INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

U·M·I

University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600

Order Number 9325134

Synthesis of archaebacterial tetraether lipid models

Pan, Dongfeng, Ph.D.

City University of New York, 1993

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

SYNTHESIS OF ARCHAEBACTERIAL TETRAETHER LIPID MODELS

by

DONGFENG PAN

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1993

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

April 27, 1993
Date

Robert Bittman
Chair of Examining Committee

4/27/93
Date

Executive Officer

William Frost Berkowitz

Thomas H. Haines

Supervisory Committee

The City University of New York

Abstract

SYNTHESIS OF ARCHAEBACTERIAL TETRAETHER LIPID MODELS

by

DONGFENG PAN

Advisor: Professor Robert Bittman

Since it is difficult to obtain substantial amounts of archaebacterial tetraether lipids from natural sources, a synthetic strategy has been developed to prepare a simpler, acyclic, straight-chain tetraether model, 1,1'-di-*O*-(1,32-dotriacontanediyl)-2,2'-di-*O*-hexadecyl-3,3'-di-*O*-benzyl-bis-glycerol **18**. This coupling strategy may be applicable to the more difficult task of assembling the cyclic tetraether. The key steps of this synthetic strategy are (a) BF_3-catalyzed alcoholysis of glycidyl derivatives and (b) silver metal catalyzed Grignard reagent coupling method to connect two diether synthons to form the tetraether lipid.

ACKNOWLEDGMENTS

I would like to thank Professor William F. Berkowitz and Professor Robert Bittman for the intellectual and financial support which made completion of this work possible. My sincere appreciation to Professor Thomas H. Haines for his interest in my progress. I would like to thank Dr. Hoe-Sup Byun for his valuable discussions and suggestions. I am especially appreciative to Dr. 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 acknowledged. I would also especially like to thank Dr. George Axelrad for his help during my years at Queens College. Lastly, and of course not leastly, I gratefully acknowledge the patience and support of my family.

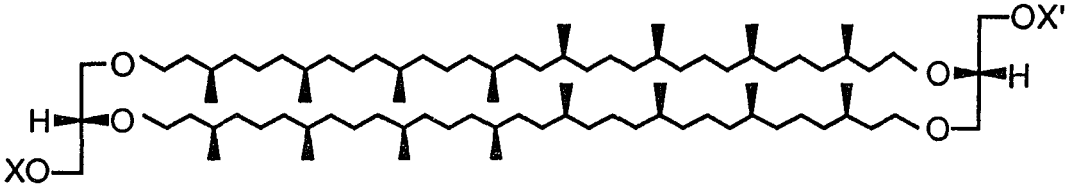
TABLE OF CONTENTS

CHAPTER 1

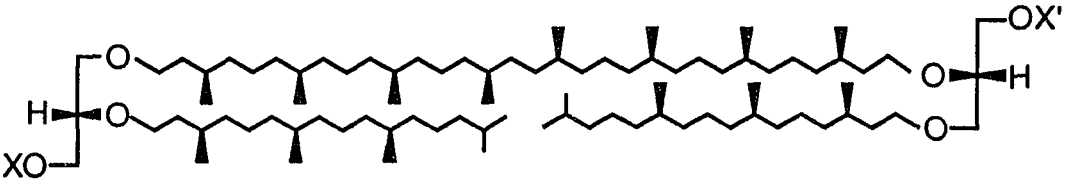
INTRODUCTION

A new approach to the synthesis of archaebacterial lipids

The discovery of the methanogenic, halophilic, and thermoacidophilic archaebacteria, which thrive in harsh environments, has stimulated research into the unique structural, biochemical, and physical properties of their membrane lipids.[1-15] The ability of these organisms to survive under extreme conditions such as high temperature (80-90 °C) and low pH (about 2)[2] suggests an important difference of stability compared with normal bilayer



1



2

Figure 1 X, X' = sugar or phosphate-containing group

membranes. Indeed, unique bipolar diglycerol tetraether lipids were separated and identified in archaebacteria, thermoplasma, sulfolobus, and

methanogens.[16-25]

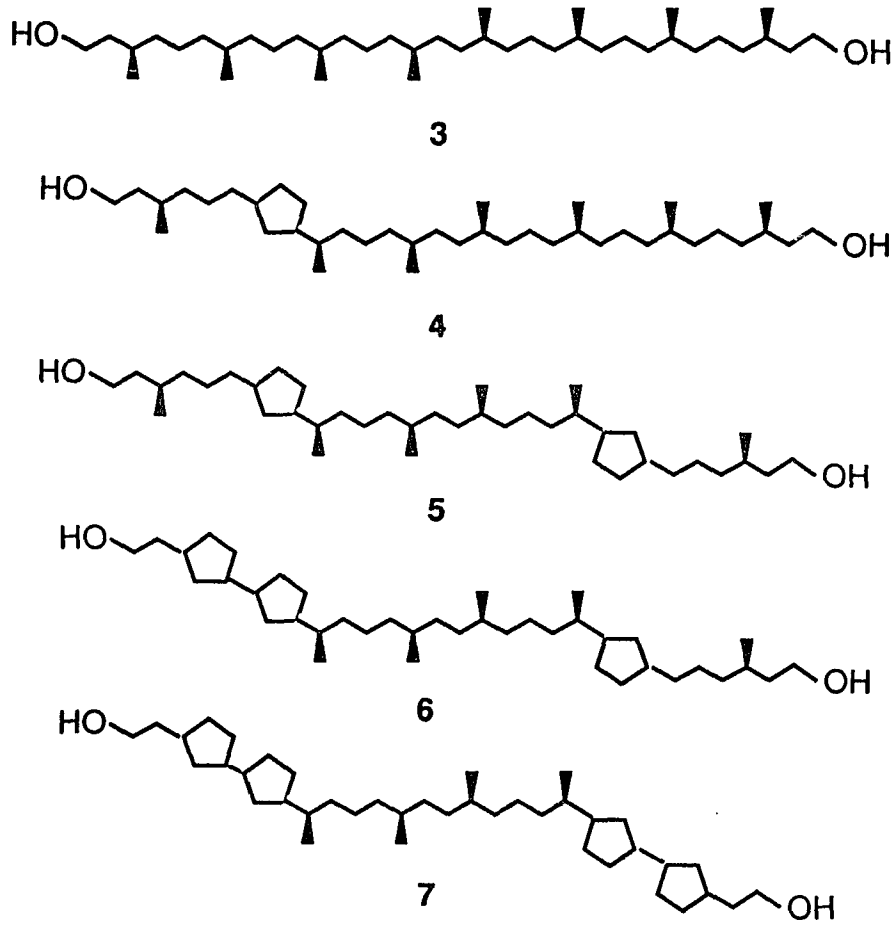


Figure 2

The tetraether lipids so far identified feature the unusual structure of C_{20}- or C_{40}-isoprenoid chains bonded through ether linkages to glycerols containing polar groups[26] (Figure 1). The two glycerol groups of the tetraethers **1** and **2** are connected by at least one hydrocarbon chain **3** (Figure 2).[27] The chain **3** may vary by containing up to four cyclopentane rings, originated by the formation of C-C bonds between methyl groups at 3, 7, 26, and 30 and methylenes at 6, 10, 23, and 27, respectively,[28-30] as shown in Figure 2. The

tetraethers in lipids of methanogenic bacteria[19-21] contain only acyclic biphytanyl chains **3**.

The absolute stereochemistry of the glycerol has been determined,[31] and the stereostructure of the C_{40}-diol **3** (biphytane-1,32-diol) has been established as (3*R*,7*R*,11*R*,15*S*,18*S*,22*R*,26*R*,30*R*)-3,7,11,15,18,22,26,30-octamethyldotriacontane-1,32-diol by synthesis.[27]

In recent years, liposomes have been studied extensively for their potential to serve as carriers for the delivery of drugs, antigens, hormones, enzymes, and other biological compounds.[32-35] The selective fusion of liposomes with particular kinds of cells is a promising means of controlling the delivery of drugs to target cells.

Monolayer membranes[36-38] formed from the diglycerol tetraether lipids reflect the uncommon resistance of archaebacteria to extreme environments.[39,40] Because of the stability of these monolayer membranes,[26,40,41] we expect that the bipolar derivatives of the tetraethers could be very useful as new materials for drug delivery. Since it is difficult to obtain these bacterial lipids from natural sources, there is much current interest in the chemical synthesis[40-44] and behavior of these lipids in membranes. Before the complex isoprenoid segment becomes readly available, the chemical synthesis and study of the properties of tetraether lipids have been limited to straight-chain models.

Before discussion of our work, all of the approaches to this kind of tetraether model examined by other groups are summarized in the following

section.

(1) The tetraether model **1 3** (Figure 3) of Kim and Thompson[44]

The overall yield from commercially available eicosanedioic acid **8** to 1,1'-*O*-eicosamethylene-2,2'-*O*-didecyl-*rac*-digycerol tetraether **1 3** was 2.8%.

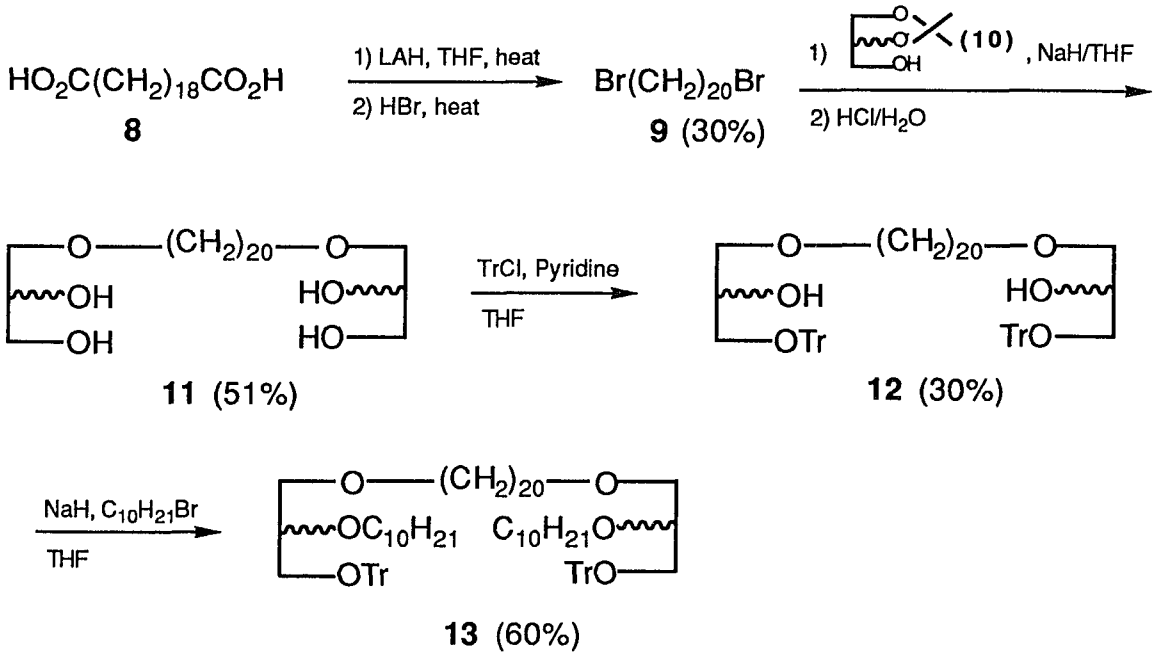


Figure 3

(2) The tetraether model **1 8** (Figure 4) of Yamauchi et al.[40]

The overall yield from 3-*O*-benzyl-*sn*-glycerol **1 4** to 1,32-dotriaconta-methylene bis(2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol) **1 8** was 11.7%.[45] 3-*O*-Benzyl-*sn*-glycerol **1 4** was made from D-mannitol in 4 steps in 50% overall yield. Furthermore, 1,32-dibromodotricosane **1 6** was synthesized in 9 steps from eicosanedioyl chloride in 46% overall yield.[42,46-48]

The procedure of Yamauchi et al.[40] (**14** to **18**) was repeated but in higher overall yield (22%) by Moss et al.[42]

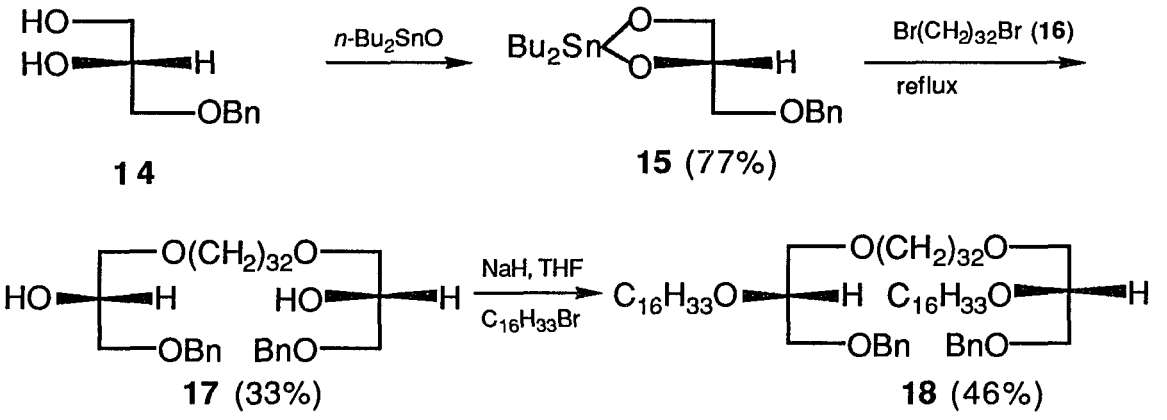


Figure 4

Recently, Yamauchi et al. reported the syntheses of tetraether model **22** (Figure 5) in overall yields of 2.5% (a) and 6.5% (b),[41,43] using essentially the same procedure as shown in Figure 4.

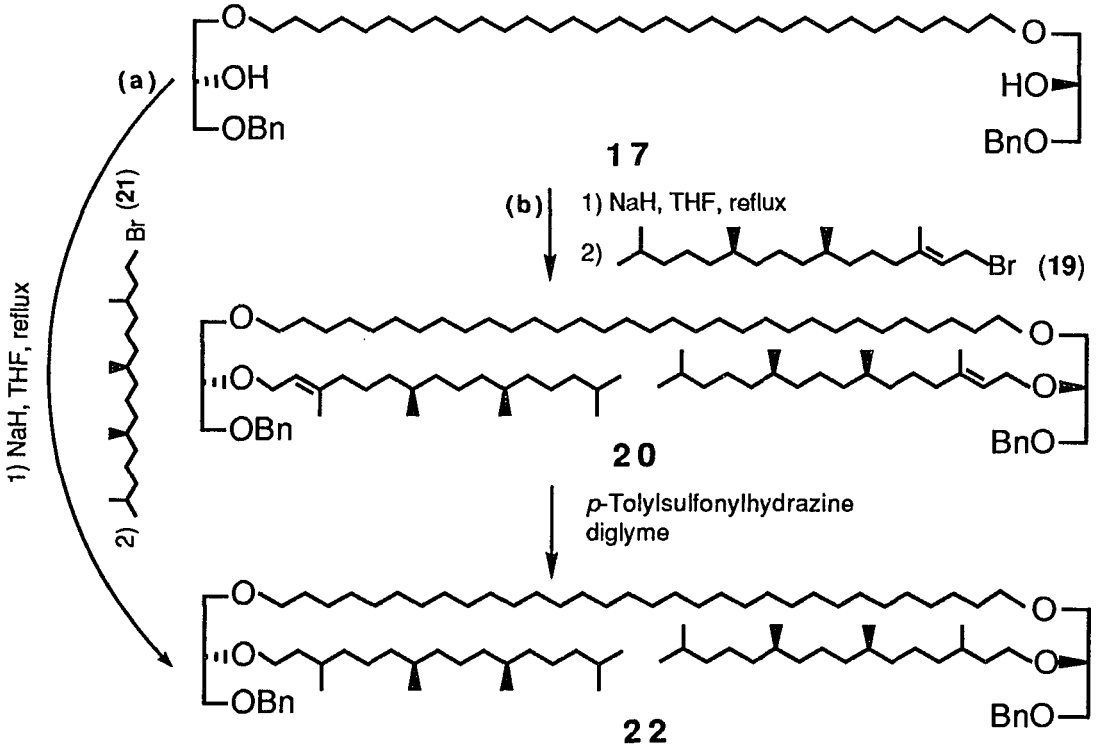


Figure 5

All of the previous lipid tetraethers have been prepared primarily by modifications of the Williamson ether synthesis, employing α,ω-dibromoalkanes, preparation of which has varied from one to several steps.

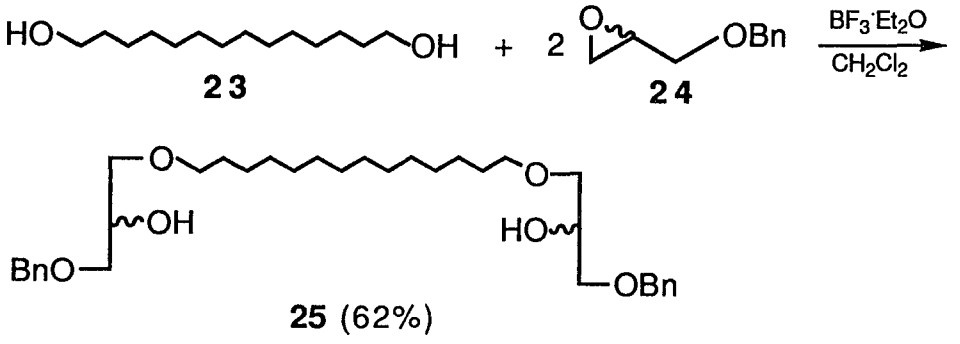


Figure 6

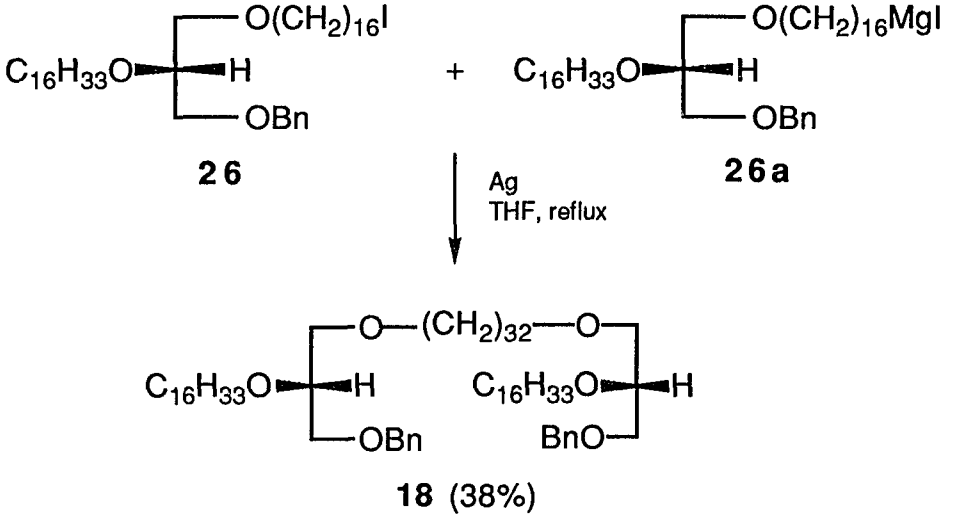


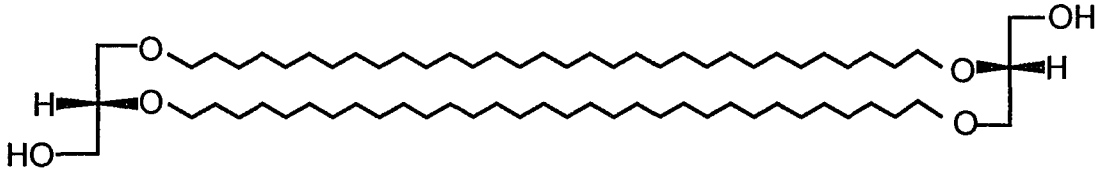
Figure 7

In this thesis, Bittman's procedure,[49-53] BF_3 etherate catalyzed ring opening of a glycidol derivative by an alcohol, was applied as an efficient and simple way to form the ether bond. As a mimic of the usual Williamson

approach, as shown in Figure 6, 1,14-tetradecanediol **23** was used to make model lipid diol **25**.

Finally, a coupling strategy has been developed and applied to a simpler, known, acyclic, straight-chain tetraether model **18** (Figure 7).[40]

This coupling strategy may be applicable to the more difficult task of assembling the cyclic tetraether **27**. The overall yield of **18** from commercially available 16-hydroxyhexadecanoic acid **60** (Scheme 7) in this procedure is 27%.



27

Authentic diol 3

A pure sample of authentic archaebacterial diol **3** has been isolated from frozen cells of *Methanobacterium thermoautotrophicum* (see experiment section) for two reasons: (1) to see if the cells could be used as a source of sufficient diol to enable us to synthesize cyclic tetraether **27**; (2) failing that, to provide us with an authentic sample for comparison with diol prepared by a totally synthetic route. In fact, the amount of diol obtained from the cells was too small to be considered as a primary source.

