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SYNTHESIS OF CHIRAL ARCHAEBACTERIAL MEMBRANE LIPID SYNTHONS

by

YANZHONG WU

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

1997

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

6/27/97
Date

W F Berkowitz
Chair of Examining Committee

July 1, 1997
Date

Executive Officer

W F Berkowitz
William F. Berkowitz

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Robert Bittman

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Richard W. Franck

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

SYNTHESIS OF CHIRAL ARCHAEBACTERIAL MEMBRANE LIPID SYNTHONS

by

YANZHONG WU

Adviser: Dr. **W. F. Berkowitz**

2,6-dimethyl 1,6-heptadiene has been synthesized with improved yield (65%) by cross coupling between 4-bromo-2-methyl-1-butene or the tosylate of 3-methyl-3-butene-1-ol with the Grignard reagent of 3-chloro-2-methylpropene in the presence of Li_2CuCl_4. Stereospecific cyclic hydroboration of the resulting diene with thexylborane, followed by carbonylation/oxidation gave *mseo*-3,7-dimethylcyclooctanone as a pure diastereoisomer in a one-pot synthetic procedure in 51% yield. The key step in the synthesis of the desired C_{10} chiron was the asymmetric depro-

tonation of *meso*-3,7-dimethylcyclooctanone with the lithium salt of (+)-bis-[(*R*)-1-phenylethyl]amine and "internal quench" with excess trimethylsilylchloride to give [((3*S*,7*R*)-3,7-dimethyl-1-cyclo-octen-1-yl)oxy]trimethyl-silane in good yield (85%) and in high optical purity (98% ee). Ozonolysis reaction of the resulting enol silyl ether gave C_{10} chiron (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoic acid in 27% overall yield in 5 steps. We believe this chiron will be applicable to the synthesis of archaebacterial lipids.

Copper-catalyzed cross-coupling of alkylsamarium reagents with alkyl halides was investigated. SmI_2/HMPA converts alkyl iodides and bromides to alkylsamarium reagents which can be cross-coupled with primary iodides, bromides, and secondary iodides in the presence of Cu(I) halides or Li_2CuCl_4 at room temperature. The alkylation of primary iodides gives high yields of cross-coupling products with negligible homo-coupling products. The method is especially useful for small scale cross-coupling reactions.

Archaebacterial lipid C_{20} chiron, methyl 16-[(*t*-butyldiphenyl-silyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexadecanoate was synthesized by using both copper-catalyzed coupling of the Grignard reagent

of 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*R*,7*S*)-3,7-dimethyloctane with methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate, and copper-catalyzed cross-coupling of the samarium reagent of 8-(*t*-butyldiphenylsilyloxy)-1-iodo-(2*R*,7*S*)-3,7-dimethyloctane with methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate, in 71% and 81% yields, respectively. A C_{20} dibromide, 1,16-dibromo-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethylhexadecane was synthesized by copper-catalyzed Grignard homo-coupling of 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(2*S*,6*R*)-2,6-dimethyloctane, followed by desilylation and bromination. A vitamin E side chain synthon, (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol (98% ee), was synthesized in 19% overall yield in 9 steps.

Dedicated to my dear wife and to our newly born daughter Jennifer; to my parents, and my elder sisters and younger brother.

ACKNOWLEDGMENTS

I would like to thank Dr. William F. Berkowitz for the intellectual and financial support which made the completion of this work possible. I would also like to thank Dr. R. W. Franck and Dr. R. Bittman for their valuable discussions and suggestions. I am especially grateful to Prof. David C. Locke who performed most of the GC/MS analysis which facilitated interpretation of the experimental results. I am appreciative to my fellow graduate students.

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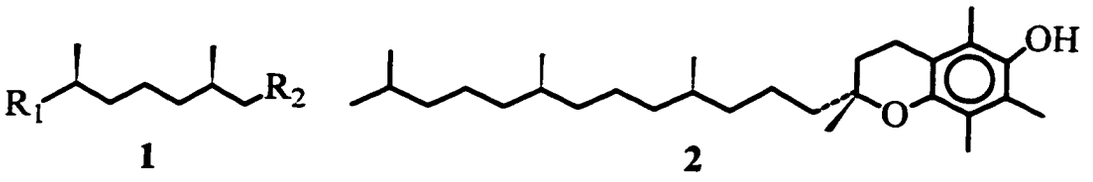
Chapter 1. Introduction

1.1 Background

The chiral *syn*-1,5-dimethylalkyl subunit **1** (R_1, R_2 = different functional groups) is found in many natural products: e.g., the ubiquitous phytol[1] side chains of vitamins E (**2**)[2] and K (**3**);[3] chlorophyll (**4**);[4] lycopadiene (**5**) produced by microalga *Botryococcus braunii*;[5] some marine natural products (e.g., fasciculatin (**6**),[6] a marine sponge sesquiterpenoid); and pheromones of pine sawflies (**7**),[7,8] tsetse flies (**8**),[8,9] red flour beetles (**9**),[8,10] male stink bugs,[8] mountain ash bentwings, and alfalfa blotch leaf miners.[8] This structural element is also found in membrane lipids (e.g., **10**, **11**, and **12**) of archaebacteria,[11] a type of microorganism living under extreme conditions such as high temperature, high salt concentration, low pH, or absence of oxygen. The membrane lipids[12] of archaebacteria may be an important factor in the unusual adaptation of such organisms to extreme conditions.[13] An important feature is the fact their membrane lipids include isoprenoid glycerol ether linkages instead of the usual fatty acid glycerol ester linkages.



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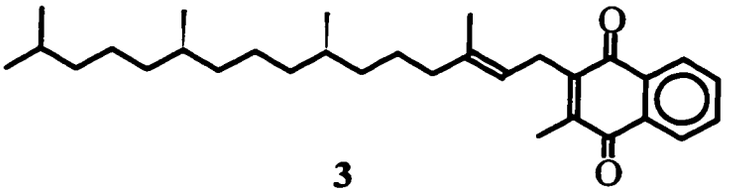

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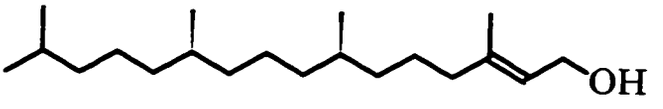

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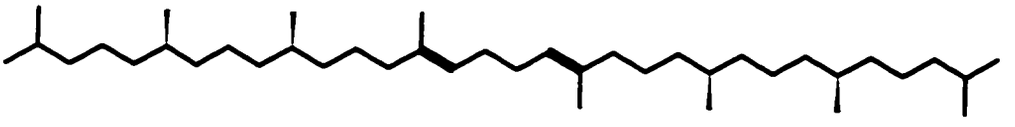

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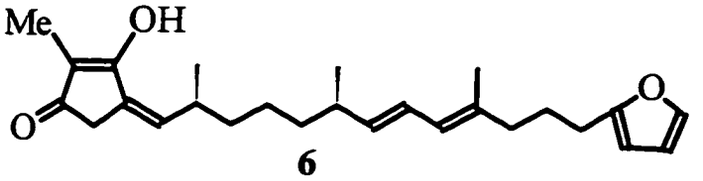

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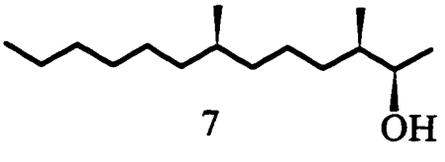

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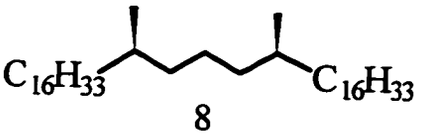

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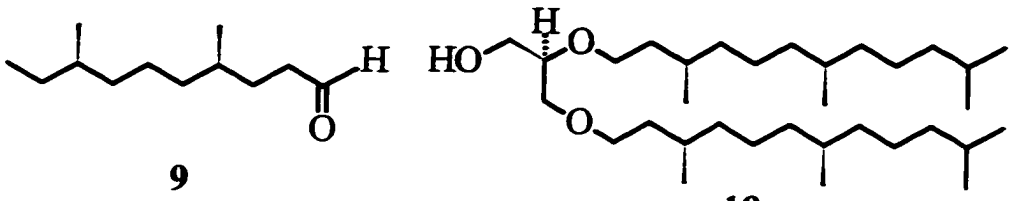

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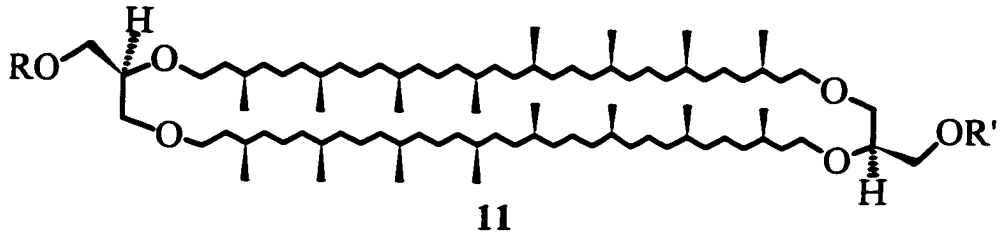
Among the most common lipids isolated from these prokaryotes are derivatives of two[13] C_2-symmetric, *sn*-2,3-bisbiphytanylglycerol tetraethers **11** and **12** (R, R` = glycoside, phosphate ester, hexitol, etc.). Model studies by Kakinuma[14] have employed sequential bonding of two unmethylated 16-substituted hexadecyl glycerol diethers to produce both of the C_2-symmetric forms of the cyclic, unmethylated, straight-chain, 72-membered ring glycerol tetraethers, closing the 72-membered rings using a McMurry reaction.

It is apparent that the same strategy can be applied to the ultimate syntheses of the natural polymethylated lipids **11** and **12**. As isolation of even the most predominant archaebacterial lipids in a sufficient quantity to attempt liposome formation is a monumental task, further biomedical study will require their synthesis.

The synthesis of the chiron C_{10} (**1**) and C_{20} (**14**) is the main subject of this dissertation.[15,16]



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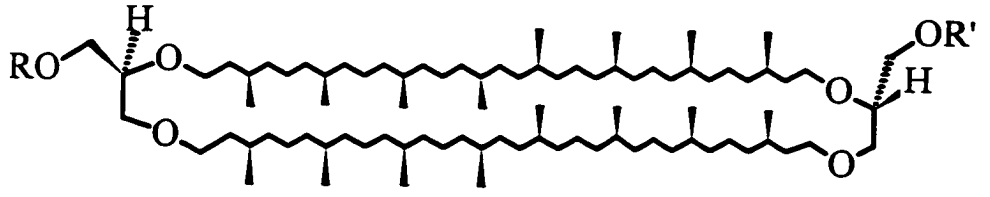

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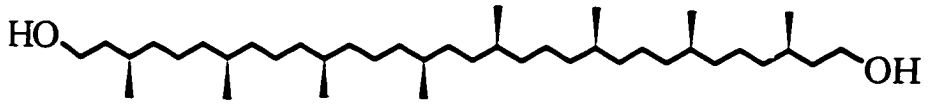

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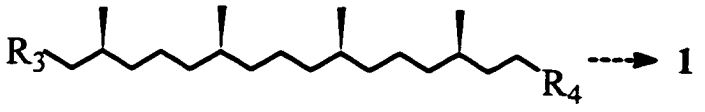

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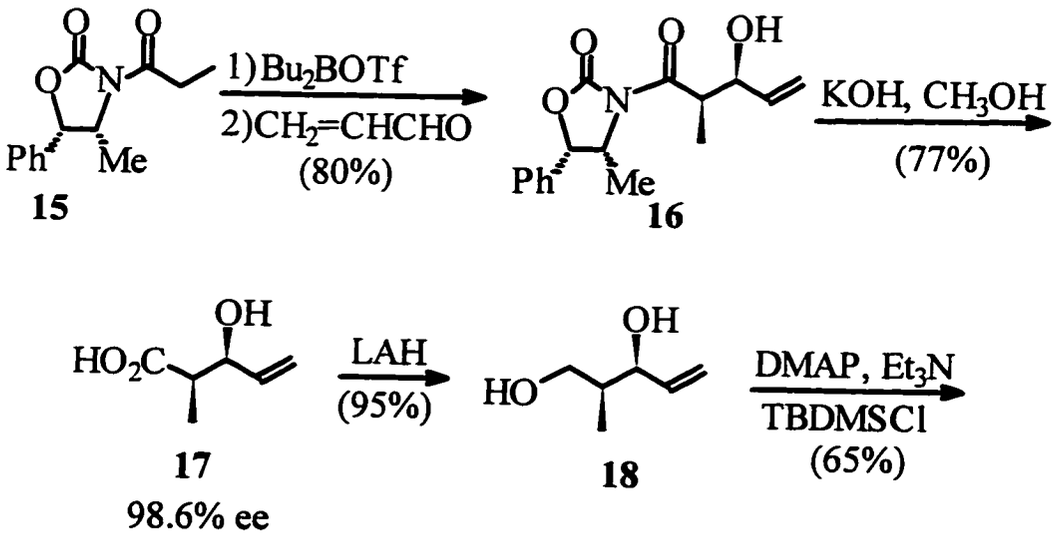
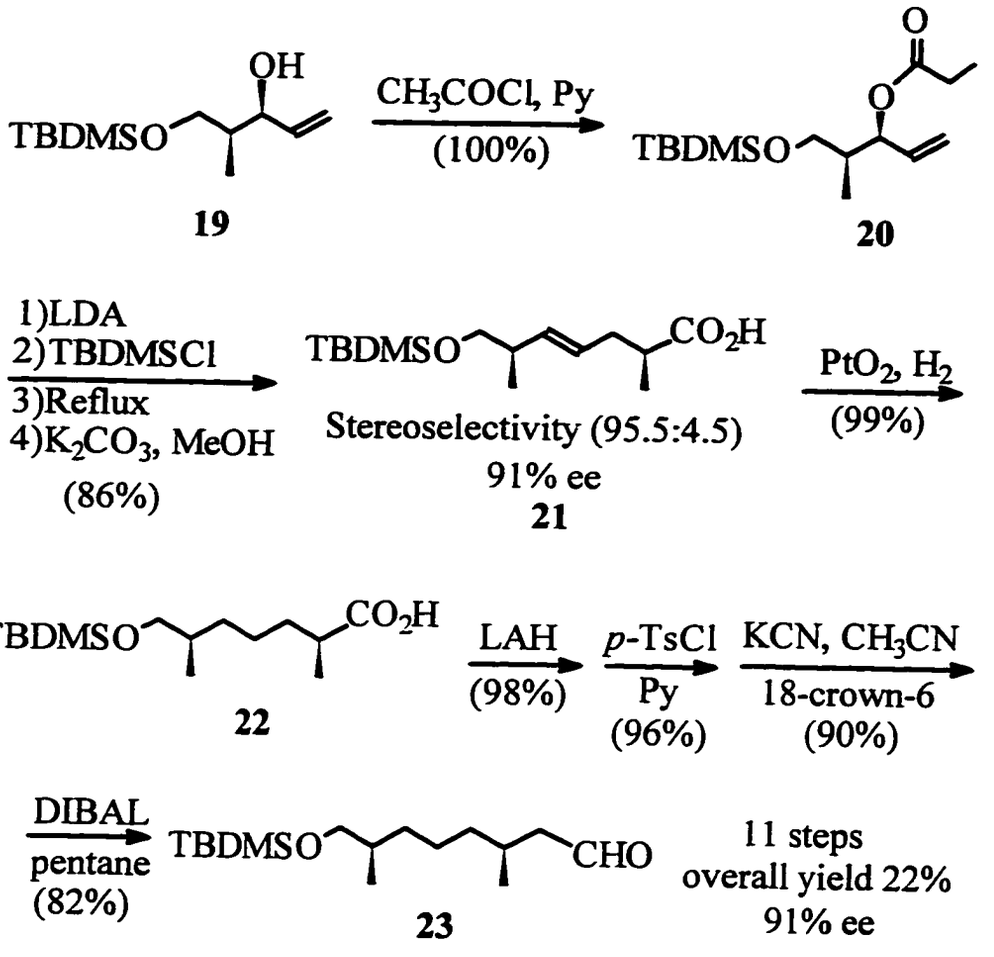
1.2 Synthesis of *syn*-1,5-dimethyl C_{10} units

1.2.1 Using a chiral auxiliary

Heathcock et al.[17] have synthesized the enantiomerically enriched unit **1** by using a chiral auxiliary oxazolidinone (**15**). A highly 1,2-diastereoselective aldol reaction (**17**: 98.6% ee) followed by a 1,5-stereoselective (**21**, 95.5:4.5) Ireland-Claisen rearrangement and final workup gave a scalemic compound **23** (91% ee, 22% overall yield, 11 steps), as shown in Scheme 1.

Scheme **1.** Heathcock et al. sequence

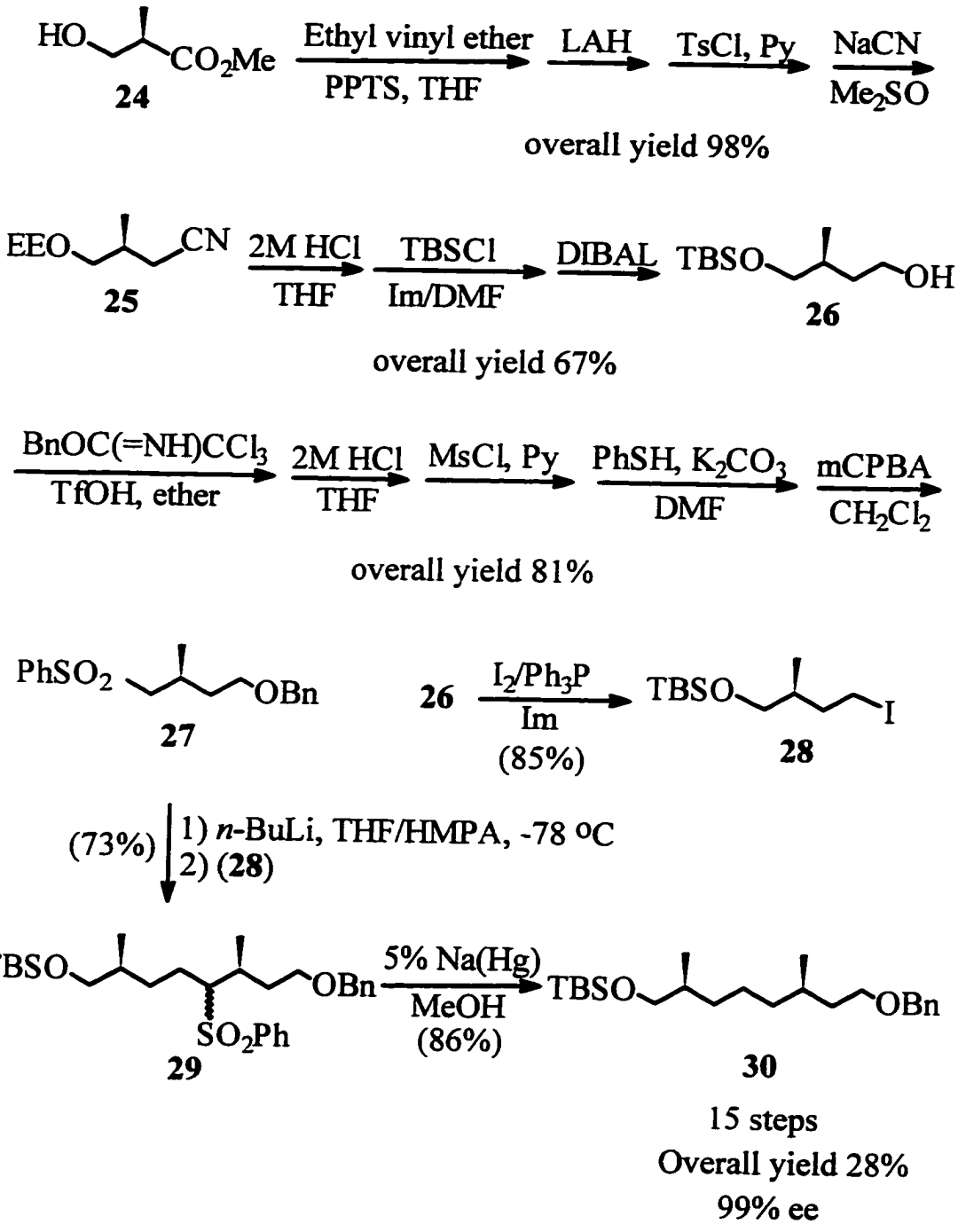




1.2.2 Using chiral compounds as starting materials

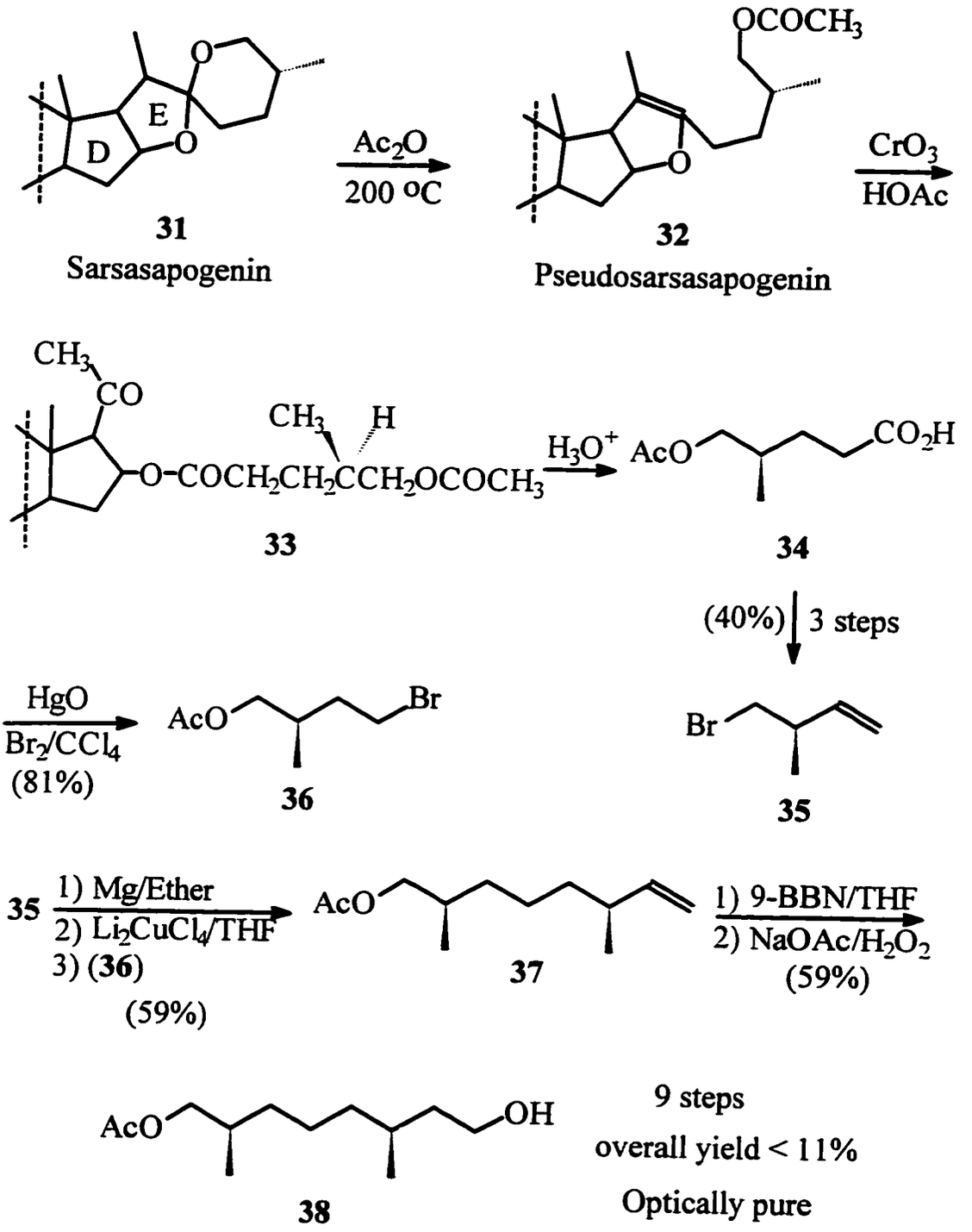
Kakinuma *et al.*[18] have synthesized optically pure, differentially protected C_{10} units by starting with a commercially available methyl (*R*)-3-hydroxy-2-methylpropionate **24** (99% ee). A C_{10} chiral unit **30** was synthesized in 28% overall yield after 15 steps, as shown in Scheme 2.

Scheme 2. Kakinuma et al. sequence



Czeskis *et al.*[19] have synthesized optically pure, differentially protected C_{10} units **38** in a more classical manner by linking two chiral C_5 precursors (**35**, **36**) using copper-catalyzed Grignard coupling. These C_5 units were made by the decarboxylation of a C_6 unit which is formed as a result of the oxidative cleavage of the side chain of diosgenin and other (25*R*)-sapogenins[20], as shown in Scheme 3. The overall maximum yield of **38** may be 11% from the following sequence because the authors[19,20] did not give the yield of **34**.

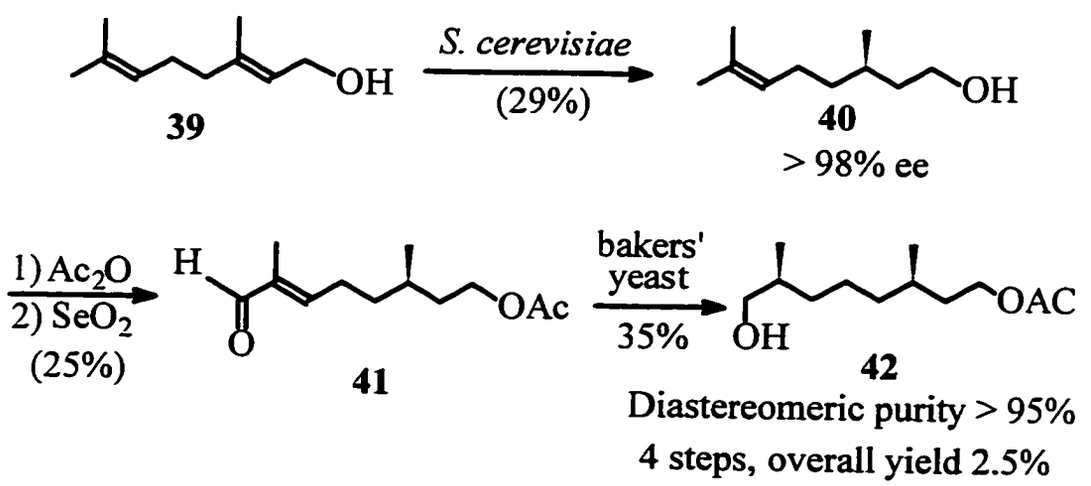
Scheme 3. Czeskis et al. sequence



1.2.3 Using an enzyme to produce chiral centers

A much shorter route was developed by Gramatica et al.[21] for the preparation of an optically pure C_{10} fragment, hydroxy ester **42**, via two microbial reductions, from geraniol (**39**) in 4 steps with 2.5% overall yield, as shown in Scheme 4.

Scheme 4. Gramatica et al. sequence

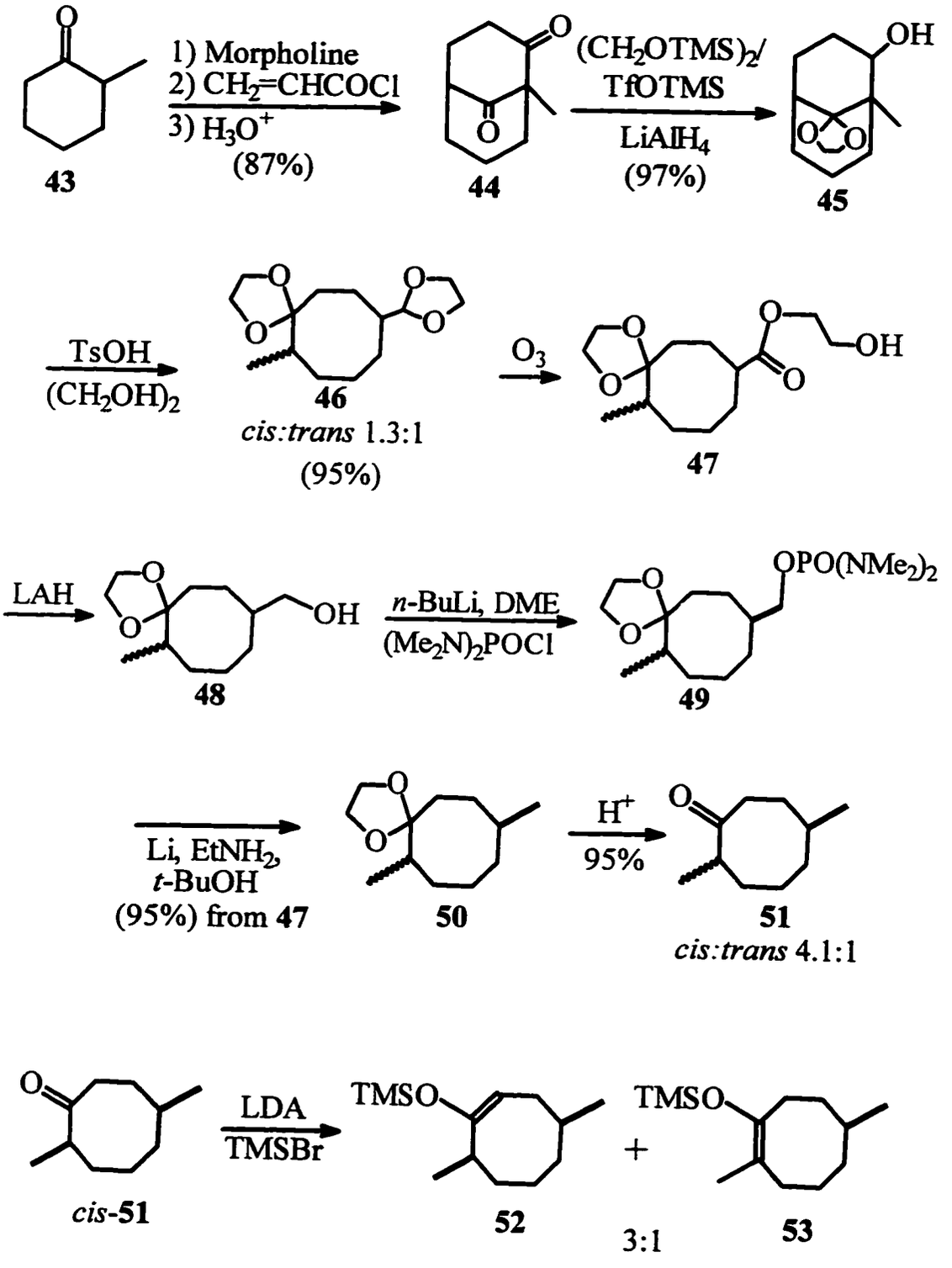


1.2.4 Racemic C_{10} unit produced by ring cleavage

Gambacorta *et al.*[22] have synthesized a racemic *syn*-1,5-dimethylalkyl unit by a ring cleavage, as shown in Scheme 5. They started from selective ketalization of dione[23] **44** which was made from the reaction of the morpholine enamine of 2-methylcyclohexanone with

acryloyl chloride, followed by reduction with LAH. Subsequent rearrangement afforded two epimers **46** (1.3:1). Conversion of the protected formyl group into a methyl group of **49** was accomplished after ozonolysis of ketal **46** to ester **47**, LAH reduction of ester **47** to alcohol **48**, deprotonation of the primary alcohol **48** with *n*-BuLi, reaction of the resulting anion with $(Me_2N)_2POCl$ to give **49**, and final reduction of **49** with lithium to **50**. Hydrolysis of the ketal **50** in acid afforded two easily separable epimers of **51** (4.1:1). Kinetic silylation (LDA, TMSBr) of *cis*-**51** gave a mixture of the corresponding silyl enol ethers (**52**, **53**, regioselectivity 3:1). Ozonolysis, reduction *in situ*, and methylation gave a separable mixture of the target *syn*-isoprenoid unit **54** as a racemic mixture in 48% overall yields for 13 steps.

