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Total Synthesis of Analogs of Topostin B, A DNA Topoisomerase I Inhibitor. Part 3. Improved Synthesis of Topostin B-1 Analogs

Hideyasu Fujiwara, Toyohiko Aoyama,* and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

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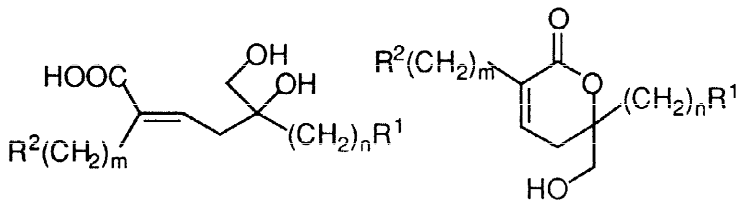
Abstract: Analogs of (*E*)-topostin B-1 (**1a–c**) and (*Z*)-topostin B-1 (**2a–c**), an inhibitor of mammalian DNA topoisomerase I, have been synthesized in a convenient manner.

We already described[1,2] a synthesis of analogs of (*E*)-topostin B-1 and (*Z*)-topostin B-1, the latter of which was easily converted to the lactone form, and these (*E*) and (*Z*)-topostin B-1 analogs and its derivatives have weak activity as DNA topoisomerase I inhibitors.[3] However, because this synthetic route needs many steps for the synthesis of (*E*) and (*Z*)-topostin B-1 analogs, it is difficult to apply to the preparation of many other topostin B-1 analogs.



Topostin B-1 $R^1 = CONH_2$, $R^2 = Me$
Topostin B-2 $R^1 = Me$, $R^2 = CONH_2$
$m + n = 25, 26$ (*E*) or (*Z*),(*S*) or (*R*)

We now wish to report a new convenient synthesis of topostin B-1 analogs from the terminal alkyne **6** according to the retrosynthetic route, shown in Scheme 1. This new synthetic route requires shorter steps (18 steps) for the synthesis of topostin B-1 analogs than the previous route (21 steps).[1,2] Because the absolute stereostructure of topostin B has not been fully clarified yet, we adopted a stereorandom strategy to synthesize topostin B-1 analogs.

An obvious cleaving point for the retrosynthesis of analogs of (*E*)-topostin B-1 (**1**) and (*Z*)-topostin B-1 lactone (**2**) will be the double bond. Thus, topostin B-1 analogs **1** and **2** would be constructed by the Horner-Emmons reaction of the aldehyde **4** with the phosphonate **3**. The right fragment **4** would be produced from the halide **7** and the terminal alkyne **6** which would be obtained through the aldol reaction of the aldehyde **9** with methyl acetate (**10**). The left fragment **3** would be produced by alkylation of the phosphonate **5** with the halide **8**. According to this retrosynthetic scheme, we started the synthesis of **1** and **2** (Scheme 1).

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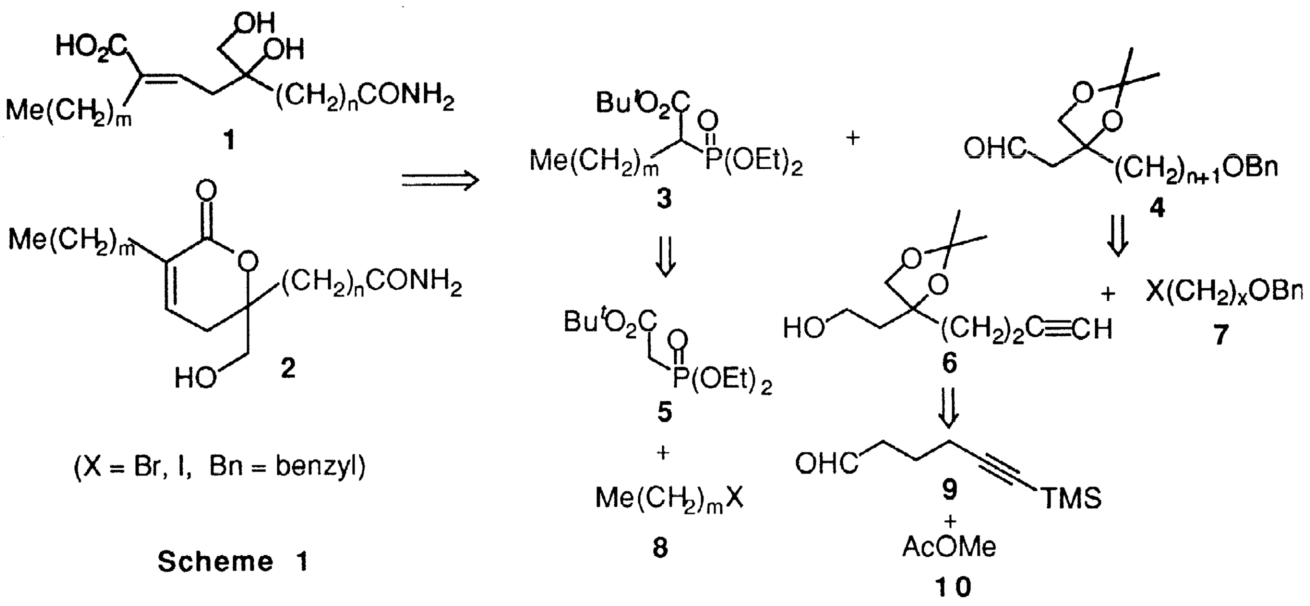
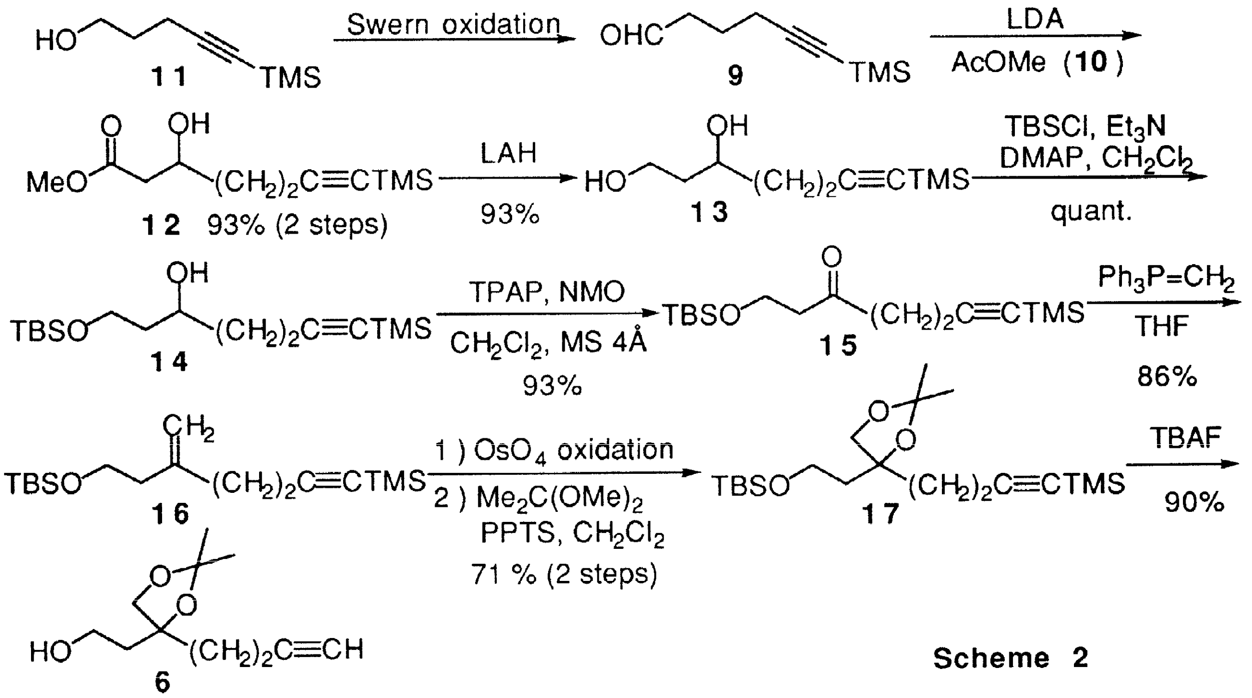


