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Total Synthesis of Analogs of Topostin B, A DNA Topoisomerase I Inhibitor. Part 2. Synthesis of Topostin B-1 Analogs

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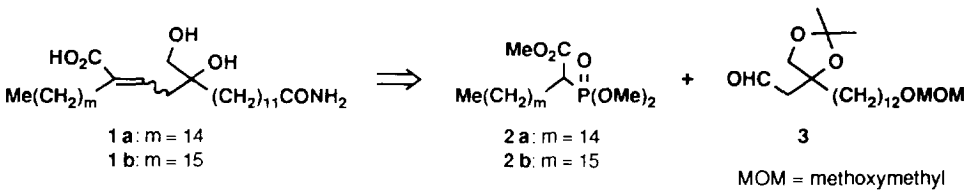
Abstract: The analogs **1a** and **1b** of topostin B-1, an inhibitor of mammalian DNA topoisomerase I, has been synthesized in a convenient manner.

In our preceding paper,[1] we described a convenient synthesis of the left and right building blocks **2** and **3** for the analogs **1** of topostin B, an inhibitor of mammalian DNA topoisomerase I.[2] We now wish to report a total synthesis of topostin B-1[3] analogs **1a** and **1b** from **2** and **3** according to the retrosynthetic route shown in Scheme 1. Since the absolute stereostructure of topostin B has not been fully clarified yet, we adopted a stereo-random strategy to synthesize topostin B-1 analogs.



1a: m = 14
1b: m = 15

2a: m = 14
2b: m = 15

3

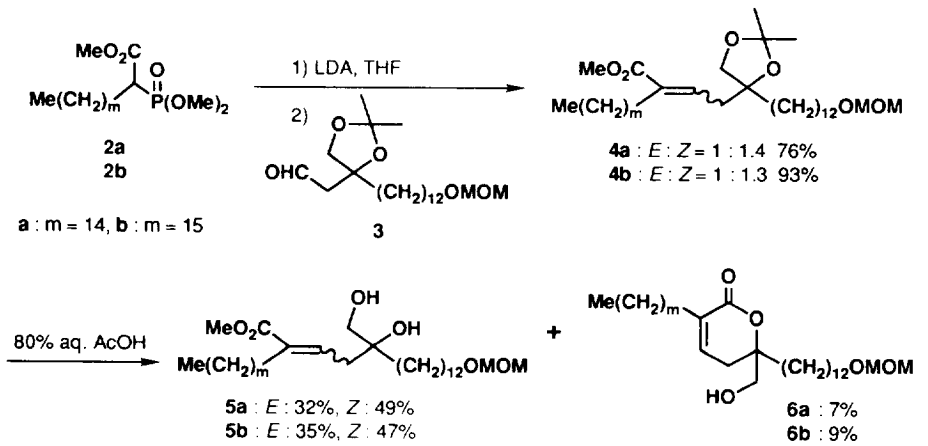
MOM = methoxymethyl

Scheme 1

The Horner-Emmons reaction of the phosphonate **2a** with the aldehyde **3** afforded a mixture of the *Z*- and *E*-isomers **4a** in a ratio of 1.4:1. Analogous coupling of **2b** with **3** produced a mixture of the geometrical isomers **4b** in a ratio of 1.3:1. Their stereochemistry was unambiguously determined by the measurement of the difference-NOE NMR spectra. Deacetalization of the coupling products **4a** and **4b**, respectively, followed by separation on a silica gel column afforded a mixture of the (*E*)- and (*Z*)-diols (**5a** and **5b**), as shown in Scheme 2. The lactones **6a** and **6b** formed by cyclization of (*Z*)-**5** were also obtained.

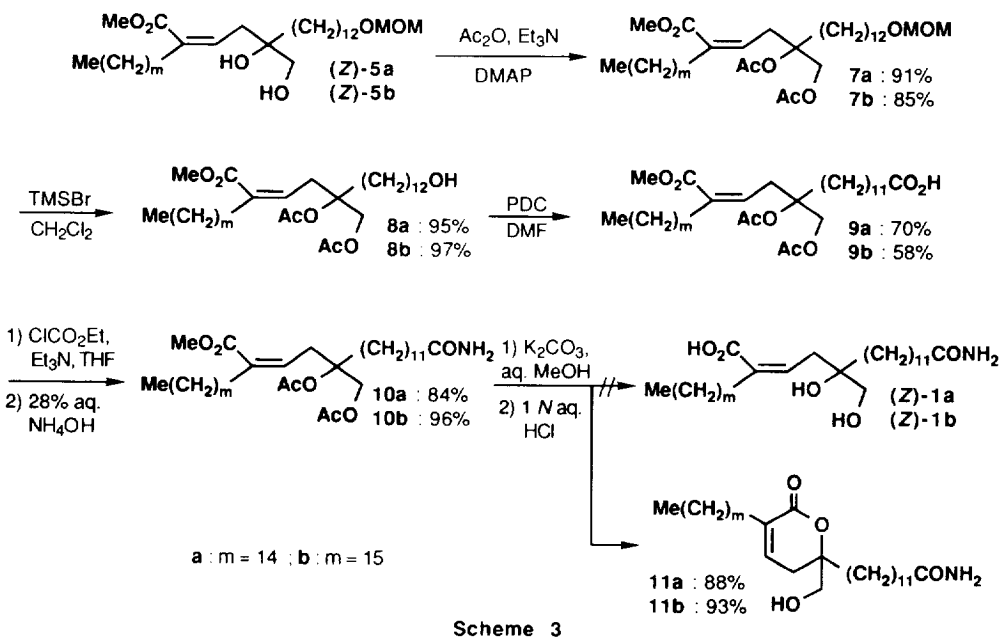
Synthesis of the Cyclized Analogs of (*Z*)-Topostin B-1

With three kinds of compounds having the full carbon skeleton of topostin B-1 in hand, we first accomplished the synthesis of (*Z*)-topostin B-1, as shown in Scheme 3. Acetylation of the (*Z*)-diol **5a** followed by removal of the methoxymethyl (MOM) group with bromotrimethylsilane (TMSBr) afforded the alcohol **8a**, which was oxidized with pyridinium dichromate (PDC) to give the carboxylic acid **9a**. After conversion to the mixed anhydride, **9a** was converted to the amide **10a**. Removal of the diacetyl function with 1*N* aqueous NaOH afforded a mixture of various products. However, treatment of **10a** with potassium



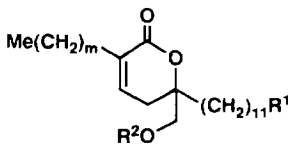
Scheme 2

carbonate in aqueous methanol produced the lactone **11a**, the cyclized analog of topostin B-1, in good yield. The desired topostin B-1 analog (**Z**)-**1a** could not be obtained at all. Analogously, the (*Z*)-diol **5b** was easily converted to the lactone **11b** in good overall yield.



Scheme 3

Alternatively, the cyclized analogs **11** of topostin B-1 were efficiently obtained from the lactones **6** through the same sequence of reactions, as outlined in Scheme 4.



a : m = 14 ; **b** : m = 15

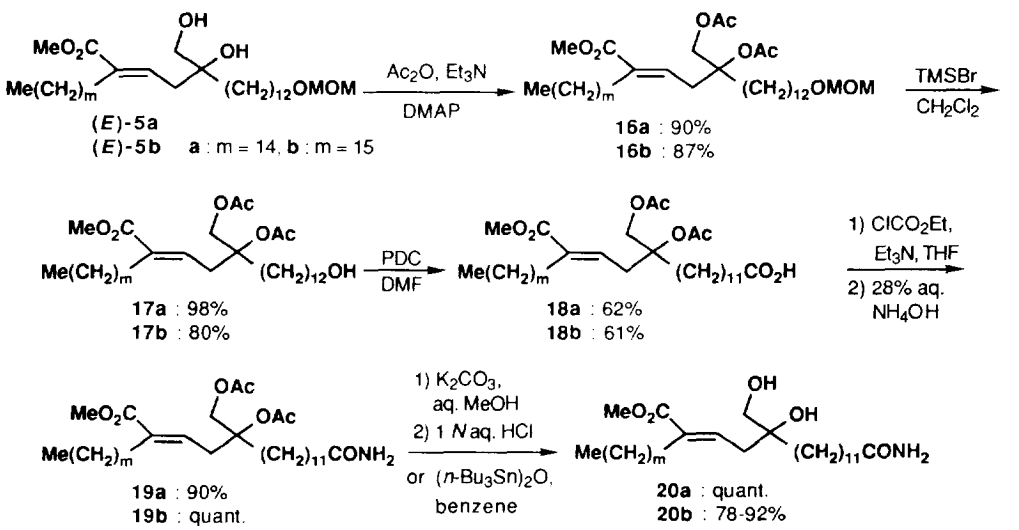
1) Ac_2O, Et_3N, DMAP
2) TMSBr, CH_2Cl_2
3) PDC, DMF
4) a) $ClCO_2Et$, Et_3N, THF
b) 28% aq. NH_4OH
5) a) K_2CO_3, aq. MeOH
b) 1*N* aq. HCl

	R^1	R^2		Yield, %
6a	CH_2OMOM	OH		
b	CH_2OMOM	OH	1)	85
12a	CH_2OMOM	OAc		92
b	CH_2OMOM	OAc	2)	82
13a	CH_2OH	OAc		81
b	CH_2OH	OAc	3)	66
14a	CO_2H	OAc		71
b	CO_2H	OAc	4)	91
15a	$CONH_2$	OAc		quant.
b	$CONH_2$	OAc	5)	90
11a	$CONH_2$	OH		89
b	$CONH_2$	OH		