Scheme 5. Gambacorta et al. sequence

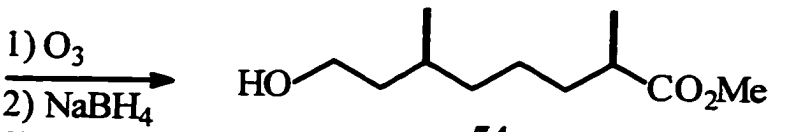


43 44 45 46 47 48 49 50 51 52 53

cis:*trans* 1.3:1 (95%)

cis:*trans* 4.1:1

cis-51



54

13 steps

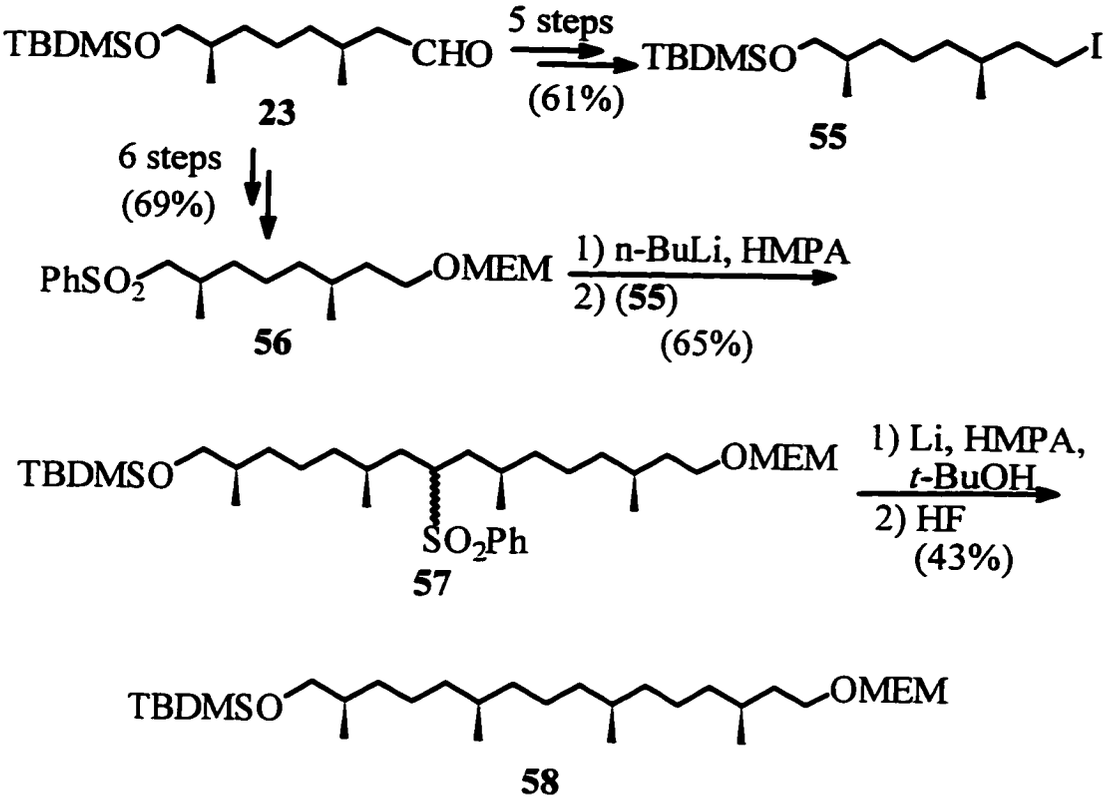
Overall yield 48%

1.3 Synthesis of C_{20} units

There are two major reactions in the synthetic literature to construct C_{20} units from C_{10} units. One is the alkylation of a sulfonate with an alkyl halide which was used by Heathcock et al.[17] and Kakinuma et al. .[18] Another is the copper-catalyzed Grignard reaction, which was used by Czeskis et al.[19]

Heathcock et al. started from aldehyde **23** (Scheme 1) to give iodide **55** and sulfonate **56** after 11 steps of functional group changes. Alkylation of **56** with **55** to give **57**, reduction of **57** with lithium to remove the sulfonyl group, and desilylation of the resulting crude product gave C_{20} **58** in 2.3% overall yield, as shown in Scheme 6.

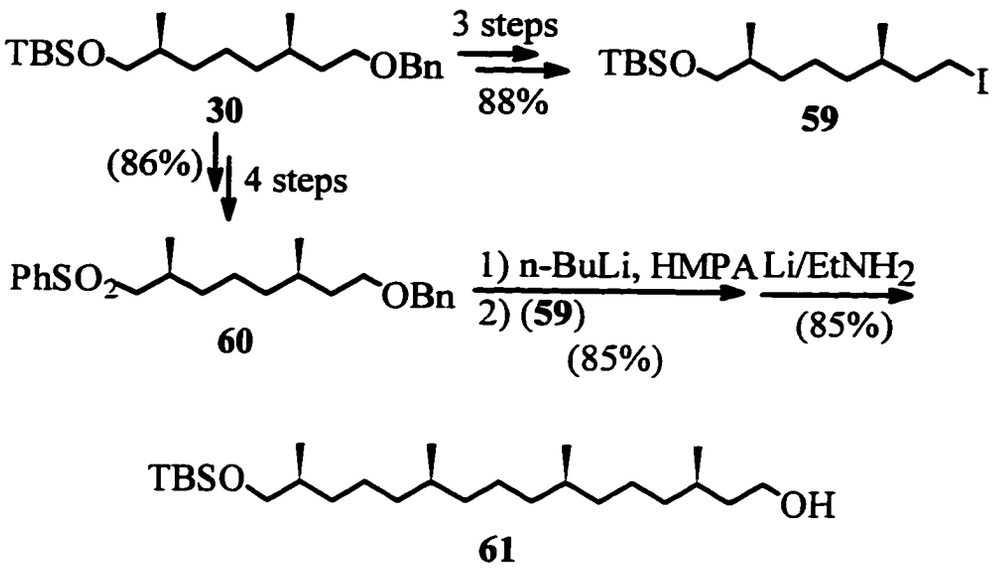
Scheme 6. Synthesis of C_{20} unit by Heathcock et al.



25 steps from **15**
Overall yield 2.3%

Kakinuma et al. used the same method as Heathcock et al. to synthesize a sulfonate **60** starting with **30** (Scheme 2). Alkylation of **60** with **59** and reduction of the resulting product with lithium to remove the sulfonyl and benzyl groups gave C_{20} **61** in 15% overall yield, as shown in Scheme 7.

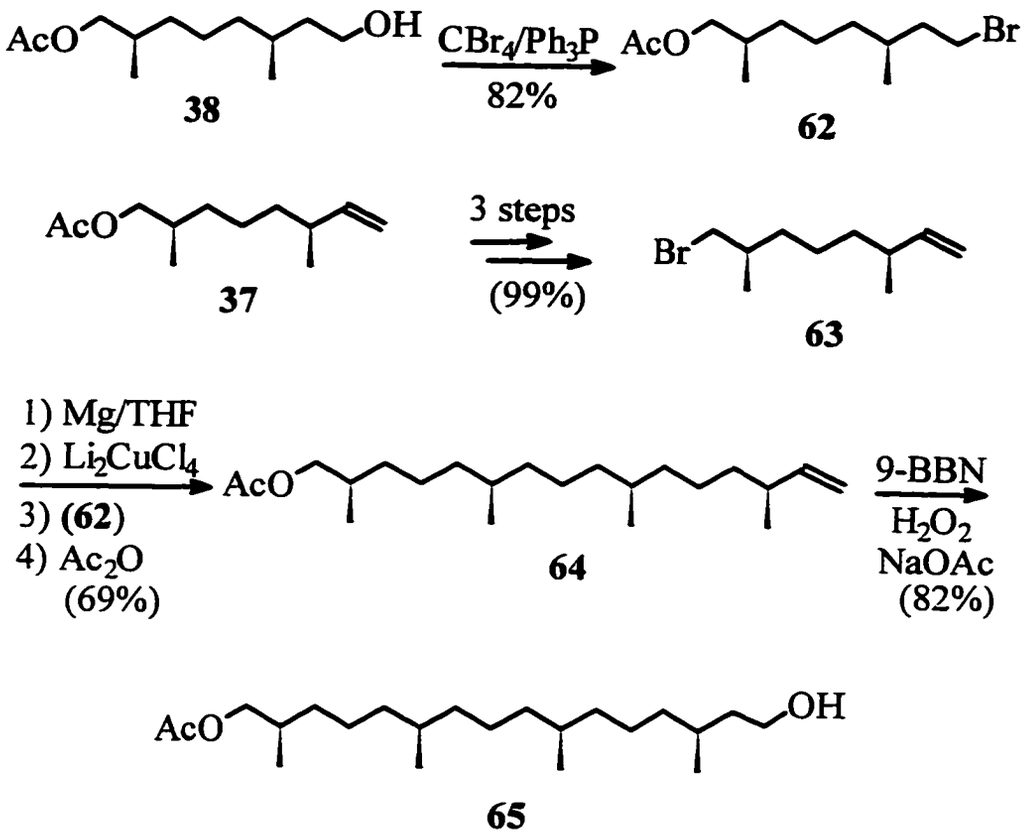
Scheme 7. Synthesis of C_{20} unit by Kakinuma et al.



24 steps from 24
Overall yield 15%

Czeskis et al. coupled two bromides **62**, **63** made from **37**, **38** (Scheme 3) using Kochi conditions[24] to give **64**. Hydroboration and oxidation of **64** yielded a difunctional C_{20} unit **65** in less than 5% overall yield, as shown in Scheme 8.

Scheme 8. Synthesis of C_{20} unit by Czeskis et al.



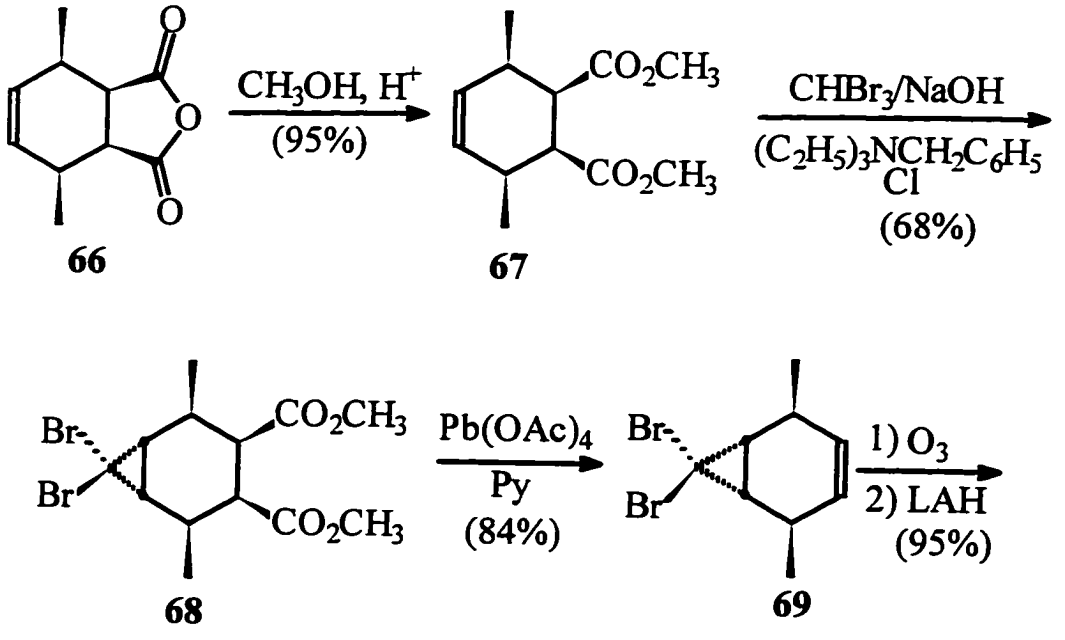
16 steps from **31**
Overall yield less 5%

1.4 Synthesis of *syn*-1,5-dimethyl C_9 units

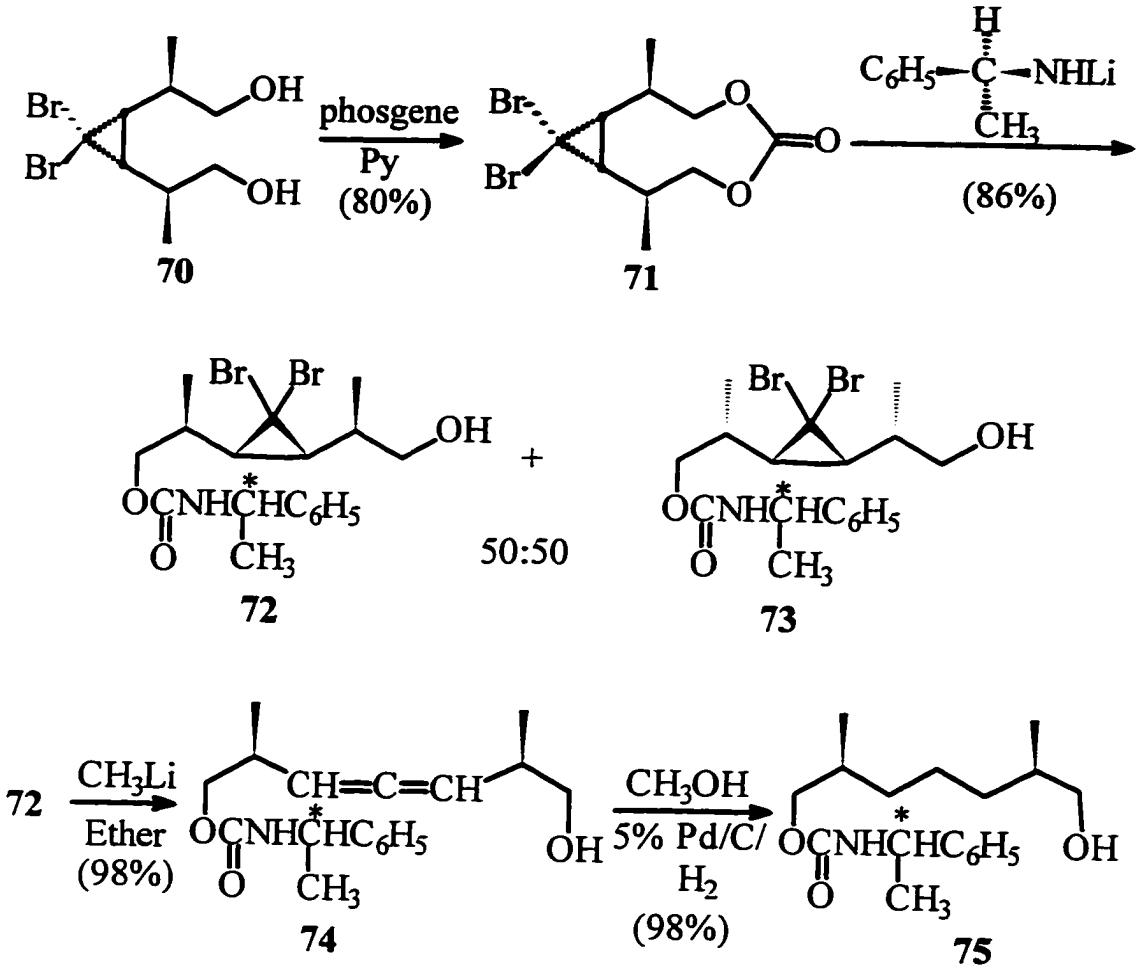
Although C_9 fragments cannot be used to build C_{20} units directly, as can coupling of two C_{10} fragments, the synthesis of C_9 fragments is of pertinent interest.

Deslongchamps et al.[25] desymmetrized *meso*-C_9-diol **70** using aminolysis of a cyclic carbonate **71** with a chiral amine, as shown in Scheme 9.

Scheme **9**. Deslongchamp et al. sequence



66 **67** **68** **69**



9 steps, overall yield 18%
Optically pure

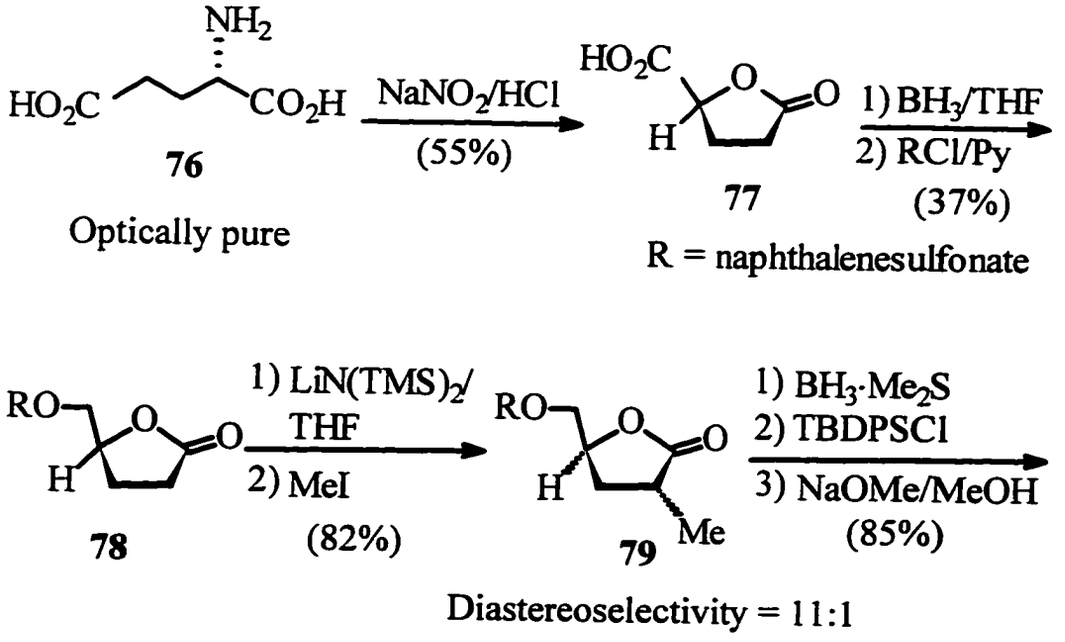
The C_9 fragment was constructed by insertion of a carbon via cyclopropanation of meso dimethyl cyclohexene diester **67**. Ozonolysis and reduction of the resulting product **69** of oxidative decarboxylation of **68** gave a meso-C_9-diol **70**, and then **70** was transformed into the symmetric nine-membered cyclic carbonate **71** with (-)-α-phenylethylamine, yield-

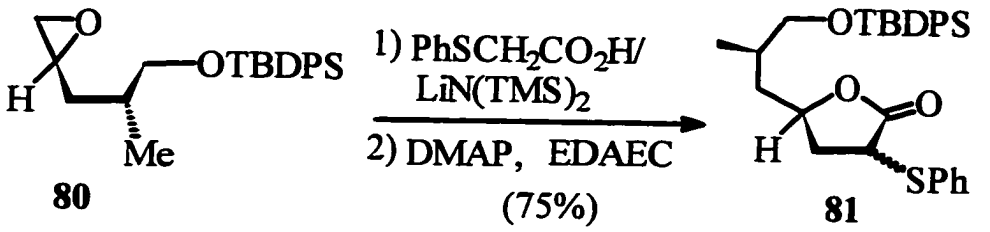
ing a mixture of optically active diastereoisomeric urethanes **72** and **73** which were separable. Ring opening of cyclopropane of **72** to allene **74** and hydrogenation of allene **74** gave an optically pure fragment C_9 **75** in 18% overall yield in 9 steps.

Hanessian et al.[26a] developed stereocontrolled methylation of a scalemic butyrolactone derived from *S*-glutamic acid[26b] to produce a C_9 fragment, as shown in Scheme 10. The commercially available optically pure *S*-glutamic acid **76** was converted to the carboxylic acid lactone **77** with complete retention of configuration. Selective reduction of this acid lactone with borane and treatment of the resulting alcohol with naphthalenesulfonyl chloride in pyridine gave a lactone **78** with one face blocked by the bulky naphthalenesulfonate group. Treatment of **78** with lithium hexamethyldisilazide followed by methyl iodide, and chromatographic purification of the mixture of isomers (>11:1) gave **79** as the major product. Reduction of this lactone, preferential silylation, and treatment with sodium methoxide gave the epoxide **80** in excellent overall yield. A two-carbon extension by treatment with dilithium 2-phenylthioacetate, followed by lactonization with ethyl(dimethylaminoethyl)-carbodiimide led to **81** as a mixture of isomers at C-2. Raney-nickel desulfurization

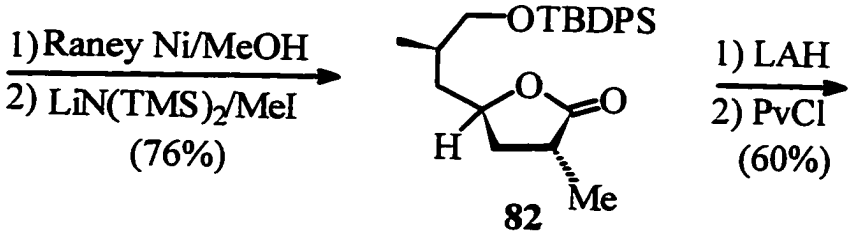
and methylation again gave lactone **82** as the major product (>11:1). Reduction and sequential esterification of **82** with pivaloyl chloride gave a secondary alcohol **83**. Treatment of **83** with methanesulfonyl chloride and reduction of the resulting product with LAH gave a C_9 unit **85** in 3.4% overall yield.

Scheme **10**. Hanessian et al. sequence



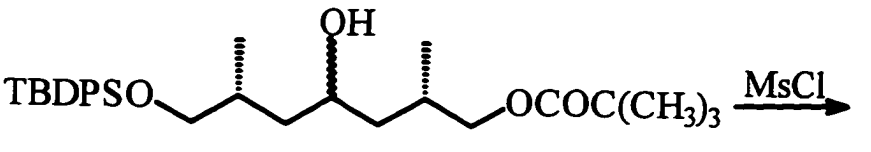


80 81



82

Diastereoselectivity = 11:1



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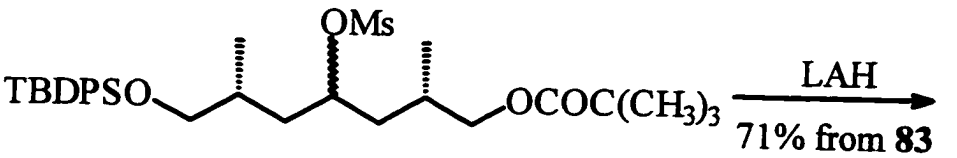

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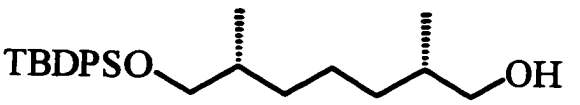


85

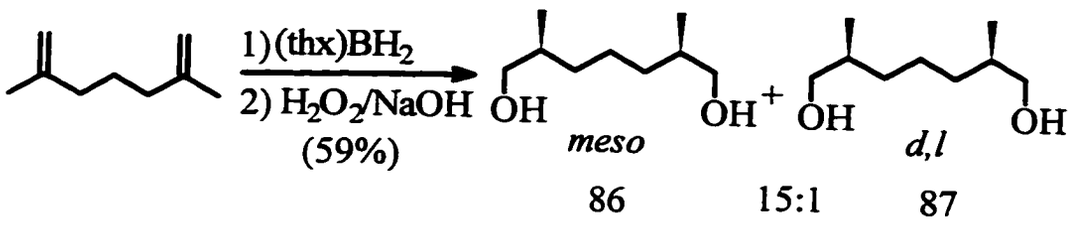
15 steps
Overall yield 3.4%
Optically pure

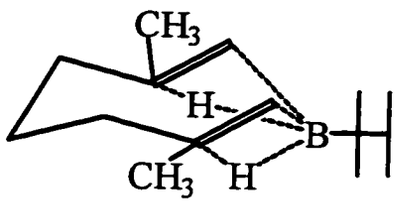
Still et al.[27a] provided an efficient new way to build a *meso syn*-1,5-dimethyl fragment in one reaction. The cyclic hydroboration of 2,6-

dimethyl-1,6-heptadiene with thexylborane at -78 °C followed by an oxidative workup gave the meso-diol as the major product (*meso:dl* = 15:1, 73%). They suggested that the transition state is a low-energy conformational substructure found in a number of rings having more than six atoms, and the transition state should not experience substantially more strain than that inherent to the ring formed. Hence, to the extent that the hydroboration is intramolecular, the product should be *meso*.

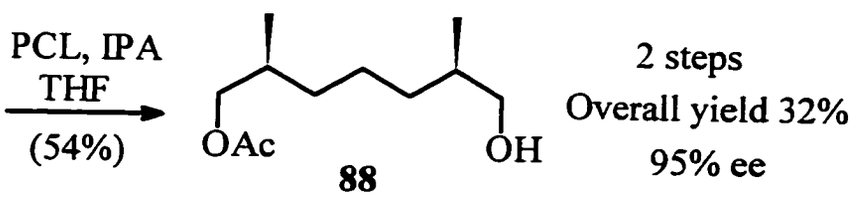
Using the Still method, Chenevert et al.[27b] also made *meso*-2,6-dimethyl-1,7-heptanediol, and esterified it enzymatically with isopropenyl acetate (IPA) in the presence of *Pseudmonas cepacia* lipase (PCL) in organic medium to provide the 2*R*,6*S*-nonracemic monoester **88** in high enantiomeric excess (over 95% ee), as shown in Scheme 11.

Scheme 11. Chenevert et al.sequence





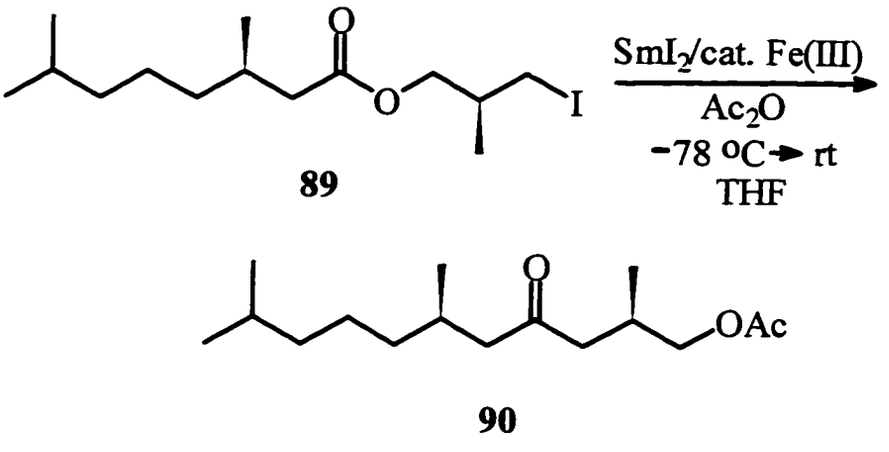
Transition state



The enzymatic reaction was performed on the *meso/d,l* (15:1) mixture. This enantioselective lipase-catalyzed reaction can separate all three stereoisomers in a mixture of meso and racemic isomers. PCL favored the *S* stereocenter (vide infra), so the meso (*R*,*S*)-isomer was monoacetylated, the (*S*,*S*)-enantiomer was diacetylated, and the (*R*,*R*)-enantiomer did not react. The monoacetate **88** was easily separated from the reaction mixture in 32% overall yield with an ee > 95%.

It should also be noted that the recently described intramolecular nucleophilic acyl substitution (INAS)[28] reaction of Molander et al. is clearly also capable of being applied to the synthesis of C_9 or C_{10} fragments, as shown in Scheme 12.

Scheme **12**. Molander's sequence

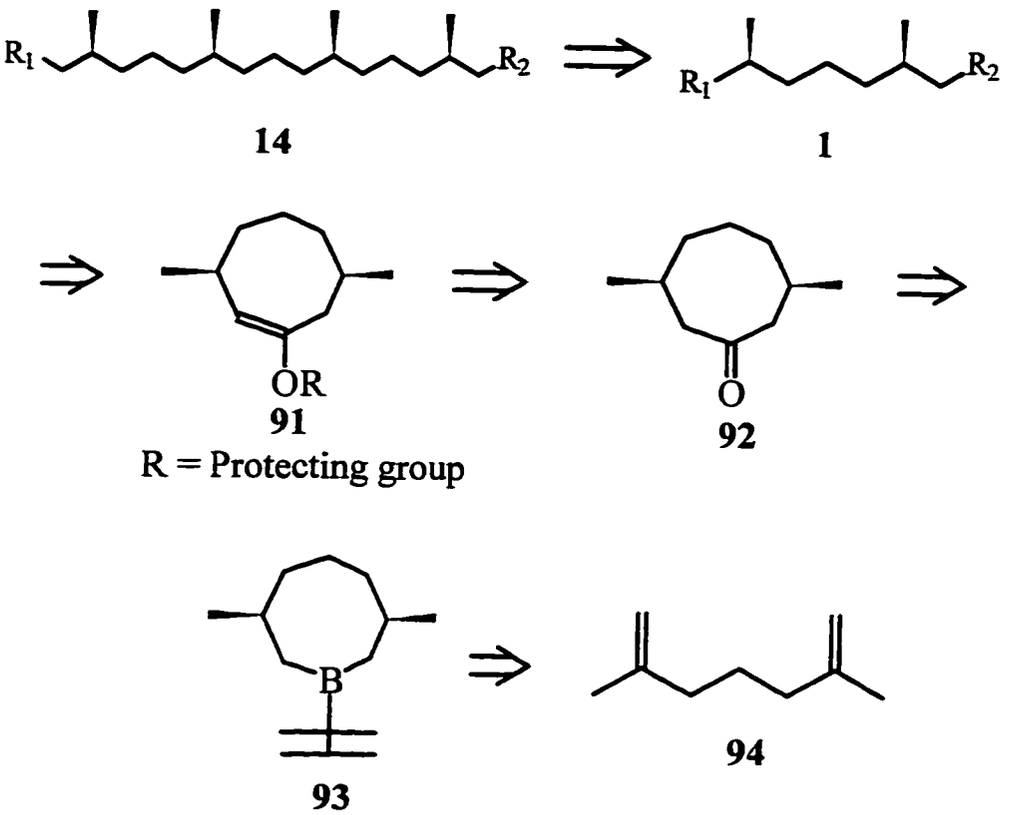


89 **90**

1.5 Retrosynthesis of our target C_{10} chiron

Retrosynthetic analysis of molecule **14** C_{20} reveals that an efficient route is the coupling of two C_{10} fragments, as shown in Scheme 13. Still and Chenevert's methods suggested to us that the C_{10} fragment, *syn*-1,5-dimethyl unit **1**, could be obtained by addition of one more carbon to the C_9 fragment diol **86** (Scheme 12). This lead us to investigate formation and asymmetric cleavage of cyclooctanone **92**.

Scheme 13. Retrosynthetic analysis

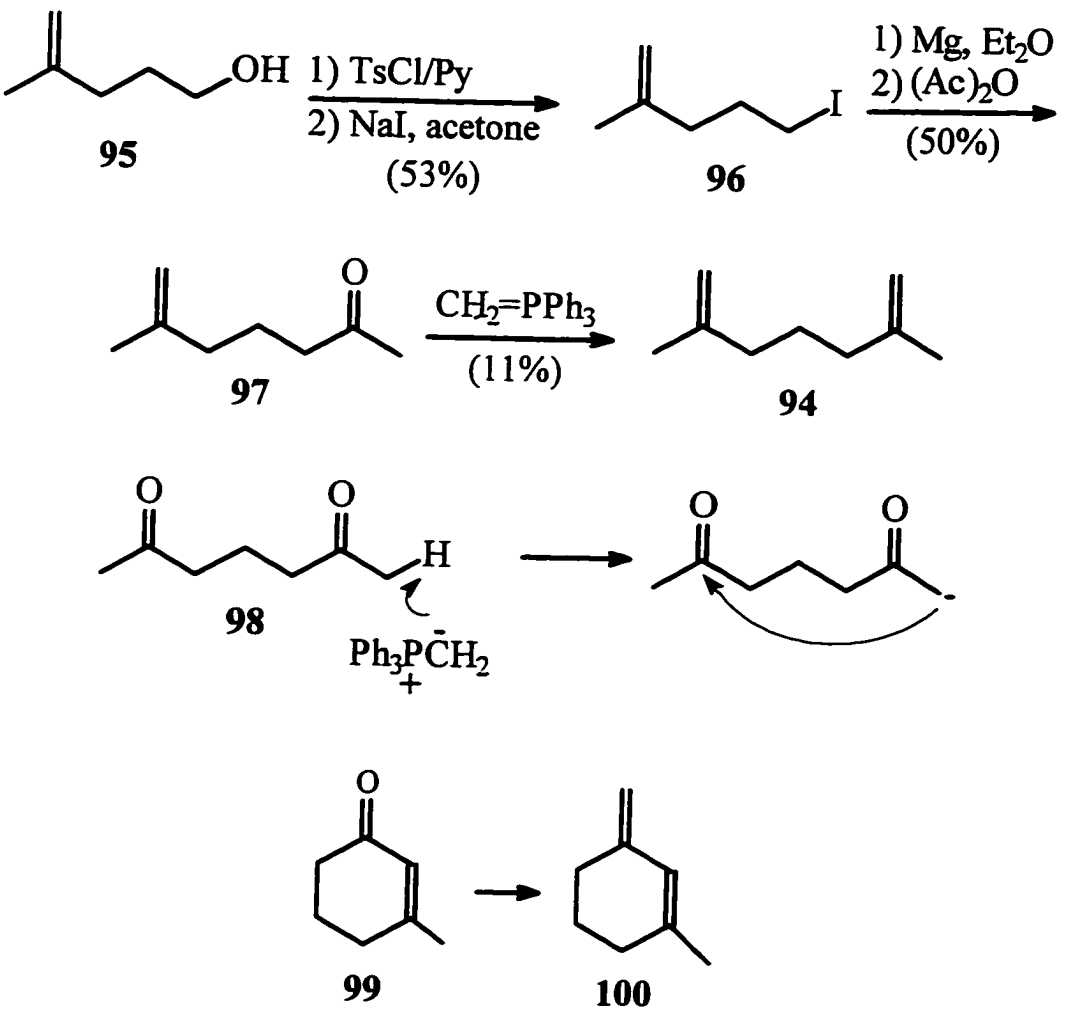


Thus compound **91** could be obtained by asymmetric deprotonation and silylation of a cycloketone **92**, which can be obtained by standard hydroboration/carbonylation from diene **94**.

According to our retrosynsthesis, 2,6-dimethyl-1,6-heptadiene (**94**) is our key starting material. 2,6-Dimethyl-1,6-heptadiene is not available commercially. It was first synthesized by Ansell and Thomas[29] in 1961 in

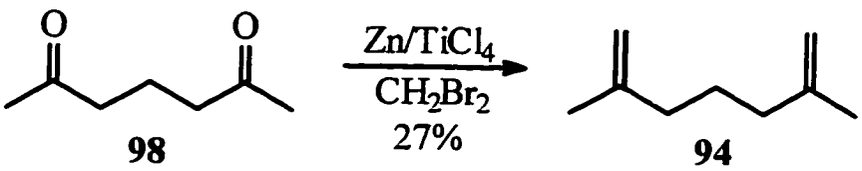
only 11% yield, as shown in Scheme 14. Their alternative route to this diene, the action of methylenetriphenylphosphorane on heptane-2,6-dione, yielded a mixture of diene **94** and cyclodiene **100**.

