Studies Directed Towards the Stereoselective Total Synthesis of Miyakolide

by

Jinhua Song

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy
in Organic Chemistry

at the
Massachusetts Institute of Technology

February, 1999

Signature of Author:_____
Department of Chemistry
September 25, 1998

Certified by:_____
Professor Satoru Masamune
A. C. Cope Professor of Chemistry
Thesis Supervisor

Accepted by:_____
Professor Dietmar Seyferth, Chairman
Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Timothy M. Swager _____
Chairman

Professor Satoru Masamune _____
Thesis Supervisor

Professor Rick L. Danheiser _____

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Abstract

Presented are the stereoselective syntheses of the **A** (C18-C28), **B** (C14-C17), **C** (C6-C13), **D** (C1-C5), **C'D'** (C1-C13) fragments and the efficient coupling of **B** and **C'D'** fragments of the marine natural product miyakolide, a 24-membered polyketide macrolide which exhibits anti-cancer activity.

Fragment **A** was synthesized from the chiral aldehyde **4-4** through the successful application of the newly developed boron mediated *anti*-selective aldol methodology using the chiral ester **3-4**. This demonstrated the usefulness of this method in the double asymmetric aldol reactions and it constitutes a reliable and general method for the direct construction of the *anti*-aldol subunits embedded in the polyketide-type natural products.

Fragment **C** synthesis started with an asymmetric *anti*-selective aldol reaction involving the chiral ester **3-4** and the aldehyde **5-1**. Then the two stereogenic centers at C7 and C8 were installed conveniently through a double asymmetric Sharpless dihydroxylation reaction of the allylic chloride **5-5**.

Fragment **D**, a vinyl iodide, was synthesized efficiently by employing a regio- and stereoselective conjugate addition of the tri-*n*-butyltin cuprate to the acetylenic ester **6-3**, followed by the metal-halogen exchange.

The vinyl anion **7-1** generated from fragment **D** failed to couple with fragment **C**.

In a revised coupling strategy, fragment **C'** (C5-C13) synthesized from fragment **C** was coupled with fragment **D'** (C1-C4, derived from the chiral aldehyde (*R*)-**8-7**) through an aldol reaction. The stereoselective introduction of the exocyclic α, β-unsaturated ester at C5 was achieved by using a substrate-controlled Peterson olefination reaction.

Fragment **B** was prepared from the chiral aldehyde (*S*)-**8-7** in a straightforward manner. The coupling of fragments **B** and **C'D'** features the chemoselective nucleophilic addition of the cuprate derived from fragment **B** to the aldehyde in fragment **C'D'** without significant interference with the benzyl ester at C1 and the exocyclic α, β-unsaturated ester at C5.

Thesis Supervisor: Satoru Masamune
Title: A. C. Cope Professor of Chemistry

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First and foremost, I would like to thank my thesis supervisor Professor Satoru Masamune for all the guidance and support he has provided to me throughout the course of my graduate work at MIT. He has been and continues to be the best model for me to follow as I develop as a chemist.

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Finally, but most of all, I would like to thank my dear wife, Amy for the unconditional love and support she has given me. I love you!

To my parents, my sister and Amy...

Table of Contents

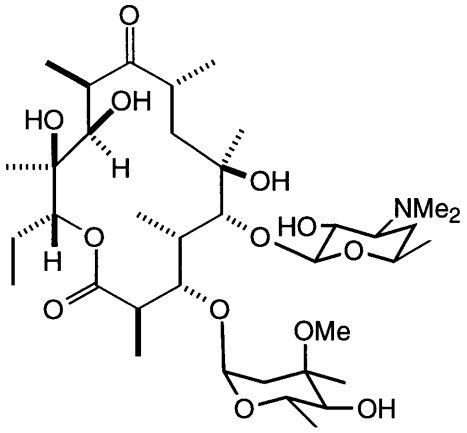
List of Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
Bz	benzoyl
DDQ	2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DET	diethyl tartrate
DMAP	4-(dimethylamino)pyridine
LDBB	lithium di-*t*-butyldibenzyl
LiHMDS	lithium hexamethyldisilizide
Mes	2, 4, 6-trimethylphenyl
MPM	*p*-methoxybenzyl
NaHMDS	sodium hexamethyldisilizide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
TBAF	tetrabutylamonium fluoride
TBHP	*t*-butylhydroperoxide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
TMS	trimethylsilyl

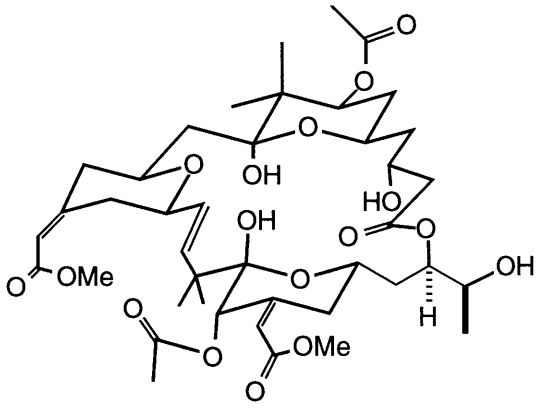
Chapter 1

Introduction to Miyakolide

Nature seems to produce an unlimited number of secondary metabolites with novel molecular architecture. An important class of these compounds includes macrolides[1] of polyketide origin. These molecules often display one or more of a broad range of biological activity including antitumor, antiviral and antibacterial activities, and are an important and valuable source of lead structures for human pharmaceuticals. Some of them, for example erythromycins,[2] have been used as antibiotics for many years. Others, such as bryostatins,[3] are being investigated in the clinic as potential anti-cancer drugs.



erythromycin A

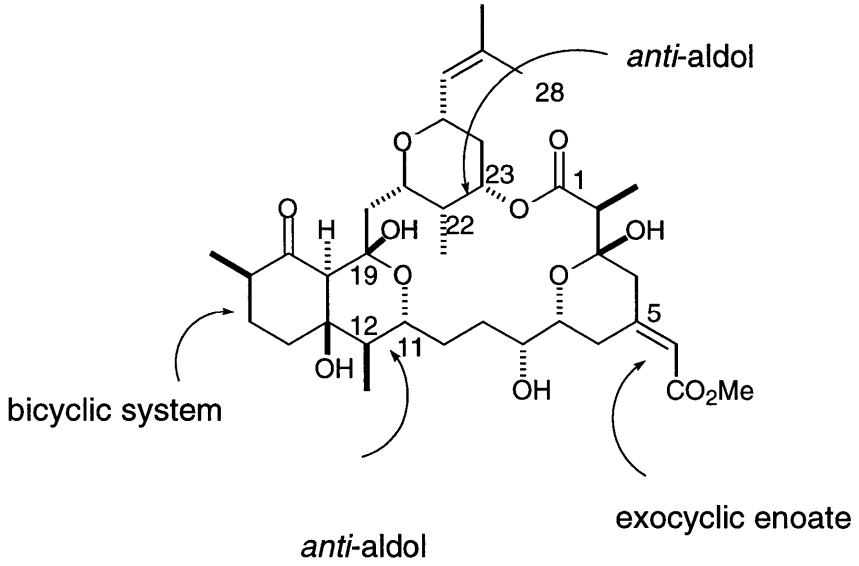


bryostatin 7

Recently miyakolide (**1-1**, Scheme 1.1),[4] a 24-membered macrolide was isolated from a marine sponge *Polyfibrospongia sp.* collected off the island of Miyako in Japan. It was shown to exhibit in vitro (IC_{50} 17.5 μg/ml) and in vivo (T/C 127% at 800 μg/kg) antitumor activities against P388 mouse leukemia. The structure and relative stereochemistry of miyakolide were elucidated through the NMR techniques and confirmed unambiguously by X-ray crystallography. The determination of the absolute

stereochemistry, however, must await either the total synthesis or the degradation studies of the natural product.

Scheme 1.1



miyakolide (**1-1**)

Our interest in the synthesis of compounds such as miyakolide stems not only from their biological activity and their potential as chemotherapeutic agents, but also from their novel structural features which call for innovative synthetic methods and designs. As will be detailed in Chapters 2 and 3, the construction of the *anti*-aldol subunits at C11-C12 and C22-C23, the exocyclic enoate at C5 and the likely fragile bicyclic system (C11-C19) in the miyakolide framework present great synthetic challenges. In addition, the success of this type of synthetic projects often relies on the careful and sometimes creative selection of protecting groups for the polyoxygenated intermediates. In order to accomplish this, extensive research is usually needed to study the subtle differences in the reactivity of multiple functionalities in complex structures. It is our hope that such synthetic endeavors

would truly define the scope and limitations of synthetic methodologies and provide solutions not only to the problems in the miyakolide project, but also to the problems of general synthetic interest.

Chapter 2

Background of Macrolide Synthesis

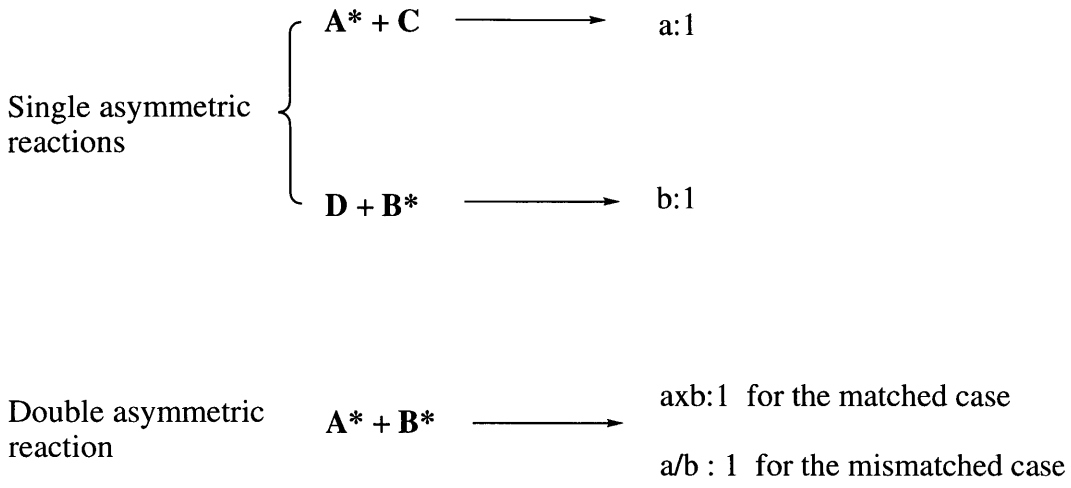
2.1 Double asymmetric synthesis

The stereochemical control of a reaction is of prime importance and interest in modern organic chemistry. Before 1980, this task was achieved by taking advantage of the intrinsic stereochemical bias of the chiral substrate(s) in a particular reaction (substrate-controlled strategy).[5] In most cases, only one out of two or more possible diastereomers can be directly accessible through a substrate-controlled reaction. Moreover, the success of this approach often relies on the presence of cyclic structures in the substrates. Consequently, it cannot be applied efficiently to the stereochemical control of acyclic systems.

Double asymmetric synthesis, in which two chiral reactants **A*** and **B*** (* denotes enantiomerically pure chiral compounds, Scheme 2.1) are allowed to react with each other, is frequently encountered in the synthesis of stereochemically complex natural products exemplified by macrolides. Based on the results of the studies on a variety of double asymmetric reactions, it was found that the overall stereochemical course of this reaction can be understood and evaluated in terms of the intrinsic diastereofacial selectivities (ds) of **A*** and **B*** estimated by the single asymmetric reactions with achiral model compounds **C** and **D**, respectively. In general, the degree of double asymmetric induction is approximated to be the product (axb) for the matched case or the quotient (a/b) for the mismatched case. This phenomenon has been observed for many types of reactions such as aldol reactions, catalytic hydrogenation, epoxidation and Diels-Alder reactions.

Scheme 2.1

Double Asymmetric Synthesis



2.2 Reagent-controlled asymmetric synthesis

Based on the phenomenon of double asymmetric synthesis, a powerful new strategy for the predictable creation of new stereogenic centers in both cyclic and acyclic systems was formulated. In this process, a chiral reagent (e.g. **A***) with a very high ds (e.g. a=100) is allowed to react with a substrate (e.g. **B***) of a usually low ds (e.g. b=5). The chiral reagent **A*** completely controls the overall stereochemical outcome of this double asymmetric reaction, by enhancing the apparent facial selectivity of the substrate (**B***) in the matched pair reaction (ds=100x5) and overriding it in the mismatched pair reaction (ds=100/5). Therefore both diastereomers can now be obtained in a predictable manner simply by choosing the right enantiomer of the chiral reagent **A***. Since the overall stereochemistry is determined by the chiral reagent, but not the substrate, this approach is termed a "reagent-controlled" strategy as opposed to the classical "substrate-controlled" strategy.

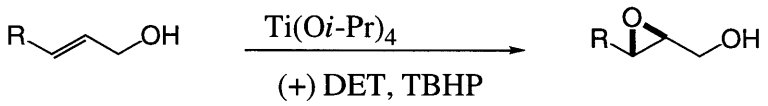
It has been well recognized that many reagents are enantioselective, but only a few such reagents are powerful enough to be also diastereoselective in both matched and

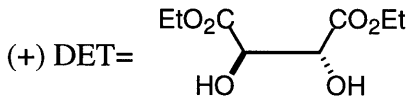
mismatched sense.[7] Therefore an enantioselective chiral reagent or process must be tested in the context of double asymmetric reactions to establish their usefulness. The chiral enolate **2-1** (Scheme 2.2) for the asymmetric *syn*-selective aldol reactions[8] and the chiral titanium catalyst [9] for the catalytic asymmetric epoxidation of primary allylic alcohols† are two such reagents that meet this demand. The wide applications of these chiral reagents in the natural product synthesis[10] are exemplary of this new "reagent-controlled" strategy.

Scheme 2.2

Chiral Reagents for Double Asymmetric Synthesis

2-1





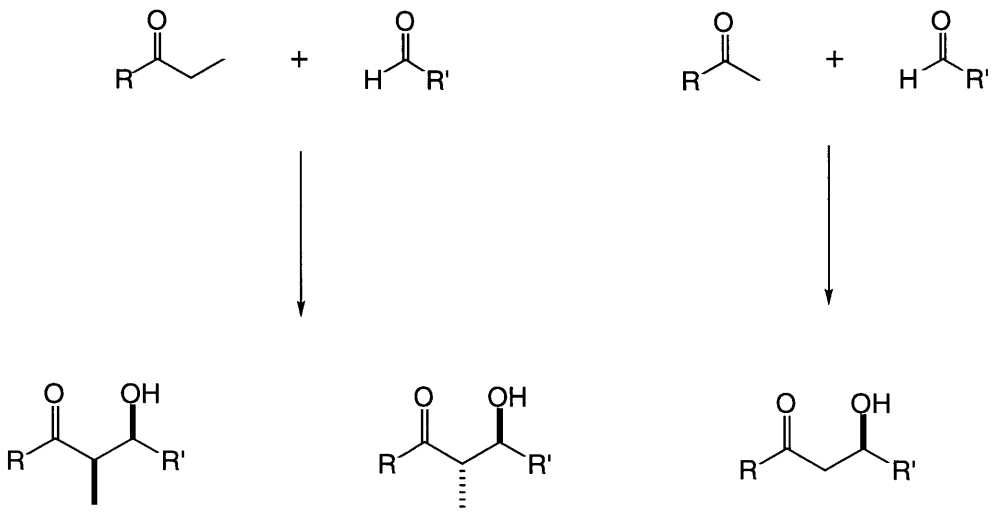
2.3 Double asymmetric aldol reactions: *syn*- and *anti*-aldols

Stereospecific aldol reactions have been a subject of extensive investigation over the past two decades because of their wide applicability to the synthesis of stereochemically complex polyketide natural products.[11]

† In the asymmetric epoxidation of chiral 1-substituted allylic alcohols (secondary allylic alcohols) with this catalytic system, kinetic resolution occurs. Therefore, only one of the two possible diastereomeric epoxides could be obtained with good stereoselectivities. See reference 9b for detailed discussion.

Scheme 2.3

Aldol Reactions

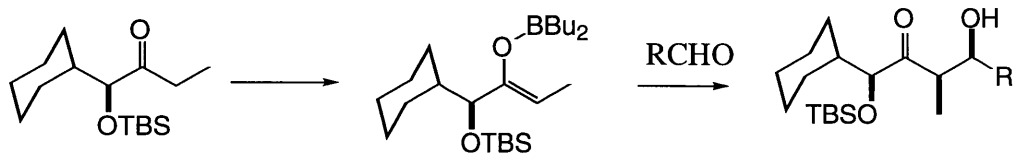


syn-propionate aldol *anti*-propionate aldol acetate aldol

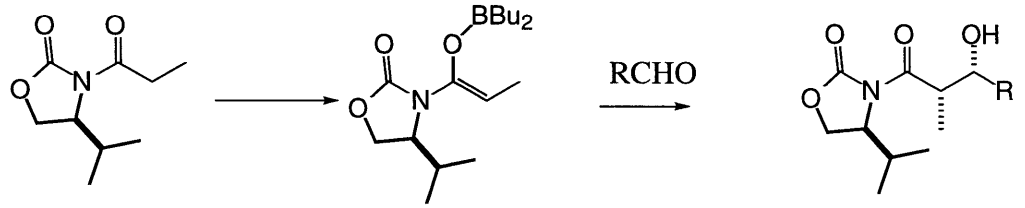
Three major product types, namely *syn*-propionate, *anti*-propionate and acetate aldols resulting from an aldol reaction were distinguished (Scheme 2.3). Several efficient and practical chiral reagents have been made available for the asymmetric *syn*-propionate additions. Two examples are the mandelic acid-derived chiral ketone **2-2** designed and synthesized in these laboratories,[8] and the amino alcohol-derived chiral oxazolidinone auxiliary **2-3** reported by the Evans' group (Scheme 2.4).[12] Because of the high diastereofacial selectivity and proven reliability of these reagents, the *syn*-selective aldol reaction has become one of the standard reactions in macrolide synthesis.

Scheme 2.4

Chiral Reagents for *Syn*-selective Aldol Reactions



2-2 **2-1** (S. Masamune)

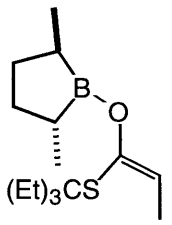


2-3 (D. Evans)

In contrast to the fruitful development of chiral reagents for the *syn*-selective aldol reactions, the development of chiral reagents for the asymmetric *anti*-selective aldol reactions has met with limited success. Several representative methods are listed in Scheme 2.5.[13] However, in many cases these methods appear to present problems in terms of the availability of reagents, the generality of reactions and conditions required for reactions. For example, Lewis acid mediated aldol reactions involving **2-7**[13c] and **2-9**[13e] usually cannot be applied successfully to highly oxygenated substrates because of unpredictable chelations.

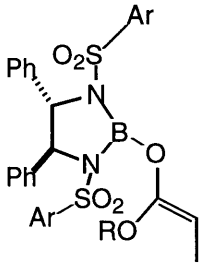
Scheme 2.5

Chiral Reagents for *Anti*-selective Aldol Reactions



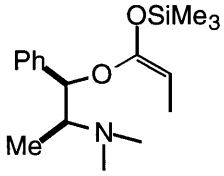
2-5

Masamune



2-6

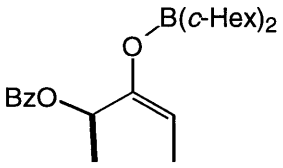
Corey



$TiCl_4$

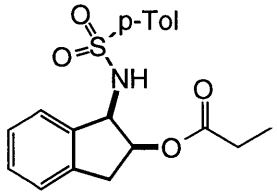
2-7

Gennari



2-8

Paterson



$TiCl_4$, Hunig's base

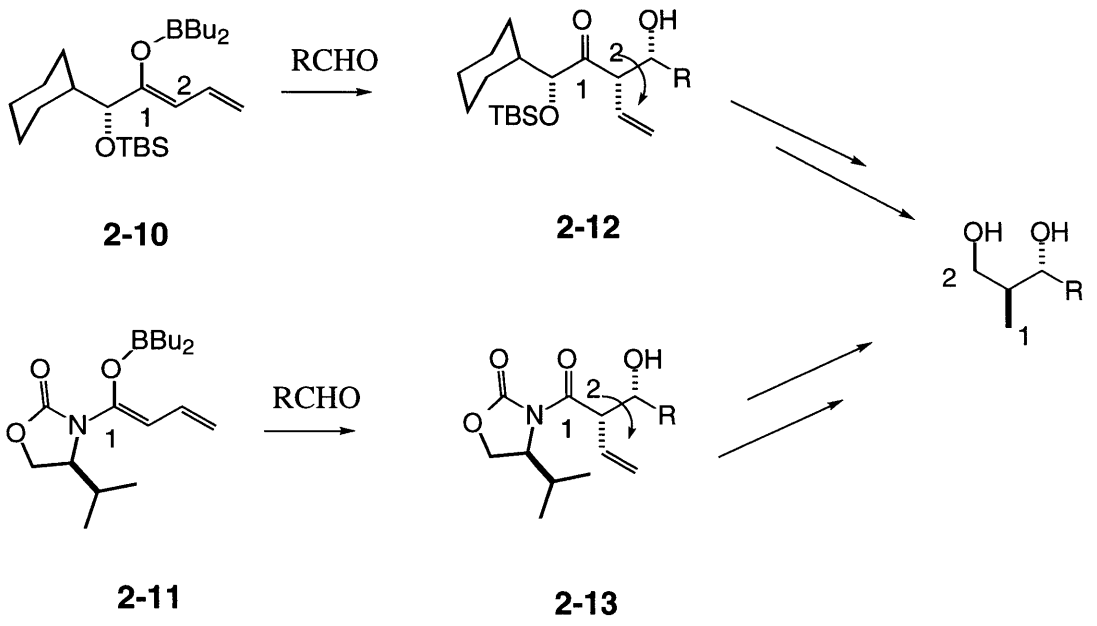
2-9

Ghosh

Before the discovery of the boron mediated *anti*-selective aldol reaction using the norephedrine based chiral ester reagent in the Masamune laboratories in 1997 (see Chapter 4),[14] most *anti*-aldol subunits were constructed by indirect means. For example, chiral enolates such as **2-10**[15] and **2-11**[16] react with aldehydes in a *syn*-selective manner to give aldols **2-12** and **2-13**, respectively (Scheme 2.6). Then cleavage of the auxiliary, deoxygenation at C1 and ozonolysis/reduction of the terminal olefin accomplish the net transformation of an *anti*-selective aldol reaction.

Scheme 2.6

Indirect Routes to *Anti*-aldol Subunits



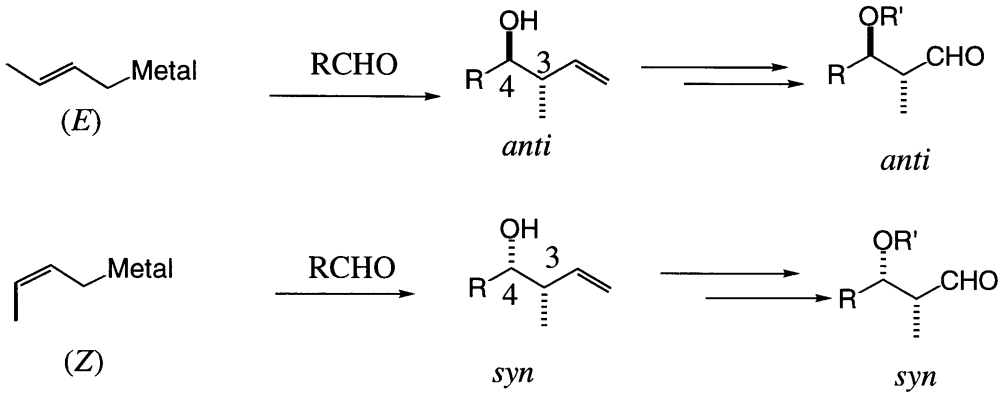
2-10 **2-12**

2-11 **2-13**

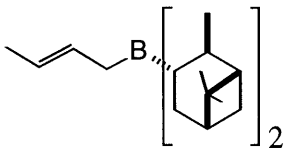
Crotyllation of aldehydes with chiral crotylmetal reagents constitutes an alternative approach for the construction of both *syn*- and *anti*-aldol subunits (Scheme 2.7).[17] The geometry of double bonds in the crotylmetal reagents can be transmitted into the products as long as the reactions proceed via closed, cyclic transition states. Specifically, the *E* reagents generate the C3-C4 *anti* relationship, while the *Z* reagents provide the C3-C4 *syn* diastereomer. Several useful chiral (*E*)-crotylmetal reagents are now available for the stereoselective synthesis of the *anti*-aldol subunits,[17a] and two such reagents (**2-14**,[17b,c,f] **2-15**[17d,e]) are presented in Scheme 2.7.

Scheme 2.7

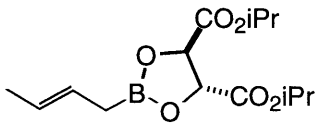
Crotylmetallation of Aldehydes



R'=protecting group



Brown **2-14**

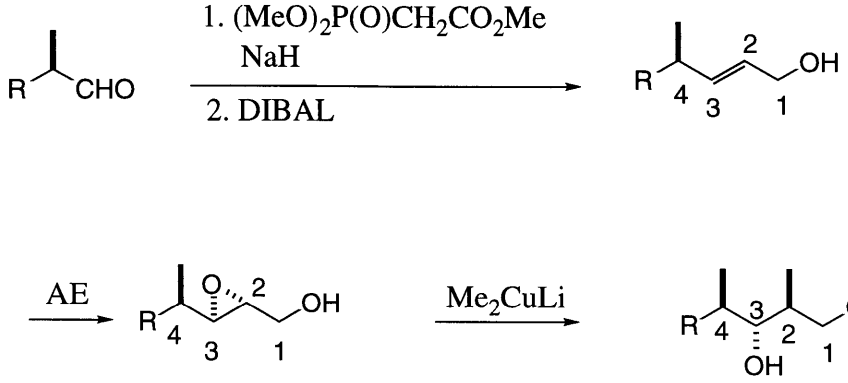


Roush **2-15**

Another commonly employed indirect method to achieve the apparent *anti*-aldol transformation requires four synthetic operations with Sharpless asymmetric epoxidation (AE)[9] and the ring opening by Me_2CuLi as the key steps (Scheme 2.8).[18] It should be pointed out that the presence of the methyl group at C4 is critical because it controls the regiochemistry of the ring opening.[18] Without this methyl group, the last step in this sequence gives a significant amount (~30%-50%) of the undesired 1, 2-diol besides the desired 1, 3-diol. Usually these two regio-isomers cannot be separated by chromatography.

Scheme 2.8

Sharpless AE Followed by Epoxide Opening



The above discussion shows that the indirect methods often require multiple synthetic steps, thus leading to inefficient synthesis. Therefore a general and reliable method for the direct elaboration of the *anti*-aldol subunits is highly desirable. Indeed this was one of the major problems encountered at the outset of the miyakolide project, because miyakolide contains two *anti*-aldol linkages (C11-C12 and C22-C23).

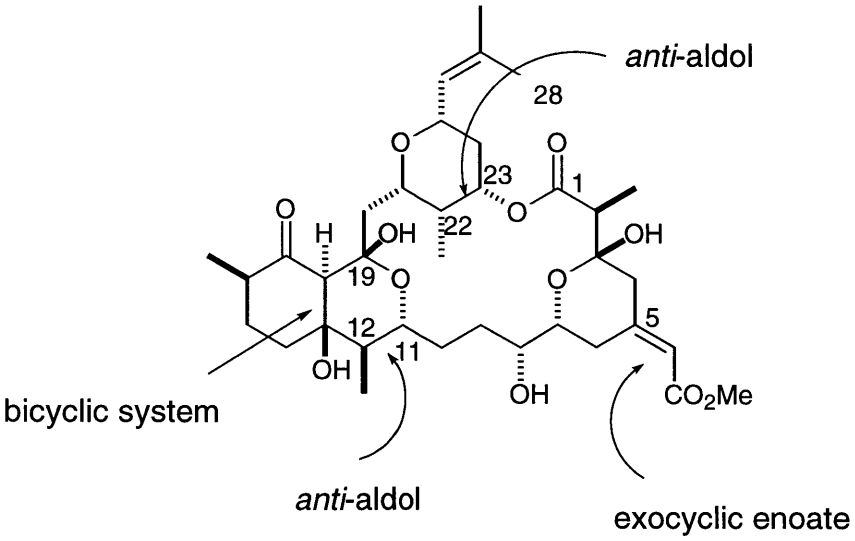
Chapter 3

Retrosynthesis of Miyakolide

3.1 Overview of the disconnection of miyakolide

Upon close inspection, several unique structural features in the miyakolide framework were identified (Scheme 3.1) : 1) the stereochemical relationships of the methyl and hydroxy groups at both C11-C12 and C22-C23 are *anti*, which call for the *anti*-selective aldol reactions; 2) the control of the geometry of the exocyclic enoate at C5 is challenging; 3) the C11-C19 bicyclic system appears very fragile. The construction of these structures present challenges and will be addressed in the retrosynthetic analysis.

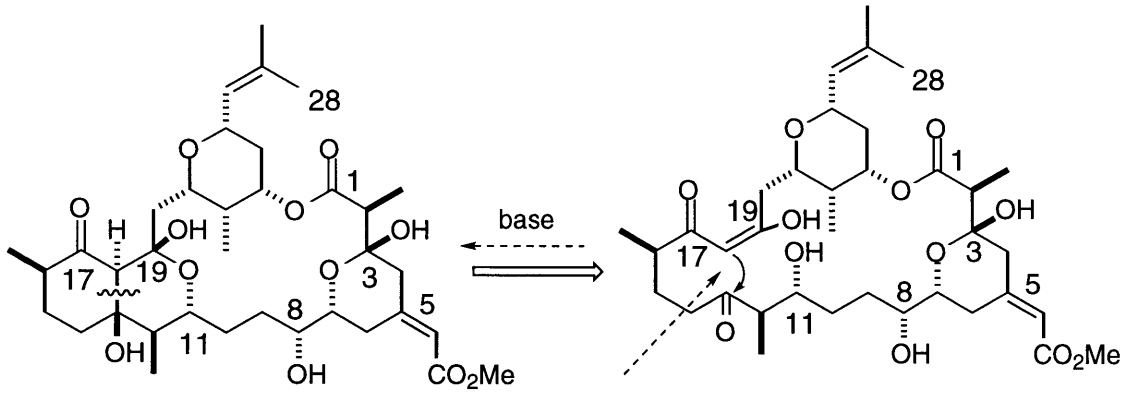
Scheme 3.1



miyakolide (**1-1**)

The retrosynthesis of miyakolide starts with the sensitive bicyclic portion of the molecule (C11-C19). The C13-C18 bond could conceivably be constructed using an intramolecular aldol cyclization from a triketone precursor such as **3-1** (Scheme 3.2).[19] We felt that the absolute configurations of the newly formed stereogenic centers at C13, C18 and C19 in the projected transannular aldol reaction should be secured due to the fact that the bicyclic system adopts the most stable chair-chair conformation as shown by the X-ray studies on miyakolide.[4] It is also anticipated that the rigidity of the 24-membered macrocyclic lactone would hold the molecule in a favorable conformation for the reaction to occur in the desired fashion. The advantage of this proposed transannular cyclization is that the relatively sensitive aldol linkage can be incorporated in the late stage of the synthesis.

