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Stereoselective total synthesis of muconin

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Abstract—An antitumor acetogenin, muconin, was synthesized through a coupling reaction of a THF–THP segment and a terminal butenolide. The key reactions include successive ether-ring formation reaction under acidic and basic conditions or one-pot double cyclization promoted by TBAF and stereoselective reduction of acyclic ketones adjacent to the 2,6-cis THP with $Zn(BH_4)_2$.

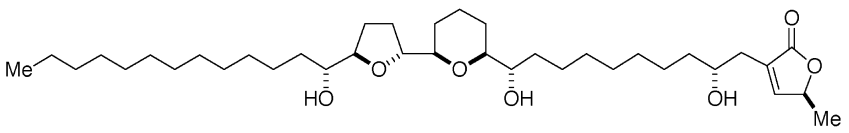
1. Introduction

Annonaceous acetogenins are a relatively new class of natural products that have a wide range of biological activities such as cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal and immunosuppressive effects.[1] They are characterized by the presence of one to three tetrahydrofuran (THF) rings in the center of a long alkyl chain with a butenolide moiety at the end, and classified into three types according to the number of THF rings and their connection patterns, i.e. the adjacent bis-THF, nonadjacent bis-THF, and mono-THF. Their structural diversity and remarkable biological activities have attracted much attention of synthetic organic chemists, and this has consequently stimulated synthetic efforts.[2]

Recently, acetogenins have been discovered that also bear a tetrahydropyran (THP) ring additional to the usual THF rings.[3,4] A representative member of that group is muconin (**1**),[5] which was isolated from the leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae) by McLaughlin et al. in 1996 (Fig. 1). Muconin (**1**) is structurally related to the cytotoxic acetogenin, jimenezin, differing remarkably in the stereorelationship of the THP and THF rings and bearing no hydroxyl group on the THP ring. Compound **1** showed potent and selective in vitro cytotoxicity to MCF-7 (breast cancer) and PACA-2 in a panel of six human solid tumor cell lines. Recently, we have been engaged in synthetic studies on the THP-acetogenins, resulting in the total synthesis of mucocin[6] and jimenezin.[7] As part of our continuing studies in this field, we describe herein the details of the total synthesis[8] of **1** in a stereocontrolled manner.[9]

2. Results and discussion

Our synthetic strategy directed toward **1** was based on a convergent process which involves a Pd-catalyzed cross-coupling reaction of the THF–THP segment **2** and a vinyl iodide **3**,[6e,10] as illustrated in Scheme 1. Disconnection of the acetylene unit and cleavage of the THF ring in **2** lead to a THP derivative **4**, which would be synthesized from an epoxy alcohol **5** through a 6-*exo* cyclization and stereoinversion at the C-8 position. For effective inversion, we planned to utilize a stereoselective reduction of an acyclic ketone adjacent to the 2,6-*cis* THP ring. The usefulness of the method has been already demonstrated in our total synthesis of mucocin[6a,d] and jimenezin.[7]



Muconin (**1**)

Figure 1.

Keywords: annonaceous acetogenin; antitumor agent; muconin; $Zn(BH_4)_2$ reduction.
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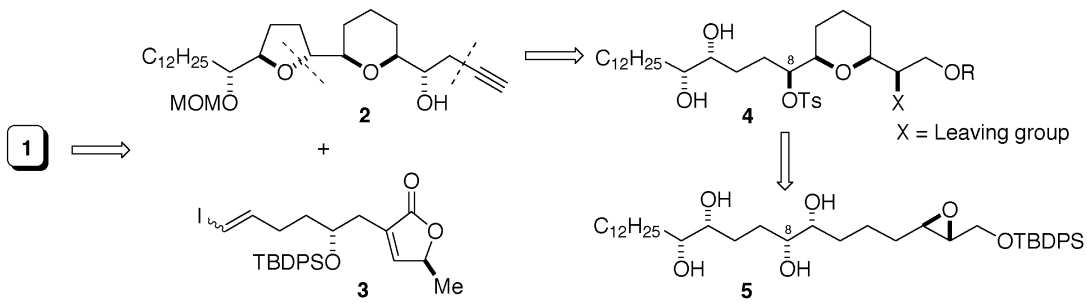
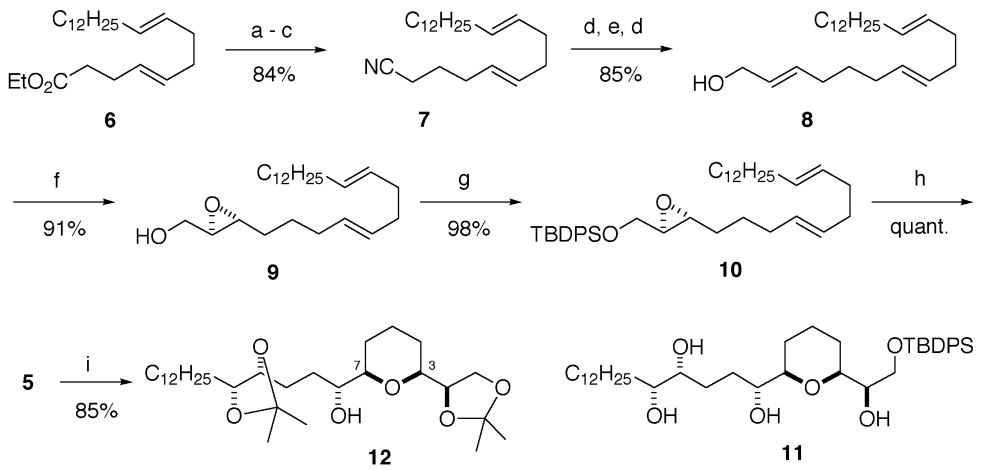
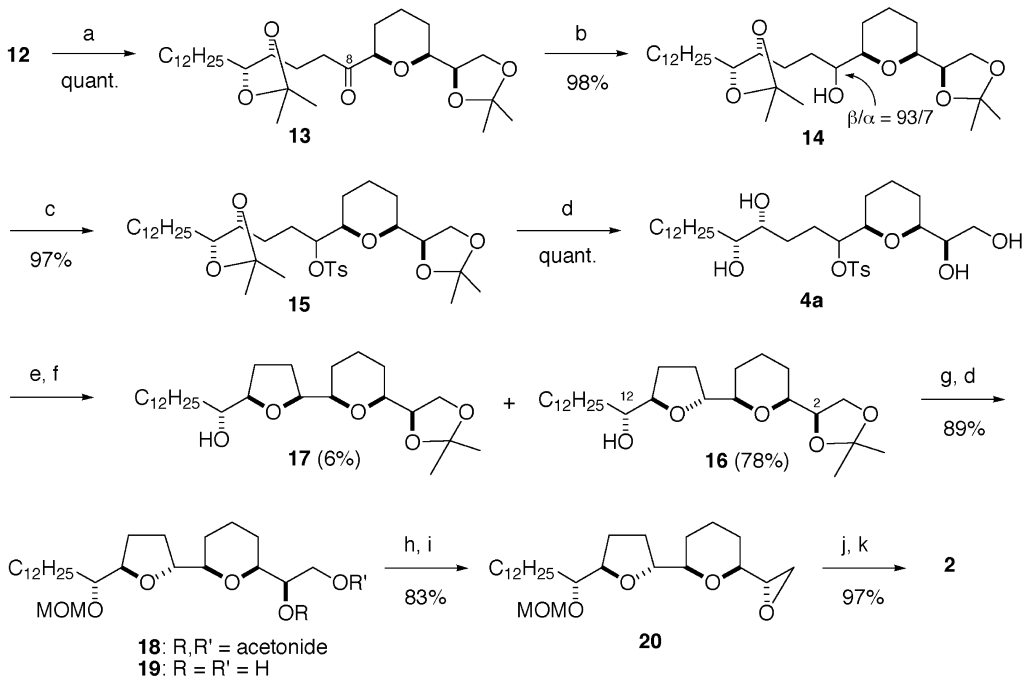


Scheme 1. Retrosynthetic scheme of muconin (**1**).



Scheme 2. (a) $LiAlH_4$, THF, 0°C; (b) *p*-TsCl, pyridine, 0°C; (c) NaCN, DMSO, rt ~60°C; (d) DIBAL, CH_2Cl_2, −78°C; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C; (f) D-DET, $Ti(Oi\text{-}Pr)_4$, *t*-BuO_2H, MS4A, CH_2Cl_2, −23°C; (g) TBDPSCl, imidazole, DMF–CH_2Cl_2, rt; (h) AD-mix β, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0°C; (i) CSA, CH_2Cl_2, rt, then MeOH, conc., and $(MeO)_2CMe_2$–CH_2Cl_2, rt.



Scheme 3. (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (b) $Zn(BH_4)_2$, Et_2O, −10°C; (c) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0°C ~rt; (d) AcOH–H_2O, rt; (e) NaOMe, MeOH, rt ~50°C; (f) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, rt; (g) MOMBr, *i*-Pr_2NEt, CH_2Cl_2, rt; (h) BzCl, pyridine, CH_2Cl_2, −20 ~5°C, and then MsCl, −20 ~0°C; (i) aq. NaOH, MeOH–THF, −20 ~5°C; (j) lithium (trimethylsilyl)acetylide, $BF_3{\cdot}Et_2O$, THF, −78°C; (k) K_2CO_3, MeOH, rt.

