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A NEW APPROACH TO THE SYNTHESIS OF ARCHAEBACTERIAL TETRAETHER LIPIDS

By
MENGXIAO SHI

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ABSTRACT

A NEW APPROACH TO THE SYNTHESIS OF ARCHAEBACTERIAL TETRAETHER LIPIDS

By MENGXIAO SHI

Advisor: Professor William F. Berkowitz

Archaebacterial tetraether lipids have received considerable attention because of their unique structure and potential properties. In particular the cyclic 2,3'; 3, 2'-bisbiphytanyl-di-sn-glycerol tetraether 1 and 2 , containing a 72-membered ring with 16 chiral methyl groups, has not yet been made. A synthetic strategy has been developed to prepare a straight chain tetraether model 77, which will supply a new synthetic route to approach the nature archaebacterial tetraether lipids. The key steps of this synthetic method are (a) BF_3-catalyzed alcoholysis of glycidyl derivatives, (b) Julia type alkylation or copper (I) catalyzed Grignard reagent cross coupling method to connect two triether fragments, (c) McMurry coupling for making the macrocyclic compound.

ACKNOWLEDGMENTS

I would like to thank Professor William F. Berkowitz for the intellectual support which made completion of this work possible. My sincere appreciation to Professor Richard Franck and Professor Robert Engel for their valuable suggestions. I am especially appreciative to Professor David, C. Locke who most graciously performed all of the GC/MS analysis which facilitated interpretation of the experimental results. The assistance offered by my fellow graduate students, stockroom personnel and secretaries are gratefully acknowledge. I would also especially like to thank the Chemistry Department of Queens College for its financial support. Lastly, I gratefully acknowledge the patience and support of my family.

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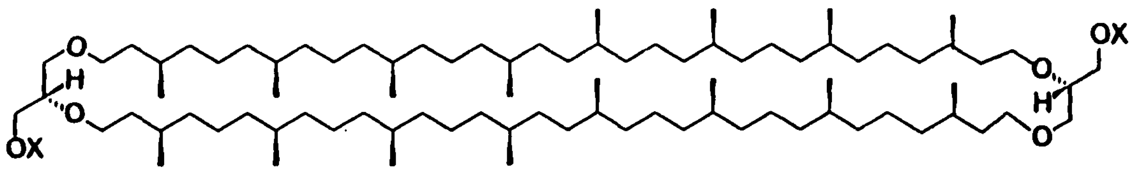
CHAPTER 1

INTRODUCTION

Background

(a). *The unique structural lipids of archaebacteria living in extreme environments*

Archaebacteria (including methanogenic, halophilic, thermo-acidophilic and alkaliophilic archaebacteria) are quite interesting single cell organisms which can survive under extremely harsh environment- al conditions,[1-5] such as (a) high temperature: the thermoacdiophilic archaebacterium, *sulfolobus solfataricus* can grow between 75 and 90 °C;[2] (b) low or high pH values: on the one hand, *Bacillus* species can grow at pH 10, and on the other, *sulfolobus solfataricus* was isolated from an acid hot spring with a pH value of 1-3;[1] (c) saturated salt solution: the halophilic bacteria grow optimally in 20-25% aqueous sodium chloride solution.[1] The ability of these organisms to survive under extreme conditions suggests an important difference in stability compared to organisms with normal bilayer



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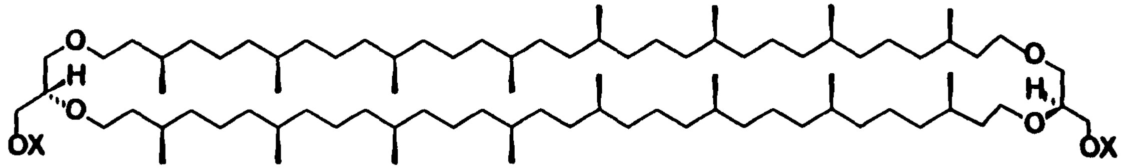


2

(1 / 2 : 45 / 55)

X = sugar or phosphate-containing group

Figure 1 The common structures of the natural archaebacterial tetraether lipids membranes. One contributing cause is due to the bipolar diglycerol tetraether lipids which have been found in the cell walls of the archaebacteria.[6-28] The more common structural types are the cyclic glycerol tetraethers **1** and **2** (Figure 1),[28] consisting of a 72-membered ring with 18 stereo centers, formed from two *sn*-2,3-glycerol units bridged through ether linkages to two isoprenoid C_{40} diols **3** formally derived from head to head linkage of two phytanol residues.[3] Compared to the eubacterial and eukaryotic diacyl glycerol membrane lipids, archaebacteria lipids possess several unusual structural features:[9,14,17] (1) The hydrocarbon chains bond through ether linkages rather than the usual ester linkages to glycerol. This could imply the obvious advantage of hydrolytic stability of the lipids to both high aqueous temperature, acid or base, and esterases. (2) The hydrocarbon chains of the most common lipid form a macrocycle, any special function of which has not yet been made clear. (3) Each hydrocarbon chain is substituted with eight methyl groups in a polyisoprenoid pattern or in several lipids, cyclopentane rings resulting from fusion of a methyl group with the chain **4-7** (Figure 2). Each methyl group is configurationally unique, that is, the chains are scalemic; nature

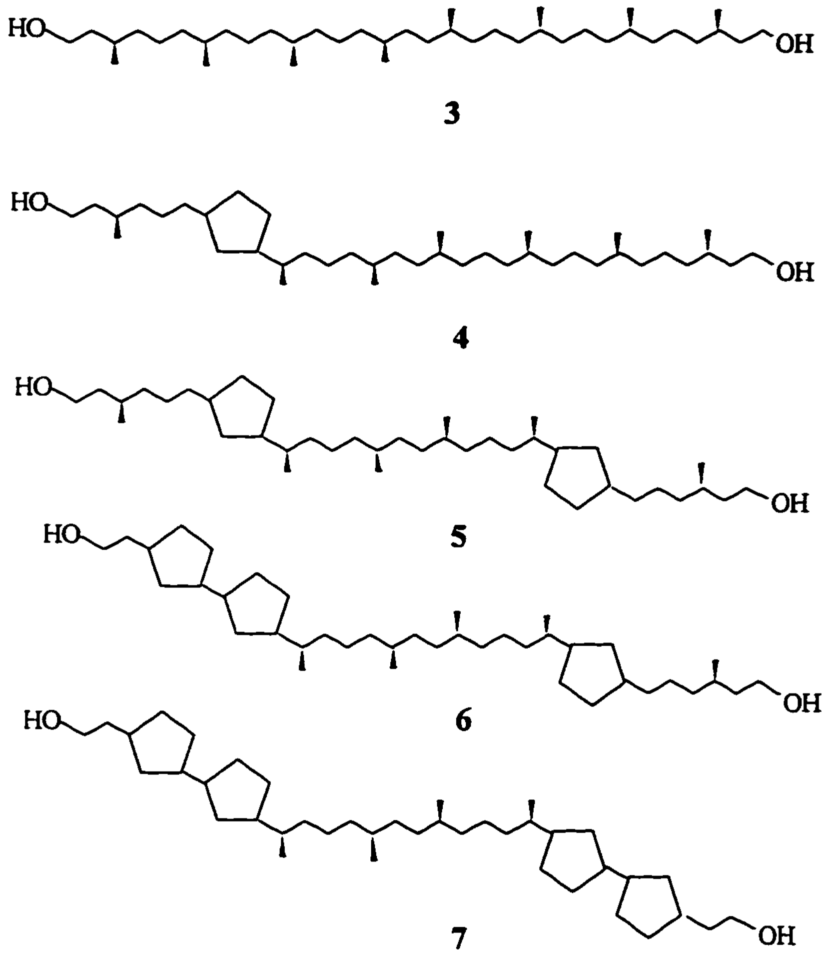


Figure 2 The hydrocarbon chains found in archaebacterial lipids

produces only one enantiomer. These substituents could possibly enhance the rigidity of the chains.[29-33] In addition, the absolute stereochemistry of the glycerol moiety was determined[15] and the stereo structure of the C_{40} chain **3** was identified, as 3R, 7R, 11R, 15S, 18S, 22R, 26R, 30R, 3, 7, 11, 15, 18, 22, 26,30- octamethyldotriacontane-1,32-diol.[34,35] Arigoni[28] also determined the connectivity of two common structures as **1** : C_2 rotation axis perpendicular to the molecular plane, and **2** : C_2 rotation axis in the molecular plane (perpendicular to the long axis). These two structures are commonly found in a ratio of 45 to 55 by degradation of the natural lipids (Figure 3).[28]

(b). Preparation of liposomes from tetraether lipids, and their stabilities

Normal fatty acid diester bilayer liposomes were first described in 1965,[36] and in recent years have been extensively studied for their potential use in medical fields as carriers for the delivery of drugs, antigens, hormones, enzymes and other biologicals (Figure 4).[37-39] The

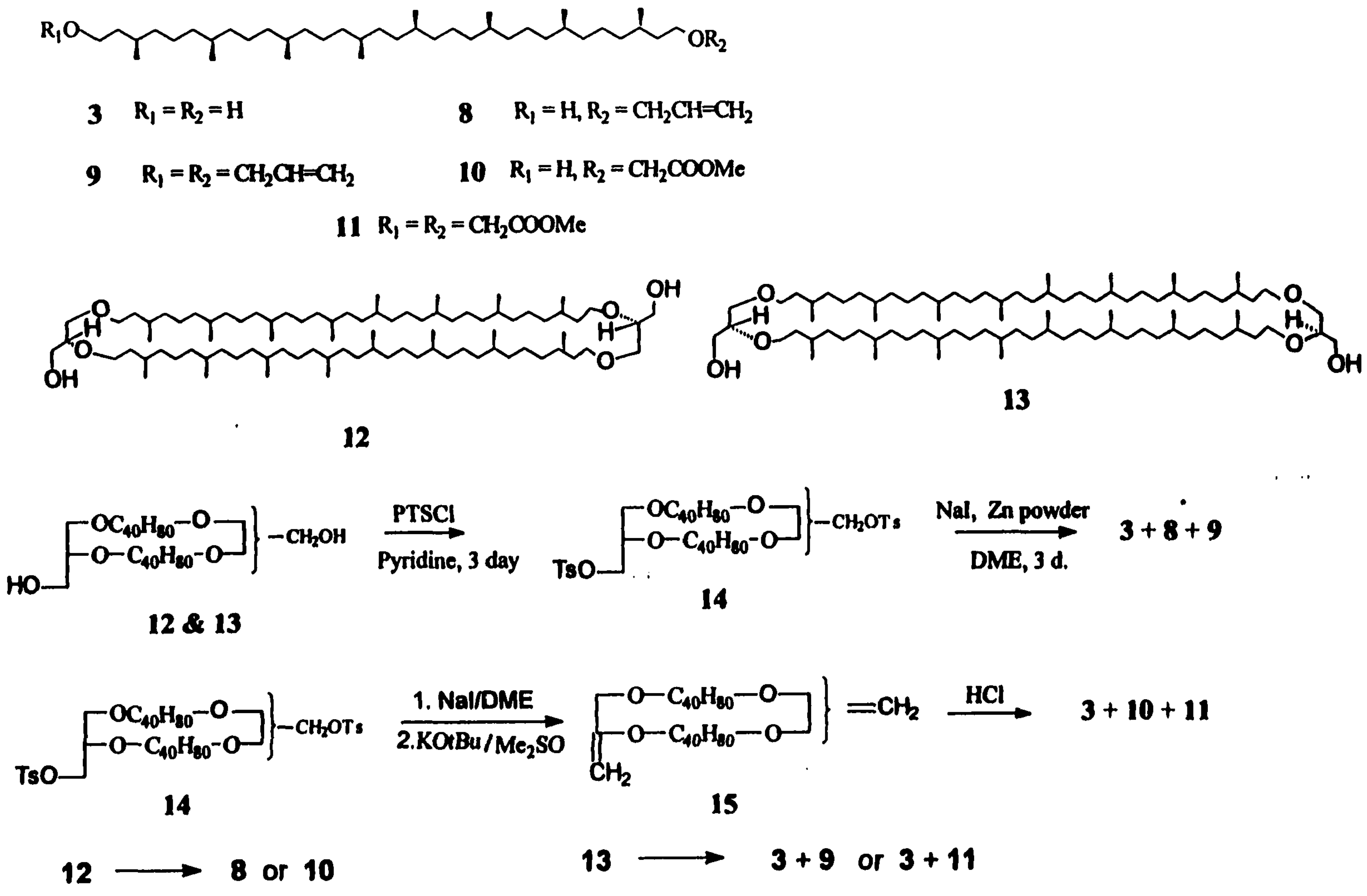
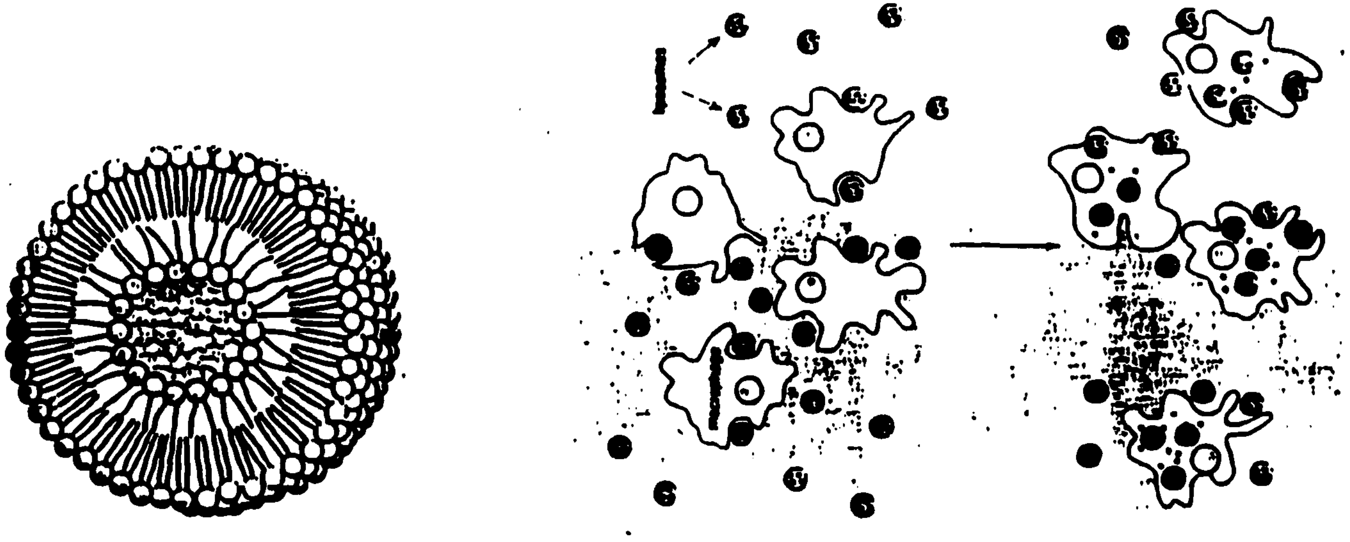


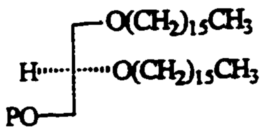
Figure 3 Arigoni's method on determination of regioisomeric macrocyclic tetraether lipids

stability and longevity of such liposomes have also received considerable attention. Due to the special structure of archaebacterial tetraether lipids, it is quite possible that the monolayer liposomes formed from them may have advantages for the delivery of drugs, such as resistance to hydrolysis and different drug effusions rates. Liposomes made from the tetraether lipids have drawn considerable attention. The research results show that closed and stable unilamellar liposomes can be made from the mixture of polar lipids extracted from various archaebacteria, e.g. methanogens,[40] including *Methanococcus volate*, *Methanosarcina mazei*, *Methanosaeta concilii*, and *Methanococcus jannaschii*, and *Sulfolobus acdiocaldarius*.[43] Electron microscopy indicated that a true monolayer liposome has been made from these tetraether lipids.[40-44] In addition beef heart cytochrome c-oxidase, bacteriorhodopsin and the leucine transport carrier of L. lactis have been functionally reconstituted in the monolayer. Some of these liposomes were also shown to be closed, intact vesicles capable of retaining entrapped [^{14}C] sucrose for extended periods of time (after two weeks incubation at 4 °C, at least 92% of the [^{14}C] sucrose was still present in the liposomes). On the other hand a study of liposome formation from model ether-linked lipids showed interesting results. When the lipids L-20, L-32, DCPC, and DSPC (Figure 5) were sonicated at 30 Watts at 10 °C in distilled water or 0.05-0.10 M HCL buffer (pH 7), like many phosphatidylcholines, DCPC and DSPC gave to rise bilayer structure liposomes. However, L-20 provided a monomolecular layered sausage-like liposome, while L-32 always gave only a sheet-like mono-molecular layer membrane, and did not form closed vesicles or a folded membrane with strong curvature.[53] Repeating using somewhat different conditions, sonication at 20-70 °C at 30 Watt for 25 min in the same solvent system, L-32-Phy also furnished stable unilamellar vesicles of 400-1000 Å diameter and about 50-Å thickness.[45] However, unlike the usual monopolar double chain amphiphiles, the bipolar lipid bent into a U-form at a water-air interface to produce the Langmuir membrane.[52] As expected, further study proved that the archaeal liposomes or ether linkage liposomes did show additional stability against external conditions,[46-50] such as high temperature [49-50] and high salt concentrations[45] (Figure 6).

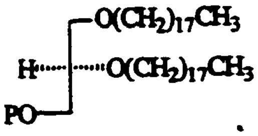


Bilayer liposomes **Serve as the drug's carriers**

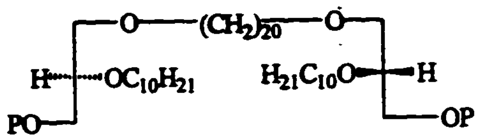
Figure 4 Typical structure of liposomes and their potential use



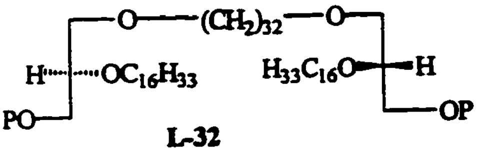
DCPC
19



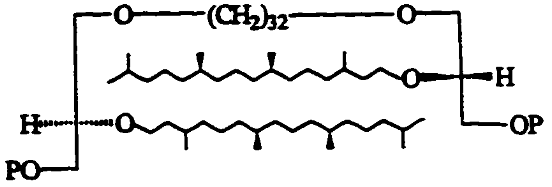
DSPC
20



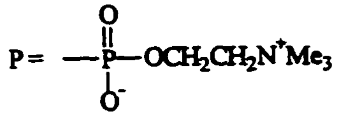
L-20
21



L-32
22



L-32
23



$$P = -\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle O^-}{\underset{|}{P}}}}-OCH_2CH_2N^+Me_3$$

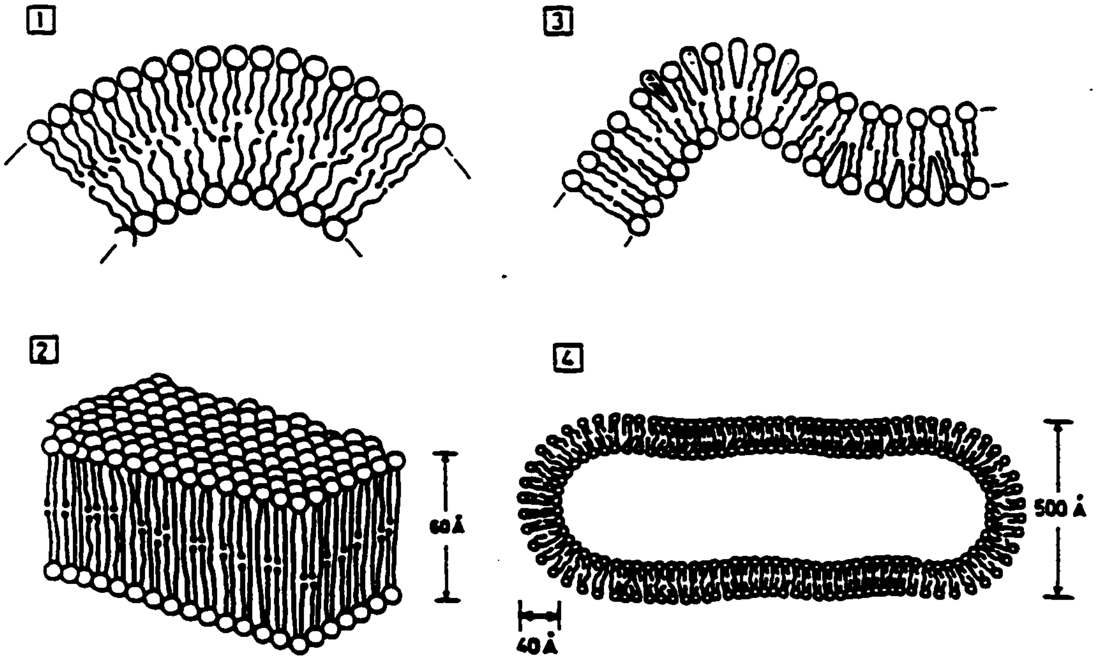
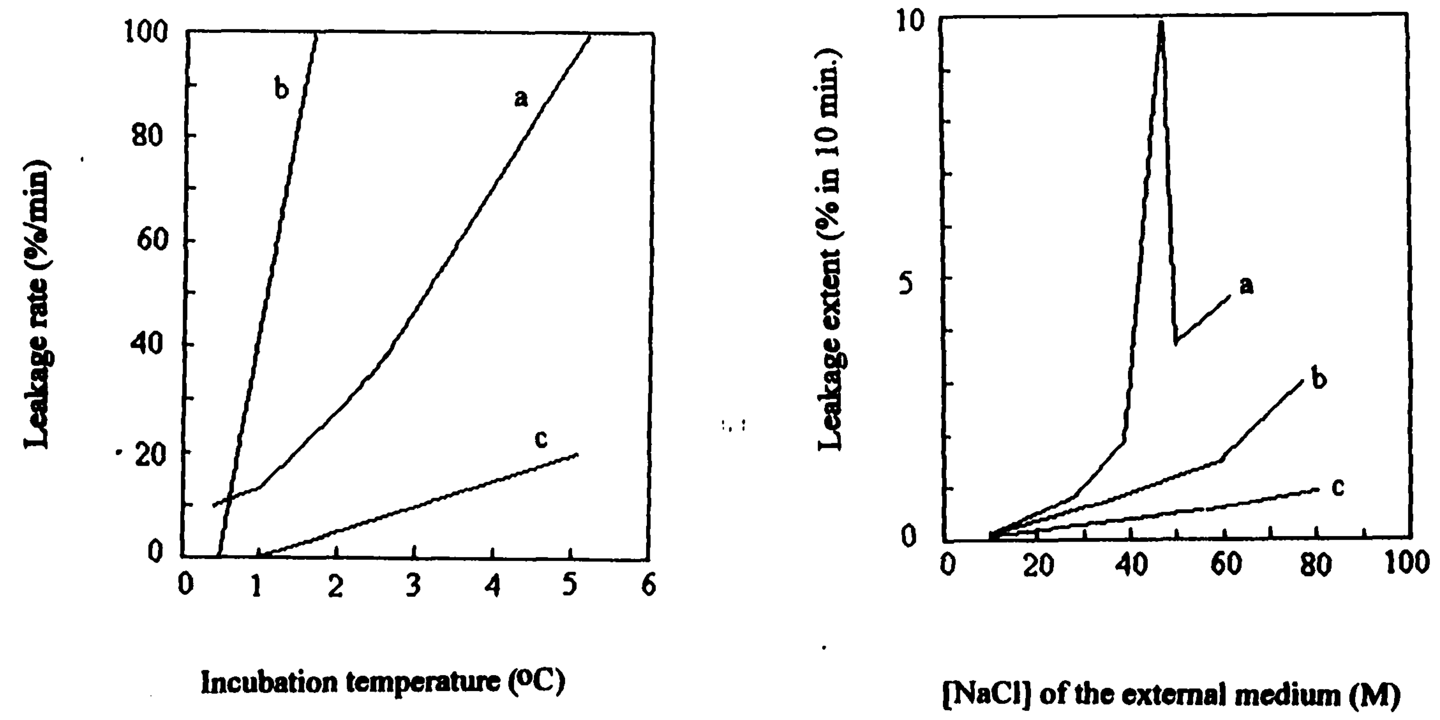


Figure 5 Illustrations of membrane structure (1) DSPC; (2) L-32; (3) a mixture of L-32 and additives (marked shadow) Such as cholesterol and DPPC; (4) L-20

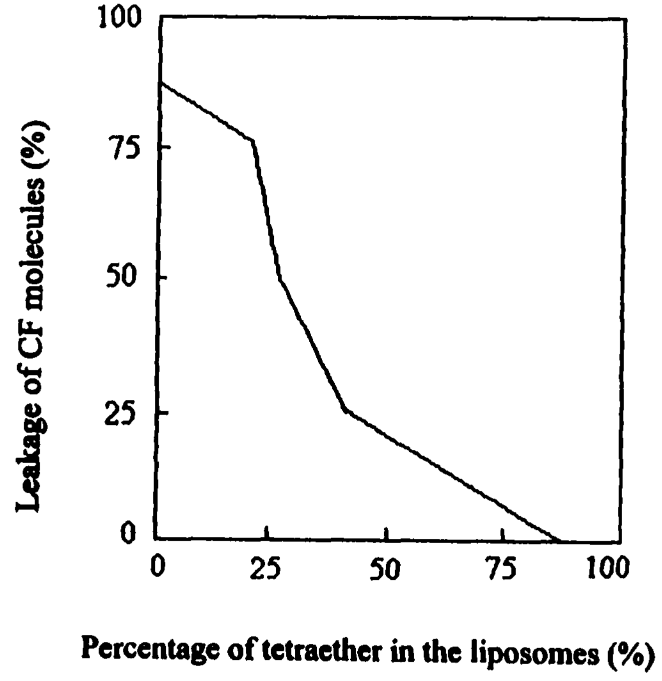


Initial leakage extent (%) of CF molecules per min. from the liposomes of DPPC* (a); egg-yolk lecithin* (b) and (R)-DphyPC* (c) as a function of temperature; Solvent : 0.05 M Tris-HCl (PH 7.8).

