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How the Stereochemistry of a Central Cyclopentyl Ring Influences the Self-Assembling Properties of Archaeal Lipid Analogues: Synthesis and CryoTEM Observations

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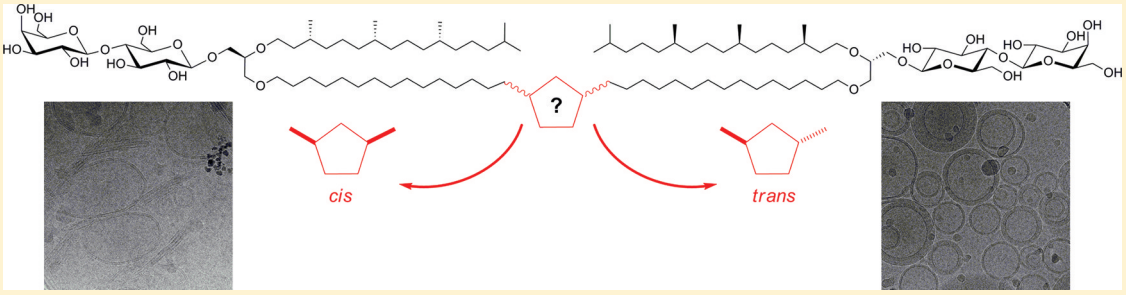
Supporting Information



ABSTRACT: The relative stereochemistry (cis or trans) of a 1,3-disubstituted cyclopentane unit placed in the middle of tetraether archaeal bipolar lipid analogues was found to have a dramatic influence on their supramolecular self-assembling properties. The synthesis of two diastereomers varying only by the stereochemistry of the cyclopentyl unit was achieved following a multistep diastereoselective route. The corresponding lipid films were hydrated and were observed by cryoTEM. The micrographs showed several types of unilamellar nano-objects such as lamellas or irregular vesicles for the cis-isomer, whereas the trans-isomer exhibited exclusively multilamellar vesicles with a regular spherical shape. Even if the cyclopentyl ring takes part of a long alkyl chain (32 carbon atoms), the pseudorotation of the carbocycle would influence the global conformation of the bipolar lipid and consequently would modify the orientation of the lactosyl polar headgroups.

INTRODUCTION

Physicochemical and theoretical studies of lipid self-assembling are extensively described in the literature, which allows at some points to predict the global behavior of some novel amphiphilic structures.[1] However, the impact of stereochemical features is still difficult to assess and still requires the physical study of well-defined stereoisomers. The stereochemistry is known to undergo clear changes in the self-assembly of amphiphilic molecules. Several research groups described, for instance, chirality transfer from molecular to supramolecular level or physicochemical comparative studies of diastereomers.[2] These latter examples usually illustrate stereochemical effects between diastereomeric compounds in which the variable stereogenic centers are relatively close one to each other and mainly near the polar domain. This is probably a consequence of the structure of the common natural lipids that almost do not bear stereogenic centers in their hydrophobic parts. By contrast, some organisms such as archaea developed membrane lipids containing a relatively high number of stereogenic centers, which might play a role on the self-assembling properties of their cell-membranes. These lipids or analogues may therefore represent an ideal model of study of the stereochemical influence on the self-assembling properties of amphiphiles in general.

Archaea organisms represent the third phyla of life with bacteria and eukarya. They are known as extreme organisms that grow under harsh conditions such as low pH, extreme temperature, highly salted media, and anaerobia.[3] These unusual conditions, compared to that of mesophiles, coerced the archaea to develop the required tools to circumvent what can be considered as hostile media. Among the differences between mesophiles and archaea, the lipid composition of archaeal membranes is of particular interest, as it involves both atypical hydrophobic cores and hydrophilic polar head groups.[4] The most remarkable hydrophobic structures involve two glyceryl units linked one to the other by two isoprenoid chains leading to a 70 atom macrocycle tetraether (Figure 1).[5,6] The particular features of these archaeal lipids are related to (1) the ability of these tetraethers to adopt a transmembrane

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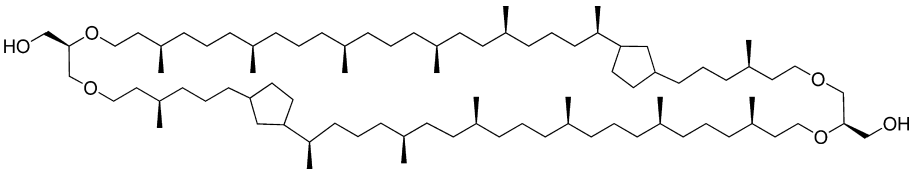


Figure 1. Example of natural archaeal tetraether lipid structure (hydrophobic domain).

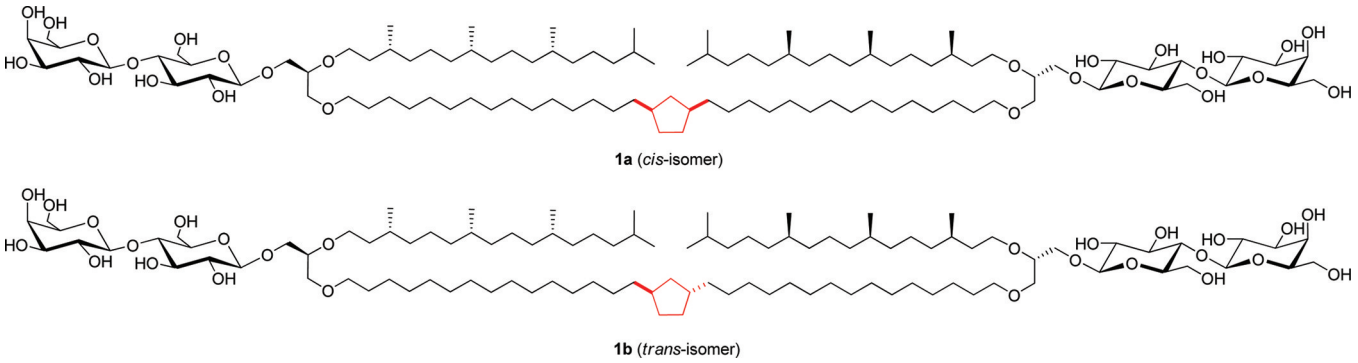
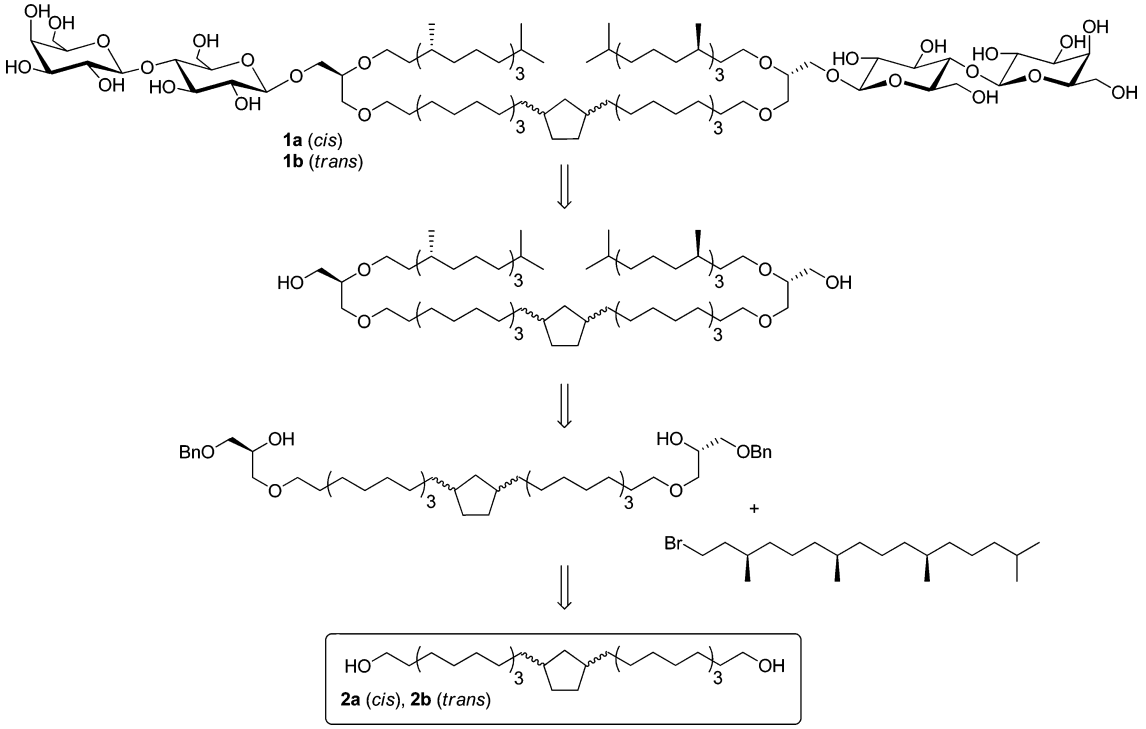


Figure 2. Structure of synthetic archaeal lipid analogues bearing a *cis*- or *trans*-1,3-disubstituted cyclopentane ring.

Scheme 1. Retrosynthesis of Bipolar Lipids 1a,b



conformation within the archaeal membrane that is responsible for its exceptional thermostability; (2) the less hydrolyzable ether-linkages compared to the ester-linkages commonly found in other forms of life; and (3) the presence of cyclopentane rings in the isoprenoid chains for which the number is associated with the living temperature of the considered organisms.[7] In terms of stereochemistry, absolute and relative configurations of glyceryl residues, isopranyl chains, and five-membered rings present on natural tetraether structures have been determined.[8,9] From these studies, the stereochemistry of the glyceryl moieties was found to be opposite of that of conventional glycerolipids. More recently, the trans configuration of the 1,3-disubstituted cyclopentane rings, as well as its absolute configuration, was determined by the synthesis of models and the comparison of their optical rotation and NMR spectroscopic data.[8]

Over the last 20 years, a considerable effort has been devoted to the synthesis of bipolar lipids[10] (also named "bolaamphiphiles") that retain some of the essential structural features of archaeal membrane lipids.[6] However, only a few studies provided evidence for a crucial stereochemical impact of branched chains and/or glyceryl units on the self-assembling properties of bipolar lipids.[11] Moreover, the precise role of the *trans*-1,3-disubstituted cyclopentane remains unknown in

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archaeal lipids. Indeed, the cyclopentane is known to adopt numerous conformations of close energies that originate from the pseudorotation of the carbocycle.[12] Ruiz del Ballesteros et al.[13] have shown by computational analysis that the energy profiles of the two diastereomers of a 1,3-disubstituted cyclopentane (cis or trans) are rather similar in terms of energy level. However, the main difference lay on the distance between the two substituents all along the pseudorotation circuit. This distance is relatively stable for the trans-isomer (4.5−4.8 Å) but varies from 3.2 to 4.8 Å when considering the cis-isomer (for two methyl groups). Within a hydrophobic structure, these differences could be at the origin of important changes in the conformational behavior of a lipid.

