Synthetic Approaches to Novel Archaeal Tetraether Glycolipid Analogues†

Grégory Lecollinet,‡ Rachel Auzély-Velty,‡ Mathieu Danel,‡ Thierry Benvegnu,*,‡ Grahame Mackenzie,§ John W. Goodby,§ and Daniel Plusquellec‡

Ecole Nationale Supérieure de Chimie de Rennes, Laboratoire de Synthèses et Activations de Biomolécules, associé au CNRS, Avenue du Général Leclerc, 35700 Rennes, France, and The Department of Chemistry, Faculty of Science and the Environment, The University of Hull, Hull HU6 7RX, U.K.

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Symmetrical and unsymmetrical archaeal tetraether glycolipid analogues have been prepared. The syntheses are based upon the elaboration of lipid cores from versatile chiral starting materials followed by simultaneous or sequential introduction of polar headgroups. Three pathways (A−C) were elaborated for the synthesis of stereochemically defined lipids **14**−**16** characterized by a straight bridging spacer and two dihydrocitronellyl chains attached to glycerol units at the *sn*-3 and *sn*-2 positions, respectively. Pathway C appeared to be particularly advantageous for the synthesis of tetraether **9**, which possesses a cyclopentane unit as found in thermoacidophilic lipids. Diglycosylated lipids **4**−**6** were produced in 49−53% yields by reaction of diols **14**−**16** with β-D-galactofuranosyl donor **31**, whereas unsymmetrical lipids possessing either two different carbohydrate units **7** or a saccharidic moiety and a phosphate group **8** were efficiently prepared from monoprotected diol **35**. These compounds represent the first examples of tetraether-type analogues containing a phosphate unit and/or glycosyl moieties.

Introduction

The Archaea domain is composed of a variety of microorganisms that proliferate under extreme environments such as acidic conditions, high temperatures, or high salt concentrations and/or absence of oxygen.[1] Archaebacteria are classified into three phenotypes on the basis of their living habitats: methanogens, halobacteria, and thermoacidophiles. All three types of organisms are characterized by membrane components that have a high degree of chemical stability. The archaea membrane core lipids are composed of saturated isoprenoid chains attached to glycerol by ether linkages with an *sn*-2 stereochemistry opposite to that of conventional mesophilic lipids.[2] Of particular interest are the unusual bipolar tetraether lipids present in thermoacidophilic and methanogenic species.[2] These lipids consist of tetraether 72-membered macrocycles that have usually been represented as **1** (Figure 1). Heathcock et al. have established the relative stereochemistry of the macrocyclic lipid core,[3a,b] and Gräther and Arigoni have recently demonstrated that the macrocycles from several archaea are actually a regioisomeric mixture of **1** and **2**.[3c] A

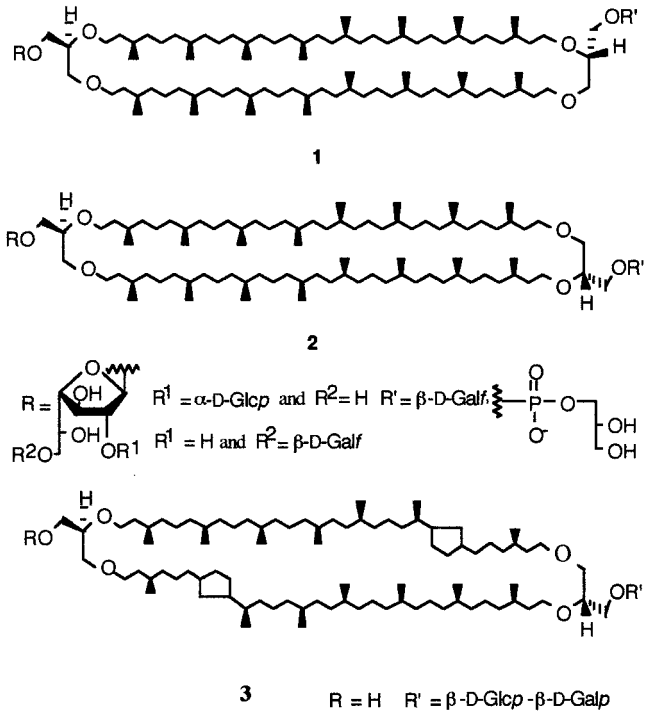

Figure 1. Bipolar tetraether-type glycolipids found in methanogenic[2e] (**1** and **2**) and in thermoacidophilic[4] (**3**) Archaea.

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‡ Ecole Nationale Supérieure de Chimie de Rennes.

§ The University of Hull.

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particularly attractive point concerns the increasing proportion of cyclopentane rings in thermoacidophilic lipids with increasing environmental temperature.[4a] Indeed, the presence of cyclopentane rings as in compound **3** are supposed to fine-tune the rigidity of the membrane in direct response to the growth temperature of the organisms.[4b] Another striking feature of archaeal lipids is the occurrence of unusual carbohydrates and/or phosphate units as polar headgroups that are expected to ensure the rigidity of the membrane and to reduce their permeability.[2e] These macrocyclic molecular components give rise to monolayered thermostable membranes, which have boosted interest in biotechnologies.[5]

To elucidate the relationship between lipidic molecular structures and the stability of their supramolecular assemblies in aqueous media, sufficient amounts of pure archaeal lipids are required. Well-defined amphiphiles, however, are difficult to isolate from natural membrane extracts, and chemical synthesis appears therefore as an important means of producing model lipids that mimic the natural compounds.

Approaches to synthetic tetraethers related to archaebacterial membranes have been reported by several groups during the last decade. These routes are based either on acid-catalyzed regioselective opening of glycidol intermediates by α,ω-polymethylene diols[6] or on alkylation of glycerol derivatives such as isopropylidene glycerol and 1-*O*-benzylglycerol with α,ω-dibromoalkanes.[7] Hemimacrocyclic backbones bearing a bridging chain and two aliphatic chains having a combined length equal to that of the former have also been generated. A dimerization process was also developed by applying Kochi's coupling procedure.[8] Macrocyclic ring formation was recently achieved via McMurry,[9] Glaser,[10] or olefin metathesis[11] coupling reactions leading to 72-membered ring skeletons.

Most of the synthetic efforts were directed toward the preparation of tetraethers bearing phosphate moieties as polar headgroups. Yamauchi et al.[12] and others[13] have

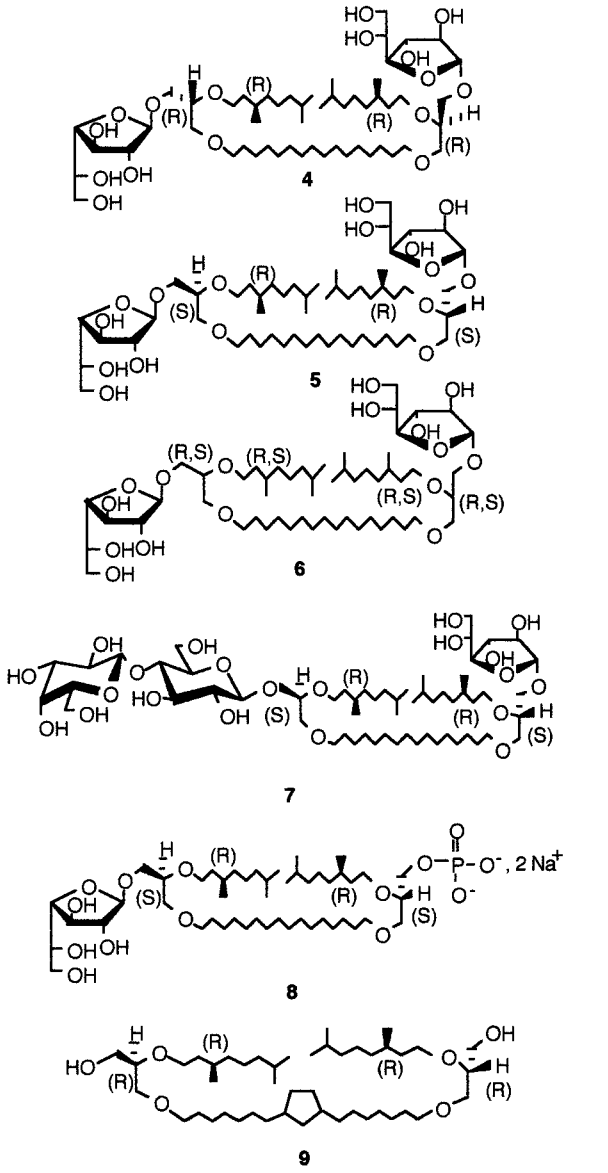

Figure 2. Synthetic symmetrical and unsymmetrical quasi-macrocyclic lipid analogues **4**−**9** of natural methanogenic or thermoacidophilic lipids **1**−**3**.

readily demonstrated that glycosidic polar heads may exert tremendous influence on the membrane stability through highly cooperative polar interactions between polyol heads. However, no reports had appeared on the synthesis of glycosylated tetraethers until our preliminary reports on the synthesis and the physicochemical studies of archaeal tetraether-type glycolipids.[14,15] In this paper, we report full details of our preparation of hemimacrocyclic model compounds **4**−**8** that mimic natural mono- or diglycosylated lipids (Figure 2). The preparation of diol **9** possessing a cyclopentane unit, as an analogue of thermoacidophilic lipid **3**, is also described. Our synthetic approaches consisted of the development of convenient procedures to prepare stereochemically well-defined compounds from commercially available chiral starting materials. The different strategies we used offer

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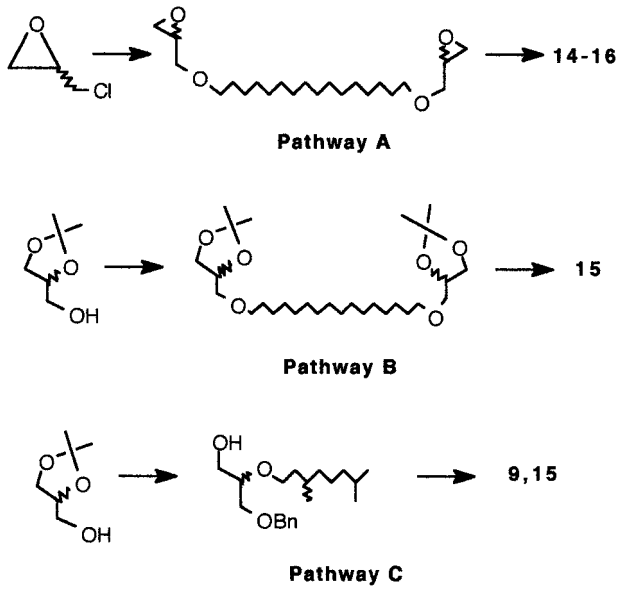
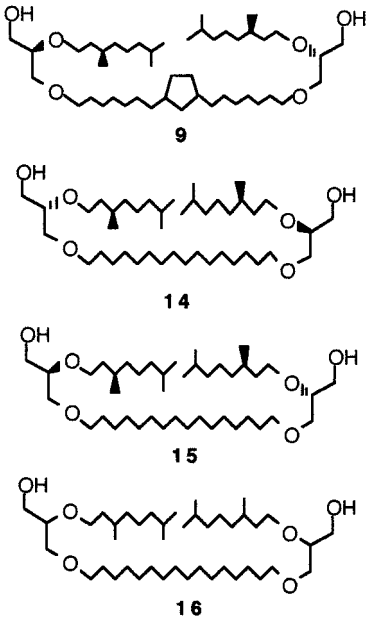
the possibility of modulating the stereochemistry of glyceryl moieties and aliphatic branched chains and of introducing phosphate groups and/or polar carbohydrate moieties on both glycerol units. These novel quasimacrocyclic compounds are characterized by the following: (1) the presence of a hexadecamethylene spacer or a spacer group containing a cyclopentane unit attached to two glycerols at primary positions; (2) two (*R*)- or (*R*,*S*)-dihydrocitronellyl chains bearing methyl groups that should allow the fluidity to be maintained at values comparable with that found in natural archaeal membranes; (3) two optically pure (*R* or *S*) or racemic glyceryl units linked to hydrophobic segments by stable ether bonds; and (4) phosphate moiety and/or glycosydic polar headgroups derived from D-galactose in a furanoid cyclic form as found in a number of natural methanogenic lipids.[2d,e] The presence of furanosidic units in such glycolipids is a striking feature since hexoses appear only in a pyranoside configuration in mammalian glycolipids and glycoproteins.[16]

