Pergamon

Tetrahedron 54 (1998) 565–572

TETRAHEDRON

Total Synthesis of Analogs of Topostin B, A DNA Topoisomerase I Inhibitor. Part 4. Synthesis of Topostin B-2 Analogs

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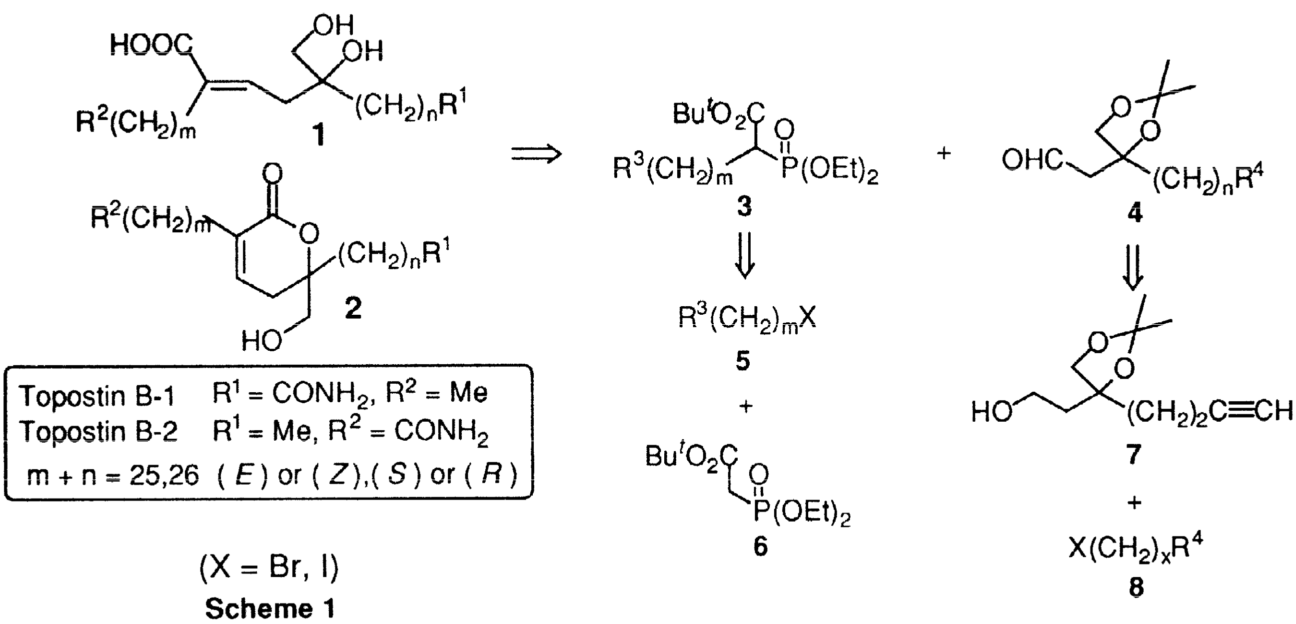
Received 9 September 1997; revised 4 November 1997; accepted 6 November 1997

Abstract: Analogs of topostin B-2, an inhibitor of mammalian DNA topoisomerase I, have been synthesized in a convenient manner.

In our preceding paper,[1] we described a convenient synthesis of analogs of topostin B-1 having inhibitory activity against DNA topoisomerase I.[2] We now succeeded in the synthesis of topostin B-2 analogs in a convenient manner. Because the fundamental structure of analogs of topostin B-1 and B-2 are the same as shown in Scheme 1, the synthetic routes analogous to those used for the synthesis of topostin B-1 analogs could be applied to the synthesis of topostin B-2 analogs. We adopted a stereorandom strategy to synthesize topostin B-2 analogs because the absolute stereostructure of topostin B has not been clarified.