(X = Br, I, Bn = benzyl)

Scheme 1

Preparation of the Terminal Alkyne 6

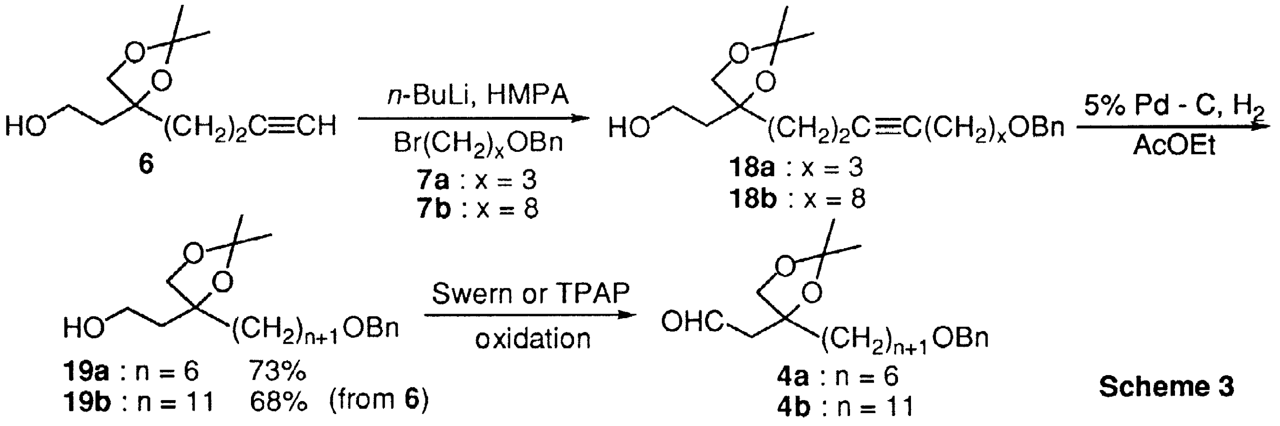
The aldol reaction of the aldehyde **9**, which was obtained by oxidation of the alcohol **11**,[4] with methyl acetate (**10**) afforded the β-hydroxyester **12**, as shown in Scheme 2. Reduction with lithium aluminum hydride followed by selective protection of the primary alcoholic function of the diol **13** with tert-butylchlorodimethylsilane (TBSCl) afforded the mono-alcohol **14**, which underwent the TPAP ($Pr_4N^+RuO_3^-$) oxidation[5] to give the ketone **15**. The Wittig methylenation smoothly afforded the exo-methylene compound **16**. Conversion of the exo-methylene function to the 1,2-diol one proceeded to give the diol, and treatment of the diol with dimethoxypropane under acidic conditions afforded the acetal **17**, of which the TBS group and trimethylsilyl (TMS) group were smoothly cleaved with tetrabutylammonium fluoride (TBAF), giving the required terminal alkyne **6**.



Scheme 2

Preparation of the Right Fragment 4.

First, alkylation of the lithium acetylide, which was generated by lithiation of the terminal alkyne **6** with butyllithium in THF-HMPA at -30°C, with the halide **7a**[6] at 0°C or room temperature failed to give the compound **18a**. However, the addition of the halide **7a** followed by evaporation of hexane, a solvent of butyllithium, afforded the alkylated alkyne **18a** in low yield. Furthermore, the alkyne **18a** was obtained in good yield by replacement of THF with diethyl ether through evaporation of the volatiles in vacuo, followed by reaction at room temperature. Alkylation of the halide **7b**[6] also smoothly proceeded under the analogous conditions. Catalytic hydrogenation of the alkynes **18a** and **18b** over 5% Pd-C, respectively, furnished the saturated compounds **19a** and **19b** without removal of the benzyl group. Swern oxidation of the primary alcohol **19a** easily afforded the right fragment **4a**, while TPAP oxidation of the alcohol **19b** afforded the right fragment **4b**. The alcohol **19b** was found to resist the Swern oxidation.



Scheme 3

Table 1

(**a** : m = 3, **b**: m = 6, **c** : m = 9, **d** : m = 14, **e** : m = 19, **f** : m = 21)

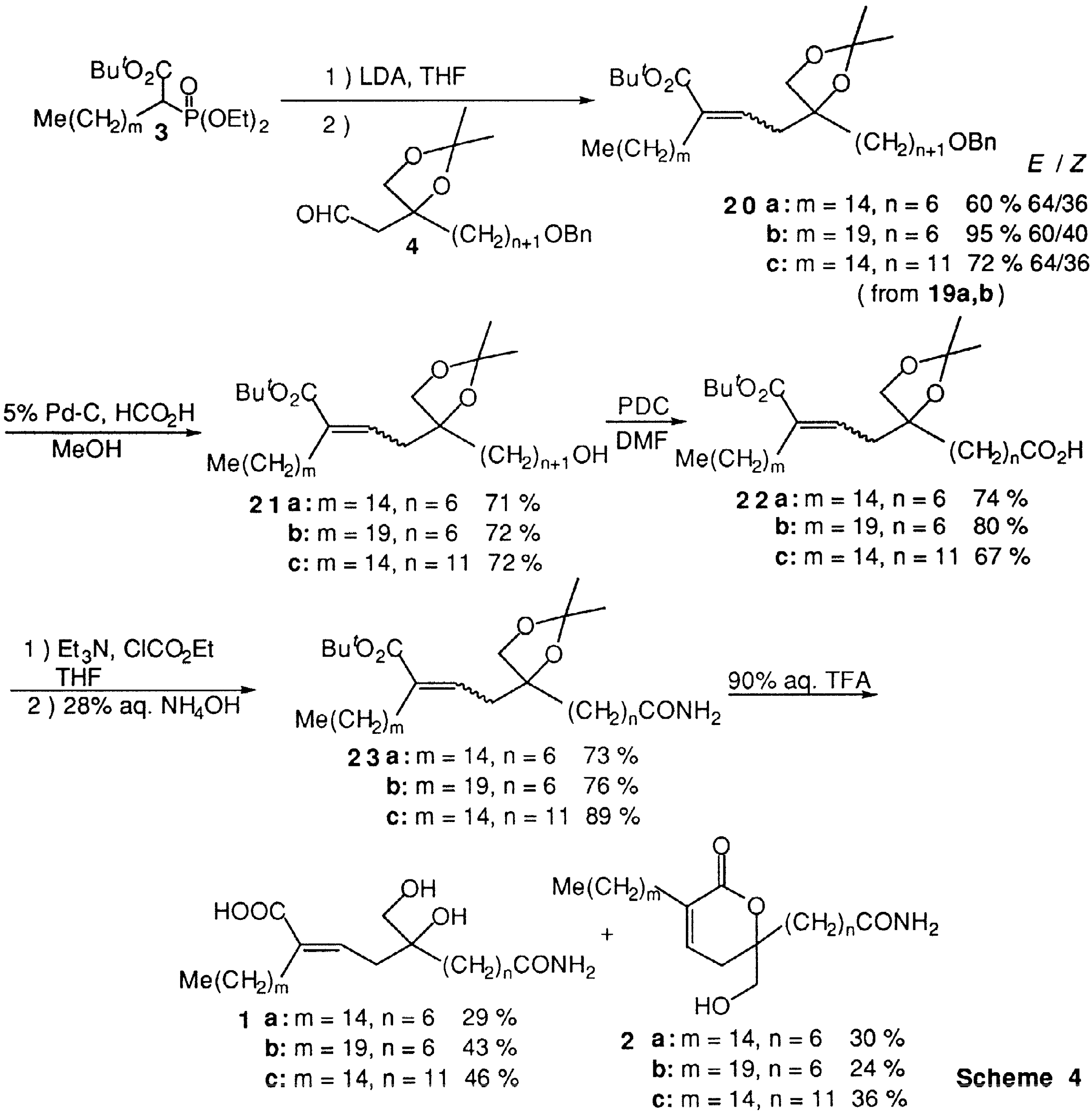
Entry	m	X	Method	Yield (%)
1	3	Br	A	70
2	6	Br	A	75
3	6	Br	B	31
4	9	Br	B	66
5	14	I	B	69
6	19	Br	B	72
7	21	Br	A	0
8	21	Br	B	50