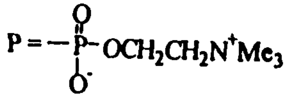
Leakage of CF molecules through a breakdown of liposomes of DPPC* (a); egg-yolk lecithin* (b) and (RS)-DphyPC* (c) in aqueous NaCl at ambient temperature (20-25 oC); solvent: 0.2 M CF (inside), from 0.5 to 5 M NaCl (outside)

Figure 6-1 Stability of the ether linkage lipids

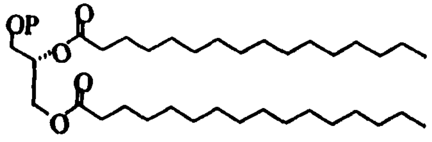
*** See structure on figure 6-2**



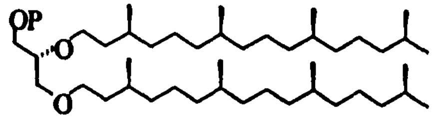
Correlation between tetraether lipids content and stability to autoclaving.



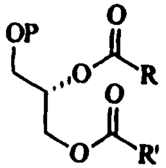
$P = -\overset{O}{\overset{\|}{\underset{O^-}{\underset{|}{P}}}}-OCH_2CH_2N^+Me_3$



DPPC
16



DPhyPC
17



Egg yolk PC : R and R' are saturated and unsaturated fat acid Chain
18

Figure 6-2 Stability of the tetraether lipids

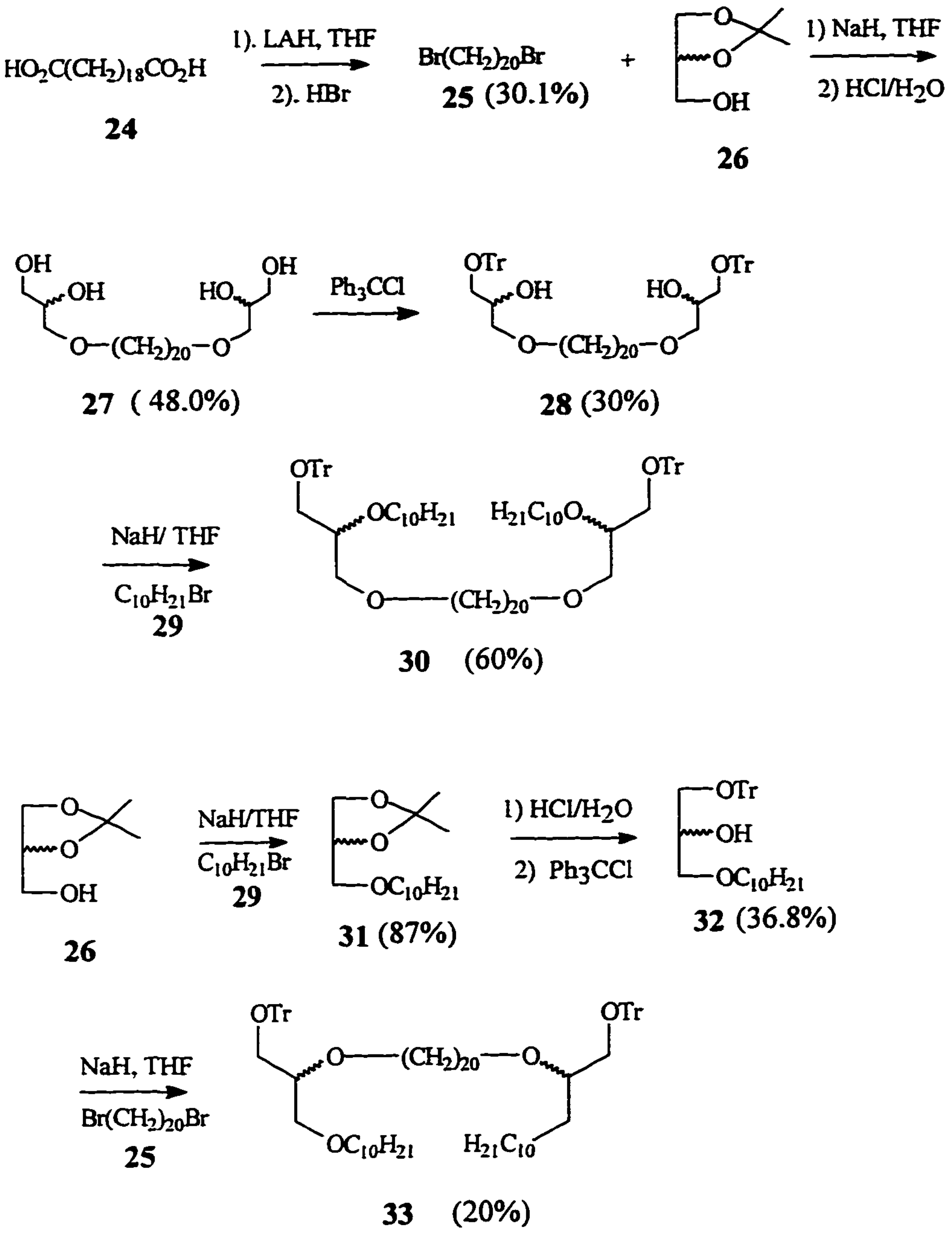
Synthetic Strategy

(a). Synthetic background

Because of the potential use and the limited sources of tetraether lipids, their synthesis has merited attention.[51-63] Furthermore, the synthesis of a 72-membered ring with the correct C-2 symmetry presents a not insignificant synthetic challenge.[51-63] Previous approaches to this kind of tetraether model by other groups are summarized in the following section.

*(1). The tetraether model **30** and **33** of Thompson et al. (Scheme 1)*[51]

Thompson et al.[51(a)] reported a sequence using a classical protection-deprotection route to the tetraether models **30** and **33**. The overall yields from commercially available eicosanedioic acid **24** to 1,1'-O-eicosamethylene-2,2'-O-didecyl-rac-digycerol tetraether **30** and 1,1'-didecyl-O-eicosamethylene-rac-diglycerol **33** were 2.6% and 6.4%. Yamauchi et al.[51(b,c)] made tetraether models by a similar method.



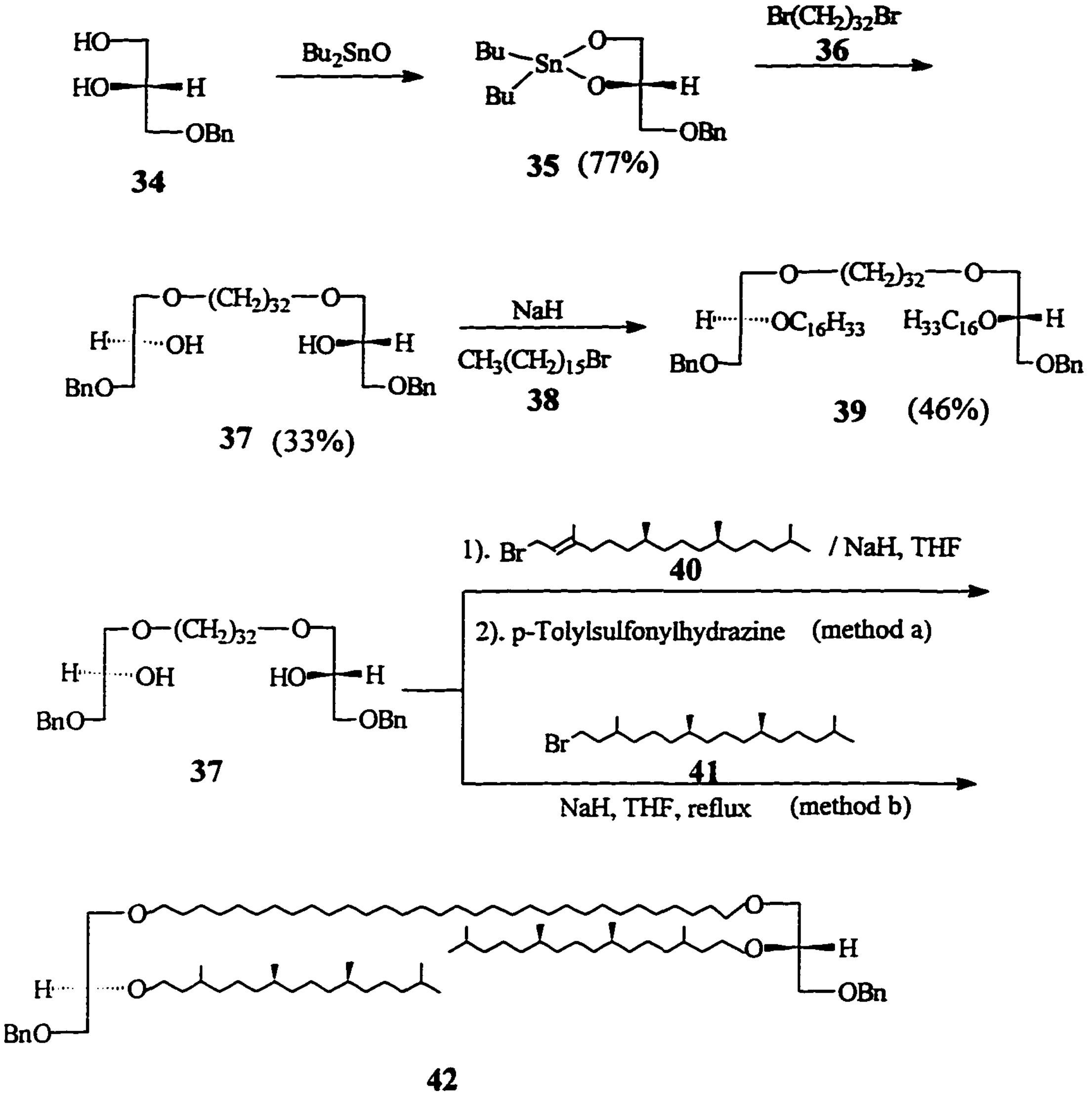
Scheme 1 Thompson's approach

*(2). The tetraether model **39** and **42** of Yamauchi et al. (Scheme 2)*[52-53]

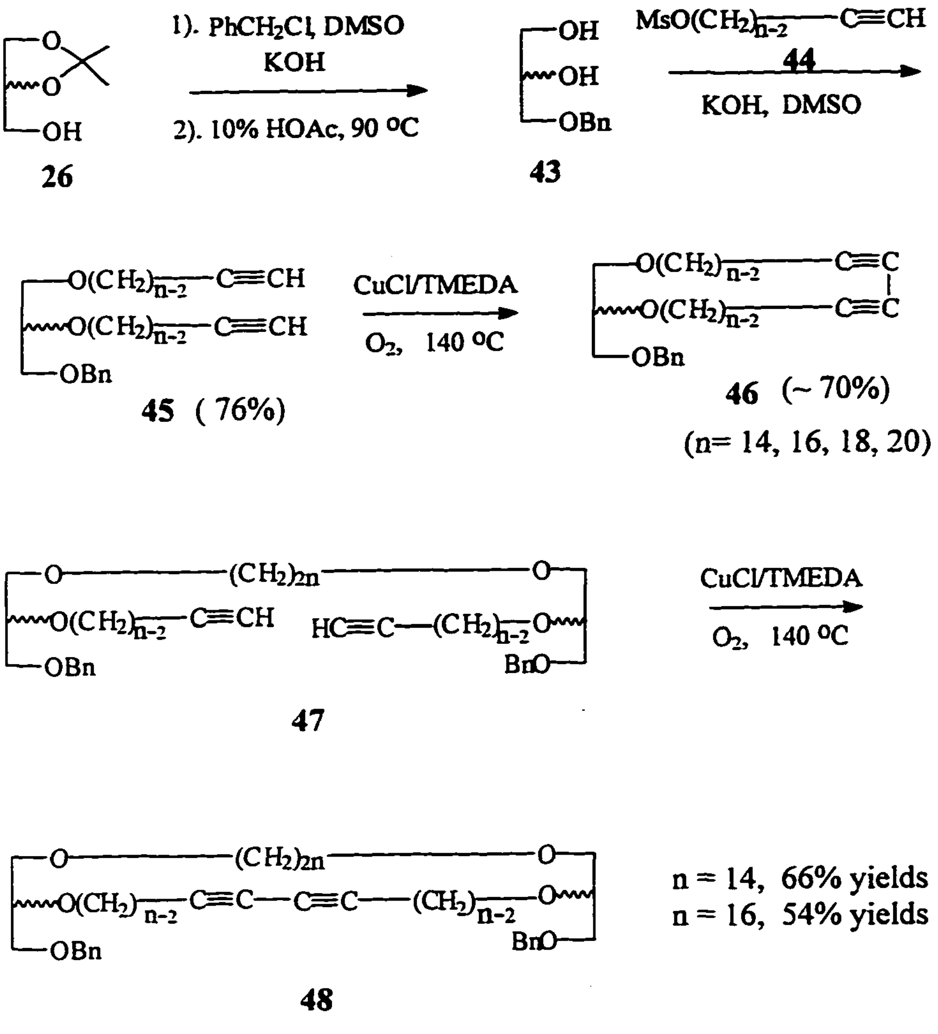
The overall yield from 3-O-benzyl-*sn*-glycerol **34** to 1,32-dotriacontamethylene bis(2-O-hexadecyl-3-benzyl-*sn*-glycerol) **39** was 11.7%. 3-O-Benzyl-*sn*-glycerol **34** was made from D-mannitol in 4 steps in 50 % overall yield and 1,32-dibromodotricosane **36** was synthesized in 9 steps from eicosanedioyl chloride in 46% overall yield. Later the procedure of Yamauchi et al.[53] (**34** to **39**) was repeated by Moss et al.[54] in a higher overall yield (22%). In 1991, Yamauchi et al.[52] reported the synthesis of tetraether **42** in overall yields of 2.5% (method b) and 6.5% (method a).

*(3). The 72-membered macrocyclic tetraether model **48** of Menger et al. (Scheme 3)*[55-56]

In 1992, Menger et al.[56] first reported the synthesis of a macrocyclic, 72 or 36 membered ring, molecule (**48** and **46**) by using Glaser oxidation reaction of two intro-molecule acetylene groups in a reasonable yield. Later, in 1991, Juest et al.[69] also reported a synthesis of macrocyclic compound by using the same method. Unfortunately, this type of coupling, involving four carbon atoms,



Scheme 2 Yamauchi's approach



Scheme 3 Menger's approach

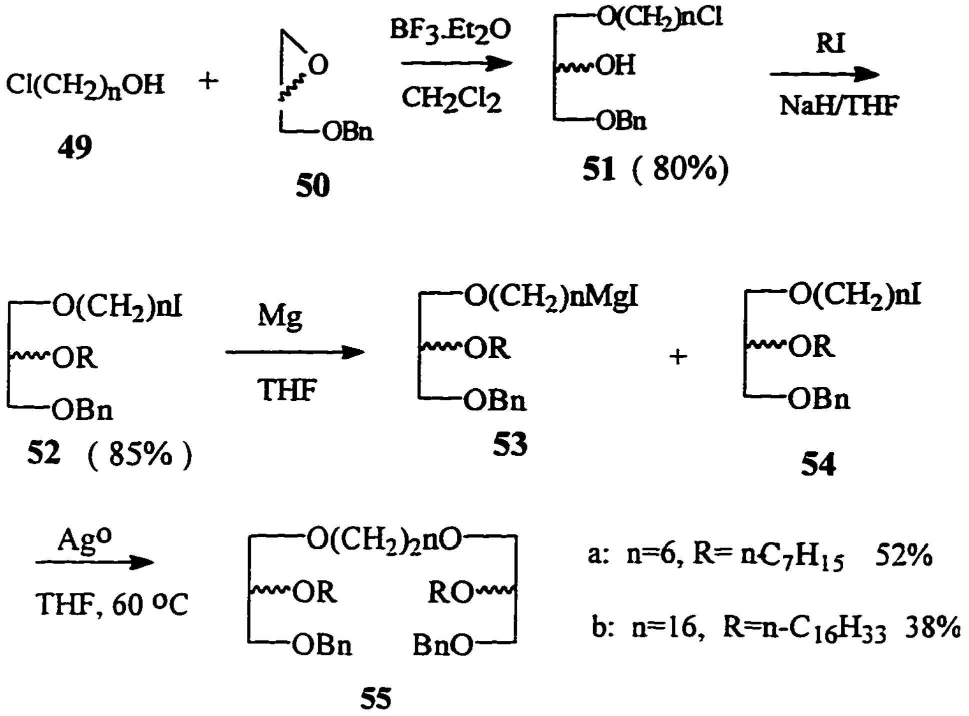
cannot readily be applied to the synthesis of the natural archaebacterial tetraether lipids which contain methyl branches near the point of ring closure.

(4). Tetraether lipid model of W. F Berkowitz et al. (Scheme 4)[60]

Berkowitz et al. employed Bittman's procedure,[63] BF_3 etherate catalyzed ring opening a glycidol derivative by an alcohol, as an efficient and simple way to form the ether bond to the primary position. Connection of a second, different, ether group to the 2-position of glycerol was accomplished by the usual Williamson ether coupling.

(5). The 36-membered macrocyclic diether model ***59*** *of Kakinuma et al. (Scheme 5)*[57-58]

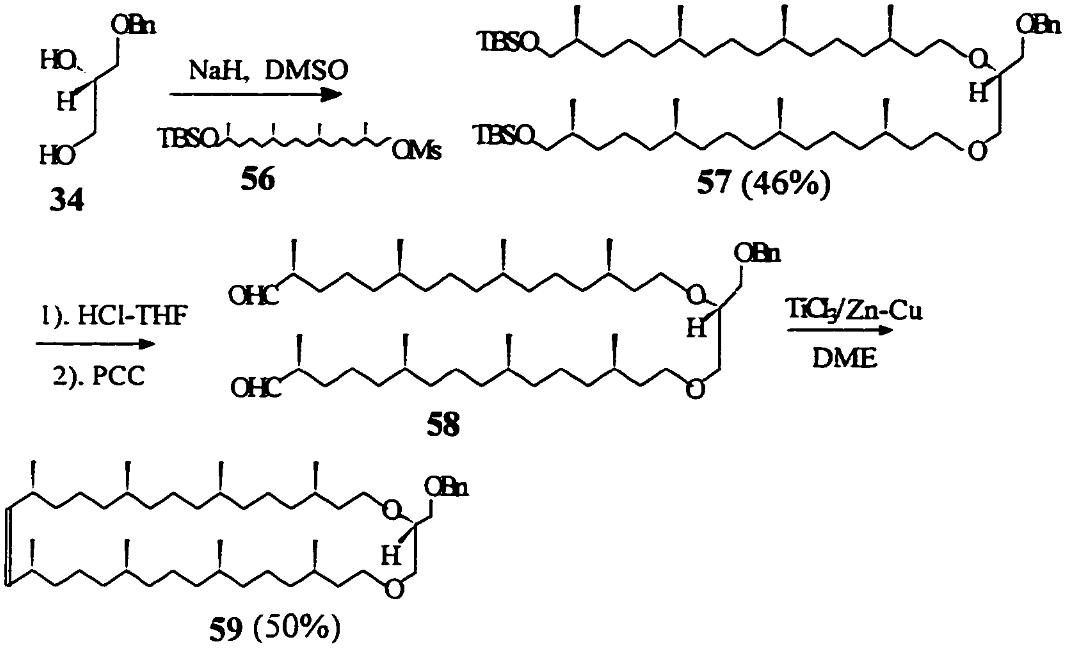
In 1994 Kakinuma et al.[58] reported the following procedure of synthesis of 36-membered macrocyclic diether lipid **59** by using Williamson ether synthesis and McMurry coupling reaction in a overall yield as 2.2%.



Scheme 4 Berkowitz's approach

(6) Triether lipids model of Makriyannis et al. (Scheme 6)[61]

In 1989, Makriyannis et al.[61] reported a sequence for the synthesis of the triether **64** in which the reduction of compound **61** by lithium aluminum hydride-aluminum chloride to give **62** in 79% as a major product is the key step. This was the first approach which allowed the introduction of different chains at C-1 and C-2 of glycerol.

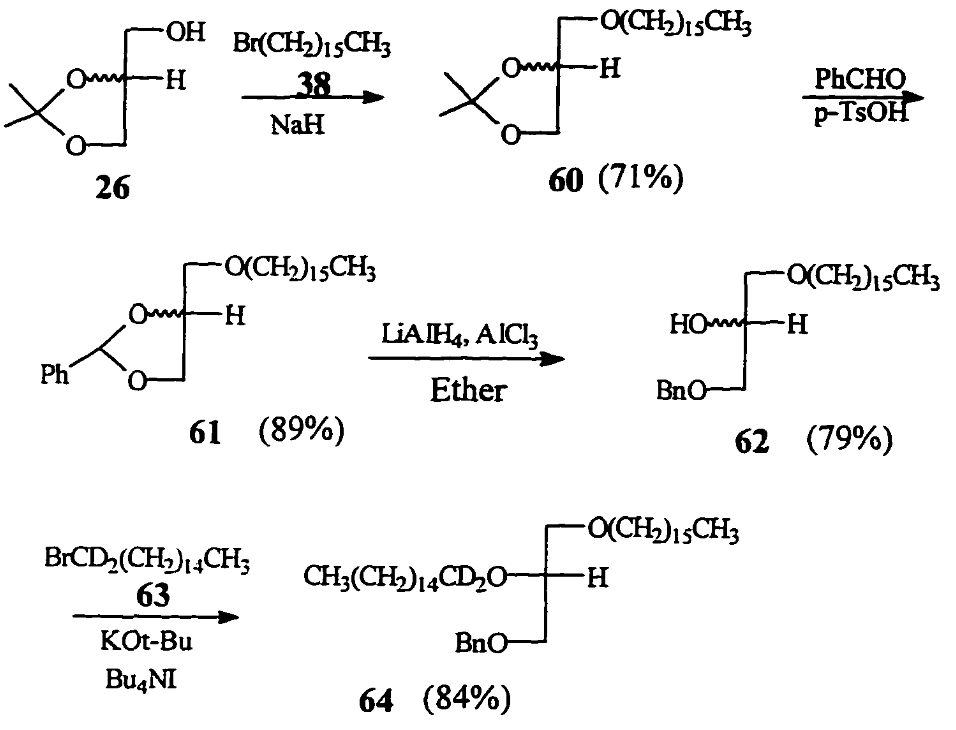


Scheme 5 Kakinuma's approach

Kakinuma (Scheme 7) used a variation of this approach in the synthesis of a 72-membered ring lipid model.