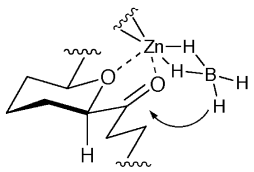
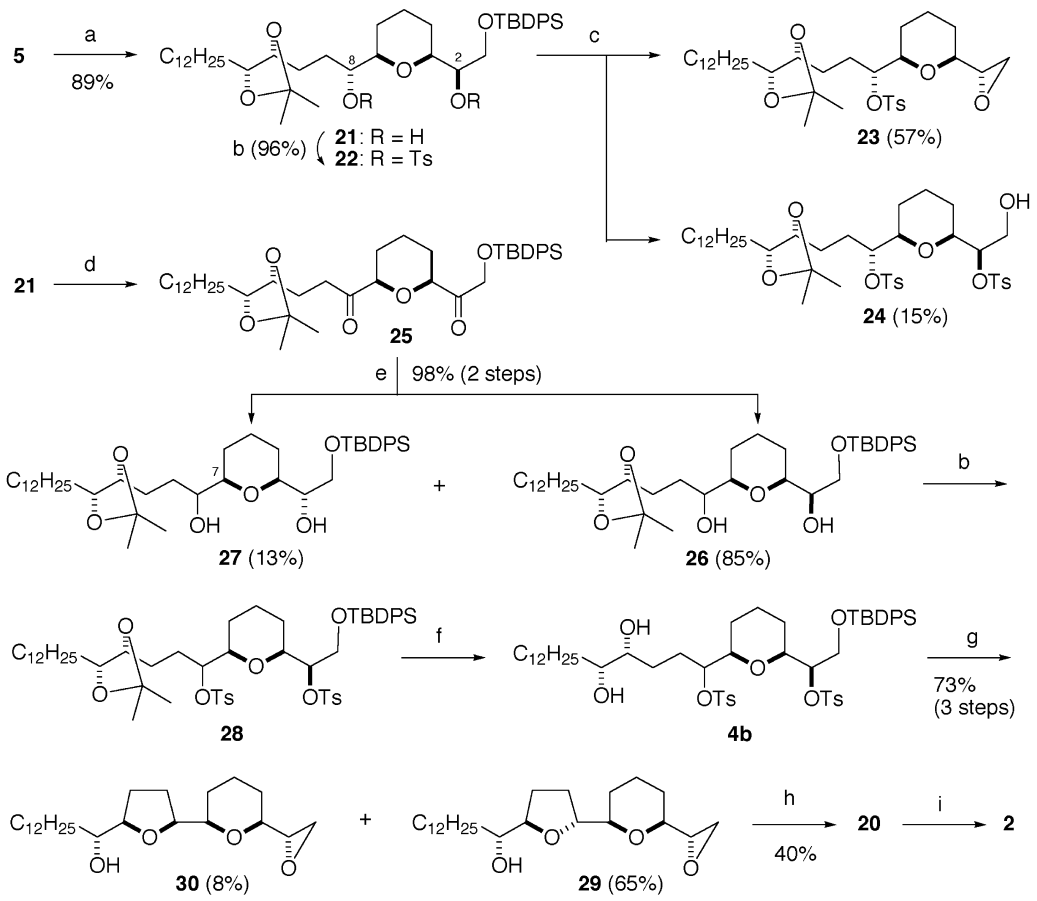


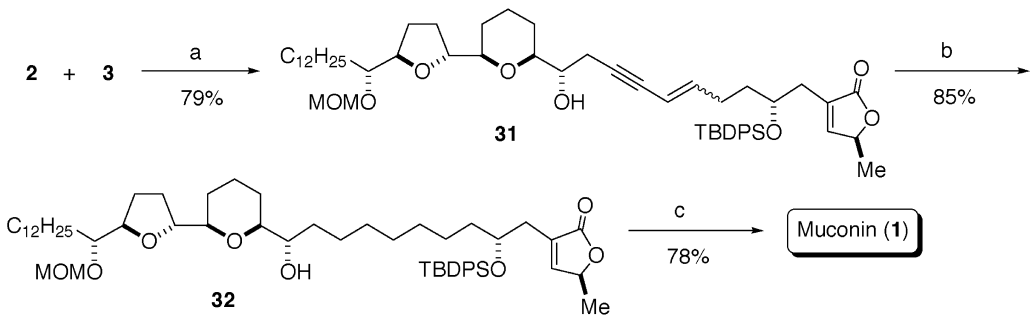
Figure 2.

Synthesis began from reduction of an unsaturated ester **6**, which was prepared by Keinan and Sinha's procedure (Scheme 2).[11] The resulting alcohol was subjected to tosylation to afford the corresponding tosylate. Treatment of this with sodium cyanide gave a nitrile **7** in 84% overall yield from **6**. The nitrile **7** was converted into an allyl alcohol **8** by the following sequence: (1) reduction of the nitrile function with DIBAL, (2) Wittig reaction, (3) DIBAL reduction of ester carbonyl (85% overall yield). Installation of the requisite oxygen function into the carbon backbone was accomplished by the Sharpless protocol.[12] Initially, **8** was epoxidized with $Ti(O\textit{i}\text{-}Pr)_4$ and $\textit{t}\text{-}BuO_2H$ in the presence of D-diethyl tartrate to give an epoxide **9** in 91% yield. The optical purity was determined to be >94% e.e. by the ^1H NMR analyses of the corresponding MTPA esters. After silylation with chloro *t*-butyldiphenylsilane and imidazole, the resulting silylether **10** reacted with AD-mix β in the presence of methanesulfonamide (2.0 equiv.) in *t*-BuOH–water to give the tetraol **5** in almost quantitative yield. Although this compound included a trace amount of the diastereomers, the undesired isomers could be separated at a later stage (vide infra). Upon treatment of **5** with *d*-camphorsulfonic acid (CSA) in CH_2Cl_2, 6-*exo* cyclization occurred to produce a THP derivative **11** in 86% yield. From a practical point of view, isolation after the following hydroxy protection was found to be more efficient. Hence, after completion of the cyclization, the reaction mixture was treated with methanol in order to hydrolyze the TBDPS ether, concentrated in vacuo and then reacted with 2,2-dimethoxypropane in CH_2Cl_2 in one pot to give a diacetonide **12** in 85% overall yield. In the ^1H NMR spectra of **12**, the signals corresponding to the protons of H-3 and 7 were observed at 3.30 ppm (ddd, $J_{3,4}$=11, $J_{2,3}$=6.7, $J_{3,4'}$=1.9 Hz) and 3.21 ppm (1H, ddd, $J_{6,7}$=11, $J_{7,8}$=6.3, $J_{6',7}$=1.9 Hz), respectively. The large coupling constant of two protons indicates that the compound **12** has the desired THP ring system. Furthermore, the optical purity of **12** was determined to be >98% e.e. by the ^1H NMR analyses of the corresponding MTPA esters.

The alcohol **12** was oxidized with Dess–Martin periodinane to give a ketone **13**, which was reduced with $Zn(BH_4)_2$[13] in ether (Scheme 3). As expected, the reduction at −10 ~ 0°C proceeded stereoselectively to afford a 93:7 mixture of the desired β-alcohol and its epimer **14** in 98% yield; the reaction at low temperature (−78°C) slightly decreased the selectivity (β/α=ca 90/10, ~96%). The similar results (β/α=93/7, ~98%) were also obtained when CH_2Cl_2 was employed as a solvent. This high stereoselectivity would be explained by the α-chelation as shown in Figure 2. As



Scheme 4. (a) CSA, CH_2Cl_2, rt, and then $(MeO)_2CMe_2$, rt; (b) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, rt; (c) TBAF, THF, rt; (d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (e) $Zn(BH_4)_2$, Et_2O, −10°C; (f) AcOH–H_2O, rt ~50°C; (g) TBAF, THF, rt ~50°C; (h) *n*-BuLi, MOMCl, THF, −23°C~rt; (i) See Scheme 3.



Scheme 5. (a) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, rt; (b) $(Ph_3P)_3RhCl$, H_2, benzene–EtOH, rt; (c) 10% HCl–MeOH, CH_2Cl_2, rt.

separation of these isomers was found to be difficult at this stage, **14** was transformed into the corresponding tosylate **15** by treatment with *p*-toluenesulfonyl chloride (TsCl) and triethylamine (Et_3N) in the presence of *N*,*N*-dimethylaminopyridine (DMAP). Acidic hydrolysis of **15** afforded a C-8 epimeric mixture of tetraols **4a** (97% yield). Formation of the second ether-ring was achieved by heating **4a** with sodium methoxide (8.4 equiv.) in methanol at rt ~50°C, and subsequent isopropylidenation provided a mixture of cyclized products, from which the desired bicyclic ether **16** was isolated in 78% yield after chromatography on silica gel. In addition, a minor isomer **17** was also obtained, which could be quite useful for preparation of pharmacologically important analogues of **1**. The remaining task was introduction of an ethynyl group through a stereoinversion at the C-2 position in **16**. Prior to the transformation, the 12-hydroxyl group in **16** was protected as a methoxymethyl (MOM) ether (MOMBr, *N*,*N*-diisopropylethylamine), and subsequent hydrolysis of **18** gave a diol **19** in 89% yield. Successive treatment of **19** with benzoyl chloride and methanesulfonyl chloride in pyridine provided a mesyl benzoate. Exposure of this to alkaline conditions led to an oxirane formation to give **20** in 83% yield from **19**. The epoxide **20** reacted with lithium trimethylsilylacetylide in the presence of $BF_3{\cdot}E_2O$ to produce a terminal acetylene **2** in 97% yield after de-silylation (potassium carbonate, MeOH).

Furthermore, we have also developed an alternative route for short-step synthesis of **2** (Scheme 4). Initially, the epoxy tetraol **5** was transformed into the corresponding acetonide **21** in 86% yield according to the one-pot sequence. After tosylation of **21**, the resulting ditosylate **22** was employed to an S_N2 reaction. Attempts for the simultaneous inversion at the C-2, and 8 positions of **22** under several conditions (e. g. NaOBz or CsOAc in the presence of 18-Crown-6 in toluene, HMPA and so on) gave unsatisfactory results, while treatment of **22** with *n*-tetrabutylammonium fluoride (TBAF) at rt caused an intramolecular etherification, giving a terminal epoxide **23** in 57% yield along with a hydroxytosylate **24** (15%). These results prompted us to conduct an intramolecular double ether-cyclization as follows. In order to prepare the substrate needed for such cyclization, the two hydroxyl groups in **21** was simultaneously oxidized to afford a diketone **25** in 95% yield. $Zn(BH_4)_2$ reduction of **25** in Et_2O gave two products, which were separated into a low polar (R_f value 0.38 on silica gel HPTLC, with 2:1 Et_2O–hexane) substance (85%) and a high polar compound (13%) with R_f value 0.27 by chromatography on silica gel. The ^1H- and ^{13}C NMR analyses revealed that each compound consisted of an unseparable mixture of two carbinols[†] and that a minor component of the low polar substance was identical with the starting alcohol **21**. Based on the α-chelation mechanism of $Zn(BH_4)_2$ reduction, we estimated that the major component of the low polar substance should be the desired 2*R*,8*S*-isomer and tentatively assigned the structure of the low polar substance and the high polar one to be **26** and **27**, respectively. This assumption was confirmed by chemical transformation into the known compounds (vide infra).[‡] The low polar substance **26** was tosylated, and the resulting ditosylate **28** was hydrolyzed to afford a diol **4b** in good yield. Double cyclization of **4b** into a tricyclic system was performed by treatment of **4b** with TBAF at rt ~50°C, giving a 8,11-*trans* THF derivative **29** and the corresponding *cis* isomer **30** in 65 and 8% yield, respectively. Each isomer was easily separated by chromatography on silica gel. Methoxymethylation (*n*-BuLi, MOMCl) of the *trans* isomer **29** furnished the key intermediate **20**, from which preparation of the left half segment **2** has been already established. This new route was quite simple and required only 9 steps[§] from **5** for preparation of **2** (cf. 13 steps in the previous Scheme).

