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# Synthetic Studies of Archaeal Macrocyclic Tetraether Lipids: Practical Synthesis of 72-Membered Tetraether Model Compounds

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Archaeal 72-membered macrocyclic tetraether model compounds (**5** and **6**) were synthesized by intramolecular dicarbonyl coupling with the aid of low-valent titanium, which is known as McMurry coupling. This synthetic methodology is the first practical way to obtain the two regioisomeric structures in quantity and appears to be applicable to the natural 72-membered tetraether lipids (**3** and **4**). Also described is the synthesis of the corresponding acyclic tetraether model counterparts (**7** and **8**) in reference to the cyclic lipids.

The archaea (archaebacteria) including thermophiles, halophiles, thermoacidophiles, alkalophiles, and methanogens form a unique kingdom distinct from other bacteria (eubacteria) and eucarya.[1] Archaea, which usually habitat under rather extraordinary environments such as high temperature, high acidic, salt-rich conditions, or complete absence of oxygen, possess structurally unique core membrane lipids.[1,2] Archaeal cell membrane lipids consist of hydrophobic isoprenoid chains linked to glycerol at the *sn*-2 and 3-positions by ether linkages, such as **1** in Fig. 1. The hydrophilic polar head group such as phosphate or carbohydrate is attached to the hydroxyl group at the *sn*-1-position of glycerol.[2] In contrast, core lipids found in eubacterial and eucaryal lipids are completely *sn*-1,2-diacylglycerol-based lipids.

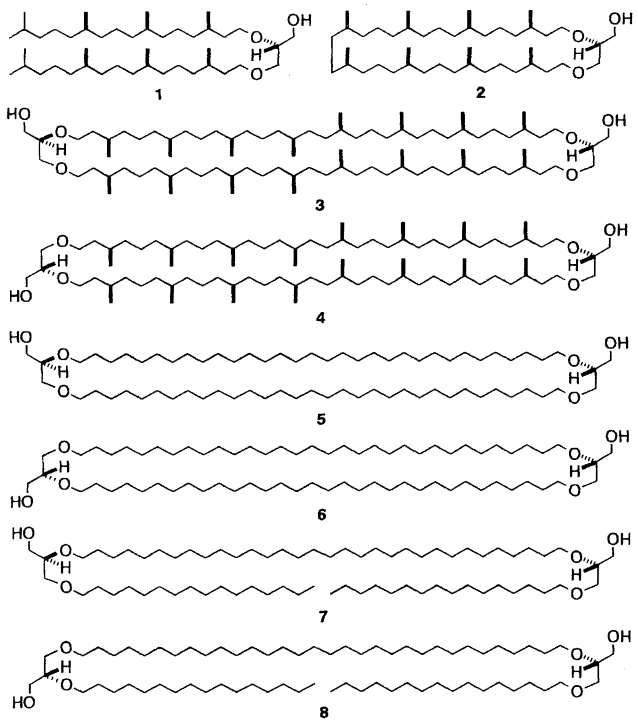



Fig. 1. Structures of archaeal core membrane lipids (**1**—**4**) and their tetraether model compounds (**5**—**8**).

Among the most striking features of the archaeal ether lipids is the presence of macrocyclic structures as large as 36- to 72-membered rings (**2**, **3**, and **4**) as shown in Fig. 1.[2] Recently, Arigoni et al. reported that the 72-membered lipids from several archaea exist as a mixture of regioisomers in terms of the glycerol arrangements such as **3** and **4**.[3] The physical nature of a membrane composed of these macrocyclic lipids is quite intriguing. The 72-membered lipids are considered to form a unimolecular membrane structure, in contrast to the ubiquitous bilayer assembly, or to constitute a trans-membrane orientation.[2,4] Several modeling and synthetic studies of these macrocyclic lipids have been reported in order to investigate the stability and permeability of the archaeal membrane lipids, especially in terms of their thermostability,[4] since these membrane lipids may provide a clue to the development of heat-resistant membranous materials. While we previously proposed the biosynthetic pathway of the lipid in the halophiles and the thermoacidophiles,[5] our interests have also been focusing on the biochemical significance of the macrocyclic molecular structures. One prerequisite in the studies to this end is to develop synthetic methods of the macrocyclic lipids on a significant scale. Along this line, we recently published the first synthesis of the 36-membered desmethylated analogs and natural lipid.[6a,6b,6d] Furthermore most recently, we have communicated the synthesis of desmethylated analogs of the regioisomeric 72-membered tetraether lipids as well.[6c] Menger et al. recently reported the synthesis of a 72-membered lipid model by using Glaser coupling as a key reaction.[4n] In this paper, we wish to describe the full details of our synthesis of archaeal macrocyclic model compounds (**5** and **6**) featuring the 72-membered ring, as well as the corresponding acyclic tetraether core lipids (**7** and **8**) as acyclic counterparts.

## Results and Discussion

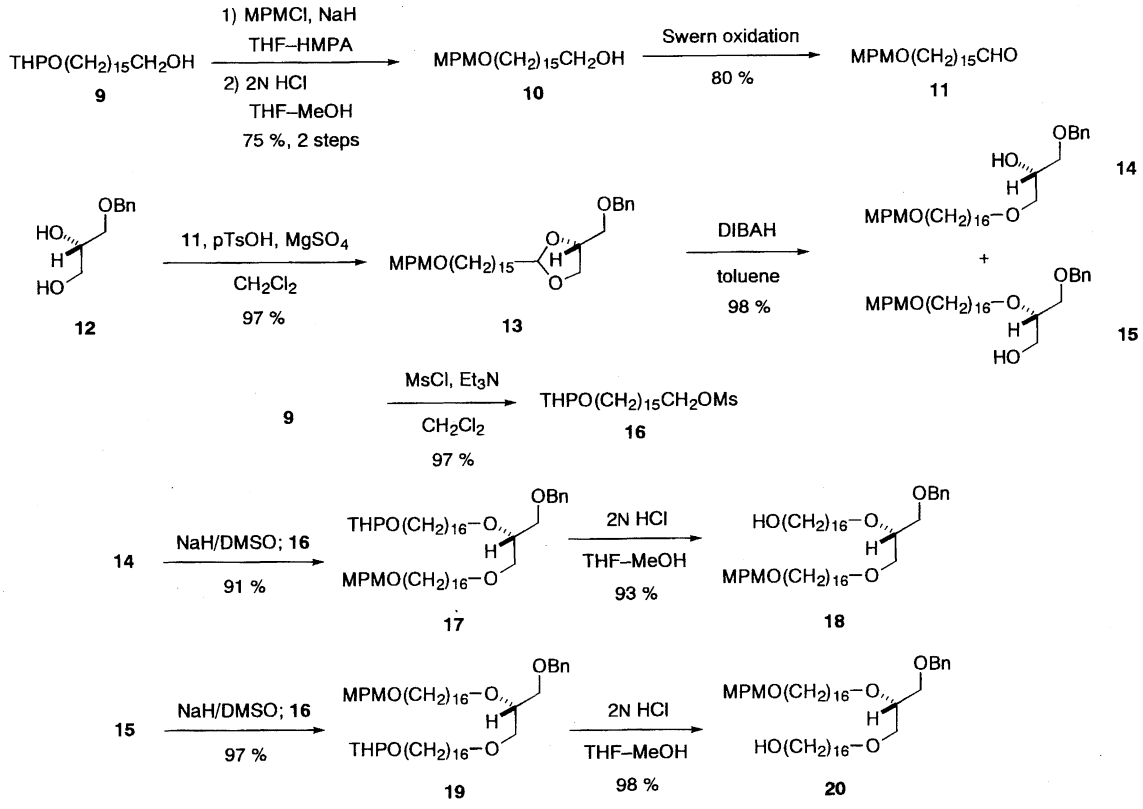
The basic synthetic plan was to prepare the functionalized half-sized diether compounds first, and then appropriately dimerize through Julia coupling,[7] and finally carry out macrocyclization of suitable dialdehydes by McMurry coupling.[8] This strategy appears to have an advantage of applicability to the natural 72-membered tetraether lipids **3** and **4**, in contrast to a disadvantage of Glaser coupling, which requires a diacetylene structure for macrocyclization.

The synthesis started with 1,16-hexadecanediol mono-THP ether **9** as shown in Eq. 1 (Scheme 1).[6a] The mono-THP ether **9** was first converted into mono MPM ether **10**. The alcohol **10** was then oxidized under Swern conditions to give aldehyde **11**, which was subjected to acetal formation with *sn*-1-*O*-benzylglycerol **12** in the presence of *p*-toluenesulfonic acid and $MgSO_4$ to give acetal derivative **13** in 97% yield as a 3 : 1 diastereomeric mixture. The acetal derivative **13** was treated as it stood with DIBAL-H to give a positionally isomeric mixture of mono-alkylated benzylglycerol derivatives, which were easily separable by a silica-gel column chromatography to afford *sn*-3-*O*-alkylated benzylglycerol derivative **14** and *sn*-2-*O*-alkylated benzylglycerol derivative **15** in 53 and 44% yield, respectively.[9] The *sn*-3-*O*-alkylated glycerol **14** was further alkylated via its sodium alkoxide with mesylate **16**, derived from **9** under the usual conditions, to afford 2,3-*O*-disubstituted *sn*-1-*O*-benzylglycerol **17**. Subsequent acid hydrolysis afforded half-sized diether compound **18** in 85% yield (two steps). The *sn*-2-*O*-alkylated glycerol **15** was treated in the same manner as the synthesis of **18** to give **20** in 95% yield (two steps).