(7) The 72-membered macrocyclic tetraether models 74 and 75 of Kakinuma et al. (Scheme 7)[59]

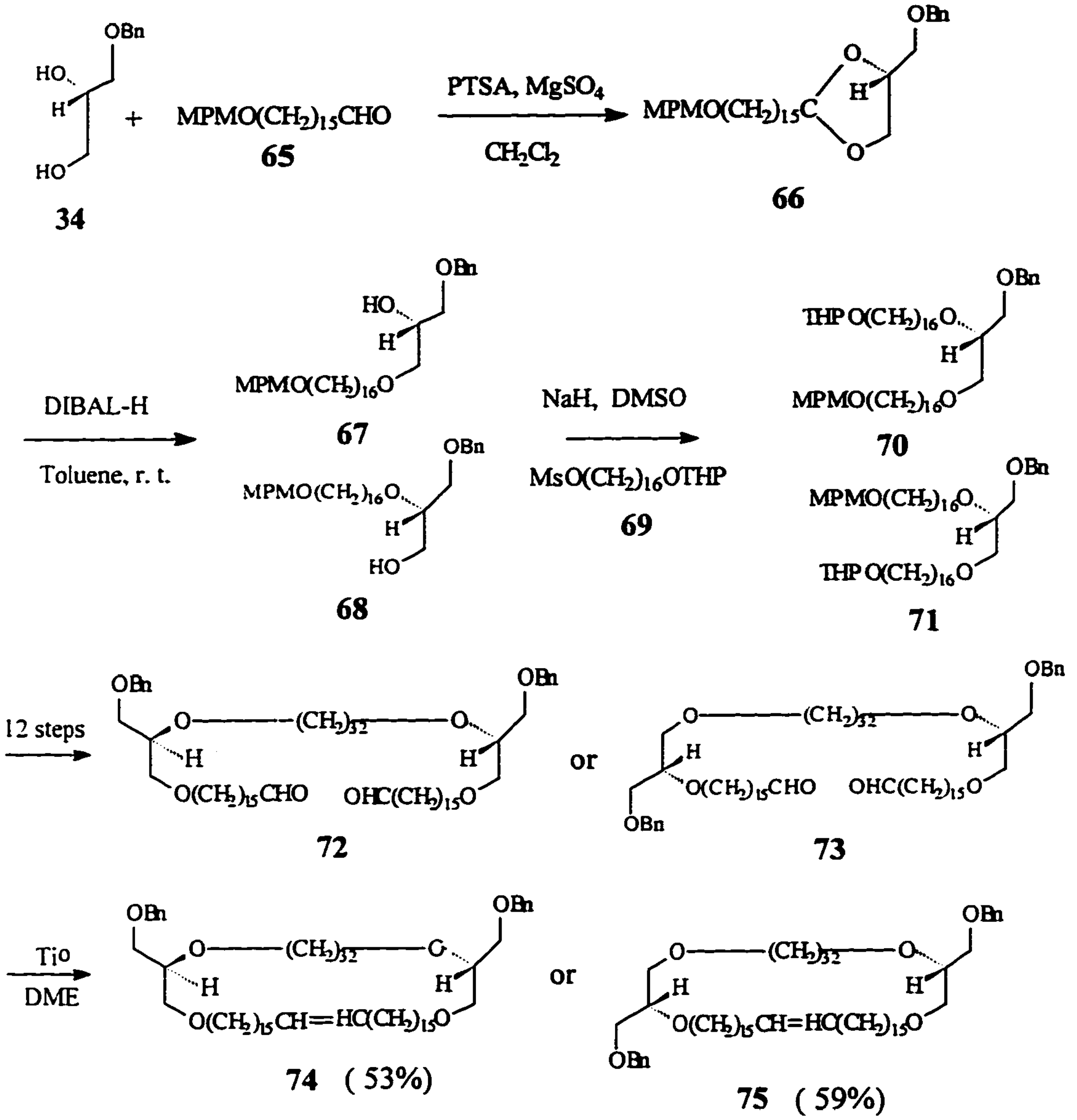
Finally, in early 1996 Kakinuma et al. reported[59] the synthesis of macrocyclic, 72-membered ring tetraether lipid models **74** and **75** (Scheme 7) in 20 steps and in 0.4% overall yield. We will say more about this significant result below.



Scheme 6 Makriyannis's approach

(b). Synthetic strategy for compound 77 (Figure 7)

In conclusion, most of the above approaches lead to the type 2 symmetry archaebacterial lipid. Only the sequences of Makriyannis (Scheme 6), Kakinuma (Scheme 7) and Berkowitz (Scheme 4)



Scheme 7 Kakinuma's approach.

provide the chance to build up the both **1** and **2** type archaebacterial lipids. In this thesis, the model compounds related to the synthesis of a type **1** archaebacterial tetraether lipid, containing a 72-membered ring and a C_2 rotation axis perpendicular to the molecular plane are well studied. As a preliminary to attempting the synthesis of a type **1** archaebacterial lipid, we studied the synthesis of a straight-chain cyclic model 77 first. In 1993, based on the previous work done in our group,[60] we proposed the synthetic route shown in figure 7 Compound **76** could be made by cross coupling two glycerol triether fragments **80** and **81**, which can be made from opening epoxide[63-64] **83** with 16-membered chain alcohols which contain either ω-halo **82** or ω-trityloxy **84** groups, followed by Williamson ether linkage.[51-62] The C_{16}-C_{17} bond could be formed by the coupling of two aldehyde groups using the McMurry reaction,[65-68] followed by hydrogenation of the double bond to give the target molecule 77. Obviously it may be difficult to form such a large ring (72-membered), yet the results of other groups[55-58, 69] lead us to believe that it is possible to get a reasonable yield by running the reaction at a highly diluted condition. The C'_{16}-C'_{17} bond could be made ether by Kochi reaction: [60, 70] silver

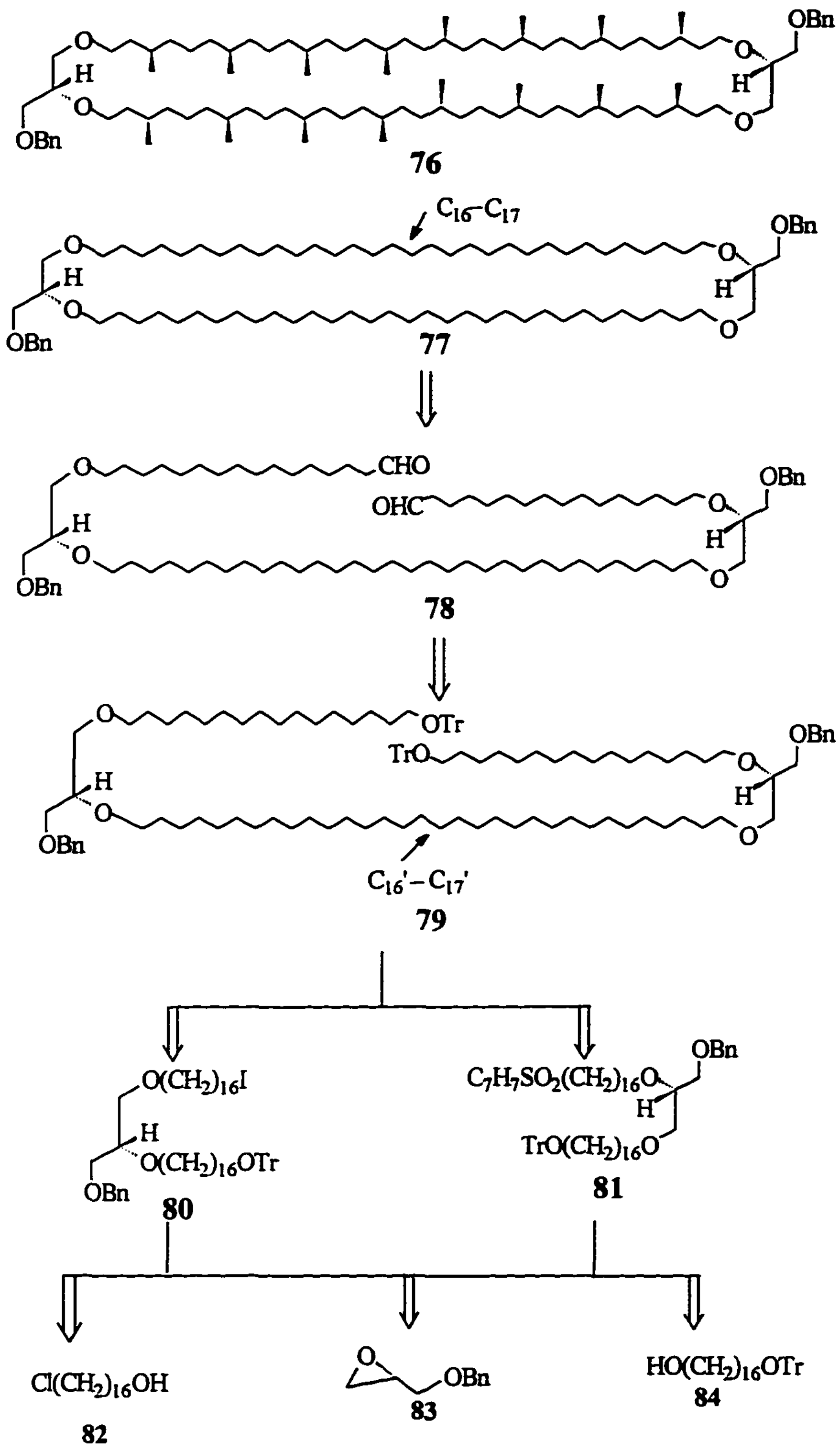


Figure 7 The retro-synthesis

or Cu(I) catalyzed cross coupling of two alkyl halide compounds, or by using a Julia type alkylation reaction.[57,71,83,84] In this synthetic proposal we chose commercially available hexadecanolide **85** and 2-benzyloxy methyl oxirane **83** as our starting materials.

CHAPTER 2

RESULT AND DISCUSSION

(*a*). *Preparation of the 16-membered chain containing two different* functional *groups at the end, which will be used to build up the triether fragments. (Figure 8, 9, and 10).*

Hexadecanolide **85**, which is commercially available, was separately treated with a catalytic amount of boron trifluoride etherate ($BF_3.Et_2O$) in methanol, and with 10% potassium hydroxide in methanol solution under reflux conditions for about 12 hours, and was quantitatively converted, respectively, to two known compounds, methyl 16 hydroxy-hexadecanoate **86**[73] and 16-hydroxyhexadecanoic acid **87**[74] (Figure 8).

The hydroxyl group on hydroxyl ester **86** was protected by a trityloxyl group[75] to give methyl 16-trityloxyhexadecanoate **88**. Reduction[76] of **88** with $LiAlH_4$ gave 16-trityloxyhexadecanol **84** in a 93.9% overall yield. At the same time, the hydroxyl acid **87** was converted to 16-chlorohexadecanol **82** via 16-chlorohexadecanoyl chloride **89** though an alane reduction[78] in ether at room temperature

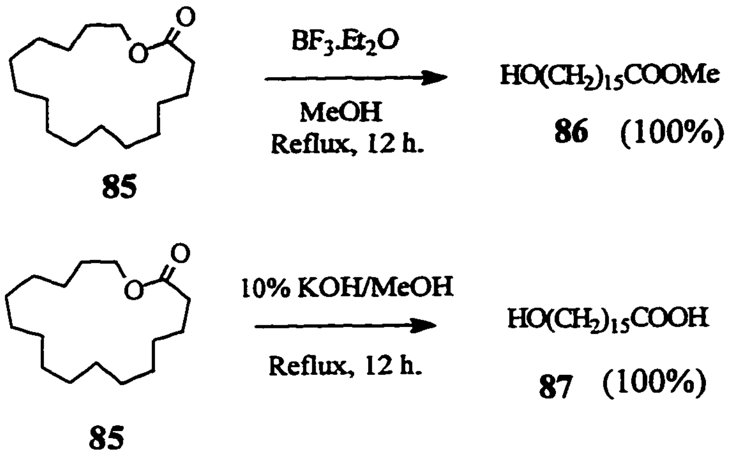


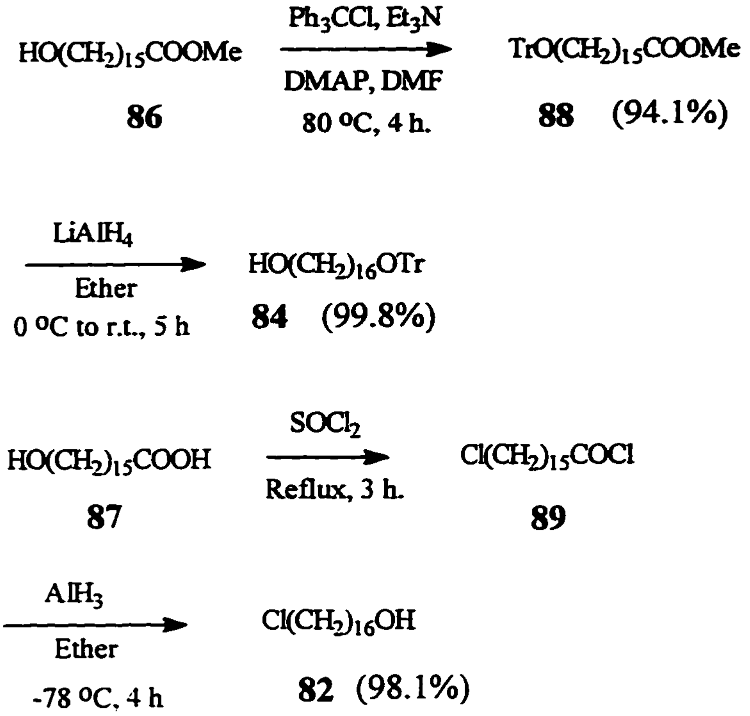
Figure 8 Preparation of the 16-membered chains (part

or -78°C in a high yield (Figure 9).

Then the trityloxy- and chloro- alcohols **84** and **82** were converted to the corresponding tosylates[79] **90** and **93**, mesylates[80] **92** and 94, or iodide[81] **91** in good yields. These were used in the Williamson ether synthesis steps (Figure 10).

(b). Preparation of triether fragments.

The triether skeleton was made by using Bittman's procedure,[60,63] $BF_3.Et_2O$ catalyzed ring opening of a glycidol derivative by an alcohol (Figure 11). Compound **95** was obtained in good yield (90.3%) and high regioselectivity by using the chloro alcohol **82** to



$$\underset{\textbf{86}}{HO(CH_2)_{15}COOMe} \xrightarrow[\text{DMAP, DMF; 80 °C, 4 h.}]{Ph_3CCl,\ Et_3N} \underset{\textbf{88}\ (94.1\%)}{TrO(CH_2)_{15}COOMe} \xrightarrow[\text{Ether; 0 °C to r.t., 5 h}]{LiAlH_4} \underset{\textbf{84}\ (99.8\%)}{HO(CH_2)_{16}OTr}$$

$$\underset{\textbf{87}}{HO(CH_2)_{15}COOH} \xrightarrow[\text{Reflux, 3 h.}]{SOCl_2} \underset{\textbf{89}}{Cl(CH_2)_{15}COCl} \xrightarrow[\text{Ether; -78 °C, 4 h}]{AlH_3} \underset{\textbf{82}\ (98.1\%)}{Cl(CH_2)_{16}OH}$$

Figure 9 Preparation of the 16-membered chains (Part II)

open commercially available epoxide **83**, with catalysis by $BF_3.Et_2O$ in methylene chloride solution. Since the trityloxyl group is not stable in acid conditions, trityloxyl alcohol **84** is not suitable for this type reaction. Furthermore, a poor yield was obtained when we tried to make compound **96** by using **84** and **83** under the basic conditions. Consequently, instead of **84** we used methyl 16-hydroxyhexadecanoate **86** to open epoxide **83**, with $BF_3.Et_2O$, and successfully obtained **97** in a good yield (82.1%) and high regioselectivity. After reduction and tritylation, compound **97** then was converted to target compound **96** in 65.1% overall yield.

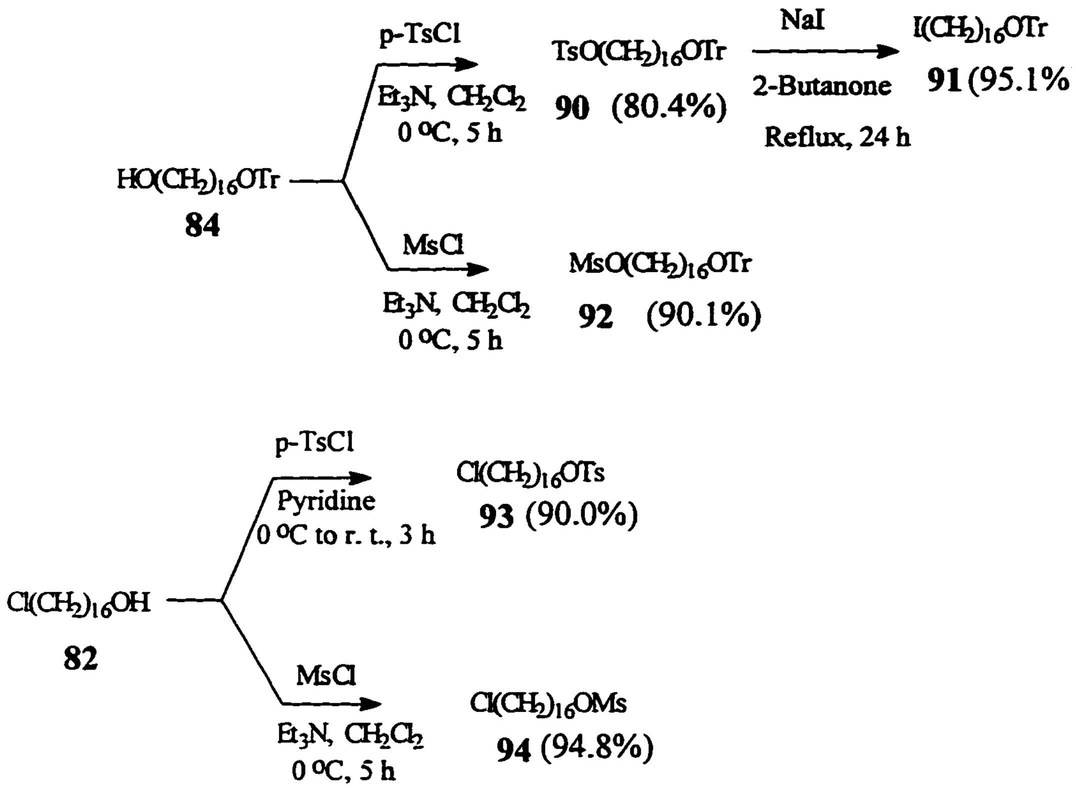


Figure 10 Preparation of the 16-membered chains (part III)

Now we are ready to build up the triether fragments. We combined racemic (±) **96** with **93** and (±) **95** with **90** to form the corresponding triethers **99** and **100** in yields of 63.4% and 65.3% by

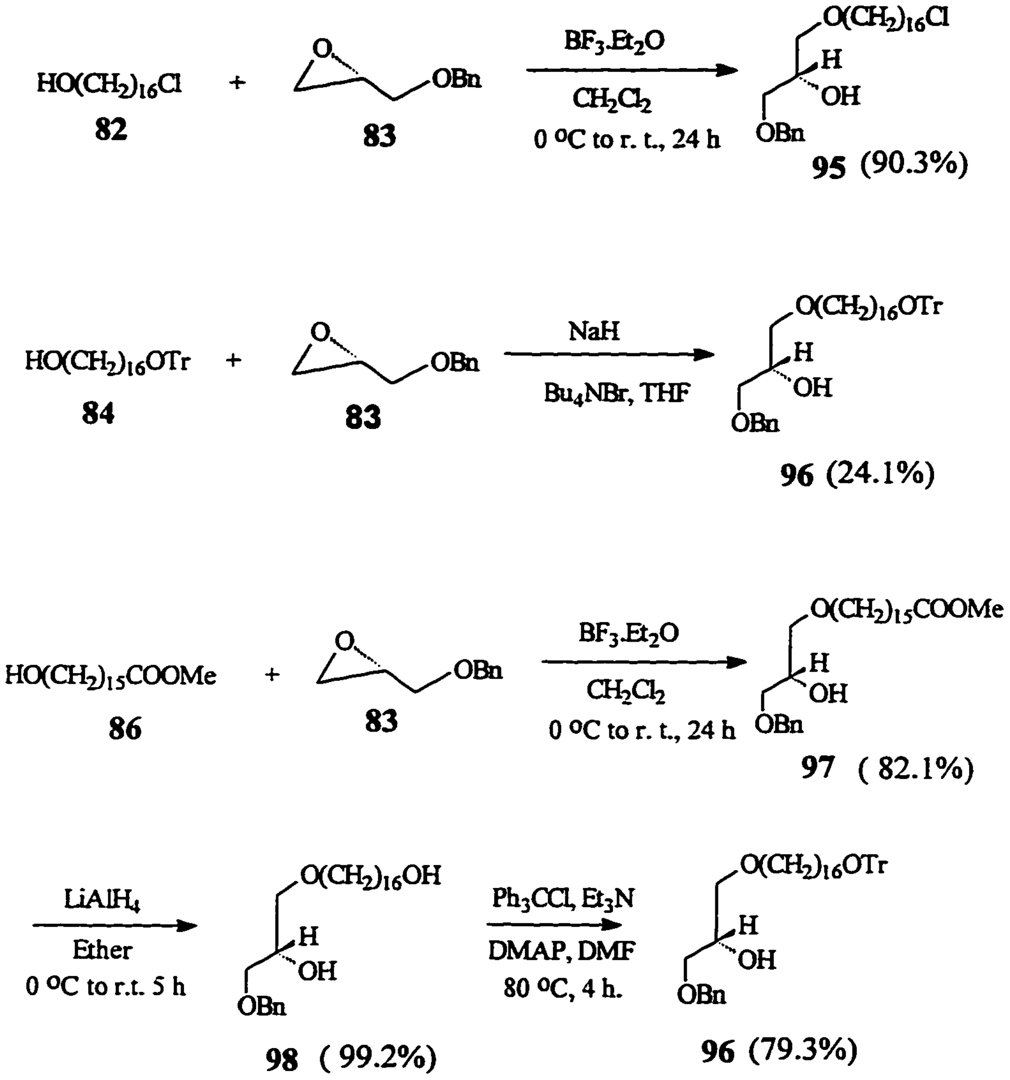


Figure 11 Preparation of the triether fragments (Opening of the epoxide)

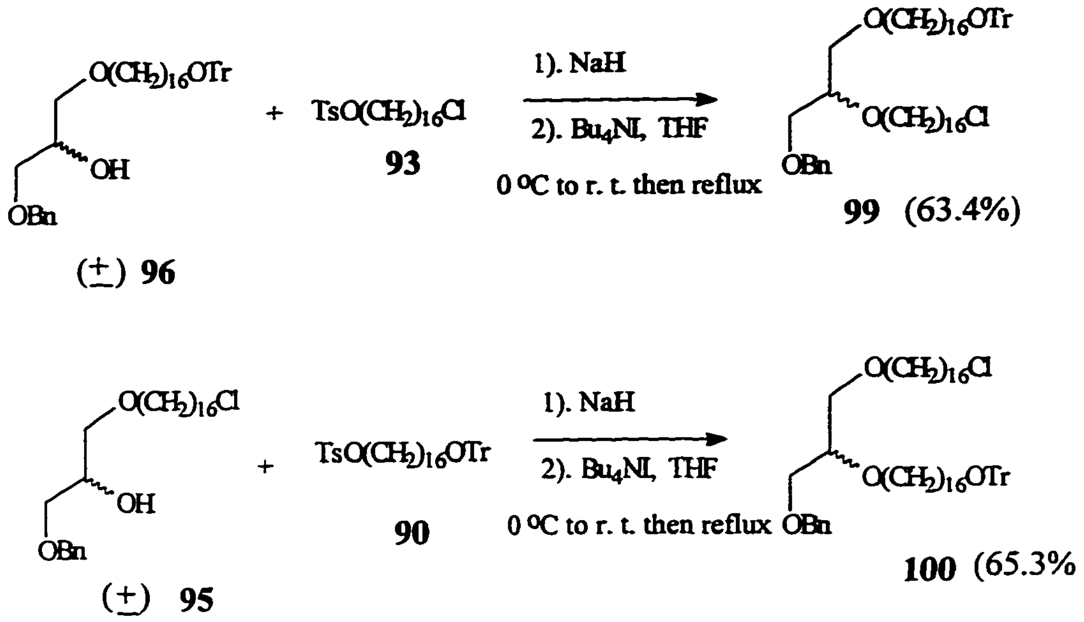


Figure 12 Preparation of the triether fragments (ether linkage reaction)

using a modification of the Williamson ether synthesis [61,62] (Figure 12). In order to improve the yield of the ether synthesis reaction, we modified the reaction conditions[55,57,61,62, 82] (details shown Tables 1 and 2) by changing reaction time, reaction temperature, reaction solvent system, bases, and leaving groups.