CHAPTER 2

RESULTS AND DISCUSSION

(a) Tetraether from *Methanobacterium thermoautotrophicum*

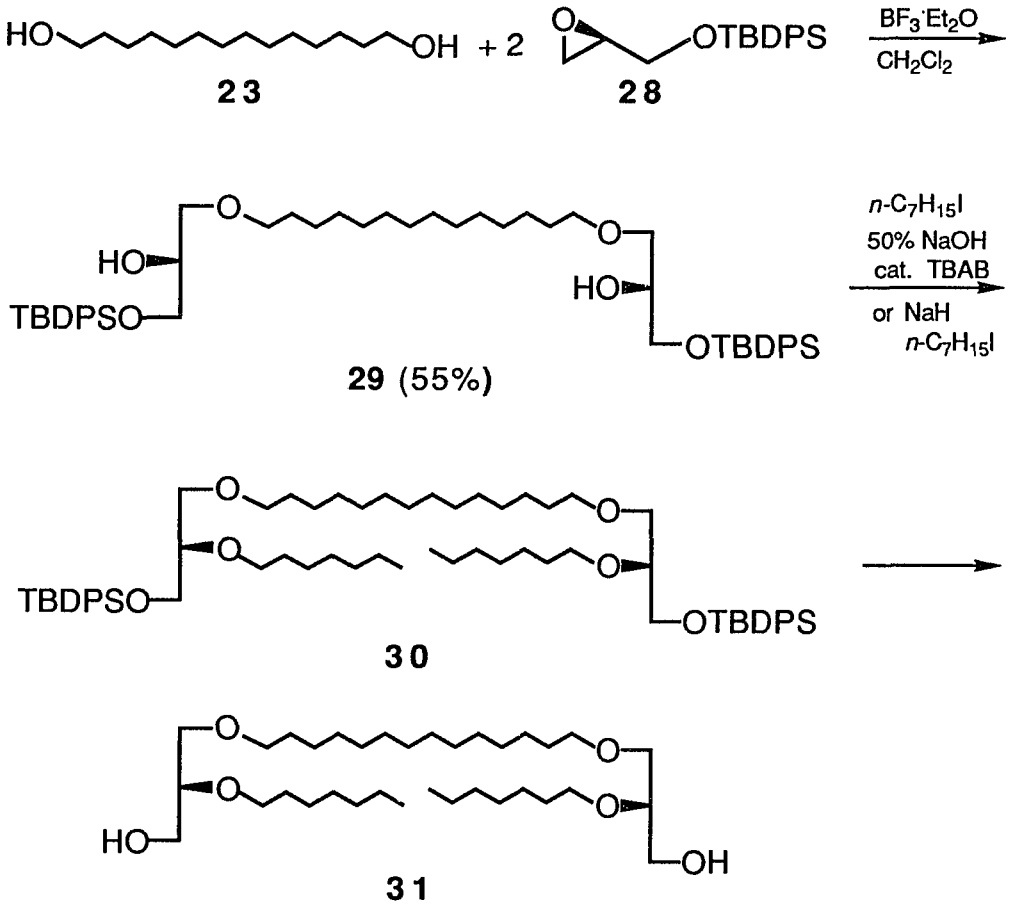
The percentage of water in frozen *M. thermoautotrophicum* cells[54] was determined. The cell mixture (2.04 g) was heated in an oil bath at 90 °C under vacuum for 6 h. Dehydrated cells (0.426 g) were obtained and the percentage of water of the frozen cell mixture was calculated to be 80%. Lipid extraction was performed by the method of Bligh and Dyer.[55] Following hydrolysis[56] dibiphytanyl diglycerol **1** was isolated and identified by spectra of high resolution (+) LISMS, 400-MHz ^{1}H NMR, 75 MHz ^{13}C NMR and IR. TLC comparison with the authentic sample[57] supplied by Professor M. Kates was also made. The yield of this tetraether from frozen cells was 0.14%. Obviously, the natural source of biphytan-1,32-diol **3** is very limited.

(b) Acyclic tetraether model from 1,14-tetradecanediol

Experiments designed to produce a tetraether such as **31** were pursued in order to find an efficient method for coupling two glycerol fragments. The sequence shown in Scheme 1 was tried first.

Different conditions were sought to enhance the yield of **29**. First, THF was used as solvent in order to increase the diol solubility. Second, sodium dodecyl sulfate (1 eq.) was added to a methylene chloride solution of the diol to

enhance solubility. Third, dilithium 1,14-tetradecane-dioxide was used to open the ring of the glycidyl ether. No improvement over the standard BF_3-catalyzed epoxide reaction[50] was obtained. The yield of diether **29** was 55%. The byproducts **32** and **33** were also purified and identified.

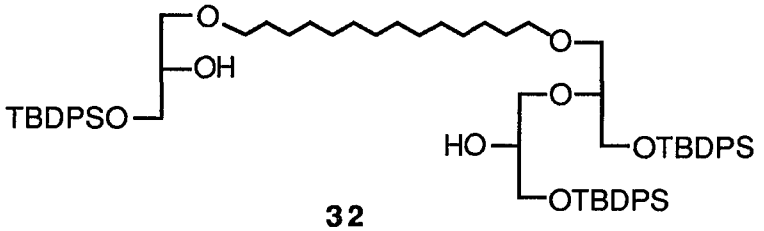


TBDPS = *t*-butyldiphenylsilyl
TBAB = tetra-*n*-butylammonium bisulfate

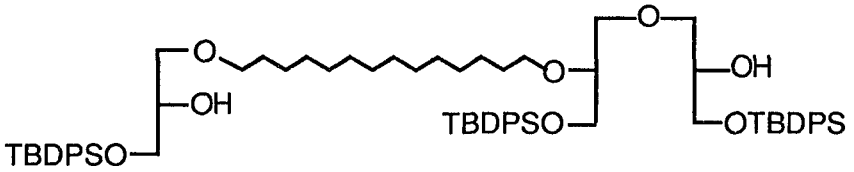
Scheme 1

Compound **29** was treated with *n*-heptyl iodide to form tetraether **30** by a phase-transfer catalyzed pathway using tetra-*n*-butylammonium hydrogen

sulfate as catalyst in 50% aqueous sodium hydroxide. Various conditions were tried but none was successful. Finally, the standard Williamson conditions were used:[40,41,43,44] compound **29** was converted to the dialkoxide using sodium hydride in DMF first, and then treated with *n*-heptyl iodide. Thin-layer chromatography showed that the reaction mixture was very complicated, and it was impossible to single out any one pure component. After several months of fruitless efforts, it was realized that the *tert*- butyldipenylsilyl protecting group was too vulnerable to endure the reaction conditions; therefore, alternative protecting groups were considered.



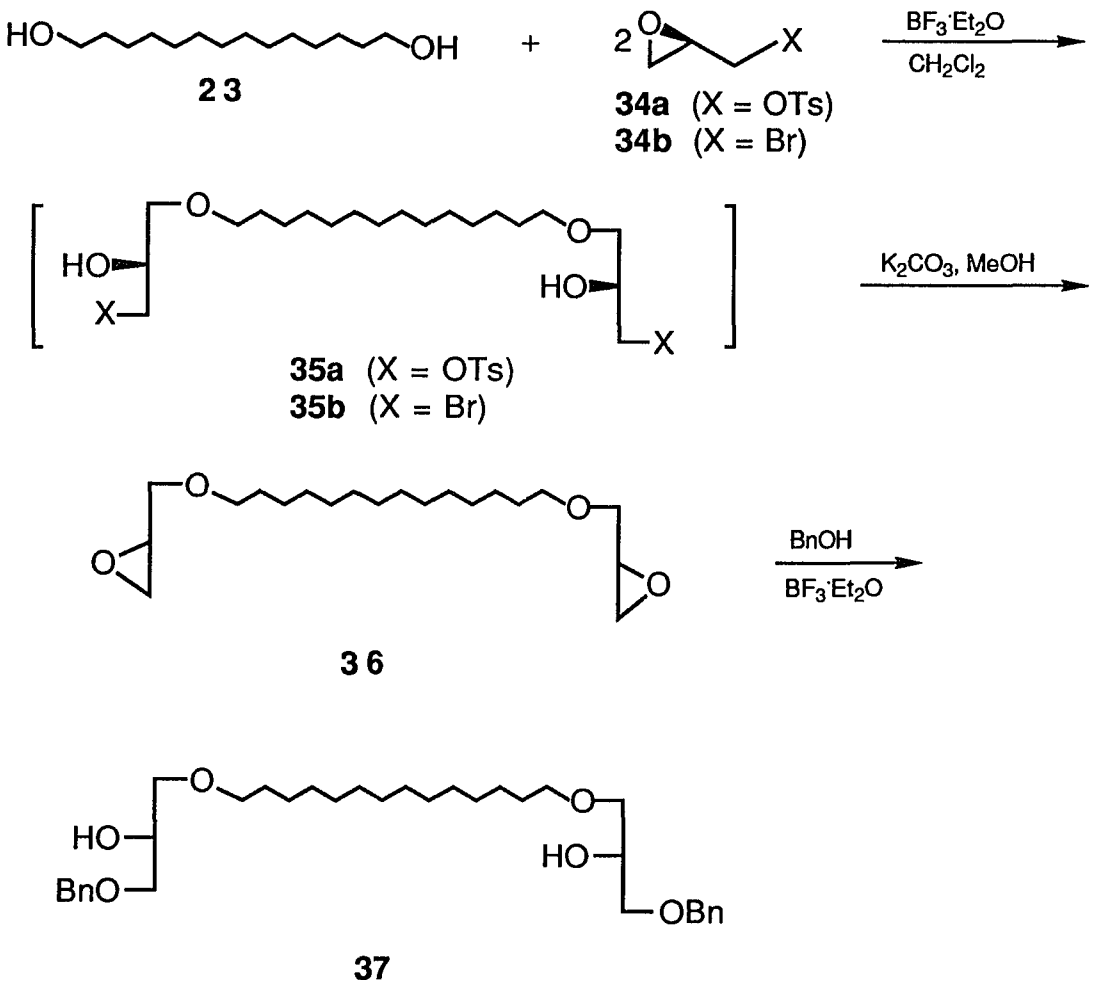
32



33

As a second protected glycidol, tosylate **34a** was used because of its known excellent regioselectivity in the ring-opening reaction;[50] **34a** reacted with diol **23**, and the tosyl group was replaced by a benzyl ether in a subsequent step (Scheme 2). Both glycidyl tosylate **34a** and epibromohydrin **34b** were reacted with 1,14-tetradecanediol **23** in methylene chloride with boron trifluoride etherate[49,50] as catalyst. After the solvent was removed, the

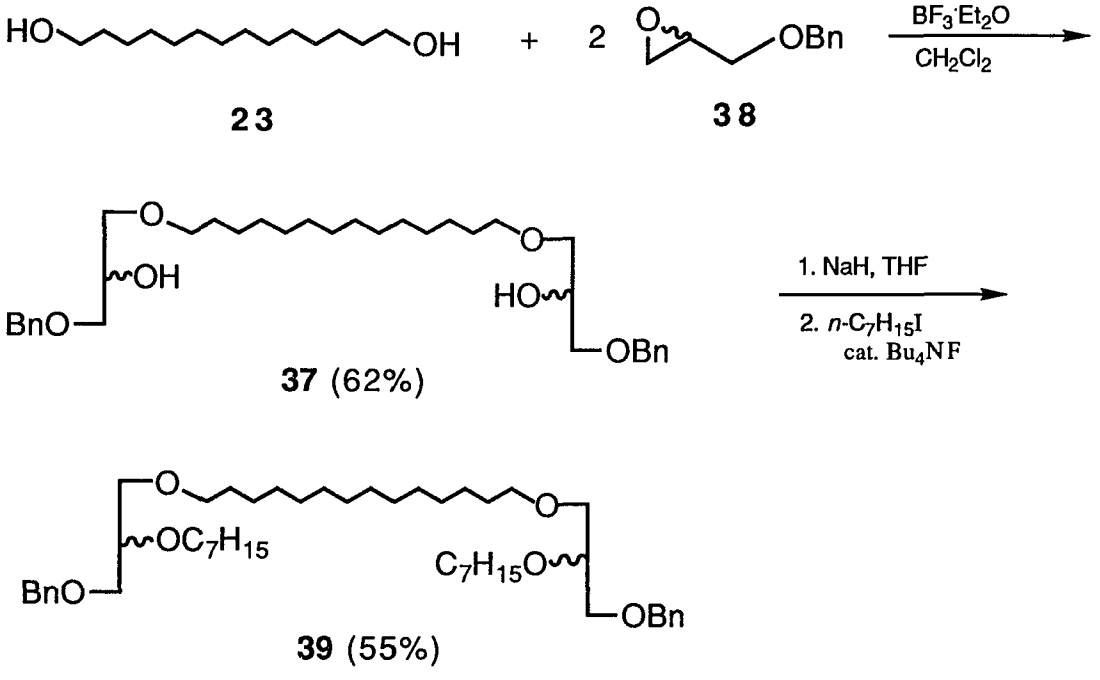
residue was dissolved in methanol and stirred with anhydrous potassium carbonate.[58] Again, TLC showed that the reaction mixtures were hopelessly complicated.



Scheme 2

As a third protecting group for glycidol, benzyl glycidyl ether was used. The reaction of 1,14-tetradecanediol **23** with benzyl glycidyl ether **38** was run, even though it was expected that the regioisomeric products would be hard to separate. Fortunately, the result was not as bad as our expectation (Scheme 3).

At first, C_{14} diol **23** reacted with benzyl glycidyl ether **38** to give **37**. The benzyl ether **38** was made from epibromohydrin and benzyl alcohol by the procedure of Bacon and Collis;[59] the yield was improved from 35% to 50%. It was very difficult to separate **37** from the reaction mixture; some pure **37** was obtained by preparative HPLC for identification. The mixture which contained **37** was directly alkylated with *n*-heptyl iodide in the presence of Bu_4NF to give **39**.[60,61] The separation of **39** was much simpler and it was isolated from the reaction mixture by flash chromatography, affording **39** in 55% yield. The alkylation reaction in the absence of Bu_4NF did not appear to proceed as well. The overall yield of **39** was 17%, which is better than previous procedures for analogous compounds.



Scheme 3

The disadvantage of preparing a long chain-diol or its derivative,

however, still exists as a barrier to the preparation of tetraethers **18** and **27**. If the two glycerol diethers **40** and **41** could be coupled (Figure 8) to produce a diglycerol tetraether **1**,[25,31,62-67] we would not only make the preparation of necessary starting materials, α,ω-difunctionalized hydrocarbon chains, shorter,

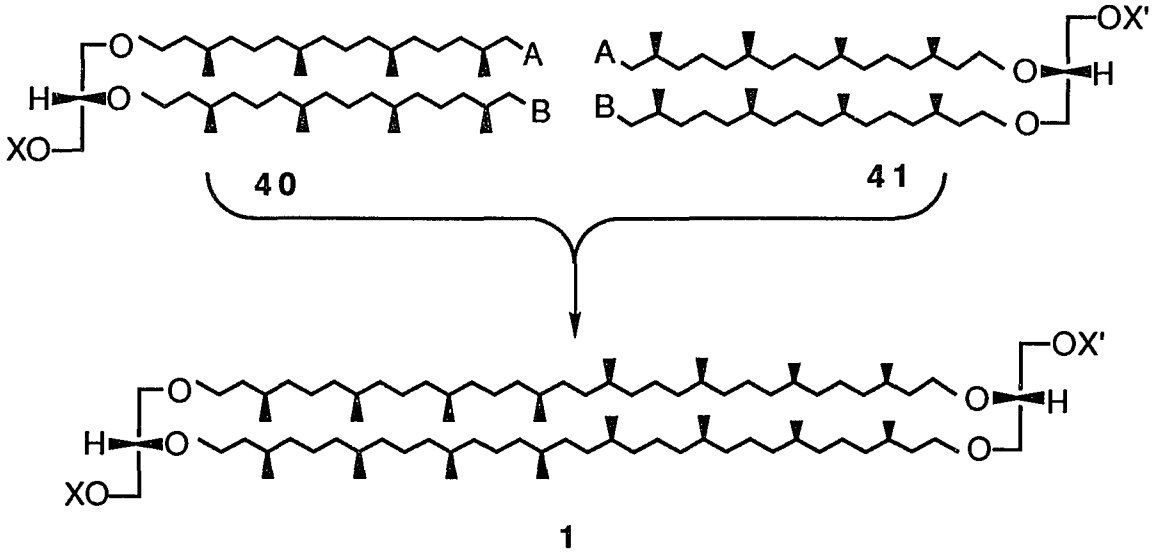
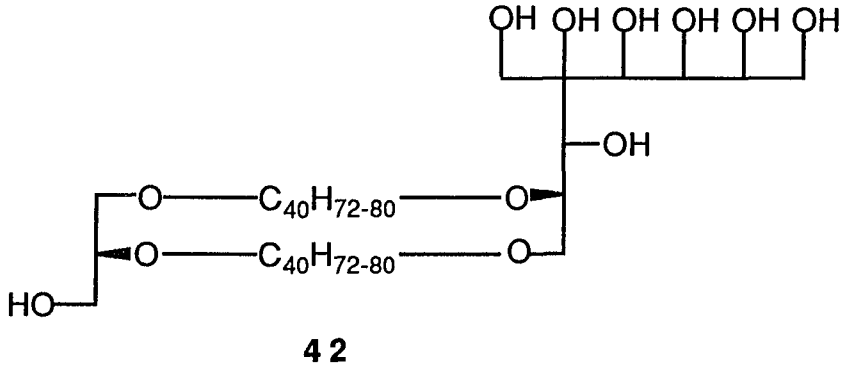


Figure 8

but also open a route to the unsymmetrical naturally occurring tetraethers,[2] which also include glycerol-dialkylnonitol tetraether **42**.[62,63]



42

(c) Acyclic tetraether model from two diethers

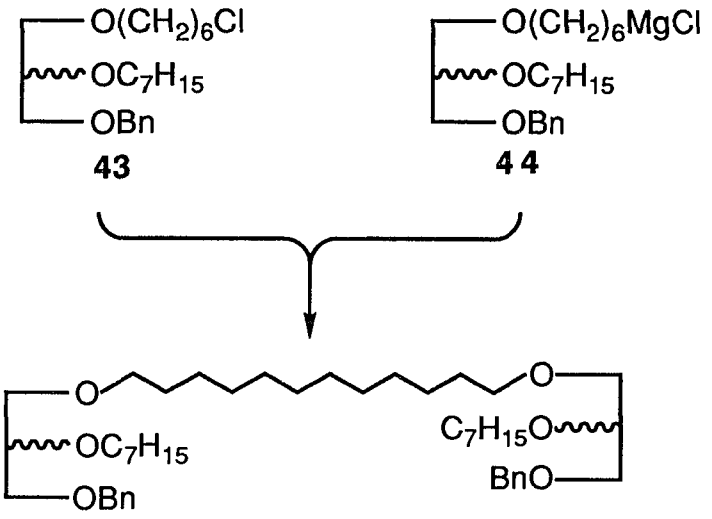
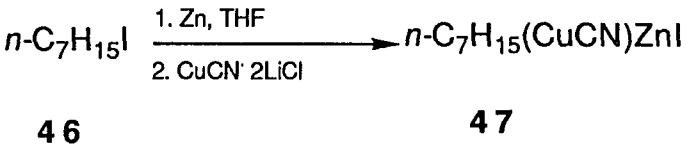
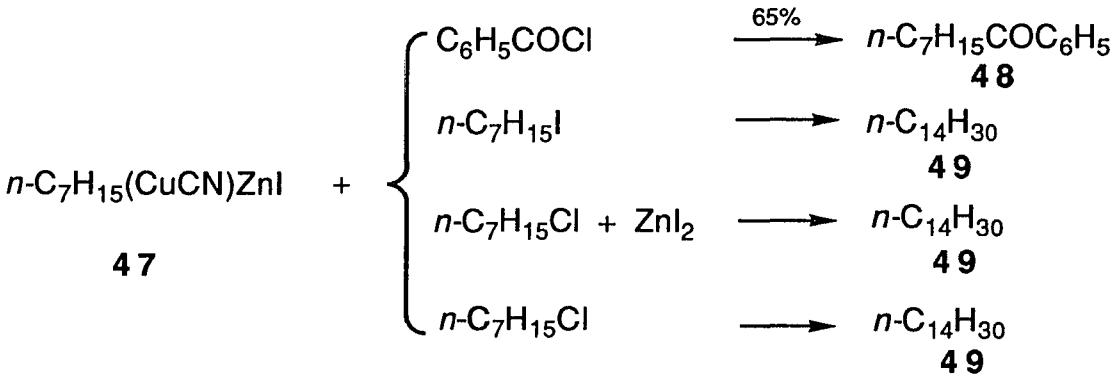


