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

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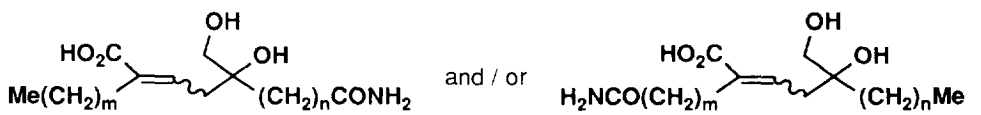
Abstract: Synthesis of the right and left building blocks, **36** and **5**, for the analog **3** of topostin B-1, an inhibitor of mammalian DNA topoisomerase I, has been achieved in a convenient manner.

Topostins, isolated by Andoh and co-workers[1,2] from a culture broth of *Flexibacter topostinus* sp. nov., B-572, are structurally novel inhibitors of mammalian DNA topoisomerase I. Topostin B is most active among topostins and has specific activity of 22,000 U/mg. One of the noteworthy features of topostin B on biological activity is that it exhibits cytotoxic activity against the camptothesin resistance tumor cell CPT-K5.[3] Since DNA topoisomerase I inhibitors will be regarded as a potential anticancer agent,[3,4] topostin B is quite an interesting compound to investigate its biological profile in detail. However, scarce availability in nature precludes the detailed investigation. Furthermore, topostin B comprises two components, topostin B-1 and B-2, with the molecular weights of 553 and 567 in an equimolecular ratio. Their structures have been tentatively assigned to be **1** and/or **2**, shown below.[5] Neither stereochemistry at the double bond nor the absolute configuration at the single stereogenic center has been determined.



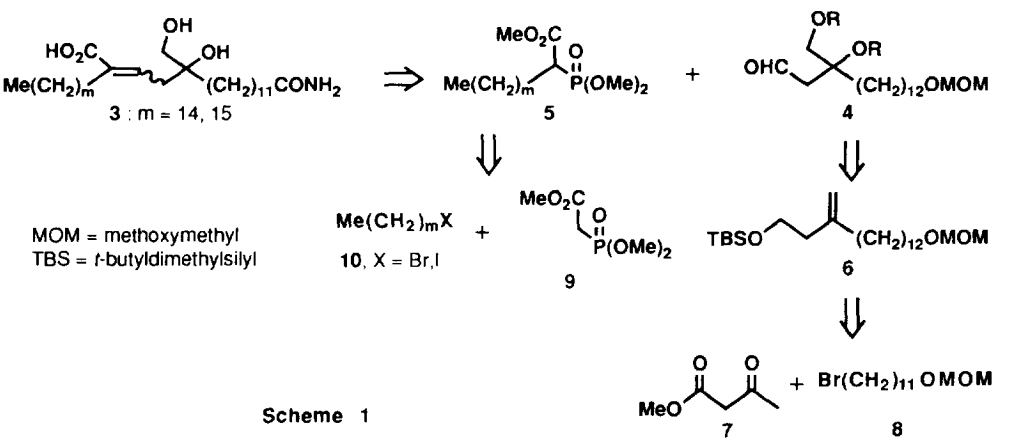
Topostin B - 1 (**1**) Topostin B - 2 (**2**)

m + n = 25 or 26

We have been quite interested in their biological activities as well as unique structures, and launched the synthesis of topostin B. Our aim is twofold:(1) determination of their structures by total synthesis, and (2) creation of a novel anticancer agent regarding topostin B as a leading compound. Our first target was topostin B-1 analogs **3** (m=14 and 15, n=11 in the structure **1**) in their racemic modification. We describe here synthesis of the right and left fragments and will disclose the total synthesis of the analogs **3** of topostin B-1 in

the following paper.[6]

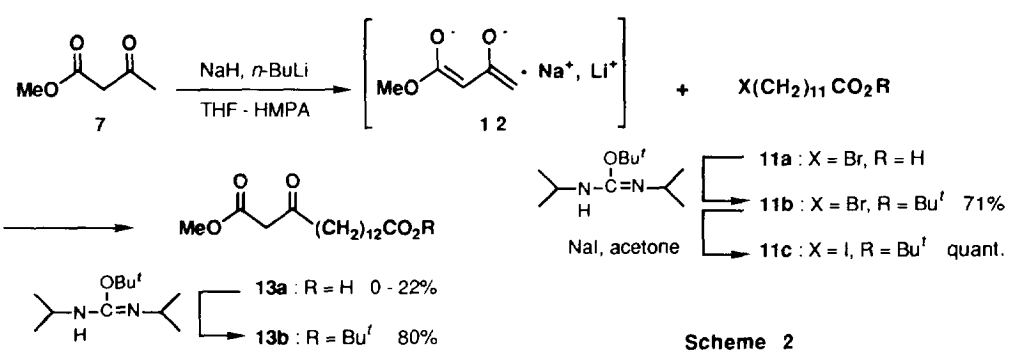
The overall strategy for the synthesis of **3** is shown in Scheme 1. Since any stereochemistry of topostin B has not been determined yet, stereorandom synthesis producing several congeners at the same time will be preferable. An obvious cleaving point for the retrosynthesis of **3** will be the double bond. Thus, the topostin B-1 analogs **3** would be constructed by the Horner-Emmons reaction of the aldehyde **4** with the phosphonate **5**. The right fragment **4** would be produced from the alkene **6** which would be obtained through alkylation of the dianion of methyl acetoacetate (**7**) with the bromide **8**. The left fragment **5** would be produced by alkylation of trimethyl phosphonoacetate (**9**) with the halide **10**. According to this retrosynthetic scheme, we started the synthesis of **3**.



Scheme 1

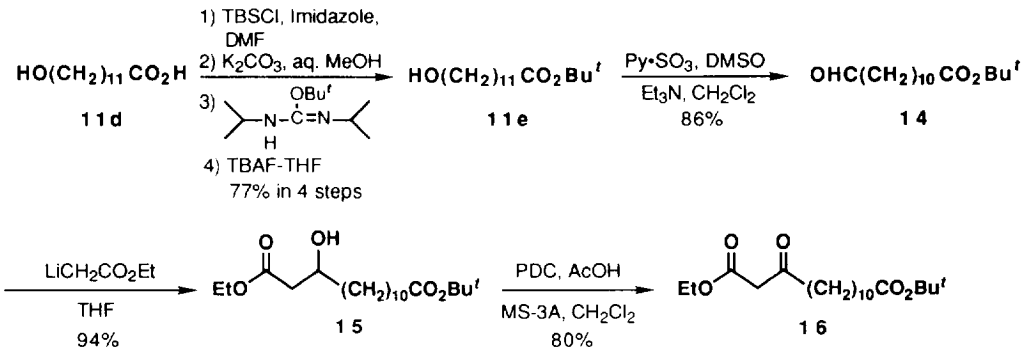
Preparation of the Right Fragment

First attempt to synthesize the right fragment **4** started from 12-bromododecanoic acid (**11a**), which was converted to the iodo tert-butyl ester **11c** *via* the bromo tert-butyl ester **11b**[7]. Attempted γ-alkylation of the dianion **12**,[8] generated from methyl acetoacetate (**7**), with either the bromide **11b** or iodide **11c** resulted in 40-90% recovery of the halide together with unknown by-products. Replacement of the tert-butyl ester **11b** or **11c** with the sodium salt[9] of **11a** afforded the γ-alkylated acid **13a** though in low yield, which was converted to the tert-butyl ester **13b**, as shown in Scheme 2.