(X = Br, I)

Scheme 1

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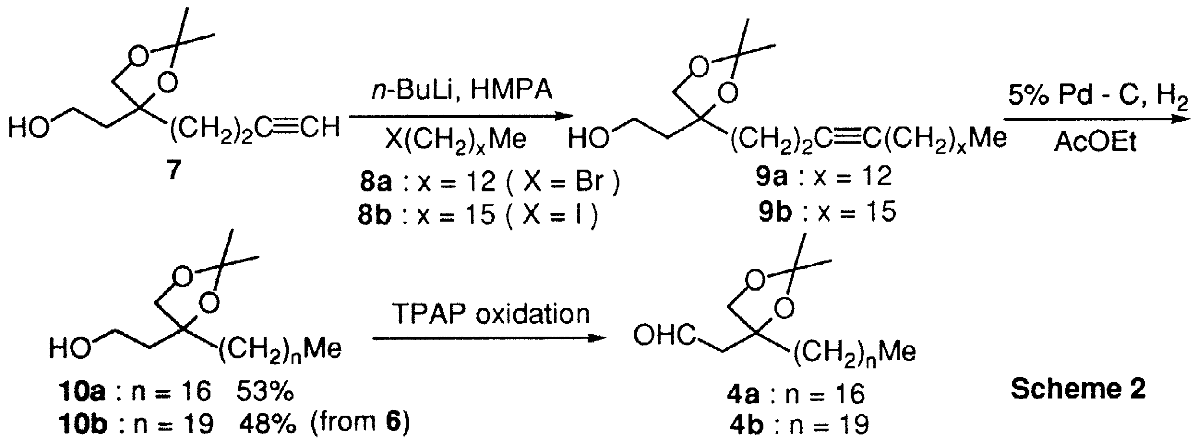
PII: S0040-4020(97)10316-7

Preparation of the Right Fragment 4.

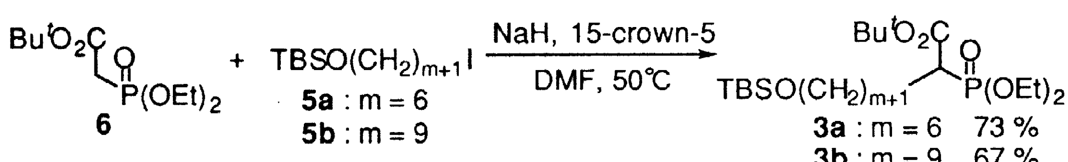
Alkylation of the lithium acetylide, which was generated by lithiation of the terminal alkyne **7**[1] with butyllithium in Et_2O-HMPA, with the alkyl halides **8a,b** gave the compounds **9a** and **9b** in good yield under conditions analogous to those in the preceding paper. Catalytic hydrogenation of the alkynes **9a** and **9b** over 5% Pd-C, respectively, furnished the saturated compounds **10a** and **10b**, followed by TPAP ($Pr_4N^+RuO_3^-$) oxidation[3] of the primary alcohol easily to give the right fragments **4a** and **4b** (Scheme 2).



Scheme 2

Preparation of the Left Fragment 3

The left fragments **3a** and **3b** of topostin B-2 analogs were respectively prepared by alkylation of the phosphonate **6** with the halides **5a** and **5b**,[4] as shown in Scheme 3.[6]