Scheme 4

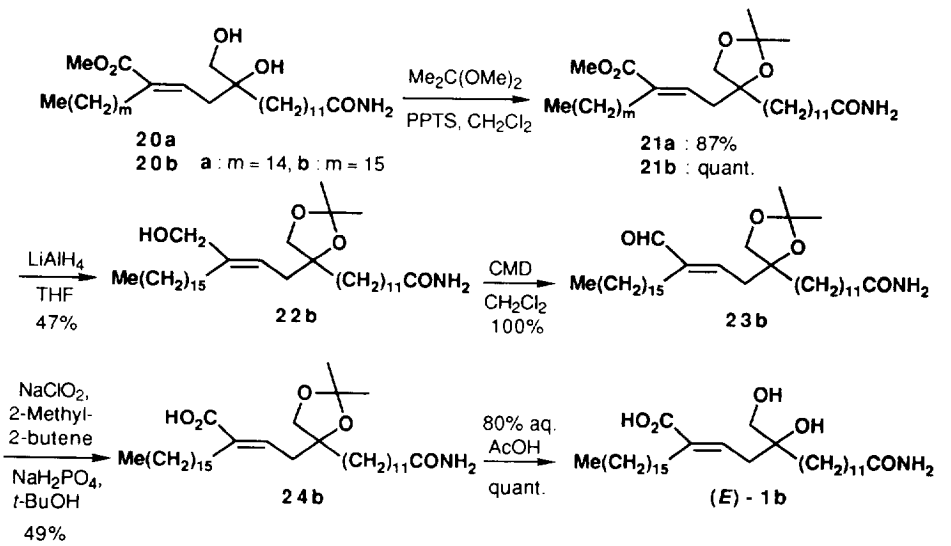
Synthesis of (*E*)-Topostin B-1 Analogs

Synthesis of (*E*)-topostin B-1 analogs was also attempted from the (*E*)-diols **5** by use of the same reaction sequence as that of (*Z*)-topostin B-1 lactones. As shown in Scheme 5, the (*E*)-diols **5a** and **5b** were smoothly converted to the amide methyl esters **19a** and **19b**, respectively, in 5 steps. Analogous treatment of **19** with potassium carbonate in aqueous methanol did not afford the desired (*E*)-topostin B-1 (**(*E*)-1**). Instead, the methyl esters **20** were obtained in good yield. To our surprise, various basic or acidic reaction conditions (LiOH, NaOH, 3.5*N* aq. HCl, CF_3CO_2H-THF, or BBr_3) failed to convert **19** to **(*E*)-1**. The neutral conditions using bis(tributyltin) oxide[4] again afforded the methyl ester **20a**, but not **(*E*)-1**.



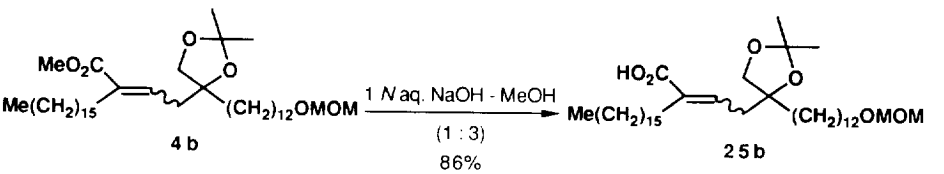
Scheme 5

Thus, we had to adopt the rather longer roundabout route to exchange the ester function to the carboxyl one, as outlined in Scheme 6. The methyl esters **20** were first converted to the acetals **21**. The acetal **21b** was treated with $LiAlH_4$ to give the alcohol **22b**. Oxidation of the primary hydroxyl function of **22b** was achieved in two steps : treatment with chemical manganese dioxide (CMD)[5] followed by sodium chlorite. The acetal **24b** thus obtained was treated under usual acidic conditions to give the desired (*E*)-topostin B-1 analogs , **(*E*)-1b**.



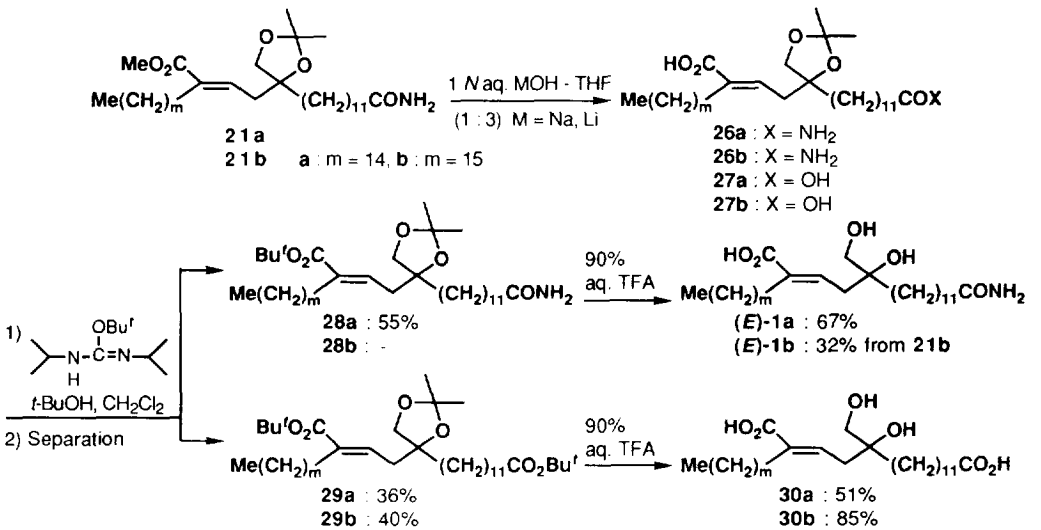
Scheme 6

Next, we investigated the conversion of the methyl ester group to the carboxylic function as their acetal derivatives. First, the MOM methyl ester **4b**, chosen as a model for this conversion, was treated with 1*N* aqueous sodium hydroxide-methanol (1:3) under reflux for 41 h, giving the carboxylic acid **25b** in good yield.



However, application of similar reaction conditions to the amide methyl ester **21a** resulted in its decomposition after only 6 h's refluxing. Milder reaction conditions at 45°C in THF afforded a mixture of the amide carboxylic acid **26a** and the dicarboxylic acid **27a**. After tert-butyl esterification, separation on a silica gel column afforded the mono-tert-butyl ester **28a** and the di-tert-butyl ester **29a**, as shown in Scheme 7. Treatment of **28a** with 90% aqueous trifluoroacetic acid (TFA) yielded (*E*)-**1a**, the desired (*E*)-topostin B-1. Analogously, the methyl ester **21b** underwent hydrolysis with lithium hydroxide to give a mixture of **26b** and **27b**. Further analogous treatment of the mixture afforded the mono- and di-tert-butyl esters **28b** and **29b**, the former of which gave (*E*)-**1b** by acidic treatment. The proof of the skeleton of (*E*)-**1a** and **1b** was obtained by their conversion to the methyl esters **20a** and **20b**, respectively, with trimethylsilyldiazomethane in methanol.[6] Furthermore, acidic treatment of the di-tert-butyl esters **29** afforded the di-carboxylic acids **30**.

Thus, we have accomplished a total synthesis of the compounds corresponding to topostin B-1. Spectral comparisons of our synthesized compounds with natural topostin B have revealed that they are different from each other. However, some of the synthesized compounds, e.g. (*E*)-**1**, **9**, **14**, **18**, and **30**, exhibit an inhibition action against mammalian DNA topoisomerase I, though weaker than topostin B itself.[7] This positive result encourages us to continue the synthesis of topostin B-1 analogs in order to find out novel anti-cancer agents. Further work is actively in progress on this matter.



Scheme 7

Experimental

All melting and boiling points ware uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8100 spectrometer. ^{1}H NMR spectra were recorded on a JEOL EX-270 or GSX-400 spectrometer with $CHCl_3$ as an internal standard. Mass spectra were recorded on a JEOL DX-300 spectrometer. Column chromatography was carried out on silica gel BW-820MH, BW-200, or BW-300 (purchased from Fuji Davison Co.). Analytical thin layer chromatography was carried out on silica gel plate (Merck Art. 5715).

Methyl 17-Methoxymethoxy-2-pentadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl) -2-heptadecenoate (4a)

To a stirred solution of lithium diisopropylamide (LDA) (prepared from *i*-Pr_2NH (560 μl, 4.26 mM) and *n*-BuLi (1.60 M in hexane, 2.76 ml, 4.42 mM) in THF (10.0 ml)) was added dropwise a solution of **2a** (1.18 g, 3.16 mM) in THF (10.0 ml) at 0°C, and the mixture was stirred at 0°C for 2 h under argon. A solution of **3** (1.49 g, 3.80 mM) in THF (10.0 ml) was added at 0°C. The mixture was stirred at room temperature for 1 h and quenched with H_2O. The mixture was extracted with Et_2O (120 ml x 2), successively washed with 10% aqueous citric acid, H_2O, and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 120 g, hexane:EtOAc = 15:1) to give **4a** (1.53 g, 76%) as a colorless oil. IR ν_{max} (neat): 2986, 2926, 2855, 1718, 1646, 1466, 1437, 1379, 1370, 1252, 1113, 1057, 976, 920, 820, 722 cm^{-1}. ^{1}H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (44 H, br), 1.39 (6 H, s), 1.57 (4 H, m), 2.24 (2 H, m), 2.46 (0.8 H, dd, J = 2.3, 7.3 Hz), 2.73 (1.2 H, dq, J = 6.9, 10.6 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.73 (3 H, s), 3.75 (0.8 H, s), 3.78 (1.2 H, s), 4.62 (2 H, s), 5.97 (0.6 H, t, J = 7.3 Hz), 6.76 (0.4 H, t, J = 7.3 Hz). FAB-MS m/z: 639 (MH^+). Anal. Calcd for $C_{39}H_{74}O_6$: C, 73.31; H, 11.67. Found: C, 73.57; H, 11.60.