In view of establishing the influence of stereochemical features on both supramolecular structures and properties, we have embarked on a program to synthesize and investigate the lyotropic behavior of diastereomers **1a,b** (Figure 2) possessing the same chemical structure but a different relative stereochemistry of the cyclopentane unit (cis or trans). These bipolar molecules are characterized by a hydrophobic backbone constructed around a bridging chain incorporating a central 1,3-disubtituted cyclopentane unit. On both ends, a stereocontrolled glyceryl unit makes the tripodal link between the bridging chain, an optically pure phytanyl chain and a lactosyl polar headgroup. The latter brings the tetrather structures to an adequate hydrophilic/hydrophobic balance. Additionally, the presence of neutral sugar headgroups instead of charged phosphorylated derivatives is expected to provide a higher sensitivity of the self-assembling properties of these glycolipids toward minor changes in their hydrophobic cores, such as the stereochemical variations we describe hereafter.[14]

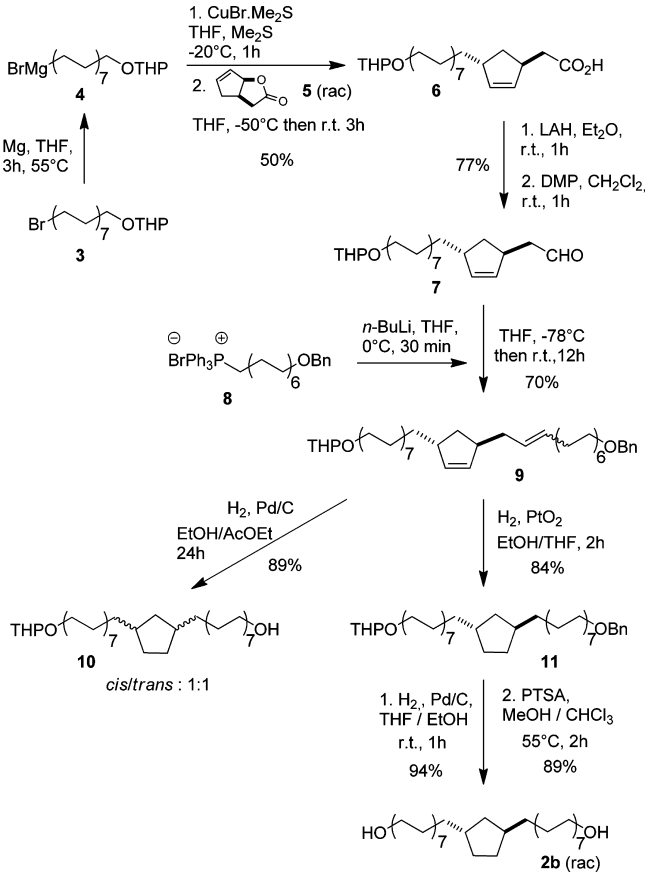
Thus, we described herein the synthesis of the two diastereomers **1a,b** (Figure 2) and the corresponding long-range effect of this stereochemical variation through comparative cryogenic transmission electron microscopy (cryo-TEM) observations of the resulting supramolecular assemblies in water (1 mg mL^{-1}).

RESULTS AND DISCUSSION

Synthesis of Tetraether Lipids 1a,b. The strategic plan for the synthesis of the two diastereomers **1a** and **1b** is based on the functionalization of α,ω-dihydroxylated alkanes containing a 1,3-disubstituted cyclopentane ring at their midpart and characterized by a cis or trans relative configuration (**2a,b**) (Scheme 1). The symmetrical construction of the tetraether backbones involved the stereocontrolled bisalkylation of diols **2a,b** with two (*S*)-epichlorhydrins and the regiospecific opening of the resulting epoxides that ensured the final configuration of the glyceryl units. The introduction of two (*R,R,R*)-phytanyl chains by a Williamson etherification reaction led to the formation of tetraether structures. Finally, the cleavage of the protecting groups permitted the introduction of the polar head groups by a double *O*-lactosylation under standard conditions.

The synthesis of the bridging chain **2a** (cis), resulting from the oxidative cleavage of norbornene, has been already reported by our research group.[15] The preparation of the trans-isomer, which has never been described, required a totally different strategy. Indeed, the access to *trans*-1,3-disubtituted cyclopentanes is not extensively described in the literature. We based our synthetic scheme on the use of lactone **5** (rac), which is known to be selectively opened by an organocuprate to provide a clean reaction in favor of a *trans*-1,3-disubtituted cyclopentene (Scheme 2).[8,16] The reaction proceeds through a 1,4-addition on the unsaturated lactone, leading to the corresponding

Scheme 2. Synthesis of Diol 2b Including a *trans*-1,3-Disubtituted Cyclopentane



carboxylic acid. One difficulty laid on the synthesis of the long alkyl chain organomagnesium halide used for the preparation of the required organocuprate. Conversion of the ω-tetrahydropyranyloxy-α-bromopentadecane **3**[17] into the corresponding organomagnesium bromide **4** required freshly purified starting materials and the heating of the reaction mixture for 3 h at 55 °C in THF.[17] The Grignard reagent was then engaged in the alkylation reaction of lactone **5** in the presence of CuBr·Me_2S in THF/Me_2S. The 1,4-addition proceeded cleanly and provided the carboxylic acid **6** with a trans configuration (confirmed by NOE NMR experiments) in 50% yield. This acid **6** can be isolated or used without purification in the next step, which consisted of the reduction of the carboxylic acid function followed by a reoxidation by the Dess−Martin periodinane to the aldehyde stage. Aldehyde **7** was obtained in 77% yield and was engaged in a Wittig olefination step to introduce the second arm of the bridging chain that fixed the length of the tetraether. Indeed, treatment of phosphonium salt **8** in THF with 1 equiv of *n*-BuLi gave the corresponding phosphorane, which was treated with aldehyde **7** for 12 h to provide olefin **9** in 70% yield. The conversion of the lactone **5** into the olefin **9** was optimized by removing the purification steps at the stage of the carboxylic acid **6** and aldehyde **7**; a single careful purification was then required after the olefination reaction to provide compound **9** in 65% yield (from **5**), compared to 27% yield if each step was performed from pure products. The

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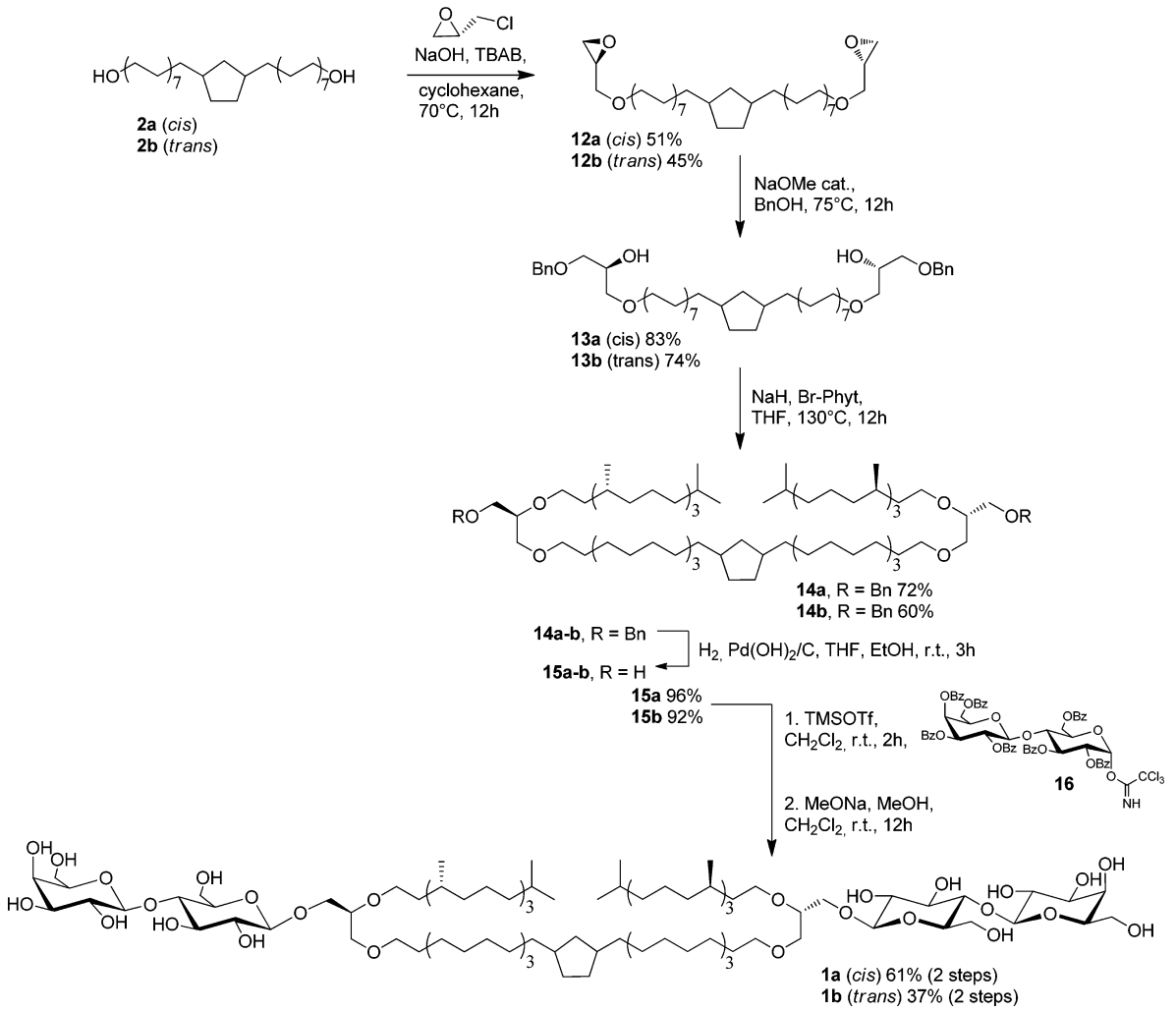
Scheme 3. Preparation of Tetraethers 1a (cis) and 1b (trans)



simultaneous hydrogenation of benzyloxy groups and double bonds was tried out in the presence of Pd/C. These conditions were chemically efficient but resulted in a loss of the stereochemistry of the cyclopentane ring; thus, alcohol **10** was isolated as a cis/trans 1:1 mixture. The replacement of the Pd/C catalytic system by PtO_2, which is known to proceed without double bond isomerization,[8,18] afforded pure trans-isomer **11** in 84% yield. The cleavage of the protecting groups was achieved by successive hydrogenolysis (H_2, Pd/C, 94%) and acidic methanolysis (PTSA, 89%). Thus, diol **2b** bearing a *trans* 1,3-disubtituted cyclopentane ring in a racemic form was obtained in seven steps from lactone **5** (overall yield of 46%).