method A : NaH, THF, reflux

method B : NaH, 15-crown-5, DMF, 50°C

Preparation of the Left Fragment 3

The left fragments **3a~f** of topostin B-1 analogs was prepared by alkylation of the phosphonate **5** with the alkyl halides **8** by either method A[7] or B[8], analogously to our former procedure,[1,2] as shown in Table 1. The method A seemed to be superior in the alkylation with the alkyl halides having a shorter alkyl chain while the method B seemed to be suitable for the alkyl halide having a longer alkyl chain.



Scheme 4

Synthesis of Topostin B-1 analogs

With two kinds of the left fragment **3** (m = 14, 19) and two kinds of the right fragment **4** (n = 6, 11) in hand, we accomplished the synthesis of topostin B-1 analogs, as shown in Scheme 4. The Horner-Emmons reaction of the phosphonate **3** with the aldehyde **4** afforded a mixture of the (*E*) and (*Z*)- isomers **20a~c** in a ratio of 60 : 40 ~ 64 : 36. Their stereochemistry was unambiguously determined by the measurement of the difference-NOE NMR spectra. Selective debenzylation of the coupling products **20a~c** by transfer hydrogenation, respectively, afforded the alcohols **21a~c**, in which trisubstituted olefin remained intact. Oxidation of the alcohols **21a~c** with pyridinium dichromate (PDC) afforded the carboxylic acids **22a~c**, which afforded the amides **23a~c** via the mixed anhydrides. Removal of the acetal and *t*-butyl functions with 90% aqueous trifluoroacetic acid (TFA) afforded the (*E*)-topostin B-1 analogs **1a~c** and the lactones **2a~c**, the latter of which were the cyclized products of (Z)-topostin B-1 analogs.

Thus, we have succeeded in synthesizing three kinds of topostin B-1 analogs in a convenient way (18 steps), which will be useful for detailed investigation of biological activity of topostin B-1.[9]

Experimental

General.

Melting points were determined on a YAMATO MP-21 apparatus or a YANAGIMOTO micro melting point apparatus. Distillation was carried out by a Kugelrohr apparatus. Infrared (IR) spectra were measured with a SHIMADZU FT IR-8100 spectrometer. ^{1}H NMR spectra were recorded on a JEOL EX-270 with tetramethylsilane or chloroform as an internal standard. Silica gel (BW-820 MH) was used for column chromatography. Methyltriphenylphosphonium bromide and molecular sieves 4Å (MS 4Å) powder were dried at 80°C for 12 h and 140°C for 24 h before use, respectively.

Methyl 3-Hydroxy-7-trimethylsilyl-6-heptynoate (12). To a stirred solution of $(COCl)_2$ (37.0 ml, 435 mM) in CH_2Cl_2 (50 ml) was added dropwise DMSO (36.9 ml, 520 mM) at -78°C under argon and the mixture was stirred for 30 min. A solution of the alcohol **11** (47.4 g, 290 mM) in CH_2Cl_2 (25 ml) was added and the mixture was stirred for 30 min at -78°C. After addition of Et_3N (20.2 ml, 1.45 M), the whole was warmed to room temperature and stirred for 1 h. The mixture was quenched with H_2O, and extracted with Et_2O (80 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the aldehyde **9** (50 g) as a yellow oil, which was used for the next step without further purification.

To a stirred solution of lithium diisopropylamide (LDA), prepared from $(i\text{-Pr})_2NH$ (42 ml, 300 mM) and *n*-BuLi (1.64 M in hexane, 183 ml, 300 mM) in THF (300 ml) was added dropwise methyl acetate (24 ml, 300 mM) at -78°C, and the mixture was stirred at -78°C for 30 min under argon. After a solution of the aldehyde **9** in THF (50 ml) was added, the mixture was stirred at -78°C for 30 min, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (300 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 400 g, hexane:EtOAc = 3:1) to give **12** (61.6 g, 93 %) as a colorless oil. IR ν_{max} (neat): 3473, 2176, 1738, 1439, 1410, 1374, 1250, 1198, 1157, 1075, 1051, 843, 760 cm^{-1}. ^{1}H NMR δ: 0.14 (9H, s), 1.68 (2H, m), 2.39 (2H, t, J=7.10), 2.50 (2H, m), 3.72 (3H, s), 4.13 (1H, m). Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83. Found: C, 57.50; H, 8.80.

7-Trimethylsilyl-6-heptyne-1,3-diol (13). To a solution of **12** (2.02 g, 8.85 mM) in Et_2O (80 ml) was added $LiAlH_4$ (671 mg, 17.7 mM) at 0°C under argon. After being stirred at room temperature overnight, EtOAc and then 1*N* aqueous HCl were added to the mixture at 0°C and the mixture was extracted with EtOAc (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-820 MH, 100 g, hexane:EtOAc = 1:2) to give **13** (1.64 g, 93 %) as a colorless oil. IR ν_{max} (neat): 3366, 2957, 2901, 2176, 1449, 1250, 1169, 1086, 1061, 1005, 999, 843, 760 cm^{-1}. ^1H NMR δ: 0.15 (9H, s), 1.73 (4H, m), 2.36 (2H, t, J=6.77 Hz), 3.86 (2H, m), 4.03 (1H, m). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.78; H, 10.19.

1-*t*-Butyldimethylsilyloxy-3-hydroxy-7-trimethylsilyl-6-heptyne (14). To a stirred solution of **13** (25.3 mg, 126 mM) in CH_2Cl_2 (200 ml) was added Et_3N (21 ml, 150 mM), 4-dimethylaminopyridine (DMAP) (616 mg, 5.0 mM) and then tert-butylchlorodimethylsilane (TBSCl) (20.9 mg, 139 mM) at room temperature. After being stirred at room temperature for 2 h, the mixture was diluted with H_2O and extracted with Et_2O (300 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-820 MH, 100 g, hexane:Et_2O = 3:1) to give **14** (39.6 g, 100 %), as a colorless oil. IR ν_{max} (neat): 3400, 2176, 1472, 1464, 1431, 1408, 1389, 1362, 1306, 1250, 1186, 1094, 1005, 959, 938, 839, 814, 777, 760, 731 cm^{-1}. ^{1}NMR δ: 0.08 (6H, s), 0.14 (9H, s), 0.91 (9H, s), 1.67 (4H, m), 2.37 (2H, t, J=7.26 Hz), 3.85 (3H, m). Anal. Calcd for $C_{16}H_{34}O_2Si_2$: C, 61.08; H, 10.89. Found: C, 61.12; H, 11.14.

