3) to yield the monoacetonide **12a** (340 mg, 92%) as colorless oil, $[\alpha]_D$: −255.6 (c = 0.50, $CHCl_3$); ^{1}H NMR: 5.72 (dt, $J = 7.9$ and 7.8 Hz, 1H), 5.30 (t, $J = 9.2$ Hz, 1H), 4.07 (t, $J = 7.2$ Hz, 1H), 3.97 (q, $J = 7.2$ Hz, 1H), 3.93−3.77 (m, 4H), 3.46 (m, 1H), 3.42 (m, 1H), 3.25−3.15 (m, 2H), 2.95 (br s, 1H), 2.78 (br s, 1H), 2.15−1.35 (m, 15H), 1.39 (s, 3H), 1.33 (s, 3H), 1.35−1.15 (m and br s, 12H), 0.86 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR: 137.0, 127.1, 109.3, 83.0, 80.1, 79.8, 78.1, 77.8, 73.7, 73.3, 70.0, 67.3, 31.8, 30.8, 29.7, 29.4, 29.3, 29.2, 29.0, 28.9, 28.5, 28.4, 27.9, 26.6, 26.5, 25.2, 22.6, 14.1; HRMS: found 631.2638 ($C_{28}H_{50}O_7Cs$ = 631.2611, MCs^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-3,6:11,15-Dioxido-1,2-(isopropylidenedioxy)-7,10,14-tris(methoxyethoxymethoxy)-pentadodec-16-ene, 12b. *iso*-Pr_2NEt (1.47 mL, 8.4 mmol) and MEM-chloride (0.48 mL, 4.2 mmol) were added sequentially to a solution of compound **12a** (340 mg, 0.68 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 16 h and then worked-up with water−CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, and the crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 3:2) to yield **12b** (373 mg, 72%) in the form of a colorless oil, $[\alpha]_D$: −26.6 (c = 2.8, $CHCl_3$); ^{1}H NMR: 5.52 (dt, $J = 10.9$, 7.3 Hz, 1H), 5.27 (t, $J = 10.9$ Hz, 1H), 4.70 (m, 6H), 4.06−3.40 (m, 22H), 3.34−3.33 (overlapped s, 9H), 2.17−1.43 (m, 14H), 1.34 (s, 3H), 1.29 (s, 3H), 1.24−1.19 (br s, 12H), 0.83 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR: 134.9, 128.1, 109.2, 95.7, 95.4, 94.2, 81.9, 79.9, 79.4, 78.5, 78.1, 75.1, 71.7, 67.6, 67.2, 66.7, 59.0, 31.8, 30.1, 29.6, 29.5, 29.3, 29.2, 29.1,28.3, 26.9, 26.6, 26.0, 25.6, 25.3, 22.6, 14.1; HRMS: found 895.4153 ($C_{40}H_{74}O_{13}Cs$ = 895.4184, MCs^+).

(16*Z*,2*R*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-3,6:11,15-Dioxido-7,10,14-tris(methoxyethoxymethoxy)-pentadodec-16-ene-1,2-diol, 13. Acetonide **12b** (330 mg, 0.43 mmol) was mixed with a 3:2 solution of glacial AcOH and water (5 mL), and the mixture was stirred at 30 °C for 4 h. The solvents were removed under reduced pressure at room temperature, and the crude product was purified by column chromatography (silica gel, CH_2Cl_2−methanol, 19:1) to yield diol **13** (310 mg, 99.2%) in the form of a colorless oil, $[\alpha]_D$: −25.2 (c = 0.50, CH_2Cl_2); ^{1}H NMR: 5.52 (dt, $J = 10.8$, 7.4 Hz, 1H), 5.26 (t, $J = 10.2$ Hz, 1H), 4.81−4.59 (m, 6H), 3.94−3.15 (m, 22H), 3.32 (s, 9H), 2.70 (br s, 2H), 2.16−1.40 (m, 14H), 1.28−1.20 (br s, 12H), 0.81 (t, $J = 6.0$ Hz, 3H);^{13}C NMR: 134.9, 128.0, 95.7, 95.3, 94.2, 81.7, 79.7, 79.4, 78.4, 76.7, 75.1,73.3, 71.8, 67.2, 66.7, 63.8, 58.9, 31.8, 30.0, 29.6, 29.5, 29.3, 29.2, 28.5,28.2, 27.8, 26.9, 25.9, 25.6, 22.6, 14.1; HRMS: found 855.3836 ($C_{37}H_{70}O_{13}Cs$ = 855.3871, MCs^+).