Figure 9



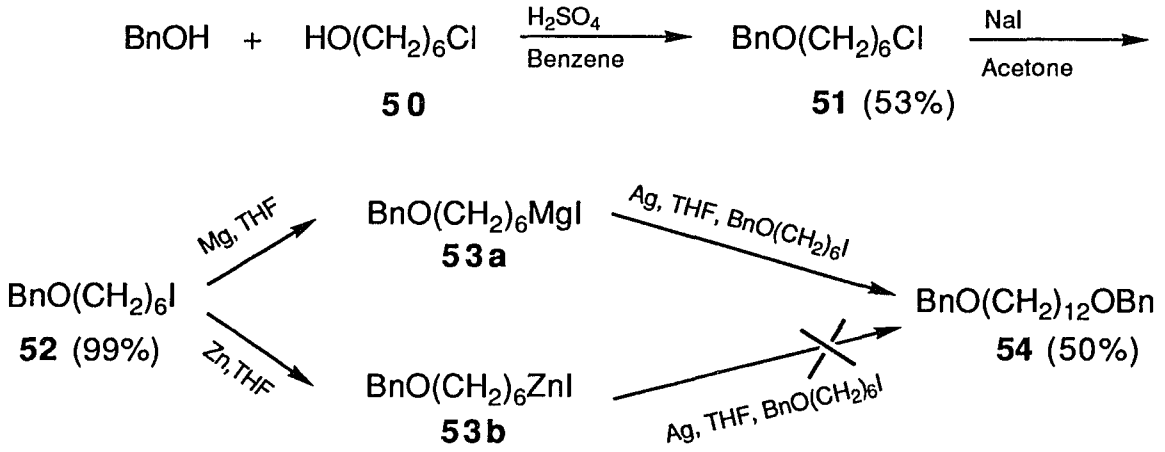


Scheme 4

The original thought was to couple an alkyl chloride **43** with its metal

derivative **44** to produce a tetraether **45** (Figure 9)

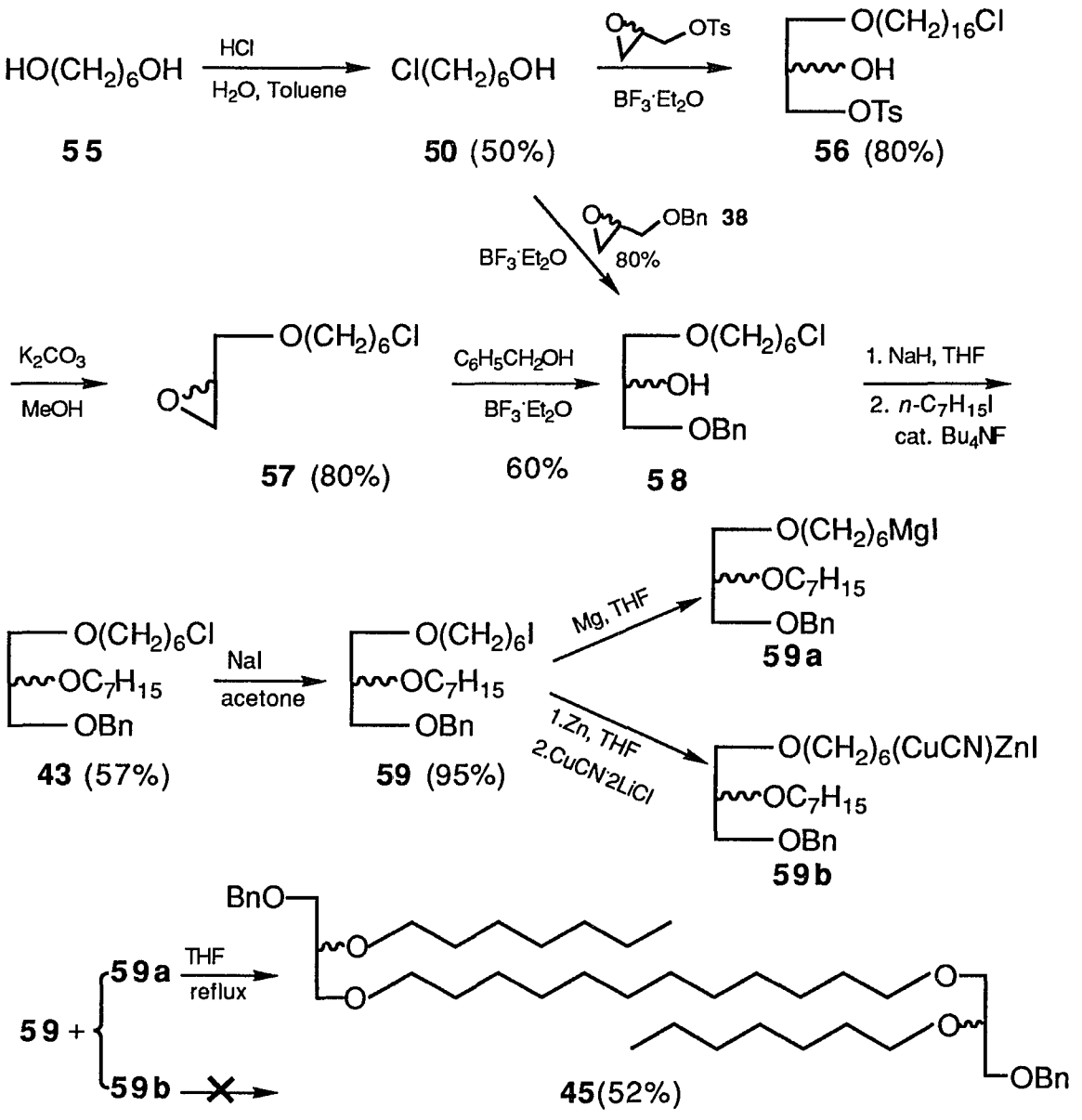
To test the feasibility of this key step before extensive work with glycerol ethers, the coupling of two C_7 units was attempted. A Zn-Cu reagent was tried first because it is mild enough to allow other functional groups to survive,[68] for example, an ester. Following Knochel's method,[68] heptyl iodide **46** was converted to a "copper" reagent **47** (Scheme 4). Coupling of the copper reagent **47** was separately tried with (1) benzoyl chloride; (2) *n*-heptyl iodide; (3) *n*-heptyl chloride with a catalytic amount (10% mol) of zinc iodide; (4) *n*-heptyl chloride in THF. *n*-Heptyl phenyl ketone **48** was obtained in 65% yield, which indicated that the alkyl copper or zinc reagent **47** was formed successfully. It seems that coupling of two alkyl halides by the copper reagent does not work.



Scheme 5

Then, attention was focused on Grignard reagent coupling. Heathcock et al. coupled two C_{20} alkyl chains by an oxidation reaction of an alkylmagnesium bromide with silver nitrate, but the yield was only 27%.[27] Using the procedure

of Tamura and Kochi,[69] model reactions using benzyl ether **52** successfully coupled with the corresponding Grignard reagent **53a** with a silver metal as catalyst. The reaction failed when applied to the corresponding zinc reagent (Scheme 5).



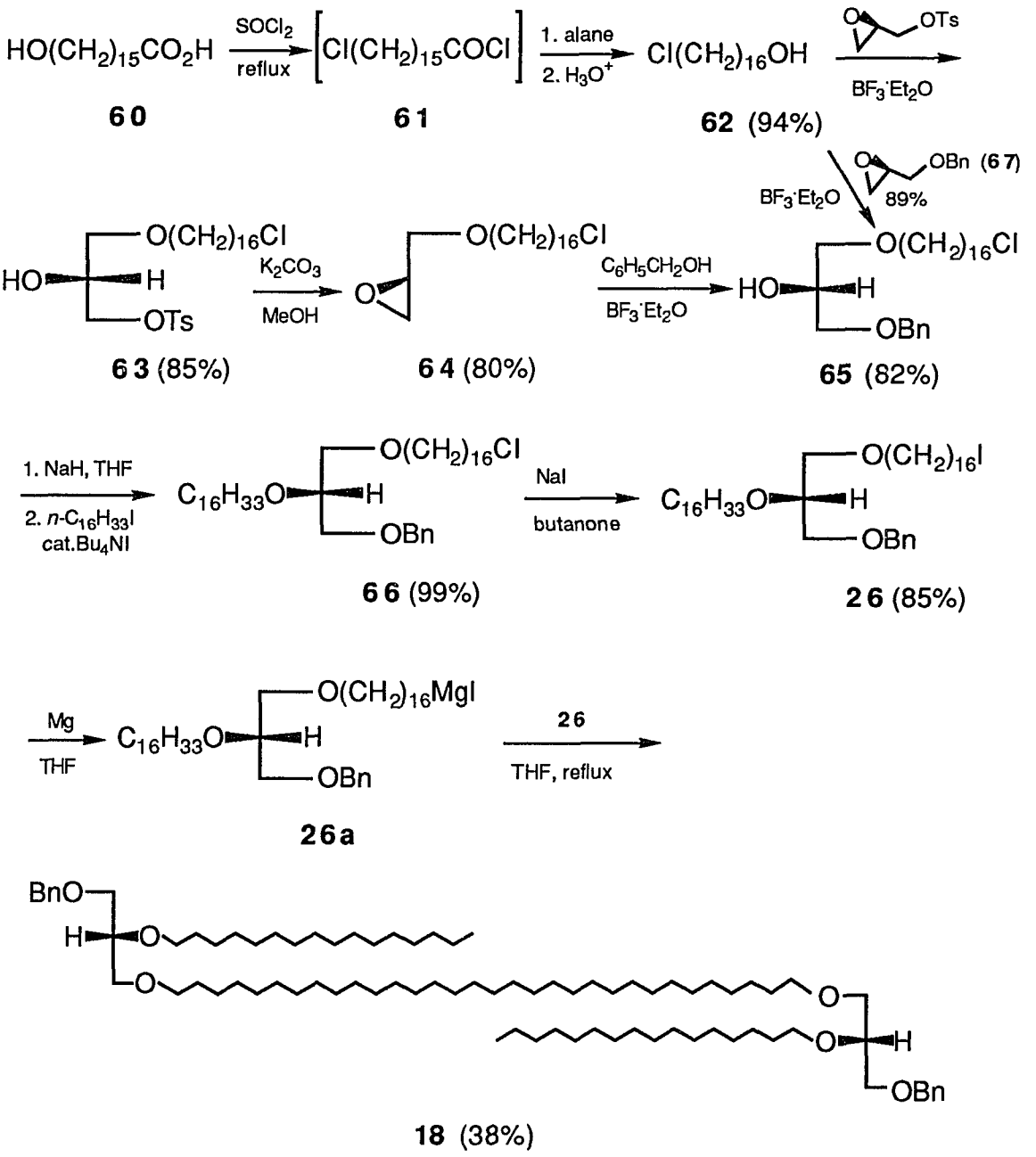
Scheme 6

The silver-catalyzed coupling method was applied to the coupling of two

glycerol diethers (Scheme 6). First, hexamethylene chlorohydrin **50** was synthesized from 1,6-hexanediol **55** in 50% yield.[70] The hexamethylene chlorohydrin reacted with (*rac*)-glycidyl tosylate to form 1-(6-chlorohexyl)-3-tosyl glycerol **56** (80%). The tosylate **56** was then stirred with potassium carbonate in methanol to give (6-chlorohexyl) glycidyl ether **57** (80%).[58] This was converted to the benzyl ether 1-*O*-(6-chlorohexyl)-3-*O*-benzylglycerol **58** by BF_3-catalyzed alcoholysis in 60% yield.[49,50] Compound **58** was also prepared in 80% yield in one step by direct reaction of hexamethylene chlorohydrin **50** with benzyl glycidyl ether **38**. Compound **58** was then treated with sodium hydride in THF, followed by *n*-heptyl iodide to give 1-*O*-(6-chlorohexyl)-2-*O*-heptyl-3-*O*-benzylglycerol **43** (57%).[60,61] The alkyl chloride **43** was converted to iodide **59** (95%) with sodium iodide in acetone.[71] The intermediates **59a** and **59b** were made from iodide **59** separately. The coupling was successful with the magnesium reagent while it failed with the zinc reagent.

The same coupling method was used to obtain tetraether lipid **18** (Scheme 7). The yields were generally improved. Commercial 16-hydroxyhexadecanoic acid **60** was converted to 16-chlorohexadecanoyl chloride **61** by refluxing with thionyl chloride, and was immediately selectively reduced to 16-chlorohexadecanol **62** by alane.[72] The combined yield of the two steps was excellent (94%). The alcohol **62** reacted with commercial (*R*)-(-)-glycidyl tosylate with BF_3 catalysis to give 1-*O*-(16-chlorohexadecyl)-3-*O*-tosyl-*sn*-glycerol **63** (85%),[50] which was treated with potassium carbonate in

methanol at 0 °C to yield (2*R*)-(+)-2-(16-chlorohexadecyloxymethyl)-oxirane **64** (80%).[58] 1-*O*-(16-Chlorohexadecyl)-3-*O*-benzyl-*sn*-glycerol **64** (82%) was



Scheme 7

obtained by reacting the epoxide **64** with benzyl alcohol/BF_3 etherate.[49,50]

Compound **64** was also made directly from hexadecamethylene chlorohydrin **62** and (*R*)-(-)-2-(benzyloxymethyl)-oxirane in 86% yield.[73] Compound **64** was alkylated with 1-iodohexadecane in the presence of a phase-transfer catalyst to give 1-*O*-(16-chlorohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol **66** (71%).[60,61]

Preparation of compound **26** from **66** with sodium iodide gave difficulty even after the reaction mixture was refluxed two days in acetone solution; only about 50% of the chloride was converted to the iodide (judging by ^{1}H NMR spectroscopy). Use of a higher reflux temperature completed the conversion; **66** was converted to **26** in 85% yield by refluxing with NaI in 2-butanone solution. Compound **26** was then reacted with magnesium in THF solution to form Grignard reagent **26a**, which gave tetraether **18** (38%) with a second equivalent of **26** and silver as catalyst.

(d) Macrocyclic tetraether 27

With the success of the coupling method, attention was given to the more challenging macrocyclic tetraether **68** (Scheme 8). It was realized that tetraether **68** could come via **69** from two distinguishable and consecutive coupling reactions of two diether synthons **70** and **71** (Figure 10).

According to this analysis, Scheme 8 was designed. Compounds **72a** and **73** could be coupled by the well-established Kochi method.[69] Then, the trityloxy groups of **74** would be converted to dialdehyde **75** by triphenylcarbenium tetrafluoroborate.[74] Dialdehyde **75** would undergo

reductive dimerization to yield olefin **76** by the McMurry reaction.[75-77] Hydrogenation of **76** would give tetraether **27**.

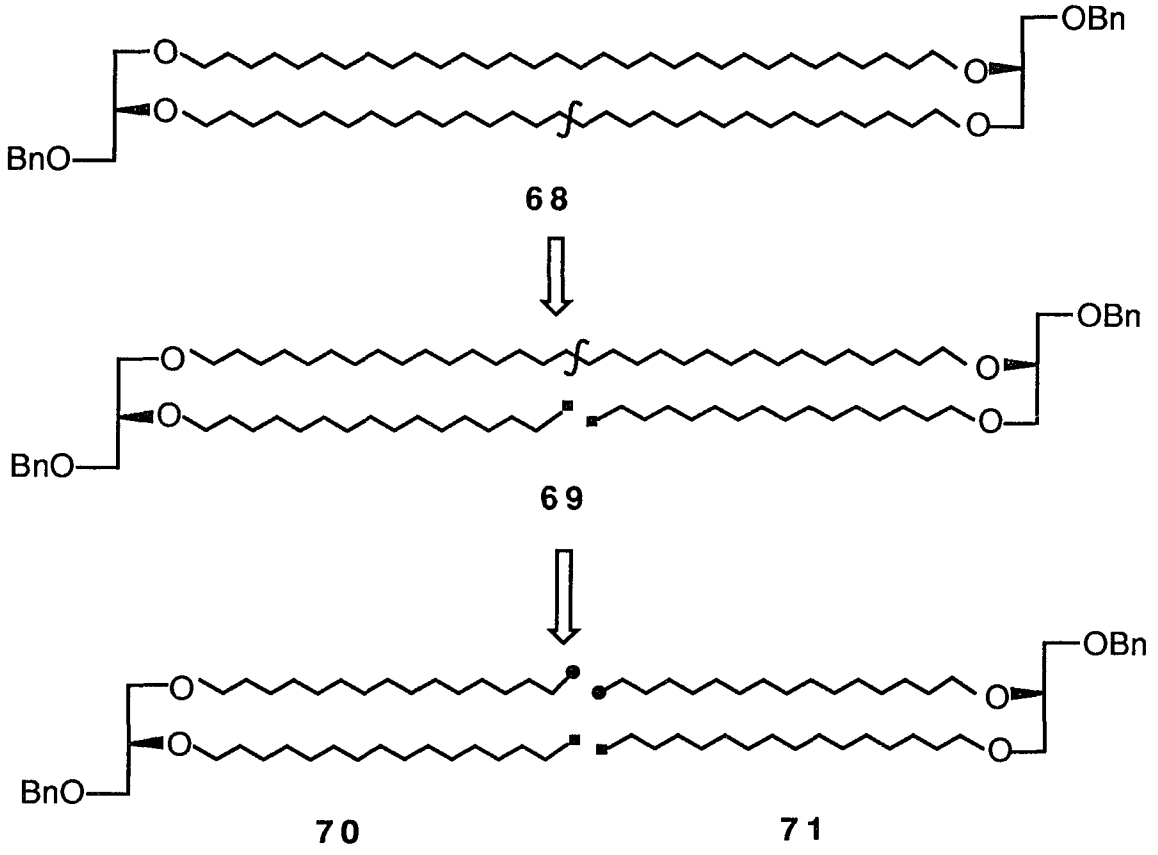
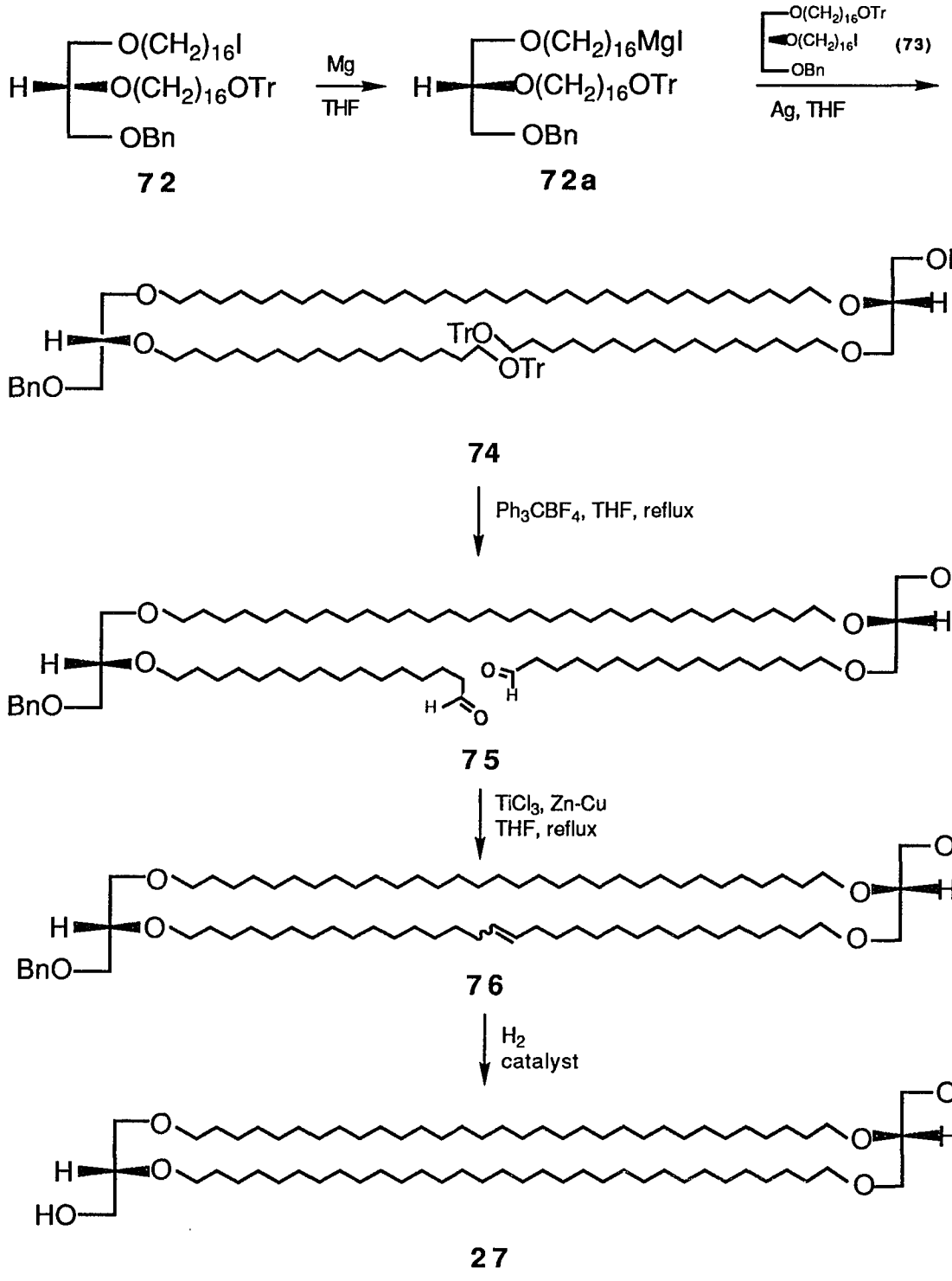