Table 1. **Reaction condition study on formation of the triether 99**

alcohol	Alkyl tosylate	base	solvent	tempera-ture	reaction time	Yields
96 1.0eq.	**93** 1.1 eq.	NaH 1.1 eq.	THF	0°C to r.t.	24 h.	no reaction
96 1.0eq.	**93** 1.5 eq.	NaH 1.5 eq.	DMSO	r.t.	48 h.	6.7%
96 1.0 eq.	**93** 3.0 eq.	NaH 3.0 eq.	THF/ Bu$_4$NBr	0 °C to r.t. to reflux	2 h. 16 h.	50.2%
96 1.0 eq.	**93** 3.0 eq.	NaH 3.0 eq.	THF/ Bu$_4$NBr	0 °C to r.t. reflux	24 h. 5 h.	59.3%
96 1.0 eq.	**93** 3.0 eq.	NaH 3.0 eq.	THF/ Bu$_4$NI	0 °C to r.t. reflux	20 h. 3 h.	63.5%
96 1.0 eq.	**93** 1.3 eq.	NaH 1.3 eq.	THF/ Bu$_4$NI	0 °C to r.t. reflux	17.5 h. 5 h.	52.5%
96 1.0 eq.	**94** 1.3 eq	KOH 10 eq.	Xylene	reflux	16 h.	14.4%
96 1.0 eq.	**94** 1.1 eq	NaH 3.0 eq.	DMSO	r.t.	3 h.	22.1%
96 1.0 eq.	**94** 1.1 eq	KOH 3.0 eq.	DMSO	r.t.	16 h.	38.5%

Table 2. **Reaction condition study on formation of the triether 100**

alcohol	Alkyl tosylate	base	solvent	temperature	reaction time	Yields
95 1.0 eq.	**90** 1.1 eq.	NaH 1.1 eq.	THF	r.t.	48 h.	no reaction
95 1.0 eq.	**90** 1.1 eq.	NaH 1.2 eq.	DMSO	r.t.	48 h.	5.2%
95 1.0 eq.	**90** 2.0 eq.	NaH 2.0 eq.	THF/ Bu_4NBr	0 °C to r.t.	24 h.	7.2%
95 1.0 eq.	**90** 2.0 eq.	NaH 2.6 eq.	THF/ Bu_4NBr	0 °C to r.t. reflux	2 h. 16 h.	47.6%
95 1.0 eq.	**90** 3.0 eq.	NaH 3.0 eq.	THF/ Bu_4NBr	0 °C to r.t. reflux	24 h. 5 h.	59.5%
95 1.0 eq.	**90** 3.0 eq.	NaH 3.0 eq.	THF/ Bu_4NI	0 °C to r.t. reflux	20 h. 3 h.	65.1%
95 1.0 eq.	**90** 1.3 eq.	NaH 1.3 eq.	THF/ Bu_4NI	0 °C to r.t. reflux	17.5 h. 5 h.	54.3%
95 1.0 eq.	**91** 1.1 eq.	NaH 2.0 eq.	THF/ Bu_4NBr	0 °C to r.t. reflux	16 h.	30.2%
95 1.0 eq.	**92** 1.1 eq.	NaH 2.3 eq.	THF/ Bu4NBr	0 °C to r.t. reflux	16 h. 4 h.	36.4%
95 1.0 eq.	**92** 1.1 eq.	KOH 5.0 eq.	DMSO	r.t.	16 h.	30.5%

(*c*). *Preparation of the tetraether by cross-coupling of two triether fragments.*

Since the products of homo-coupling **102** and hetero-coupling **104** of the two triether fragments **101** and **103** (Figure 13) may have closely related physical and chemical properties, and can be separated only with difficulty, we chose a procedure which would avoid the possibility of homo-coupling.

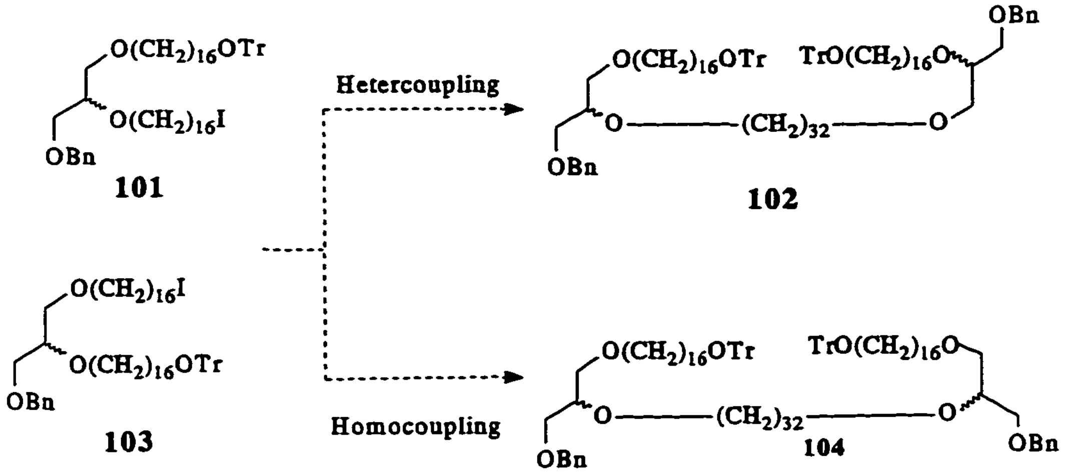


Figure 13 The two possible results of coupling reaction between the two triethers

Based on this idea, we chose to investigate Julia[83,84] coupling of an aldehyde or an alkyl halide with a sulfone anion. Compounds **99** and **100** were first successfully converted to the corresponding alkyl iodides **101** and **102** , then the sulfone compound **105** was made from compound **101** in a good yield in a one step substitution reaction[85,86] (Figure 14). In order to find good reaction conditions for this

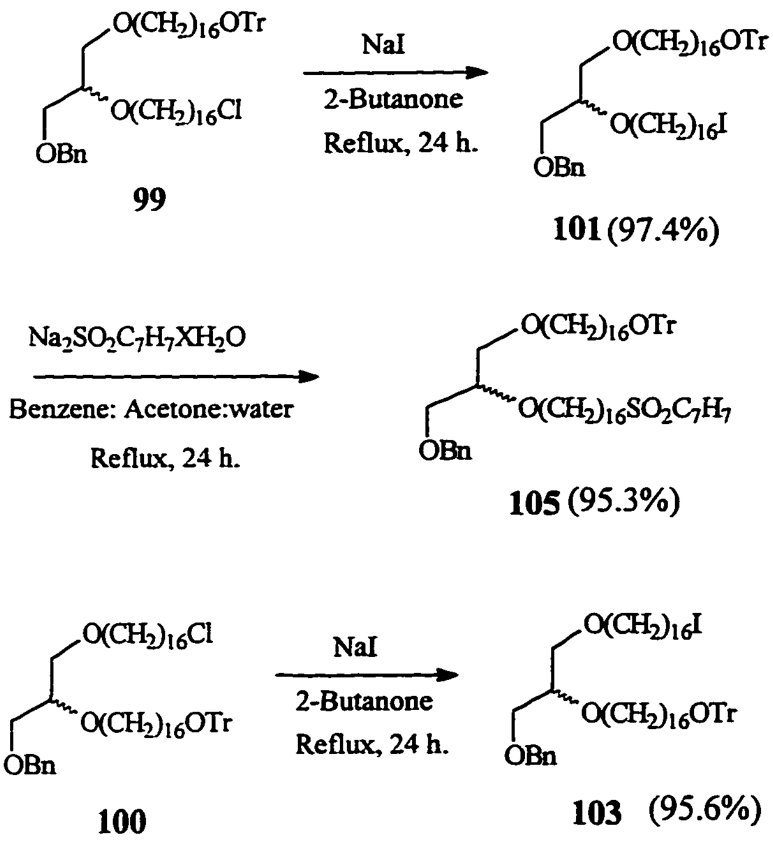


Figure 14 Preparation of the teraethers (part I)

coupling, several model reactions were tested.[83,84,87,57,71] We prepared iodide **108** as shown, then oxidized[97,98] it to aldehyde **109** (Figure 15). These two were reacted with the anion of sulfone **110**, affording coupling products **111** (73%) and **112** (44%) respectively. Application of the alkylation sequence gave **113** (57.6%) from alkyl iodide **103** and sulfone **105** using n-BuLi, LDA, or *t*-BuLi as the base to make the anion (Figure 15). At the same time 56.4% and 33.3% of starting materials **103** and **105** were recovered. Different reaction systems were tested for the alkylation reaction , and we found that the glycerol chain system was really sensitive to the strong base (n-BuLi etc.), higher temperatures (even at 0 °C), or HMPA, which, although they are typical ways to improve the yield of alkylation reactions, here caused our reactants to decompose.

(*d*). *Preparation of the macrocyclic tetraether.*

Having the compound **113** on hand, we attempted to close the 72-membered ring by McMurry coupling between two aldehyde groups. In 1972 Doyle et al.[88] reported a procedure for converting a trityloxyl group directly to an aldehyde in one step, so we tried this

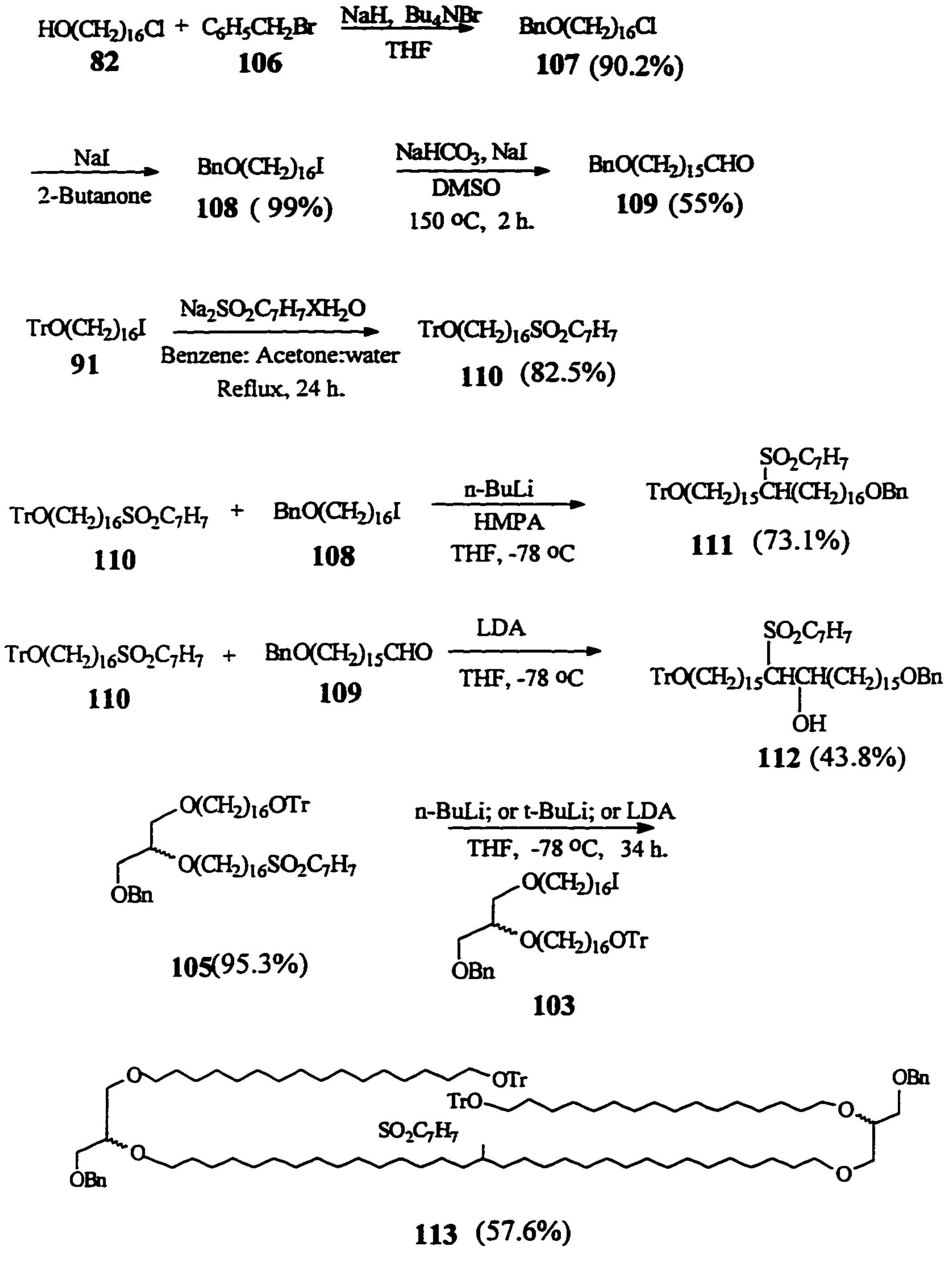


Figure 15 Perparation of the tetraether (part II)

method first. The model reaction, oxidation of trityloxy-hexadecane **115** using triphenyl carbenium tetrafluoroborate as the catalyst in methylene chloride, gave hexadecanal **116** in 52.1% yield. Although the yield was not exciting, because only one step is involved it was worth trying. Upon oxidation, compound **113**, using the same conditions, always gave a mixture of monoaldehyde-alcohols **117** (Figure 16). Consequently we changed the plan to remove[89] the trityl group first then follow with a Swern oxidation,[90] which method gave us a good yield (overall 76.7%) of compound **121** (Figure 17). Before we continued to the McMurry coupling reaction,[65-68] we tried model reactions first. The successful result of the formation of compound **122** (80% yield) encouraged us and we continued with the McMurry coupling of compound **121.** Our initial experiment resulted in a low conversion (25%) to a substance which proved to be a mixture. Given these preliminary and negative results, and the publication of Kakinuma's very similar work, we discontinued this line of research (Figure 18).

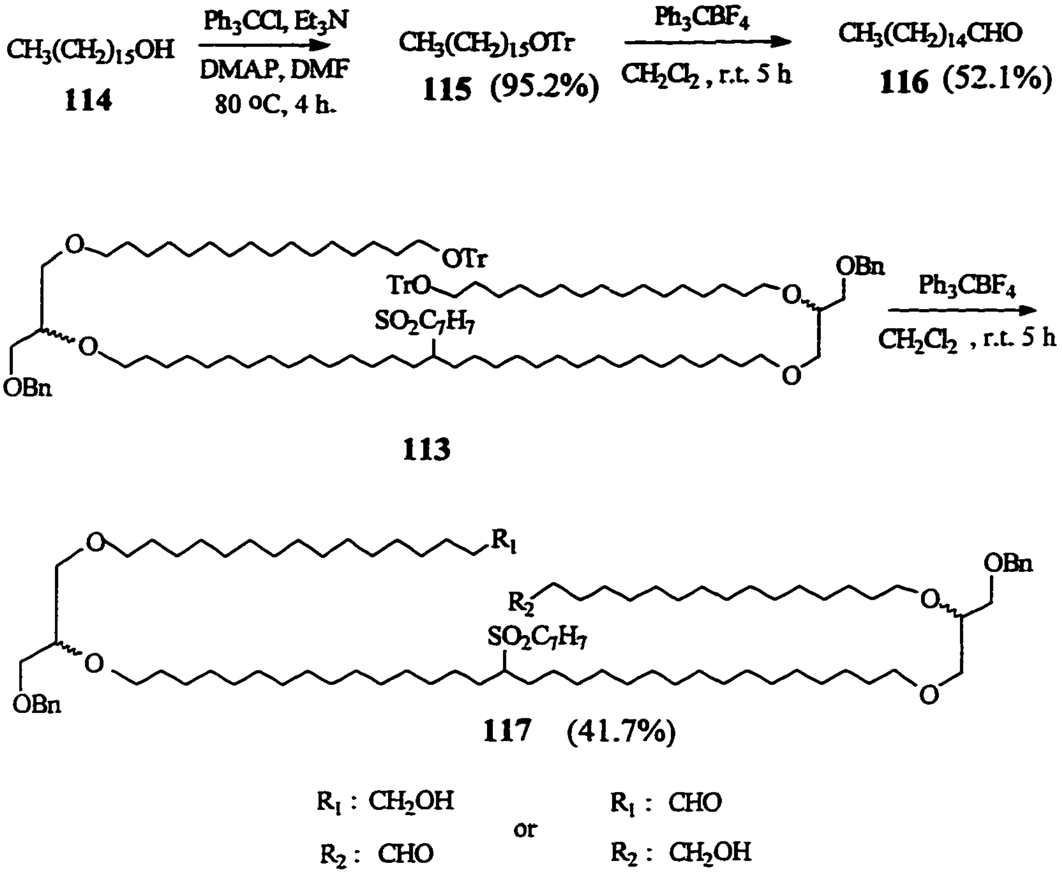


Figure 16 Oxidation of the trityl group to aldehyde

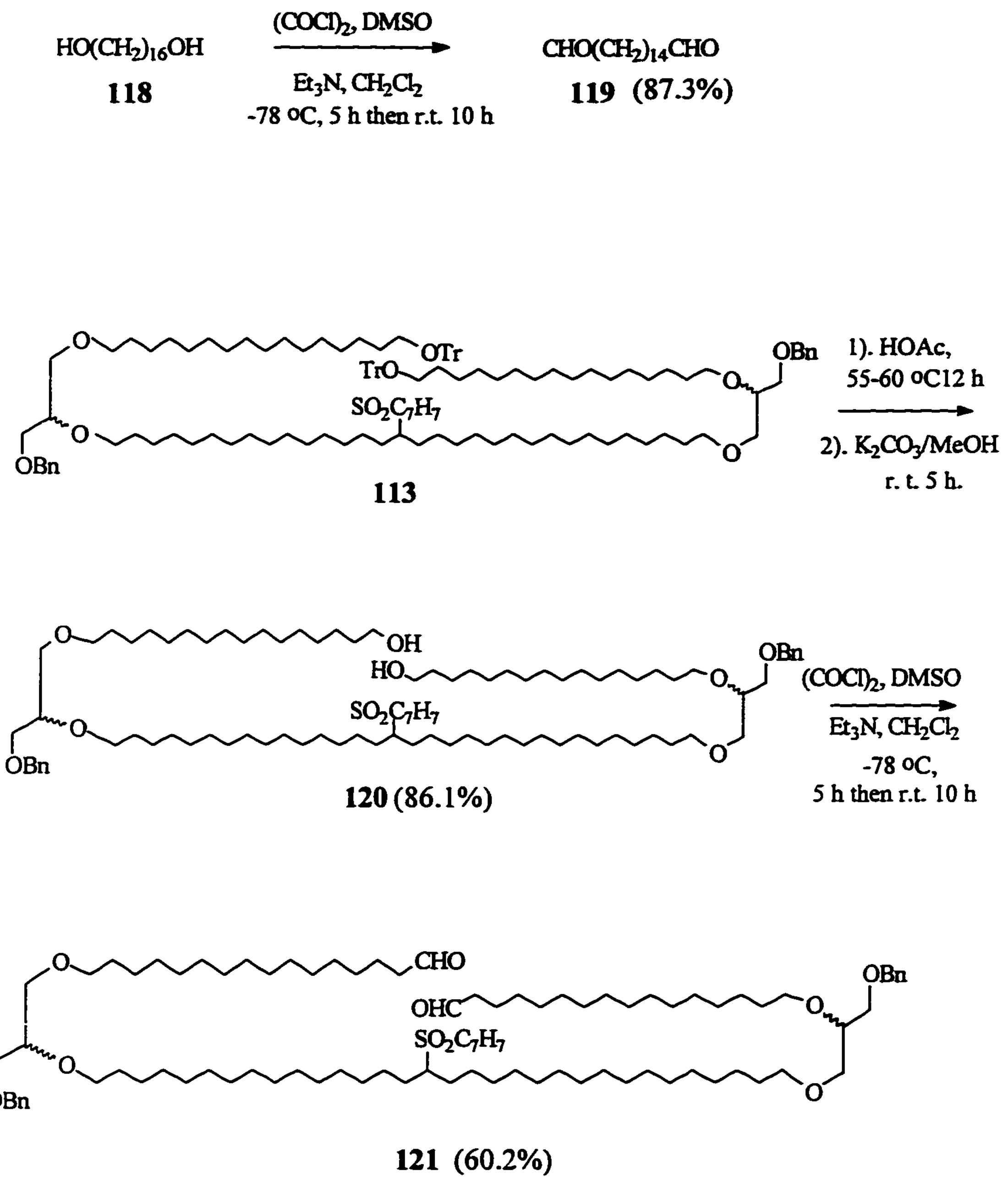
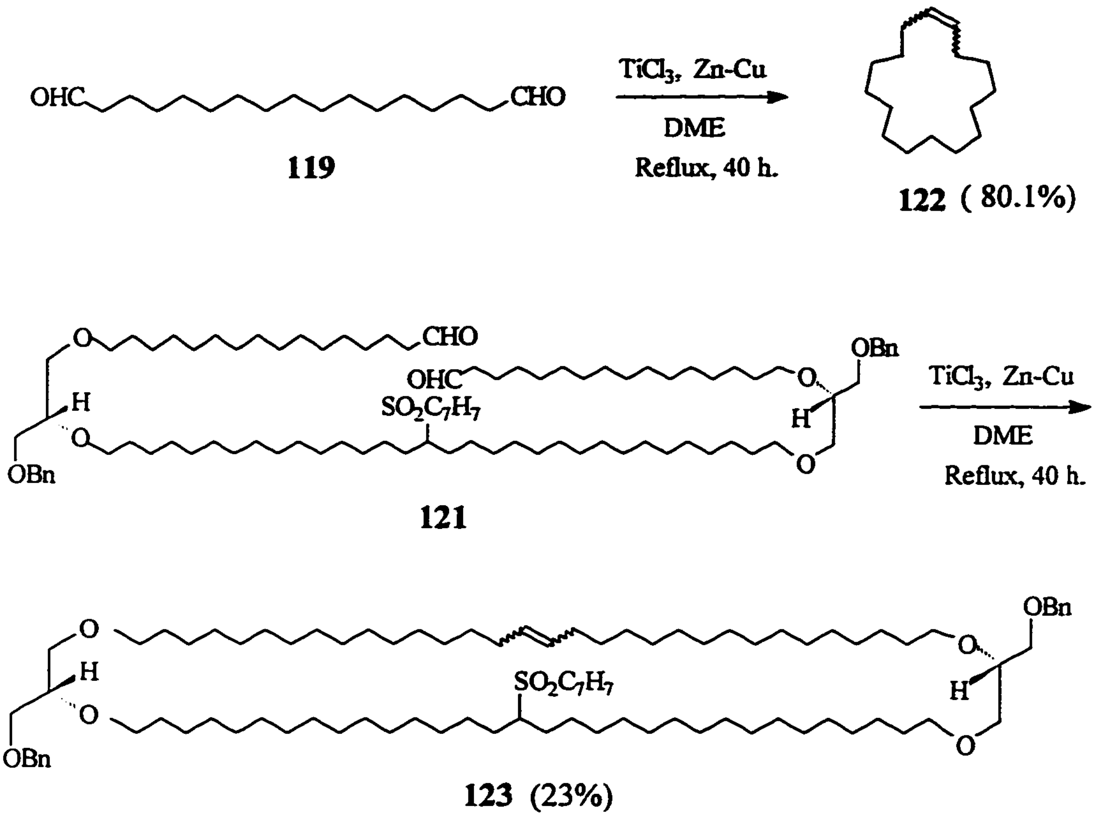


Figure 17 Oxidation of the tetraether



119

122 (80.1%)

121

123 (23%)