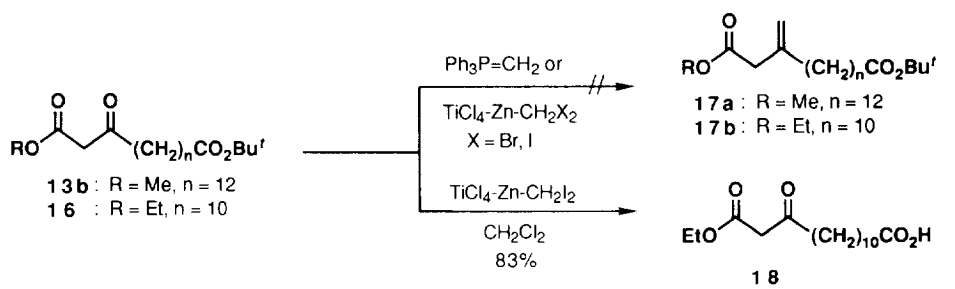
Scheme 2

This unsatisfactory result of the alkylation led us to investigate the utilization of the aldol reaction. After protection of the hydroxyl group of 12-hydroxydodecanoic acid (**11d**) with tert-butyldimethylsilyl (TBS) chloride, tert-butyl esterification followed by removal of the TBS group with tetrabutylammonium fluoride (TBAF) afforded tert-butyl 12-hydroxydodecanoate (**11e**),[10] which was oxidized with dimethyl sulfoxide under the Parikh-Doering conditions[11] to give the aldehyde **14**, shown in Scheme 3. The aldol reaction of the aldehyde **14** with lithio ethyl acetate smoothly proceeded to give the β–hydroxy ester **15**, which underwent the oxidation with pyridinium dichromate (PDC)[12] to give the β–ketoester **16**.



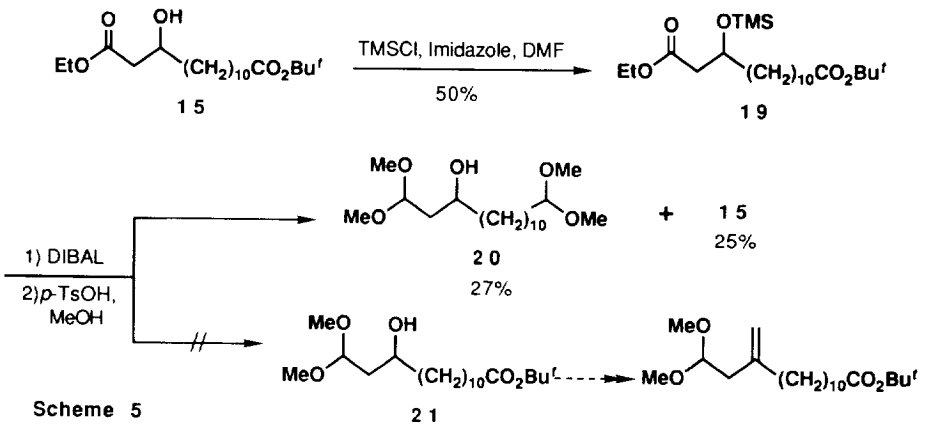
Scheme 3

Attempted methylenation of the carbonyl group of the β–ketoester **13b** or **16** by use of methylenetriphenylphosphorane resulted in the recovery of the starting material. The Nozaki[13] or Nozaki-Lombardo[14] methylenation using titanium tetrachloride-zinc-dihalomethane was also unsuccessful to give the exo-methylene compound **17**. When dichloromethane was used in place of tetrahydrofuran which was an ordinary solvent in the Nozaki's method,[13,14] removal of the tert-butyl function only occurred to give the acid **18** in 83% yield, as shown in Scheme 4.



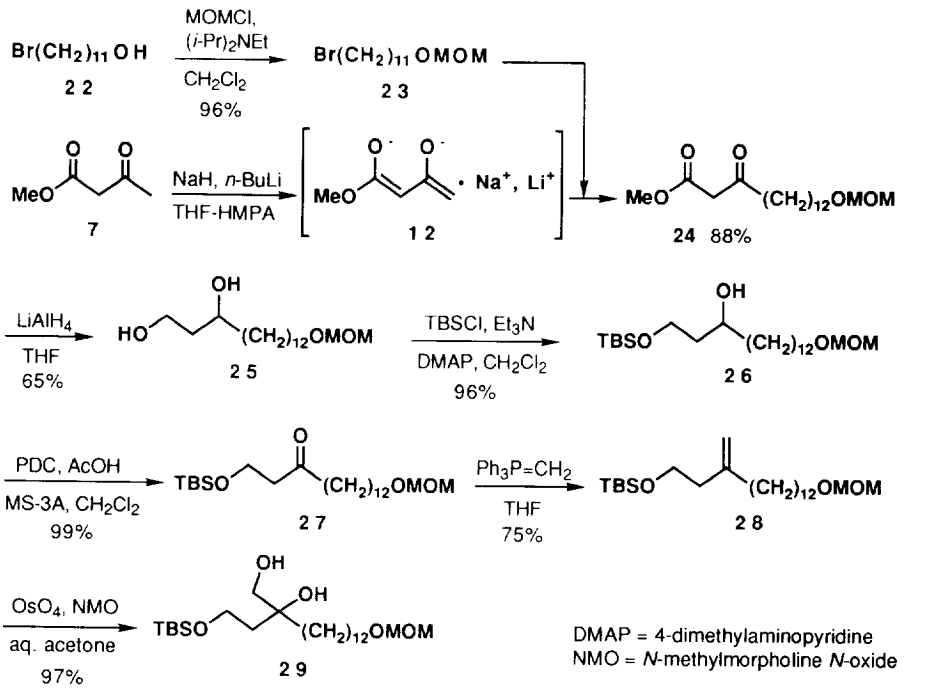
Scheme 4

Next, we attempted the methylenation of the protected β–keto aldehyde instead of the β–keto ester. After protection of the hydroxyl group of **15** with trimethylsilyl (TMS) chloride, attempt of the selective reduction of the ethyl ester **19** with diisobutylaluminum hydride (DIBAL) followed by the methyl acetalization resulted in the reduction of the both ester functions, giving the bisdimethylacetal **20** in low yield but no desired monoacetal **21**, shown in Scheme 5.