Having completed the stereoselective synthesis of the left-half segment **2**, we turned to the final steps of the synthesis (Scheme 5). The acetylene **2** was coupled with the γ-lactone **3** in the presence of $(PPh_3)_2PdCl_2$ and CuI in triethylamine[14] at rt to afford an enyne **31** in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst to give a partially protected muconin **32**, in which all protecting groups were subsequently cleaved by hydrogen chloride in methanol–CH_2Cl_2 to give muconin (**1**). The spectroscopic and physical properties of **1** were identical those of natural **1**.

In summary, we have succeeded in a convergent synthesis of **1** via successive ether-ring formation reaction under acidic and basic conditions or one-pot double cyclization promoted by TBAF and stereoselective reduction of acyclic ketones as the key steps.

[†] The isomer ratio was 89/11 (for **26**) or 56/44 (for **27**). The major constituent of **27** was estimated to be an 8β-alcohol by comparison with the ^1H NMR data (the chemical shifts and splitting pattern of H-7) of **26**; see, Section 3.

[‡] Desilylation (TBAF, THF), isopropylidenation and Dess–Martin oxidation of **26** afforded **13** in high yield. Compound **27** could be taken back to the starting diketone **25** by the oxidation.

[§] This synthesis proceeded in 18% overall yield. On the other hand, the previous procedure resulted in 45% overall yield.

3. Experimental

3.1. General procedures

Melting points were determined using a Yanaco MP-500 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR spectra were recorded with a JASCO VALOR-III spectrophotometer. ^{1}H NMR spectra were recorded at 270 or 400 MHz with JEOL EX-270 or JNM-α 400 spectrometers, using tetramethylsilane as the internal standard. Column chromatography was performed on Kanto silica gel 60N (spherical, neutral; 40–100 μm). Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, was used for analytical thin-layer chromatography. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 40–42°C.

3.1.1. (*E*,*E*)-5,9-Docosadienonitrile (7). To a stirred suspension of $LiAlH_4$ (1.07 g, 28.2 mmol) in THF (40 ml) was added dropwise a solution of **6** (10.3 g, 29.3 mmol) in THF (10 ml) at 0°C, and the mixture was stirred at 0°C ~rt for 12 h. At 0°C, water (1.0 ml), 15% NaOH solution (1.0 ml) and water (3.0 ml) was added sequentially to produce a heterogeneous mixture, which was stirred at 0°C~rt for 1 h. The resulting mixture was filtered through a pad of celite and $MgSO_4$, and concentrated to give a dienol as a crystalline solid (8.74 g, 97%).

To a stirred solution of the above dienol (21.5 g, 69.7 mmol) in pyridine (150 ml) was added *p*-TsCl (17.4 g, 91.2 mmol) at 0°C, and the mixture was stirred at the same temperature for 16 h. After addition of ice-water, the resulting mixture was stirred for 10 h, and then extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried, and concentrated. The residue was dissolved in dimethylsulfoxide (50 ml) and sodium cyanide (5.2 g, 0.11 mol) was added to the solution. The mixture was stirred at rt for 12 h and 60°C for 4 h, and then poured into ice-water. The resulting mixture was extracted with ether. The extracts were washed with water, brine, dried, and concentrated. Chromatography on silica gel with hexane–hexane-EtOAc (20:1) gave **7** (19.3 g, 87%) as a colorless oil. IR (neat) 2925, 2247, 1460, 1458, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=6.3 Hz), 1.22–1.38 (20H, m), 1.70 (1H, dd, *J*=15.4, 7.2 Hz), 1.72 (1H, dd, *J*=15, 6.8 Hz), 1.96 (2H, m), 2.05 (4H, brs), 2.14 (2H, m), 2.31 (2H, t, *J*=7.3 Hz), 5.28–5.54 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 16.3, 22.8, 25.2, 29.3, 29.4, 29.6, 29.7, 29.8, 31.3, 32.0, 32.6, 32.7, 119.5, 127.4, 129.2, 130.9, 132.9.

Anal. Found: C, 83.01; H, 12.52; N, 4.29. Calcd for $C_{22}H_{39}N$: C, 83.21; H, 12.38; N, 4.41.

3.1.2. (*E*,*E*,*E*)-2,7,11-Tetracosatrien-1-ol (8). To a stirred solution of **7** (17.0 g, 53.5 mmol) in CH_2Cl_2 (150 ml) was added dropwise a 0.93 M hexane solution of DIBAL (75 ml, 69.9 mmol) at −78°C. After stirring at −78°C for 1.5 h, the mixture was quenched with *i*-PrOH (19 ml) and water (19 ml) at −78°C and returned to rt. After addition of silica gel, the resulting mixture was stirred for 1 h, diluted with EtOAc and filtered through a pad of celite. The filtrate was concentrated to give an aldehyde (17.2 g). To a stirred suspension of NaH (60% oil suspension, 3.21 g, 80.3 mmol) in THF (150 ml) was added dropwise triethyl phosphonoacetate (18.0 g, 80.3 mmol) at 0°C, and the mixture was stirred at 0°C for 1 h. To this solution was added a solution of the above aldehyde (17.2 g) in THF (50 ml) at 0°C and the mixture was stirred at 0°C for 1 h. After addition of water, the mixture was extracted with ether. The extracts were washed successively with water and brine, dried, and concentrated. The residue was passed through a short column of silica gel {hexane–hexane-EtOAc (50:1)} to give an unsaturated ester (19.5 g). To a stirred solution of the ester (19.5 g) in CH_2Cl_2 (300 ml) was added dropwise a 0.93 M hexane solution of DIBAL (134 ml, 0.12 mol) at −78°C. After stirring at −78°C for 2.5 h, the mixture was quenched with *i*-PrOH (34 ml) and water (34 ml) at −78°C and returned to rt. After addition of silica gel, the resulting mixture was stirred for 1 h, diluted with EtOAc, filtered through a pad of celite, and concentrated. Chromatography on silica gel with hexane–EtOAc (10:1) as the eluent yielded **8** (15.9 g, 85% from **7**) as a colorless oil. IR ($CHCl_3$) 3300–3200, 2918, 1472, 1461, 1082, 962, 907 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=6.3 Hz), 1.22–1.48 (22H, m), 1.94–2.07 (10H, m), 4.05–4.13 (2H, brd), 5.34–5.44 (4H, m), 5.63 (1H, ddd, *J*=15, 5.3, 4.8 Hz), 5.69 (1H, ddd, *J*=15, 6.3, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 29.0, 29.3, 29.4, 29.6, 29.7, 29.8, 31.8, 32.0, 32.1, 32.7, 32.8, 63.9, 128.9, 129.5, 129.9, 130.2, 130.7, 133.2.

Anal. Found: C, 82.67; H, 12.81. Calcd for $C_{24}H_{44}O$: C, 82.69; H, 12.72.

3.1.3. (*E*,*E*,2*R*,3*R*)-2,3-Oxido-7,11-tetracosadien-1-ol (9). D-(−)-Diethyltartrate (1.01 g, 4.30 mmol) and Ti(O*i*-Pr)$_4$ (0.93 ml, 3.16 mmol) was added sequentially to a suspension of **8** (1.00 g, 2.87 mmol) and MS 4A (1.5 g) in CH_2Cl_2 (22 ml) at −23°C, and the mixture was stirred at the same temperature for 20 min. A 5.2 M isooctane solution of *t*-BuO_2H (0.86 ml) was added, and the mixture was stirred at −23°C for 18 h. After addition of dimethylsulfide (2 ml) and sat. Na_2SO_4 solution, the resulting mixture was stirred at the same temperature for 1 h, allowed to warm to rt over 1 h, and then extracted with EtOAc. The extracts were washed with brine, dried, and concentrated. Chromatography on silica gel with hexane–EtOAc (10:1–4:1) as the eluent yielded **9** (953 mg, 91%) as an amorphous powder. $[\alpha]_D^{23}$=+16.9 (*c* 0.69, $CHCl_3$); IR (KBr) 3280, 3157, 2918, 1460, 1041, 992, 963, 878 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=6.3 Hz), 1.22–1.35 (20H, m), 1.45–1.60 (4H, m), 1.85–2.05 (9H, m), 2.90–2.96 (2H, m), 3.61 (1H, ddd, *J*=13, 6.8, 4.4 Hz), 3.90 (1H, ddd, *J*=13, 5.3, 2.4 Hz), 5.32–5.46 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.9, 29.3, 29.4, 29.6, 29.7, 29.8, 31.0, 32.0, 32.3, 32.6, 32.7, 32.8, 129.4, 129.5, 130.5, 130.7; HRMS calcd for $C_{24}H_{44}O_2Na$ $[M+Na]^+$ 387.3239, found 387.3231.

Anal. Found: C, 79.10; H, 12.25. Calcd for $C_{24}H_{44}O_2$: C, 79.06; H, 12.16.