1-*t*-Butyldimethylsilyloxy-3-oxo-7-trimethylsilyl-6-heptyne (15). To a mixture of **14** (39.6 g, 126 mM), *N*-methylmorpholine-*N*-oxide (NMO) (22.1 g, 189 mM) and MS 4Å (63 g) in CH_2Cl_2 (700 ml) was added tetrapropylammonium perrutenate (TPAP) (2.2 g, 6.3 mM) at 0°C. After being stirred at room temperature for 1 h, the mixture was filtrated, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 400 g, hexane:EtOH = 4:1) to give **15** (36.6 g, 93 %) as a colorless oil. IR ν_{max} (neat): 2957, 2930, 2859, 2178, 1717, 1472, 1469, 1410, 1389, 1362, 1252, 1217, 1094, 1061, 1007, 968, 939, 841, 812, 777, 760 cm^{-1}. ^{1}NMR δ: 0.05 (6H, s), 0.13 (9H, s), 0.87 (9H, s), 2.47 (2H, dd, J=5.94 Hz, 2.64 Hz), 2.61 (2H, t, J=6.27 Hz), 2.71 (2H, dd, J=5.74 Hz, 2.64 Hz), 3.89 (2H, t, J=6.27 Hz). Anal. Calcd for $C_{16}H_{32}O_2Si_2$: C, 61.48; H, 10.32. Found: C, 61.32 H, 10.58.

1-*t*-Butyldimethylsilyloxy-3-methylene-7-trimethylsilyl-6-heptyne (16). To a stirred suspension of methyltriphenylphosphonium bromide (4.97 g, 13.9 mM) in THF (70 ml) was added dropwise *n*-BuLi (1.66 M in hexane, 8.40 ml, 13.9 mM) at -10°C under argon and the mixture was stirred at room temperature for 1 h. A solution of **15** (3.63 g, 11.6 mM) in THF (10 ml) was added dropwise to the mixture at -10°C and then warmed to room temperature. After being stirred at room temperature for 2 h, the mixture was quenched with H_2O and extracted with Et_2O (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-820 MH, 100 g, hexane:EtOAC = 2:1) to give **16** (3.09 g, 86 %) as a colorless oil. IR ν_{max} (neat): 2957, 2930, 2897, 2859, 2118, 1472, 1464, 1435, 1408, 1389, 1362, 1327, 1250, 1159, 1102, 1059, 938, 924, 885, 839, 812, 776, 760 cm^{-1}. ^{1}NMR δ: 0.05 (6H, s), 0.14 (9H, s), 0.89 (9H, s), 2.30 (6H, m), 3.70 (2H, t, J=6.93 Hz), 4.79 (2H, br). Anal. Calcd for $C_{17}H_{34}O_1Si_2$: C, 65.73; H, 11.03. Found: C, 65.53; H, 10.79.

1-*t*-Butyldimethylsilyloxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-7-trimethylsilyl-6-heptyne (17). To a mixture of **16** (30.4 g, 98 mM), $K_3Fe(CN)_6$ (70.3 g, 294 mM), K_2CO_3 (40.6 g, 294 mM) and $Me_2SO_2NH_2$ (9.38 g, 98.0 mM) in *t*-BuOH-H_2O (300 ml-300 ml) was added dropwise OsO_4 (0.1 M in toluene, 19.6 ml, 1.96 mM) at 0°C. After being stirred at 4°C for 15 h, the mixture was diluted with saturated aqueous $NaHSO_3$ and extracted with EtOAc (500 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 1,2-diol (26.2 g) as a colorless oil, which was used for the next step without further purification. IR ν_{max} (neat): 3440, 2957, 2930, 2859, 2176, 1472, 1464, 1408, 1391, 1362, 1250, 1092, 1049, 1005, 974, 939, 887, 839, 810, 777, 760 cm^{-1}. ^{1}H NMR δ: 0.09 (6H, s), 0.14 (9H, s), 0.90 (9H, s), 1.79 (2H, t, J=7.43 Hz), 1.77 (2H, m), 2.34 (2H, t, J=7.43 Hz), 2.89 (1H, t, J=7.67 Hz), 3.49 (2H, m), 3.70 (1H, br), 3.87 (2H, m). Anal. Calcd for $C_{17}H_{36}O_3Si_2$: C, 59.25; H, 10.53 Found: C, 58.98; H, 10.50.

To a stirred solution of the 1,2-diol in CH_2Cl_2 (30 ml) was added 2,2-dimethoxypropane (12 ml, 98 mM) and pyridinium *p*-toluenesulfonate (PPTS) (23 mg, 0.09 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-820 MH, 60 g, hexane:Et_2O = 10:1) to give **17** (26.8 g, 71 %) as a colorless oil. IR ν_{max} (neat): 2986, 2957, 2930, 2859, 2176, 1472, 1464, 1379, 1370, 1252, 1213, 1159, 1096, 1061, 1007, 980, 939, 895, 841, 812, 776, 760, 735 cm^{-1}. ^{1}H NMR δ: 0.05 (6H, s), 0.14 (9H, s), 0.89 (9H, s), 1.36 (3H, s), 1.39 (3H, s), 1.86 (4H, m), 2.30 (2H, m), 3.70 (2H, t, J=6.27 Hz), 3.85 (2H, ABq, J=8.90 Hz). Anal. Calcd for $C_{20}H_{41}O_3Si_2$: C, 62.28; H, 10.70 Found: C, 62.55; H, 10.60.

3-(5-Spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-6-heptyne-1-ol (6). A mixture of **17** (3.86 g, 10 mM) and TBAF (7.84 g, 30 mM) in THF (50 ml) was stirred at room temperature for 2 h. After 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-820 MH, 20 g, hexane:EtOAc = 3:1) to give **6** (1.78 mg, 90 %) as a colorless oil. IR ν_{max} (neat): 3445, 3293, 2988, 2882, 2118, 1383, 1372, 1252, 1213, 1157, 1084, 1053, 980, 868 cm^{-1}. ^{1}H NMR δ: 1.41 (3H, s), 1.43 (3H, s), 1.95 (5H, m), 2.27 (2H, m), 2.32 (1H, br), 3.85 (2H, m), 3.89 (2H, ABq, J=8.75 Hz). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.35; H, 9.21.

10-Benzyloxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-6-decyne-1-ol (18a). To a solution of **6** (395 mg, 2.0 mM) in HMPA-Et_2O (2 ml-4 ml) was added dropwise *n*-BuLi (1.69 M in hexane, 2.6 ml, 4.4 mM) at -30°C under argon, and the mixture was stirred at -10°C for 1.5 h. After a solution of **7a** (551 g, 2.4 mM) in Et_2O (2 ml) was added dropwise, hexane and Et_2O were evaporated *in vacuo* and the mixture was stirred at room temperature for 24 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with Et_2O (60 ml x 2). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the alkyne **18a** (534 mg) as a colorless oil, which was used for the next step without further purification. IR ν_{max} (neat): 3400, 1497, 1478, 1455, 1381, 1370, 1252, 1211, 1156, 1103, 1055, 1028, 980, 911, 870, 824, 737 cm^{-1}. ^{1}H NMR δ: 1.26 (2H, t, J=7.10 Hz), 1.40 (3H, s), 1.43 (3H, s), 1.90 (4H, m), 2.17 (4H, m), 2.57 (1H, m), 3.46 (2H, t, J=6.60 Hz), 3.80 (4H, m), 4.50 (2H, s), 7.30 (5H, m).