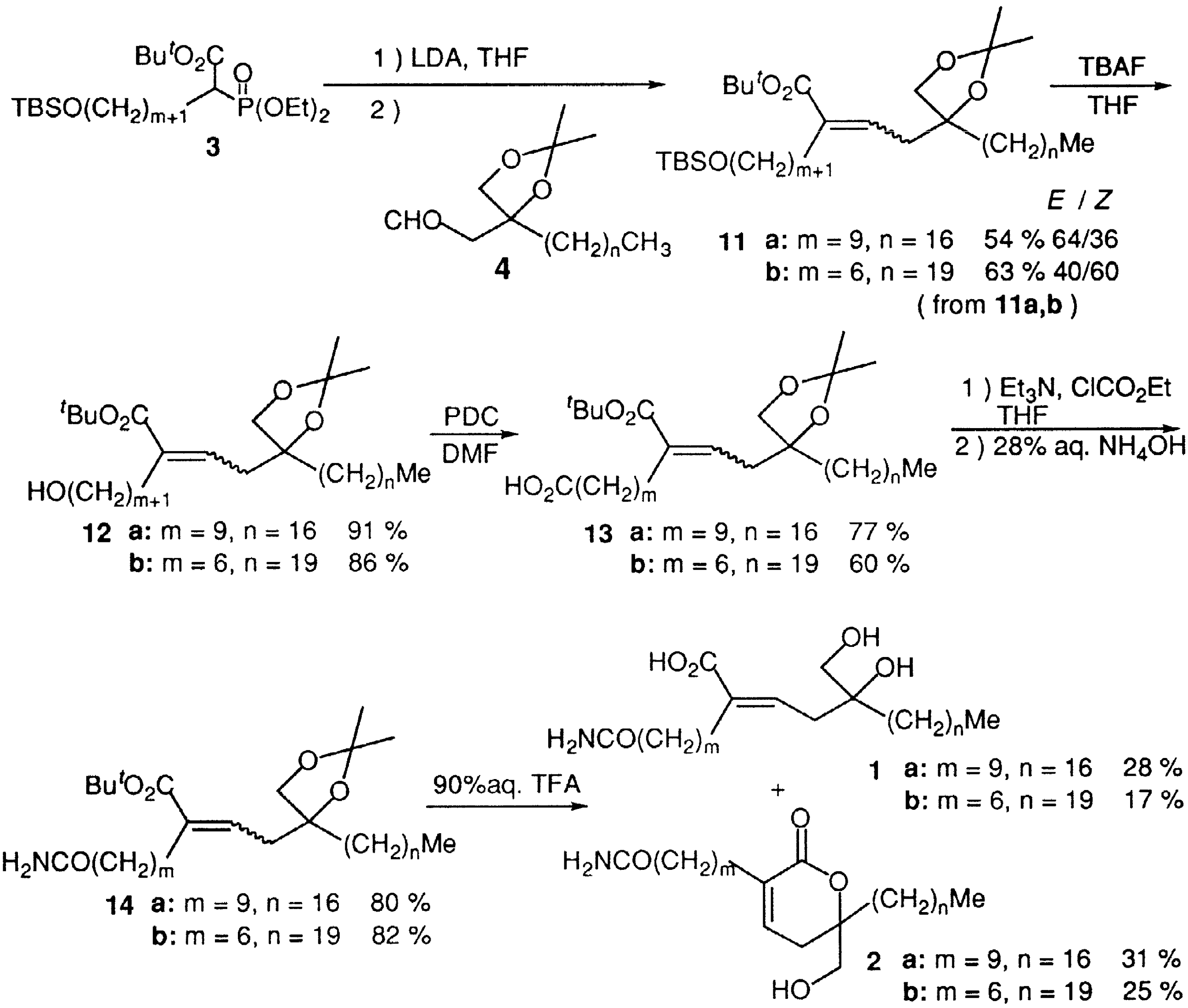


Scheme 3

Synthesis of Topostin B-2 Analogs

With two kinds of the left fragments **3** (m = 6, 9) and two kinds of right fragments **4** (n = 16, 19) in hand, we accomplished the topostin B-2 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 **11a** and **11b** in a ratio of 40 : 60 ~ 64 : 36. Their stereochemistry was unambiguously determined by the measurement of the difference-NOE NMR spectra. Respective desilylation of the coupling products **11a** and **11b** afforded the alcohols **12a** and **12b**, which were oxidized with pyridinium dichromate (PDC) to give the carboxylic acids **13a** and **13b**. After conversion to the mixed anhydrides, **13a** and **13b** was converted to the amides **14a** and **14b**. Respective removal of the acetonide and *t*-butyl functions with 90% aqueous trifluoroacetic acid (TFA) afforded (*E*)-topostin B-2 analogs **1a** and **1b** and the lactones **2a** and **2b** which were the cyclization products of (Z)-topostin B-2.