Figure 18 Preparetion of the macrocyclic compound

(*e*). *Alternative approach to cross coupling triether fragments.*

Based on the previous work done in our lab we planned to used the Kochi type reaction to couple the two triethers. Although the Julia coupling worked, in order to cut the reaction steps and improve the yield, we explored an alternative cross coupling reaction between alkyl iodides **101** and **103** using a the Kochi protocol[70] we employed in earlier work[60] (Scheme 4), silver or copper catalyzed coupling between a Grignard reagent and an alkyl halide. Several different reaction conditions were tested,[91,92,93] (Figure 19 &20). Initially, model reactions (Figure 19) gave poor yields of Grignard reagents. n-Hexadecyl bromide **38** did work better than 1-octadecyl chloride **124**, but 36% of the starting alkyl bromide still remained after a long reaction time. We found that in order to get the best Grignard reagent, the magnesium turnings needed to be activated by being stirred under argon for 24 hour before use and reactions proceeded best when initiated by addition of 1,2-dibromoethane (Figure 20). Specifically, we attempted coupling of the Grignard reagent **133** of hexadecyl bromide with decyl iodide **134**, and the Grignard reagent **137** of the THP[94] derivative of 16-hydroxyhexadecyl bromide with the trityl[89]

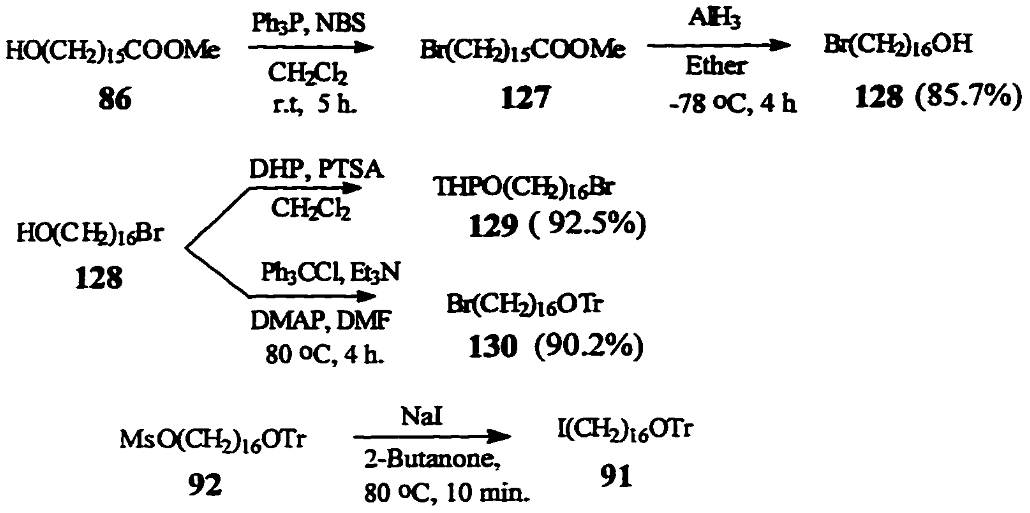


Figure 19 Preparatio of the 16-membered chain for the Grignard Reaction

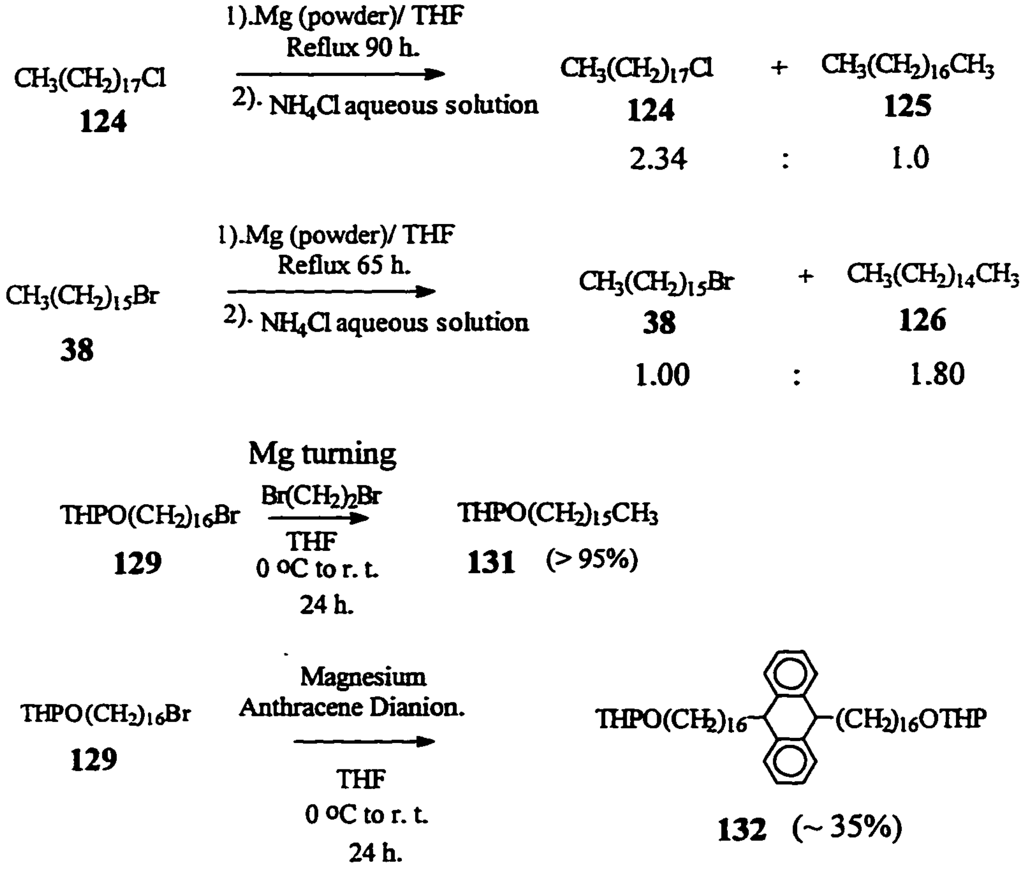


Figure 20 Preparation of the Grignard reagent by different methods

derivatives of both 16-hydroxyhexadecyl iodide[95] **91** and bromide **130**, catalyzed by Li_2CuCl_4. The simple alkyl halides gave a high yield of the hetero-coupling product **135**, with little homo-coupling product **136** (Figure 21). The ethers first were not as successful, however. We had some difficulty in preparing the Grignard reagent of THP derivative **129**. Initially, only the reduced product **131** was obtained. Further attempts to prepare the Grignard reagent by exchange with the magnesium salt of anthracene dianion gave bis-alkylation product **132** (Figure 20). Finally, conditions which gave the desired Grignard reagent **137** with copper catalysis also afforded the heterocoupling product **138** with trityliodide derivative **91** in moderate yields with little homo-coupling (Figure 21). Attempted coupling with the corresponding tritylbromide dervative **130** gave no hetero-coupling product. And also one trial of the coupling reaction between the two triether deratives **142** and **103** gave no desired product.

(f). Our sequence verse Kakinuma's method.

In the early 1996, Kakinuma et al[58] reported the synthesis of the identical cyclic, straight chain, 72-membered ring model of the

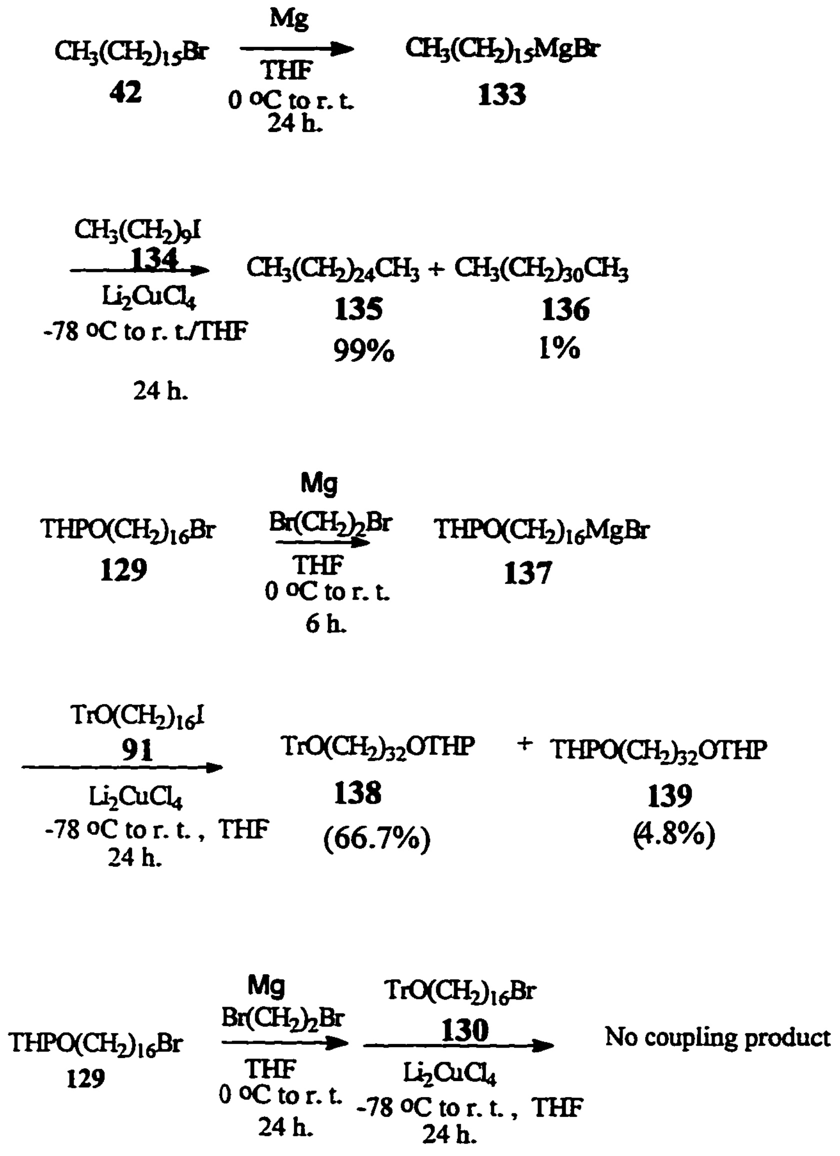


Figure 21 Cross coupling reaction catalyzed by Cu(I)

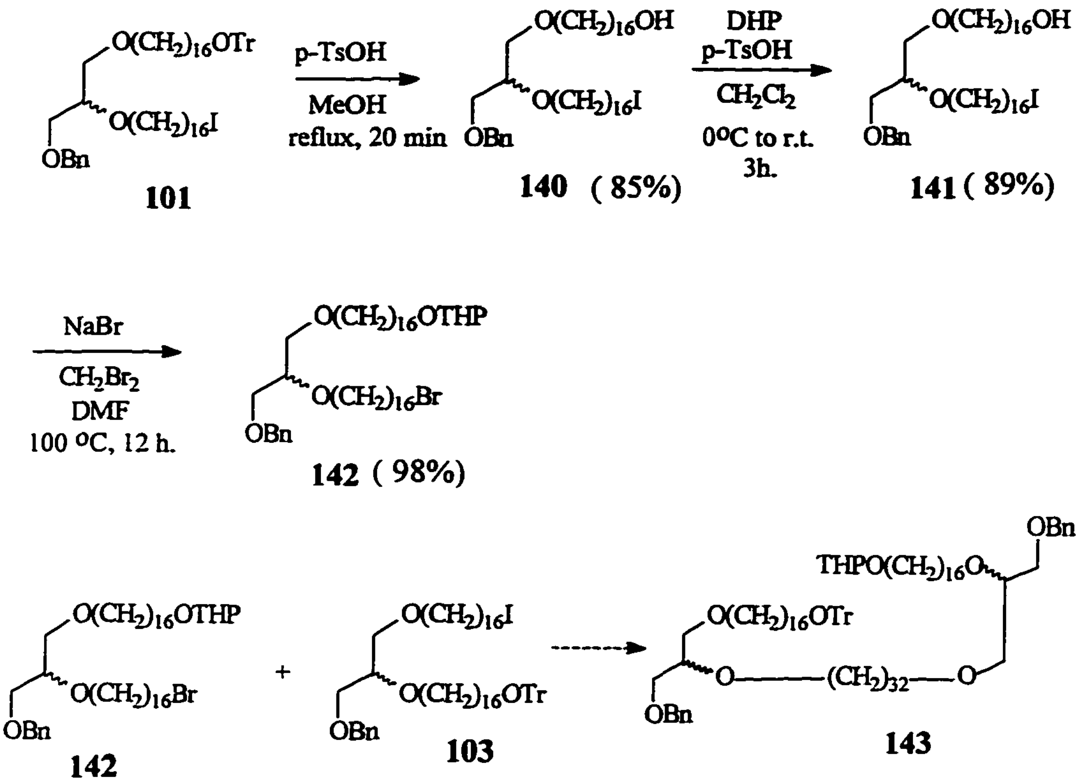
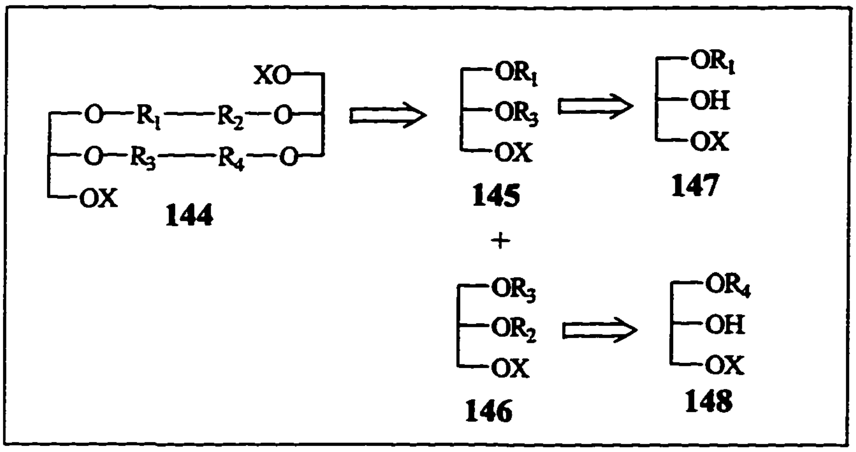


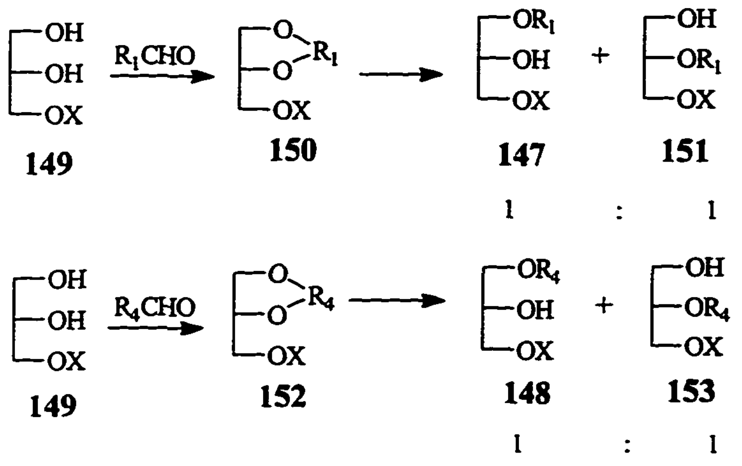
Figure 22 Preparation the triethers for the Kochi type cross coupling reaction

archaebacterial tetraether lipids (Scheme 7) that we have been attempting to make, and used a method very similar to that which we proposed (to NIH) in 1993. The main difference lies in the way of building the triethers fragments (Scheme 8). Kakinuma's method leads to lipids with only identical chains attached at the C-2 and C-3 positions of glycerol, while our method allows independent attachment of two different chains at these positions. Thus we can prepare lipids with variable methyl substitution patterns and chain lengths, inherently offering greater flexibility for the synthesis of different tetraethers.

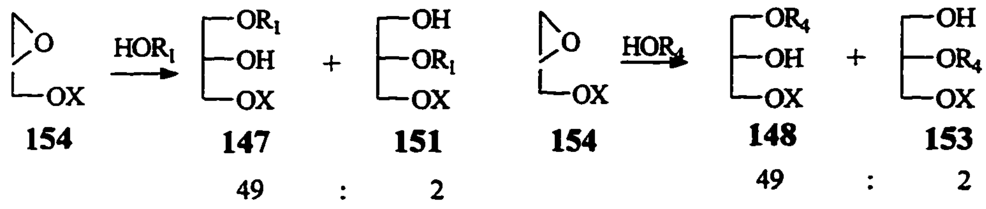
Since the biochemical properties of these kind of lipids have drawn more and more attention, particularly in stabilization studies[45-50] of the liposomes made from tetraether lipids, it is apparent that the structure of the hydrophobic chains play a very important role[29-33] in determining the physical properties of the lipids. A full study of the effects of the methyl substituents which are so enantiospecifically incorporated in the lipid chain would require synthesis of chains of varying substitution pattern, perhaps removing the methyl groups from one chain while leaving them on the other, using chains which are



Kakinuma's method



Berkowitz's method



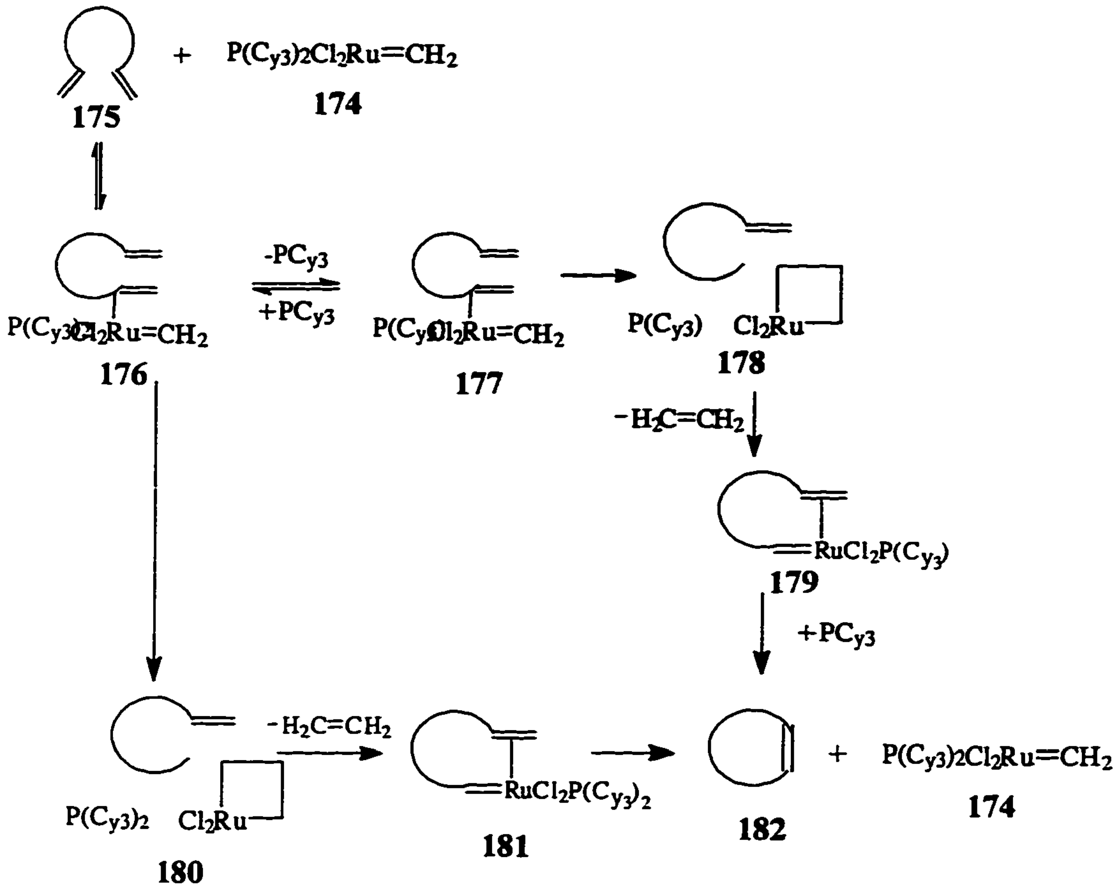
Scheme 8 Comparison between the two methods

epimeric at corresponding positions, or of different lengths.

In addition, the method reported by Grubbs et al.[101] recently offered a new possible alternative route to synthesize the macrocycling molecules (Scheme 9).

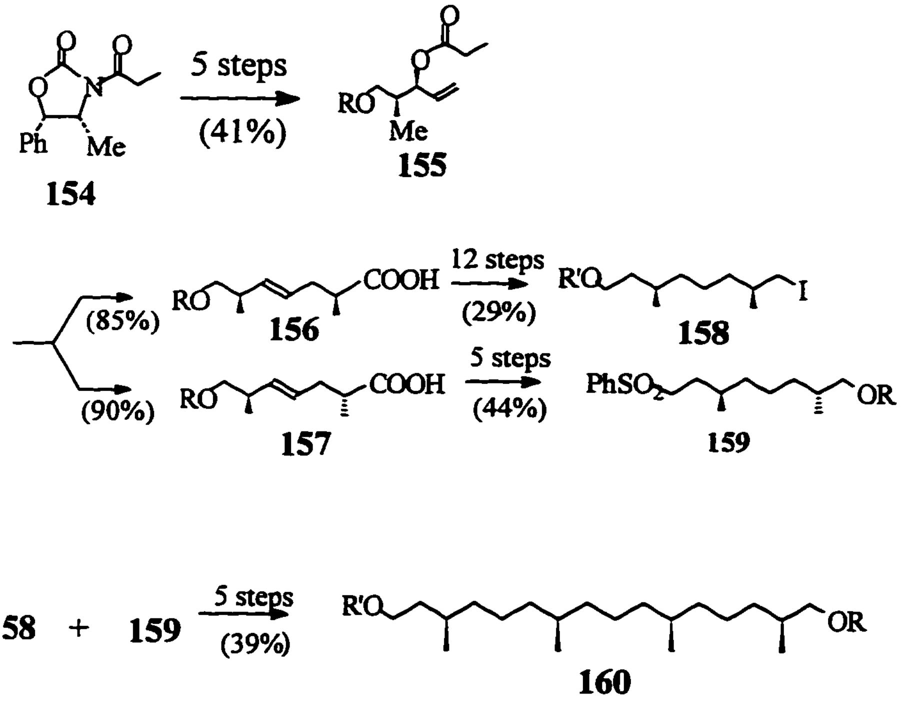
(g). Conclusion.

We designed a synthetic route for making a straight chain model archaebacterial lipid **77** starting from commercially available hexadecanolide **85** and 2-benzyloxymethyl oxirane **83**, using $BF_3.Et_2O$ catalyzed ring opening of the epoxide, cross coupling of two C-2, C-3 differentially substituted glycerol triethers, with a McMurry ring closure the key steps. The strategy used for the synthesis of the straight chain model **77** could be readily be applied to the synthesis of the natural archaebacterial tetraether lipid by using a 1,16 disubstituted C_{20}-phytane instead of the straight chain compounds. Indeed several sequences of syntheses of 1, 16 disubstituted C_{20}-phytane have already been reported. Heathcock et al.[35] first synthesized **160**-like chains using a combination of enolate-Claisen rearrangement and aldol condensation (Scheme 10). Later

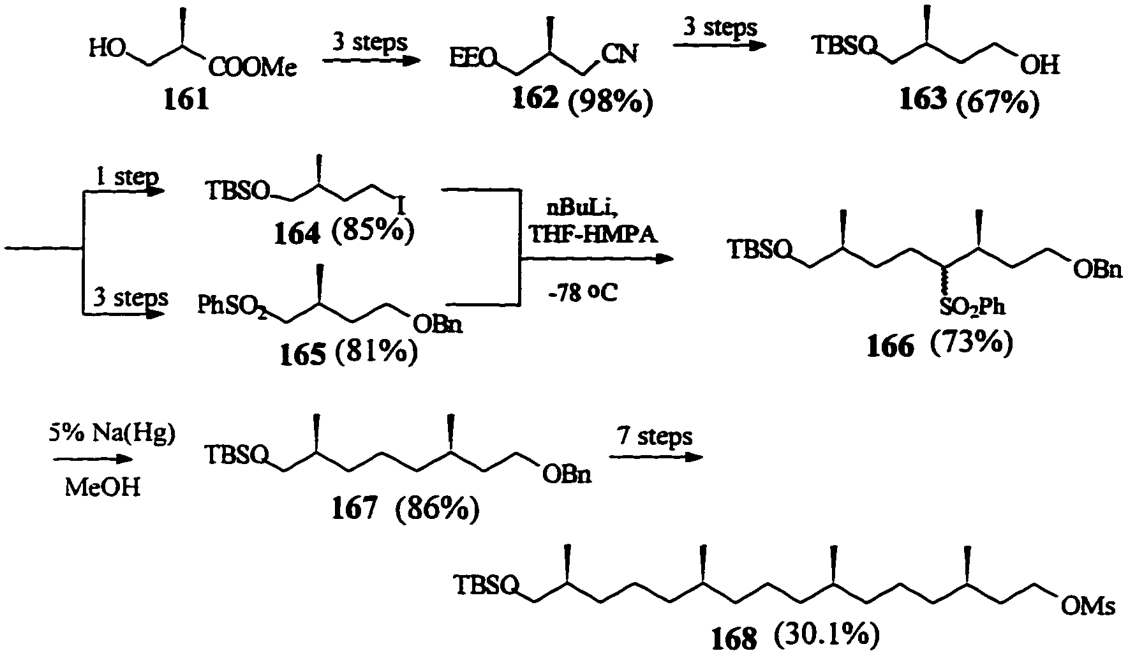


Scheme 9 Grubbs et al.'s method

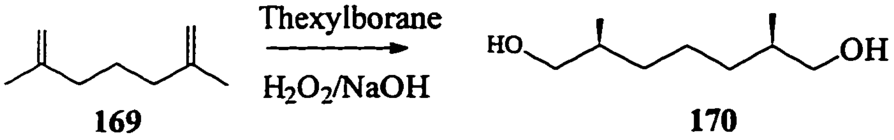
Kakinuma[58] and Czeskis[102] synthesized optically pure, differentially protected C_{20}-phytane units by a more classical method, linking four optically resolved C_5 precursor units (Scheme 11). Our group is presently working on a new, very short, method which will supply a C_{10} unit with two correct chiral centers starting from the nonchiral compounds, elaborating on Still's method[72] of cyclic hydroboration of a 1,6-heptadiene (Scheme 12) [103].