Methyl 17-Methoxymethoxy-2-hexadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenoate (4b)

The phosphonate **2b** (1.31 g, 3.23 mM) was condensed with the aldehyde **3** (1.0 g, 2.69 mM) as described for **2a** to give **4b** (1.63 g, 93%) as a colorless oil. IR ν_{max} (neat): 2986, 2926, 2855, 1719, 1647, 1466, 1437, 1379, 1310, 1250, 1213, 1151, 1113, 1057, 920, 820, 722 cm^{-1}. ^{1}H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (46 H, br), 1.39 (6 H, s), 1.55 (4 H, m), 2.24 (2 H, m), 2.46 (0.8 H, dd, J = 2.3, 7.3 Hz), 2.73 (1.2 H, m), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.73 (3 H, s), 3.75 (0.8 H, s), 3.78 (1.2 H, s),

4.62 (2 H, s), 5.97 (0.6 H, t, J = 7.3 Hz), 6.76 (0.4 H, t, J = 7.3 Hz). Anal. Calcd for $C_{40}H_{76}O_6$: C, 73.57; H, 11.73. Found: C, 73.73; H, 11.64.

(*E*)-Methyl 5-Hydroxy-5-hydroxymethyl-17-methoxymethoxy-2-pentadecanyl-2-heptadecenoate (*E*-5a), (*Z*)-Methyl 5-Hydroxy-5-hydroxymethyl-17-methoxymethoxy-2-pentadecanyl-2-heptadecenoate (*Z*-5a), and 5-Hydroxymethyl-5-(12-methoxymethoxydodecanyl)-2-pentadecanyl-2-penten-5-olide (6a)

A mixture of **4a** (1.49 g, 2.34 mM) and 80% aqueous AcOH (150 ml) was stirred at room temperature for 5 days. The mixture was quenched with 1*N* aqueous NaOH at 0°C, and extracted with EtOAc (300 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was carefully purified by silica gel column chromatography (BW-200, 150 g, hexane:EtOAc = 7:2, then BW-200, 150 g, benzene:EtOAc = 5:1) to give **(*E*)-5a** (454 mg, 32%), **(*Z*)-5a** (679 mg, 49%), and **6a** (115 mg, 9%).

Compound (*E*)-5a. A colorless oil. IR ν_{max} (neat): 3700-3100, 2924, 2855, 1717, 1642, 1466, 1437, 1379, 1262, 1213, 1150, 1113, 1048, 920, 824, 749, 722 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.8 Hz), 1.25 (44 H, br), 1.40-1.70 (4 H, m), 1.92 (1 H, br), 2.02 (1 H, s), 2.30 (2 H, t, J = 7.9 Hz), 2.40 (2 H, d, J = 7.6 Hz), 3.36 (3 H, s), 3.51 (4 H, m), 3.73 (3 H, s), 4.61 (2 H, s), 6.78 (1 H, t, J = 7.3 Hz). DIF-NOE C3-H - C4-H 4.1%. FAB-MS m/z: 599 (MH^+). Anal. Calcd for $C_{36}H_{70}O_6$: C, 72.19; H, 11.78. Found: C, 72.36; H, 11.73.

Compound (*Z*)-5a. A colorless oil. IR ν_{max} (neat): 3700-3100, 2924, 2855, 1717, 1644, 1466, 1439, 1379, 1302, 1219, 1150, 1113, 1046, 920, 722, 677 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (46 H, br), 1.57 (2 H, m), 2.27 (2 H, m), 2.43 (1 H, dd, J = 7.9, 13.9 Hz), 2.63 (1 H, dd, J = 9.6, 13.9 Hz), 3.03 (1 H, s), 3.12 (1 H, t, J = 6.9 Hz), 3.36 (3 H, s), 3.32-3.47 (2 H, m), 3.51 (2 H, t, J = 6.6 Hz), 3.76 (3 H, s), 4.62 (2 H, s), 5.91 (1 H, t, J = 7.9 Hz). DIF-NOE C3-H - C4-H 6.4%, C3H - C1′-H 8.0% . Anal. Calcd for $C_{36}H_{70}O_6$: C, 72.19; H, 11.78. Found: C, 72.47; H, 11.73.

Compound 6a. A colorless oil. IR ν_{max} (neat): 3700-3100, 2924, 2853, 1717, 1466, 1441, 1379, 1240, 1150, 1111, 1046, 945, 920, 872, 824, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (42 H, br), 1.40-1.80 (6 H, m), 1.93 (1 H, t, J = 6.3 Hz), 2.20-2.30 (3 H, m), 2.74 (1 H, d, J = 7.2 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.52 (1 H, m), 3.71 (1 H, dd, J = 5.6, 11.9 Hz), 4.62 (2 H, s), 6.44 (1 H, br). Anal. Calcd for $C_{35}H_{66}O_5$: C, 74.15; H, 11.73. Found: C, 74.56; H, 11.60.

(*E*)-Methyl 2-Hexadecanyl-5-hydroxy-5-hydroxymethyl-17-methoxymethoxy-2-heptadecenoate (*E*-5b), (*Z*)-Methyl 2-Hexadecanyl-5-hydroxy-5-hydroxymethyl-17-methoxymethoxy-2-heptadecenoate (*Z*-5b), and 2-Hexadecanyl-5-hydroxymethyl-5-(12-methoxymethoxydodecanyl)-2-penten-5-olide (6b)

The acetonide **4b** (109 mg, 0.167 mM) was treated as described for **4a** to give **(*E*)-5b** (36 mg, 35%), **(*Z*)-5b** (48 mg, 47%), and **6b** (7 mg, 7%).

Compound (*E*)-5b. A white wax, mp 36-37°C. IR ν_{max} (neat): 3700-3100, 2924, 2855, 1717, 1642, 1466, 1437, 1267, 1215, 1150, 1113, 1047, 920, 824, 754, 721 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (46 H, br), 1.47-1.58 (4 H, m), 1.84 (1 H, br), 1.96 (1 H, br), 2.30 (2 H, t, J = 6.6 Hz), 2.41 (2 H, d, J = 7.6 Hz), 3.36 (3 H, s), 3.51 (4 H, m), 3.74 (3 H, s), 4.62 (2 H, s), 6.79 (1 H, t, J = 7.6 Hz). DIF-NOE C3-H - C4-H 5.2%. FAB-MS m/z: 613 (MH^+) ; Anal. Calcd for $C_{37}H_{72}O_6$: C, 72.50; H, 11.84. Found: C, 72.44; H, 11.67.

Compound (*Z*)-5b. A coloress oil. IR ν_{max} (neat): 3700-3100, 2926, 2853, 1717, 1466, 1439, 1379, 1302, 1223, 1150, 1113, 1046, 920, 804, 722 cm^{-1}. ^1H NMR δ 0.87 (3 H, t, J = 6.9 Hz), 1.25 (48 H, br), 1.58 (2 H, quint, J = 6.9 Hz), 2.27 (2 H, m), 2.43 (1 H, dd, J = 7.9, 13.9 Hz), 2.63 (1 H, dd, J = 9.6, 13.9 Hz), 3.09 (1 H, s), 3.11 (1 H, t, J = 6.6 Hz), 3.35 (3 H, s), 3.38 (2 H, ddd, J = 7.0, 11.2, 12.8 Hz), 3.51 (2 H, t, J = 6.6 Hz), 3.76 (3 H, s), 4.61 (2 H, s), 5.91 (1 H, t, J = 7.9 Hz). DIF-NOE C3-H - C4-H 10.2%, C3H - C1′-H 6.8%. Anal. Calcd for $C_{37}H_{72}O_6$: C, 72.50; H, 11.84. Found: C, 72.37; H,

11.58.

Compound 6b. A white wax, mp 57-59°C. IR ν_{max} (neat): 3700-3100, 2918, 2851, 1715, 1684, 1470, 1387, 1231, 1156, 1111, 1082, 1048, 958, 939, 918, 822, 720 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.41-1.75 (6 H, m), 1.96 (1 H, dd, J = 5.9, 7.6 Hz), 2.17-2.38 (3 H, m), 2.70-2.78 (1 H, m), 3.35 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.52 (1 H, m), 3.71 (1 H, dd, J = 5.9, 11.9 Hz), 4.61 (2 H, s), 6.43 (1 H, dd, J = 3.6, 5.0 Hz). Anal. Calcd for $C_{36}H_{68}O_5$: C, 74.43; H, 11.80. Found: C, 74.14; H, 11.67.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-17-methoxymethoxy-2-pentadecanyl-2-heptadecenoate (7a)

A mixture of **(Z)-5a** (632 mg, 1.06 mM), Et_3N (1.76 ml, 12.6 mM), DMAP (12.2 mg, 0.1 mM) and Ac_2O (990 μl, 10.5 mM) was stirred at room temperature for 29 h, and diluted with H_2O. The mixture was extracted with Et_2O (100 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100 g, hexane:Et_2O = 4:1) to give **7a** (655 mg, 91%) as a colorless oil. IR ν_{max} (neat): 2926, 2855, 1744, 1721, 1647, 1466, 1439, 1368, 1224, 1150, 1111, 1048, 941, 920, 819, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (44 H, br), 1.58 (2 H, m), 1.84 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.25 (2 H, t, J = 7.3 Hz), 3.01 (2 H, d, J = 7.3 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.27 (1 H, d, J = 11.5 Hz), 4.34 (1 H, d, J = 11.6 Hz), 4.62 (2 H, s), 5.79 (1 H, t, J = 7.3 Hz). FAB-MS m/z: 683 (MH^+). Anal. Calcd for $C_{40}H_{74}O_8$: C, 70.34; H, 10.92. Found: C, 70.60; H, 10.82.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-17-methoxymethoxy-2-heptadecenoate (7b)