Having the diols **2a,b** in hand, the next step involved the introduction of the glyceryl moieties through the reaction of diols **2a,b** with (*S*)-epichlorhydrin that ensured a *sn*-2,3 absolute configuration of the final product (Scheme 3). The bis-glycidyl derivatives **12a,b** were isolated respectively in 51 and 45% yields, in addition to monoglycidylation products (~40%), which can be recycled in another glycidylation reaction to furnish additional diepoxide products. The glycidyl derivatives **12a,b** were easily opened by an excess of benzylic alcohol in the presence of a catalytic amount of sodium methoxide yielding diols **13a,b** (~80%). The phytanyl chains were next introduced from (3*R*,7*R*,11*R*)-phytanylbromide. The latter was synthesized from 7*R*,11*R*-phytol by asymmetric reduction based on Noyori's procedure,[19] followed by bromination of the resulting alcohol in aqueous HBr.[15,20] The diastereoisomeric ratio (100:3) was determined by integrable ^{13}C NMR experiments on the (3*R*,7*R*,11*R*)-phytanol. Reaction of phytanylbromide (Br-phyt) with diols **13a,b** was carried out in the presence of sodium hydride at 130 °C, which permitted the removal of the solvent, allowing the reaction to proceed under solvent-free conditions for 12 h. This double Williamson reaction led to the dibenzylated tetraethers **14a,b** in 72 and 60% yields, respectively. After hydrogenolysis of the benzyloxy groups, a glycosylation reaction of the resulting diol **15** was performed using the trichloroacetimidate lactosyl derivative **16**. A catalytic amount of trimethylsilyltriflate promoted a stereoselective double glycosylation (92−76% yield), and final methanolysis of the benzoate groups provided dilactosyl-tetraethers **1a,b** in 66 and 48% yields, respectively. These modest yields are mainly due to the tricky purification steps of such amphiphilic compounds.

CryoTEM Observations. CryoTEM was carried out on both tetraether lipids (**1a,b**), which gave access to direct observations of their self-assemblies in aqueous media. The samples were prepared at a concentration of 1 mg mL^{-1} by hydration at 45 °C of lipid films that were obtained by evaporation of a chloroform/methanol solution. The temperature of hydration was fixed to 45 °C to ensure a fluidic state of

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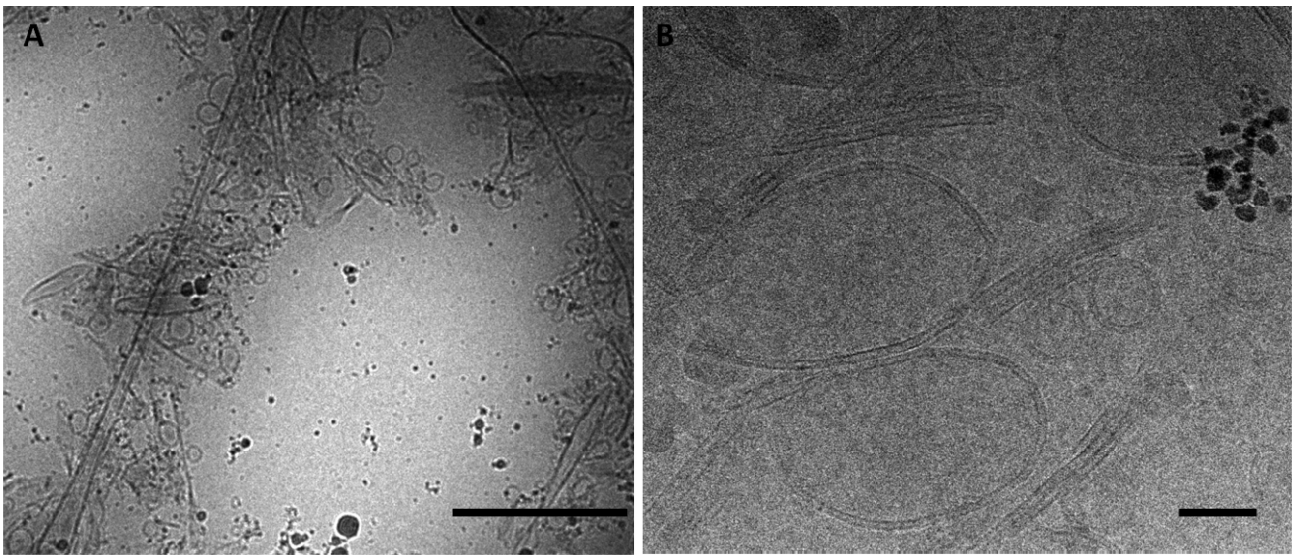

Figure 3. CryoTEM observations of aqueous dispersions of tetraether **1a** (1 mg mL^{-1}). Scale bars 1 μm (A) and 50 nm (B).

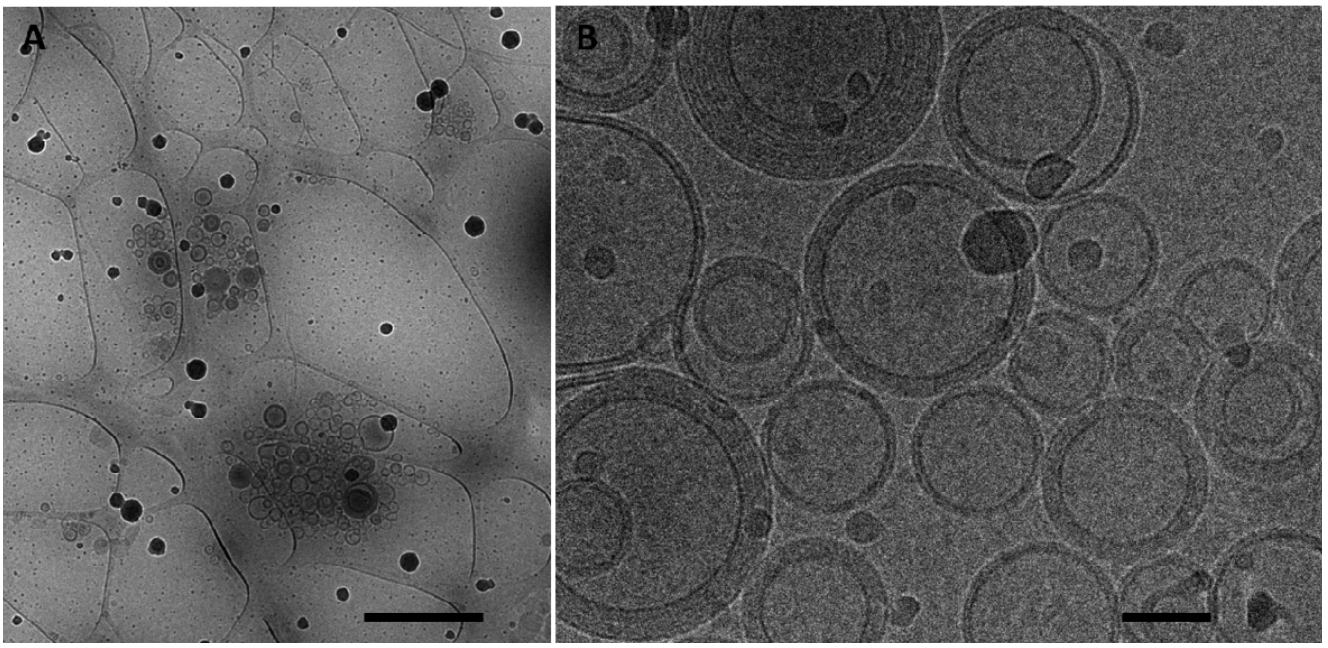

Figure 4. CryoTEM observations of aqueous dispersions of tetraether **1b** (1 mg mL^{-1}). Note that the membranes of unilamellar and bilamellar liposomes are ~6 and ~12 nm thick, respectively. Scale bars 1 μm (A) and 50 nm (B).

the alkyl chains (confirmed by SAXS studies, data not shown). Macroscopically, the hydration of the cis-isomer **1a** led to a transparent aqueous solution resulting from a easy dispersion of the lipid film in water. Conversely, the trans-isomer **1b** (following strictly the same conditions of preparation) led to a homogeneous solution that did not appear as a clear transparent solution. CryoTEM observations of frozen-hydrated samples supported on carbon grids with holes were performed under low-dose conditions. The micrographs shown in Figure 3 (cis-isomer **1a**) and Figure 4 (trans-isomer **1b**) also demonstrated contrasting behavior at a nanoscale level.

Concerning the cis-isomer **1a**, the cryoTEM analysis led to the observation of various nanostructures including lamellae, unilamellar and irregular vesicles, or flat structures (Figure 3). Additionally, most of the membranes involved in these nanostructures are not pairing to one another, leading mainly to unilamellar objects. Independent of the nature of the nano-objects, the thickness of the membrane was estimated to be ~6 nm.

However, the cryoTEM study of the trans-isomer **1b** sample led to the observation of regular vesicles with sizes ranging from 50 to 200 nm that have a tendency to interact with one another, leading to a relative aggregation phenomenon (Figure 4A). Furthermore, most of the vesicles are multilamellar structures with strong interactions between lamellae (Figure 4B). Also, when a vesicle contained a sufficiently smaller one, the latter usually stacked on one side of the larger vesicles. The thickness of the membranes are also very regular and were determined to be more or less the same as for the cis-isomer **1a** (~ 6 nm).