Scheme 5

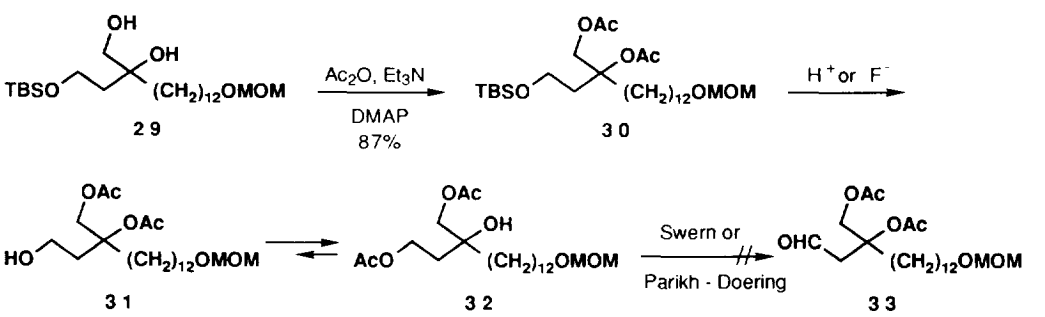
Since the above access to the right fragment **4** of topostin B-1 failed, we now employed a relatively longer pathway using the primary alcohol function instead of the ester function, as summarized in Scheme 6. Indeed, this replacement worked with great success. The γ-alkylation of the dianion **12**, generated from methyl acetoacetate (**7**), with 1-bromo-11-methoxymethoxyundecane (**23**), obtained by methoxymethylation of 11-bromoundecanol (**22**), was found to proceed smoothly to give the β-keto ester **24**. Reduction with lithium aluminum hydride followed by selective protection of the primary alcoholic function of the diol **25** with TBSCl afforded the mono-alcohol **26**, which underwent the PDC oxidation[12] to give the ketone **27**. The Wittig



Scheme 6

methylenation now smoothly afforded the exo-methylene compound **28**. Conversion of the exo-methylene function to the 1,2-diol one easily proceeded to give the diol **29**.

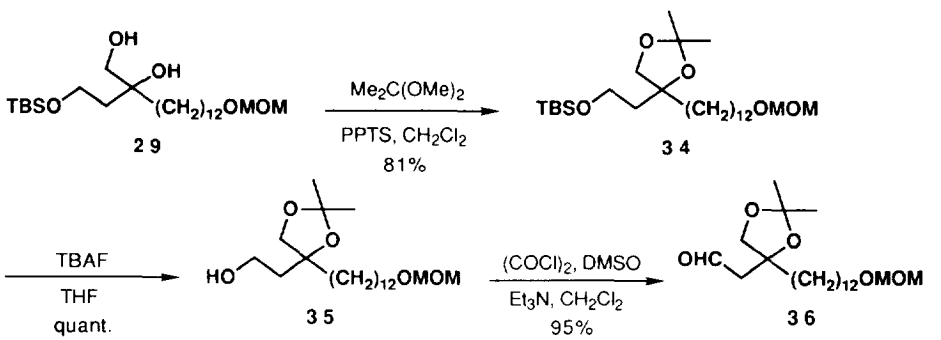
Acetylation of the diol **29** afforded the diacetate **30** in good yield. Desilylation of **30** with TBAF followed by oxidative treatment under the Swern or Parikh-Doering conditions[11] did not produce the aldehyde **33** at all. Careful inspection of the ^1H NMR spectrum of the desilylated product revealed that its methylene protons attached at the primary alcoholic functions shifted 0.5 ppm toward the lower field (δ 3.7 to 4.2 ppm), proving that the desilylated product was actually the tertiary alcohol **32** formed by the acetyl migration. Although the desilylation of **30** was also tried under acidic conditions as shown in Scheme 7, the yield of the desired primary alcohol **31** was unsatisfactory due to the concomitant formation of the tertiary alcohol **32**. Poor reproducibility of the reaction posed the problem too. Furthermore, the primary alcohol **31** spontaneously transformed to the tertiary alcohol **32** upon being kept at ambient temperature.



Reaction Conditions		Yield **31** : **32**
TBAF - THF	rt, 1 h	– : 84%
p-TsOH - 90% aq. MeOH	rt, 1 h	9% : 75%
AcOH - THF - H_2O (1 : 1 : 1)	rt., 11 h	59% : 25%

Scheme 7

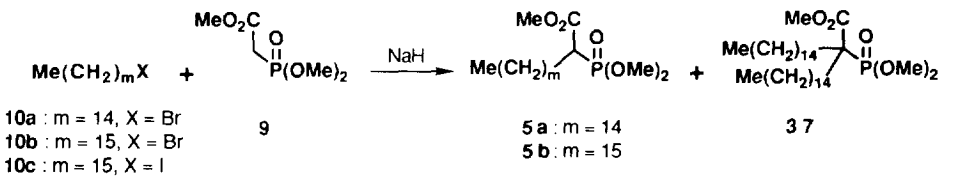
Thus, we decided to change the acetyl protection to the acetal one, shown in Scheme 8. Treatment of the diol **29** with dimethoxypropane under acidic conditions afforded the acetal **34**, of which the TBS group was smoothly cleaved with TBAF without any migration, giving the required primary alcohol **35**. Swern oxidation of **35** finally afforded the required right fragment **36** of topostin B-1. The overall yield of the aldehyde **36** from 11-bromoundecanol (**22**) was 29% in 10 steps.



Scheme 8

Preparation of the Left Fragment

The left fragment **5b** of topostin B-1 was prepared by alkylation[15] of trimethyl phosphonoacetate (**9**) with 1-bromohexadecane (**10b**), as shown in Scheme 9. In the alkylation with the bromide **10b** in tetrahydrofuran, both sodium and potassium hydrides were more effective bases than lithium diisopropylamide. Addition of hexamethylphosphortriamide to tetrahydrofuran gave a complex mixture of the products. Interestingly, use of 1-iodohexadecane (**10c**) in place of the bromide **10b** resulted in a quantitative recovery of the starting iodide. So far, the maximum 36% yield of **5b** was obtained when 4 equivalent excess of the bromide **10b** was used. Although none of the dialkylation products could be found in the alkylation in refluxing tetrahydrofuran with **10b**, analogous alkylation of **9** with 1-bromopentadecane (**10a**) yielded a mixture of the mono- and di-alkylated products **5a** and **37**. Use of 1.05 equivalents of sodium hydride in 1,2-dimethoxyethane decreased the formation of **37**, giving **5a** and **37** in 29 and 7% yields, respectively. Although the yields of alkylation of **9** were not superior in either case, we have not investigated the reaction conditions further because of easy availability of the starting materials **9**, **10a**, and **10b**.



Scheme 9

We now succeeded in synthesizing two important building units **36** and **5** for the topostin B-1 analogs in a convenient way, which will be useful for the total synthesis of the topostin B-1 analogs.[6]

Experimental

All melting and boiling points were uncorrected. Distillation was carried out by a Kugelrohr apparatus. IR spectra were measured with 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 obtained on a JEOL DX-300 spectrometer. Silica gel BW-820MH, BW-200, or BW-300 (purchased from Fuji Davison Co.) was used for column chromatography. Analytical thin layer chromatography was carried out on a silica gel plate (Merck Art. 5715). Methyltriphenylphosphonium bromide and molecular sieves 3A (MS-3A) powder were dried at 80°C for 12 h and 140°C for 3 days before use, respectively.

