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Synthesis of Archaeal Bipolar Lipid Analogues: A Way to Versatile Drug/Gene Delivery Systems

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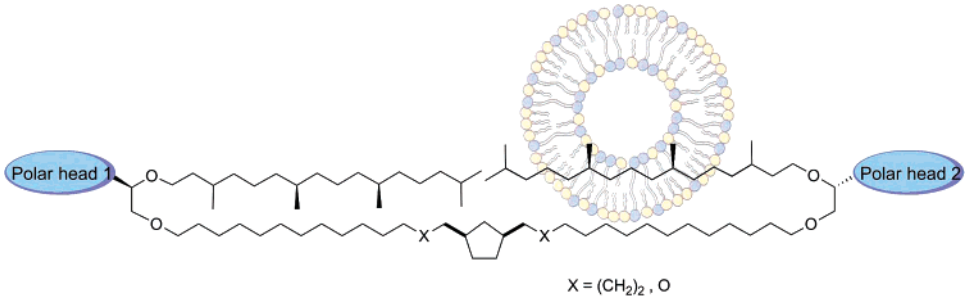

A synthetic route for the preparation of symmetrical and unsymmetrical archaeal tetraether-like analogues has been described. The syntheses are based upon the elaboration of hemimacrocyclic tetraether lipid cores from versatile building blocks followed by simultaneous or sequential introduction of polar head groups. Functionalizations of the tetraether lipids with neutral lactose or phosphatidylcholine polar heads and cationic glycine betaine moieties were envisaged both to increase membrane stability and to exhibit interactions with charged nucleic acids. Additionally, mannose and lactose triantennary clusters designed as multivalent ligands for selective interaction with lectin-type receptors were also efficiently synthesized for active cell/tissue targeting.

Introduction

Phospholipid liposomes or synthetic lipid-containing vesicles are self-assembled colloidal particles resulting from the organization of amphiphilic molecules in aqueous media. The hydrophilic head groups of the lipids forming liposomes are oriented toward the aqueous environments present inside and outside the liposomes, whereas the hydrophobic regions of the lipids are sandwiched between the polar head groups and away from the aqueous environments. Liposomes termed unilamellar vesicles (ULV) are composed of a single bilayer, and multilamellar vesicles (MLV, onion-like structure) contain multiple bilayers with an aqueous space separating the bilayers from one to the other. As liposome structures induce the presence of both hydrophobic and hydrophilic domains, they are able to entrap both hydrophilic and hydrophobic molecules, which is particularly attractive for encapsulation and drug delivery applications. An ideal vehicle or vector in drug delivery should be highly efficient in delivering the drug in a target-specific manner, stable in vitro as well as in vivo, nontoxic, non-immunogenic, and it should reduce the need for multiple administrations. Liposome delivery systems answer most of these conditions, and numerous studies have thus demonstrated the potentiality of liposomes as carriers of drugs, vaccines, genes, imaging agents, or antioxidants.[1−6]

However, a major drawback of liposome formulations is their lack of stability all along the extracellular route to the target sites, reducing the circulation time. Especially if an oral administration is considered, their poor stability at low pH and their tendency to be attacked by bile salts, gastrointestinal tract enzymes, or lipoproteins have considerably limited the interest

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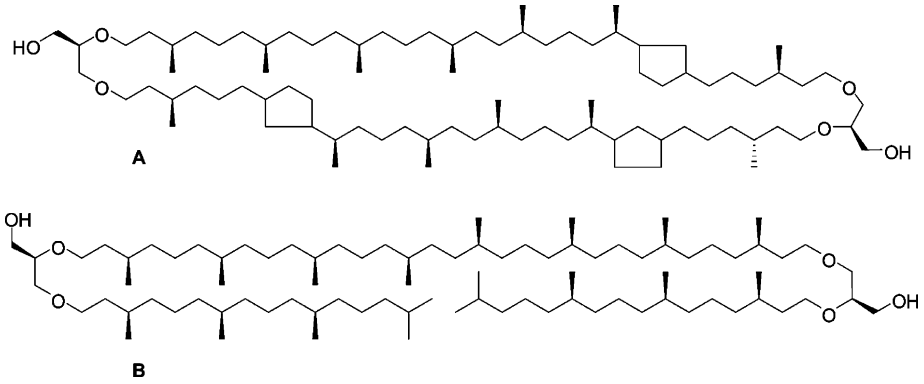

FIGURE 1. Typical basic structures of macrocyclic and hemimacrocyclic natural archaeal lipids.

of liposome systems in the delivery of medicines. Attempts to improve their stability either by incorporation of high amounts of cholesterol in the bilayer (improve mechanical properties, such as an increased stretching elastic modulus, resulting in stronger membranes and reduced permeability) or by coating the liposome surface with hydrophilic polyethyleneglycol polymers (sterically stabilized liposomes, called stealth liposomes, to reduce interactions with blood proteins) have increased the resident time and therefore have permitted better efficacy and passive targeting. Nevertheless, these improvements have not solved all the problems encountered with liposome technology, notably insufficient in vivo stability and lack of active targeting.

Archaeosomes are liposomes which are made from natural lipids found in archaea or from synthetically derived lipids that have the unique structure characteristics of archaeal membrane lipids.[7,8] The lipid components of archaea are strikingly different than those found in other forms of life, and they are considered as specific and useful markers of this evolutive line. Apart from the archaea domain, all forms of life usually have lipids that contain ester linking groups. However, for archaea, the lipids contain ether linkages and saturated isopranyl units (Figure 1). The ether linkages are chemically and enzymatically more stable than esters located in comparable positions within the structures of the lipids, and the branching methyl groups help to keep the membrane in a fluid state. In addition to possessing saturated branched residues and ether moieties, lipids of the archaea domain can also possess aliphatic phytanyl chains ether-linked to two *sn*-2,3-glycerol units that span the membrane from the inner to the outer side. When two chains of a particular head group span the membrane to another head group on the opposing surface, a macrocyclic unit is formed (Figure 1, type **A**), and when only one chain spans the membrane, a hemimacrocycle is formed (Figure 1, type **B**). The monolayer-type membrane organizations obtained from these tetraether derivatives inhibit lipid lateral diffusion phenomena and reduce flip-flop dynamics in comparison with standard bilayer systems.[9] In some cases, cyclopentyl units are incorporated into the spanning chains, and their number (up to 8) usually increases with the roughness of the life conditions.[10,11]

Thus, membranes of the archaea domain are relatively more stable than those of other forms of life, thereby enabling organisms containing membranes of this type to survive under extreme conditions of pH, temperature, pressure, salt concentration, and anaerobia. Within this context, natural archaeal lipids have been used as innovative materials in liposome formulations, exploiting their ability to enhance lipid membrane stabilities.[12,13] The poor availability of pure natural archaeal lipids forces scientists to design and synthesize realistic analogues. Indeed, approaches to synthetic hemimacrocyclic and macrocyclic tetraethers related to archaeal membranes have been reported during the past 20 years.[14−22] These synthetic bipolar compounds generally contain branched phytanyl chains and/or linear oligomethylene bridging chains; in some cases, aromatic or heterocyclic rings are also incorporated into the hydrophobic core. However, among the number of analogues already prepared so far, neither contains the specific cyclopentane rings and only few synthetic compounds reach the same length as in natural archaeal lipids. Additionally, most of the synthetic efforts were directed toward the preparation of tetraethers bearing phosphate moieties as polar head groups. No reports had appeared on the synthesis of neutral glycosylated or cationic tetraethers until our preliminary reports on the development of lactose- or glycine betaine-containing tetraethers for the development of drug or gene delivery systems.[23,24] Our strategy aims at fine-tuning the properties of conventional liposome mem-

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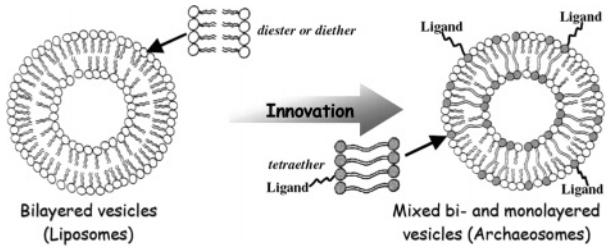

FIGURE 2. Stabilization of conventional liposome via the introduction of tetraether lipids.

branes (rigidity, fluidity) via the controlled modulation of its lipid composition (bilayer/monolayer-forming lipids) as natural archaea do. This work takes advantage of the outstanding properties of archaeal lipids to improve both the stability of the delivery system and the anchoring of cell-surface ligands into the lipid membrane (Figure 2).

In this paper, we report full details of the preparation of symmetrical and unsymmetrical neutral or cationic tetraether-type compounds **1**−**5** (Figure 3). Furthermore, with the aim to develop site-specific drug targeting, novel unsymmetrical synthetic tetraethers **6** and **7** containing a triantennary sugar (lactose or mannose) moiety were designed and synthesized in order to bind to lectin-type receptors (over)expressed on the cell surfaces.

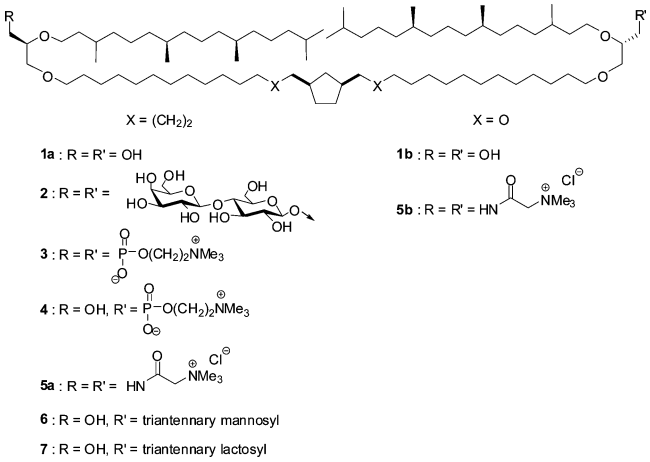

FIGURE 3. Synthetic analogues of archaeal membrane bipolar lipids.

The synthetic hemimacrocyclic bipolar lipids are actually characterized by the following: (1) the presence of a 31 or 33 atom-long bridging chain containing a cyclopentane ring (supposed to increase the lipid dispersion into water)[16] linked at both ends to two (*S*)-glycerol moieties via ether bonds, (2) two phytanyl chains having a combined length equivalent to that of the bridging chain, and (3) neutral hydroxyl groups (lipids **1a,b**), lactosyl moieties (lipid **2**), phosphatidylcholine units (lipids **3** and **4**), positive quaternary ammonium groups derived from glycine betaine to provide electrostatic interactions with negatively charged DNA (lipids **5a,b**), or a hydroxyl unit and a trimannosylated or trilactosylated ligand introduced at opposite ends of the lipophilic backbone (**6** and **7**). The presence of oxygen atoms within the spanning chains of lipids **1b** and **5b** results from our aim to simplify the synthetic pathway initially developed for tetraethers **1a**, **2**−**4**, **5a**, **6**, and **7**.

Results and Discussion

Preparation of Tetraether Diols. Intrigued by the presence of cyclopentane rings in natural archaeal lipids and their influence on the membrane structure, we have investigated and designed synthetic pathways that permit the introduction of five-membered rings into the hydrophobic core (Figure 4). Actually, the role of the cyclopentane residues in membrane properties was modeled by Chong et al., who clearly showed significant changes in the packing arrangement of structures containing such rings or not (0 or 4 rings).[25] These preliminary models denote a thinner and more packed membrane for the tetraether containing four rings than for the tetraether without any ring. In the present study, we focused on a *cis*-configured 1,3-disubstituted cyclopentyl unit; however, it is important to note that Montenegro et al. determined recently, by synthesis and NMR comparisons, the cyclopentane configuration in a natural archaeal lipid to be *trans*.[26] Our synthetic strategy is based on a final coupling between a phytanylated glycerol **8** and a symmetrical cyclopentane-containing bridging chain **9a,b** (Figure 4). Building block **8** was synthesized from phytol **10** and (*R*)-solketal **11**, and spacers **9a,b** were prepared from diol **12**, which results from an ozonolysis/reduction sequence on norbornene **13**.

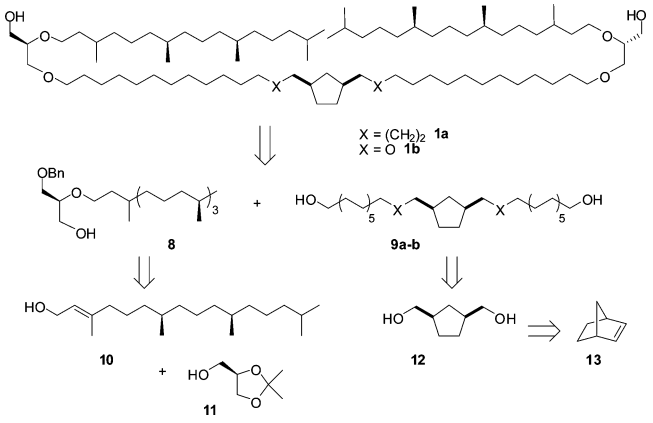

FIGURE 4. Retrosynthesis scheme tetraether analogues **1a,b**.