(15Z,2S,5S,6S,9S,10S,13R,14S)-2,5:10,14-Dioxido-6,9,13-tris-(methoxyethoxymethoxy)-pentadodec-15-en-1-al, 14. $NaIO_4$ (0.18 g, 0.83 mmol) and water (0.5 mL) were added to a solution of **13** (300 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) and acetone (3 mL) at 0 °C. The mixture was stirred for 2 h, dried over Na_2SO_4, and filtered through Celite. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, CH_2Cl_2−MeOH, 49:1) to yield **14** (275 mg, 95.0%) in the form of a colorless oil, ^{1}H NMR: 9.63 (d, $J = 1.92$ Hz, 1H), 5.56 (dt, $J = 11.0$, 7.1 Hz, 1H), 5.30 (t, $J = 8.7$ Hz, 1H), 4.81−4.59 (m, 6H), 4.29 (dd, $J = 7.9$, 1.8 Hz, 1H) 4.09 (dt, $J = 8.2$, 6.0 Hz, 1H), 3.90 (t, $J = 8.8$ Hz, 1H), 3.72−3.62 (m, 6H), 3.52−3.39 (m, 9H), 3.37 (s, 9H), 3.29 (m, 1H), 2.23−1.42 (m, 14H), 1.33−1.23 (br s, 12H), 0.86 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR: 203.0,134.9, 128.0, 99.8, 95.5, 94.2, 82.2, 79.5, 79.2, 78.4, 75.1, 71.8, 71.7, 67.3, 66.8, 59.0, 31.9, 30.1, 29.6, 29.5, 29.4, 29.3, 28.3, 27.7, 27.3, 26.0, 25.7, 25.6, 22.7, 14.1; HRMS: found 823.3576 ($C_{36}H_{66}O_{12}$ = 823.3609, MCs^+).

(16*Z*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-1,1-Dibromo-3,6:11,15-dioxido-7,10,14-tris(methoxyethoxymethoxy)-pentadodeca-1,16-diene, 15. PPh_3 (0.39 g, 1.48 mmol) and CBr_4 (0.25 g, 0.74 mmol) were added to solution of **14** (255 mg, 0.37 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 15 min and then quenched by addition of solid $NaHCO_3$ followed by water (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, benzene−EtOAc, 2:3) to furnish **15** (300 mg, 96%) in the form of a pale yellow oil, $[\alpha]_D$: −16.9 (c = 0.65, CH_2Cl_2); ^{1}H NMR: 6.47 (d, $J = 7.5$ Hz, 1H), 5.57 (dt, $J = 11.0$, 7.6 Hz, 1H), 5.30 (t, $J = 9.9$ Hz, 1H), 4.86−4.63 (m, 6H), 4.53 (q, $J =$ 7.4 Hz, 1H), 4.00 (q, $J = 6.2$ Hz, 1H), 3.90 (t, $J = 8.8$ Hz, 1H), 3.72−3.51 (m, 6H), 3.53−3.51 (m, 8H), 3.42 (m, 1H), 3.37−3.36 (overlapped s, 9H), 3.30 (m, 1H), 2.17 (br s, 2H), 2.05 (m, 2H), 1.98 (br s, 1H), 1.65−1.24 (m and br s, 21H), 0.86 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR: 139.8, 134.9, 128.0, 95.8, 95.5, 94.2, 81.7, 79.5, 79.1, 78.5, 75.2, 71.8, 71.7,67.3, 66.8, 59.0, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 28.3, 26.1, 22.7, 14.1; HRMS: found 977.2058 ($C_{37}H_{66}Br_2O_{11}Cs$ = 977.2026, MCs^+).

(16*Z*,3*S*,6*S*,7*S*,10*S*,11*S*,14*R*,15*S*)-3,6:11,15-dioxido-7,10,14-tris-(methoxyethoxymethoxy)-pentadodec-16-en-1-yne, 16. n-BuLi (0.165 mL, 0.265 mmol) was added dropwise to a solution of **15** (70 mg, 0.106 mmol) in THF at −78 °C, and the mixture was warmed slowly to −50 °C over 2 h and then quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2 × 5 mL). The organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2−MeOH, 99:1) to furnish **16** (37 mg, 50%) in the form of a colorless oil and corresponding monobromoalkene (14 mg, 20%). Physical data of **16**: $[\alpha]_D$: −31.6 (*c* = 0.80, CH_2Cl_2); ^{1}H NMR: 5.56 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.29 (t, *J* = 8.7 Hz, 1H), 4.82−4.61 (m, 6H), 4.15 (dd, *J* = 13.0, 6.4 Hz, 1H), 3.87 (t, *J* = 9.0 Hz, 1H), 3.70−3.62 (m, 7H), 3.52 (m, 8H), 3.45 (m, 1H), 3.36 (s, 9H), 3.27 (m, 1H), 2.39 (dt, *J* = 2.8, 2.2 Hz, 1H), 2.25−1.90 (m, 5H), 1.70−1.24 (m, 21H), 0.85 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR: 134.9, 128.1, 95.8, 95.6, 94.2, 83.8, 80.8, 79.4, 79.2, 78.5, 75.2, 72.5, 71.7, 68.0, 67.3, 66.7, 59.0, 33.3, 31.9, 30.1, 29.6, 29.5, 29.4, 29.3, 28.3, 27.4, 27.1, 26.3, 25.7, 22.7, 14.1; HRMS: found 819.3624 ($C_{37}H_{66}O_{11}Cs$ = 819.3659, MCs^+).