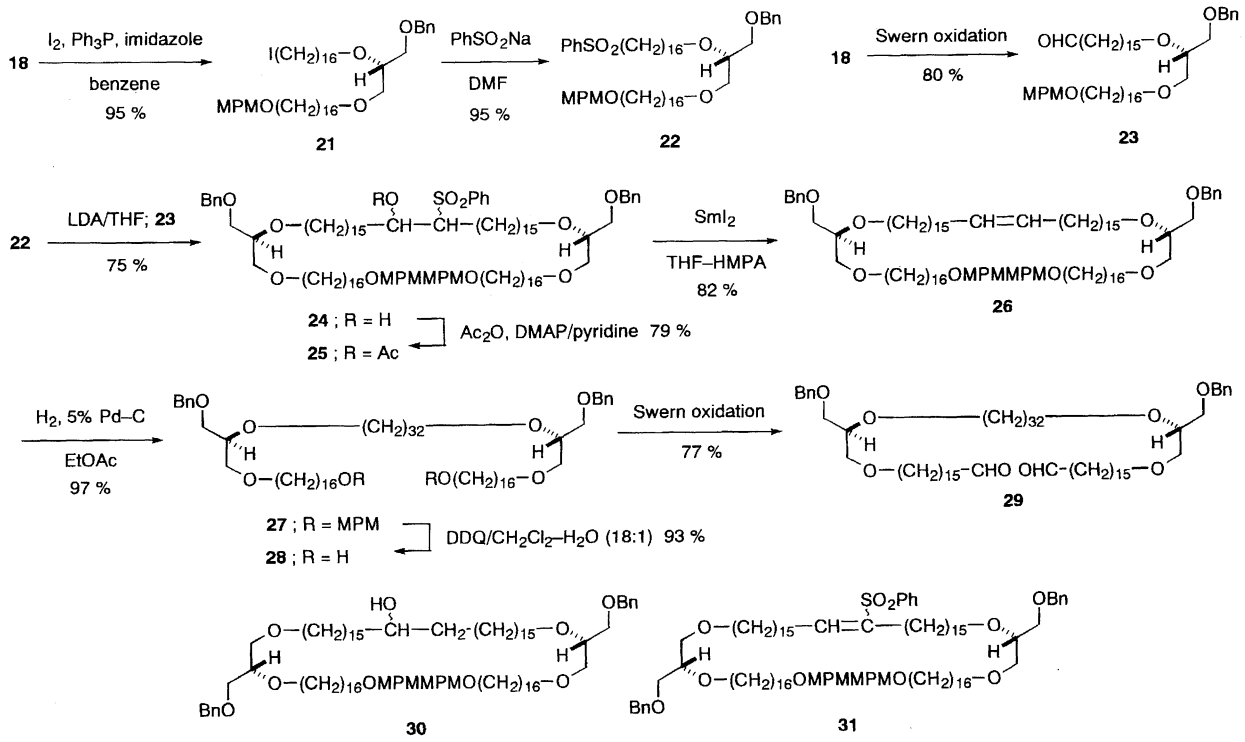
The half-sized diether lipid **18** was converted into two appropriate coupling precursors, the sulfone **22** and the aldehyde **23**, which were then coupled together by Julia coupling to lead to a precursor of McMurry coupling.

As shown in Eq. 2 (Scheme 2), the compound **18** was treated with $I_2$–$Ph_3P$–imidazole in benzene to give iodide **21** in 95% yield. The iodide **21** was reacted with $PhSO_2Na$ in DMF to afford sulfone **22** in 95% yield. The other coupling partner of Julia method, aldehyde **23**, was prepared from **18** under Swern oxidation in 80% yield.

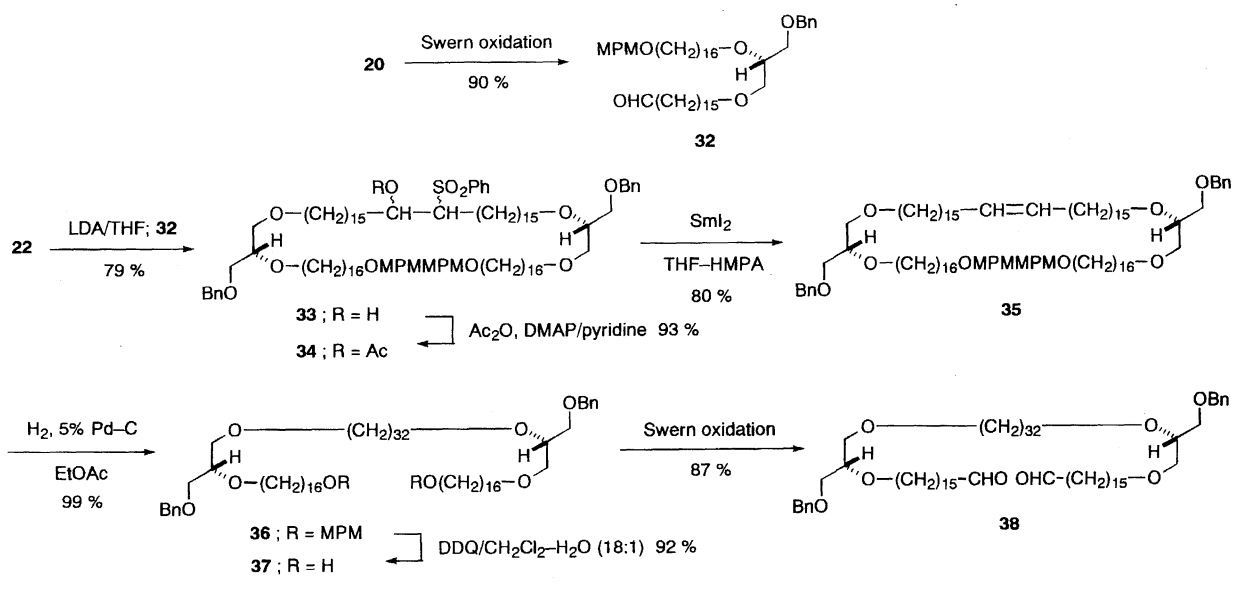
In a preliminary experiment, we used the iodide **21** and the sulfone **22** for the coupling reaction according to our previous synthesis of the 36-membered archaeal macrocyclic lipid.[6b,6d] However, the sequential reactions of coupling and desulfonylation resulted in low yield (27% in two steps). Therefore, we switched to using the aldehyde **23** for the coupling reaction. Thus, lithium carbanion prepared from the sulfone **22** with lithium diisopropylamide was treated with the aldehyde **23** in THF at −20 °C to successfully furnish $\beta$-hydroxy sulfone **24** in 79% yield. After acetylation of **24**, a reductive elimination reaction was carried out with Na–Hg according to the original Julia's method[7] with little success (the yield was less than 50%). Under these conditions, alcohol **30** and vinyl sulfone **31** were generated as by-products in 10—25% yields. Since Fukumoto et al. recently reported a devised method of reductive elimination of $\beta$-acetoxy sul-




Scheme 1.



Scheme 2.

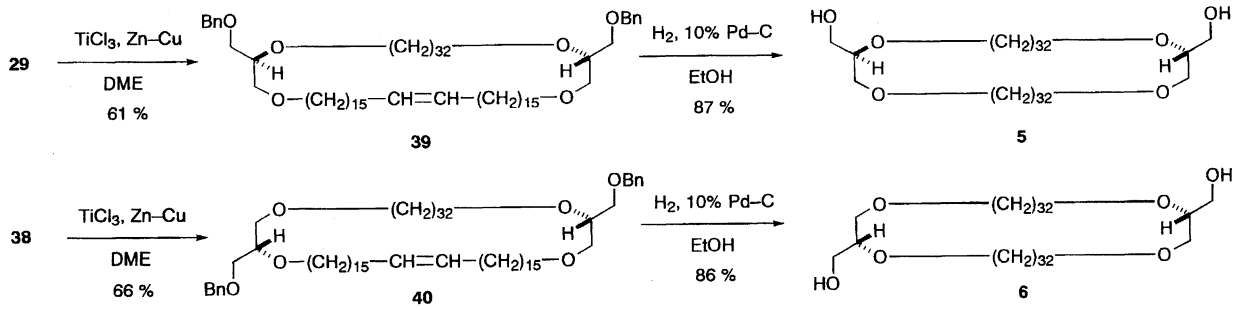


Scheme 3.

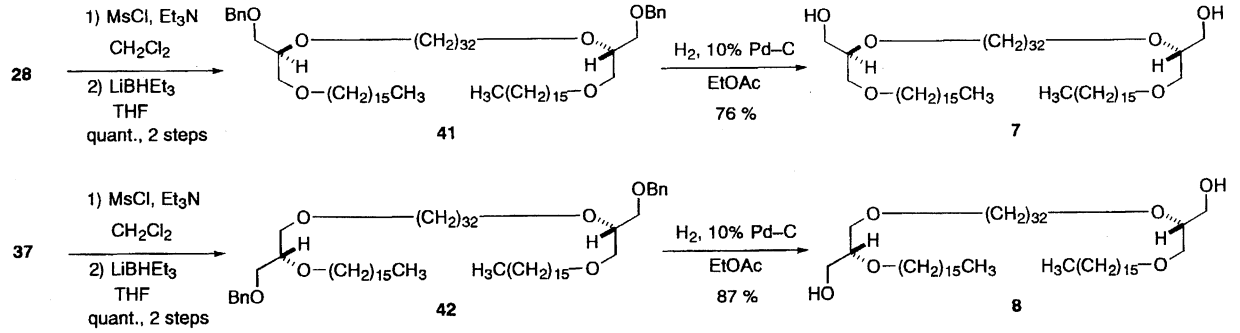
fone with $SmI_2$,[10] we applied this procedure to the reductive elimination reaction of **25**. Reaction of **25** with 4.5 molar amounts of $SmI_2$ smoothly proceeded to give olefins **26** in an excellent yield (82%) as a mixture of the geometrical isomers. The isomeric ratio was estimated as ca. 2—3 : 1 (*trans*/*cis*) from the chemical shifts and intensities of $^{13}C$ NMR signals. The double bond of the olefin **26** was hydrogenated on Pd–C to give **27** in an excellent yield. Deprotection of the MPM group with DDQ in $CH_2Cl_2$–$H_2O$ was performed to afford diol **28** in 93% yield. Precursory dialdehyde for McMurry coupling **29** was then prepared from diol **28** by subsequent oxidation under Swern conditions in 77% yield.