The results on the preparation of the glyceryl alcohol **8** have been previously reported;[20,27,28] however, due to low regioselectivity and/or insufficient efficiency of the syntheses, we improved its preparation from (*R*)-solketal **11** and phytol **10**. In brief, commercially available (*R*)-solketal **11** was benzylated (BnBr, NaH) at the primary position, and the acetonide moiety was cleaved under acidic conditions (IR-120, MeOH) to afford the diol **14** (85%, two steps) (Scheme 1). The latter was then monoprotected with trityl chloride (68% yield), and **15** reacted with phytanyl bromide[29] to furnish the differentially protected

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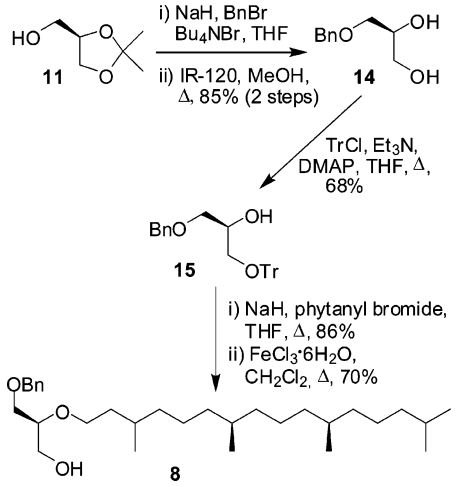
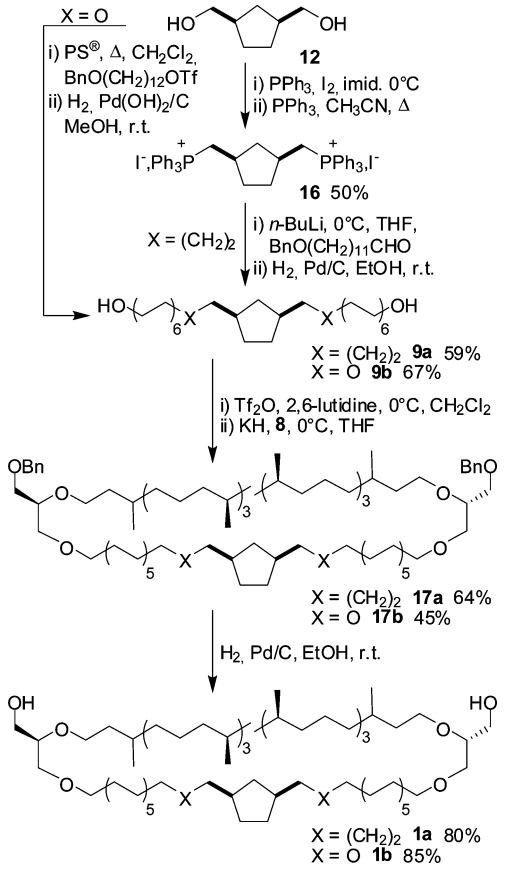
SCHEME 1. Preparation of Glyceryl Derivative 8



monophytanyl glycerol derivative. Final cleavage of the trityl group with iron chloride hexahydrate provided the targeted building block **8** in good yield (70%).[30] At this stage, we have been able to scale-up the synthesis of compound **8** to a 40 g scale with an overall yield of 35% (five steps).

The introduction of two oxygen atoms into the middle of the lipidic skeleton (**1b**) is an important structural difference, and the corresponding analogues dissent from natural archaeal lipids. However, our choice results from an easier synthetic route developed for the preparation of these tetraether-type analogues. Indeed, the bridging chain (**9b**) of compound **1b** was synthesized via a more efficient and a shorter reaction sequence than for its counterpart lipid **1a**, starting from the same diol **12**[16] (Scheme 2). Treatment of diol **12** with triphenylphosphine and iodine led to the formation of the corresponding 1,3-bis(iodomethyl)-cyclopentane, which underwent a nucleophilic displacement with triphenylphosphine in acetonitrile, providing the diphosphonium salt **16** in 50% yield (two steps).[31] Addition of 2 equiv of *n*BuLi conduced to the corresponding diylide that performed a double Wittig olefination with 12-benzyloxydodecancarboxaldehyde. A subsequent pallado-catalyzed hydrogenation of the resulting dialkene furnished in a one-pot reaction the saturated and deprotected diol **9a** in 30% overall yield (four steps from diol **12**). Coupling of 2 equiv of 12-benzyloxydodecanetriflate with diol **12** in the presence of proton sponge (PS) followed by a pallado-catalyzed hydrogenolysis of the benzyloxy groups provided the hydrophobic chain **9b**. The quality of the triflate anhydride was found to have a dramatic influence on the reaction yield. The best yield achieved for this two-step sequence was 80%, with an average of 65% for repeated runs. In addition, replacement of proton sponge by hydride bases such as NaH or KH was found to be ineffective and led mainly to elimination byproducts. The use of mesylated compounds also failed whatever the base used. Treatment of alcohol **8** with KH at 0 °C in dry THF followed by coupling with the ditriflates of diols **9a,b** afforded dibenzylated tetraethers **17a,b** in 64 and 45% yield, respectively. A final hydrogenolysis of the benzyloxy groups was conduced in the presence of palladium on carbon and concretized the preparation of our archaeal lipid analogues **1a** and **1b** in overall yields of 15 (seven steps) and 26% (five steps), respectively. We were able at this stage to scale-up the

SCHEME 2. Synthesis of Archaeal Lipid Analogues 1a,b



preparation of both bipolar lipids **1a** and **1b** to multigram quantities. However, concerning the preparation of **1a**, optimized yields were obtained when performing multiple batches of the double Wittig olefination instead of a unique large scale batch.

Introduction of Polar Heads. Having the diols **1a,b** in hand, our next goal was to introduce various polar head groups at one end or at both ends of these hemimacrocyclic structures. Indeed, to fine-tune the properties of our archaeal-like lipids, we envisaged further functionalizations of diols **1a,b** with neutral, zwitterionic, or cationic moieties. A series of mono- and difunctionalized tetraethers were thus prepared from diol **1a** (Scheme 3). Sugar polar heads are common in archaeal membrane lipids, and they exert tremendous influence on the membrane stability through highly cooperative polar interactions between polyol heads. Thus, we investigated the introduction of disaccharidic lactosyl groups in order to bring a sufficient hydrophilic character to our synthetic glycolipids. A double glycosylation reaction was carried out under standard thioglycoside chemistry[32] (NIS, Et_3SiOTf_{cat}) and proceeded at 0 °C to provide exclusively β-linked bislactosyl lipids. The β-selectivity resulted from neighboring group participation of the C-2 acetyl donor functionality. A final deprotection of the hydroxyl groups by a Zemplèn procedure (MeONa, MeOH) provided the fully deprotected dilactosyl tetraether **2** in 32% yield (two steps). The introduction of two phosphatidylcholine groups was performed via the double condensation of diol **1a** on bromomethyl phosphorodichloridate at room temperature, providing the corresponding diphosphonate, which reacts subsequently with

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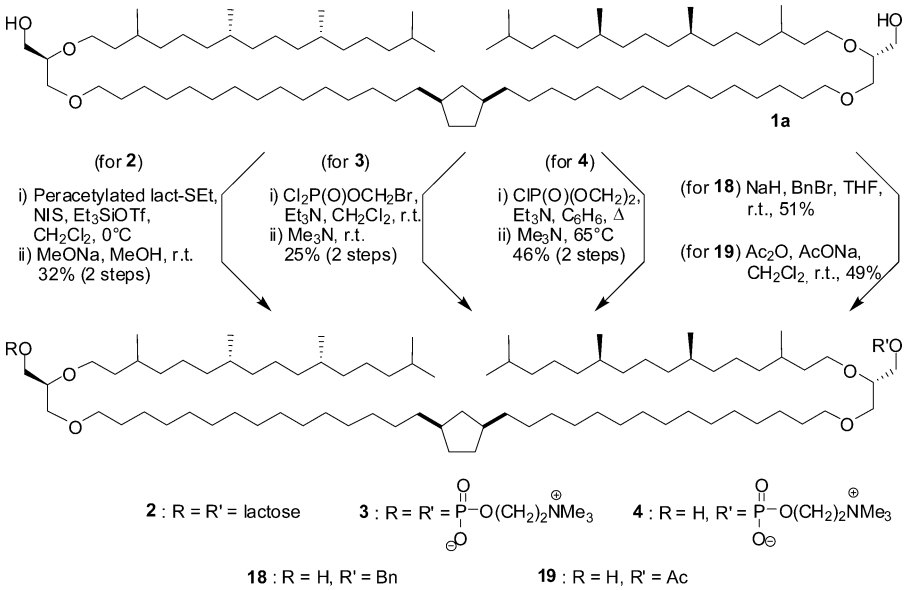
SCHEME 3. Introduction of Phosphatidylcholine, Lactose, Benzyl, and Acetyl Groups onto Diol 1a



trimethylamine in 4 days to give the diphosphatidylcholine tetraether **3** in 25% yield (two steps). Interestingly, the reaction of an excess of 2-chloro-2-oxo-1,2,3-dioxaphospholane[33−35] provided a selective monofunctionalization of diol **1a**. The following condensation of trimethylamine at 65 °C afforded the corresponding monophosphatidylcholine tetraether **4** in a relatively good yield (46%, two steps). Except for the latter example, the efficient monofunctionalization of **1a** required a selective protection of one of the two hydroxyl groups. We therefore investigated two types of monoprotection reaction (benzylation or acetylation). The benzyl bromide/NaH system provided clean monobenzylated tetraether **18** (51% yield), whereas monoacetylation of diol **1a** with acetic anhydride in the presence of triethylamine afforded monoacetylated tetraether **19** in 49% yield (recyclable diacetylated tetraether and remaining diol **1a** were isolated in 33 and 17% yield, respectively).

These bipolar lipids are supposed to exhibit properties in terms of membrane stability and permeability similar to those of lipids from natural thermoacidophile organisms.[29,34,36−38] In a previous study, these synthetic analogues were found to provide stable liposomes over wide temperature, in acidic conditions (pH 2) or/and in the presence of fetal calf serum (FCS) or sodium cholate (reflecting a bile salt-containing media).[23] In particular, incorporation of 30% of dilactosyl tetraether **2** into egg PC liposome formulations remarkably lowered the leakage of encapsulated 5(6)-carboxyfluorescein (CF) in 0.4% sodium cholate and serum (FCS) media. Additionally, archaeosomes made from exclusively diPC tetraether **3** have a pH stability that compares favorably to the stability of liposomes composed of natural *Thermoplasma acidophilium* tetraether lipids, which lost 20−30% of the marker after 10 min at pH 2.

Another application of archaeosomes as innovative gene delivery systems was additionally envisaged via the use of new synthetic cationic tetraether lipids. The prerequisite for gene therapy is carrier systems that envelop the therapeutic nucleic acid and facilitate incorporation by the target cell. This special problem of drug delivery needs to take into account the special properties of negatively charged nucleic acids. Typically, cationic lipids can be used to complex nucleic acids, thereby forming so-called lipoplexes; these complexes are then able to deliver genes into cells.[39−41] Numerous combinations of DNA with suspensions of vesicles composed of cationic lipids and neutral "helper" lipids, such as DOPE (dioleoylphosphatidylethanolamine) or cholesterol, were developed for transfection, but their use in clinical gene therapy trials was relatively unsatisfactory. Within this context, dicationic tetraethers **5a,b** were thus prepared from diols **1a,b** by introducing glycine betaine groups. Glycine betaine is a quaternary ammonium salt representing an important byproduct of the sugar industry (27% w/w of the molasses of sugar beet), and for this reason, it can be regarded as an interesting renewable raw material (Scheme 4).[42] A three-step sequence involving (1) a mesylation of the diols **1** by mesyl chloride, (2) a condensation of sodium azide in DMF at reflux, and (3) a pallado-catalyzed hydrogenation in EtOH/THF 1:1 provided diamines **20a,b** in 76 and 77% overall yields, respectively (three steps). *N*-Acylations of the tetraether diamines **20** were efficiently performed with the *N*-acyl thiazolidine-2-thione derivative **21**[43] of glycine betaine, affording dicationic tetraethers **5a,b** in 80% yield.