Thus, we have succeeded in synthesizing two kinds of topostin B-2 analogs **1** and **2** in an analogous manner to the synthesis of topostin B-1 analogs.[1] Our method will be useful for the preparation of various analogs of topostin B.



Scheme 4

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.

3-(5-Spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-6-icosyne-1-ol (9a). To a solution of **7** (192 mg, 1.0 M) in HMPA-Et_2O (1 ml-2 ml) was added dropwise *n*-BuLi (1.71 M in hexane, 1.23 ml, 2.1 mM) at -30°C under argon, and the mixture was stirred at -10°C for 1.5 h. After a solution of **8a** (395 g, 1.5 mM) in Et_2O (1.0 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 (30 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 **9a** (262 mg) as a colorless oil, which was used for the next step without further purification. IR ν_{max} (neat): 3360, 2930, 1379, 1126, 1095, 949, 845 cm^{-1}. ^1H NMR δ: 0.89 (3H, m), 1.24 (22H, m), 1.40 (3H, s), 1.43 (3H, s), 1.88 (4H, m), 2.17 (4H, m), 2.57 (1H, br), 3.85 (4H, m).

3-(5-Spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-6-tricosyne-1-ol (9b). The alkyne **6** (260 mg, 1.3 mM) was alkylated with the alkyl halide **8b** (705 mg, 2.0 mM) as described for **8a** to give **9b** (311 mg) as a pale yellow oil, which was used for the next step without further purification. IR ν_{max} (neat): 3400, 2926, 2855, 1466, 1379, 1255, 1211, 1157, 1057, 980, 871, 721 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.30 Hz), 1.25 (28H, m), 1.40 (3H, s), 1.43 (3H, s), 1.90 (4H, m), 2.15 (4H, m), 2.61 (1H, br), 3.80 (4H, m).

3-(5-Spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-1-icosanol (10a). A mixture of the alkyne **9a** (262 mg) and 5% Pd-C (90 mg) in EtOAc (100 ml) was stirred for 30 min at room temperature under H_2 atmosphere. The mixture was filtrated, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820 MH, 10 g, hexane:EtOAc = 5:1) to give **10a** (206 mg, 53 %) as a colorless oil. IR ν_{max} (neat): 3375, 2924, 1466, 1309, 1254, 1057, 871 cm^{-1}. ^1H NMR δ: 0.89 (3H, t, J=6.63 Hz), 1.25 (30H, m), 1.40 (3H, s), 1.43 (3H, s), 1.85 (4H, m), 2.69 (1H, br), 3.85 (4H, m). Anal. Calcd for $C_{24}H_{48}O_3$: C, 74.94; H, 12.58. Found: C, 74.69; H, 12.59.

3-(5-Spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-1-tricosanol (10b). The alkyne **9b** (311 mg) was reduced as descried for **9a** to give **10b** (268 mg, 48 %) as a colorless oil. IR ν_{max} (neat): 3400, 2986, 2914, 1471, 1253, 1213, 1053, 1018, 987, 868, 821,717 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.30 Hz), 1.25 (36H, m), 1,40 (3H, s) 1,43 (3H, s), 1.85 (4H, m), 2.69 (1H, br), 3.80 (4H, m). Anal. Calcd for $C_{27}H_{54}O_3$: C, 76.00; H, 12.75. Found: C, 75.58; H, 12.66.