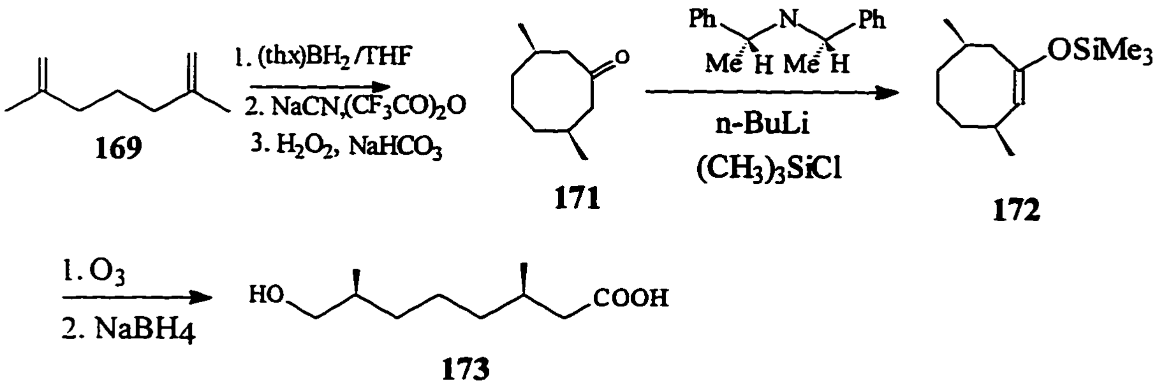
Scheme 10 Heathcock's sequence



Scheme 11 Kakinuma's sequence



Still's method



Scheme 12 Berkowitz's sequence

CHAPTER 3

EXPERIMENTAL SECTION

General Methods : ^1H NMR and ^{13}C NMR spectra were recorded on an IBM WP 200SY (200 MHz) spectrometer and a Bruker CXP400 NMR spectrometer in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are reported in parts per million down field from Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectro- photometer. Optical rotations were measured in a 1.0 dm cell on a JASCO Model DIP-140 digital polarimeter. Melting point were determined in open capillaries tube by using a Thomas-Hoover Uni-melt apparatus. Silica gel G TLC plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with iodine vapor, UV-lamp or 10% sulfuric acid in ethanol to visualize the spots. E. Merck silica gel 60 (230-400 ASTM mesh) was used for flash chromatography. Analytical and preparative HPLC were carried out on a Waters Associates system consisting of Waters RCM 8 × 10 or 25 × 10 Cartridges, and a 6000 SDS pump, U6K injector, as well as a Model 401 differential refractometer. GC/MS analyses were performed by Dr. David C. Locke at Queens College on a HP 5972 GC/MS 30 × 0.25 mm DB-5 fused silica capillary column gas chromatography-mass spectrometer. Elemental analyses were done by Galbraith Laboratories, Knoxville, TN.

Solvents were dried as follows: Dichloromethane was distilled from calcium hydride before using. Ether and tetrahydrofuran were refluxed over sodium under nitrogen atmosphere for several hours by using benzophenone as indicator and then distilled and used immediately. Ethylene glycol dimethyl ether was refluxed over sodium under nitrogen gas for 2 days and distilled before using. N, N-dimethylformamide was dried over CaH_2, distilled, and stored over 4 A molecular sieves. All amines were distilled under reduced pressure and stored over sodium hydroxide. Dimethyl sulfoxide was distilled from BaO and stored over 4 A molecular sieves. All air-sensitive reactions were carried out under an argon or nitrogen atmosphere. (R)-(-)-glycidyl benzyl ether $[\alpha]_D^{20}$ -4.9° ($CHCl_3$) was obtained from Aldrich Chemical Co. (Milwaukee, WI), and 16-hexadecanolide was obtained from Lancaster Synthesis, Ltd. (Windham, NH), and International Flavor and Fragrance Inc.(Union, NJ).

Methyl 16-hydroxyhexadecanoate (86)[73]

To a 250 mL round bottom flask was added 10.0 g (39.9 mmol) of 16-hexadecanolide **85**, 100 mL of dry methanol and a few drops of BF_3Et_2O. The reaction mixture was stirred and refluxed under nitrogen for 24 h. TLC (elution by hexane/EtOAc 7:1) showed that only one new compound was formed and all starting materials were gone. Methanol was removed by rotary evaporation, the solid residue was dissolved in 250 mL of ether, then washed with three 100 mL portions of water. The ethereal solution was dried over anhydrous sodium sulfate, filtered and concentrated to give pure methyl 16-hydroxyhexadecanoate **86** as a white solid (11.2 g, 99.0% yield), mp.55-56 °C (lit[73]).

^1H NMR (200 MHz, in $CDCl_3$) δ 1.26 (br., 22 H, 11×CH_2), 1.55 (m, 5 H), 2.28 (t, 2 H, J=6.6 Hz, CH_2COOMe), 3.60 (t, 2 H, J=6.6 Hz, CH_2OH), 3.67 (s, 3 H, $COOCH_3$).

IR ($CDCl_3$, cm^{-1}) 3630, 2920, 2850, 1725, 1020.

MS (m/e) 256, 98, 87, 74 , 55 (base peak).

16-Hydroxyhexadecanoic acid (87)[74]

To a 250 mL round bottom flask was added 10.0 g (39.9 mmol) of 16-hexadecanolide **85**, 100 mL of dry methanol and 10.0 g of potassium hydroxide. The reaction mixture was stirred and refluxed for 24 h. TLC (elution by hexane/EtOAc 7:1) showed that all starting materials were gone. Methanol was removed by rotary evaporation and the solid residue was neutralized by 400 mL of 10% hydrochloric acid. Crude 16-Hydroxyhexadecanoic crystallized when the solution was cooled to room temperature. Pure acid **87** (10.7 g 100% yield) was obtained by recrystalization from ethanol: mp. 94-96°C (lit[74]).

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.24 (br., 22 H, 11×CH_2), 1.57 (m, 5 H), 2.32 (t, 2 H, J=7.5 Hz, CH_2COOH), 3.62 ((t, 2 H, J=6.5 Hz, CH_2OH), 9.70 (s, 1 H, COOH).

IR ($CDCl_3$, cm^{-1}) 3280, 3210-2350 (br.) 2912, 2874, 1700, 1470.

16-chlorohexadecanoyl chloride (89)[77]

To a 250 mL round bottom flask was added 10.0 g (36.7 mmol) of 16-hydroxyhexadecanoic acid **87** and 50 g (0.42 mol) of freshly distilled thionyl chloride. The reaction mixture was stirred at room temperature for 30 min, and refluxed for 3 h. The excess thionyl chloride was distilled out and the residue was pumped by an oil pump at 100 °C for 3 h. IR spectroscopy of the residue confirmed the absence of hydroxyl and carboxyl groups, and the carbonyl group of the acyl chloride appeared at 1790 cm^{-1}. The residue can be directly reduced to 16-chlorohexdecanol **82** without purification.

16-Chlorohexadecanol (82)[78]

Method a (alane reduction) : Preparation of the alane solution[78]: To dry aluminum trichloride (4.92 g 36.9 mmol) in a 250 mL round bottom flask was added dropwise 35 mL of freshly distilled ether. The solution boiled spontaneously during the addition of the ether. The solution was then transferred to another flask which already contained lithium aluminum hydride (1.40 g, 36.9 mmol) in 35 mL of ether. The gray suspension of alane which formed was introduced dropwise to an ethereal solution of crude 16-chlorohexadecanoyl chloride **89.** The reaction mixture was stirred at room temperature for 3 h, then diluted with 70 mL of 10 % aqueous tartaric acid. The ethereal layer was separated and the aqueous layer was extracted with three 100 mL portions of ether. The combined organic layers were washed twice with 200 mL of brine, then dried over anhydrous sodium sulfate. After the organic solution was filtered and concentrated, the residue was purified by flash chromatography (elution with hexane/EtOAc 8:1). 16-chlorohexadecanol **82** 9.90 g (91.0%) was obtained as a white solid; mp 44 °C .

Method b ($LiAlH_4$ reduction): To a 250 mL round bottom flask was added 0.60 g (16 mmol) of lithium aluminum hydride and 80 mL of freshly distilled dry ether. The solution was stirred at room temperature for 1 h, then cooled to -78°C. Crude 16-chlorohexadecanoyl chloride **89**, which was made from 3.65 g (13.4 mmol) of 16-hydroxyhexadecanic acid, in 60 mL of ether was added dropwise through an air balanced dropping funnel. The solution was stirred at -78°C for 4 h, the temperature was raised to room temperature, and the mixture was neutralized by 100 mL of 6 N aqueous H_2SO_4. The ethereal layer was separated and the aqueous layer was extracted three times with 100 mL portions ether. The combined organic layers were washed with two 200 mL portions of brine, then dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (elution with hexane/EtOAc 8:1). 16-chlorohexadecanol **82** 3.64 g (98.1%) was obtained as a white solid; mp 44 °C .

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.26 (br., 24 H, $12XCH_2$), 1.56 (m, 2 H, CH_2), 1.77 (m, 2 H, CH_2), 3.53 (t, 2 H, J=6.7 Hz, CH_2Cl), 3.64 (t, 2 H, J=6.5 Hz, CH_2OH).

IR ($CDCl_3$, cm^{-1}) 3620, 2920, 2850.

MS (m/e) 258/260 (3:1), 55 (base peak).

Elemental analysis: Calculated: C 69.41; H 12.01

Found: C 69.18; H 12.19

16-Chlorohexadecyl tosylate (94)[79]

To a 250 mL round bottom flask equipped with a drying tube was added 9.90 g (35.7 mmol) of 16-chlorohexadecanol **82** and 11.9 g (150 mmol) of pyridine. The mixture was stirred at room temperature for 20 min. then cooled to below 10 °C. At this temperature 7.50 g (39.3 mmol) of p-toluenesulfonyl chloride was introduced in portions during a 5 min. period. After the addition the mixture was stirred at room temperature for 3.5 h, then neutralized with 30 mL of concentration hydrochloric acid in 100 g of ice. The solid ester was collected by vacuum filtration and the crude solids were recrystallized from 60 mL of ethanol. The yield of the tosylate **94** was 13.88 g (90.0%); mp 56-58 °C.

^{1}H NMR (200 MHz, in CDCl$_3$) δ 1.24 (br., 24 H, 12XCH$_2$), 1.59 (m, 2 H, CH$_2$), 1.76 (m, 2 H, CH$_2$), 2.44 (s, 3 H, CH$_3$), 3.53 (t, 2 H, J=6.7 Hz, CH$_2$Cl), 4.02 (t, 2 H, J=6.5 Hz CH$_2$OTs), 7.34 (d, 2 H, J=8.25 Hz), 7.78 (d, 2 H, J=8.2 Hz).

IR (CDCl$_3$, cm^{-1}) 2927, 2855, 1465, 1371, 1188, 1178, 1099, 968.

Elemental analysis: Calculated: C 64.09; H 9.12; S 7.44

Found: C 64.24; H 9.49; S 7.82

Methyl 16-trityloxyhexadecanoate (88)[75]

To a 500 mL round bottom flask was added 9.30 g (36.0 mmol) of methyl 16-hydroxy-hexadecanoate **86**, 10. 05 g (37.5 mmol) of triphenylmethyl chloride, 12 mL (84 mmol) of triethylamine, 0.70 g

(6 mmol) of DMAP and 400 mL of dry DMF. The mixture was stirred under nitrogen atmosphere at room temperature for 48 h, then refluxed for 5 h, then poured into 300 g of ice-water, and extracted three times with 200 mL portions of methylene chloride. The combined organic solutions were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (elution with hexane/EtOAc 8:1) to obtain 17.93 g (94.1%) of methyl 16-trityloxyhexadecanoate **88**, as a thick liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.24 (br., 22 H, 11×CH_2), 1.60 (m, 4 H, CH_2), 2.29 (t, 2 H, J=6.6 Hz, CH_2COOMe), 3.03 (t, 2 H, J=6.7 Hz CH_2OTr), 3.67 (s, 3 $COOCH_3$), 7.17 (m, 3 H), 7.29 (m, 6 H), 7.44 (m, 6 H).

IR ($CDCl_3$, cm^{-1}) 3061, 2927, 2855, 1750, 1596, 1465.

Elemental analysis: Calculated: C 81.77 H 9.15

Found: C 82.18 H 9.17

16-Trityloyxhexadecanol (84)[76]

To a 250 mL round bottom flask was added 1.36 g (36.0 mmol) of lithium aluminum hydride and 150 mL of freshly distilled dry ether, and the solution was stirred at room temperature for 30 min., then cooled to 0°C. At this temperature 18.3 g (34.6 mmol) of methyl trityloxy hexadecanoate **88** in 60 mL of dry ether solution was added dropwise through a pressure-equalized dropping funnel. The reaction mixture was stirred at room temperature for 3 h and the resulting gray solution was diluted with 300 mL of 10% aqueous tartaric acid , then extracted with 300 mL of ether. The ethereal layer was dried over anhydrous sodium sulfate, and after removal of the ether, the residues were purified by flash chromatography (elution with hexane/EtOAc 5:1). to obtain 17.31 g (99.8%) of 16-trityloxyhexadecanol **84** as a thick liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.20 (br., 24 H, 12XCH_2), 1.55 (m, 5H), 3.03 (t, 2 H, J=6.6 Hz, CH_2OTr), 3.63 (t, 2 H, J=6.6 Hz, CH_2OH), 7.20 (m. 3 H), 7.32 (m, 6 H), 7.45 (m, 6 H).

IR ($CDCl_3$, cm^{-1}) 3625, 3061, 2927, 2855, 1596, 1490, 1465, 1221, 1069.

Elemental analysis: Calculated: C 83.95; H 9.66

Found: C 84.05; H 9.77

16-Trityloxyhexadecyl tosylate (90)[80]

To a 250 mL round bottom flask as added 14.63 g (29.20 mmol) of 16-trityloxyhexadecanol **84**, 3.65 g (35.0 mmol) of triethylamine, 0.40 g (3.3 mmol) of DMAP, and 150 mL of distilled methylene chloride. The reaction mixture was stirred at room temperature for 30 min., then cooled to 0 °C. p-Toluenesulfonyl chloride 6.68 g (35.0 mmol) was introduced to the reaction mixture, which was then refluxing for 24 h. The resulting organic solution was washed with three 100 mL portions of solution, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 10:1) to obtain 16-trityloxyhexadecyl tosylate **90** 15.39 g (80.4%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.24 (br., 24 H, 12×CH_2), 1.59 (m, 4 H, 2×CH_2), 2.44 (s, 3 H, CH_3), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr).

4.01(t, 2 H, J=6.5 Hz CH_2OTs), 7.25~7.42 (m. 17 H), 7.79 (d, 2 H, J= 8.27 Hz).

IR ($CDCl_3$, cm^{-1}) 3061, 2927, 2855, 1598, 1490, 1357, 1189, 1176, 1069, 961.

Elemental analysis:	Calculated:	C 77.02; H 8.31; S 4.89
	Found:	C 77.11; H 8.49; S 5.06

16-Trityloxyhexadecyl mesylate(92)[80]

To a 100 mL round bottom flask was added 3.62 g (7.22 mmol) of 16-trityloxyhexadecanol **84**, 1.51 mL (10.83 mmol) of triethyl amine, and 40 mL of distilled methylene chloride. The reaction mixture was stirred at room temperature for 10 min., then cooled to 0 °C and at this temperature 0.67 mL (8.66 mmol) of methanesulfonyl chloride was introduced to the reaction mixture, followed by stirring at 0 °C for 1 h. The reaction was quenched by adding 50 mL of ice-water and the resulting organic solution was washed with 30 mL of aqueous 0.1 M HCl and 30 mL of brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 6:1) to obtain 16-

trityloxyhexadecyl mesylate **92,** 3.77 g (90.1%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.25 (br., 24 H, 12×CH_2), 1.62 (m, 2 H, CH_2), 1.73 (m, 2 H), 2.99 (s, 3 H, CH_3), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 4.22 (t, 2 H, J=6.68 Hz CH_2OMs), 7.26 (m. 9 H), 7.44 (d, 6 H, J= 7.50 Hz).

IR ($CDCl_3$, cm^{-1}) 3061, 2927, 2855, 1598, 1490, 1357, 1189, 1176, 1069, 961.

16-Chlorohexadecyl mesylate (94)[80]

To a 100 mL round bottom flask as added 2.00 g (7.22 mmol) of 16-chlorohexadecanol **82,** 1.51 mL (10.83 mmol) of triethylamine, and 40 mL of distilled methylene chloride. The reaction mixture was stirred at room temperature for 10 min., then cooled to 0 °C. At this temperature 0.67 mL (8.66 mmol) of methanesulfonyl chloride was introduced to the reaction mixture, which was stirred at 0 °C for 1 h. The reaction was quenched by adding 50 mL of ice-water and the resulting organic solution was washed with 30 mL of aqueous 0.1 M HCl and 30 mL of brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 6:1) to obtain 16-chlorohexadecyl mesylate **94**, 3.77 g (90.1%), as a solid, mp 49-50 °C

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.25 (br., 24 H, 10XCH_2), 1.73 (m, 4 H), 3.00 (s, 3 H, CH_3), 3.53 (t, 2 H, J=6.72 Hz, CH_2Cl). 4.24 (t, 2 H, J=6.64 Hz CH_2OMs).

IR ($CDCl_3$, cm^{-1}) 2927.3, 2855, 1466, 1368, 1347, 1178.6, 969.4, 947, 807.

1-Iodo-16-trityloxyhexadecane (91)[81]

To a 50 mL round-bottom flask was added 3.30 g (5.0 mmol) of 16-trityloxyhexadecyl tosylate **90**, 1.49 g (10.0 mmol) of sodium iodide and 20 mL of 2-butanone. The reaction mixture was stirred and refluxed for 30 min, then cooled to room temperature, diluted with 40 mL of ether, filtered and dried over anhydrous sodium sulfate. The resulting solution was filtered, concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc 10:1) to obtain 1-iodo-16-trityloxyhexadecane **91**, 2.96 g (98.7%), as a solid;

mp 48-49 °C.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 24 H, 12×CH_2), 1.62 (m ,2 H, CH_2), 1.81 (m, 2 H), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.18 (t, 2 H, J=6.68 Hz CH_2I), 7.30 (m. 9 H), 7.45 (d, 6 H, J= 7.8 Hz).

IR ($CDCl_3$, cm-^{1}) 3062, 2928, 2855, 1560, 1490, 1448, 1272, 1221, 1070.

Elemental analysis:	Calculated:	C 68.83; H 7.76
	Found:	C 68.66; H 7.67

1-O-(16-chlorohexadecyl)-3-O-benzyl-glycerol (95)[60,63]

To a 50 mL round bottom flask was added 1.69 g (6.10 mmol) of 16-chlorohexadecanol **82**, 1.0 g (6.10 mmol) of 2-(**R**)-(-)-benzyloxymethyloxirane **83**, and 30 mL of freshly distilled dry methylene chloride. The reaction mixture was cooled to 0°C for 15 min., five drops of $BF_3.Et_2O$ were added, and the mixture was stirred at room temperature for 20 h. Then the reaction mixture was washed with three 20 mL portions of water, the organic layer was dried and concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc, 6:1) to obtain 1-O-(16-chlorohexadecyl)-3-O-benzylglycerol **95**, 2.30 g (86.0%), as a white solid; mp 55-57 °C.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.26 (br., 24 H, 12×CH_2), 1.53 (m, 2 H), 1.77 (m, 2 H, CH_2), 3.41~3.56 (m, 6 H), 3.63 (t, 2 H, J=6.7 Hz, CH_2Cl), 3.97 (m, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.33 (m, 5 H).

IR ($CDCl_3$, cm^{-1}) 3570,2910, 2840, 1450, 1250, 1100.

Elemental analysis: Calculated: C 70.88; H 10.28

Found: C 70.83; H 10.09

Methyl 16-(2-hydroxy-3-benzyloxypropanoxy) hexadecanoate (97)[60,63]

To a 100 mL round bottom flask was added 2.87 g (10.0 mmol) of methyl 16-hydroxyhexadecanoate **86**,1.69 g (10.0 mmol) of 2-(R)-(-)-benzyloxymethyloxirane **83**, and 30 mL of freshly distilled dry methylene chloride. The reaction mixture was cooled to 0°C for 30 min., five drops of $BF_3.Et_2O$ were added, and the mixture was stirred at room temperature for 20 h. Then the reaction mixture was washed with three 20 mL portions of water, the organic layer was dried and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc, 6:1) to obtain methyl 16-(2-hydroxy-3-benzyloxypropanoxy) hexadecanoate **97**, 2.85 g (82.1%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.27 (br., 22 H, 12×CH_2), 1.53~1.66 (m, 4 H, CH_2), 2.26 (t, J=6.5 Hz CH_2COOMe), 3.45 (m, 6 H), 3.66 (s, 3 H, COOMe), 4.00 (m, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.33 (m, 5 H).

IR ($CDCl_3$, cm^{-1}) 3618, 3182, 3065, 2928, 2855, 1731, 1455, 1247, 1074.

1-O-(16-hydroxyhexadecyl)-3-O-benzyl-glycerol (98)[76]

To a 250 mL round bottom flask was added 1.0 g (24.9 mmol) of lithium aluminum hydride and 100 mL of freshly distilled dry ether. The solution was stirred at room temperature for 30 min., then cooled to 0°C. At this temperature 11.22 g (24.9 mmol) of methyl 16-(2-hydroxy-3-benzyloxypropanoxy) hexadecanoate **97** in 60 mL dry ether solution was added dropwise through a pressure-equalized dropping funnel. The reaction mixture was stirred at room temperature for 5 h, and the resulting gray solution was diluted with 300 mL of 10% aqueous tartaric acid, then extracted with three 100 mL portions of ether. The combined ethereal layers were dried over anhydrous sodium sulfate. After removal of the ether, the residues were purified by flash chromatography (elution with hexane/EtOAc 4:1) to obtain 8.75 g (90.0%) of 1-O-(16-hydroxyhexadecyl)-3-O-benzylglycerol **98** as a white solid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.20 (br., 24 H, 12XCH_2), 1.56 (m, 4 H, 2XCH_2), 3.53, 3.60 (m, 8 H), 3.98 (s, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.33 (m, 5 H).

IR ($CDCl_3$, cm^{-1}) 3626, 3065, 2928, 2854, 1247, 1074.