The reduction of the diazides to diamines **20** needs more comments. Indeed, when this step was done in a mixture of chlorinated solvents and ethanol ($CHCl_3$ or CH_2Cl_2/EtOH 1:1), a side reaction was encountered consisting of a monochlorination

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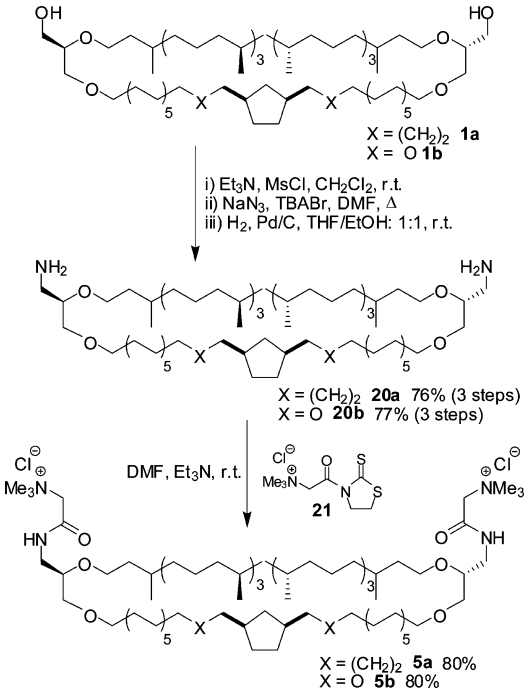
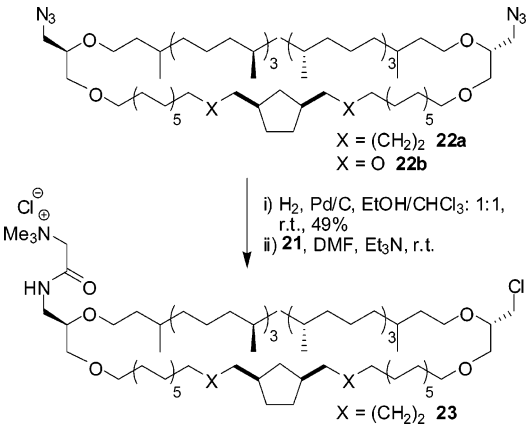
SCHEME 4. Preparation of Dicationic Archaeal Lipid Derivatives 5a,b



SCHEME 5. Chlorination/Reduction of Diazide 22a



of the diazide **22a** simultaneously with the reduction of the second azide. The subsequent acylation with **21** conduced to the corresponding monocationic tetraether **23** (Scheme 5).

From a physicochemical point of view, we studied the membrane organization of liposomes containing solely lipid **5a** or a lipid **5a**/DOPE (95:5 w/w) mixture by freeze fracture electron microscopy (FFEM), with the samples being etched before shadowing in order to better visualize the fracture propagation path. Interestingly, dispersion of bipolar lipid **5a** yielded at room temperature vesicles which were not fractured in the usual way along the midplane of the membrane (Figure 5). As previously described for diPC tetraether **3**,[23] the absence of a fracture midplane clearly indicates that the bipolar lipids span the membrane, forming a monolayer as with natural tetraethers (Figure 5a). The addition of 5% of DOPE yielded a small number of vesicles with midplane-fractured membranes (Figure 5b). Nevertheless, even in the presence of the bilayer-forming DOPE, the predominant structures observed were small cross-fractured vesicles due to the membrane-spanning tetraether lipids.

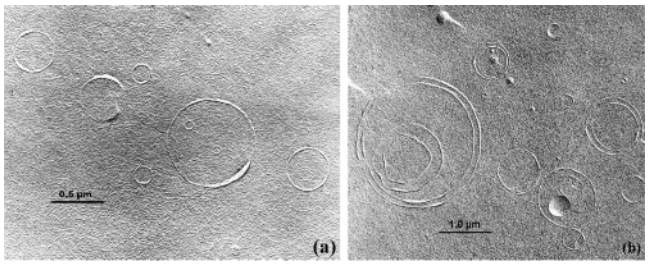
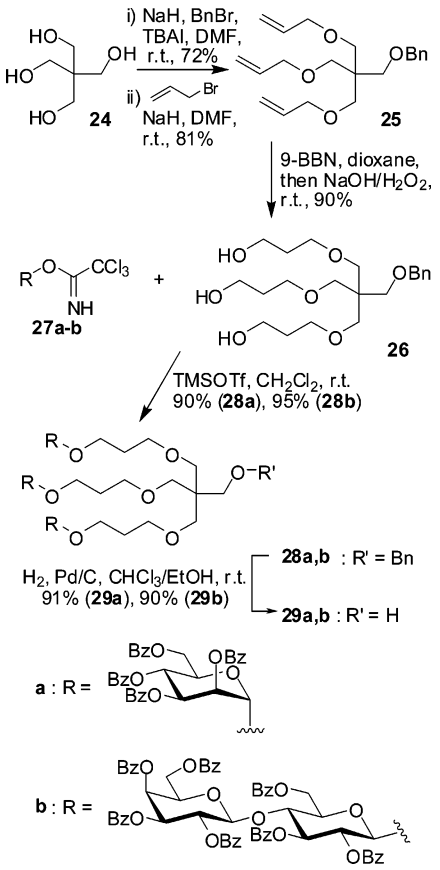


FIGURE 5. Freeze-fracture electron micrographs of cationic liposomes formed by (a) lipid **5a** and (b) lipid **5a**/DOPE (95:5 w/w).

SCHEME 6. Synthesis of Trimannosyl and Trilactosyl Clusters



Preliminary studies clearly revealed that combinations of DNA with suspensions of vesicles composed of these cationic tetraethers **5a,b** and neutral helper lipids such as DOPE exhibited efficient in vitro gene transfection properties. Cationic archaeosomes represent a new approach for modulating the lipidic membrane rigidity of the complexes they form with DNA.[24]

Targeting Archaeal Lipids. Lactose and mannose glycoconjugates are known to have specific interactions with lectin-type receptors and thus are good candidates for active targeting delivery. Lactosylated polymeric micelles exhibited higher transfection efficiency against cultured HepG2 cells possessing the asialoglycoprotein receptor in comparison to nontargeted micelles due to the contribution of a receptor-mediated endocytosis mechanism.[44] In the same way, mannosylated liposomes were recognized by macrophages via the mannose receptor and

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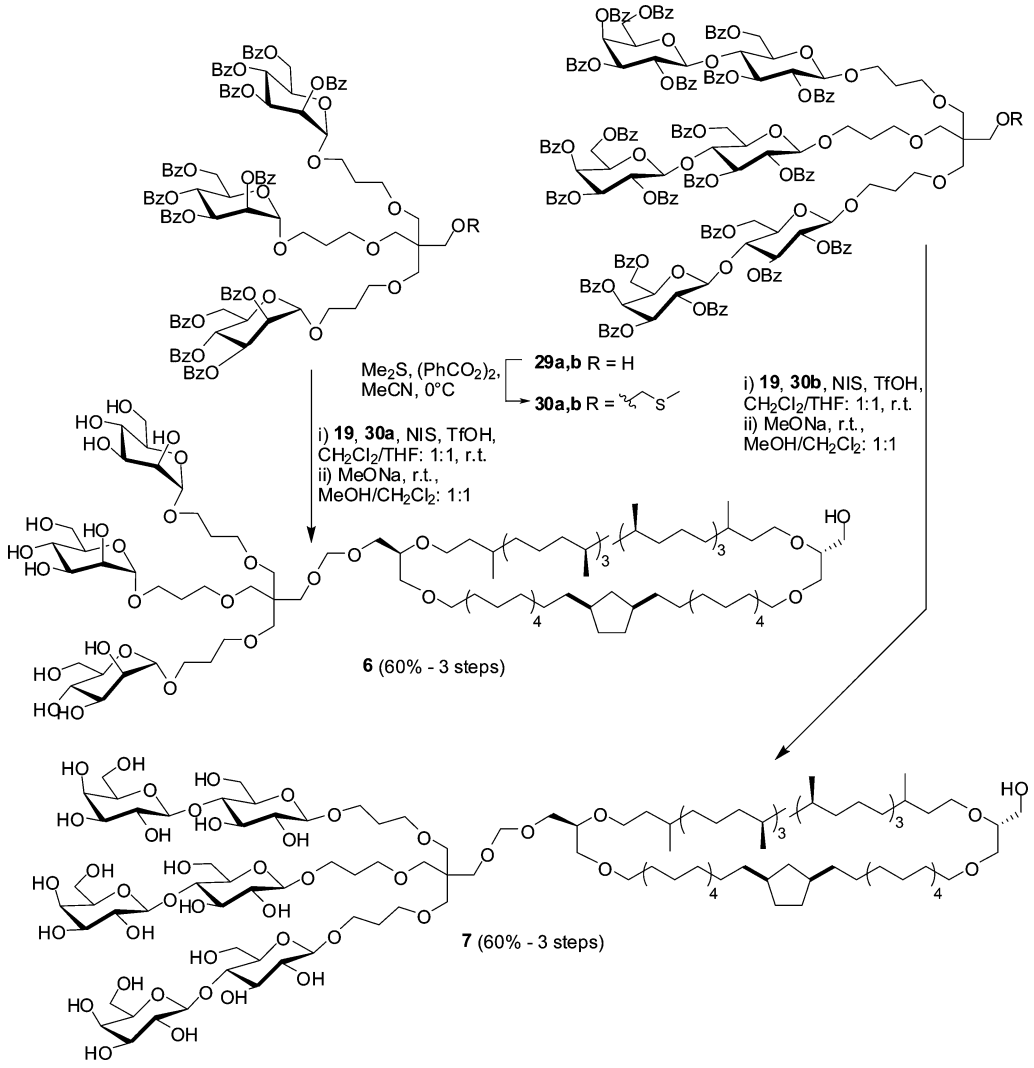
SCHEME 7. Introduction of Trimannosyl and Trilactosyl Clusters on Tetraether Lipids



led to specific biodistribution profiles.[45] Dilactosyl tetraether **2** may interact with cell surface; however, the promiscuity between the lipid and the ligand would probably inhibit interactions with the targeted cells. We thus designed elongated triglycosyl-type clusters which are known to increase significantly cell recognition.[46−48] These clusters are based on a pentaerythritol skeleton which is particularly adapted to that purpose. Monobenzylation of pentaerythritol (**24**) was achieved through a one-step alkylation with 0.25 equiv of benzyl bromide in the presence of tetrabutylammonium iodide and NaH (0.28 equiv).[49] The triallylation of the resulting triol with allyl bromide gave compound **25**[50] in good yield (81%) (Scheme 6). Hydroboration reactions with 9-BBN followed by the in situ conversion to the corresponding triol under oxidative/basic conditions provided triol **26** (90% yield).[51] Triglycosylation under standard glycosylation conditions with readily available trichloroacetamidate derivatives **27a,b**[52,53] permitted an easy access to trimannoside α-anomers and trilactoside β-anomers **28a,b** in 90 and 95% yields, respectively. The reactions were promoted by TMSOTf in CH_2Cl_2 at room temperature and needed the use of an excess of the donors (20 equiv). Finally, hydrogenolysis of the benzyloxy groups provided alcohols **29a,b** in good yields (91 and 90%, respectively).

Trimannosyl and trilactosyl clusters **29a,b** were then converted into hemimethylthioacetals **30a,b** in the presence of dimethyl sulfide and benzoyl peroxide in acetonitrile (Scheme 7). The two partners **30a** or **30b** and monoacetylated tetraether **19** were thus ready to accomplish the final coupling. The introduction of the sugar clusters on **19** was therefore achieved in the presence of *N*-iodosuccinimide and catalytic triflic acid. The final deacylation of all hydroxyl groups under Zemplèn conditions (MeONa, MeOH) furnished the two targeting lipids **6** and **7** in quite fair yields (60%, three steps). The trimannosyl tetraether **6** was easily and fully characterized by NMR (^{1}H and ^{13}C) and mass spectrometry. However, compound **7** was found

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to be insoluble in most of common organic solvents but d_5-pyridine in which ^{1}H NMR spectra could be easily recorded. The structure of **7** was also confirmed by high-resolution mass spectrometry. This drawback could make its formulation less easy than for its mannosyl counterpart, but it would not prevent the formation of archaeosomes including few percents of this trilactosyl tetraether.

Conclusions

In summary, we have synthesized a series of functionalized hemimacrocyclic symmetrical or unsymmetrical tetraethers where a cyclopentane ring is incorporated into the middle of the bridging chain, which reminds one of the structure of thermoacidophile archaeal lipids. The preparation of tetraether-type diols **1a,b** could be scaled up to multigram quantities that permit one to envisage numerous functionalizations and potential uses in drug/gene delivery. The introduction of various polar head groups (lactose, mannose, phosphatidylcholine, glycine betaine) provides a new generation of highly stable liposomes. Tetraether **1a** was also coupled with lactose and mannose triantennary clusters for the development of targeting archaeosomes. The efficiency and flexibility of the synthetic routes allow us to envisage the optimization of the ligand/receptor interaction by modulating the length and the molecular structure of the cluster between the lipidic core and the ligand.