(4*S*,2′*R*)-2-(2′-(*tert*-Butyldiphenylsilyloxy)-6′-hydroxyheptan-1-yl)-pent-2-en-1,4-olide, 21. 9-BBN (0.5 M, 1.25 mL, 0.62 mmol) was added to a solution of **20** (180 mg, 0.41 mmol) in THF (10 mL) at 0 °C and stirred overnight. 1 N NaOH (1.8 mL) and H_2O_2 (0.6 mL) were added slowly to the reaction mixture at 0 °C and stirred for 2 h at room temperature. The reaction mixture was extracted with Et_2O (3 × 10 mL), and the combined ether fractions were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Residue was chromatographed over SiO_2 gel and eluted with hexanes−EtOAc (6:4) to afford **21** as an oil (100 mg, 54%), ^{1}H NMR: 7.63 (m, 4H), 7.39 (m, 6H), 6.92 (d, *J* = 1.4 Hz, 1H), 4.89 (dq, *J* = 6.8, 1.4 Hz, 1H), 4.01 (dt, *J* = 11.3, 5.5 Hz, 1H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.43 (d, *J* = 5.4 Hz, 2H), 1.60 (br s, 1H), 1.43−1.23 (m, 6H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR: 174.1, 151.7, 135.8, 134.0, 130.4, 129.7, 127.7, 77.5, 71.6, 62.4, 35.8, 32.3, 31.6, 27.0, 20.8, 19.9, 18.9.

(4*S*,2′*R*)-2-(2′-(*tert*-Butyldiphenylsilyloxy)hexan-6′-al-1-yl)pent-2-en-1,4-olide, 22. PCC (71 mg, 0.33 mmol) and Celite (71 mg) were added to a solution of alcohol **21** (100 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) and stirred for 2 h at room temperature. The reaction mixture was passed through silica gel (hexanes: EtOAc, 3:7) to yield aldehyde **22** (89 mg, 90%), ^{1}H NMR: 9.58 (t, *J* = 1.6 Hz, 1H), 7.60 (m, 4H), 7.35 (m, 6H), 6.88 (d, *J* = 1.4 Hz, 1H), 4.85 (qd, *J* = 6.8, 1.4 Hz, 1H), 3.98 (m, 1H), 2.41 (m, 2H), 2.13 (m, 2H), 1.51 (m, 2H), 1.36 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 9H); ^{13}C NMR: 202.3, 173.9, 151.6, 135.8, 133.8, 130.2, 129.8, 127.6, 77.5, 71.2, 43.4, 35.4, 31.7, 26.9, 19.3, 18.9, 17.3.

(4*S*,2′*S*)-2-(2′-(*tert*-Butyldiphenylsilyloxy)-7′-iodohept-6′-en-1′-yl)-pent-2-en-1,4-olide, 17. A mixture of aldehyde **22** (78 mg, 0.17 mmol) and iodoform (136 mg 0.35 mmol) in THF (3 mL) was added dropwise to a solution of $CrCl_2$ (125 mg, 1.02 mmol) in dry THF (1 mL) at 0 °C and stirred for 4 h at the same temperature. The reaction was quenched by addition of water and extracted with Et_2O (3 × 5 mL). The combined ether layer was washed with brine, dried over $MgSO_4$, and evaporated to a residue which was chromatographed over SiO_2 gel (hexanes−EtOAc, 9:1) to yield iodide **17** (87 mg, 88%) as a mixture of trans and cis isomers (4:1) in the form of an oil, ^{1}H NMR: 7.64 (m, 4H), 7.38 (m, 6H), 6.91 (d, *J* = 1.4 Hz, 1H), 6.32 and 6.10 (dt, *J* = 14.4, 7.1 Hz and dt, *J* = 7.3, 1.3 Hz, together 1H), 5.96 and 5.82 (q, *J* = 6.7 Hz and dt, *J* = 14.3, 1.4 Hz, together 1H), 4.90 (m, 1H), 4.00 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.42 (m, 2H), 1.92 and 1.81 (m, together 1H), 1.42−1.23 (m, 4H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR: 173.9, 151.5, 146.1, 135.8, 133.4, 130.4, 129.7, 127.6, 82.6, 75.5, 71.4, 35.6, 35.4, 31.8, 27.0, 23.4, 19.3, 18.9.