Results and Discussion

The strategic plan for the synthesis of glycolipids **4**−**8** involved a suitable synthesis of hemimacrocyclic diols **14**−**16** and a subsequent introduction of the polar headgroups. Three pathways A−C were developed for the preparation of diols **9** and **14**−**16** as outlined in Scheme 1. The key differences in these three strategies result from (1) the structure of the chiral starting material, epichlorohydrin or solketal, used as the precursor for the glycerol moiety and (2) the coupling of the spacer group to the glycerol units. In pathways A and B, the introduction of the spacer was performed in the first step of the synthesis. Conversely, according to pathway C, the construction of the aliphatic linker between the two glycerols was achieved in the final steps by the use of a glycerol derivative possessing the branched chain at the *sn*-2 position. This latter strategy is more advantageous for the preparation of various hemimacrocyclic diols insofar as it allows us to modulate more easily the structure of the spacer.

Scheme 1





Preparation of Quasimacrocyclic Diols 14−16 via Pathway A. Tetraether **14** was obtained from (*R*)-epichlorohydrin in a five-step procedure (Scheme 2). After experimentation, we found that bisalkylation of hexadecanediol with two (*R*)-epoxide units using phase-transfer catalysis conditions yielded bis-(*S*)-glycidol **10**. Reaction of an excess of (*R*)-epichlorohydrin with hexadecanediol was performed in a two-phase system composed of aqueous sodium hydroxide and *n*-hexane, in the presence of a catalytic amount of tetrabutylammonium bromide at 70 °C for 4 h. The formation of **10** (55% yield) resulted from the nucleophilic attack of the diol at the less hindered position of the two oxirane rings followed by in situ recyclization due to internal displacement of the chloride ions. This reaction therefore provided complete inversion at the *sn*-2 carbon. Comparison of $[\alpha]_D$ values of **10** and that of the same product obtained by the synthetic pathway derived from Thompson's procedure[6a] allowed confirmation of the absolute configuration at the glycidol stereocenters (Scheme 3). Double nucleophilic addition of hexadecanediol onto (*R*)-oxiranemethanol-3-nitrobenzenesulfonate in the presence of 1% triflic acid afforded the (*R*)-bolalipid intermediate **17** (58% yield). High optical purity of **17** was demonstrated by Thompson and co-workers using NMR analysis and chiral resolution Pirkle-phase HPLC.[6a] Finally, treatment of diol **17** with K_2CO_3 in methanol gave the (*S*)-bisglycidol ether **10** in 65% yield. Compound **10** resulting from the two synthetic pathways showed identical $[\alpha]_D$ values ($[\alpha]^{20}_D$ +7.9, *c* 1, CH_2Cl_2) that supported the proposed mechanism.

In the next step, treatment of **10** with allyl alcohol and a catalytic amount of sodium methoxide resulted in the regiospecific opening of the two epoxides, affording bis-(3-allyl-*sn*-glycerol) **11** in 90% yield (Scheme 2). Dialkoxide generated by deprotonation of **11** with NaH in dry THF was treated with 5 equiv of commercially available (*R*)-(−)-citronellyl bromide to give allyl-protected glycerol derivative **12** (80% yield). The cleavage of allyl ethers with a catalytic amount of palladium on activated char-

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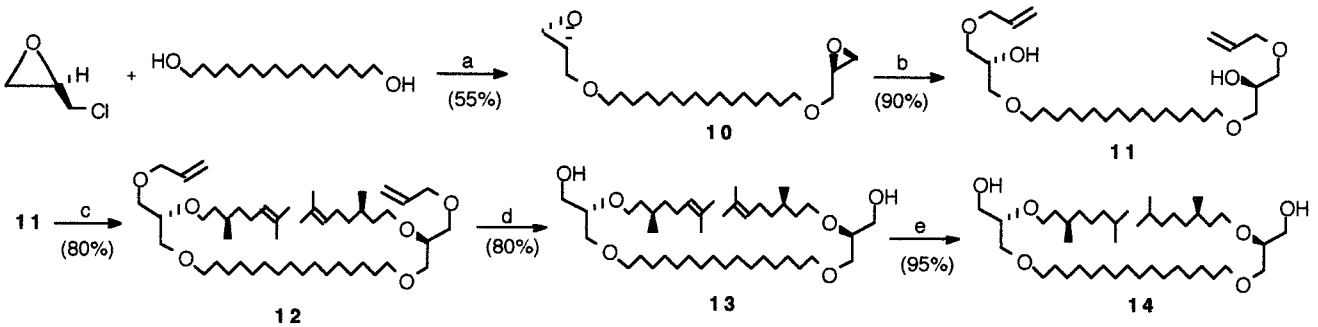
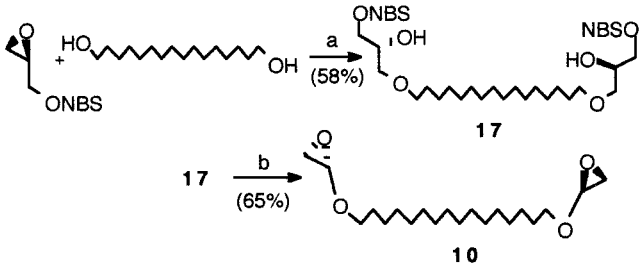
Scheme 2[a]



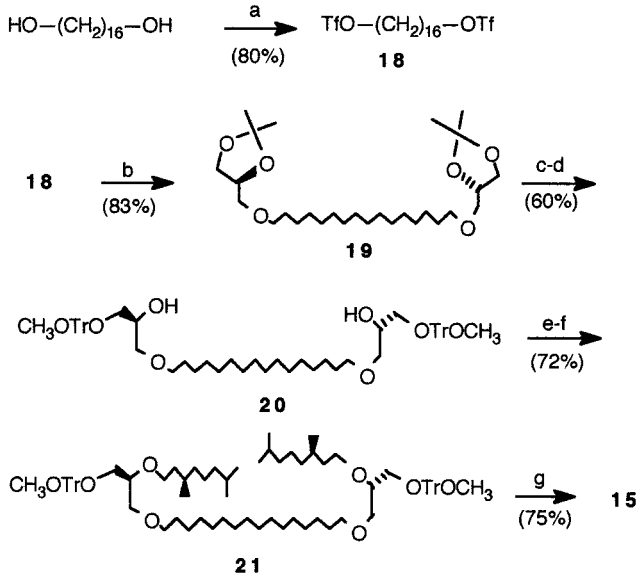
[a] Reagents: (a) 50% NaOH, *n*-hexane, Bu_4NBr, 70 °C; (b) allyl alcohol, NaOMe; (c) (*R*)-(−)-citronellyl bromide, NaH; (d) $(Ph_3P)_3RhCl$, EtOH, toluene, water (7:3:1, v/v); (e) Raney nickel, H_2, EtOH.

Scheme 3[a]



[a] Reagents: (a) TfOH cat., CH_2Cl_2 (NBS; 4-nitrobenzenesulfonate); (b) K_2CO_3, CH_3OH.

Scheme 4[a]



[a] Reagents: (a) $(CF_3SO_2)_2O$, 2,6-lutidine, CH_2Cl_2, 0 °C, then room temperature; (b) (*S*)-(+)-solketal, PS, CH_2Cl_2, reflux; (c) Dowex H^+ resin, CH_3OH, reflux; (d) CH_3O−TrCl, pyridine, DMAP, THF, reflux; (e) (*R*)-citronellyl bromide, NaH, 130 °C; (f) H_2, Pd/C, Et_3N, AcOEt; (g) HCOOH, Et_2O.

coal and a catalytic amount of *p*-toluenesulfonic acid was ineffective. The *O*-allyl groups were therefore efficiently removed in the presence of Wilkinson catalyst[17] in a refluxing mixture of ethanol, toluene, and water (7:3:1, v/v) via isomerization of allyl ethers to vinyl ethers followed by in situ hydrolysis (80% yield). Conversion of **13** into saturated compound **14** was attempted using various reducing conditions. Palladium-catalyzed hydrogenation of **13** led to the formation of side products due to the unexpected partial cleavage of ether linkages at *sn*-2 glycerol sites. As shown in Scheme 2, reduction of the double bonds could be easily performed by catalytic hydrogenation over Raney nickel to yield (*S*,*S*) tetraether **14** ($[\alpha]^{20}_D$ −10.2, *c* 0.65, CH_2Cl_2) in 95% yield. The best yield we were able to obtain in this overall sequence was 35%, and the representative 30% yield was an average of repeated runs.

A procedure similar to that described for quasimacrocyclic diol **14** was used to synthesize the isomeric (*R*,*R*) diol **15** ($[\alpha]^{20}_D$ +12.9, *c* 0.86, CH_2Cl_2) and the racemic diol **16** (30−33% overall yields) starting from commercially available (*S*)- or (*R*,*S*)-epichlorohydrins, respectively. In the case of compound **16**, the double *O*-alkylation at the *sn*-2 position of glyceryl units was accomplished by using (*R*,*S*)-dihydrocitronellyl bromide; this noncommercially available product was prepared by hydrogenation of (*R*,*S*) citronellol over Raney nickel and conversion of the saturated alcohol into the corresponding bromide using aqueous 48% HBr.

Preparation of Diol 15 via Pathway B. With the aim of developing a practical synthesis of tetraether-type analogues on a multigram scale, we then investigated a second approach based on the use of 2,2-dimethyl-1,3-dioxolan-4-ylmethanol (solketal) as the starting material. (*S*)-(+)-Solketal and its (*R*)-(−)-isomer are currently available on a kilogram scale, thus making entry into larger amounts of chiral lipids easier. At this stage, we chose to test this second strategy for the preparation of diol **15** possessing a glycerol stereochemistry similar to that of the natural glycolipids. Compound **15** was prepared via Williamson coupling reactions from (*S*)-solketal, hexadecane-1,16-diyl ditriflate **18**, and (*R*)-(−)-citronellyl bromide (Scheme 4). Reaction of hexadecane-1,16-diol with Tf_2O in the presence of pyridine resulted in the formation of the 1,16-hexadecanedipyridinium salt in addition to the expected ditriflate. Minimization of this side-compound formation was successfully achieved by replacement of pyridine by the less nucleophilic 2,6-lutidine. Separation of the ditriflate from the base by flash chromatography afforded the triflate derivative in 80% yield. Alkylation of two (*S*)-solketal units with **18** proceeded efficiently (83%) in CH_2Cl_2 heated at reflux for 24 h using 1,8-bis(dimethylamino)-naphthalene (PS) as a base.[6a] Removal of the isopropylidene groups in the presence of a Dowex acidic resin in refluxing methanol yielded the expected tetraol in 73%

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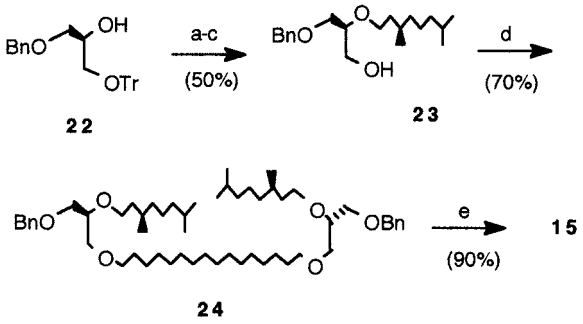
Scheme 5[a]



[a] Reagents: (a) (*R*)-citronellyl bromide, NaH, 130 °C; (b) H_2, Pd/C, Et_3N, AcOEt; (c) HCOOH, Et_2O; (d) KH, **18**, THF; (e) H_2, Pd/C, AcOEt.

yield. Selective protection of the two primary hydroxy functions with *p*-methoxytrityl chloride followed by Williamsom coupling using commercially available (*R*)-(−)-citronellyl bromide and a palladium-catalyzed hydrogenation in the presence of triethylamine provided the saturated hexaether **21**. Conversion into the key diol **15** was finally accomplished by the subsequent removal of the trityl groups under acidic conditions.