Scheme **14.** Ansell and Thomas's sequence



Compared to Ansell and Thomas, Irrgang et al.[30] improved the yield for making diene **94** from heptane-2,6-dione (**98**) by using zinc and titanium(IV) chloride; however, the yield was only 27%, as shown in Scheme 15.

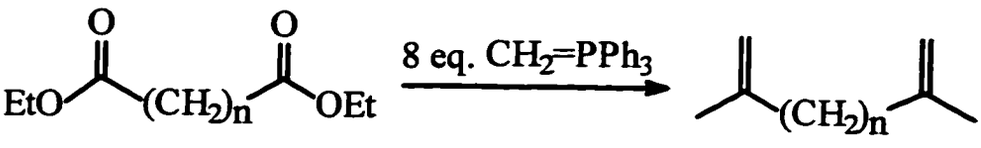
Scheme **15**. Irrgang's sequence



98 **94**

Uijttewaal et al.[31] synthesized this diene by reaction of diethyl glutarate (**101**, n = 3) with excess methylenetriphenylphosphorane. When the distance between the ester groups is small ($RO_2C(CH_2)_nCO_2R$, $n \leq 3$) appreciable interaction between the functional groups occurs, as evidenced by the low yields of olefins. When the ester groups are separated by four carbon atoms or more, reaction with 8 equivalents of salt-free ylide proceeds satisfactorily, and good yields of corresponding bis(isopropenyl) compounds were obtained, as shown in Scheme 16.

Scheme 16. Uijttewaal et al. sequence



101

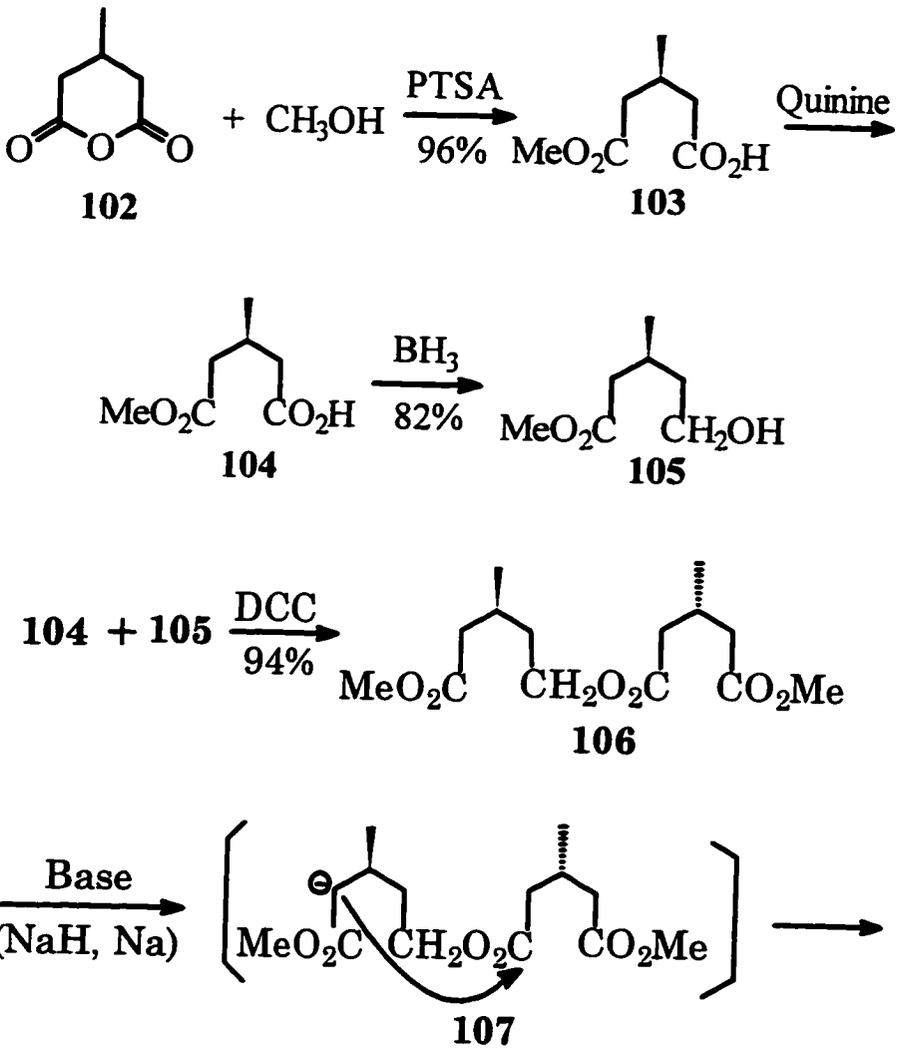
n	2	3	4	5	10
yield (%)	13	15	75	63	81

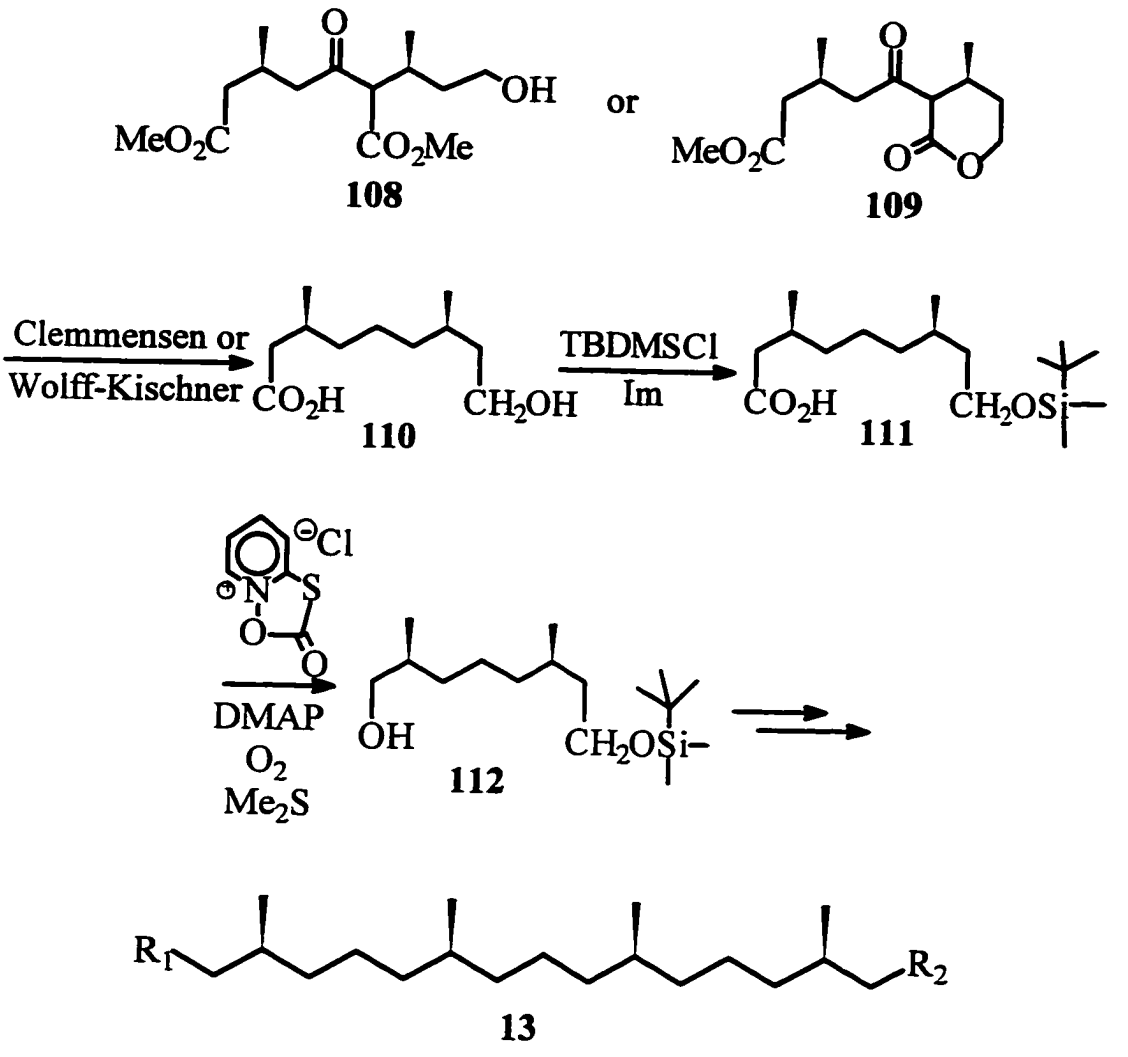
Chapter 2. Results and Discussion

2.1 Our initial proposal

Our initial proposal, as outlined in Scheme **17** is similar to the sequence of Molander (Scheme 12).[28]

Scheme **17.** Our initial proposal

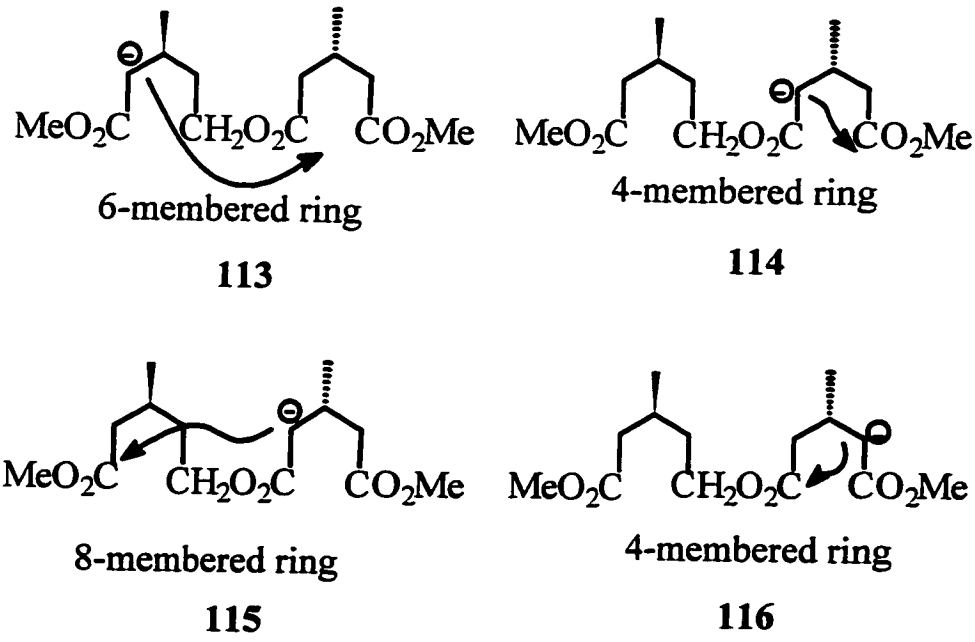




We started with 3-methylglutaric anhydride (**102**) bought from Aldrich, and used racemic methyl hydrogen 3-methylglutarate as starting material to construct triester **106**. We hoped triester **106** would undergo an intramolecular Dieckmann condensation. Then, Clemmensen or Wolff-Kishner reduction with concomitant hydrolysis and decarboxylation, should give a C_{10} synthon, hydroxy-acid **108, 109**. The key step is

the change of triester **106** to **108** or lactone **109**. In theory, when triester **106** is treated with strong bases, there are three positions which will form anions, but only the more favorable 6-membered ring **113**, compared to the alternate 4 or 7 or 8-membered rings (**114**, **115**, **116**), should produce product, as shown in Scheme 18.

Scheme **18**. Intermediates for Dieckmann condensation



Three different bases (NaH, LDA, Na) in different solvents (toluene, benzene, hexene, THF) at different reaction temperatures were selected. Some of them are shown in Table 1. Unfortunately, none of the

desired products were obtained. Most of reactions gave dimethyl 3-methylglutarate, and some of them gave β-methyl-δ-valerolactone. In nonpolar solvent, we think an *O*-anion attacks another carbonyl group to give a lactone and dimethyl ester, probably following the mechanism, as shown in Scheme 19.

Scheme **19**. Mechanism for Dieckmann reactions

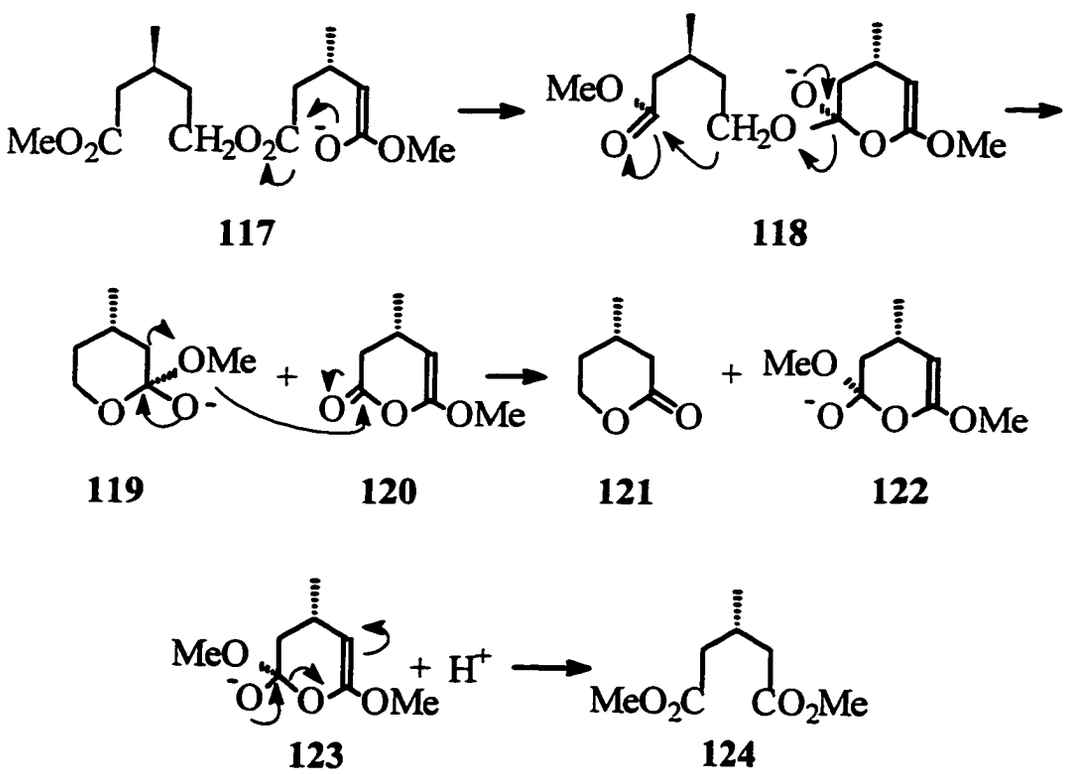


Table 1. Dieckmann reactions in different conditions

Base	Solvent	Temp. °C	Reaction time, hr.	Result
NaH	Benzene	Reflux	16	A*, B
NaH	Hexane	52	2	72% of C recovered
NaH	Hexane	rt	6	40% of C recovered
NaH	THF	rt	19	7 side products
Na	Toluene	Reflux	4	B, polymers
Na	Benzene	rt	73	No reaction
Na	THF	Reflux	2	A, B and polymers
Na	THF	rt	2.5	B, polymers
LDA	THF	-78	7	76% of C recovered
LDA	THF	-78	28	28% of C and 5 side products

A: 3-methylvalerolactone, B: dimethyl 3-methylglutarate
C: starting material (Reaction condition: 1 g of starting material in 50mL solvent with one equiv. of base).

Chenevert's approach, desymmetrization of *meso* diol **86** is inefficient in two ways: 1) resolution gives only a 32% yield of a chiral synthon, and 2) the product is a C_9 structure, entailing addition of one more

carbon before coupling. We were hopeful that carbonylation of the borocane intermediate **93** leading to **92** (see Scheme 17), followed by asymmetric enolization of the resulting cyclooctanone **92** would lead to single enantiomeric C_{10} synthon. The results are summarized in Scheme 20, 21 and 25.

2.2 Synthesis of 2,6-dimethyl-1,6-heptadiene (94)

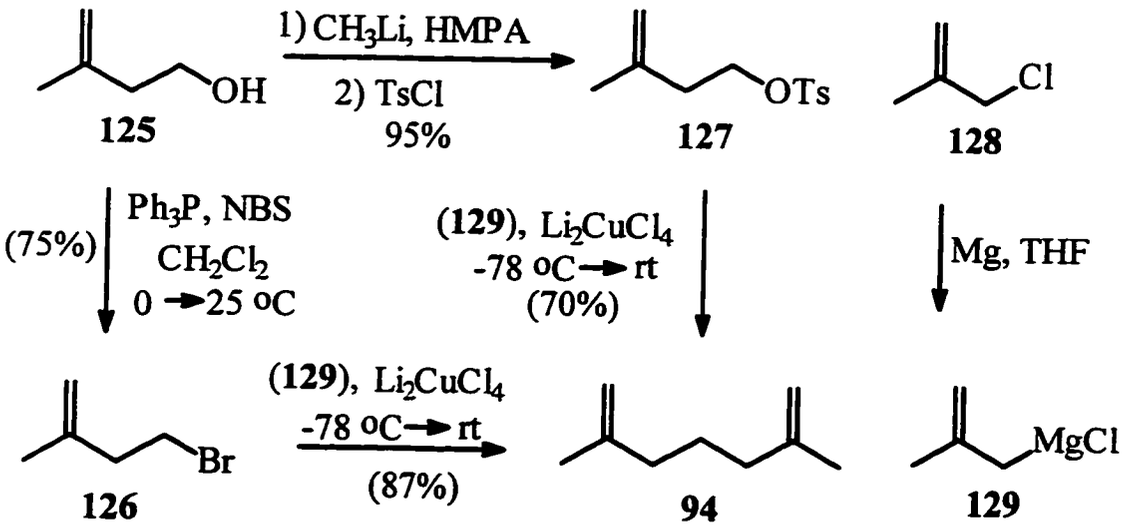
Cross coupling between 4-bromo-2-methyl-1-butene[32] (**126**) or the tosylate[32] **127** of 3-methyl-3-butene-1-ol (**125**) with the Grignard[33] reagent of 3-chloro-2-methylpropene (**128**) in the presence of Li_2CuCl_4[24] gave 2,6-dimethyl-1,6-heptadiene (**94**) in 65% yield (from 3-methyl-3-buten-1-ol), a considerable improvement over previous methods (11%[29],15%[31], 27%[30]). Although 17% of the homocoupling by-product, 2,5-dimethyl-1,6-hexadiene, was also found, the main product can be obtained by distillation.

The coupling reaction between 4-bromo-2-methyl-1-butene **126** and the Grignard reagent gave a higher yield (87%) and less polymer side product (from distillation residue) than did the tosylate **127** (70%). As

4-bromo-2-methyl-1-butene is very volatile, some of it evaporated during the preparation, and the isolated yield is only 75%, although 3-methyl-3-buten-1-ol was completely converted to the bromide **126** (Ph_3P, NBS).

Conversely, the tosylate of 3-methyl-3-butene-1-ol was prepared in better yield (95%), although there was some inconvenience in handling CH_3Li). The overall yields for both two-step sequences are about the same, but the route **125** to **126** to **94** was preferred.

Scheme **20**. Synthesis of 2,6-dimethyl-1,6-heptadiene



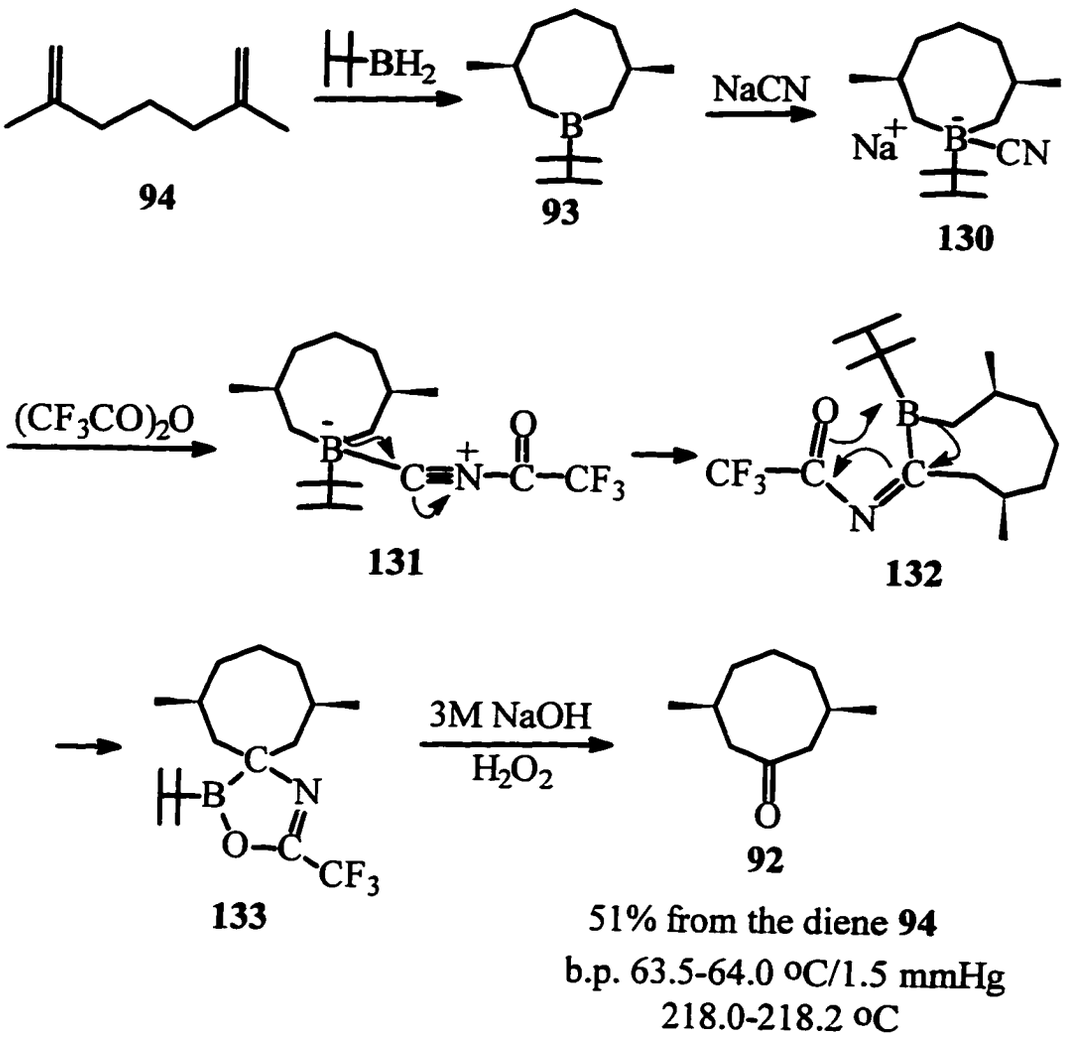
2.3 Synthesis of *meso*-3,7-dimethylcyclooctanone

2.3.1 Cyclic hydroboration

Cyclic hydroboration/oxidation of diene **94** with thexylborane[34] was found by Still at al.[27a] (and confirmed by Chenevert et al.[27b]) to give predominately *meso*-diol in 73% (59%) yield (*meso* / *d,l* = 15/1). On the other hand, cyclic hydroboration with thexyl borane followed by carbonylation/oxidation[35] of the crude product produced *meso*-3,7-dimethylcyclooctanone **92** as a pure diastereoisomer in 51% yield, as shown in Scheme 21.

GC-MS showed one other component with M^+ 154 but of negligible intensity (0-0.2%), and ^{13}C NMR showed no peaks consistent with the *d,l* diastereoisomer.

Scheme 21. Synthesis of 3,7-dimethylcyclooctanone



94 93 130

131 132

133

92

51% from the diene **94**

b.p. 63.5-64.0 °C/1.5 mmHg

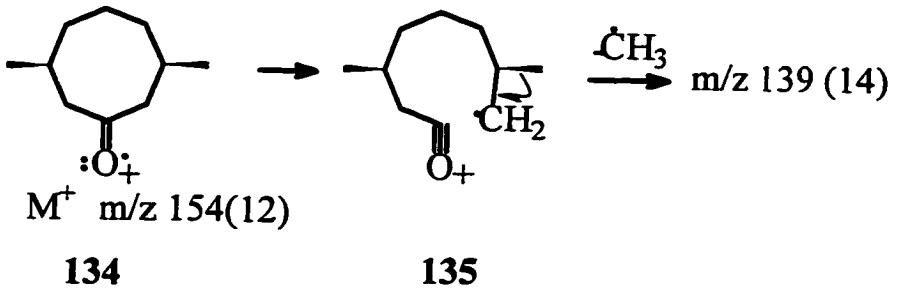
218.0-218.2 °C

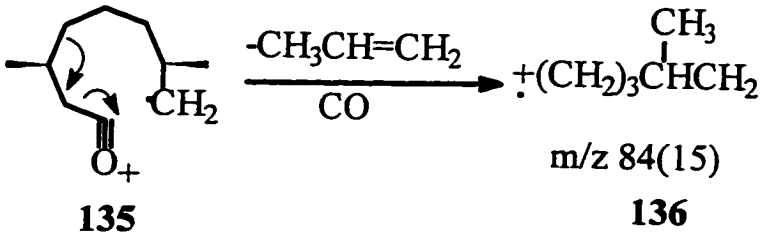
Structure elucidation:

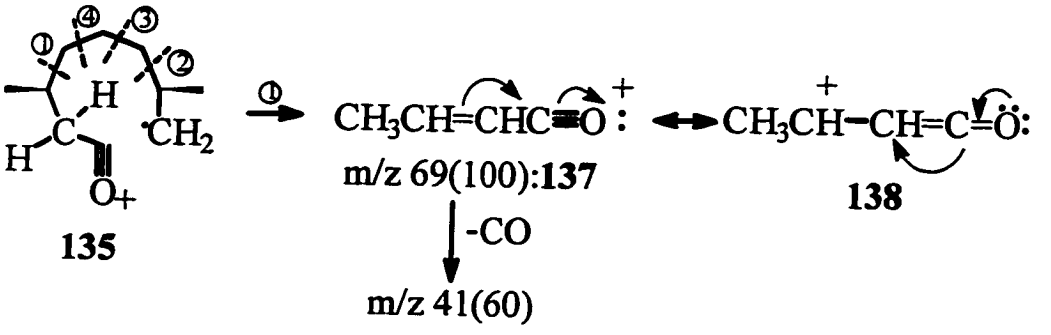
The signals in ^{1}H NMR and ^{13}C NMR spectra of all of the synthesized compounds were assigned by DEPT, 2-D COSY, and 2-D HETCOR in the experimental section.

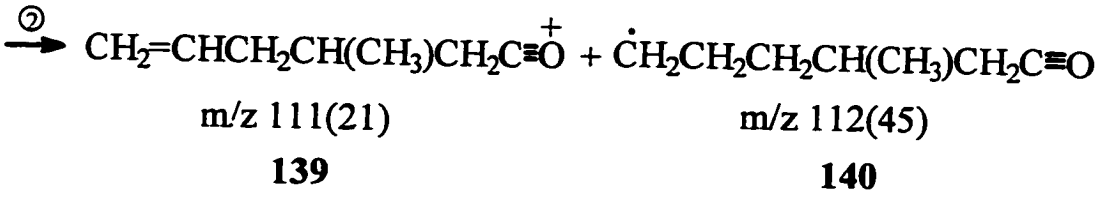
The GC-MS spectrum gave a molecular ion peak with prominent intensity (M+, 12): Some of the distinctive peaks are rationalized, as shown in Scheme 22.

Scheme **22.** Fragmentation of *cis*-3,7-dimethylcyclooctanone





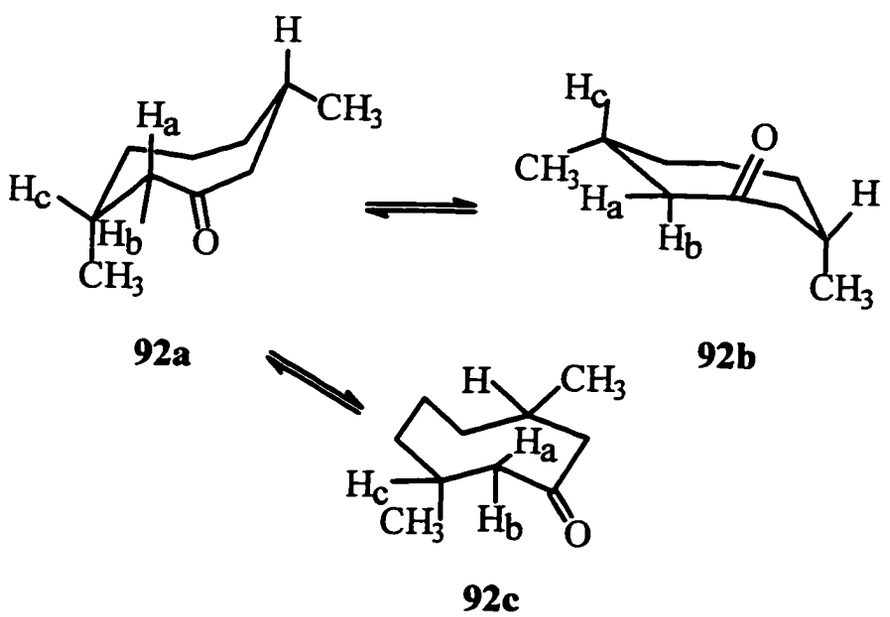




$M^+ \xrightarrow{③}$ m/z 97(16), 98(17). $M^+ \xrightarrow[-CO]{④}$ m/z 56(35), 55(52).

Interestingly, *cis*-3,7-dimethylcyclooctanone (**92**) exhibits a big difference in chemical shift between the α and α' protons (AB-quartet) on C-2 and C-8 ($\Delta\nu = 0.37$ppm, with $J_{ab} = 18$ Hz). This big difference is caused by the rigid ring structure and the adjacent methyl groups, as shown in Scheme 23.

Scheme **23**. Probable conformations of ketone **92**



92a **92b**

92c

There may be three conformations of **92**, chair-like (**92a**, **92b**) or boat-like (**92c**). H_a and H_b are in different environments in all the three conformations.

2.3.2 Stereoselectivity of cyclic hydroboration

It is likely that the Still/Chenevert's results (Scheme 11) were due to the presence of appreciable polymeric borane besides the desired (cyclic) borocane **93** and oxidation of this mixture gave the *meso/d,l* diol (**86**, **87**) product mixture actually isolated. Carbonylation, on the other hand, could have proceeded only from **93**, which resulted from a highly stereoselective cyclic hydroboration as Still had predicted.

According to Brown et al.[34] and Pelter et al.,[34f] hydroboration of dienes with thexylborane in many cases gives high yields of cyclic boranes, especially 1,4-pentadiene, 1,5-hexadiene, and 1,5-cyclooctadiene. On the other hand, the corresponding reaction of 1,7-octadiene does not, and hydroboration of 1,6-heptadiene using BH_2Cl[34b-e] gives polymeric product, although depolymerization at high temperature gives the monomeric product. Thus, it is more difficult to make an 8-membered ring borane

without polymerization. This is probably the reason we only obtained a moderate yield of *cis*-3,7-dimethylcyclooctanone.

There are three methods to mix thexylborane with diene: addition of borane-to-diene, diene-to-borane, and the simultaneous addition of thexylborane and a diene. Brown et al.[34a] favored the first procedure (borane-to-diene) as more convenient, and they found the simultaneous addition did not offer any noticeable advantage. We tried all three approaches, and Still's method (addition of the diene to borane) gave the best result so far.

We found that the reaction temperatures and ratios of diene **94** to thexylborane affected the yields of diols, and the ratio of *meso/d,l* diols, as shown in Table 2.

Table 2. The effect of the reaction temperatures and reactant ratios on the yield and ratio (*meso/d,l*) of diol.