The diol **(Z)-5b** (626 mg, 1.02 mM) was acetylated as described for **(Z)-5a** to give **7b** (606 mg, 85%) as a colorless oil. IR ν_{max} (neat): 2926, 2855, 1748, 1744, 1721, 1647, 1466, 1439, 1368, 1225, 1150, 1111, 1047, 941, 920, 822, 793, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (46 H, br), 1.59 (2 H, m), 1.84 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.25 (2 H, t, J = 7.3 Hz), 3.02 (2 H, d, J = 7.3 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.27 (1 H, d, J = 11.5 Hz), 4.34 (1 H, d, J = 11.6 Hz), 4.62 (2 H, s), 5.79 (1 H, t, J = 6.9 Hz). Anal. Calcd for $C_{41}H_{76}O_8$: C, 70.65; H, 10.99. Found: C, 70.44; H, 10.82.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-17-hydroxy-2-pentadecanyl-2-heptadecenoate (8a)

To a stirred solution of **7a** (52 mg, 0.076 mM) in CH_2Cl_2 (1.0 ml) was added dropwise bromotrimethylsilane (TMSBr) (163 μl, 1.22 mM) at -30°C under argon. After being stirred at -30°C for 1.5 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (30 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 3:1) to give **8a** (46 mg, 95%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 2926, 2855, 1744, 1721, 1647, 1466, 1437, 1368, 1227, 1150, 1049, 1024, 820, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.49 (1 H, br), 1.57 (2 H, m), 1.82 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.25 (2 H, t, J = 7.3 Hz), 3.02 (2 H, d, J = 7.3 Hz), 3.64 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.26 (1 H, d, J = 11.9 Hz), 4.34 (1 H, d, J = 11.9 Hz), 5.79 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{70}O_7$: C, 71.43; H, 11.04. Found: C, 71.14; H, 10.81.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-17-hydroxy-2-heptadecenoate (8b)

The diacetate **7b** (53 mg, 0.076 mM) was demethoxymethylated as described for **7a** to give **8b** (48 mg, 97%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 2926, 2855, 1744, 1721, 1644, 1466, 1439, 1368, 1225, 1150, 1049, 1024, 820, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (46 H, br), 1.55 (3 H, m), 1.84 (2 H, br), 2.01 (3 H, s), 2.07 (3 H, s), 2.25 (2 H, t, J = 7.3 Hz), 3.01 (2 H, d, J = 7.6 Hz), 3.64

(2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.26 (1 H, d, J = 11.5 Hz), 4.34 (1 H, d, J = 11.5 Hz), 5.79 (1 H, t, J = 7.3 Hz). FAB-MS m/z: 653 (MH^+). Anal. Calcd for $C_{39}H_{72}O_7$: C, 71.74; H, 11.11. Found: C, 71.53; H, 11.03.

(Z)-1-Methyl 17-Hydrogen 5-Acetoxy-5-acetoxymethyl-2-pentadecanyl-2-heptadecenedioate (9a)

To a solution of the alcohol **8a** (51 mg, 0.08 mM) in DMF (500 μl) was added pyridinium dichromate (PDC) (211 mg, 0.560 mM) at room temperature. After being stirred at room temperature for 2 h, the mixture was diluted with Et_2O. The ethereal solution was washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 5:2) to give **9a** (37 mg, 70%) as a pale yellow oil. IR ν_{max} (neat): 3700-2000, 2926, 2855, 1744, 1713, 1466, 1437, 1368, 1225, 1154, 1103, 1049, 1022, 943, 804, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.63 (2 H, quint, J = 7.6 Hz), 1.83 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.25 (2 H, t, J = 7.6 Hz), 2.34 (2 H, t, J = 7.6 Hz), 3.01 (2 H, d, J = 7.3 Hz), 3.73 (3 H, s), 4.26 (1 H, d, J = 11.5 Hz), 4.34 (1 H, d, J = 11.5 Hz), 5.79 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{68}O_8$: C, 69.90; H, 10.50. Found: C, 70.07; H, 10.44.

(Z)-1-Methyl 17-Hydrogen 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-2-heptadecenedioate (9b)

The alcohol **8b** (32 mg, 0.049 mM) was oxidized as described for **8a** to give **9b** (19 mg, 58%) as a pale yellow oil. IR ν_{max} (neat): 3750-2300, 2926, 2855, 1744, 1713, 1466, 1437, 1368, 1227, 1154, 1107, 1048, 1021, 943, 822, 795, 722 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.63 (2 H, quint, J = 7.3 Hz), 1.84 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.25 (2 H, t, J = 7.6 Hz), 2.34 (2 H, t, J = 7.6 Hz), 3.01 (2 H, d, J = 7.6 Hz), 3.73 (3 H, s), 4.26 (1 H, d, J = 11.9 Hz), 4.34 (1 H, d, J = 11.5 Hz), 5.79 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{39}H_{70}O_8$: C, 70.23; H, 10.58. Found: C, 70.56; H, 10.59.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-16-carbamoyl-2-pentadecanyl-2-hexadecenoate (10a)

To a stirred solution of **9a** (352 mg, 0.540 mM) and Et_3N (83 μl, 0.594 mM) in THF (5.0 ml) was added dropwise $ClCO_2Et$ (57 μl, 0.594 mM) at 0°C. The mixture was stirred at 0°C for 30 min, and then 28% aqueous NH_4OH (110 μl, 1.620 mM) was added dropwise. After being stirred at 0°C for 30 min, the mixture was quenched with H_2O, and extracted with EtOAc (40 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 30 g, hexane:EtOAc = 1:1 to 1:3) to give **10a** (295 mg, 84%) as a white wax, mp 63-64°C. IR ν_{max} ($CHCl_3$): 3360, 3200, 2928, 2855, 1732, 1676, 1609, 1466, 1437, 1387, 1370, 1217, 1148, 1022, 668 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.63 (2 H, m), 1.84 (2 H, br), 2.01 (3 H, s), 2.06 (3 H, s), 2.22 (2 H, t, J = 7.6 Hz), 2.25 (2 H, m), 3.01 (2 H, d, J = 7.3 Hz), 3.73 (3 H, s), 4.26 (1 H, d, J = 11.5 Hz), 4.33 (1 H, d, J = 11.9 Hz), 5.30 (2 H, br), 5.79 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{69}NO_7$: C, 70.01; H, 10.67; N, 2.15. Found: C, 69.77; H, 10.50; N, 2.06.

(Z)-Methyl 5-Acetoxy-5-acetoxymethyl-16-carbamoyl-2-hexadecanyl-2-hexadecenoate (10b)

The carboxylic acid **9b** (22 mg, 0.033 mM) was amidated as described for **9a** to give **10b** (21 mg, 96%) as a white wax, mp 55-57°C. IR ν_{max} ($CHCl_3$): 3360, 3200, 2926, 2855, 1738, 1669, 1466, 1439, 1368, 1229, 1105, 1048, 1022, 801, 724, 668 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.63 (2 H, quint, J = 7.3 Hz), 1.83 (2 H, br), 2.01 (3 H, s), 2.05 (3 H, s), 2.21 (2 H, t, J = 7.3 Hz), 2.24 (2 H, m), 3.01 (2 H, d, J = 7.3 Hz), 3.73 (3 H, s), 4.26 (1 H, d, J = 11.5 Hz), 4.33 (1 H, d, J = 11.9 Hz), 5.46 (2 H, br), 5.78 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{39}H_{71}NO_7 \cdot {}^1/_4H_2O$: C, 69.86; H, 10.75; N, 2.09. Found: C, 69.84; H, 10.62; N, 1.99.

5-(11-Carbamoylundecanyl)-5-hydroxymethyl-2-pentadecanyl-2-penten-5-olide (11a)

i) From 10a. To a stirred solution of **10a** (80 mg, 0.123 mM) in 90% aqueous MeOH (5.0 ml) was added K_2CO_3 (509 mg, 3.686 mM). After being stirred at room temperature for 1 h, the mixture was quenched with 1*N* aqueous HCl and extracted with $CHCl_3$ (30 ml x 5). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, $CHCl_3$:MeOH = 30:1) to give **11a** (58 mg, 88%) as a white wax, mp 89-90°C. IR ν_{max} ($CHCl_3$): 3700-3100, 3353, 3187, 2917, 2849, 1684, 1667, 1638, 1469, 1430, 1387, 1215, 1161, 1134, 1111, 955, 720, 669 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.6 Hz), 1.25 (40 H, br), 1.46 (2 H, m), 1.50-1.84 (4 H, m), 1.85 (1 H, br), 2.22 (2 H, t, J = 7.6 Hz), 2.31 (3 H, m), 2.74 (1 H, d, J = 8.1 Hz), 3.53 (1 H, d, J = 11.9 Hz), 3.70 (1 H, d, J = 11.9 Hz), 5.51(2 H, br), 6.44 (1 H, br). Anal. Calcd for $C_{33}H_{61}NO_4$: C, 73.97; H, 11.47; N, 2.61. Found: C, 74.01; H, 11.47; N, 2.55.

ii) From 15a. To a stirred solution of **15a** (12 mg, 0.021 mM) was added H_2O (0.2 ml) and K_2CO_3 (58 mg, 0.416 mM). After being stirred at ambient temperature for 1h, the mixture was neutralized with 1 *N* aq. HCl. The whole mixture was extracted with $CHCl_3$ (30 ml x 5), washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a white wax. The crude wax was purified by silica gel column chromatography (BW-300, 10 g, $CHCl_3$:MeOH = 35:1) to give **11a** (10 mg, 90%) as a white wax.