Preparation of Diol 15 via Pathway C. We next focused our attention on the development of a third approach which could allow more synthetic flexibility for the design of various tetraether-type diols containing different kinds of aliphatic spacers. Scheme 5 shows the synthetic pathway C for the preparation of diol **15** from the key intermediate 1-*O*-benzyl-2-*O*-(*R*)-3,7-dimethyloctyl-*sn*-glycerol **23**. Compound **23** was readily produced by etherification of 3-*O*-trityl-1-*O*-benzyl-*sn*-glycerol **22** with (*R*)-(−)-citronellyl bromide followed by reduction of the double bond and removal of the trityl group under the same conditions as described in pathway B (50% yield over three steps). The starting alcohol **22** was prepared following a conventional sequence[18] based on successive O-benzylation of (*R*)-solketal (BnBr, NaH), removal of the acetonide group with aqueous acetic acid, and selective tritylation of the primary free hydroxyl group (TrCl, (i-Pr)$_2$NEt). Alkylation of **23** with ditriflate **18** in refluxing CH_2Cl_2 using PS was ineffective. Conversely, treatment of alcohol **23** with **18** and potassium hydride at room temperature resulted in a smooth conversion to **24** in 70% yield. After hydrogenolysis of the benzyloxy group, diol **15** was obtained in 90% yield. This synthetic route represents a novel efficient strategy to prepare various hemimacrocyclic diols from the same key intermediate **23**, which is easily available on a large scale from (*R*)-solketal.

Synthesis of Diol 9 Containing a Cyclopentane Unit via Pathway C. At this stage, we envisaged the application of pathway C to the preparation of diol **9**, which incorporates for the first time, to our knowledge, a cyclopentane ring. Our synthetic plan involved the connection of the (*S*)-glycerol derivative **23** and diol **28** bearing a cyclopentane ring (Scheme 6). Our strategy for the synthesis of **28** was based upon a double Wittig reaction of the key *cis*-1,3-diformylcyclopentane **25** with phosphonium salt **26** (Scheme 6). Compound **25** could be prepared by oxidation of norbornene with $KMnO_4$ in acetone−water or by OsO_4/$NaIO_4$ in dioxane−water.[19,20] However, these oxidative conditions led to the formation of polyaldehydes with varying amounts of free formyl groups, depending upon the amount of water present and the temperature.[21] We decided to investigate the ozonolysis of norbornene in CH_2Cl_2 followed by treatment of triphenylphosphine. This procedure smoothly provided dialdehyde **25** in 55−70% yield. This route has a number of practical advantages: (1) the starting norbornene is cheap; (2) the reaction can be conducted on a multigram scale according to a simple and inexpensive process; (3) pure dialdehyde was isolated after chromatographic purification without side products resulting from polycondensation; and (4) dialdehyde **25** can be stored for several days under nitrogen at −4 °C without any degradation.

Phosphonium salt **26** was readily prepared using conventional procedures as reported in the literature.[22] The next crucial step involved the connection of two fragments **26** with the *cis*-1,3-disubstituted cyclopentane **25** via a double Wittig[23] reaction. Treatment of salt **26** in THF with 1.05 equiv of *n*-BuLi at 0 °C led to the formation of the corresponding phosphorane, which was then treated, after the solution was warmed to room temperature, with 0.5 equiv of *cis*-1,3-diformylcyclopentane **25**. After workup, compound **27** resulting from a one-pot double Wittig reaction was isolated in 70% yield as a mixture containing predominantly the cis isomers. Removal of the THP groups with pTSA in MeOH followed by a palladium-catalyzed hydrogenation provided diol **28** in 81% yield. ^1H and ^{13}C NMR studies including $^1H-^{13}C$ correlation spectra from compound **28** revealed that the *cis*-1,3-diformylcyclopentane **25** underwent some partial isomerization to the trans isomer under the conditions of the Wittig reaction, leading to a 4:1 mixture of cis−trans isomers, respectively. The presence of two distinct chemical shifts for the protons of the methylene group $CHCH_2CH$ of the cyclopentane moiety for the cis isomer (H: 1.87 ppm and H′: 0.62 ppm) and a single signal for the trans isomer (H, H′: 1.32 ppm) allowed us to quantify by integration of the peak at 0.62 ppm the cis−trans ratio. Reaction of diol **28** with Tf_2O in the presence of 2,6-lutidine provided ditriflate **29** in 77% yield. Treatment of alcohol **23** with **29** and potassium hydride at room temperature resulted in the formation of the dibenzylated ether **30** (79% yield), which was then submitted to hydrogenolysis to give the target diol **9** as a diastereoisomeric mixture due to the presence of the stereogenic centers of the cyclopentane ring.

Synthesis of Symmetrical Diglycosylated Lipids 4−6. Glycosylation reactions of diols **14**, **15**, or **16** were investigated from *n*-pentenyl D-galactofuranoside **31** as an inseparable mixture of anomers (α/β = 40/60), available in a one-pot procedure from D-galactose and 4-penten-1-ol[24] (Scheme 7). The glycosylation was carried out under

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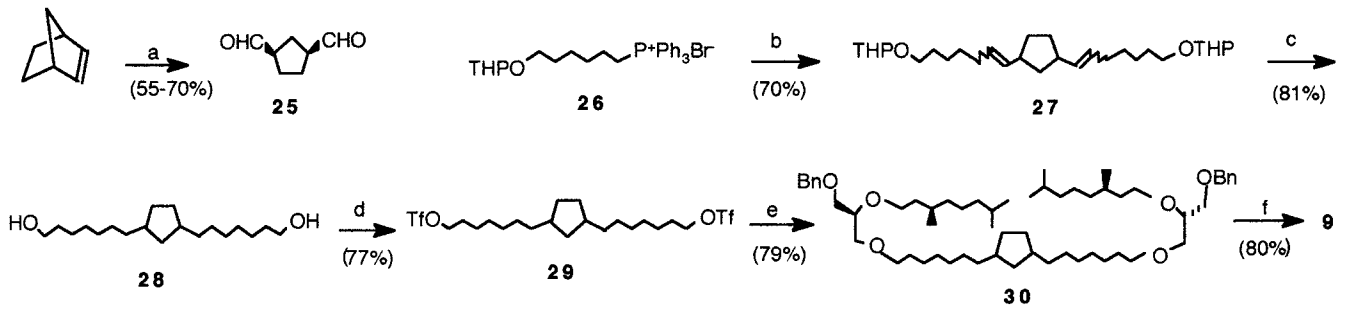
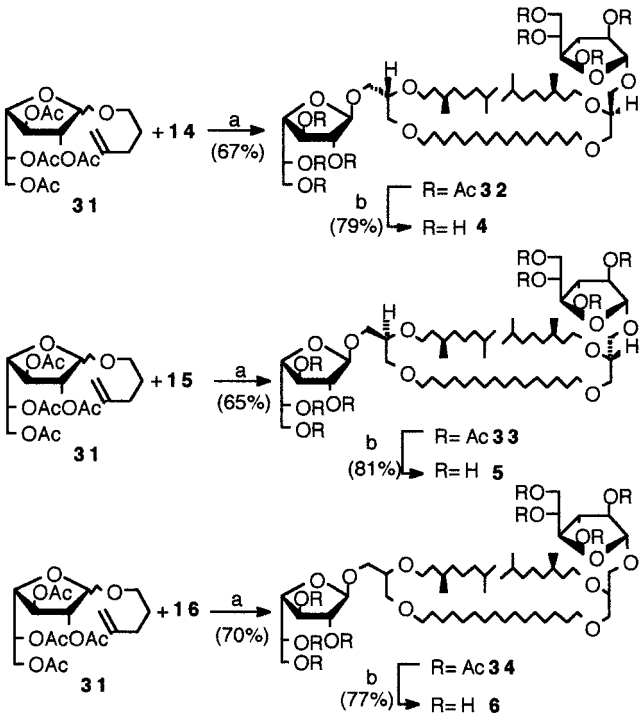
Scheme 6[a]



[a] Reagents: (a) O_3, CH_2Cl_2, −78 °C then PPh_3, rt; (b) *n*-BuLi, THF, 0 °C, then **25**, rt; (c) pTSA, CH_3OH, H_2, Pd/C, CH_3OH; (d) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, then rt; Et_2O; (e) KH, **23**, THF; (f) H_2, Pd/C, AcOEt.

Scheme 7[a]



[a] Reagents: (a) NIS, Et_3SiOTf, CH_2Cl_2; (b) CH_3ONa, CH_3OH.

standard *n*-pentenyl glycoside chemistry[25] (NIS, 1.3 equiv; Et_3SiOTf, 0.3 equiv with respect to the donor) and proceeded smoothly and quickly (10−15 min) at room temperature to provide exclusively the β-linked bis-galactofuranoside lipids. The high β-selectivity resulted from neighboring group participation of the C-2 acetyl donor functionality. Deacylation of the symmetrical glycolipids with sodium methoxide in methanol gave the corresponding diglycosylated compounds **4**, **5**, or **6**. 2D-COSY ^1H NMR and $^1H-^{13}C$ correlation spectra allowed the assignment of most of ^1H and ^{13}C signals, providing evidence of the β-anomeric configuration of the galactofuranosyl rings. The low-field resonance (δ 109.7 ppm) observed for the anomeric carbons as well as the values for $J_{H1,H2} < 2$ Hz are indicative of a trans relationship between H-1 and H-2 in the glycosyl moieties.

Synthesis of Unsymmetrical Lipids 7 and 8. Our attention was next directed toward the synthesis of unsymmetrical glycolipids **7** and **8**. These compounds are supposed to self-assemble into monolayer membranes, and the presence of two headgroups with different sizes and water solubilities is expected to induce membrane curvature.[12] The major difficulties in constructing such structures lay in the desymmetrization of the quasi-macrocyclic diol as well as the introduction of two different polar groups under conditions compatible with the presence of highly hydrolyzable glycosidic or phosphate ester linkages. The use of the McDougal process[26] involving the formation of the sodiomonoalkoxide corresponding to diol **15** and the subsequent treatment by benzyl bromide resulted in the formation of a mixture of the unreacted diol (31% yield), the expected monoprotected compound (43% yield), and the totally protected derivative (7% yield). An improvement in the selectivity of the monobenzylation reaction was obtained by using the Sauvé methodology.[27] Reaction of **15** with Ag_2O and BnBr in CH_2Cl_2 led to the formation of the monobenzylated product **35** (50% yield) in addition to the dibenzylated derivative (10% yield) and the unreacted recyclable diol (36%). The introduction of the β-D-galactofuranoside unit was performed by using the same procedure as for symmetrical lipids **4**−**6** to provide stereospecifically the corresponding β-glycoside in 80% yield. Removal of the benzyl group afforded the monoglycosylated lipid **36** in 91% yield (Scheme 8).