Figure 10

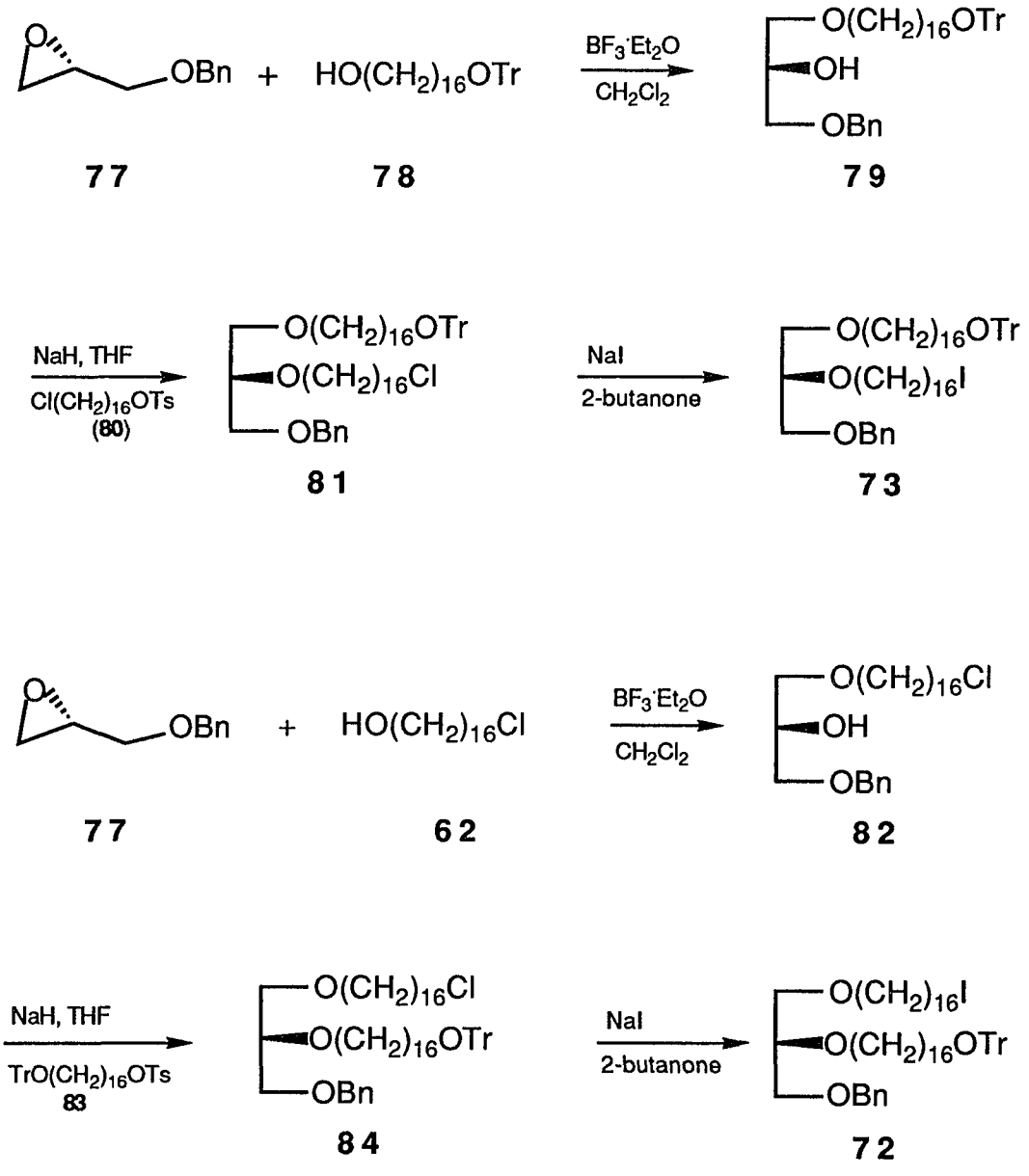
The two glycerol diethers required, **72** and **73**, could be made by the procedure shown in Scheme 9. To prepare diethers **72** and **73**, four different α,ω-disubstituted hexadecanes, **62**, **78**, **80**, and **83**, are required (Scheme 10). They may be made from an inexpensive starting material, 16-hexadecanolide **85**. Compounds **62**, **78**, and **80** have been made and identified (see Experimental Section). Compound **83** will be made from **78**.



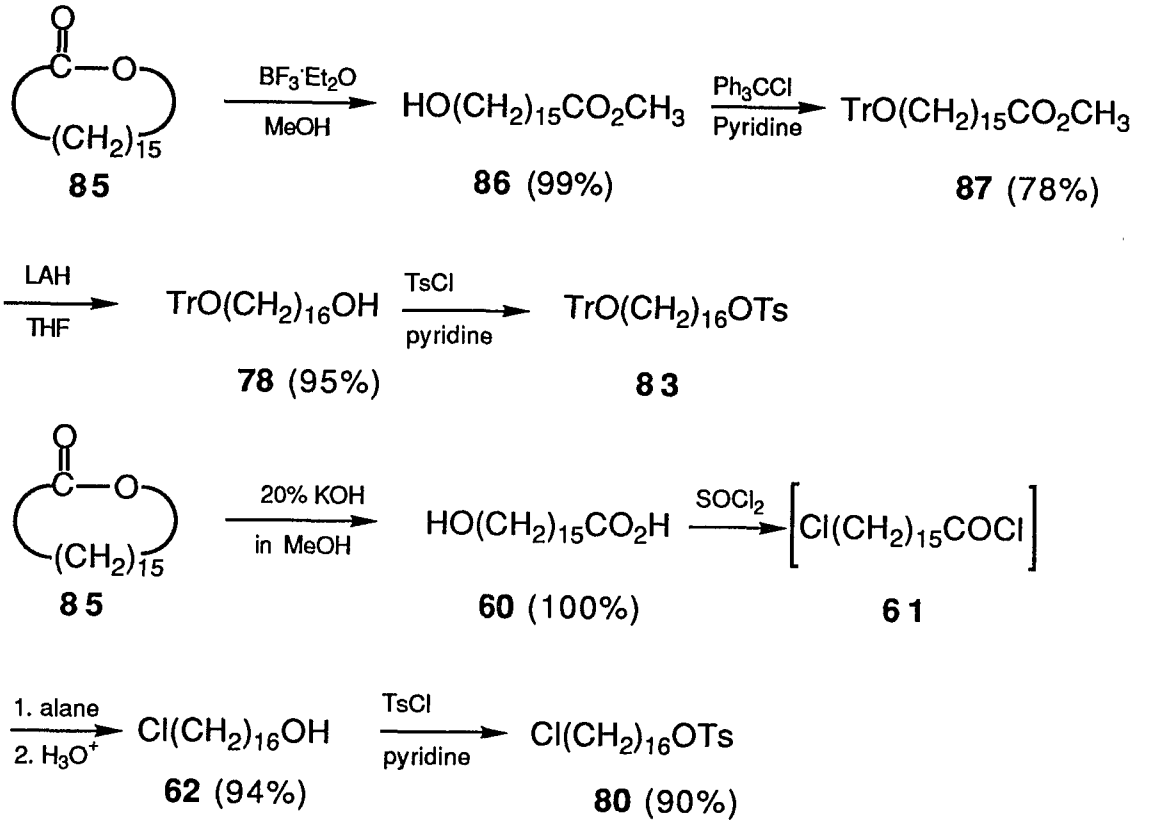
Scheme 8

Before trityl was used as the protecting group, the route shown in

Scheme 11 was tried. 16-Hexadecanolide **85** was reduced with DIBAL to the hydroxyaldehyde **88** and protected as the ketal **89**. Coupling with benzyl glycidyl ether **77** gave **90** in 75% yield. The NMR and IR spectra showed that both **89** and **90** are accompanied by a small amount of unprotected aldehyde



Scheme 9



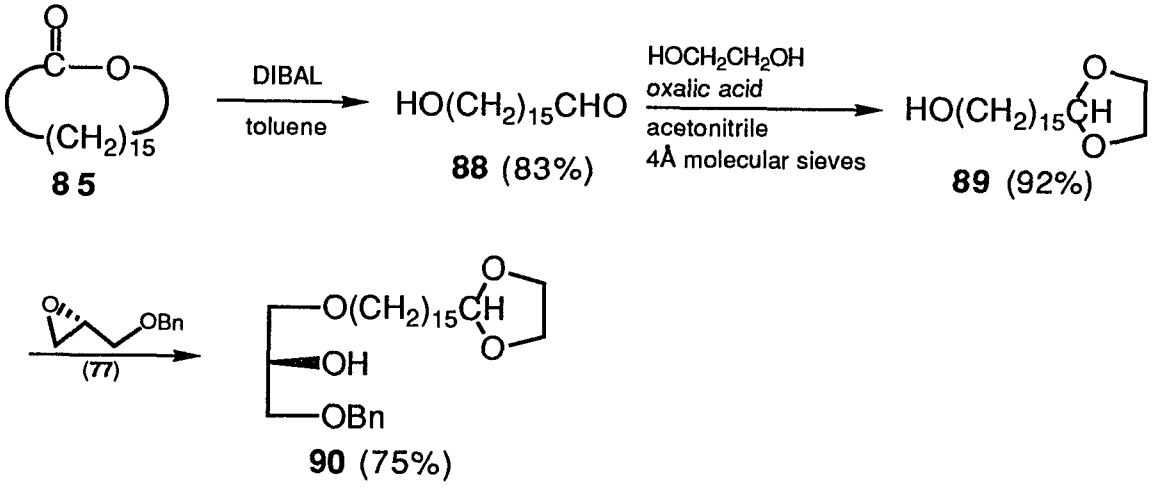
85 → HO(CH2)15CO2CH3 **86** (99%) → TrO(CH2)15CO2CH3 **87** (78%)

→ TrO(CH2)16OH **78** (95%) → TrO(CH2)16OTs **83**

85 → HO(CH2)15CO2H **60** (100%) → [Cl(CH2)15COCl] **61**

→ Cl(CH2)16OH **62** (94%) → Cl(CH2)16OTs **80** (90%)

Scheme 10



85 → HO(CH2)15CHO **88** (83%) → HO(CH2)15CH(O,O) **89** (92%)

→ O(CH2)15CH(O,O), OH, OBn **90** (75%)

Scheme 11

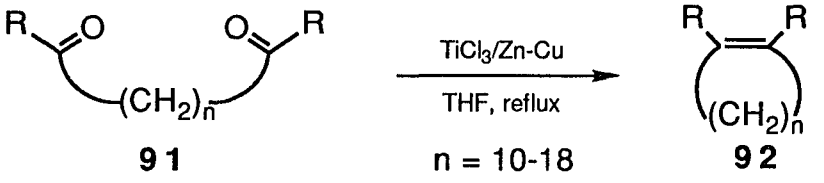
isomers which were hard to remove completely. It was expected that the aldehyde would retard the preparation of the required Grignard reagents, so this procedure (Scheme 11) was abandoned.

CHAPTER 3

ALTERNATIVE COUPLING APPROACHES

It is clear that the first coupling of synthons **70** and **71** is a cross-coupling and the second is a cyclization (Figure 10).

Scheme 8 shows the cross-coupling reaction to be completed by Kochi's method[69] and the cyclization to be accomplised by the McMurry reaction.[75-77] McMurry showed that rings of sizes from 12 to 20 carbon atoms (Figure 11) may be formed in yields higher than 80%, and it is believed that there is no reason to suspect that still larger rings would not form smoothly.[75]



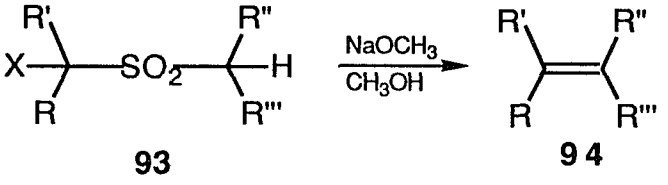
91 **92**

Figure 11

Alternative alkyl condensation methods have also been considered. For the first cross-coupling reaction the following methods represent alternative choices.

(a) Ramberg-Backlund rearrangement (Figure 13)[78-80]

Ramberg-Backlund rearrangement reaction (Figure 12) has been an efficient carbon-carbon coupling method. A Ramberg-Backlund rearrangement coupling of **84** and **95** was designed as shown in Figure 13.



93 **94**

Figure 12

Using the method of Bieniarz and Cornwell,[81] alkyl chloride **84** may be converted to mercaptan **93** in high yield. Reaction of the sodium salt of mercaptan **93** with alkyl chloride **81** will give sulfide **96**.[82] Halogenation of sulfide **96** with *N*-chlorosuccinimide (NCS) in carbon tetrachloride solution will form a pair of regioisomers **97a** and **97b**,[83-89] which then will be oxidized to α-chlorosulfones **98a** and **98b** by *m*-chloroperbenzoic acid in chloroform.[90-92] α-Chlorosulfones **98a,b** may undergo the Ramberg-Backlund rearrangement to yield tetraether alkene **99**.[78,80,93-96] The advantage of this method is that the unwanted symmetrical dimerization could be definitely avoided since the two alkyl groups would be connected with sulfur in separate steps.

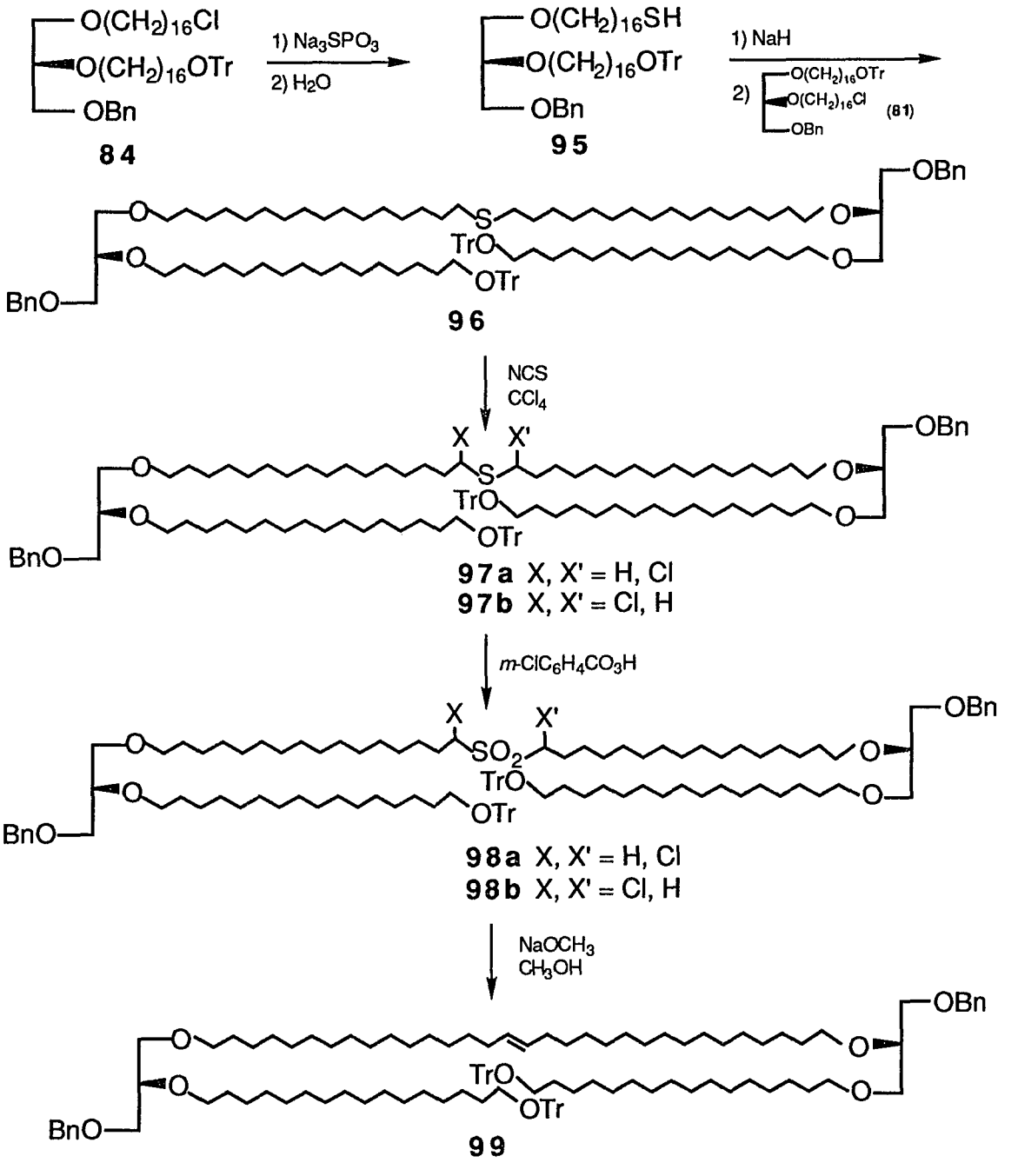

O(CH2)16Cl
O(CH2)16OTr
OBn
84
1) Na3SPO3
2) H2O
O(CH2)16SH
O(CH2)16OTr
OBn
95
1) NaH
2)
O(CH2)16OTr
O(CH2)16Cl
OBn
(81)
OBn
S
TrO
OTr
BnO
96
NCS
CCl4
X
X'
97a X, X' = H, Cl
97b X, X' = Cl, H
m-ClC6H4CO3H
SO2
98a X, X' = H, Cl
98b X, X' = Cl, H
NaOCH3
CH3OH
99

Figure 13

(b) Copper-catalyzed alkylation of an organomanganese chloride reagent (Figure 15)[97]

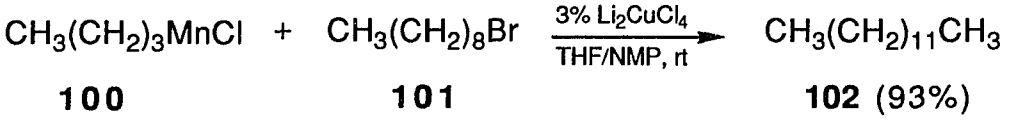


Figure 14

Cahiez and Marquis showed that alkylation of organomagnese chloride reagent **100** with alkyl halide **101** is an interesting coupling method because of the high yield (Figure 14).[97] Based on this reaction, an alternative route shown in Figure 15 was designed.