Scheme 3.2

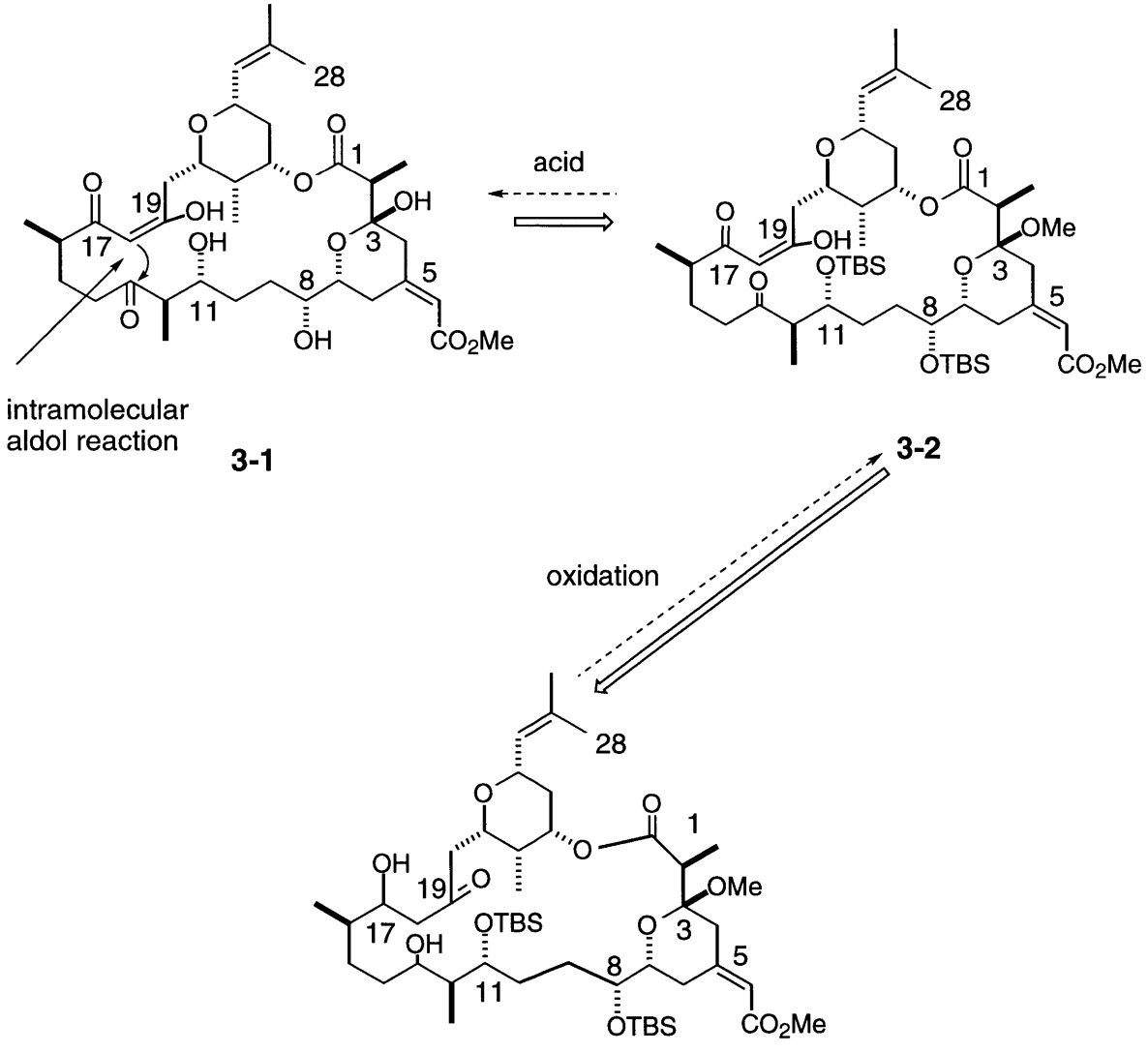


miyakolide (**1-1**)

3-1

We propose to prepare the 1, 3, 7-triketone in **3-2** by oxidizing[20] the corresponding hydroxy ketone **3-3**, as shown in Scheme 3.3. In the forward synthesis, treatment of compound **3-2** with acid would simultaneously deprotect the C8, C11 alcohols and the C3 mixed methyl ketal to deliver the intermediate **3-1**, which would then be induced to cyclize into miyakolide upon exposure to weak base.

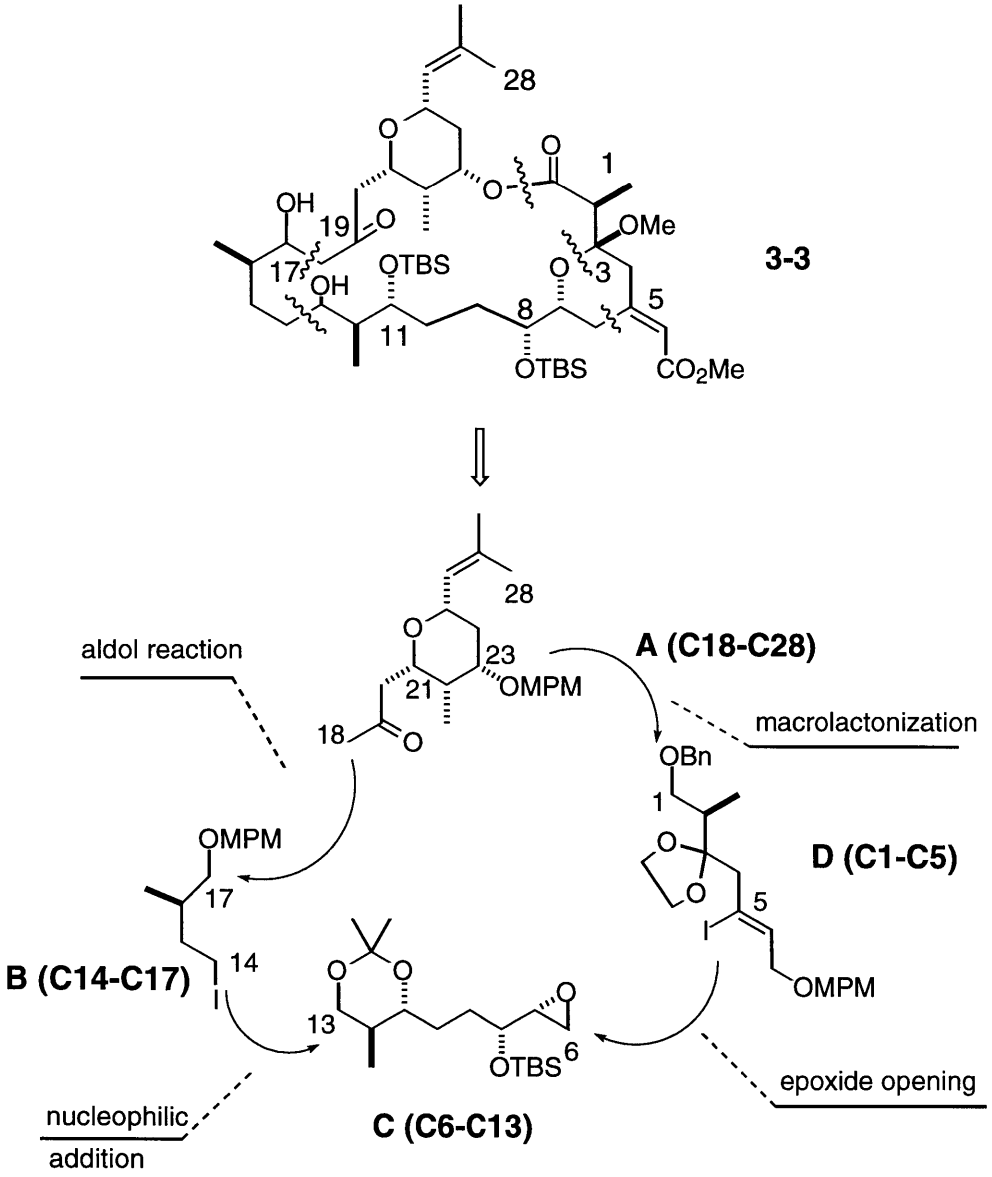
Scheme 3.3



3-3

The key synthetic intermediate **3-3** was further disconnected in a convergent manner to furnish four fragments **A** (C18-C28), **B** (C14-C17), **C** (C6-C13) and **D** (C1-C5) (Scheme 3.4). In the synthetic direction, the sequential coupling of **D**, **C**, **B**, **A** would give the fully assembled carbon skeleton of miyakolide, as indicated below. Through a few necessary manipulations, compound **3-3** could be converted into the requisite precursor **3-1** to participate in the proposed transannular aldol cyclization to reach the target molecule.

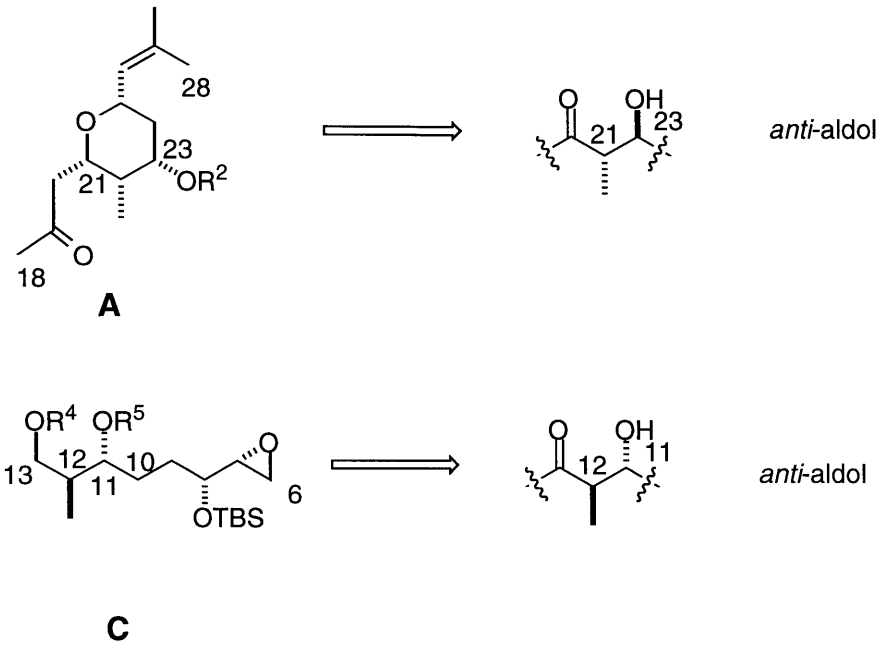
Scheme 3.4



3.2 Retrosynthesis of fragments **A** and **C**

3.2.1 *Anti*-aldol subunits in fragments **A** and **C**

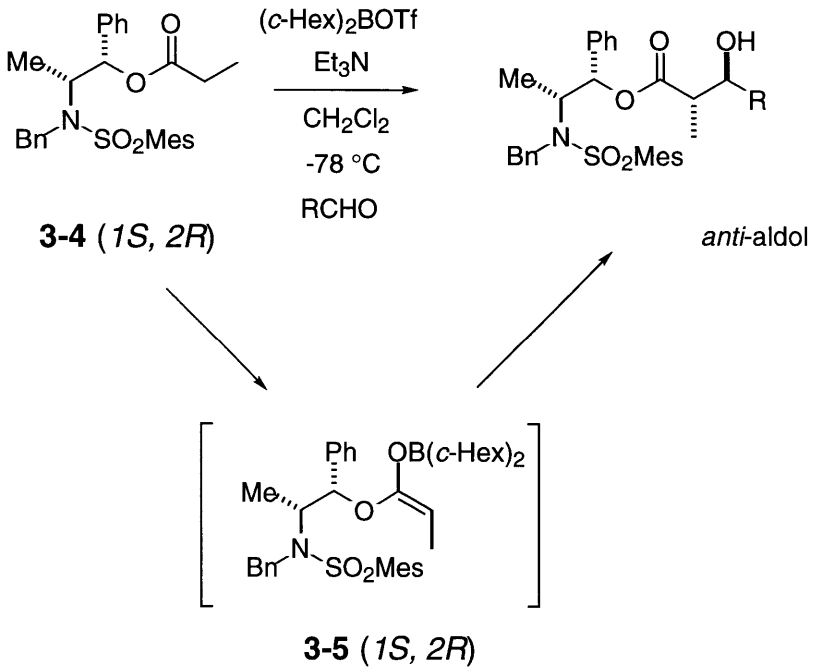
Retrosynthetic analysis revealed that both fragments **A** and **C** contain the *anti*-aldol subunits.



As discussed in Chapter 2, the synthesis of the *anti*-aldol subunit is not as straightforward as the synthesis of the *syn*-aldol counterpart. In order to construct this stereochemical subunit efficiently, new chiral reagents need to be developed. This was accomplished by Drs. Abiko and Liu in the Masamune laboratories. They found that the enolization of the chiral ester **3-4** with dicyclohexylboron triflate and triethylamine led to the formation of the *E*(*O*) enolate **3-5** selectively and upon reaction with aldehydes, it gave *anti*-aldols with excellent enantio- and diastereoselectivities (Scheme 3.5, see Chapter 4 for more discussion).[14] This timely discovery provided an excellent methodology for the construction of the *anti*-aldol subunits existing in fragments **A** and **C** of miyakolide.

Scheme 3.5

A New Chiral Auxiliary for *Anti*-selective Aldol Reactions

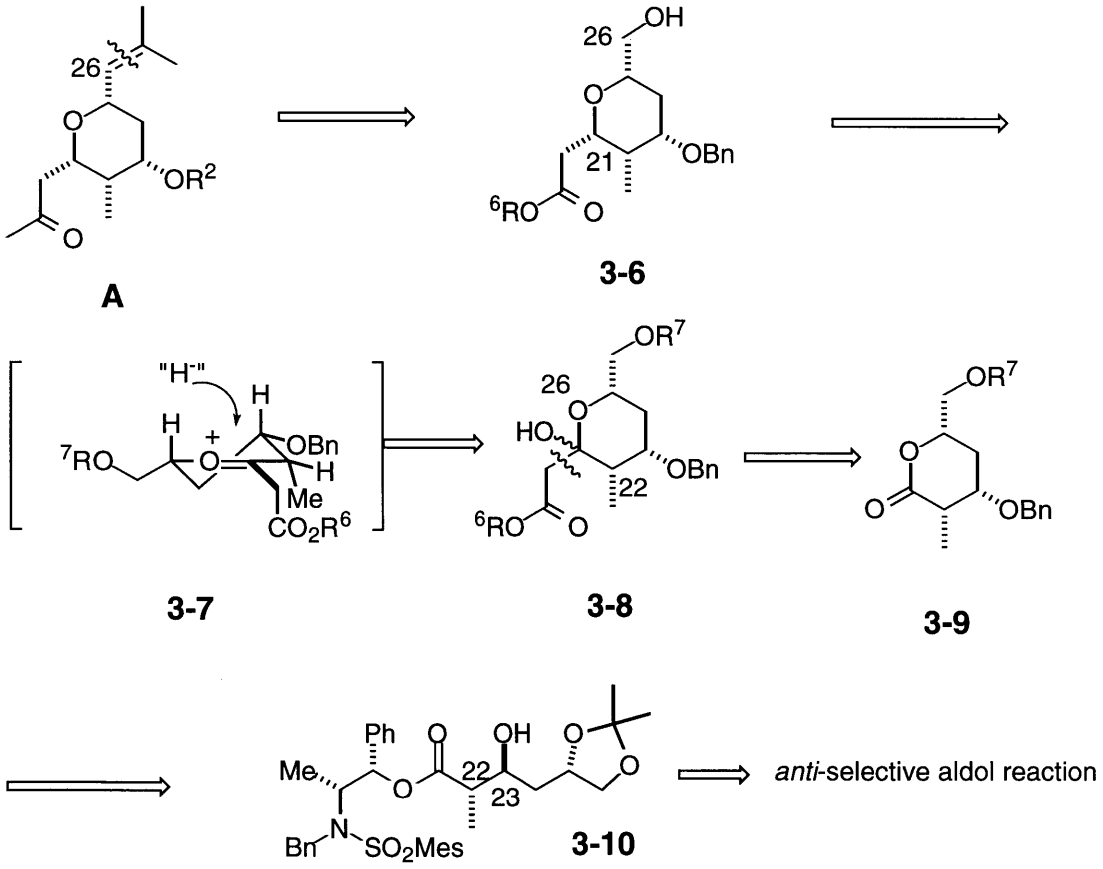


It should also be noted that the frequently employed method, i.e. a sequence of reactions involving Sharpless AE followed by the ring opening with Me_2CuLi, cannot be applied to the synthesis of either fragment **A** or fragment **C**, because there are no methyl groups at C24 and C10 to dictate the regiochemistry of the ring opening.[18] The aldol approach seems to be the only rational choice.

3.2.2 Retrosynthesis of fragment **A**

Compound **3-6** was considered as a viable intermediate which could be manipulated into fragment **A** through a few standard synthetic operations including a Wittig olefination at C26 (Scheme 3.6). The stereogenic center at C21 could, in principle, arise from a substrate-controlled hydride addition into an oxonium ion, such as **3-7**, which could be generated from the hemiketal **3-8** under the influence of a Lewis acid. The stereochemical course of this type of reactions has been well documented.[21] In the present case, both the anomeric and the steric effects (the axially positioned methyl group at C22) are expected to favor the desired facial selectivity. Retrosynthetic scission across the C20-C21 bond then delivered the lactone **3-9** which could be prepared by applying the asymmetric *anti*-selective aldol reaction.

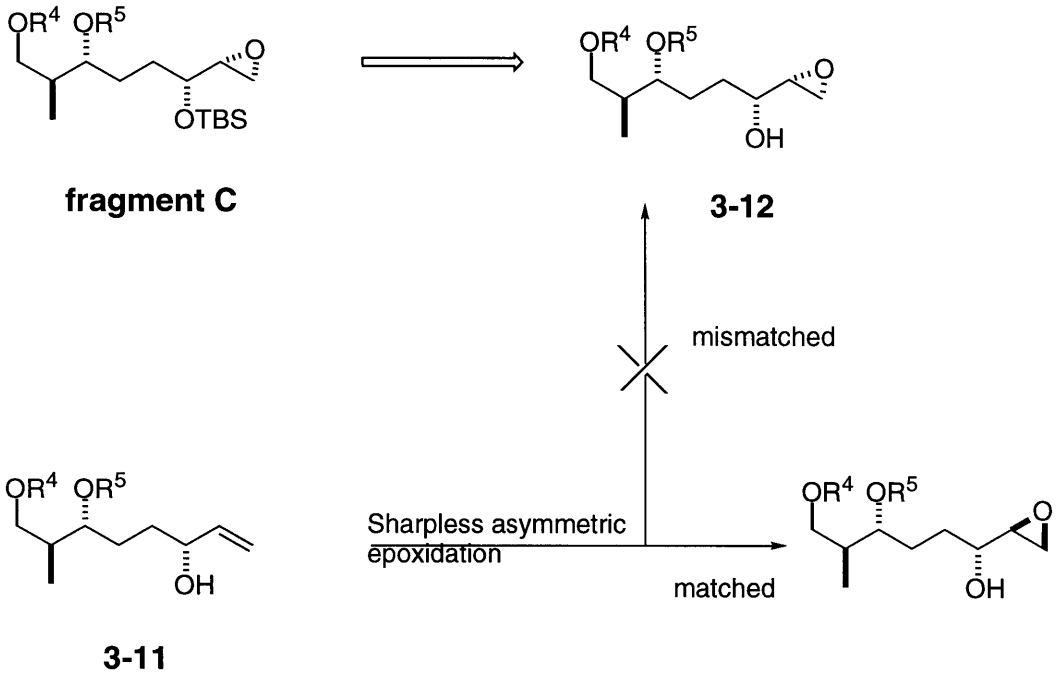
Scheme 3.6



3.2.3 Retrosynthesis of fragment **C**

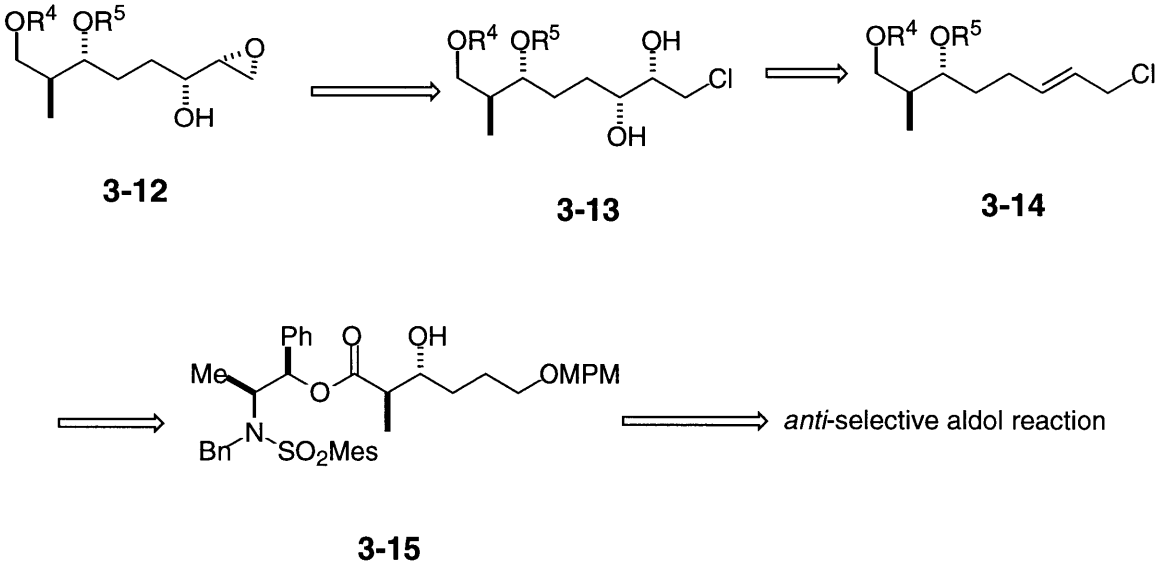
In the asymmetric epoxidation of chiral 1-substituted allylic alcohols (secondary allylic alcohols) with Sharpless epoxidation catalyst, kinetic resolution occurs. Therefore, only one of the two possible diastereomeric α-hydroxy epoxides could be obtained with good stereoselectivities.[9b] In the present case, Sharpless AE on the chiral allylic alcohol **3-11** leading to the desired α-hydroxy epoxide **3-12** happens to be a mismatched double asymmetric reaction predicted by the Sharpless empirical mnemonic (Scheme 3.7).[9b]

Scheme 3.7



Alternatively, this functionality could be obtained from the ring closure of the chlorohydrin **3-13**, which could be constructed using a Sharpless AD reaction[22a] from the corresponding allylic chloride **3-14** (Scheme 3.8).[22b] Compound **3-14** would then be synthesized from the *anti*-aldol **3-15**.

Scheme 3.8



The retrosyntheses of fragments **B** and **D** are straightforward and will be discussed later in the appropriate chapters.

Chapter 4

Fragment A Synthesis

4.1 Development of the chiral reagent for the *anti*-selective aldol reactions

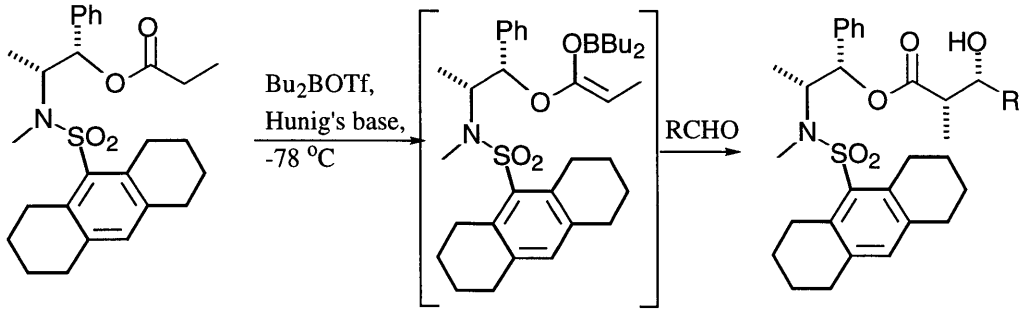
As pointed out in Chapter 3, the successful synthesis of fragment **A** is very much due to the development of a new chiral reagent **3-4** for the asymmetric *anti*-selective aldol reactions. This development was achieved by Drs. Abiko and Liu[14] and is outlined in this section.

For many years, it has been assumed that simple carboxylic esters cannot be enolized with the use of a dialkylboron trifluoromethanesulfonate and an amine, reagents which are commonly used for the enolization of other carbonyl compounds such as ketones and thioesters.[10a,23] During the course of their research, Drs. Abiko and Liu unexpectedly discovered that carboxylic esters can be enolized under these "standard conditions" and react with aldehydes to give aldols in high yields.[24]

More importantly, the geometry of the enolate can be controlled by the judicious choice of enolization conditions. The combination of dibutylboron triflate and diisopropylethylamine leads to the predominant formation of the *Z*(*O*)-enolate of the parent ester. After screening a series of propionate esters bearing different chiral alcohol residues, it was found that the chiral *Z*(O)-enolate derived from the chiral ester **4-1**[25] showed the best diastereofacial selectivities (ds for *syn* >97:3) in the *syn*-selective aldol reactions with aldehydes (Scheme 4.1).

On the other hand, the enolization of an ester with dicyclohexylboron triflate and triethylamine affords the corresponding *E*(*O*)-enolate selectively. Through a systematic screening, the chiral *E*(O)-enolate **3-5** derived from the chiral ester **3-4** was found to exhibit excellent diastereofacial selectivities (ds for *anti* >95:5) in the *anti*-selective aldol reactions with a variety of aldehydes (Scheme 4.1).[14]

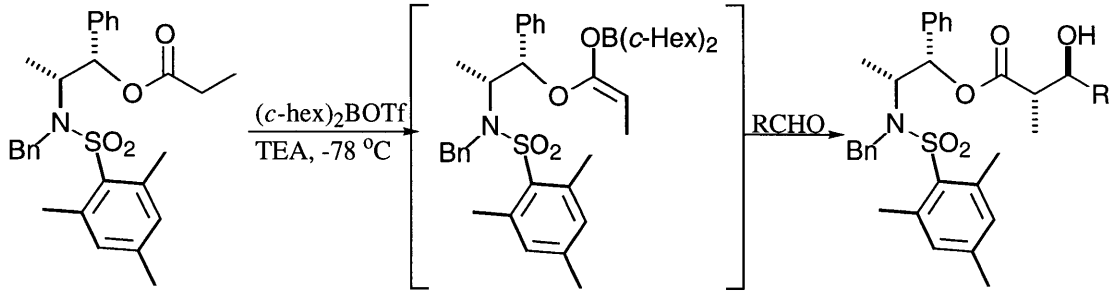
Scheme 4.1



4-1

syn -aldol reagent

syn:*anti* 95:5; ds for *syn* 97:3



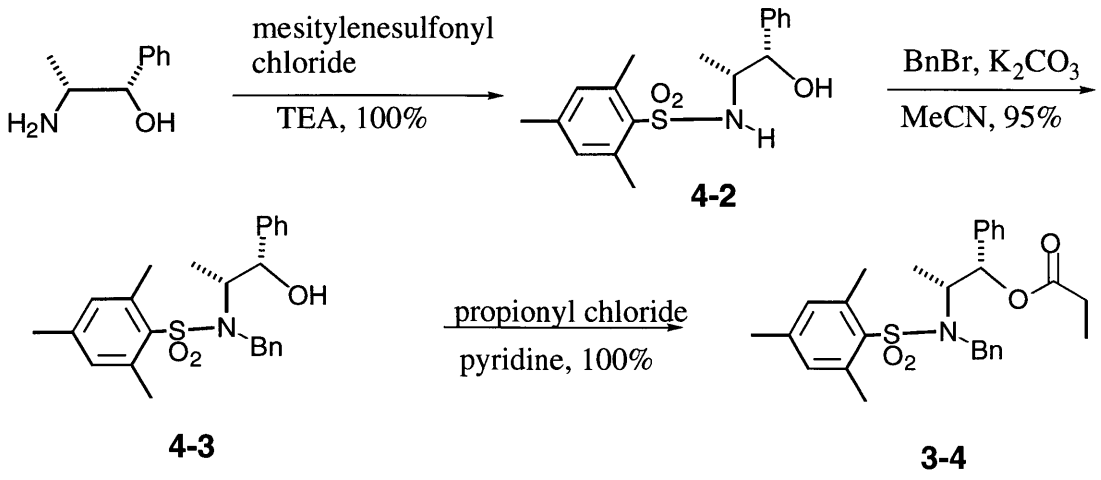
3-4 **3-5**

anti-aldol reagent

anti:*syn* >97:3; ds for *anti* >95:5

Several advantageous features of the boron mediated *anti*-selective aldol methodology using **3-4** are easily noticed. The reagent is prepared in three easy steps from the inexpensive starting material norephedrine (Scheme 4.2).[14] All intermediates including **3-4** are crystalline compounds and no chromatography is needed for purification. After serving in the aldol reaction, the chiral auxiliary **4-3** can be recovered in nearly quantitative yield. It has also been shown that no Lewis acid catalyzed reaction pathway is available in this type of aldol reactions. Therefore it should be, in principle, applicable to highly oxygenated substrates without the complication of unwanted chelations.

Scheme 4.2



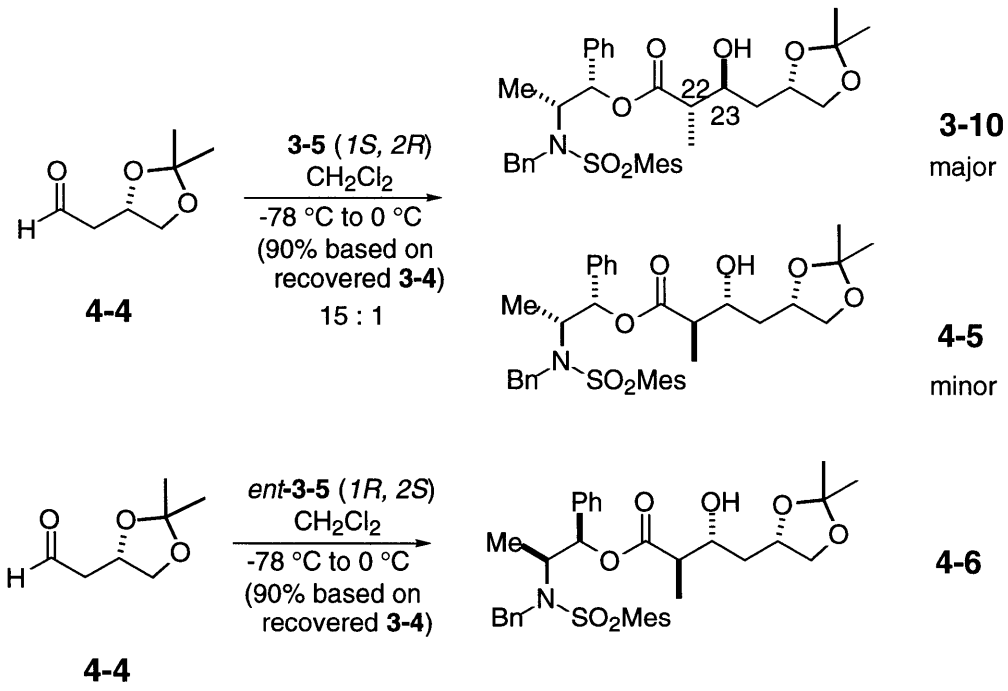
4-2 **4-3** **3-4**

4.2 Double asymmetric *anti*-selective aldol reactions in fragment **A** synthesis[26]

The construction of the stereogenic centers at C22 and C23 in fragment **A** requires a double asymmetric *anti*-selective aldol reaction.