(8*(EZ)*,25*Z*)-4-(*tert*-Butyldiphenylsilyloxy)-16,19,23-tris(methoxy-ethoxymethoxy)mucocin-8,25-dien-10-yne, 18. CuI (3.0 mg, 15 μmol) and $Pd(PPh_3)_2Cl_2$ (3.4 mg, 4.7 μmol) were added to a solution of the alkyne **16** (32 mg, 47 μmol) and the iodide **17** (45 mg, 82 μmol) in Et_3N (2 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h, the Et_3N was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 6:4) to yield **18** (29 mg, 55%), ^{1}H NMR: 7.67−7.60 (m, 4H), 7.52−7.24 (m, 6H), 6.90 (s, 1H), 5.97 (dt, *J* = 15.8, 7.7 Hz, 1H), 5.61 (dt, *J* = 11.2, 7.0 Hz, 1H), 5.35 (m, 2H), 4.93−4.68 (m, 7H), 4.15 (dd, *J* = 7.2, 6.7 Hz, 1H), 4.03 (t, *J* = 4.9 Hz, 1H), 3.94 (t, *J* = 8.7 Hz, 1H), 3.75−3.65 (m, 7H), 3.56−3.54 (m, 8H), 3.47 (m, 1H), 3.41 (overlapped s, 9H), 3.33 (m, 1H), 2.45 (br s, 2H), 2.24−1.28 (m and br s, 32H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.06 (s, 9H), 0.86 (t, *J* = 6.8 Hz, 3H); HRMS: found 1265.5869 ($C_{65}H_{100}O_{14}SiCs$ = 1265.5937, MCs^+).

4-(*tert*-Butyldiphenylsilyloxy)-16,19,23-tris(methoxyethoxymethoxy)-mucocin, 19. $Rh(PPh_3)_3Cl$ (10 mg, 11 μmol) was added to a solution of **18** (29 mg, 25.6 μmol) in benzene−ethanol (1:1, 2 mL). The solution was stirred at room temperature under H_2 atmosphere for 48 h, the solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to yield **19** (25 mg, 86%), ^{1}H NMR: 7.64 (m, 4H), 7.51−7.27 (m, 6H), 6.89 (d, *J* = 1.4 Hz, 1H), 4.94−4.66 (m, 7H), 4.00−3.93 (m, 2H), 3.81 (m, 1H), 3.74−3.63 (m, 6H), 3.54−3.47 (m, 8H), 3.37 (s, 3H), 3.36 (s, 6H), 3.32 (m, 1H), 3.21 (m, 1H), 3.05 (dt, *J* = 7.6, 2.1 Hz, 1H), 2.41 (m, 2H), 2.23 (m, 1H), 1.92 (m, 2H), 1.73−1.33 (m, 41H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 0.85 (t, *J* = 6.7 Hz, 3H). HRMS: found 1273.6555 ($C_{65}H_{108}O_{14}SiCs$ = 1273.6563, MCs^+).

Mucocin, 1. A solution of 5% AcCl in MeOH (1 mL) was added to a stirred solution of protected **19** (25 mg, 21.9 μmol) in dichloromethane (1 mL) and stirred at room temperature for 16 h. The solvent was evaporated, and the residue was taken up in EtOAc (10 mL). The ethyl acetate extract was washed with saturated $NaHCO_3$ solution (2 × 2 mL) and brine (3 × 2 mL), dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed (silica gel, hexanes−EtOAc, 1:4) to yield **1** (9 mg, 64%), $[\alpha]_D$: −13.4 (*c* = 0.27, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): 7.16 (s, 1H), 5.05 (q, *J* = 7.0 Hz, 1H), 3.86−3.82 (m, 2H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.46 (m, 1H), 3.42 (t, *J* = 7.5 Hz, 1H), 3.26 (dt, *J* = 9.8, 5.0 Hz, 1H), 3.15 (br t, *J* = 7.0 Hz, 1H), 3.04 (dt, *J* = 9.0, 2.5 Hz, 1H), 2.50 (d, *J* = 13.6 Hz, 1H), 2.38 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.10 (m, 1H), 1.99 (m, 2H), 1.81 (m, 1H), 1.75−1.20 (m and br s, 44H), 1.42 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 174.6, 151.8, 131.2, 82.0, 80.1, 79.3, 78.0, 73.8, 73.5, 70.6, 69.9, 37.4, 35.6, 33.3, 32.6, 32.4, 32.0, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 28.3, 26.9, 26.2, 25.5, 22.7, 19.1, 14.1 ppm; HRMS: found: 771.3841 ($C_{37}H_{66}O_8Cs$ = 771.3812, MCs^+).

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **1**, **3**, **5**, **8**, **10a**, **12a**, **16**, and **17**; ^{13}C NMR spectra of compounds **1**, **3**, **5**, **8**, **10a**, **12a**, and **16** (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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