The supramolecular morphologies determined by cryoTEM experiments revealed different lyotropic self-assembling properties for the tetraether glycolipids **1a** and **1b**, with a significant

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dependence on the relative stereochemistry of the cyclopentane unit. A more extensive comparative study is in progress to confirm this stereochemical effect. As a potential interpretation, we suggest that the trans-isomer **1b** adopts a specific conformation leading to a unique type of nano-object (vesicle). This preferred conformation would favor the formation of a hydrogen-bonding network between the sugar moieties, as shown by the observation of a multilamellar system as well as by the partial contacts of internal vesicles within larger ones. Conversely, a wider range of nano-objects was observed from the cis-isomer **1a**. Indeed, the effect of the pseudorotation of the cyclopentyl ring discussed before could explain a relative conformational inconstancy of the lipid within the membrane. Additionally, the absence of multilamellar structures seems to reveal a low tendency for the formation of a hydrogen-bonding network. These clear differences would demonstrate the stereochemical importance of the cyclopentane on the self-organizing properties of these bipolar lipids. The presence of the five-membered ring with either a cis or a trans stereochemistry, even placed in the middle of a long bipolar lipid, would therefore influence in a different way (1) its conformation, leading to a different nature of nano-objects, and (2) the orientation of the lactosyl polar headgroups attached to the tetraether backbone, thus favoring or inhibiting the formation of hydrogen bonds.

■ CONCLUSIONS

The multistep synthesis of two diastereomers containing a central cyclopentyl ring was achieved in 13 steps. It permits reaching sufficient amounts of material to start a physicochemical comparative study (i.e., >100 mg). The comparison of the micrographs obtained by cryoTEM analysis demonstrates the remarkable influence of the stereochemistry of a tetraether-type lipid structure (archaeal lipid analogues). The sole change of the relative stereochemistry of a cyclopentane ring placed in the middle of a 32 carbon atom chain already induces dramatic changes in the behavior of such bipolar lipids in aqueous solutions. Indeed, the cis-isomer would provide a more flexible conformation to the lipid and led to a lower number of interactions (hydrogen bonds) between lipids within a membrane. The trans-isomer seems to reach a higher conformational rigidity that can be compared to the natural lipids bearing the same stereochemistry. These conclusions required several other studies such as small angle X-ray scattering (SAXS) and pressure isotherm monolayers that would provide additional evidence of the relationships between stereochemistry and self-assembling properties. Thanks to the synthetic scheme described in this article, these studies will be reported in a near future.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage over a column of activated alumina; dichloromethane (CH_2Cl_2) was distilled over calcium hydride. All other reagents were used directly from the supplier without further purification unless noted. Analytical thin layer chromatography (TLC) was performed on 60 F_{254} silica gel nonactivated plates. A solution of 5% H_2SO_4 in EtOH or ultraviolet fluorescence was used to develop the plates. Column chromatography was performed on silica gel 60 H (5−40 μm). Nuclear magnetic resonance spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). For $CDCl_3$, CD_3OD, and pyridine-d_5 solutions, the chemical shifts (δ) are reported as parts per million (ppm) referenced to the appropriate residual solvent peak. Coupling constants are reported in Hertz (Hz). Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens, attribution). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), bs (broad singlet), CyP (cyclopentyl). The NMR peak assignments were determined from 2D NMR experiments such as COSY, HSQC, and HMBC. High-resolution mass spectra (accurate mass) were performed on a MS/MS-TOF mass spectrometer and are reported as m/z. Accurate masses are reported for the molecular ion $[M + Na]^+$, $[M + H]^+$, or $[M]^+$.

(15-(Tetrahydro-2*H*-pyran-2-yloxy)pentadecyl)magnesium Bromide 4. A solution of freshly purified ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]pentadecane **3** (6.42 g, 1 equiv, 16.40 mmol, in dry THF (33 mL)) was added dropwise with stirring to magnesium turnings (598 mg, 1.5 equiv, 24.60 mmol) under an argon atmosphere. After the exothermic reaction had subsided, the mixture was stirred at 55 °C for 3 h. The Grignard solution of **4** was titrated with a *sec*-butanol solution (0.5 mol/L) in the presence of *ortho*-phenanthroline and was used rapidly in the next step.

2-(4-(5-(Tetrahydro-2*H*-pyran-2-yloxy)pentadecyl)trans-cyclopent-2-enyl)acetic Acid 6. To a solution of CuBr-Me_2S (2.0 g, 1.2 equiv, 9.67 mmol) in Me_2S (20 mL) and THF (40 mL) at 0 °C was added Grignard solution **4** (33 mL titrated at 0.29 mol/L, 1.2 equiv, 9.67 mmol). After the mixture was stirred 1 h at room temperature and cooled at −50 °C, a cold solution of lactone **5** (1 g in THF (32 mL), 1 equiv, 8.06 mmol) was added dropwise via a syringe. The resulting mixture was stirred and slowly warmed up to room temperature (3 h) and then quenched with 1 N HCl. After extraction with ether, the organic phase was washed with brine and water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product solubilized in chloroform was filtered, and the filtrate was concentrated under reduced pressure. Purification by column chromatography (cyclohexane/AcOEt 85:15) gave acid **6** (1.76 g, 4.03 mmol, 50%) as a white solid: R_f = 0.27 (AcOEt/PE 10:90); mp = 58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.24−1.73 (m, 36H, 18CH_2), 2.31 (dd, J = 15.4, 8.1 Hz, 1H, CH_2C═O), 2.40 (dd, J = 15.4, 6.9 Hz, 1H, CH_2C═O), 2.69 (m, 1H, CyP), 3.11 (m, 1H, CyP), 3.38 (dt, J = 9.6, 6.7 Hz, 1H, CH_2CH_2O), 3.51 (m, 1H, THP), 3.73 (dt, J = 9.6, 6.9 Hz, 1H, CH_2CH_2O), 3.88 (m, 1H, THP), 4.59 (m, 1H, THP), 5.66 (dt, J = 5.6, 2.0 Hz, 1H, CyP), 5.73 (dt, J = 5.5, 1.9 Hz, 1H, CyP); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 25.5, 26.2, 27.9, 29.5 (4CH_2), 29.6 (4CH_2), 29.7, 29.8, 30.8, 35.8, 36.4 (5CH_2), 41.2 (CH_2C═O), 42.5 (CH, CyP), 44.6 (CH, CyP), 62.3 (CH_2, THP), 67.7 (CH_2O), 98.8 (CH, THP), 132.7 (CH, CyP), 136.4 (CH, CyP), 176.1 (C═O); Accurate mass calcd for $C_{27}H_{48}O_4Na$ $(M + Na)^+$ 459.34503, found 459.3450; Accurate mass calcd for $C_{27}H_{47}O_4Na_2$ $(M - H + 2Na)^+$ 481.32697, found 481.3260.

2-(4-(15-(Tetrahydro-2*H*-pyran-2-yloxy)pentadecyl)trans-cyclopent-2-enyl)acetaldehyde 7. To a suspension of $LiAlH_4$ (107 mg, 3 equiv, 2.66 mmol) in diethyl ether (40 mL) at 0 °C was added dropwise a solution of acid **6** (0.41 g, 1 equiv, 0.89 mmol) in diethyl ether (20 mL). The mixture was stirred at 0 °C for 1 h, followed by dropwise addition of water and 1 M aqueous NaOH solution, until gas evolution had ceased. The suspension was filtered, and the white residue was washed with diethyl ether. The filtrate was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the intermediary alcohol (375 mg, 0.89 mmol, quant.) as a white solid: R_f = 0.39 (AcOEt/PE 20:80); mp = 35 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.24−1.87 (m, 38H, 19CH_2), 2.66 (m, 1H, CyP), 2.79 (m, 1H, CyP), 3.38 (dt, J = 9.6, 6.7 Hz, 1H, CH_2CH_2O), 3.59 (m, 1H, THP), 3.70 (m, 3H, CH_2CH_2O and CH_2−OH), 3.87 (m, 1H, THP), 4.57 (m, 1H, THP), 5.67 (dt, J = 5.7, 1.9 Hz, 1H, CyP), 5.69 (dt, J = 5.7, 1.7 Hz, 1H, CyP); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 22.3, 25.5, 26.2, 28.0, 29.5, 29.59, 29.61, 29.66, 29.74, 29.9, 30.8, 38.9 (18CH_2), 41.3 (CH, CyP), 44.8 (CH; CyP), 61.9 (CH_2−OH), 62.3 (CH_2, THP), 67.7 (CH_2O), 98.8 (CH, THP), 133.8 (CH, CyP), 135.4 (CH, CyP). Dess−Martin periodinane (DMP) in DCM (1.1 mL, 1.1 equiv, 0.98 mmol) was added to a solution of the previous alcohol (375 mg, 1 equiv, 0.89 mmol) in dichloromethane

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(14 mL). The mixture was stirred for 1 h at room temperature and then quenched by the addition of saturated aq $NaHCO_3$/saturated aq $Na_2S_2O_3$ 1:1 (30 mL). The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with saturated aq $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (PE/AcOEt 95:5) gave aldehyde **7** (288 mg, 0.68 mmol, 77%) as a white solid: R_f = 0.33 (PE/AcOEt 95:5); mp = 29 °C; ^{1}H NMR($CDCl_3$, 400 MHz) δ (ppm) 1.24−1.36 (m, 24H, 12CH_2), 1.49−1.84 (m, 12H, (2CH_2, THP), (CH_2, CyP), 3CH_2), 2.40 (ddd, J = 16.5, 7.8, 2.1 Hz, 1H, CH_2CHO), 2.49 (ddd, J = 16.6, 6.4, 1.9 Hz, 1H, CH_2CHO), 2.67 (m, 1H, CyP), 3.16 (m, 1H, CyP), 3.38 (dt, J = 9.6, 6.7 Hz, 1H, CH_2O), 3.49 (m, 1H, THP), 3.73 (dt, J = 9.6, 6.9 Hz, 1H, CH_2O), 3.86 (m, 1H, THP), 4.57 (m, 1H, THP), 5.64 (dt, J = 5.6, 2.1 Hz, 1H, CyP), 5.73 (dt, J = 5.6, 2.0 Hz, 1H, CyP), 9.77 (t, J = 2.0 Hz, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 25.5, 26.2, 27.9, 29.5, 29.59, 29.60 (9CH_2), 29.63 (2CH_2), 29.64 (CH_2), 29.66 (3CH_2), 30.8, 35.8, 36.4 (3CH_2), 39.0 (CH, CyP), 44.7 (CH, CyP), 49.9 (*C*H_2CHO), 62.3 (CH_2, THP), 67.7 (CH_2O), 98.8 (CH, THP), 132.5 (CH, CyP), 136.5 (CH, CyP), 202.5 (CHO); Accurate mass calcd for C_{27} H_{48} O_3 Na (M + Na)$^+$ 443.35012, found 443.3512. Anal. for C_{27} H_{48} O_3 calcd C, 77.09; H, 11.50. Found C, 76.96; H, 11.70.