15-Benzyloxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-6-pentadecyne-1-ol (18b). The alkyne **6** (217 mg, 1.1 mM) was alkylated with the alkyl halide **7b** (385 mg, 1.35 mM) as described for **7a** to give the alkyne **18b** (316 mg) as a pale yellow oil, which was used for the next step without further purification. IR ν_{max} (neat): 3455, 1496, 1455, 1435, 1379, 1370, 1331, 1252, 1211, 1156, 1096, 1057, 1028, 980, 939, 911, 872, 824, 737 cm^{-1}. ^{1}H NMR δ: 1.23 (8H, m), 1.40 (3H, s), 1.43 (3H, s), 1.90 (8H, m), 2.15 (4H, m), 2.61 (1H, brs), 3.55 (2H, t, J=6.41 Hz), 3.80 (4H, m), 4.51 (2H, s), 7.32 (5H, m).

10-Benzyloxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-1-decanol (19a). A mixture of the alkyne **18a** (534 mg) and 5% Pd-C (130 mg) in EtOAc (390 ml) was stirred for 30 min at room temperature under H_2 atmosphere. The mixture was filtratered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 50 g, hexane:EtOAc = 2:1) to give **19a** (512 mg, 73 %) as a colorless oil. IR ν_{max} (neat): 3417, 2928, 2855, 1472, 1461, 1379, 1370, 1254, 1215, 1159, 1094, 1061, 1007, 895, 837, 812, 776 cm^{-1}. ^{1}H NMR δ: 1.30 (10H, m), 1,40 (3H, s) 1,43 (3H, s), 1.52 (2H, m), 1.86 (2H, m), 2.50 (1H, br), 3.46 (2H, t, J=6.60 Hz), 3.75 (4H, m), 4.50 (2H, s), 7.35 (5H, m). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.67; H, 9.87.

15-Benzyloxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-1-pentadecanol (19b). The alkyne **18b** (316 mg) was reduced as described for **18a** to give **19b** (314 mg, 68 %) as a colorless oil. IR ν_{max} (neat): 3455, 2928, 2855, 1497, 1456, 1379, 1368, 1254, 1213, 1157, 1102, 1059, 1028, 984, 872, 820, 735 cm^{-1}. ^{1}H NMR δ: 1.30 (20H, m), 1,40 (3H, s) 1,43 (3H, s), 1.54 (2H, m), 1.85 (2H, m), 2.69 (1H, brs), 3.46 (2H, t, J=6.60 Hz), 3.75 (4H, m), 4.50 (2H, s), 7.33 (5H, m). Anal. Calcd for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found: C, 73.92; H, 10.56.

***t*-Butyl 2-Butyl-2-diethylphosphonoacetate (3a).** To a stirred suspension of NaH (60% oil dispersion, 132 mg, 3.3 mM) in THF (3.3 ml) was added dropwise a solution of **5** (828 mg, 3.3 mM) in THF (3.3 ml) at 0°C under argon, and the mixture was stirred at room temperature for 2 h. A solution of **8a** (904 mg, 6.6 mM) in THF (6.6 ml) was added dropwise and the mixture was refluxed overnight, then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (50 ml x 2), washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation to give **3a** (712 mg, 70 %) as a colorless oil; b.p. 120°C / 1.0 mmHg (Kugelrohr). IR ν_{max} (neat): 2930, 2859, 1732, 1480, 1256, 1393, 1370, 1337, 1254, 1154, 1131, 1097, 1055, 1026, 968, 905, 853, 791, 752, 712 cm^{-1}. ^{1}H NMR δ: 0.90 (3H, s), 1.33 (10H, m), 1.48 (9H, s), 2.00 (2H, m), 2.84 (1H, dquint, J=3.96 Hz, 7.16 Hz), 4.15 (4H, m). Anal. Calcd for $C_{14}H_{29}O_5P$: C, 54.53; H, 9.48. Found: C, 54.23; H, 9.30.

***t*-Butyl 2-Heptanyl-2-diethylphosphonoacetate (3b).** The phosphonate **5** (252 mg, 1.0 mM) was alkylated with the alkyl halide **8b** (358 g, 2.0 mM) as described for **8a** to give **3b** (1.06 g, 75 %) as a colorless oil; b.p. 140°C / 1.0 mmHg (Kugelrohr). IR ν_{max} (neat): 2930, 2859, 1732, 1445, 1393, 1368, 1333, 1256, 1154, 1117, 1098, 1053, 1026, 968, 847, 791, 752 cm^{-1}. ^{1}H NMR δ: 0.89 (3H, t, J=6.44 Hz), 1.30 (16H, m), 1.47 (9H, s), 1.90 (2H, m), 2,82 (1H, m), 4.15 (4H, m). Anal. Calcd for $C_{17}H_{35}O_5P$: C, 58.27; H, 10.07. Found: C, 57.97; H, 9.84

t-Butyl 2-Decanyl-2-diethylphosphonoacetate (3c). To a stirred suspension of NaH (60% oil dispersion, 40 mg, 1.0 mM) in DMF (2.5 ml) was added dropwise a solution of **5** (252 mg, 1.0 mM) in DMF (2.0 ml) at 0°C under argon, and the mixture was stirred at room temperature for 1 h. A solution of **8c** (414 ml, 2.0 mM) in DMF (1 ml) and 15-Crown-5 (20 µl, 0.1 mM) was added dropwise and the mixture was stirred at 50°C overnight, then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (50 ml x 2), washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation to give **3c** (260 mg, 66 %) as a colorless oil; b.p. 150°C / 1.0 mmHg (Kugelrohr). IR ν_{max} (neat): 2926, 2858, 1732, 1468, 1458, 1446, 1393, 1368, 1337, 1258, 1150, 1117, 1100, 1055, 1028, 967, 843, 791, 752, 722 cm^{-1}. ^1H NMR δ: 0.89 (3H, t, J=6.60 Hz), 1.25 (22H, m), 1.47 (9H, s), 1,85 (2H, brd, J=34.97 Hz), 2.82 (1H, dquint, J=3.79 Hz, 7.55 Hz), 4.15 (4H, m). Anal. Calcd for $C_{20}H_{41}O_5P \cdot 1/2H_2O$: C, 59.83; H, 10.54. Found: C, 59.85; H,10.45.

t-Butyl 2-Pentadecanyl-2-diethylphosphonoacetate (3d). The phosphonate **5** (757 mg, 3.0 mM) was alkylated with the alkyl halide **8d** (1.52 g, 4.5 mM) as described for **8c** to give **3d** (958 mg, 69 %) as a colorless oil. IR ν_{max} (neat) 2926, 2855, 1732, 1464, 1456, 1393, 1368, 1337, 1256, 1152, 1188, 1098, 1055, 1028, 968, 843, 793, 756, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.24 (32H, m) 1.47 (9H, s), 1.84 (2H, brd, J=33.7 Hz), 2.82 (1H, dquint, J=3.63, 7.46 Hz), 4.14 (4H, m). Anal. Calcd for $C_{25}H_{51}O_5P$: C, 64.90; H, 11.11. Found: C, 64.67; H, 11.20.