3.1.4. (*E*,*E*,2*R*,3*R*)-1-*t*-Butyldiphenylsilyloxy-7,11-tetracosadien-2,3-oxido (10). To a stirred solution of **9**

(824 mg, 2.26 mmol) and imidazole (462 mg, 6.78 mmol) in DMF–CH_2Cl_2 (4:1, 20 ml) was added TBDPSCl (0.65 ml, 2.49 mmol) at 0°C, and the mixture was stirred at 0°C ~rt for 12 h, poured into ice-water. The resulting mixture was stirred for 1 h and extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried and concentrated. Chromatography on silica gel with hexane–EtOAc (50:1–30:1) as the eluent afforded **10** (1.33 g, 98%) as a colorless oil. $[\alpha]_D^{22}$=+10.9 (*c* 0.25, $CHCl_3$); IR (neat) 2926, 1464, 1428, 1113, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J*=6.8 Hz), 1.08 (9H, s), 1.25–1.63 (24H, m), 1.94–2.10 (8H, m), 2.80 (1H, m), 2.91 (1H, m), 3.75 (1H, dd, *J*=12, 4.3 Hz), 3.79 (1H, dd, *J*=12, 3.8 Hz), 5.38–5.48 (4H, m), 7.38–7.48 (6H, m), 7.70 (4H, brd, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.3, 22.8, 25.9, 26.8, 29.3, 29.4, 29.6, 29.7, 29.8, 31.1, 32.0, 32.3, 32.7, 32.8, 56.3, 58.5, 64.3, 127.6, 129.5, 129.6, 129.7, 130.4, 130.7, 133.2, 135.4.

Anal. Found: C, 79.27; H, 10.50. Calcd for $C_{40}H_{62}O_2Si$: C, 79.67; H, 10.36.

3.1.5. (2*R*,3*R*,7*R*,8*R*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-2,3-oxido-7,8,11,12-tetracosanetetraol (5). To a stirred suspension of AD-mix β (4.72 g) and methanesulfonamide (0.32 g, 3.34 mmol) in *t*-BuOH-water (1:1, 20 ml) was added dropwise **10** (0.94 g, 1.56 mmol) at 0°C, and the mixture was vigorously stirred at the same temperature for 14 h. After quenching with $Na_2S_2O_3$ (2.9 g), the reaction mixture was gradually warmed to rt over 1.5 h with stirring, and then concentrated. The residue was diluted with water and CH_2Cl_2, and then extracted with EtOAc. The extracts were washed successively with brine, dried and concentrated. The residue was passed through a short column of silica gel {hexane-EtOAc (1:1)–EtOAc} to afford **5** (1.03 g, 99%) as an amorphous solid, which contained a trace amount of methanesulfonamide. This compound was employed to the next step without further purification. IR (KBr) 3280, 3157, 2918, 1460, 1143, 1114, 963, 878 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ 0.88 (3H, t, *J*=6.8 Hz), 1.05 (9H, s), 1.22–1.70 (32H, m), 2.23 (1H, d, *J*=4.8 Hz), 2.43 (1H, d, *J*=4.4 Hz), 2.80 (1H, m), 2.90 (1H, m), 3.21 (1H, brs), 3.30 (1H, brs), 3.33–3.43 (4H, m), 3.69 (1H, dd, *J*=12, 4.8 Hz), 3.81 (1H, dd, *J*=12, 3.4 Hz), 7.38–7.43 (6H, m), 7.66–7.68 (4H, m); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.3, 19.5, 22.8, 23.1, 26.1, 27.0, 29.8, 30.0, 30.1, 30.6, 30.7, 31.9, 32.3, 33.6, 34.1, 56.4, 58.7, 64.7, 74.8, 74.9, 75.0, 127.9, 129.9, 133.6, 135.7; HRMS calcd for $C_{40}H_{66}O_6SiNa$ $[M+Na]^+$ 693.4526, found 693.4516.

3.1.6. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-1,2:11,12-(Diisopropylidenedioxy)-3,7-oxido-8-tetracosanol (12). A mixture of **5** (265 mg, 0.39 mmol) and *d*-camphorsulfonic acid (60 mg, 0.26 mmol) in CH_2Cl_2 (5 ml) was stirred at rt for 2 h, concentrated, and then diluted with methanol (3 ml). The mixture was stirred at rt for 18 h, concentrated, co-evaporated with benzene, and then diluted with 2,2-dimethoxypropane–CH_2Cl_2 (1:2, 3 ml). The resulting mixture was stirred at rt for 5 h, and then diluted with ether. The ethereal solution was washed successively with sat. $NaHCO_3$ solution, water, brine, dried, and concentrated. Chromatography on silica gel with hexane–EtOAc (4:1) as the eluent yielded **12** (171 mg, 85%) as a colorless oil. $[\alpha]_D^{25}$=+27.8 (*c* 0.24, $CHCl_3$); IR (neat) 3490, 2926, 1251, 1214, 1073, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.22–1.82 (31H, m), 1.35 (3H, s), 1.36 (6H, s), 1.39 (3H, s), 1.89–1.93 (1H, m), 2.72 (1H, brs), 3.21 (1H, ddd, *J*=11, 6.3, 1.9 Hz), 3.30 (1H, ddd, *J*=11, 6.7, 1.9 Hz), 3.45 (1H, brq, *J*=6.3 Hz), 3.59 (2H, m), 3.87 (1H, dd, *J*=7.2, 5.8 Hz), 3.95 (1H, dd, *J*=12, 6.3 Hz), 4.30 (1H, dd, *J*=8.3, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.6, 22.7, 25.3, 26.2, 26.7, 27.2, 27.3, 27.4, 27.8, 29.1, 29.4, 29.6, 29.7, 29.8, 31.9, 32.9, 66.8, 73.6, 78.1, 78.7, 80.7, 80.8, 80.9, 107.7, 109.2; HRMS calcd for $C_{30}H_{57}O_6$ $[M+H]^+$ 513.4155, found 513.4150.

Anal. Found: C, 70.19; H, 11.21. Calcd for $C_{30}H_{56}O_6$: C, 70.27; H, 11.01.

3.1.7. (2*R*,3*S*,7*R*,11*R*,12*R*)-1,2:11,12-(Diisopropylidenedioxy)-3,7-oxido-8-tetracosanone (13). To a stirred mixture of **12** (24.0 mg, 0.05 mmol) and a trace amount of $NaHCO_3$ in CH_2Cl_2 (0.5 ml) was added Dess–Martin periodinane (33.0 mg, 0.08 mmol) at rt. The resulting suspension was stirred at the same temperature for 6 h, diluted with sat. $NaHCO_3$/$Na_2S_2O_3$ solution, and then extracted with ether. The extracts were washed successively with water, brine, dried, and concentrated to give **13** (27 mg), which was employed to the next step without further purification. An analytical sample was prepared by chromatography on silica gel {hexane–EtOAc (4:1)}. Colorless oil; $[\alpha]_D^{23}$=+58.5 (*c* 0.62, $CHCl_3$); IR (neat) 2926, 1719, 1379, 1369, 1250, 1215, 1098, 1070, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*=6.8 Hz), 1.22–1.96 (30H, m), 1.35 (9H, s), 1.40 (3H, s), 2.67 (1H, ddd, *J*=18.7, 8.7, 6.8 Hz), 2.76 (1H, ddd, *J*=18.7, 9.1, 5.7 Hz), 3.33 (1H, ddd, *J*=11, 6.8, 2.0 Hz), 3.52–3.61 (2H, m), 3.82 (1H, dd, *J*=12, 2.4 Hz), 3.93–3.99 (2H, m), 4.07 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.5, 26.0, 26.1, 26.8, 27.3, 27.4, 27.9, 28.0, 29.4, 29.6, 29.7, 29.8, 31.9, 32.9, 34.5, 66.9, 78.1, 78.6, 80.0, 80.9, 82.8, 209.9; HRMS calcd for $C_{30}H_{54}O_6Na$ $[M+Na]^+$ 533.3818, found 533.3815.

Anal. Found: C, 70.58; H, 10.69. Calcd for $C_{30}H_{54}O_6$: C, 70.55; H, 10.66.

3.1.8. (2*R*,3*S*,7*R*,8*RS*,11*R*,12*R*)-1,2:11,12-(Diisopropylidenedioxy)-3,7-oxido-8-tetracosanol (14). To a stirred solution of the above ketone **13** (27 mg, ca 0.05 mmol) in ether (0.4 ml) was added dropwise a 0.14 M solution of $Zn(BH_4)_2$ (2.0 ml) in ether at −10°C, and the mixture was stirred at the same temperature for 0.5 h. After quenching with sat. NH_4Cl solution, the resulting mixture was dried over $MgSO_4$, filtered through a pad of celite, and concentrated. Chromatography on silica gel with hexane–EtOAc (4:1) as the eluent gave **14** (23.6 mg, 98%) as a stereoisomeric mixture (β/α=ca 93/7 by ^1H NMR analysis). Colorless oil; IR (neat) 3477, 2926, 1251, 1215, 1068, 1046, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.22–2.20 (45H, m), 3.21 (0.07H, ddd, *J*=11, 6.3, 1.9 Hz), 3.25–3.35 (1.93H, m), 3.45 (0.07H, brq, *J*=6.3 Hz), 3.55–3.63 (2.93H, m), 3.87–3.98 (2H, m), 4.01–4.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.6, 22.7, 25.3, 26.2, 26.8, 27.2, 27.3, 27.4, 28.3, 29.1,

29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 31.9, 32.8, 32.9, 66.8, 67.0, 73.5, 73.6, 78.1, 78.2, 78.7, 78.9, 80.4, 80.7, 80.8, 80.9, 81.1, 81.2, 107.8, 109.2; HRMS calcd for $C_{30}H_{56}O_6Na$ $[M+Na]^+$ 535.3975, found 535.3969.

Anal. Found: C, 70.24; H, 11.03. Calcd for $C_{30}H_{56}O_6$: C, 70.27; H, 11.01.