(13-(Benzyloxy)tridecyl)triphenylphosphonium Bromide 8. To a solution of bromide derivative (0.62 g, 1.0 equiv, 1.67 mmol) in AcOEt (10 mL) was added triphenylphosphine (0.88 g, 2.0 equiv, 3.33 mmol), and the resulting mixture was refluxed for 4 days. After the mixture was cooled to room temperature, the crystallized triphenylphosphine oxide was filtered and washed with cold toluene. Column chromatography over silica gel (CH_2Cl_2/MeOH 100:0 then 95:5) gave the phosphonium salt **8** (0.40 g, 0.63 mmol, 38%) as a yellow oil: R_f = 0.36 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.18 (m, 16H, 8CH_2), 1.63 (m, 6H, 3CH_2), 3.45 (t, J = 6.7 Hz, 2H, CH_2OBn), 3.70 (m, 2H, CH_2P), 4.49 (s, 2H, CH_2Ph), 7.31 (m, 5H, *Ph*CH_2), 7.70 (m, 6H, (H_{meta}, Ph_3P)), 7.81 (m, 9H, $H_{ortho/para}$, Ph_3P); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.64 (d, J = 4 Hz, CH_2−CH_2−CH_2−P), 22.69 (d, J = 49 Hz, CH_2P), 26.15, 29.15, 29.23, 29.43, 29.47 (5CH_2), 29.50 (2CH_2), 29.61, 29.74 (2CH_2), 30.37 (d, J = 16 Hz, *C*H_2−CH_2−P), 70.52 (CH_2OBn), 72.82 (CH_2Ph), 118.49 (d, J = 85 Hz, 3Cquat (PPh_3)), 127.42 (CH(OBn)), 127.59 (2CH(OBn)), 128.30 (2CHOBn), 130.42 (d, J = 12 Hz, 3CHortho-(Ph_3)), 133.70 (d, J = 10 Hz, 3CHmeta(Ph_3)), 134.89 (d, J = 3 Hz, 3CHpara(Ph_3)), 138.68 (Cquat(OBn)); ^{31}P NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.5; Accurate mass calcd for C_{38} H_{48} O P (M)$^+$ 551.34428, found 551.3446.

2-(15-(4-(15-(Benzyloxy)pentadec-2-enyl)trans-cyclopent-2-enyl)pentadecyloxy)tetrahydro-2*H*-pyran 9. To a suspension of dried phosphonium bromide **8** (1.5 g, 1.5 equiv, 2.36 mmol) in dry THF (14 mL), *n*-butyllithium (1.35 mol/L in hexane, 1.76 mL, 1.5 equiv, 2.36 mmol) was added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and aldehyde **7** (666 mg, 1.0 equiv, 1.58 mmol) dissolved in dry THF (2 mL) was added at −20 °C. After stirring for 12 h at room temperature and cooling at 0 °C, the reaction was quenched with water and diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 60:40) to yield **9** (780 mg, 1.12 mmol, 71%) as a colorless oil: R_f = 0.62 (PE/AcOEt 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.34 (m, 40H, 20CH_2), 1.60 (m, 15H, (2CH_2, THP), (CH_2, CyP), 5CH_2), 1.82 (m, 1H, (CH_2, THP)), 2.01 (m, 4H, 2CH_2), 2.72 (m, 2H, CyP), 3.38 (dt, J = 9.6, 6.7 Hz, 1H, CH_2O), 3.46 (t, J = 6.7 Hz, 2H, CH_2OBn), 3.49 (m, 1H, THP), 3.73 (dt, J = 9.6, 6.9 Hz, 1H, CH_2O), 3.87 (ddd, J = 11.1, 7.6, 3.6 Hz, 1H, THP), 4.50 (s, 2H, CH_2Ph), 4.58 (m, 1H, THP), 5.38 (m, 2H, CH═CH), 5.65 (dt, J = 5.7, 1.8 Hz, 1H, CyP), 5.67 (dt, J = 5.7, 1.8 Hz, 1H, CyP), 7.33 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 25.5, 29.19, 29.24 (3CH_2), 27.3 (CH_2), 28.0, 29.3 (2CH_2), 29.49 (2CH_2), 29.55 (CH_2), 29.60 (5CH_2), 29.66 (CH_2), 29.68 (6CH_2), 29.73, 29.75, 29.76, 29.90 (4CH_2), 30.8 (CH_2, THP), 33.4 (CH_2), 36.12, 36.17 (2CH_2), 44.8 (CH, CyP), 45.0 (CH, CyP), 62.3 (CH_2, THP), 67.7 (CH_2O), 70.5 (CH_2OBn), 72.8 (*C*H_2Ph), 98.8 (CH, THP), 127.4 (CH, Ph), 127.6 (2CH, Ph), 128.2 (CH=), 128.3 (2CH, Ph), 130.7 (CH=), 134.2 (CH, CyP), 135.2 (CH, CyP), 138.7 (C, Ph); Accurate mass calcd for C_{47} H_{80} O_3 Na (M + Na)$^+$ 715.60052, found 715.6016. Anal. for C_{47} H_{80} O_3 calcd C, 81.44; H, 11.63. Found C, 81.60; H, 11.63.

2-(15-((3-(15-(Benzyloxy)pentadecyl)-trans-cyclopentyl)-pentadecyloxy)tetrahydro-2*H*-pyran 11. A solution of **9** (1.0 g, 1.0 equiv, 1.44 mmol) in THF/EtOH 1:1 (100 mL) was stirred in the presence of PtO_2 (100 mg, 10% wt) under a 10 bar pressure of hydrogen gas at room temperature for 1 h. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (cyclohexane/CH_2Cl_2 60:40) to afford compound **11** (0.99 g, 1.42 mmol, 84%) as a white solid: R_f = 0.32 (cyclohexane/CH_2Cl_2 60:40); mp = 41 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.00−1.14 (m, 2H, CyP), 1.25−1.34 (m, 52H, 26CH_2), 1.47−1.65 (m, 10H, (CH_2, THP), 4CH_2), 1.68−1.87 (m, 6H, (4CH, CyP), (CH_2, THP)), 3.38 (td, J = 6.7, 9.6 Hz, 1H, CH_2O), 3.46 (t, J = 6.6 Hz, 2H, CH_2OBn), 3.49 (m, 1H, THP), 3.73 (td, J = 6.9, 9.6 Hz, 1H, CH_2O), 3.87 (ddd, J = 11.2, 7.4, 3.6 Hz, 1H, THP), 4.50 (s, 2H, CH_2Ph), 4.57 (m, 1H, THP), 7.27−7.34 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 25.5, 26.19, 26.24 (4CH_2), 28.7 (2CH_2), 29.6 (4CH_2), 29.66 (3CH_2), 29.69 (9CH_2), 29.73 (3CH_2), 29.76 (2CH_2), 29.9 (2CH_2), 30.8 (CH_2, THP), 33.0 (2CH_2), 36.8 (2CH_2), 38.8 (3C, CyP), 62.3 (CH_2, THP), 67.7 (CH_2O), 70.5 (CH_2OBn), 72.8 (CH_2Ph), 98.8 (CH, THP), 127.4 (CH, Ph), 127.6 (2CH, Ph), 128.3 (2CH, Ph), 138.7 (C, Ph); Accurate mass calcd for C_{47} H_{84} O_3 Na (M + Na)$^+$ 719.63182, found 719.6318. Anal. for C_{47} H_{84} O_3 calcd C, 80.97; H, 12.14. Found C, 80.98; H, 12.16.

15,15′-((*trans*-Cyclopentane-1,3-diyl)dipentadecan-1-ol 2b. A solution of **11** (1.0 g, 1.0 equiv, 1.43 mmol) in THF/EtOH 1:1 (100 mL) was stirred in the presence of 10% palladium on activated charcoal (300 mg, 0.2 equiv, 0.28 mmol) under an atmosphere of hydrogen gas at room temperature for 1 h. The catalyst was removed by filtration after heating to 40 °C and washed with a hot EtOH/THF mixture, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by flash silica gel column chromatography (cyclohexane/AcOEt 80:20) to give the THP ether compound (0.81 g, 1.33 mmol, 94%) as a white solid: R_f = 0.43 (cyclohexane/AcOEt 90:10); mp = 59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.02−1.14 (m, 2H, CyP), 1.25−1.36 (m, 52H, 26CH_2), 1.49−1.61 (m, 11H, (CH_2, THP), 4CH_2, OH), 1.68−1.87 (m, 6H, (CH, CyP), (CH_2, THP)), 3.38 (td, J = 6.7, 9.6 Hz, 1H, CH_2O), 3.50 (m, 1H, THP), 3.64 (m, 2H, CH_2OH), 3.72 (td, J = 6.9, 9.6 Hz, 1H, CH_2O), 3.87 (m, 1H, THP), 4.57 (m, 1H, THP); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (CH_2, THP), 25.5, 25.7, 26.2 (3CH_2), 28.7 (2CH_2), 29.4, 29.5 (2CH_2), 29.60 (2CH_2), 29.61 (2CH_2), 29.65 (2CH_2), 29.68 (2CH_2), 29.72 (2CH_2), 29.75 (1CH_2), 29.9 (2CH_2), 30.8 (CH_2, THP), 32.8 (CH_2), 33.0 (2CH, CyP), 36.8 (2CH_2), 38.8 (3C, CyP), 62.3 (CH_2, THP), 63.1 (CH_2OH), 67.7 (CH_2O), 98.8 (CH, THP); Accurate mass calcd for C_{40} H_{78} O_3 Na (M + Na)$^+$ 629.58487, found 629.5833. Anal. for C_{40} H_{78} O_3 calcd C, 79.14; H, 12.95. Found C, 79.05; H, 12.90. A solution of the previous THP ether (1.3 g, 1.0 equiv, 2.14 mmol) and PTSA (100 mg, 0.1 equiv, 0.21 mmol) in $CHCl_3$/MeOH 1:1 (100 mL) was stirred at 55 °C for 2 h. The reaction mixture was quenched with saturated aq $NaHCO_3$ and extracted three times with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/AcOEt 80:20) gave the diol **2b** (0.76 g, 1.45 mmol, 89%) as a white solid: R_f = 0.3 (cyclohexane/AcOEt 80:20); mp = 89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.02−1.14 (m, 2H, CyP), 1.25−1.36 (m, 54H, 27CH_2), 1.53−1.60 (m, 6H, 2CH_2, 2OH), 1.75−1.83 (m, 4H, CyP), 3.64 (t, J = 6.6 Hz, 4H, 2CH_2OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 25.7 (3CH_2), 28.7 (2CH_2), 29.4 (3CH_2), 29.59 (2CH_2), 29.61 (2CH_2), 29.65 (2CH_2), 29.68 (8CH_2), 29.72 (CH_2), 29.9 (2CH_2), 32.9 (2CH_2), 33.0 (CH, CyP), 36.8 (CH_2), 38.8 (3C, CyP), 63.1 (2CH_2OH); Accurate mass calcd for C_{35} H_{70} O_2 Na (M + Na)$^+$ 545.52735, found 545.5267; Accurate mass calcd for C_{35}