***t*-Butyl Diethyl-2-(1-*t*-butyldimethylsiloxyheptanyl)phosphonoacetate (3a).** To a stirred suspension of NaH (60% oil dispersion, 110 mg, 2.7 mM) in DMF (8 ml) was added dropwise a solution of **6** (570 mg, 2.26 mM) in DMF (15 ml) at 0°C under argon, and the mixture was stirred at room temperature for 1 h. A solution of **5a** (962 mg, 2.7 mM) in DMF (10 ml) and 15-Crown-5 (120 µl, 0.6 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 silica gel column chromatography (BW-820 MH, 50 g, hexane:EtOAc = 5:1) to give **3a** (787 mg, 73 %) as a colorless oil. IR ν_{max} (neat) 2933, 1738, 1392, 1255, 1163, 1097, 1053, 1026, 970, 837, 775 cm^{-1}. ^1H NMR δ: 0.38 (6H, s), 0.89 (9H, s), 1.30 (16H, m), 1.47 (9H, s), 1.90 (2H, brd, J=40.60 Hz), 2.92 (1H, dquint, J=3.80, 11.22 Hz), 3.58 (2H, t, J=6.6 Hz), 4.26 (4H, m). Anal. Calcd for $C_{23}H_{49}O_6PSi \cdot H_2O$: C, 55.39; H, 10.31. Found: C, 55.06; H, 9.94.

***t*-Butyl Diethyl-2-(1-*t*-butyldimethylsiloxydecanyl)phosphonoacetate (3b).** The phosphonate **6** (1.26 g, 5.0 mM) was alkylated with the alkyl halide **5b** (2.67 g, 6.71 mM) as described for **5a** to give **3b** (1.69 g, 67 %) as a colorless oil. IR ν_{max} (neat): 2930, 1732, 1368, 1256, 1105, 1028, 966, 837 cm^{-1}. ^{1}H NMR δ: 0.44 (6H, s), 0.89 (9H, s), 1.39 (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), 3.58 (2H, t, J=6.6 Hz), 4.15 (4H, m). Anal. Calcd for $C_{26}H_{55}O_6PSi$: C, 59.74; H, 10.06. Found: C, 59.70; H, 10.00.

***t*-Butyl 2-(10-*t*-Butyldimethylsiloxydecanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxa-cyclopentyl)-2-henicosenoate (11a).** To a mixture of **10a** (134 mg, 0.35 mM), *N*-methylmorpholine-*N*-oxide (NMO) (62 mg, 0.75 mM) and MS 4Å (180 mg) in CH_2Cl_2 (3.5 ml) was added tetrapropylammonium perrutenate (TPAP) (6 mg, 0.018 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 **4a** (140 mg) 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-Pr)$_2$NH (74 µl, 0.42 mM) and *n*-BuLi (1.56 M in hexane, 272 µl, 0.42 mM) in THF (1 ml)) was added dropwise a solution of **3b** (195 mg, 0.39 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 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, 10 g, hexane:EtOAc = 10:1) to give **11a** (141 mg, 54 %) as a colorless oil. IR ν_{max} (neat): 2926, 2855, 1709, 1640, 1256, 1213, 1156, 1100, 835 cm^{-1}. ^{1}H NMR δ: 0.43 (6H, s), 0.87 (12H, m), 1.25 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.47 (9H, s), 2.22(2H, m), 2.43 (1.28H, d, J=7.58 Hz), 2.68 (0.72H, m), 3.59 (2H, t, J=6.60 Hz), 3.76 (2H, m), 5.81 (0.36H, t, J=7.26 Hz), 6.66 (0.64H, t, J=7.40 Hz). Anal. Calcd for $C_{46}H_{90}O_5Si$: C, 73.54; H, 12.07. Found: C,73.51; H, 11.97.