1-O-(16-trityloxyhexadecyl)-3-O-Benzyl-glycerol (96)[75]

To a 100 mL round bottom flask was added 2.23 g (5.10 mmol) of 1-O-(16-hydroxyhexadecyl)-3-O-benzyl glycerol **98**, 1.47 g (5.3 mmol) of triphenylmethyl chloride, 1.3 mL of triethyl amine, 0.05 g (0.3 mmol) of DMAP and 50 mL of dry DMF. The mixture was stirred under nitrogen at room temperature for 48 h, followed by refluxing 5 h, then poured into 50 g of ice-water and extracted three times with 50 mL portions of methylene chloride. The combined organic solutions were washed with brine solution and dried over anhydrous sodium sulfate. Removal of the organic solvent and, purification of the residue by flash chromatography (elution with hexane/EtOAc 6:1) gave 1.66 g (65.1%) of 1-O-(16-trityloxyhexadecyl)-3-O- benzyl glycerol **96** as a viscous liquid.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.24 (br., 24 H, 12×CH_2), 1.60 (m, 4 H, CH_2), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.44, 3.50, 3.63 (m, 6 H), 3.97 (m, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.22~7.29 (m, 11 H), 7.42~7.46 (m, 9 H).

IR ($CDCl_3$, cm^{-1}) 3583, 3182, 3062, 3033, 2928, 2855, 1590, 1490, 1488, 1247, 1072.

Elemental analysis	Calculated:.	C 81.28; H 49.09.
	Found:	C 81.53; H 49.36.

1-O-(16-trityloxyhexadecyl)-2-O-(16-chlorohexadecyl)-3-O-benzyl glycerol (99)[60,61]

To a 100 mL round bottom flask was added 0.13 g (5.6 mmol) of sodium hydride, 2.08 g (3.14 mmol) of 1-O-(16-trityloxyhexadecyl)-3-O-benzyl glycerol (±) **96** and 20 mL of freshly distilled, dry, THF. The solution was stirred at room temperature for 3 h, then cooled to 0°C, when 4.07 g (9.44 mmol) of 16-chlorohexadecanol tosylate **93** and 0.20 g (0.55 mmol) of tetrabutylamonium iodide dissolved in 30 mL of dry THF were introduced by syringe. The reaction mixture was stirred at room temperature for another 24 h, then refluxed for 5 h, and finally was filtered through celite to remove the inorganic salts. After the celite was rinsed with 50 mL of ether, the combined organic solutions were concentrated by rotary evaporation, and, the residue was purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 1-O-(16-trityloxyhexadecyl)-2-(16-chlorohexadecyl)-3-O-benzyl glycerol **99**, 1.92 g (66.1%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.25 (br., 48 H, 24×CH_2), 1.58 (m, 6 H, 3×CH_2), 1.77 (m, 2 H CH_2), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.42-3.59 (m, 10 H OCH_2), 4.01 (m, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.20-7.42 (m, 12 H), 7.44-7.46 (m, 8 H).

IR ($CDCl_3$, cm^{-1}) 3063, 3033, 2927, 2855, 1596, 1490, 1465, 1445, 1220, 1090, 1030, 920.

^{13}C NMR (200 MHz, in $CDCl_3$) 26.18, 26.94, 28.93, 29.56, 29.70, 30.20, 32.74, 45.10, 63.77, 70.64, 70.91, 71.75, 73.44, 126.80, 127.68, 128.31, 128.79, 138.64, 144.68.

Elemental analysis	Calculated:	C 79.31; H 9.93.
	Found:	C 79.26; H 10.26

1-O-(16-chlorohexadecyl)-2-O-(16-trityloxyhexadecyl)-3-O-benzyl glycerol (100)[60,61]

To a 100 mL round bottom flask was added 0.13 g (5.60 mmol) of sodium hydride, 1.10 g (2.40 mmol) of 1-O-(16-chlorohexadecyl)-3-O-benzyl glycerol (±) **95** and 20 mL of freshly distilled dry THF. The solution was stirred at room temperature for 3 h, then cooled to 0°C, when 3.40 g (4.70 mmol) of 16-trityloxyhexadecanol tosylate **90** and 0.20 g (0.55 mmol) of tetrabutylamonium iodide dissolved in 30 mL of dry THF were introduced by syringe. The reaction mixture was stirred at room temperature for another 24 h, then refluxed for 5 h, and finally filtered through celite to remove the inorganic salts. After the celite was rinsed with 50 mL of ether, the combined organic solutions were concentrated by rotary evaporation, and the residue was purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 1-O-(16-chlorohexadecyl)-2-(16-trityloxyhexadecyl)-3-O-benzyl glycerol **100**, 1.32 g (60.1%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.25 (br., 48 H, 24×CH_2), 1.58 (m, 6 H, 3×CH_2), 1.77 (m 2 H CH_2), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.42-3.59 (m, 10 H OCH_2), 4.01(m, 1 H), 4.56 (s, 2 H, OCH_2Ph), 7.20-7.42 (m, 12 H), 7.44-7.46 (m, 8 H).

IR ($CDCl_3$, cm^{-1}) 3063, 3033, 2927, 2855, 1596, 1490, 1465, 1445, 1220, 1090, 1030, 920.

^{13}C NMR (200 MHz, in $CDCl_3$) δ 2 26.18, 26.94, 28.93, 29.56, 29.70, 30.20, 32.74, 45.10, 63.77, 70.64, 70.91, 71.75, 73.44, 126.80, 127.68, 128.31, 128.79, 138.64, 144.68.

Elemental analysis Calculated: C 79.31; H 9.93.

Found: C 79.41; H 10.21.

1-O-(16-trityloxyhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol (101)[81]

To a 100 mL round bottom flask was added 0.10 g (0.11 mmol) of 1-O-(16-trityloxyhexadecyl)-2-O-(16-chlorohexadecyl)-3-O-benzyl glycerol **99**, 0.16 g (1.1 mmol) of sodium iodide, 0.1 g of tetrabutylammonium iodide, and 40 mL of 2-butanone. The reaction mixture was stirred and refluxed under nitrogen for 48 h, then cooled and concentrated. The residue was dissolved in 100 mL of ether, and was washed twice with 50 mL portions of brine. The organic layer was dried over anhydrous sodium sulfate, concentrated and then purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 1-O-(16-trityloxyhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **101**, 0.11 g (100%), as a viscous liquid.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 48 H, 24×CH_2), 1.57 (m, 6 H, 3×CH_2), 1.81 (m, 2 H CH_2), 3.04 (t, 2 H J=6.7 Hz, CH_2OTr), 3.18 (t, 2 H J=6.2 Hz CH_2I), 3.38-3.60 (m, 9 H, OCH_2), 4.55 (s, 2 H, OCH_2Ph) , 7.28-7.42 (m, 14 H), 7.42-7.46 (m, 6 H).

IR ($CDCl_3$, cm^{-1}) 3062, 3032, 2926, 2854, 1596, 1490, 1448, 1365, 1227, 1221, 1090.

1-O-(16-iodohexadecyl)-2-O-(16-trityloxyhexadecyl)-3-O-benzyl glycerol (103)[81]

To a 100 mL round bottom flask was added 0.10 g (0.11 mmol) of 1-O-(16-chlorohexadecyl)-2-O-(16-trityloxyhexadecyl)-3-O-benzyl glycerol **100**, 0.16 g (1.1 mmol) of sodium iodide, 0.1 g of tetrabutyl-ammonium iodide and 40 mL of 2-butanone. The reaction mixture was stirred and refluxed under nitrogen for 48 h, then cooled and concentrated . The residue was dissolved in 100 mL of ether, and was washed twice with 50 mL portions of brine. The organic layer was dried over anhydrous sodium sulfate, and was concentrated and purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 1-O-(16-iodohexadecyl)-2-O-(16-trityloxyhexadecyl)-3-O-benzyl glycerol **103**, 0.11 g (100%), as a viscous liquid.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.26 (br., 48 H, 24×CH_2),1.58 (m, 6 H, 3×CH_2), 1.80 (m, 2 H, CH_2), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.17 (t, 2 H, J=7.0 Hz, CH_2I), 3.42-3.60 (m, 9 H, OCH_2), 4.55 (s, 2 H, OCH_2Ph) , 7.25-7.32 (m, 14 H), 7.45-7.47 (m, 6 H).

IR ($CDCl_3$, cm^{-1}) 3062, 3032, 2926, 2854, 1596, 1448, 1365, 1227, 1221,1090

Elemental analysis Calculated: C 72.16; H 9.03;

Found: C 72.15; H 8.75;

1-O-(16-trityloxyhexadecyl)-2-O-(16-p-toluenesulfonylhexadecyl)-3-O-benzyl glycerol (105)[85,86]

To a 100 mL round bottom flask was added 3.00 g (2.90 mmol) of 1-O-(16-trityloxyhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **101**, 0.79 g (4.43 mmol) of sodium p-toluenesulfinate salt, 0.20 g of tetrabutylamonium iodide and 48 mL of a mixture of 1:1:2 benzene: acetone: water. The reaction mixture was stirred and refluxed under nitrogen for 48 h, then extracted three times with 40 mL portions of ether. The combined organic solutions were dried over anhydrous sodium sulfate, concentrated and the residue was purified by flash chromatography (elution with hexane/EtOAc 7:1) to obtain 1-O-(16-trityloxyhexadecyl)-2-O-(16-p-toluenesulfonylhexadecyl)-3-O-benzyl glycerol **105**, 2.94 g (95.3%), as a viscous liquid.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.24 (br., 48 H, 24×CH_2), 1.48~1.55 (m, 8 H, 4×CH_2), 2.44 (s, 3 H, $PhCH_3$), 3.04 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.06 (t, 2 H, CH_2Ts), 3.39-3.60 (m, 9 H, OCH_2), 4.55 (s, 2 H, OCH_2Ph), 7.17-7.42 (m, 16 H), 7.47 (m, 6 H), 7.77 (d, 2 H, J= 8.18 Hz).

IR ($CDCl_3$, cm^{-1}) 3087.6, 3062.7, 3032.7, 2926.6, 2864.7, 1598.4, 1491.5, 1465.7, 1449, 1371, 1324.7, 1302, 1239, 1149.6, 1090, 1048.2, 908.3.

Elemental analysis	Calculated:	C 78.27; H 9.47; S 3.07.
	Found:	C78.59; H 9.63; S 2.75

1-[3-benzyloxy-2-(16-trityloxyhexadecyloxy)propanoxy]-32-[(1-benzyloxymethyl)-2-(16-trityloxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane (113)[84,87]

To a 100 mL round bottom flask equipped with a balloon filled with nitrogen was added 480.1 mg (0.460 mmol) of 1-O-(16-trityloxyhexadecyl)-2-O-(16-p-toluenesulfonylhexadecyl)-3-O-benzyl glycerol **105** and 30 mL of dry THF. The solution was stirred at -75 °C for 10 min., and 0.60 mL of 1.7 M n-BuLi in hexanes solution was added through a syringe. After 10 min an orange colored solution was obtained. Stirring was continued at -75 °C for another 3 h, then 424.0 mg (0.418 mmol) of 1- O-(16-iodohexadecyl)-2-O-(16 trityloxyhexadecyl)-3-O-benzyl glycerol **103** in 10 mL of dry THF was added. The reaction mixture was stirred at -75 °C under nitrogen for another 30 h, then quenched by adding 2 mL of 1.0 N aqueous hydrochloric acid. The temperature of the mixture was raised to room temperature and the THF was removed by rotary evaporation. The residue was dissolved in 50 mL of ether, was washed with two 30 mL portions of brine. The organic layer was separated and dried over anhydrous sodium sulfate. The resulting solution was concentrated and the residue was purified by flash chromatography (elution with hexane/EtOAc 9:1) to obtain 1-[3-benzyloxy-2-(16-trityloxyhexadecyl) propanoxyl]-32-[(1-benzyloxymethyl)]-2-(16-trityloxyhexadecyl)-ethoxy]-16-p-toluenesulfonyl dotridecane **113**, 202.2 mg (57.6%), and recovered starting materials **103**, 239.1 mg (56.7%), and **105**, 160.0 mg (33%).

^1H NMR (400 MHz, in $CDCl_3$) δ 1.24 (br., 102 H, 51×CH_2), 1.56 (m, 12 H, 6×CH_2), 2.45 (s, 3 H, $PhCH_3$), 2.89 (m, 1 H), 3.03 (t, 4 H, J=6.4 Hz, CH_2OTr), 3.38-3.60 (m, 18 H), 4.55 (s, 4 H, OCH_2Ph) , 7.17-7.38 (m, 24 H), 742-7.46 (m, 18 H), 7.77 (d, 2 H, J=8.11 Hz).

IR ($CDCl_3$, cm^{-1}) 3087.6, 3062.7, 3032.7, 2927, 2864.7, 1598.4, 1491.5, 1449, 1239, 1088.

Elemental analysis	Calculated:	C 80.24; H 9.81; S 1.66
	Found:	C 79.87; H 9.95; S 1.48

1-[3-benzyloxy-2-(16-hydroxyhexadecyloxy)propanoxy]-32-[(1-benzyloxymethyl)-2-(16-hydroxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane (120)[89]

To a 50 mL round bottom flask was added 39.2 mg (0.0203 mmol) of 1-[3-benzyloxy-2 -(16-trityloxyhexadecyloxy) propanoxy]-32-[(1-benzyloxymethyl)-2-(16-trityloxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane **113** and 25 mL of acetic acid. The reaction mixture was stirred at 55-60 °C for 16 h, then poured into 50 g of ice-water and neutralized with saturated aqueous potassium carbonate. The resulting mixture was extracted three times with 50 mL portions of ether. The ether layers were combined and concentrated, and 0.5 g of potassium carbonate and 20 mL of methanol were added to the residue. The mixture was stirred at room temperature for 5 h, then concentrated. The residue was dissolved in 100 mL of ether and washed twice with 50 mL portions of brine solution. The combined organic layers were concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc 4:1) to obtain 25.3 mg (86.1%) of 1-[3-benzyloxy-2-(16-hydroxyhexadecyloxy) propanoxy]-32-[(1-benzyloxy-methyl)-2-(16-hydroxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane **120**.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 102 H, 51×CH_2), 1.43 (m, 2 H), 1.54 (m, 12 H, 6×CH_2), 2.44 (s, 3 H, $PhCH_3$), 2.89 (m, 1 H), 3.40-3.63 (m, 22 H), 4.55 (s, 4 H, OCH_2Ph) , 7.30~7.35 (m, 12 H), 7.74 (d, 2 H, J=8.16 Hz).

IR ($CDCl_3$, cm^{-1}) 3560, 3061, 2927, 2854, 1548, 1440, 1372, 1120.

1-[3-benzyloxy-2-(16-oxohexadecyloxy)propanoxy]-32-[(1-benzyloxymethyl)-2-(16-oxohexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane (121)[90]

To a 100 mL round bottom flask was added 0.10 mL (1.15 mmol) of oxalychloride and 30 mL of freshly distilled methylene chloride. The mixture was cooled to -78 °C, and 0.19 mL (2.14 mmol) of DMSO was introduced through a syringe. The mixture was stirred at -78 °C for 20 min. and 27.3 mg (0.0189 mmol) of 1-[3-benzyloxy-2-(hydroxyhexadecyloxy) propanoxyl]-32-[(1-benzyloxy-methyl)-2-(16-hydroxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane **120** dissolved in 25 mL of methylene chloride was added. The reaction mixture was stirred at -78 °C for one hour, then 0.7 mL (5.0 mmol) of triethylamine was added. Stirring was continued at -78 °C for another two hours. The temperature was then slowly raised to room temperature. The reaction mixture was washed three times with 60 mL portions of brine. The organic layer was separated and dried over anhydrous magnesium sulfate, concentrated and the residue was purified by flash chromatography (elution with hexane/EtOAc 5:1) to obtain 24.2 mg (88.6%) 1-[3-benzyloxy-2-(16-oxohexadecyloxy) propanoxy]-32-[(1-benzyloxy-methyl)-2-(16-oxohexadecyloxy)-ethoxy]-16-p-toluenesulfonyldotridecane **121.**

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.24 (br., 102 H, 51×CH_2), 1.57 (m, 12 H, 6×CH_2), 2.41 (t, 4 H, J= 5.56 Hz, 2×CH_2-CHO), 2.44 (s, 3 H, $PhCH_3$), 2.89 (m, 1 H), 3.40-3.59 (m, 18 H), 4.55 (s, 4 H, OCH_2Ph), 7.30 (m, 6 H), 7.43 (m, 6 H), 7.74 (d, 2 H, J= 8.28 Hz), 9.76 (t, J=1.88 Hz, 2H, CHO).

^{13}CNMR (400 MHz, in $CDCl_3$) δ 22.09, 26.79, 27.92, 29.17, 29.29, 29.37, 29.44, 29.53, 29.60, 29.65, 29.68, 29.73, 30.11, 30.32, 43.93, 70.29, 70.62, 70.71, 71.67, 73.69, 125.89, 127.50, 128.80, 129.70, 138.45, 204.0.

IR ($CDCl_3$, cm^{-1}) 2927, 2855, 1727,1, 1527.2, 1451, 1302, 1114.

Cyclohexadecene (122)[66-68]

To a 500 mL three neck flask equipped with a condenser was added 2.50 g $TiCl_3$ and 50 mL of dry DME. The reaction mixture was stirred under reflux conditions under nitrogen for 50 h 3.1 g of Zn-Cu and 120 mL of DME were added and stirring was continued under nitrogen for another 12 h Then 0.10 g (0.40 mmol) of 1,16 hexadecanedial **119** in 50 mL of DME was added by a syringe pump during a 12 h period. The reaction mixture was stirred for a further 24 h. The reaction mixture was finally diluted with distilled hexane and filtered through silca gel. The resulting solution was concentrated and the residue was purified by flash chromatography (elution with hexane) to obtain cyclohexadecenes **122** (cis and trans), 0.0798 g (80.0%).

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.28 (br. 24 H), 2.05 (m, 4 H), 5.35 (m, 2 H).

^{13}C NMR (400 MHz, in $CDCl_3$) d 14.14, 22.71, 23.51,24.09, 25.03, 25.41, 27.46, 29.38, 29.71, 31.65, 31.94, 131.65.

IR ($CDCl_3$, cm^{-1}) 2926.4, 2854.3, 1601.5, 1463.5, 1377.2, 971.7.

MS (m/e) 28, 41, 55, 70, 82, 83, 96, 109, 123, 127, 137, 152, 165, 193, 222 (M^+).

Compound 123

To a 250 mL two neck flask equipped with a condenser was added 0.50 g (33.5 mmol) $TiCl_3$, 0.50 g (7.7 mmol) of Zn-Cu and 20 mL of dry DME. The reaction mixture was stirred under reflux conditions under nitrogen for 1 h Then 0.020 g (0.080 mmol) of dialdehyde **121** in 30 mL of DME was added by a syringe pump during a 6 h period. The reaction mixture was stirred for a further 12 h at 80 °C. The reaction mixture was finally diluted with distilled pentane and filtered through silca gel. The resulting solution was concentrated and the residue was purified by flash chromatography (elution with hexane) to obtain 0.002 g (10%) of, possibly, compound **123**.

^1H NMR (400 MHz, in $CDCl_3$) δ 25 (br. 98 H), 1.55 (m, 12 H), 2.04 (m, 4 H), 2.44 (s, 3 H), 2.98 (m, 1 H), 3.40~3.66 (m, 18 H), 4.55 (s, 4 H), 5.37 (m, 2 H), 7.30 (m, 10 H), 7.45 (d, 2 H, J=7.48 Hz), 7.75 (d, 2 H, J=7.88 Hz).

Hexadecanal (116)[88]

To a 50 mL round-bottom flask was added 0.48 g (1.0 mmol) of 16-trityloxyhexadecane **115** and 0.17 g (0.5 mmol) of triphenyl carbenium tetrafluoroborate in 10 mL of dry methylene chloride. The reaction mixture was stirred at room temperature under nitrogen for 6 h, then 10 mL of water was introduced. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography (elution by hexane/EtOAc, 16 :1) to obtain the monoaldehyde **116** 0.124 g (52.1% yield).

^{1}H NMR (200 MHz, in $CDCl_3$) δ 0.85 (t, 3 H, CH_3), 1.23 (br., 24 H, CH_2), 1.52 (m, 2H), 2.40 (m. 2H), 9.74 (t, 1 H, CHO).

IR ($CDCl_3$, cm^{-1}) 2927, 2854, 1721.3.

Monoaldehyde (117)[88]

To a 50 mL round-bottom flask was added 29.8 mg (0.0154 mmol) of 1-[3-benzyloxy-2-(16-trityloxyhexadecyloxy) propanoxy]-2-[(1-benzyloxy-methyl)-2-(16-trityloxyhexadecyloxy)-ethoxy]-16-p-toluenesulfonyl-dotridecane **113** and 12.0 m g (0.04 mmol) of triphenyl carbenium tetrafluoroborate in 10 mL of dry methylene chloride. The reaction mixture was stirred at room temperature under nitrogen for 4 h, then 10 mL of water was introduced. The organic layer was separated dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (elution by hexane/EtOAc, 4 :1) to a **117** 0.058 g (41.7% yield).

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.24 (br., 102 H), 1.52 (m, 13 H), 2.41 (t, 2H, J=5.60 Hz), 2.44 (s, 3 H), 2.89 (m, 1 H), 3.4-3.6 (m, 20 H), 4.55 (s, 4 H) 7.35-7.45 (m, 12 H), 7.79 (d, 2H, J= 8.2 Hz), 9.80 (t, 1 H, CHO).

IR ($CDCl_3$, cm^{-1}) 3450 (OH), 3100, 2927, 2854, 1722.2, 1489.

16-Trityloxyhexadecyl-p-toluenesulfone (110)[85,86]

To a 50 mL round-bottom flask was added 2.30 g (3.77 mmol) of 1-iodo-16-trityloxyhexadecane **91**, 1.34 g (7.50 mmol) of sodium-p-toluenesulfinate salt, 0.32 g (1.0 mmol) of tetrabutylammonium bromide, and 20 mL of a mixture of 1:1:2 benzene: acetone : water.

The reaction mixture was stirred under reflux conditions for 48 h, then extracted with ether (3X30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash chromatography (elution with hexane/EtOAc 7:1) to obtain 16-trityloxyhexadecyl-p-toluenesulfone **110**, 1.88 g (78.0%), as a viscous liquid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.23-1.26 (br., 24 h, CH_2), 1.62 (m, 4 H), 2.43 (s, 3 H), 3.03 (t, 2 H, J=6.7 Hz), 3.07 (t, 2 H, J= 6.64 Hz), 7.42-7.47 (m, 17 H), 7.76 (d, 2H, J= 8.27 Hz).
IR ($CDCl_3$, cm-^{1}) 3087, 3061.5, 3033.6, 2926.9, 2864.9, 1598.4, 1487.0, 1465.7, 1448.6, 1404, 1381, 1324, 1239, 1150, 1089, 1072, 1033.

16-Chloro-1-benzyloxyhexadecane (107)[37]

To a 50 mL round-bottom flask was added 1.00 g (3.61 mmol) of 16-chlorohexadecanol **82**, 0.18 g (7.2 mmol) of sodium hydride and 10 mL of THF. The reaction mixture was stirred at room temperature for 3 h, then 0.68 g (3.97 mmol) of benzyl bromide was added. Stirring was continued at room temperature for another 24 h. The reaction mixture was then diluted with 10 mL of ether and filtered through celite. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by radial chromatography (elution with hexane/EtOAc 40:1) to obtain 16-chloro-1-benzyloxyhexadecane **107,** 1.31 g (90.2%), as a solid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.26 (br., 24 H, CH_2), 1.58 (m, 2 H), 1.82 (m, 2 H), 3.46 (t, 2 H, J=6.6 Hz) 3.53 (t, J=6.7 Hz, 2 H), 4.51(s, 2 H), 7.33 (m, 5 H).

IR ($CDCl_3$, cm-^{1}) 3087.6,3062.7, 3032.7, 2927, 2855, 1598.2, 1492.1, 1448.9, 1315.6, 1301.7, 1146, 1088.

16-Iodo-1-benzyloxyhexadecane (108)[81]

To a 50 mL round-bottom flask was added 1.31 g (3.61 mmol) of 16-chlorobenzyloxyhexadecane **107**, 5.40 g (36.1 mmol) of sodium iodide and 20 mL of 2-butanone. The reaction mixture was stirred under reflux conditions for 24 h, then cooled to room temperature, diluted with 40 mL of ether, filtered and dried over anhydrous sodium sulfate. The resulting solution was concentrated and purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 16-iodo-1-benzyloxyhexadecane **108**, 1.36 g (82.4%), as a solid.