3.1.9. (2*R*,3*S*,7*R*,8*RS*,11*R*,12*R*)-1,2:11,12-(Diisopropylidenedioxy)-3,7-oxido-8-tetracosanol *p*-toluenesulfonate (15). To a stirred mixture of **14** (23.6 mg, 0.05 mmol), *N*,*N*-dimethylaminopyridine (6.1 mg, 0.05 mmol) and triethylamine (50μl) in CH_2Cl_2 (0.3 ml) was added *p*-toluenesulfonyl chloride (19.0 mg, 0.10 mmol) at 0°C, and then the mixture was stirred at 0°C~rt for 12 h. After addition of ice-water, the resulting mixture was extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried and concentrated. Chromatography on silica gel with hexane–EtOAc (10:1) as the eluent gave **15** (29.7 mg, 97%) as a colorless oil. IR (neat) 2927, 1601, 1368, 1189, 1177, 1096, 1072, 921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 1.22–1.90 (44H, m), 2.40 (0.21H, s), 2.44 (2.79H, s), 3.09–3.19 (1H, m), 3.35–3.51 (3H, m), 3.59–3.64 (1H, m), 3.73–3.79 (1H, m), 3.88–3.93 (1H, m), 4.52 (0.93H, ddd, J=8.7, 4.3, 3.9 Hz), 4.58 (0.07H, m), 7.31 (2H, d, J=7.8 Hz), 7.77 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.6, 22.4, 22.6, 22.7, 25.3, 26.2, 26.4, 26.7, 26.8, 27.3, 27.8, 28.0, 28.2, 28.6, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 67.0, 67.1, 77.8, 77.9, 78.9, 79.1, 80.2, 80.6, 80.8, 80.9, 85.1, 85.2, 107.7, 109.0, 127.6, 129.3, 129.4, 134.7, 144.1; HRMS calcd for $C_{37}H_{62}O_8SNa$ $[M+Na]^+$ 689.4063, found 689.4083.

Anal. Found: C, 66.66; H, 9.51; S, 5.14. Calcd for $C_{37}H_{62}O_8S$: C, 66.63; H, 9.37; S, 4.81.

3.1.10. (2*R*,3*S*,7*R*,8*RS*,11*R*,12*R*)-3,7-Oxido-8-(*p*-toluenesulfonyloxy)-1,2,11,12-tetracosanetetraol (4a). A solution of **15** (441 mg, 0.66 mmol) in AcOH–water (7:1, 12 ml) was stirred at rt for 24 h, concentrated, and then co-evaporated with toluene (×5) to give **4a** (387 mg, quant.), which was employed to the next step without further purification. An analytical sample was prepared by preparative TLC {$CHCl_3$–MeOH (10:1), 2 developments}. Colorless oil; IR (neat) 3409, 2926, 1566, 1457, 1367, 1188, 1176, 1096, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.10–2.00 (32H, m), 2.43 (3H, s), 3.18–3.31 (5H, m), 3.33–3.55 (3H, m), 3.57–3.82 (3H, m), 4.50–4.65 (1H, m), 7.32 (2H, d, J=8.2 Hz), 7.77 (1H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.7, 22.7, 22.8, 25.6, 25.8, 26.2, 26.6, 26.8, 26.9, 27.0, 28.3, 29.4, 29.6, 29.8, 31.9, 33.1, 33.5, 62.9, 74.0, 77.5, 79.3, 84.7, 127.6, 129.6, 134.2, 144.5; HRMS calcd for $C_{31}H_{54}O_8SNa$ $[M+Na]^+$ 609.3437, found 609.3420.

3.1.11. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-1,2-(Isopropylidenedioxy)-3,7:8,11-dioxido-12-tetracosanol (16) and (2*R*,3*S*,7*R*,8*S*,11*R*,12*R*)-1,2-(isopropylidenedioxy)-3,7:8,11-dioxido-12-tetracosanol (17). A mixture of the above tetraol **4a** (387 mg, 0.66 mmol) and sodium methoxide (300 mg, 5.55 mmol) in methanol (1.5 ml) was stirred at rt for 1 h and 50°C for 5 h, and then treated with Dowex 50W X-8 (H^+) resin. The suspension was filtered, concentrated, and diluted with 2,2-dimethoxypropane–CH_2Cl_2 (1:10, 12 ml). To a stirred mixture was added *d*-camphorsulfonic acid (40 mg, 0.17 mmol), and the mixture was stirred at rt for 0.5 h, diluted with ether, and then washed successively with sat. $NaHCO_3$ solution, water, brine, dried, and concentrated. Chromatography on silica gel with hexane–ether (3:1) as the eluent yielded **16** (145 mg, 48% from **15**), and a mixture of **16** and **17**, which was separated by preparative TLC {hexane–EtOAc (4:1), 3 developments}to afford more additional **16** (88 mg, 30%) and **17** (17 mg, 6%).

16; colorless oil; $[\alpha]_D^{25}$=+17.8 (c 0.23, $CHCl_3$); IR (neat) 3480, 2925, 1251, 1210, 1075, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 1.22–1.97 (32H, m), 1.35 (3H, s), 1.41 (3H, s), 2.45 (1H, brs), 3.25–3.31 (2H, m), 3.37 (1H, brq, J=6.5 Hz), 3.79 (1H, dd, J=7.9, 6.5 Hz), 3.85 (1H, ddd, J=7.9, 5.8, 5.6 Hz), 3.91–4.04 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 22.9, 25.4, 25.7, 26.8, 27.3, 28.0, 28.3, 28.4, 29.4, 29.7, 29.8, 31.9, 33.5, 66.9, 74.1, 78.3. 78.6, 80.2, 81.1, 82.7, 109.1; HRMS calcd for $C_{27}H_{51}O_5$ $[M+H]^+$ 455.3737, found 455.3738.

Anal. Found: C, 71.06; H, 11.26. Calcd for $C_{27}H_{50}O_5$: C, 71.32 H, 11.08.

17; amorphous solid; $[\alpha]_D^{21}$=−0.48 (c 0.42, $CHCl_3$); IR ($CHCl_3$) 3426, 2919, 1263, 1097, 1046, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 1.22–2.01 (32H, m), 1.33 (3H, s), 1.39 (3H, s), 2.70 (1H, d, J=6.7 Hz), 3.28 (1H, ddd, J=11, 6.8, 1.5 Hz), 3.30 (1H, m), 3.45 (1H, ddd, J=11, 4.9, 2.0 Hz), 3.81–3.91 (3H, m), 4.08 (1H, ddd, J=10, 8.7, 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.3, 25.9, 26.6, 26.8, 28.2, 28.4, 28.5, 29.4, 29.7, 29.8, 31.9, 34.6, 67.5, 74.8, 78.1, 78.9, 79.2, 82.1, 82.2, 109.0; HRMS calcd for $C_{27}H_{51}O_5$ $[M+H]^+$ 455.3737, found 455.3744.

Anal. Found: C, 71.23; H, 11.07. Calcd for $C_{27}H_{50}O_5$: C, 71.32 H, 11.08.

3.1.12. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-1,2-(Isopropylidenedioxy)-12-(methoxymethoxy)-3,7:8,11-dioxidotetracosane (18). To a stirred mixture of **16** (462 mg, 1.02 mmol) and *N*,*N*-diisopropylethylamine (0.71 ml, 4.06 mmol) in CH_2Cl_2 (2.0 ml) was added dropwise bromomethyl methyl ether (0.17 ml, 2.03 mmol) at 0°C. The mixture was stirred at rt for 12 h, and then poured into ice–water. The resulting mixture was extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried and concentrated. Chromatography on silica gel with hexane–ethyl acetate (10:1) as the eluent yielded **18** (462 mg, 91%) as a colorless oil. $[\alpha]_D^{22}$=+33.2 (c 0.40, $CHCl_3$); IR (neat) 2925, 1210, 1150, 1100, 1076, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, J=6.8 Hz), 1.23–1.95 (32H, m), 1.33 (3H, s), 1.39 (3H, s), 3.26–3.26 (2H, m), 3.38 (3H, s), 3.40–3.47 (1H, m), 3.82–4.03 (5H, m), 4.65, 4.82 (2H, each d, J=6.8 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.2, 22.7, 22.9, 25.5, 25.6, 26.8, 27.3, 28.3, 28.4, 29.4, 29.7, 29.9, 31.2, 31.9, 55.7, 67.1, 71.4, 78.4, 78.6, 79.4, 80.0, 80.9,

81.7, 96.5, 108.9; HRMS calcd for $C_{29}H_{54}O_6Na$ $[M+Na]^+$ 521.3818, found 521.3835.

Anal. Found: C, 70.24; H, 11.05. Calcd for $C_{29}H_{54}O_6$: C, 69.84; H, 10.91.

3.1.13. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-12-(Methoxymethoxy)-3,7:8,11-dioxido-1,2-tetracosanediol (19). A solution of **18** (371 mg, 0.74 mmol) in AcOH–water (10:1, 3.3 ml) was stirred at rt for 12 h, concentrated, and then co-evaporated with toluene (×5). Chromatography on silica gel with hexane–EtOAc (1:1)–EtOAc as the eluent yielded **19** (334 mg, 98%) as a colorless oil. $[\alpha]_D^{20}=+28.3$ (*c* 0.50, $CHCl_3$); IR (neat) 3420, 2925, 1149, 1087, 1039, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.20–1.74 (29H, m), 1.88–1.96 (3H, m), 2.80 (2H, brs), 3.28 (1H, ddd, *J*=11, 5.4, 1.5 Hz), 3.38 (3H, s), 3.42–3.49 (2H, m), 3.54 (1H, dd, *J*=9.3, 4.9 Hz), 3.67 (1H, dd, *J*=11.7, 3.9 Hz), 3.76 (1H, dd, *J*=11.7, 4.9 Hz), 3.84 (1H, ddd, *J*=8.3, 5.8, 5.8 Hz), 3.96 (1H, ddd, *J*=8.3, 7.3, 6.4 Hz), 4.66, 4.80 (2H, each d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 22.9, 25.5, 27.3, 27.4, 28.1, 28.5, 29.4, 29.6, 29.7, 29.8, 29.9, 31.0, 31.2, 31.9, 55.8, 63.8, 73.6, 79.6, 80.1, 80.3, 81.2, 81.8, 96.6; HRMS calcd for $C_{26}H_{50}O_6Na$ $[M+Na]^+$ 481.3505, found 481.3534.