5-(11-Carbamoylundecanyl)-2-hexadecanyl-5-hydroxymethyl-2-penten-5-olide (11b)

i) From 10b. The amide **10b** (68 mg, 0.102 mM) was treated as described for **10a** to give **11b** (52 mg, 93%) as a white wax, mp 90-91°C. IR ν_{max} ($CHCl_3$): 3700-3100, 3357, 3190, 2923, 2849, 1684, 1669, 1636, 1472, 1431, 1387, 1215, 1161, 1134, 1111, 955, 920, 885, 850, 829, 720, 669 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.45 (2 H, m), 1.50-1,84 (4 H, m), 1.85 (1 H, br), 2.21 (2 H, t, J = 7.6 Hz), 2.31 (3 H, m), 2.73 (1 H, d, J = 8.5 Hz), 3.53 (1 H, d, J = 11.9 Hz), 3.70 (1 H, d, J = 11.9 Hz), 5.52(2 H, br), 6.44 (1 H, br). Anal. Calcd for $C_{34}H_{63}NO_4 \cdot {}^1/_4H_2O$: C, 73.66; H, 11.54; N, 2.53. Found: C, 73.72; H, 11.42; N, 2.41.

ii) From 15b. The monoacetate **15b** (17 mg, 0.029 mM) was treated as described for **15a** to give **11b** (14 mg, 89%) as a white wax.

5-Acetoxymethyl-5-(12-methoxymethoxydodecanyl)-2-pentadecanyl-2-penten-5-olide (12a)

A mixture of **6a** (105 mg, 0.186 mM), Et_3N (155 μl, 1.11 mM), DMAP (2 mg, 0.01 mM), and Ac_2O (88 μl, 0.93 mM) was stirred at room temperature for 1.5 h and diluted with H_2O. The mixture was extracted with Et_2O (50 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:Et_2O = 7:3) to give **12a** (96 mg, 85%) as a white wax, mp 39-40°C. IR ν_{max} ($CHCl_3$): 3019, 2926, 2855, 1744, 1713, 1655, 1466, 1381, 1368, 1217, 1169, 1048, 953, 920, 826, 668 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.40-1.80 (6 H, m), 2.08 (3 H, s), 2.27 (2 H, m), 2.45 (2 H, m), 3.36 (3 H, s), 3.51 (2 H, t, J= 6.6 Hz), 4.15 (2 H, dd, J = 11.5, 16.2 Hz), 4.62 (2 H, s), 6.40 (1 H, t, J = 4.6 Hz). Anal. Calcd for $C_{37}H_{68}O_6$: C, 72.98; H, 11.26. Found: C, 72.73; H, 11.05.

5-Acetoxymethyl-2-hexadecanyl-5-(12-methoxymethoxydodecanyl)-2-penten-5-olide (12b)

The alcohol **6b** (55 mg, 0.095 mM) was acetylated as described for **6a** to give **12b** (54 mg, 92%) as a pale yellow wax, mp 48-49°C. IR ν_{max} (neat): 3019, 2926, 2853, 1736, 1709, 1468, 1379, 1368, 1227, 1132, 1113, 1051, 955, 723, 648 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.40-1.80 (6 H, m), 2.08 (3 H, s), 2.27 (2 H, m), 2.45 (2 H, m), 3.36 (3 H, s), 3.51 (2 H, t, J= 6.6 Hz), 4.15 (2 H, dd, J = 11.5, 16.2 Hz), 4.62 (2 H, s), 6.40 (1 H, br). Anal. Calcd for $C_{38}H_{70}O_6$: C, 73.27; H, 11.33. Found: C, 73.32; H, 11.22.

5-Acetoxymethyl-5-(12-hydroxydodecanyl)-2-pentadecanyl-2-penten-5-olide (13a)

To a stirred solution of **12a** (84 mg, 0.138 mM) in CH_2Cl_2 (2.0 ml) was added dropwise TMSBr (75

μl, 0.553 mM) at -30°C under argon. After being stirred at -30°C for 2 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (50 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 7:2) to give **13a** (64 mg, 82%) as a white wax, mp 47-48°C. IR ν_{max} (neat): 3700-3100, 2924, 2853, 1752, 1721, 1466, 1439, 1379, 1368, 1229, 1129, 1107, 1051, 953, 889, 826 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.40-1.80 (7 H, m), 2.08 (3 H, s), 2.28 (2 H, m), 2.45 (2 H, m), 3.63 (2 H, t, J= 6.6 Hz), 4.14 (2 H, dd, J = 11.5, 16.2 Hz), 6.40 (1 H, t, J = 4.6 Hz). FAB-MS m/z: 565 (MH^+). Anal. Calcd for $C_{35}H_{64}O_5 \cdot {}^1/_4H_2O$: C, 73.87; H, 11.42. Found: C, 73.91; H, 11.15.

5-Acetoxymethyl-2-hexadecanyl-5-(12-hydroxydodecanyl)-2-penten-5-olide (13b)

The methoxymethyl derivative **12b** (73 mg, 0.117 mM) was treated as described for **12a** to give **13b** (55 mg, 81%) as a white wax, mp 35-36°C. IR ν_{max} (neat): 3700-3100, 2924, 2855, 1750, 1721, 1466, 1437, 1379, 1368, 1129, 1107, 1051, 951, 828 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.40-1.80 (7 H, m), 2.08 (3 H, s), 2.27 (2 H, m), 2.45 (2 H, m), 3.63 (2 H, t, J= 6.6 Hz), 4.14 (2 H, dd, J = 11.5, 16.2 Hz), 6.39 (1 H, t, J = 4.3 Hz). Anal. Calcd for $C_{36}H_{66}O_5$: C, 74.69; H, 11.49. Found: C, 74.40; H, 11.49.

5-Acetoxymethyl-5-(11-carboxyundecanyl)-2-pentadecanyl-2-penten-5-olide (14a)

To a solution of the alcohol **13a** (56 mg, 0.099 mM) in DMF (500 μl) was added PDC (261 mg 0.695 mM) at room temperature. After being stirred at room temperature for 2.5 h, the mixture was diluted with Et_2O. The ethereal solution was washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 7:2) to give **14a** (38 mg, 66%) as a white wax, mp 31-32°C. IR ν_{max} (neat): 3700-2000, 2851, 1732, 1715, 1700, 1468, 1392, 1368, 1229, 1132, 1107, 1049, 953, 831, 722 cm^{-1}. ^1H NMR δ: 0.86 (3 H, t, J = 6.6 Hz), 1.24 (40 H, br), 1.45 (2 H, m), 1.50-1.80 (4 H, m), 2.07 (3 H, s), 2.27 (2 H, m), 2.33 (2 H, t, J = 7.6 Hz), 2.45 (2 H, m), 4.14 (2 H, dd, J = 11.5, 16.5 Hz), 6.39 (1 H, t, J = 4.3 Hz). Anal. Calcd for $C_{35}H_{62}O_6$: C, 72.62; H, 10.80. Found: C, 72.16; H, 10.61.

5-Acetoxymethyl-5-(11-carboxyundecanyl)-2-hexadecanyl-2-penten-5-olide (14b)

The alcohol **13b** (51 mg, 0.088 mM) was oxidized as described for **13a** to give **14b** (37 mg, 71%) as a white wax, mp 49-51°C. IR ν_{max} ($CHCl_3$): 3700-2000, 2855, 1744, 1713, 1466, 1379, 1368, 1229, 1129, 1107, 1049, 953 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.6 Hz), 1.25 (42 H, br), 1.46 (2 H, m), 1.50-1.80 (4 H, m), 2.08 (3 H, s), 2.30 (2 H, m), 2.34 (2 H, t, J = 7.6 Hz), 2.45 (2 H, m), 4.14 (2 H, dd, J = 11.5, 16.5 Hz), 6.40 (1 H, br). Anal. Calcd for $C_{36}H_{64}O_6$: C, 72.93; H, 10.88. Found: C, 72.60; H, 10.58.

5-Acetoxymethyl-5-(11-carbamoylundecanyl)-2-pentadecanyl-2-penten-5-olide (15a)

To a stirred solution of **14a** (22 mg, 0.038 mM) and Et_3N (2% solution of THF, 292 μl, 0.042 mM) in THF (900 μl) was added dropwise $ClCO_2Et$ (2% solution of THF, 201 μl, 0.042 mM) at 0°C. The mixture was stirred at 0°C for 30 min and then 28% aqueous NH_4OH (2% solution of THF, 387 μl, 0.114 mM) was added dropwise. After being stirred at 0°C for 30 min, the mixture was quenched with H_2O, and extracted with EtOAc (30 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 1:1 to 1:3) to give **15a** (20 mg, 91%) as a white wax, mp 65-67°C. IR ν_{max} (neat): 3418, 3198, 2928, 2855, 1744, 1720, 1684, 1466, 1391, 1236, 1105, 1049 cm^{-1}. ^1H NMR δ: 0.86 (3 H, t, J = 6.9 Hz), 1.24 (40 H, br), 1.45 (2 H, m), 1.50-1.80 (4 H, m), 2.07 (3 H, s), 2.20 (2 H, t, J = 7.6 Hz), 2.28 (2 H, m), 2.45 (2 H, m), 4.13 (2 H, dd, J = 11.5, 15.8 Hz), 5.51 (2 H, br), 6.39 (1 H, br). Anal Calcd for $C_{35}H_{63}NO_5$: C, 72.75; H, 10.99; N, 2.42. Found: C, 72.31; H, 10.78; N, 2.44.