***t*-Butyl 2-(7-*t*-Butyldimethylsiloxyheptaanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxa-cyclopentyl)-2-tetracosenoate (11b).** The phosphonate **3a** (125 mg, 0.26 mM) was coupled with the aldehyde **4b**, which was obtained by oxidation of alcohol **10b** (91 mg, 0.213 mM), as described for the preparation of **10a** to give **11b** (101 mg, 63 %) as a colorless oil. IR ν_{max} (neat): 2928, 2855, 2359, 1714, 1464, 1379, 1369, 1255, 1213, 1099, 1061, 835, 775, 721 cm^{-1}. ^{1}H NMR δ: 0.04 (6H, s), 0.89 (12H, m), 1.25 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.47 (9H, s), 2.28 (2H, m), 2.46 (0.8H, d, J=6.60 Hz), 2.73 (1.2H, m), 3.59 (2H, t, J=6.60 Hz), 3.76 (2H, m), 5.94 (0.6H, t, J=6.90 Hz), 6.76 (0.4H, t, J=7.30 Hz). Anal. Calcd for $C_{46}H_{90}O_5Si \cdot 1/4H_2O$: C, 73.10; H, 12.07. Found: C, 73.03; H, 11.96.

***t*-Butyl 2-(10-Hydroxydecanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-henicosenoate (12a).** A mixture of **11a** (134 mg, 0.78 mM) and tetrabutylammonium fluoride (TBAF) (91.5 mg, 0.35 mM) in THF (1.5 ml) was stirred at room temperature for 2 h, diluted with H_2O, and the mixture was 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-820 MH, 10 g, hexane:EtOAc = 3:1) to give **12a** (105 mg, 91 %) as a colorless oil. IR ν_{max} (neat): 3427, 2924, 2855, 1709, 1647, 1466, 1368, 1251 ,1213, 1157, 870 cm^{-1}. ^{1}H NMR δ: 0.89 (3H, t, J=6.10 Hz), 1.25 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.47 (9H, s), 2.21 (2H, m), 2.43 (1.28H, d, J=7.59

Hz), 2.68 (0.72H, m), 3.64 (2H, t, J=6.60 Hz), 3.76 (2H, m), 5.83 (0.36H, t, J=7.09 Hz), 6.66 (0.64H, t, J=7.43 Hz). Anal. Calcd for $C_{40}H_{76}O_5$: C, 75.42; H, 12.02. Found: C, 75.32; H, 11.82.

***t*-Butyl 2-(7-Hydroxyheptanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-tetracosenoate (12b)**. The silylether **11b** (89 mg, 0.12 mM) was desilylated as described for **11a** to give **12b** (66 mg, 86 %) as a colorless oil. IR ν_{max} (neat): 3420, 2924, 2855, 2316, 1714, 1464, 1379, 1369, 1252, 1213, 1157, 1059, 875, 721 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.90 Hz), 1.25 (48H, m), 1.39 (3H, s), 1.41 (3H, s), 1.47 (9H, s), 2.27 (2H, m), 2.43 (0.8H, d, J=7.59 Hz), 2.68 (1.2H, m), 3.56 (1H, br), 3.62 (2H, m), 3.76 (2H, m), 5.95 (0.6H, t, J=6.90 Hz), 6.77 (0.4H, t, J=7.30 Hz). Anal. Calcd for $C_{40}H_{76}O_5$: C, 75.42; H, 12.02. Found: C, 75.15; H, 12.05.

***t*-Butyl 2-(9-Carboxynonanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-henicosenoate (13a)**. To a solution of the alcohol **12a** (110 mg, 0.173 mM) in DMF (1 ml) was added pyridinium dichromate (PDC) (455 mg, 1.21 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 **13a** (87 mg, 77 %) as a colorless oil. IR ν_{max} (neat): 3218, 2926, 2855, 1740, 1709, 1646, 1464, 1456, 1391, 1379, 1368, 1252, 1213, 1156, 1061, 974, 938, 872, 853, 820, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.25 (46H, m), 1.39 (3H, s) 1.41 (3H, s) 1.48 (9H, s), 2.24 (2H, m), 2.34 (2H, t, J=7.43 Hz), 2.44 (1.28H, d, J=7.25 Hz), 2.68 (0.72H, m), 3.77 (2H, m), 5.81 (0.36H, t, J=7.26 Hz), 6.66 (0.64H, t, J=7.59 Hz). Anal. Calcd for $C_{40}H_{74}O_6$: C, 73.80; H, 11.46. Found: C, 73.76; H, 11.28.