***t*-Butyl 12-Bromododecanoate (11b)**

To a stirred solution of 12-bromododecanoic acid (**11a**) (1.0 g, 3.58 mM) in CH_2Cl_2 (5.0 ml) was added *t*-BuOH (10.0 ml) and then *O*-*t*-Bu-*N*,*N*′-diisopropylisourea (8.2 ml, 35.8 mM). After being stirred at room temperature for 17 h, the mixture was filtered through the pad of celite and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 400 g, hexane:Et_2O = 5:1) to give **11b** (855 mg, 71%) as a colorless oil, bp 115°C / 0.005 mmHg. IR ν_{max} (neat): 1732, 1458, 1368, 1256, 1156, 848, 723 cm^{-1}. ^{1}H NMR δ: 1.27 (14 H, br), 1.43 (9 H, s), 1.57 (2 H, m), 1.85 (2 H, quint, J = 6.9 Hz), 2.19 (2 H, t, J = 7.6 Hz), 3.40 (2 H, t, J = 6.9 Hz). Anal. Calcd for $C_{16}H_{31}BrO_2$: C, 57.31; H, 9.32. Found: C, 57.18; H, 9.30.

t-Butyl 12-Iodododecanoate (11c)

A mixture of **11b** (991 mg, 2.96 mM) and NaI (3.55 g, 23.68 mM) in acetone (20 ml) was refluxed for 2 h and diluted with Et_2O. The ethereal solution was washed with H_2O, aqueous $Na_2S_2O_3$, and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residual oil was distilled to give **11c** (1.13 g, quant.) as a colorless oil, bp 120-140°C / 0.005 mmHg. IR ν_{max} (neat): 1732, 1458, 1391, 1366, 1256, 1156, 849, 756 cm^{-1}. ^1H NMR δ: 1.20-1.43 (14 H, br), 1.44 (9 H, s), 1.56 (2 H, m), 1.81 (2 H, quint, J = 6.9 Hz), 2.19 (2 H, t, J = 7.6 Hz), 3.18 (2 H, t, J = 6.9 Hz). Anal. Calcd for $C_{16}H_{31}IO_2$: C, 50.27; H, 8.17. Found: C, 50.56; H, 8.36.

1-Methyl 16-Hydrogen 3-Oxohexadecanedioate (13a)

To a stirred suspension of NaH (60% oil dispersion, 71.6 mg, 1.79 mM) in THF (7.0 ml) was added dropwise a solution of **11a** (500 mg, 1.79 mM) in THF (3.0 ml) at 0°C under argon and the mixture was stirred at room temperature for 5 h. The mixture was cooled to 0°C and then a solution of dienolate **12** (prepared from methyl acetoacetate (**7**) (251 μl, 2.33 mM), NaH (60% oil dispersion, 96.4 mg, 2.41 mM), and *n*-BuLi (1.64 M in hexane, 1.47 ml, 2.41 mM) in THF-HMPA (8.0 ml-935 μl)) was added dropwise at 0°C. After being stirred at room temperature for 63 h, the mixture was quenched with 1*N* aqueous HCl and extracted with Et_2O (80 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, 100 g, hexane:acetone = 8:1 to 5:1) to give **13a** (113 mg, 20%), accompanied by recovered **11a** (368 mg, 74%) as a white wax. **13a**, mp 85-87°C. IR ν_{max} (nujol): 3700-2000, 1744, 1713, 1698, 1650-1550, 1464, 1439, 1408, 1321, 1262, 1163, 1088, 1001, 939, 723, 660 cm^{-1}. ^1H NMR δ: 1.26 (16 H, br), 1.61 (4 H, m), 1.65-2.30 (1 H, br), 2.34 (2 H, t, J = 7.6 Hz), 2.53 (2 H, t, J = 7.3 Hz), 3.45 (2 H, s), 3.74 (3 H, s). FAB-MS m/z: 315 (MH^+). Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.83; H, 9.22.

1-Methyl 16-t-Butyl 3-Oxohexadecanedioate (13b)

To a stirred solution of **13a** (110 mg, 0.35 mM) in CH_2Cl_2 (1.6 ml) was added *t*-BuOH (330 μl, 3.50 mM) and then *O*-*t*-Bu-*N,N'*-diisopropylisourea (418 μl, 1.75 mM). After being stirred at room temperature for 10 h, *O*-*t*-Bu-*N,N'*-diisopropylisourea (150 μl, 0.62 mM) and *t*-BuOH (150 μl, 1.60 mM) were added to the mixture. The mixture was stirred at 40°C for 4 h and diluted with Et_2O. The ethereal solution was filtered through the pad of celite and concentrated *in vacuo*. The residue was extracted with Et_2O (30 ml x 3), 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, 25 g, hexane:EtOAc = 15:1) to give **13b** (104 mg, 80%) as a white wax, mp 42-44°C. IR ν_{max} (nujol): 1752, 1713, 1650-1600, 1379, 1366, 1256, 1163, 1113, 1084, 1003, 717, 658, 586 cm^{-1}. ^1H NMR δ: 1.25 (16 H, br), 1.44 (9 H, s), 1.56 (4 H, m), 2.16 (2 H, t, J = 7.6 Hz), 2.52 (2 H, t, J = 7.3 Hz), 3.45 (2 H, s), 3.73 (3 H, s). Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.88; H, 10.29.

t-Butyl 12-Hydroxydodecanoate (11e)

To a stirred solution of 12-hydroxydodecanoic acid (**11d**) (216 mg, 1.0 mM) in *N,N*-dimethylformamide (DMF) (1.0 ml) was added imidazole (340 mg, 5.0 mM) and then TBSCl (452 mg, 3.0 mM). After being stirred at room temperature for 12 h, the mixture was diluted with Et_2O. The ethereal solution was washed with 10% aqueous citric acid, H_2O, and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a colorless oil (542 mg). The crude product was used for the next step without further purification.

A solution of the above crude oil (542 mg) in MeOH (19 ml) was added to an aqueous solution of K_2CO_3 (690 mg, 5.0 mM) in H_2O (6.6 ml) at 0°C. After being stirred at room temperature for 2.5 h, the mixture was quenched with 10% aqueous citric acid 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 a colorless oil (384 mg), which was used for the next step without further purification.

A mixture of the above oil (384 mg), CH_2Cl_2 (5.0 ml), *t*-BuOH (940 μl, 10.0 mM), and *O*-*t*-Bu-*N,N'*-diisopropylisourea (1.2 ml, 5.0 mM) was stirred at room temperature for 15 h. The mixture was filtered through the pad of celite and concentrated *in vacuo* to give a yellow oil. The residue was diluted with Et_2O and washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil (523 mg). The crude product was used for the next step without further purification.

To a stirred solution of the above oil (523 mg) in THF (10.0 ml) was added TBAF (783 mg, 3 mM). After being stirred at room temperature for 2 h, the mixture was quenched with H_2O and 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-820MH, 20 g, hexane:EtOAc = 5:1) to give **11e** (197 mg, 72%) as a colorless oil, bp 140-150°C / 1.8 mmHg. IR ν_{max} (neat): 3750-3100, 1742, 1458, 1397, 1367, 1256, 1057, 849 cm^{-1}. ^1H NMR δ: 1.26 (14 H, br), 1.43 (9 H, s), 1.63 (5 H, m), 2.19 (2 H, t, J = 7.6 Hz), 3.63 (2 H, t, J = 6.6 Hz). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.84; H, 11.90.

t-Butyl 11-Formylundecanoate (14)

To a stirred solution of **11e** (275 mg, 1.01 mM) and Et_3N (418 μl, 3.0 mM) in CH_2Cl_2 (3.0 ml) was added a solution of pyridine-sulfur trioxide (Py•SO_3) (477 mg, 3.0 mM) in dimethylsulfoxide (DMSO) (3.0 ml) at -10°C. After being stirred at room temperature for 10 min, the mixture was poured into ice-cooling saturated brine and extracted with Et_2O (50 ml x 2). The extracts were washed with 10% aqueous citric acid and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 20 g, hexane:EtOAc = 7:1) to give **14** (235 mg, 86%) as a white wax, mp 23-25°C. IR ν_{max} (neat): 1720, 1717, 1389, 1368, 1250, 1163, 851, 758, 722 cm^{-1}. ^1H NMR δ: 1.28 (12 H, br), 1.44 (9 H, s), 1.60 (4 H, m), 2.20 (2 H, t, J = 7.6 Hz), 2.42 (2 H, dt, J = 2.0, 7.3 Hz), 9.76 (1 H, t, J = 2.0 Hz). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.70; H, 11.03.