Grignard reagent **72a** may be converted to organomanganese reagent **103**.[97] The copper-catalyzed alkylation of **103** with iodide **73** will yield tetraether **74**. Cahiez and Marquis showed that the influence of *N*-methylpyrrolidine (NMP) is very important.[97]

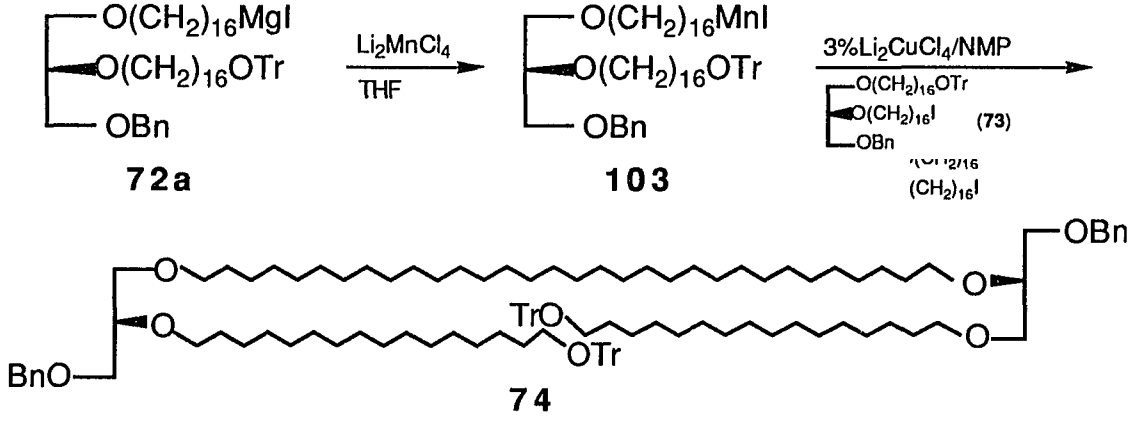


Figure 15

(c) Cyclization by Ramberg-Backlund rearrangement (Figure 16)[78-80]

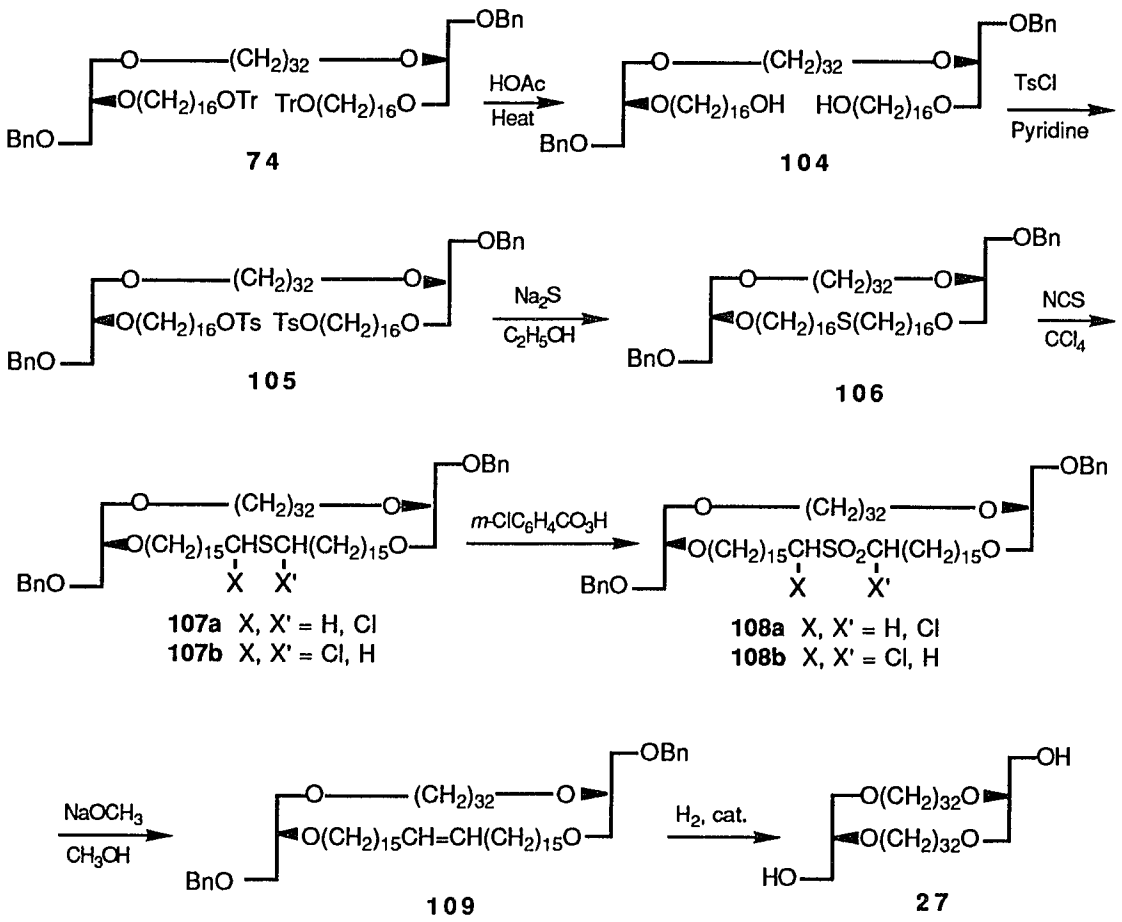
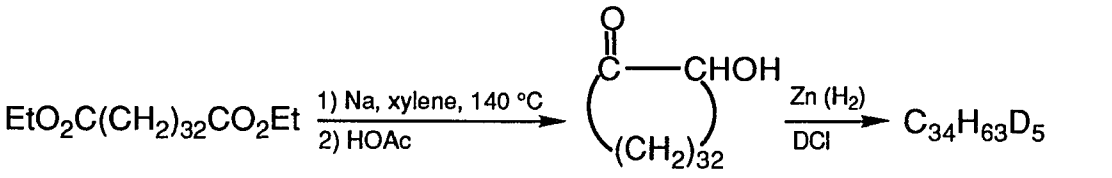


Figure 16

In place of the McMurry reaction, the cyclization step also could be done by Ramberg-Backlund rearrangement. Detritylation of **74** will give diol **104**,[98] which then could be converted to ditosylate **105** by tosyl chloride.[99] Reaction of tosylate **105** with sodium sulfide in ethanol solution may yield thiacyclo compound **106** based on Regen's method.[100] Following α–halogenation and oxidation of sulfide **106**, tetraether alkene **109** could be obtained by Ramberg-Backlund rearrangement of compounds **108a** and **b**. Hydrogenation of **109**

will yield tetraether **27**.

(d) Acyloin cyclization by Wasserman's method (Figure 18)[101-105]

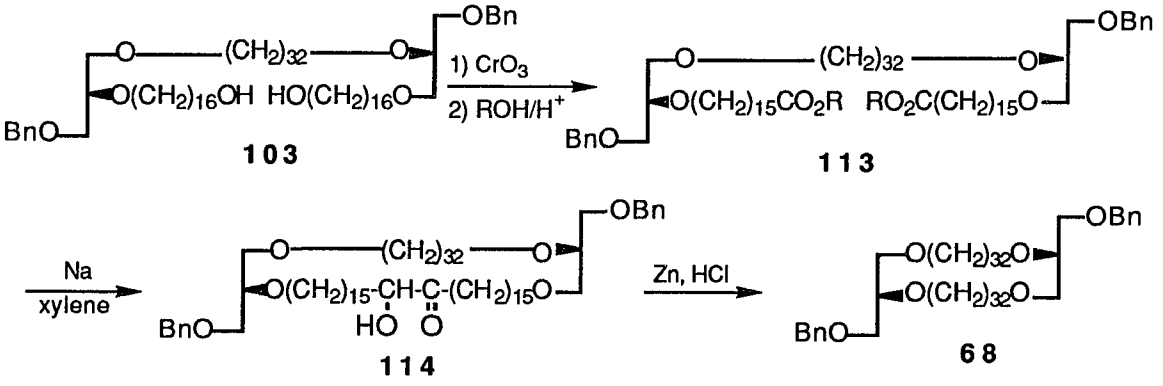


110 **111** **112**

(50% overall)

Figure 17

As a traditional macroring cyclization reaction, Wasserman's method is still attractive because the yield of the macrocyclization reaction (Figure 17) is quite good, and this reaction has been reproduced by several laboratory.[102-105] Therefore, this is another alternative method (Figure 18).



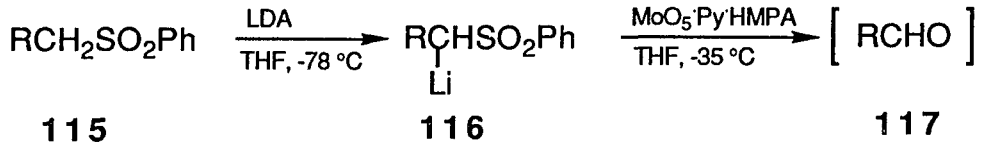
103 **113** **114** **68**

Figure 18

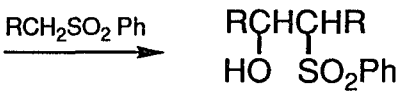
Diol **104** may be oxidized and esterified to yield diester **113**. This could in turn be cyclized to the acyloin **114** by Wasserman's method.[101-105]

Tetraether **6 8** will be obtained by Clemmensen reduction of acyloin **11 4**.

(e) Coupling by Julia's method (Figure 20)[113]



115 **116** **117**



118

(70-90% overall yield)

R = geranyl

Figure 19

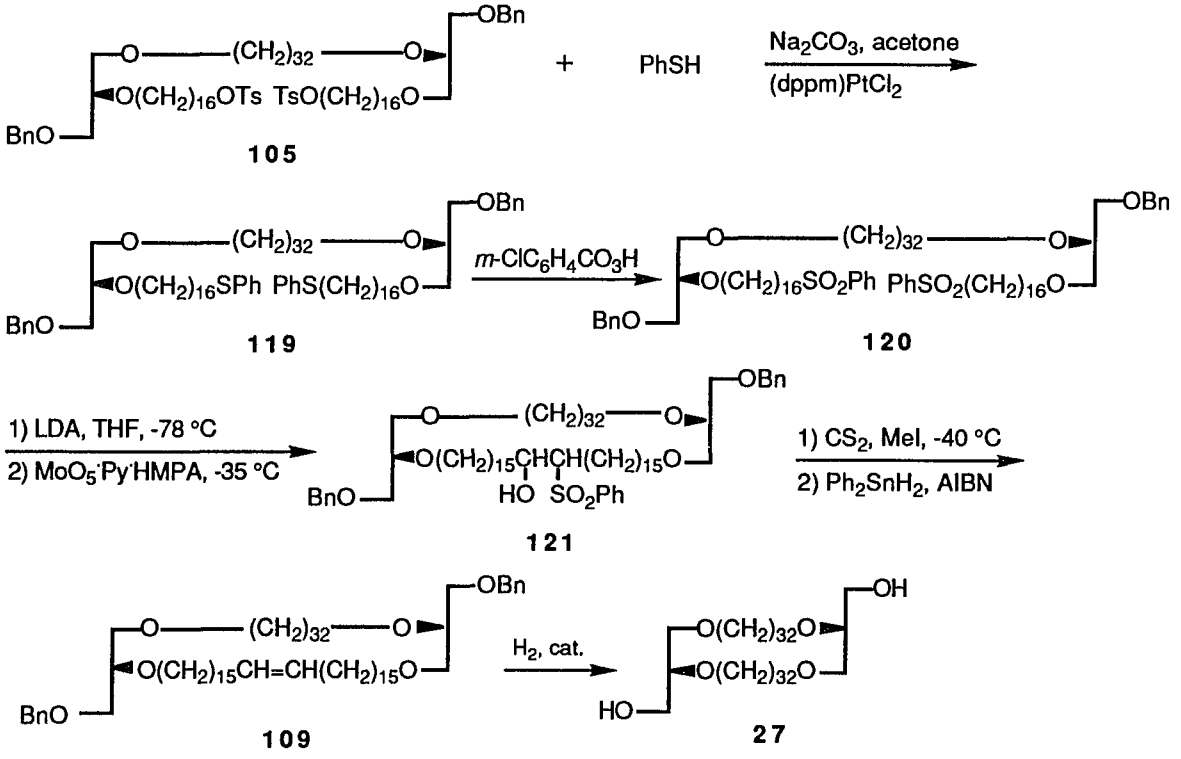


Figure 20

Julia et al.[113] have shown that the oxidative desulfonylation of primary sulfonyl anions with the molybdenum peroxide reagent, MoO_5·Py·HMPA, leads directly to β-hydroxysulfones through condensation of the starting α-sulfonyl anion with the aldehyde formed in situ (Figure 19).

As an alternative approach, ditosylate **105** could be converted to sulfide **119** by reaction with thiophenol and sodium carbonate in acetone with small amount of bis(diphenylphosphino)methane platinum dichloride [(dppm)$PtCl_2$] as catalyst.[114] After oxidation of disulfide **119**, disulfone **120** would undergo Julia condensation[113] to yield β-hydroxysulfone **121**, which could be reduced to alkene **109**,[115] and then to tetraether **27**.

CHAPTER 4

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on an IBM WP 200 SY (200 MHz) spectrometer in $CDCl_3$ with Me_4Si as the internal standard. ^{1}H NMR (400 MHz) were acquired using a JEOL GX-400 MHz spectrometer at Hunter College by Dr. Michael Blumenstein. Chemical shifts are reported in parts per million downfield from Me_4Si. *J* values are reported in Hz. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and brs (broad). Infrared spectra were recorded on a Perkin-Elmer IR 598 or 1600 series FTIR instrument.

Melting points were determined in open capillaries by using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Silica gel G TLC plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with iodine vapor or 10% sulfuric acid in methanol to visualize the spots.

GC/MS analyses were performed by Dr. David C. Locke at Queens College on a Hewlett Packard 5988a GC/MS instrument with a cross-linked methylsilicone column. For separation of polar compounds, a Carbowax column was used. High resolution (+) LSIMS spectra were done by Hoffmann-La Roche Inc. or by Dr. Bev Chamberlin of Michigan State University. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Optical rotations were measured in a 1-dm cell on a JASCO model DIP-140 digital polarimeter.

E. Merck silica gel 60 (230-400 ASTM mesh) was used for flash chromatography.[106] For medium pressure chromatography, Merck Lichroprep Si 60 (40-63 μm) was used in a commercial Lobar (1 cm) column. Analytical HPLC was conducted with a Waters Associates system consisting of two 4 mm X 30 cm μ-Porasil silica columns in series, a 6000 SDS pump, U6K injector, and a Model 401 differential refractometer.

Solvents were dried as follows. Dichloromethane and acetonitrile were distilled from calcium hydride and stored over 3Å molecular sieves; benzene and hexane were distilled from and stored over sodium; methanol was dried over anhydrous potassium carbonate; ether and tetrahydrofuran were refluxed over sodium benzophenone ketyl for several hours and then distilled and used immediately; acetone and 2-butanone were stored over anhydrous calcium sulfate for at least one week.

(*R*)-(+)-Glycidyl *tert*-butyldiphenylsilyl ether was prepared by the procedure of Gao et al.;[107] $[\alpha]^{30}_D$ +2.65° (*c* 1.62, $CHCl_3$) [lit.[107] $[\alpha]^{25}_D$ +2.40°, 96% ee]. (*R*)-(-)-Glycidyl tosylate [$[\alpha]^{25}_D$ -17.1° (*c* 2.75, $CHCl_3$)] [lit.[107] $[\alpha]^{25}_D$ -17.1°, 92% ee] and (*R*)-(-)-glycidyl benzyl ether [$[\alpha]^{20}_D$ -4.9° ($CHCl_3$)] were obtained from Aldrich. 16-Hexanolide was obtained from Lancaster Synthesis, Ltd. (Windham, NH).

Dibiphytanyl diglycerol tetraether (1) from *Methanobacteria thermoautotrophicum.*

Lipid extraction was performed by the method of Bligh and Dyer.[55] A

100-g sample of the frozen cell mixture[54] was homogenized with a mixture of 100 mL of chloroform and 200 mL of methanol for 2 h. To the mixture was then added 100 mL of chloroform, and after blending for 1 h, 100 mL of distilled water was added and blending was continued for another hour. The homogenate was filtered through Whatman No. 1 filter paper and the residue, with filter paper, was blended with 100 mL of chloroform. The mixture was filtered and the residue was rinsed with a total of 50 mL of chloroform. The filtrate was mixed with the original filtrate, transferred to a 1-L graduated cylinder, and kept for 30 min until separation and clarification was complete. The top alcoholic layer was removed and the chloroform layer was concentrated. The residue was fractionated on a column of silica gel with hexane, followed by benzene and finally chloroform to remove nonpolar lipids. The remaining polar glycolipids and phospholipids were recovered by eluting with a mixture of chloroform and methanol (2:1 by volume) and methanol, and the eluates were pooled and concentrated to give 231 mg (0.23% of frozen cells) of polar lipids. The residue was dissolved in 50 mL of methanolic-HCl (3%) in a 75-mL screw-capped Teflon-lined pressure tube and heated in an oil bath at 80 °C for 5 h, then diluted with 10 mL of aqueous sodium hydroxide solution (7N) and refluxed for 1.5 h.[108] The mixture was extracted with petroleum ether (30-60 °C, 4 X 50 mL). The combined extracts were concentrated and applied to a column of silica gel, and eluted with hexane and ethyl acetate (7:1). Dibiphytanyl diglycerol tetraether **1** (136 mg) (0.14% of frozen cells) was obtained as a colorless oil; $[\alpha]^{20}_{D}$ +9.03° (*c* 1.65, $CHCl_3$)

[lit.[31,66] $[\alpha]^{25}_D$ +8.7° ($CHCl_3$)]; R_f 0.30 (hexane/EtOAc 4:1); R_f 0.19 (hexane/diethyl ether/acetic acid, 80:20:1) [lit.[23] R_f 0.19 (hexane/diethyl ether/acetic acid, 80:20:1)]. The spectral data (^1H NMR, ^{13}C NMR, and IR) obtained matched those reported in the literature.[27]

^1H NMR ($CDCl_3$, 400 MHz) δ 0.840 (m, 18H, 6 X CH_3), 0.857 (m, 18H, 6X CH_3), 0.878 (d, 6H, J = 6.8 Hz, 2 X CH_3), 0.885 (d, 6H, J = 6.8 Hz, 2 X CH_3), 1.076-1.395 (m, 96H, 40 X CH_2, 16 X CH), 1.557-1.634 (m, 8H, 4 X $C\underline{H}_2CH_2O$), 2.202 (t, 2H, J = 9.8 Hz, 2 X OH), 3.444-3.703 (m, 18H, 8 X OCH_2, 2 X OCH).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.68 (CH_3), 19.75 (CH_3), 19.77 (CH_3), 19.80 (CH_3), 24.36 (CH_2), 24.45 (CH_2), 24.47 (CH_2), 29.50 (CH), 32.80 (2 x CH), 33.05 (CH), 34.30 (CH_2), 37.30 (CH_2), 37.40 (3 x CH_2), 37.50 (CH_2), 37.55 (CH_2), 39.90 (CH_2), 61.30 (CH_2).

IR ($CDCl_3$, cm^{-1}): 3590, 2970, 2950, 2895, 2840, 1460, 1362, 1130, 1110.

High resolution (+) LSIMS. $C_{86}H_{172}O_6$ M^++H Calculated: 1302.3240 for $C_{86}H_{173}O_6$. Observed: 1302.3238.

1,14-Di-[3-(*tert*-butyldiphenylsilyloxy)-(2*R*)-2-hydroxypropanoxy]-tetradecane (29)

(*R*)-(+)-Glycidyl *tert*-butyldiphenylsilyl ether[107] **28** [$[\alpha]^{30}_D$ +2.65° (*c* 1.62, $CHCl_3$)] was synthesized by the Sharpless method[107] starting from allyl alcohol. To a solution of 144 mg (0.625 mmol) of tetradecanediol **23** and 399 mg (1.250 mmol) of (*R*)-(+)-glycidyl *tert*-butyldiphenylsilyl ether **28** in 30 mL of freshly distilled methylene chloride (dried over CaH_2) was added 9 mg (0.06 mmol) of BF_3·etherate.[49,50] The mixture was stirred overnight under a nitrogen atmosphere at room temperature. Additional (*R*)-glycidyl TBDPS ether (200 mg, 0.625 mmol) was added, and the mixture was stirred for 24 h. The reaction mixture was diluted with 15 mL of water, then extracted with methylene chloride (3 X 35 mL). The combined organic solutions were dried over anhydrous magnesium sulfate, filtered, concentrated, and the residue was chromatographed on silica gel (60-200 mesh), eluting with a mixture of hexane and ethyl acetate (6.5/1). Four fractions were collected (20 mL each). The fourth fraction was concentrated to afford 295 mg (55%) of compound **29**; $[\alpha]^{31}_D$ +0.29° (*c* 2.04, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.1 (s, 18H, *tert*-butyl), 1.3 (s, 24H, CH_2), 3.4-3.8 (m, 14H, HCO), 3.9 (br s, 2H, OH), 7.3-7.7 (m, 20H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9 (CH_3), 26.12 (CH_2), 26.87 (CH_2), 29.51 (CH_2), 29.63 (CH_2), 29.66 (CH_2), 64.89 (OCH), 70.78 (OCH_2), 71.48 (OCH_2), 71.68 (OCH_2), 127.73, 129.75, 133.80, 135.56 (C_6H_5).

IR (CCl_4, cm^{-1}): 3573, 3300, 3072, 3008, 2962, 2926, 2862, 1729, 1652, 1583, 1474, 1437, 1428, 1383, 1364, 1241, 1114, 1027.

Elemental analysis: Calc. for $C_{52}H_{78}O_6$: C 73.01, H 9.19. Found: C 72.69, H 8.87.

Compound 32. ^1H NMR ($CDCl_3$, 200 MHz) δ 1. 04 (s, 18H, *tert*- butyl), 1.06 (s, 9H, *tert*- butyl), 1.23 (s, 20H, CH_2), 1.51-1.54 (m, 4H, CH_2), 2.35 (br s, 2H, OH), 3.38-3.88 (m, 19H, OCH_2, OCH), 7.24-7.68 (m, 30H, C_6H_5).

Elemental analysis: Calc. for $C_{71}H_{102}O_8Si_3$: C 73.02, H 8.80. Found: C 72.73, H 8.71.

Compound 33. ^1H NMR ($CDCl_3$, 200 MHz) δ 1. 04, 1.05, 1.06 (three s, 27H, *tert*- butyl), 1.51 (s, 20H, CH_2), 1.59-1.60 (m, 4H, CH_2), 2.15 (br s, 2H, OH), 3.39-3.72 (m, 19H, OCH_2, OCH), 7.24-7.68 (m, 30H, C_6H_5).

Elemental analysis: Calc. for $C_{71}H_{102}O_8Si_3$: C 73.02, H 8.80. Found: C 72.91, H 8.56.

1-Benzyloxyl-2,3-epoxypropane (38)

According to the procedure of Bacon and Collis,[59] to a solution of benzyl alcohol (21.6 g, 0.2 mol) and 100 mL of toluene in a 500-mL two-necked round

bottom flask was added freshly cut sodium (4.6 g, 0.2 mol). The mixture was stirred until all of the sodium had reacted. The white sodium salt slurry was cooled to room temperature and epibromohydrin (100 g, 0.73 mol) was added slowly through a dropping funnel over a 1-h period while the solution was stirred. After all of the epibromohydrin was added, the mixture was heated gently until an exothermic reaction commenced at 75 °C. The heating mantle was removed until the exothermic reaction had subsided (T_{max} = 80 °C), and the mixture was then maintained at 80 °C for 30 min. Subsequently, the mixture was heated under reflux and stirred for 90 min, cooled, and filtered. Toluene and excess epibromohydrin were distilled out under vacuum. The residue was distilled through a spinning band column; 16.7 g (50%) of benzyl glycidyl ether **38** was collected as a colorless liquid (bp 80 °C/0.8 mmHg) [lit.[59] bp 70-75 °C/4 mmHg].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.61 (dd, 1H, *J* = 4.7 Hz, *J* = 2.5 Hz), 2.80 (t, 1H, *J* = 4.6 Hz), 3.20 (m, 1H), 3.46 (dd, 1H, *J* = 11.4 Hz, *J* = 6.0 Hz), 3.78 (dd, 1H, *J* = 11.4 Hz, *J* = 3.4 Hz), 4.60 (m, 2H, $PhCH_2$), 7.25-7.45 (m, 5H, C_6H_5).