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H_{71} O_2 $(M + H)^+$ 523.54541, found 523.5462. Anal. for C_{35} H_{70} O_2 calcd C, 80.39; H, 13.49. Found C, 80.71; H, 13.32.

1,1′-*O*-((16,19-Methylidene)tetratriacontane)bis-(*R*)-glycidol 12a,b. To a solution of diol **2** (1.0 g, 1.0 equiv, 1.91 mmol) in hot cyclohexane (5 mL), a NaOH aqueous solution (50% wt, 1.83 g, 12 equiv, 22.9 mmol) and TBAB (370 mg, 0.6 equiv, 1.15 mmol) were added. After the mixture was stirred for 15 min at room temperature, epichlorhydrine (1.79 mL, 1.0 equiv, 1.9 mmol) was added. The resulting mixture was stirred at 70 °C for 12 h, cooled to room temperature, and then diluted with water. The viscous precipitate was filtered out and washed with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt and then with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by silica gel chromatography (cyclohexane/AcOEt 90:10) to yield diepoxyde **12** (0.54 g, 0.85 mmol) as white solid (monoepoxyde alcohol (0.40 g, 0.69 mmol) was also isolated): R_f = 0.56 (cyclohexane/AcOEt 80:20). ***cis* (12a)**: yield = 51%; mp = 60 °C; $[\alpha]_D^{20}$ = −4.0 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (1H, dt, J = 11.8, 9.9 Hz, CyP), 1.02−1.13 (2H, m, CyP), 1.25−1.34 (52H, m, 26CH_2), 1.54−1.62 (4H, m, 2CH_2), 1.74−1.82 (4H, m, CyP), 1.90 (1H, m, CyP), 2.61 (2H, dd, J = 5.0, 2.7 Hz, (CH_2, epoxide)), 2.80 (2H, dd, J = 5.0, 4.1 Hz, (CH_2, epoxide)), 3.14 (2H, m, (CH, epoxide)), 3.38 (2H, dd, J = 11.5, 5.6 Hz, CH_2O), 3.47 (2H, td, J = 6.7, 9.3 Hz, CH_2O), 3.49 (2H, td, J = 6.7, 9.3 Hz, CH_2O), 3.69 (2H, dd, J = 11.5, 3.1 Hz, CH_2O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.1 (2CH_2), 28.7 (2CH_2), 29.5 (2CH_2), 29.59 (2CH_2), 29.61 (2CH_2), 29.66 (2CH_2), 29.69 (10CH_2), 29.73 (2CH_2), 30.0 (2CH_2), 31.6 (2CH, CyP), 36.8 (2CH_2), 40.1 (2CH, CyP), 40.7 (CH_2, CyP), 44.7 (2CH_2O), 50.9 (2CHO), 71.5 (2CH_2O), 71.7 (2CH_2O); Accurate mass calcd for C_{41} H_{78} O_4 Na $(M + Na)^+$ 657.57978, found 657.5786. Anal. for C_{41} H_{78} O_4 calcd C, 77.54; H, 12.38. Found C, 77.39; H, 12.42. ***trans* (12b)**: yield = 45%; mp = 60 °C; $[\alpha]_D^{20}$ = −3.6 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.02−1.13 (2H, m, CyP), 1.25−1.34 (54H, m, 27CH_2), 1.54−1.62 (4H, m, 2CH_2), 1.74−1.82 (4H, m, CyP), 2.61 (2H, dd, J = 5.0, 2.7 Hz, (CH_2, epoxide)), 2.80 (2H, dd, J = 5.0, 4.1 Hz, (CH_2, epoxide)), 3.14 (2H, m, (CH, epoxide)), 3.38 (2H, dd, J = 11.5, 5.6 Hz, CH_2O), 3.47 (2H, td, J = 6.7, 9.3 Hz, CH_2O), 3.49 (2H, td, J = 6.7, 9.3 Hz, CH_2O), 3.69 (2H, dd, J = 11.5, 3.1 Hz, CH_2O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.1 (2CH_2), 28.7 (2CH_2), 29.5 (2CH_2), 29.59 (2CH_2), 29.61 (2CH_2), 29.66 (2CH_2), 29.69 (10CH_2), 29.73 (2CH_2), 30.0 (2CH_2), 33.0 (2CH, CyP), 36.8 (2CH_2), 38.8 (3C, CyP), 44.7 (2CH_2O), 50.9 (2CHO), 71.5 (2CH_2O 1), 71.7 (2CH_2O); Accurate mass calcd for C_{41} H_{78} O_4 Na $(M + Na)^+$ 657.57978, found 657.5794. Anal. for C_{41} H_{78} O_4 calcd C, 77.54; H, 12.38. Found C, 77.58; H, 12.51.

1,1′-Di-*O*-benzyle-3,3′-*O*-((16,19-methylidene)-tetratriacontan)-di-*sn*-glycerol 13a,b. Diepoxyde **12** (924 mg, 1.0 equiv, 1.45 mmol), commercially available sodium methanolate (15 mg, 0.1 equiv, 0.15 mmol) and benzyl alcohol (3.0 mL, 20 equiv, 29 mmol) were vigorously stirred at 70 °C for 12 h. At room temperature, the reaction mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aq NaCl, dried ($MgSO_4$), concentrated, and freeze-dried. Purification by silica gel column chromatography (cyclohexane/AcOEt 80:20) gave the compound **13** (1.09 g, 1.28 mmol) as a white solid: R_f = 0.23 (cyclohexane/AcOEt 80:20). ***cis* (13a)**: yield = 83%; mp = 52 °C; $[\alpha]_D^{20}$ = −5.0 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (1H, dt, J = 11.0, 9.9 Hz, CyP), 1.00−1.14 (2H, m, CyP), 1.25−1.34 (52H, m, 26CH_2), 1.21−1.58 (4H, m, 2CH_2), 1.67−1.81 (4H, m, CyP), 1.87−1.91 (1H, m, CyP), 2.48 (2H, d, J = 4.2 Hz, 2OH), 3.42−3.58 (12H, m, 6CH_2O), 3.99 (2H, m, 2CHO), 4.56 (4H, s, 2CH_2Ph), 7.26−7.38 (10H, m, 2Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.1 (2CH_2), 28.7 (2CH_2), 29.5 (2CH_2), 29.60 (2CH_2), 29.61 (2CH_2), 29.67 (2CH_2), 29.70 (10CH_2), 29.73 (2CH_2), 30.0 (2CH_2), 31.6 (2CH, CyP), 36.8 (2CH_2), 40.1 (2CH, CyP), 40.7 (CH_2, CyP), 69.5 (2CHO), 71.4 (2CH_2O), 71.7 (2CH_2O), 71.8 (2CH_2O), 73.4 (2CH_2Ph), 127.7 (6CH, Ph), 128.4 (4CH, Ph), 130.0 (2C, Ph). ***trans* (13b)**: yield = 74%; mp = 52 °C; $[\alpha]_D^{20}$ = −4.8 (c 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.00−1.14 (2H, m, CyP), 1.25−1.34 (54H, m, 27CH_2), 1.21−1.58 (4H, m, 2CH_2), 1.67−1.81 (4H, m, (4CH, CyP), 2.48 (2H, d, J = 4.2 Hz, 2OH), 3.42−3.58 (12H, m, 6CH_2O), 3.99 (2H, m, 2CHO), 4.56 (4H, s, 2CH_2Ph), 7.26−7.38 (10H, m, 2Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.1 (2CH_2), 28.7 (2CH_2), 29.5 (2CH_2), 29.60 (2CH_2), 29.61 (2CH_2), 29.67 (2CH_2), 29.70 (10CH_2), 29.73 (2CH_2), 30.0 (2CH_2), 33.0 (2CH, CyP), 36.8 (2CH_2), 38.76 (3C, CyP), 69.5 (2CHO), 71.4 (2CH_2O), 71.7 (2CH_2O), 71.8 (2CH_2O), 73.5 (2CH_2Ph), 127.7 (6CH, Ph), 128.4 (4CH, Ph), 130.0 (2C, Ph); Accurate mass calcd for C_{55} H_{94} O_6 Na $(M + Na)^+$ 873.69426, found 873.6946. Anal. for C_{55} H_{94} O_6 calcd C, 77.59; H, 11.13. Found C, 76.99; H, 11.07.