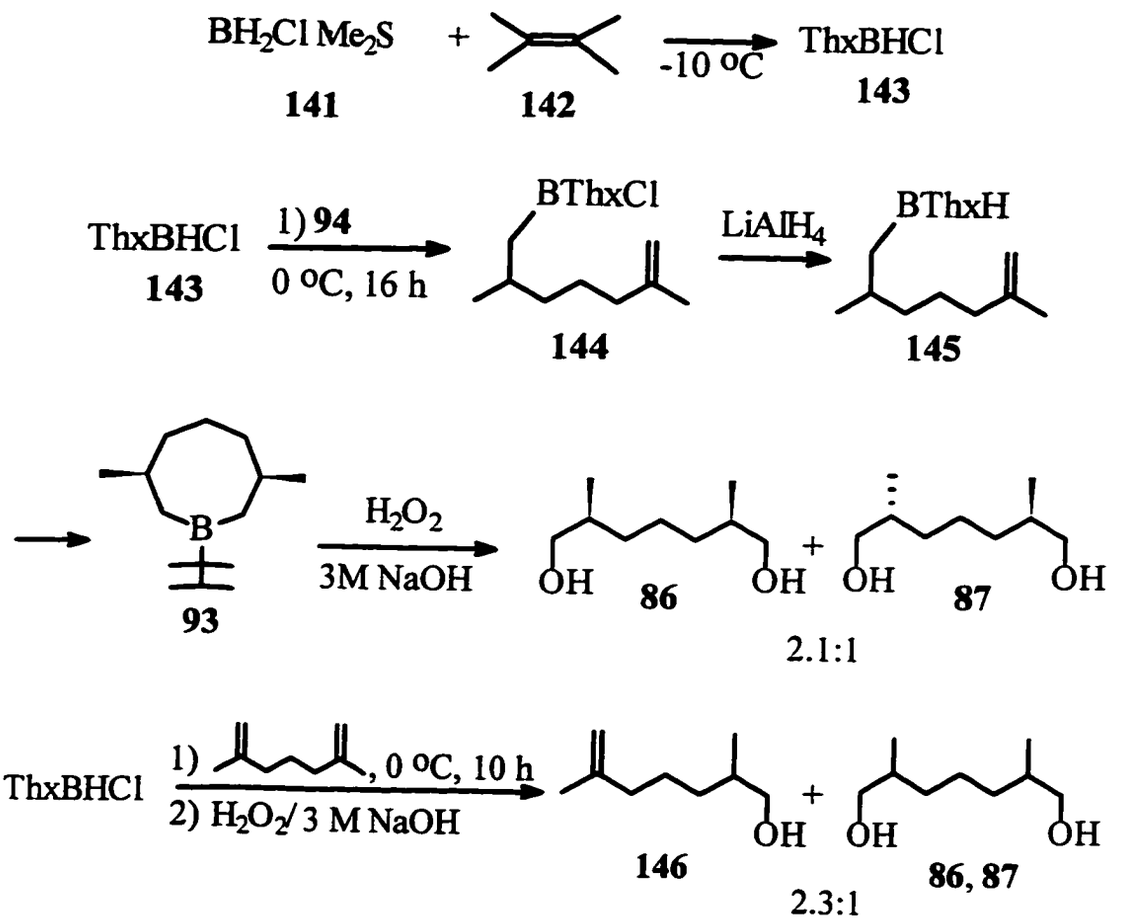
BH_3/Diene	Temp. (^{0}C)	Time (h)	*meso/d,l**	Yield (%)
1.1/1.0	-78-rt	18	9.0/1	61
3.0/1.0	-78-rt	18	4.5/1	83
1.1/1.0	-78-reflux	4	6.5/1	86
1.1/1.0	0-reflux	4	4.8/1	81

*According to ^{13}C NMR. 5 mmol of the diene in 50 mL of THF was used in each experiment.

We attempted to increase the yield of cyclic hydroboration by a stepwise route, as shown in Scheme 24. Stepwise hydroboration of two different alkenes followed by replacement of the borane by a carbonyl group is one of the important routes for the synthesis of unsymmetrical ketone.[35] Thexylchloroborane[36] can be readily prepared from $BH_2Cl{\cdot}Me_2S$. We tried the following reactions, as shown in Scheme 24. We hoped that hydroboration of one double bond of diene **94** with thexylchloroborane (**143**), followed by reduction of the chloroborane adduct **144** and intramolecular hydroboration of **145** would give *meso* product **86** in higher yield. Unfortunately, the results were not satisfactory.

Hydroboration of diene (**94,** 1 eq) with thexylchloroborane (1e q.) gave a mixture of diol and mono-enol.

Scheme 24. Stepwise hydroboration of diene **94**



Another important consideration is that during carbonylation of tri-alkylboranes proceeds via intramolecular transfer of alkyl groups from boron to carbon, the migratory aptitude of a tertiary alkyl group, such as

the thexyl (2,3-dimethyl-2-butyl) group, is much lower than that of a primary or a secondary groups. Consequently, carbonylation-oxidation of thexylboranes is almost quantitative, as shown in Scheme 21. Similarly, the reaction of organoboranes with NaCN is quantitative prior to addition of an electrophile such as benzoyl chloride, *N*-phenylbenzimidoyl chloride, or trifluoroacetic anhydride. We chose trifluoroacetic anhydride as an acylating reagent since it gives the best yield[34f] in this kind of reaction, and the reaction occurred readily below room temperature.

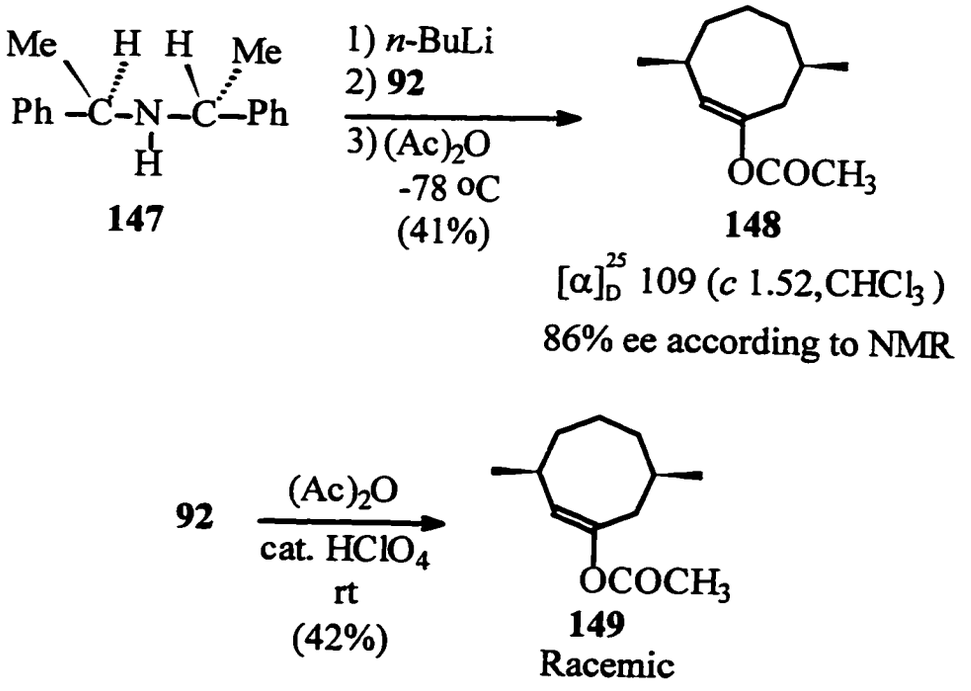
2.4 Synthesis of C_{10} chirons

Deprotonation of a ketone followed by a reaction of the resulting enolate with an electrophile is one of the fundamental reaction sequences in organic synthesis. During recent years, a growing number of papers dealing with enantioselective deprotonation[37] of cyclic ketones (most of them are 6-membered rings) with a number of chiral lithium amides have appeared. However, no enantioselective deprotonation of an 8-membered ring has been reported yet. There are many chiral bases which can be used. We used (+)-bis-[(*R*)-1-phenylethyl]-amine, since both enantiomers are commercially available. In the event, the reaction was gratify-

ingly enantioselective for *cis*-3,7-dimethylcyclooctanone with the amide of this base.

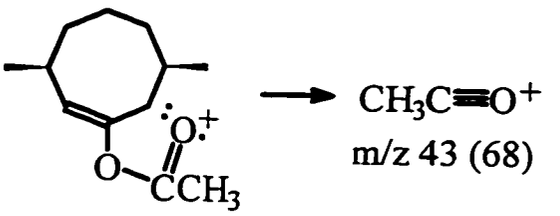
Deprotonation of the above ketone with the lithium salt of (+)-bis-[(*R*)-1-phenylethyl]amine (**147**) and quenching the resulting enolate with acetic anhydride yielded an enol acetate **148** in 42% yield, as shown in Scheme 25.

Scheme **25**. Synthesis of C_{10} chirons

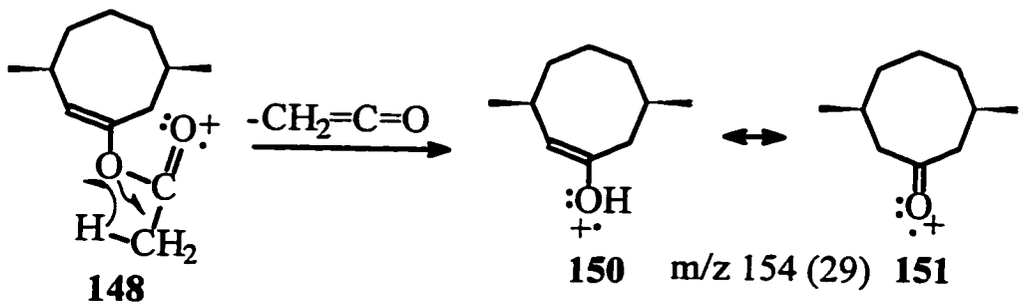


The GC-MS spectrum of enol acetate **148** gave a molecular ion peak with the visible intensity (M^+,1). Some of the distinctive peaks are rationalized, as shown in Scheme 26.

Scheme **26**. Fragmentation of (3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-ol acetate

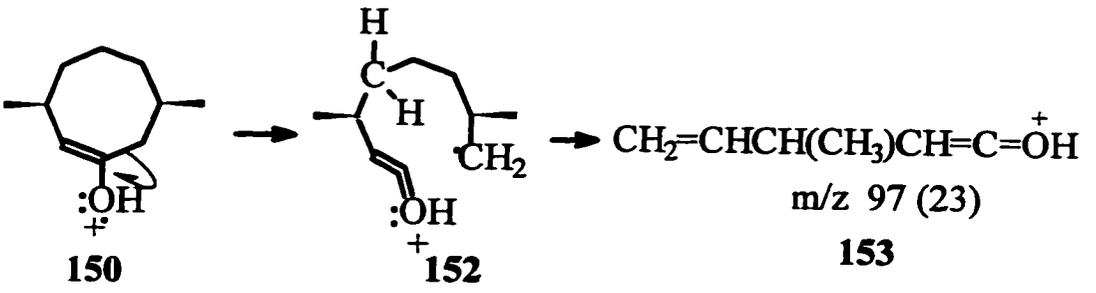


148
m^+/z 196 (1)

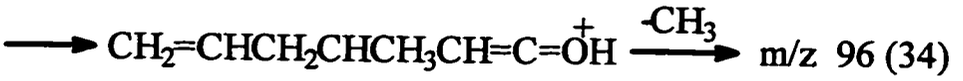


148 **150** m/z 154 (29) **151**

same as ketone → 139 (20), 98 (20), 97 (23), 69 (44), 55 (27), 41 (34), 111 (100), 112 (92).



150 **152** **153**



154

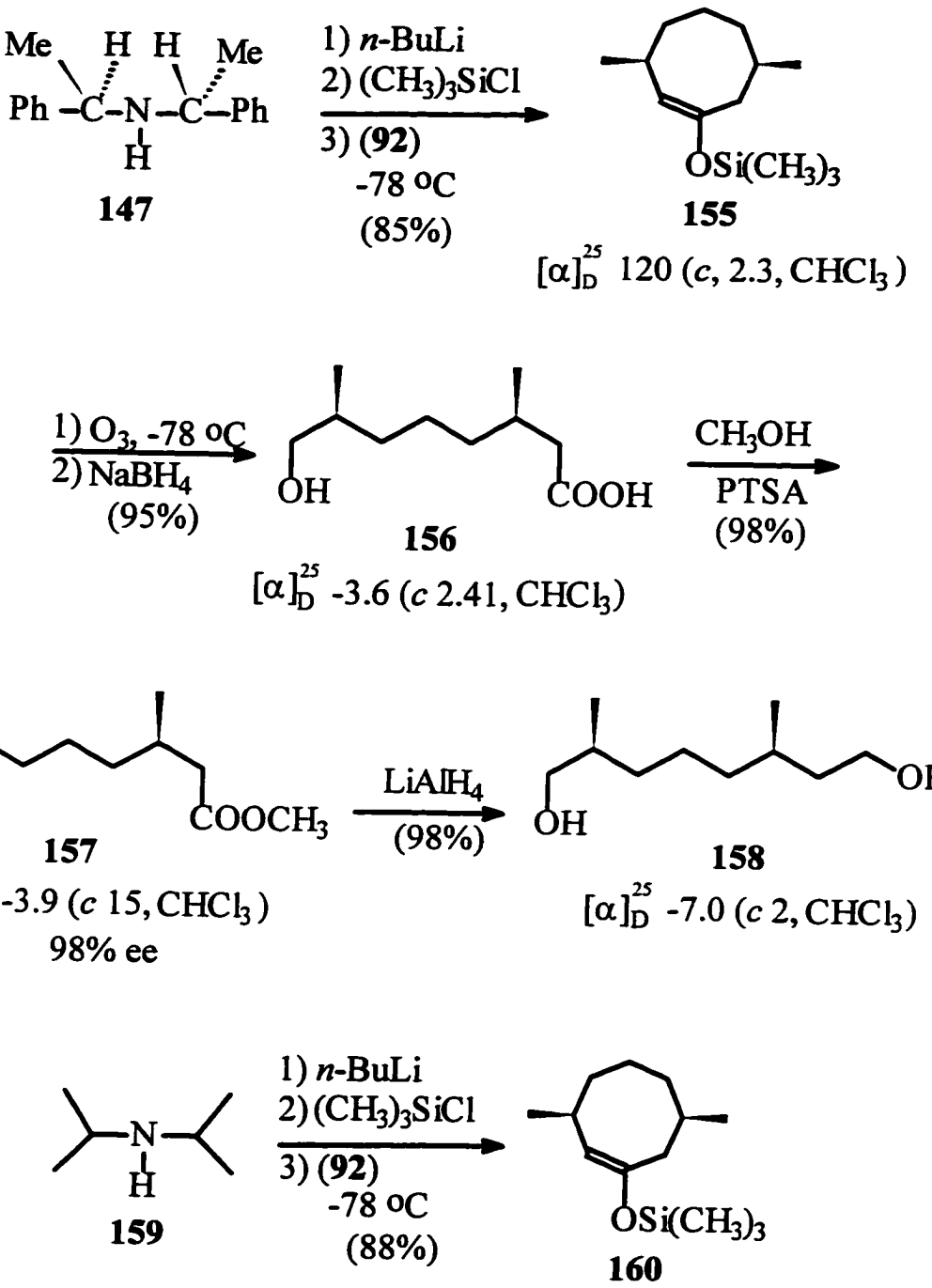
In comparison, the racemic enol acetate **149** was made from ketone **92** with acetic anhydride in the presence of $HClO_4$[38]. Chiral shift reagent Eu(hfc)$_3$ (tris(3-heptafluorobutyryl-*d*-camphorato)europium(III)) induced separation of the ^{1}H NMR position of the two methyl groups of racemic enol acetate (**149**). One of the methyl groups (δ 0.93, d, J = 6.6 Hz) on the ring was split into two doublets (δ1.11, 1.17, J = 6.6 Hz) with 1:1 ratio and baseline separation.

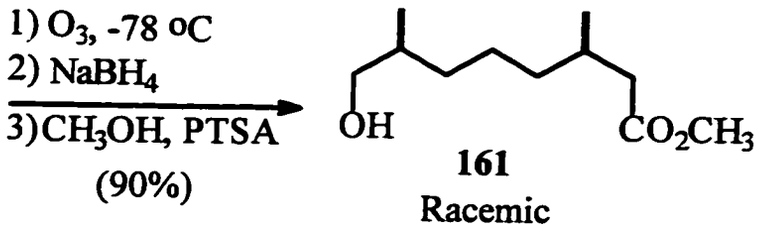
Chiral shift reagent Eu(hfc)$_3$ (tris(3-heptafluorobutyryl-*d*-camphorato)europium(III)) was also applied to the enantiomerically enriched enol acetate **148**. The methyl group (δ 0.93, J = 6.6 Hz) was

split into two doublets (δ 1.10, 1.16, J = 6.6 Hz) with a 7:93 ratio (86% ee).

Silylation according to the "internal quench" technique[39a] has been proven to lead to the best results as far as reactions of ketones of C_s symmetry are concerned. *cis*-3,7-Dimethylcyclooctanone was deprotonated by the lithium salt of (+)-bis-[(*R*)-1-phenylethyl]amine (**147**) and the resulting enolate was internally quenched with excess trimethylsilyl chloride to give the corresponding enol trimethylsilyl ether **155** in 85% yield. The chiral shift reagent had no observable effect on **155**. The ring of **155** was opened by ozonolysis/reduction,[39b] and the corresponding hydroxy acid **156** was converted in turn to the hydroxy ester **157** and diol **158**. In comparison, *cis*-3,7-dimethylcyclooctanone was deprotonated by LDA and quenched with excess trimethylsilyl chloride to give the corresponding racemic enol silyl ether **160** in 88% yield. The ring was opened by ozonolysis followed by a reduction workup, and esterification with methanol to give a racemic methyl (3*R*,7*S* and 3*S*,7*R*)-3,7-dimethyl-8-hydroxyoctanate (**161**), as shown in Scheme 27.

Scheme 27. Synthesis of C_{10} Chirons





161
Racemic

Chiral shift reagent $Eu(hfc)_3$ induced separation of the ^1H NMR positions of the methoxyl groups of the enantiomers of hydroxy ester **161**. The methyl group (δ 3.67, s, $COOCH_3$) was split into a doublet (δ 4.16, 4.11) with 1:1 ratio and base line separation.

Chiral shift reagent $Eu(hfc)_3$ was also applied to chiral hydroxy ester **157**. The methyl group (δ 3.67, s, $COOCH_3$) was split into a doublet (δ 4.15, 4.10) in a 99:1 ratio, as shown in Figure 1.

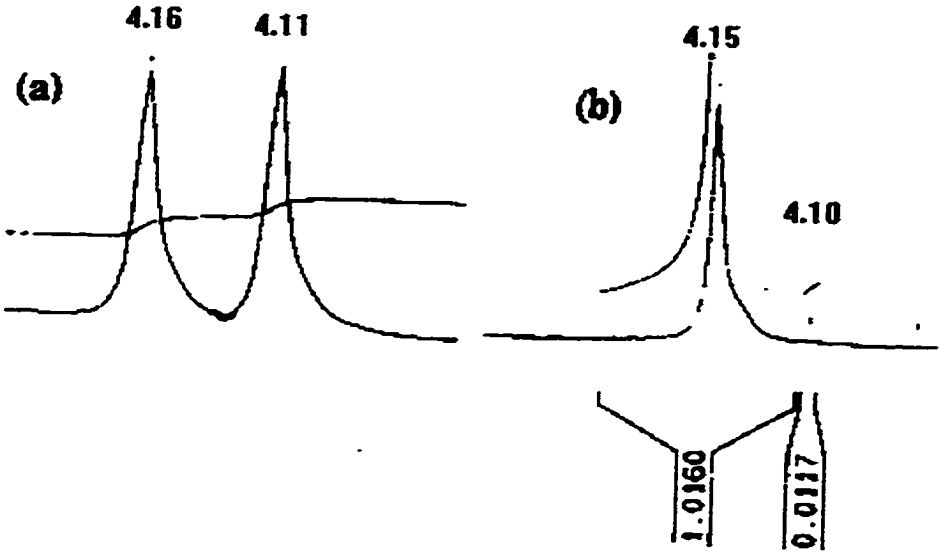
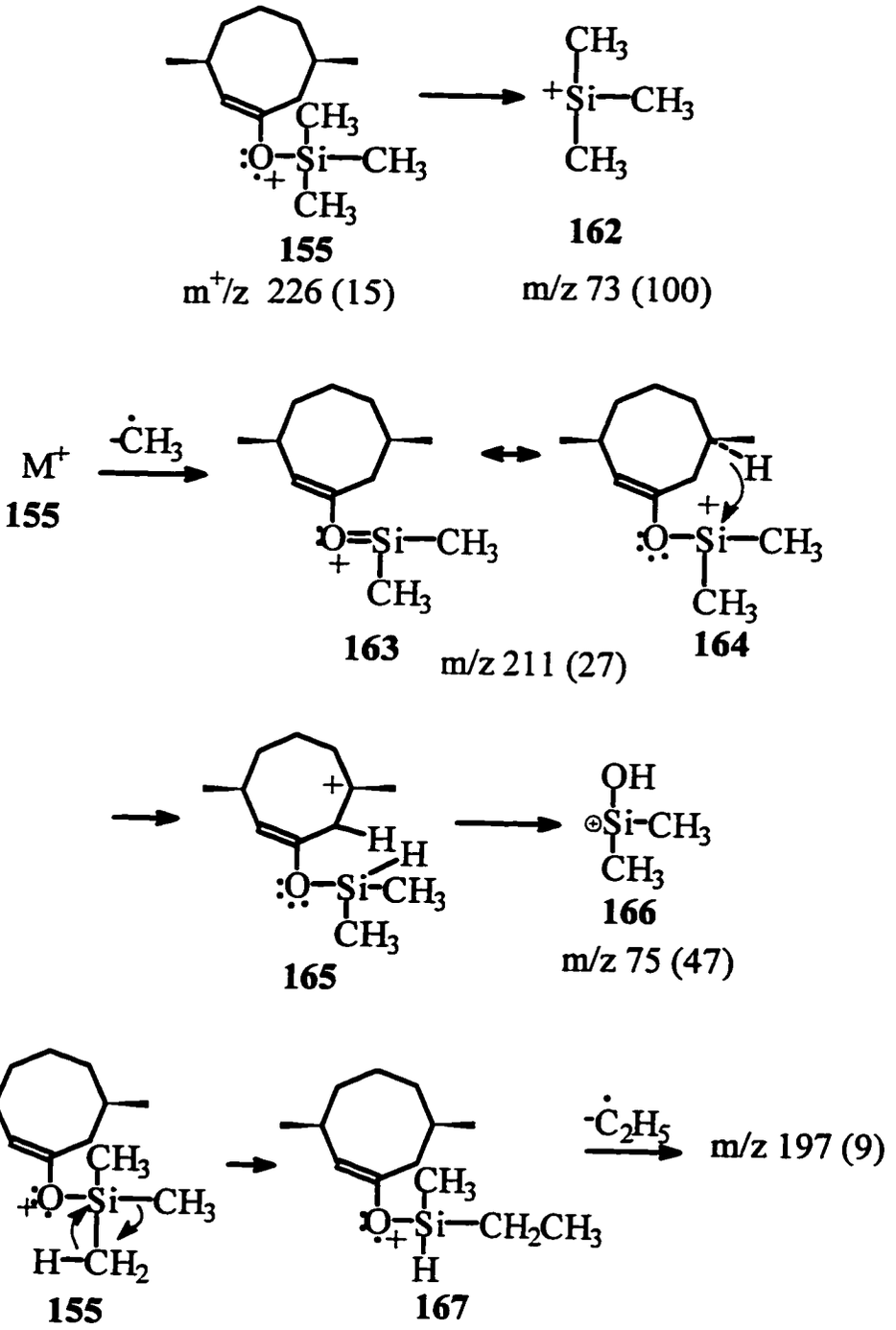


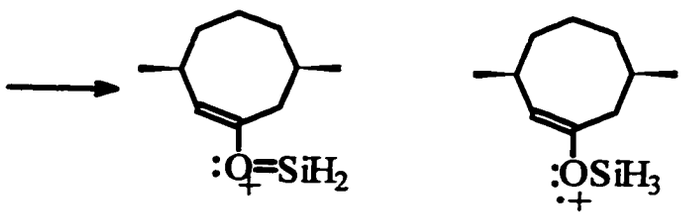
Fig. 1. Partial ^{1}H NMR of methyl 8-hydroxy-3,7-dimethylcyclooctanoate (a) racemic **161**, (b) optically active **157**.

The ee of hydroxy ester **157** is thus 98%, and consequently so is the enol silyl ether, as no subsequent transformation would have epimerized any position. This result also proves that cyclooctanone **92** was the *meso*-dimethyl diastereomer, as the chiral diastereoisomer would have given a racemic mixture upon deprotonation/silylation.

Some of distinctive peaks of enol trimethylsilyl ether **157** in the GC-MS spectrum are rationalized as shown in Scheme 28.

Scheme 28. Fragmentation of [((3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane



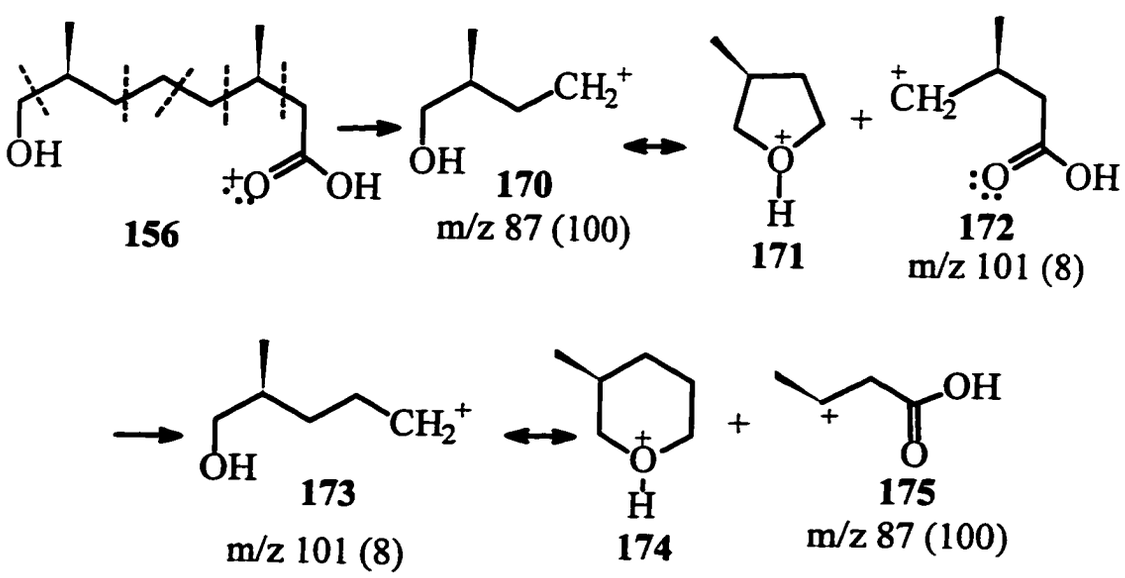


168
m/z 183 (64)

169
m/z 184 (23)

Some of the distinctive peaks of (3*R*,7*S*)-3,7-dimethyl-8-hydroxy-octanoic acid (**156**) in the GC-MS spectrum are rationalized, as shown in Scheme 29.

Scheme **29**. Fragmentation of (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoic acid.



156

170
m/z 87 (100)

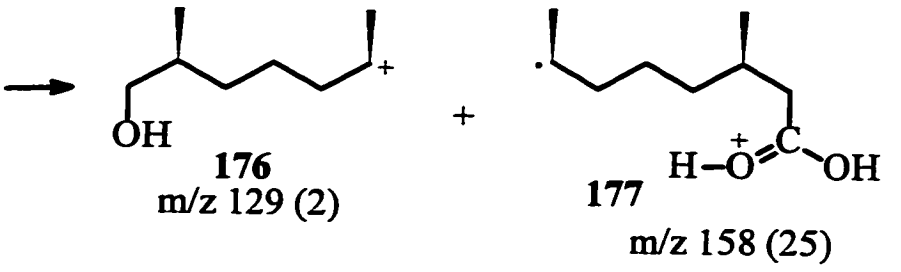
171

172
m/z 101 (8)

173
m/z 101 (8)

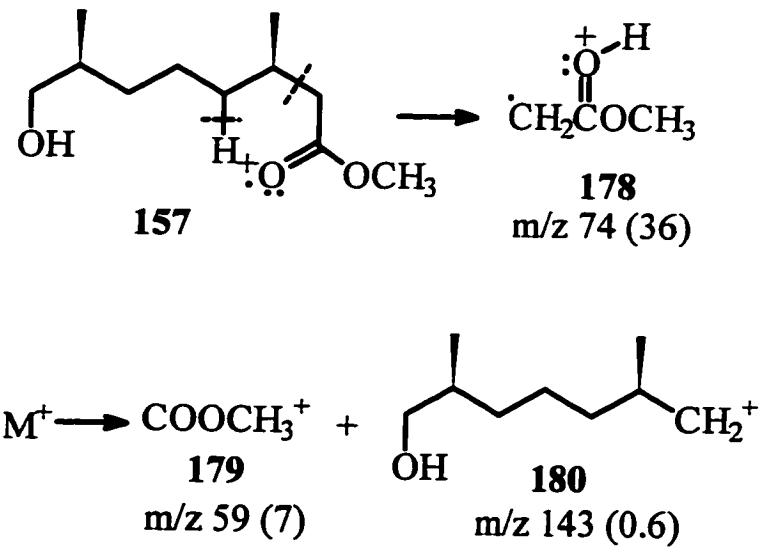
174

175
m/z 87 (100)

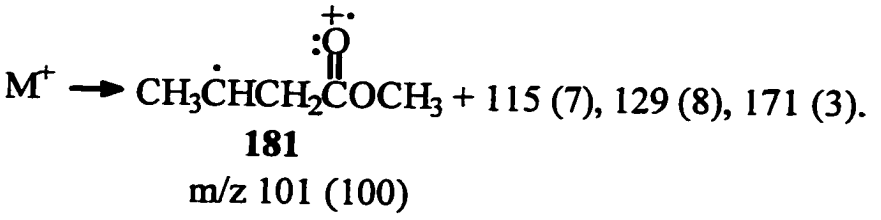


Some of the distinctive peaks of methyl (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoate (**157**) in the GC-MS spectrum are rationalized as shown in Scheme 30.

Scheme **30**. Fragmentation of methyl (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoate

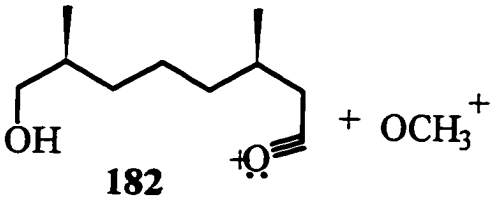


→ 129 (9), 101 (100), 87), 73 (6), 59 (17).



181

m/z 101 (100)



182

m/z 171 (3)

m/z 31 (9)

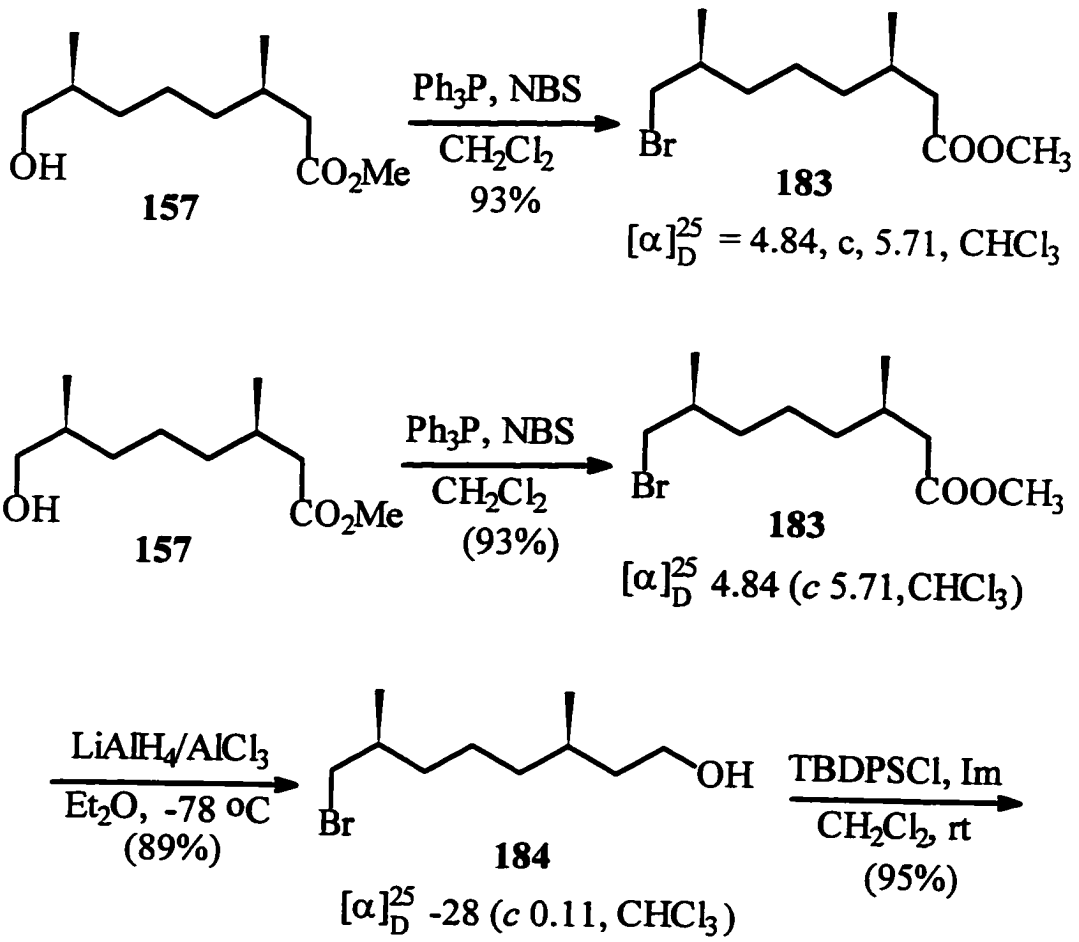
Finally, the optical purity of **157** was determined by reduction with $LiAlH_4$ to the known (2*S*,6*R*)-2,6-dimethyloctane-1,8-diol with $[\alpha]_D^{25}$ -7.0 (*c* 2.1, $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ -6.3 (*c* 9.5, $CHCl_3$), >98% ee, from geraniol, as shown in Scheme 4. Our results (NMR, IR) matched the reference.

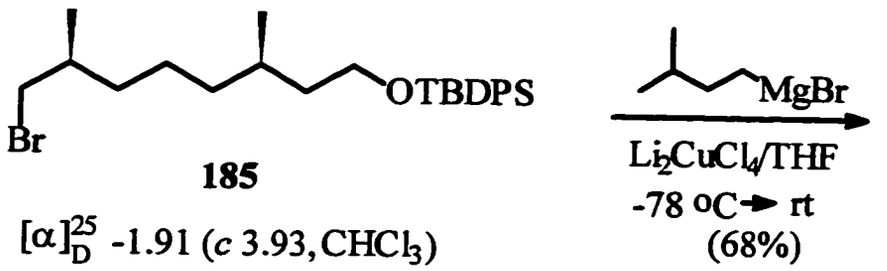
2.5 Synthesis of a vitamin E side chain synthon

In recent years, vitamin E (α-tocopherol), a potent antioxidant and radical scavenger in chemical and biological systems, has receieved increasing attention with regard to clinical and nutritional application in

human heath.[40] Phytanol (**187**) (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol[41,42] served as a key intermediate in the total synthesis of vitamin E.[43] A C_{10} chiron (**157**) obtained from hydroboration/asymmetric deprotonation/ozonolysis[1] of diene **94** can be easily transformed into **187**, as shown in Scheme 31.