1,1'-Di-*O*- (1,14-tetradecanediyl)-3,3'-di-*O*- benzyl-di-glycerol (37)

To a solution of tetradecanediol **23** (1.152 g, 5.0 mmol) and $BF_3{\cdot}Et_2O$ (2 drops) in 30 mL of freshly distilled methylene chloride (dried over CaH_2) in an ice bath was very slowly added overnight a solution of benzyl glycidyl ether (4.105 g, 25 mmol) in 20 mL of methylene chloride under nitrogen. After the

addition was complete, TLC showed that only a trace of diol was left. The mixture was concentrated and separated by flash chromatography (elution with hexane/EtOAc, 3:1), giving **37** (1.725 g, 50%). The crude product was purified by HPLC for identification.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20-1.35 (s, 20H, 10 X CH_2), 1.50-1.65 (m, 4H, 2 X $C\underline{H}_2CH_2O$), 2.4 (br s, 2H, 2 X OH), 3.41-3.55 (m, 8H, 4 X OCH_2), 3.63 (t, 4H, J = 6.6 Hz, 2 X OCH_2), 3.94-4.04 (m, 2H, 2 X OCH), 4.56 (s, 4H, 2 X $PhCH_2$), 7.25-7.35 (m, 10H, 2 X C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.74 (CH_2), 26.10 (CH_2), 29.44 (CH_2), 29.55 (CH_2), 29.60 (CH_2), 32.84 (CH_2), 63.07 (OCH_2), 69.63 (OCH_2), 71.72 (OCH_2), 71.88 (OCH), 73.49 ($PhCH_2$), 127.67, 127.68, 128.40, 138.17 (C_6H_5).

IR (CCl_4, cm^{-1}): 3628, 3165, 2932, 2860, 1340, 1360, 1295, 1190, 910, 730, 650.

Elemental analysis: Calc. for $C_{34}H_{54}O_6$: C 73.08, H 9.74. Found: C 73.18, H 9.58.

1,1'-Di-*O*- (1,14-tetradecanediyl)-2,2'-di-*O*- heptyl-3,3'-di-*O*-benzyl-diglycerol (39)

Oil dispersed (54%) sodium hydride (70 mg, 1.58 mmol) in a 15-mL

round-bottom flask was washed twice with dry hexane. Compound **37** (177 mg, 0.32 mmol) in 5 mL of THF was added, and the mixture was stirred at 0 °C for 0.5 h. *n*-Heptyl iodide (717 mg, 4.65 mmol) and tetra-*n*-butylammonium chloride[60,61] (5 mg, 0.02 mmol) were added and the mixture was stirred at room temperature for 48 h. Ether (200 mL) was added and the mixture was washed with aqueous sodium bicarbonate twice. The organic layer was dried and filtered, and the solvents were removed. The residue was separated by medium pressure chromatography (elution with hexane/EtOAC, 10:1). Tetraether **39** was collected as a colorless oil (130 mg, 55%). In the absence of tetrabutylammonium chloride, the alkylation reaction did not proceed well, as evidenced by TLC examination of the reaction mixture.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, 6H, J = 6.5 Hz, 2 X CH_3), 1.21 (m, 36H, 18 x CH_2), 1.56 (m, 8H, 4 x CH_2), 3.48-3.62 (m, 18H, 8 X OCH_2, 2 X OCH), 4.55 (s, 4H, 2 X $PhCH_2$), 7.30 (s, 10H, 2 X C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.06 (CH_3), 22.64 (CH_2), 25.79 (CH_2), 26.13 (CH_2), 29.18 (CH_2), 29.48 (CH_2), 29.54 (CH_2), 29.64 (CH_2), 29.72 (CH_2), 30.19 (CH_2), 31.89 (CH_2), 32.88 (CH_2), 63.13 (OCH_2), 70.51 (OCH_2), 70.65 (OCH_2), 70.90 (OCH_2), 71.72 (OCH), 73.42 ($PhCH_2$), 127.51, 127.60, 128.33, 138.59 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3030, 2930, 2860, 1452, 1100, 860, 690.

MS (m/e): 664 (M^+-Bn), 557, 231, 181, 133, 91 (base peak), 77, 65, 51.

Elemental analysis: Calc. for $C_{48}H_{82}O_6$: C 76.34, H 10.95. Found: C 76.19, H 10.68.

Hexamethylene chlorohydrin (50)

According to the method of Campbell and Sommers,[70] a solution of 1,6-hexanediol (23.0 g, 0.195 mol), concentrated hydrochloric acid (440 mL), water (70 mL), and toluene (30 mL) in a liquid-liquid extractor was heated at 111 °C overnight. The toluene solution was separated and concentrated. The residue was distilled on a spinning-band column. Hexamethylene chlorohydrin **50** (13.3 g, 50%) was collected as a colorless oil; bp 97 °C /11 mmHg.

1-*O*-(6-Chlorohexyl)-3-*O*-tosylglycerol (56)

To a solution of hexamethylene chlorohydrin **50** (51.7 mg, 0.38 mmol) and glycidyl tosylate (57.6 mg, 0.25 mmol) in 2 mL of methylene chloride was added 1 drop of distilled boron trifluoride etherate. The mixture was stirred at room temperature for 4 h. The mixture was then concentrated under vacuum and the residue was separated by medium pressure column chromatography (hexane/EtOAc, 6:1). 1-*O*-(6-Chlorohexyl)-3-*O*-tosylglycerol **56** was collected as a colorless oil (73.7 mg, 80%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35-1.50 (m, 4H, 2 x CH_2), 1.60 (p, 2H, CH_2),

1.78 (p, 2H, CH_2), 2.55 (br s, 1H, OH), 3.39 (s, 3H, $C_6H_4C\underline{H}_3$), 3.42-3.48 (m, 6H, 3 X OCH_2), 3.54 (t, 2H, J = 6.6 Hz, $ClCH_2$), 3.98 (m, 1H, OCH), 7.33-7.82 (dd, 4H, J = 7.2 Hz, J = 7.2 Hz, C_6H_4Me).

IR ($CDCl_3$, cm^{-1}): 3590, 2925, 2885, 1600, 1446, 1360, 1188, 1175, 1115, 980, 830, 810.

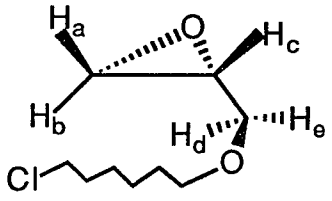
Elemental analysis: Calc. for $C_{16}H_{25}O_5ClS$: C 52.67, H 6.91, Cl 9.72. Found: C 52.41, H 7.10, Cl 10.00.

6-Chlorohexyl glycidyl ether (57)

To a solution of compound **56** (1.23 g, 3.37 mmol) in 10 mL of methanol in an ice bath was added 1.5 g of potassium carbonate. The mixture was stirred for 3 h at 0 °C, then stirred overnight at room temperature. TLC (hexane/EtOAc, 7:1) showed that the starting material had all disappeared (the R_f value of the epoxide, 0.45). Ether (100 mL) was added and the mixture was stirred for 10 min. The mixture was filtered and concentrated under vacuum. The residue was separated by flash chromatography (elution with hexane/EtOAc, 10:1). 6-Chlorohexyl glycidyl ether **57** (0.65 g, 80%) was collected as a colorless oil.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30-1.50 (m, 4H, 2 x CH_2), 1.60 (p, 2H, CH_2), 1.79 (p, 2H, CH_2), 2.61 (dd, $1H_a$, J = 5.0 Hz, J = 2.7 Hz), 2.80 (dd, $1H_b$, J = 5.0 Hz, J = 4.2 Hz), 3.15 (m, $1H_c$), 3.37 (dd, $1H_e$, J = 11.5 Hz, J = 5.8 Hz), 3.44-3.52 (m, 2H, OCH_2), 3.54 (t, 2H, J = 6.6 Hz, CH_2Cl), 3.72 (dd, $1H_d$, J = 11.5 Hz, J =

3.0 Hz).



IR ($CDCl_3$, cm^{-1}): 2940, 2860, 1465, 1380, 920, 890, 755, 710, 645.

Elemental analysis: Calc. for $C_9H_{17}O_2Cl$: C 56.33, H 9.12.

Found: C 56.10, H 8.89.

1-*O*-(6-Chlorohexyl)-3-*O*-benzylglycerol (58)

(a) To a solution of 6-chlorohexyl glycidyl ether (374 mg, 1.94 mmol) and benzyl alcohol (420 mg, 3.88 mmol) in 15 mL of methylene chloride was added 5 drops of boron trifluoride etherate. The mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by medium pressure chromatography (elution with hexane/EtOAc, 4:1). 1-*O*-(6-Chlorohexyl)-3-*O*- benzylglycerol **58** was collected as a colorless oil (350 mg, 60%).

(b) To a 50-mL round-bottom flask were added hexamethylene chlorohydrin **50** (2.05 g, 15.0 mmol), methylene chloride (20 mL), and boron trifluoride etherate (93 μL, 106 mg, 0.75 mmol). The flask was chilled to -78 °C under dry nitrogen gas protection. Benzyl glycidyl ether **38** (2.96 g, 18.0 mmol)

in 2 mL of methylene chloride was added by a syringe, and the the solution was stirred for 24 h at -78 °C. TLC (hexane/EtOAc, 4:1) showed that there was no hexamethylene chlorohydrin left. The solvent was removed by rotary evaporation. The residue was separated by flash chromatography (elution with hexane/EtOAc, 5:1). 1-*O*-(6-Chlorohexyl)-3-*O*-benzylglycerol **58** was collected as a colorless oil (3.58 g, 80%).

The two preparations of **58** resulted in identical products, as determined by comparision of their TLC retention times [R_f 0.33 (hexane/EtOAc, 4:1)], and ^{1}H NMR and IR spectra.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30-1.50 (m, 4H, 2 x CH_2), 1.58 (p, 2H, CH_2), 1.75 (p, 2H, CH_2), 2.57 (d, 1H, J = 4.1 Hz, OH), 3.40-3.59 (m, 8H, 3 X OCH_2, CH_2 Cl), 3.98 (m, 1H, OCH), 4.56 (s, 2H, $PhCH_2$), 7.33 (m, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.47, 26.72, 29.48, 32.59 (4 X CH_2), 44.97 (CH_2Cl), 69.65, 71.49, 71.50 (3 X OCH_2), 71.95 (OCH), 73.53 ($PhCH_2$), 127.75, 128.18, 128.45, 138.15 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3580, 3159, 2939, 2865, 1815, 1793, 1450, 1382, 1095, 910, 730, 658.

MS (m/e): 300 (M^+)/302 (3:1), 282/284 (3:1), 91 (base peak).

Elemental analysis: Calc. for $C_{16}H_{25}O_3Cl$: C 62.49, H 8.22.

Found: C 62.88, H 8.38.

1-*O*-(6-Chlorohexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol (43)

Oil dispersed (54%) sodium hydride (729 mg, 16.4 mmol) in a 50-mL round-bottom flask was washed twice with dry hexane. Compound **58** (2.46 g, 8.19 mmol) in 20 mL of THF was added, and the reaction mixture was stirred at 0 °C for 0.5 h. *n*-Heptyl iodide (9.26 g, 41 mmol) and tetra-*n*-butylammonium chloride[60,61] (121 mg, 0.4 mmol, 5%) were added, and the mixture was stirred at room temperature for 24 h. After ether (400 mL) was added the mixture was washed successively with water (50 mL), 10% aqueous sodium thiosulfate (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried, filtered, and the solvent was removed. The residue was separated by flash chromatography (elution with hexane/EtOAc, 25:1). 1-*O*-(6-Chlorohexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol **43** was collected as a colorless oil (2.78 g, 85%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 1.28 (s, 8H, 4 x CH_2), 1.33-1.44 (m, 4H, 2 x CH_2), 1.50-1.62 (m, 4H, 2 x $C\underline{H}_2CH_2O$), 1.68-1.82 (p, 2H, $C\underline{H}_2CH_2I$), 3.40-3.60 (m, 11H, 4 X OCH_2,CH_2Cl, OCH), 4.56 (s, 2H, $PhCH_2$), 7.31 (m, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07 (CH_3), 22.65, 25.50, 26.11, 26.74, 29.17, 29.54, 30.19, 31.87, 32.63 (9 X CH_2), 44.85 (CH_2Cl), 70.45, 70.59, 70.95, 71.36 (4 X OCH_2), 73.41 (OCH), 78.08 ($PhCH_2$), 127.48, 127.55, 128.29, 138.60

(C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3030, 2935, 2860, 1794, 1468, 1454, 1380, 1095, 905, 730, 646.

MS (m/e): 398 (M^+)/400 (3:1), 119, 91(base peak).

Elemental analysis: Calc. for $C_{23}H_{39}O_3Cl$: C 69.56, H 10.03, Cl 8.89. Found: C 69.23, H 9.85, Cl 8.61.

(*rac*)-1-*O*-(6-Iodohexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol (59)

A dry, one-necked, 25-mL round-bottom flask equipped with a magnetic stirring bar and a reflux condenser with a gas inlet at the top was charged with 1.290 g (3.23 mmol) of compound **43**, 1.211 g (8.08 mmol) of sodium iodide, and 10 mL of acetone.[71] The reaction mixture was stirred and refluxed under nitrogen for 24 h. The solvent was removed by rotary evaporation and the resulting solid was dissolved in 30 mL of methylene chloride and 20 mL of water. The layers were separated and the aqueous layer was extracted with two 20-mL portions of methylene chloride. The combined organic extracts were washed successively with 10% aqueous sodium thiosulfate (20 mL), water (3 X 20 mL), and brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate. After filtration and concentration of the solution, the residue was separated by medium pressure chromatography (elution with

hexane/EtOAc, 25:1). (*rac*)-1-*O*- (6-Iodohexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol **59** was collected as a colorless liquid (1.506 g, 95%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 1.28-1.38 (m, 12H, 6 x CH_2), 1.52-1.58 (m, 4H, 2 x $C\underline{H}_2CH_2O$), 1.80 (p, 2H, $C\underline{H}_2CH_2I$), 3.16 (t, 2H, J = 7.1 Hz, CH_2I), 3.39-3.63 (m, 9H, 4 X OCH_2, OCH), 4.55 (s, 2H, $PhCH_2$), 7.32 (m, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.65 (CH_2I), 14.05 (CH_3), 22.55, 25.05, 26.02, 29.08, 29.39, 30.08, 30.23, 31.78, 33.42 (9 X CH_2), 70.29, 70.47, 70.80, 71.23 (4 X OCH_2), 73.27 (OCH), 77.93 ($PhCH_2$), 127.40, 127.42, 128.18, 138.44 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3030, 2910, 2860, 1450, 1350, 1200, 1100.

MS (m/e): 262 (M^+-$(CH_2)_6I$), 91 (base peak).

Elemental analysis: Calc. for $C_{23}H_{39}O_3I$: C 56.32, H 8.02.
Found: C 56.58, H 8.19.

(*rac*)-1-*O*-(6-Iodomagnesiumhexyl)-2-*O*-*n*-heptyl-3-*O*-benzyl-glycerol (59a)

A 25-mL round-bottom three-necked flask containing magnesium (14.3 mg, 0.59 mmol) and a stirring bar, and fitted with a condenser with a drying tube and two septa, was heated by flame and flushed with dry nitrogen alternately three times to make sure that it was dry. (*rac*)-1-*O*- (6-Iodohexyl)-2-*O*-*n*- heptyl-3-*O*- benzylglycerol **59** (240 mg, 0.49 mmol) and iodine (2 mg) in 5 mL of dry THF were added by syringe. The solution was stirred and heated in an oil bath at 50 °C for 2 h. Most of the magnesium disappeared, indicating that the Grignard reagent had formed.

Soluble silver catalyst[69]

A solution of soluble silver was prepared by reacting silver nitrate (5.0 mmol) in THF (70 mL) with 30 mL of a 1.0 M solution of ethylmagnesium bromide at 0 °C for 3 h in the dark. The supernatant solution, 0.05 M "soluble silver," could be stored for prolonged periods at -20 °C.

1,1'-Di-*O*-(1,12-dodecanediyl)-2,2'-di-*O*-heptyl-3,3'-di-*O*-benzyl-bis-glycerol (45)

To the solution of (*rac*)-1-*O*- (6-iodomagnesiumhexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol **59a** (see above), a solution of soluble silver[69] (100 mL) and (*rac*)-1-*O*-(6-iodohexyl)-2-*O*-*n*-heptyl-3-*O*-benzylglycerol **59** (240 mg, 0.49 mmol) in 5 mL of THF was added by syringe. The mixture was stirred for 24 h at 60 °C (oil bath). The grey magnesium iodide solid precipitate was then removed using a short Celite column. The filtrate was diluted with 25 mL of

methylene chloride and washed with 10% aqueous sodium thiosulfate solution (15 mL) and water (20 mL) consecutively. The organic layer was dried and concentrated, and the residue was chromatographed on a medium pressure column (elution with hexane/EtOAc, 10:1). (*rac*)-1,1'-di-*O*- (1,12-Dodecanediyl)-2,2'-di-*O*-heptyl-3,3'-di-*O*- benzyl-bis-glycerol **45** was collected as a colorless oil (184.4 mg, 52%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 6H, *J* = 6.3 Hz, 2 X CH_3), 1.27 (s, 32H, 16 x CH_2), 1.51-1.60 (m, 8H, 4 x $C\underline{H}_2CH_2O$), 3.39-3.60 (m, 18H, 8 X OCH_2, 2 X OCH), 4.55 (s, 4H, 2 X $PhCH_2$), 7.27-7.34 (m, 10H, 2 X C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07 (2 X CH_3), 22.62 (2 X CH_2), 26.11 (2 X CH_2), 26.17 (2 X CH_2), 29.17 (2 X CH_2), 29.54 (2 X CH_2), 29.66 (4 X CH_2), 29.71 (2 X CH_2), 30.17 (2 X CH_2), 31.87 (2 X CH_2), 70.49 (2 X OCH_2), 70.62 (2 X OCH_2), 70.86 (2 X OCH_2), 71.71 (2 X OCH_2), 73.41 (2 X OCH), 78.05 (2 X $PhCH_2$), 127.48, 127.57, 128.29, 138.57 (2 X C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3030, 2915, 2860, 1452, 1100.

M S (m/e): 636 (M^+-91), 91 (base peak).

High resolution (+) LSIMS

M^++H Calculated for $C_{46}H_{78}O_6$: 727.5876. Observed: 727.5877.

_n_-Heptylcopper reagent (47)[68]

A suspension of 1.7 g (26 mmol) of zinc (99.999% purity, Aldrich) in 2 mL of THF containing 190 mg (1.0 mmol) of 1,2-dibromoethane was heated to 65 °C , and 0.1 mL (0.8 mmol) of chlorotrimethylsilane was added. After 15 min at 25 °C, a solution of *n*-heptyl iodide (5.65 g, 25 mmol) in 10 mL of THF was added slowly. When the addition was completed, the reaction mixture was stirred for 12 h at 25-30 °C. The dark grey solution was cooled to -10 °C , and a solution of 1.98 g (22 mmol) of CuCN and 1.9 g (44 mmol) of LiCl (both salts were predried at 150 °C under vacuum for 1 h) in 22 mL of THF was added rapidly. The resulting dark green solution was stirred at 0 °C for 10 min and was then used immediately.

_n_-Heptyl phenyl ketone (48)[68]

Benzoyl chloride (2.61 g, 18.7 mmol) was slowly added to the above prepared solution of the copper reagent at -25 °C. The reaction mixture was then stirred overnight at 0 °C. To the mixture was added 40 mL of ether and 40 mL of saturated aqueous sodium bicarbonate, and the mixture stirred for 10 min. The ether layer was concentrated and the residue was separated by flash chromatography (elution with hexane/EtOAc, 6:1). *n*-Heptyl phenyl ketone **48** was obtained as a colorless liquid (2.29 g, 60%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, J = 6.7 Hz, CH_3), 1.28-1.35 (m, 8H, 4 X CH_2), 1.68-1.80 (m, 2H, CH_2), 2.96 (t, 2H, J = 7.3 Hz, CH_2CO), 7.40-8.05 (m,

5H, C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3060, 2996, 2820, 1682, 1600, 1580, 1450, 1360, 1260, 955, 760, 690, 586.

MS (m/e): 204 (M^+), 133, 120, 105, 77 (base peak), 65, 51.