Having the free alcohol **36** in hand, the last crucial step involved the introduction of the second polar headgroup under mild conditions in order to prevent any hydrolysis of the β-D-galactofuranosidic bond. First, we envisaged to introduce a lactosyl unit to obtain compound **7** possessing two sugar units with different sizes at opposite sides. Glycosylation of **36** was performed using lactosyl thioglycoside **37** as a donor. The latter was efficiently prepared from peracetylated lactose by reaction with ethanethiol in the presence of $BF_3 \cdot Et_2O$.[28] The coupling reaction was carried out under NIS−Et_3SiOTf conditions and provided the β-*O*-bisglycoside in 70% yield. The conventional deprotection of hydroxy groups by sodium methoxide in methanol proceeded smoothly to give the totally unprotected bipolar lipid **7** in 93% yield.

Our next goal was to introduce a phosphate group onto intermediate **36** to obtain an unsymmetrical lipid bearing both a glycosyl unit and an anionic group at opposite ends. A striking feature concerning the organization of such lipids in natural archaeal methanogenic and ther-

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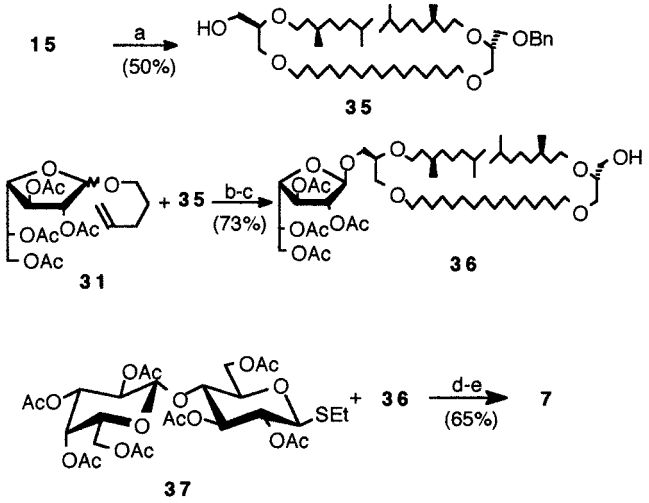
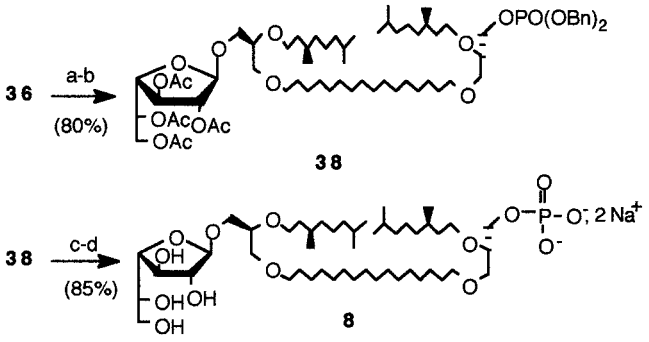
Scheme 8[a]



[a] Reagents: (a) Ag_2O, BnBr, CH_2Cl_2; (b) NIS, Et_3SiOTf, CH_2Cl_2; (c) H_2, Pd/C, EtOH; (d) NIS, Et_3SiOTf, CH_2Cl_2; (e) CH_3ONa, CH_3OH.

Scheme 9[a]



[a] Reagents: (a) 1*H*-tetrazole, $(BnO)_2PN(i\text{-}Pr)_2$, CH_2Cl_2; (b) *m*-CPBA, CH_2Cl_2, −40 to 0 °C; (c) CH_3ONa, CH_3OH; (d) (1) H_2, Pd/C, CH_3OH, acetate buffer (pH 5) (3:1 v/v), (2) Amberlite IR-120 (Na^+), CH_3OH, (3) gel filtration on Sephadex LH-20.

moacidophilic membranes has been reported in the literature.[2c] Glycosyl groups were shown to be located at the exterior membrane side and the anionic phosphate groups were found into the inner membrane layer, thus placing a highly negatively charged surface density onto one side of the membrane. Within this context, physicochemical studies from synthetic compounds should give further information about these unusual self-assembling properties in archaeal membranes. Alkyl dibenzyl phosphate **38** was prepared by reacting alcohol **36** with *N*,*N*-diethyl dibenzylphosphoramidite/1*H*-tetrazole followed by in situ mild oxidation of the resulting phosphite with 3-chloroperoxybenzoic acid (80% yield)[29] (Scheme 9). The transformation of **38** into the phosphate salt **8** was performed by sequential deacetylation of the galactosyl unit, catalytic hydrogenolysis (Pd/C) in a buffered solvent mixture (methanol−acetic acid−sodium acetate, pH 5) avoiding the glycoside hydrolysis, and treatment with Amberlite IR-120 (Na^+ form, water). Purification by gel filtration chromatography with Sephadex LH-20 furnished the targeted unsymmetrical glycolipid **8** in 85% yield. The structure of these original glycolipids **7** and **8** was confirmed by NMR (^{31}P and/or ^{13}C, ^1H) and by positive-ion FAB high-resolution mass spectroscopy. The presence of two distinct chemical shifts for the secondary carbons of the two glyceryl sites (C-2: 78.82; 79.19 for **7**; 78.75; 79.11 for **8**) was fully consistent with the unsymmetrical structure of the molecules.

In summary, we have accomplished and optimized the synthesis of novel symmetrical and unsymmetrical archaeal glycolipid analogues, which include for the first time, to our knowledge, galactose units in a furanose cyclic form and lactose or phosphate moieties. A particularly attractive approach for the construction of the lipidic backbone was developed that allowed the efficient access of chiral diols on a large scale. The flexibility of this methodology was clearly demonstrated by preparing a novel hemimacrocyclic diol possessing a cyclopentane unit.

Experimental Section

General Methods. ^1H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz. Melting points are uncorrected. Merck 60H (5−40 μm) silica gel was used for column chromatography. Analytical TLC was performed on Merck 60 F_{254} silica gel nonactivated plates. A solution of 5% H_2SO_4 in EtOH was used to develop the plates. The solvent systems for the chromatographies were as follows [system code (volume ratio)]: for petroleum ether/EtOAc, A (19:1), B (9:1), C (4:1), D (7:3), E (2:1), F (2:1), G (1:1), H (2:3); for petroleum ether/diethyl ether, I (7:3). Pent-4-enyl 2,3,5,6-tetra-*O*-α,*β*-D-galactofuranoside **31** was prepared as previously described.[24] (*S*)-(+)-Solketal and its (*R*)-(−) isomer were obtained on a kilogram scale from Chemi. S.p.A., 20092 Cinisello Balsamo, Italy. Other chemicals were purchased from Acros or Fluka Chemika Co. Solvents were of reagent grade and were distilled under N_2 before use: THF from sodium benzophenone ketyl, CH_2Cl_2 from P_2O_5. Unless otherwise noted, nonaqueous reactions were carried out under nitrogen atmosphere.

1,1′-*O*-(1,16-Hexadecamethylene)bis[(*S*)-glycidol] (10). 1,16-Hexadecanediol (2.30 g, 8.92 mmol), 50% aqueous NaOH solution (4.28 g), *n*-hexane (10 mL), and tetrabutylammonium bromide (0.29 g, 0.89 mmol) were combined in a 50-mL two-neck round-bottom flask. The mixture was stirred vigorously at room temperature for about 5 min. (*R*)-Epichlorohydrin (3.14 mL, 40.12 mmol) was then added, and the mixture was heated at 70 °C for 4 h. After cooling, the mixture was diluted with ether, washed successively with water, 5% aqueous HCl, and brine, dried over $MgSO_4$, and rotoevaporated. The crude product was purified by silica gel chromatography. Elution with a mixture of petroleum ether and EtOAc (4:1 v/v) gave the desired product as a white solid (1.82 g, 55%), which was recrystallized from *n*-hexane, R_f = 0.60 (solvent D). **10**: mp 59 °C; $[\alpha]^{20}_D$ +7.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25−1.33 (m, 24H), 1.55−1.62 (m, 4H), 2.61 (dd, 2H, J = 2.7, 5.0 Hz), 2.80 (t-like, 2H), 3.15 (m, 2H), 3.38 (dd, 2H, J = 5.8, 11.5 Hz), 3.48 (m, 4H), 3.71 (dd, 2H, J = 3.1, 11.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.07, 29.47, 29.58, 29.60, 29.65, 29.66, 29.68, 44.34, 50.90, 71.45, 71.72. Anal. Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.72; H, 11.42.

1,1′-*O*-(1,16-Hexadecamethylene)bis(3-*O*-allyl-*sn*-glycerol) (11). To a solution of sodium methoxide (0.02 g, 0.40 mmol) in allyl alcohol (5.4 mL, 80 mmol) was added **10** (1.48 g, 4.0 mmol). The mixture was stirred at 75 °C overnight. The allyl alcohol was then removed under high vacuum using a dry ice trap, and the solid residue was purified by silica gel chromatography. Elution with a mixture of petroleum ether and EtOAc (1:1 v/v) gave the desired product as a white solid (1.71 g, 90%), which was recrystallized from *n*-hexane, R_f = 0.51 (solvent H). **11**: mp 41 °C; $[\alpha]^{20}_D$ +0.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 24H), 1.55−1.60 (m, 4H), 3.40−3.54 (m, 12H), 3.96 (m, 2H), 4.03 (m, 4H), 5.19 (dt, 2H, J = 10.4 Hz), 5.28 (dt, 2H, J = 17.2 Hz), 5.86−5.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.07, 29.45, 29.57, 29.58, 29.59,

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29.64, 69.46, 71.30, 71.66, 71.77, 72.33, 117.24, 134.49. Anal. Calcd for $C_{28}H_{54}O_6$: C, 69.10; H, 11.18. Found: C, 69.44; H, 11.56.

1,1′-*O*-(1,16-Hexadecamethylene)bis[2-*O*-(*R*)-citronellyl-3-*O*-allyl-*sn*-glycerol] (12). A mixture of sodium hydride (60% in oil, 0.72 g, 18 mmol) and 1,1′-*O*-(1,16-hexadecamethylene)bis(3-*O*-allyl-*sn*-glycerol) **11** (0.80 g, 1.64 mmol) in dry tetrahydrofuran (15 mL) was stirred under nitrogen at 40 °C for 1 h. (*R*)-Citronellyl bromide (1.62 mL, 8.20 mmol) was added to the resulting alkoxide solution, and the mixture was heated at about 140 °C for 5 h; the solvent was distilled out during heating. After cooling, a few drops of CH_3OH were added, and the reaction mixture was diluted with ether. The organic layer was washed with water and brine and dried over $MgSO_4$. Rotovaporation of solvent gave a residue that was purified by silica gel chromatography, eluting with a mixture of petroleum ether and EtOAc (the volume ratio was changed from 39:1 to 19:1) to yield the desired product as a colorless oil (1.0 g, 80%), $R_f = 0.46$ (solvent B). **12**: $[\alpha]^{20}_D$ +0.9 (*c* 1.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 6H, $J = 6.6$ Hz), 1.10−1.41 and 1.51−1.66 (2m, 38H), 1.60 and 1.68 (2s, 12H), 1.97 (m, 4H), 3.42−3.66 (m, 18H), 4.01 (dt, 4H, $J = 5.5$ Hz), 5.09 (m, 2H), 5.17 and 5.27 (2m, 4H), 5.85−5.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.63, 19.52, 25.46, 25.72, 26.13, 29.46, 29.51, 29.66, 29.70, 29.71, 37.00, 37.24, 68.82, 70.26, 70.71, 71.65, 72.33, 77.92, 116.82, 124.88, 131.05, 134.85. Anal. Calcd for $C_{48}H_{90}O_6$: C, 75.54; H, 11.88. Found: C, 75.59; H, 11.93.