Experimental Section

(*cis*-16,19-Methylidene)tetratriaconta-1,33-diol 9a. Wittig Olefination. To a suspension of phosphonium salt **16** (300 mg, 0.34 mmol, 1 equiv) in dry THF (6 mL) was added a solution of *n*-butyllithium (360 μL, 0.72 mmol, 2.1 equiv) in hexane (2 M) at 0 °C. The resulting orange mixture was stirred at 0 °C for 15 min. A solution of 12-benzyloxydodecancarboxaldehyde (239 mg, 0.69 mmol, 2.0 equiv) in THF (6 mL) was added, and the reaction mixture was stirred until discoloration. Water was added, and the aqueous phase was extracted with (PE/EtOAc 6:4). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 99:1) to yield unsaturated and dibenzylated product (150 mg, 63%) as a white solid: R_f = 0.6 (PE/EtOAc 8:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) (major isomer) 0.95−1.04 (m, 1H), 1.25−1.40 (m, 42H), 1.57−1.63 (m, 4H), 1.74−2.00 (m, 3H), 2.03 (m, 4H), 2.78 (m, 2H), 3.46 (t, J = 6.6 Hz, 4H), 4.50 (s, 4H), 5.27−5.37 (m, 4H), 7.24−7.34 (m, 10H); ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) (major isomer) 26.2, 27.5, 29.3, 29.5, 29.6, 29.7, 29.8, 30.0, 32.8, 38.2, 42.2, 70.5, 72.8, 127.4, 126.6, 128.3, 128.7, 135.0, 138.7. Anal. Calcd for $C_{49}H_{78}O_2$: C, 84.18; H, 11.25. Found: C, 83.70; H, 10.84.

Hydrogenation. A mixture of the previous compound (1.93 g, 2.8 mmol, 1 equiv) and palladium on activated carbon (500 mg, 25% w/w) in EtOH (150 mL) was stirred overnight at room temperature under hydrogen atmosphere. The reaction mixture was warmed (40−45 °C) and filtered on Celite. The filtrate was concentrated under reduced pressure to yield **9a** (1.34 g, 93%) as a white solid: R_f = 0.4 (PE/EtOAc 6:4); mp 89−92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.67 (m, 1H), 1.29 (m, 54H), 1.59 (m, 6H), 1.76 (m, 4H), 1.92 (m, 1H), 3.66 (t, J = 6.6 Hz, 4H); ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 25.9, 28.8, 29.6, 29.70, 29.72, 29.78, 29.81, 30.1, 31.9, 33.0, 36.9, 39.0, 40.4, 40.9, 63.2.

***cis*-1,3-Bis((dodecan-1-ol)oxymethyl)cyclopentane 9b.** Triflic anhydride (5.67 mL, 34.2 mmol, 2 equiv) was added dropwise to a solution of 2,6-lutidine (3.98 mL, 34.2 mmol, 2 equiv) in dry dichloromethane (50 mL) at 0 °C. The resulting red solution was stirred at 0 °C for 15 min. A solution of 12-benzyloxydodecanol (5 g, 17.1 mmol, 1 equiv) in dry dichloromethane (20 mL) was added, and the reaction mixture was stirred at room temperature for 1.5 h. Five percent aqueous HCl was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were successively washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 9:1) to yield corresponding 12-benzyloxydodecanetriflate (6.05 g, 83%) as a brown oil. Due to its relative instability, the compound was not characterized and was used rapidly in the next step.

A mixture of diol **12** (400 mg, 14.3 mmol, 1.1 equiv) and proton sponge (1.98 g, 9.2 mmol, 3 equiv) in dry dichloromethane (50 mL) was stirred at room temperature for 1 h. A solution of fresh 12-benzyloxydodecanetriflate in dry dichloromethane (10 mL) was added, and the reaction mixture was stirred at reflux for 5 days. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (PE/EtOAc 96:4) to yield benzylated product (1.58 g, 79%) as a white solid: R_f = 0.2 (PE/EtOAc 8:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90−0.98 (dt, J = 9.1, 12.7 Hz, 1H), 1.23−1.38 (m, 34H), 1.50−1.58 (m, 8H), 1.68−1.78 (m, 2H), 1.91−1.99 (m, 1H), 2.13−2.24 (m, 2H), 3.28 (d, J = 7.1 Hz, 4H), 3.39 (t, J = 6.6 Hz, 4H), 3.62 (t, J = 6.6 Hz, 4H), 4.50 (s, 4H), 7.25−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.59, 26.60, 29.3, 29.90, 29.91, 30.0, 30.1, 30.2, 34.3, 40.1, 70.9, 71.6, 73.2, 76.0, 127.9, 128.0, 128.8, 139.1; HRMS (ESI+) calcd for $C_{45}H_{74}O_4$ $(M + Na)^+$ 701.5485, found 701.5490; $(M + K)^+$ 717.5224, found 717.5227. Anal. Calcd for $C_{45}H_{74}O_4$: C, 79.59; H, 10.98. Found: C, 79.99; H, 10.90.

A mixture of previous dibenzylated diol (2.7 g, 4 mmol, 1 equiv) in THF/MeOH (100 mL, 3:1) and palladium dihydroxide (700 mg, 5% w/w) was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction mixture was warmed (40−45 °C) and filtered on Celite. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from cyclohexane to yield **9b** (1.7 g, 90%) as a white solid: R_f = 0.2 (PE/EtOAc 8:2); mp 63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90−0.98 (dt, J = 9.1, 12.7 Hz, 1H), 1.23−1.38 (m, 34H), 1.50−1.58 (m, 10H), 1.68−1.78 (m, 2H), 1.91−1.99 (m, 1H), 2.13−2.24 (m, J = 6.6 Hz, 2H), 3.28 (d, J = 7.1 Hz, 4H), 3.39 (t, J = 6.6 Hz, 4H), 3.63 (t, J = 6.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.1, 26.6, 29.2, 29.8, 29.8, 29.96, 29.98, 30.1, 33.2, 34.3, 40.1, 63.5, 71.5, 76.0; HRMS (ESI+) calcd for $C_{31}H_{62}O_4$ $(M + Na)^+$ 521.4546, found 521.4542. Anal. Calcd for $C_{31}H_{62}O_4$: C, 74.64; H, 12.53. Found: C, 74.61; H, 12.20.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-*sn*-diglycerol 1a. Triflic anhydride (611 μL, 3.6 mmol, 3.8 equiv) was added dropwise to a solution of 2,6-lutidine (423 μL, 7.6 mmol, 3.8 equiv) in dry dichloromethane (20 mL) at 0 °C, and the resulting red solution was stirred at 0 °C for 15 min. The diol **9a** (500 mg, 0.96 mmol, 1 equiv) was added, and the reaction mixture was stirred at room temperature and then at 30 °C until the complete dissolution of **9a**. Water was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were successively washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 9:1) to yield the corresponding ditriflate as a white solid: R_f = 0.8 (PE/EtOAc 9:1). Due to its relative instability the compound was not further characterized and was rapidly used in the next step.

To a suspension of potassium hydride (438 mg, 3.8 mmol, 4 equiv) and alcohol **8** (1.32 g, 2.87 mmol, 3 equiv) in dry THF (12 mL) was added a solution of ditriflate (750 mg, 0.96 mmol, 1 equiv) in dry THF (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Water was added, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 10:0 then

95:5) to yield **17a** (860 mg, 64%) as a yellow oil: $R_f = 0.8$ (PE/EtOAc 9:1); $[\alpha]^{20}_D$ +2.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.59−0.64 (m, 1H), 0.83−1.07 (m, 30H), 1.07−1.78 (m, 110H), 1.88 (m, 1H), 3.38−3.66 (m, 18H), 4.55 (s, 4H), 7.26−7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7, 19.77, 19.84, 22.7, 22.8, 24.5, 24.6, 24.9, 26.2, 28.1, 28.9, 29.6, 29.7, 29.8, 29.9, 30.1, 31.7, 32.9, 36.8, 37.16, 37.24, 37.4, 37.47, 37.54, 37.59, 38.9, 39.4, 40.2, 40.8, 69.0, 70.4, 70.8, 71.7, 73.4, 78.0, 127.6, 127.7, 128.4, 138.5. Anal. Calcd for $C_{95}H_{174}O_6$: C, 80.79; H, 12.42. Found: C, 81.19; H, 12.50.

A mixture of **17a** (1.77 g, 1.2 mmol, 1 equiv) and palladium dihydroxide (200 mg, 5% w/w) in THF/EtOH (50 mL, 1:1) was stirred at room temperature overnight under hydrogen atmosphere. The reaction mixture was warmed (40−45 °C) and filtered on Celite. The filtrate was concentrated under reduced pressure to yield **1a** (1.2 g, 80%) as a colorless oil: $R_f = 0.3$ (PE/EtOAc 8:2); $[\alpha]^{20}_D$ +8.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.58−0.66 (m, 1H), 0.84−0.89 (m, 30H), 1.05−1.83 (m, 110H), 1.86−1.95 (m, 1H), 2.22−2.29 (m, 2H), 3.4−3.7 (m, 18H); ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 19.66, 19.73, 19.77, 22.7, 22.8, 24.4, 24.5, 24.9, 26.2, 28.0, 28.8, 29.5, 29.7, 29.8, 29.9, 30.0, 32.8, 36.8, 37.1, 37.2, 37.34, 37.39, 37.44, 37.5, 38.8, 39.4, 40.2, 40.8, 63.06, 63.08, 68.70, 70.9, 71.0, 71.9, 78.4; HRMS (ESI+) calcd for $C_{81}H_{162}O_6$ $(M + Na)^+$ 1254.2269, found 1254.2264; $(M + K)^+$ 1270.2009, found 1270.2015. Anal. Calcd for $C_{81}H_{162}O_6$: C, 78.96; H, 13.25. Found: C, 79.26; H, 13.25.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methoxy]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-*sn*-diglycerol 1b. Compound **1b** was prepared from diol **9b** (1.0 g, 2.0 mmol) and alcohol **8** (2.78 g, 6.0 mmol) following a procedure similar to that of **1a**. Flash chromatography on silica gel (PE/EtOAc 99:1) provided **17b** (1.32 g, 45%) as a colorless oil: $R_f = 0.66$ (PE/EtOAc 90:10); $[\alpha]^{20}_D$ +1.7 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83−0.87 (m, 31H), 1.06−1.66 (m, 90H), 1.68−1.78 (m, 2H), 1.91−1.99 (m, 1H), 2.13−2.24 (m, 2H), 3.28 (d, $J = 7.1$ Hz, 4H), 3.39 (t, $J = 6.6$ Hz, 4H), 3.43 (t, $J = 6.6$ Hz, 8H), 3.50−3.70 (m, 10H), 4.54 (s, 4H), 7.26−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7, 19.77, 19.84, 19.86, 22.7, 22.8, 24.5, 24.56, 24.58, 24.9, 26.2, 26.3, 29.61, 29.62, 29.73, 29.75, 29.82, 29.9, 32.86, 32.88, 34.0, 39.8, 69.0, 70.4, 70.8, 71.2, 71.8, 73.4, 75.7, 78.0, 127.6, 127.7, 128.4, 138.5. Anal. Calcd for $C_{91}H_{166}O_8$: C, 78.73; H, 12.05. Found: C, 78.49; H, 12.17.