1-Benzyloxy-6-chlorohexane (51)[109]

To a solution of hexamethylene chlorohydrin (11.10 g, 81 mmol) and concentrated sulfuric acid (1 mL) in benzene was added a solution of benzyl alcohol (7.32 g, 68 mmol) in benzene (15 mL) dropwise during 10 min while the mixture was stirred and refluxed in an oil bath (90 °C). After 4 h, the solution became cloudy because of the formation of water. The reaction mixture was cooled to room temperature and 30 mL of benzene was added. The mixture was washed consecutively with water (30 mL), 5% aqueous sodium bicarbonate (30 mL), and water (30 mL). The organic layer was dried over anhydrous magnesium sulfate for 30 min. The solution was filtered and concentrated, and the residue was distilled under reduced pressure. 1-Benzyloxy-6-chlorohexane was collected as a colorless liquid (8.10 g, 53%); bp 118-125 °C /0.5 mmHg [lit.[110] bp 138 °C /1mmHg].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.45 (m, 4H, 2 x CH_2), 1.63 (m, 2H, $C\underline{H}_2CH_2O$), 1.77 (m, 2H, $C\underline{H}_2CH_2Cl$), 3.47 (t, 2H, J = 6.4 Hz, OCH_2), 3.52 (t,

2H, J = 6.7 Hz, $ClCH_2$), 4.50 (s, 2H, $PhCH_2$), 7.30-7.34 (m, 5H, C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3065, 3030, 2938, 2862, 1495, 1452, 1360, 1095, 900, 725, 645.

MS (m/e): 226 (M^+)/228 (3:1), 135, 91 (base peak),77, 65, 51.

1-Benzyloxy-6-iodohexane (52)

A dry, one-necked, 50-mL, round-bottom flask equipped with a magnetic stirring bar and a reflux condenser with a gas inlet at the top was charged with 0.55 g (2.43 mmol) of compound **51**, 1.31 g (8.74 mmol) of sodium iodide, and 8 mL of acetone.[71] The reaction mixture was stirred and refluxed under nitrogen for 24 h. The solvent was removed on a rotary evaporator and the resulting solid was dissolved in 30 mL of methylene chloride and 20 mL of water. The layers were separated and the aqueous layer was extracted with two 20-mL portions of methylene chloride. The combined organic extracts were washed successively with 10% aqueous sodium thiosulfate (20 mL), water (3 X 20 mL), and brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate. After filtration and concentration of the solution, the residue was separated by medium pressure chromatography (elution with hexane/EtOAc, 80:1). 1-Benzyloxy-6-iodohexane **52** was obtained as a colorless liquid (0.77 g, 2.42 mmol, 99%).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40-1.42 (m, 4H, 2 x CH_2), 1.62 (m, 2H, $C\underline{H}_2CH_2O$), 1.83 (m, 2H, $C\underline{H}_2CH_2I$), 3.18 (t, 2H, J = 6.9 Hz, CH_2 I), 3.47 (t, 2H, J = 6.2 Hz, OCH_2), 4.50 (s, 2H, $PhCH_2$), 7.33 (m, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.83 (CH_2I), 25.20, 29.56, 30.30, 33.49 (4 X CH_2), 70.22 (OCH_2), 72.91 ($PhCH_2$), 127.10, 127.57, 128.32, 138.70 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3068, 3035, 2932, 2860, 1453, 1361, 1277, 1205, 1096, 905, 760, 648.

MS (m/e): 318 (M^+), 227, 197, 91 (base peak), 77, 65, 41.

6-Benzyloxyhexylmagnesium iodide (53a)

A 25-mL round-bottom three-necked flask containing magnesium (54 mg, 2.2 mmol) and a stirring bar, and fitted with a condenser with a drying tube and two septa was heated by flame and flushed with dry nitrogen alternately three times to make sure that it was dry. 1-Benzyloxy-6-iodohexane **52** (633 mg, 2.0 mmol) in 10 mL of dry THF was added by syringe. The mixture was stirred and heated in an oil bath at 50 °C for 2 h. The magnesium disappeared, indicating that the Grignard reagent had formed.

1,12-Dibenzyloxydodecane (54)

To the 6-benzyloxyhexylmagnesium iodide **53a** solution (see above), a

solution containing soluble silver[69] (30 μL) and 1-benzyloxy-6-iodohexane **52** (633 mg, 2.0 mmol) in 5 mL of THF was added by syringe. The mixture was stirred for 24 h at room temperature, then diluted with ether (150 mL) and washed consecutively with saturated aqueous ammonium chloride (100 mL) and water (100 mL). The ether layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by medium pressure chromatography (elution with hexane/EtOAc, 60:1). 1,12-Dibenzyloxydodecane (381 mg, 50%) was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 16H, 8 X CH_2), 1.56-1.64 (m, 4H, 2 X $C\underline{H}_2CH_2O$), 3.46 (t, 4H, J = 6.6 Hz, 2 X OCH_2), 4.50 (s, 4H, 2 X $PhCH_2$), 7.33 (s, 10H, 2 X C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.24 (2 X CH_2), 29.51 (2 X CH_2), 29.60 (4 X CH_2), 29.82 (2 X CH_2), 70.59 (2 X OCH_2), 72.87 (2 X $PhCH_2$), 127.42, 127.59, 128.32, 138.87 (2 X C_6H_5).

IR (CCl_4, cm^{-1}): 2928, 2860, 1452, 1370, 1245, 1090, 900, 725, 645.

MS (m/e): 291 (M^+-Bn), 274, 107, 91 (base peak), 77, 65, 41.

16-Chlorohexadecanoyl chloride (61)

To a solution of 16-hydroxyhexadecanoic acid (2.90 g, 10.64 mmol) and

benzene (10 mL) in a 100-mL three-necked flask which was fitted with a condenser carrying a drying tube and two septa was added freshly distilled thionyl chloride (12.66 g, 106.4 mmol) by syringe. The mixture was stirred at room temperature for 30 min and then refluxed for 3 h. The excess thionyl chloride and benzene were distilled out, and the residue was pumped at 100 °C for 1 h by using an oil pump. IR spectroscopy of the residue confirmed the absence of hydroxyl and carboxylic hydroxyl groups, and the carbonyl group of the acyl chloride appeared at 1790 cm^{-1}. The residue was reduced directly to 16-chlorohexadecanol by alane without purification.

16-Chlorohexadecanol (62)

Preparation of the alane solution:[72] To aluminum trichloride (1.419 g, 10.64 mmol) in a 25-mL flask was added dropwise 10 mL of freshly distilled ether. The solution was kept gently boiling during the addition. This solution was added dropwise to a solution of lithium aluminum hydride (0.404 g, 10.64 mmol) in 10 mL of ether. The grey suspension of alane was added then to a solution of the crude 16-chlorohexadecanoyl chloride in 15 mL of ether at a rate which kept the solution gently refluxing. The mixture was then stirred at room temperature for 3 h. Water (20 mL) and 6N sulfuric acid (15 mL) were added consecutively. The ether layer was separated and the aqueous layer was extracted with ether (3 X 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (elution with

hexane/EtOAc, 7:1). 16-Chlorohexadecanol **62** (2.78 g, 94%) was obtained as a white solid; mp 44 °C [lit.[111] 43 °C].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 22H, 11 X CH_2), 1.38-1.45 (m, 2H, CH_2), 1.50-1.60 (m, 2H, $C\underline{H}_2CH_2O$), 1.70-1.84 (p, 2H, $C\underline{H}_2CH_2Cl$), 3.53 (t, 2H, J = 6.7 Hz, CH_2 Cl), 3.64 (t, 2H, J = 6.5 Hz, $C\underline{H}_2OH$).

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

MS (m/e): 258 (M^+-H_2O)/260 (3:1), 55 (base peak).

Elemental analysis: Calc. for $C_{16}H_{33}OCl$: C 69.41, H 12.01.
Found: C 69.18, H 12.19.

1-*O*-(16-Chlorohexadecyl)-3-*O*-tosyl-*sn*-glycerol (63)

To a 50-mL round-bottom flask was added a stirring bar, 2.10 g (7.58 mmol) of 16-chlorohexadecanol, and 1.904 g (8.34 mmol) of (*R*)-(-)-glycidyl tosylate ($[\alpha]^{25}_D$ -17.1° (*c* 2.4, $CHCl_3$); 92% ee).[107] The mixture was dried under vacuum at 100 °C for 1 h. Freshly distilled methylene chloride (20 mL) and a catalytic amount of boron trifluoride etherate (54 mg, 1 drop) were added consecutively to the flask. The solution was stirred overnight. TLC (hexane/EtOAc, 4:1) showed that most of the 16-chlorohexadecanol and all of the glycidyl tosylate had disappeared. The solvent was removed by rotary

evaporation, giving a residue that was purified by medium pressure chromatography (elution with hexane/EtOAc, 2:1). 1-*O*-(16-Chlorohexadecyl)-3-*O*-tosyl-*sn*-glycerol **63** (3.255 g, 85%) was obtained as a white solid; mp 64.5-66.5 °C; $[\alpha]^{25}_{D}$ -3.04° (*c* 4.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 24H, 12 X CH_2), 1.38-1.51 (m, 2H, $C\underline{H}_2CH_2O$), 1.73-1.80 (m, 2H, $C\underline{H}_2CH_2Cl$), 2.45 (s, 3H, $C_6H_4C\underline{H}_3$), 2.55 (s, 1H, OH), 3.39 (t, 2H, *J* = 6.6 Hz, OCH_2R), 3.43 (d, 2H, *J* = 3.9 Hz, $OC\underline{H}_2CH$), 3.52 (t, 2H, *J* = 6.7 Hz, CH_2Cl), 3.96 (m, 1H, OCH), 4.06 (t, 2H, *J* = 5.2 Hz, CH_2OTs), 7.35-7.80 (dd, 4H, Ar).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.26 (CH_3), 26.03 (CH_2), 26.90 (CH_2), 28.90 (CH_2), 29.45 (2 X CH_2), 29.54 (3 X CH_2), 29.65 (5 X CH_2), 32.69 (CH_2), 45.13 (CH_2Cl), 68.37 (OCH_2), 70.54 (OCH_2), 70.67 (OCH_2), 71.80 (OCH), 128.02, 129.90, 132.90, 144.94 (C_6H_4).

IR ($CDCl_3$, cm^{-1}): 3580, 3150, 2920, 2850, 1780, 1595, 1460, 1360, 1245, 1185, 1175, 1095, 982, 900, 730, 645, 550.

MS (m/e): 331 (M^+-TsOH-H)/333 (3:1), 289/291 (3:1), 173, 155, 91, 57 (base peak).

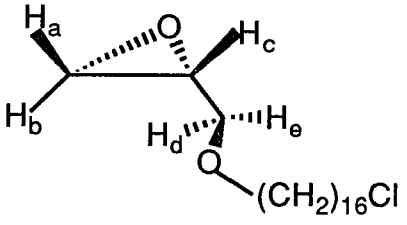
High resolution (+) LSIMS. M^+ Calculated for $C_{26}H_{45}O_5ClS$: 504.2679.

Observed: 504.2676.

(*R*)-(+)-Oxiranemethyl 16-chlorohexadecyl ether (64)

To a solution of 1-*O*-(16-chlorohexadecyl)-3-*O*-tosyl-*sn*-glycerol **63** (2.54 g, 5.03 mmol) in 15 mL of absolute methanol in a 50-mL round-bottom flask submerged in an ice bath and precooled for 15 min was added potassium carbonate (2.086 g, 15.08 mmol). The reaction mixture was stirred for 3 h at 0 °C. To the mixture was added 100 mL of ether, and the solution was filtered through a short Celite column. The filtrate was concentrated and the product was separated by flash chromatography (elution with hexane/EtOAc, 10:1). (*R*)-(+)-Oxiranemethyl 16-chlorohexadecyl ether **64** was obtained as a white solid (1.34 g, 80%); mp 51-54 °C; $[\alpha]^{25}_{D}$ +1.60° (*c* 2.09, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26-1.45 (s, 24H, 12 X CH_2), 1.58 (p, 2H, *J* = 6.6 Hz, $C\underline{H}_2CH_2O$), 1.77 (p, 2H, *J* = 7.0 Hz, $C\underline{H}_2CH_2Cl$), 2.60 (dd, $1H_a$, *J* = 5.0 Hz, *J* = 2.7 Hz), 2.78 (t, $1H_b$, *J* = 4.6 Hz), 3.14 (m, $1H_c$), 3.52 (t, 2H, *J* = 6.7 Hz, CH_2Cl), 3.33-3.73 (m, 4H, 2 X OCH_2).



^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.14 (CH_2), 26.96 (CH_2), 28.93 (CH_2), 29.51 (3

X CH_2), 29.64 (4 X CH_2), 29.77 (3 X CH_2), 32.75 (CH_2), 45.03 (CH_2Cl), 44.26, 50.87 (epoxide), 71.50 (OCH_2), 71.74 (OCH_2).

IR ($CDCl_3$, cm^{-1}): 2910, 2850, 1455, 1335, 1300, 1250, 1100.

MS (m/e): 287/289 (3:1), 111, 97, 83, 71, 69, 57, 55 (base peak).

Elemental analysis: Calc. for $C_{19}H_{37}O_2Cl$: C 68.54, H 11.20.
Found: C 68.38, H 10.96.

1-*O*-(16-Chlorohexadecanyl)-3-*O*-benzyl-*sn*-glycerol (65)

(a) To a 50-mL round-bottom flask was added a solution of 1.14 g (3.42 mmol) of ether **64** and 4.04 g (34.20 mmol) of benzyl alcohol in 15 mL of methylene chloride. Powdered, activated 4Å molecular sieves and a stirring bar were added. The mixture was stirred for 2 h. Boron trifluoride etherate (40 μL) was added, and the reaction mixture was stirred at room temperature for 3 h. TLC (hexane/EtOAc, 7:1) showed that all of the epoxide disappeared. The mixture was diluted with 100 mL of methylene chloride and filtered through Celite. Methylene chloride was removed by rotary evaporation, and excess benzyl alcohol was distilled out under 5 mmHg pressure (bp 75 °C/5 mmHg). The residue was purified by flash chromatography (elution with hexane/EtOAc, 10:1). 1-*O*-(16-Chlorohexadecyl)-3-*O*-benzyl-*sn*-glycerol **65** (1.24 g, 82%) was obtained as an oil; $[\alpha]^{25}_D$ +1.33° (*c* 2.5, $CHCl_3$).

(b) To a 50-mL round-bottom flask were added 16-chlorohexadecanol **62** (214 mg, 0.77 mmol), benzyl glycidyl ether **38** (152 mg, 0.93 mmol), methylene chloride (15 mL), and a stirring bar. The flask was cooled to 0 °C under dry nitrogen gas protection. A drop of boron trifluoride etherate was added the solution was stirred overnight at 0 °C. An additional amount of ether **38** (38 mg, 0.23 mmol) was added to the solution, and stirring was continued for another 24 h. TLC (hexane/EtOAc, 5:1) showed that there was no 16-chlorohexadecanol **62** left. The solvent was removed by rotary evaporation. The residue was separated by flash chromatography (elution with hexane/EtOAc, 10:1). 1-*O*-(6-Chlorohexadecyl)-3-*O*-benzyl-*sn*-glycerol **65** was collected as a colorless oil (293 mg, 86%).

The two preparations of **65** resulted in identical products, as determined by comparision of their TLC retention times [R_f 0.30 (hexane/EtOAc, 5:1)] and ^{1}H NMR and IR spectra.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26-1.40 (s, 24H, 12 X CH_2), 1.5 (m, 2H, $C\underline{H}_2CH_2O$), 1.75 (p, 2H, J = 7.0 Hz, $C\underline{H}_2CH_2Cl$), 2.62 (d, 1H, J = 4.1 Hz, OH), 3.40-3.57 (m, 8H, 3 X OCH_2, CH_2Cl), 3.96 (m, 1H, OCH), 4.55 (s, 2H, CH_2Ph), 7.32 (s, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.16 (CH_2), 26.95 (CH_2), 28.93 (CH_2), 29.67 (10 X CH_2), 32.74 (CH_2), 45.09 (CH_2Cl), 69.66 (OCH_2), 71.60 (OCH_2), 71.76 (OCH_2), 71.93 (OCH), 73.54 (CH_2Ph), 127.73, 128.45, 138.22 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 3570, 2910, 2840, 1450, 1205, 1100.

MS (m/e): 440 (M^+)/442 (3:1), 91 (base peak).

Elemental analysis: Calc. for $C_{26}H_{45}O_3Cl$: C 70.80, H 10.28. Found: C 70.83, H 10.09.

1-*O*-(16-Chlorohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol (66)

To a 50-mL round bottom flask loaded with a drying tube and a stirring bar was added 1-*O*-(16-chlorohexadecyl)-3-*O*-benzyl-*sn*-glycerol **65** (837 mg, 1.89 mmol) and freshly distilled THF (10 mL). The flask was cooled in an ice bath for 10 min, and sodium hydride powder (neat) (81.5 mg, 3.26 mmol) was added. The mixture was stirred for 0.5 h at 0 °C. 1-Iodohexadecane (2.872 g, 8.15 mmol) and tetrabutylammonium iodide (35 mg, 0.03 mmol) were added, and the temperature was raised to room temperature, then to reflux overnight. TLC (hexane/EtOAc, 10:1) showed that most of the alcohol **65** had been converted to ether **66**. The reaction mixture was diluted with 100 mL of ether and filtered through Celite. The filtrate was concentrated and the product was purified by flash chromatography (elution with hexane/EtOAc, 50:1). 1-*O*-(16-Chlorohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol **66** was collected as a colorless oil (1.25 g, 99%); $[\alpha]^{25}_D$ +0.19° (*c* 4.68, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, J = 6.6 Hz, CH_3), 1.26 (s, 50H, 25 X CH_2), 1.51-1.60 (m, 4H, 2 X CH_2), 1.76 (p, 2H, J = 7.0 Hz, $C\underline{H}_2CH_2Cl$), 3.36 (s, 3H, OCH_3), 3.39-3.59 (m, 11H, 4 X OCH_2, CH_2Cl, OCH), 4.55 (s, 2H, CH_2Ph), 7.32 (s, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07 (CH_3), 20.65 (CH_2), 22.81 (CH_2), 26.26 (2 X CH_2), 27.10 (CH_2), 29.10 (CH_2), 29.60 (CH_2), 29.80 (18 X CH_2), 30.26 (CH_2), 32.05 (CH_2), 32.81 (CH_2), 45.15 (CH_2Cl), 70.45 (OCH_2), 70.59 (OCH_2), 70.95 (OCH_2), 71.36 (OCH_2), 73.41 (OCH), 78.14 (CH_2Ph), 127.53, 127.69, 128.42, 138.59 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 2920, 2855, 1455, 1105, 900, 810, 600.

MS (m/e): 543/545 (3:1), 287/289 (3:1), 91 (base peak).

Elemental analysis: Calc. for $C_{42}H_{77}O_3Cl$: C 75.55, H 11.66.
Found: C 75.00, H 11.66.

High resolution (+) LSIMS. M^+ Calculated for $C_{42}H_{77}O_3Cl$: 664.5565.
Observed: 664.5562.

1-*O*-(16-Iodohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol (26)

A dry, one-necked, 25-mL round-bottom flask equipped with a magnetic

stirring bar and a reflux condenser with a gas inlet at the top was charged with 2.59 g (3.38 mmol) of compound **6 6**, 5.07 g (33.80 mmol) of sodium iodide, and 10 mL of 2-butanone. The reaction mixture was stirred and refluxed under nitrogen for 48 h. The reaction mixture was cooled and mixed with 100 mL of ether and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (elution with hexane/EtOAc, 75:1). 1-*O*-(16-Iodohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol **2 6** was collected as a colorless liquid (2.5 g, 85%); $[\alpha]^{30}_{D}$ +0.17° (*c* 5.30, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, *J* = 6.6 Hz, CH_3), 1.26 (m, 30H, 25 x CH_2), 1.54 (m, 4H, 2 x $C\underline{H}_2CH_2O$), 1.81 (p, 2H, *J* = 7.1 Hz, $C\underline{H}_2CH_2I$), 3.18 (t, 2H, *J* = 7.1 Hz, CH_2I), 3.42 (t, 4H, *J* = 6.6 Hz, 2 X OCH_2), 3.48-3.60 (m, 5H, 2 X OCH_2, OCH), 4.55 (s, 2H, $PhCH_2$), 7.28-7.34 (m, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.04 (CH_2I), 14.11 (CH_3), 22.70 (CH_2), 26.15 (CH_2), 28.57 (CH_2), 29.70 (21 X CH_2), 30.14 (CH_2), 30.53 (CH_2), 31.94 (CH_2), 33.62 (CH_2Cl), 70.42 (OCH_2), 70.62 (OCH_2), 70.82 (OCH_2), 71.68 (OCH_2), 73.40 (OCH), 78.01 (CH_2Ph), 127.48, 127.56, 128.29, 138.52 (C_6H_5).

IR ($CDCl_3$, cm^{-1}): 2930, 2860, 1450, 1290, 1100.

High resolution (+) LSIMS. M^+ Calculated for $C_{42}H_{77}O_3I$: 756.4921. Observed: 756.4918.

1-*O*-(16-Iodomagnesiumhexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol (26a)

A 25-mL round-bottom three-necked flask containing magnesium (14.5 mg, 0.60 mmol) and a stirring bar, and fitted with a condenser with a drying tube and two septa, was heated by flame and flushed with dry nitrogen alternately three times to make sure that it was dry. 1-*O*-(16-Iodohexadecyl)-2-*O*-hexadecyl-3-*O*-benzyl-*sn*-glycerol **26** (0.41 g, 0.54 mmol) and iodine (2 mg) in 5 mL of dry THF were added by syringe. The solution was stirred and heated in an oil bath at 50 °C overnight. Most of the magnesium disappeared, indicating that the Grignard reagent had formed.