1,1′-*O*-(1,16-Hexadecamethylene)bis[2-*O*-(*R*)-citronellyl-*sn*-glycerol] (13). A suspension of **12** (1.15 g, 1.5 mmol) in a mixture of ethanol, toluene, and water (44 mL, 7:3:1 v/v/v) containing $(Ph_3P)_3RhCl$ (0.225 g, 0.24 mmol) was stirred at 100 °C for 40 h. The mixture was then concentrated and fractionated between water and ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and rotoevaporated. The crude product was purified by silica gel chromatography. Elution with a mixture of CH_2Cl_2 and acetone (the volume ratio was changed from 19:1 to 9:1) gave the desired product as a pale yellow oil (0.82 g, 80%), $R_f = 0.44$ (solvent E). **13**: $[\alpha]^{20}_D$ −9.0 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 6H, $J = 6.5$ Hz), 1.11−1.44 and 1.50−1.65 (2m, 38H), 1.60 and 1.68 (2s, 12H), 1.97 (m, 4H), 3.41−3.75 (m, 18H), 5.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.64, 19.54, 25.46, 25.71, 26.10, 29.41, 29.47, 29.60, 29.61, 29.67, 29.68, 36.99, 37.15, 63.08, 68.55, 70.87, 71.85, 78.29. Anal. Calcd for $C_{42}H_{82}O_6$: C, 73.85; H, 12.09. Found: C, 73.60; H, 12.21.

1,1′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (14). A suspension of **13** (0.50 g, 0.73 mmol) in ethanol (10 mL) containing Raney nickel (ready for use, Acros, 2 g) was stirred under atmospheric pressure of hydrogen at room temperature for 1 h. After removal of the catalyst by filtration with Celite, rotoevaporation of solvent gave a colorless oil that was purified by silica gel chromatography. Elution with a mixture of petroleum ether and EtOAc (2:1 v/v) yielded the desired product as a colorless oil (0.467 g, 95%), $R_f = 0.50$ (solvent E). **14**: $[\alpha]^{20}_D$ −10.2 (c 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 18H), 1.07−1.41 and 1.47−1.65 (2m, 48H), 3.40−3.75 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.63, 22.59, 22.69, 24.64, 26.09, 27.94, 29.47, 29.60, 29.61, 29.66, 29.68, 29.77, 37.06, 37.34, 39.25, 63.06, 68.62, 70.88, 71.84, 78.28. Anal. Calcd for $C_{42}H_{86}O_6$: C, 73.41; H, 12.62. Found: C, 73.50; H, 13.02.

Following the same synthetic pathway A from (*S*)-epichlorohydrin, **15** was obtained in 30% overall yield.

3,3′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (15): $[\alpha]^{20}_D$ +12.9 (c 0.86, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 18H), 1.06−1.41 and 1.47−1.67 (2m, 48H), 3.42−3.75 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.64, 22.59, 22.69, 24.65, 26.09, 27.97, 29.47, 29.60, 29.61, 29.66, 29.68, 29.79, 37.08, 37.34, 39.26, 63.04, 68.63, 70.91, 71.84, 78.31; FABMS (*m*-nitrobenzyl alcohol matrix) calcd for $[M + H]^+$ 687.6502, found 687.6510.

Following the same synthetic pathway A from (*R*,*S*)-epichlorohydrin, diol **16** was obtained in 33% overall yield.

1,1′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*rac*-glycerol} (16): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 18H), 1.07−1.42 and 1.47−1.67 (2m, 48H), 3.42−3.75 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.66, 22.61, 22.71, 24.67, 26.12, 27.97, 29.49, 29.62, 29.61, 29.64, 29.70, 29.81, 29.82, 29.94, 37.10, 37.36, 39.26, 63.11, 63.12, 68.65, 70.93, 70.95, 71.88, 71.27, 78.29. Anal. Calcd for $C_{42}H_{86}O_6$: C, 73.41; H, 12.62. Found: C, 73.56; H, 12.82.

Hexadecane-1,16-diyl Ditriflate (18). A solution of 2,6-lutidine (1.17 mL, 10 mmol) in 10 mL of dry CH_2Cl_2 was cooled to 0 °C under nitrogen. Triflic anhydride (1.64 mL, 10 mmol) was slowly introduced, and after a few minutes hexadecane-1,16-diol (1 g, 3.87 mmol) was added. The mixture was stirred for 15 min before water was added. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic phase was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with a mixture of petroleum ether and EtOAc (19:1) to afford compound **18** as a white solid (1.5 g, 80%), $R_f = 0.67$ (solvent C). **18**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.22−1.42 (m, 24H), 1.79 (m, 4H), 4.53 (t, 4H, $J = 6.41$ Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 25.22, 29.04, 29.39, 29.53, 29.67, 29.79, 29.83, 78.56, 119.0.

1,1′-*O*-(1,16-Hexadecamethylene)bis[(*S*)-solketal] (19). To a solution of ditriflate derivative **18** (1.44 g, 2.75 mmol) in 5 mL of dry CH_2Cl_2 was added a mixture of (*S*)-solketal (1.46 g, 11.05 mmol) and *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine (PS) (1.53 g, 7.46 mmol) dissolved in 5 mL of CH_2Cl_2. The mixture was refluxed for 15 h, cooled to room temperature, and filtered through a silica gel pad. The solvent was evaporated, and the residue was flash chromatographed over silica gel with petroleum ether−EtOAc (7:3) as the eluent to give bis-(*S*)-solketal **19** as a white solid (1.12 g, 83%), $R_f = 0.70$ (solvent I). **19**: mp 47−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (m, 24H), 1.35 (s, 6H), 1.41 (s, 6H) 1.56 (m, 4H), 3,46 (m, 8H) 3.71 (dd, 2H), 4.05 (dd, 2H), 4.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.51, 26.14, 26.86, 29.56, 29.64, 29.68, 29.70, 29.75, 29,76, 67.02, 71.90, 71.98, 74.84. Anal. Calcd for $C_{28}H_{54}O_6$: C, 69.09; H, 11.18. Found: C, 69.11; H, 11.06.

3,3′-*O*-(1,16-Hexadecamethylene)bis(1-*O*-*p*-methoxyphenyldiphenylmethyl-*sn*-glycerol) (20). Compound **19** (4 g, 8.22 mmol) was dissolved in 25 mL of CH_3OH, and 400 mg of an acidic resin Dowex 50 × 8−100 was added. The solution was refluxed for 20 h and then cooled to room temperature. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the crude residue was purified by recrystallization in EtOAc to give 3,3′-*O*-(1,16-hexadecamethylene)bis(*sn*-glycerol) as a white solid (3.1 g, 93%), $R_f =$ 0.60 (THF); mp 112−113 °C; ^{1}H NMR (400 MHz, pyridine-d_5 + D_2O) δ 1.21−1,38 (m, 24H), 1.62 (m, 4H), 3,52 (m, 4H) 3.85 (dd, 2H), 4.42 (m, 2H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 23.11, 26.27, 29.57, 29.66, 29.71, 29.84, 29.95, 64.53, 71.47, 71.81, 73.41. To a solution of this tetraol (755 mg, 1.86 mmol) in THF (10 mL) were added Et_3N (2.07 mL, 14.9 mmol), DMAP (90 mg, 0.74 mmol), and *p*-methoxyphenyldiphenylmethyl chloride (1.43 g, 4.65 mmol). After being stirred for 4 h under refluxing, the solution was cooled to room temperature, diluted with CH_2Cl_2, and washed with water. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography with petroleum ether−EtOAc (4:1) as the eluent, giving **20** as a syrup (1.40 g, 80%), $R_f = 0.54$ (solvent D). **20**: $[\alpha]^{20}_D$ −3.65 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1,32 (m, 24H), 1.52 (m, 4H), 2.49 (d, 2H, $J = 4.07$ Hz), 3.19 (m, 4H), 3.38−3.56 (m, 8H), 3.77 (s, 6H), 3.94 (m, 2H), 6.80−7.46 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.10−29.67, 55.16, 64.51, 69.85, 71.62, 72.07, 86.29, 113.07−158.53. Anal. Calcd for $C_{62}H_{78}O_8$: C, 78.28; H, 8.26. Found: C, 78.19; H, 8.16.

3,3′-*O*-(1,16-Hexadecamethylene)bis{1-*O*-*p*-methoxyphenyldiphenylmethyl-2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (21). In a 20 mL double-neck flask equipped with a Dean−Stark apparatus was slowly added NaH (60% in oil, 376 mg, 9.41 mmol) to a solution of **20** (895 mg, 0.95 mmol) in 8 mL of dry THF. When gas evolution ceased, (*R*)-citronellyl

bromide (930 μL, 4.07 mmol) was added, and the resulting mixture was stirred at 120 °C for 3 h; the solvent was distilled out during heating. After cooling, a few drops of CH_3OH were added, and the reaction mixture was diluted with ether, quenched with water, and extracted with ether. The combined extracts were washed with 5% aqueous HCl and water, dried, and concentrated to leave a residue, chromatography of which on silica gel (elution with petroleum ether−EtOAc 19:1) provided 3,3′-*O*-(1,16-hexadecamethylene)bis[1-*O*-*p*-methoxyphenyldiphenyl methyl-2-*O*-(*R*)-citronellyl-*sn*-glycerol] as a colorless oil (924 mg, 80%): $R_f = 0.46$ (solvent B); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 6H, $J = 6.5$ Hz), 1.10−1.44 and 1.48−1.65 (2m, 38H), 1.59−1.68 (m, 12H), 1.97 (m, 4H), 3.16 (m, 4H), 3.39−3.61 (m, 14H), 3.78 (m, 6H), 5.08 (m, 2H), 6.80−7.46 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.72, 19.63, 25.57, 25.79, 26.21, 29.57, 29.63, 29.73, 29.77, 29.79, 29.81, 29.82, 37.16, 37.36, 55.24, 63.61, 68.97, 71.31, 71.70, 78.44, 86.24, 124.97, 131.13, 113.05−158.51. A solution of this compound (924 mg) in EtOAc (10 mL) containing triethylamine (106 μL, 1 equiv) and 10% palladium on carbon (90 mg) was stirred under an atmosphere of hydrogen gas at room temperature for 8 h. The catalyst was removed by filtration, and the filtrate was concentrated under vacuum to give **21** as a colorless oil (834 mg, 90%), $R_f = 0.59$ (solvent B). **21**: $[\alpha]^{20}_D$ −4.71 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, 12H, $J = 6.6$ Hz), 0.86 (d, 6H, $J = 6.6$ Hz), 1.07−1.42 and 1.45−1.68 (2m, 48H), 3.16 (m, 4H), 3.39−3.61 (m, 14H), 3.78 (s, 6H), 6.80−7.46 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.67, 22.61, 22.71, 24.70, 26.12, 27.97, 29.56, 29.66, 29.70, 29.74, 29.77, 37.16, 37.42, 39.31, 55.17, 63.52, 68.93, 71.24, 71.62, 78.34, 86.22, 112.97−158.42. Anal. Calcd for $C_{82}H_{118}O_8$: C, 79.95; H, 9.65. Found: C, 79.68; H, 9.68.