1-Ethyl 14-*t*-Butyl 3-Hydroxytetradecanedioate (15)

To a stirred solution of lithium diisopropylamide (LDA) (prepared from *i*-Pr_2NH (1.04 ml, 7.41 mM) and *n*-BuLi (1.64 M in hexane, 4.52 ml, 7.41 mM) in THF (20 ml)) was added dropwise a solution of EtOAc (725 μl, 7.41 mM) in THF (6.0 ml) over 10 min period at -78°C. After being stirred at -78°C for 20 min, a solution of **14** (1.82 g, 6.74 mM) in THF (6.0 ml) was added dropwise over 15 min period at -78°C. The whole was stirred at -78°C for 10 min and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (150 ml x 3), 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-820MH, 150 g, hexane:EtOAc = 8:1) to give **15** (2.27 g, 94%) as a pale yellow oil. IR ν_{max} (neat): 3600-3050, 1732, 1458, 1368, 1256, 1156, 1032, 947, 849, 756, 722 cm^{-1}. ^1H NMR δ: 1.27 (19 H, br), 1.44 (9 H, s), 1.59 (4 H, m), 2.19 (2 H, t, J = 7.6 Hz), 2.38 (1 H, dd, J = 9.0, 16.5 Hz), 2.93 (1 H, d, J = 3.6 Hz), 3.98 (1 H, br), 4.17 (2 H, q, J = 7.3 Hz). FAB-MS m/z: 359 (MH^+). Anal. Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 66.80; H, 10.62.

1-Ethyl 14-*t*-Butyl 3-Oxotetradecanedioate (16)

To a stirred solution of **15** (1.97 g, 5.5 mM) in CH_2Cl_2 (27.5 ml) was added pyridinium dichromate (PDC) (3.1 g, 8.25 mM) and MS-3A powder (4.4 g) and then AcOH (550 μl) at 0°C, and the mixture was stirred at room temperature for 50 min. Celite (2.75 g) was added and the mixture was stirred at room temperature for 20 min and filtered through the pad of celite. The filtrate was concentrated *in vacuo* to give a dark brown residue. The residue was dissolved in toluene and again concentrated *in vacuo*. The residue was dissolved in Et_2O and filtered through the pad of $MgSO_4$. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 120 g, hexane:EtOAc = 19:1) to give **16** (1.57 g, 80%) as a white wax, mp 31-32°C. IR ν_{max} (neat): 3700-3000, 1739, 1721, 1710, 1670-1600,

1472, 1368, 1240, 1159, 1111, 1038, 853 cm^{-1}. ^1H NMR δ: 1.27 (15 H, br), 1.44 (9 H, s), 1.57 (4 H, s), 2.19 (2 H, t, J = 7.3 Hz), 2.53 (1.6 H, t, J = 7.6 Hz), 3.42 (1.6 H, s), 4.20 (2 H, q, J = 7.3 Hz), 4.98 (0.4 H, s), 12.10 (0.4 H, s). FAB-MS m/z: 357 (MH^+). Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.09; H, 10.62.

1-Hydrogen 14-Ethyl 12-Oxotetradecanedioate (18)

To a stirred suspension of Zn dust (1.2 g, 18.0 mM) in CH_2Cl_2 (10.0 ml) was added dropwise CH_2I_2 (800 μl, 10.0 mM) under argon and the mixture was stirred at room temperature for 30 min. A solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 2.0 ml, 2.0 mM) was added dropwise at 0°C. The mixture was stirred at room temperature for 30 min and a solution of **16** (184 mg, 0.52 mM) in CH_2Cl_2 (1.0 ml) was added dropwise at room temperature. After being stirred at room temperature for 40 h, the mixture was quenched with 1*N* aqueous HCl 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-200, 50 g, hexane:acetone = 6:1) to give **18** (129 mg, 83%) as a white wax, mp 52-53°C. IR ν_{max} (nujol): 3650-2000 2917, 2851, 1742, 1713, 1694, 1600-1500, 1470, 1435, 1412, 1383, 1333, 1304, 1275, 1244, 1215, 1192, 1167, 1115, 1098, 1051, 1042, 1021, 988, 922, 847, 779, 722, 716, 683, 656, 625, 586 cm^{-1}. ^1H NMR δ: 1.28 (15 H, br), 1.50-1.70 (4 H, m), 2.35 (2 H, t, J = 7.3 Hz), 2.52 (2 H, t, J = 7.6 Hz), 3.43 (2 H, s), 4.19 (2 H, quint, J = 7.3 Hz). FAB-MS m/z: 301 (MH^+).

1-Ethyl 14-*t*-Butyl 3-Trimethylsilyloxytetradecanedioate (19)

To a stirred solution of **15** (88 mg, 0.246 mM) in DMF (250 μl) was added imidazole (100 mg, 1.27 mM) and trimethylsilyl chloride (TMSCl) (114 μl, 0.885 mM). After being stirred at room temperature for 41 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-820MH, 10 g, hexane:Et_2O = 12:1) to give **19** (53 mg, 50%) as a colorless oil, bp 180-190°C / 2.0 mmHg. IR ν_{max} (neat): 2930, 2857, 1738, 1732, 1589, 1559, 1456, 1368, 1250, 1098, 1035, 951, 843 cm^{-1}. ^1H NMR δ: 0.10 (9 H, s), 1.26 (19 H, br), 1.44 (9 H, s), 1.54 (2 H, m), 2.20 (2 H, t, J = 7.3 Hz), 2.42 (2 H, d, J = 6.6 Hz), 4.12 (3 H, m). FAB-MS m/z: 431 (MH^+). Anal. Calcd for $C_{23}H_{46}O_5Si$: C, 64.14; H, 10.76. Found: C, 64.38; H, 10.56.

3-Hydroxy-1,14-tetradecanedial-bis-dimethylacetal (20)

To a stirred solution of **19** (50 mg, 0.116 mM) in CH_2Cl_2 (1.0 ml) was added dropwise diisobutylaluminum hydride (DIBAL) (1.0 M in toluene, 116 μl, 0.116 mM) at -78°C under argon. After being stirred at -78°C for 1 h, the mixture was quenched with 1 M aqueous $KHSO_4$ and extracted with Et_2O (30 ml x 3). The extracts were washed with H_2O, saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil (56 mg), which was used for the next step without further purification.