5-Acetoxymethyl-5-(11-carbamoylundecanyl)-2-hexadecanyl-2-penten-5-olide (15b)

The carboxylic acid **14b** (10 mg, 0.017 mM) was amidated as described for **14a** to give **15b** (10 mg, 100%) as a white wax, mp 71-72°C. IR ν_{max} (neat): 3397, 3202, 2924, 2853, 1736, 1709, 1657, 1628, 1466, 1391, 1229, 1107, 1049, 953, 876 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.46 (2 H, quint, J = 6.9 Hz), 1.50-1.80 (4 H, m), 2.08 (3 H, s), 2.22 (2 H, t, J = 7.3 Hz), 2.28 (2 H, m), 2.46 (2 H, m), 4.14 (2 H, dd, J = 11.5, 15.8 Hz), 5.20 - 5.50 (2 H, br), 6.40 (1 H, t, J = 4.3 Hz). Anal. Calcd for $C_{36}H_{65}NO_5 \cdot {}^1/_2H_2O$: C, 71.96; H, 11.07; N, 2.37. Found: C, 71.71; H, 10.69; N 2.33.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-17-methoxymethoxy-2-pentadecanyl-2-heptadecenoate (16a)

A mixture of **(*E*)-5a** (405 mg, 0.677 mM), Et_3N (1.13 ml, 8.12 mM), DMAP (8.3 mg, 0.068 mM), and Ac_2O (638 μl, 6.77 mM) was stirred at room temperature for 9 h and diluted with H_2O. The mixture was extracted with Et_2O (50 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100 g, hexane:Et_2O = 4:1) to give **16a** (418 mg, 90%) as a colorless oil. IR ν_{max} (neat): 2926, 2855, 1748, 1718, 1646, 1466, 1437, 1368, 1225, 1150, 1111, 1048, 920, 824, 739, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.59 (2 H, m), 1.87 (2 H, m), 2.02 (3 H, s), 2.07 (3 H, s), 2.28 (2 H, t, J = 7.9 Hz), 2.77 (2 H, m), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.25 (1 H, d, J = 11.9 Hz), 4.36 (1 H, d, J = 11.5 Hz), 4.62 (2 H, s), 6.67 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{40}H_{74}O_8$: C, 70.34; H, 10.92. Found: C, 70.44; H, 10.88.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-17-methoxymethoxy-2-heptadecenoate (16b)

The diol **(*E*)-5b** (398 mg, 0.650 mM) was acetylated as described for **(*E*)-5a** to give **16b** (396 mg, 87%) as a pale yellow oil. IR ν_{max} (neat): 2926, 2855, 1748, 1744, 1719, 1647, 1466, 1437, 1368, 1225, 1150, 1113, 1048, 920, 824, 756, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.8 Hz), 1.26 (46 H, br), 1.57 (2 H, m), 1.87 (2 H, m), 2.02 (3 H, s), 2.07 (3 H, s), 2.28 (2 H, t, J = 7.3 Hz), 2.72 (1 H, dd, J = 5.3, 16.2 Hz), 2.79 (1 H, dd, J = 5.3, 16.5 Hz), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.25 (1 H, d, J = 11.5 Hz), 4.36 (1 H, d, J = 11.6 Hz), 4.62 (2 H, s), 6.68 (1 H, t, J = 7.6 Hz). Anal. Calcd for $C_{41}H_{76}O_8$: C, 70.65; H, 10.99. Found: C, 71.00; H, 11.00.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-17-hydroxy-2-pentadecanyl-2-heptadecenoate (17a)

To a stirred solution of **16a** (50 mg, 0.073 mM) in CH_2Cl_2 (1.0 ml) was added dropwise TMSBr (39 μl, 0.293 mM) at -30°C under argon. After being stirred at -30°C for 1.5 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (30 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 7:2) to give **17a** (46 mg, 98%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 2926, 2855, 1744, 1719, 1646, 1466, 1437, 1368, 1227, 1134, 1049, 957, 749, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.56 (2 H, m), 1.87 (2 H, m), 2.02 (3 H, s), 2.07 (3 H, s), 2.28 (2 H, t, J = 7.6 Hz), 2.76 (2 H, m), 3.63 (2 H, t, J = 6.6 Hz), 3.74 (3 H, s), 4.25 (1 H, d, J = 11.9 Hz), 4.36 (1 H, d, J = 11.9 Hz), 6.67 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{70}O_7$: C, 71.43; H, 11.04. Found: C, 70.83; H, 10.74.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-17-hydroxy-2-heptadecenoate (17b)

The diacetate **16b** (12 mg, 0.017 mM) was demethoxymethylated as described for **16a** to give **17b** (9 mg, 80%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 2926, 2855, 1744, 1719, 1644, 1466, 1437, 1368, 1227, 1049, 959, 747, 722 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.25 (46 H, br), 1.51-1.64 (3 H, m), 1.86 (2 H, m), 2.02 (3 H, s), 2.06 (3 H, s), 2.27 (2 H, dd, J = 5.0, 7.3 Hz), 2.72 (1 H, dd, J = 7.3, 15.7 Hz), 2.79 (1 H, dd, J = 7.3, 15.5 Hz), 3.63 (2 H, t, J = 6.6 Hz), 3.73 (3 H, s), 4.25 (1 H, d, J = 11.9

Hz), 4.36 (1 H, d, J = 11.6 Hz), 6.67 (1 H, t, J = 7.3 Hz). FAB-MS m/z: 653 (MH^+). Anal. Calcd for $C_{39}H_{72}O_7$: C, 71.74; H, 11.11. Found: C, 72.03; H, 11.08.

(*E*)-1-Methyl 17-Hydrogen 5-Acetoxy-5-acetoxymethyl-2-pentadecanyl-2-heptadecenedioate (18a)

To a solution of the alcohol **17a** (52 mg, 0.082 mM) in DMF (500 µl) was added PDC (215 mg, 0.570 mM) at room temperature. After being stirred at room temperature for 2.5 h, the mixture was diluted with Et_2O. The ethereal solution was washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, hexane:EtOAc = 7:2) to give **18a** (33 mg, 62%) as a pale yellow oil. IR ν_{max} (neat): 3700-2300, 2926, 2855, 1744, 1717, 1647, 1466, 1437, 1368, 1227, 1134, 1049, 1022, 947, 799, 722 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.24 (42 H, br), 1.62 (2 H, quint, J = 7.3 Hz), 1.86 (2 H, br), 2.02 (3 H, s), 2.06 (3 H, s), 2.27 (2 H, m), 2.33 (2 H, t, J = 7.6 Hz), 2.72 (1 H, dd, J = 7.3, 15.8 Hz), 2.79 (1 H, dd, J = 7.3, 15.8 Hz), 3.73 (3 H, s), 4.24 (1 H, d, J = 11.9 Hz), 4.36 (1 H, d, J = 11.5 Hz), 6.67 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{68}O_8$: C, 69.90; H, 10.50. Found: C, 69.65; H, 10.33.

(*E*)-1-Methyl 17-Hydrogen 5-Acetoxy-5-acetoxymethyl-2-hexadecanyl-2-heptadecenedioate (18b)

The alcohol **17b** (100 mg, 0.153 mM) was oxidized as described for **17a** to give **18b** (62 mg, 61%) as a pale yellow oil. IR ν_{max} (neat): 3700-2300, 2926, 2855, 1744, 1717, 1647, 1466, 1437, 1368, 1227, 1048, 949, 799, 722 cm^{-1}. ^1H NMR δ 0.88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.63 (2 H, quint, J = 7.3 Hz), 1.87 (2 H, m), 2.02 (3 H, s), 2.07 (3 H, s), 2.27 (2 H, m), 2.34 (2 H, t, J = 7.3 Hz), 2.73 (1 H, dd, J = 7.9, 16.2 Hz), 2.80 (1 H, dd, J = 7.9, 15.8 Hz), 3.73 (3 H, s), 4.25 (1 H, d, J = 11.5 Hz), 4.36 (1 H, d, J = 11.6 Hz), 6.67 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{39}H_{70}O_8$: C, 70.23; H, 10.58. Found: C, 70.48; H, 10.45.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-16-carbamoyl-2-pentadecanyl-2-hexadecenoate (19a)

To a stirred solution of **18a** (199 mg, 0.305 mM) and Et_3N (47 µl, 0.336 mM) in THF (3.0 ml) was added dropwise $ClCO_2Et$ (32 µl, 0.336 mM) at 0°C. The mixture was stirred at 0°C for 30 min and then 28% aqueous NH_4OH (62 µl, 0.916 mM) was added dropwise. After being stirred at 0°C for 30 min, the mixture was quenched with H_2O, and extracted with EtOAc (50 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 30 g, hexane:EtOAc = 2:3 to 1:3) to give **19a** (178 mg, 90%) as a white wax, mp 66-68°C. IR ν_{max} ($CHCl_3$): 3353, 3212, 3021, 2928, 2855, 1732, 1713, 1678, 1613, 1466, 1437, 1387, 1370, 1217, 1132, 1049, 1022, 955, 930,845, 826, 668 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.63 (2 H, m), 1.87 (2 H, br), 2.02 (3 H, s), 2.07 (3 H, s), 2.22 (2 H, t, J = 7.3 Hz), 2.28 (2 H, m), 2.77 (2 H, m), 3.74 (3 H, s), 4.25 (1 H, d, J = 11.5 Hz), 4.36 (1 H, d, J = 11.9 Hz), 5.10-5.70 (2 H, br), 6.67 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{69}NO_7$: C, 70.01; H, 10.67; N, 2.15. Found: C, 69.82; H, 10.50; N, 2.10.