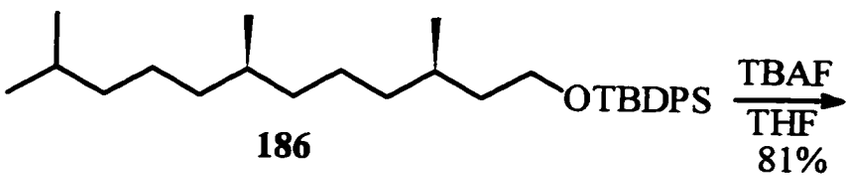
Scheme **31**. Synthesis of Phytanol (**187**)





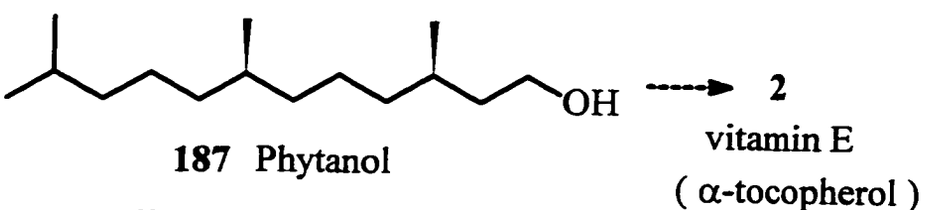
185

$[\alpha]_D^{25}$ -1.91 (*c* 3.93, $CHCl_3$)



186

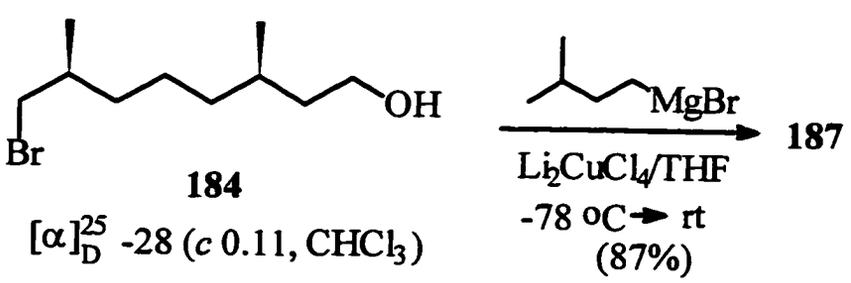
$[\alpha]_D^{25}$ -1.45 (*c* 1.72, $CHCl_3$)



187 Phytanol

$[\alpha]_D^{25}$ 3.53 (*c* 1.205, $CHCl_3$)

lit.[42] $[\alpha]_D^{23}$ 3.56 (*c* 1.805, $CHCl_3$)



184

$[\alpha]_D^{25}$ -28 (*c* 0.11, $CHCl_3$)

Hydroxy ester **157** was converted to bromo ester **183** with Ph_3P/NBS[44] in CH_2Cl_2 in 93% yield. Alane reduction[45] of **183** at -78°C in

ether gave bromo alcohol **184** in 89% yield. Silylation[46] of **184** using *tert*-butyldiphenylsilyl chloride in methylene chloride to protect the hydroxy group provided **185** in 95% yield. Cross coupling between **185** with excess Grignard reagent (10 eq) of 1-bromo-3-methylbutane in the presence of Li_2CuCl_4 gave a protected Phytanol **113** in 68% yield. Deprotection of **186** with TBAF gave Phytanol **187** in 81% yield. Directly from cross coupling between bromo alcohol **184** with the excess Grignard reagent (10 eq) of 1-bromo-3-methylbutane in the presence of Li_2CuCl_4 also gave **187** in 87% yield, and TLC showed all of the bromo alcohol was consumed. The optically active (98% ee) C_{15} alcohol was thus prepared in 7 steps from diene **94** in 29% overall yield. The IR, ^1H NMR, ^{13}C NMR, and optical rotation of **187** matched the reference[42].

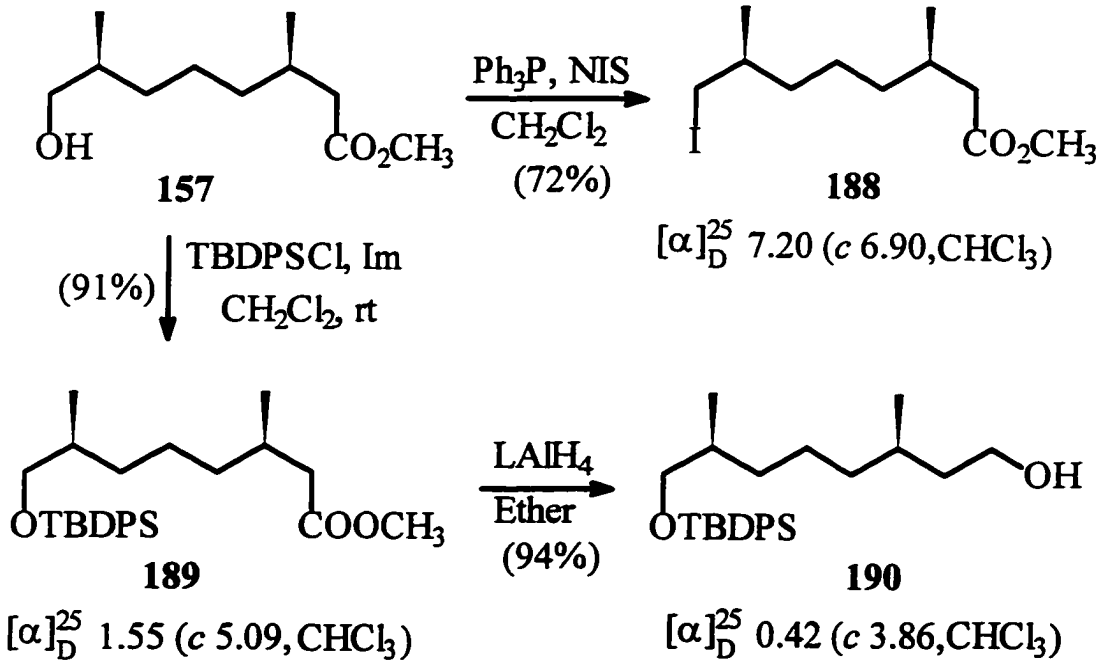
2.6 Synthesis of a C_{20} chiron using a Grignard reagent

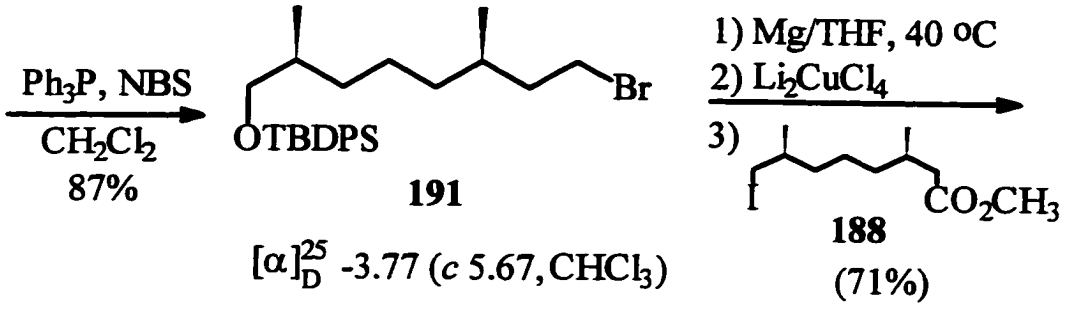
Head to tail coupling two C_{10} units will give the desired C_{20} synthon **13** applicable to the synthesis of archaebacterial lipids **10** and **11**. Hydroxy ester **157** was converted to iodo ester **188** with Ph_3P/NIS in CH_2Cl_2 in 72% yield, as shown in Scheme 32. In the meantime, hydroxy ester **157** was protected by *tert*-butyldiphenylsilyl chloride[46] to give **189**

in 91% yield, then reduced with LAH to give **190** in 94% yield, and converted to bromide **191** with Ph_3P/NBS in 87% yield.

Cross-coupling between the Grignard reagent of **191** (2 eq) and iodo ester **188** (1 eq) at 0 °C in the presence of Li_2CuCl_4 in THF gave C_{20} chiron **192** in 71% yield. The ^1H NMR, ^{13}C NMR, IR, and ESI-MS ($M+H^+$, 581.3) spectra matched this compound.

Scheme **32**. Synthesis of C_{20} chiron



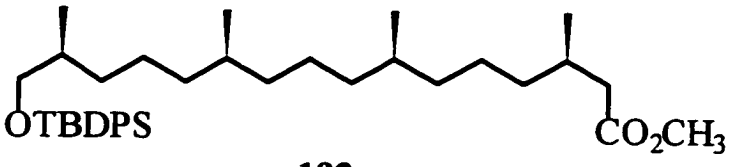


191

$[\alpha]_D^{25}$ -3.77 (*c* 5.67, $CHCl_3$)

188

(71%)

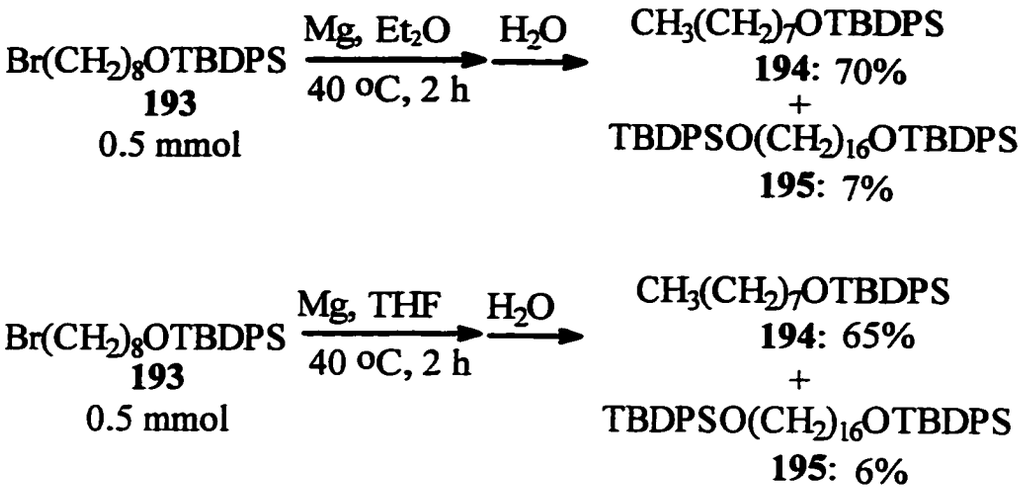


192

$[\alpha]_D^{25}$ 1.50 (*c* 1.70, $CHCl_3$)

In order to maximize the yield of the cross-coupling reaction between the Grignard reagent of **191** and iodo ester **188**, the following model reactions were investigated, as shown in Scheme 33.

Scheme 33. Model study on Grignard reactions



Upon conversion of bromide **193** to the Grignard reagent in ether 14% of the bromide was homo-coupled. The result was essentially unchanged in THF.

In order to avoid homo-coupling during Grignard formation, model studies on samarium mediated cross-coupling reactions were initiated.

2.7 Copper-catalyzed cross-coupling of alkylsamarium reagents with alkyl halides

2.7.1 Model studies on cross-coupling reaction

In order to find a new way to increase the yield of C-C bond formation of a small scale reaction, cross-coupling of organosamarium species with organic halides was investigated.

SmI_2 is a powerful one-electron reducing agent that can be prepared in moderate concentrations (0.1 M) in THF using several different reactions with samarium metal. Preparation times vary from 1 h to 12 h.[47,48]

$$Sm + ICH_2CH_2I \xrightarrow[rt,\ 1\ h]{THF} SmI_2 + CH_2{=}CH_2$$

$$Sm + ICH_2I \xrightarrow[rt,\ 1\ h]{THF} SmI_2 + 0.5\,CH_2{=}CH_2$$

$$Sm + I_2 \xrightarrow[12\ h]{THF} SmI_2$$

Deep blue solutions of SmI_2 are generated in virtually quantitative yields by all of these methods, but diiodomethane or diiodoethane need to

be purified. For reproducible synthetic purposes, SmI_2 is freshly made and used within several days, although THF solutions of SmI_2 are commercially available. SmI_2 is easily handled by standard techniques for the manipulation of air-sensitive materials.

The development of samarium(II) reagents for the reduction of organic functional groups and for carbon-carbon bond formation has received a great deal of attention[49] since Kagan and coworkers developed a convenient synthesis of SmI_2 and provided an outline for its reactivity with organic functional groups.[50] It is believed that the reduction of organic halides by SmI_2/HMPA,[49e] or $Sm(OTf)_2$[51] under "Grignard" conditions forms organosamarium(III) intermediates. The development of copper-catalyzed conjugate additions of such reagents by Curran and Wipf[52] led us to wonder if they might also be used for copper-catalyzed cross-coupling of alkyl halides. This is indeed the case, as summarized in Table 3 and 4.

From Table 3, it can be seen that CuBr is the most effective catalyst for cross-coupling (90%). CuCl and CuI gave moderate yields of cross-coupling product (entries 2,3). Li_2CuCl_4 (0.1 M in THF) also give good results (75%), and was easier to handle. Replacement of CuBr with

$FeCl_3$ or $ZnCl_2$ in the above experiments failed to give any homo or cross-coupling product. In the absence of Cu catalyst, no coupling was observed.

Table 3. Cross-coupling of alkyl halides catalyzed by different copper salts[a]

Entry	RX	R'X	Catalyst	R-R[b]	R'-R'[c]	R-R'[c]
1	*n*-$C_7H_{15}Br$	*n*-$C_6H_{13}I$	CuBr	0	3	90
2	*n*-$C_7H_{15}Br$	*n*-$C_6H_{13}I$	CuCl	3	8	77
3	*n*-$C_7H_{15}Br$	*n*-$C_6H_{13}I$	CuI	8	3	68
4	*n*-$C_7H_{15}Br$	*n*-$C_6H_{13}I$	Li_2CuCl_4	5	2	75(85[d])

2.5 eq SmI2, 8.3 eq of HMPA, 1.0 eq of RX, 0.17 eq of catalyst, and 0.83 eq of R'X, 15 min, rt. [a] Yields were determined by GC. Structures and yields were identified by GC/MS comparison with known materials. [b] Yield based on RX. [c] yield based on R'X. [d] 1.0 eq of RX and 0.5 eq of R'X were used.

From Table 4, it can be seen that coupling of primary or secondary alkylsamarium reagents, from bromides or iodides, with primary iodides affords useable yields of cross coupling products with little or no homocoupling by-product. On the other hand, coupling of a primary alkylsamarium with benzyl bromide or isopropyl iodide is less efficient,

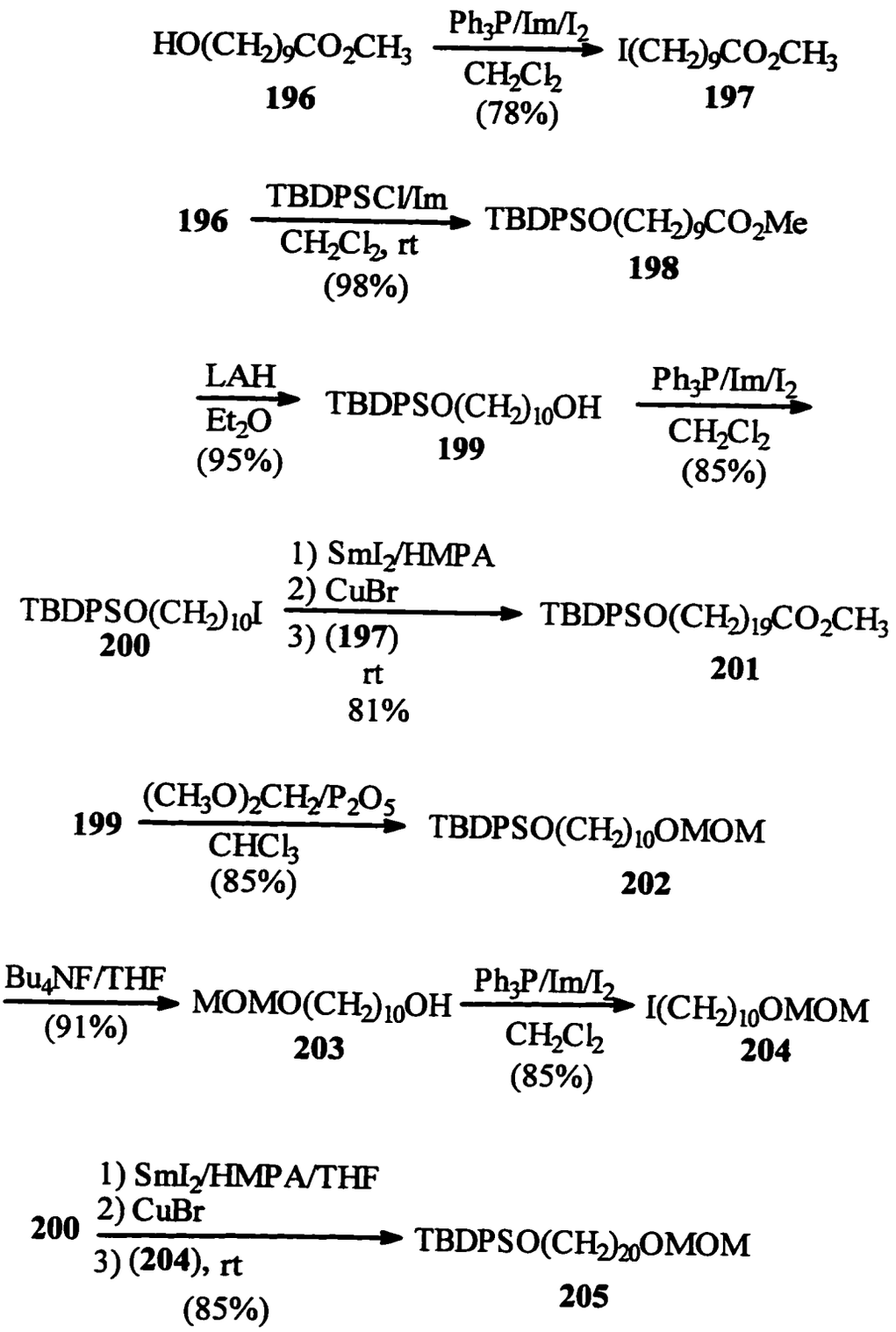
and is useless with an alkyl bromide. We also tried to make organo-samarium reagents from iodobenzene, bromobenzene, methyl 2-bromoacetate, methyl 3-bromopropanoate, the tosylate of 1-hexanol, 1,6-dibromo-hexane, ethyl 5-bromopentanoate, and methyl 8-iodooctanoate, and then couple them with 1-iodohexane, but in no case was a cross-coupling product observed. Although alkylsamarium "Grignard" reagents appear to react with an ester group,[53] here, coupling via the copper derivative with an ω-iodoester was quite efficient, as shown in Scheme 34.

Table 4. Cross-coupling of several alkyl halides, catalyzed by CuBr[a]

Entry	RX	R'X	R-R[b]	R'-R'[c]	R-R'[c]
1	*n*-$C_7H_{15}I$	*n*-$C_6H_{13}I$	5	1	87(92[d])
2	2-bromoheptane	*n*-$C_6H_{13}I$	0	2	48(60[e])
3	*n*-$C_6H_{13}I$	*n*-$C_7H_{15}Br$	3	0	9
4	*n*-$C_{10}H_{21}Br$	*n*-C_3H_7Br	0	nd	63[f]
5	*n*-$C_6H_{13}I$	$C_6H_5CH_2Br$	9	nd	32
6	$C_6H_5CH_2Br$	*n*-$C_6H_{13}I$	nd	8	53
7	n-$C_{10}H_{21}Br$	2-iodopropane	nd	nd	51[e]

Reaction conditions and a,b,c,d as in Table 3. [e] 6 h. [f] 20 h.
nd: not determined.

Scheme **34**. Cross-coupling of several functionalized alkyl halides

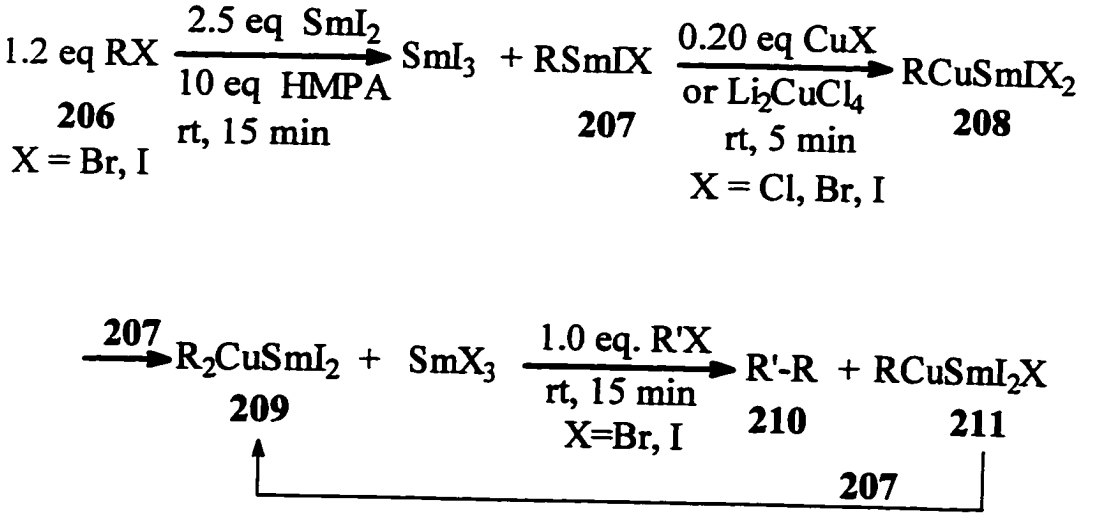


Methyl 10-hydroxydecanoate (available from Aldrich) **196** was converted to iodoester **197** with $Ph_3P/Im/I_2$ in CH_2Cl_2 in 78% yield. In the meantime, **196** was protected by *tert*-butyldiphenylsilyl chloride to give **198** in 98% yield, then reduced with LAH to give **199** in 95% yield, and converted to iodide **200** with $Ph_3P/Im/I_2$ in 85% yield. Cross-coupling between 10-(*t*-butyldiphenylsilyloxy)-1-iododecane **200** (1.2 eq) using SmI_2 (2.5 eq) / HMPA (10 eq) / CuBr (0.2 eq) and methyl 10-iododecanoate **197** (1 eq) at room temperature afforded methyl 20-(*t*-butyldiphenylsilyloxy)icosanoate **201** in 71% yield, and when 2 equivalent of 10-(*t*-butyldiphenylsilyloxy)-1-iododecane **200** were used, the yield was 81%. In order to examine the effect of the other functional group on the yield of the coupling reaction, 10-(*t*-butyldiphenylsilyloxy)-decan-1-ol **199** was transformed to 10-(*t*-butyldiphenylsilyloxy)-1-(methoxymethoxy)decane **202** with methylal/P_2O_5 in $CHCl_3$ in 85% yield. Desilylation of **202** with Bu_4NF/THF gave 10-(methoxymethoxy)decan-1-ol **203** in 91% yield and which was further transformed into 10-(methoxymethoxy)-1-iododecane **204** with $Ph_3P/Im/I_2$ in 85% yield. Cross-coupling between 10-(*t*-butyldiphenylsilyloxy)-1-iododecane **200** (1.2 eq) using SmI_2 (2.5 eq) / HMPA (10 eq) / CuBr (0.2 eq) and 10-

(methoxymethoxy)-1-iododecane **204** (1 eq) at room temperature afforded 10-[(*t*-butyldiphenylsilyl)oxy]-1-(methoxymethoxy)icosane **205** in 85% yield, and when 2 equivalent of 10-(*t*-butyldiphenylsilyloxy)-1-iododecane **200** was used, the yield was 89%. Thus, a MOM protecting group is better in this reaction than an ester group.

The mechanism proposed by Totleben, Curran and Wipf[52a] for the copper catalyzed conjugate addition of alkylsamarium reagents may be adapted to the cross-coupling reactions, as shown in Scheme 35.

Scheme **35**. Mechanism for samarium mediated crossing-coupling reaction

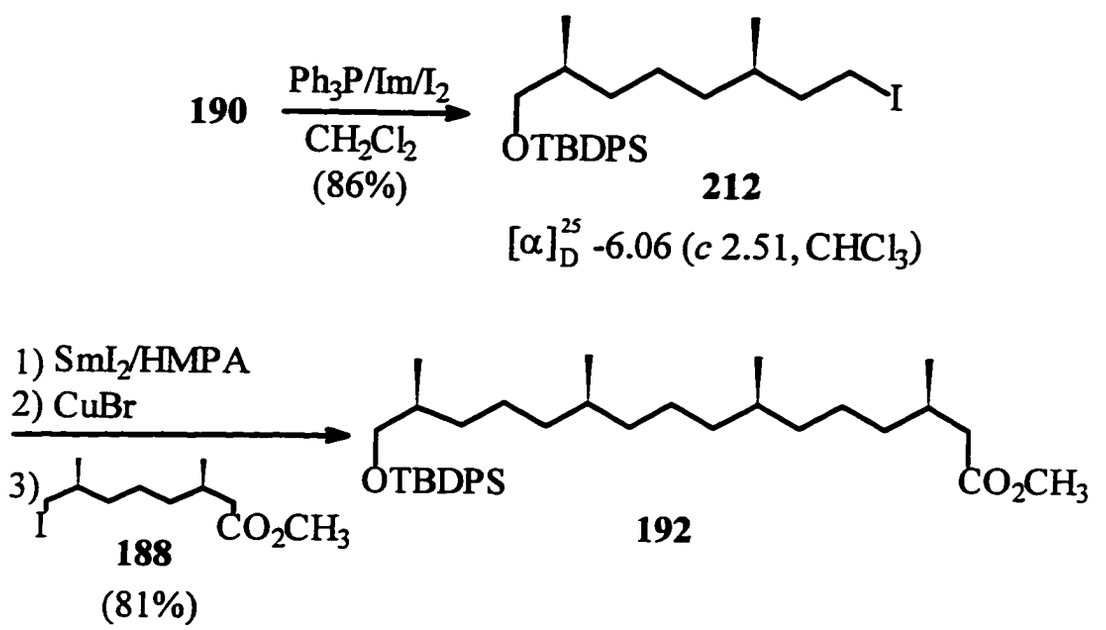


Alkylsamarium **207** is the presumed product of the reduction of alkyl iodides or bromides in THF/HMPA at room temperature. Alkylsamarium **207** is transmetalated smoothly *in situ* to monoalkyl copper samarium species **208** with copper salts. The nucleophilic ability of this species is only marginal. It then reacts with a second equivalent of organosamarium reagent **207** to form a dialkylsamarium copper complex **209**. It is this complex **209** that is coupled with another alkyl halide to give the cross-coupling product **210**. Because the by-product of the coupling reaction, **211**, can combine with another equivalent of organosamarium reagent **207** to regenerate dialkylsamarium copper complex **209**, only a catalytic amount of Copper(I) is needed. In fact, when 1 full equivalent of copper salt was used, no cross coupling product was observed, presumably because there was not sufficient RSmIX **207** remaining to form dialkylsamarium copper complex **209**.

2.7.2 Synthesis of a C_{20} chiron using samarium

The reaction conditions for model studies were applied to the synthesis of enantiomerically pure compounds, as shown in Scheme 36.

Scheme **36**. Synthesis of a C_{20} chiron by using samarium



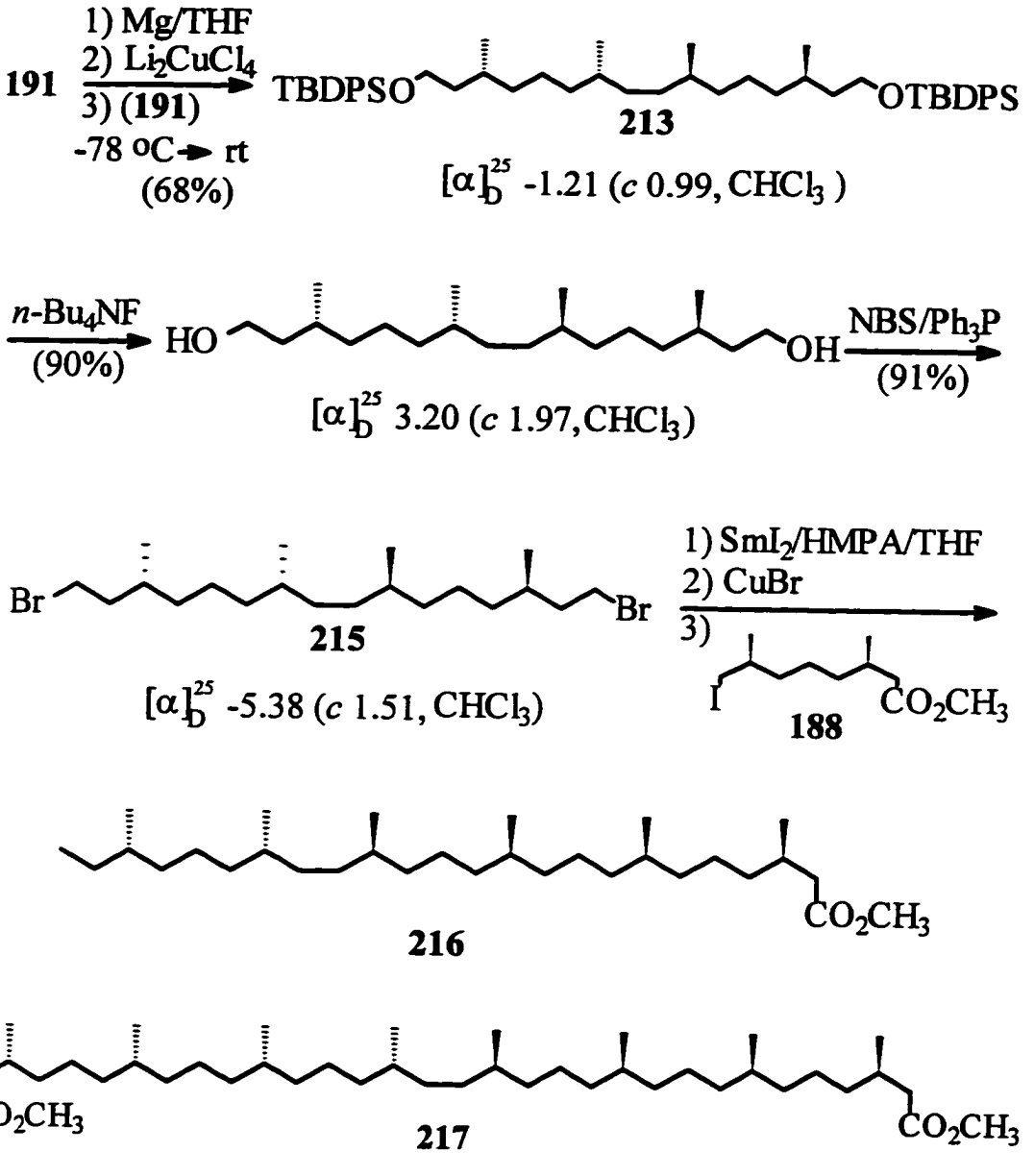
Cross-coupling between 8-(*t*-butyldiphenylsilyloxy)-1-iodo-(2*R*,7*S*)-3,7-dimethyloctane (**212**, 1.2 eq) and methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate (**188**, 1 eq) gave methyl 16-[(*t*-butyldiphenyl-silyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexa-decanoate (**192**) in 81% yield.

By comparison with the Grignard reaction (71%), this reaction gave a higher yield of **192**, and the reaction proceeded within 1 h. Alkylsamarium reagents can be easily prepared by SmI_2 reduction of functionalized alkyl iodides and coupled smoothly with functionalized alkyl iodides at room temperature. Compared to the Grignard reactions, this methodology is considerably milder and faster and results in a better yield, especially on small scale reactions.

2.8 Attempt to synthesize a C_{40} chiron

The archaebacterial C_{40} diol can in theory be constructed efficiently from C_{10} synthons (e.g. **212**) by 1) head to head coupling followed by 2) head to tail coupling, or the reverse. Here we describe an attempt to use the first route, as shown in Scheme 37.