A mixture of the above crude product (56 mg) and *p*-toluenesulfonic acid (*p*-TsOH) (4 mg, 0.02 mM) in MeOH (3.5 ml) was stirred at room temperature for 15 h. The mixture was quenched with pyridine (20 μl) and concentrated *in vacuo*. The residue was extracted with Et_2O (30 ml x 3), 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:Et_3N = 2:1:0.006) to give **20** (11 mg, 27%) as a colorless oil, and recovered **15** (10 mg, 24%). Compound **20**. IR ν_{max} (neat): 3700-3100, 2984, 2926, 2855, 2832, 1464, 1387, 1368, 1312, 1233, 1192, 1127, 1055, 965, 914, 818, 729, 696 cm^{-1}. ^1H NMR δ: 1.26 (16 H, br), 1.57 (2 H, m), 1.72 (4 H, m), 2.85 (1 H, d, J = 2.6 Hz), 3.30 (6 H, s), 3.34 (3 H, s), 3,37 (3 H, s), 3.76 (1 H, m), 4.34 (1 H, t, J = 5.9 Hz), 4.57 (1 H, t, J = 5.9 Hz).

11-Bromoundecanyl Methoxymethyl Ether (23)

To a mixture of 11-bromoundecanol (**22**) (2.51 g, 10.0 mM) and *i*-Pr_2NEt (2.09 ml, 12.0 mM) in CH_2Cl_2 (10.0 ml) was added methoxymethyl chloride (MOMCl) (912 μl, 12.0 mM) at 0°C. After being stirred at room temperature for 2 h, the mixture was diluted with CH_2Cl_2, washed with H_2O, then saturated brine, and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by silica gel column chromatography (BW-820MH, 100 g, hexane:EtOAc = 25:1) to give **23** (2.84 g, 96%) as a colorless oil, bp 140-145°C / 2.0 mmHg. IR ν_{max} (neat) : 2928, 2855, 1464, 1215, 1152, 1113, 1046, 920, 723, 652, 625 cm^{-1}. ^1H NMR δ: 1.28 (14 H, br), 1.58 (2 H, quint, J = 6.9 Hz), 1.80 (2 H, m),3.35 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.52 (2 H, t, J = 6.6 Hz), 4.61 (2 H, s). FAB-MS m/z: 295 (MH^+), 297 (MH^++2).

Methyl 15-Methoxymethoxy-3-oxopentadecanoate (24)

To a stirred suspension of NaH (60% oil dispersion 480 mg, 12.0 mM) in tetrahydrofuran (THF)-hexamethylphosphoramide (HMPA) (20 ml-10 ml) was added dropwise a solution of methyl acetoacetate (**7**)(1.19 ml, 11.0 mM) in THF (5.0 ml) at 0°C under argon. After being stirred at 0°C for 30 min, *n*-BuLi (1.64 M in hexane 7.32 ml, 12.0 mM) was added dropwise to the mixture at 0°C and the mixture was stirred for 30 min. A solution of **23** (2.95 g, 10.0 mM) in THF (10.0 ml) was added dropwise at 0°C to this mixture. After being stirred at room temperature for 3 h, the mixture was quenched with 1*N* aqueous HCl and extracted with Et_2O (100 ml x 2). The extracts were washed with H_2O and saturated brine, and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by silica gel column chromatography (BW-200, 150 g, hexane:Et_2O = 4:1 to 3:1) to give **24** (2.9 g, 88%) as a white wax, mp 30-33°C. IR ν_{max} (neat): 2928, 2857, 1748, 1717, 1651, 1628, 1437, 1320, 1152, 1111, 1046, 918, 733, 648 cm^{-1}. ^1H NMR δ: 1.26 (16 H, br), 1.59 (4 H, m), 2.53 (2 H, t, J = 7.3 Hz), 3.36 (3 H, s), 3.37 (2 H, s), 3.51 (2 H, t, J = 7.6 Hz), 3.74 (3 H, s), 4.62 (2 H, s). Anal. Calcd for $C_{18}H_{34}O_5$: C, 65.42; H, 10.37. Found: C, 65.72; H, 10.45.

15-Methoxymethoxy-1,3-pentadecanediol (25)

To a stirred solution of **24** (115 mg, 0.5 mM) in THF (7.0 ml) was added $LiAlH_4$ (95 mg, 2.5 mM) at 0°C under argon. After being stirred at room temperature for 20 h, EtOAc and then 1*N* aqueous HCl were added to the mixture at 0°C and the mixture was 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, 20 g, hexane:EtOAc = 2:3) to give **25** (69 mg, 65%) as a white wax, mp 37-38°C. IR ν_{max} (nujol): 3700-3100, 2919, 2851, 1339, 1154, 1111, 1075, 1043, 941, 916, 722 cm^{-1}. ^{1}NMR δ: 1.27 (18 H, br), 1.35-1.78 (6 H, m), 2.19 (1 H, d, J = 4.9 Hz), 2.23 (1 H, t, J = 5.6 Hz), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.6 Hz), 3.87 (3 H, m), 4.62 (2 H, s). FAB-MS m/z: 305 (MH^+). Anal. Calcd for $C_{17}H_{36}O_4$: C, 67.06; H, 11.92. Found: C, 67.19; H, 11.78.

1-*t*-Butyldimethylsilyloxy-15-methoxymethoxy-3-pentadecanol (26)

To a stirred solution of **25** (875 mg, 2.88 mM) in CH_2Cl_2 (5.8 ml) was added Et_3N (401 μl, 3.45 mM), 4-dimethylaminopyridine (DMAP) (14 mg, 0.115 mM) and then *t*-butyldimethylsilyl chloride (TBSCl) (477 mg, 3.17 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 (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-820MH, 100 g, hexane:Et_2O = 3:1) to give **26** (1.14 g, 95%), as a colorless oil, bp 195-210°C / 1.0 mmHg. IR ν_{max} (neat): 3700-3100, 2928, 2857, 1559, 1464, 1256, 1148, 1111, 1090, 1046, 837, 777 cm^{-1}. ^{1}NMR δ: 0.08 (6 H, s), 0.90 (9 H, s), 1.26 (20 H, br), 1.63 (4 H, m), 3.36 (3 H, s), 3.39 (1 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.78-3.93 (3 H, m), 4.62 (2 H, s). FAB-MS m/z: 419 (MH^+). Anal. Calcd for $C_{23}H_{50}O_4Si$: C, 65.97; H, 12.04. Found: C, 65.87; H, 11.80.