***t*-Butyl 2-(6-Carboxyhexanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-tetracosenoate (13b)**. The alcohol **12b** (19 mg, 0.031 mM) was oxidized as described for the preparation of **12a** to give **13b** (12 mg, 60 %) as a colorless oil. IR ν_{max} (neat): 3420, 2926, 2855, 1738, 1713, 1464, 1379, 1369, 1252, 1213, 1157, 1097, 1061, 976, 875, 817, 721 cm^{-1}. ^1H NMR δ: 0.88 (3H, m), 1.25 (46H, m), 2.25 (4H, m), 2.46 (0.8H, d, J=7.30 Hz), 2.70 (1.2H, m), 3.75 (2H, m), 5.95 (0.6H, m), 6.77 (0.4H, m). Anal. Calcd for $C_{40}H_{74}O_6 \cdot 1/4C_6H_{14}$: C, 74.11; H, 11.61. Found: C, 74.59; H, 11.25.

***t*-Butyl 2-(9-Carbamoylnonanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-henicosenoate (14a)**. To a stirred solution of **13a** (61 mg, 0.094 mM) and Et_3N (14 µl, 0.103 mM) in THF (1 ml) was added dropwise $ClCO_2Et$ (10 µl, 0.10 mM) at 0°C. The mixture was stirred at 0°C for 30 min and then 28% aqueous NH_4OH (19 µl, 0.282 mM) was added dropwise. After being stirred at 0°C for 30 min, the mixture was quenched with H_2O, and extracted with EtOAc (10 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 **14a** (49 mg, 80 %) as a colorless oil. IR ν_{max} (neat): 3432, 3368, 3218, 2926, 2855, 1705, 1669, 1464, 1456, 1368, 1252, 1213, 1156, 1061, 872, 855, 722 cm^{-1}. ^1H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.25 (46H, m) 1.39 (3H, s), 1.41 (3H, s), 1.47 (9H, s), 2.21 (4H, t, J=7.59 Hz), 2.43 (1.28H, d, J=7.25 Hz), 2.67 (0.72H, m), 3.76 (2H, m), 5.38 (2H, br), 5.80 (0.36H, t, J=7.26 Hz), 6.66 (0.64H, J=7.43 Hz). Anal. Calcd for

$C_{40}H_{75}NO_5$: C, 73.91; H, 11.63; N, 2.15. Found: C, 73.58; H, 11.46, N, 2.31.

***t*-Butyl 2-(6-Carbamoylhexanyl)-5-(5-spiro-3,3-dimethyl-1,3-dioxacyclopentyl)-2-tetracosenoate (14b).** The carboxylic acid **13b** (13 mg, 0.021 mM) was amidated as described for the preparation of **13a** to give **14b** (11 mg, 82 %) as a colorless oil. IR ν_{max} (neat): 3400, 3200, 2924, 2853, 1714, 1682, 1651, 1614, 1469, 1456, 1062, 976, 721 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, m), 1.25 (46H, m), 1.39 (6H, s), 1.48 (9H, s), 2.28 (4H, m), 2.45 (0.8H, d, J=7.25 Hz), 2.75 (1.2H, m), 3.78 (2H, m), 5.32 (2H, m), 5.95 (0.6H, m), 6.79 (0.4H, m). Anal. Calcd for $C_{40}H_{75}O_5N$: C, 73.91; H, 11.63; N, 2.15. Found: C, 73.74; H, 11.51; N, 2.04.

(E)-2-(9-Carbamoylnonanyl)-5-hydroxy-5-hydroxymethyl-2-henicosenoic Acid (1a) and 5-Heptadecanyl-5-hydroxymethyl-2-(9-carbamoylnonanyl)-2-penten-5-olide (2a)

A mixture of **14a** (42 mg, 0.065 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, 28 %) as a white waxy solid; m.p. 57-59°C and **2a** (10 mg, 31 %) as a white waxy solid; m.p. 90-91°C.