Scheme 4.3

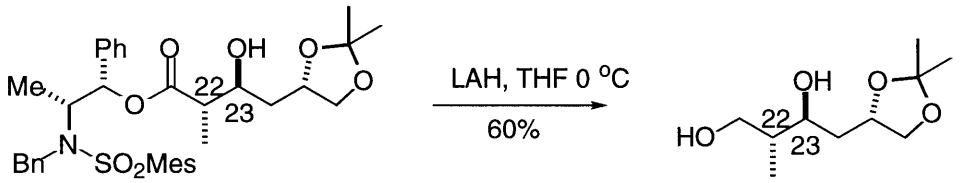
Double Asymmetric *Anti*-selective Aldol Reactions



4-4 **3-10** major **4-5** minor **4-6**

Chiral aldehyde **4-4** [27] was allowed to react with the enol borinate **3-5** (*1S, 2R*) under the optimized conditions to provide the *anti*-aldol **3-10** along with compound **4-5** as the minor isomer in a ratio of 15:1, whereas the reaction of **4-4** with the *ent*-**3-5** (*1R, 2S*) resulted in the formation of the *anti*-aldol **4-6** as the only detectable isomer (Scheme 4-3). This result is noteworthy because it implies that the directing effect of the chiral enol borinate **3-5** is high enough to overcome the intrinsic stereochemical bias of the chiral aldehyde, thereby dictating the stereochemical outcome in both matched and mismatched double asymmetric aldol reactions.[6] Reagent **3-4** meets the stringent demand set by the reagent-controlled strategy and constitutes a general and reliable method for the construction of the *anti*-aldol subunits in the synthesis of complex structures.

Scheme 4.4



3-10 **4-7**

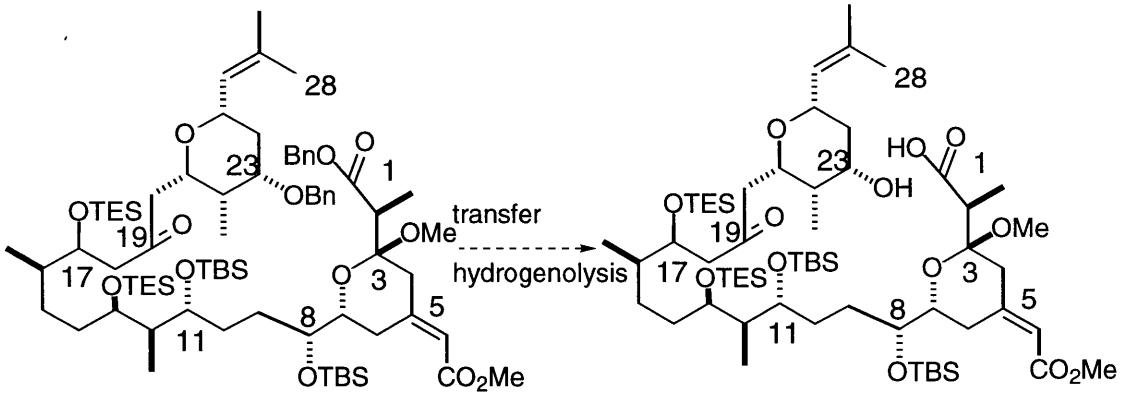
The major aldol isomer **3-10** was readily separated from the minor isomer **4-5** by column chromatography. Then the chiral auxiliary was reductively cleaved by LAH to give the diol **4-7** (Scheme 4.4).

4.3. A note on the protecting group for the C23 alcohol

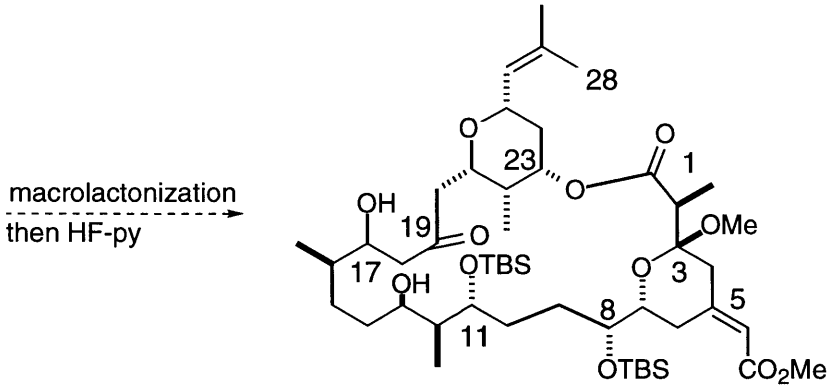
In our planned synthesis of the target molecule, the C23 alcohol and the C1 carboxylic acid need to be liberated selectively in the presence of the trisubstituted double bond at C26-C27 and the exocyclic enoate at C5 for the macrolactonization. At the outset of

the project, we had planned to protect the C23 alcohol as its benzyl ether and the C1 carboxylic acid as its benzyl ester (**4-8**, Scheme 4.5) and had hoped that the mild conditions such as transfer hydrogenolysis[28] would deprotect the benzyl ether and benzyl ester simultaneously to deliver the free hydroxy acid **4-9** for the macrocyclization. This protecting group arrangement was based on literature precedents[28, 29] and was expected to simplify the isolation and purification of the polar free hydroxy acid. Accordingly, fragment **A** was synthesized with the C23 alcohol protected with a benzyl group.

Scheme 4.5



4-8 **4-9**



3-3

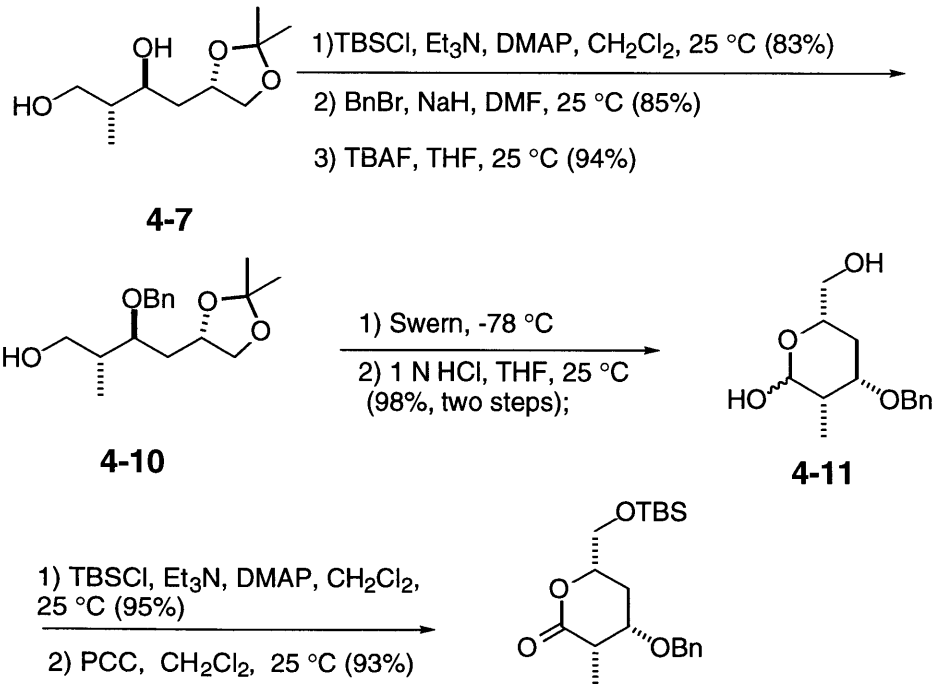
However, it was found recently that the deprotection of the benzyl ether proved to be problematic in the presence of the exocyclic enoate at C5. While benzyl ester could be

removed efficiently by transfer hydrogenolysis, the deprotection of the benzyl ether under these and several other sets of conditions was slow and always accompanied by the partial reduction of the α, β-unsaturated ester at C5. These results raised the concern that the benzyl group might cause problems later in the synthesis. Therefore the syntheses of the C23 benzyloxy-fragment **A** as well as the C23 *p*-methoxybenzyloxy-fragment **A** are both described below.

4.4 Completion of fragment **A** synthesis

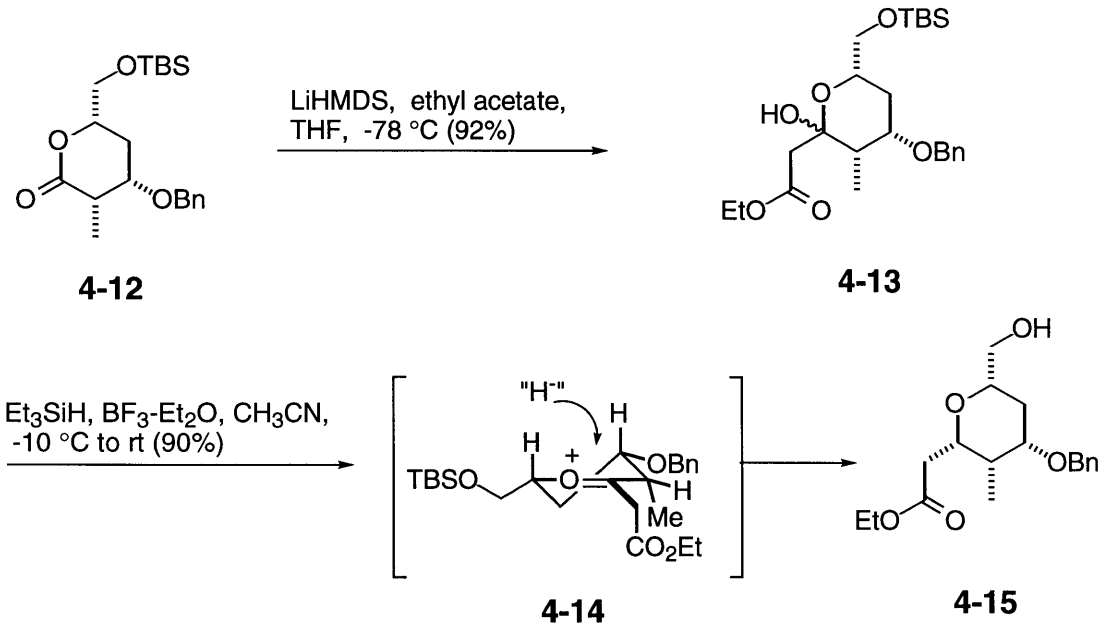
Standard protecting group manipulation of the diol **4-7** afforded the primary alcohol **4-10** which was then oxidized to the aldehyde using Swern oxidation[30] (Scheme 4.6). Acid hydrolysis of the acetonide (1 N HCl/THF), followed by *in situ* cyclization, gave hemiacetal **4-11** in good yield. Selective silylation of the primary alcohol and PCC oxidation[31] of the lactol furnished the key intermediate lactone **4-12**.

Scheme 4.6



As planned, the last stereogenic center (at C21) in fragment **A** was introduced by a substrate-controlled stereoselective reduction (Scheme 4.7). Treatment of lactone **4-12** with lithium ethyl acetate in THF gave the expected aldol adduct **4-13** which was then reduced with triethylsilane at -10 °C in the presence of boron trifluoride etherate, via an intermediate oxonium ion **4-14**, to furnish compound **4-15** as the major diastereomer (ds>95:5).[21] Under these conditions the primary TBS group was cleanly removed. The excellent selectivity observed in the reduction step was attributed to the synergistic action of the anomeric and steric effects as expected.

Scheme 4.7

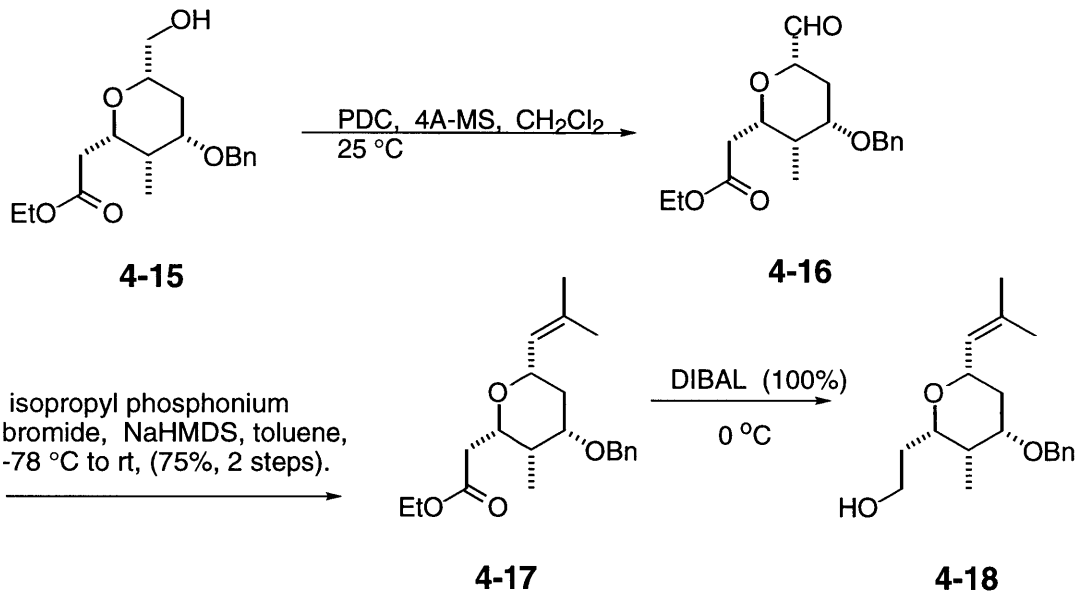


4-12 **4-13** **4-14** **4-15**

The oxidation of the alcohol **4-15** to the corresponding aldehyde **4-16** proved to be problematic (Scheme 4.8). Conditions such as Swern oxidation,[30] PCC [31] and Dess-Martin oxidation[20b] gave either a complicated mixture of several compounds or rapid decomposition of the aldehyde product upon workup. Finally it was found that oxidation

with PDC[32] and filtration through a florisil column afforded the desired aldehyde in fairly good yield. Reaction time longer than one hour resulted in the partial oxidation of the C23 benzyl ether to the benzoyl ester. It is also very important not to let the aldehyde stay on the florisil column for longer than 15 minutes. A mixture of 30% ethyl acetate in hexane, not ethyl ether, was found to be the most effective in flushing the aldehyde off the column in a short time. The labile aldehyde was then used immediately in the subsequent Wittig olefination.

Scheme 4.8



4-15 **4-16** **4-17** **4-18**

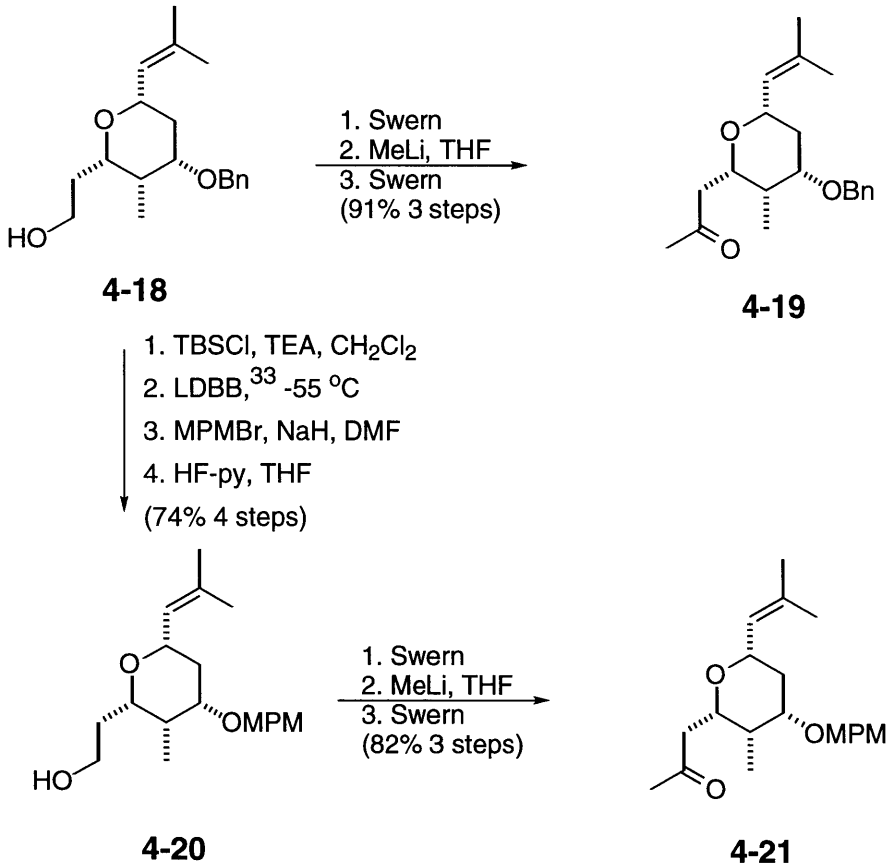
The generation of the isopropylidenephosphorane was best accomplished by treating the isopropyl phosphonium bromide with NaHMDS in toluene at 0 °C (Scheme 4.8). The aldehyde reacted with the isopropylidenephosphorane at -78 °C instantly to form the betaine, which collapsed gradually at room temperature to give the desired olefin **4-17**. The combination of other bases and solvents such as *n*-BuLi/THF resulted in the slow deprotonation of the isopropyl phosphonium bromide and sluggish nucleophilic addition of

the formed isopropylidenephosphorane to the aldehyde even at 0 °C. The longer reaction time has caused the decomposition of the unstable aldehyde.

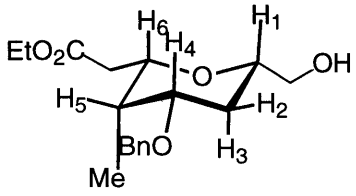
Reduction of **4-17** with DIBAL then gave the alcohol **4-18** in quantitative yield.

The synthesis diverged at this point to give either the C23 benzyloxy fragment **A** (**4-19**) or the C23 *p*-methoxybenzyloxy fragment **A** (**4-21**) through a few standard synthetic operations as shown in Scheme 4.9.

Scheme 4.9

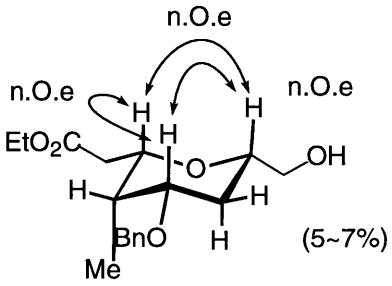


To ensure our stereochemical assignment of fragment **A**, ^{1}H NMR spectra of both compounds **4-15** and **4-17** have been analyzed. The coupling constants and nOe measurements are shown below.

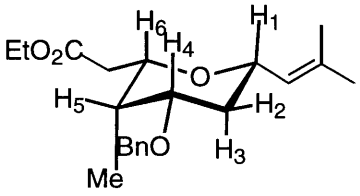


$J_{1,2}$ (ae)=3.8 Hz
$J_{1,3}$ (aa)=11.4 Hz
$J_{2,4}$ (ae)=5.0 Hz
$J_{3,4}$ (aa)=11.3 Hz
$J_{4,5}$ (ae)=5.0 Hz
$J_{5,6}$ (ae)=1.9 Hz

4-15

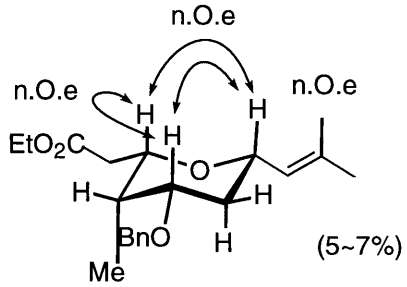


4-15



$J_{1,2}$ (ae)=1.9 Hz
$J_{1,3}$ (aa)=11.5 Hz
$J_{2,4}$ (ae)=4.6 Hz
$J_{3,4}$ (aa)=11.6 Hz
$J_{4,5}$ (ae)=4.6 Hz
$J_{5,6}$ (ae)=1.8 Hz

4-17



4-17

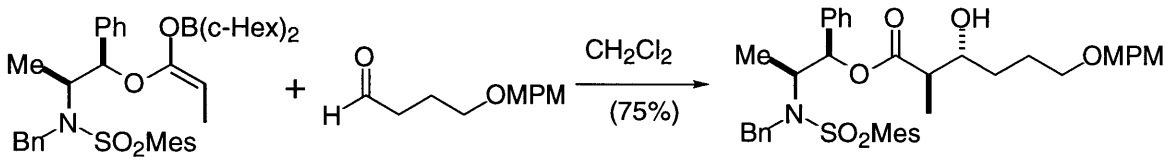
Chapter 5

Fragment C Synthesis

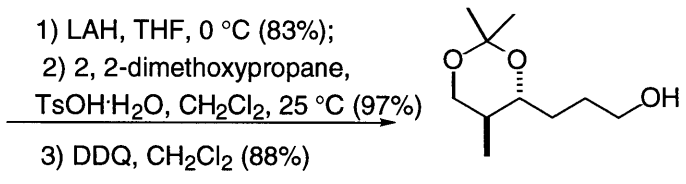
5.1 *Anti*-selective aldol reaction in fragment **C** synthesis[26]

The synthesis of fragment **C** involves another asymmetric *anti*-selective aldol reaction[14] and a Sharpless asymmetric dihydroxylation (AD).[22] The readily synthesized aldehyde **5-1**[34] was treated with the chiral enol borinate *ent*-**3-5** (*1R, 2S*) to give the *anti*-aldol **3-15** in 75% yield with good selectivity (*ca.* 13:1 on a 36 mmole scale, Scheme 5.1). The major isomer **3-15** was obtained in pure form after chromatography. After the reductive removal of the auxiliary, the diol was protected as its acetonide. Then the MPM group was deprotected to give the alcohol **5-2**.[35]

Scheme 5.1



(*ent*)-**3-5** **5-1** **3-15**



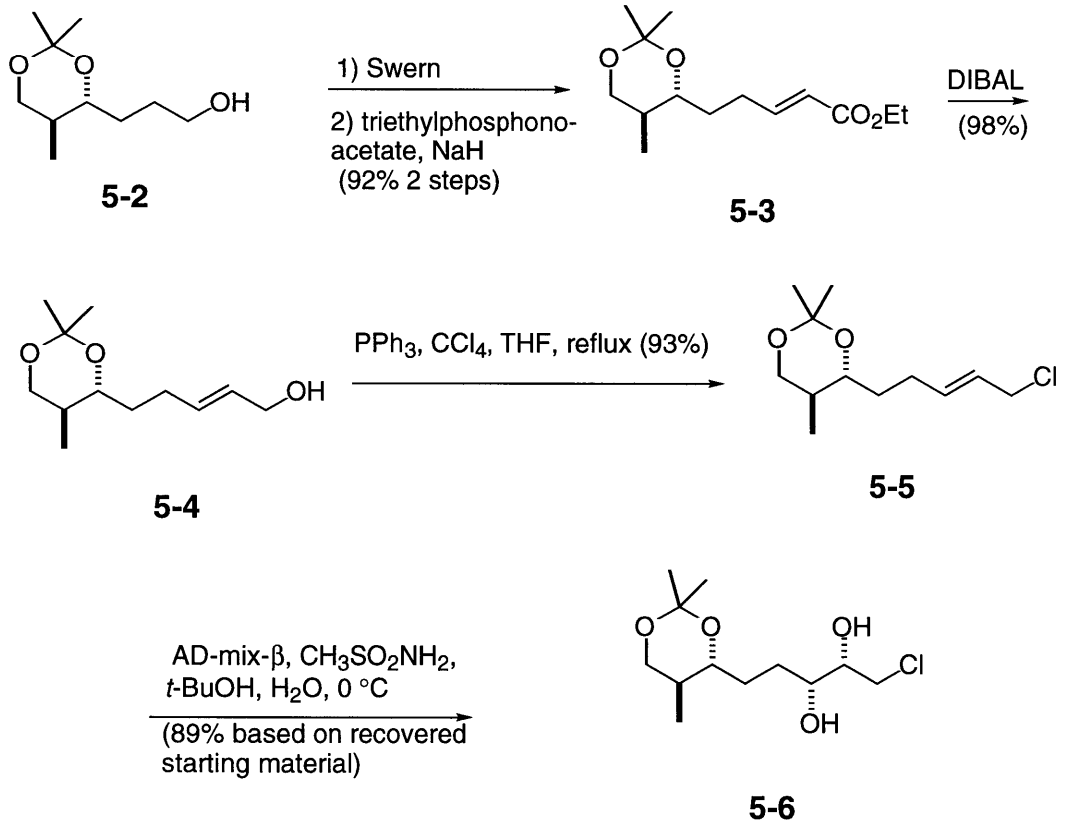
5-2

The synthesis of fragment **C** was first achieved by Dr. G.-Q. Wang, and later modified and improved by the author.

5.2 Completion of fragment **C** synthesis

Compound **5-2** was converted into the α, β-unsaturated ester **5-3** through an HWE reaction. Reduction of the ester and halogenation (Ph_3P, CCl_4, THF, reflux)[36] of the resulting allylic alcohol **5-4** proceeded uneventfully to deliver the allylic chloride **5-5** which was then subjected to the so-called "buffered" Sharpless dihydroxylation conditions (AD-mix-β, $CH_3SO_2NH_2$, $NaHCO_3$, *t*-BuOH/H_2O, Scheme 5.2).[22b]

Scheme 5.2

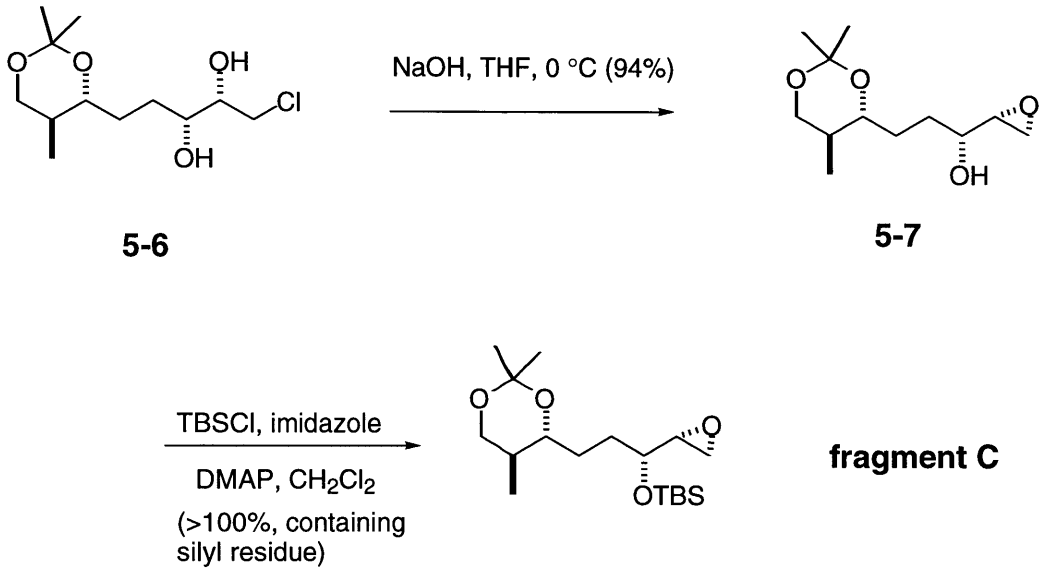


5-2 **5-3** **5-4** **5-5** **5-6**

Sharpless and coworkers have found that the use of $NaHCO_3$ greatly suppressed the side reactions, such as the solvolysis of the allylic chloride and the closure of the formed chlorohydrin into the epoxide. This double asymmetric reaction proceeded at 0 °C slowly yet smoothly to give the chlorohydrin **5-6** with a diastereoselectivity of ~15:1. Lower selectivity (*ca.* 6:1) was observed when the reaction was carried out at room

temperature. Dihydroxylation of the allylic chloride **5-5** using AD-mix-α gave the other isomer with a modest selectivity (*ca.* 3:1).

Scheme 5.3



5-6 **5-7** **fragment C**

Brief exposure of **5-6** to freshly pulverized sodium hydroxide in THF at room temperature led to the formation of the α-hydroxy epoxide **5-7** (94%, Scheme 5.3) which was subsequently silylated (TBSCl, imidazole, CH_2Cl_2, DMAP, >100%, containing some silyl residue) to furnish fragment **C** in excellent yield. It was noted that silylation using TBSOTf/ 2, 6-lutidine at -78 ^oC gave poor yield due to the decomposition of the starting material.

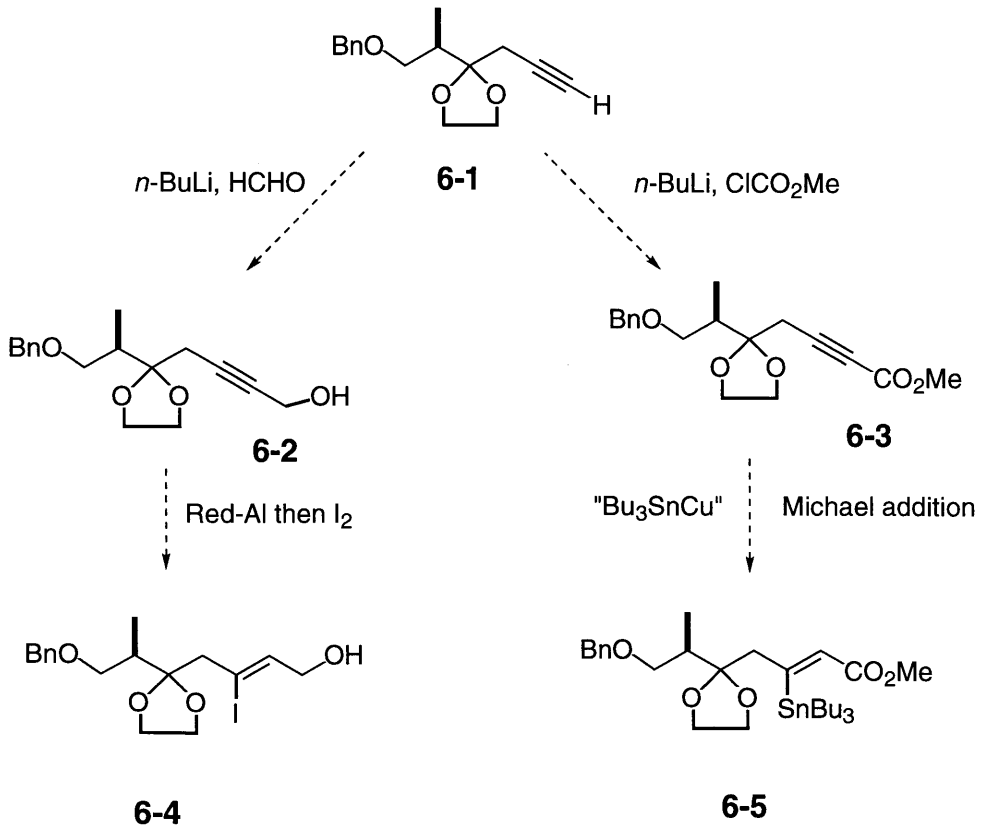
Chapter 6

Fragment D Synthesis

6.1 Strategies for the synthesis of fragment **D**

We plan to construct the trisubstituted double bond in fragment **D** by the stereoselective reduction of the propargyl alcohol **6-2** or by the stereoselective Michael addition of a "tin cuprate" to the acetylenic ester **6-3** (Scheme 6.1). Metal-halogen exchange would then deliver the requisite vinyl iodide. Both **6-2** and **6-3** could be readily prepared from the common precursor **6-1**.