Titled product **1b** was obtained from **17b** in 85% yield as a colorless oil: $R_f = 0.23$ (PE/EtOAc 85:15); $[\alpha]^{20}_D$ +9.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.80−0.88 (m, 31H), 1.06−1.67 (m, 90H), 1.68−1.78 (m, 2H), 1.91−1.98 (m, 1H), 2.14−2.28 (m, 4H), 3.28 (d, $J = 7.1$ Hz, 4H), 3.40 (t, $J = 6.6$ Hz, 4H), 3.43 (t, $J = 6.6$ Hz, 8H), 3.50−3.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.70, 19.71, 19.76, 19.83, 22.71, 22.74, 22.76, 22.80, 24.4, 24.55, 24.56, 24.9, 26.18, 26.25, 28.05, 28.9, 29.55, 29.60, 29.7, 29.8, 29.9, 32.85, 34.01, 37.1, 37.2, 37.36, 37.39, 37.42, 37.46, 37.48, 37.52, 37.6, 38.8, 39.4, 39.8, 63.2, 68.7, 71.0, 71.2, 71.9, 75.7, 78.4; HRMS (ESI+) calcd for $C_{77}H_{154}O_8$ $(M + Na)^+$ 1230.1541, found 1230.1524; $(M + K)^+$ 1246.1281, found 1246.1234. Anal. Calcd for $C_{77}H_{154}O_8$: C, 76.56; H, 12.85. Found: C, 76.33; H, 12.90.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-di-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]-*sn*-diglycerol 2. Glycosylation. To a mixture of diol **1a** (21 mg, 0.017 mmol, 1 equiv) and peracetylated ethylthiolactoside (35 mg, 0.051 mmol, 3 equiv) in dichloromethane (3 mL) were added *N*-iodosuccinimide (15.3 mg, 0.068 mmol, 4 equiv) and triethylsilyl triflate (1.5 μL, 0.007 mmol, 0.4 equiv) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 10 min. Triethylamine then dichloromethane were added, and the organic phase was washed with 10% aqueous $Na_2S_2O_3$, water, and saturated NH_4Cl. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 9:1 then 7:3) to yield the peracetylated dilactosyl tetraether (15 mg, 36%) as a gum: $R_f = 0.4$ (PE/EtOAc 6:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.51−0.59 (m, 1H), 0.71−0.81 (m, 30H), 1.00−1.65 (m, 110H), 1.81−1.85 (m, 1H), 1.90−2.09 (s, 42H), 3.31−3.52 (m, 18H), 3.72 (t, $J = 9.2$ Hz, 2H), 3.79−3.82 (m, 4H), 4.00−4.08 (m, 6H), 4.39−4.42 (m, 4H), 4.47 (d, $J = 7.9$ Hz, 2H), 4.82−4.90 (m, 4H), 5.04 (dd, $J = 7.9$, 10.4 Hz, 2H), 5.12 (t, $J = 9.4$ Hz, 2H), 5.28 (d, $J = 2.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.65, 19.70, 19.76, 19.83, 20.6, 20.7, 20.8, 20.9, 21.0, 22.7, 22.8, 24.5, 24.6, 24.9, 26.2, 28.1, 28.9, 29.6, 29.65, 29.73, 29.76, 29.82, 29.9, 30.0, 30.1, 31.7, 32.9, 36.8, 37.4, 37.46, 37.49, 37.54, 37.7, 38.8, 39.4, 40.2, 40.8, 60.9, 62.1, 66.7, 69.15, 69.23, 69.4, 70.5, 70.7, 71.1, 71.7, 71.9, 72.6, 73.0, 76.4, 77.9, 78.0, 100.9, 101.2, 169.2, 169.6, 169.9, 170.2, 170.3, 170.46, 170.47.

Deacetylation. A solution of previous peracetylated derivative (15 mg, 0.006 mmol, 1 equiv) in MeOH/MeONa (2 mL, 0.05 M) was stirred at room temperature for 2 h. A solution of acetic acid in MeOH was added, and the reaction mixture was concentrated under reduced pressure. The residue was purified on LH-20 Sephadex gel ($CHCl_3$/MeOH/H_2O 7:3:0 then 7:3:0.5) to yield **2** (10 mg, 88%) as a gum: $R_f = 0.6$ ($CHCl_3$/MeOH/H_2O 8:2:0.5); $[\alpha]^{20}_D$ −5.3 (*c* 1, $CHCl_3$/MeOH 2:1); ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 0.51−0.61 (m, 1H), 0.74−0.82 (m, 30H), 0.90−1.70 (m, 110H), 1.80−1.84 (m, 1H), 3.26−3.95 (m, 42H), 4.25 (d, $J = 7.6$ Hz, 4H); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 19.7, 19.9, 20.0, 22.8, 22.9, 24.7, 24.8, 25.1, 26.4, 28.3, 29.1, 29.8, 29.9, 29.99, 30.03, 30.1, 30.2, 30.3, 32.0, 33.1, 37.1, 37.2, 37.3, 37.6, 37.7, 37.8, 38.0, 39.2, 39.7, 40.5, 41.1, 61.6, 61.8, 69.3, 69.4, 69.5, 70.5, 71.6, 72.2, 73.6, 73.9, 75.1, 75.3, 76.0, 78.2, 80.4, 103.7, 104.1; HRMS (FAB) calcd for $C_{105}H_{202}O_{26}$ $(M + Na)^+$ 1902.4382, found 1902.4383.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-di-*O*-(phosphatidylcholine)-*sn*-diglycerol 3. Nitrogen gas was bubbled in a solution of phosphoryl chloride (12 mL, 130 mmol, 1.7 equiv) in dry toluene (5 mL) for 15 min. 2-Bromoethanol (5.4 mL, 76 mmol, 1 equiv) was slowly added over 30 min, HCl was trapped by an aqueous solution (2 M KOH), and the reaction mixture was stirred at room temperature overnight under nitrogen atmosphere. The residue was distilled under reduced pressure (120 °C, 10 mmHg) to yield bromoethyldichlorophosphate (5.52 g).[54]

To a solution of bromoethyldichlorophosphate (118 mg, 0.49 mmol, 20 equiv) in dry dichloromethane (2 mL) were slowly added triethylamine (136 μL, 0.97 mmol, 40 equiv) and a solution of diol **1a** (30 mg, 0.024 mmol, 1 equiv) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 3 days under darkness and nitrogen atmosphere, 2:1 $CHCl_3$/MeOH and brine were added, and the aqueous phase was washed with 2:1 $CHCl_3$/MeOH. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on Sephadex LH-20 gel ($CHCl_3$/MeOH 2:1) and then on silica gel ($CHCl_3$/MeOH 9:1 then 8:2) to yield the bromide derivative (35 mg, 90%) as a colorless oil: $R_f = 0.3$ ($CHCl_3$/MeOH 2:1). Due to its relative instability, the compound was not further characterized and was used rapidly in the next step.

A solution of the previous bromide derivative (35 mg, 0.022 mmol, 1 equiv) in $CHCl_3$/*i*-PrOH/H_2O (2.7:2.25:0.75) and trimethylamine (1.95 mL, 31−35% in EtOH) was stirred at room temperature for 4 days. $CHCl_3$/MeOH (2:1) and aqueous NaCl were added, and the aqueous phase was extracted with 2:1 $CHCl_3$/MeOH. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on LH-20 Sephadex gel ($CHCl_3$/MeOH 2:1) and then on silica gel ($CHCl_3$/

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MeOH/H_2O/NH_4OH 65:35:5.5:0.5) to yield **3** (9.5 mg, 25%) as a gum: R_f = 0.1 ($CHCl_3$/MeOH/H_2O/NH_4OH 65:35:5.5:0.5); IR (neat) ν (cm^{-1}) 1087, 1232, 1467−1377, 2340, 2921−2852; ^1H NMR (CD_3OD/$CDCl_3$ 1:1, 400 MHz) δ (ppm) 0.61−0.63 (m, 1H), 0.83−0.87 (m, 30H), 1.06−1.75 (m, 110H), 1.90 (m, 1H), 3.32 (s, 18H), 3.40−3.65 (m, 14H), 3.73 (m, 4H), 3.90−3.93 (m, 4H), 4.24 (m, 4H); ^{13}C NMR (CD_3OD/$CDCl_3$ 1:1, 100 MHz) δ (ppm) 20.08, 20.13, 20.18, 20.19, 23.1, 23.2, 25.3, 25.6, 27.0, 28.8, 29.5, 30.4, 30.5, 30.56, 30.58, 32.5, 33.6, 37.6, 38.0, 38.1, 38.2, 40.2, 41.0, 41.5, 54.6, 60.2, 67.0, 69.6, 71.3, 72.5, 77.9; ^{31}P NMR (CD_3OD/$CDCl_3$ 1:1, 162 MHz) δ (ppm) 0.64 (s, 1P).

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1′-*O*-(phosphatidylcholine)-*sn*-diglycerol 4. To a solution of diol **1a** (50 mg, 0.04 mmol, 1 equiv) in benzene (2 mL) were added triethylamine (113 μL, 80 mmol, 20 equiv) and 2-chloro-2-oxo-1,2,3-dioxaphospholane (74 μL, 80 mmol, 20 equiv) at 0 °C, and the yellow mixture was stirred at room temperature for 36 h. The precipitate was filtered off, washed with toluene, and the solvents were evaporated under reduced pressure. The residue in acetonitrile was placed in an autoclave, and trimethylamine (1 mL) was added at −80 °C. In the autoclave, the reaction mixture was then warmed at 65 °C for 48 h and was concentrated under reduced pressure. The residue was purified on silica gel ($CHCl_3$/MeOH/H_2O/NH_4OH 60:40:0:0 then 65:35:5.5:0.5) to yield **4** (26 mg, 46%) as a gum: R_f = 0.6 ($CHCl_3$/MeOH/H_2O/NH_4OH 65:35:5.5:0.5); $[\alpha]^{20}_D$ −2.2 (*c* 1, $CHCl_3$/MeOH 2:1); ^1H NMR (CD_3OD/$CDCl_3$ 1:1, 400 MHz) δ (ppm) 0.61−0.63 (m, 1H), 0.83−0.87 (m, 30H), 1.06−1.75 (m, 110H), 1.90 (m, 1H), 3.35 (s, 9H), 3.44−3.68 (m, 14H), 3.75 (m, 2H), 3.89−3.96 (m, 4H), 4.26 (m, 2H); ^{13}C NMR (CD_3OD/$CDCl_3$ 1:1, 100 MHz) δ (ppm) 20.0, 20.07, 20.14, 23.0, 23.1, 24.98, 25.02, 25.4, 25.8, 26.7, 28.5, 29.0, 30.1, 30.3, 30.4, 30.5, 32.2, 33.32, 33.34, 37.3, 37.65, 37.73, 37.8, 37.9, 38.0, 38.1, 38.2, 39.3, 39.9, 40.7, 41.3, 47.0, 51.9, 62.4, 62.5, 65.3, 65.4, 67.58, 67.64, 69.4, 69.6, 71.0, 71.1, 72.3, 78.0; ^{31}P NMR (CD_3OD/$CDCl_3$ 1:1, 162 MHz) δ (ppm) 1.69 (s, 1P); HRMS (FAB) calcd for $C_{86}H_{175}NO_9P$ $(M + H)^+$ 1397.3005, found 1397.3010.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methoxy]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-*O*-diamino-*sn*-diglycerol 20a. Dimesylate. To a mixture of diol **1a** (200 mg, 0.16 mmol, 1 equiv) and triethylamine (67.9 μL, 0.49 mmol, 3 equiv) in dry dichloromethane (10 mL) was added mesyl chloride (75.6 μL, 1.02 mmol, 6 equiv) at 0 °C, and the reaction mixture was stirred overnight at room temperature. Water was added, and the organic phase was washed with saturated $NaHCO_3$ and brine. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 9:1) to yield the dimesylate derivative (214 mg, 95%) as a colorless oil: R_f = 0.5 (PE/EtOAc 8:2); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.61 (m, 1H), 0.83−0.88 (m, 30H), 1.02−1.81 (m, 110H), 1.88 (m, 1H), 3.04 (s, 6H), 3.41−3.69 (m, 14H), 4.24 (dd, J = 5.7, 10.8 Hz, 2H), 4.38 (dd, J = 3.6, 10.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.5, 19.57, 19.58, 19.61, 19.64, 19.67, 19.74, 22.6, 22.7, 24.4, 24.46, 24.48, 24.8, 26.1, 28.0, 28.7, 28.8, 29.5, 29.57, 29.60, 29.63, 29.68, 29.71, 29.73, 29.8, 30.0, 31.6, 32.76, 32.78, 36.7, 36.8, 36.9, 37.0, 37.27, 37.31, 37.33, 37.35, 37.37, 37.39, 37.40, 37.44, 37.48, 37.50, 38.8, 39.3, 40.1, 40.7, 69.0, 69.1, 69.70, 69.73, 71.9, 76.4.

Diazide 22a. A mixture of the previous dimesylate derivative (75 mg, 0.054 mmol, 1 equiv), sodium azide (10.5 mg, 0.15 mmol, 3 equiv), and tetrabutylammonium bromide (8.7 mg, 0.25 mmol, 0.5 equiv) in dry DMF (1 mL) was placed under nitrogen atmosphere. The resulting orange and heterogeneous mixture was stirred at reflux for 1 h. Water was added, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/Et_2O 98:2) to yield the diazide **22a** derivative (62 mg, 90%) as a colorless oil; R_f = 0.8 (CH_2Cl_2/Et_2O 98:2); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (m, 1H), 0.80−0.88 (m, 30H), 1.01−1.80 (m, 110H), 1.90 (m, 1H), 3.28−3.65 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.65, 19.68, 19.8, 22.6, 22.7, 24.3, 24.47, 24.49, 24.8, 26.1, 28.0, 28.8, 29.5, 29.6, 29.7, 30.0, 31.6, 32.8, 36.7, 37.0, 37.1, 37.3, 37.4, 37.4, 37.5, 38.8, 39.4, 40.2, 40.7, 52.1, 68.9, 70.1, 71.8, 77.88, 77.91; HRMS (ESI+) calcd for $C_{81}H_{160}N_6O_4$ $(M + Na)^+$ 1304.2399, found 1304.2454.