3.1.14. (2*S*,3*S*,7*R*,8*R*,11*R*,12*R*)-12-(Methoxymethoxy)-1,2:3,7:8,11-trioxido-tetracosane (20). *From* **19**. To a stirred solution of **19** (179 mg, 0.39 mmol) in pyridine (1.5 ml) was added dropwise a solution of benzoyl chloride (55 μl, 0.47 mmol) in CH_2Cl_2 (0.4 ml) at −20°C, and the mixture was stirred at −20 to 5°C for 12 h. Methanesulfonyl chloride (70 μl, 0.90 mmol) was added at −20°C, and the mixture was stirred at −20 to 0°C for 7 h, then poured into ice–water. The resulting mixture was extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried and concentrated to give a syrup (271 mg). To a stirred solution of the syrup (271 mg) in THF–methanol (1:1, 1.6 ml) was added a 4 M solution of NaOH (0.2 ml) at −20°C. The mixture was stirred at −20 to 5°C for 17 h, diluted with CH_2Cl_2, and washed successively with water, brine, dried, and concentrated. Chromatography on silica gel with hexane–EtOAc (10:1–4:1) as the eluent yielded **20** (143 mg, 83% from **19**).

From **29**. To a stirred solution of **29** (49.4 mg, 0.12 mmol) in THF (0.5 ml) was added dropwise a 1.6 M hexane solution of *n*-BuLi (0.1 ml, 0.16 mmol) at −23°C, and the mixture was stirred at −23°C for 15 min. Chloromethyl methyl ether (12 μl, 0.16 mmol) was added, and the mixture was stirred at −23°C ~rt for 18 h. After quenching with sat. NH_4Cl solution, the resulting mixture was extracted with ether. The extracts were washed successively with water, brine, dried and concentrated. Chromatography on silica gel {hexane–EtOAC (4:1)} followed by purification by preparative TLC {hexane–EtOAc (2:1), 3 developments} yielded **20** (22.0 mg, 40%). Colorless oil; $[\alpha]_D^{23}=+24.3$ (*c* 1.07, $CHCl_3$); IR (neat) 2925, 1150, 1105, 1089, 1040, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.23–1.95 (32H, m), 2.67 (1H, dd, *J*=4.9, 2.9 Hz), 2.74 (1H, t, *J*=4.9 Hz), 1.81–1.91 (1H, m), 3.00 (1H, m), 3.24 (1H, ddd, *J*=11, 3.9, 2.0 Hz), 3.31 (1H, ddd, *J*=11, 4.9, 2.0 Hz), 3.91 (1H, m), 4.02 (1H, m), 4.68, 4.82 (2H, each d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.3, 23.1, 23.3, 25.9, 27.3, 27.9, 28.4, 28.7, 29.8, 30.0, 30.1, 30.3, 31.5, 32.4, 44.0, 54.5, 55.8, 78.7, 80.2, 80.3, 81.6, 81.9, 97.0; HRMS calcd for $C_{26}H_{48}O_5Na$ $[M+Na]^+$ 463.3399, found 463.3405.

Anal. Found: C, 70.87; H, 11.10. Calcd for $C_{26}H_{48}O_5$: C, 70.87; H, 10.98.

3.1.15. (4*S*,5*S*,9*R*,10*R*,13*R*,14*R*)-14-(Methoxymethoxy)-5,9:10,13-dioxido-1-hexacosyn-4-ol (2). To a stirred solution of trimethylsilylacetylene (0.2 ml, 1.42 mmol) in THF (1.5 ml) was added dropwise a 1.59 M solution of *n*-butyllithium in hexane (0.84 ml, 1.34 mmol) at −78°C, and the mixture was stirred at the same temperature for 1 h. A solution of **20** (194 mg, 0.44 mmol) in THF (0.6 ml) and $BF_3{\cdot}Et_2O$ (0.17 ml, 1.34 mmol) was added sequentially to the above solution at −78°C. The mixture was stirred at the same temperature for 2 h, poured into sat. NH_4Cl solution, and extracted with ether. The extracts were washed successively with water, brine, dried, concentrated, and passed through a short column of silica gel {hexane–EtOAc (10:1–4:1)} to give a syrup (232 mg). A mixture of the syrup (232 mg) and potassium carbonate (31 mg) in methanol (2.0 ml) was stirred at rt for 5 h, and then concentrated. The residue was purified by chromatography on silica gel {hexane–EtOAc (10:1–4:1)} to give **2** (199 mg, 97%) as a colorless oil. $[\alpha]_D^{23}=+39.4$ (*c* 0.40, $CHCl_3$); IR (neat) 3449, 3314, 2924, 2120, 1101, 1084, 1039, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.22–1.75 (29H, m), 1.86–1.94 (3H, m), 1.99 (1H, t, *J*=2.4 Hz), 2.38 (1H, ddd, *J*=17, 5.9, 2.4 Hz), 2.48 (1H, ddd, *J*=17, 5.9, 2.4 Hz), 3.33 (1H, ddd, *J*=11, 5.9, 2.0 Hz), 3.35–3.48 (2H, m), 3.38 (3H, s), 3.59 (1H, dd, *J*=11, 5.9 Hz), 3.89 (1H, ddd, *J*=7.3, 6.3, 5.8 Hz), 3.96 (1H, ddd, *J*=8.3, 6.4, 6.3 Hz), 4.66, 4.81 (2H, each d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 22.8, 23.0, 25.5, 26.9, 27.0, 27.7, 28.4, 29.3, 29.5, 29.6, 29.8, 31.1, 31.9, 69.9, 72.4, 78.8, 79.4, 80.0, 80.9, 81.0, 81.8, 96.5; HRMS calcd for $C_{28}H_{50}O_5Na$ $[M+Na]^+$ 489.3556, found 489.3551.

Anal. Found: C, 72.37; H, 10.89. Calcd for $C_{28}H_{50}O_5$: C, 72.06; H, 10.80.

3.1.16. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanediol (21). To a stirred solution of **5** (240 mg, 0.36 mmol) in CH_2Cl_2 (4.5 ml) was added *d*-camphorsulfonic acid (54 mg, 0.23 mmol) at rt, and the mixture was stirred at rt for 3 h. 2,2-Dimethoxypropane (0.1 ml) was added and stirring was further continued for 3.5 h. After addition of triethylamine, the resulting mixture was concentrated. Chromatography on silica gel with hexane–EtOAc (4:1–2:1) as the eluent yielded **21** (226 mg, 89%) as a colorless oil. $[\alpha]_D^{23}=+15.5$ (*c* 0.96, $CHCl_3$); IR (neat) 3441, 2928, 1428, 1239, 1113, 1087, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=6.8 Hz), 1.07 (9H, s), 1.22–1.93 (35H, m), 1.34 (3H, s), 2.47 (1H, brs), 2.58 (1H, brs), 3.17 (1H, ddd, *J*=11, 6.3, 2.0 Hz, H-7), 3.37 (1H, ddd, *J*=11, 6.3, 2.0 Hz, H-3), 3.42 (1H, m, H-8), 3.55–3.62 (2H,

m, H-11, 12), 3.65 (1H, m, H-2), 3.72 (1H, dd, J=10, 6.3 Hz, H-1), 3.77 (1H, dd, J=10, 4.4 Hz, H-1′), 7.38–7.45 (6H, m), 7.65 (4H, brd, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.4, 22.8, 26.2, 26.9, 27.0, 27.2, 27.3, 27.4, 28.7, 29.1, 29.4, 29.6, 29.7, 29.9, 31.9, 32.9, 64.7, 73.7, 74.1, 77.8, 80.7, 80.8, 80.9, 107.8, 127.7, 128.2, 129.7, 132.9, 135.4.

Anal. Found: C, 72.67; H, 10.09. Calcd for $C_{43}H_{70}O_6Si$: C, 72.63; H, 9.92.

3.1.17. (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanediol di-*p*-toluenesulfonate (22). Treatment of **21** (143 mg, 0.21 mmol) as described for preparation of **15** yielded **22** (149 mg), which was employed to the next step without further purification. An analytical sample was prepared by chromatography on silica gel {hexane–EtOAc (4:1)}. Colorless oil; $[\alpha]_D^{23}$=+7.7 (c 0.97, $CHCl_3$); IR (neat) 3072, 2928, 1599, 1463, 1428, 1367, 1189, 1177, 1113, 1097, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.00 (9H, s), 1.20–1.83 (32H, m), 1.31 (3H, s), 1.34 (3H, s), 2.37 (3H, s), 2.40 (3H, s), 3.37–3.43 (3H, m), 3.58 (1H, dd, J=11, 3.9 Hz), 3.63 (1H, m), 3.66 (1H, dd, J=11, 3.8 Hz), 4.39 (1H, dd, J=9.6, 4.3 Hz), 4.54 (1H, dd, J=10.7, 6.2 Hz), 7.22 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.7 Hz), 7.37–7.43 (6H, m), 7.55–7.59 (4H, m), 7.71 (2H, d, J=8.7 Hz), 7.72 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.2, 21.5, 21.6, 22.5, 22.7, 25.6, 26.1, 26.4, 26.7, 27.2, 27.3, 28.3, 29.3, 29.5, 29.6, 29.8, 31.9, 32.8, 61.8, 75.5, 77.4, 80.4, 81.0, 83.6, 83.7, 107.9, 127.7, 127.8, 127.9, 129.5, 129.6, 129.7, 129.8, 132.9, 133.0, 134.3, 134.4, 135.4, 135.6, 144.3, 144.4; HRMS calcd for $C_{57}H_{82}O_{10}SiS_2Na$ [M+Na]$^+$ 1041.5016, found 1041.5010.

3.1.18. (2*S*,3*S*,7*R*,8*R*,11*R*,12*R*)-11,12-(Isopropylidenedioxy)-1,2:3,7-dioxido-8-tetracosanol *p*-toluenesulfonate (23) and (2*R*,3*S*,7*R*,8*R*,11*R*,12*R*)-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-di-*p*-toluenesulfonyloxy-1-tetracosanol (24). To a stirred solution of **22** (103 mg, 0.10 mmol) in THF (0.5 ml) was added a 1.0 M THF solution of TBAF (0.12 ml, 0.12 mmol) at rt, and the mixture was stirred at rt for 2d, then concentrated. The residue was passed through a short column of silica gel {hexane–EtOAc (4:1)} and then purified by preparative TLC {hexane–EtOAc (4:1)} to give **23** (35.1 mg, 57%), and **24** (11.5 mg, 15%).