Scheme 37. Attempt to synthesis the C_{40} chiron

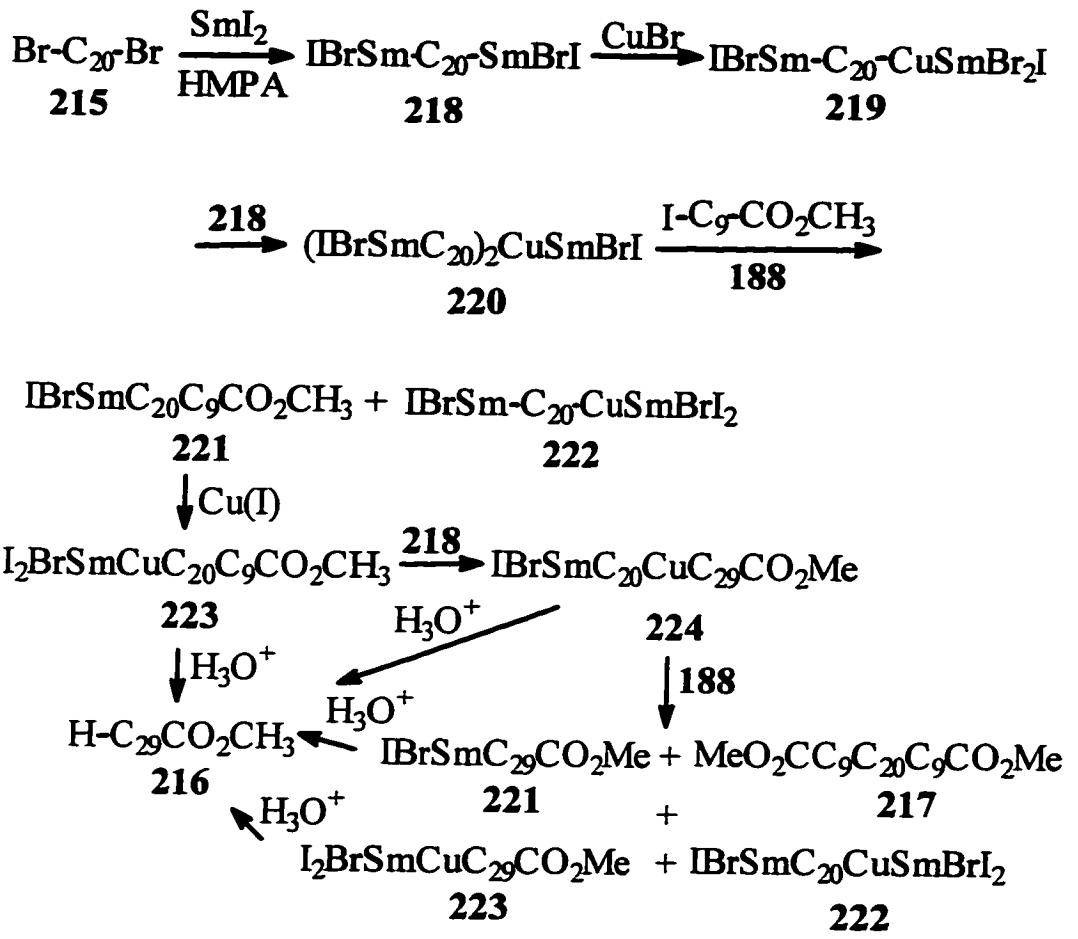


Homocoupling of **191** under Kochi conditions gave a C_2-symmetrical C_{20} chiron **213** in 68% yield. Desilylation of **213** with TBAF in THF yielded a C_{20} diol **214** in 90% yield. Double bromination

with NBS/Ph_3P in CH_2Cl_2 afforded a C_{20} dibromide **215** in 91% yield. Treatment of this dibromide **215** with 5 equivalent of SmI_2 and 20 equivalent HMPA, followed by a catalytic amount of CuBr, and 2 equivalents of iodoester **188** gave only a trace of the desired product **217** (identified by its high resolution mass spectrum: M+H, 467.4838). The products or mono-coupling and mono-reduction, methyl (3*R*,7*R*,11*S*,15*S*,-18*S*,22*S*)-3,7,11,15,18,22-hexamethyl-hexa-icosanoate (**216**) was the major product, in 68% yield.

The reason there is efficient mono coupling but only trace double coupling product **217** may be that the competition of the various samarium complexes for the available copper, limits formation of **224**, and that there are many intermediates which can produce **216** when the reaction mixture is acidified, as shown in Scheme 38.

Scheme 38. Possible mechanism for the above coupling reaction



2.9 Conclusions

2,6-dimethyl 1,6-heptadiene has been synthesized with improved yield (65%) by cross coupling between 4-bromo-2-methyl-1-butene or the tosylate of 3-methyl-3-butene-1-ol with the Grignard reagent of 3-chloro-2-methylpropene in the presence of Li_2CuCl_4. Stereospecific cyclic hydroboration of the resulting diene with thexylborane, followed by carbonylation/oxidation gave *mseo*-3,7-dimethylcyclooctanone as a pure diastereoisomer in a one-pot synthetic procedure in 51% yield. The key step in the synthesis of C_{10} was the asymmetric deprotonation of *mseo*-3,7-dimethylcyclooctanone with the lithium salt of (+)-bis-[(*R*)-1-phenylethyl]amine and "internal quench" with excess trimethylsilyl-chloride to give [((3*S*,7*R*)-3,7-dimethyl-1-cyclo-octen-1-yl)oxy]trimethyl-silane in good yield (85%) and in high optical purity (98% ee). Ozonolysis reaction of the resulting enol silyl ether gave C_{10} chiron (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoic acid in 27% overall yield in 5 steps. We believe this chiron will be applicable to the synthesis of archaebacterial lipids.

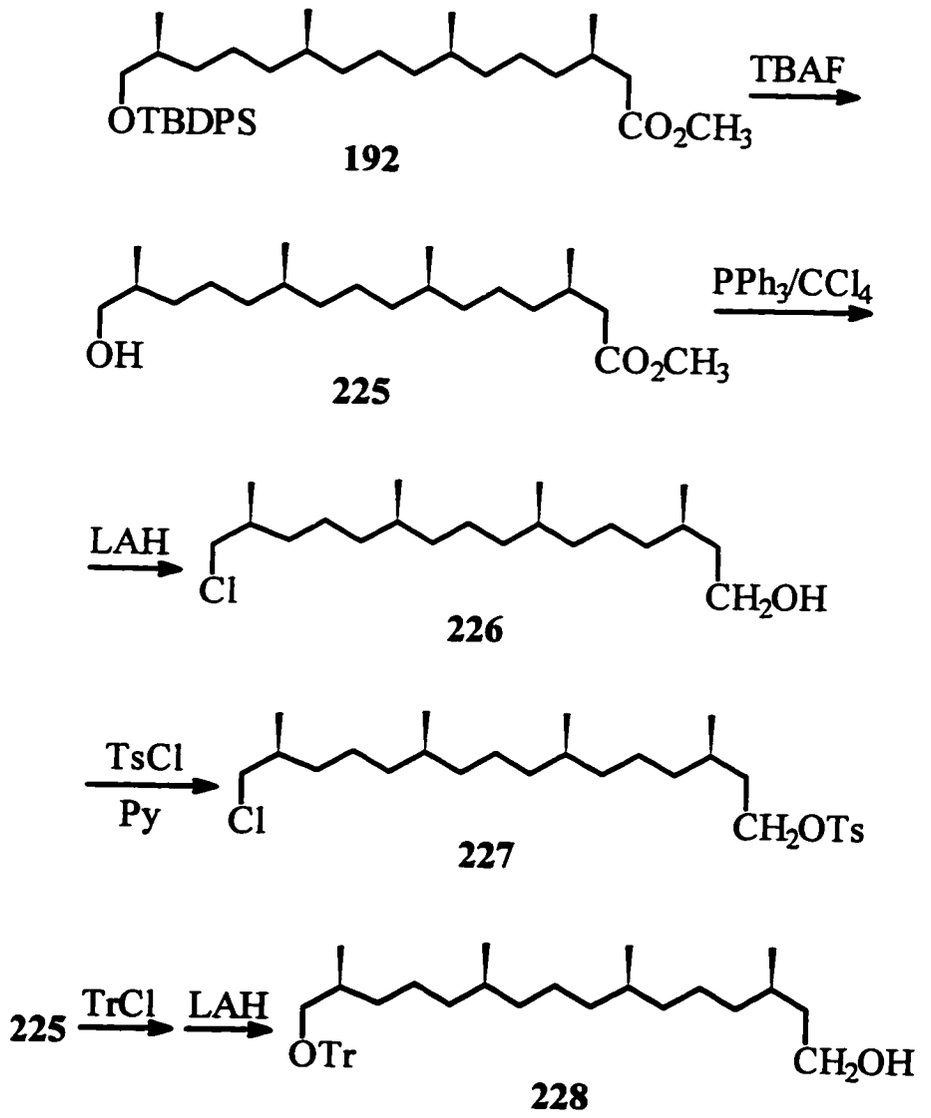
Copper-catalyzed cross-coupling of alkylsamarium reagents with alkyl halides was investigated. SmI_2/HMPA converts alkyl iodides and

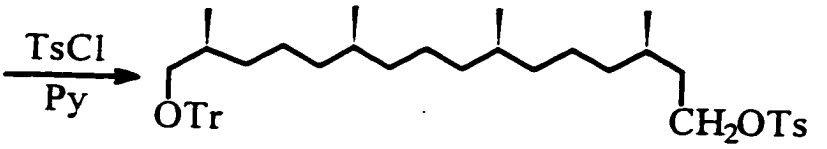
bromides to alkylsamarium reagents which can be cross-coupled with primary iodides, bromides, and secondary iodides in the presence of Cu(I) halides or Li_2CuCl_4 at room temperature. The alkylation of primary iodides gives high yields of cross-coupling products with negligible homo-coupling products. The method is especially useful for small scale cross-coupling reactions.

Archaebacterial lipid C_{20} chirons, methyl 16-[(*t*-butyldiphenylsilyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexadecanoate was synthesized by using both copper-catalyzed Grignard reaction of 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*R*,7*S*)-3,7-dimethyloctane with methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate and copper-catalyzed cross-coupling of the samarium reagent of 8-(*t*-butyldiphenylsilyloxy)-1-iodo-(2*R*,7*S*)-3,7-dimethyloctane with methyl (3*R*,7*S*)-3,7-dimethyl-8-iodo-octanoate in 71% and 81% yields, respectively. A C_{20} dibromide, 1,16-dibromo-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecane was synthesized by copper-catalyzed homo-coupling of 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(2*S*,6*R*)-2,6-dimethyloctane, followed by desilylation and bromination. A vitamin E side chain synthon, (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol (98% ee), was synthesized in 19% overall yield in 9 steps.

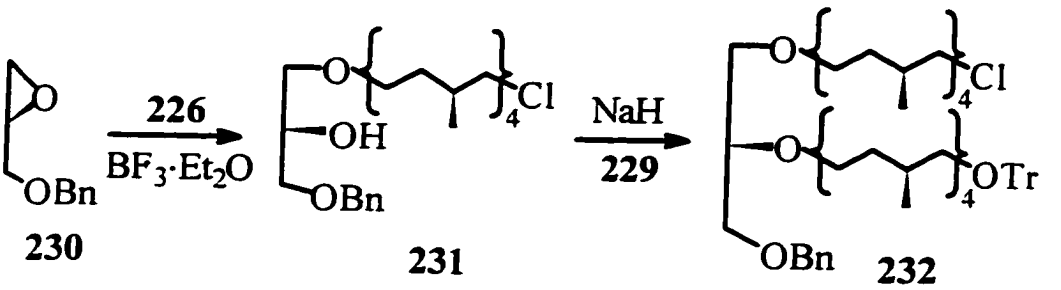
2.10 Suggestion for further work

Scheme 39. Suggestion for the total synthesis of archaebacterial membered lipid **11** or **12**.

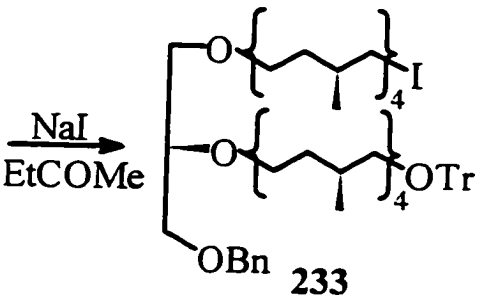




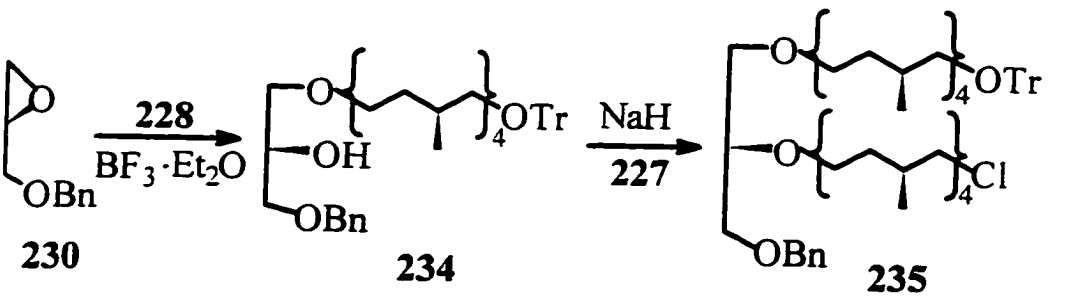
229



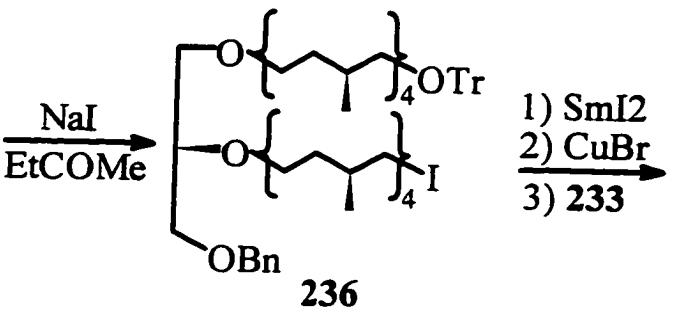
230 231 232



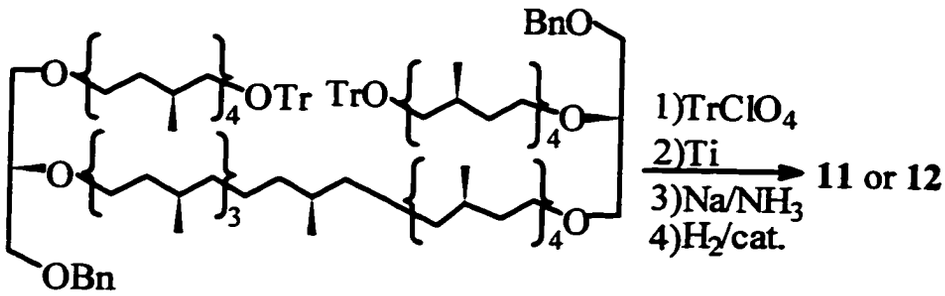
233



230 234 235



236



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Chapter 3. Experimental Section

General. All air-sensitive reactions were carried out under argon or nitrogen. Diethyl ether and THF were distilled under nitrogen from sodium and benzophenone. CH_2Cl_2 was distilled from CaH_2. All amines were distilled under reduced pressure. Trimethylsilyl chloride was distilled from CaH_2 and used immediately. HMPA was distilled from CaH_2 and deoxygenated with argon. Sm metal and Cu salts were bought from Aldrich and used directly.

IR spectra were recorded on a Perkin-Elmer 1600-Series FTIR spectrophotometer. ^1H NMR, ^{13}C NMR, 2D-COSY, 1D-DEPT and, 2D-HETCOR spectra were recorded on a Bruker CXP400 spectrometer operating at 100.6MHzfor ^{13}C and 400 MHz for ^1H. Chemical shifts were reported in δ (from internal Me_4Si). Optical rotations were measured in a 1.0-dm cell on a JASCO Model DIP-140 digital polarimeter. Gas chromatographic analyses were performed on a Shimadzu GC-8A gas chromatography with a column (2% OV-1), using helium as carrier gas. GC-MS spectra were recorded on a HP 5972 GC/MS 30x0.25 mm DB-5 fused silica capillary column gas chromatography-mass spectrometer. TLC was carried out on silica gel GF Analtech Uniplates. Flash column chromatography was

performed on silica gel 60 (230-400 mesh ASTM). Distillations were performed with either a column packed with glass helices or an annular teflon spinning band column. All organic solvents were dried over anhydrous $MgSO_4$, unless otherwise noted. Solutions were concentrated under reduced pressure on rotary evaporator (water pump), unless otherwise noted.

Synthesis of methyl hydrogen 3-methylglutarate (103):

Stallberg's method was used.[54] A mixture of 3-methylglutaric anhydride (**102**, 62.7 g, 0.490 mol) and anhydrous methanol (23.9 mL, 0.588 mol) was refluxed for 1.25 h. The mixture was concentrated on a rotary evaporator and vacuum distilled to yield 76.1 g (97%) of methyl hydrogen 3-methylglutarate, bp 114-117 °C/1.7 mmHg (lit.[54] bp 107-108 °C/0.5 mmHg); IR (CCl_4) 2500-3500 (br), 2953.3, 2674.2, 1740.1 (s), 1708.3 (s), 1458.0, 1436.4, 1413.6, 1370.0, 1293.8, 1209.3, 1161.3, 1083.9 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (d, 3H, J = 6.3 Hz, CH_3), 2.27-2.48 (m, 5H, $2CH_2$, CH), 3.68 (s, 3H, OCH_3).

Synthesis of racemic methyl 5-hydroxy-3-methylpentanoate (105):

Herold's method was used.[55] A 10 M solution of $BH_3 \cdot Me_2S$ (8.13 mmol, 0.81 mL) was added during 1.5 h to a solution of methyl hydrogen 3-methylglutarate (0.89 mL, 6.25 mmol) in dry THF (7 mL) cooled to -20 °C (2:3 methanol/water dry ice) under nitrogen. The mixture was warmed to room temperature and stirred at 22 °C for 21 h, then cooled to 0 °C. Water (7 mL) was carefully added and the solvent was removed *in vacuo*. The residue was extracted with ether (3x20 mL), and the combined extracts were washed with 1 N HCl, aqueous $NaHCO_3$, and brine, then dried and concentrated on a rotary evaporator and the residue was purified by flash chromatography (SiO_2, 10/1, CH_2Cl_2:EtOAc) to afford 7.46 g (82%) of (**105**); IR (CCl_4) 3634.5, 3528.7 (br), 2952.9, 2929.4, 2870.7, 2360.3, 2341.4, 1741.2, 1454.0, 1436.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (d, J = 6 Hz, 3H, CH_3), 1.48-1.61 (m, 2H, O-C-CH_2), 1.78 (s, 1H, OH), 2.10-2.38 (m, 3H, CH_2CO, CH), 3.65-3.71 (m, 5H, O-CH_2, OCH_3).

Synthesis of 4-methoxycarbonyl-3-methylbutyl methyl 3-methyl-pentanedioate (106):

Paquette's method was used.[56] To a solution of methyl hydrogen 3-methylglutarate (**103**) (7.40 g, 46.2 mmol) in anhydrous ether (25 mL) was added a solution of dicyclohexylcarbodiimide (9.50 g, 46.2 mmol) in anhydrous ether (5 mL) during 35 min. at 0 °C. Following this, 4-(dimethylamino)pyridine (0.14 g, 1.18 mmol) was added in one portion at 0°C, and the mixture was stirred at room temperature for 22 h. The mixture was filtered and concentrated. The residue was chromatographed on silica gel (elution with 4:1 hexane / ethyl acetate), giving 9.50 g (96%) of **106**, and GC showed a single peak at t_R = 15.6 min. (temp:column, 180 °C, Det/Inj, 220 °C); IR (CCl_4) 2952.9, 2876.4, 2843.7, 1740.2 (s), 1458.8, 1436.1, 1369.4, 1265.9, 1194.2, 1173.3, 1083.2, 1013.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98, 1.01 (2d, J = 8.0, 6.0 Hz, 6H), 1.43-1.82 (m, 2H), 2.02-2.53 (m, 8H), 3.68 (s, 6H), 4.07-4.18 (m, 2H); Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.43; H, 8.52.

Synthesis of the tosylate of 3-methyl-3-butene-1-ol (127):

Stock's[32d] method, using methyllithium in place of pyridine, was used. To a dry, 500 mL, three necked flask equipped with a magnetic stirrer, a pressure equalizing dropping funnel, and an argon inlet tube, were added under an argon atmosphere 3-methyl-3-buten-1-ol (10.0 g, 0.116 mol), freshly distilled HMPA (20.2 mL, 0.116 mol), and triphenylmethane (20 mg). The stirred solution was cooled to 0°C with an ice bath, and methyllithium (82.9 mL, 0.116 mol, in ether) was added during 30 min. After the addition was complete, the funnel was rinsed with ether (10 mL), and a pink solution was obtained. A solution of *p*-toluenesulfonyl chloride (23.3 g, 0.122 mol) in ether (80 mL) was added during a period of 30 min to the cold mixture. The temperature was raised to room temperature, and the mixture was stirred for 3 h, then poured into water (100 mL). The flask was washed with ether (100 mL), and the combined organic phases were washed with water (4x100 mL), and brine (100 mL), then dried. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 10:1 hexane/ether) to yield 26.1g (94%) of tosylate of 3-methyl-3-buten-1-ol. TLC (5:1, hexane:ethyl acetate) showed one spot; IR[32a] (CCl_4) 3080.0, 2973.9, 2921.8, 1652.1, 1599.1, 1446.1, 1368.5, 1188.9, 1178.5, 1098.3, 1020.8, 969.8, 899.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (s, 3H,

CH_3C=), 2.35 (t, J = 6.8 Hz, 2H, CH_2C=), 2.45 (s, 3H, CH_3), 4.13 (t, J = 6.9 Hz, 2H, OCH_2), 4.68, 4.79 (2brs, 2H, =CH_2), 7.35 (d, J = 8.1 Hz, 2H, CH), 7.79 (d, J = 8.3 Hz, 2H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.65 (CH_3 on phenyl), 22.34 (CH_3 on C-3), 36.74 (C-2), 68.53 (C-1), 113.12 (C-4), 127.93 (C on phenyl), 129.83 (C on phenyl), 133.13 (C on phenyl), 140.14 (C on phenyl), 144.75 (C-3).

Synthesis of 4-bromo-2-methyl-1-butene[32a] (126):

The method of Bose[44] was used. To a dry, 1 liter, round-bottomed, two-necked flask equipped with a septum inlet and a magnetic stirrer flushed with a slow flow of nitrogen were added 3-methyl-3-butene-1-ol (50.5 mL, 0.500 mol), triphenylphosphine (144 g, 0.550 mol) and dry CH_2Cl_2 (100 mL). The solution was cooled in an ice bath, and N-bromosuccinimide (97.9 g, 0.550 mol) was added in several portions with vigorous stirring. Stirring was continued for 3 h at room temperature. Then, hexane (300 mL) was added to the flask, the mixture was filtered through a short silica gel pad, which was washed with hexane (200 mL). The solvents were removed by distillation at 1 atm, and the residue was distilled under reduced pressure to yield 55.9 g (75%) of 4-bromo-2-bromo-1-butene, bp 63-65 °C/90 mmHg, and GC-MS showed a single peak at t_R =

4.92min. Lit.[32a] bp 40°C/40 mmHg; IR (CCl_4): 3038.5, 2972.2, 2938.5, 2917.8, 1651.5, 1448.6, 1375.9, 1253.6, 1210.4, 898.3 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H, CH_3), 2.58 (t, J = 7.4 Hz, 2H, CH_2C=), 3.48 (t, J = 7.3 Hz, 2H, CH_2Br), 4.78, 4.86 (2s, 2H, =CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.94 (CH_3 on C-2), 30.80 (C-4), 40.90 (C-3), 112.68 (C-1), 142.41 (C-2); MS (EI) m/z (relative intensity), 151 (M+1, 0.8), 150 (M^+, ^{81}Br, 13), 148 (M^+, ^{79}Br, 14), 135 (0.4), 133 (0.5), 95 (2.3), 93 (2.5), 82 (1.3), 80 (1.3), 70 (5.5), 69 (100), 68 (9.1), 67 (16), 55 (20), 53 (21), 41 (81), 39 (46), 27 (22).

Synthesis of 2,6-dimethyl-1,6-heptadiene[29,30,31] (94) from 4-bromo-2-methyl-1-butene (126):

Kochi's coupling method was employed.[24] To a dried, 500 mL, argon-filled three-neck flask were added magnesium turnings (29.2 g, 1.20 mol) and dry THF (200 mL). While the magnesium-THF mixture was stirred vigorously at 0°C, a solution of 3-chloro-2-methyl-1-propene (**128**, 59.2 mL, 0.60 mol) in dry THF (200 mL) was added dropwise during a period of 8 h. The mixture was stirred overnight at room temperature. The resulting Grignard reagent was siphoned into a 1 liter three-necked flask which contained 4-bromo-2-methyl-1-butene (**126**, 44.8 g, 0.30 mol),

Li_2CuCl_4 (30 ml, 3.00 mmol, 0.1 M in THF), and dry THF (200 mL) at -78 °C. The mixture was stirred for 1 h at -78 °C, then for 6 h at 0 °C, and 18 h at room temperature. Then, saturated aqueous aqueous NaCl (100 mL) was added, the resulting mixture was filtered through a short pad of Celite 545, which was washed with ether (150 mL). The aqueous layer was separated and extracted with ether (3x50 mL). The combined organic extracts were washed with brine, and dried, and then the solvent was removed by distillation. The residue was distilled to yield 32.43 g (87%) of 2,6-dimethyl-1,6-heptadiene, bp 135-136°C (lit.[29] bp 138-139 °C) and GC-MS showed a single peak at t_R = 6.32 min; IR (CCl_4) 3075.1, 2969.9, 2937.4, 1648.8, 1446.1, 1373.9, 889.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57 (p, J = 7.6 Hz, 2H, CH_2), 1.72 (s, 6H, $2CH_3$), 2.00 (t, J = 7.7 Hz, 4H, CH_2), 4.68, 4.71 (2s, 4H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.41 (CH_3 on C-2,6), 25.56 (C-4), 37.38 (C-3,5), 109.83 (C-2,6), 145.94 (C-1,7); MS (EI) m/z (relative intensity), 124 (M^+, 2), 109 (24), 96 (14), 81 (20), 68 (100), 57 (12), 53 (18), 41 (61).

Synthesis of 2,6-dimethyl-1,6-heptadiene (94) from the tosylate of 3-methyl-3-butene-1-ol (127):

Kochi's coupling method was employed.[24] To a dried, 250 mL, argon-filled three-neck flask were added magnesium turnings (5.47 g, 0.225 mol) and dry THF (100 mL). While the magnesium-THF mixture was stirred vigorously at 0 °C, a solution of 3-chloro-2-methyl-1-propene (14.8 mL, 0.150 mol) in dry THF (50 mL) was added dropwise during a period of 4.5 h. The mixture was stirred for 3 h at room temperature, the resulting Grignard reagent was cooled to -78 °C and siphoned into a 500 mL three-necked flask which contained the tosylate of 3-methyl-3-butene-1-ol (**127**, 18.02 g, 0.075 mol) in dry THF (100 mL) at -78 °C. A solution of Li_2CuCl_4 (7.5 mL, 0.75 mmol, 0.1 M) in THF was injected into the flask. The mixture was stirred for 1 h at -78 °C, then for 6 h at 0 °C, and 15 h at room temperature. Then, 100 mL of saturated aqueous aqueous NaCl was added, the resulting mixture was filtered through a short pad of Celite 545, which was washed with pentane (100 mL). The aqueous layer was separated and extracted with pentane (2x30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and dried. The solvent was removed by distillation at 1 atm and the residue was distilled to yield 10.96 g (70%) of 2,6-dimethyl-1,6-heptadiene (**94**), bp

135-136 °C. Comparison of spectra and GC-MS retention time (t_R = 6.33 min) showed the two samples of **94** to be identical.

Synthesis of cis-3,7-dimethylcyclooctanone (92):

Brown's method was used.[34] An oven dried, 3-neck flask was fitted with an L-shaped solid-addition tube, an injection septum, a magnetic stir-ring bar, and a vacuum/nitrogen inlet. Into the sidearm was placed dry, finely divided sodium cyanide (1.08 g, 22.0 mmol). The apparatus was then evacuated and filled with nitrogen, which was then maintained at a positive pressure until the oxidation step was complete. Tetrahydrofuran (200 mL) and borane-THF (22.0 mL of 1.0 M, 22.0 mmol) were introduced and the temperature was lowered to -25 °C. By syringe, 2,3-dimethylbut-2-ene (2.62 mL, 22.0 mmol) was slowly added to the stirred solution. The mixture was stirred for 2 h at 0 °C, then the temperature was lowered to -78 °C and 2,6-dimethyl-1,6-heptadiene (**94**, 2.48 g, 20.0 mmol) was added during 15 min. The cooling bath was removed after addition of the diene, and the mixture was allowed to warm to room temperature and stirred for 20 h.

The solid addition sidearm was then rotated so that the sodium

cyanide was introduced (Caution HCN gas!). The mixture was stirred for 2 h, during which time most of the sodium cyanide dissolved. The mixture was cooled to -78 °C, trifluoroacetic anhydride (3.38 mL, 24.0 mmol) was added dropwise with vigorous stirring, and the mixture was allowed to warm to room temperature during 1 h. The flask was cooled to 0 °C and NaOH solution (15 mL, 3 M), followed H_2O_2 (28 mL, 30%) were added. This mixture was stirred for 3 h at room temperature and 20 min. at 50 °C. The solution was then saturated aqueous with sodium chloride and the organic phase was separated, washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$) and filtered. The solvent was distilled at 1 atm and the residue was purified by flash chromatography (Silica gel, hexane/ethyl acetate : 40/1), then distilled to yield 1.58g (51%) of *cis*-3,7-dimethylcyclooctanone (**92**), bp 63.5-64.0°C/1.5 mmHg and 218.0-218.2 °C; GC-MS showed a single peak at t_R = 13.11 min; IR (CCl_4) 2956.8, 2928.5, 2872.9, 1697.6, 1457.6, 1266.2, 1180.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, J = 6.4 Hz, 6H), 1.23-1.37 (m, 3H), 1.40-1.54 (m, 1H), 1.60-1.75 (m, 2H), 2.15-2.22 (m, 4H), 2.53 (q, J = 18.0, 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.44 (CH_3 on C-3,7), 22.63 (C-5), 32.49 (C-3,7), 36.42 (C-4,6), 50.45 (C-2,8), 215.3 (C-1); MS (EI) m/z (relative intensity), 155 (M+1, 1), 154 (M^+, 12), 139 (14), 125 (11), 121 (9), 112 (45), 98

(17), 84 (15), 81 (9), 69 (100), 55 (52), 41 (60), 39 (29), 27 (16). Anal Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C,77.51, H, 11.72.

Synthesis of [((3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane (101):

Gleave's method was used.[37c] To a cold (-78 °C) 100 mL, flame dried three necked flask which contained (+)-bis[(*R*)-1-phenylethyl]amine (**147**, 1.4 g, 6.50 mmol) in dry THF (65 mL) was added dropwise n-butyllithium (6.25 mmol, 2.50 mL of 2.5 M solution in hexane). After 5 min, the cooling bath was rev and the mixture was allowed to warm to room temperature during 35 min and then again lowered to -78 °C. Freshly distilled TMSCl (3.17 mL, 25.0 mmol) in THF (6 mL) was added dropwise. The cold mixture was stirred for 8 min, then *cis*-3,7-dimethylcyclooctanone (**92**, 0.770 g, 5.00 mmol) in THF (15 mL) was added dropwise during 40 min. The resulting solution was stirred at -78 °C for 3 h, then Et_3N (9 mL) was added. The solution was allowed to warm to room temperature, saturated aqueous $NaHCO_3$ solution (30 mL) was added, and the solvents were removed under vacuum and the residue was extracted with pentane (3x50 mL). The combined extracts were washed with 0.1 M aqueous citric acid (2x50 mL) and water (50 mL), dried ($MgSO_4$), and the solvent was removed

under reduced pressure to give the crude product which was purified by flash chromatography (SiO_2, pentane) to yield 0.96 g (85%) of enol silyl ether (0.96 g, 85 %) as a colorless oil; GC-MS showed a single peak at t_R = 14.36 min; $[\alpha]_D^{25}$ 120 (*c* 2.315, $CHCl_3$); IR (CCl_4) 2957.8, 2925.2, 2870.1, 1655.0, 1457.6, 1380.0, 1251.9, 1201.3, 1169.6, 875.8, 848.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 9H), 0.95 (d, *J* = 5.0 Hz, 3H), 0.97 (d, *J* = 4.8 Hz, 3H), 1.08-1.18 (m, 1H), 1.20-1.40 (m, 2H), 1.52-1.62 (m, 2H), 1.70-1.80 (m, 2H), 1.88-1.98 (m, 1H), 2.2-2.3 (m, 1H), 2.60 (q, *J* = 14.0, 4.9 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.41 ($Si(CH_3)_3$), 21.63 (CH_3 on C-7), 23.59 (CH_3 on C-3), 24.81 (C-5), 32.08 (C-3), 33.79 (C-7), 34.28 (C-6), 37.18 (C-8), 39.82 (C-4), 113.44 (C-2), 150.06 (C-1); MS (EI) m/z (relative intensity), 228 (M+2, 0.8), 227 (M+1, 2.6), 226 (M^+, 15), 211 (28.6), 197 (9.2), 184 (23.4), 183 (63.9), 169 (15.3), 157 (93.2), 144 (12.9), 130 (14.5), 121 (6.2), 115 (13.8), 99 (3.8), 93 (5.5), 75 (47), 73 (100), 55 (12.0), 45 (17.5), 39 (6.9). Anal. Calcd. for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.58; H, 11.32.