Diamine 20a. A mixture of diazide **22a** (90 mg, 0.07 mmol, 1 equiv) and palladium on activated carbon (9 mg, 10% w/w) in THF/EtOH (10 mL, 1:1) was stirred at room temperature for 5 h under hydrogen atmosphere. The reaction mixture was filtered on Celite, and the solvents were evaporated under reduced pressure to yield the diamine **20a** (77 mg, 90%) as a yellow oil: R_f = 0.5 (MeOH/Et_3N 99:1); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.60−0.63 (m, 1H), 0.83−0.87 (m, 30H), 0.98−1.93 (m, 111H), 3.07−3.12 (m, 2H), 3.21−3.25 (m, 2H), 3.41−3.77 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.5, 19.6, 19.66, 19.74, 22.6, 22.7, 24.40, 24.44, 24.5, 24.8, 26.0, 28.0, 28.59, 28.60, 29.59, 29.63, 29.68, 29.74, 29.81, 29.83, 29.9, 31.7, 32.80, 32.83, 33.0, 36.7, 36.9, 37.0, 37.3, 37.40, 37.44, 37.5, 39.4, 40.1, 40.5, 41.3, 68.8, 68.9, 70.4, 72.0, 73.9.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methoxy]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-*O*-diamino-*sn*-diglycerol 20b. Compound **20b** was prepared from diol **1b** (200 mg, 0.17 mmol, 1 equiv) following a procedure similar to that of **20a**.

Dimesylate. The crude material was purified by flash chromatography on silica gel (PE/EtOAc 9:1) to yield the dimesylate derivative (95%) as a colorless oil: R_f = 0.5 (PE/EtOAc 8:2); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83−0.88 (m, 31H), 1.01−1.63 (m, 90H), 1.68−1.77 (m, 2H), 1.95 (dt, J = 12.7, 7.2 Hz, 1H), 2.12−2.23 (m, 2H), 2.97 (s, 6H), 3.28 (d, J = 7.1 Hz, 4H), 3.39 (t, J = 6.6 Hz, 4H), 3.43 (t, J = 6.6 Hz, 4H), 3.46−3.69 (m, 10H), 4.18 (ddd, J = 1.0, 5.7, 10.9 Hz, 2H), 4.31 (dd, J = 3.6, 10.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.5, 19.56, 19.58, 19.60, 19.63, 19.67, 19.73, 22.6, 22.7, 24.3, 24.45, 24.47, 24.8, 26.1, 26.16, 26.18, 28.0, 28.8, 29.46, 29.51, 29.57, 29.60, 29.7, 29.75, 29.77, 32.8, 33.9, 36.87, 36.89, 36.96, 36.97, 37.26, 37.30, 37.32, 37.35, 37.38, 37.40, 37.43, 37.47, 39.3, 39.7, 69.00, 69.04, 69.1, 69.70, 69.73, 71.1, 71.9, 75.6, 76.3.

Diazide 22b. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2/Et_2O 98:2) to yield the diazide **22b** (90%) as a colorless oil: R_f = 0.8 (CH_2Cl_2/Et_2O 98:2); $[\alpha]^{20}_D$ +3.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83−0.87 (m, 31H), 1.06−1.66 (m, 90H), 1.68−1.78 (m, 2H), 1.95 (dt, J = 12.6, 7.5 Hz, 1H), 2.13−2.24 (m, 2H), 3.28 (d, J = 7.1 Hz, 4H), 3.33 (m, 4H), 3.38 (t, J = 6.6 Hz, 4H), 3.41−3.65 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.65, 19.68, 19.8, 22.6, 22.7, 24.3, 24.46, 24.48, 24.8, 26.1, 26.18, 26.20, 28.0, 28.7, 28.8, 29.47, 29.52, 29.6, 29.7, 29.8, 32.77, 32.79, 33.9, 36.97, 36.99, 37.05, 37.08, 37.28, 37.34, 37.40, 37.44, 37.5, 39.4, 39.7, 52.1, 68.88, 68.90, 70.1, 71.0, 71.1, 71.8, 75.6, 77.85, 77.89. Anal. Calcd for $C_{77}H_{152}N_6O_6$: C, 73.51; H, 12.18; N, 6.68. Found: C, 73.82; H, 12.71; N, 6.63.

Diamine 20b. The crude material was filtered on Celite, and the solvents were evaporated under reduced pressure to yield the diamine **20b** (90%) as a yellow oil: R_f = 0.5 (MeOH/Et_3N 99:1); $[\alpha]^{20}_D$ +12.9 (*c* 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.82−0.86 (m, 31H), 1.06−1.66 (m, 96H), 1.91−1.99 (m, 1H), 2.12−2.22 (m, 2H), 3.04−3.09 (m, 2H), 3.19−3.62 (m, 22H), 3.72−3.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.67, 19.74, 22.6, 22.7, 24.41, 24.43, 24.5, 24.8, 26.0, 26.15, 26.17, 28.0, 28.8, 29.45, 29.51, 29.54, 29.56, 29.6, 29.69, 29.71, 29.74, 29.81, 29.84, 32.8, 33.9, 36.85, 36.93, 37.29, 37.30, 37.39, 37.43, 37.47, 37.50, 37.52, 39.4, 39.7, 41.4, 68.7, 68.9, 70.9, 71.09, 71.13, 72.1, 73.7, 75.57, 75.59; HRMS (ESI+) calcd for $C_{77}H_{156}N_2O_6$ $(M + H)^+$ 1206.2041; $(M + Na)^+$ 1228.1861, found 1206.2041; 1228.1914.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-*O*-dibetaine-*sn*-diglycerol 5a. A mixture of diamine **20a** (90 mg, 0.07 mmol, 1 equiv) and activated glycine betaine **21** (56 mg, 0.22 mmol, 3 equiv) in DMF/Et_3N (11 mL, 10:1) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel ($CHCl_3$/acetone/MeOH/NH_4OH 8:6:5:1) to yield **5a** (84 mg, 80%) as a red gum: R_f = 0.4 ($CHCl_3$/acetone/MeOH/NH_4OH 8:6:5:1); $[\alpha]^{20}_D$ +13.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.60−0.63 (m, 1H), 0.83−0.87 (m, 30H), 1.00−1.80 (m, 110H), 1.91 (m, 1H), 3.39−3.7 (m, 18H), 3.44 (s, 18H), 4.58 (m, 2H), 4.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.0, 20.1, 20.3, 23.05, 23.15, 25.2, 26.1, 26.6, 28.4, 30.1, 30.2, 30.4, 32.1, 33.20, 33.22, 33.24, 37.2, 37.7, 37.8, 37.85, 37.89, 39.8, 40.6, 55.4, 65.7, 69.0, 69.1, 72.2, 73.6, 165.4; HRMS (ESI+) calcd for $C_{91}H_{184}N_4O_6$ (M^{2+}) 714.7108, found 714.7103.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methoxy]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1,1′-*O*-dibetaine-*sn*-diglycerol 5b. Compound **5b** was prepared from **20b** following a similar procedure to that of **5a**. The crude material was purified by flash chromatography on silica gel ($CHCl_3$/acetone/MeOH/NH_4OH 8:6:5:1) to yield **5b** (80%) as a red gum: R_f = 0.4 ($CHCl_3$/acetone/MeOH/NH_4OH 8:6:5:1); $[\alpha]^{20}_D$ +13.1 (*c* 0.81, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 1.05−1.08 (m, 30H), 1.23−2.15 (m, 96H), 3.46−3.83 (m, 26H), 3.54 (s, 18H), 4.39 (s, 4H); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 20.65, 20.71, 20.86, 20.91, 23.7, 23.8, 26.0, 26.4, 27.0, 27.8, 29.6, 30.1, 30.3, 31.1, 31.2, 31.27, 31.33, 31.52, 31.57, 31.61, 34.39, 34.42, 35.3, 38.8, 38.9, 38.98, 39.04, 41.0, 40.5, 41.8, 55.3, 66.3, 69.8, 70.1, 72.5, 72.7, 73.1, 77.0, 78.7, 78.9, 164.9; HRMS (ESI+) calcd for $C_{87}H_{176}N_4O_8$ (M^{2+}) 702.6744, found 702.6745.

Monocationic Tetraether 23. Compound **23** was prepared from **22a** following a similar procedure to that of **5a** except that the reduction of **22a** was done in 1:1 $CHCl_3$/MeOH instead of 1:1 THF/MeOH: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.57−0.65 (m, 1H), 0.83−0.88 (m, 30H), 1.04−1.97 (m, 111H), 3.35−3.70 (m, 18H), 3.46 (s, 9H), 4.60 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.56, 19.63, 19.7, 22.6, 22.7, 24.28, 24.34, 24.41, 24.44, 24.8, 26.0, 26.1, 27.9, 28.7, 29.52, 29.54, 29.57, 29.63, 29.65, 29.69, 29.77, 29.84, 29.93, 29.94, 31.6, 32.71, 32.73, 32.8, 33.0, 36.7, 36.86, 36.93, 37.2, 37.35, 37.42, 37.5, 38.7, 39.3, 40.1, 40.31, 40.33, 40.7, 43.90, 43.92, 45.8, 54.7, 65.4, 68.5, 68.6, 68.8, 69.92, 69.93, 70.86, 70.89, 71.71, 76.74, 76.8, 78.2, 78.3, 163.0; HRMS (ESI+) calcd for $C_{86}H_{172}N_2O_5Cl$ (M^+) 1348.2949, found 1348.2907.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1-*O*-benzyl-*sn*-diglycerol 18. To a solution of diol **1a** (584 mg, 0.47 mmol, 1 equiv) and [15]-crown-5 ether (50 μL) in dry THF (18 mL) was added sodium hydride (60% in mineral oil, 18.8 mg, 0.47 mmol, 1 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. Benzyl bromide (84 μL, 0.70 mmol, 1.5 equiv) was added dropwise, and the reaction mixture was stirred under reflux for 36 h. Et_2O and water were added, and the aqueous phase was extracted with Et_2O and EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 9:1 then 7:3) to yield **18** (320 mg, 51%) as a yellow oil: R_f = 0.5 (PE/EtOAc 9:1); $[\alpha]^{20}_D$ +3.3 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.60 (m, 1H), 0.75−0.80 (m, 30H), 1.00−1.80 (m, 110H), 1.80−1.96 (m, 1H), 2.17 (t, *J* = 6.2 Hz, 1H), 3.34−3.66 (m, 18H), 4.48 (s, 2H), 7.18−7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.67, 19.74, 22.6, 22.7, 24.4, 24.5, 24.8, 26.1, 28.0, 28.8, 29.47, 29.50, 29.65, 29.71, 29.8, 30.0, 31.6, 32.8, 36.7, 37.28, 37.34, 37.38, 37.44, 38.8, 39.4, 40.1, 40.7, 63.1, 68.6, 68.9, 70.3, 70.7, 70.9, 71.7, 71.9, 73.3, 77.9, 78.2, 127.5, 127.6, 128.3, 138.4.

3,3′-*O*-[1,33-Tetratriaconta-(*cis*-16,19-methylidene)methylene]-2,2′-di-*O*-[3,7-(*R*),11-(*R*),15-tetramethylhexadecyl]-1-*O*-acetyl-*sn*-diglycerol 19. A mixture of diol **1a** (1.01 g, 0.821 mmol, 1 equiv), acetic anhydride (293 mg, 2.9 mmol, 3.5 equiv), and sodium acetate (101 mg, 1.23 mmol, 1.5 equiv) in dry dichloromethane (50 mL) was stirred at reflux for 6.5 h. Water was added, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 8:2) to yield **19** (512 mg, 49%) as a colorless oil: R_f = 0.5 (PE/EtOAc 8:2); $[\alpha]^{20}_D$ +9.4° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.60 (m, 1H), 0.84−0.89 (m, 30H), 1.05−1.83 (m, 110H), 1.86−1.95 (m, 1H), 2.09 (s, 3H), 2.17 (t, *J* = 6.2 Hz, 1H), 3.40−3.78 (m, 16H), 4.11 (dd, *J* = 5.9, 11.6 Hz, 1H), 4.23 (dd, *J* = 4.1, 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.5, 19.56, 19.62, 19.67, 19.74, 20.9, 22.6, 22.7, 24.3, 24.46, 24.48, 24.8, 26.1, 28.0, 28.8, 29.5, 29.6, 29.7, 29.8, 30.0, 31.6, 32.8, 33.0, 36.7, 36.8, 36.9, 37.0, 37.1, 37.23, 37.33, 37.38, 37.44, 37.5, 38.8, 39.4, 40.1, 40.7, 63.08, 63.10, 64.1, 68.6, 68.90, 68.91, 70.19, 70.21, 70.9, 71.8, 71.9, 76.5, 78.2, 78.3, 171.0; HRMS (ESI+) calcd for $C_{83}H_{164}O_7$ ($M + Na$)$^+$ 1296.2375, found 1296.2378.