3,3′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (15). A solution of bis trityl ether **21** (440 mg, 0.36 mmol) in ether (6 mL) was treated with formic acid (5 mL), and the resulting mixture was stirred at room temperature for 45 min. The reaction was quenched with brine, and the organic layer was washed twice with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed over silica gel with petroleum ether−EtOAc (17:1) to give diol **15** as a colorless oil (183 mg, 75%), $R_f = 0.33$ (solvent C). **15**: $[\alpha]^{20}_D$ +13.8 (*c* 0.70, CH_2Cl_2). For NMR data, see pathway A.

1-*O*-Benzyl-2-*O*-(*R*)-3,7-dimethyloctyl-*sn*-glycerol (23). A mixture of sodium hydride (60% in oil, 552 mg, 13.8 mmol) and 3-*O*-trityl-1-*O*-benzyl-*sn*-glycerol **22** (1.46 g, 3.44 mmol)[18] in 20 mL of dry THF was stirred at room temperature until gas evolution ceased. (*R*)-(−)-Citronellyl bromide (1.63 mL, 8.24 mmol) was added, and the resulting mixture was stirred at 120 °C for 2.5 h; the solvent was distilled out during heating. After cooling, a few drops of CH_3OH were added, and the reaction mixture was diluted with ether, quenched with water, and extracted with ether. The combined ether extracts were washed with 5% aqueous HCl and water, dried, and concentrated to leave a residue, chromatography of which on silica gel (elution with petroleum ether−EtOAc 49:1) provided 3-*O*-trityl-2-*O*-(*R*)-citronellyl-1-*O*-benzyl-*sn*-glycerol as a colorless oil (1.33 g, 68%), $R_f = 0.81$ (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, $J = 6.10$ Hz), 1.10−1.42 (m, 5H), 1.59 and 1.68 (2s, 6H), 1.95 (m, 2H), 3.21 (d, 2H), 3.51−3.66 (m, 5H), 4.51 (m, 2H), 5.08 (m, 1H), 7.21−7.42 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.06, 19.97, 25.89, 26.14, 29.95, 37.50, 37.70, 63.91, 69.37, 70.93, 73.68, 78.79, 86.97, 125.3, 131.5, 127.3−144.5. A solution of this compound (1.20 g, 2.13 mmol) in EtOAc (10 mL) containing triethylamine (297 μL, 2.13 mmol) and 10% palladium on carbon (100 mg) was stirred under an atmosphere of hydrogen gas at room temperature for 18 h. The catalyst was removed by filtration on Celite, and the filtrate was concentrated under vacuum to give 3-*O*-trityl-2-*O*-(*R*)-3,7-dimethyloctyl-1-*O*-benzyl-*sn*-glycerol as a colorless syrup (1.03 g, 98%), $R_f = 0.83$ (solvent C). This crude product (1.03 g) in ether (6 mL) was treated with HCO_2H (6 mL) until appearance of a yellow color, and the resulting mixture was stirred at room temperature for 20 min. The reaction was quenched with brine, and the organic layer was washed twice with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed over silica gel with petroleum ether−EtOAc (9:1) to give alcohol **23** as a colorless oil (504 mg, 75%), $R_f = 0.42$ (solvent C). **23**: $[\alpha]^{20}_D$ −12.7 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.88 (d, 9H), 1.08−1.66 (m, 10H), 2.25 (t, 1H), 3.50−3.76 (2m, 7H), 4.51 (s, 2H), 7.21−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.65, 22.60, 22.70, 24.65, 27.95, 29.78, 37.08, 37.34, 39.26, 62.84, 68.68, 69.97, 73.50, 78.52, 127.63, 127.70, 128.41, 138.00. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.82; H, 10.81.

3,3′-*O*-(1,16-Hexadecamethylene)bis{1-*O*-benzyl-2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (24). A solution of 0.105 g (0.20 mmol) of ditriflate **18** in 2 mL of tetrahydrofuran was added to a suspension of 133 mg (0.60 mmol) of alcohol **23** and 137 mg of potassium hydride (35% in oil) in 2 mL of tetrahydrofuran. The suspension was allowed to stir at room temperature for 1 h before water was added, and the resulting mixture was extracted with ether. The combined extracts were dried over magnesium sulfate, and the solvent was removed at reduced pressure. The residue was purified by flash chromatography upon elution with petroleum ether−ether (19:1) to yield **24** as a colorless oil (121 mg, 70%), $R_f = 0.72$ (solvent C). **24**: $[\alpha]^{20}_D$ +1.22 (*c* 0.82 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.87 (d, 18H), 1.07−1.42 and 1.47−1.68 (2m, 48H), 3.41−3.66 (m, 18H), 4.55 (s, 4H), 7.26−7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.74, 22.69, 22.79, 24.75, 26.21, 28.04, 29.59, 29.74, 29.79, 29.85, 37.19, 39.37, 68.95, 70.36, 70.82, 71.74, 73.43, 78.00, 127.57, 127.66, 128.37, 138.49. Anal. Calcd for $C_{56}H_{98}O_6$: C, 77.54; H, 11.39. Found: C, 77.93; H, 10.91,

3,3′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (15). A solution of compound **24** (105 mg, 0.12 mmol) in AcOEt (2 mL) containing 10% palladium on carbon (15 mg) was stirred under an atmosphere of hydrogen gas at room temperature for 3 h. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography upon elution with petroleum ether−AcOEt (4:1) to give **15** as a colorless oil (75 mg, 90%). **15**: $[\alpha]^{20}_D$ +15.0 (*c* 1.02, CH_2Cl_2). For NMR data, see pathway A.

***cis*-1,3-Diformylcyclopentane (25).** A solution of norbornene (5 g, 53.1 mmol) in 200 mL of CH_2Cl_2 at −78 °C was ozonized until a faint blue color persisted, and the mixture was purged with oxygen for 10 min. The ozonide was reduced with triphenylphosphine (42 g, 160.1 mmol) at −78 °C, and the resulting mixture was allowed to warm to room temperature. The reaction was stirred for overnight. After removal of solvent, the crude product was purified by silica gel chromatography with petroleum ether and then petroleum ether−AcOEt (1:1 v/v) to give dialdehyde **25** as a colorless oil (3.65 g, 55%),[19,20] $R_f = 0.40$ (solvent G); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84−1.88 (m, 4H), 1.94−2.02 (dt, 1H, $J = 8.64$, 13.73 Hz), 2.16−2.25 (dt, 1H, $J = 6.61$ Hz), 2.77−2.88 (m, 2H), 9.59 (d, 2H, $J = 2.03$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.90, 26.21, 51.36, 202.63.

1,3-Bis(7-tetrahydropyranyloxyhept-1-enyl)cyclopentane (27). To 4.89 mmol (2.58 g) of dry (6-tetrahydropyranyloxyhexyl)triphenyphosphonium bromide[22] in 16 mL of THF under N_2 was added at 0 °C 2.33 equiv of *n*-BuLi (3.2 mL, 1.6 M solution in hexane, 5.13 mmol). After 25 min at 0 °C, a solution of *cis*-1,3-diformylcyclopentane (278 mg, 2.20 mmol) in 2.5 mL of THF was added. The reaction was stirred at room temperature for 1 h. The solution was subjected to an extractive workup (quenching with water and extraction with diethyl ether), and the product was purified by silica gel chromatography. Elution with a mixture of petroleum ether, EtOAc, and Et_3N (94:5:1, v/v) yielded compound **27** as a colorless oil (703 mg, 70%), $R_f = 0.20$ (solvent A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91−1.03 (dt, 1H, $J = 10.68$, 12.21 Hz), 1.22−1.41 (m, 10H), 1.44−1.62 (m, 10H), 1.64−1.88 (m, 9H), 1.93−2.08 (m, 4H), 2.69−2.83 (m, 2H), 3.30−3.39 (dt, 2H, $J = 6.61$, 9.16 Hz), 3.42−3.51 (m, 2H), 3.65−3.74 (dt, 2H, $J = 7.12$ Hz), 3.79−3.88 (m, 2H), 4.56 (t, 2H, $J = 3.06$ Hz), 5.18−5.36 (m, 4H, $J = 5.60$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.68, 25.53, 25.92, 27.46,

29.74, 29.80, 30.78, 32.81, 38.27, 42.14, 62.28, 67.61, 98.82, 128.42, 135.33. Anal. Calcd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.27; H, 10.89.

1,3-Bis(7-hydroxyheptyl)cyclopentane (28). To a solution of pTSA (12 mg, 0.07 mmol) in methanol (20 mL) was added 1,3-bis(7-tetrahydropyranyloxyhept-1-enyl)cyclopentane **27** (607 mg, 1.31 mmol). The reaction mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and the solution was washed with water. The organic layers were dried ($MgSO_4$) and concentrated. A solution of the resulting residue in CH_3OH (20 mL) containing 10% palladium on carbon (80 mg) was stirred under an atmosphere of hydrogen gas at room temperature for 2 h. The catalyst was removed by filtration on Celite, and the filtrate was concentrated under vacuum. The crude product was purified by silica gel chromatography with petroleum ether−AcOEt (1:1 v/v) as the eluent to provide diol **28** (317 mg, 81%) as a white solid, $R_f = 0.30$ (solvent G). **28**: mp 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92−1.91 (m, 32H), 2.60 (s, 2H), 3.56 (t, 4H, $J = 6.61$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.78, 28.68, 29.48, 29.89, 31.61, 32.72, 36.69, 36.75, 38.74, 40.11, 40.68, 62.75. Anal. Calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.36; H, 13.01.

3,3′-*O*-[1,18-Octadecan-(8,11-methylidene)methylene]-bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (9). A solution of 2,6-lutidine (755 μL, 6.35 mmol) in 8 mL of dry CH_2Cl_2 was cooled to 0 °C under nitrogen. Triflic anhydride (1.05 mL, 3.35 mmol) was slowly introduced, and after a few minutes diol **28** (500 mg, 1.67 mmol) was added. The mixture was stirred for 15 min before water was added. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic phase was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with a mixture of petroleum ether and EtOAc (19:1) to afford compound **29** as a colorless oil (675 mg, 77%). A solution of 675 mg (1.28 mmol) of ditriflate **29** in 5 mL of tetrahydrofuran was added to a suspension of 1.61 g (0.60 mmol) of alcohol **23** and 1.14 g of potassium hydride (35% in oil) in 15 mL of tetrahydrofuran. The suspension was allowed to stir at room temperature for 1 h before water was added, and the resulting mixture was extracted with ether. The combined extracts were dried over magnesium sulfate, and the solvent was removed at reduced pressure. The residue was purified by flash chromatography upon elution with petroleum ether−ether (19:1) to yield **30** as a colorless oil (920 mg, 79%), $R_f = 0.55$ (solvent B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.74, 22.69, 22.80, 24.75, 26.21, 28.04, 28.72, 29.62, 29.74, 29.85, 29.97, 31.69, 33.1, 36.78, 37.18, 37.45, 38.83, 39.38, 40.19, 40.79, 68.94, 70.34, 70.81, 73.42, 77.99, 127.57, 127.66, 128.38, 128.38, 138.49. A solution of compound **30** (139 mg, 0.153 mmol) in AcOEt (3 mL) containing 10% palladium on carbon (15 mg) was stirred under an atmosphere of hydrogen gas at room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography upon elution with petroleum ether−AcOEt (4:1) to give **9** as a colorless oil (87 mg, 80%), $R_f = 0.54$ (solvent D). **9**: $[\alpha]^{20}_D$ +12.4 (*c* 0.82, CH_2Cl_2); ^{13}C NMR δ 17.71, 24.73, 26.16, 28.01, 28.67, 28.74, 29.57, 29.68, 29.86, 29.93, 31.68, 33.08, 36.75, 36.83, 37.14, 37.41, 38.81, 39.33, 40.17, 40.76, 63.13, 68.70, 70.98, 71.92, 78.35. Anal. Calcd for $C_{45}H_{90}O_6$: C, 74.32; H, 12.47. Found: C, 74.45; H, 12.56.