1,1′-Di-*O*-benzyle-2,2′-di-*O*-(3,7,11(*R*)-3,7,11,15-tetramethyl-hexadecyl)-3,3′-*O*-((16,19-methylidene)tetratriacontane)-di-*sn*-glycerol 14a,b. Sodium hydride (60% in oil, 246 mg, 5.0 equiv, 6.16 mmol) dispersed in dry THF (20 mL) and diol **13** (1.05 g, 1.0 equiv, 1.23 mmol) was added in solution in THF (20 mL). The reaction mixture was stirred for 1.5 h at room temperature, and then PhytBr (1.07 g, 2.4 equiv, 2.96 mmol) was added in solution in THF (4 mL). The solvent was distilled out during heating, and the reaction mixture was kept at 130 °C for 12 h. After cooling, water was added, and the reaction mixture was diluted with ether. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting crude mixture was purified by silica gel chromatography (cyclohexane/CH_2Cl_2 1:1) to afford **14** as a colorless oil: R_f = 0.23 (cyclohexane/CH_2Cl_2 1:1). ***cis* (14a)**: yield = 72%; $[\alpha]_D^{20}$ = +1.3 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (1H, dt, J = 11.0, 9.9 Hz, CyP), 0.83−0.87 (30H, m, 10CH_3), 1.01−1.40 (98H, m, 48CH_2, (CH_2, CyP)), 1.49−1.66 (8H, m, 8C*H*CH_3), 1.72−1.83 (4H, m, (2CH, CH_2, CyP)), 1.87−1.90 (1H, m, (CH_2, CyP)), 3.42 (4H, t, J = 6.7 Hz, 2CH_2O), 3.46−3.66 (14H, m, 6CH_2O, 2CHO), 4.55 (4H, s, 2CH_2Ph), 7.26−7.34 (10H, m, 10CH, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (2CH_3), 19.75 (2CH_3), 19.78 (2CH_3), 22.6 (2CH_3), 22.7 (2CH_3), 24.4 (2CH_2), 24.5 (2CH_2), 24.8 (2CH_2), 26.1 (2CH_2), 28.0 (2CH), 28.7 (2CH_2), 29.5 (2CH), 29.7 (16CH_2), 29.8 (2CH_2), 30.0 (2CH), 31.6 (2CH_2, CyP), 33.0 (2CH_2), 36.8 (2CH_2), 37.1 (4CH_2), 37.3 (4CH_2), 37.4 (2CH_2), 37.46 (2CH_2), 37.52 (2CH_2), 39.4 (2CH_2), 40.1 (2CH, CyP), 40.7 (CH_2, CyP), 68.9 (2CH_2O), 70.3 (2CH_2O), 70.8 (2CH_2O), 71.7 (CH_2O), 73.4 (2CH_2Ph), 77.9 (2CHO), 127.5 (2CH, Ph), 127.6 (4CH, Ph), 128.3 (4CH, Ph), 138.4 (2C, Ph). ***trans* (14b)**: yield = 60%; $[\alpha]_D^{20}$ = +1.2 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83−0.87 (30H, m, 10CH_3), 1.01−1.40 (100H, m, 48CH_2, (2CH_2, CyP)), 1.49−1.66 (8H, m, 8C*H*CH_3), 1.72−1.83 (4H, m, 2CH, CH_2, CyP), 3.42 (4H, t, J = 6,7 Hz, 2CH_2O), 3.46−3.66 (14H, m, 6CH_2O, 2CHO), 4.55 (4H, s, 2CH_2Ph), 7.26−7.34 (10H, m, 10CH, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 (2CH_3), 19.75 (2CH_3), 19.78 (2CH_3), 22.6 (2CH_3), 22.7 (2CH_3), 24.4 (2CH_2), 24.5 (2CH_2), 24.8 (2CH_2), 26.1 (2CH_2), 28.0 (2CH), 28.7 (2CH_2), 29.5 (2CH), 29.65, 29.71 (16CH_2), 29.8 (2CH_2), 30.0 (2CH), 32.8 (2CH_2, CyP), 33.0 (2CH_2), 36.8 (2CH_2), 37.1 (4CH_2), 37.3 (4CH_2), 37.4 (2CH_2), 37.46 (2CH_2), 37.52 (2CH_2), 38.8 (3C, CyP), 39.4 (2CH_2), 68.9 (2CH_2O), 70.3 (2CH_2O), 70.8 (2CH_2O), 71.7 (CH_2O), 73.4 (2CH_2Ph), 77.9 (2CH), 127.5 (2CH, Ph), 127.6 (4CH, Ph), 128.3 (4CH, Ph), 138.4 (2C, Ph); Accurate mass calcd for C_{95} H_{174} O_6 Na $(M + Na)^+$ 1434.32081, found 1434.3189. Anal. for C_{95} H_{174} O_6 calcd C, 80.79; H, 12.42. Found C, 80.89; H, 12.08.

2,2′-Di-*O*-(3,7,11(*R*)-3,7,11,15-tetramethyl-hexadecyl)-3,3′-*O*-((16,19-methylidene)tetratriacontane)-di-*sn*-glycerol 15a,b. A solution of **11** (797 mg, 1.0 equiv, 0.56 mmol) in THF/EtOH 1:1 (15 mL) was stirred in the presence of 20% $Pd(OH)_2/C$ (80 mg) under an atmosphere of hydrogen gas at room temperature for 3 h. The catalyst was removed by filtration after the solvent was heated to 40 °C and washed with the hot EtOH/THF mixture, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by flash silica gel column chromatography (cyclohexane/AcOEt 80:20) to give the tetraether **15** as a white solid: R_f = 0.17 (cyclohexane/AcOEt 90:10). ***cis* (15a)**: yield = 96%; mp = 35 °C; $[\alpha]_D^{20}$ = +4.6 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (1H, m, CyP), 0.83−0.89 (30H, m, 10CH_3), 1.03−1.40

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(98H, m, 48CH_2, (CH_2, CyP)), 1.47−1.66 (8H, m, 8CH), 1.73−1.85 (4H, m, (2CH, CH_2, CyP), 1.85−1.89 (1H, m, CyP), 2.17 (2H, t, J = 6.7, OH), 3.41−3.75 (18H, m, 8CH_2O, 2CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.68, 19.74, 19.76 (6CH_3), 22.6 (2CH_3), 22.7 (2CH_3), 24.4 (2CH_2), 24.5 (2CH_2), 24.8 (2CH_2), 26.1 (2CH_2), 26.9 (2CH_2), 28.0 (2CH), 28.7 (2CH_2), 29.5 (2CH), 29.61 (2CH_2), 29.62 (2CH_2), 29.7 (10CH_2), 29.8 (2CH_2), 30.0 (2CH_2), 31.6 (2CH_2, CyP), 32.8 (4CH), 36.8 (2CH_2), 37.1 (2CH_2), 37.3 (4CH_2), 37.35 (4CH_2), 37.38 (2CH_2), 37.45 (2CH_2), 37.49 (2CH_2), 39.4 (2CH_2), 40.2 (CH, CyP), 40.7 (CH_2, CyP), 63.1, 68.6, 71.0, 71.9, 78.3 (8CH_2O, 2CHO); Accurate mass calcd for C_{81} H_{162} O_6 Na (M + Na)$^+$ 1254.22691, found 1254.2295. Anal. for C_{81} H_{162} O_6 calcd C, 78.96; H, 13.25. Found C, 78.68; H, 13.29. ***trans*** **(15b)**: yield = 92%; mp = 34 °C; $[\alpha]_D^{20}$ = +4.9 (c 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83−0.89 (30H, m, 10CH_3), 1.03−1.40 (100H, m, 48CH_2, 2CH_2, CyP), 1.47−1.66 (8H, m, 8CH), 1.73−1.85 (4H, m, CyP), 2.17 (2H, t, J = 6.7, OH), 3.41−3.75 (18H, m, 8CH_2O, 2CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.68, 19.74, 19.76 (6CH_3), 22.6 (2CH_3), 22.7 (2CH_3), 24.4 (2CH_2), 24.5 (2CH_2), 24.8 (2CH_2), 26.1 (2CH_2), 26.9 (2CH_2), 28.0 (2CH), 28.7 (2CH_2), 29.5 (2CH), 29.61 (2CH_2), 29.62 (2CH_2), 29.7 (10CH_2), 29.8 (2CH_2), 30.0 (2CH_2), 32.8 (4CH), 33.0 (CH_2, CyP), 36.8 (2CH_2), 37.1 (2CH_2), 37.3 (4CH_2), 37.35 (4CH_2), 37.38 (2CH_2), 37.45 (2CH_2), 37.49 (2CH_2), 38.8 (3C, CyP), 39.4 (2CH_2), 63.1, 68.6, 71.0, 71.9, 78.3 (8CH_2O, 2CHO); Accurate mass calcd for C_{81} H_{162} O_6 Na (M + Na)$^+$ 1254.22691, found 1254.2291. Anal. for C_{81} H_{162} O_6 calcd C, 78.96; H, 13.25. Found C, 79.37; H, 13.31.