Benzyloxymethyl Trisallyloxymethylmethane 25. Monobenzylation. To a solution of pentaerythritol **24** (20 g, 147 mmol, 1 equiv) and tetrabutylammonium iodide (1.5 g) in DMF (100 mL) was added slowly at 0 °C sodium hydride (1.47 g, 36.8 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 1 h. Benzyl bromide (4.4 mL, 36.8 mmol, 0.25 equiv) was added, and the reaction mixture was stirred at room temperature for 12 h. MeOH was added, and the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with water. The organic phase was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with water, and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to yield monobenzylated derivative (5.8 g, 72%) as a white solid: R_f = 0.3 (EtOAc/PE/MeOH 10:5:1); mp 73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.22 (br s, 3H), 3.48 (s, 2H), 3.68 (s, 6H), 4.48 (s, 2H), 7.29−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 45.02, 64.22, 72.23, 73.71, 127.53, 127.82, 128.50, 137.66. These analytical data are in total agreement with previously published data.[55]

Triallylation. To a solution of the previous triol (1.45 g, 6.4 mmol, 1 equiv) and allyl bromide (2.8 mL, 32 mmol, 5 equiv) in DMF (90 mL) was added slowly at 0 °C sodium hydride (60% in mineral oil, 1.02 g, 25.6 mmol, 4 equiv), and the reaction mixture was stirred at room temperature for 12 h. MeOH was added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 7:3) to yield **25** (1.80 g, 81%) as a colorless oil: R_f = 0.76 (PE/EtOAc 6:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.56 (s, 6H), 3.60 (s, 2H), 4.02 (dt, *J* = 5.4, 1.5 Hz, 6H), 4.58 (s, 2H), 5.20 (dq, *J* = 10.4, 1.5 Hz, 3H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 3H), 5.95 (ddt, *J* = 10.4, 17.2, 5.4 Hz, 3H), 7.31−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 45.4, 69.3, 69.5, 72.2, 73.2, 116.1, 127.2 (2C), 128.2, 135.2, 139.0; HRMS (ESI+) calcd for $C_{21}H_{30}O_4$ ($M + Na$)$^+$ 369.2042, found 369.2036.

Benzyloxymethyl Tris(propanol-3-oxymethyl)methane 26. To a solution of **25** (797 mg, 2.3 mmol, 1 equiv) in dry dioxane (20 mL) was added at 0 °C 9-borabicylco[3.3.1]nonane (41 mL, 20.7 mmol, 9 equiv), and the reaction mixture was stirred at room temperature for 24 h. An aqueous solution of sodium hydroxide (50 mL, 3M) and a solution of H_2O_2 (8 mL, 30%) were added at 0 °C, and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was extracted with EtOAc, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/PE/MeOH 10:5:1) to yield **26**

(55) Dunn, T. J.; Neumann, W. L.; Rogic, M. M.; Woulfe, S. R. *J. Org. Chem.* **1990**, *55*, 6368−6373.

(830 mg, 90%) as a gum: $R_f = 0.25$ (EtOAc/PE/MeOH 10:5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.77 (m, 6H), 3.21 (br s, 3H), 3.40 (s, 2H), 3.41 (s, 6H), 3.56 (t, $J = 4.8$ Hz, 6H), 3.72 (t, $J = 5.4$ Hz, 6H), 4.47 (s, 2H), 7.27−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 31.6, 44.7, 61.5, 69.6, 70.5, 70.9, 73.3, 127.4, 127.5, 128.3, 138.4. Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 62.65; H, 8.75.

Benzyloxymethyl Tris(1-(perbenzoyl-D-mannosyl)propan-3-oxymethyl)methane 28a. To a mixture of the mannosyl donor **27a** (2.5 g, 3.4 mmol, 20 equiv) and triol **26** (68 mg, 0.17 mmol, 1 equiv) in dry dichloromethane (5 mL) was added a solution of trimethylsilyl trifluoromethane sulfonate (62 μL, 5% in dichloromethane), and the reaction mixture was stirred at room temperature for 12 h. $NaHCO_3$ (1 g) was added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 6:4) to yield **28a** (327 mg, 90%) as a white solid: $R_f = 0.23$ (PE/EtOAc 6:4); $[\alpha]^{20}_D$ −25.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.95 (m, 6H), 3.48 (s, 6H), 3.49 (s, 2H), 3.54 (m, 6H), 3.65 (m, 3H), 3.88 (m, 3H), 4.39−4.44 (m, 6H), 4.46 (m, 2H), 4.68 (dd, $J =$ 12.0, 2.3 Hz, 3H), 5.06 (d, $J = 1.6$ Hz, 3H), 5.69 (dd, $J = 3.0$, 1.8 Hz, 3H), 5.91 (dd, $J = 7.4$, 4.0 Hz, 3H), 6.12 (t, $J = 10.2$ Hz, 3H), 7.17−7.43 (m, 32H), 7.47 (t, $J = 7.4$ Hz, 3H), 7.56 (m, 6H), 7.82 (d, $J = 8.4$ Hz, 6H), 7.93 (d, $J = 8.4$ Hz, 6H), 8.03 (d, $J = 8.4$ Hz, 6H), 8.09 (d, $J = 8.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 30.1, 45.9, 63.2, 66.3, 67.3, 68.3, 69.2, 70.2, 70.6, 70.9, 73.7, 98.1, 127.67, 127.72, 128.6, 128.7, 128.8, 128.9, 129.0, 129.4, 129.5, 129.8, 130.1, 130.19, 130.23, 130.3, 133.4, 133.5, 133.8, 139.3, 165.7, 165.9, 166.5; HRMS (ESI+) calcd for $C_{123}H_{114}O_{34}$ $(M + Na)^+$ 2157.7090, found 2157.7075.

Benzyloxymethyl Tris(1-(perbenzoyl-D-lactosyl)propan-3-oxymethyl)methane 28b. To a mixture of the lactosyl donor **27b** (3.9 g, 3.2 mmol, 20 equiv) and triol **26** (64 mg, 0.16 mmol, 1 equiv) in dry dichloromethane (25 mL) was added a solution of trimethylsilyl trifluoromethane sulfonate (25 μL, 5% in dichloromethane). The reaction mixture was stirred at room temperature for 12 h. $NaHCO_3$ (1 g) was added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 6:4) to yield **28b** (541 mg, 95%) as a white solid: $R_f = 0.14$ (PE/EtOAc 6:4); $[\alpha]^{20}_D$ +34.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.52 (m, 6H), 2.86 (dd, $J = 8.9$, 12.7 Hz, 6H), 3.02 (t, $J = 6.1$ Hz, 6H), 3.06 (s, 2H), 3.30−3.38 (dt, $J = 6.3$, 13.2 Hz, 3H), 3.55−3.68 (m, 9H), 3.70 (dt, $J = 6.3$, 13.2 Hz, 3H), 3.79 (m, 3H), 4.15 (t, $J = 9.4$ Hz, 3H), 4.23 (s, 2H), 4.35−4.51 (dd, $J = 4.1$, 12.2 Hz, 6H), 4.49 (d, $J = 7.9$ Hz, 3H), 4.78 (d, $J = 7.9$ Hz, 3H), 5.25−5.37 (m, 6H), 5.61−5.71 (m, 9H), 7.06 (t, $J = 7.8$ Hz, 6H), 7.13 (t, $J = 7.6$ Hz, 8H), 7.17−7.56 (m, 54H), 7.65 (d, $J = 8.4$ Hz, 6H), 7.82 (d, $J =$ 8.1 Hz, 12H), 7.91 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 29.7, 45.0, 61.1, 62.4, 67.48, 67.53, 69.4, 69.9, 71.4, 71.78, 71.83, 72.9, 73.0, 76.0, 101.0, 101.3, 127.0, 127.4, 128.3, 128.4, 128.61, 128.64, 128.7, 128.9, 129.3, 129.4, 129.5, 129.6, 129.68, 129.74, 129.78, 129.82, 130.0, 133.2, 133.3, 133.5, 133.6, 139.0, 164.8, 165.2, 165.3, 165.4, 165.6, 165.9; HRMS (ESI+) calcd for $C_{204}H_{180}O_{58}$ $(M + Na)^+$ 3580.1033, found 3580.1019.

Tris(1-(perbenzoyl-D-mannosyl)propan-3-oxymethyl)methanol 29a. A mixture of **28a** (80 mg, 0.04 mmol, 1 equiv) and palladium on activated carbon (15 mg, 20% w/w) in $CHCl_3$/MeOH (6 mL, 1:1) was stirred at room temperature for 3 h under hydrogen atmosphere. The reaction mixture was filtered on Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 6:4) to yield **29a** (69 mg, 91%) as a white solid: $R_f = 0.5$ (PE/EtOAc 6:4); $[\alpha]^{20}_D$ −34.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.90 (m, 6H), 2.90 (t, $J = 5.9$ Hz, 1H), 3.46 (s, 6H), 3.51 (t, $J = 6.1$ Hz, 6H), 3.59 (m, 3H), 3.75 (d, $J = 5.0$ Hz, 2H), 3.88 (m, 3H), 4.35 (m, 3H), 4.41 (dd, $J = 12.0$, 4.4 Hz, 3H), 4.63 (dd, $J =$ 12.0, 2.3 Hz, 3H), 5.02 (d, $J = 1.6$ Hz, 3H), 5.62 (dd, $J = 3.0$, 1.8 Hz, 3H), 5.84 (dd, $J = 7.4$, 4.0 Hz, 3H), 6.05 (t, $J = 10.0$ Hz, 3H), 7.18 (m, 6H), 7.24−7.35 (m, 21H), 7.40 (t, $J = 7.5$ Hz, 3H), 7.49 (m, 6H), 7.75 (d, $J = 8.4$ Hz, 6H), 7.87 (d, $J = 8.5$ Hz, 6H), 7.96 (d, $J = 8.4$ Hz, 6H), 8.02 (d, $J = 8.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 30.1, 45.4, 63.2, 66.0, 66.1, 67.3, 68.6, 69.2, 70.6, 70.9, 71.9, 98.1, 128.7, 128.8, 128.9, 129.0, 129.4, 129.5, 129.8, 130.1, 130.2, 130.25, 130.29, 133.5, 133.6, 133.8, 165.8, 165.89, 166.6; HRMS (ESI+) calcd for $C_{116}H_{108}O_{34}$ $(M + Na)^+$ 2067.6618, found 2067.6662. Anal. Calcd for $C_{116}H_{108}O_{34}$: C, 68.09; H, 5.32. Found: C, 68.37; H, 5.50.

Tris(1-(perbenzoyl lactosyl)propan-3-oxymethyl)methanol 29b. A mixture of **28b** (120 mg, 0.04 mmol, 1 equiv) and palladium on activated carbon (24 mg, 20% w/w) in $CHCl_3$/EtOH (20 mL, 1:1) was stirred at room temperature for 3 h under hydrogen atmosphere. The reaction mixture was filtered on Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 1:1) to yield **29b** (105 mg, 90%) as a white solid: $R_f = 0.5$ (PE/EtOAc 1:1); $[\alpha]^{20}_D$ +53.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.52 (m, 6H), 2.79 (d, $J = 9.2$ Hz, 3H), 2.87 (d, $J = 9.2$ Hz, 3H), 3.02 (t, $J = 6.4$ Hz, 6H), 3.22 (s, 2H), 3.30−3.38 (m, 3H), 3.58−3.67 (m, 7H), 3.70−3.75 (m, 6H), 3.80 (t, $J = 6.8$ Hz, 3H), 4.15 (t, $J =$ 9.4 Hz, 3H), 4.40 (dd, $J = 4.1$, 12.2 Hz, 3H), 4.49 (d, $J = 10.8$ Hz, 3H), 4.57 (d, $J = 7.9$ Hz, 3H), 4.78 (d, $J = 7.9$ Hz, 3H), 5.25−5.37 (m, 6H), 5.61−5.71 (m, 9H), 7.06 (t, $J = 7.7$ Hz, 6H), 7.13 (t, $J = 7.7$ Hz, 6H), 7.20−7.50 (m, 48H), 7.54 (t, $J = 7.5$ Hz, 3H), 7.65 (d, $J = 7.2$ Hz, 6H), 7.81−7.84 (m, 12H), 7.86−7.94 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 29.6, 44.3, 61.1, 62.4, 65.6, 67.2, 67.5, 67.8, 69.9, 71.1, 71.4, 71.8, 72.9, 73.0, 76.1, 101.0, 101.2, 128.3, 128.4, 128.56, 128.60, 128.63, 128.7, 128.9, 129.3, 129.4, 129.5, 129.6, 129.67, 129.70, 129.8, 130.0, 133.2, 133.26, 133.30, 133.5, 133.6, 164.8, 165.2, 165.3, 165.5 (2C), 165.6, 165.9; HRMS (ESI+) calcd for $C_{197}H_{174}O_{58}$ $(M + Na)^+$ 3490.0564, found 3490.0558; $(M + K)^+$ calcd 3506.0303, found 3506.0339. Anal. Calcd for $C_{197}H_{174}O_{58}$: C, 68.20; H, 5.06. Found: C, 67.92; H, 5.08.