t-Butyl 2-Icosanyl-2-diethylphosphonoacetate (3e). The phosphonate **5** (1.26 g, 5.0 mM) was alkylated with the alkyl halide **8e** (3.62 g, 10 mM) as described for **8c** to give **3e** (1.91 g, 72 %) as a white waxy solid; m.p. 60-61°C. IR ν_{max} ($CHCl_3$): 2926, 2855, 1732, 1468, 1393, 1368, 1337, 1258, 1154, 1121, 1100, 1055, 1028, 965, 847, 791, 752, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.77 Hz), 1,26 (42H, m), 1.47 (9H, s), 1.80 (2H, brd, J=32,33 Hz), 2.82 (1H, dquint, J=3.79 Hz, 7.42 Hz), 4.14 (4H, m). Anal. Calcd for $C_{30}H_{61}O_5P$: C, 67.63; H, 11.54. Found: C, 67.33; H, 11.49.

t-Butyl 2-Docosanyl-2-diethylphosphonoacetate (3f). The phosphonate **5** (151 mg, 0.60 mM) was alkylated with the alkyl halide **8f** (280 mg, 0.72 mM) as described for **8c** to give **3f** (168 mg, 50 %) as a white solid; m.p. 70-71°C. IR ν_{max} ($CHCl_3$): 2980, 2953, 1728, 1470, 1456, 1393, 1368, 1337, 1256, 1154, 1119, 1098, 1055, 1026, 968, 845, 791, 752, 721 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.26 (46H, m), 1.47 (9H, s), 1.84 (2H, brd, J=33.7 Hz), 2.82 (1H, dquint, J=3.86 Hz, 6,92 Hz), 4.14 (4H, m). Anal. Calcd for $C_{32}H_{65}O_5P$: C, 67.45; H, 11.67. Found: C, 67.71; H, 11.92.

t-Butyl 12-Benzyloxy-2-pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-dodecenoate (20a). To a stirred solution of $(COCl)_2$ (64 µl, 0.75 mM) in CH_2Cl_2 (3 ml) was added dropwise DMSO (64 µl, 0.9 mM) at -78 °C under argon, and the mixture was stirred for 30 min. A solution of **19a** (175 mg, 0.50 mM) was added, and the mixture was stirred for 30 min. After addition of Et_3N (349 µl, 2.5 mM), the whole was warmed to room temperature and stirred for 1 h. The mixture was quenched with H_2O, and extracted with Et_2O (30 ml x 3). The extracts were washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **4a** (170 mg) as a colorless oil, which was used for the next step without further purification.

To a stirred solution of lithium diisopropylamide (LDA) (prepared from (*i*-Pr)$_2$NH (85 μl, 0.61 mM) and *n*-BuLi (1.69 M in hexane, 361 μl, 0.61 mM) in THF (1.5 ml)) was added dropwise a solution of **3d** (254 mg, 0.55 mM) in THF (1.5 ml) at 0°C, and the mixture was stirred at 0°C for 2 h under argon. A solution of the aldehyde **4a** in THF (1.5 ml) was added at 0°C. The mixture was stirred at room temperature for 2 h and quenched with H_2O. The mixture was extracted with Et_2O (30 ml x 2), successively washed with saturated aqueous NH_4Cl, H_2O, and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 50 g, hexane:EtOAc = 15:1) to give **20a** (197 mg, 60 %) as a colorless oil. IR ν_{max} (neat): 2979, 2926, 2855, 1709, 1646, 1456, 1393, 1368, 1252, 1213, 1156, 1115, 1103, 1061, 1028, 976, 870, 833, 818, 735 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.44 (38H, m), 1.48 (9H, s), 2.24 (2H, m), 2.43 (1.28H, d, J=7.59 Hz), 2.67 (0.72H, m), 3.45 (2H, t, J=6.60 Hz), 3.76 (2H, s), 4.50 (2H, s), 5.80 (0.36H, t, J=7.10 Hz), 6.66 (0.64H, t, J=7.43 Hz) 7,32 (5H, m). Anal. Calcd for $C_{42}H_{72}O_5$: C, 76.78; H, 11.05. Found: C, 76.59; H, 11.00.

***t*-Butyl 12-Benzyloxy-2-icosanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-dodecenoate (20b)**. The phosphonate 3e (293 mg, 0.55 mM) was coupled with the aldehyde **4a**, which was obtained by oxidation of alcohol **19a** (175 mg, 0.50 mM), as described for **19a** to give **20b** (347 mg, 95 %) as a colorless oil. IR ν_{max} (neat): 2979, 2926, 2855, 1709, 1646, 1497, 1466, 1456, 1391, 1379, 1368, 1252, 1213, 1156, 1103, 1061, 1028, 870, 853, 818, 733 cm^{-1}. ^{1}H NMR δ: 0.87 (3H, m), 1.31 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 2.34 (2H, m), 2.43 (1.20H, d, J=7.59 Hz), 2.68 (0.80H, m), 3.46 (2H, t, J=6.60 Hz), 3.74 (2H, s), 5.80 (0.40H, t, J=7.26 Hz), 6.66 (0.60 Hz, t, J=7.43 Hz), 7.29 (5H, m). Anal. Calcd for $C_{47}H_{82}O_5$: C, 77.63; H, 11.37. Found: C, 77.42; H, 11.45.

***t*-Butyl 17-Benzyloxy-2-pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenoate (20c)**. To a mixture of **19b** (200 mg, 0.475 mM), NMO (88 ml, 0.75 mM) and MS 4Å (250 mg) in CH_2Cl_2 (5 ml) was added tetrapropylammonium perrutenate (TPAP) (8.8 mg, 0.025 mM) at 0°C. After being stirred at room temperature for 30 min, the mixture was filtrated, and the filtrate was concentrated *in vacuo* to give the aldehyde **4b** (200 mg) as a colorless oil, which was used for the next step without further purification.

To a stirred solution of lithium diisopropylamide (LDA) (prepared from (*i*-Pr)$_2$NH (80 μl, 0.57 mM) and *n*-BuLi (1.69 M in hexane, 337 μl, 0.57 mM) in THF (1.5 ml)) was added dropwise a solution of **3d** (242 mg, 0.52 mM) in THF (1.5 ml) at 0°C, and the mixture was stirred at 0°C for 2 h under argon. A solution of the aldehyde **4b** in THF (1.5 ml) was added at 0°C. The mixture was stirred at room temperature for 2 h and quenched with H_2O. The mixture was extracted with Et_2O (30 ml x 2), successively washed with saturated aqueous NH_4Cl, H_2O, and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 120 g, hexane:EtOAc = 15:1) to give **20c** (250 mg, 72 %) as a colorless oil. IR ν_{max} (neat): 2979, 2926, 2855, 1709, 1644, 1495, 1456, 1391, 1379, 1368, 1252, 1213, 1156, 1061, 1028, 853, 733 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.35 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 2.23 (2H, m), 2.43 (1.28H, d, J=7.26 Hz), 2.68 (0.72H, quint, J=7.59 Hz), 3.48 (2H, t, J=6.60 Hz), 3.76 (2H, s), 4.50 (2H, s), 5.81 (0.36H, t, J=7.10 Hz), 6.66 (0.64H, t, J=6.43 Hz), 7.47 (5H, m). Anal. Calcd for $C_{47}H_{82}O_5$: C, 77.63; H, 11.37. Found: C, 77.36; H, 11.61.