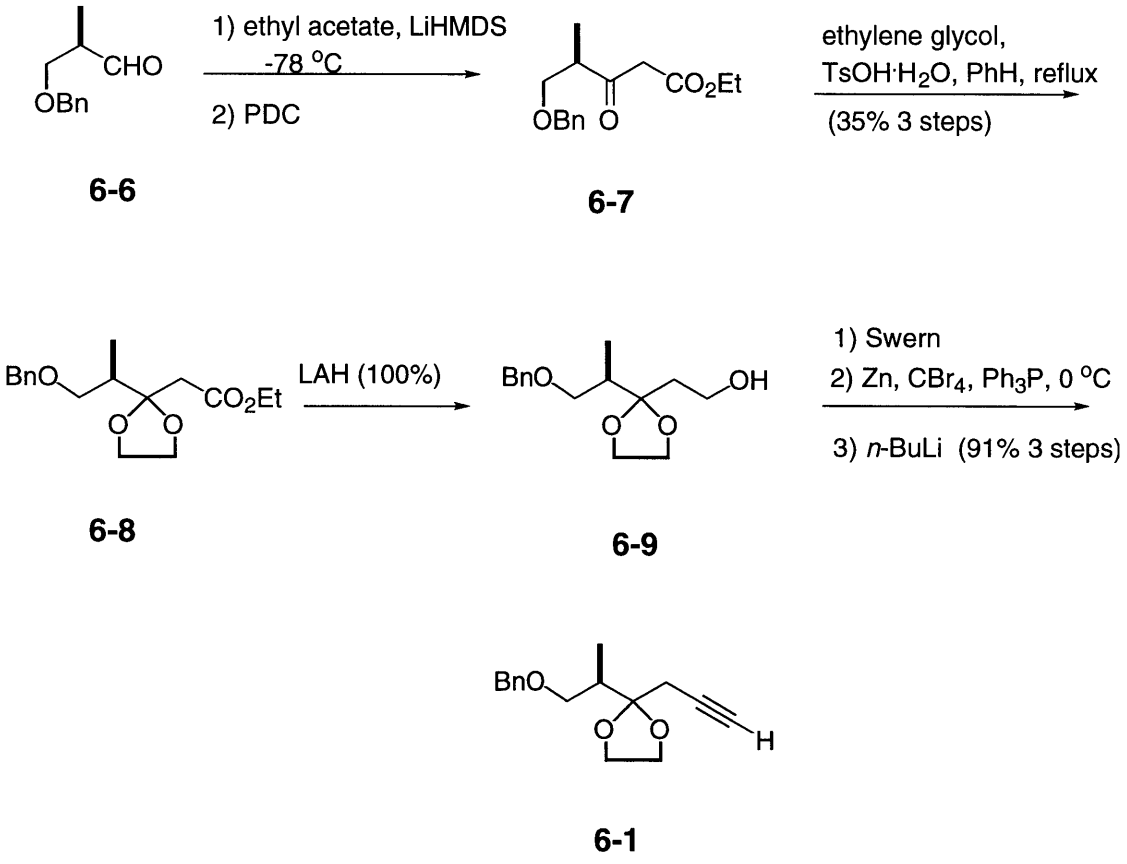
Scheme 6.1



6.2 Syntheses of the propargyl alcohol **6-2** and the acetylenic ester **6-3**

An efficient synthesis of **6-1** is depicted in Scheme 6.2. The known aldehyde **6-6** was converted into the β-keto ester **6-7** in two steps. After the ketone was protected selectively over the ester as its cyclic ketal **6-8**, the ester was reduced with LAH to give the alcohol **6-9**. Then oxidation of **6-9** to the aldehyde and one carbon elongation[37] furnished the key acetylene **6-1** in very good yield.

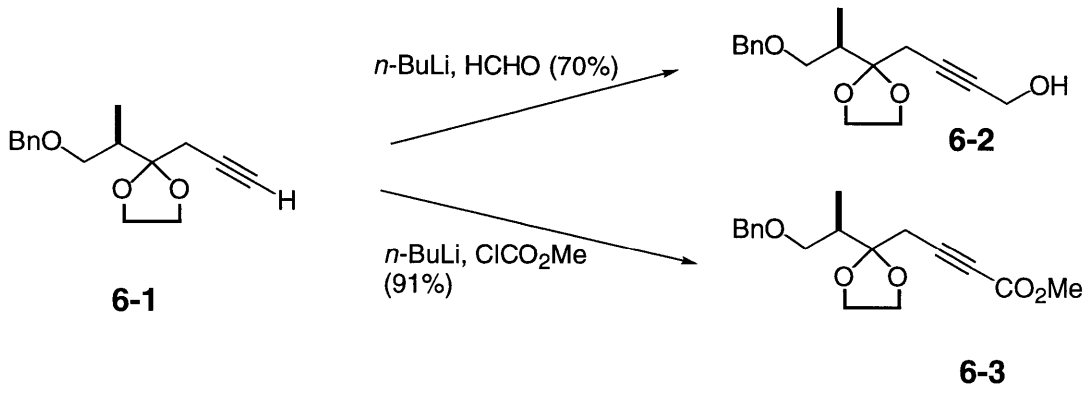
Scheme 6.2



6-6 **6-7** **6-8** **6-9** **6-1**

The lithium anion of **6-1** generated by using *n*-BuLi was then allowed to react with either formaldehyde or methyl chloroformate to provide compounds **6-2** and **6-3** for further elaboration.

Scheme 6.3



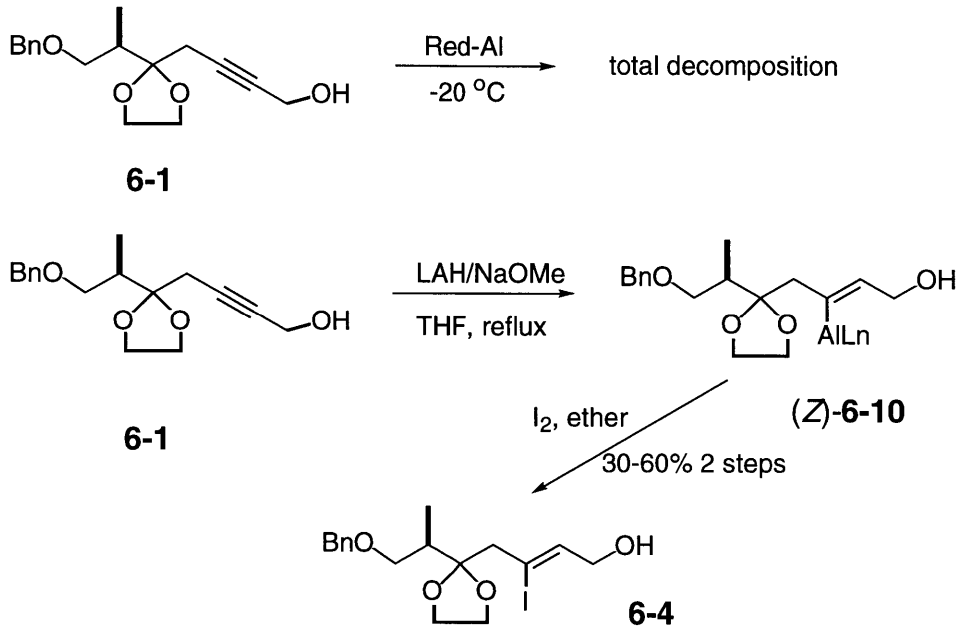
6.3 Red-Al and related reduction of the propargyl alcohol **6-2**

The Red-Al type reduction of the propargyl alcohol **6-2** was first attempted. The original protocol for the hydroxy group directed hydride reduction of propargyl alcohols using LAH/NaOMe in refluxing THF was described by Corey.[38] More recently Denmark[39] reported that Red-Al effected the same transformation at lower temperature with better yield and selectivity.

To our surprise, the Red-Al reduction of the propargyl alcohol **6-2** gave total decomposition even at -20 °C. Reduction of **6-2** using Corey's protocol (LAH/NaOMe/60 °C, Scheme 6.4) gave the expected alanate (*Z*)-**6-10** and its *E* isomer in a ratio of 9:1, which was then converted into the desired vinyl iodide **6-4** by treatment with I_2. These results are puzzling because the "harsher " conditions proved to be more productive. We suggested that the stronger Lewis acidity of Red-Al than that of LAH might be held responsible for the decomposition of the substrate in the reaction. Although the vinyl iodide **6-4** can be obtained using the LAH/NaOMe method, the yield is variable and

unsatisfactory (~ 30-60%). It was concluded that this route is not optimal for the efficient construction of the trisubstituted double bond.

Scheme 6.4

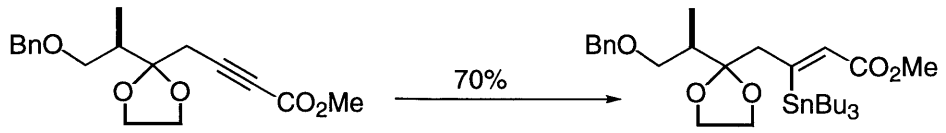


6.4 Michael addition of a "tin cuprate" to the acetylenic ester **6-3**

Alternatively, the trisubstituted double bond can be constructed by using a Michael addition reaction of a "tin cuprate" to the acetylenic ester such as **6-3**. The geometry of the resulting double bond can be controlled by using either the kinetic or the thermodynamic conditions.[40]

Thus $Bu_3SnBuCNCuLi_2$, generated by using Bu_3SnH, *n*-BuLi and CuCN,[40b] was allowed to react with the acetylenic ester **6-3** under thermodynamic conditions to give, after quenching with MeOH, the desired *Z*-olefin **6-5** as the single isomer in good yield (Scheme 6.5).

Scheme 6.5



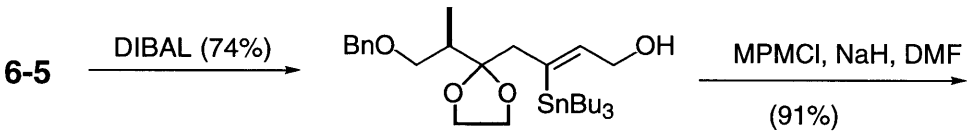
6-3 **6-5**

The geometry of the double bond was determined to be *Z* based on the observed Sn-H coupling constant (J_{Sn-H}=110 Hz) in the ^{1}H NMR spectrum of **6-5**.

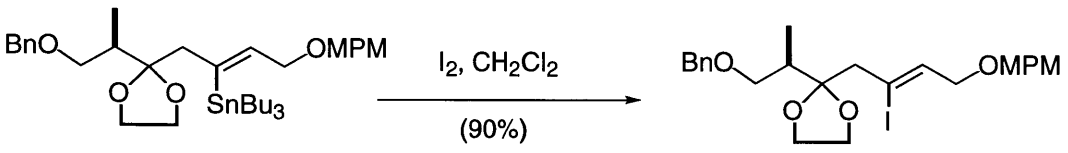
6.5 Completion of fragment **D** synthesis

With **6-5** in hand, the ester was reduced to the allylic alcohol **6-11** using DIBAL, and then the alcohol was protected as its MPM ether **6-12** (Scheme 6.6). Finally the Sn-I exchange furnished fragment **D** in high yield.

Scheme 6.6



6-11



6-12 **fragment D**

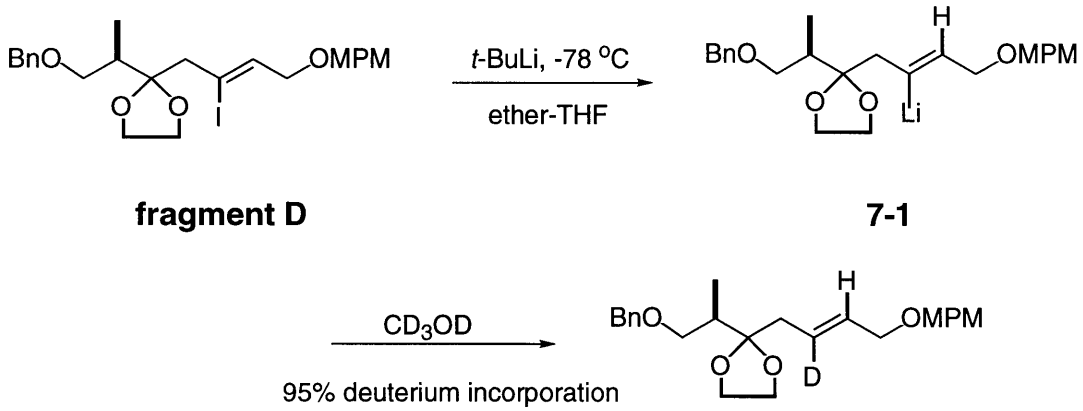
Chapter 7

Attempted Coupling of Fragments D and C

7.1 Generation of the vinyl anion from fragment **D**

The planned coupling of fragments **D** and **C** involves the regioselective opening of the epoxide in fragment **C** by the vinyl anion **7-1** derived from fragment **D**.[41] Among several sets of conditions examined, the treatment of the vinyl iodide using 2.1 eq of *t*-BuLi in ether/THF (10:1) gave the desired vinyl lithium **7-1** in nearly quantitative yield (Scheme 7.1).[42] This was confirmed by quenching the vinyl anion with CD_3OD. The isotopic incorporation is determined by ^1H NMR to be greater than 95%.

Scheme 7.1

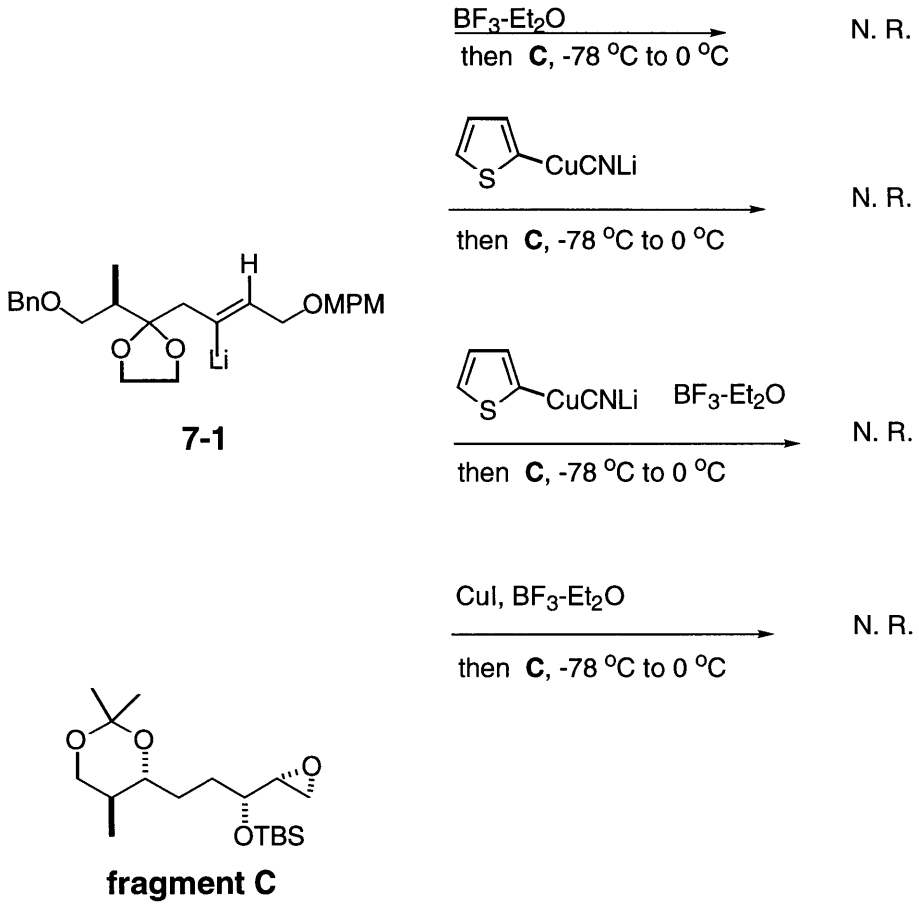


7.2 The nucleophilicity of the vinyl anion generated from fragment **D**

With the vinyl anion **7-1** secured, the coupling of fragments **D** and **C** was attempted. We were disappointed to find that no reaction occurred under several sets of coupling conditions (Scheme 7.2). These results were disturbing and raised the concern that the reactivity of the vinyl anion **7-1** is unexpectedly low towards alkylating agents.

Scheme 7.2

Attempted Coupling of Fragments D and C



7-1

fragment C

After extensive experimentation, it was found that the vinyl anion **7-1** did react with reactive electrophiles such as aldehydes and MeI, but it proved to be unreactive towards epoxides and unactivated alkyl iodide. In view of these results, we decided to abandon this coupling strategy and redesign our synthesis based on the available fragments.

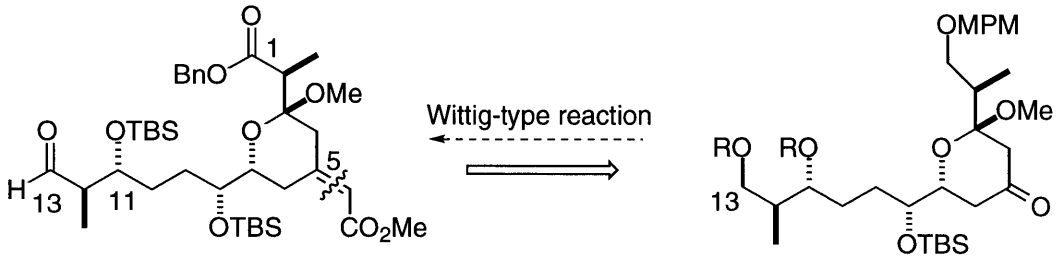
Chapter 8

Revised Retrosynthesis of Miyakolide

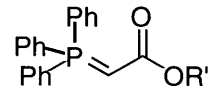
8.1 Revised strategy for the construction of the exocyclic enoate at C5

The low nucleophilicity of the vinyl anion **7-1** led us to revise our strategy for the construction of the exocyclic enoate in the C1-C13 segment. In this context a more straightforward method, i.e. the Wittig-type olefination[43] of a ketone such as **8-1**, was considered (Scheme 8.1).

Scheme 8.1

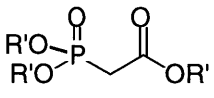


C1-C13 segment **8-1**



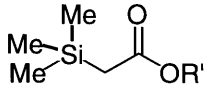
Wittig reagent

8-2



HWE reagent

8-3



Peterson reagent

8-4

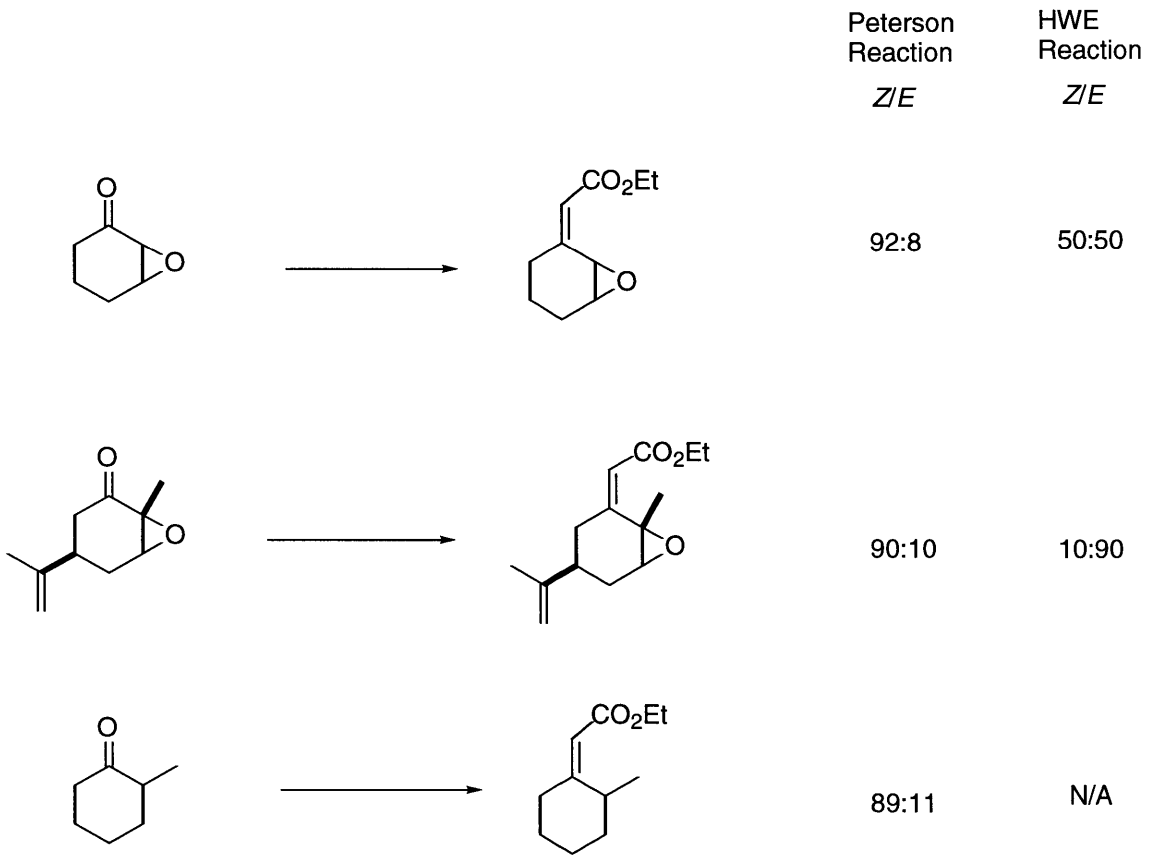
Conventionally, the stereoselective introduction of an exocyclic enoate, such as in the miyakolide framework, through the Wittig-type olefination relies on the proper selection of reagents and reaction conditions. It is generally accepted that the reactions between a carbonyl compound and the Wittig reagent **8-2** or the HWE reagent **8-3** are reversible and

usually favor the formation of the olefin with the *E* configuration which is thermodynamically more stable than the *Z* isomer.[43] For carbonyl compounds such as aldehydes or ketones with different substitutions at the α and α' positions, excellent to modest *E*-selectivities have been observed. However, for ketones with no substitutions at the α and α'-positions such as **8-1**, no such selectivity was anticipated for their reactions with reagents **8-2** or **8-3**.

In recent years, the Peterson reaction[44] has become an increasingly important alternative to the Wittig or HWE reactions for the stereoselective preparation of conjugated olefinic compounds. One of the distinct advantages of the Peterson reaction is that the stabilized α-silyl carbanions are generally more reactive than the corresponding phosphorus stabilized carbanions and therefore the Peterson reaction involves the irreversible addition of the stabilized α-silyl carbanion to the carbonyl group followed by the elimination of the four-membered ring intermediate to give the α, β-unsaturated carbonyl compounds. The irreversibility of the nucleophilic addition to the carbonyl group in the first step often results in different *Z*/*E*-selectivities from those observed in the Wittig or HWE reactions. Indeed it has been reported[45] that in several cases, good *Z*-stereoselectivities were achieved in the Peterson reactions between reagent **8-4** and α-substituted-α'-methylene cyclohexanones where HWE reactions gave little or opposite selectivities (Scheme 8.2). Although there is no established precedent for the stereoselective Peterson reaction with α, α'-unsubstituted cyclohexanones, such as in our case, we felt that the different reactivities between reagents **8-2**, **8-3** and **8-4** would offer us different *Z*/*E*-selectivities. At least, we expected to obtain a mixture of geometric isomers enriched in the desired *E*-olefin.

Scheme 8.2

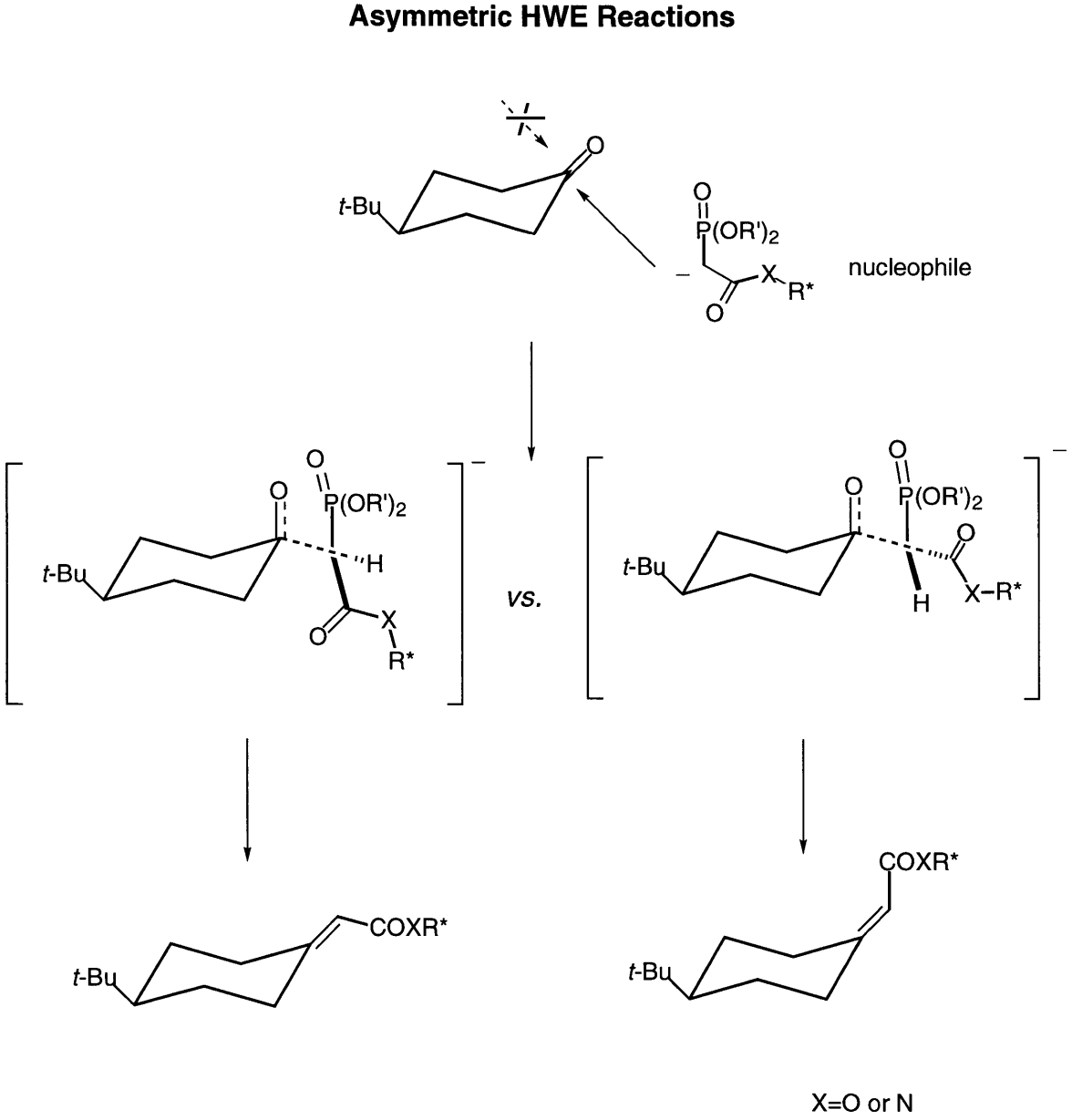
Comparison of HWE and Peterson Reactions



Besides the previously discussed substrate-controlled approach to the stereoselective introduction of the exocyclic enoate, another strategy for this transformation was also considered, in which the use of a **chiral** Wittig-type reagent controls the **geometry** of the exocyclic trisubstituted enoate.[46] In an asymmetric HWE reaction with 4-*t*-butylcyclohexanone, the nucleophile can only attack the carbonyl group from the more accessible exo-face, as indicated in Scheme 8.3. Since the nucleophile is carrying a chiral

auxiliary (R*), the two possible diastereomeric transition states should, in principle, be differentiated, thus leading to the stereoselective formation of the exocyclic α, β-unsaturated carbonyl compounds.

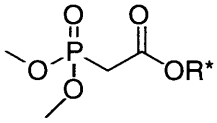
Scheme 8.3



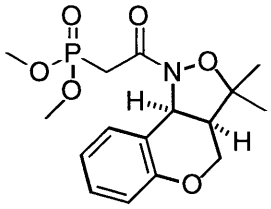
Although this approach seems to be the most direct method for the stereoselective construction of exocyclic α, β-unsaturated carbonyl compounds, the development of chiral reagents for this purpose has not been explored extensively. All of the few chiral reagents reported to date are chiral keto-phosphonates to effect asymmetric HWE reactions.[46] Two such reagents are presented in Scheme 8.4.[46a, d, e] The utility of these methodologies has not been fully demonstrated in the synthesis of complex structures. Since this reagent-controlled approach would potentially enable us to control the geometry of the exocyclic double bond by simply choosing the right enantiomer of the chiral reagents, we decided to investigate the applicability of these methods to our synthesis.

Scheme 8.4

Selected Chiral Reagents for Asymmetric HWE Reactions



8-5 R*=menthyl,
8-6 R*=8-phenyl menthyl

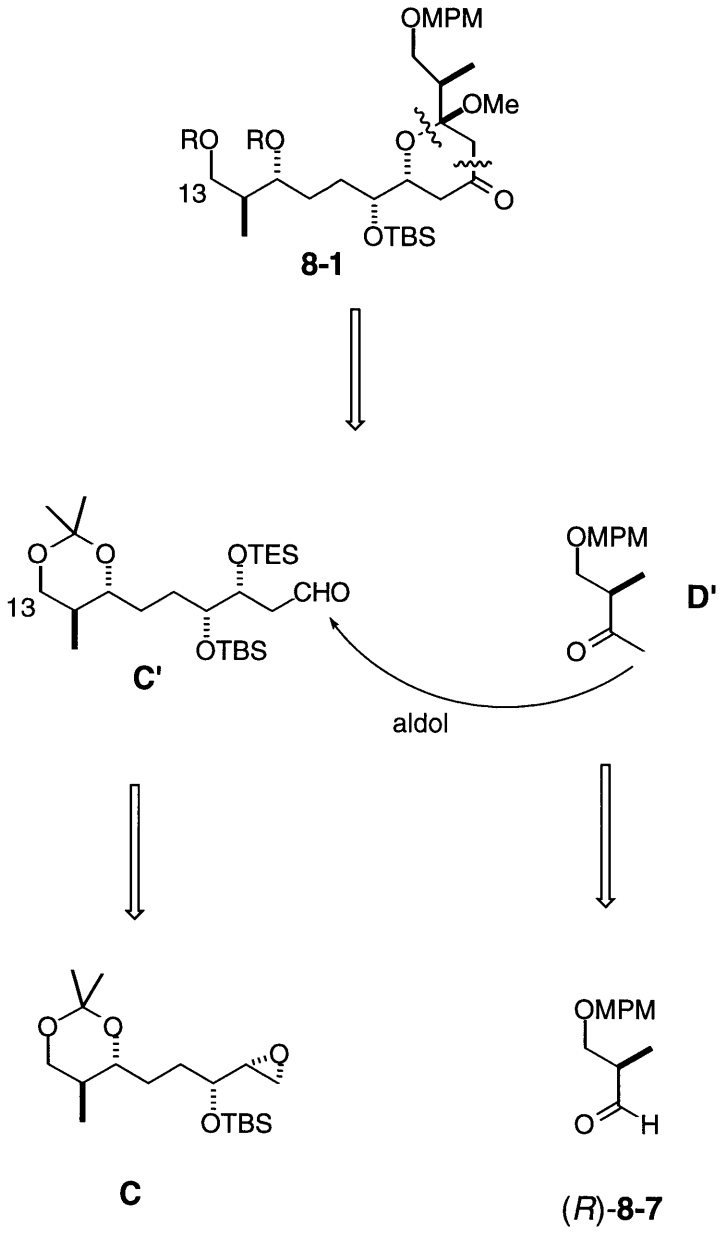


8.2 Retrosynthesis of ketone **8-1**

Ketone **8-1** was disconnected into fragments **C'** and **D'** to be joined through an aldol reaction (Scheme 8.5). Fragment **C'** could be easily prepared from fragment **C**. Fragment **D'** could be synthesized from the known aldehyde (*R*)-**8-7** as indicated. If this revised scheme works, we can make the most use of the available fragments and minimize the extra work due to this revision.