Trimannosyl Cluster Tetraether 6. Preparation of 30a. A solution of **29a** (50 mg, 0.024 mmol, 1 equiv) in dry acetonitrile was concentrated under reduced pressure and dried under reduced pressure for 2 h. The residue (**29a**) was dissolved in degassed dry acetonitrile (0.5 mL), then dimethyl sulfide (16 μL, 192 mmol, 8 equiv) and benzoyl peroxide (26 mg, 96 mmol, 4 equiv) were added at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, EtOAc was added, and the organic phase was washed with brine. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 98:2) to yield **30a** (33 mg, 80%) as a white solid. The product was rapidly characterized (some impurities were found in the NMR spectra) and was used as such in the next step: $R_f = 0.3$ (PE/EtOAc 6:4); ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.94 (m, 6H), 2.1 (s, 3H), 3.38 (s, 6H), 3.51 (m, 8H), 3.62 (m, 3H), 3.86 (m, 3H), 4.35−4.44 (m, 6H), 4.52 (s, 2H), 4.66 (dd, $J = 12.0$, 2.3 Hz, 3H), 5.04 (d, $J = 1.6$ Hz, 3H), 5.66 (dd, $J = 3.1$, 1.8 Hz, 3H), 5.87 (dd, $J = 7.4$, 4.0 Hz, 3H), 6.09 (t, $J = 10.2$ Hz, 3H), 7.15−7.55 (m, 36H), 7.75 (d, $J = 8.4$ Hz, 6H), 7.87 (d, $J = 8.4$ Hz, 6H), 7.97 (d, $J = 8.4$ Hz, 6H), 8.02 (d, $J =$ 8.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 13.9, 29.8, 45.4, 62.9, 65.9, 67.0, 68.0, 68.9, 69.9, 70.2, 70.6, 75.8, 97.8, 128.4, 128.48, 128.52, 128.6, 129.1, 129.2, 129.4, 129.8, 129.87, 129.91, 130.0, 130.3, 133.1, 133.2, 133.5, 165.43, 165.44, 166.2.

Preparation of 6 (Protected). A mixture of **30a** (20 mg, 0.010 mmol, 1 equiv) and **19** (14 mg, 0.012 mmol, 1.2 equiv) in dry dichloromethane (2 mL) was concentrated under reduced pressure and dried under reduced pressure for 2 h. The residue was dissolved in CH_2Cl_2/THF (0.3 mL, 1:1), molecular sieves (15 mg, 4 Å) was added, and the reaction mixture was stirred at room temperature for 15 min. A solution of *N*-iodosuccinimide (1.25 equiv) and triflic acid (0.12 equiv) in CH_2Cl_2/THF (0.4 mL, 1:1) was added at 0 °C, and the reaction mixture was stirred for 5 min. Pyridine (0.5 mL) and dichloromethane were added, and the organic phase was washed

with aqueous 1 M $Na_2S_2O_3$ and 10% aqueous $NaHCO_3$. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc 7:3) to yield **6** (protected) (19 mg, 60%, two steps) as a colorless oil: $R_f = 0.5$ (PE/EtOAc 7:3); $[\alpha]^{20}_D$ −24.3 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.57 (m, 1H), 0.80−0.88 (m, 30H), 0.98−1.80 (m, 110H), 1.94 (m, 7H), 2.1 (s, 3H), 3.38−3.70 (m, 33H), 3.86 (m, 3H), 4.05 (dd, $J = 5.8$, 11.5 Hz, 1H), 4.18 (dd, $J = 4.1$, 11.5 Hz, 1H), 4.36−4.46 (m, 6H), 4.65−4.68 (m, 5H), 5.04 (d, $J = 1.6$ Hz, 3H), 5.66 (dd, $J = 1.7$, 3.0 Hz, 3H), 5.87 (dd, $J = 4.0$, 7.4 Hz, 3H), 6.09 (t, $J = 10.2$ Hz, 3H), 7.19 (t, $J = 7.7$ Hz, 6H), 7.25−7.37 (m, 21H), 7.41 (t, $J = 7.4$ Hz, 3H), 7.51 (t, $J = 7.5$ Hz, 6H), 7.78 (d, $J = 8.4$ Hz, 6H), 7.89 (d, $J = 8.4$ Hz, 6H), 7.99 (d, $J = 8.4$ Hz, 6H), 8.05 (d, $J = 8.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.67, 19.74, 19.8, 21.0, 22.7, 22.8, 24.4−24.6, 24.9, 26.16, 26.22, 28.0, 28.8, 29.6, 29.7−29.9, 30.1, 31.7, 32.9, 36.8, 36.9, 37.0, 37.1, 37.15, 37.24, 37.4, 37.4−37.6, 37.7, 38.8, 39.4, 40.2, 40.8, 45.2, 62.8, 64.2, 65.9, 66.9, 67.3, 67.6, 68.1, 68.8, 69.0, 69.9, 70.2−70.3, 70.6, 71.1, 71.7, 71.8, 76.6, 77.9, 78.0, 96.3, 97.8, 128.3, 128.46, 128.50, 128.6, 129.0, 129.2, 129.4, 129.8, 129.85, 129.89, 130.0, 133.1, 133.2, 133.4, 165.4, 165.49, 165.51, 166.2; HRMS (ESI+) calcd for $C_{200}H_{272}O_{41}$ $(M + Na)^+$ 3352.9297, found 3352.9113; $(M + K)^+$ calcd 3368.8836, found 3368.8761.

Preparation of 6. To a solution of previous **6** (protected) (100 mg, 0.030 mmol, 1 equiv) in CH_2Cl_2/MeOH (20 mL, 1:1) was added a 0.1 M solution of MeONa (5 mL), and the reaction mixture was stirred at room temperature for 48 h. Amberlite resin (IR120) was added, the reaction mixture was filtered, and the solvents were evaporated under reduced pressure. The residue was purified on LH-20 Sephadex gel (CH_2Cl_2/MeOH 1:1) to yield **7** (60 mg, quantitative) as a colorless oil: $R_f = 0.5$ (EtOAc/MeOH/H_2O 5:3:2); $[\alpha]^{20}_D$ −14.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (CD_3OD/$CDCl_3$ 1:1, 400 MHz) δ (ppm) 0.61 (m, 1H), 0.83−0.88 (m, 30H), 1.04−1.89 (m, 117H), 3.33−3.83 (m, 56H), 4.64 (s, 2H), 4.75 (d, $J = 1.6$ Hz, 3H); ^{13}C NMR (CD_3OD/$CDCl_3$ 1:1, 100 MHz) δ (ppm) 19.2−19.3, 22.15, 22.24, 24.1, 24.2, 24.5, 25.3, 25.80, 25.83, 27.7, 28.4, 29.2−29.6, 31.3, 32.5, 36.5, 36.8−37.2, 39.1, 39.9, 49.2, 61.2, 61.3, 64.1, 64.3, 66.8, 66.9, 67.0−67.2, 67.8, 68.0, 68.5, 68.6, 69.4, 70.4−70.6, 71.1, 71.4, 71.5, 72.3, 78.8, 78.9, 95.9, 99.9. HRMS (ESI+) calcd for $C_{114}H_{222}O_{28}$ $(M + Na)^+$ 2062.5845, found 2062.5853.

Trilactosyl Cluster Tetraether 7. Preparation of 30b. Compound **30b** was prepared from **29b** (100 mg, 0.029 mmol, 1 equiv) following a similar procedure to that of **30a**. The product was rapidly characterized (some impurities were found in the NMR spectra) and was used as such in the next step: $R_f = 0.1$ (PE/EtOAc 6:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.52 (m, 6H), 2.1 (s, 3H), 2.86 (s, 6H), 3.02 (t, $J = 6.4$ Hz, 6H), 3.06 (s, 2H), 3.30−3.38 (dt, $J = 6.3$, 13.2 Hz, 3H), 3.55−3.68 (m, 9H), 3.70 (dt, $J = 6.3$, 13.2 Hz, 3H), 3.79 (m, 3H), 4.15 (t, $J = 9.4$ Hz, 3H), 4.35−4.51 (dd, $J = 4.1$, 12.2 Hz, 6H), 4.49 (d, $J = 7.9$ Hz, 3H), 4.52 (s, 2H), 4.78 (d, $J = 7.9$ Hz, 3H), 5.25−5.37 (m, 6H), 5.61−5.71 (m, 9H), 7.05−7.97 (m, 105H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.1, 30.0, 45.0, 60.8, 61.4, 62.8, 67.9, 68.0, 69.7, 70.3, 71.8, 72.2, 73.3, 76.4, 101.4, 101.6, 128.7, 128.8, 128.9, 128.97, 129.03, 129.2, 129.7, 129.8, 129.9, 130.0, 130.05, 130.08, 130.11, 130.2, 130.4, 130.6, 133.6, 133.7, 133.8, 134.0, 134.1, 165.2, 165.55, 165.64, 165.8, 166.0, 166.2.

Preparation of 7 (Protected). Compound **7** (Protected) (28.5 mg, 60%, two steps) was prepared from **30b** (40 mg, 0.010 mmol, 1 equiv) and **19** (14 mg, 0.0125 mmol, 1.2 equiv) following a similar procedure to that of **7** (protected). Colorless oil: $R_f = 0.6$ (PE/EtOAc 65:35); $[\alpha]^{20}_D$ +41.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.62 (m, 1H), 0.81−0.88 (m, 30H), 1.02−1.93 (m, 111H), 2.07 (s, 3H), 2.89 (m, 6H), 3.07 (t, $J = 6.4$ Hz, 6H), 3.17 (s, 2H), 3.34−3.81 (m, 37H), 3.86 (t, $J = 6.6$ Hz, 3H), 4.10 (dd, $J = 5.8$, 11.6 Hz, 1H), 4.21 (dd, $J = 4.0$, 7.4 Hz, 1H), 4.25 (t, $J = 9.4$ Hz, 3H), 4.45 (s, 2H), 4.48 (dd, $J = 4.1$, 12.2 Hz, 3H), 4.56 (d, $J = 10.6$ Hz, 3H), 4.62 (d, $J = 7.9$ Hz, 3H), 4.86 (d, $J = 7.9$ Hz, 3H), 5.35 (dd, $J = 3.4$, 10.3 Hz, 3H), 5.35 (dd, $J = 8.0$, 9.9 Hz, 3H), 5.71 (m, 6H), 5.77 (t, $J = 9.4$ Hz, 3H), 7.14 (t, $J = 7.7$ Hz, 6H), 7.21 (t, $J = 7.7$ Hz, 6H), 7.27−7.64 (m, 51H), 7.72 (d, $J = 8.5$ Hz, 6H), 7.87−7.90 (m, 12H), 7.96−8.01 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.6, 19.67, 19.74, 20.9, 22.6, 22.7, 24.3, 24.5, 24.8, 25.5, 26.08, 26.13, 28.0, 28.8, 28.9, 29.49, 29.52, 29.56, 29.62, 29.69, 29.72, 29.77, 29.82, 29.84, 29.99, 30.01, 31.6, 32.78, 32.84, 36.7, 37.28, 37.34, 37.4, 37.6, 38.6, 39.4, 40.1, 40.8, 45.6, 61.0, 61.7, 62.4, 67.5, 67.7, 68.9, 69.8, 69.9, 70.2, 71.3, 71.7, 71.8, 72.9, 76.0, 76.5, 96.0, 101.0, 101.2, 128.2, 128.3, 128.5, 128.55, 128.61, 128.64, 128.8, 129.3, 129.4, 129.47, 129.54, 129.6, 129.65, 129.74, 129.8, 130.0, 133.1, 133.2, 133.4, 133.5, 164.8, 165.1, 165.2, 165.37, 165.38, 165.5, 165.8; HRMS (ESI+) calcd for $C_{281}H_{338}O_{65}Na$ $(M + Na)^+$ 4775.3041, found 4775.3036.

Preparation of 7. Compound **7** was prepared from **7** (protected) following a similar procedure to that of **6**. Compound **7** was found to be insoluble in most of common organic solvents. Only ^{1}H NMR could be recorded in d_5-pyridine: ^{1}H NMR (d_5-pyridine, 400 MHz) δ (ppm) 0.70 (m, 1H), 0.88−0.97 (m, 30H), 1.10−2.02 (m, 117H), 3.52−4.54 (m, 74H), 4.78 (d, $J = 7.8$ Hz, 3H), 4.88 (s, 2H), 5.09 (d, $J = 7.9$ Hz, 3H); HRMS (ESI+) calcd for $C_{132}H_{252}O_{43}$ $(M + Na)^+$ 2548.7430, found 2548.7441.

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Supporting Information Available: Experimental procedure for the synthesis of known compounds **8**, **14**, and **15**. Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**−**7**, **9a**, **18**−**20**, **22**, **23**, **25**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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