As also shown in Eq. 3 (Scheme 3), the other half-sized diether lipid **20** was converted into the aldehyde **32**, and then the same series of reactions involving Julia coupling between the sulfone **22** and the aldehyde **32**, the reductive elimination with $SmI_2$, hydrogenation, deprotection of MPM groups, and Swern oxidation gave the additional precursor **38** for McMurry coupling.

The crucial 72-membered ring formation reaction was performed with these dialdehydes with the aid of a low-valent titanium coupling known as McMurry coupling. Intramolecular coupling of the dialdehyde **29** was carried out under high dilution conditions for a prolonged time. The reaction pro-




Scheme 4.




Scheme 5.

ceeded quite smoothly to yield macrocyclic tetraether compound **39** as a geometric mixture (ca. 4 : 1) of the double-bond in 61% yield. Usually, the yield of this coupling reaction ranged from 50—65%. The EI-MS spectrum of the coupling product showed the following relevant ion peaks: *m/z* 1255 ($M^+$) and 1164 ($M^+$−benzyl). These results supported the 72-membered structure of **39**. The major product of **39** was assigned to be *E*-isomer from $^{13}C$ NMR signals of the olefinic carbons [$\delta$ = 130.35 (major), 129.89 (minor)] and the allylic carbons [$\delta$ = 32.58 (major), 27.16 (minor)]. This finding was quite similar to the case of the formation of 36-membered desmethylated compound.[6a] Finally, deprotection of the benzyl group and reduction of the double bond of **39** were performed simultaneously by catalytic hydrogenation over Pd–C in refluxing ethanol to afford the 72-membered tetraether core lipid **5** in 87% yield as shown in Eq. 4 (Scheme 4). The EI-MS spectrum of the product; *m/z* 1077 ($M^+$), 1059 ($M^+-H_2O$) firmly supported the structure of **5**.

The positional isomer **38** was also applied to the McMurry coupling to afford the macrocyclic compound **40** in 66% yield by the same method. The geometric ratio of **40** was same to that of **39**. The regioisomeric 72-membered core lipid **6** was obtained from **40** by catalytic hydrogenation in 86% yield.

We were thus successful in synthesizing the archaeal 72-membered lipid model by the McMurry coupling. For detailed investigations of this 72-membered lipid, it is necessary to compare the macrocyclic lipids with non-cyclized counterparts **7** and **8**. Therefore, we here prepared **7** and **8**, as shown in Eq. 5 (Scheme 5). The intermediates **28** and **37** were appropriate precursors for syntheses of **7** and **8**. The diol **28** was treated with methanesulfonyl chloride, followed by reduction with Superhydride® to afford acyclic tetraether **41** in an excellent yield. The tetraether **41** was subjected to catalytic hydrogenation in the presence of Pd–C to give the acyclic tetraether core lipid **7** in 76% yield. The other diol **37** was also transformed into the acyclic tetraether core lipid **8** similarly.

In summary, we have accomplished the synthesis of 72-membered macrocyclic tetraether model lipids using McMurry coupling. This methodology is applicable to the natural 72-membered tetraether lipids, such application is currently underway in our laboratory. The phosphorylation of their tetraether model lipids and their characterization are currently in progress and will be reported in due course.

## Experimental

Melting points were measured with a Yanagimoto BY-1 melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi 285 infrared spectrometer and/or a Horiba FT-710 fourier transform infrared spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on JEOL EX-270, LA-300, and/or LA-400 spectrometers. Deuteriochloroform (99.8 atom% enriched, Merck) was used for the NMR solvent. $^1H$ NMR and $^{13}C$ NMR chemical shifts were reported in $\delta$ value based on internal TMS ($\delta_H$ = 0), or solvent signal ($CDCl_3$ $\delta_C$ = 77.0) as reference. Mass spectra were obtained by using a JEOL AX-505HA mass spectrometer. Column chromatography was carried out with a Kieselgel 60 (70—230 mesh or 230—400 mesh, Merck). All reactions, except for catalytic hydrogenation reactions, were carried out in an inert (Ar or $N_2$) atmosphere. THF and DME were distilled from sodium/benzophenone ketyl prior to use. Pyridine and triethylamine were distilled from potassium hydroxide. DMF was distilled from $CaSO_4$, and benzene, DMSO, $CH_2Cl_2$, HMPA, and toluene were distilled from calcium hydride.

**16-(4-Methoxybenzyloxy)-1-hexadecanol (10).** Pre-washed

NaH (11 g containing oil, 275 mmol) was added to a solution of 16-(2-tetrahydropyranyl)oxy-1-hexadecanol (**9**) (61.7 g, 180 mmol) in THF (200 ml). After the mixture was stirred at room temperature for 1 h, HMPA (50 ml) and 4-methoxybenzyl chloride (37 ml, 271 mmol) were added, and stirring was continued for 62 h at 40 °C. Water was added and the mixture was extracted with hexane. The organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. A mixture of the residual wax and 2 M HCl (50 ml, 1 M = 1 mol dm$^{-3}$) in THF (230 ml) and methanol (200 ml) was stirred at room temperature for 12 h. The mixture was concentrated in vacuo, and saturated $NaHCO_3$ and EtOAc were added. The organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was recrystallized from hexane to give alcohol (**10**) as a colorless powder (51.3 g, 75%). Mp 65—66 °C; $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 24H), 1.57 (m, 4H), 3.43 (t, $J$ = 6.6 Hz, 2H), 3.64 (t, $J$ = 6.6 Hz, 2H), 3.81 (s, 3H), 4.43 (s, 2H), 6.88 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.27 (dt, $J$ = 8.8, 2.2 Hz, 2H); $^{13}$C NMR (75 MHz) $\delta$ = 25.71, 26.18, 29.41, 29.48, 29.59, 29.61, 29.63, 29.74, 32.77, 55.25, 63.07, 70.21, 72.47, 113.68, 129.22, 130.73, 159.01; IR ($CHCl_3$) 1039, 1223, 1462, 2852, 2935, 3455 cm$^{-1}$. Found: C, 76.33; H, 11.37%. Calcd for $C_{24}H_{42}O_3$: C, 76.16; H, 11.18%.

**16-(4-Methoxybenzyloxy)hexadecanal (11).** To a stirred solution of oxalyl chloride (7.0 ml, 81.6 mmol) in $CH_2Cl_2$ (100 ml) was slowly added DMSO (8.0 ml, 112 mmol) at −78 °C. The mixture was stirred with a mechanical stirrer for 10 min and was warmed to −20 °C. A solution of alcohol (**10**) (10 g, 25.8 mmol) in $CH_2Cl_2$ (100 ml) was added dropwise over 7 min. The mixture was stirred for 30 min, then cooled to −30 °C, and $Et_3N$ (18 ml, 130 mmol) was added. The mixture was warmed gradually to 0 °C, and saturated $NH_4Cl$ was added. The mixture was extracted three times with $CHCl_3$. The organic phase was washed with saturated $NaHCO_3$, and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (19 : 1 to 9 : 1) to give aldehyde (**11**) (8.0 g, 80%) as a white solid. Mp 51—52 °C; $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 22H), 1.60 (m, 4H), 2.42 (dt, $J$ = 2.0, 7.3 Hz, 2H), 3.43 (t, $J$ = 6.6 Hz, 2H), 3.80 (s, 3H), 4.29 (s, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.27 (dt, $J$ = 8.8, 2.2 Hz, 2H), 9.76 (t, $J$ = 2.0 Hz, 1H); $^{13}$C NMR (75 MHz) $\delta$ = 22.06, 26.18, 29.14, 29.33, 29.40, 29.47, 29.55, 28.58, 29.50, 29.62, 29.75, 43.90, 55.24, 70.21, 72.47, 113.69, 129.29, 130.77, 159.04, 202.98; IR ($CHCl_3$) 1039, 1223, 1462, 1725, 2852, 2935 cm$^{-1}$. Found: C, 76.39; H, 10.90%. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71%.

**(4*R*)-4-Benzyloxymethyl-2-[15-(4-methoxybenzyloxy)pentadecanyl]-1,3-dioxolane (13).** A mixture of aldehyde (**11**) (2.84 g 7.54 mmol), 1-*O*-benzyl-*sn*-glycerol (**12**) (1.58 g 8.65 mmol), *p*-toluenesulfonic acid (89 mg 0.536 mmol), and $MgSO_4$ (1.20 g 9.93 mmol) in $CH_2Cl_2$ (80 ml) was stirred at room temperature for 18 h. Saturated $NaHCO_3$ and EtOAc were added and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (10 : 1 to 2 : 1) to give acetal (**13**) as a diastereoisomeric mixture (ca. 3 : 1, 97%). $^1$H NMR (400 MHz) $\delta$ = 1.24 (br, 24H), 1.56—1.69 (m, 4H), 3.41—3.61 (m, 4H), 3.64 (dd, $J$ = 7.1, 8.3 Hz, 0.25H), 3.78 (dd, $J$ = 5.1, 8.0 Hz, 0.75H), 3.80 (s, 3H), 3.90 (dd, $J$ = 7.1, 8.0 Hz, 0.75H), 4.12 (dd, $J$ = 6.6, 8.3 Hz, 0.25H), 4.21—4.31 (m, 1H), 4.43 (s, 2H), 4.54—4.61 (m, 2H), 4.88 (t, $J$ = 4.8 Hz, 0.75H), 4.97 (t, $J$ = 4.9 Hz, 0.25H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.24—7.35 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ = 23.95, 23.97, 26.19, 29.48, 29.53, 29.60, 29.65, 29.75, 33.95, 33.99, 55.24, 67.43, 67.51, 70.22, 70.45, 71.02, 72.47, 73.46, 74.50, 74.74, 104.69, 105.15, 113.70, 127.68, 127.72, 127.74, 128.39, 129.19, 130.79, 137.91, 159.05; IR ($CHCl_3$) 1038, 1095, 1140, 1243, 1508, 2850, 2925 cm$^{-1}$. Found: C, 75.32; H, 9.65%. Calcd for $C_{34}H_{52}O_5$: C, 75.52; H, 9.69%;.