Scheme 8.5

Retrosynthesis of Ketone 8-1



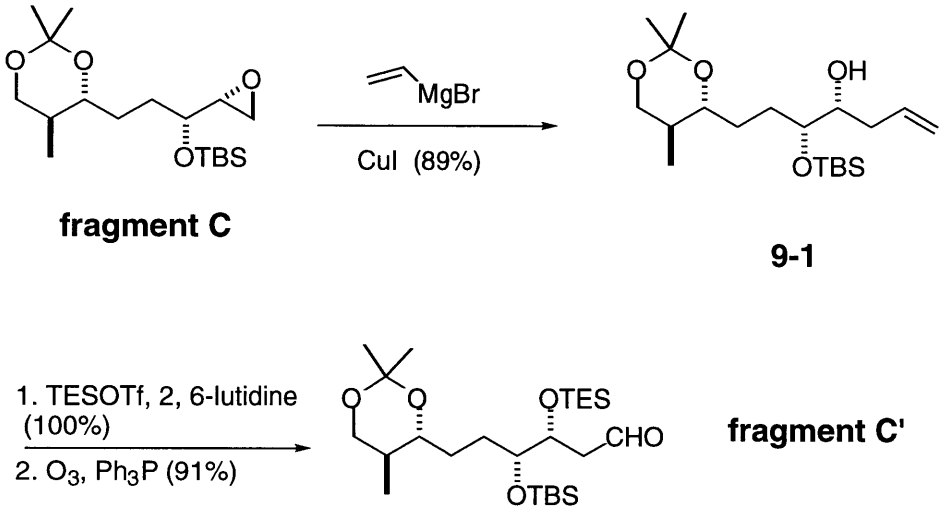
Chapter 9

Synthesis of Fragment C'D'

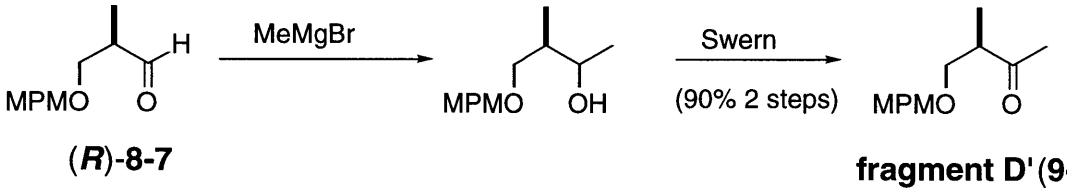
9.1 Synthesis of fragments **C'** and **D'**

Starting with fragment **C**, we synthesized fragment **C'** in three easy steps as shown in Scheme 9.1. The epoxide was regioselectively opened by vinyl Grignard reagent in the presence of a catalytic amount of CuI to give the alcohol **9-1**.[47] After the alcohol was protected as its TES ether, ozonolysis-reduction of the terminal olefin afforded the requisite aldehyde (fragment **C'**).

Scheme 9.1



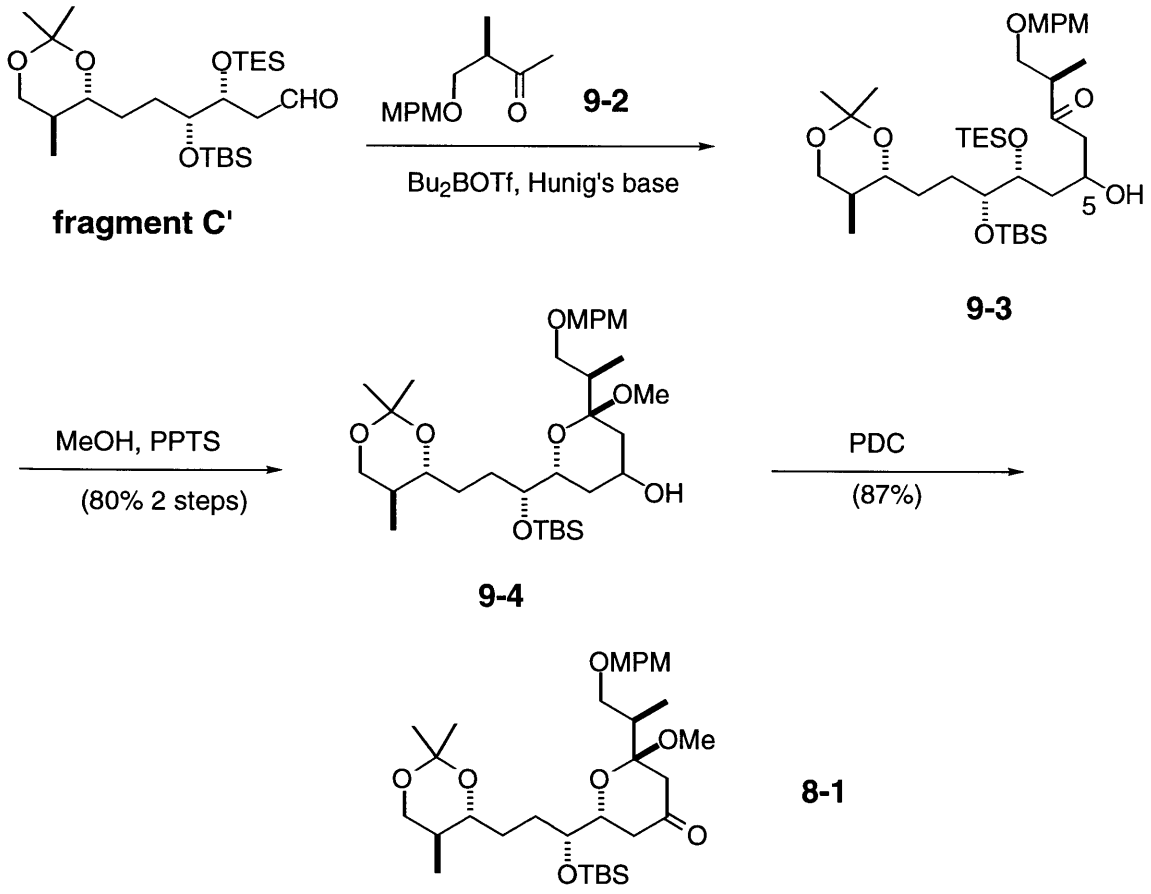
Fragment **D'** (**9-2**) was synthesized in a straightforward manner as shown below.



9.2 Synthesis of ketone **8-1**

Fragments **C'** and **D'** were coupled through an aldol reaction as planned (Scheme 9.2). Methyl ketone **9-2** was enolized with the use of Bu_2BOTf and Hunig's base and was then allowed to react with the aldehyde (fragment **C'**) to give the aldol **9-3** which appeared to be a single diastereomer by ^1H NMR analysis. The absolute stereochemistry of the C5 alcohol in compound **9-3** was not determined. Treatment of **9-3** with a catalytic amount of PPTS in methanol removed the TES group selectively, and at the same time led to the rapid formation of the mixed methyl ketal **9-4**. PDC oxidation[32] of **9-4** furnished the ketone **8-1**, which was ready for the Peterson or asymmetric HWE reactions.

Scheme 9.2

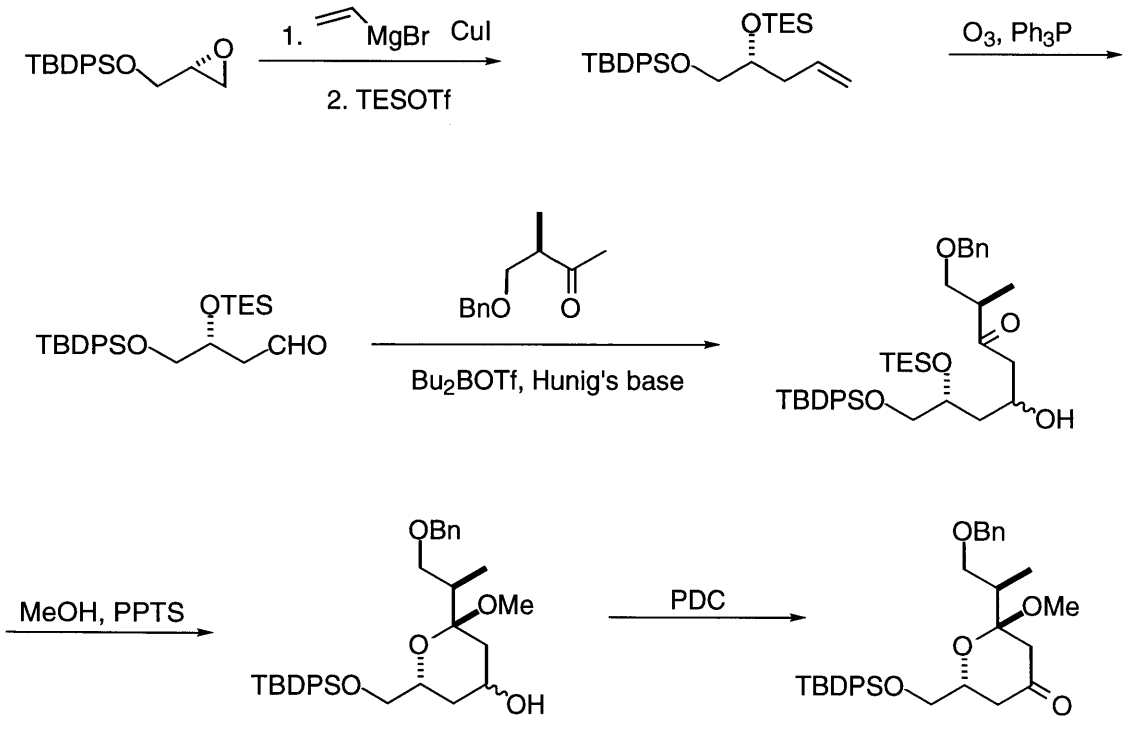


9.3 Model Studies on the Peterson and asymmetric HWE reactions

In order to gain more information about the applicability of the proposed Peterson or asymmetric HWE reactions to the ketone **8-1**, we carried out systematic studies on a model ketone **9-5**. The synthesis of **9-5** parallels that of the ketone **8-1** and is shown in Scheme 9.3.

Scheme 9.3

Synthesis of Model Ketone



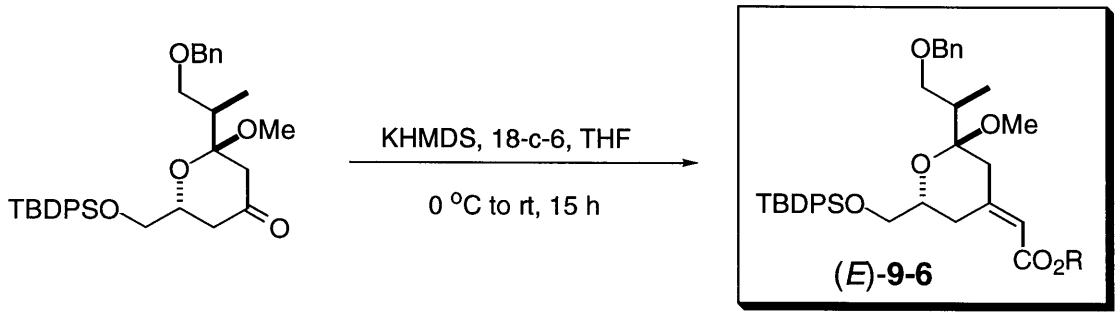
9-5

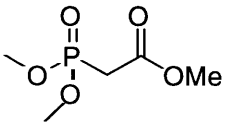
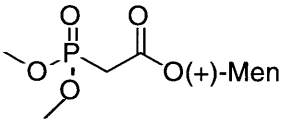
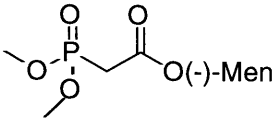
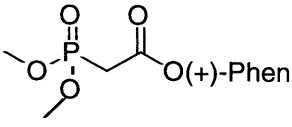
9.3.1 Asymmetric HWE reactions

The single asymmetric HWE reaction between the chiral ketone **9-5** and the achiral trimethyl phosphonoacetate provided a 1:1 mixture of (*E*)-**9-6** and (*Z*)-**9-6** (Scheme 9.4). Chiral keto-phosphonates **8-5**[46d, e] and **8-6**[46d, e] were chosen for our initial sets of

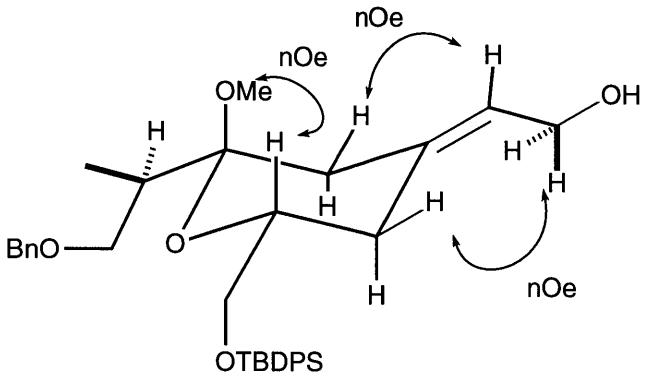
double asymmetric HWE reactions, because they are easily prepared from simple starting materials. To our satisfaction, both chiral reagents were successful in controlling the geometry of the double bond in a predictable sense with moderate selectivities (Scheme 9.4).

Scheme 9.4



		E : *Z*
		1 : 1
	**(-)-8-5**	2.3 : 1
	**(+)-8-5**	1 : 6
	**8-6**	1 : 3.3

To determine the absolute configuration of the products, compound **9-6** was reduced to the corresponding allylic alcohol **9-7**. Then the geometry of the double bond was assigned based on the nOe measurements shown below.



9-7

Although we were able to control the geometry of the double bond by applying the asymmetric HWE reactions, we also noticed that the HWE reactions proceeded very slowly even at room temperature and this has caused significant decomposition of the ketone. In view of the low reactivities of the asymmetric HWE reactions, we next turned our attention to the Peterson olefination reaction.

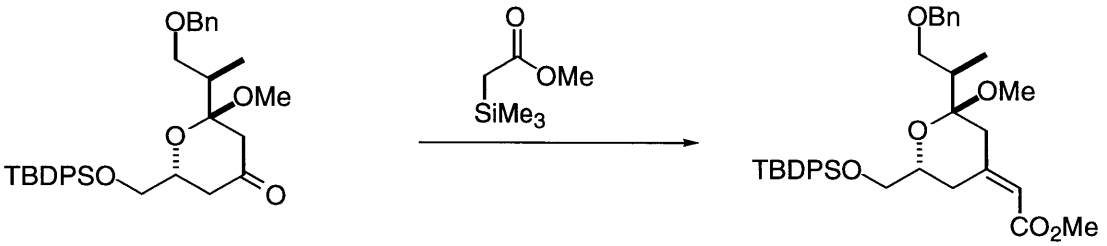
9.3.2 Peterson reaction

Unlike the HWE reaction, the Peterson reaction[44] usually proceeds at lower temperatures because of the higher reactivity of the stabilized α-silyl carbanion. The reaction between the ketone **9-5** and the lithium enolate of the α-trimethylsilyl methyl acetate occurred instantly at -78 ^{o}C to give a mixture of two isomeric enoates **9-6** with a selectivity of *E/Z*=2.6:1 (Scheme 9.5). Interestingly, when the sodium enolate of the α-trimethylsilyl methyl acetate was allowed to react with the ketone **9-5** at -78 ^{o}C, a reversed selectivity was observed (*E/Z*=1:6). Therefore, the geometry of the double bond can be controlled simply by choosing the appropriate base for the Peterson reaction. With these

results in hands, we were confident that the exocyclic enoate in the miyakolide framework could be synthesized stereoselectively.

Scheme 9.5

Peterson Reacion



(*E*)-9-6

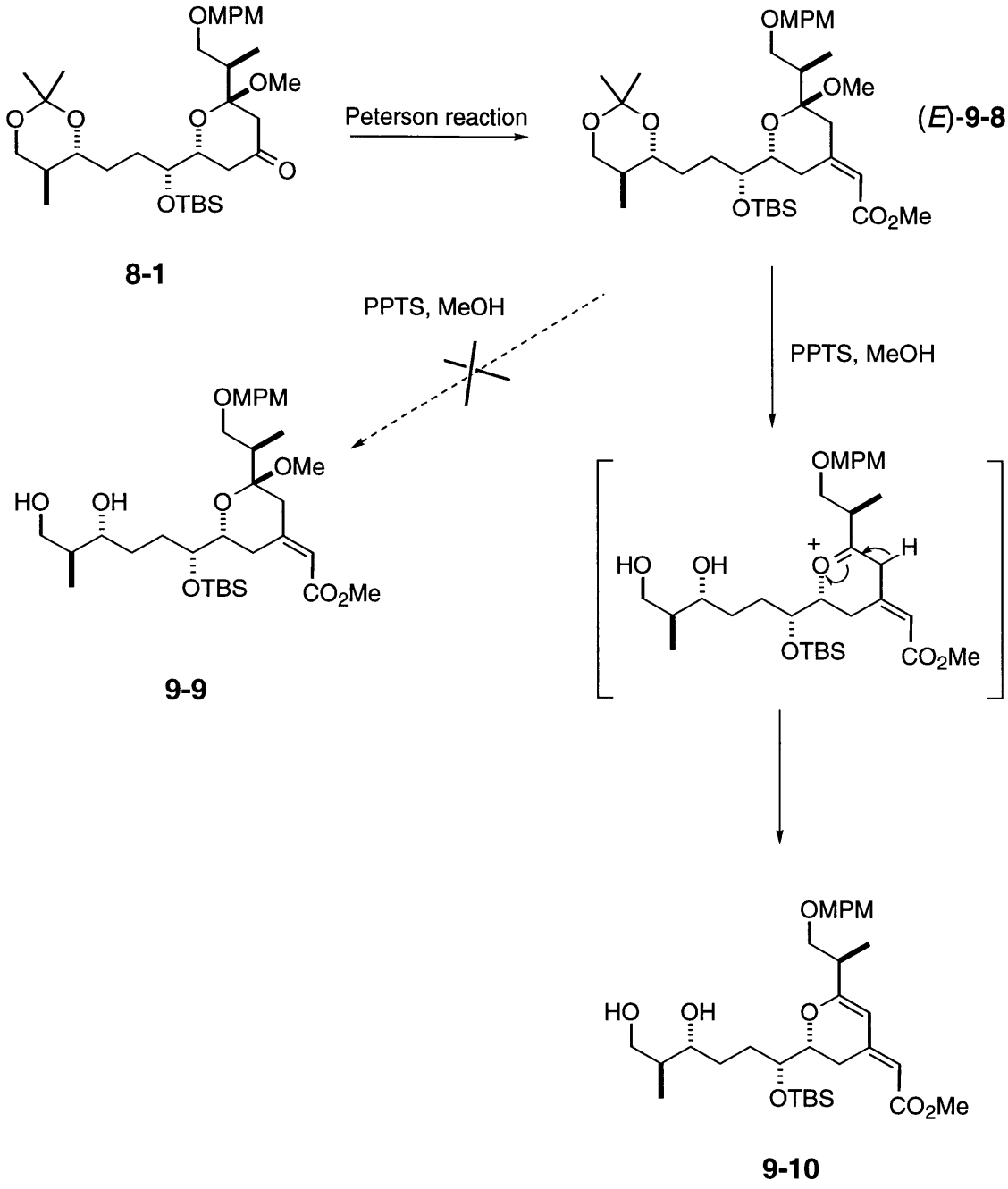
E : Z

LiHMDS, THF, -78 °C	2.6 : 1
NaHMDS, THF, -78 °C	1: 6.0

9.4 Synthesis of fragment **C'D'** through the Peterson reaction

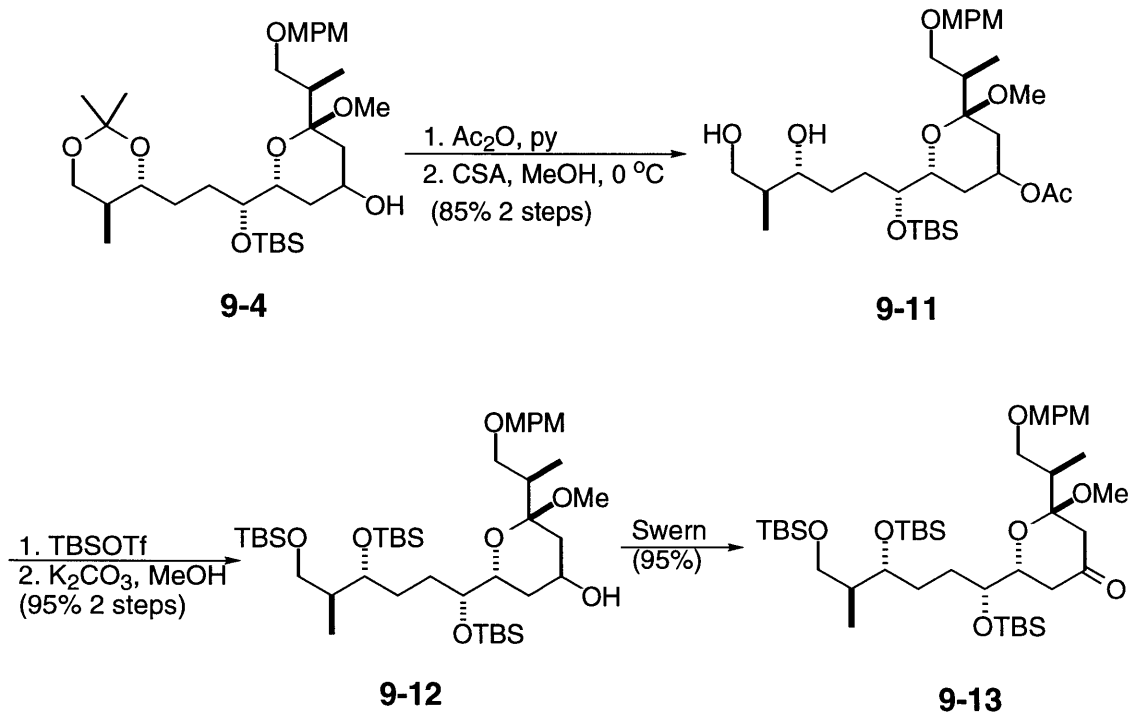
When the ketone **8-1** was treated with the lithium enolate of the α-trimethylsilyl methyl acetate at -78 °C for 5 minutes, the enoate (*E*)-**9-8** was obtained as the major isomer in a ratio of 2.5:1 as expected from the model experiments (Scheme 9.6). When we were trying to deprotect the acetonide in (*E*)-**9-8** with PPTS in MeOH, the methyl ketal was eliminated to give **9-10** through the oxonium ion intermediate as depicted below.

Scheme 9.6


OMPM
OMe
O
O
O
O
OTBS
8-1
Peterson reaction
OMPM
OMe
O
O
OTBS
CO2Me
(E)-9-8
PPTS, MeOH
PPTS, MeOH
OMPM
OMe
HO
OH
O
OTBS
CO2Me
9-9
OMPM
HO
OH
+
O
H
OTBS
CO2Me
OMPM
HO
OH
O
OTBS
CO2Me
9-10

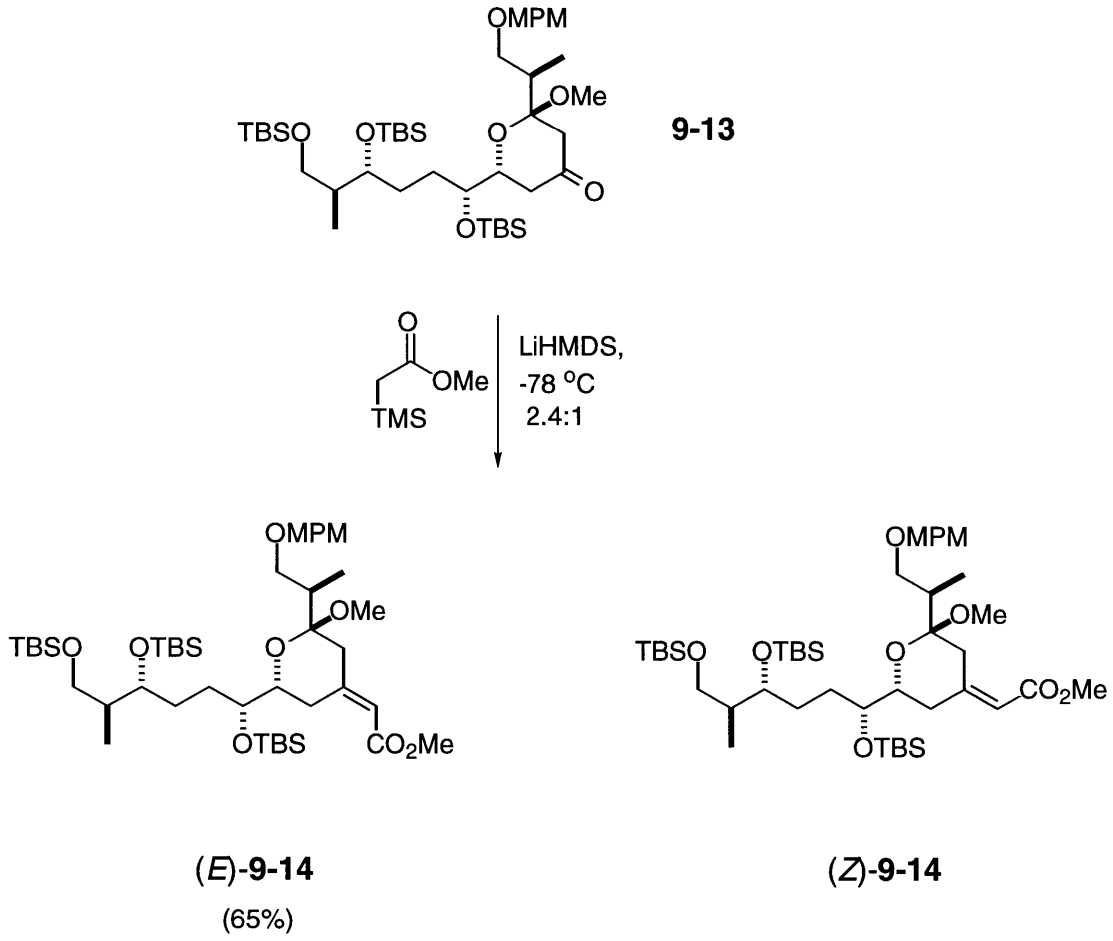
One obvious solution to this problem is to change the protecting groups for the diol before the introduction of the unsaturation at C5. Accordingly the alcohol **9-4** was masked as its acetate and then the acetonide was deprotected with CSA in MeOH at 0 ^{o}C without any problem to give the diol **9-11** (Scheme 9.7). Silylation and deacetylation then furnished the compound **9-12** which was oxidized to the ketone **9-13** smoothly by using the Swern procedure.[30]

Scheme 9.7



Again, the Peterson olefination of the ketone **9-13** with the lithium enolate of the α-trimethylsilyl methyl acetate provided the desired (*E*)-**9-14** with a selectivity of 2.4:1 (Scheme 9.8). The added advantage of the use of TBS groups is that the *E*-**9-14** is readily separated from its *Z* isomer by column chromatography.

Scheme 9.8

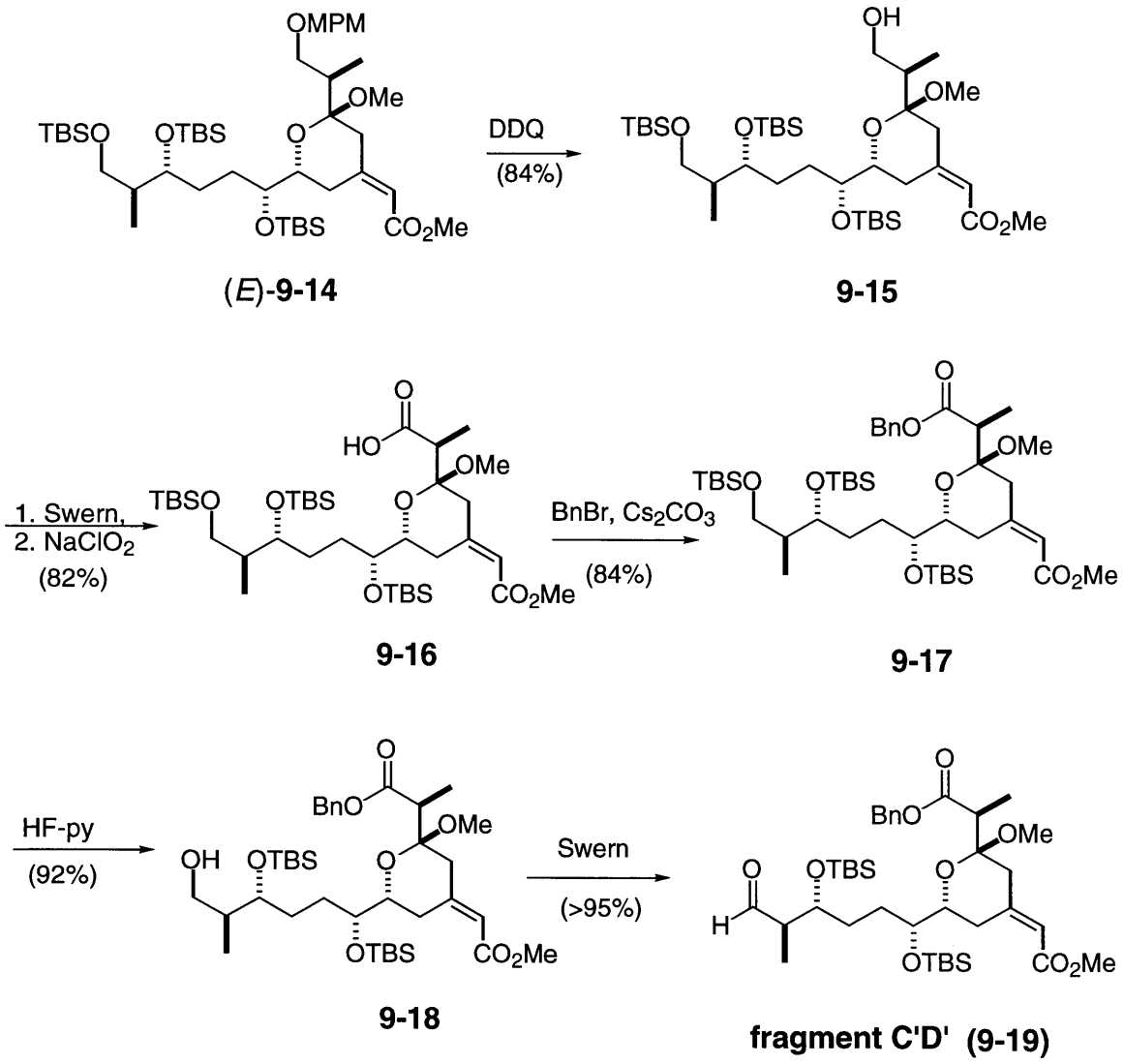


(*E*)-**9-14**
(65%)

(*Z*)-**9-14**

The MPM group was then removed by DDQ oxidation[35] in wet CH_2Cl_2 to give the primary alcohol **9-15** which was oxidized[48] to the corresponding carboxylic acid **9-16** uneventfully (Scheme 9.9). The benzyl ester was introduced with the use of Cs_2CO_3 and BnBr.[49] Then the primary TBS group was selectively removed by HF-py[50] to deliver the primary alcohol **9-18** in high yield. Finally the Swern oxidation of **9-18** gave the aldehyde **9-19** which constitutes the C1-C13 segment (fragment **C'D'**) of miyakolide.