1-*t*-Butyldimethylsilyloxy-15-methoxymethoxypentadecan-3-one (27)

To a stirred solution of **26** (1.14 g, 2.73 mM) in THF (14.0 ml) was added PDC (1.54 g, 4.09 mM)

and MS-3A powder (2.2 g) and then AcOH (273 μl) at 0°C, and the mixture was stirred at room temperature for 30 min. Celite (1.4 g) was added and the mixture was stirred at room temperature for 20 min and filtered through the pad of celite. The filtrate was concentrated *in vacuo* to give a dark brown residue. The residue was dissolved in toluene and again concentrated *in vacuo*. The residue was dissolved in Et_2O and filtered through the pad of $MgSO_4$. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 120 g, hexane:Et_2O = 8:1) to give **27** (1.13 g, 99%) as a colorless oil, bp 190-205°C / 1.0 mmHg. IR ν_{max} (neat): 2930, 2857, 1717, 1464, 1389, 1250, 1148, 1111, 1048, 920, 837, 777 cm^{-1}. ^{1}NMR δ: 0.04 (6 H, s), 0.87 (9 H, s), 1.31 (18 H, br), 1.55 (2 H, m), 2.43 (2 H, t, J = 7.6 Hz), 2.59 (2 H, t, J = 6.3 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.88 (2 H, t, J = 6.3 Hz), 4.62 (2 H, s). FAB-MS m/z: 417 (MH^+). Anal. Calcd for $C_{23}H_{48}O_4Si$: C, 66.29; H, 11.61. Found: C, 66.38; H, 11.46.

1-*t*-Butyldimethylsilyloxy-15-methoxymethoxy-3-methylenepentadecane (28)

To a stirred suspension of methyltriphenylphosphonium bromide (1.15 g, 3.21 mM) in THF (20.0 ml) was added dropwise *n*-BuLi (1.68 M in hexane, 1.96 ml, 3.21 mM) at -10°C under argon and the mixture was stirred at room temperature for 1 h. A solution of **27** (1.11 g, 2.68 mM) in THF (10.0 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 (80 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-820MH, 90 g, hexane:Et_2O = 25:1) to give **28** (830 mg, 75%) as a colorless oil, bp 180-195°C / 1.2 mmHg. IR ν_{max} (neat): 2928, 2856, 1646, 1464, 1387, 1256, 1151, 1111, 1048, 837, 777 cm^{-1}. ^{1}NMR δ: 0.05 (6 H, s), 0.89 (9 H, s), 1.26 (18 H, br), 1.56 (2 H, m), 2.00 (2 H, t, J = 7.6 Hz), 2.23 (2 H, t, J = 7.3 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.69 (2 H, t, J = 7.3 Hz), 4.62 (2 H, s), 4.76 (2 H, d, J = 6.3 Hz). FAB-MS m/z: 415 (MH^+). Anal. Calcd for $C_{24}H_{50}O_3Si$: C, 69.50; H, 12.15. Found: C, 69.72; H, 11.97.

1-*t*-Butyldimethylsilyloxy-3-hydroxy-3-hydroxymethyl-14-methoxymethoxypentadecane (29)

To a stirred solution of **28** (153 mg, 0.37 mM), *N*-methylmorpholine *N*-oxide (NMO) (109 mg, 0.925 mM) in 90% aqueous acetone (2.0 ml) was added OsO_4 (0.2 mM in toluene, 185 μl, 0.037 mM). After being stirred at room temperature for 2 h, the mixture was quenched with $NaHSO_4$ (130 mg) 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 column chromatography (BW-820MH, 15 g, hexane:EtOAc = 4:1 to 3:1) to give **29** (160 mg, 97%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 1464, 1256, 1150, 1111, 1088, 1048, 920, 837, 777 cm^{-1}. ^{1}NMR δ: 0.10 (6 H, s), 0.91 (9 H, s), 1.27 (18 H, br), 1.50-1.84 (6 H, m), 2.89 (1 H, dd, J = 6.3, 7.3 Hz), 3.36 (3 H, s), 3.37-3.53 (5 H, m), 3.83 (2 H, m), 4.62 (2 H, s). FAB-MS m/z: 449 (MH^+). Anal. Calcd for $C_{24}H_{52}O_5Si$: C, 64.24; H, 11.68. Found: C, 64.29; H, 11.49.

3-Acetoxy-3-acetoxymethyl-1-*t*-butyldimethylsilyloxy-15-methoxymethoxypentadecane (30)

A mixture of **29** (509 mg, 1.14 mM), Et_3N (1.9 ml, 13.63 mM), DMAP (6 mg, 0.045 mM) and Ac_2O (1.07 ml, 11.36 mM) was stirred at room temperature for 24 h and diluted with H_2O. The mixture was 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-200, 50 g, hexane:Et_2O = 4:1) to give **30** (430 mg, 71%) as a colorless oil. IR ν_{max} (neat): 2930, 2857, 1748, 1740, 1464, 1368, 1252, 1111, 1046, 837, 777 cm^{-1}. ^{1}H NMR δ: 0.04 (6 H, s), 0.88 (9 H, s), 1.25 (18 H, br), 1.55 (2 H, m), 1.87 (2 H, br), 1.97-2.21 (2 H, m), 2.00 (3 H, s), 2.07 (3 H, s), 3.36 (3 H, s), 3.51 (2 H, t,

J = 6.6 Hz), 3.67 (2 H, t, J = 6.9 Hz), 4.35 (2 H, d, J = 3.0 Hz), 4.62 (2 H, s). Anal. Calcd for $C_{28}H_{56}O_7Si$: C, 63.12; H, 10.59. Found: C, 63.29; H, 10.55.

3-Acetoxy-3-acetoxymethyl-15-methoxymethoxy-1-pentadecanol (31) and 1-Acetoxy-3-acetoxymethyl-15-methoxymethoxy-3-pentadecanol (32)

To a solution of **30** (26 mg, 0.049 mM) in THF (500 μl) and H_2O (500 μl) was added AcOH (500 μl) at 0°C. After being stirred at room temperature for 11 h, the mixture was quenched with Et_3N, diluted 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*. The residue was purified by silica gel column chromatography (BW-820MH, 25 g, hexane:EtOAc = 5:2) to give **31** (12 mg, 59%) and **32** (5 mg, 25%):

Compound 31. A colorless oil. IR ν_{max} (neat): 3700-3100, 2928, 2855, 1740, 1466, 1370, 1237, 1150, 1111, 1044, 920 cm^{-1}. ^1H NMR δ: 1.26 (19 H, br), 1.58 (2 H, quint, J = 6.6 Hz), 1.95 (2 H, m), 2.01 (3 H, s), 2.03-2.23 (2 H, m), 2.08 (3 H, s), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.73 (2 H, t, J = 6.6 Hz), 4.33 (1 H, d, J = 11.9 Hz), 4.40 (1 H, d, J = 11.5 Hz), 4.62 (2 H, s):

Compound 32. A colorless oil. IR ν_{max} (neat): 3700-3100, 2928, 2855, 1744, 1466, 1368, 1240, 1150, 1111, 1044, 920 cm^{-1}. ^1H NMR δ: 1.27 (18 H, br), 1.55 (2 H, m), 1.87 (2 H, t, J = 6.9 Hz), 1.97-2.21 (2 H, m), 2.05 (4 H, br), 2.11 (3 H, s), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.6 Hz), 4.02 (2 H, s), 4.22 (2 H, t, J = 6.9 Hz), 4.62 (2 H, s). Anal. Calcd for $C_{22}H_{42}O_7$: C, 63.13; H, 10.11. Found: C, 62.90; H, 10.00.