**1-*O*-Benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol (14) and 1-*O*-Benzyl-2-*O*-[16-(4-methoxybenzyloxy)-hexadecanyl]-*sn*-glycerol (15).** A solution of DIBAL-H (1 M in toluene, 6.2 ml, 6.2 mmol) was added to a solution of acetal (**13**) (1.12 g, 2.07 mmol) in toluene (20 ml) at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture was quenched by addition of saturated $NH_4Cl$ and the mixture was stirred for 10 min. Ether and 2 M HCl were added. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (10 : 1 to 5 : 1) to give a less polar product (**14**) (479 mg, 43%) and a more polar product (**15**) (665 mg, 59%), **14**: Mp 36—37 °C. $[\alpha]_D^{30}$ −1.31° (*c* 1.22, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 24H), 1.57 (m, 4H), 2.59 (d, $J$ = 3.4 Hz, 1H), 3.41—3.57 (m, 8H), 3.79 (s, 3H), 3.98 (m, 1H), 4.42 (s, 2H), 4.55 (s, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.24—7.37 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ = 26.03, 26.14, 29.42, 29.44, 29.56, 29.62, 29.71, 55.18, 69.46, 70.16, 71.33, 71.62, 71.72, 72.42, 73.36, 113.65, 127.65, 128.35, 129.14, 130.73, 137.96, 159.00; IR ($CHCl_3$) 1042, 1100, 1255, 1520, 1740, 2852, 2935, 3020, 3590 cm$^{-1}$. Found: C, 75.35; H, 10.18%. Calcd for $C_{34}H_{54}O_5$: C, 75.24; H, 10.03%.

**15:** Mp 37 °C. $[\alpha]_D^{30}$ −7.35° (*c* 0.893, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 24H), 1.59 (m, 4H), 2.15 (t, $J$ = 6.0 Hz, 1H), 3.41—3.76 (m, 9H), 3.80 (s, 3H), 4.43 (s, 2H), 4.54 (s, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.24—7.35 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ = 26.06, 26.17, 29.44, 29.46, 29.58, 29.64, 29.73, 30.03, 55.21, 62.82, 69.94, 70.19, 70.39, 72.45, 73.46, 78.40, 113.67, 127.59, 127.66, 128.37, 129.17, 130.75, 137.97, 159.02; IR ($CHCl_3$) 1042, 1100, 1255, 1520, 1740, 2852, 2935, 3020, 3590 cm$^{-1}$. Found: C, 74.96; H, 9.90%. Calcd for $C_{34}H_{54}O_5$: C, 75.24; H, 10.03%.

**1-*O*-Benzyl-2-*O*-[16-(2-tetrahydropyranyloxy)hexadecanyl]-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol (17).** Methanesulfonyl chloride (5.2 ml, 66 mmol) was added to a mixture of THP ether (**9**) (13 g, 37.7 mmol) and $Et_3N$ (26 ml, 188 mmol) in $CH_2Cl_2$ (140 ml) at 0 °C, and the mixture was stirred for 30 min at room temperature. Ether and 1 M HCl were added and the organic phase was separated. The aqueous phase was extracted with ether. The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel (600 g) with hexane–EtOAc (10 : 1 to 7 : 1) to give mesylate (**16**) (15.4 g, 97%). A solution of mesylate (**16**) (1.82 g, 4.33 mmol) in DMSO (16 ml) was added to an alkoxide solution, which had been prepared separately by adding a solution of glycerol derivative (**14**) (1.77 g, 3.26 mmol) in DMSO (17 ml) to prewashed NaH (378 mg containing oil, 9.50 mmol) and stirring at room temperature for 30 min. The mixture was stirred at room temperature for 12 h. Saturated $NH_4Cl$ was added and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (10 : 1 to 7 : 1) to yield diether (**17**) (3.29 g, 97%) as a wax. $[\alpha]_D^{26}$ +0.11° (*c* 0.997, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 48H), 1.49—1.87 (m, 14H), 3.38 (dt, $J$ = 9.5, 6.6 Hz, 1H), 3.41—3.62 (m, 12H), 3.73 (dt, $J$ = 9.5, 7.1 Hz, 1H), 3.79 (s, 3H), 3.87 (m, 1H), 4.42 (s, 2H), 4.55 (s, 2H), 4.58 (m, 1H), 6.87 (dt, $J$ = 8.5, 2.0 Hz, 2H), 7.24—7.34 (m, 7H); $^{13}$C NMR (100 MHz)

$\delta$ = 19.64, 25.45, 26.05, 26.07, 26.16, 26.19, 29.45, 29.56, 29.58, 29.60, 29.64, 29.71, 29.72, 30.04, 30.73, 55.17, 62.24, 67.62, 70.16, 70.22, 70.54, 70.65, 71.59, 72.43, 73.28, 77.84, 98.75, 113.65, 127.42, 127.50, 128.23, 129.13, 130.74, 138.38, 159.00; IR (neat) 1040, 1100, 1250, 1470, 2855, 2940 $cm^{-1}$. Found: C, 76.38; H, 10.90%. Calcd for $C_{55}H_{94}O_7$: C, 76.16; H, 10.92%.

**1-*O*-Benzyl-2-*O*-(16-hydroxyhexadecanyl)-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol (18).** A mixture of diether (**17**) (9.94 g, 11.5 mmol), 2 M HCl (12 ml) in THF (85 ml) and methanol (42 ml) was stirred at room temperature for 11 h. The mixture was concentrated in vacuo, and then saturated aqueous $NaHCO_3$ and EtOAc were added. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was purified by flash-chromatography over silica gel with hexane–EtOAc (7 : 1 to 4 : 1) to give alcohol (**18**) (8.32 g, 93%) as a wax. $[\alpha]_D^{27}$ −0.16° (*c* 0.853, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 48H), 1.51—1.62 (m, 8H), 3.41—3.62 (m, 13H), 3.79 (s, 3H), 4.42 (s, 2H), 4.55 (s, 2H), 6.87 (dt, *J* = 8.5, 1.9 Hz, 2H), 7.24—7.33 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ = 25.69, 26.03, 26.05, 26.13, 29.38, 29.44, 29.58, 29.60, 29.63, 29.69, 30.02, 32.72, 55.15, 62.86, 70.14, 70.18, 70.53, 70.62, 71.57, 72.41, 73.26, 77.82, 113.63, 127.42, 127.49, 128.22, 129.13, 130.68, 138.33, 158.98; IR ($CHCl_3$) 1038, 1100, 1248, 1469, 1516, 1615, 2852, 2940, 3360 $cm^{-1}$. Found: C, 76.54; H, 11.14%. Calcd for $C_{50}H_{86}O_6$: C, 76.68; H, 11.07%.

**1-*O*-Benzyl-2-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-3-*O*-[16-(2-tetrahydropyranyl)oxyhexadecanyl]-*sn*-glycerol (19).** A glycerol derivative (**15**) (2.13 g, 3.93 mmol) was treated with mesylate (**16**) (2.23 g, 5.30 mmol) in the same manner as described for the preparation of diether (**17**) to give diether (**19**) (3.29 g, 97%) as a wax. $[\alpha]_D^{27}$ −0.04° (*c* 0.953, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 48H), 1.52—1.87 (m, 14H), 3.38 (dt, *J* = 9.5, 6.6 Hz, 1H), 3.41—3.62 (m, 12H), 3.73 (dt, *J* = 9.5, 6.8 Hz, 1H), 3.80 (s, 3H), 3.87 (m, 1H), 4.43 (s, 2H), 4.55 (s, 2H), 4.57 (m, 1H), 6.87 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.24—7.34 (m, 7H); $^{13}$C NMR (75 MHz) $\delta$ = 19.69, 25.48, 26.10, 26.20, 26.23, 29.50, 29.65, 29.69, 30.08, 30.77, 55.22, 62.33, 67.69, 70.22, 70.59, 70.67, 71.65, 72.48, 73.32, 77.86, 98.80, 113.69, 127.48, 127.57, 128.29, 129.20, 130.77, 138.41, 159.04; IR ($CHCl_3$) 1038, 1100, 1248, 1459, 2852, 2935 $cm^{-1}$. Found: C, 76.21; H, 11.21%. Calcd for $C_{55}H_{94}O_7$: C, 76.16; H, 10.92%.

**1-*O*-Benzyl-2-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-3-*O*-(16-hydroxyhexadecanyl)-*sn*-glycerol (20).** Diether (**19**) (1.61 g, 1.85 mmol) was treated in the same manner as described for the preparation of alcohol (**18**) to give alcohol (**20**) (1.45 g, 98%) as a wax. $[\alpha]_D^{27}$ −0.13° (*c* 0.843, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 48H), 1.50—1.64 (m, 8H), 3.41—3.65 (m, 13H), 3.80 (s, 3H), 4.43 (s, 2H), 4.55 (s, 2H), 6.88 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.25—7.34 (m, 7H); $^{13}$C NMR (75 MHz) $\delta$ = 25.71, 26.08, 26.16, 29.42, 29.48, 29.63, 30.05, 32.77, 55.24, 63.01, 70.20, 70.58, 70.65, 71.62, 72.45, 73.30, 77.84, 113.67, 127.47, 127.55, 128.27, 129.20, 130.73, 138.37, 159.01; IR ($CHCl_3$) 1038, 1100, 1248, 1469, 1516, 1615, 2852, 2940, 3360 $cm^{-1}$. Found: C, 76.38; H, 11.04%. Calcd for $C_{50}H_{86}O_6$: C, 76.68; H, 11.07%.