(*E*)-Methyl 5-Acetoxy-5-acetoxymethyl-16-carbamoyl-2-hexadecanyl-2-hexadecenoate (19b)

The carboxylic acid **18b** (11 mg, 0.017 mM) was amidated as described for **18a** to give **19b** (11 mg, 100%) as a white wax, mp 55-57°C. IR ν_{max} ($CHCl_3$): 3600-3000, 3586, 3021, 2928, 2855, 1733, 1709, 1671, 1466, 1458, 1437, 1370, 1215, 1048, 756, 668 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 7.3 Hz), 1.25 (44 H, br), 1.64 (2 H, m), 1.86 (2 H, m), 2.02 (3 H, s), 2.07 (3 H, s), 2.22 (2 H, t, J = 7.3 Hz), 2.28 (2 H, m), 2.73 (1 H, dd, J = 7.6, 15.8 Hz), 2.80 (1 H, dd, J = 7.6, 15.8 Hz), 3.73 (3 H, s), 4.25 (1 H, d, J = 11.6 Hz), 4.36 (1 H, d, J = 11.9 Hz), 5.25-5.60 (2 H, br), 6.67 (1 H, t, J = 7.6 Hz). Anal. Calcd for $C_{39}H_{71}NO_7$: C, 70.34; H, 10.75; N, 2.10. Found: C, 69.92; H, 10.62; N, 2.02.

(*E*)-Methyl 16-Carbamoyl-5-hydroxy-5-hydroxymethyl-2-pentadecanyl-2-hexadecenoate (20a)

To a stirred solution of **19a** (16 mg, 0.025 mM) in 90% aqueous MeOH (1.5 ml) was added K_2CO_3 (102 mg, 0.737 mM). After being stirred at room temperature for 2 h, the mixture was quenched with 1*N* aqueous HCl and extracted with $CHCl_3$ (30 ml x 4). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 60:1 to 50:1 to 40:1) to give **20a** (14 mg, 100%) as a white wax, mp 40-42 °C. IR ν_{max} ($CHCl_3$): 3700-3100, 3410, 3210, 3017, 2926, 2855, 1705, 1669, 1613, 1466, 1437, 1406, 1262, 1215, 1075, 1050, 926, 668 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.9 Hz), 1.24 (42 H, br), 1.48 (2 H, br), 1.62 (2 H, quint, J = 7.3 Hz), 2.14 (2 H, br), 2.20 (2 H, t, J = 7.3 Hz), 2.29 (2 H, t, J = 7.9 Hz), 2.39 (2 H, d, J = 7.6 Hz), 3.47 (3 H, s), 5.58 (2 H, br), 6.79 (1 H, t, J = 7.3 Hz). Anal Calcd for $C_{34}H_{65}NO_5$: C, 71.91; H, 11.54; N, 2.47. Found: C, 71.59; H, 11.55; N, 2.37.

(*E*)-Methyl 16-Carbamoyl-2-hexadecanyl-5-hydroxy-5-hydroxymethyl-2-hexadecenoate (20b)

A mixture of **19b** (10 mg, 0.015 mM) and bis(tributyltin) oxide (BBTO) (46 μl, 0.090 mM) in benzene (1.0 ml) was refluxed for 3 days under argon and quenched with 1*N* aqueous HCl. The mixture was extracted with $CHCl_3$ (30 ml x 4), washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 8 g, $CHCl_3$:MeOH = 35:1) to give **20b** (8 mg, 92%) as a white wax, mp 70-71°C. IR ν_{max} ($CHCl_3$): 3700-3100, 3409, 3208, 1709, 1667, 1617, 1468, 1435, 1418, 1377, 1347, 1266, 1208, 1140, 1117, 1071, 1051, 959, 906, 824, 785, 735, 650 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.24 (44 H, br), 1.49 (2 H, br), 1.63 (2 H, t, J = 6.9 Hz), 1.84 (2 H, br), 2.23 (2 H, t, J = 7.3 Hz), 2.30 (2 H, m), 2.41 (2 H, d, J = 6.6 Hz), 3.49 (2 H, s), 3.73 (3 H, s), 5.54 (2 H, br), 6.79 (1 H, t, J = 7.3 Hz). Anal Calcd for $C_{35}H_{67}NO_5 \cdot {}^1/_2H_2O$: C, 71.14; H, 11.60; N, 2.37. Found: C, 71.10; H, 11.33; N, 2.22.

(*E*)-Methyl 16-Carbamoyl-2-pentadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenate (21a)

To a stirred solution of **20a** (14 mg, 0.025 mM) in CH_2Cl_2 (1.4 ml) was added 2,2-dimethoxypropane (30 μl, 0.25 mM) and pyridinium *p*-toluenesulfonate (PPTS) (0.6 mg, 0.002 mM) at room temperature. After being stirred at room temperature for 4 h, the mixture was diluted with Et_2O. The ethereal solution was washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 60:1) to give **21a** (13 mg, 87%) as a white wax. IR ν_{max} ($CHCl_3$): 3416, 3196, 2986, 2926, 2855, 1713, 1674, 1613, 1466, 1437, 1408, 1381, 1370, 1252, 1215, 1154, 1061, 976, 922, 870, 818, 723, 668 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (40 H, br), 1.38 (3 H, s), 1.41 (3 H, s), 1.60 (6 H, br), 2.22 (2 H, t, J = 7.3 Hz), 2.28 (2 H, m), 2.46 (2 H, m), 3.73 (3 H, s), 3.78 (2 H, s), 5.43 (2 H, br), 6.76 (1 H, t, J = 7.3 Hz).

(*E*)-Methyl 16-Carbamoyl-2-hexadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenate (21b)

The diol **20b** (8 mg, 0.014 mM) was treated as described for **20a** to give **21b** (9 mg, quant.) as a white wax, mp 37-38°C. IR ν_{max} ($CHCl_3$): 3355, 3195, 2984, 2926, 2855, 1709, 1674, 1613, 1466, 1437, 1406, 1381, 1372, 1254, 1213, 1152, 1098, 1061, 976, 909, 872, 820, 735, 648 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.6 Hz), 1.25 (42 H, br), 1.38 (3 H, s), 1.41 (3 H, s), 1.50-1.70 (6 H, m), 2.22 (2 H, t, J = 7.3 Hz), 2.28 (2 H, m), 2.46 (2 H, m), 3.73 (3 H, s), 3.78 (2 H, s), 5.46 (2 H, br), 6.76 (1 H, t, J = 7.3 Hz). Anal. Calcd for $C_{38}H_{71}N0_5 \cdot {}^1/_4H_2O$: C, 72.85; H, 11.50; N, 2.24. Found: C, 72.72; H, 11.21; N, 2.05.

(*E*)-16-Carbamoyl-2-hexadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenol (22b)

To a stirred solution of **21b** (9 mg, 0.015 mM) in THF (1.0 ml) was added $LiAlH_4$ (6 mg, 0.145 mM) at 0°C under argon. After being stirred at 0°C for 1 h, the mixture was quenched with EtOAc and extracted with $CHCl_3$ (20 ml x 5). The extracts were successively washed with 1*N* aqueous HCl, H_2O, and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 40:1) to give **22b** (4 mg, 47%) as a white wax. IR ν_{max} ($CHCl_3$): 3700-3100, 2986, 2926, 2855, 1671, 1466, 1458, 1380, 1372, 1250, 1215, 1159, 666 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 6.6 Hz), 1.25 (42 H, br), 1.38 (3 H, s), 1.40 (3 H, s), 1.50-1.70 (7 H, m), 2.08 (2 H, t, J = 7.3 Hz), 2.22 (2 H, t, J = 7.3 Hz), 2.34 (2 H, m), 3.73 (3 H, s), 3.76 (2 H, s), 4.06 (2 H, s), 5.43 (3 H, br.t, J = 7.3 Hz).

(*E*)-16-Carbamoyl-2-hexadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenal (23b)

To a stirred solution of **22b** (4 mg, 0.007 mM) in CH_2Cl_2 (200 μl) was added CMD-1 (12 mg, 0.132 mM). After being stirred at room temperature for 2 days, the mixture was diluted with CH_2Cl_2 and filtered through the pad of celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 50:1) to give **23b** (4 mg, 100%) as a colorless oil. IR ν_{max} ($CHCl_3$): 3497, 3412, 3019, 2928, 2855, 1719, 1682, 1610, 1466, 1406, 1381, 1372, 1262, 1215, 1156, 1098, 1059, 928, 864, 669 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.40 (3 H, s), 1.43 (3 H, s), 1.60 (6 H, br), 2.22 (4 H, t, J = 7.3 Hz), 2.63 (2 H, d, J = 7.3 Hz), 3.81 (2 H, dd, J = 8.9, 13.5 Hz), 5.42 (2 H, br), 6.56 (1 H, t, J = 7.3 Hz), 9.40 (1 H, s).

(*E*)-16-Carbamoyl-2-hexadecanyl-5-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenoic acid (24b)

A mixture of **23b** (4 mg, 0.007 mM), *t*-BuOH (200 μl) and 2-methyl-2-butene (100 μl) was added dropwise to a 1.0 M solution of $NaClO_2$ in 20% aqueous NaH_2PO_4 (68 ml, 0.068 mM). After being stirred at room temperature for 30 min, the mixture was quenched with 10% aqueous $NaHSO_3$ and extracted with $CHCl_3$ (20 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 50:1) to give **24b** (2 mg, 49%) as a white wax. IR ν_{max} ($CHCl_3$): 3700-3000, 3501, 3196, 3019, 2928, 2855, 1684, 1595, 1466, 1416, 1381, 1372, 1262, 1215, 1098, 1057, 1026, 928, 866, 804, 669 cm^{-1}. ^1H NMR δ 0.88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.38 (3 H, s), 1.42 (3 H, s), 1.50-1.70 (6 H, br), 2.24 (2 H, t, J = 7.3 Hz), 2.29 (2 H, m), 2.49 (2 H, m), 3.79 (2 H, s), 5.50 (1 H, br), 6.05 (1 H, br), 6.86 (1 H, t, J = 7.3 Hz).