Scheme 9.9



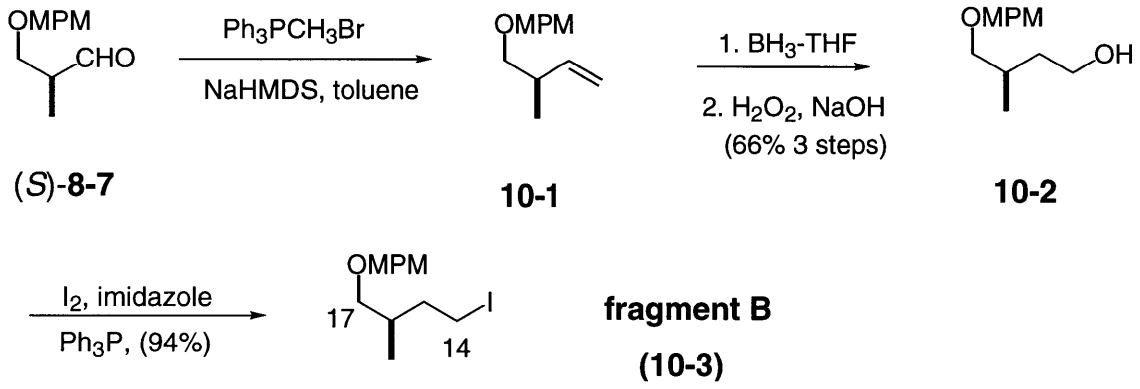
Chapter 10

Coupling of Fragments B and C'D'

10.1 Synthesis of fragment **B**

Fragment **B** was synthesized from the known aldehyde (*S*)-**8-7** in four steps as shown in Scheme 10.1.

Scheme 10.1



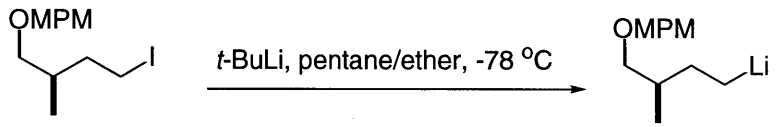
10.2 Coupling of fragments **B** and **C'D'**

The coupling of fragments **B** and **C'D'** involves the nucleophilic addition of the carbanion derived from **B** to the aldehyde at C13 in fragment **C'D'**. Traditionally the coupling at unactivated carbon center relies heavily on the employment of auxiliaries such as sulfones[51] to facilitate the generation of the carbanions. However, these strategies usually entail the removal of the auxiliary, which might not be readily achieved for molecules with multiple functionalities.

The results presented in Chapter 10 were obtained by Dr. J.-F. Liu.

Alternatively, the direct generation of carbanions at the unactivated carbon centers could be achieved by the metal-halogen exchange reactions.[52] When fragment **B** (**10-3**) was treated with 2.0 equivalent of *t*-BuLi in pentane/ether (3:2) at -78 °C the primary alkyl lithium **10-4** was generated cleanly in high yield (Scheme 10.2).

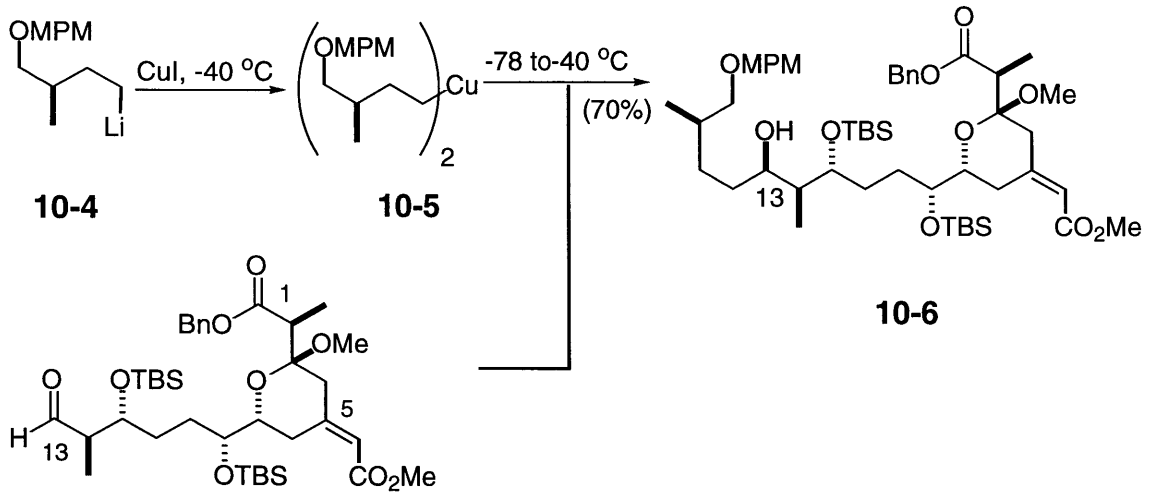
Scheme 10.2



fragment B (10-3) **10-4**

After extensive experimentation, it was found that the dialkyl cuprate[53] **10-5** which was derived from the primary alkyl lithium **10-4** reacted chemo- and stereoselectively with the aldehyde **9-19** at -40 °C to afford the alcohol **10-6** as the major isomer (~5:1) without significant interference with the benzyl ester at C1 and the exocyclic α, β-unsaturated ester at C5. The configuration at C13 in **10-6** was tentatively assigned to be *R* , which reflects the Felkin-Anh addition of the nucleophile to the aldehyde.

Scheme 10.1



10-4 **10-5** **10-6**

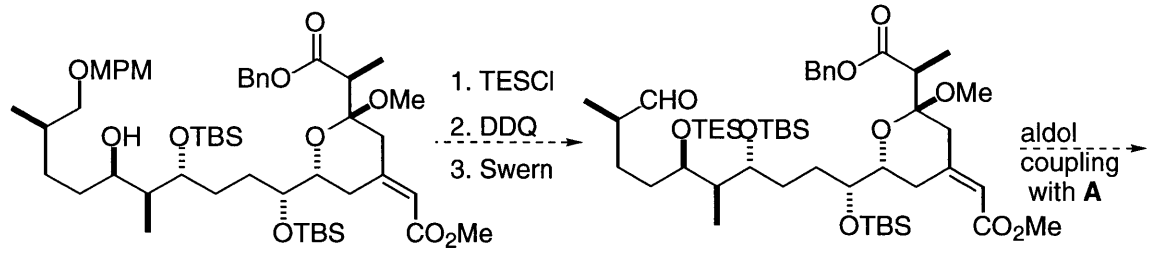
fragment C'D' (9-19)

Chapter 11

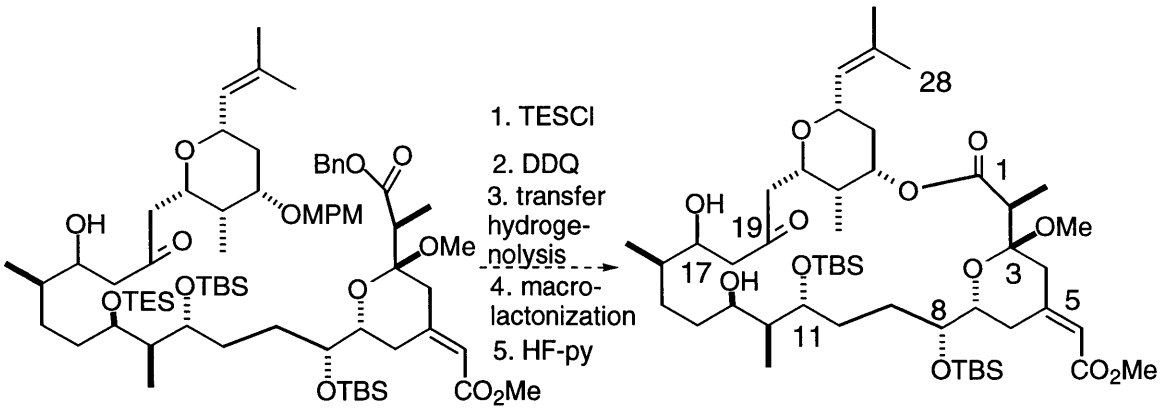
Future Plans

To complete the total synthesis of miyakolide, the following schemes would be pursued.

The advanced intermediate **10-6** would be converted into the aldehyde **11-1** which would be coupled with fragment **A** (**4-21**) through an aldol reaction to give the intermediate **11-2**. Protecting group manipulation would lead to the formation of the free hydroxy acid which could undergo macrolactonization and selective deprotection of the TES groups to afford compound **3-3**.

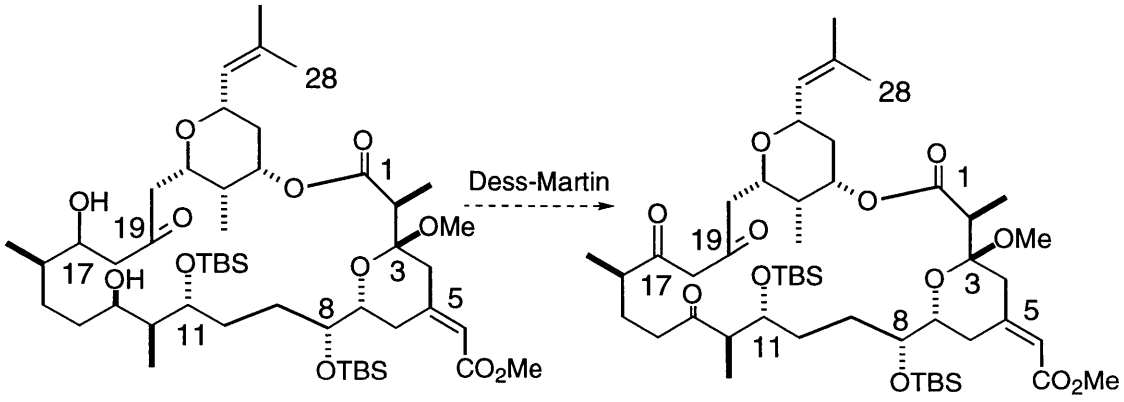


10-6 **11-1**

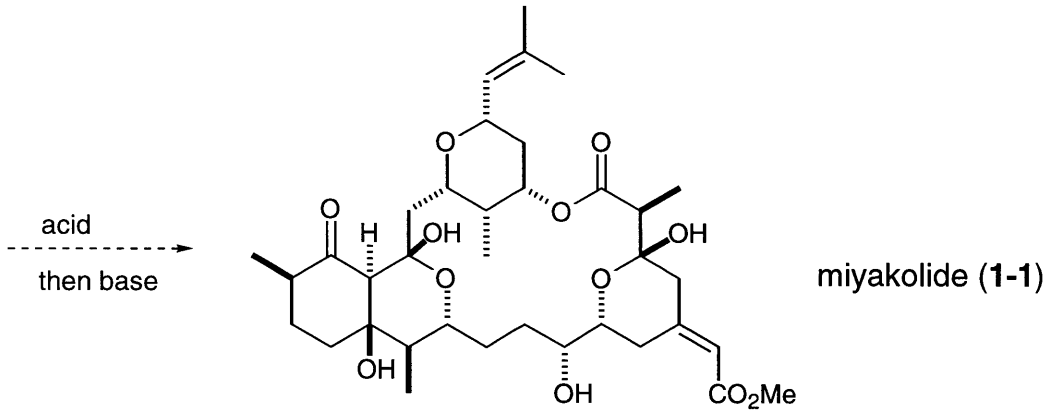


11-2 **3-3**

Oxidation of compound **3-3** to the 1, 3, 7-triketone **3-2** could be achieved by the Dess-Martin oxidation[20] and then the sequential treatment of the **3-2** with acid and base would complete the total synthesis of miyakolide.



3-3 **3-2**



miyakolide (**1-1**)

Chapter 12

Experimental Section

General Procedures: Reaction mixtures were stirred using a magnetic stirring apparatus unless otherwise indicated. All moisture or air sensitive reactions were carried out under a positive pressure of argon, and were performed in glassware that was oven and / or flame dried. Solvents and liquid reagents were transferred via syringe or cannula. Reactions were monitored by thin layer chromatography as described below. Organic solvents were removed through concentration using a Büchi rotary evaporator at 20 - 40 mmHg.

Materials : Commercial solvents and reagents were used without further purification with the following exceptions:

Solvents

Methylene chloride was distilled under nitrogen from calcium hydride.

Ethyl ether was distilled under argon from sodium benzophenone ketyl.

Hexanes were distilled under nitrogen from calcium hydride.

Tetrahydrofuran was distilled under argon from sodium benzophenone ketyl.

Toluene was distilled under nitrogen from sodium.

Triethylamine was distilled under nitrogen from calcium hydride.

Chromatography

Flash column chromatography was performed using ICN silica gel (230-400 mesh) according to the method of Still.[54] HPLC grade solvents were used.

Thin layer chromatography (TLC) was performed as an analytical tool using Analtech high performance precoated glass silica gel (SiO_2, approx. 5μm particle size) plates (200 μm thickness). The plates were impregnated with 254 nm fluorescent indicator. The procedure used was to elute using the solvent mixture indicated in the text, followed by an observation by illumination with a 254 nm ultraviolet light, and staining by dipping in either an ethanolic solution of 2.5% *p* - anisaldehyde (3.5 % sulfuric acid and

1.0 % acetic acid) or an ethanolic solution of phosphomolybdic acid (20% wt.) followed by heating on a hot plate.

Physical Data

Melting points were determined on Mel-temp II manufactured by Laboratory Devices, USA and were uncorrected.

Optical rotations were determined using a Perkin-Elmer 241 polarimeter using a sodium lamp (D line) at 23 °C, and are reported in degrees. Concentration (c) is indicated as units of 10 mg / mL.

FTIR spectra were recorded on a Perkin-Elmer spectrometer equipped with an internal polystyrene sample as a reference.

^{1}H NMR were recorded on either a Varian XL 300 MHz spectrometer, a Varian Unity 300 MHz spectrometer or a Varian VXR 500 MHz spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.0) using the residual deuterated chloroform signal (δ 7.24) or deuterated benzene signal (δ 7.16) as a standard. Multiplicities are reported in the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublets of doublets), *etc.*

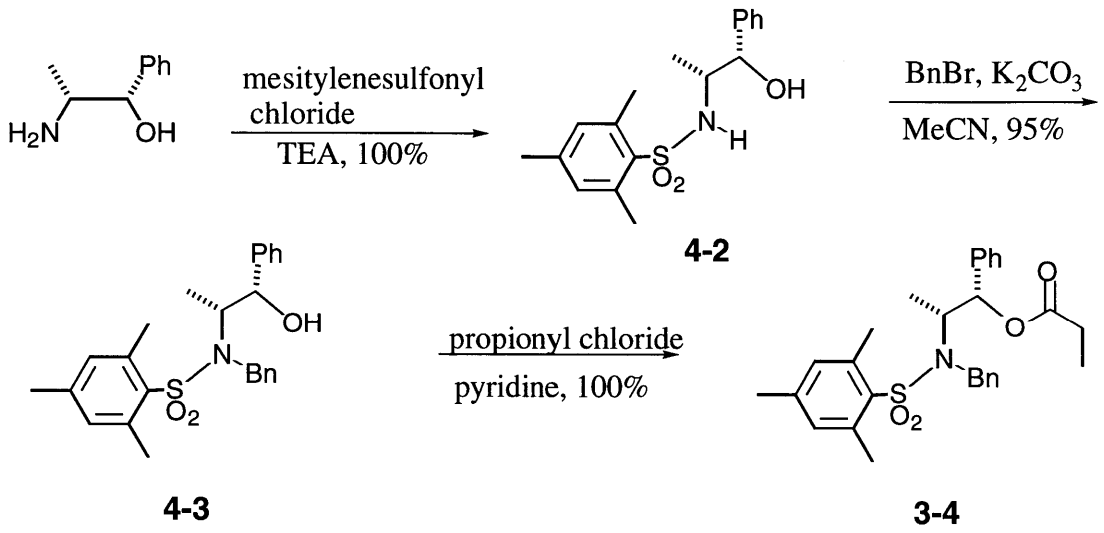
^{13}C NMR were recorded on either a Varian 300 NMR at 75 MHz or a Varian 500 NMR at 125 MHz. The deuteriochloroform signal (δ 77.01) or deuterated benzene signal (δ 128.5) was used as a standard.

Mass spectra and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT System 8200, double focusing, magnetic sector, mass spectrometer. The spectra were recorded using either electron impact (EI), generating (M^++1), or fast atom bombardment (FAB) with sodium iodide in 3-nitrobenzyl alcohol , generating ($M+Na^+$). Spectra were recorded in units of mass to charge (m/e).

All compounds were judged to be greater than or equal to 95% pure based on their ^{1}H NMR spectra.

Preparations of chiral ester 3-4 and dicyclohexylboron trifluoromethanesulfonate:

At the request of Prof. Masamune, the preparations of the chiral reagent **3-4** for the *anti*-selective aldol reaction and the (*c*-Hex)$_2$BOTf are described here.[13]



4-2: To a solution of (1*S*, 2*R*)-(-)-norephedrine (7.6 g, 50 mmol) and TEA (8.4 mL, 60 mmol) in 200 mL of CH_2Cl_2 at 0 °C was added mesitylenesulfonyl chloride (11.0 g, 50 mmol). The reaction mixture was stirred at 0 °C to room temperature for 2 hours before being diluted with ether (200 mL) and the mixture was poured into water (100 mL). The organic layer was then washed with 1 N HCl, water, saturated $NaHCO_3$ aqueous solution and brine. The organic layer was dried over $MgSO_4$ and then concentrated. Recrystallization from CH_2Cl_2/hexane afforded **4-2** (16.7 g, 100%).

mp 120.5-121.5 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.36 (m, 5H), 6.95 (s, 2H), 4.97 (d, J = 8.9 Hz, 1H), 4.75 (dd, J = 3.3, 4.7 Hz, 1H), 3.42-3.58 (m, 1H), 2.71 (d, J = 4.7 Hz, 1H), 2.65 (s, 6H), 2.29 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 140.5, 138.8, 134.2, 131.9, 128.2, 127.4, 125.8, 75.6, 54.5, 22.8, 20.8, 14.2.

$[\alpha]_D^{24}$=+12.8 (c=2.1, $CHCl_3$)

Anal. Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.94; H, 6.98; N, 4.17.

4-3: A solution of **4-2** (3.3 g, 10.0 mmol), BnBr (1.43 mL, 12.1 mmol) and K_2CO_3 (2.1 g, 15.1 mmol) in CH_3CN (40 mL) was refluxed for 7 hours. Then the reaction mixture was cooled to room temperature and filtered. The salts were washed with ether. The combined organics were concentrated. Recrystallization from CH_2Cl_2/hexane afforded **4-3** (4.0 g, 95%).

mp 123.0-124.0 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-7.36 (m, 8H), 7.04-7.08 (m, 2H), 6.91 (s, 2H), 4.98 (br s, 1H), 4.77 (d, *J* = 16.1 Hz, 1H), 4.54 (d, *J* = 16.1 Hz, 1H), 3.82 (dd, *J* = 1.9, 7.1 Hz, 1H), 2.63 (s, 6H), 2.28 (s, 3H), 2.22 (d, *J* = 3.4 Hz, 1H), 1.02 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 142.1, 140.0, 138.6, 133.4, 132.0, 128.4, 128.0, 127.6, 127.2, 127.1, 125.4, 76.5, 59.5, 48.9, 22.8, 20.8, 10.1.

$[\alpha]_D^{24}$=+6.4 (c=2.0, $CHCl_3$)

Anal. Calcd for $C_{25}H_{29}NO_3S$: C, 70.89; H, 6.90; N, 3.31. Found: C, 70.91; H, 6.95; N, 3.32.

3-4: To a solution of **4-3** (15.0 g, 35.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added pyridine (3.7 mL, 46.0 mmol) and propionyl chloride (3.8 mL, 42.5 mmol). The reaction mixture was stirred overnight and diluted with ether (300 mL) and water (200 mL). The organic layer was then washed with 1 N HCl and saturated $NaHCO_3$ aqueous solution and brine. The solvent was removed and the residue was recrystallized from ethyl acetate and hexane to afford **3-4** (16.8 g, 100%).

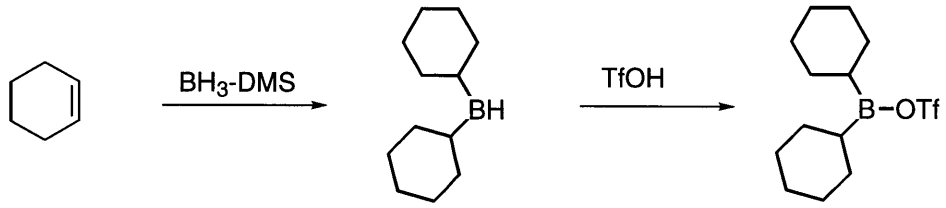
mp 147.0-148.0 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.35 (m, 8H), 6.88-6.96 (m, 2H), 6.87 (s, 2H), 5.84 (d, *J* = 3.9 Hz, 1H), 4.72 (d, *J* = 16.6 Hz, 1H), 4.60 (d, *J* = 16.6 Hz, 1H), 4.04 (dq, *J* = 4.0, 7.0 Hz, 1H), 2.51 (s, 6H), 2.27 (s, 3H), 2.14 (m, 2H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 142.3, 139.9, 138.5, 138.4, 133.2, 131.9, 128.1, 127.5, 127.1, 126.8, 125.6, 77.7, 56.5, 47.9, 27.1, 22.7, 20.6, 12.3, 8.54.

$[\alpha]_D^{24}$=-11.1 (c=2.2, $CHCl_3$)

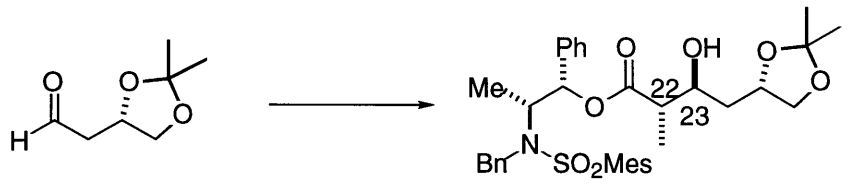
Anal. Calcd for $C_{28}H_{33}NO_4S$: C, 70.12; H, 6.93; N, 2.92. Found: C, 70.40; H, 6.97; N, 2.90.



dicyclohexylboron trifluoromethanesulfonate:

To a solution of cyclohexene (36.5 mL, 360 mmol) in ether (180 mL) at 0 °C was added BH3-DMS (~10.5 M, 14.2 mL, 150 mmol). White precipitation was observed in about 10 minutes. The reaction mixture was kept at 0 °C for 1.5 h and room temperature for 0.5 h. The white slurry was then filtered under argon and washed with ether several times. Then the residual ether was pumped off to afford the dicyclohexylborane as a white solid (22.1 g, 83%). The borane is very air-sensitive as a solid. So it is very important to carry out the filtration and subsequent manipulations under argon.

The borane was suspended in anhydrous hexane (90 mL). TfOH (11.0 mL, 124 mmol) was added dropwise. At the end of the addition, the solid disappeared and the solution became clear. This procedure gave a 1.0 M stock solution of (*c*-Hex)2BOTf in hexane.



4-4 **3-10**

3-10: To a solution of **3-4** (*1S, 2R*) (1.0 g, 2.11 mmol) in 30 mL of CH_2Cl_2 at -78 °C were added TEA (1.18 mL, 8.44 mmol) and (*c*-Hex)$_2$BOTf (0.4 M in hexane, 10.6 mL, 4.24 mmol) diluted in 5 mL of CH_2Cl_2 (precooled to -78 °C). After 2 hours at -78 °C, aldehyde **4-4** (about 253 mg, 1.76 mmol) in 5 mL of CH_2Cl_2 (2 mL rinse) was added dropwise into the enolate solution at the same temperature. The reaction mixture was stirred at -78 °C for one hour and 0 °C for an additional hour before it was quenched by adding 10 mL of MeOH, 10 mL of pH 7 buffer, and 10 mL of 30% H_2O_2. The heterogeneous mixture was stirred vigorously for 12 hours and then extracted with CH_2Cl_2 thoroughly. The combined organics were dried over $MgSO_4$, filtered, concentrated to give a yellow oil which was purified by flash chromatography (30% EtOAc/hexane) to provide a mixture of two isomers (major **3-10**, minor **4-5**). Further chromatography (5% ether/CH_2Cl_2) resulted in the separation of these two isomers to give 438 mg (90% based on the recovered **3-4**) **3-10** in pure form, along with minute quantities (30 mg) of **4-5**.

For **3-10**: **^{1}H NMR** (300 MHz, C_6D_6) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.8 Hz, 2H), 6.96-7.10 (m, 6H), 6.50 (s, 2H), 6.25 (d, *J* = 3.9 Hz, 1H), 4.92 (d, *J* = 16.2 Hz, 1H), 4.64 (d, *J* = 16.2 Hz, 1H), 4.39 (ddd, *J* = 4.5, 7.2, 14.1 Hz, 1H), 4.14 (m, 1H), 3.91 (m, 1H), 3.83 (dd, *J* = 6.0, 8.1 Hz, 1H), 3.42 (t, *J* = 8.1 Hz, 1H), 2.73 (br s, 1H), 2.56 (s, 6H), 2.38 (ddd, *J* = 6.9, 6.9, 14.7 Hz, 1H), 1.88 (s, 3H), 1.60 (ddd, *J* = 2.4, 7.2, 14.1 Hz, 1H), 1.44 (dd, *J* = 4.8, 9.9 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 174.4, 142.7, 141.0, 139.8, 139.6, 135.0, 132.8, 129.2, 129.0, 128.6, 127.9, 127.0, 109.3, 79.2, 74.4, 71.4, 70.5, 58.1, 49.4, 47.1, 38.8, 27.9, 26.6, 23.9, 21.4, 14.5, 6.5.

IR (neat) 3455, 2984, 2938, 1738, 1324, 1153, 1055 cm^{-1}

$[\alpha]_D^{24}$=-18.0 (c=0.55, $CHCl_3$)

HRMS $C_{35}H_{45}O_7NS$ $[M-CH_3]^+$ calculated: 608.2682, found: 608.2681.

For **4-5**: **^{1}H NMR** (300 MHz, C_6D_6) δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 2H), 6.98 (m, 6H), 6.51 (s, 2H), 6.20 (d, *J* = 3.9 Hz, 1H), 4.93 (d, *J* = 16.8 Hz, 1H), 4.70 (d, *J* = 16.5 Hz, 1H), 4.36 (ddd, *J* = 3.6, 7.2, 14.4 Hz, 1H), 3.96 (m, 1H), 3.88 (m, 1H), 3.63 (dd, *J* = 6.0, 8.1 Hz, 1H), 3.40 (d, *J* = 2.1 Hz, 1H), 3.15 (dd, *J* = 8.1, 8.6 Hz, 1H), 2.60 (m, 1H), 2.57 (s, 6H), 1.89 (s, 3H), 1.43 (m, 1H), 1.28 (d, *J* = 7.3 Hz, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.08 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 205.2, 186.6, 173.4, 142.7, 141.0, 140.0, 135.1, 132.8, 129.1, 129.0, 127.8, 110.0, 107.2, 79.2, 76.3, 73.1, 70.3, 58.0, 49.9, 46.7, 37.7, 27.6, 26.5, 23.9, 21.3, 14.3, 13.3.

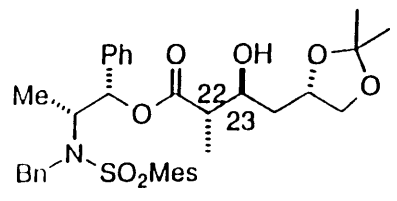
$[\alpha]_D^{24}$=-24.3 (c=1.4, $CHCl_3$)

Aldol reaction between *ent*-**3-4** (*1R, 2S*) and aldehyde **4-4** was carried out in a similar manner to give desired compound **4-6** as the only detectable isomer.

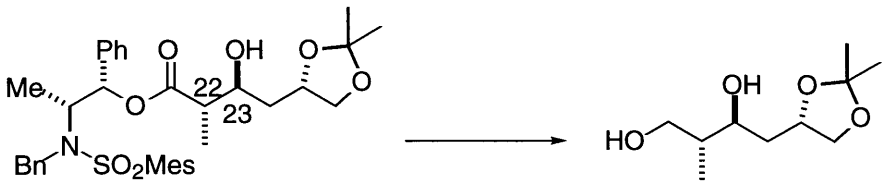
^{1}H NMR (300 MHz, C_6D_6) δ 7.53 (d, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 2H), 7.01 (m, 6H), 6.53 (s, 2H), 6.25 (d, *J* = 3.6 Hz, 1H), 5.00 (d, *J* = 16.6 Hz, 1H), 4.76 (d, *J* = 16.6 Hz, 1H), 4.35 (m, 1H), 3.94 (m, 2H), 3.65 (t, *J* = 8.0 Hz, 1H), 3.46 (s, 1H), 3.19 (t, *J* = 7.3 Hz, 1H), 2.58 (s, 9H), 2.58 (m, 1H), 1.88 (s, 3H), 1.30-1.50 (m, 3H), 1.28 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.20 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 174.2, 142.7, 141.0, 140.2, 140.0, 135.1, 132.8, 129.1, 129.0, 128.6, 127.8, 126.8, 109.8, 79.0, 75.9, 73.2, 70.2, 70.2, 58.0, 49.2, 46.5, 37.6, 27.4, 26.3, 23.7, 21.1, 13.9, 13.6.

$[\alpha]_D^{24}$=+20.5 (c=2.0, $CHCl_3$)



3-10



3-10 **4-7**

<u>4-7</u>: To a solution of **3-10** (500 mg, 0.82 mmol) in 25 mL of THF at 0 °C was added LAH (0.15 g, 4.00 mmol) as powders. After 30 minutes, the reaction was quenched by the addition of 50 mL of EtOAc and 50 mL of saturated sodium potassium tartrate aqueous solution. The biphasic mixture was stirred vigorously overnight at which time the two layers became clear. The aqueous layer was extracted with EtOAc thoroughly and the combined organics were dried over Na_2SO_4, filtered, concentrated. The residual oil was purified by flash column chromatography (85% EtOAc/hexane) to provide 100 mg (60%) of diol **4-7** as a clear oil.