1,1′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-3-*O*-(β-D-galactofuranosyl)-*sn*-glycerol} (4). Compound **14** (0.535 g, 0.779 mmol) and pent-4-enyl 2,3,5,6-tetra-*O*-acetyl-α,β-D-galactofuranoside **31**[24] (0.822 g, 1.974 mmol) were combined, rotoevapored twice with toluene, and then dried for 2 h under vacuum. A solution of this mixture in dry methylene chloride (20 mL) at room temperature was treated under nitrogen with *N*-iodosuccinimide (577 mg, 2.565 mmol) followed by dropwise addition of triethylsilyl trifluoromethanesulfonate (0.13 mL, 0.592 mmol). The mixture was stirred until TLC analysis indicated complete disappearance of the starting acceptor (10−15 min). Several drops of triethylamine were added to the reaction mixture until it turned into a yellow solution. The resulting solution was diluted with CH_2Cl_2, washed successively with 10% aqueous sodium thiosulfate, 0.5% aqueous HCl, and brine, and then dried over $MgSO_4$, and rotoevaporated. The crude product was purified by silica gel chromatography, eluting with a mixture of CH_2Cl_2 and acetone (the volume ratio was changed from 39:1 to 19:1) to yield 1,1′-*O*-(1,16-hexadecamethylene)bis{2-*O*-[5(*R*)-3,7-dimethyloctyl]-3-*O*-[2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl]-*sn*-glycerol} **32** as a colorless oil (0.702 g, 67%), $R_f = 0.31$ (solvent H). **32**: $[\alpha]^{20}_D$ −27.5 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 18H), 1.07−1.39 and 1.47−1.66 (2m, 48H), 2.06−2.14 (4s, 24H), 3.40−3.66 (m, 16H), 3.71 (dd, 1H, $J = 4.3$, 9.2 Hz), 4.21 (dd, 2H, $J = 7.2$, 11.8 Hz), 4.26 (dd, 2H, $J = 3.8$, 5.9 Hz), 4.34 (dd, 2H, $J = 4.3$, 11.8 Hz), 4.99 (dd, 2H, $J = 1.6$ Hz), 5.05−5.07 (m, 4H), 5.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.58, 20.65, 20.70, 20.76, 20.81, 22.58, 22.68, 24.63, 26.11, 27.93, 29.51, 29.64, 29.66, 29.70, 29.71, 29.79, 29.96, 37.05, 37.44, 39.26, 62.66, 67.32, 69.05, 69.21, 70.37, 71.71, 76.55, 77.64, 79.87, 81.22, 105.51, 169.55, 169.93, 170.02, 170.49. To a suspension of **32** (0.50 g, 0.371 mmol) in dry CH_3OH (10 mL) was added a 0.1 M solution of sodium methoxide in CH_3OH (5 mL). The mixture was stirred for 2 h at room temperature, neutralized with aqueous acetic acid, and rotoevaporated. The crude product was purified by silica gel chromatography, eluting with a mixture of CH_2Cl_2 and CH_3OH (the volume ratio was changed gradually from 9:1 to 17:3), to yield the desired product as a syrup (295 mg, 79%), $R_f = 0.51$ (solvent I). **4**: $[\alpha]^{20}_D$ −46.2 (*c* 0.84, CH_2Cl_2−CH_3OH (2:3 v/v)); ^{1}H NMR (400 MHz, pyridine−D_2O) δ 0.87−0.93 (m, 18H), 1.06−1.78 (m, 48H), 3.49−3.85 (m, 12H), 3.87,4.18 (m, 4H), 3.96 (m, 2H), 4.34 (m, 4H), 4.75 (m, 2H), 4.85 (m, 4H), 5.01 (dd, 2H, $J = 4.1$, 6.5 Hz), 5.58 (d, 2H, $J = 1.96$ Hz); ^{13}C NMR (100 MHz, pyridine−D_2O) δ 19.72−22.84, 24.80−39.48, 64.30, 67.88, 68.81, 71.59, 71.66, 72.22, 78.42, 78.92, 84.68, 109.65. Anal. Calcd for $C_{54}H_{106}O_{16}$: C, 64.13; H, 10.56. Found: C, 64.15; H, 10.86.

3,3′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(β-D-galactofuranosyl)-*sn*-glycerol} (5). Following the same strategy as for compound **4** and starting from diol **15** compound **5** was obtained (diglycosylation: 65% yield; deprotection: 81% yield). **5**: $[\alpha]^{20}_D$ −40.1 (*c* 0.80, CH_2Cl_2−CH_3OH (2:3 v/v)); ^{1}H NMR (400 MHz, pyridine−D_2O) δ 0.87−0.93 (m, 18H), 1.06−1.78 (m, 48H), 3.49−3.83 (m, 12H), 3.49−3.83 (m, 8H), 3.85, 4.19 (2dd, 4H, $J = 4.8$, 6.5 Hz and $J = 4.58$, 10.3 Hz), 3.95 (m, 2H), 4.37 (m, 4H), 4.58 (m, 2H), 4.87 (m, 4H), 5.03 (dd, 2H, $J = 4.1$, 6.2 Hz), 5.60 (d, 2H, $J = 1.80$ Hz); ^{13}C NMR (100 MHz, pyridine−D_2O) δ 19.72−22.84, 24.80−39.48, 64.43, 68.13, 68.81, 71.61, 71.70, 72.41, 78.62, 83.04, 84.88, 109.77. Anal. Calcd for $C_{54}H_{106}O_{16}$: C, 64.13; H, 10.56. Found: C, 64.13; H, 10.96.

1,1′-*O*-(1,16-Hexadecamethylene)bis{2-*O*-[(*R,S*)-3,7-dimethyloctyl]-3-*O*-(β-D-galactofuranosyl)-*rac*-glycerol} (6). Following the same strategy as for compound **4** and starting from diol **16**, compound **6** was obtained (diglycosylation: 70% yield; deprotection: 77% yield). **6**: $[\alpha]^{20}_D$ −50.7 (*c* 0.87, CH_2Cl_2−CH_3OH (2:3 v/v)); ^{1}H NMR (400 MHz, pyridine−D_2O) δ 0.87−0.93 (m, 18H), 1.06−1.78 (m, 48H), 3.48−3.83 (m, 12H), 3.84−3.90 and 4.17−4.22 (m, 4H), 3.95 (m, 2H), 4.38 (m, 4H), 4.58 (m, 2H), 4.89 (m, 4H), 5.05 (m, 2H), 5.60 (m, 2H); ^{13}C NMR (100 MHz, pyridine−D_2O) δ 19.72−22.84, 24.80−39.48, 64.49, 67.95, 68.16, 68.67−68.85, 71.57−71.67, 72.50, 78.40−78.67, 83.11, 84.93, 84.96, 109.84, 109.87. Anal. Calcd for $C_{54}H_{106}O_{16}$: C, 64.13; H, 10.56. Found: C, 63.85; H, 10.56.

3,3′-*O*-(1,16-Hexadecamethylene)-2,2′-*O*-[(*R*)-3,7-dimethyloctyl]-1′-*O*-benzyl-*sn*-diglycerol (35). To a stirred solution of diol **15** (514 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) were added Ag_2O (260 mg, 1.12 mmol) and benzyl bromide (124 μL, 1.05 mmol). The reaction was refluxed for 3 days in the dark and filtered through a silica gel pad. Evaporation of the solvent followed by flash chromatography, eluting with a mixture of petroleum ether and EtOAc (the volume ratio was changed from 9:1 to 3:1), gave the monobenzylated product **35** as a colorless oil (291 mg, 50%) in addition to the starting material **15** (36%) and the diprotected diol (10%), $R_f = 0.67$ (solvent D). **35**: $[\alpha]^{20}_D$ +8 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ

0.86−0.91 (m, 18H), 1.06−1.42 and 1.47−1.68 (2m, 48H), 2.2 (m, 1H), 3.40−3.76 (m, 18H), 4.55 (s, 2H), 7.27−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.72, 19.74, 22.68, 22.78, 24.74, 26.18, 26.21, 28.03, 29.56, 29.87, 37.16, 37.18, 37.42, 37.34, 39.34, 39.37, 63.17, 68.70, 68.94, 70.34, 70.81, 71.01, 71.94, 73.42, 77.99, 78.32, 127.57−138.49. Anal. Calcd for $C_{49}H_{92}O_6$: C, 75.52; H, 11.93. Found: C, 75.33; H, 11.81.

3,3′-*O*-(1,16-Hexadecamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(2,3,5,6-tetra-*O*-acetyl-*β*-D-galactofuranosyl)-*sn*-diglycerol (36). Compound **35** (145 mg, 0.186 mmol) and pent-4-enyl 2,3,5,6-tetra-*O*-acetyl-α,*β*-D-galactofuranoside **31**[24] (124 mg, 0.298 mmol) were combined, rotoevaporated twice with toluene, and then dried for 2 h under vacuum. A solution of this mixture in dry CH_2Cl_2 (6 mL) at room temperature was treated under nitrogen with *N*-iodosuccinimide (87 mg, 0.372 mmol) followed by dropwise addition of triethysilyl trifluoromethanesulfonate (21 μL, 0.084 mmol). The mixture was stirred until TLC analysis indicated complete disappearance of the starting acceptor **35** (10−15 min). Several drops of triethylamine were added to the reaction mixture until it turned into a yellow solution. The resulting solution was diluted with CH_2Cl_2, washed successively with 10% aqueous sodium thiosulfate, 0.5% aqueous HCl, and brine, dried over $MgSO_4$ and rotoevaporated. The crude product was purified by silica gel chromatography with petroleum ether−EtOAc (4:1) to yield 3,3′-*O*-(1,16-hexadecamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(2,3,5,6-tetra-*O*-acetyl-*β*-D-galactofuranosyl)-1′-*O*-benzyl-*sn*-diglycerol as a colorless oil (164 mg, 80%), R_f = 0.31 (solvent C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.88 (m, 18H), 1.04−1.42 and 1.46−1.68 (2m, 48H), 2.05−2.12 (4s, 12H), 3.39−3.66 (m, 17H), 3.72−3.78 (dd, 1H, J = 4.57, 10.17 Hz), 4.22 (dd, 1H, J = 7.12, 11.70 Hz), 4.25 (dd, 1H, J = 3.56, 6.11 Hz), 4.34 (dd, 1H, J = 4.07 Hz), 4.55 (s, 2H), 4.99 (m, 1H), 5.06−5.09 (m, 2H), 5.39 (m, 1H), 7.27−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.68, 19.73, 22.68, 22.78, 24.75, 20.79, 20.83, 20.91, 24.73, 26.21, 28.03, 29.59−29.84, 37.15, 37.18, 37.44, 39.37, 62.81, 67.52, 68.93, 69.01, 69.35, 70.35, 70.51, 70.82, 71.73, 71.85, 73.41, 76.65, 77.99, 79.93, 81.29, 105.82, 127.56−138.50, 169.60, 170.03, 170.11, 170.58. A solution of this compound (164 mg) in EtOH (3 mL) was stirred in the presence of 10% palladium on activated charcoal (20 mg) and under an atmosphere of hydrogen gas at room temperature until TLC analysis indicated complete disappearance of the starting material. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under vacuum to give the deprotected monoglycosylated lipid **36** as a colorless oil (137 mg, 91%), R_f = 0.54 (solvent G). **36**: $[\alpha]^{20}_D$ −16.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.88 (m, 18H), 1.05−1.43 and 1.47−1.69 (2m, 48H), 2.04−2.18 (4s, 12H), 2.2 (t, 1H, J = 6.10 Hz), 3.39−3.77 (m, 18H), 4.21 (dd, 1H, J = 7.12, 11.70 Hz), 4.25 (dd, 1H, J = 3.56, 5.80 Hz), 4.34 (dd, 1H, J = 4.07 Hz), 4.99 (m, 1H), 5.06−5.09 (m, 2H), 5.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.62, 19.65, 20.68−20.83, 22.60, 22.71, 24.66, 26.11, 26.14, 27.95, 29.48−29.80, 37.09, 37.35, 37.37, 39.27, 62.74, 63.09, 67.45, 68.63, 68.94, 69.29, 70.35, 70.44, 70.95, 71.78, 71.86, 76.58, 77.61, 78.28, 79.87, 81.21, 105.76, 169.53−170.51. Anal. Calcd for $C_{56}H_{104}O_{15}$: C, 66.11; H, 10.30. Found: C, 65.87; H, 10.29.