**1-*O*-Benzyl-2-*O*-(16-iodohexadecanyl)-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol (21).** A mixture of alcohol (**18**) (3.86 g, 4.93 mmol), imidazole (839 mg, 12.3 mmol), triphenylphosphine (3.26 g, 12.4 mmol), and $I_2$ (2.51 g, 9.89 mmol) in benzene (60 ml) was stirred at room temperature for 40 min. Saturated $Na_2S_2O_3$ was added and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was purified by chromatography over silica gel with benzene–EtOAc (50 : 1) to give iodide (**21**) (4.16 g, 95%) as a wax. $[\alpha]_D^{27}$ +0.02° (*c* 1.42, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 48H), 1.50—1.64 (m, 6H), 1.81 (q, *J* = 7.1 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 3.39—3.62 (m, 11H), 3.80 (s, 3H), 4.43 (s, 2H), 4.56 (s, 2H), 6.88 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.24—7.36 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ = 7.27, 26.03, 26.14, 28.48, 29.36, 29.43, 29.49, 29.58, 29.71, 30.02, 30.44, 33.49, 55.16, 70.14, 70.18, 70.53, 70.62, 71.57, 72.41, 73.25, 77.82, 113.63, 127.42, 127.49, 128.23, 129.12, 130.69, 138.34, 158.97; IR (neat) 1100, 1248, 1460, 1516, 1615, 2848, 2920 $cm^{-1}$. Found: C, 67.44; H, 9.70%. Calcd for $C_{50}H_{85}IO_5$: C, 67.24; H, 9.59%.

**1-*O*-Benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-2-*O*-(16-phenylsufonylhexadecanyl)-*sn*-glycerol (22).** A mixture of iodide (**21**) (4.03 g, 4.51 mmol) and sodium benzenesulfinate dihydrate (4.48 g, 22.4 mmol) in DMF (33 ml) was stirred at room temperature for 12 h. EtOAc and water were added and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with water and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (7 : 1 to 4 : 1) to give phenylsulfone (**22**) (3.90 g, 95%) as a white solid. Mp 42—43 °C; $[\alpha]_D^{27}$ +0.02° (*c* 0.963, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 48H), 1.52—1.63 (m, 6H), 1.66—1.74 (m, 2H), 3.07 (m, 2H), 3.41—3.62 (m, 11H), 3.80 (s, 3H), 4.43 (s, 2H), 4.55 (s, 2H), 6.87 (dt, *J* = 8.8, 2.2, 2H), 7.25—7.34 (m, 7H), 7.54—7.59 (m, 2H), 7.63—7.67 (m, 1H), 7.90—7.93 (m, 2H); $^{13}$C NMR (100 MHz) $\delta$ = 22.59, 26.07, 26.09, 26.17, 28.23, 28.96, 29.20, 29.44, 29.48, 29.54, 29.61, 29.64, 29.67, 29.74, 30.062, 55.22, 56.28, 70.20, 70.24, 70.57, 70.66, 71.62, 72.46, 73.30, 77.86, 113.68, 127.46, 127.53, 128.01, 128.27, 129.17, 129.20, 130.76, 133.55, 138.40, 139.18, 159.02; IR (neat) 1095, 1155, 1255, 1304, 1473, 1517, 1516, 1620, 2860, 2940 $cm^{-1}$. Found: C, 74.33; H, 10.29%. Calcd for $C_{56}H_{90}O_7S$: C, 74.13; H, 10.00%.

**1-*O*-Benzyl-2-*O*-(15-formylpentadecany)-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol (23).** To a stirred solution of oxalyl chloride (6.3 ml, 73.5 mmol) in $CH_2Cl_2$ (150 ml) was slowly added DMSO (7.3 ml, 100 mmol) at −70 °C. The mixture was stirred with a mechanical stirrer for 15 min and warmed to −20 °C. A solution of alcohol (**18**) (10.6 g, 13.5 mmol) in $CH_2Cl_2$ (100 ml) was added dropwise over the period of 15 min. The mixture was stirred for 1 h and cooled to −56 °C, and then $Et_3N$ (15 ml, 108 mmol) was added. The mixture was gradually warmed to 0 °C, and saturated $NH_4Cl$ was added. EtOAc was added and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (9 : 1 to 7 : 1) to give aldehyde (**23**) (8.47 g, 80%) as a wax. $[\alpha]_D^{29}$ +0.16° (*c* 0.833, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 46H), 1.50—1.67 (m, 8H), 2.42 (dt, *J* = 1.7, 7.3 Hz, 2H), 3.40—3.64 (m, 11H), 3.80 (s, 3H), 4.43 (s, 2H), 4.55 (s, 2H), 6.87 (dt, *J* = 8.8, 2.2 Hz, 2H), 7.24—7.34 (m, 7H), 9.76 (t, *J* = 1.7 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ = 21.95, 25.83, 26.01, 26.10, 29.05, 29.18, 29.27, 29.34, 29.40, 29.54, 29.60, 29.98, 43.79, 55.09, 70.09, 70.47, 70.56, 71.53, 72.37, 73.21, 77.77, 113.58, 127.38, 127.46, 128.19, 129.08, 130.62, 138.28, 158.93, 202.82; IR (neat) 1105, 1250, 1473, 1509, 1740, 2855, 2935 $cm^{-1}$. Found: C, 77.13; H, 10.93%. Calcd for $C_{50}H_{84}O_6$: C, 76.87; H, 10.84%.

**2,2′-*O*-[(16-Hydroxy-17-phenylsulfonyl)-1,32-dotriacontanediyl]bis{1-*O*-benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol} (24).** To a stirred solution of diisopropylamine

(0.51 ml, 3.7 mmol) in THF (7 ml) was added butyllithium in hexane (1.52 M, 2.2 ml, 3.3 mmol) at −78 °C. The mixture was warmed to 0 °C and stirred for 2 h at the same temperature, and then recooled to −20 °C. A solution of sulfone (**22**) (1.94 g, 2.1 mmol) in THF (15 ml) was added. The mixture was warmed to 0 °C and stirred for 30 min at the same temperature, and then recooled to −20 °C, and a solution of aldehyde (**23**) (1.67 g, 2.13 mmol) in THF (13 ml) was added. The mixture was stirred for 10 min, gradually warmed to 0 °C, and saturated $NH_4Cl$ was added. The mixture was extracted twice with EtOAc. The combined organic phase was neutralized with saturated $NaHCO_3$, washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (7 : 1 to 5 : 1) to give $\beta$-hydroxy sulfone (**24**) (2.83 g, 79% as a diastereomeric mixture) as an oil. $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 96H), 1.50—1.69 (m, 14H), 1.84 (m, 2H), 2.89 (t, $J$ = 5.1 Hz, 1H), 3.08 (d, $J$ = 5.0 Hz, 0.5H) 3.41—3.63 (m, 22H), 3.80 (s, 6H), 4.12 (br, 1H), 4.43 (s, 4H), 4.56 (s, 4H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.24—7.35 (m, 14H), 7.59 (m, 2H), 7.68 (m, 1H), 7.91 (m, 2H); $^{13}$C NMR (75 MHz) $\delta$ = 22.39, 25.68, 25.71, 25.90, 25.97, 26.01, 26.03, 26.11, 27.38, 28.98, 29.03, 29.05, 29.14, 29.29, 29.34, 29.37, 29.42, 29.44, 29.48, 29.55, 29.57, 29.60, 29.62, 29.67, 30.00, 33.91, 34.06, 55.13, 68.26, 68.61, 69.24, 69.94, 70.08, 70.11, 70.49, 70.54, 71.55, 72.39, 73.22, 77.75, 113.58, 127.40, 127.48, 127.95, 128.21, 128.46, 128.48, 129.08, 129.13, 129.21, 130.62, 133.67, 133.83, 137.91, 138.28, 138.76, 158.93; IR ($CHCl_3$) 1100, 1150, 1250, 1360, 1463, 1508, 2850, 2925, 3530 cm$^{-1}$. Found: C, 75.62; H, 10.57%. Calcd for $C_{106}H_{174}O_{13}S$: C, 75.40; H, 10.39%.

**2,2′-*O*-[1,32-(16-Acetoxy-17-phenylsulfonyl)dotriacontanediyl]bis{1-*O*-benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol} (25).** A mixture of $\beta$-hydroxy sulfone (**24**) (2.47 g, 1.46 mmol), acetic anhydride (0.6 ml, 6.36 ml), and a small crystal of DMAP in pyridine was stirred overnight. EtOAc and 2 M HCl were added and the organic phase was separated. The organic phase was successively washed with 2 M HCl, saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (7 : 1 to 5 : 1) to give $\beta$-acetoxy sulfone (**25**) (2.03 g, 79% as a diastereomeric mixture) as an oil. $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 96H), 1.51—1.62 (m, 14H), 1.65—2.09 (m, 2H), 1.80 (s, 1.5H), 1.90 (s, 1.5H), 3.07 (dt, $J$ = 1.7, 5.8 Hz, 0.5H), 3.32 (ddd, $J$ = 2.7, 5.1, 10.5 Hz, 0.5H), 3.40—3.61 (m, 22H), 3.80 (s, 6H), 4.42 (s, 4H), 4.55 (s, 4H), 5.09 (dt, $J$ = 3.0, 10.5 Hz, 0.5H), 5.29 (ddd, $J$ = 1.7, 5.6, 6.8 Hz, 0.5 H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.23—7.35 (m, 14H), 7.53—7.67 (m, 3H), 7.87—7.93 (m, 2H); $^{13}$C NMR (100 MHz) $\delta$ = 20.71, 20.75, 23.98, 25.56, 25.81, 26.05, 26.06, 26.14, 27.58, 28.68, 28.95, 29.13, 29.18, 29.23, 29.26, 29.32, 29.45, 29.50, 29.56, 29.60, 29.63, 29.71, 30.04, 32.23, 55.17, 65.89, 66.61, 70.16, 70.21, 70.34, 70.53, 70.62, 71.53, 71.58, 72.42, 73.27, 77.83, 113.64, 127.42, 127.50, 128.23, 128.58, 128.92, 129.01 129.13, 130.73, 133.52, 133.63, 138.37, 138.59, 139.16, 158.99, 169.95, 170.12; IR ($CHCl_3$) 1100, 1158, 1250, 1370, 1463, 1508, 1748, 2850, 2925 cm$^{-1}$. Found: C, 74.69; H, 10.24%. Calcd for $C_{108}H_{176}O_{14}S$: C, 74.95; H, 10.25%.