23; colorless oil; $[\alpha]_D^{24}$=+29.6 (c 0.51, $CHCl_3$); IR (neat) 2927, 1599, 1457, 1366, 1188, 1176, 1096, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 1.20–1.92 (32H, m), 1.31 (3H, s), 1.33 (3H, s), 2.40 (3H, s), 2.58 (1H, dd, J=4.9, 2.5 Hz), 2.71 (1H, t, J=4.9 Hz), 2.88 (1H, ddd, J=7.3, 4.9, 2.5 Hz), 3.10 (1H, ddd, J=11, 5.8, 2.0 Hz), 3.38–3.45 (2H, m), 3.51 (1H, ddd, J=11, 4.9, 1.9 Hz), 3.55 (1H, ddd, J=11, 6.8, 1.9 Hz), 4.77 (1H, dd, J=8.7, 4.7 Hz), 7.31 (2H, d, J=7.8 Hz), 7.81 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.7, 22.6, 22.7, 25.4, 26.2, 26.6, 27.2, 27.3, 28.4, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 43.8, 54.0, 77.2, 78.7, 80.4, 80.9, 83.8, 107.8, 127.8, 129.4, 134.2, 144.2; HRMS calcd for $C_{34}H_{56}O_7SNa$ [M+Na]$^+$ 631.3644, found 631.3638.

Anal. Found: C, 67.07; H, 9.39; S, 5.43. Calcd for $C_{34}H_{56}O_7S$: C, 67.07; H, 9.27; S, 5.27.

24; colorless oil; $[\alpha]_D^{23}$=+20.9 (c 0.22, $CHCl_3$); IR (neat) 3546, 2927, 1599, 1457, 1366, 1189, 1177, 1096, 920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.20–1.90 (32H, m), 1.29 (3H, s), 1.33 (3H, s), 2.40 (1H, t, J=6.3 Hz), 2.44 (3H, s), 2.45 (3H, s), 3.38–3.48 (3H, m), 3.55 (1H, ddd, J=11, 6.8, 1.9 Hz), 3.67 (1H, ddd, J=13, 6.8, 2.9 Hz), 3.77 (1H, ddd, J=13, 6.3, 4.4 Hz), 4.37 (1H, dd, J=6.7, 3.4 Hz), 4.54 (1H, dd, J=7.2, 4.8 Hz), 7.33 (4H, m), 7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.7, 21.8, 22.6, 22.8, 26.1, 26.2, 26.8, 27.2, 27.3, 27.5, 27.9, 29.4, 29.6, 29.7, 29.8, 31.9, 32.8, 61.4, 76.3, 77.9, 80.1, 80.7, 83.7, 84.1, 107.9, 127.6, 127.8, 129.6, 129.8, 133.6, 134.3, 144.5; HRMS calcd for $C_{41}H_{64}O_{10}S_2Na$ [M+Na]$^+$ 803.3839, found 803.3830.

3.1.19. (3*S*,7*R*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanedione (25). Treatment of **21** (136.1 mg, 0.19 mmol) as described for preparation of **13** yielded **25** (149 mg), which was employed to the next step without further purification. An analytical sample was prepared by chromatography on silica gel {hexane–EtOAc (4:1)}. Colorless oil; $[\alpha]_D^{23}$=+15.3 (c 0.74, $CHCl_3$); IR (neat) 3070, 2928, 1740, 1720, 1428, 1378, 1367, 1240, 1205, 1113, 1110, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.11 (9H, s), 1.20–1.94 (30H, m), 1.33 (3H, s), 1.34 (3H, s), 2.61 (1H, ddd, J=19.3, 7.8, 7.3 Hz), 2.66 (1H, ddd, J=19.3, 8.7, 5.3 Hz), 3.50–3.60 (2H, m), 3.75 (1H, brd, J=11.6 Hz), 3.95 (1H, brd, J=11.6 Hz), 4.61 (1H, brd, J=18.8 Hz), 4.65 (1H, brd, J=18.8 Hz), 7.37–7.46 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.4, 22.7, 25.9, 26.1, 26.8, 27.3, 27.4, 29.4, 29.6, 29.7, 29.8, 32.0, 32.8, 34.4, 67.1, 79.9, 81.1, 81.5, 82.6, 107.8, 127.6, 129.7, 132.7, 135.4, 205.9, 209.2.

Anal. Found: C, 72.94; H, 9.49. Calcd for $C_{43}H_{66}O_6Si$: C, 73.04; H, 9.41.

3.1.20. (2*R*,3*S*,7*R*,8*RS*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanediol (26) and (2*S*,3*S*,7*R*,8*RS*,11*R*,12*R*)-1-*t*-butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanediol (27). Treatment of the above ketone **25** (149 mg, ca 0.19 mmol) as described for preparation of **14** yielded **26** (117 mg, 85%) as a C-8 epimeric mixture (β/α=ca 89/11 by ^{1}H NMR analysis) and **27** (17 mg, 13%) as a C-8 epimeric mixture (β/α=ca 56/44).

26; colorless oil; IR (neat) 3449, 3072, 2928, 1597, 1428, 1377, 1367, 1239, 1219, 1113, 1087, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.07 (9H, s), 1.22–1.94 (38H, m), 2.40 (2H, brs), 3.17 (0.11H, ddd, J=11.7, 6.3, 1.8 Hz, H-7$_{minor}$), 3.23 (0.89H, ddd, J=12, 3.3, 2.0 Hz, H-7$_{major}$), 3.36–3.46 (1H, m), 3.52–3.81 (5H, m), 7.37–7.46 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.4, 22.8, 25.5, 26.0, 26.2, 26.9, 27.0, 27.2, 27.3, 27.4, 28.7, 29.1, 29.4, 29.6, 29.7, 29.9, 32.0, 32.9, 64.4, 64.7, 73.5, 73.7, 74.0, 74.1, 77.8, 80.4, 80.7, 80.8, 80.9, 81.1, 81.2, 107.8, 127.6, 127.7, 129.7,

132.9, 133.0, 135.4; HRMS calcd for $C_{43}H_{70}O_6SiNa$ $[M+Na]^+$ 733.4839, found 733.4854.

Anal. Found: C, 72.69; H, 10.09. Calcd for $C_{43}H_{70}O_6Si$: C, 72.63; H, 9.92.

27; colorless oil; IR (neat) 3400, 3060, 2929, 1597, 1428, 1377, 1367, 1239, 1219, 1113, 1066, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.8 Hz), 1.06 (9H, s), 1.22–1.94 (32H, m), 1.37 (3H, s), 1.38 (3H, s), 2.26 (2H, brs), 3.23 (0.44H, ddd, J=11.7, 5.9, 1.8 Hz, H-7_{minor}), 3.30 (0.56H, ddd, J=11.8, 3.5, 1.8 Hz, H-7_{major}), 3.45–3.65 (4H, m), 3.66–3.76 (2H, m), 7.37–7.46 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.3, 22.7, 22.9, 24.8, 26.2, 26.9, 27.1, 27.3, 27.4, 28.7, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 32.9, 64.3, 64.4, 73.4, 73.6, 74.4, 80.5, 80.7, 80.8, 80.9, 81.0, 81.2, 96.0, 107.7, 127.5, 127.6, 129.5, 129.6, 133.1, 133.2, 135.3; HRMS calcd for $C_{43}H_{70}O_6SiNa$ $[M+Na]^+$ 733.4839, found 733.4855.

Anal. Found: C, 72.55; H, 10.08. Calcd for $C_{43}H_{70}O_6Si$: C, 72.63; H, 9.92.

3.1.21. (2*R*,3*S*,7*R*,8*RS*,11*R*,12*R*)-1-*t*-Butyldiphenylsilyloxy-11,12-(isopropylidenedioxy)-3,7-oxido-2,8-tetracosanediol di-*p*-toluenesulfonate (28). To a stirred mixture of **26** (67.2 mg, 0.09 mmol), *N*,*N*-dimethylaminopyridine (23.1 mg, 0.19 mmol) and triethylamine (0.2 ml) in CH_2Cl_2 (1.0 ml) was added *p*-toluenesulfonyl chloride (54 mg, 0.28 mmol) at rt, and then the mixture was stirred at rt for 12 h. More *p*-toluenesulfonyl chloride (27 mg, 0.14 mmol) was added, and stirring was further continued for 10 h. After addition of ice–water, the resulting mixture was vigorously stirred for 30 min and then extracted with ether. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried, and concentrated. The residue was passed through a short column of silica gel {hexane–EtOAc (10:1–4:1)} to give **28** (99.0 mg), which was employed to the next step without further purification. Analytical sample was prepared by preparative TLC {hexane–EtOAc (4:1)}. Colorless oil; IR (neat) 3070, 3050, 2929, 2927, 1599, 1367, 1189, 1177, 1113, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 0.99 (9H, s), 1.22–1.84 (38H, m), 2.37, 2.38, 2.39, 2.40 (total 6H, each s), 3.18–3.25 (1H, m), 3.38–3.70 (5H, m), 4.05 (0.89H, m), 4.35 (0.89H, m), 4.38 (0.11H, m), 4.34 (0.11H, m), 7.19–7.21 (2H, m), 7.30–7.58 (10H, m), 7.65–7.74 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.3, 21.6, 21.7, 22.4, 22.5, 22.7, 25.3, 25.6, 26.2, 26.8, 27.3, 27.4, 29.1, 29.4, 29.6, 29.7, 29.9, 32.0, 32.9, 61.5, 61.8, 74.4, 75.5, 78.3, 80.4, 80.7, 81.0, 81.1, 83.3, 83.6, 83.7, 85.2, 107.8, 127.6, 129.2, 129.4, 129.5, 129.6, 132.7, 132.9, 134.2, 134.4, 134.7, 135.3, 135.4, 144.2, 144.3; HRMS calcd for $C_{57}H_{82}O_{10}SiS_2Na$ $[M+Na]^+$ 1041.5016, found 1041.5020.