***t*-Butyl 12-Hydroxy-2-tetradecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-**

dodecenoate (21a). To a mixture of **20a** (110 mg, 0.167 mM) and 5% Pd-C (110 mg) in Et_2O-MeOH (0.6 ml-10 ml) was added dropwise HCO_2H (1.0 ml) at 0°C under argon. After being stirred at room temperature for 2 h, the reaction mixture was filtrated, and the filtrate was concentrated *in vacuo*. The residue was purification by silica gel column chromatography (BW-820 MH, 50 g, hexane:EtOAc = 5:1) to give **21a** (73 mg, 71 %) as a colorless oil. IR ν_{max} (neat): 3426, 2980, 2926, 2855, 1709, 1646, 1456, 1391, 1379, 1368, 1252, 1213, 1156, 1061, 868, 853, 818, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.43 (38H, m), 1.48 (9H, s), 2.21 (2H, m), 2.43 (1.28H, d, J=7.26 Hz), 2.61 (0.72H, m), 3.64 (2H, t, J=6.60 Hz), 3.76 (2H, s), 5.81 (0.36H, t, J=7.10 Hz), 6.66 (0.64H, t, J=7.43 Hz). Anal. Calcd for $C_{35}H_{66}O_5$: C, 73.90; H, 11.82. Found: C, 74.15; H, 11.73.

***t*-Butyl 12-Hydroxy-2-nonadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-dodecenoate (21b).** The benzyl ether **20b** (140 mg, 0.19 mM) was debenzylated as described for **20a** to give **21b** (88 mg, 72 %) as a colorless oil. IR ν_{max} (neat): 3442, 2980, 2926, 2855, 1709, 1646, 1464, 1456, 1391, 1379, 1368, 1252, 1213, 1157, 1061, 976, 918, 870, 853, 818, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.43 (48H, m), 1.48 (9H, s), 2.16 (2H, m), 2.45 (1.20H, d, J=7.26 Hz), 2.65 (0.8H, m), 3.63 (2H, m), 3.75 (2H, m), 5.80 (0.4H, t, J=6.60 Hz), 6.65 (0.60H, t, J=7.43 Hz). Anal. Calcd for $C_{40}H_{76}O_5$: C, 75.42; H, 12.02. Found: C, 75.07; H, 11.84.

***t*-Butyl 17-Hydroxy-2-tetradecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenoate (21c).** The benzyl ether **20c** (73 mg, 0.10 mM) was debenzylated as described for **20a** to give **21c** (46 mg, 72 %) as a colorless oil. IR ν_{max} (neat): 3400, 2926, 2855, 1709, 1644, 1464, 1393, 1379, 1368, 1252, 1213, 1157, 1061, 976, 853, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.43 (48H, m), 1.48 (9H, s), 2.23 (2H, m), 2.44 (1.28H, d, J=7.26 Hz), 2.59 (0.72H, m), 3.64 (2H, t, J=6.44 Hz), 3.76 (2H, s), 5.71 (0.36H, t, J=7.10 Hz), 6.56 (0.64H, t, J=6.43 Hz). Anal. Calcd for $C_{40}H_{76}O_5$: C, 75.42; H, 12.02. Found: C, 75.39; H, 12.14.

***t*-Butyl 12-Hydrogen 2-pentadecanyl -5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-dodecenedioate (22a).** To a solution of the alcohol **21a** (62 mg, 0.11 mM) in DMF (0.5 ml) was added pyridinium dichromate (PDC) (290 mg, 0.77 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-820 MH, 10 g, hexane:EtOAc = 1:1) to give **22a** (47 mg, 74 %) as a colorless oil. IR ν_{max} (neat): 3240, 2924, 2855, 1740, 1709, 1644, 1462, 1390, 1379, 1368, 1258, 1213, 1157, 1063, 803 cm^{-1}. ^1H NMR δ: 0.90 (3H, t, J=6.93 Hz), 1.25 (37H, m), 1.39 (3H, m), 1.41 (3H, s), 1.48 (9H, s), 2.21 (2H, m), 2.35 (2H, m), 2.43 (1.32H, d, J=7.59 Hz), 2.67 (0.66H, m), 3.76 (2H, m), 5.81 (0.34H, t, J=7.43 Hz), 6.66 (0.66H, J=7.43 Hz). Anal. Calcd for $C_{35}H_{64}O_6$: C, 72.37; H, 11.10. Found: C,72.55; H, 11.87.

***t*-Butyl 12-Hydrogen 2-icosanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-dodecenedioate (22b).** The alcohol **21b** (90 mg, 0.14 mM) was oxidized as described for **21a** to give **22b** (73 mg, 80 %) as a colorless oil. IR ν_{max} (neat): 3200, 2926, 2855, 1738, 1709, 1640, 1466, 1391, 1379, 1368, 1252, 1213, 1156, 1061, 976, 918, 852, 818, 733 cm^{-1}. ^1H NMR δ: 0.91 (3H, t, J=6.93 Hz), 1.25 (47H, m), 1.39 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 2.25 (2H, m), 2.35 (2H, t, J=7.42 Hz), 2.43 (1.28H, d, J=7.59 Hz), 2.64 (0.72H, m), 3.76 (2H, m), 5.80 (0.36H, t, J=7.26 Hz), 6.65 (0.64H, t, J=7.43 Hz). Anal. Calcd for $C_{40}H_{74}O_6$: C, 73.80; H, 11.46. Found: C, 73.71; H, 11.42.

***t*-Butyl 17-Hydrogen 2-pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-heptadecenedioate (22c).** The alcohol **21c** (15 mg, 0.023 mM) was oxidized as described for **21a** to give **22c** (10 mg, 67 %) as a colorless oil. IR ν_{max} (neat): 3000, 2926, 2855, 1738, 1711, 1646, 1559, 1541, 1507, 1464, 1456, 1418, 1393, 1379, 1368, 1252, 1213, 1157, 1061, 976, 870, 853, 818, 722 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.25 (47H, m), 1.39 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 2.24 (2H, m), 2.34 (2H, t, J=7.42 Hz), 2.42 (1.28H, d, J=6.93 Hz), 2.68 (0.72H, m), 3.77 (2H, s), 5.81 (0.36H, t, J=6.80 Hz), 6.66 (0.64H, t, J=6.43 Hz). Anal. Calcd for $C_{40}H_{74}O_6$: C, 73.80; H, 11.46. Found: C, 73.90; H, 11.63.

***t*-Butyl 16-Carbamoyl-2 pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenate (23a).** To a stirred solution of **22a** (72 mg, 0.125 mM) and Et_3N (20 µl, 0.14 mM) in THF (1 ml) was added dropwise $ClCO_2Et$ (13 µl, 0.14 mM) at 0°C. The mixture was stirred at 0°C for 30 min and then 28% aqueous NH_4OH (25 µl, 140 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-820 MH, 10 g, hexane:EtOAc = 1:1) to give **23a** (42 mg, 73 %) as a colorless oil. IR δ_{max} (neat): 3410, 3200, 1705, 1669, 1635, 1456, 1367, 1252, 1213, 1157, 1061, 853 cm^{-1}. ^{1}H NMR δ: 0.87 (3H, t, J=6.60 Hz), 1.25 (36H, m), 1.40 (6H, s), 1.48 (9H, s), 2.22 (4H, t, J=7.10 Hz), 2.42 (1.26H, d, J=7.25 Hz), 2.67 (0.74H, m), 3.76 (2H, s), 5.45 (2H, m), 5.79 (0.36H, m), 6.64 (0.64H, t, J=7.45 Hz). Anal. Calcd for $C_{35}H_{65}O_5N$: C, 72.49; H, 11.30; N, 2.42. Found: C,72.32; H, 11.39; N, 2.28.