1-*t*-Butyldimethylsilyloxy-15-methoxymethoxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)pentadecane (34)

To a stirred solution of **29** (489 mg, 1.09 mM) in CH_2Cl_2 (2.0 ml) was added 2,2-dimethoxypropane (1.34 ml, 10.9 mM) and pyridinium *p*-toluenesulfonate (PPTS) (27.4 mg, 0.109 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-820MH, 60 g, hexane:Et_2O = 10:1) to give **34** (432 mg, 81%) as a colorless oil. IR ν_{max} (neat): 2930, 2857, 1472, 1464, 1379, 1368, 1256, 1213, 1151, 1111, 1053, 939, 837, 776, 723, 662 cm^{-1}. ^1H NMR δ: 0.05 (6 H, s), 0.89 (9 H, s), 1.26 (18 H, br), 1.37 (3 H, s), 1.39 (3 H, s), 1.56 (4 H, m), 1.84 (2 H, t, J = 7.3 Hz), 3.36 (3 H, s), 3.51 (2 H, t, J = 6.6 Hz), 3.64-3.78 (2 H, m), 3.40 (1 H, d, J = 8.9 Hz), 3.86 (1 H, d, J = 8.6 Hz), 4.62 (2 H, s). Anal. Calcd for $C_{27}H_{56}O_5Si$: C, 66.34; H, 11.55. Found: C, 66.41; H, 11.40.

15-Methoxymethoxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-1-pentadecanol (35)

A mixture of **34** (308 mg, 0.63 mM) and tetrabutylammonium fluoride (TBAF) (330 mg, 1.26 mM) in THF (5.0 ml) was stirred at room temperature for 30 min, and diluted with H_2O. The mixture was extracted with Et_2O (50 ml x 3) and 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-820MH, 20 g, hexane:EtOAc = 3:1) to give **35** (227 mg, 96%) as a colorless oil. IR ν_{max} (neat): 3700-3100, 1466, 1456, 1379, 1369, 1250, 1213, 1152, 1113, 1094, 984, 920, 872, 822, 722 cm^{-1}. ^1H NMR δ: 1.27 (18 H, br), 1.40 (3 H, s), 1.44 (3 H, s), 1.54-1.89 (6 H, m), 2.68 (1 H, dd, J = 4.3, 6.6 Hz), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.6 Hz), 3.71-3.89 (4 H, m), 4.62 (2 H, s). FAB-MS m/z: 375 (MH^+). Anal. Calcd for $C_{21}H_{42}O_5$: C, 67.34; H, 1130. Found: C, 67.34; H, 11.11.

15-Methoxymethoxy-3-(5-spiro-2,2-dimethyl-1,3-dioxacyclopentyl)-1-pentadecanal (36)

To a stirred solution of $(COCl)_2$ (439 μl, 5.03 mM) in CH_2Cl_2 (25.0 ml) was added dropwise DMSO (428 μl, 6.04 mM) at -78°C under argon and the mixture was stirred for 30 min. A solution of **35** (1.25 g, 3.35 mM) was added and the mixture was stirred for 30 min. After addition of Et_3N (2.34 ml, 16.77 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 (80 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-820MH, 70 g, hexane:Et_2O = 3:1) to give **36** (1.18 g, 95%) as a colorless oil. IR ν_{max} (neat): 2988, 2928, 2855, 1725, 1466, 1381, 1254, 1213, 1152, 1111, 1049, 984, 920, 862, 722 cm^{-1}. ^1H NMR δ: 1.26 (18 H, br), 1.39 (3 H, s), 1.42 (3 H, s), 1.54-1.76 (4 H, m), 2.61 (1 H, dd, J = 2.6, 5.5 Hz), 2.71 (1 H, dd, J = 2.3, 5.5 Hz), 3.36 (3 H, s), 3.52 (2 H, t, J = 6.6 Hz), 3.86 (2 H, s), 4.62 (2 H, s), 9.82 (1 H, t, J = 2.3 Hz). Anal. Calcd for $C_{21}H_{40}O_5$: C, 67.71; H, 10.82. Found: C, 67.80; H, 10.77.

Trimethyl 2-Pentadecanylphosphonoacetate (5a)

To a stirred suspension of NaH (60% oil dispersion, 120 mg, 1.84 mM) in 1,2-dimethoxyethane (DME) (5.0 ml) was added dropwise a solution of **9** (278 μl, 1.72 mM) in DME (3.0 ml) at 0°C under argon and the mixture was stirred at room temperature for 2 h. A solution of **10a** (1.0 g, 3.44 mM) in DME (3.0 ml) was added dropwise and the mixture was refluxed for 12 h, then quenched with 10% aqueous citric acid. The mixture was extracted with Et_2O (80 ml x 3), 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, 70 g, hexane:EtOAc = 11:9 to 9:11 to 7:11) to give **5a** (192 mg, 29%) and **37** (73 mg, 7%) together with recovered **10a** (518 mg, 52%).

Compound 5a. A colorless oil. IR ν_{max} (neat): 2955, 2924, 2855, 1740, 1466, 1337, 1260, 1188, 1159, 1057, 1032, 866, 826, 776, 722 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.6 Hz), 1.25 (26 H, br), 1.70-2.20 (2 H, br), 2.97 (1 H, ddd, J = 4.0, 10.9, 22.4 Hz), 3.76 (3 H, s), 3.77 (3 H, d, J = 6.6 Hz), 3.81 (3 H, d, J = 4.0 Hz). FAB-MS m/z: 393 (MH^+). Anal. Calcd for $C_{20}H_{41}O_5P$: C, 61.20; H, 10.53. Found: C, 61.61; H, 10.53.

Compound 37. A colorless oil. IR ν_{max} (neat): 2953, 2924, 2853, 1738, 1466, 1377, 1254, 1184, 1156, 1059, 1034, 828, 774, 722 cm^{-1}. ^1H NMR δ: 0.88 (6 H, t, J = 6.6 Hz), 1.25 (52 H, br), 1.70-2.20 (4 H, br), 3.76 (3 H, s), 3.74 (3 H, s), 3.76 (3 H, s), 3.80 (3 H, s).

Trimethyl 2-Hexadecanylphosphonoacetate (5b)

To a stirred suspension of NaH (60% oil dispersion, 36 mg, 0.90 mM) in THF (5.0 ml) was added dropwise a solution of **9** (133 μl, 0.82 mM) in THF (3.0 ml) at 0°C under argon and the mixture was stirred at room temperature for 2 h. A solution of **10b** (1.0 g, 3.28 mM) in THF (4.0 ml) was added dropwise and the mixture was refluxed for 12 h, then quenched with 10% aqueous citric acid. The mixture was extracted with Et_2O (80 ml x 3), 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-820MH, 50 g, hexane:acetone = 4:1) to give **5b** (121 mg, 36%) as a colorless oil. IR ν_{max} (neat): 2923, 2853, 1738, 1468, 1337, 1258, 1188, 1159, 1055, 1032, 828, 777 cm^{-1}. ^1H NMR δ: 0.88 (3 H, t, J = 6.9 Hz), 1.25 (28 H, br), 1.70-2.10 (2 H, br), 2.97 (1 H, ddd, J = 4.0, 10.9, 22.4 Hz), 3.77 (6 H, d, J = 4.0 Hz), 3.81 (3 H, d, J = 4.0 Hz). FAB-MS m/z: 407 (MH^+). Anal. Calcd for $C_{21}H_{43}O_5P$: C, 62.04; H, 10.66. Found: C, 62.09; H, 10.57.

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