3.1.22. (2*S*,3*S*,7*R*,8*R*,11*R*,12*R*)-1,2:3,7:8,11-Trioxido-12-tetracosanol (29) and (2*S*,3*S*,7*R*,8*S*,11*R*,12*R*)-1,2:3,7:8,11-trioxido-12-tetracosanol (30). A solution of the above ditosylate **28** (99.0 mg, 0.66 mmol) in AcOH–water (20:1, 2.1 ml) was stirred at rt for 3d and then at 50°C for 6 h, concentrated, and then co-evaporated with toluene. The residue was passed through a short column of silica gel {hexane–EtOAc (10:1–4:1)} to give **4b** (387 mg, 0.66 mmol), which was dissolved in THF (1 ml). A 1.0 M THF solution of TBAF (0.2 ml, 0.2 mmol) was added to the solution, and the mixture was stirred at rt for 24 h and at 50°C for 3 h, and then concentrated. Chromatography on silica gel with hexane–EtOAc (10:1–4:1) as the eluent yielded **29** (22.1 mg, 59% from **26**), and a mixture of **29** and **30**, which was separated by preparative TLC {hexane–EtOAc (1:1)} to afford more additional **29** (2.4 mg, 6%) and **30** (3.1 mg, 8%).

29; colorless oil; $[\alpha]_D^{24}$=+8.0 (*c* 0.41, $CHCl_3$); IR (neat) 3475, 2925, 1467, 1441, 1087, 1047, 904 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz), 1.22–2.00 (33H, m), 2.66 (1H, dd, J=4.8, 2.5 Hz), 2.76 (1H, t, J=4.8 Hz), 3.02 (1H, m), 3.22 (1H, ddd, J=11.2, 7.3, 1.9 Hz), 3.31 (1H, ddd, J=11.2, 6.8, 1.5 Hz), 3.36 (1H, dd, J=6.8, 5.8 Hz), 3.81 (1H, ddd, J=6.8, 6.8, 6.3 Hz), 3.89 (1H, ddd, J=8.3, 5.8, 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 22.8, 25.6, 26.7, 27.3, 28.2, 28.3, 29.3, 29.5, 29.6, 29.7, 31.9, 33.2, 43.8, 54.1, 74.0, 77.8. 79.9, 80.9, 82.8; HRMS calcd for $C_{24}H_{44}O_4Na$ $[M+Na]^+$ 419.3137, found 419.3126.

Anal. Found: C, 72.50; H, 11.24. Calcd for $C_{24}H_{44}O_4$: C, 72.68 H, 11.18.

30; white solid; mp 63–65°C; $[\alpha]_D^{21}$=−6.7 (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 3401, 2920, 1465, 1095, 1077, 1064, 1051, 902 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ 0.87 (3H, t, J=6.8 Hz), 1.22–1.98 (32H, m), 2.59 (1H, dd, J=5.4, 2.9 Hz), 2.66 (1H, brs), 2.70 (1H, t, J=5.4 Hz), 2.91 (1H, m), 3.15 (1H, ddd, J=11.1, 5.8, 1.9 Hz), 3.31 (1H, m), 3.38 (1H, ddd, J=11.2, 6.3, 1.9 Hz), 3.76 (1H, dd, J=6.2, 5.4 Hz), 3.84 (1H, ddd, J=6.8, 6.8, 4.3 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 14.4, 23.1, 23.2, 26.3, 27.1, 27.9, 28.1, 28.5, 29.8, 30.1, 30.2, 32.4, 34.7, 43.9, 54.4, 74.5, 78.8. 79.6, 82.2, 82.9.

Anal. Found: C, 72.59; H, 11.17. Calcd for $C_{24}H_{44}O_4$: C, 72.68 H, 11.18.

3.1.23. Butenolide (31). To a stirred solution of **2** (57.5 mg, 0.12 mmol) and **3** (114 mg, 0.20 mmol) in Et_3N (2 ml) were added $(Ph_3P)_2PdCl_2$ (9.1 mg, 0.01 mmol) and CuI (7.3 mg, 0.04 mmol) at rt, and the reaction mixture was stirred at rt for 2 h, poured into ice–water. The resulting mixture was extracted wtih EtOAc. The extracts were washed successively with cold HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried, concentrated. Chromatography on silica gel with hexane–EtOAc (10:1–4:1–1:1) as the eluent yielded an enyne **31** (87.2 mg, 79%) as a colorless oil. IR (neat) 3464, 2927, 1758, 1428, 1104, 1081, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) of ca 3/1 of an isomeric mixture: δ 0.87 (3H, t, J=6.8 Hz), 1.04 (9H, s), 1.21–2.04 (37H, m), 1.31 (3H, d, J=6.8 Hz), 2.18–2.60 (4H, m), 3.28–3.60 (4H, m), 3.39 (3H, s), 3.86–4.06 (3H, m), 4.65, 4.66, 4.81, 4.83 (total 2H, each d, J=6.8 Hz), 4.88 (1H, qd, J=6.8, 1.5 Hz), 5.30 (0.74H, brd, J=16.1 Hz), 5.33 (0.26H, brd, J=10.7 Hz), 5.51 (0.26H, ddd, J=10.7, 7.8, 7.3 Hz), 5.82 (0.74H, ddd, J=16.1, 7.3, 6.8 Hz), 6.88 (0.74H, brd, J=1.5 Hz), 6.92 (0.26H, brd, J=1.5 Hz), 7.35–7.44 (6H,

m), 7.62–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 18.9, 19.3, 22.6, 22.8, 23.9, 25.5, 26.9, 27.7, 28.3, 28.4, 29.3, 29.6, 29.8, 31.1, 31.7, 31.9, 35.2, 55.7, 71.1, 72.7, 78.8, 79.1, 79.4, 80.0, 80.6, 80.9, 81.8, 84.9, 96.5, 109.6, 110.0, 127.6, 129.7, 130.3, 133.8, 135.8, 141.8, 142.8, 151.4, 173.8; HRMS calcd for $C_{55}H_{82}O_8SiNa$ $[M+Na]^+$ 921.5677, found 921.5691.

3.1.24. Muconin 4-*O*-(*t*-butyldiphenylsilyl)-22-*O*-(methoxymethyl) diether (32). A mixture of **31** (41.3 mg, 46 μmol) and tris(triphenylphosphine)rhodium chloride (21.0 mg, 23 μmol) in benzene–ethanol (4:1, 0.75 ml) was stirred at rt for 7 h under hydrogen atmosphere, and concentrated. The residue was purified by chromatography on silica gel {hexane–EtOAc (10:1–4:1–2:1)} to give **32** (35.5 mg, 85%) as a colorless oil. $[\alpha]_D^{22}=+2.7$ (*c* 0.70, $CHCl_3$); IR (neat) 2927, 1759, 1460, 1321, 1210, 1104, 1077, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.03 (9H, s), 1.10–1.76 (46H, m), 1.31 (3H, d, *J*=6.8 Hz), 2.37–2.46 (2H, m), 3.14 (1H, ddd, *J*=11, 6.8, 1.9 Hz), 3.30 (1H, ddd, *J*=11, 5.3, 1.9 Hz), 3.38 (1H, m), 3.39 (3H, s), 3.46 (1H, m), 3.89 (1H, ddd, *J*=7.8, 5.9, 5.9 Hz), 3.95–4.04 (2H, m), 4.66, 4.82 (2H, each d, *J*=6.8 Hz), 4.88 (1H, qd, *J*=6.8, 1.5 Hz), 6.91 (1H, m), 7.34–7.42 (6H, m), 7.62–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 18.9, 19.3, 22.6, 22.9, 24.8, 25.3, 25.5, 26.9, 27.1, 27.8, 28.4, 29.3, 29.4, 29.6, 29.8, 31.1, 31.7, 31.9, 32.5, 36.3, 71.7, 74.2, 77.4, 79.4, 79.9, 80.8, 81.1, 81.8, 96.6, 127.5, 129.6, 130.6, 134.1, 135.8, 151.1, 173.9; HRMS calcd for $C_{55}H_{88}O_8SiNa$ $[M+Na]^+$ 927.6146, found 927.6149.

Anal. Found: C, 72.88; H, 9.54. Calcd for $C_{55}H_{88}O_8Si$: C, 72.96; H, 9.80.

3.1.25. Muconin (1). To a stirred solution of **32** (8.9 mg, 9.8 μmol) in CH_2Cl_2–MeOH (2:1, 0.9 ml) was added a 10% HCl solution in MeOH (0.3 ml) at rt, and the mixture was stirred at rt for 1 day. After addition of $NaHCO_3$, the resulting mixture was filtered through a pad of celite, and then concentrated. The residue was purified by preparative TLC (EtOAc, 3 developments) to afford **1**. (4.8 mg, 78%) as a white powder. $[\alpha]_D^{23}=+12.9$ (*c* 0.21, $CHCl_3$); IR (KBr) 3441, 2923, 1755, 1464, 1073, 1050, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=6.8 Hz), 1.20–2.00 (46H, m), 1.43 (3H, d, *J*=6.8 Hz), 2.30–2.62 (3H, m), 2.38 (1H, dd, *J*=15.1, 8.2 Hz), 2.51 (1H, ddd, *J*=15.1, 2.0, 1.5 Hz), 3.16 (1H, m), 3.30 (1H, m), 3.37 (1H, m), 3.42 (1H, m), 3.80 (1H, m), 3.84 (1H, m), 3.88 (1H, m), 5.05 (1H, qd, *J*=6.8, 1.0 Hz), 7.18 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.1, 22.7, 22.9, 25.2, 25.5, 25.6, 27.0, 27.1, 28.3, 29.3, 29.4, 29.6, 29.7, 31.9, 32.4, 33.3, 37.3, 69.9, 74.0, 74.1, 78.0, 80.9, 81.3, 82.9, 131.1, 151.8, 174.6; HRMS (FAB) calcd for $C_{37}H_{66}O_7Na$ 645.4706, found 645.4714.

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