***t*-Butyl 16-Carbamoyl-2-icosanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-undecenoate (23b).** The carboxylic acid **22b** (78 mg, 0.12 mM) was amidated as described for **22a** to give **23b** (59 mg, 76 %) as a colorless oil. IR ν_{max} (neat): 3410, 3350, 3200, 2924, 2853, 1709, 1670, 1646, 1464, 1456, 1368, 1257, 1213, 1157, 1061, 853 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.27 Hz), 1.25 (46H, m), 1.39 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 2.22 (4H, t, J=7.10 Hz), 2.42 (1.2H, d, J=7.25 Hz), 2.65 (0.8H, m), 3.75 (2H, m), 5.36 (2H, m), 5.80 (0.4H, J=7.42 Hz), 6.69 (0.6H, t, J=7.43 Hz). Anal. Calcd for $C_{40}H_{75}O_5N$: C, 72.49; H, 11.30; N, 2.13. Found: C, 72.78; H, 11.41; N, 2.47.

***t*-Butyl 16-Carbamoyl-2-pentadecanyl-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-hexadecenate (23c).** The carboxylic acid **22c** (17 mg, 0.026 mM) was amidated as described for **22a** to give **23c** (15 mg, 89 %) as a colorless oil. IR ν_{max} (neat): 3706, 3456, 3199, 2926, 2855, 1707, 1675, 1641, 1456, 1450, 1368, 1250, 1264, 1213, 1156, 1059, 851 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.25 (46H, m), 1.41 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 2.22 (4H, m), 2.43 (1.28H, d, J=7.26 Hz), 2.64 (0.72H, m), 3.76 (2H, m), 5.35 (2H, m), 5.79 (0.36H, t, J=7.42 Hz), 6.66 (0.64H, t, J=7.59 Hz). Anal. Calcd for $C_{40}H_{75}O_5N \cdot 1/2H_2O$: C, 72.90; H, 11.62; N, 2.13. Found: C,73.03; H, 11.63; N, 2.38.

(*E*)-16-Carbamoyl-5-hydroxy-5-hydroxymethyl-2-pentadecanyl-2-undecenoic Acid (1a) and 5-(11-Carbamoylhexanyl)-5-hydroxymethyl-2-pentadecanyl-2-penten-5-olide (2a). A mixture of **23a** (42 mg, 0.073 mM) and 90% aqueous TFA (0.5 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 preparative thin layer chromatography (Merck Art 5717, 20 cm x 20 cm, $CHCl_3$:EtOH = 4:1) to give **1a** (10 mg, 29 %) as a colorless oil and **2a** (10 mg, 30 %) as a colorless oil.

Compound 1a. IR ν_{max} ($CHCl_3$): 3340, 3200, 3019, 2928, 2855, 1682, 1641, 1466, 1414, 1260, 1071, 1049, 928, 669 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.3 Hz), 1.25 (32H, br), 1.49 (2H, br), 1.60 (2H, br), 2.28 (6H, m), 3.70 (2H, m), 5.55 (1H, br), 6.32 (1H, br), 6.77 (1H, br). FABHRMS Calcd for $C_{28}H_{52}O_5N$ $(M-H)^-$: 482.3843. Found: 482.3872.

Compound 2a. IR ν_{max} ($CHCl_3$): 3451, 3240, 2917, 2849, 1675, 1661, 1642, 1459, 1428, 1260, 1167, 1111, 1025, 810, 722 cm^{-1}. ^1H NMR δ: 0.86 (3H, t, J=6.93 Hz), 1.25 (30H, br), 1.46 (2H, m), 1.60 (4H, m), 1.85 (1H, br), 2.25 (5H, m), 2.73 (1H, m), 3.56 (1H, m), 3.65 (1H, m), 5.38 (2H, br), 6.45 (1H, br). FABHRMS Calcd for $C_{28}H_{50}O_4N$ $(M-H)^-$: 464.3737. Found: 464.3721.

(*E*)-16-Carbamoyl-5-hydroxy-5-hydroxymethyl-2-icosenyl-2-undecenoic Acid (1b) and 5-(11-Carbamoylhexanyl)-5-hydroxymethyl-2-icosenyl-2-penten-5-olide (2b). The compound **23b** (30 mg, 0.046 mM) was treated as described for **23a** to give **1b** (11 mg, 43 %) as a white waxy solid; m.p. 57-59°C and **2b** (6 mg, 24 %) as a white waxy solid; m.p. 89-90°C.

Compound 1b. IR ν_{max} ($CHCl_3$): 3350, 3200, 3015, 2928, 2855, 1682, 1638, 1466, 1414, 1261, 1071, 1049, 928, 669 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.6 Hz), 1.25 (42H, br), 1.47 (2H, br), 1.63 (2H, br), 2.30 (6H, m), 3.72 (2H, m), 5.68 (1H, br), 6.30 (1H, br), 6.77 (1H, br). FABHRMS Calcd for $C_{33}H_{62}O_5N$ $(M-H)^-$: 552.4625. Found: 552.4683.

Compound 2b. IR ν_{max} ($CHCl_3$): 3453, 3246, 2917, 2849, 1675, 1661, 1468, 1430, 1260, 1167, 1111, 1028, 803, 722 cm^{-1}. ^1H NMR δ: 0.87 (3H, t, J=6.6 Hz), 1.25 (40H, br), 1.46 (2H, m), 1.60 (4H, m), 1.85 (1H, br), 2.25 (5H, m), 2.74 (1H, m), 3.53 (1H, m), 3.70 (1H, m), 5.35(2H, br), 6.45 (1H, br). FABHRMS Calcd for $C_{33}H_{60}O_4N$ $(M-H)^-$: 534.4519. Found: 534.4522.

(*E*)-16-Carbamoyl-5-hydroxy-5-hydroxymethyl-2-pentadecanyl-2-hexadecenoic Acid (1c) and 5-(11-Carbamoylundecanyl)-5-hydroxymethyl-2-pentadecanyl-2-penten-5-olide (2c). The compound **23c** (41 mg, 0.063 mM) was treated as described for **23a** to give **1c** (16 mg, 46 %) as a white waxy solid; m.p. 57-59°C and **2c** (12 mg, 36 %) as a white waxy solid; m.p. 89-90°C, which were identified by spectroscopic comparison with the authentic sample.[2]

Compound 1c. IR ν_{max} ($CHCl_3$): 3351, 3204, 3019, 2928, 2855, 1682, 1645, 1466, 1415, 1261, 1069, 1049, 928, 673 cm^{-1}. ^1H NMR δ: 0.87 (3H, t, J=5.9 Hz), 1.25 (42H, br), 1.47 (2H, br), 1.63 (2H, br), 2.24 (4H, br), 2.42 (2H, d, J=5.9 Hz), 3.50 (2H, br), 5.63 (1H, br), 6.30 (1H, br), 6.80 (1H, br).

Compound 2c. IR ν_{max} ($CHCl_3$): 3353, 3187, 2917, 2849, 1684, 1667, 1638, 1469, 1430, 1387, 1215, 1161, 1134, 1111, 955, 720, 669 cm^{-1}. ^1H NMR δ: 0.87 (3H, t, J=6.6 Hz), 1.25 (40H, br), 1.46 (2H, m), 1.70 (4H, m), 1.85 (1H, br), 2.22 (2H, t, J=7.6 Hz), 2.31 (3H, m), 2.74 (1H, d, J=8.1 Hz), 3.53 (1H, d, J=11.9 Hz), 3.70 (1H, d, J=11.9 Hz), 5.51(2H, br), 6.44 (1H, br).

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