Compound 1a. IR ν_{max} ($CHCl_3$): 3351, 3204, 3019, 2928, 2855, 1682, 1464, 1417, 1381, 1286, 1275, 1123, 1075, 1039, 963, 743 cm^{-1}. ^{1}H 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), 6.10 (1H, br), 6.90 (1H, br). FABHRMS Calcd for $C_{33}H_{62}O_5N$ $(M-H)^-$: 552.4625. Found: 552.4671.

Compound 2a. IR ν_{max} ($CHCl_3$): 3399, 3198, 2926, 2853, 1728, 1684, 1657, 1469, 1430, 1387, 1215, 1161, 1134, 1111, 955, 720, 669 cm^{-1}. ^{1}H NMR δ: 0.87 (3H, t, J=6.9 Hz), 1.25 (40H, br), 1.45 (2H, m), 1.60 (4H, m), 2.11 (1H, br), 2.21 (5H, m), 2.73 (1H, d, J=8.5 Hz), 3.62 (2H, d, J=11.9 Hz), 5.41(2H, br), 6.44 (1H, br). FABHRMS Calcd for $C_{33}H_{60}O_4N$ $(M-H)^-$: 534.4519. Found: 534.4507.

(E)-2-(6-Carbamoylhexanyl)-5-hydroxy-5-hydroxymethyl-2-tetracosenoic Acid (1b) and 5-Nonadecanyl-5-hydroxymethyl-2-(6-Carbamoylhexanyl)-2-penten-5-olide (2b). The compound **14b** (38 mg, 0.058 mM) was treated as described for **14a** and **2a** to give **1b** (5 mg, 17 %) as a white waxy solid; m.p. 64-66°C and **2b** (8 mg, 25 %) as a white waxy solid; m.p. 91-93°C.

Compound 1b. IR ν_{max} ($CHCl_3$): 3400, 2922, 2853, 1713, 1682, 1651, 1464, 1261, 1217, 1095, 1047, 802, 760, 721 cm^{-1}. ^{1}H NMR δ: 0.88 (3H, t, J=6.60 Hz), 1.25 (42H, m), 1.47 (2H, br), 1.63 (2H, br), 2.22 (2H, t, J=7.10 Hz), 2.31 (2H, t, J=7.40 Hz), 2.42 (2H, t, J=7.60 Hz), 3.49 (2H, m), 5.50 (2H, br), 6.79 (1H, t, J=7.10 Hz). FABHRMS Calcd for $C_{33}H_{62}O_4N$ $(M+H-H_2O)^+$: 536.4675. Found: 536.4683.

Compound 2b. IR ν_{max} ($CHCl_3$): 3400, 2918, 2851, 1713, 1682, 1651, 1469, 1216, 1159, 962, 835, 802, 719 cm^{-1}. ^{1}H NMR δ: 0.87 (3H, m), 1.25 (48H, m), 2.03-2.35 (4H, m), 3.46-3.74 (2H, m), 5.41 (2H, br), 6.45 (1H, br). FABHRMS Calcd for $C_{33}H_{62}O_4N$ $(M+H)^+$: 536.4675. Found: 536.4681.

Acknowledgment : This work was supported in part by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. The authors thanks Professor Toshiwo Andoh of Soka University for biological assay.

References and Notes

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4. The halides **5** were obtained from the alcohol **15**[5] as shown below, and the crude products were used for the next step without further purification.

$$\underset{\textbf{15}}{\mathrm{TBSO(CH_2)_{m+1}OH}} \xrightarrow[\text{2) NaI, acetone, reflux}]{\text{1) MsCl, Et}_3\text{N, CH}_2\text{Cl}_2\text{, 0°C}} \underset{\textbf{5}\text{ (}\textbf{a}\text{ : m = 6, }\textbf{b}\text{ : m = 9)}}{\mathrm{TBSO(CH_2)_{m+1}I}}$$

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