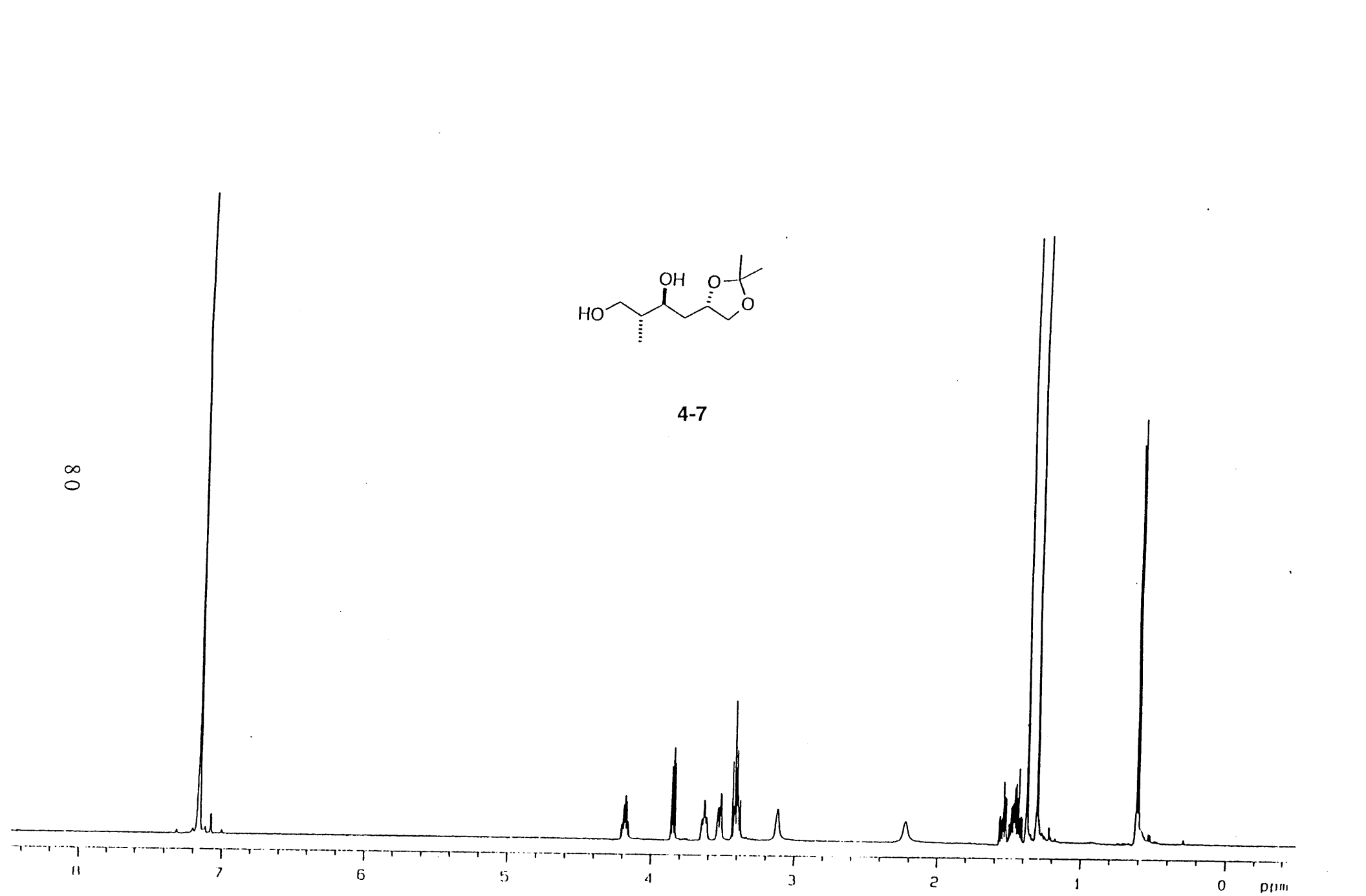
^{1}H NMR (300 MHz, C_6D_6) δ 4.18 (m, 1H), 3.85 (dd, J = 6.3, 8.1 Hz, 1H), 3.63 (br m, 1H), 3.53 (dd, J = 3.9, 10.8 Hz, 1H), 3.42 (m, 2H), 3.05 (br s, 1H), 2.18 (br s, 1H), 1.40-1.60 (m, 3H), 1.39 (s, 3H), 1.21 (s, 3H), 0.63 (d, J = 7.0 Hz, 3H).

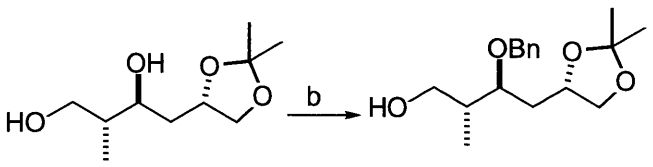
^{13}C NMR (75 MHz, C_6D_6) δ 109.3, 74.7, 74.5, 67.8, 41.4, 39.3, 27.9, 26.6, 14.6.

IR (neat) 3384, 2984, 1371, 1218, 1059 cm^{-1}

$[\alpha]_D^{24}$=-22.0 (c=1.0, $CHCl_3$)

HRMS $C_{10}H_{20}O_4$ $[M-CH_3]^+$ calculated: 189.1127, found: 189.1127.


OH
O
HO
O
4-7
80
8
7
6
5
4
3
2
1
0
ppm



4-7 **4-10**

4-10: To a solution of **4-7** (82 mg, 0.43 mmol) in 5 mL of CH_2Cl_2 at room temperature were added TEA (0.56 mL), TBSCl (122 mg, 0.81 mmol) and DMAP (catalytic amount). After 5 hours, the reaction mixture was poured into 5 mL of saturated $NaHCO_3$ aqueous solution and 50 mL of ether. The ether layer was washed successively with 1 M $CuSO_4$ aqueous solution, H_2O and brine. After being dried over $MgSO_4$, the organic layer was concentrated to give an oil which was purified by column chromatography (15% EtOAc/hexane) to afford 106 mg (83%) primary-TBS protected compound as a clear oil.

^{1}H NMR (300 MHz, C_6D_6) δ 4.39 (ddd, J = 5.7, 6.5, 12.8 Hz, 1H), 4.03 (dd, J = 6.0, 8.1 Hz, 1H), 3.77 (ddd, J = 2.8, 3.9, 13.6 Hz, 1H), 3.58 (m, 2H), 3.45 (dd, J = 6.7, 10.0 Hz, 1H), 3.29 (d, J = 4.0 Hz, 1H), 1.77 (ddd, J = 2.4, 7.1, 13.8 Hz, 1H), 1.50-1.61 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 0.90 (s, 3H), 0.72 (d, J = 7.2 Hz, 3H), 0.00 (s, 6H).

^{13}C NMR (75 MHz, C_6D_6) δ 109.3, 107.5, 75.3, 73.8, 71.3, 70.9, 68.5, 42.0, 40.0, 28.3, 27.0, 19.3, 14.6, 5.0.

IR (neat) 3478, 2930, 1471, 1369, 1255, 1157, 1058, 834, 776 cm^{-1}

$[\alpha]_D^{24}$=-12.9 (c=1.0, $CHCl_3$)

The TBS ether was then dissolved in 3 mL of DMF and treated with NaH (133 mg, 3.30 mmol) and BnBr (80 μL, 0.66 mmol). After 5 hours, the reaction was quenched by adding 10 mL of saturated NH_4Cl aqueous solution and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$, concentrated and the residual oil was purified by column chromatography (5% EtOAc/hexane) to provide 116 mg (85%) of the fully protected compound.

^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (d, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.08 (m, 1H), 4.12 (d, *J* = 14.1 Hz, 1H), 4.41 (d, *J* = 14.1 Hz, 1H), 4.39 (m, 1H), 3.86 (dd, *J* = 6.2, 8.1 Hz, 1H), 3.81 (m, 1H), 3.40-3.51 (m, 3H), 2.04 (quint, *J* = 6.3 Hz, 1H), 1.66 (dd, *J* = 8.3, 11.4 Hz, 1H), 1.55 (dd, *J* = 4.6, 10.5 Hz, 1H), 1.43 (s, 3H), 1.31, (s, 3H), 0.98 (s, 9H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.02 (s, 6H).

^{13}C NMR (75 MHz, C_6D_6) δ 139.8, 128.6, 128.0, 127.7, 108.6, 77.8, 74.1, 72.3, 70.5, 65.6, 39.0, 35.4, 27.6, 26.3, 18.6, 11.9, 5.2.

IR (neat) 2990, 2857, 1462, 1378, 1252, 1160, 1063, 837 cm^{-1}

$[\alpha]_D^{24}$=-27.7 (c=0.83, $CHCl_3$)

To a solution of this fully protected compound (116 mg, 0.28 mmol) in 4 mL of THF was added dropwise a solution of TBAF (1.0 M in THF, 0.34 mL, 0.34 mmol). The reaction mixture was stirred for one hour and the solvent was removed under vacuum. The residual oil was purified by flash column chromatography (40% EtOAc/hexane) to furnish 78 mg (94%) of the desired primary alcohol **4-10** as a clear oil.

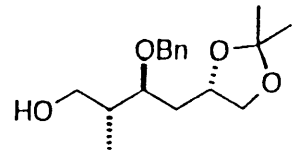
^{1}H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 7.5 Hz, 2H), 7.16 (m, 2H), 7.05 (m, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.18 (m, 1H), 3.80 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.67 (m, 1H), 3.45 (m, 1H), 3.38 (m, 1H), 3.37 (t, *J* = 8.5 Hz, 1H), 1.82 (m, 1H), 1.49-1.53 (m, 2H), 1.40 (s, 3H), 1.30 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 139.8, 129.1, 128.4, 109.1, 79.7, 74.3, 73.1, 70.6, 65.6, 39.5, 36.6, 27.8, 26.6, 13.2.

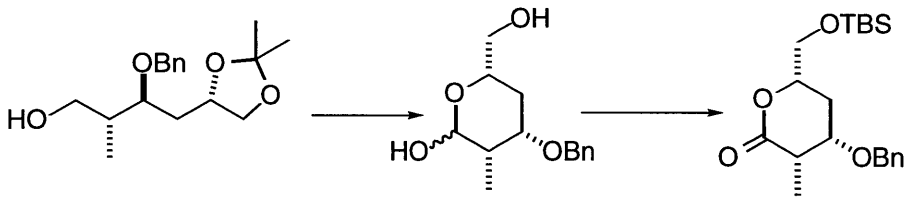
IR (neat) 3430, 2934, 1455, 1370, 1215, 1158, 1028 cm^{-1}

$[\alpha]_D^{24}$=-33.3 (c=0.42, $CHCl_3$)

HRMS $C_{17}H_{26}O_4$ $[M-CH_3]^+$ calculated: 279.1596, found: 279.1597.



4-10



4-10 **4-11** **4-12**

4-12: Using the standard Swern procedure, **4-10** was oxidized to the corresponding aldehyde smoothly and it was used as crude in the following reaction.

^{1}H NMR (300 MHz, C_6D_6) δ 9.46 (d, *J* = 2.0 Hz, 1H), 7.07-7.28 (m, 5H), 4.30 (s, 2H), 4.14 (m, 1H), 3.88 (ddd, *J* = 4.2, 4.2, 8.4 Hz, 1H), 3.74 (dd, *J* = 6.0, 7.8 Hz, 1H), 3.28 (dd, *J* = 6.9, 7.5 Hz, 1H), 2.30 (m, 1H), 1.45 (m, 2H), 1.40 (s, 3H), 1.32 (s, 3H), 0.90 (d, *J* = 7.4 Hz, 3H).

To a solution of the aldehyde in 3 mL of THF was added 3 mL of 1 N HCl. After 3 hours of vigorous stirring, the reaction was quenched by adding 5 mL of saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated to give an oil which was subjected to flash column chromatography (5% MeOH/CH_2Cl_2) to give 54 mg (98%) of the hemiacetal **4-11** as an anomeric mixture.

To a solution of hemiacetal **4-11** (54 mg, 0.22 mmol) in 4 mL of CH_2Cl_2 were added TEA (0.15 mL), TBSCl (65 mg, 0.43 mmol) and DMAP (catalytic amount). The stirring was continued for 5 hours and the reaction mixture was poured into 5 mL of saturated $NaHCO_3$ aqueous solution and 50 mL of ether. The ether layer was washed successively with 1 M $CuSO_4$ aqueous solution, H_2O and brine. After being dried over $MgSO_4$, the organic layer was concentrated to give an oil which was purified by flash column chromatography (20% EtOAc/hexane) to afford 75 mg (95%) of the primary-TBS protected hemiacetal.

The hemiacetal (75 mg, 0.20 mmol) was dissolved in 4 mL of CH_2Cl_2. To this solution, 4 Å molecular sieves (70 mg) and PCC (88 mg, 0.41mmol) were added. The reaction completed after 4 hours at which time the reaction mixture was diluted with 10 mL

of ether and filtered through a florisil pad (washed with an additional 20 mL of ether). Concentration afforded 69 mg (93%) of lactone **4-12** as a white solid.

^{1}H NMR (300 MHz, C_6D_6) δ 7.05-7.20 (m, 5H), 4.26 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.73 (ddd, *J* = 4.8, 4.8, 9.3 Hz, 1H), 3.54 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.48 (dd, *J* = 5.1, 10.8 Hz, 1H), 3.22 (ddd, *J* = 4.5, 4.5, 6.6 Hz, 1H), 2.16 (dq, *J* = 3.9, 6.9 Hz, 1H), 1.70 (ddd, *J* = 4.8, 10.8, 14.7 Hz, 1H), 1.51 (ddd, *J* = 4.8, 7.2, 14.4 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 0.96 (s, 9H), 0.10 (s, 3 H), 0.09 (s, 3H).

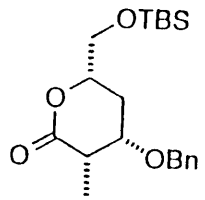
^{13}C NMR (75 MHz, C_6D_6) δ 172.8, 139.3, 129.4, 128.6, 76.5, 74.5, 71.3, 66.1, 40.3, 30.8, 26.8, 19.3, 12.8, 4.4.

mp 70.2-71.0 °C

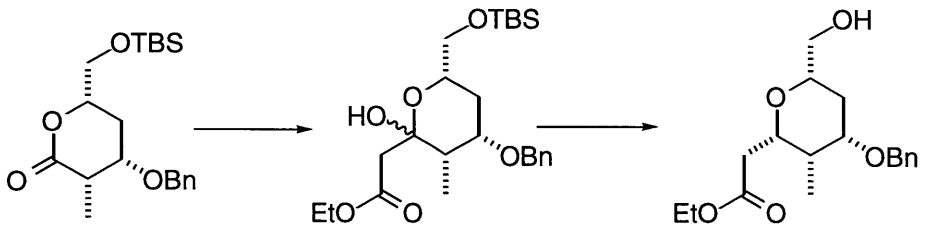
IR (neat) 2930, 1753, 1078, 1026 cm^{-1}

$[\alpha]_D^{24}$=+39.8 (c=0.85, $CHCl_3$)

HRMS $C_{20}H_{32}O_4Si$ $[M]^+$ calculated: 364.2070, found: 364.2070.



4-12



4-12 **4-13** **4-15**

4-15: To a solution of LiHMDS (1.0 M in THF, 1.33 mL, 1.33 mmol) in 6 mL of THF at -78 °C was added EtOAc (0.19 mL, 1.89 mmol). After 0.5 hour, a solution of lactone **4-12** (69 mg, 0.19 mmol) in 2 mL of THF at -78 °C was cannulated into this enolate solution. The reaction was instant and it was quenched at -78 °C by adding 10 mL of saturated NH_4Cl aqueous solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over $MgSO_4$, filtered, concentrated and the residual oil was purified by flash column chromatography (7% EtOAc/hexane) to give 78 mg (92%) of the aldol adduct **4-13.**

To a solution of aldol adduct **4-13** (78 mg, 0.17 mmol) in 6 mL of CH_3CN at -10 °C were added Et_3SiH (0.28 mL, 1.73 mmol) and BF_3-Et_2O (0.11 mL, 0.86 mmol). The reaction mixture was allowed to warm up to room temperature over 30 minutes and the reaction was quenched by adding 10 mL of saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over Na_2SO_4, filtered, concentrated. The residual oil was purified by flash column chromatography (7% EtOAc/hexane) to give 50 mg (90%) of alcohol **4-15** as a colorless oil.

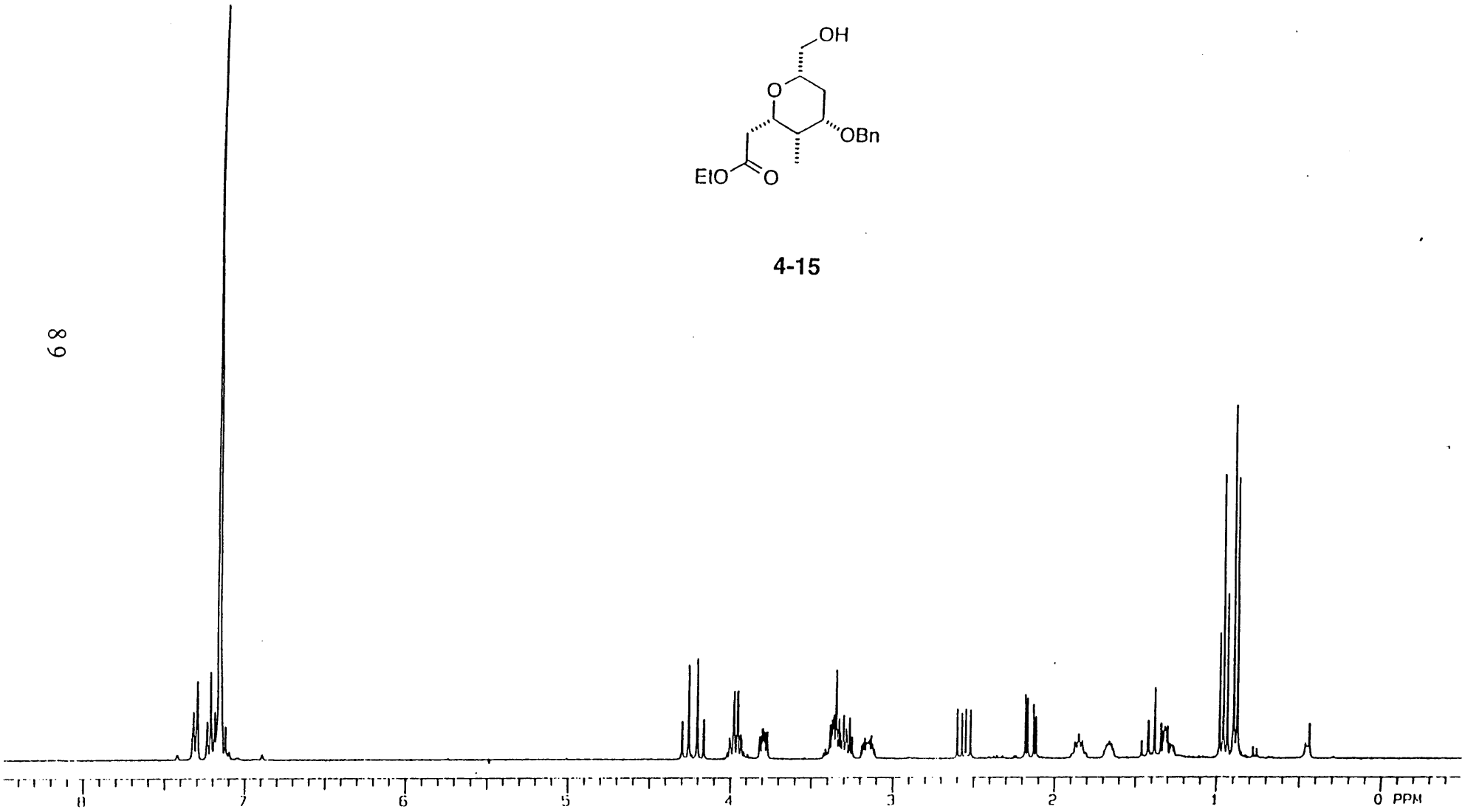
^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (d, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.12 (m, 1H), 4.28 (d, *J* = 12.0 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 3.97 (dq, *J* = 1.8, 7.2 Hz, 2H), 3.78 (ddd, *J* = 2.1, 5.0, 8.6 Hz, 1H), 3.31-3.40 (m, 2H), 3.29 (ddd, *J* = 5.0, 5.0, 11.5 Hz, 1H), 3.15 (m, 1H), 2.54 (dd, *J* = 8.7, 15.6 Hz, 1H), 2.15 (dd, *J* = 4.8, 15.4 Hz, 1H), 1.85 (m, 1H), 1.66 (m, 1H), 1.40 (q, *J* = 11.5 Hz, 1H), 1.30 (ddd, *J* = 2.7, 4.4, 12.6 Hz, 1H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 171.0, 139.7, 128.7, 127.8, 127.7, 77.7, 77.3, 75.5, 69.5, 66.0, 60.5, 38.5, 35.5, 28.5, 14.4, 5.7.

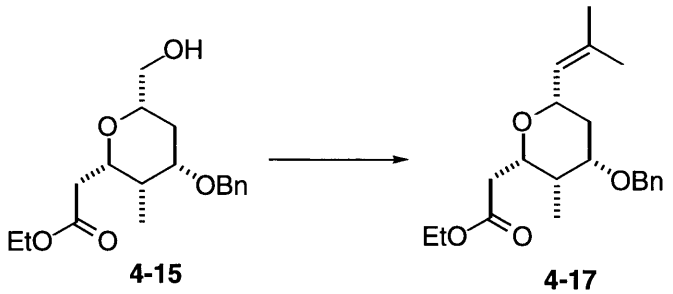
IR (neat) 3449, 2977, 2938, 2868, 1733, 1367, 1186, 1103, 1028 cm^{-1}

$[\alpha]_D^{24}$=-28.0 (c=0.65, $CHCl_3$)

HRMS $C_{18}H_{26}O_5$: $[M]^+$ calculated: 322.1780, found: 322.1777.



4-15



4-15 **4-17**

4-17: To a solution of **4-15** (30 mg, 0.093 mmol) in 5 mL of CH_2Cl_2 at room temperature were added 4 Å molecular sieves (30 mg) and PDC (140 mg, 0.36 mmol). The alcohol was consumed within 30 minutes. The reaction mixture was diluted with ether and filtered through a florisil column using 30% ethyl acetate/hexane. Concentration of the filtrate provided the sensitive aldehyde **4-16** which was used immediately in the next step without any further purification.

^{1}H NMR (300 MHz, C_6D_6) δ 9.42 (d, *J* = 1.2 Hz, 1H), 7.10-7.30 (m, 5H), 4.19 (d, *J* = 12.2 Hz, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 4.98 (dq, *J* = 1.6, 7.3 Hz, 2H), 3.75 (ddd, *J* = 1.9, 4.6, 8.3 Hz, 1H), 3.27 (dd, *J* = 2.9, 12.3 Hz, 1H), 3.16 (ddd, *J* = 4.6, 4.6, 11.5 Hz, 1H), 2.59 (dd, *J* = 8.7, 15.8 Hz, 1H), 2.07 (dd, *J* = 4.6, 15.8 Hz, 1H), 1.78 (m, 2H), 1.30 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.82 (d, *J* = 7.2 Hz, 3H).

Isopropyl phosphonium bromide (300 mg, 0.78 mmol) was suspended in 6 mL of toluene at -78 °C. Then NaHMDS (1.0 M in THF, 0.52 mL, 0.52 mmol) was added dropwise. After 15 minutes at -78 °C, the suspension was warmed up to 0 °C and stirred for five minutes and recooled to -78 °C. Aldehyde **4-16** in 2 mL of toluene (2 mL rinse) was added dropwise into this orange ylid solution at -78 °C. The reaction mixture was kept at -78 °C for 15 minutes and warmed up to room temperature. After two hours, the reaction was quenched by adding EtOH (1 mL). The reaction mixture was passed through a short silica column (30% EtOAc/hexane) and concentrated. A more careful column chromatography (5% EtOAc/hexane) furnished 24 mg (75%) of **4-17** as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.33 (d, *J* = 6.5 Hz, 2H), 7.21 (m, 2H), 7.12 (m, 1H), 5.30 (d, *J* = 7.5 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H),

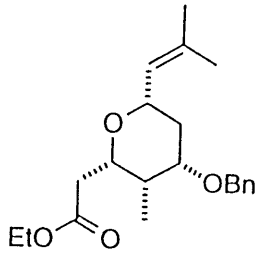
4.06-3.90 (m, 4H), 3.44 (ddd, J = 4.5, 4.5, 11.5 Hz, 1H), 2.69 (dd, J = 8.5, 15.5 Hz, 1H), 2.21 (dd, J = 5.0, 15.5 Hz, 1H), 1.92 (m, 1H), 1.70-1.60 (m, 2H), 1.58 (s, 3H), 1.55 (s, 3H), 1.01 (d, J = 7.3 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 171.4, 135.3, 129.2, 127.9, 127.6, 127.1, 78.4, 75.8, 74.4, 69.9, 60.9, 39.4, 35.8, 26.3, 19.1, 15.0, 6.4, -6.5.

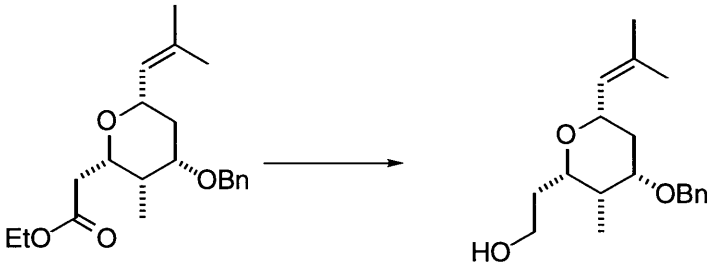
IR (neat) 2926, 2855, 1736, 1454, 1376, 1182, 1072, 1026 cm^{-1}

$[\alpha]_D^{24}$=-25.0 (c=0.50, $CHCl_3$)

HRMS $C_{21}H_{30}O_4$: $[M]^+$ calculated: 347.2222, found: 347.2225.



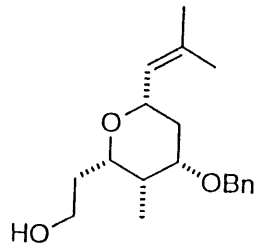
4-17



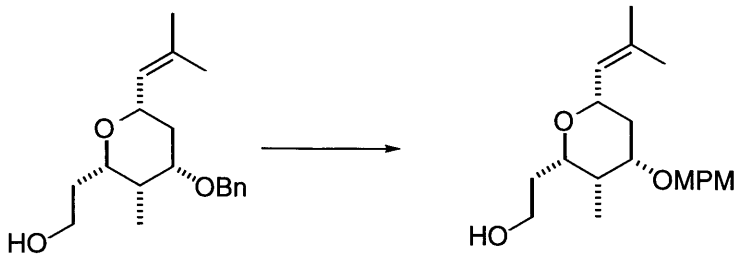
4-17 **4-18**

4-18: To a solution of **4-17** (40 mg, 0.12 mmol) in 2 mL of ether at -78 ^{o}C was added DIBAL (1.0 M in hexane, 0.46 mL, 0.46 mmol). The reaction was allowed to warm up to 0 ^{o}C and then quenched carefully with MeOH. Usual workup gave a crude oil (**4-18**, 36 mg, 100%)which was used as crude in the next step. An analytical sample was obtained by flash column chromatography (35% ethyl acetate/hexane).

^{1}H NMR (500 MHz, C_6D_6) δ 7.35 (d, J = 7.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 7.13 (m, 1H), 5.26 (d, J = 8.0 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.28 (d, J = 11.5 Hz, 1H), 3.92 (ddd, J = 3.0, 7.5, 10.5 Hz, 1H), 3.72 (m, 1H), 3.66 (m, 2H), 3.39 (ddd, J = 4.5, 4.5, 10.5 Hz, 1H), 3.31 (d, J = 10.0 Hz, 1H), 2.24 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.66 (m, 2H), 1.51 (s, 6H), 1.03 (d, J = 7.5 Hz, 3H).



4-18



4-18 **4-20**

4-20: To a solution of the alcohol **4-18** (20 mg, crude) in CH_2Cl_2 (2.5 mL) were added TEA (0.18 mL) and TBSCl (30 mg, 0.20 mmol). After 3 hours, the reaction mixture was poured into water and ether. Usual workup gave a crude oil which was purified by column chromatography (4% ethyl acetate/hexane) to afford the TBS ether (26 mg, 100%).

To a solution of the TBS ether (26 mg, 0.066 mmol) in THF (2 mL) at -55 ^oC was added LDBB stock solution dropwise (2 mL). After 15 minutes, the reaction was quenched by adding saturated NH_4Cl aqueous solution. Extraction with CH_2Cl_2, drying and concentration gave a crude oil which was purified by flash column chromatography (13% ethyl acetate/hexane) to afford the alcohol as a colorless oil (20 mg, 98%).

To a solution of the secondary alcohol (20 mg, 0.061 mmol) in DMF (2 mL) were added NaH (25 mg, 60% suspension in mineral oil, 0.62 mmol) and MPMBr (50 μL, 0.33 mmol). After 5 hours, the reaction was carefully quenched with H_2O and the aqueous layer was extracted with ether. Drying over Na_2SO_4 and concentration gave a crude oil which was purified by column chromatography (4% ethyl acetate/hexane) to afford the MPM ether (22 mg, 81%).

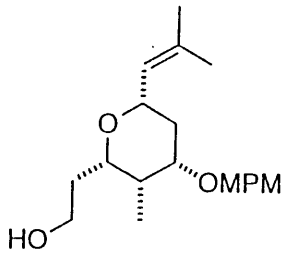
To a solution of the MPM ether (22 mg, 0.049 mmol) in THF (1 mL) was added HF-py stock solution (1 mL). Two hours later, the reaction was neutralized with saturated $NaHCO_3$ aqueous solution and the aqueous layer was extracted with CH_2Cl_2. Drying over Na_2SO_4 and removal of the solvents gave a crude oil which was purified by colunmn

chromatography (20% ethyl acetate/hexane) to afford the primary alcohol **4-20** as a colorless oil (15.5 mg, 93%).

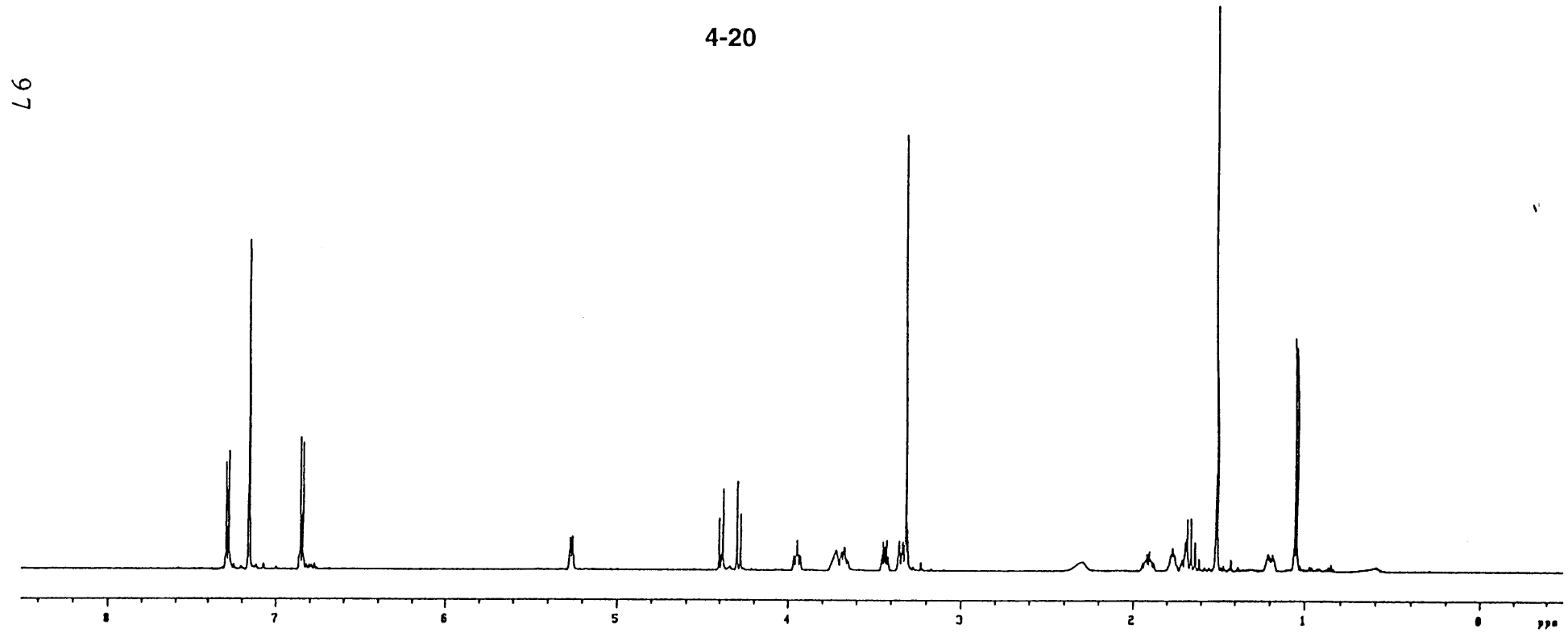
^{1}H NMR (500 MHz, C_6D_6) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 7.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 3.95 (ddd, *J* = 3.0, 7.5, 10.5 Hz, 1H), 3.72 (m, 1H), 3.67 (m, 1H), 3.44 (ddd, *J* = 5.0, 5.0, 10.0 Hz, 1H), 3.34 (dd, *J* = 2.5, 10.5 Hz, 1H), 3.32 (s, 3H), 2.30 (br s, 1H), 1.92 (m, 1H), 1.79 (m, 1H), 1.65 (m, 2H), 1.51 (s, 6H), 1.20 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H).