**2,2′-*O*-(Dotriacont-16-ene-1,32-diyl)bis{1-*O*-benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol} (26).** To a stirred solution of $SmI_2$ in THF (0.1 M, 440 ml, 44 mmol) was slowly added HMPA (22 ml, 126 mmol) at room temperature. After 45 min, a solution of $\beta$-acetoxysulfone (**25**) (17.0 g, 9.80 mmol) in THF (105 ml) was added and the mixture was stirred for 1 h. After dilution with ether, the mixture was washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (9 : 1 to 4 : 1) to afford alkene (**26**) (12.3 g, 82%, $E$ : $Z$ = ca. 2.5 : 1) as a wax. $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 96H), 1.52—1.63 (m, 12H), 1.94—2.03 (m, 4H), 3.41—3.63 (m, 22H), 3.80 (s, 6H), 4.43 (s, 4H), 4.55 (s, 4H), 5.33—5.39 (m, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.23—7.33 (m, 14H); $^{13}$C NMR (100 MHz) $\delta$ = 26.09, 26.11, 26.19, 27.20 (*Z*), 29.19, 29.32, 29.49, 29.54, 29.58, 29.64, 29.66, 29.69, 29.76, 30.08, 32.61 (*E*), 55.23, 70.21, 70.25, 70.59, 70.68, 71.64, 72.47, 73.32, 77.88, 113.69, 127.47, 127.55, 128.28, 129.18, 129.86 (*Z*), 130.32 (*E*), 130.78, 138.42, 159.04; IR (neat) 975, 1105, 1250, 1460, 1515, 1608, 2850, 2910 cm$^{-1}$. Found: C, 78.54; H, 11.36%. Calcd for $C_{100}H_{168}O_{10}$: C, 78.48; H, 11.06%.

**2,2′-*O*-(1,32-Dotriacontanediyl)bis{1-*O*-benzyl-3-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-*sn*-glycerol} (27).** A mixture of alkene (**26**) (819 mg, 0.534 mmol) and 5% Pd–C (77 mg) in EtOAc (40 ml) was stirred under $H_2$ at room temperature for 2.5 h. The mixture was filtered through a Celite pad and concentrated to dryness to give (**27**) (793 mg, 97%) as a wax. $[\alpha]_D^{29}$ +0.26° (*c* 0.1.30, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 104H), 1.51—1.63 (m, 12H), 3.41—3.62 (m, 22H), 3.80 (s, 6H), 4.43 (s, 4H), 4.55 (s, 4H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.25—7.34 (m, 14H); $^{13}$C NMR (100 MHz) $\delta$ = 26.09, 26.11, 26.19, 29.50, 29.65, 29.69, 29.72, 29.76, 30.09, 55.24, 70.23, 70.26, 70.60, 70.69, 71.64, 72.48, 73.33, 77.88, 113.70, 127.47, 127.56, 128.28, 129.19, 130.79, 138.42, 159.04; IR ($CHCl_3$) 1100, 1252, 1465, 1509, 1608, 2855, 2935 cm$^{-1}$. Found: C, 78.08; H, 11.28%. Calcd for $C_{100}H_{170}O_{10}$: C, 78.38; H, 11.18%.

**2,2′-*O*-(1,32-Dotriacontanediyl)bis{[1-*O*-benzyl-3-*O*-(16-hydroxyhexadecanyl)]-*sn*-glycerol} (28).** To a stirred solution of di-MPM ether (**27**) (17.6 g, 11.5 mmol) in $CH_2Cl_2$ (135 ml) and $H_2O$ (7.5 ml) at room temperature was added 2,3-dichloro-5,6-dicyanobenzoquinone (8.5 g, 35.9 mmol), this mixture was stirred for 50 min. Saturated $NaHCO_3$ and $CHCl_3$ were added, the organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with $CHCl_3$–EtOAc (9 : 1) to afford diol (**28**) (13.7 g, 93%), which was recrystallized from EtOAc to give a colorless powder. Mp 64—65 °C; $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 104H), 1.51—1.57 (m, 12H), 3.41—3.64 (m, 22H), 4.55 (s, 4H), 7.26—7.34 (m, 10H); $^{13}$C NMR (100 MHz) $\delta$ = 25.71, 26.08, 29.41, 29.48, 29.64, 29.69, 30.06, 32.76, 62.99, 70.23, 70.58, 70.67, 71.62, 73.31, 77.86, 127.45, 127.54, 128.26, 138.38; IR ($CHCl_3$) 1103, 1468, 2858, 2940, 3620 cm$^{-1}$. Found: C, 77.84; H, 11.74%. Calcd for $C_{84}H_{154}O_8$: C, 78.08; H, 12.01%.

**2,2′-*O*-(1,32-Dotriacontanediyl)bis{1-*O*-benzyl-[3-*O*-(15-formylpentadecanyl)]-*sn*-glycerol} (29).** To a stirred solution of oxalyl chloride (3.20 ml, 37.3 mmol) in $CH_2Cl_2$ (60 ml) was slowly added DMSO (5.00 ml, 70.4 mmol) in $CH_2Cl_2$ (5 ml) at −78 °C. The mixture was stirred for 15 min and warmed to −20 °C. The diol (**28**) (6.02 g, 4.66 mmol) in $CH_2Cl_2$ (60 ml) was added dropwise over 15 min. The mixture was stirred at −15 °C for 25 min, and cooled to −30 °C, and then $Et_3N$ (10.0 ml, 71.7 mmol) was added. The mixture was warmed gradually to room temperature, and saturated $NH_4Cl$ was added. The mixture was extracted three times with EtOAc. The combined organic phase was washed with saturated $NaHCO_3$, and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was subjected to flash-chromatography over silica gel with hexane–EtOAc (20 : 1 to 7 : 1) to give dialdehyde (**29**) (4.60 g, 77%) as a solid. Mp 51—52 °C; $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 100H), 1.51—1.66 (m, 12H), 2.42 (dt, $J$ = 1.9, 7.3 Hz, 4H), 3.41—3.62 (m, 18H), 4.55 (s, 4H),

7.25—7.34 (m, 10H), 9.76 (t, $J$ = 1.9 Hz, 2H); $^{13}$C NMR (100 MHz) $\delta$ = 22.03, 26.05, 29.10, 29.32, 29.38, 29.47, 29.60, 29.67, 30.04, 43.86, 70.20, 70.54, 70.65, 71.59, 73.27, 77.84, 127.42, 127.51, 128.24, 138.38, 202.84; IR ($CHCl_3$) 1100, 1460, 1723, 2853, 2940 cm$^{-1}$. Found: C, 78.10; H, 11.70%. Calcd for $C_{84}H_{150}O_8$: C, 78.33; H, 11.74%.

**1-*O*-Benzyl-2-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]-3-*O*-(15-formylpentadecany)-*sn*-glycerol (32).** Alcohol (**20**) (2.44 g, 3.11 mmol) was treated in the same manner as described for the preparation of aldehyde (**23**) to give aldehyde (**32**) (2.15 g, 90%) as a wax. $[\alpha]_D^{30}$ +0.35° ($c$ 0.1.38, $CHCl_3$); $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 46H), 1.59—1.67 (m, 8H), 2.42 (dt, $J$ = 1.7, 7.3 Hz, 2H), 3.40—3.62 (m, 11H), 3.80 (s, 3H), 4.43 (s, 2H), 4.55 (s, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.23—7.35 (m, 7H), 9.76 (t, $J$ = 1.7 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ = 22.05, 26.09, 26.18, 29.14, 29.34, 29.42, 29.49, 29.62, 29.74, 30.07, 43.90, 55.22, 70.20, 70.58, 70.65, 71.62, 72.47, 73.31, 77.86, 113.67, 127.46, 127.55, 128.28, 129.18, 130.75, 138.39, 159.02, 202.95; IR ($CHCl_3$) 1100, 1245, 1460, 1509, 1722, 2853, 2935 cm$^{-1}$. Found: C, 76.75; H, 11.10%. Calcd for $C_{50}H_{84}O_6$: C, 76.87; H, 10.84%.

**2,3′-*O*-(16-Hydroxy-17-phenylsulfonyl-1,32-dotriacontanediyl)-2′,3-bis-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]bis(1-*O*-benzyl-*sn*-glycerol) (33).** Sulfone (**22**) (1.76 g, 1.94 mmol) was reacted with aldehyde (**32**) (1.57 g, 2.01 mmol) in the same manner as described for the preparation of $\beta$-hydroxy sulfone (**24**) to give $\beta$-hydroxysulfone (**33**) (2.41 g, 75% as a diastereomeric mixture) as an oil. $^1$H NMR (270 MHz) $\delta$ = 1.25 (br, 96H), 1.50—1.65 (m, 14H), 1.86 (m, 2H), 2.89 (t, $J$ = 5.1 Hz, 0.5H), 3.04—3.10 (m, 0.5H), 3.37—3.63 (m, 22H), 3.79 (s, 6H), 4.00—4.08 (m, 0.5H), 4.10—4.15 (m, 0.5H), 4.43 (s, 4H), 4.55 (s, 4H), 6.87 (dt, $J$ = 8.6, 2.0 Hz, 4H), 7.24—7.34 (m, 14H), 7.54—7.70 (m, 3H), 7.88—7.92 (m, 2H); $^{13}$C NMR (75 MHz) $\delta$ = 22.40, 25.71, 25.87, 26.01, 26.03, 26.12, 27.38, 28.99, 29.03, 29.05, 29.14, 29.29, 29.42, 29.55, 29.58, 29.63, 29.68, 30.00, 33.90, 34.07, 55.13, 68.22, 68.62, 69.24, 69.95, 70.08, 70.12, 70.49, 70.54, 71.55, 72.39, 73.22, 77.75, 113.58, 127.41, 127.48, 128.21, 128.47, 129.09, 129.14, 129.22, 130.62, 133.67, 133.83, 137.90, 138.28, 138.74, 158.92; IR ($CHCl_3$) 1100, 1150, 1250, 1363, 1463, 1508, 2850, 2925, 3530 cm$^{-1}$. Found: C, 75.68; H, 10.53%. Calcd for $C_{106}H_{174}O_{13}S$: C, 75.40; H, 10.39%.