(*E,Z*)-2-Hexadecanyl-17-methoxymethoxy-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenoic acid (25b)

To a stirred solution of the ester **4b** (7 mg, 0.011 mM) in MeOH (1.5 ml) was added 1*N* aqueous NaOH (500 μl). After being stirred at room temperature for 5h, then refluxed for 41 h, the mixture was quenched with 1*N* aqueous HCl and extracted with Et_2O (30 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, hexane:EtOAc = 5:1) to give **25b** (6 mg, 88%) as a colorless oil. IR ν_{max} ($CHCl_3$): 3600-3000, 2928, 2855, 1686, 1466, 1383, 1372, 1262, 1215, 1152, 1107, 1048, 806, 650 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.3 Hz), 1.25 (46 H, br), 1.39 (3 H, s), 1.41 (3 H, s), 1.58 (4 H, quint, J = 6.6 Hz), 2.30 (2 H, m), 2.48 (0.8 H, d, J = 7.6 Hz), 2.62 (0.6 H, q, J = 7.3 Hz), 2.80 (0.6 H, q, J = 7.3 Hz), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.9 Hz), 3.78 (0.8 H, s), 3.80 (1.2 H, s), 4.62 (2 H, s), 6.03 (0.6 H, t, J = 7.3 Hz), 6.56 (0.4 H, t, J = 7.6 Hz).

(*E*)-*t*-Butyl 16-Carbamoyl-2-pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenate (28a) and (*E*)-Di-*t*-butyl 2-Pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenedioate (29a)

To a stirred solution of **21a** (12 mg, 0.02 mM) in THF (750 μl) was added 1*N* aqueous NaOH (250 μl). After being stirred at room temperature for 1 week, then warmed to 45°C and stirred for 3 weeks. The mixture was quenched with 1*N* aqueous HCl, and extracted with $CHCl_3$ (20 ml x 5). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next step without further purification.

The crude oil was dissolved in CH_2Cl_2 (200 μl), *t*-BuOH (100 μl) and *O*-*t*-Bu-*N,N'*-diisopropylisourea (50 μl, 0.2 mM) was added. After being stirred at room temperature for 24 h, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 100:1 to 60:1) to give **28a** (7 mg, 55%) and **29a** (5 mg, 36%) as colorless oils, respectively.

Compound 28a. IR ν_{max} ($CHCl_3$): 3341, 3198, 2926, 2855, 1694, 1674, 1613, 1522, 1464, 1458, 1393, 1381, 1370, 1254, 1215, 1157, 1132, 1097, 1061, 976, 922, 866, 853, 804, 723, 668 cm^{-1}. ^1H NMR δ: 0 88 (3 H, t, J = 6.0 Hz), 1.25 (42 H, br), 1.34 (3 H, s), 1.41 (3 H, s), 1.48 (9 H, s), 1.63 (4 H, m), 2.22 (4 H, t, J = 7.3 Hz), 2.43 (2 H, d, J = 7.6 Hz), 3.76 (2 H, s), 5.40 (2 H, br), 6.66 (1 H, t, J = 7.3 Hz).

Compound 29a. IR ν_{max} ($CHCl_3$): 2979, 2928, 2855, 1728, 1707, 1646, 1466, 1458, 1393, 1379, 1368, 1258, 1215, 1156, 1102, 1063, 976, 920, 868, 851, 804, 668 cm^{-1}. ^1H NMR δ 0 87 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.39 (3 H, s), 1.40 (3 H, s), 1.44 (9 H, s), 1.47 (9 H, s), 1.59 (4 H, m), 2.19 (4 H, t, J = 7.6 Hz), 2.42 (2 H, d, J = 7.3 Hz), 3.76 (2 H, s), 6.66 (1 H, t, J = 7.3 Hz).

(*E*)-16-Carbamoyl-5-hydroxy-5hydroxymethyl-2-pentadecanyl-2-hexadecenoic acid (*E*-1a)

A mixture of **28a** (7 mg, 2.34 mM) and 90% aqueous trifluoroacetic acid (TFA) (1.0 ml) was stirred at room temperature for 2 days. After addition of H_2O, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH:AcOH = 100:1:1 to 100:3:1) to give **(*E*)-1a** (4 mg, 67%) as a white waxy solid, mp 57-59°C. IR ν_{max} ($CHCl_3$): 3700-3100, 3700-2100, 3351, 3204, 3019, 2928, 2855, 1682, 1466, 1414, 1261, 1071, 1049, 928, 669 cm^{-1}. ^1H NMR δ: 0.87 (3 H, t, J = 5.9 Hz), 1.25 (42 H, br), 1.47 (2 H, br), 1.63 (2 H, br), 2.24 (4 H, br), 2.42 (2 H, d, J = 5.9 Hz), 3.50 (2 H, br), 5.63 (1 H, br), 6.10-6.40 (1 H, br), 6.90 (1 H, br).

(*E*)-16-Carbamoyl-5-hydroxy-5hydroxymethyl-2-hexadecanyl-2-hexadecenoic acid (*E*-1b) and (*E*)-Di-*t*-butyl 2-Hexadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxocyclopentyl)-2-heptadecenedioate (29b)

i) From 21b. To a stirred solution of **21b** (24 mg, 0.039 mM) in THF (1.5 ml) was added 1*N* aqueous LiOH (500 μl). After being stirred at 40°C for 3 weeks, the mixture was quenched with 1*N* aqueous HCl, and extracted with $CHCl_3$ (20 ml x 5). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next step without further purification.

The crude oil was dissolved in CH_2Cl_2 (500 μl), and *t*-BuOH (250 μl) and *O*-*t*-Bu-*N,N'*-diisopropylisourea (100 μl, 0.42 mM) were added. After being stirred at room temperature for 48 h, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 100:1 to 60:1) to give **29b** (11 mg, 40%) as a colorless oil and a crude **28b**. The crude **28b** was used for the next step without further purification.

Compound 29b. IR ν_{max} ($CHCl_3$): 3019, 2980, 2928, 2855, 1717, 1707, 1646, 1466, 1458, 1393, 1368, 1254, 1215, 1156, 1061, 976, 926, 851, 668 cm^{-1}. ^1H NMR δ 0 87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.39 (3 H, s), 1.40 (3 H, s), 1.44 (9 H, s), 1.47 (9 H, s), 1.50-1.70 (4 H, br), 2.19 (2 H, t, J = 7.6 Hz), 2.23 (2 H, m), 2.42 (2 H, d, J = 7.6 Hz), 3.76 (2 H, s), 6.66 (1 H, t, J = 7.6 Hz).

A mixture of the above crude **28b** and 90% aqueous TFA (2.0 ml) was stirred at room temperature for 2 days. The mixture was added to H_2O and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH:AcOH = 100:1:1 to 100:3:1) to give **(*E*)-1b** (7 mg, 32% from **21b**) as a white waxy solid, mp 67-70 °C.

ii) From 24b. A mixture of **24b** (2 mg, 0.003 mM) and 80% aqueous AcOH (200 µl) was stirred ambient temperature for 40 h. The mixture was concentrated *in vacuo*, to give pale yellow wax. The crude wax was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 20:1 to 15:1 to 10:1) to give **(*E*)-1b** (2 mg, quant.) as a white wax. IR ν_{max} ($CHCl_3$): 3700-3100, 3700-2100, 3335, 3212, 3019, 2924, 2851, 1686, 1667, 1468, 1416, 1273, 1262, 1215, 1121, 1069, 1049, 930, 907, 669 cm^{-1}. ^1H NMR δ: 0 87 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.50 (2 H, br), 1.62 (2 H, br), 2.27 (4 H, br), 2.41 (2 H, br), 3.49 (2 H, br), 5.50-6.00 (1 H, br), 6.00-6.70 (1 H, br), 6.90 (1 H, br), 8.50-8.60 (1 H, br). Anal. Calcd for $C_{34}H_{65}N0_5 \cdot CF_3COOH \cdot H_2O$: C, 61.78; H, 9.78; N, 2.00. Found: C, 61.96; H, 9.54; N, 2.06.

(*E*)-2-Pentadecanyl-5-hydroxy-5-hydroxymethyl-2-heptadecenedioic acid (30a)

A mixture of **29a** (5 mg, 0.007 mM) and 90% aqueous TFA (1.0 ml) was stirred at room temperature for 15 h. The mixture was added to H_2O and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-300, 1.2 g, $CHCl_3$:MeOH = 50:1) to give **30a** (2 mg, 51%) as a white wax. IR ν_{max} ($CHCl_3$): 3700-3100, 3700-2100, 3019, 2926, 2855, 1700, 1638, 1466, 1414, 1273, 1262, 1215, 1073, 1046, 928, 669 cm^{-1}. ^1H NMR δ: 0 88 (3 H, t, J = 6.9 Hz), 1.25 (42 H, br), 1.49 (2 H, br), 1.64 (4 H, br), 2.35 (4 H, br), 2.41 (2 H, br), 3.49 (2 H, s), 6.94 (1 H, br).

(*E*)-2-Hexadecanyl-5-hydroxy-5-hydroxymethyl-2-heptadecenedioic acid (30b)

The *tert*-butyl ester **29b** (9 mg, 0.013 mM) was treated as described for **29a** to give **30b** (6 mg, 85%) as a white wax. IR ν_{max} ($CHCl_3$): 3700-3100, 3700-2100, 3021, 2928, 2855, 1698, 1638, 1466, 1418, 1262, 1215, 1048, 929, 669 cm^{-1}. ^1H NMR δ: 0 88 (3 H, t, J = 6.9 Hz), 1.25 (44 H, br), 1.48 (2 H, br), 1.63 (4 H, br), 2.30 (4 H, br), 2.63 (2 H, d, J = 9.2 Hz), 3.49 (2 H, s), 6.94 (1 H, br).

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