***Synthesis of (3S,7R)*-3,7-dimethyl-1-cycloocten-1-ol acetate (148):**

To a 50 mL, flame dried three necked flask which contained (+)-bis[(*R*)-1-phenylethyl]amine (**147**, 0.293 g, 1.00 mmol) in dry THF (20 mL) was added dropwise n-butyllithium (1.20 mmol, 0.48 mL of a 2.5 M solution in hexane) at -78 °C. After 5 min, the cooling bath was removed, the temperature was allowed to warm to room temperature during 35min. and then again lowered to -78 °C. Then, *cis*-3,7-dimethylcyclooctanone (**92**, 0.154 g, 1.00 mmol) in THF (5 mL) was added dropwise during 5 min. The resulting solution was stirred at -78 °C for 2 h, freshly distilled acetic anhydride (0.28 mL, 3.00 mmol) was added dropwise during 1 min. and the mixture was stirred for 1h at -78 °C. Saturated aqueous NH_4Cl (10 mL) was added, the solution was allowed to warm to room temperature. The solvents were removed under vacuum and the residue was extracted with ether (3x20 mL). The combined ether extracts were washed with 0.1M aqueous citric acid (2x30 mL) and saturated aqueous $NaHCO_3$ (35 mL), dried ($MgSO_4$), and the solvent was removed to give the crude product which was purified by flash chromatography (SiO_2, 30:1 hexane/EtOAc) to yield 0.0386g (41%) of enol acetate **148** and 0.0801g of unreacted ketone **92**.

Addition of 10mg of chiral shift reagent Eu(hfc)$_3$(tris(3-heptafluorobutyryl-*d*-camphorato)-europium (III)) to 6mg of chiral enol acetate **148** in 0.7mL of $CDCl_3$, the methyl group (0.93, J = 6.6 Hz) was split into two doublets (1.10, 1.16, J = 6.6 Hz) with a 7:93 ratio (86% ee). $[\alpha]_D^{25}$ 109 (*c* 1.52, $CHCl_3$); IR (CCl_4) 2959.1, 2926.7, 2826.1, 1754.6, 1460.2, 1366.6, 1224.4, 1057.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 1.15-1.46 (m, 3H), 1.55-1.67 (m, 2H), 1.75-1.85 (m, 1H), 1.90-2.03 (m, 2H, 7-CH), 2.09 (s, 3H), 2.38-2.48 (m, 1H), 2.69 (q, J = 15.6, 5.2 Hz, 1H), 5.01 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.59 ($COCH_3$), 21.80 (CH_3 on C-7), 22.77 (CH_3 on C-3), 24.30 (C-5), 31.52 (C-3), 33.22 (C-7), 34.29 (C-4 or 6), 34.94 (C-8), 38.92 (C-6 or 4), 123.57 (C-2), 147.52 (C-1), 169.75 (C=O); MS (EI) m/z (relative intensity), 196 (M^+, 1), 154 (29), 139 (20), 125 (12), 112 (92), 111 (100), 98 (20), 97 (23), 96 (34), 85 (27), 69 (44), 55 (27), 43 (68), 41 (34). Anal Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.15; H, 10.41.

Synthesis of racemic (3*R*,7*S*) and (3*S*,7*R*)-3,7-dimethyl-1-cyclooctenyl acetate (149):

House's method was employed.[57] To a 50mL, flame dried three necked flask which contained *cis*-3,7-dimethylcyclooctanone (**92**, 0.154 g, 1.00 mmol) and freshly distilled acetic anhydride (0.57 mL, 6.00 mmol) in CCl_4 (3 mL) was added $HClO_4$ (0.017 mL, 70% aqueous solution) at room temperature. The mixture was allowed to stand at room temperature for 1 h. and then treated with saturated aqueous $NaHCO_3$ (10 mL) and ether (20 mL). The aqueous phase was separated and extracted with ether (2x10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10ml), brine, and dried. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 30:1 hexane/EtOAc) to yield 81.9 mg (42%) of racemic (3*R*,7*S*) and (3*S*,7*R*)-3,7-dimethyl-1-cyclooctenyl acetate **149** and 27.0mg of unreacted ketone (**92**); The spectra of were identical with **148**. Addition of 10mg of chiral shift reagent $Eu(hfc)_3$(tris(3-heptafluorobutyryl-*d*-camphorato)-europium (III)) to 6mg of the racemic enol acetate (**149**) in 0.7mL of $CDCl_3$ gave rise to two diastereomeric complexes. The methyl group (0.93, d, J = 6.6 Hz) on the ring was split into two doublets (1.11, 1.17, J = 6.6 Hz) with 1:1 ratio and base line separation.

Synthesis of racemic [((3*R*,7*S*) and (3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane (160):

Corey's method was employed.[39a] To a cold (-78 °C) 25 mL, flame dried three necked flask which contained diisopropylamine (0.14 mL, 1.1 mmol) in dry THF (2 mL) was added n-butyllithium (1.1 mmol, 0.44 mL of 2.5 M solution in hexane) by syringe. This mixture was stirred for 10 min. at -78 °C, then freshly distilled TMSCl (0.89 mL, 7.0 mmol) in THF (2 mL) was added dropwise, followed by *cis*-3,7-dimethylcyclooctanone (**92**, 0.154 g, 1.0 mmol) in THF (2 mL). The resulting solution was stirred at -78 °C for 20min., and still at -78 °C, Et_3N (2 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) were added. The solution was allowed to warm to room temperature, and the solvents were removed under reduced pressure. The residue was extracted with ether (3x10 mL), and the combined ether extracts were washed with 0.1 M aqueous citric acid (2x10 mL), water (10 mL), and dried ($MgSO_4$). The solvents were removed under reduced pressure to give the crude product which was purified by flash chromatography (SiO_2, pentane) to yield 0.20 g (88%) of racemic **160** [((3*R*,7*S*) and (3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane. GC-MS showed a single peak at t_R = 14.35 min; IR (CCl_4) 2957.8, 2925.2, 2870.1, 1655.0, 1457.6,

1380.0, 1251.9, 1201.3, 1169.6, 875.8, 848.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 9H), 0.95 (d, *J* = 5.0 Hz, 3H), 0.97 (d, *J* = 4.8 Hz, 3H), 1.08-1.18 (m, 1H), 1.20-1.40 (m, 2H), 1.52-1.62 (m, 2H), 1.70-1.80 (m, 2H), 1.88-1.98 (m, 1H), 2.2-2.3 (m, 1H), 2.60 (q, *J* = 14.0, 4.9 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.41 (Si $(CH_3)_3$), 21.63 (CH_3 on C-7), 23.59 (CH_3 on C-3), 24.81 (C-5), 32.08 (C-3), 33.79 (C-7), 34.28 (C-6), 37.18 (C-8), 39.82 (C-4), 113.44 (C-2), 150.06 (C-1); MS (EI) m/z (relative intensity), 228 (M+2, 0.8), 227 (M+1, 3), 226 (M^+, 15), 211 (27), 197 (9), 184 (23), 183 (64), 169 (15), 157 (93), 144 (13), 130 (15), 121 (6), 115 (14), 99 (4), 93 (6), 75 (47), 73 (100), 55 (12), 45 (18), 39 (7).

Addition of chiral Eu shift reagent had no effect on the ^1H NMR spectrum of **160**.

Synthesis of (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoic acid (156):

Heathcock's method was employed[39b]. In a 250 mL, three necked flask, [((3*S*,7*R*)-3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane (**155**, 0.800 g, 3.54 mmol) in methanol (20 mL) and CH_2Cl_2 (20 mL) was treated with excess O_3 at -78°C until the solution turned blue. After purging with nitrogen, the cold solution was reduced with excess sodium borohydride (1.34 g, 35.4 mmol), allowed to warm to room temperature, and stirred

overnight. After the solvent was evaporated on a rotary evaporator, the residue was treated with HCl (20 mL, 10% aqueous), and extracted with ether (3x50 mL), and the combined ether extracts were washed with brine, dried ($MgSO_4$), and the solvent was evaporated to give the crude product which was purified by flash chromatography (SiO_2, hexane/acetone, 1:1) to yield 0.632 g (95%) (3*R*,7S)-3,7-dimethyl-8-hydroxy-octanoic acid; $[\alpha]_D^{25}$ 3.6 (*c* 2.4, $CHCl_3$); IR (CCl_4) 2962.8, 2929.1, 2871.7, 1707.7, 1252.1, 1217.6, 1005.0, 978.6 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.02-1.48 (m, 7H), 1.62 (m, 1H), 1.96 (m, 1H), 2.16 (q, J = 15.0, 8.0 Hz, 1H), 2.34 (q, J = 15.0, 6.1 Hz, 1H), 3.47 (m, 2H), 5.0-6.5 (br, 1H, COOH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.57 (CH_3 on C-3), 19.78 (CH_3 on C-7), 24.21 (C-5), 30.13 (C-7), 33.12 (C-4), 35.65 (C-3), 36.87 (C-6), 41.45 (C-2), 68.25 (C-8), 178.85 (C=O); MS (EI) m/z (relative intensity), 159 (3), 158 (25), 152 (1), 139 (3), 129 (2), 115 (8), 111 (8), 110 (13), 97 (22), 95 (9), 87 (100), 83 (10), 81 (9), 69 (51), 55 (57), 45 (16), 41 (44), 31 (20), 28 (22), 18 (19). Anal Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.76; H,10.88.

Synthesis of methyl (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoate (157):

A mixture of (3*R*,7*S*)-dimethyl-8-hydroxyoctanoic acid (**156**, 0.632 g, 3.36 mmol) acid, methanol (50 mL), and p-toluenesulfonic acid (20 mg) were refluxed for 24 h. Then, the solvent was evaporated under reduced pressure, and the residue was extracted with ether (3x30 mL), and washed with saturated aqueous $NaHCO_3$ solution (40 mL), brine and dried. The solvent was evaporated to yield crude product, which was purified by flash chromatography (SiO_2, hexane/EtOAc, 6:1) to yield 0.665 g (98%) of methyl (3*R*,7*S*)-dimethyl-8-hydroxyl-octanoate as a colorless oil, GC-MS showed a single peak at $t_R = 17.45$ min.

Addition of 6.5 mg of chiral shift reagent $Eu(hfc)_3$ (tris(3-heptafluorobutyryl-*d*-camphorato)-europium (III)) to 3.7 mg of the racemic hydroxyl ester (**161**) in 0.7mL of $CDCl_3$ gave rise to two diastereomeric complexes. The methyl group (3.67, s, $COOCH_3$) was split into a doublet (4.16, 4.11) with 1:1 ratio and base line separation.

The shift reagent was also applied to the non-racemic hydroxy ester (**157**). The methyl group (3.67, s, $COOCH_3$) was split into a doublet (4.15, 4.10) with a 99:1 ratio (98% ee); $[\alpha]_D^{25}$ 3.91 (*c* 15.0, $CHCl_3$); IR (CCl_4) 3640.6, 2953.1, 2929.5, 2873.2, 1740.0, 1458.3, 1436.0, 1196.9, 1166.5, 1029.0 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.0 Hz, 6H), 1.05-

1.45 (m, 7H), 1.55-1.65 (m, 1H), 1.90-2.00 (m, 1H), 2.21 (q, J = 14.7, 8.1 Hz, 1H), 2.31 (q, J = 14.7, 6.1 Hz, 1H), 3.38-3.53 (m, 2H), 3.67 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.58 (CH_3 on C-3), 19.80 (CH_3 on C-7), 24.25 (C-5), 30.32 (C-7), 33.18 (C-4), 35.71 (C-3), 36.95 (C-6), 41.62 (C-2), 51.40 (OCH_3), 68.29 (C-8), 173.81 (C=O); MS (EI) m/z (relative intensity), 172 (M-30, 36), 157 (4), 152 (4), 139 (5), 129 (9), 128 (4), 115 (8), 112 (5), 111 (12), 110 (16), 109 (8), 101 (100), 97 (17), 87 (7), 81 (7), 74 (36), 69 (44), 59 (17), 55 (30), 43 (12), 41 (18). Anal Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C,64.93; H, 11.23.

Synthesis of (2*S*,6*R*)-2,6-dimethyl-1,8-octanediol (158):

To a dried, 100 mL, three necked flask flushed with nitrogen and charged with $LiAlH_4$ (0.100 g, 2.50 mmol) in dry ether (10 mL) was added methyl (3*R*,7*S*)-dimethyl-8-hydroxyoctanate (**157**, 50.0 g, 0.250 mmol) in dry ether (10 mL) during a period of 7min. The resulting mixture was stirred for 4 h, then cooled to 0 °C, and a mixture of ether (4 mL) and methanol (4 mL) added dropwise, followed by HCl (10 ml, 1 M aqueous). The aqueous layer was extracted with ether (3x10 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, and dried. The solvent was evaporated to yield crude product, which was puri-

fied by flash chromatography (SiO_2, hexane/EtOAc, 2:1) to yield 42.6 mg (98%) of the diol **158** as a colorless oil; $[\alpha]_D^{25}$ 7.0 (*c* 2.1, $CHCl_3$; Lit.[21] $[\alpha]_D^{25}$ 6.3 (*c* 9.5, $CHCl_3$); IR (CCl_4) 3733.9, 3628.2, 2948.5, 2929.2, 2863.5, 1457.2, 1374.3, 1030.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.0 Hz, 6H), 1.04-1.48 (m, 9H), 1.55-1.70 (m, 3H), 3.42 (q, J = 10.5, 5.9 Hz, 1H), 3.51 (q, J = 10.4, 6.5 Hz, 1H), 3.65-3.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.62 (CH_3 on C-6), 19.68 (CH_3 on C-2), 24.25 (C-4), 29.45 (C-2), 33.35 (C-3), 35.76 (C-6), 37.38 (C-5), 39.89 (C-7), 61.21 (C-8), 68.33 (C-1); MS (EI) m/z (relative intensity), 144 (0.1), 137 (0.3), 126 (5), 123 (7),112 (2), 109 (15), 99 (7), 97 (7), 81 (46), 70 (38), 69 (82), 56 (36), 55 (100), 43 (39), 41 (73), 39 (18), 31 (56). Anal Calcd. for $C_{10}H_{22}O_2$: C, 68.92; H, 12.72. Found: C, 68.63; H, 12.40.

Synthesis of racemic methyl (3*R*,7*S* and 3*S*,7*R*)-3,7-dimethyl-8-hydroxyoctanate (161):

In a 25 mL, three necked flask, racemic 3,7-dimethyl-1-cycloocten-1-yl)oxy]trimethylsilane (**160**, 0.200 g, 0.880 mmol) in methanol (5 mL) and CH_2Cl_2 (5 mL) was treated with excess O_3 at -78 °C until the solution turned blue. After purging with nitrogen, the cold solution was reduced with ex-

cess sodium borohydride (0.400 g, 10.6 mmol), then allowed to warm to room temperature during 0.5 h. The solvent was evaporated under reduced pressure, and the residue was treated with HCl (5 mL, 10% aqueous), and extracted with ether (3x20 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and the solvent was evaporated to give the crude product, racemic (*3R*,7S and 3*S*,7*R*)-dimethyl-8-hydroxyoctanoic acid. Without further separation, this acid was dissolved in methanol (15 mL) and p-toluenesulfonic acid (8 mg) was added. The resulting solution was heated to reflux for 15 h. The solvent was evaporated under reduced pressure and the residue was extracted into ether (50 mL), and washed with saturated aqueous aqueous $NaHCO_3$ (40 mL), brine, and dried. The solvent was evaporated under reduced pressure to yield crude product which was purified by flash chromatography (SiO_2, hexane/EtOAc, 6:1) to yield 0.16 g (90%) of **161**; IR (CCl_4) 3640.0, 2952.9, 2929.7, 2873.5, 1739.9, 1461.7, 1436.0, 1197.0, 1166.9, 1028.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.0 Hz, 6H), 1.05-1.45 (m, 7H), 1.55-1.65 (m, 1H), 1.90-2.00 (m, 1H), 2.21 (q, J = 14.7, 8.1 Hz, 1H), 2.31 (q, J = 14.7, 6.1 Hz, 1H), 3.38-3.53 (m, 2H), 3.67 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.58 (CH_3 on C-3), 19.80 (CH_3 on C-7), 24.25 (C-5), 30.32 (C-7), 33.18 (C-4), 35.71 (C-3), 36.95 (C-6), 41.62 (C-2), 51.40 (OCH_3), 68.29 (C-8), 173.81 (C=O); MS

(EI) m/z (relative intensity), 172 (36), 157 (4), 152 (4), 139 (5), 129 (9), 128 (4), 115 (8), 112 (5), 111 (12), 110 (16), 109 (8), 101 (100), 97 (17), 87 (7), 81 (7), 74 (36), 69 (44), 59 (17), 55 (30), 43 (12), 41 (18).

Synthesis of methyl 8-bromo-(3*R*,7*S*)-3,7-dimethyloctanoate (110):

To a mixture of 0.101 g (0.500 mmol) of methyl (3*R*,7*S*)-3,7-dimethyl 8-hydroxyoctanoate (**157**) and 0.144 g (0.550 mmol) of Ph_3P in dry CH_2Cl_2 (3.5 mL) at -23°C was added 0.107 g (0.600 mmol) of NBS at one portion. The mixture was allowed to warm to room temperature and stirred for 3 h, then methanol (0.5 mL) was added and continuously stirred for 0.5 h, then, diluted with a mixture of hexane/EtOAc (6:1, 20 ml). The solvents were evaporated and the residue was filtered through a short silica gel pad, which was washed with hexane/EtOAc (6:1, 100 ml). The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 40:1) to give 0.124g (93%) of methyl 8-bromo-(*3R*,7S)-3,7-dimethyloctanoate (**183**) as a colorless oil; $[\alpha]_D^{25}$ 4.84 (*c* 5.71, $CHCl_3$); IR (CCl_4) 2962.7, 2931.6, 2858.3, 1740.1, 1458.6, 1435.8, 1171.3, 1119.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.13-1.48 (m, 6H), 1.82 (m, 1H), 1.96 (m, 1H), 2.12 (q, J = 14.7, 8.0 Hz, 1H), 2.31 (q, J = 14.7, 6.1 Hz, 1H), 3.32 (q, J = 9.8, 6.1 Hz, 1H), 3.39 (q, J = 9.8, 5.0 Hz,

1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.81 (CH_3 on C-3), 19.72 (CH_3 on C-7), 24.71 (CH_2), 30.25 (CH), 34.87 (CH_2), 35.11 (CH), 36.68 (CH_2), 41.43 (CH_2Br), 41.60 (CH_2CO), 51.41 (OCH_3), 173.70 (CO), MS (EI) m/z (relative intensity), 266 (M-Br, 0.04), 264 (M-Br, 0.05), 233 (2.8), 235 (2.7, M-OCH_3), 101 (100), 185 (4.5, M-Br), 153 (14), 74 (100), 69 (24), 55 (21), 41 (30). Anal Calcd. for $C_{11}H_{21}BrO_2$: C, 49.82, H, 7.98, Br, 30.01. Found: C, 49.77; H, 7.72, Br 30.25.

Synthesis of 8-bromo-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (184):

Nystrom's method was used.[45] To a mixture of $LiAlH_4$ (0.517 mmol, 0.0196 g) in dry ether (5 mL) was added a solution of $AlCl_3$ (0.0689 g, 0.517 mmol) in dry ether (5 mL) by syringe. The resulting solution was cooled to -78 °C, and a solution of 8-bromo-(3*R*,7*S*)-3,7-dimethyloctanoate (**183**, 0.137 , 0.517 mmol) in ether (5 mL) was added during a period of 10 min. The resulting mixture was stirred for 3.5 h at -78 °C, then a mixture of methanol (1 mL) and ether (9 mL) was added to destroy the excess hydride. Then, 3M HCl (10 mL) was added after the mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with ether (3x20 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine, than dried. The

solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 6:1) to give 0.110 g (89%) of 8-bromo-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (**184**) as a colorless oil; $[\alpha]_D^{25}$ -28.0 (*c* 0.11, $CHCl_3$); IR (CCl_4) 3636.3, 2955.8, 2929.9, 1461.5, 1378.9, 1230.4, 1055.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz) δ 0.90 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.08-1.65 (m, 11H), 1.89 (m, 1H), 3.33 (q, J = 9.7, 6.1 Hz, 1H), 3.39 (q, J = 9.7, 5.0 Hz, 1H), 3.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.85 (CH_3), 19.59 (CH_3), 24.21 (CH_2), 29.41 (CH), 35.06 (CH_2), 35.18 (CH), 37.15 (CH_2), 39.89 (CH_2), 41.53 (CH_2Br), 61.17 (CH_2O); MS (EI) m/z (relative intensity), 192 (M-CH_2CH_2-H_2O, 4.0), 190 (M-CH_2CH_2-H_2O, 4.0), 178 (4.5), 176 (4.7), 111 (15), 97 (30), 83 (70), 69 (89), 55 (100), 43 (33), 41 (81), 31 (29). Anal Calcd. for $C_{11}H_{21}BrO$: C, 50.64; H, 8.91; Br, 33.69. Found: C, 50.62; H, 8.94; Br, 34.01.

Synthesis of 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*S*,6*R*)-2,6-dimethyl-octane (185):

Hanessian's method was used,[46] with CH_2Cl_2 as solvent. A mixture of imidazole (0.557 mmol, 0.0379 g) and *t*-butyl-chlorodiphenylsilane (0.072 mL, 0.278 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature, then a solution of 8-bromo-(3*R*,7*S*)-3,7-dimethyloctan-1-ol

(**184**, 0.060 g, 0.253 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise during a period of 1min. The resulting mixture was stirred for 5.5 h at room temperature, then, CH_2Cl_2 (50 mL) was added, the reaction mixture was washed with water (20 mL), saturated aqueous $CuSO_4$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 40:1) to give 0.114 g (95%) of 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*S*,6*R*)-2,6-dimethyloctane (**185**) as a colorless oil; $[\alpha]_D^{25}$ -1.91 (*c* 3.93, $CHCl_3$); IR (CCl_4) 3071.7, 3052.5, 2957.7, 2930.2, 2858.0, 1427.9, 1111.6 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3), 1.05 (s, 9H), 1.06-1.65 (m, 9H), 1.78 (m, 1H), 3.31 (q, J = 9.7, 6.2 Hz, 1H), 3.39 (q, J = 9.7, 4.8 Hz, 1H), 3.67 (m, 2H), 7.41 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ18.85 (CH_3), 19.21 (C-Si), 19.72 (CH_3), 24.21 (CH_2), 26.88 (CH_3), 29.29 (CH), 35.07 (CH_2), 35.20 (CH), 37.05 (CH_2), 39.57 (CH_2), 41.58 (CH_2Br), 62.14 (CH_2O), 127.58, 129.51, 134.12, 135.58 (phenyl); MS (EI) m/z (relative intensity), 342 (M-C_6H_5-*t*-Butyl, 0.1), 340 (M-C_6H_5-*t*-Butyl, 0.1), 263 (19), 261 (19), 199 (23), 183 (15), 181 (14), 97 (24), 83 (100), 69 (49), 57 (32), 55 (24). Anal Calcd. for $C_{26}H_{29}BrOSi$: C, 65.66; H, 8.27; Br, 16.80. Found: C,65.82; H, 8.33; Br,16.46.

Synthesis of 12-(*t*-butyldiphenylsilyloxy)-(6*S*,10*R*)-2,6,10-trimethyldodecane (186):

To a 25mL three necked flask in which was placed ground Mg turnings (0.50 g, 20 mmol) and THF (5 mL) under argon was added 1-bromo-3-methylbutane (0.50 mL, 4.2 mmol) during a period of 20 min. The resulting mixture was stirred at room temperature for 1 h, then the solution was siphoned by argon pressure into another flask which contained 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*S*,6*R*)-2,6-dimethyloctane (**185**, 0.095 g, 0.20 mmol) and Li_2CuCl_4 (0.142 mmol, 1.42 mL of 0.1 M in THF) in THF (1 mL) at -78 °C. The resulting solution was allowed to warm to room temperature and stirred for 20 h, then saturated aqueous NH_4Cl solution (30 mL) was added. The organic solvent was evaporated and the residue was extracted with ether (3x30 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 40:1) to give 0.0635 g (68%) of 12-(*t*-butyldiphenylsilyloxy)-(6*S*,10*R*)-2,6,10-trimethyldodecane (**186**) as a colorless oil; $[\alpha]_D^{25}$ -1.45 (*c* 1.72, $CHCl_3$); IR ($CDCl_3$) 3071.5, 2954.3, 2927.8, 2857.4, 1462.1, 1426.9, 1110.2 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80-

0.88 (m, 12H, $4CH_3$), 1.04 (s, 9H, $C(CH_3)_3$), 1.05-1.40 (m, 14H, CH_2, $2(CH_2)_3$), 1.48-1.52 (m, 3H, 3CH), 3.70 (m, 2H, CH_2O), 7.40 (m, 6H, phenyl), 7.66 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.21 (C-Si), 19.75 (CH_3), 19.79 (CH_3), 24.64 (CH_3), 22.73 (CH_3), 24.40 (CH_2), 24.81 (CH_2), 26.87 (($CH_3)_3$), 27.98 (CH), 29.40 (CH), 32.80 (CH), 37.30, 37.36, 37.47 (($CH_2)_3$), 39.37 (CH_2), 39.66 (CH_2), 62.25 (CH_2O), 127.56, 129.47, 134.18, 135.58 (phenyl); MS (EI) m/z (relative intensity), 253 (1), 239 (*t*-$BuPh_2Si$, 1), 227 (M-$^tBuPh_2Si$, 2), 213 (21), 199 (Ph_2SiOH, 100), 183 (63), 135 (21), 123 (14), 111 (22), 97 (34), 83 (32), 71 (48), 57 (44), 43 (53). Anal Calcd. for $C_{31}H_{50}OSi$: C, 79.76; H, 10.80. Found: C,79.82; H,10.74.

Synthesis of (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol (187):

A mixture of 12-(*t*-butyldiphenylsilyloxy)-(6*S*,10*R*)-2,6,10-trimethyldodecane (**186,** 0.060 g, 0.13 mmol) and tetra-n-butylammonium fluoride (0.5 mL, 1 M in THF) was stirred at room temperature for 16 h, then ether (50 mL) was added, and the aqueous phase was extracted with ether (2x10 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 6:1) to give 0.0241 g (81%) of (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol (**187**) as a col-

orless oil; $[\alpha]_D^{25}$ 3.53 (*c* 1.205, $CHCl_3$); (Lit.[42] $[\alpha]_D^{25}$ 3.56 (*c* 1.805, $CHCl_3$); IR (CCl_4) 3634.6, 2954.3, 2925.4, 2869.0, 1461.6, 1376.8, 1055.2 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, J = 6.7 Hz, 3H, CH_3), 0.86 (d, J = 6.7, 6H, $2CH_3$), 0.89 (J = 6.6 Hz, 3H, CH_3), 1.00-1.65 (m, 18H, 7(CH_2), 3(CH), OH), 3.68 (m, 2H, CH_2O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.69 (CH_3), 19.74 (CH_3), 22.63 (CH_3), 22.73 (CH_3), 24.38 (CH_2), 24.79 (CH_2), 27.98 (CH), 29.53 (CH), 32.80 (CH), 37.27, 37.36, 37.50 ((CH_2)$_3$), 39.36 (CH_2), 39.98 (CH_2), 61.29 (CH_2O); MS (EI) m/z (relative intensity), 210 (M-H_2O, 2), 182 (M-H_2O-C_2H_4, 7), 140 (6), 126 (20), 125 (23), 112 (17), 111 (22), 97 (44), 85 (20), 84 (25), 83 (47), 81 (21), 71 (99), 70 (63), 69 (86), 57 (100), 56 (54), 55 (85).

Synthesis of (3*R*,7*R*)-(+)-3,7,11-trimethyldodecan-1-ol (187) directly from 8-bromo-(3*R*,7*S*)-3,7-dimethyloctanol (184):

To a 25 mL three necked flask which was placed grounded Mg turnings (0.50 g, 20 mmol) in THF (5 mL) under argon was added 1-bromo-3-methylbutane (0.50 mL, 4.2 mmol) during a period of 20 min. The resulting mixture was stirred at room temperature for 1 h, then, the solution was siphoned into another flask which contained 8-bromo-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (**184**) and Li_2CuCl_4 (0.142 mmol, 1.42 mL of 0.1 M in

THF) in THF (1 mL) at -78 °C. The resulting solution was allowed to warm to room temperature and stirred for 48 h, then 3M HCl (30 mL) was added. The organic solvent was evaporated and the residue was extracted with ether (3x30 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 10:1) to give 0.0515 g (87%) of (3R,7R)-(+)-3,7,11-trimethyldodecan-1-ol (**187**) as a colorless oil. GC-MS, IR, and NMR spectra matched the values in the references[43], and comparison of spectra and GC-MS showed the two samples of **187** to be identical.

Synthesis of Methyl (3*R*,7*S*)-3,7-Dimethyl-8-iodooctanoate (188):

Bose's method was used[44]. To a mixture of methyl (3*R*,7*S*)-3,7-dimethyl-8-hydroxyoctanoate (**157**, 0.242 g, 1.20 mmol) of and Ph_3P (0.330g, 0.550 mmol) in dry CH_2Cl_2 (15 mL) at -23 °C was added N-iodosuccinimide (NIS) (0.313 g, 1.32 mmol) at one portion. The mixture was allowed to warm to room temperature and stirred for 20 h, diluted with methanol (0.5 mL) and stirred for an additional 0.5 h. Then, a mixture of hexane/EtOAc (6:1, 20ml) was added to precipitate Ph_3PO. Two thirds of the solvents were evaporated and the residue was filtered with a short silica

gel pad, washed with hexane/EtOAc (6:1, 150 ml). The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to give 0.271 g (72%) of methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate (**188**) as a colorless oil; $[\alpha]_D^{25}$ 7.20 (*c* 6.90, $CHCl_3$); IR (CCl_4) 2957.7, 2929.3, 2853.0, 1739.3, 1459.7, 1434.6, 1193.6, 1171.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, *J* = 6.6 Hz, 3H, CH_3), 0.97 (d, *J* = 6.4 Hz, 3H, CH_3), 1.10-1.50 (m, 6H), 1.83 (m, 1H), 1.95 (m, 1H, CH), 2.12 (q, *J* = 14.7, 8.0 Hz, 1H), 2.30 (q, *J* = 14.7, 6.1 Hz, 1H), 3.15 (q, *J* = 9.5, 5.8 Hz, 1H), 3.22 (q, *J* = 9.6, 4.6 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.79 (CH_2I), 19.72 (CH_3), 20.62 (CH_3), 24.20 (CH_2), 30.24 (CH), 34.64 (CH), 36.47 (CH_2), 36.63 (CH_2), 41.60 (CH_2CO), 51.41 (OCH_3), 173.69 (CO); MS (EI) m/z (relative intensity), 281 (M-CH3O, 8), 185 (M-I, 43), 169 (7), 153 (54), 135 (9), 111 (43), 83 (26), 74 (26), 69 (100), 59 (32), 55 (54), 43 (30), 41 (50). Anal Calcd. for $C_{11}H_{21}IO_2$: C, 42.32; H, 6.78; I, 40.65. Found: C, 42.64; H, 7.08; I, 40.33.

Synthesis of Methyl 8-(*t*-Butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyl-octanoate (189):

A mixture of imidazole (7.70 mmol, 0.524 g) and *t*-butyl-chlorodiphenylsilane (1.00 ml, 3.85 mmol) in dry CH_2Cl_2 (15 mL) was stirred for 1h at room temperature, then a solution of methyl 8-hydroxy-(3*R*,7*S*)-3,7-dimethyloctanoate (**188**, 0.707 g, 3.50 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise during a period of 20min. The resulting mixture was stirred at room temperature for 4 h, then, CH_2Cl_2 (100 mL) was added. The reaction mixture was washed with water (40 mL), saturated aqueous $CuSO_4$ (2x50 mL), and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to give 1.40 g (91%) of methyl 8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyloctanoate (**189**) as a colorless oil; $[\alpha]_D^{25}$ 1.55 (*c* 5.09, $CHCl_3$); IR (CCl_4) 3071.1, 2953.8, 2929.2, 2857.5, 1740.4, 1426.9, 1111.1cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91(d, *J* = 6.6 Hz, 6H), 1.05 (s, 9H), 1.06-1.48 (m, 6H), 1.62 (m, 1H, CH), 1.82 (m, 1H), 2.09 (q, *J* = 14.7, 8.3 Hz, 1H), 2.29 (q, *J* = 14.7, 5.9 Hz, 1H), 3.43 (q, *J* = 9.7, 6.4 Hz, 1H), 3.50 (q, *J* = 9.80, 5.8 Hz, 1H), 3.66 (s, 3H), 7.40 (m, 6H), 7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.92 (CH_3), 19.31 (C-Si), 19.75 (CH_3), 24.26 (CH_2),

26.88 (CH_3), 30.36 (CH), 33.22 (CH_2), 35.66 (CH), 37.00 (CH_2), 41.65 (CH_2CO), 51.35 (OCH_3), 68.82 (CH_2O), 127.56, 129.48, 134.09, 135.62 (phenyl), 173.80 (C=O); MS (EI) m/z (relative intensity), 383 (M-^{t}Bu, 100), 351 (M-^{t}Bu-CH_3OH, 12), 331 (3), 305 (7), 293 (5), 273 (8), 247 (8), 213 ($Ph_2SiHOCH_2$, 69), 199 (Ph_2SiOH, 98), 183 (33), 153 (38), 135 (31), 123 (12), 109 (18), 69 (62), 55 (26). Anal Calcd. for $C_{27}H_{40}O_3Si$: C, 73.59; H, 9.15. Found: C, 73.90; H, 9.03.