**2,3′-*O*-(16-Acetoxy-17-phenylsulfonyldotriacontane-1,32-diyl)-2′,3-bis-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]bis(1-*O*-benzyl-*sn*-glycerol) (34).** $\beta$-Hydroxy sulfone (**33**) (2.01 g, 1.19 mmol) was treated in the same manner as described for the preparation of $\beta$-acetoxy sulfone (**25**) to give $\beta$-acetoxy sulfone (**34**) (1.94 g, 93%) as an oil. $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 96H), 1.50—2.09 (m, 16H), 1.81 (s, 1.5H), 1.91 (s, 1.5H), 3.07 (dt, $J$ = 1.7, 5.6, 0.5H), 3.33 (m, 0.5H), 3.40—3.63 (m, 22H), 3.80 (s, 6H), 4.43 (s, 4H), 4.56 (s, 4H), 5.1 (dt, $J$ = 5.0, 10.5 Hz, 0.5H), 5.29 (dt, $J$ = 1.9, 5.6 Hz, 0.5 H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.23—7.35 (m, 14H), 7.53—7.67 (m, 3H), 7.87—7.93 (m, 2H); $^{13}$C NMR (100 MHz) $\delta$ = 20.73, 23.97, 25.57, 25.81, 26.05, 26.14, 27.59, 28.68, 28.96, 29.14, 29.27, 29.32, 29.45, 29.60, 29.63, 29.71, 30.04, 32.23, 55.16, 65.88, 66.59, 70.16, 70.34, 70.53, 70.60, 71.59, 72.43, 73.27, 77.82, 113.63, 127.42, 127.51, 128.24, 128.59, 128.92, 129.01 129.14, 130.71, 133.55, 133.66, 138.37, 139.12, 158.99, 169.99, 170.14; IR ($CHCl_3$) 1100, 1158, 1249 1370, 1463, 1509, 1748, 2850, 2930 cm$^{-1}$. Found: C, 75.23; H, 10.43%. Calcd for $C_{108}H_{176}O_{14}S$: C, 74.95; H, 10.25%.

**2,3′-*O*-(1,32-Dotriacont-16-ene-diyl)-2′,3-bis-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]bis(1-*O*-benzyl-*sn*-glycerol) (35).** $\beta$-Acetoxy sulfone (**34**) (18.3 g, 10.6 mmol) was treated in the same manner as described for the preparation of alkene (**26**) to give alkene (**35**) (13.0 g, 80%, $E$ : $Z$ = ca. 2.5 : 1) as a wax. $^1$H NMR (300 MHz) $\delta$ = 1.25 (br), 1.52—1.62 (m, 12H), 1.96 (m, 4H), 3.40—3.61 (m, 22H), 3.80 (s, 6H), 4.43 (s, 4H), 4.55 (s, 4H), 5.33—5.39 (m, 2H), 6.87 (dt, $J$ = 8.8, 2.2 Hz, 4H), 7.25—7.33 (m, 14H); $^{13}$C NMR (100 MHz) $\delta$ = 26.07, 26.16, 27.15 ($Z$), 29.14, 29.27, 29.45, 29.51, 29.60, 29.65, 29.73, 30.04, 32.56 ($E$), 55.15, 70.14, 70.18, 70.53, 70.62, 71.57, 72.43, 73.25, 77.82, 113.63, 127.40, 127.49, 128.23, 129.12, 129.80 ($Z$), 130.27 ($E$), 130.71, 138.36, 158.99; IR (neat) 975, 1105, 1250, 1460, 1515, 1608, 2850, 2910 cm$^{-1}$. Found: C, 78.54; H, 11.36%. Calcd for $C_{100}H_{168}O_{10}$: C, 78.48; H, 11.06%.

**2,3′-*O*-(1,32-Dotriacontanediyl)-2′,3-bis-*O*-[16-(4-methoxybenzyloxy)hexadecanyl]bis(1-*O*-benzyl-*sn*-glycerol) (36).** Alkene (**35**) (15.6 g, 10.2 mmol) was treated in the same manner as described for the preparation of (**27**) to give (**36**) (15.5 g, 99%) as a wax. $[\alpha]_D^{30}$ +0.02° ($c$ 1.47, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 104H), 1.50—1.64 (m, 12H), 3.40—3.62 (m, 22H), 3.80 (s, 6H), 4.43 (s, 4H), 4.55 (s, 4H), 6.87 (dt, $J$ = 8.8, 2.0 Hz, 4H), 7.24—7.34 (m, 14H); $^{13}$C NMR (75 MHz) $\delta$ = 26.10, 26.19, 29.50, 29.65, 29.71, 30.08, 55.25, 70.21, 70.59, 70.67, 71.64, 72.47, 73.32, 77.86, 113.68, 127.48, 127.56, 128.28, 129.20, 130.76, 138.40, 159.02; IR (neat) 1100, 1252, 1465, 1506, 1607, 2855, 2935 cm$^{-1}$. Found: C, 78.59; H, 11.44%. Calcd for $C_{100}H_{170}O_{10}$: C, 78.38; H, 11.18%.

**2,3′-*O*-(1,32-Dotriacontanediyl)-2′,3-bis-*O*-(16-hydroxyhexadecanyl)bis(1-*O*-benzyl-*sn*-glycerol) (37).** Di-MPM ether (**36**) (1.10 g, 0.718 mmol) was treated in the same manner as described for the preparation of diol (**28**) to give diol (**37**) (850 mg, 92%) as a colorless powder. Mp 56—57 °C; $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 104H), 1.51—1.59 (m, 12H), 3.40—3.63 (m, 22H), 4.55 (s, 4H), 7.26—7.34 (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ = 25.71, 26.04, 26.06, 29.40, 29.46, 29.55, 29.59, 29.63, 29.67, 30.04, 32.74, 62.90, 70.19, 70.55, 70.64, 71.60, 73.28, 77.84, 127.43, 127.52, 128.23, 138.34; IR ($CHCl_3$) 1100, 1460, 2851, 2940, 3625 cm$^{-1}$. Found: C, 77.84; H, 11.97%. Calcd for $C_{84}H_{154}O_8$: C, 78.08; H, 12.01%.

**2,3′-*O*-(1,32-Dotriacontanediyl)-2′,3-bis-*O*-(15-formylpentadecanyl)bis(1-*O*-benzyl-*sn*-glycerol) (38).** Diol (**37**) (198 mg, 0.153 mmol) was treated in the same manner as described for the preparation of dialdehyde (**29**) to give dialdehyde (**38**) (172 mg, 87%) as a solid. Mp 46—48 °C; $^1$H NMR (400 MHz) $\delta$ = 1.25 (br, 100H), 1.52—1.67 (m, 12H), 2.42 (dt, $J$ = 1.9, 7.4 Hz, 4H), 3.40—3.62 (m, 18H), 4.55 (s, 4H), 7.26—7.34 (m, 10H), 9.76 (t, $J$ = 1.9 Hz, 2H); $^{13}$C NMR (75 MHz) $\delta$ = 22.05, 26.07, 26.10, 29.14, 29.34, 29.41, 29.49, 29.57, 29.63, 29.70, 30.07, 43.90, 70.25, 70.58, 70.68, 71.63, 73.31, 77.87, 127.46, 127.54, 128.27, 138.41, 202.92; IR ($CHCl_3$) 1100, 1460, 1725, 2860, 2940 cm$^{-1}$. Found: C, 78.03; H, 11.97%. Calcd for $C_{84}H_{150}O_8$: C, 78.33; H, 11.74%.

**(2*S*,39*S*)-2,39-Bis(benzyloxymethyl)-1,4,37,40-tetraoxacyclodoheptacont-20-ene (39).** $TiCl_3$ (3.6 g, 23.4 mmol) and Zn–Cu couple[8] (4.5 g, 67.7 mmol) were placed in a Schlenk tube under argon. DME (200 ml) was added and the mixture was refluxed for 4 h. A solution of dialdehyde (**29**) (1.50 g, 1.17 mmol) in 50 ml of DME was added to the refluxing slurry via a motor-driven syringe pump over a 50 h period. After an additional 11 h reflux period, the reaction mixture was cooled to room temperature and 20% $K_2CO_3$ (100 ml) was added. The resulting mixture was stirred for 2.5 h. The organic phase was separated, and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated $NH_4Cl$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The aqueous phase was further extracted with $CHCl_3$. The combined organic extracts were washed with saturated $NH_4Cl$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with

benzene to benzene–EtOAc (100 : 1 to 30 : 1) to give 72-membered cyclic product (**39**) (1.93 g, 61%, *E* : *Z* = ca. 4 : 1), which was recrystallized from benzene–EtOAc to give colorless powder. Mp 98—100 °C; $^1$H NMR (400 MHz) $\delta$ = 1.26 (br, 104H), 1.50—1.60 (br, 8H), 1.94—2.04 (br, 4H), 3.40—3.64 (m, 18H), 4.55 (s, 4H), 5.33—5.42 (m, 2H), 7.26—7.35 (m, 10H); $^{13}$C NMR (100 MHz) $\delta$ = 26.05, 26.12, 27.17 (*Z*), 29.10, 29.29, 29.45, 29.51, 29.63, 30.06, 32.58 (*E*), 70.22, 70.58, 71.00, 71.59, 73.32, 77.93, 127.49, 127.57, 128.30, 129.89 (*Z*), 130.35 (*E*), 138.38; IR ($CHCl_3$) 1105, 1460, 2855, 2940 cm$^{-1}$. EI-MS *m*/*z* 1255 ($M^+$), 1164 ($M^+-CH_2Ph$), 1058, 91. Found: C, 80.07; H, 12.26%. Calcd for $C_{84}H_{150}O_6$: C, 80.32; H, 12.04%.