3,3′-*O*-(1,16-Hexadecamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(*β*-D-galactofuranosyl)-1′-*O*-(*β*-lactosyl)-*sn*-diglycerol (7). Alcohol **36** (75 mg, 0.075 mmol) and lactosyl thioglycoside **37** (65 mg, 0.096 mmol) were dissolved in CH_2Cl_2 (2 mL), and 4 Å molecular sieves (100 mg) were added. The mixture was treated under nitrogen in the dark with *N*-iodosuccinimide (22 mg, 0.096 mmol) followed by dropwise addition of triethylsilyl trifluoromethanesulfonate (4 μL, 0.015 mmol). The reaction was quenched with a few drops of triethylamine after 5 min at room temperature. The resulting solution was diluted with CH_2Cl_2, washed successively with 10% aqueous sodium thiosulfate, water, and brine, dried over $MgSO_4$, and rotoevaporated. The crude product was purified by silica gel chromatography with petroleum ether−EtOAc (11:9) to give the acetylated diglycosylated lipid as a colorless oil (85 mg, 70%), R_f = 0.19 (solvent G); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.89 (m, 18H), 1.08−1.40 and 1.45−1.60 (2m, 48H), 1.96−2.16 (11s, 33H), 3.37−3.63 (m, 17H), 3.72−3.82 (m, 2H), 3.84−3.92 (m, 2H), 4.05−4.16 (m, 3H), 4.19−4.27 (m, 2H), 4.33 (dd, 1H), 4.45−4.50 (m, 2H, J = 7.63, 11.75 Hz), 4.54 (d, 1H, J = 7.63 Hz), 4.88−5.01 (m, 3H), 5.07−5.14 (m, 3H), 5.19 (dd, 1H, J = 9.16 Hz), 5.33−5.41 (m, 2H, J = 3.56 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.63, 20.68, 20.69, 20.71, 20.72, 20.73, 20.74, 20.76, 20.77, 20.78, 20.81, 20.83, 22.60, 22.73, 24.65, 26.11, 26.14, 27.96, 29.52, 29.55, 29.62, 29.65, 29.66, 29.68, 29.70, 29.72, 29.73, 37.02, 37.08, 37.32, 37.37, 39.27, 39.31, 60.78, 62.22, 62.74, 67.01, 67.46, 68.95, 69.29, 69.71, 70.45, 71.78, 73.40, 75.12, 76.31, 76.59, 77.16, 77.61, 79.88, 81.24, 100.60, 100.80, 105.82, 169.02−170.04. To a solution of this compound (85 mg) in CH_3OH (5 mL) was added a 0.1 M solution of sodium methoxide in CH_3OH (4 mL). The mixture was stirred for 10 h at room temperature, neutralized with an acidic resin (Amberlite IR 120), filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with a mixture of EtOAc−CH_3OH−H_2O (7:2.5:0.5), to yield **7** as a white solid (60 mg, 93%), R_f = 0.53 [solvent: EtOAc−CH_3OH−H_2O (7:2.5:0.5)]. **7**: mp 195−196 °C; $[\alpha]^{20}_D$ −26.7 (*c* 0.78, CH_3OH); ^{13}C NMR (100 MHz, CD_3OD) δ 20.18, 20.21, 23.08, 23.18, 25.84, 27.27, 29.14, 30.57−30.95, 38.16, 38.40, 40.50, 61.82, 62.45, 64.48, 68.40, 69.63, 69.75, 70.21, 70.24, 71.79, 71.96, 72.35, 72.52, 72.60, 74.62, 74.71, 76.27, 76.44, 77.03, 78.82, 79.17, 79.22, 80.47, 83.12, 84.53, 104.54, 104.99, 109.64; FABMS (*m*-nitrobenzyl alcohol matrix) calcd for $[M + Na]^+$ 1195.7907, found 1195.7880.

3,3′-*O*-(1,16-Hexadecamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(2,3,5,6-tetra-*O*-acetyl-*β*-D-galactofuranosyl)-1′-*O*-(dibenzylphosphono)-*sn*-diglycerol (38). To a solution of alcohol **36** (195 mg, 0.192 mmol) in CH_2Cl_2 (5 mL) were added dibenzyl diisopropylphosphoramidite (96 μL, 0.287 mmol) and 1*H*-tetrazole (41 mg, 0.576 mmol). After 2 h under stirring at room temperature, the mixture was cooled to −40 °C, and a solution of 3-chloroperoxybenzoic acid (ready for use, Acros, 70% purity with water, 95 mg, 0.384 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was heated to 0 °C and maintained at this temperature for 20 min. The solution was diluted with CH_2Cl_2 and washed with 10% aqueous $Na_2S_2O_3$, 5% aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by flash silica gel chromatography [elution with petroleum ether−EtOAc (7:3)] to provide compound **38** as a colorless oil (195 mg, 80%), R_f = 0.67 (solvent G). **38**: $[\alpha]^{20}_D$ −12.3 (*c* 0.81, CH_2Cl_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ −3.56 (s, 1P); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82−0.89 (m, 18H), 1.05−1.41 and 1.46−1.65 (2m, 48H), 2.04−2.14 (4s, 12H), 3.36−3.64 (m, 15H), 3.75 (dd, 1H, J = 4.57, 10.68 Hz), 3.99−4.15 (2m, 2H), 4.22 (dd, 1H, J = 7.12, 11.70 Hz), 4.26 (dd, 1H, J = 4.07, 6.10 Hz), 4.34 (dd, 1H, J = 4.07 Hz), 4.99 (m, 1H), 5.03−5.09 (m, 2H), 5.39 (m, 1H), 7.28−7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.62, 19.64, 20.68−20.83, 22.60, 22.71, 24.66, 26.10, 26.14, 27.95, 29.53−29.74, 37.01, 37.09, 37.33, 37.36, 39.28, 39.31, 62.74, 67.46, 68.95, 69.16, 69.21, 69.70, 70.44, 71.78, 76.59, 77.16, 77.61, 79.87, 81.23, 105.75, 127.87−135.92, 169.53−170.50. Anal. Calcd for $C_{70}H_{117}O_{18}$: C, 65.81; H, 9.23. Found: C, 65.46; H, 9.13.

3,3′-*O*-(1,16-Hexadecamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(*β*-D-galactofuranosyl)-*sn*-diglycerol-1′-*O*-phosphate, Sodium Salt (8). To a solution of compound **38** (170 mg, 0.133 mmol) in CH_3OH (5 mL) was added dropwise a 0.1 M solution of sodium methoxide in CH_3OH (4 mL). The resulting mixture was stirred for 15 min at room temperature and was treated with a solution of acetic acid diluted in CH_3OH. The solvents were evaporated, and the residue was diluted in a mixture of CH_3OH (5 mL) and 1 mL of an acetate buffer (pH 5). The mixture was stirred at room temperature in the presence of 10% palladium on charcoal (20 mg) and under an atmosphere of hydrogen gas for 1 h. The catalyst was removed by filtration and the solvent partially evaporated. Resin Amberlite IR-120 (Na^+ form, 2 mL) prewashed with water was added to the mixture, and the resulting solution was stirred for 12 h at room temperature. The residue was filtered, the filtrate was concentrated, and the crude product was purified on a Sephadex LH-20 column eluting with a

mixture of $CH_2Cl_2-CH_3OH$ (1:2) to give the phosphate derivative **8** (110 mg, 85%), $R_f = 0.24$ [solvent $CH_2Cl_2-CH_3OH-NH_3$ (5:4:1)]. **8**: $[\alpha]^{20}_D$ −26.4 (*c* 0.72, CH_3OH); ^{31}P NMR (162 MHz, CD_3OD) δ −1.67 (s, 1P); ^{13}C NMR (100 MHz, CD_3OD) δ 20.16, 20.17, 23.06, 23.16, 23.81, 25.79, 25.81, 27.21, 27.23, 29.10, 30.49−30.79, 38.09, 38.12, 38.33, 38.38, 40.47, 40.48, 64.44, 65.22, 68.36, 69.71, 69.74, 71.92, 72.26, 72.27, 72.54, 72.58, 78.76, 79.11, 79.49, 83.01, 84.55, 109.58. FABMS (*m*-nitrobenzyl alcohol matrix) calcd for $[M + H]^+$ 973.6333, found 973.6331; calcd for $[M-Na + 2H]^+$ 951.6514, found 951.6524.

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Supporting Information Available: Copies of the high-field ^1H NMR and ^{13}C NMR spectra of *cis*-1,3-diformylcyclopentane (**25**), 1,1′-*O*-(1,16-hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-3-*O*-(β-D-galactofuranosyl)-*sn*-glycerol} (**4**), 3,3′-*O*-(1,16-hexadecamethylene)bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-3-*O*-(β-D-galactofuranosyl)-*sn*-glycerol} (**5**), 1,1′-*O*-(1,16-hexadecamethylene)bis{2-*O*-[(*R*,*S*)-3,7-dimethyloctyl]-3-*O*-(β-D-galactofuranosyl)-*rac*-glycerol} (**6**), and 3,3′-*O*-[1,18-octadecan-(8,11-methylidene)methylene]bis{2-*O*-[(*R*)-3,7-dimethyloctyl]-*sn*-glycerol} (**9**). ^1H and ^{13}C NMR and $^1H-^{13}C$ correlation spectra for 1,3-bis(7-hydroxyheptyl)cyclopentane (**28**). ^{13}C NMR and DEPT spectra for 3,3′-*O*-(1,16-hexamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(β-D-galactofuranosyl)-1′-*O*-(β-D-lactosyl)-*sn*-diglycerol (**7**) and ^{13}C and ^{31}P NMR spectra for 3,3′-*O*-(1,16-hexamethylene)-2,2′-di-*O*-[(*R*)-3,7-dimethyloctyl]-1-*O*-(β-D-galactofuranosyl)-*sn*-diglycerol-1′-*O*-phosphate, sodium salt (**8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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