1,1'-Di-*O*-(1,32-dotriacontanediyl)-2,2'-di-*O*-hexadecyl-3,3'-di-*O*-benzyl-bis-glycerol (18)

To the solution of Grignard reagent **26a** (see above), a solution of soluble silver[69] (200 μL, 0.01 mmol) and iodide **26** (0.42 g, 0.55 mmol) in 5 mL of THF was added by syringe. The mixture was stirred for 48 h at 60 °C oil bath. The reaction solution was diluted with 50 mL of ether and filtered. The filtrate was concentrated and purified by medium pressure chromatography (elution with hexane/EtOAc, 25:1). 1,1'-Di-*O*-(1,32-dotriacontanediyl)-2,2'-di-*O*-hexadecyl-3,3'-di-*O*-benzyl-bis-glycerol **18** (260 mg, 38%) was collected as a pale yellowish semisolid; $[\alpha]^{25}_{D}$ +0.23° (*c* 1.61, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 6H, *J* = 6.6 Hz, 2 X CH_3), 1.25 (s, 108H,

54 x CH_2), 1.54 (m, 8H, 4 x $C\underline{H}_2CH_2O$), 3.42 (t, 8H, J = 6.6 Hz, 4 X OCH_2), 3.50-3.60 (m, 10H, 4 X OCH_2, 2 X OCH), 4.55 (s, 4H, 2 X $PhCH_2$), 7.32 (m, 10H, 2 X C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.11 (2 X CH_3), 22.70 (2 X CH_2), 26.16 (2 X CH_2), 29.38, 29.54, 29.72, 30.15 (52 X CH_2), 31.95 (2 X CH_2), 70.44 (2 X OCH_2), 70.65 (2 X OCH_2), 70.83 (2 X OCH_2), 71.71 (2 X OCH_2), 73.41 (2 X OCH), 78.00 (2 X CH_2Ph), 127.50, 127.59, 128.32, 138.54 (2 X C_6H_5).

IR ($CDCl_3$, cm^{-1}): 2930, 2886, 1460, 1100.

High resolution (+) LSIMS. M^+ Calculated for $C_{84}H_{154}O_6$: 1259.1752. Observed: 1259.1750.

Methyl 16-hydroxyhexadecanoate (86)

To a 50-mL round-bottom flask fitted with a condenser and drying tube was added a solution of 16-hexadecanolide **85** (1.00 g, 3.93 mmol) in absolute methanol (30 mL) and 100 μL of BF_3 etherate. The solution was refluxed for 24 h. TLC (hexane/EtOAc, 7:1) showed that only one new spot was formed. The solvent was removed by rotary evaporation. The residue (white crystals) was dissolved in 20 mL of ether and washed with water (15 mL X 2). The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. Pure methyl 16-hydroxyhexadecanoate **86** was obtained as a

white solid (1.10 g, 99%); mp 55-56 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 20H, 10 X CH_2), 1.44 (s, 2H, CH_2), 1.57 (p, 4H, 2 X CH_2), 2.30 (t, 2H, *J* = 6.6 Hz, CH_2), 3.64 (t, 2H, *J* = 6.6 Hz, CH_2), 3.67 (s, 3H, CH_3).

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

MS (m/e): 256 (M^+-OCH_2), 98, 87, 74, 55.

16-Hydroxyhexadecanoic acid (60)

To a 250-mL round-bottom flask was added a solution of KOH (10.00 g, 179 mmol) in 115 mL of 10% aqueous methanol and 16-hexadecanolide **85** (10.00 g, 39.3 mmol). The solution was refluxed for 24 h under N_2 protection. The solvent was removed by rotary evaporation. The sodium salt of **60** was dissolved in 500 mL of hot 10% aqueous HCl. Crude 16-hydroxyhexadecanoic acid **60** crystallized as a white solid when the solution was cooled to room temperature. The crude product was recrystallized from hot methanol to give pure 16-hydroxyhexadecanoic acid **60** (10.70 g, 100%); mp 94-96 °C [lit.[112] 97-98 °C].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 22H, 11 X CH_2), 1.58 (m, 4H, 2 X CH_2), 2.33 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CO_2H$), 3.63 (t, 2H, *J* = 6.5 Hz, $C\underline{H}_2OH$), 3.66 (brs,

1H, OH), 9.70 (s, 1H, CO_2H).

IR ($CDCl_3$, cm^{-1}): 3280, 3210-2350 (br), 2912, 2847, 1700, 1470.

16-Chlorohexadecyl tosylate (80)[99]

To a 100-mL round-bottom flask fitted with a drying tube were added 16-chlorohexadecanol (8.31 g, 30 mmol), pyridine (11.87 g, 150 mmol), and a magnetic stirring bar. The flask was placed in a water bath sufficiently cold to lower the temperature of the mixture to 10 °C. At this temperature, *p*-toluenesulfonyl chloride (6.29 g, 33 mmol) was added in portions over a 10- to 20-min period. The mixture was stirred for 3 h at a temperature below 20 °C, after which it was diluted with 25 mL of concentrated hydrochloric acid in 80 mL of ice water. The ester that crystallized was collected on a chilled Büchner funnel and sucked as dry as possible. The solid was transferred to a 100-mL beaker, 40-60 mL of ethanol was added, and the mixture was warmed on a steam bath until the ester melted. It was then cooled in a ice bath while being stirred continuously. The solid ester separated in a fairly fine state, and was collected on a Büchner funnel and allowed to dry in the air. The yield of the tosylate was 11.64 g (90%); mp 56-58 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 22H, 11 X CH_2), 1.41 (m, 2H, CH_2), 1.63 (p, 2H, CH_2), 1.77 (p, 2H, CH_2), 2.45 (s, 3H, CH_3), 3.53 (t, J = 6.7 Hz, 2H, CH_2Cl), 4.02 (t, 2H, CH_2OTs), 7.34, 7.81 (dd, 4H, Ts).

Conclusions. The method reported here allows the preparation of protected model lipid 1,3 or 2,3-*sn*-glycerol tetraethers via BF_3-catalyzed alcoholysis of glycidyl derivatives, and silver catalyzed carbon-carbon coupling of the corresponding Grignard reagent and alkyl iodide. Attempts to construct and couple appropriately substituted alkyl glycerol derivatives to form macrocyclic diglycerol tetraethers are in progress.

CHAPTER 5

REFERENCES

1. Kates, M. In *Ether Lipids: Chemistry and Biology*; Snyder, F., Ed.; Academic Press: New York, 1972, pp 351.
2. Langworthy, T. A. In *The Bacteria*; Woese, C. R., Wolfe, R. S., Eds.; Academic Press: New York, 1985, pp 459-491.
3. Woese, C. R. *Microbiol. Rev.* **1987**, *51*, 221.
4. De Rosa, M.; Lanzotti, V.; Nicolaus, B.; Trincone, A.; Gambacorta, A. In *Microbiology of Extreme Environments and Its Potential for Biotechnology*; DaCosta, M. S., Duarte, J. C., William, R. A. D., Eds.; Elsevier: New York, 1989, pp 131-151.
5. Heathcock, C.; Finkelstein, B.; Aoki, T.; Poulter, C. *Science* **1985**, 229, 862.
6. Poulter, C.; Aoki, T.; Daniels, L. *J. Am. Chem. Soc.* **1988**, 110, 2620.
7. Kaminuma, K.; Yamagishi, M.; Fijimoto, Y.; Ikekawa, W.; Oshima, T. *J. Am. Chem. Soc.* **1990**, 112, 2740.
8. Nicolaus, B.; Trincone, A.; Esposito, E.; Vaccaro, M.; Gambacorta, A.; De Rosa, M. *Biochem. J.* **1990**, 266, 785.
9. De Rosa, M.; Gambacorta, A. *Prog. Lipid Res.* **1988**, 27, 153.
10. Luzzati, V.; Vargas, R.; Gulik, A.; Mariani, P.; Seddon, J.; Rivas, E. *Biochemistry* **1992**, 31, 279.
11. Quinn, P.; Kates, M.; Tocanne, J.; Tomoaia-Cotisel, M. *Biochem. J.* **1989**, 261, 377.
12. Rolandi, R.; Schindler, H.; De Rosa, M.; Gambacorta, A. *Eur. Biophys. J.* **1986**, 14, 19.

13. Bruno, S.; Gliozzi, A.; Cannistravo, S. *J. Phys.* **1986**, 47, 1555.

14. Bruno, S.; Gliozzi, A.; Cannistravo, S.; De Rosa, M.; Gambacorta, A. *Eur. Biophys. J.* **1985**, 13, 67.

15. Steward, L.; Kates, M.; Ekiel, I.; Smith, I. C. P. *Chem. Phys. Lipids* **1990**, 54, 115.

16. De Rosa, M.; De Rosa, S.; Gambacorta, A. *Phytochemistry* **1977**, 16, 1909.

17. De Rosa, M.; De Rosa, S.; Gambacorta, A.; Minale, L.; Bu'Lock, J. D. *Phytochemistry* **1977**, 16, 1961.

18. De Rosa, M.; Gambacorta, A.; Nicolaus, B.; Sodano, S.; Bu'Lock, J. D. *Phytochemistry* **1980**, 19, 833.

19. Tornabene, T. G. *J. Mol. Evol.* **1978**, 11, 253.

20. Makula, R. A.; Singer, M. E. *Biochem. Biophys. Res. Commun.* **1978**, 82, 716.

21. Tornabene, T. G.; Langworthy, T. A. *Science* **1979**, 203, 51.

22. De Rosa, M.; Gambacorta, A.; Nicolaus, B.; Chappe, B.; Albrecht, B. *Biochim. Biophys. Acta* **1983**, 753, 249.

23. Langworthy, T. *Biochim. Biophys. Acta* **1977**, 487, 37.

24. De Rosa, M.; Gambacorta, A.; Minale, L. *J. Chem. Soc., Chem. Commun.* **1974**, 543.

25. Mayberry-Carson, K.; Langworthy, T.; Mayberry, W.; Smith, P. *Biochim. Biophys. Acta* **1974**, 360, 217.

26. Langworthy, T. *Curr. Top. Membr. Transp.* **1982**, 17, 45.

27. Heathcock, C.; Finkelstein, B.; Jarvi, E.; Radel, P.; Hadley, C. *J. Org. Chem.* **1988**, 53, 1922.

28. De Rosa, M.; Gambacorta, A. *Syst. Appl. M.* **1986**, 7, 278.

29. Langworthy, T.; Pond, J. *Syst. Appl. M.* **1986**, 7, 253.

30. Woese, C.; Wolfe, R. *The Bacteria,* Vol. VIII, Academic Press: New York, 1985, pp 172.

31. Kushwaha, S.; Kates, M.; Sprott, G.; Smith, I. C. P. *Biochim. Biophys. Acta* **1981**, 664, 156.

32. Bangham, A.; Standish, M.; Watkins, J. *J. Mol. Biol.* **1965**, 13, 238.

33. Shek, P. N.; Barker, R. F. *Fed. Proc.* **1986**, 45, 577.

34. (a) Papahadjopoulos, D.; Gabizon, A. *Ann. N. Y. Acad. Sci.* **1987**, 507, 64 . (b) Juliano, R.; Daoud, S.; Kranse, H.; Grant, C. *ibid.* **1987**, 507, 89.

35. Lelkes, P.; Goldenberg, D.; Gliozzi, A.; De Rosa, M.; Gambacorta, A.; Miller, I. *Biochim. Biophys. Acta* **1983**, 732, 714.

36. De Rosa, M. *J. Mol. Biol.* **1985**, 182, 131.

37. Luzzati, V. *Syst. Appl. M.* **1986**, 7, 262.

38. Gliozzi, A. *J. Membr. Biol.* **1983**, 75, 45.

39. Roush, W.; Grover, P.; Lin, X. *Tetrahedron Lett.* **1990**, 31, 7563.

40. Yamauchi, K.; Moriya, A.; Kinoshita, M. *Biochim. Biophys. Acta* **1989**, 1003, 151.

41. Yamauchi, K.; Sakamoto, Y.; Mariya, A; Yamada, K.; Hosokawa, T.; Higuchi, T.; Kinoshita, M. *J. Am. Chem. Soc.* **1990**, 112, 3188.

42. Moss, R.; Fujita, T.; Okamura, Y. *Langmuir* **1991**, 7, 2415.

43. Yamauchi, K.; Yamada, K.; Kinoshita, M.; Kamikawa, T. *Bull. Chem. Soc. Jpn.* **1991**, 64, 2088.

44. Kim, J.; Thomson, D. H. *Langmuir* **1992**, 8, 637.

45. Yamauchi, K.; Une, F.; Tabata, S.; Kinoshita, M. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 765.

46. Hunig, S.; Lucke, E.; Brenninger, W. *Org. Synth.* Coll. Vol. V, Baumgarten, H. E., Ed.; Wiley: New York, 1973, pp 533.

47. Caglioti, L. *Org. Synth.* Coll. Vol. VI, Noland, W. E., Ed.; Wiley: New York,

1988, pp 62.

48. Furukawa, A.; Shoji, H.; Nakaya, T.; Imoto, M. *Makromol. Chem.* **1987**, 188, 265.

49. Guivisdalsky, P.; Bittman, R. *J. Am. Chem. Soc.* **1989**, 111, 3077.

50. Guivisdalsky, P.; Bittman, R. *J. Org. Chem.* **1989**, 54, 4637.

51. Ali, S.; Bittman, R. *Biochem. Cell Biol.* **1990**, 68, 360.

52. Deveer, A.; Dijkman, R.; Leuveling-Tjeenk, M.; Berg, L.; Ransac, S.; Batenburg, M.; Egmond, M.; Verheij, H.; Naas, G. *Biochemistry* **1991**, 30, 10034.

53. Jain, M.; Tao, W.; Rogers, J.; Arenson, C.; Eibl, H.; Yu, B. *Biochemistry* **1991**, 30, 10256.

54. We thank Dr. Ralph S. Wolfe, Department of Microbiology, University of Illinois, for the frozen cells of *Methanobacterium thermoautotrophicum.*

55. Bligh, E. G.; Dyer, W. J. *Can. J. Biochem. Physiol.* **1959**, 37, 911.

56. Kates, M. *Techniques of Lipidology,* Amsterdam, North-Holland American Elsevier: New York, 1972, pp 164.

57. An authentic sample of dibiphytanyl diglycerol was provided by Professor M. Kates, Department of Biochemistry, University of Ottawa, Ottawa, Ontario, Canada.

58. Byun, H-S.; Bittman, R. *Tetrahedron Lett.* **1989**, 30, 2751.

59. Bacon, J.; Collis, M. *Chem. Ind.* (London) **1971**, 930.

60. Abdelmageed, O; Duclos, R.; Griffin, R.; Siminovitch, D.; Ruocco, M.; Makriyannis, A. *Chem. Phys. Lipids* **1989**, 50, 163.

61. Abdelmageed, O; Duclos, R.; Abushanab, E.; Makriyannis, A. *Chem. Phys. Lipids* **1990**, 54, 49.

62. Langworthy, T. A. *J. Bacteriol.* **1977**, 130, 1326.

63. De Rosa, M.; De Rosa, S.; Gambacorta, A.; Bu'lock, J. D. *Phytochemistry*

1980, 19, 249-254.

64. Mayberry-Carson, K.; Jewell, M.; Smith, P. *J. Bacteriol.* **1978**, 133, 1510.
65. Smith, P. *Biochim. Biophys. Acta* **1980**, 691, 367.
66. Kushwaha, S.; Kates, M.; Sprott, G.; Smith, I. C. P. *Science* **1981**, 211, 1163.
67. De Rosa, M.; Gambacorta, A.; Nicolaus, B.; Bu'Lock, J. D. *Phytochemistry* **1980**, 19, 791.
68. Knochel, P.; Yeh, P.; Berk, S.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390.
69. Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
70. Campbell, K.; Sommers, A. *Org. Synth.* Coll. Vol. III, Horning, E. C., Ed.; Wiley: New York, pp 446.
71. Kuwajima, I.; Urabe, H. *Org. Synth.* **1988**, 66, 87.
72. Nystrom, R. *J. Am. Chem. Soc.* **1959**, 81, 610.
73. (*R*)-(-)-2-(Benzyloxymethyl)oxirane was purchased from Aldrich.
74. Doyle, M.; DeBuyn, D.; Scholten, D. *J. Org. Chem.* **1973**, 38, 625.
75. McMurry, J. *Chem. Rev.* **1989**, 89, 1513.
76. McMurry, J.; Fleming, M.; Kees, K.; Krepski, L. *J. Org. Chem.* **1978**, 43, 3255.
77. McMurry, J.; Kees, K. *J. Org. Chem.* **1977**, 42, 2655.
78. Ramberg, L.; Backlund, B. *Ark. Kemi Minerol. Geol.* **1940**, 13A, 27 [*C.A.* **1940**, 34, 4725[5]].
79. Grossert, J. *Tetrahedron Lett.* **1974**, 15, 2805.
80. Paquette, L. *Org. React.* **1977**, 25, 1.
81. Bieniarz, C.; Cornwell, M. *Tetrahedron Lett.* **1993**, 34, 939.
82. Reid, E. *Organic Chemistry of Bivalent Sulfur*, Vol. 1, pp 21-29, 32-35; Vol. 5, pp 27-34, Chemical Publishing Company: New York, 1958.

83. Tuleen, D.; Stephens, T. *Chem. Ind.* (London) **1966**, 1555.

84. Tuleen, D.; Markum, V. *J. Org. Chem.* **1967**, 32, 204.

85. Tuleen, D. *J. Org. Chem.* **1967**, 32, 4006.

86. Tuleen, D.; Stephens, T. *J. Org. Chem.* **1969**, 34, 31.

87. Tuleen, D.; Buchanan, D. *J. Org. Chem.* **1967**, 32, 495.

88. Tuleen, D.; Bennett, R. *J. Heterocycl. Chem.* **1969**, 6, 115.

89. Vilsmaiev, E.; Sprugel, W. *Ann. Chem.* **1971**, 747, 151.

90. Paquette, L. *J. Am. Chem. Soc.* **1964**, 86, 4085.

91. Paquette, L. *J. Am. Chem. Soc.* **1964**, 86, 4089.

92. Paquette, L. *J. Am. Chem. Soc.* **1964**, 86, 4383.

93. Paquette, L. *Mechanisms of Molecular Migration*, Vol. 1, Thyagarajan, B. S., Ed., Interscience: New York, 1968, pp 121.

94. Paquette, L. *Acc. Chem. Res.* **1968**, 1, 209.

95. Burdwell, F. *Organosulfur Chemistry,* Janssen, M. J., Ed.; Interscience: New York, 1967, Ch. 16.

96. Burdwell, F. *Acc. Chem. Res.* **1970**, 3, 281.

97. Cahiez, G.; Marquis, S. *Synlett*. **1993**, 45.

98. Blickenstaff, R. *J. Am. Chem. Soc.* **1960**, 82, 3673.

99. Marvel, C. S.; Sekera, V. C. *Org. Synth.* Coll. Vol. III, Horning, E. C., Ed.; Wiley: New York, pp 366.

100. Singh, A.; Mehrotra, A.; Regen, S. *Synth. Commun.* **1981**, 11, 409.

101. Wasserman, E.; *J. Am. Chem. Soc.* **1960**, 82, 4433.

102. Hansley, V. U.S. Patent 2,228,268 (1941) [*C.A.* **1941**, 35, 2534[1]].

103. Prelog, V.; Frenkiel, L.; Kobelt, M.; Barman, P. *Helv. Chim. Acta* **1947**, 30, 1741.

104. Stoll, M.; Rouve, A. *Helv. Chim. Acta* **1947**, 30, 1822.

105. Stoll, M.; Hulstkamp, J. *Helv. Chim. Acta* **1947**, 30, 1815.

106. Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.

107. Sharpless,K.; Gao, Y. *J. Am. Chem. Soc.* **1987**, 109, 5765.

108. Langworthy, T. A. In *Ether Lipids: Biochemistry and Biomedical Aspects;* Mangold, H. K., Paltauf, F., Eds.; Academic Press: New York, pp 161-175.

109. Feuer, H.; Hooz, J.*The Chemistry of the Ether Linkage,* Patai, S., Ed. Interscience: New York, 1967, pp 457-460, 468-470.

110. Wasserman, D. *J. Org. Chem.* **1943**, 8, 73.

111. Bennett, G.; Gudgeon, H. *J. Chem. Soc., Memoirs & Proceedings* **1938**, 1679.

112. The melting point of 16-hydroxyhexadecanoic acid from Aldrich Co. is 97-99 °C.

113. Capet, M.; Cuvigny, T.; Herve Du Penhoat, C.; Julia, M.; Loomis, G. *Tetrahedron Lett.* **1987**, 28, 6273.

114. Page, P.; Klair, S.; Brown, M.; Harding, M.; Smith, C.; Maginn, S.; Mulley, S. *Tetrahedron Lett.* **1988**, 29, 4477.

115. Barton, D.; Jaszberenyi, J.; Tachdjian, C. *Tetrahedron Lett.* **1991**, 32, 2703.