**(2*S*, 38*S*)-2,38-Bis(benzyloxymethyl)-1,4,37,40-tetraoxacyclodoheptacont-20-ene (40).** Dialdehyde (**38**) (2.17 g, 1.68 mmol) was treated in the same manner as described for the preparation of 72-membered cyclic compound (**39**) to give 72-membered cyclic compound (**40**) (1.39 g, 66%, *E* : *Z* = ca. 4 : 1) as a colorless powder. Mp 100—102 °C. $^1$H NMR (300 MHz) $\delta$ = 1.25 (br, 104H), 1.50—1.61 (br, 8H), 1.93—2.05 (br, 4H), 3.40—3.63 (m, 18H), 4.55 (s, 4H), 5.32—5.38 (m, 2H), 7.24—7.34 (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ = 26.05, 26.06, 26.11, 27.17 (*Z*), 29.11, 29.43, 29.45, 29.50, 29.63, 29.65, 30.04, 32.61 (*E*), 70.21, 70.58, 71.00, 71.58, 73.32, 77.93, 127.48, 127.56, 128.29, 129.88 (*Z*), 130.30 (*E*), 138.37; IR ($CHCl_3$) 1105, 1460, 2855, 2940 cm$^{-1}$. EI-MS *m*/*z* 1255 ($M^+$), 1164 ($M^+-CH_2Ph$), 1058, 91. Found: C, 80.05; H, 12.29%. Calcd for $C_{84}H_{150}O_6$: C, 80.32; H, 12.04%.

**(2*R*, 39*R*)-2,39-Bis(hydroxymethyl)-1,4,37,40-tetraoxacyclodoheptacontane (5).** A mixture of 72-membered olefin (**39**) (550 mg, 0.438 mmol) and 10% Pd–C (200 mg) in ethanol (250 ml) was refluxed under $H_2$ for 40 h. The mixture was filtered, and concentrated to dryness to give 72-membered core lipid (**5**), which was recrystallized from EtOAc to give colorless powder (418 mg, 87%). Mp 129—130 °C; $^1$H NMR (400 MHz) $\delta$ = 1.26 (br, 112H), 1.53—1.59 (m, 8H), 2.04 (t, *J* = 6.0 Hz, 2H), 3.41—3.72 (m, 18H); $^{13}$C NMR (67.5 MHz) $\delta$ = 26.13, 29.40, 29.56, 29.63, 30.14, 63.16, 70.44, 71.23, 71.84, 78.58; IR (KBr pellet) 719, 729, 1074, 1122, 1464, 1473, 2848, 2918, 3429 cm$^{-1}$. EI-MS *m*/*z* 1077 ($M^+$), 1059 ($M^+-H_2O$), 1047, 538, 464. Found: C, 77.83; H, 13.20%. Calcd for $C_{70}H_{140}O_6$: C, 78.00; H, 13.09%.

**(2*R*, 38*R*)-2,38-Bis(hydroxymethyl)-1,4,37,40-tetraoxacyclodoheptacontane (6).** 72-Membered cyclic compound (**40**) (283 mg, 0.225 mmol) was treated in the same manner as described for the preparation of 72-membered core lipid (**5**) (209 mg, 86%) to give 72-membered core lipid (**6**) as a colorless powder. Mp 131—133 °C; $^1$H NMR (300 MHz) $\delta$ = 1.26 (br, 112H), 1.53—1.59 (br, 8H), 2.09 (t, *J* = 6.0 Hz, 2H), 3.42—3.71 (m, 18H); $^{13}$C NMR (67.5 MHz) $\delta$ = 26.13, 29.40, 29.56, 29.63, 30.14, 63.17, 70.45, 71.22, 71.85, 78.59; IR (KBr pellet) 719, 729, 1072, 1119, 1464, 1473, 2848, 2914, 3417 cm$^{-1}$. EI-MS *m*/*z* 1077 ($M^+$), 1059 ($M^+-H_2O$), 1047, 538, 464. Found: C, 77.82; H, 13.13%. Calcd for $C_{70}H_{140}O_6$: C, 78.00; H, 13.09%.

**2,2′-*O*-(1,32-Dotriacontanediyl)bis[1-*O*-benzyl-3-*O*-hexadecanyl-*sn*-glycerol] (41).** Methanesulfonyl chloride (85 μl, 1.10 mmol) was added dropwise to a solution of diol (**28**) (355 mg, 0.274 mmol) and $Et_3N$ (300 μl, 2.16 mmol) in $CH_2Cl_2$ (20 ml) at 0 °C and the mixture was stirred at 0 °C for 3 h. Water (10 ml) was added and the mixture was extracted with EtOAc. The organic phase was washed with 2 M HCl, saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness to afford a crude dimesylate. To a solution of dimesylate in THF (15 ml) was added dropwise lithium triethylhydroborate (1 M solution in THF, 2.40 ml, 2.40 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. Water (10 ml) was carefully added at 0 °C and the mixture was extracted with ether. The organic phase was washed with 2 M HCl, saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (7 : 1) to give (**41**) (348 mg, quant.) as a colorless solid. Mp 45—46 °C; $^1$H NMR (300 MHz) $\delta$ = 0.88 (t, *J* = 7.1 Hz, 6H), 1.25 (br, 108H), 1.50—1.61 (m, 8H), 3.40—3.62 (m, 18H), 4.55 (s, 4H), 7.25—7.33 (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ = 14.09, 22.67, 26.09, 26.11, 29.35, 29.49, 29.64, 29.70, 30.09, 31.91, 70.29, 70.58, 70.72, 71.63, 73.32, 77.91, 127.44, 127.53, 128.26, 138.43; IR (KBr pellet) 696, 719, 737, 1115, 1454, 1469, 2856, 2914 cm$^{-1}$. Found: C, 80.22; H, 12.43%. Calcd for $C_{84}H_{154}O_6$: C, 80.06; H, 12.32%.

**2,3′-*O*-(1,32-Dotriacontanediyl)-2′,3-di-*O*-hexadecanylbis(1-*O*-benzyl-*sn*-glycerol) (42).** By the same manner as described in the synthesis of (**41**), the compound (**37**) (680 mg, 0.526 mmol) was converted to (**42**) (669 mg, quant.) as a colorless powder. Mp 41—42 °C; $^1$H NMR (300 MHz) $\delta$ = 0.88 (t, *J* = 7.1 Hz, 6H), 1.25 (br, 108H), 1.50—1.61 (m, 8H), 3.40—3.63 (m, 18H), 4.55 (s, 4H), 7.25—7.34 (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ = 14.10, 22.68, 26.11, 29.35, 29.49, 29.64, 29.71, 30.09, 31.91, 70.26, 70.58, 70.70, 71.62, 73.32, 77.89, 127.44, 127.53, 128.26, 138.42; IR (KBr pellet) 696, 721, 733, 1119, 1454, 1468, 2848, 2914 cm$^{-1}$. Found: C, 79.97; H, 12.62%. Calcd for $C_{84}H_{154}O_6$: C, 80.06; H, 12.32%.

**2,2′-*O*-(1,32-Dotriacontanediyl)-3,3′-di-*O*-hexadecanyl-di-*sn*-glycerol (7).** A mixture of (**41**) (293 mg, 0.232 mmol) and 10% Pd–C (383 mg) in EtOAc (40 ml) was stirred at 60 °C under hydrogen atmosphere for 24 h. The catalyst was filtered through a pad of Celite and washed with $CHCl_3$. The filtrate and washings were combined and concentrated to dryness. The residue was chromatographed over silica gel with hexane–EtOAc (5 : 1) to $CHCl_3$ to give diol (**7**) (190 mg, 76%) as a colorless solid. Mp 66—67 °C; $^1$H NMR (300 MHz) $\delta$ = 0.88 (t, *J* = 7.1 Hz, 6H), 1.25 (br, 108H), 1.51—1.60 (m, 8H), 3.41—3.65 (m, 18H); $^{13}$C NMR (75 MHz) $\delta$ = 14.13, 22.69, 26.10, 29.36, 29.47, 29.62, 29.72, 30.07, 31.93, 63.09, 70.39, 70.90, 71.85, 78.19; IR (KBr pellet) 719, 1119, 1471, 2846, 2929, 3415 cm$^{-1}$. Found: C, 77.56; H, 13.50%. Calcd for $C_{70}H_{142}O_6$: C, 77.86; H, 13.25%.

**2,3′-*O*-(1,32-Dotriacontanediyl)-2′,3-di-*O*-hexadecanyl-di-*sn*-glycerol (8).** By the same manner as described in the synthesis of (**7**), the compound (**42**) (576 mg, 0.457 mmol) was converted to (**8**) (430 mg, 87%) as a colorless powder. Mp 79—81 °C; $^1$H NMR (300 MHz) $\delta$ = 0.88 (t, *J* = 7.1 Hz, 6H), 1.25 (br, 108H), 1.51—1.60 (m, 8H), 3.41—3.65 (m, 18H); $^{13}$C NMR (75 MHz) $\delta$ = 14.13, 22.69, 26.10, 29.36, 29.47, 29.62, 29.72, 30.07, 31.93, 63.09, 70.39, 70.90, 71.85, 78.19; IR (KBr pellet) 723, 1115, 1466, 2850, 2918, 3492 cm$^{-1}$. Found: C, 77.65; H, 13.21%. Calcd for $C_{70}H_{142}O_6$: C, 77.86; H, 13.25%.

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