Synthesis of 8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (190):

To a dried, 100 mL, three necked flask flushed with nitrogen and charged with $LiAlH_4$ (0.112 g, 2.95 mmol) in dry ether (50 mL) was added methyl 8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyloctanoate (**189**, 1.30 g, 2.95 mmol) in dry ether (20 mL) during a period of 25 min. The resulting mixture was stirred for 0.5h, then, a mixture of ether (4 mL) and methanol (4 mL) added dropwise, followed by 1M HCl (20 ml). The aqueous layer was extracted with ether (3x40 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, and brine, then dried. The solvent was evaporated to yield crude product, which was purified by flash chromatography (SiO_2, hexane/EtOAc, 6:1) to yield 1.15 g (95%) of

8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (**190**) as a colorless oil; $[\alpha]_D^{25}$ 0.42 (*c* 3.855, $CHCl_3$); IR (CCl_4): 3633.6, 3071.5, 2956.2, 2929.8, 2856.4, 1426.9, 1112.2 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 5.8 Hz, 3H), 1.05 (s, 9H), 1.06-1.70 (m, 11H), 3.43 (q, *J* = 9.8, 6.4 Hz, 1H), 3.51 (q, *J* = 9.7, 5.6 Hz, 1H), 3.67 (m, 2H), 7.40 (m, 6H), 7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.96 (CH_3), 19.33 (C-Si), 19.65 (CH_3), 24.27 (CH_2), 26.88 (CH_3), 29.48 (CH), 33.41 (CH_2), 35.71 (CH), 37.41 (CH_2), 39.94 (CH_2), 61.25 (CH_2O), 68.87 (CH_2OSi), 127.55, 129.47, 134.12, 135.62 (phenyl); MS (EI) m/z (relative intensity), 353 (2), 239 (2), 229 (5), 211 (2), 199 (100), 213 (2), 211 (5), 183 (12), 181 (14), 139 (18), 97 (13), 83 (54), 69 (33), 55 (23). Anal Calcd. for $C_{26}H_{40}O_2Si$: C, 75.67; H, 9.77. Found: C, 75.71; H, 9.90.

Synthesis of 1-Bromo-8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-Dimethyloctane (191):

To a mixture of 8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyloctan-1-ol (**190**, 0.994 g, 2.41mmol) and 0.692 g (2.64 mmol) of Ph_3P in dry CH_2Cl_2 (20 mL) at -23 °C was added N-bromosucinimide (NBS) (0.513 g, 2.88 mmol) at one portion. The mixture was allowed to warm to room tem-

perature and stirred for 16 h, then, methanol (1 mL) was added and continuously stirred for 0.5 h, then, a mixture of hexane/EtOAc (6:1, 20 ml) was added. The methylene chloride was evaporated and the residue was filtered with a short silica gel pad, washed with hexane/EtOAc (6:1, 100 ml). The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to give 1.00 g (87%) of 1-bromo-8-(*t*-butyldiphenylsilyloxy)-(2*R*,7*S*)-3,7-dimethyloctane (**191**); $[\alpha]_D^{25}$ -3.77 (*c* 5.67, $CHCl_3$); IR ($CDCl_3$) 3071.5, 2957.7, 2929.2, 2856.9, 1426.9, 1110.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, J = 6.4 Hz, 3H, CH_3), 0.91 (d, J = 6.7 Hz, 3H, CH_3), 1.05 (s, 9H, $C(CH_3)_3$), 1.06-1.68 (m, 9H, CH_2, CH, $(CH_2)_3$), 1.85 (m, 1H, CH), 3..37-3.53(m, 4H, CH_2Br, CH_2O), 7.40 (m, 6H, phenyl), 7.67 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.96 (CH_3), 18.84 (CH_3), 19.32 (C-Si), 24.14 (CH_2), 26.88 (CH_3), 31.62 (CH), 32.21 (CH_2Br), 33.33 (CH_2), 35.67(CH), 36.76 (CH_2), 40.00 (CH_2), 68.81 (CH_2O), 127.56, 129.48, 134.09, 135.62 (phenyl); Anal Calcd. for $C_{26}H_{39}BrOSi$: C, 65.66; H, 8.27; Br, 16.80. Found: C, 65.43; H, 8.26; Br,16.46.

Synthesis of Methyl 16-[(*t*-Butyldiphenylsilyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexadecanoate (192) using copper catalyzed Grignard coupling:

Nunomoto's method was used.[48] To a 25mL three necked flask which was placed ground Mg turning (0.50 g, 20mmol) in THF (3 mL) under argon was added 0.03 mL of $BrCH_2CH_2Br$. 5 min later, 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(3R,7S)-3,7-dimethyloctane (**191**, 0.218 g, 0.459 mmol) in THF (1 mL) was added during a period of 1 min. The resultant mixture was stirred at 40°C for 2 h, then the solution was siphoned into another flask which contained methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate (**188**, 0.0716 g, 0.230 mmol) and Li_2CuCl_4 (0.050 mmol, 0.50 ml of 0.1M in THF) (1 mL) at 0 °C. The resultant solution was allowed to warm to room temperature and stirred for 48 h, then saturated aqueous NH_4Cl (5 mL) was added. The organic solvent was evaporated and the residue was extracted with ether (3x30 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to give methyl 16-[(*t*-butyldiphenylsilyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexa-decanoate (0.0982g, 71%) as a colorless oil;

$[\alpha]_D^{25}$ 1.50 (*c* 1.70, $CHCl_3$); IR ($CDCl_3$) 3069.5, 3049.7, 2953.5, 2928.3, 2855.9, 1739.4, 1462.7, 1426.9, 1111.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, J = 6.0 Hz, 6H, $2CH_3$), 0.91 (d, J = 4.5 Hz, 3H, CH_3), 0.93 (d, J = 4.4 Hz, 3H, CH_3), 0.95-1.42 (m, 29H, $3(CH_2)_3$, 2CH, $C(CH_3)_3$), 1.62 (m, 1H, CH), 1.92 (m, 1H, CH), 2.10 (q, J = 14.6, 8.2 Hz, 1H, H_{2a}), 2.31 (q, J = 14.6, 5.9 Hz, 1H, H_{2b}), 3.43 (q, J = 9.6, 6.3 Hz, 1H, H_{16a}), 3.51 (q, J = 10.5, 6.3 Hz, 1H, H_{16b}), 3.66 (s, 3H, OCH_3), 7.40 (m, 6H, phenyl), 7.67 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.99 (CH_3), 19.32 (C-Si), 19.73 (CH_3), 19.75 (CH_3), 19.80 (CH_3), 24.35 (CH_2), 24.40 (CH_2), 24.47 (CH_2), 26.88 ($(CH_3)_3$), 30.40 (CH), 32.77 (CH), 33.49 (CH_2), 35.74(CH), 37.08 (CH_2), 37.12 (CH_2), 37.36 (CH_2), 37.40 (CH_2), 41.67 (CH_2CO), 51.34, 68.91 (CH_2O), 127.54, 129.45, 134.14, 135.63 (phenyl), 173.85 (C=O). Apparently, one CH_2 and one CH peaks were merged in the above spectrum. ESI-MS 581.3 $(M+H)^+$; MS/MS (Tandem Mass Spectrum, Parent Ion $(M+H)^+$ 581.3, Major peaks) 503.3 $[(M+H)^+-C_6H_6]$, 471.1 $[(M+H)^+-C_6H_6-HOCH_3]$, 425.3 $[(M+H)^+-2C_6H_6]$, 393.3 $[(M+H)^+-2C_6H_6-HOCH_3]$, 325.1 $[(M+H)^+-{}^tBuPh_2SiO]$, 293.3 $[(M+H)^+-t\text{-}BuPh_2SiO\text{-}HOCH_3]$, 239.3 ($t$-$BuPh_2Si^+$). Anal Calcd. for $C_{37}H_{60}O_3Si$: C, 76.49; H, 10.41. Found: C, 76.72; H, 10.29. HRMS Calcd. for $C_{37}H_{60}O_3Si$: 580.4312, found 580.4292.

Preparation of 0.1M SmI_2 in THF.

Wipf's method was used.[52] A suspension of samarium powder (1.84 g, 12 mmol) and I_2 (2.54 g, 10 mmol) in dry THF (100 mL) was stirred vigorously under argon at room temperature for 20 h, during which time the color changed from purple to rust-brown to green and finally to prussian blue.

General Procedure for the Preparation of Tridecane.

To a solution of 25 mL (2.5 mmol) of a 0.1 M of SmI_2 in THF under argon was added 1.74 mL (10 mmol) of dried HMPA. The deep purple solution was stirred at rt for 5 min and treated with 1-iodoheptane (96 μL, 0.6 mmol). The resulting light purple solution was stirred for 15 min and 14 mg (0.1 mmol) of CuBr was added. After 5 min, 74 μL (0.50 mmol) of 1-iodohexane was added. The resulting mixture was stirred for 15 min. The reaction mixture was poured into 20 mL of brine which contained 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate, and brine, then dried and concentrated.

The residue was diluted with THF to 2 mL. The concentration of tridecane was measured by GC and compared with a calibration curve.

Synthesis of Methyl 10-Iododecanoate (121):

To a stirred mixture of Ph_3P (4.72 g, 18.0 mmol), imidazole (1.53 g, 22.5 mmol) and methyl 10-hydroxydecanoate (**196**, 3.15 mL, 15.0 mmol, from Aldrich) in ether (24 mL) and CH_3CN (16 mL) was added I_2 (6.10 g, 24.0 mmol) in portions at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 30 min, then diluted with methanol (4 mL), and stirred for an additional 15 min. The mixture was diluted with ether (150 mL), washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $CuSO_4$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to yield 3.65 g (78%) of methyl 10-iododecanoate (**197**) as a colorless oil; IR ($CDCl_3$) 2930.9, 2856.2, 1731.5, 1437.8, 1205.7, 1173.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.40 (m, 10H, $(CH_2)_5$), 1.56-1.66 (m, 2H, CH_2), 1.78-1.85 (m, 2H, CH_2), 2.30 (t, J = 7.5 Hz, 2H, CH_2I), 3.19 (t, J = 8.1 Hz, 2H, CH_2OSi), 3.67 (s, 3H, CH_3O); ^{13}C NMR (CDCl3, 100 MHz) δ 7.30, 24.91, 28.46, 29.08, 29.14, 29.20, 30.46, 33.52, 34.08, 34.08, 51.46, 174.33. Anal Calcd. for $C_{11}H_{21}O_2I$: C, 42.32; H, 6.78; I, 40.46. Found: C, 42.47; H, 7.02; I, 40.45.

Synthesis of Methyl 10-(*t*-Butyldiphenylsilyloxy)decanoate (198):

A mixture of imidazole (44.0 mmol, 3.00 g) and *t*-butyl-chlorodiphenylsilane (6.24 mL, 24.0 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 1h at room temperature, then a solution of methyl 10-hydroxydecanoate (**196**, 4.20 mL, 24.0 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise during a period of 20 min. The resulting mixture was stirred at room temperature overnight, then, CH_2Cl_2 (100mL) was added. The reaction mixture was washed with water (40mL), saturated aqueous $CuSO_4$ (2x50mL), and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to give 8.63 g (98%) of methyl 10-(*t*-butyldiphenylsilyloxy)decanoate (**198**) as a colorless oil; IR ($CDCl_3$) 3071.9, 2931.7, 2857.0, 1731.4, 1471.9, 1427.9, 1199.1, 1175.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H, $C(CH_3)_3$), 1.20-1.38 (m, 10H, $(CH_2)_5$), 1.50-1.65 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H), 3.63 (t, 2H, J = 6.5 Hz), 3.66 (s, 3H, OCH_3), 7.35-7.44 (m, 6H), 7.66-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.22, 24.94, 25.74, 26.87, 29.14, 29.20, 29.31, 29.40, 32.56, 34.12, 51.45, 63.98, 127.56, 129.47, 134.17, 135.58, 174.34. Anal Calcd. for $C_{27}H_{40}O_3Si$: C, 73.59; H, 9.15. Found: C, 73.74; H, 9.14.

Synthesis of 10-(*t*-Butyldiphenylsilyloxy)decan-1-ol (199):

To a dried, 250mL, three necked flask flushed with nitrogen and charged with $LiAlH_4$ (0.696 g, 18.34 mmol) in dry ether (100 mL) was added methyl 10-(*t*-butyldiphenylsilyloxy)decanoate (**198**, 8.07 g, 18.34 mmol) in dry ether (50 mL) during a period of 25min. The resulting mixture was stirred for 15 min, then, a mixture of ether (10mL) and methanol (10mL) added dropwise, followed by 1M HCl (50mL). The aqueous layer was extracted with ether (3x40mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, and dried. The solvent was evaporated to yield a crude product, which was purified by flash chromatography (SiO_2, hexane/EtOAc, 6:1) to afford 7.18 g (95%) of 10-(*t*-butyldiphenylsilyloxy)decan-1-ol (**199**) as a colorless oil; IR ($CDCl_3$) 3625.7, 3071.9, 3052.8, 2931.2, 2857.0, 1471.9, 1427.9, 1389.9, 1111.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H, $C(CH_3)_3$), 1.22-1.40 (m, 13H, $(CH_2)_6$, OH), 1.50-1.60 (m, 4H), 3.61-3.67 (m, 4H), 7.35-7.43 (m, 6H), 7.66-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.22, 25.74, 25.76, 26.87, 29.36, 29.42, 29.54, 32.57, 32.81, 63.09, 64.00, 127.55, 129.47, 134.18, 135.57. Anal Calcd. for $C_{26}H_{40}O_2Si$: C, 75.67; H, 9.77. Found: C, 75.84; H, 9.54.

Synthesis of 10-(*t*-Butyldiphenylsilyloxy)-1-Iododecane (200):

To a stirred mixture of Ph_3P (4.80 g, 18.42 mmol), imidazole (1.57 g, 23.03 mmol) and 10-(*t*-butyldiphenylsilyloxy)decan-1-ol (**199**, 6.325 g, 15.35 mmol) in ether (30 mL) and CH_3CN (20 mL) was added I_2 (6.24 g, 24.56 mmol) in portions at 0°C. The resulting mixture was allowed to warm to rt and stirred for 30 min, then diluted with methanol (3 mL), then stirred for an additional 15 min. The mixture was diluted with ether (150 mL), washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $CuSO_4$, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 40:1) to yield 6.77 g (85%) of 10-(*t*-butyldiphenylsilyloxy)-1-iododecane (**200**) as a colorless oil; IR ($CDCl_3$) 3071.8, 3052.6, 2930.8, 2856.7, 1471.9, 1427.8, 1389.8, 1361.8, 1187.7, 1111.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H, $C(CH_3)_3$), 1.20-1.40 (m, 6H, $(CH_2)_6$), 1.50-1.60 (m, 2H), 1.75-1.85 (m, 2H), 3.18 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 7.0 Hz, 2H), 7.30-7.40 (m, 6H), 7.60-7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.34, 19.22, 25.74, 26.87, 28.52, 29.30, 29.34, 29.48, 30.51, 32.56, 33.56, 63.97, 127.55, 129.46, 134.17, 135.57. Anal Calcd. for $C_{26}H_{39}IOSi$: C, 59.76; H, 7.52; I, 24.28. Found: C,60.08; H, 7.55; I, 24.48.

Synthesis of Methyl 20-(*t*-Butyldiphenylsilyloxy)icosanoate (125):

To a solution of 12.5 mL (1.25 mmol) of a 0.1 M SmI_2 in THF under argon was added 0.87 mL (5 mmol) of HMPA. The deep purple solution was stirred at rt for 5 min, then 10-(*t*-butyldiphenylsilyloxy)-1-iododecane (**200**, 0.261 g, 0.500 mmol) in THF (1 mL) was added dropwise during a period of 2 min. The resulting light purple mixture was stirred for 15 min, and 14 mg (0.1 mmol) of CuBr was added. After 5 min, methyl 10-iododecanoate (**197**, 0.131 g, 0.42 mmol) in THF (1 mL) was added dropwise during a period of 1 min. The resulting mixture was stirred for 30 min at rt and then poured into 25 mL of brine which contained 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate, and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (hexane/EtOAc, 20:1) to yield 0.195 g (80%) of methyl 20-(*t*-butyldiphenylsilyloxy)-icosanoate (**201**) as a colorless oil; IR ($CDCl_3$) 3072.3, 3052.7, 2928.5, 2855.4, 1731.6, 1464.1, 1428.0, 1111.0 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H, $C(CH_3)_3$), 1.15-1.35 (m, 30H, $(CH_2)_{15}$), 1.50-1.65 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H, CH_2CO), 3.65 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H, OCH_3),

7.35-7.42 (m, 6H), 7.62-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.22, 23.85, 23.90, 24.97, 25.78, 26.87, 28.85, 28.94, 29.17, 29.27, 29.40, 29.47, 29.62, 29.64, 29.66, 29.69, 29.71, 32.59, 34.12, 51.43, 64.02, 127.55, 129.46, 134.19, 135.57, 174.33; ESI-MS 581.3 $(M+H)^+$. Anal Calcd. for $C_{37}H_{60}O_3Si$: C, 76.49; H, 10.41. Found: C, 76.78; H, 10.29.

Synthesis of 10-(*t*-Butyldiphenylsilyloxy)-1-(Methoxymethoxy)decane (202):

Fuji's method[47] was used. To a stirred solution of 10-(*t*-butyldiphenylsilyloxy)decan-1-ol (**199**, 1.512 g, 3.67 mmol) in chloroform (20 mL, dried over phosphorus pentoxide) were added dimethoxymethane (23 mL, 257 mmol) and phosphorus pentoxide (7.00 g) in portions. After 20 min, the solution was poured into saturated aqueous Na_2CO_3 solution (100 mL) and the solid residue was washed with saturated aqueous Na_2CO_3 solution (30 mL). The aqueous phases were extracted with CH_2Cl_2 (3x50 mL) separately and the combined organic phases were washed with brine, dried, and evaporated. The residue was purified by chromatography (hexane/EtOAc, 20:1) to yield 1.42 g (85%) of 10-(*t*-butyldiphenylsilyloxy)-1-(methoxymethoxy)decane (**202**) as a colorless oil; IR ($CDCl_3$) 3071.9, 3052.4, 2931.2, 2857.4, 1469.0, 1427.9, 1109.9, 1041.3 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ 1.04 (s, 9H, $C(CH_3)_3$), 1.20-1.40 (m, 12H, $(CH_2)_6$), 1.52-1.62 (m, 4H), 3.36 (s, 3H, OCH_3), 3.52 (t, J = 6.7 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 4.62 (s, 2H, OCH_2O), 7.30-7.40 (m, 6H), 7.60-7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.23, 25.77, 26.24, 26.87, 29.37, 29.45, 29.56, 29.77, 31.60, 32.59, 55.09, 64.01, 67.89, 96.39, 127.56, 129.47, 134.19, 135.58. Anal Calcd. for $C_{28}H_{44}O_3Si$: C, 73.63; H, 9.71. Found: C, 73.57; H, 9.87.

Synthesis of 10-(Methoxymethoxy)decan-1-ol (203):

10-(*t*-Butyldiphenylsilyloxy)-1-(methoxymethoxy)decane (**202**, 0.840 g, 1.84 mmol) was dissolved in TBAF (4 mL, 1 M in THF). The mixture was stirred overnight, then water (20 mL) was added. The resulting mixture was extracted with ether (3x50 mL) and the combined organic phases were washed with brine and dried. The solvents were evaporated and the residue was purified by chromatography (hexane/EtOAc, 6:1) to yield 0.365 g (91%) of 10-(methoxymethoxy)decan-1-ol (**53**) as a colorless oil; IR ($CDCl_3$) 3622.7, 2931.5, 2856.4, 1466.4, 1146.2, 1108.2, 1041.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (m, 13H), 1.50-1.60 (m, 4H), 3.36 (s, 3H, OCH_3), 3.52 (t, J = 6.6 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 4.62 (s, 2H,

OCH_2O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.73, 26.21, 29.41, 29.52, 29.54, 29.74, 32.81, 55.10, 63.07, 67.88, 96.39. Anal Calcd. for $C_{12}H_{26}O_3$: C, 66.01; H, 12.00. Found: C,66.17; H, 12.03.

Synthesis of 10-(Methoxymethoxy)-1-Iododecane (204):

To a stirred mixture of Ph_3P (0.453 g, 1.73 mmol), imidazole (0.148 g, 2.16 mmol) and 10-(methoxymethoxy)decan-1-ol (**127**, 0.315 g, 1.44 mmol) in ether (6 mL) and CH_3CN (4 mL) was added I_2 (0.585 g, 2.30 mmol) in portions at 0°C. The resulting mixture was allowed to warm to rt and stirred for 30 min, then diluted with methanol (1 mL), then stirred for an additional 15 min. The mixture was filtered through a short silica gel pad which was washed with hexane/EtOAc (100 mL, 6/1). The combined filtrates were evaporated and the residue was purified by chromatography (Hexane/EtOAc, 20:1) to yield 0.401 g (85%) of 10-(methoxymethoxy)-1-iododecane (**204**) as a colorless oil; IR ($CDCl_3$) 2931.1, 2856.1, 1465.8, 1212.1, 1149.0, 1108.4, 1043.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.45 (m, 12H, $(CH_2)_6$), 1.52-1.62 (m, 2H, CH_2), 1.75-1.85 (m, 2H, CH_2), 3.19 (t, J = 7.1 Hz, 2H, CH_2I), 3.36 (s, 3H, OCH_3), 3.52 (t, J = 6.7 Hz, 2H, CH_2OSi), 4.62 (s, 2H, OCH_2O); ^{13}C NMR (CDCl3, 100 MHz) δ 7.34, 26.21,

28.53, 29.36, 29.40, 29.48, 29.75, 30.50, 33.56, 55.10, 67.86, 96.40. Anal Calcd. for $C_{12}H_{25}O_2I$: C, 43.91; H, 7.68; I, 38.66. Found: C, 44.03; H, 7.52; I, 38.34.

Synthesis of 10-[(*t*-Butyldiphenylsilyl)oxy]-1-(Methoxymethoxy)-icosane (205):

To a solution of 12.5 mL (1.25 mmol) of a 0.1 M of SmI_2 in THF under argon was added 0.87 mL (5 mmol) of dried HMPA. The deep purple solution was stirred at rt for 5 min, then 10-(*t*-butyldiphenylsilyloxy)-1-iododecane (**200**, 0.261 g, 0.500 mmol) in THF (1 mL) was added dropwise during a period of 2 min. The resulting light purple mixture was stirred for 15 min, and 14 mg (0.1 mmol) of CuBr was added. After 5 min, 10-(methoxymethoxy) -1-iododecane (**204**, 0.138 g, 0.42 mmol) in THF (1 mL) was added dropwise during a period of 1 min. The resulting mixture was stirred for 30 min at rt and then poured into 25 mL of brine which contained 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (hexane/EtOAc, 20:1) to yield 0.212 g (85%) of 10-[(*t*-

butyldiphenylsilyl)-oxy]-1-(methoxy-methoxy)icosane (**205**) as a colorless oil; IR ($CDCl_3$) 3071.9, 3050.6, 2928.4, 2855.1, 1467.8, 1427.9, 1109.8, 1042.8 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H, $C(CH_3)_3$), 1.20-1.40 (m, 32H, $(CH_2)_{16}$), 1.48-1.62 (m, 4H), 3.30 (s, 3H, OCH_3), 3.51 (t, J = 6.6 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 4.62 (s, 2H, OCH_2O), 7.30-7.42 (m, 6H), 7.60-7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.23, 25.78, 26.23, 26.87, 29.40, 29.46, 29.63, 29.72 (m), 32.59, 55.08, 64.02, 67.89, 96.39, 127.55, 129.46, 134.20, 135.58; ESI-MS 597.3 $(M+H)^+$. Anal Calcd. for $C_{38}H_{64}O_3Si$: C, 76.52; H, 10.82. Found: C, 76.72; H, 10.69.

Synthesis of 8-(*t*-Butyldiphenylsilyloxy)-1-Iodo-(2*R*,7*S*)-3,7-dimethyl-octane (212):

To a mixture of 8-(*t*-butyldiphenylsilyloxy)-(3*R*,7*S*)-3,7-dimethyl-octan-1-ol (**190**, 0.60 g, 1.46 mmol), Ph_3P (0.459 g, 1.75 mmol) and imidazole (0.149 g, 2.19 mmol) in dry ether (6 mL) and CH_3CN (4 mL) at 0 °C was added I_2 (0.539 g, 2.34 mmol) in portions. The mixture was allowed to warm to room temperature and stirred for 0.5 h, diluted with methanol (1mL) and stirred for an additional 15 min. The residue was filtered through a short silica gel pad which was washed with hexane/EtOAc (6:1, 100ml). The combined organic layers were evaporated and the residue was

purified by chromatography (hexane/EtOAc, 20:1) to give 0.652 g (86%) of 8-(*t*-butyldiphenylsilyloxy)-1-iodo-(2*R*,7*S*)-3,7-dimethyl-octane (**212**) as a colorless oil; $[\alpha]_D^{25}$ -6.06 (*c* 2.51, $CHCl_3$); IR ($CDCl_3$) 3072.0, 3052.4, 2963.4, 2930.3, 2858.4, 1471.8, 1428.8, 1111.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, *J* = 6.5 Hz, 3H, CH_3), 0.92 (d, *J* = 6.7 Hz, 3H, CH_3), 1.05 (s, 9H, $C(CH_3)_3$), 1.10-1.70 (m, 9H, CH_2, CH, $(CH_2)_3$), 1.80-1.90 (m, 1H, CH), 3.10-3.16 (m, 2H, CH_2I), 3.40-3.52 (m, 2H, CH_2O), 7.30-7.40 (m, 6H, phenyl), 7.60-7.65 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.37, 16.96, 18.73, 19.32, 24.13, 26.88, 33.34, 33.84, 35.67, 36.52, 40.90, 68.81, 127.56, 129.48, 134.08, 135.62. Anal Calcd. for $C_{26}H_{39}IOSi$: C, 59.76; H, 7.52; I, 24.28. Found: C, 59.58; H, 7.50; I, 24.00.

Synthesis of Methyl 16-[(*t*-Butyldiphenylsilyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-Tetramethylhexadecanoate (192) using Samarium Diiodide:

To a solution of 5.6 mL (0.56 mmol) of a 0.1 M of SmI_2 in THF under argon was added 0.39 mL (2.24 mmol) of dried HMPA. The deep purple solution was stirred at rt for 5 min, then 8-(*t*-butyldiphenylsilyloxy)-1-iodo-(2*R*,7*S*)-3,7-dimethyloctane (**212**, 0.117 g, 0.224 mmol) in THF (1 mL) was added dropwise during a period of 4 min. The resulting light purple mixture

was stirred for 15 min, and 5 mg (0.04 mmol) of CuBr was added. After 5 min, methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate (**188**, 0.0583 g, 0.187 mmol) in THF (1 mL) was added dropwise during a period of 3 min. The resulting mixture was stirred for 30 min at rt and then poured intc 25 mL of brine which contained 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (hexane/EtOAc, 20:1) to yield 0.0883 g (81%) of methyl 16-[(*t*-butyldiphenylsilyl)oxy]-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethylhexadecanoate (**192**). Comparison of spectra showed the two samples of **192** to be identical.

Synthesis of 1,16-di[(*t*-Butyldiphenylsilyl)oxy]-(3*R*,7S,10S,14R)-3,7,-10,14-tetramethylhexadecane (213)

To a 25 mL three necked flask which was placed grounded Mg turning (0.50 g, 20 mmol) in THF (3 mL) under argon was added 0.1mL of $BrCH_2CH_2Br$. At the cessation of gas evolution, 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(2S,6R)-2,6-dimethyloctane (**191**, 0.285 g, 0.600 mmol) in THF (2mL) was added in one portion. The resultant mixture was stirred 40

°C for 2 h, then the solution was siphoned into another flask which contained 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(2S,6R)-2,6-dimethyloctane (**191**, 0.238 g, 0.500 mmol) and Li_2CuCl_4 (0.030 mmol, 0.30 ml of 0.1 M in THF) in THF (1 mL) at -78°C. The resultant solution was allowed to warm to room temperature and stirred for 72 h, then saturated aqueous NH_4Cl (5 mL) was added. The organic solvent was evaporated and the residue was extracted with ether (3x30 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 100:1) to give 1, 16-di[(*t*-Butyldiphenylsilyl)oxy]-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethylhexadecane (0.208 g, 68%) and unreacted 1-bromo-8-(*t*-butyldiphenylsilyoxy)-(2S,6R)-2,6-dimethyloctane (**213**, 0.058 g, 0.12 mmol) as a colorless oil; $[\alpha]_D^{25}$ -1.21 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3072.4, 3054.7, 2957.7, 2929.8, 2857.8, 1462.6, 1378.8, 1111.2cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, J = 6.6 Hz, 6H, $2CH_3$), 0.83 (d, J = 6.5 Hz, 6H, $2CH_3$), 0.95-1.40 (m, 38H), 1.50-1.65 (m, 4H), 3.70 (m, 4H), 7.42 (m, 12H), 7.68 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.21, 19.72, 19.80, 24.44, 26.88, 29.41, 33.08, 34.36, 37.44, 37.49, 39.67, 62.26, 127.56, 129.47, 134.19, 135.59. Anal Calcd. for $C_{52}H_{78}O_2Si_2$: C,78.92; H,9.94. Found: C, 78.94; H, 9.90.

Synthesis of (3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethylhexadecan-1,16-diol (214):

A mixture of 1,16-di[(*t*-Butyldiphenylsilyl)oxy]-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecane (**213**, 0.208 g, 0.263mmol) and tetra-n-butylammonium fluoride (2mL, 1 M in THF) was stirred at room temperature overnight, then ether (50mL) was added, and the aqueous phase was extracted wither ether (2x10mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (Hexane/EtOAc, 2:1) to give 0.0744g (90%) of (3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecan-1,16-diol (**214**) as a colorless oil; $[\alpha]_D^{25}$ 3.2 (*c* 1.97, $CHCl_3$); IR ($CHCl_3$) 3620.6, 2956.2, 2927.9, 2870.6, 1462.3, 1378.6, 1052.0, 996.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.5 Hz, 6H), 0.89 (d, J = 6.4, 6H), 1.00-1.40 (m, 18H), 1.60-1.70 (m, 4H), 1.83-1.93 (m, 2H), 3.36-3.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.70, 19.77, 24.38, 28.81, 33.06, 34.26, 37.43, 37.50, 39.95, 61.20. HRMS Calcd. for $C_{20}H_{43}O_2$: 315.3263, found: $(M+H)^+$, 315.3247.

Synthesis of 1,16-dibromo-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecane (215):

To a mixture of (3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecan-1,16-diol (**214**, 0.0744 g, 0.237 mmol) and Ph_3P (0.137 g, 0.521 mmol) in dry CH_2Cl_2 (3mL) at -23 °C was added NBS (0.101 g, 0.569 mmol) at one portion. The mixture was allowed to warm to room temperature and stirred for 1.5 h, then diluted with methanol (0.5 mL) and stirred for an additional 0.5 h. Then, a mixture of hexane/EtOAc (6:1, 20ml) was added. Two thirds of the solvents were evaporated and the residue was filtered through a short silica gel pad which was washed with hexane/EtOAc (6:1, 100ml). The combined solvents were evaporated and the residue was purified by chromatography (Hexane/EtOAc, 40:1) to give 0.095g (91%) of 1,16-dibromo-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecane (**215**) as a colorless oil; $[\alpha]_D^{25}$ -5.38 (*c* 1.51, $CHCl_3$); IR ($CHCl_3$) 2957.9, 2928.1, 2869.3, 1462.5, 1379.3, 1262.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, *J* = 6.5 Hz, 6H), 0.89 (d, *J* = 6.4 Hz, 6H), 1.00-1.40 (m, 18H), 1.60-1.70 (m, 4H), 1.83-1.93 (m, 2H), 3.36-3.52 (m,4H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.01, 19.72, 24.25, 31.68, 32.26, 33.04, 34.29, 36.84, 37.38, 40.04. HRMS Calcd. for $C_{20}H_{41}Br_2$: 439.1575. found: $(M+H)^+$, 439.1400.

Synthesis of Methyl (3*R*,7*R*,11*S*,15*S*,18*S*,22*S*)-3,7,11,15,18,22-Hexamethylhexaicosanoate (216):

To a solution of 8.5 mL (0.85 mmol) of a 0.1 M of SmI_2 in THF under argon was added 0.6 mL (3.4 mmol) of dried HMPA. The deep purple solution was stirred at rt for 5 min, then 1,16-dibromo-(3*R*,7*S*,10*S*,14*R*)-3,7,10,14-tetramethyl-hexadecane (**214**, 0.073 g, 0.17 mmol) in THF (1 mL) was added dropwise during a period of 1 min. The resulting light purple mixture was stirred for 15 min, and 8 mg (0.064 mmol) of CuBr was added. After 5 min, methyl (3*R*,7*S*)-3,7-dimethyl-8-iodooctanoate (**188**, 0.106 g, 0.34 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred for 2 h at rt and then poured into 25 mL of brine which contained 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate and brine, then dried. The solvent was evaporated and the residue was purified by chromatography (hexane/EtOAc, 20:1) to yield 0.055 g (69%) of Methyl (3R,7R,11S,15S,18S,22S)-3,7,11,15,18,22-Hexamethylhexa-icosanoate (**216**) as a colorless oil; $[\alpha]_D^{25}$ 4.26 (*c* 0.1915, $CHCl_3$); IR ($CHCl_3$) 2956.1, 2927.5, 2856.6, 1729.7, 1462.0, 1377.8cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ

0.84 (m, 18H), 0.93 (d, J = 6.68 Hz, 3H), 1.00-1.40 (m, 35H), 1.90-2.00 (m, 1H), 2.10 (q, J = 8.2 Hz, J = 14.7 Hz, 1H), 2.31 (q, J = 6.0 Hz, J = 14.7 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.28, 19.76, 19.80, 24.36, 24.48, 24.51, 24.53, 29.49, 30.41, 32.77, 32.82, 33.08, 34.33, 37.00, 37.10, 37.13, 37.38, 37.43, 37.57, 41.67, 51.34, 173.84. HRMS Calcd. for $C_{31}H_{63}O_2$: 467.4828. Found: $(M+H)^+$, 467.4838.

Chapter 4. References

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