^{1}H NMR (200 MHz in $CDCl_3$) δ 1.26 (br, .24 H, CH_2) 1.58 (m, 2 H), 1.82 (m, 2 H), 3.18 (t, 2 H, J=7.0 Hz) 3.46 (t, 2 H, J=6.6 Hz), 4.51 (s, 2 H), 7.33 (m, 5 H).

IR ($CDCl_3$, cm-^{1}) 3080, 3062.7, 3033, 2928, 2855, 1597, 1492.1, 1448, 1314, 13012, 1146, 1089.

16-Benzyloxyhexadecanal (109)[97,98]

To a 100 mL rounded-bottom flask was added 0.23 g (0.50 mmol) of 16-iodo-1-benzyloxyhexadecane **108**, 0.084 g (1.0 mmol) of sodium bicarbonate, 0.11 g (0.75 mmol) of sodium iodide, and 2 mL (4 mL/mmol) of DMSO. The reaction mixture was heated to 115 °C and stirred at this temperature for 3 h, then was dissolved in 50 mL of ether and washed by 40 mL of water. The organic layer was collected, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 62 mg (35.7%), 16-benzyloxyhexadecanal **109** as a solid.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.26 (br., 24 H, CH_2) 1.58 (m, 4 H), 2.41(t, 2 H, J=7.26 Hz) 3.46 (t, 2 H, J=6.6 Hz), 4.51(s, 2 H), 7.23-7.35 (m, 4 H), 9.76 (t, 1 H, J=1.72 Hz).

1,16-hexadecanedial(119)[90]

To a 100 mL round bottom flask was added 0.10 mL (1.15 mmol) of oxalychloride and 30 mL of freshly distilled methylene chloride. The mixture was cooled to −78 °C, 0.19 mL (2.14 mmol) of DMSO was introduced through a syringe, and, after stirring at −78 °C for 20 min., 0.41 (0.18 mmol) of 1,16-hexadecadiol **118** dissolved in 140 mL of methylene chloride was also added. The reaction mixture was stirred at −78 °C for one hour, then 0.7 mL (5.0 mmol) of triethylamine was added. Stirring was continued at −78 °C for another two hours. The temperature was raised slowly to room temperature. The reaction mixture was washed three times with 60 mL portions of brine. The combined organic layers were dried over anhydrous magnesium sulfate, concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc 5:1) to obtain 0.24 g (59.0%) of 1,16-hexadecanedial **119**, mp 44-45 °C.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.26 (br., 24 H, CH_2), 1.58 (m, 4 H), 2.41(t, 4 H, J=7.26 Hz), 9.76 (t, 2 H, J=1.72 Hz).

IR ($CDCl_3$, cm-^{1}) 2927.4, 2875, 1736, 1465, 1230.

Octadecane (125) [91]

Magnesium powder (0.34 g, 13.8 mmol) in a 25 mL round-bottom flask was washed with freshly dried ether, then dried by vacuum and stirred under nitrogen for 16 h. 1,2 dibromomethane (0.56 g, 3.0 mmol) in 2.0 mL of freshly distilled THF was added, and after the reaction started, 1.0 g (3.4 mmol) of 1-chlorooctadecane **124** in 4.0 mL of THF was slowly added by a syringe. The reaction mixture was stirred under nitrogen and refluxed for 65 h, then quenched by adding 10 mL of saturated aqueous NH_4Cl, followed by refluxing for 1 h. The mixture was extracted with ether, which was concentrated. The residue was analyzed by GC-MS. According to GC the ratio of 1-chlorooctadecane **124** (starting material) to octadecane

125 (product) is 2.34 to 1.

GC-MS: Peak #1 (m/e) 41, 57, 71, 85, 97, 111, 127, 141, 169, 183, 197, 211, 225, 254 (M^+) Peak #2 (m/e) 43, 57, 71, 91, 105, 125, 147, 161, 189, 203, 217, 252, 288 (M^+).

Hexadecane (126) [91]

Magnesium powder (0.640, 26.18 mmol) in a 25 mL round-bottom flask was washed with freshly dried ether, then dried by vacuum and stirred under nitrogen for 16 h. 1,2 dibromomethane 0.56 g (3.0 mmol) in 2.0 mL of freshly distilled THF was added, and after the reaction started, 2.0 g (6.5 mmol) of 1-bromohexadecane **38** in 4.0 mL of THF was slowly added by a syringe. The reaction mixture was stirred under nitrogen and refluxed for 65 h, then quenched by adding 10 mL of saturated aqueous NH_4Cl, followed by refluxing for 1 h. The mixture was extracted with ether and concentrated. The residue was analyzed by GC-MS. According to GC the ratio of 1-bromohexadecane **38** (starting material) to hexadecane **126** (product) is 1 to 1.78.

GC-MS: Peak #1 (m/e) 29, 43, 57, 71, 85, 97, 111, 126, 141, 155, 169, 183, 226 (M^+). Peak #2 (m/e) 43, 57, 71, 85, 109, 135, 137, 163, 177, 193, 225, 233, 249.

16-*p*-toluenesulfonyl-1-trityloxy-32-benzyloxydotridecane(111)[84,87]

To a 10 mL round-bottom flask was added 54.3 mg (0.086 mmol) of 16-trityloxyhexadecyl-p-toluenesulfone **110** and 1 mL of freshly distilled THF. The reaction mixture was cooled to -78 °C for 10 min, then 0.19 mL of 1.70 M n-BuLi in hexanes was added by syringe. Stirring was continued at -78 °C for another 40 min, then 0.38 g (2.15 mmol) of HMPA was added by syringe and the mixture was stirred for another 20 min. Then, 16-iodobenzyloxy-hexadecane **108** (73.7 mg, 0.160 mmol) in 1 mL of THF was introduced. After stirring for another 2 h at -78 °C, the reaction was quenched by adding 0.5 mL of methanol, and the temperature was raised to room temperature. The reaction mixture was diluted with 10 mL of ether and washed with saturated aqueous ammonium chloride. The organic layer was separated and dried over anhydrous sodium sulfate and concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc 50 :1) to obtain 16-p-toluenesulfonyl-1-trityloxy-32-benzyloxydotridecane **111**, 29.8 mg (73.1% yield), as an oil, plus 14.6 mg (26.9%) of recovered starting sulfone compound **110**.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.24 (br., 54 H, CH_2), 1.59 (m, 4 H), 2.441 (s, 3 H), 2.89 (m, 1 H), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.46 (t, 2 H, J=6.6 Hz, CH_2OBn), 4.51 (s, 2 H), 7.21-7.35 (m, 15 H), 7.38-7.41(m, 6 H), 7.76 (d, 2 H, J=8.07 Hz).

IR ($CDCl_3$, cm-^{1}) 3062.7, 2928, 2855, 1598.2, 1492.1, 1448.9, 1315.6, 1301.7, 1146, 1088, 908.

16-*p*-toluenesulfonyl-17-hydroxy-1-trityloxy-32-benzyloxydotridecane (112)[84,87]

To a 100 mL round-bottom flask was added 0.45 mL (3.2 mmol) of diisopropylamine and 5 mL of dry THF, the reaction mixture was cooled to −78 °C and stirred for 20 min. N-BuLi in hexanes (1.3 mL, 2.5 M) was then added through a syringe. Stirring was continued at −78 °C for another 20 min, then 0.20 g (0.30 mmol) of 16-trityloxyhexadecyl p-toluenesulfone **110** in 5 mL of THF was added through a syringe. After stirring for another 40 min. at −78 °C, 0.11 g (0.32 mmol) of 16-benzyloxyhexadecanal **109** in 5 mL of THF was added. The reaction was stirred for further 13.5 h then quenched by adding 1.0 mL of 2 N aqueous HCl. The temperature was then raised to room temperature and the reaction mixture was diluted with 10 mL of ether and washed with saturated aqueous ammonium chloride. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated, and the residue was purified by flash chromatography (elution with hexane/EtOAc 8 :1) to obtain 16-p-toluenesulfonyl-17-hydroxy-1-trityloxy-32-benzyloxydotridecane **112**, 92.1 mg (16.5%), as an oil, and to recover 51.0 mg of starting sulfone compound **110**.

^{1}H NMR (200 MHz, in $CDCl_3$) δ 1.25 (br., 48 H, CH_2), 1.58-1.60 (m, 8 H), 2.441 (s, 3 H), 2.99 (m, 1 H), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.37-3.49 (t, 2 H, J=6.6 Hz, CH_2OBn), 4.00 (m, 1 H), 4.51 (s, 2 H), 7.17-7.46 (m, 21 H), 7.75-7.79 (d, 2H, J=8.1 Hz).

Hexacosane (135)[70]

1.2 g (50 mmol) of magnesium turning was added into a 100 mL round bottom three-neck flask containing a magnetic stirring bar, and stirred under argon for 24 h Then 3.05 g (10 mmol) of 1-bromohexadecane **38** dissolved in 20 mL of dried THF was slowly added through a dropping funnel at 0 °C. The reaction mixture was stirred at room temperature for another 40 hours to obtain the hexadecyl magnesium bromide **133**. In the meantime, to another 100 mL three-neck round bottom flask was added 1.11 g (5.0 mmol) of iodododecane **134** and 20 mL of dry THF, and this solution was cooled to −78 °C. Then the preformed Grignard reagent **133** was transferred to the cold reaction solution through teflon tubing by Ar pressure, followed by 10 mL of 0.1 M Li_2CuCl_4 in THF solution. The reaction was stirred at −78 °C for one hour, followed by stirring at 0 °C for another 5 hours and another 24 hours at room temperature. The reaction was quenched by adding 10 mL of saturated aqueous NH_4Cl. The THF was diluted with 100 mL of ether and the ethereal solution was washed three times with 60 mL portions of brine. The combined organic layers were collected and dried over anhydrous magnesium sulfate and concentrated. The side product hexadecane **126**, which was made from the excess starting bromohexadecane **38** was removed by reduced pressure distillation and the residue was recrystallized from ether to obtain 1.82 g (98% yield) hexacosane **135** as a solid, mp 56.5 -58 °C (lit: Beil. **1**.179).

^{1}H NMR (400 MHz, in $CDCl_3$) δ 0.88 (t, 6 H), 1.25 (br., 48 H).
MS (m/e) 41, 57 (base peak), 71, 85, 99, 113, 141, 155, 169, 183, 211, 225, 239, 267, 281, 295, 309, 366 (M^+).

Methyl 16-bromo-hexadecanoate (127)[99]

To a 250 mL round bottom flask was added 4.0 g (14.0 mmol) of methyl 16-hydroxyhexadecanoate **86**, 4.04 g (15.4 mmol) of triphenylphosphine and 60 mL of dry methylene chloride. The reaction mixture was cooled to 0 °C., 2.62 g (15.4 mmol) of N-bromosuccinimide was added, and the mixture was stirred at 0 °C for 1 h and at room temperature for another 5 h. Then methylene chloride was removed by rotary evaporation and the residue was purified through a silica gel pad (elution with pure hexane) to obtain 4.80 g

(98.2%) of methyl, 16-bromohexadecanoate **127**.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 22 H), 1.54 (m, 2 H), 1.87 (m, 2 H), 2.29 (t, 2 H, J=7.4 Hz), 3.41 (t, 2 H, J=6.84 Hz), 3.66 (s, 3 H).

16-Bromohexadecanol (128)[78]

Preparation of the alane solution[78]: To dry aluminum trichloride (1.87 g 14.0 mmol) in a 250 mL round bottom flask was added dropwise 35 mL of freshly distilled ether. The solution boiled spontaneously during the addition of the ether. The solution was then transferred to another flask which already contained lithium aluminum hydride (0.53 g, 14.0 mmol) in 35 mL of ether to obtain the alane reagent. Then 4.80 g (13.7 mmol) of methyl 16-bromohexadecanoate **127** dissolved in 50 mL of methylene chloride was added dropwise to the alane solution. The reaction mixture was stirred at -78 °C for 3 h, then diluted with 70 mL of 10 % aqueous tartaric acid. The ethereal layer was separated and the aqueous layer was extracted with three 100 mL portions of ether. The combined organic layers were washed twice with 200 mL portions of brine, then dried over anhydrous sodium sulfate. After the solution was filtered and concentrated, the residue was purified by flash chromatography (elution with hexane/EtOAc 6:1) to give 16-bromohexadecanol **128**, 3.78 g (85.4%), as white solid; mp. 49-50.5 °C .

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 24 H), 1.55 (m, 2 H),1.87 (m, 2 H), 3.41 (t, 2 H, J=6.84 Hz), 3.65 (t, 2 H, J=6.48 Hz).

IR ($CDCl_3$, cm^{-1}) 3650, 2928, 2855, 1470, 1252, 1052.

Elemental analysis	Calculated:.	C 59.80; H 10.35
	Found:	C 59.90; H 10.19

16-Trityloxyhexadecyl bromide (130)[75]

To a 100 mL round bottom flask was added 2.13 g (6.63 mmol) of 16-bromo-hexadecanol **128** , 2.23 g (8.0 mmol) of triphenylmethyl chloride, 1.1 mL (8.0 mmol) of triethyl amine, 0.1 g of DMAP and 50 mL of dry DMF. The mixture was stirred under nitrogen at 80 °C for 4.5 h, then poured into 50 g of ice-water, and extracted three times with 50 mL portions of methylene chloride. The combined organic solutions were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporator and the residue was purified by flash chromatography (elution with hexane/EtOAc 20:1) to obtain 3.46 g (92.5%) of methyl 16-trityloxyhexadecanoate **130** as a solid, mp 49-51 °C.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.24 (br., 24 H), 1.61 (m, 2 H), 1.78 (m, 2 H), 3.03 (t, 2 H, J=6.7 Hz, CH_2OTr), 3.46 (t, 2 H, J= 6.7 Hz), 7.28 (m, 9 H), 7.44 (m, 6 H).

IR ($CDCl_3$, cm^{-1}) 3087, 3024, 3061, 2927, 2854, 1597, 1490, 1465, 1448, 1386, 1314, 1220, 1183, 1152, 1087, 1072, 1033.

16-(2-Tetrahydropyranyloxy)-hexadecyl bromide (129)[94]

To a 100 mL round bottom flask was added 2.27 g (7.06 mmol) of 16-bromohexadecanol **128** 1.48 g (17.7 mmol) of 1,2-dihydropyran and 50 mL of dry methylene chloride. The mixture was then cooled to 0 °C and 0.1 g of p-toluenesulfonic acid was introduced. The reaction mixture was stirred at room temperature for another 3 h, then washed with 30 mL of saturated aqueous $NaHCO_3$ and 30 mL of brine.

The resulting organic solution was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 10 :1) to obtain 2.12 (92.5% yield) of 16-(2-tetrahydropyranyloxy)-hexadecyl bromide **129** as a solid, mp 35-36 °C.

^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.25 (br., 22 H), 1.43 (m, 2 H), 1.55 (m, 6 H), 1.61 (m, 1 H), 1.85 (m, 3 H), 3.42 (m, 3 H), 3.52 (m, 1 H), 3.73 (m, 1 H), 3.86 (m, 1 H), 4.57 (dd, 1 H).

IR ($CDCl_3$, cm^{-1}) 2927.9, 2854.7, 1465.7, 1455, 1441, 1366, 1353.3, 1323, 1275, 1260, 1200, 1184, 1134, 1119, 1016.

MS (m/e) 41, 55, 69, 85 (base peak), 115, 135, 137, 177, 179, 191, 201, 207, 209, 333, 335, 403, 405.

Elemental analysis	Calculated:.	C 62.26; H 10.19
	Found:	C 62.60; H 10.16

Tetrahydropyranyloxyhexadecane (131)[91,92]

1.2 g (50 mmol) of magnesium turning was added into a 50 mL round bottom three-neck flask and stirred under argon for 24 h.

Then 0.38 g (0.94 mmol) of 16-(2-tetrahydro-pyranyloxy)-1-bromohexadecane **129** dissolved in 10 mL of dried THF was slowly added through a dropping funnel at 0 °C. The reaction mixture was stirred at room temperature for another 24 hours to obtain the Grignard reagent. The reaction was quenched by adding 10 mL of saturated aqueous NH_4Cl. The THF solution was layer was separated, evaporated to dryness on the rotary evaporator, and the residue was dissolved in 100 mL of ether. The ethereal solution was washed three times with 60 mL portions of brine. The organic layer was collected and dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with Hexane/EtOAc 30 :1) to obtain the 1-(2-tetrahydropyranyloxy)-hexadecane **131** as the main product (94.0 %)

^{1}H NMR (400 MHz, in $CDCl_3$) δ 0.88 (t, 3 H, J=6.24 Hz), 1.25 (br., 26 H), 1.58 (m, 6 H), 1.71 (m, 1 H), 1.84 (m, 1 H), 3.37 (m, 1 H), 3.50 (m, 1 H), 3.73 (m, 1 H), 3.86 (m, 1 H), 4.57 (dd, 1 H).

1-Tetrahydropyranyloxy-32-trityloxy-dotriacontane(138).[70,100]

Magnesium turnings (2.4 g, 100 mmol) were added into a 50 mL round bottom three-neck flask containing a magnetic stirring bar and stirred under argon for 24 h. Then 5 mL of dried THF was added, followed by 0.1 mL of 1,2-dibromoethane, which caused the reaction solution to boil. Then, 0.734 g (1.81 mmol) of 16-(2-tetrahydropyranyloxy)-1-bromohexadecane **129** dissolved in 10 mL of dried THF was slowly added through a dropping funnel at room temperature. The reaction mixture was stirred at room temperature for another 6 hours to obtain the Grignard reagent **137**. In the meantime, to another 50 mL three-neck round bottom flask was added 0.50 g (0.86 mmol) of 16-trityloxyl-1-iodohexadecane **91** and 10 mL of dry THF, and this solution was cooled to −78 °C. Then the preformed Grignard reagent was transferred to the cold reaction solution through teflon tubing by pressure, followed by adding 0.25 mL of 0.1 M Li_2CuCl_4 in THF solution. The reaction was stirred at −78 °C for one hour, then at room temperature for another 16 hours. The reaction was quenched by adding 10 mL of saturated NH_4Cl aqueous solution. The THF solution was separated, evaporated to dryness on the rotary evaporator, and the residue was dissolved in 100 mL of ether. The ethereal solution was washed three times with 60 mL portions of brine. The organic layer was collected and dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with Hexane/EtOAc 30 :1) to obtain 0.46 g (66.1% yield) of 1-(2-tetrahydropyranyloxy)-32-trityloxy dotriacontane **138** as a solid, mp 66-67.2 °C. and a trace (4.8%) amount of homo-coupling product 1,32-di-(2-tetrahydropyranyloxy)-dotriacontane **139.**

^1H NMR of **138** (400 MHz, in $CDCl_3$) δ 1.25 (br., 56 H), 1.58 (m, 8 H), 1.70 (m, 1 H), 1.85 (m, 1 H), 3.03 (t, 2 H, J=6.6 Hz), 3.40 (m, 1 H), 3.50 (m, 1 H), 3.73 (m, 1 H), 3.87 (m, 1 H), 4.57 (dd, 1 H), 7.20-7.33 (m, 9 H), 7.45 (d, 6 H, J=7.52).

^{13}C NMR (400 MHz, in $CDCl_3$) δ 25.5, 26.0, 26.2, 29.72, 29.90, 31.20, 61.5, 62.1, 67.7, 99.3, 126.7, 127.67, 128.79, 144.6.

IR (cm^{-1}, in CCl_4) 2927.6, 2854, 1560, 1445.1, 1236, 1031, 996.

Elemental analysis	Calculated.	C 83.11; H 10.95 .
	Found:	C 82.91; H 10.88.

^{1}H NMR of compound **139** (400 MHz, in $CDCl_3$) δ 1.25 (br., 56 H), 1.58 (m, 12 H), 1.72 (m, 2 H), 1.82 (m, 2 H), 3.40 (m, 2 H), 3.50 (m, 2 H), 3.73 (m, 2 H), 3.87 (m, 2 H), 4.57 (dd, 2 H).

1-O-(16-hydroxyhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzylglycerol (140)[89]

To a 50 mL round bottom flask was added 0.20 g (0.20 mmol) of 1-O-(16-trityloxy-hexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **101**, 0.05 g of p-toluene sulfonic acid and 20 mL of methylene chloride. The reaction mixture was refluxed for 30 min, then cooled to room temperature. The reaction mixture was diluted by adding another 20 mL of methylene chloride and washed with 20 mL of saturated aqueous sodium bicarbonate and 20 mL of brine. The organic solution was separated, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 5 :1) to obtain 0.15 g (94.5% yield) of 1-O-(16-hydroxylhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **140** as a viscous liquid.

^{1}H NMR of (400 MHz, in $CDCl_3$) δ 1.25 (br., 48 H), 1.55 (m, 7 H), 1.83 (m, 2 H), 3.18 m (t, 2 H, J=7.08 Hz), 3.41~3.65 (m, 11 H), 4.55 (s, 2 H), 7.32 (m, 5 H).

IR (cm^{-1}, in CCl_4) 3690, 3010, 2928, 2855, 1605, 1565, 1460, 1110.

1-O-[16-(2-tetrahydronpyranyloxyhexadecyl)]-2-O-(16-iodohexadecyl)-3-O-benzylglycerol (141)[94]

To a 50 mL round bottom flask was added 0.15 g (0.1.8 mmol) of 1-O-(16-hydroxyhexadecyl)-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **140**, 0.070 mL (0.75 mmol) of 1,2-dihydropyran and 20 mL of dry methylene chloride. The mixture was cooled to 0 °C, 0.05 g of p-toluenesulfonic acid was introduced, and the reaction mixture was stirred at room temperature for another 3 h. The organic solution was washed with 30 mL of saturated aqueous $NaHCO_3$ and 30 mL of brine, then dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 20 :1) to obtain 0.14 (89.2% yield) of 1-O-[16-(2-tetrahydro pyranyloxy- hexadecyl)]-2-O-(16-iodohexadecyl)-

3-O-benzyl glycerol **141** as a viscous liquid.

^{1}H NMR of (400 MHz, in CDCl$_3$) δ 1.25 (br., 48 H), 1.55 (m, 10 H), 1.59 (m, 1 H), 1.86 (m, 3 H), 3.18 (t, 2 H, J=7.1 Hz), 3.41~3.65 (m, 11 H), 3.72 (m, 1 H), 3.87 (m, 1 H), 4.55 (s, 2 H), 4.56 (dd, 1 H), 7.34 (m, 5 H).

IR (CDCl$_3$, cm^{-1}) 3011, 2927.9, 2854.7, 1655, 1560, 1465.7, 1455, 1441, 1366, 1230, 1134, 1120.

1-O-[16-(2-tetrahydropyranyloxyhexadecyl)]-2-O-(16-bromohexadecyl)-3-O-benzylglycerol (142)[95]

To a 50 mL round bottom flask was added O.14 g (0.16 mmol) of 1-O-[16-(2-tetrahydropyranyloxyhexadecyl)]-2-O-(16-iodohexadecyl)-3-O-benzyl glycerol **141**, 0.10 g (0.97 mmol) of sodium bromide and 12 mL of a 2:1 mixture of N, N dimethylformamide and dibromomethane. The reaction mixture was stirred at 100 °C for 12 h, then cooled to room temperature. The reaction mixture was diluted by adding another 50 mL of methylene chloride then washed with three portions of 20 mL of brine. The organic solution was separated, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 20 :1) to obtain 0.115 g (88.7% yield) of 1-O-[16-(2-tetrahydronpyranyloxyhexadecyl)]-2-O-(16-bromohexadecyl)-3-O-benzylglycerol **142** as a viscous liquid.

^{1}H NMR of (400 MHz, in $CDCl_3$) δ 1.25 (br., 48 H), 1.55 (m, 10 H), 1.58 (m, 1 H), 1.86 (m, 3 H), 3.41~3.65 (m, 11 H), 3.73 (m, 1 H), 3.86 (m, 1 H), 4.55 (s, 2H), 4.57 (dd, 1 H), 7.33 (m, 5 H).

IR ($CDCl_3$, cm^{-1}) 3011, 2927.9, 2854.7, 1655, 1560, 1465.7, 1455, 1441, 1366, 1230, 1134, 1120.

Chapter 4

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