1,1′-Di-*O*-(*β*-D-galactopyranosyl)-*β*-D-glucopyranose)-2,2′-di-*O*-(3,7,11(*R*)-3,7,11,15-tetramethyl-hexadecyl)-3,3′-*O*-((16,19-methylidene)tetratriacontane)-di-*sn*-glycerol 1a,b. Hydroxylated tetraether **15** (525 mg, 1.0 equiv, 0.43 mmol) and 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-*α*-D-glucopyranose trichloroacetimidate **16** (2.59 g, 5.0 equiv, 2.13 mmol) were dissolved in CH_2Cl_2 (45 mL). TMSOTf (5% in CH_2Cl_2, 154 μL, 0.1 equiv, 0.04 mmol) was added. After being stirred for 2 h at room temperature, the reaction was quenched with saturated aq $NaHCO_3$, and the precipitate was filtered out and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (cyclohexane/AcOEt 80:20) to give glycosylated tetraether protected-**1** (1.08 g, 0.32 mmol) as a white solid: R_f = 0.5 (cyclohexane/AcOEt 70:30), ***cis*** **(protected-1a)**: yield = 92%; mp = 71 °C; $[\alpha]_D^{20}$ = +27.5 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.58−0.66 (m, 1H, CyP), 0.70 (6H, d, J = 6.5 Hz, 2CH_3), 0.81−0.87 (26H, m, CH_3), 0.99−1.40 (104H, m, 48CH_2, 6CH, (CH_2, CyP)), 1.47−1.54 (2H, m, 2CH), 1.74−1.85 (4H, m, (2CH, CH_2, CyP)), 1.86−1.93 (m, 1H, CyP), 3.19−3.91 (26H, m, 6CH_2O, 2CHO), 4.25 (2H, t, J = 9.5 Hz, (CHO, Lact)), 4.46−4.60 (4H, m, 2CH_2O), 4.76 (2H, d, J = 7.9 Hz, CHO, Lact), 4.85 (2H, d, J = 7.9 Hz, (CHO, Lact)), 5.35 (2H, dd, J = 10.3, 3.5 Hz, (CHO, Lact)), 5.47 (2H, dd, J = 9.9, 7.9 Hz, (CHO, Lact)), 5.69−5.73 (4H, m, (CHO, Lact)), 5.79 (2H, t, J = 9.5 Hz, (CHO, Lact)), 7.11−8.02 (70H, m, (14H, Bz)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 18.4, 19.3, 19.7, 22.6 (5CH_3), 24.3, 24.5, 24.8, 26.0, 28.0 (CH_2), 28.7 (CH), 29.47, 29.52, 29.61, 29.63, 29.65, 29.69, 29.73, 29.74, 30.0, 31.6 (CH_2, CyP), 32.79, 32.80, 33.8, 36.9, 37.3, 37.37, 37.40, 37.5, 40.2 (2CH, CyP), 40.7 (CH_2, CyP), 58.5, 61.0, 62.4, 67.5 (CHO), 68.1, 69.9 (CHO), 70.4, 70.6, 71.4, 71.5, 71.6 (CHO), 71.7, 71.8 (CHO), 72.85, 72.91, 72.94 (CHO), 76.0 (CHO), 77.6, 101.0 (OCHO), 101.4 (OCHO), 128.20, 128.23, 128.3, 128.50, 128.53, 128.56, 128.62, 128.66, 128.8, 129.35, 129.41, 129.5, 129.59, 129.63, 129.73, 129.76, 130.0 (35CH, Bz), 133.1, 133.2, 133.3, 133.4, 133.5 (7C, Bz), 164.8, 165.1, 165.2, 165.4, 165.5, 165.8. ***trans*** **(protected-1b)**: yield = 76%; mp = 69 °C; $[\alpha]_D^{20}$ = +30.1 (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.70 (6H, d, J = 6.5 Hz, 2CH_3), 0.81−0.87 (26H, m, CH_3), 0.99−1.40 (106H, m, 48CH_2, 6CH(Phyt), (CH_2, CyP)), 1.47−1.54 (2H, m, 2CH), 1.74−1.85 (4H, m, (CH, CH_2, CyP), 3.19−3.91 (26H, m, 6CH_2O, 2CHO), 4.25 (2H, t, J = 9.5 Hz, (CHO, Lact)), 4.46−4.60 (4H, m, 2CH_2O), 4.76 (2H, d, J = 7.9 Hz, (OCHO, Lact)), 4.85 (2H, d, J = 7.9 Hz, (OCHO, Lact)), 5.35 (2H, dd, J = 10.3, 3.5 Hz, (CHO, Lact)), 5.47 (2H, dd, J = 9.9, 7.9 Hz, (CHO, Lact)), 5.69−5.73 (4H, m, H-2b, (CHO, Lact)), 5.79 (2H, t, J = 9.5 Hz, (CHO, Lact)), 7.11−8.02 (70H, m, (14H, Bz)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 18.4, 19.3, 19.7, 22.6 (5CH_3), 24.2, 24.5, 24.8, 26.0, 28.0 (CH_2), 28.7 (CH), 29.47, 29.52, 29.61, 29.63, 29.65, 29.69, 29.73, 29.74, 30.0, 32.79, 32.80, 33.0 (CH_2, CyP), 33.8, 36.9, 37.3, 37.37, 37.40, 37.5, 38.8 (3C, CyP), 39.4, 58.5, 61.0, 62.4, 67.5 (CHO), 68.1, 69.9 (CHO), 70.4, 70.6, 71.4, 71.5, 71.6 (CHO), 71.7, 71.8 (CHO), 72.85, 72.91, 72.94 (CHO), 76.0 (CHO), 77.6, 101.0 (OCHO), 101.4 (OCHO), 128.20, 128.23, 128.3, 128.50, 128.53, 128.56, 128.62, 128.66, 128.8, 129.35, 129.41, 129.5, 129.59, 129.63, 129.73, 129.76, 130.0 (35CH, Bz), 133.1, 133.2, 133.3, 133.4, 133.5 (7C, Bz), 164.8, 165.1, 165.2, 165.4, 165.5, 165.8. A solution of sodium methanolate in MeOH (0.1 mol/L, 16 mL, 5.0 equiv, 1.62 mmol) was added to a solution of glycosylated tetraether protected-**1** (1.0 g, 1.0 equiv, 0.32 mmol) in MeOH (25 mL) and CH_2Cl_2 (20 mL). The resulting mixture was stirred at room temperature for 12 h and neutralized by adding Amberlite IR 120 resin. After filtration and concentration, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 80:20) and recrystallization (Et_2O) to yield final compound **1** (313 mg, 0.17 mmol) as white solid. ***cis*** **(1a)**: yield = 66%; mp > 250 °C; $[\alpha]_D^{20}$ = −5.7 (c 1, $CHCl_3$/MeOH 80:20); ^{1}H NMR (pyridine-d_5, 400 MHz) δ (ppm) 0.71−0.77 (m, 1H, CyP), 0.88−0.94 (30H, m, 10CH_3), 1.10−1.53 (98H, m, 48CH_2, (CH_2, CyP), 1.59−1.72 (8H, m, 8CH), 1.83−1.90 (4H, m, 2CH, CH_2, CyP), 2.09−2.13 (m, 1H, CyP), 3.46−3.52 (4H, m, 2CH_2O), 3.71 (2H, dd, J = 9.8, 6.1 Hz, CH_2O), 3.77−3.84 (6H, m, 3CH_2O), 3.87−3.90 (2H, m, (2CH, Lact)), 3.95−4.02 (4H, m, (4CH, Lact)), 4.04−4.09 (2H, m, 2CH, Lact), 4.14−4.18 (4H, m, 4CH, Lact), 4.26−4.35 (6H, m, (6CH, Lact)), 4.37−4.43 (2H, m, CH_2O), 4.45−4.57 (10H, m, CH_2O, (6CH, Lact), 2CHO), 4.90 (2H, d, J = 7.9 Hz, OCHO), 5.12 (2H, d, J = 7.9 Hz, OCHO), 6.10−7.30(m, OH); ^{13}C NMR (pyridine-d_5, 100 MHz) δ (ppm) 20.26, 20.31, 23.1, 23.2 (CH_3), 25.1, 25.2, 25.5, 26.9 (CH_2), 28.6 (CH), 29.5, 30.2, 30.35, 30.41 (CH_2), 30.5 (CH), 30.56, 30.7, 31.8 (2CH_2, CyP), 32.3 (CH_2), 33.4, 33.5 (CH), 37.4, 37.9, 38.04, 38.07, 38.10, 38.2, 39.9 (CH_2), 40.8 (CH, CyP), 41.3 (CH_2, CyP), 62.4, 62.5, 68.2, 72.0 (CH_2), 72.8, 75.0, 75.6, 76.8, 77.0, 77.6, 78.9, 82.4 (CH, Lact), 105.2 (OCHO), 106.1 (OCHO); Accurate mass calcd for C_{105} H_{202} O_{26} Na (M + Na)$^+$ 1902.43821, found 1902.4375. ***trans*** **(1b)**: yield = 48%; mp > 250 °C; $[\alpha]_D^{20}$ = −5.3 (c 1, $CHCl_3$/MeOH 80:20); ^{1}H NMR (pyridine-d_5, 400 MHz) δ (ppm) 0.88−0.94 (30H, m, 10CH_3), 1.10−1.53 (100H, m, 48CH_2, (2CH_2, CyP)), 1.59−1.72 (8H, m, 8CH), 1.83−1.90 (4H, m, (2CH, CH_2, CyP)), 3.46−3.52 (4H, m, 2CH_2O), 3.71 (2H, dd, J = 9.8, 6.1 Hz, CH_2O), 3.77−3.84 (6H, m, 3CH_2O), 3.87−3.90 (2H, m, (2CH, Lact)), 3.95−4.02 (4H, m, (4CH, Lact)), 4.04−4.09 (2H, m, (2CH, Lact)), 4.14−4.18 (4H, m, (4CH, Lact)), 4.26−4.35 (6H, m, (6CH, Lact)), 4.37−4.43 (2H, m, CH_2O), 4.45−4.57 (10H, m, CH_2O, (5CH, Lact), 2CHO), 4.90 (2H, d, J = 7.9 Hz, OCHO), 5.12 (2H, d, J = 7.9 Hz, OCHO), 6.10−7.30 (m, OH); ^{13}C NMR (pyridine-d_5, 100 MHz) δ (ppm) 20.26, 20.31, 23.1, 23.2 (CH_3), 25.1, 25.2, 25.5, 26.9 (CH_2), 28.6 (CH), 29.5, 30.2, 30.3, 30.4 (CH_2), 30.5 (CH), 30.6, 30.66, 32.3 (CH_2), 33.4, 33.46 (CH), 33.51 (2CH_2, CyP), 37.4, 37.9, 38.04, 38.07, 38.10, 38.2, 39.9 (CH_2), 40.8 (3C, CyP), 62.4, 62.5, 68.2, 72.0 (CH_2), 72.8, 75.0, 75.6, 76.8, 77.0, 77.6, 78.9, 82.4 (CH, Lact), 105.2 (OCHO), 106.1 (OCHO); Accurate mass calcd for C_{105} H_{202} O_{26} Na (M + Na)$^+$ 1902.43821, found 1902.4379.

CryoTEM Studies. Samples used in the CryoTEM studies were prepared from a lipid film obtained by evaporation of a $CHCl_3$/MeOH 2:1 solution (1.0 mg in 1.0 mL) of the lipids (N_2 flow). The films were dried under reduced pressure overnight and hydrated by 1.0 mL of pure water at 45 °C. After one night, the samples were sonicated (2 × 5 min) at 45 °C (thermocontrolled sonic bath). Each sample (5 μL) was deposited on a grid covered with a carbon film having 2 μm diameter holes previously exposed to treatment with UV-ozone. The excess of water was removed by absorption with filter paper to form a thin layer of water suspended inside the holes. This grid was then plunged quickly in liquid ethane (−178 °C). Grids were then placed in a suitable object carrier for observing the samples at −170 °C. Observation under a microscope was carried out in the mode Low Dose, limiting the effects of beam irradiation on the lipid material.

Images were recorded using an ultrasensitive camera 2K × 2K with a pixel size of 14 μm. The electron dose used was 10−20 electrons/Å^2. The image resolution under these conditions was about 2 nm.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org/.

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