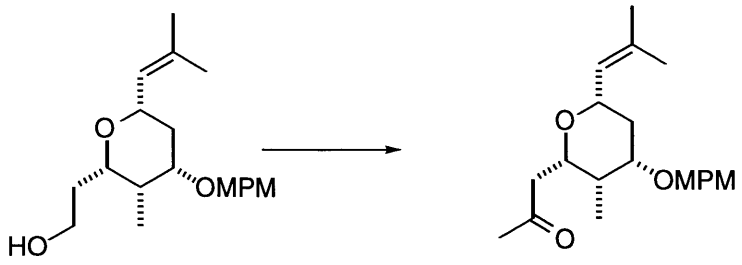
^{13}C NMR (125 MHz, C_6D_6) δ 160.2, 135.7, 132.0, 126.6, 126.9, 114.6, 79.2, 77.8, 74.3, 69.4, 62.2, 55.3, 34.4, 36.2, 33.8, 26.0, 18.8, 6.40.

IR (neat) 3438, 2946, 1613, 1514, 1248, 1073, 1036 cm^{-1}



4-20





4-20 **4-21**

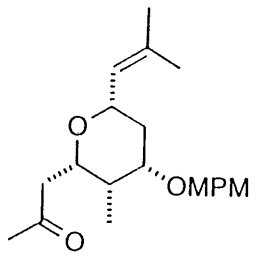
4-21: The alcohol **4-20** (16 mg, 0.046 mmol) was converted into the corresponding aldehyde by a normal Swern oxidation and the aldehyde was used immediately in the next step.

To a solution of the aldehyde in THF (2 mL) at -78 °C was added MeLi (1.4 M in ether, 70 μL, 0.70 mmol). The reaction was instant and quenched with saturated NH_4Cl aqueous solution. Extraction with CH_2Cl_2, drying over Na_2SO_4 and removal of solvents gave a yellow oil which was purified by column chromatography (20% ethyl acetate/hexane). This product was then converted into the ketone **4-21** by another Swern oxidation. Column chromatography gave the purified ketone **4-21** as a colorless oil (13 mg, 82% for 3 steps).

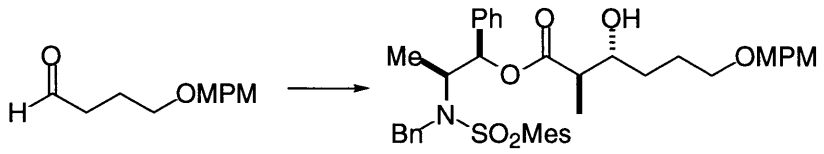
^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.40 (d, *J* = 7.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.10 (ddd, *J* = 3.0, 8.0, 11.0 Hz, 1H), 4.00 (ddd, *J* = 2.0, 4.0, 8.5 Hz, 1H), 3.60 (ddd, *J* = 5.0, 5.0, 11.5 Hz, 1H), 3.41 (s, 3H), 2.65 (dd, *J* = 9.0, 16.5 Hz, 1H), 2.04 (dd, *J* = 4.0, 16.0 Hz, 1H), 1.99 (m, 1H), 1.85 (s, 3H), 1.82-1.71 (m, 2H), 1.64 (s, 3H), 1.61 (s, 3H), 1.12 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR** (125 MHz, C_6D_6) δ 205.5, 160.2, 135.5, 132.0, 129.6, 127.9, 127.7, 114.6, 77.9, 75.2, 74.2, 69.6, 55.3, 47.1, 35.7, 33.7, 31.1, 26.0, 18.8, 6.4. **IR** (neat) 2925, 2856, 1717, 1613, 1513, 1248, 1071 cm^{-1}

$[\alpha]_D^{24}$=-6.0 (c=0.30, CH_2Cl_2)

HRMS (FAB, 3-nitrobenzyl alcohol) $C_{21}H_{30}O_4$ $[M+H]^+$ calculated: 347.2222, found: 347.2222.



4-21



5-1 **3-15**

<u>3-15</u>: Aldehyde **5-1** was readily synthesized from 1,4-butanediol.

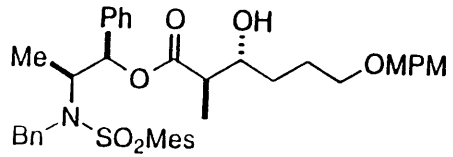
To a solution of *ent*-**3-4** (*1R, 2S*) (17.6 g, 36.6 mmol) in 350 mL of CH_2Cl_2 at -78 °C were added TEA (12.8 mL, 91.5 mmol) and (*c*-Hex)$_2$BOTf (0.89 M in hexane, 82.6 mL, 73.2 mmol). After 2 hours at -78 °C, aldehyde **5-1** (6.8 g, 1.76 mmol) in 5 mL of CH_2Cl_2 (2 mL rinse) was added dropwise at the same temperature. The reaction mixture was stirred at -78 °C for one hour and 0 °C for an additional hour before it was quenched by adding 50 mL of MeOH, 50 mL of pH 7 buffer, and 50 mL of 30% H_2O_2. The heterogeneous mixture was stirred vigorously for 12 hours and then extracted with CH_2Cl_2 thoroughly. The combined organics were dried over $MgSO_4$, filtered, concentrated to give a yellow oil. Flash column chromatography (10%-20% EtOAc/hexane) provided pure **3-15** (9.5 g, 43%) and a mixture of **3-15** and the other isomer (7.0 g, 32%). More **3-15** could be recovered through column chromatography (75% overall).

^{1}H NMR (500 MHz, C_6D_6) δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.10 (t, *J* = 7.0 Hz, 2H), 7.02-6.93 (m, 6H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.54 (s, 2H), 6.20 (d, *J* = 4.0 Hz, 1H), 5.05 (d, *J* = 16.5 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 4.34 (m, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 4.22 (d, *J* = 11.5 Hz, 1H), 3.71 (m, 1H), 3.33 (s, 3H), 3.29 (m, 2H), 3.18 (m, 1H), 2.59 (s, 6H), 2.47 (m, 1H), 1.87 (s, 3H), 1.65-1.52 (m, 3H), 1.36 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H).

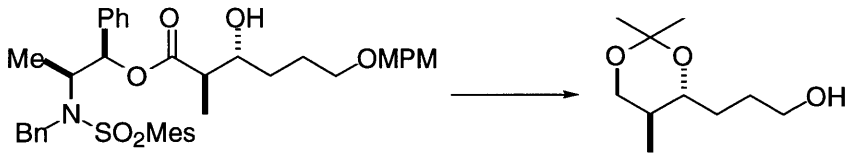
^{13}C NMR (125 MHz, C_6D_6) δ 174.9, 160.3, 142.7, 141.0, 140.4, 140.0, 135.2, 132.8, 131.1, 130.0, 129.1, 129.0, 127.7, 126.8, 114.6, 78.8, 73.8, 73.4, 70.7, 57.9, 55.3, 49.2, 46.9, 32.6, 26.9, 23.7, 21.1, 14.4, 14.1.

IR (neat) 3518, 2939, 1740, 1606, 1513, 1453, 1322, 1248, 1152 cm^{-1}

$[\alpha]_D^{24}$=+16.2 (c=0.78, CH_2Cl_2)



3-15



3-15 **5-2**

5-2: To a suspension of LAH (2.1 g, 55.3 mmol) in 200 mL of THF at 0 °C was added a solution of aldol **3-15** (9.0 g, 13.1 mmol) in 10 mL of THF. After one hour at 0 °C, the reaction was quenched by the addition of water and Na_2SO_4 (solid). The mixture was stirred vigorously until layers became clear (about two hours). The aqueous layer was extracted with CH_2Cl_2 thoroughly and the combined organics were dried over $MgSO_4$, concentrated to give a crude oil which was purified by column chromatography to give 2.8 g (83%) of the diol.

The diol (2.7 g, 10.0 mmol) was dissolved in 50 mL of CH_2Cl_2 and to this solution were added 20 mL of 2, 2-dimethoxypropane and a catalytic amount of $TsOH \cdot H_2O$. The stirring was continued for 10 minutes before the reaction was quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated, washed with brine and concentrated. Flash column chromatography (5:1 EtOAc/hexane) provided 3.0 g (97%) of desired compound.

^{1}H NMR (500 MHz, C_6D_6) δ 7.24 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 4.37 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 3.57 (dd, J = 5.0, 11.5 Hz, 1H), 3.40 (m, 2H), 3.30 (s, 3H), 3.27 (m, 1H), 1.97 (m, 1H), 1.74 (m, 2H), 1.58 (m, 1H), 1.53 (s, 3H), 1.46 (m, 1H), 1.28 (s, 3H), 0.40 (d, J = 7.0 Hz, 3H).

The fully protected compound (4.1 g, 13.3 mmol) was dissolved in CH_2Cl_2 (200 mL) and water (10 mL). To this solution was added DDQ (3.6 g, 15.8 mmol). After one hour, the reaction was quenched with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried with Na_2SO_4 and

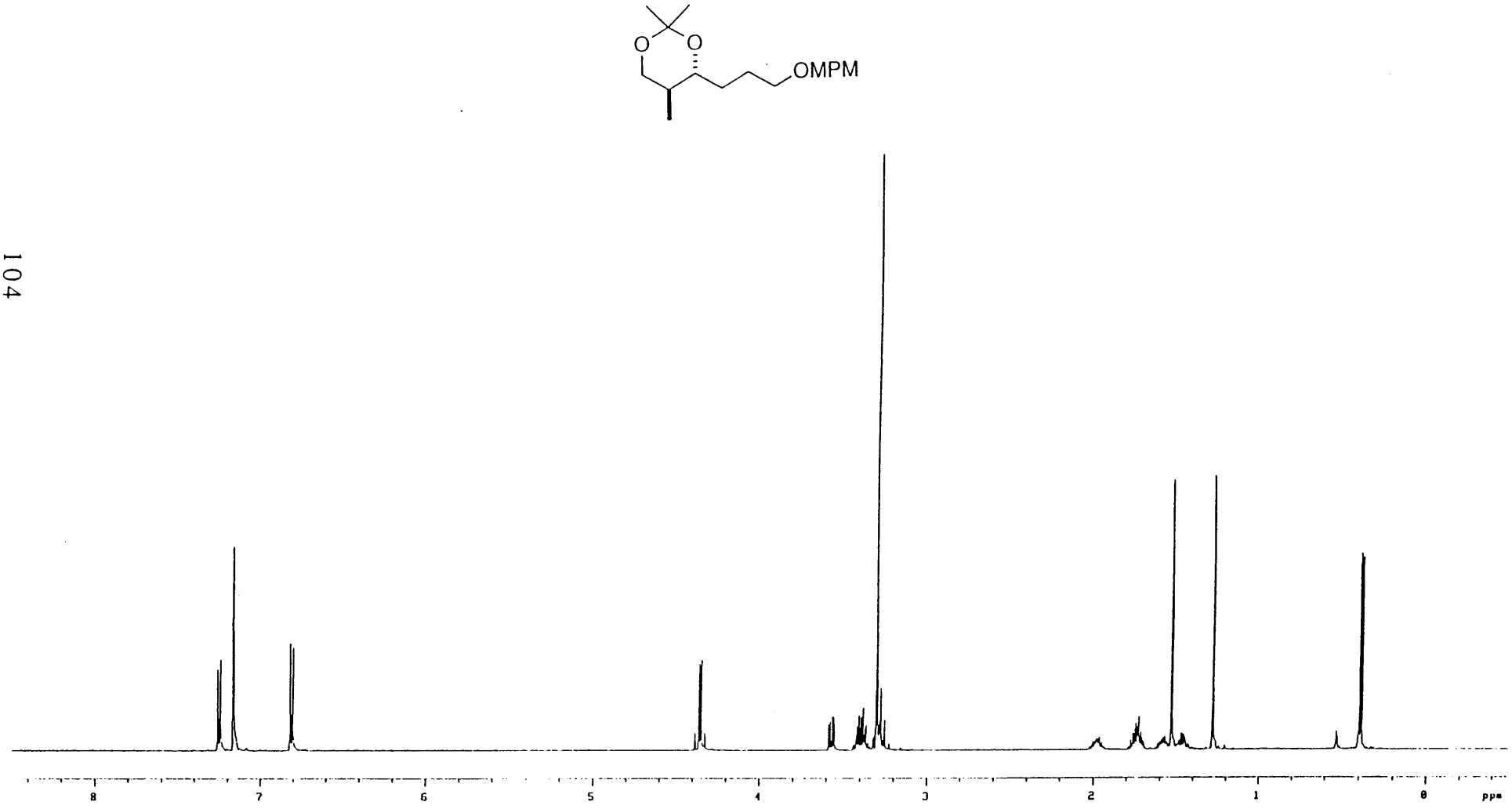
concentrated. Flash chromatography (45%-55% ethyl acetate/hexane) afforded the alcohol **5-2** (2.2 g, 88%) as a light yellow oil.

^{1}H NMR (300 MHz, C_6D_6) δ 3.57-3.45 (m, 3H), 3.28-3.20 (m, 2H), 1.70-1.46 (m, 4H), 1.50 (s, 3H), 1.42-1.25 (m, 1H), 1.27 (s, 3H), 0.36 (d, J = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 98.8, 75.7, 66.5, 63.1, 34.6, 30.5, 29.4, 19.6, 13.0.

IR (neat) 3420 cm^{-1}

$[\alpha]_D^{24}$=+36.5 (c=1.49, $CHCl_3$)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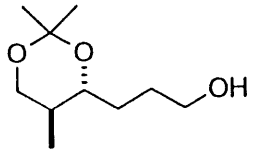
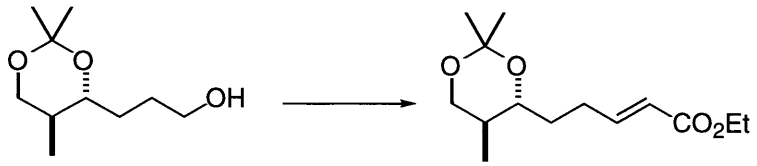


5-2



5-2 **5-3**

5-3: The alcohol **5-2** (1.2 g, 6.37 mmol) was converted into the aldehyde by a standard Swern oxidation.

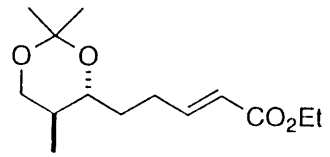
To a suspension of NaH (459 mg, 60% suspension in mineral oil, 11.5 mmol) in toluene (60 mL) at 0 °C was added triethylphosphoacetate (2.53 mL, 12.7 mmol) dropwise. After one hour at 0 °C, aldehyde dissolved in THF (10 mL) was cannulated into this enolate solution. The reaction mixture was kept at 0 °C for one hour before the reaction was quenched with saturated NH_4Cl aqueous solution. The aqueous layer was extracted with ether and the combined organics were dried over Na_2SO_4, concentrated and then the crude oil was purified by column chromatographey (6% ethyl acetate/hexane) to afford **5-3** (1.5 g, 92% for 2 steps) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.09 (ddd, J = 6.5, 7.5, 15.5 Hz, 1H), 5.92 (ddd, J = 2.0, 3.5, 16.0 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.52 (dd, J = 5.5, 11.5 Hz, 1H), 3.21 (t, J = 11.5 Hz, 1H), 3.14 (td, J = 2.5, 9.5 Hz, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 1.46 (s, 3H), 1.42 (m, 1H), 1.29 (m, 1H), 1.24 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 0.28 (d, J = 7.0 Hz, 3H).

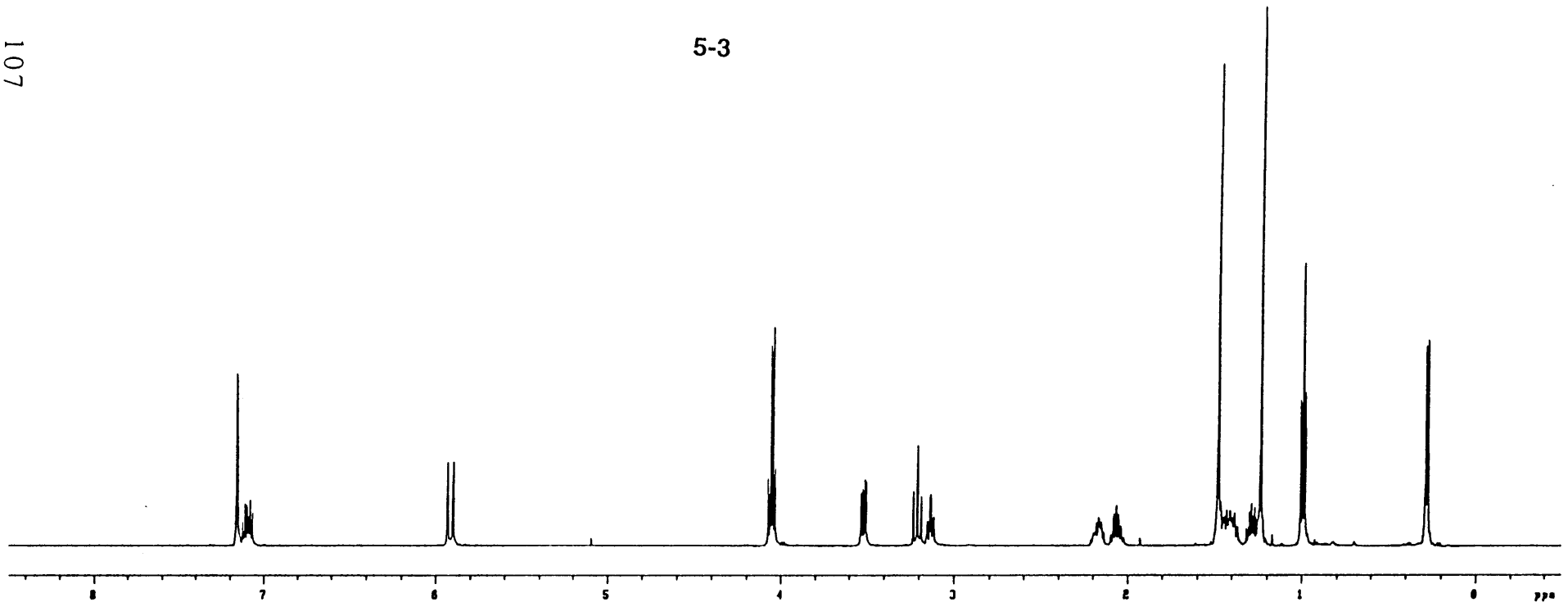
^{13}C NMR (125 MHz, C_6D_6) δ 166.7, 149.5, 122.5, 98.7, 74.5, 66.4, 60.5, 34.8, 32.1, 30.6, 28.3, 19.6, 14.8, 12.8.

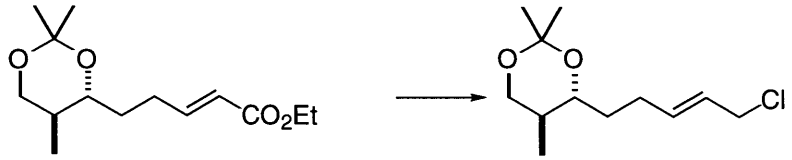
IR (neat) 2991, 2853, 1721, 1654, 1368, 1201, 1060 cm^{-1}

$[\alpha]_D^{24}$=+47.4 (c=0.58, CH_2Cl_2)



5-3





5-3 **5-5**

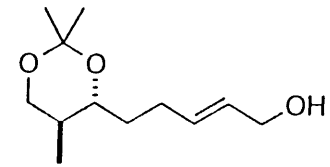
5-5: To a solution of the ester **5-3** (1.5 g, 5.85 mmol) in ether (60 mL) at -78 °C was added DIBAL (1.0 M in hexane, 14.6 mL, 14.6 mmol) dropwise. After 15 minutes at -78 °C, the reaction mixture was warmed up to 0 °C. The reaction was carefully quenched with MeOH and then sodium potassium tartrate (1 M in water, 100 mL) was added. The mixture was stirred vigorously for 3 hours. Usual extractive workup gave a crude oil which was purified by column chromatography (40% ethyl acetate/hexane) to afford the allylic alcohol **5-4** (1.2 g, 98%) as an oil.

^{1}H NMR (500 MHz, C_6D_6) δ 5.55 (m, 2H), 3.88 (s, 2H), 3.57 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.28 (t, *J* = 11.0 Hz, 1H), 2.24 (m, 1H), 2.06 (m, 1H), 1.58 (s, 3H), 1.57 (m, 2H), 1.42 (m, 1H), 1.31 (s, 3H), 0.38 (d, *J* = 6.5 Hz, 3H).

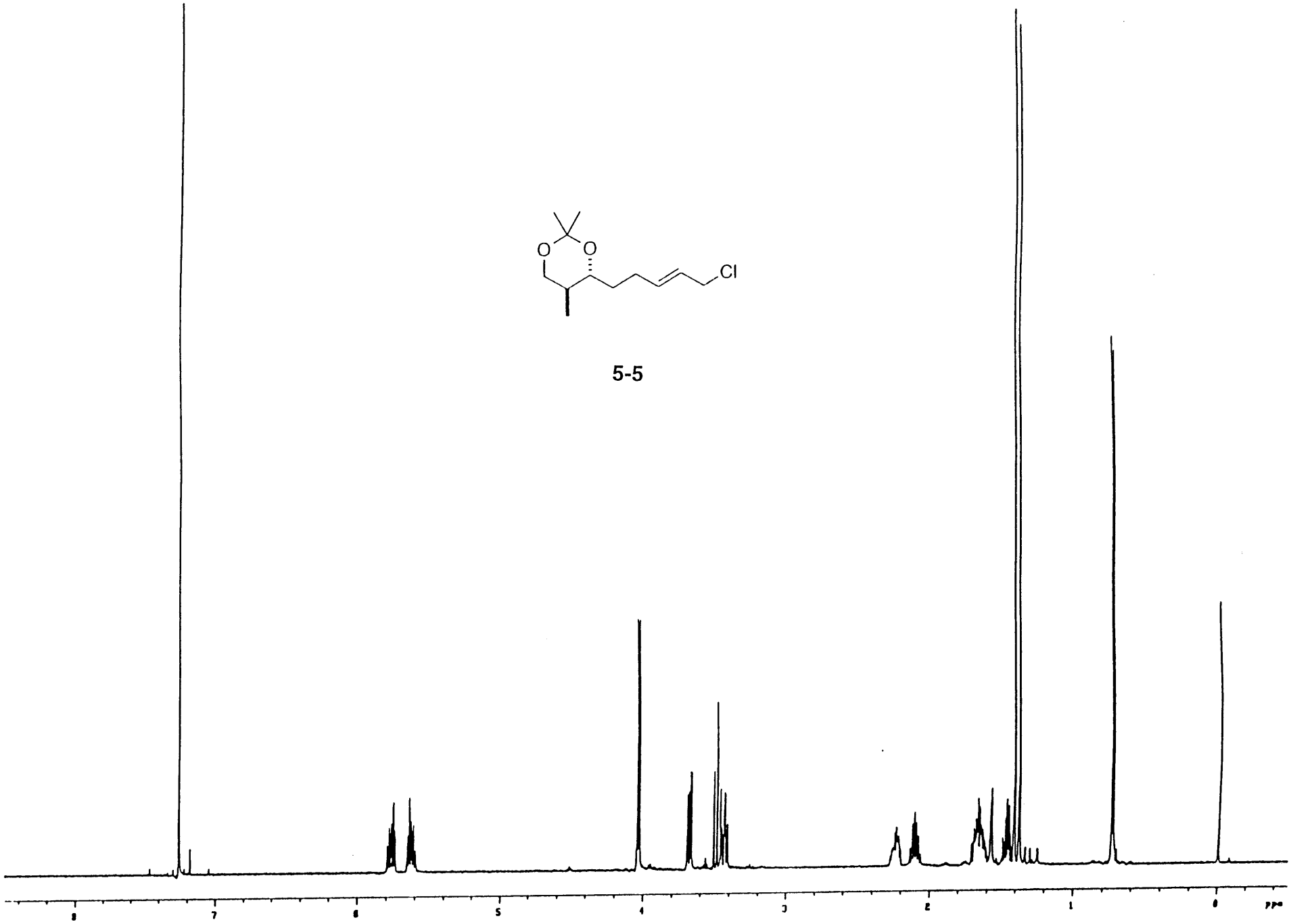
To a solution of the allylic alcohol **5-4** (1.2 g, 5.6 mmol) in 25 mL of THF and 5 mL of CCl_4 was added Ph_3P (2.9 g, 11.2 mmol). The reaction was refluxed for 3 hours. After being cooled to room temperature, the reaction mixture was diluted with ether and washed with saturated ammonium chloride aqueous solution and brine. The organics were dried over $MgSO_4$, concentrated to give an oil which was then purified by column chromatography (5% EtOAc/hexane) to afford 1.2 g (93%) of the allylic chloride **5-5**.

^{1}H NMR (500 MHz, C_6D_6) δ 5.43 (m, 2H), 3.65 (d, *J* = 2.5 Hz, 2H), 3.56 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.26 (d, *J* = 11.0 Hz, 1H), 3.20 (td, *J* = 2.5, 9.5 Hz, 1H), 2.14 (m, 1H), 2.00 (m, 1H), 1.53 (s, 3H), 1.52 (m, 1H), 1.42 (m ,1H), 1.36 (m ,1H), 1.30 (s, 3H), 0.35 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.9, 126.5, 98.4, 74.2, 66.4, 45.8, 34.4, 32.4, 30.1, 27.8, 19.5, 13.0. **IR** (neat) 2992, 2854, 1456, 1380, 1255, 1201, 1113 cm^{-1} $[\alpha]_D^{24}$=+32.2 (c=0.73, $CHCl_3$)

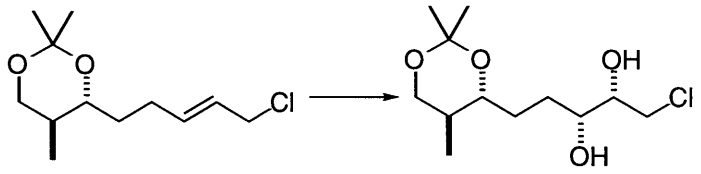
HRMS $C_{12}H_{21}O_2Cl$: $[M-CH_3]^+$ calculated: 217.0995, found: 217.0996.



5-4



5-5



5-5 **5-6**

5-6: To a solution of the allylic chloride **5-5** (1.2 g, 5.2 mmol) in aqueous *t*-BuOH (40 mL of *t*-BuOH, 40 mL of H_2O) at 0 °C were added $NaHCO_3$ (1.3 g, 15.6 mmol), $CH_3SO_2NH_2$ (495 mg, 5.2 mmol), AD-mix-β (7.3 g). The reaction was stirred at 0 °C for 10 hours before it was stopped by adding 100 mL of saturated Na_2SO_3 aqueous solution. The mixture was partitioned and extracted with ethyl acetate thoroughly and the organic layer was washed with brine, dried over $MgSO_4$, concentrated to give a crude oil which was purified by column chromatography (45% EtOAc/hexane) to provide 800 mg (89% yield, based on 426 mg of the recovered olefin) of the chlorohydrin **5-6**.

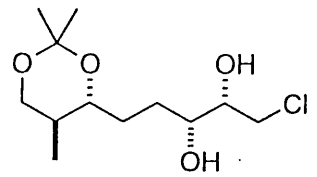
^{1}H NMR (500 MHz, C_6D_6) δ 3.58 (m, 1H), 3.50 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.35-3.48 (m, 2H), 3.61 (m, 1H), 3.20 (t, *J* = 12.5 Hz, 1H), 3.08 (q, *J* = 4.5 Hz, 1H), 2.30 (m, 1H), 1.60-1.42 (m, 3H), 1.46 (s, 3H), 1.32 (m, 1H), 1.23 (s, 3H), 0.34 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 93.9, 71.1, 69.6, 66.5, 61.2, 41.7, 29.8, 25.5, 25.0, 24.8, 14.5, 8.1.

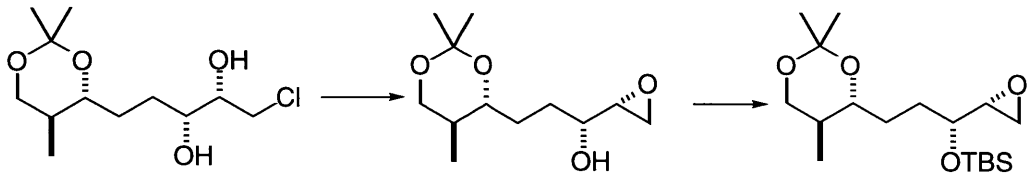
IR (neat) 3394, 2929, 2856, 1458, 1383, 1268, 1201, 1059 cm^{-1}

$[\alpha]_D^{24}$ =+25.4 (c=0.95, $CHCl_3$)

HRMS $C_{12}H_{23}O_4Cl$: $[M-CH_3]^+$ calculated: 251.1050, found: 251.1050.



5-6



5-6 **5-7** fragment C

Fragment C: To a solution of the chlorohydrin **5-6** (800 mg, 3.0 mmol) in 15 mL of THF was added pulverized NaOH (240 mg, 6.0 mmol). The reaction mixture was stirred at room temperature for 10 hours before it was diluted with CH_2Cl_2 and saturated NH_4Cl aqueous solution. The organics were washed with brine, dried over $MgSO_4$, concentrated to give a crude oil which was purified by column chromatography (45% ethyl acetate/hexane) to afford 650 mg (94%) of the terminal epoxide **5-7**.

^{1}H NMR (500 MHz, C_6D_6) δ 3.54 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.28 (m, 2H), 3.25 (t, *J* = 11.5 Hz, 1H), 2.64 (ddd, *J* = 2.5, 4.0, 4.5 Hz, 1H), 2.38 (dd, *J* = 2.5, 5.0 Hz, 1H), 2.30 (dd, *J* = 4.5, 5.0 Hz, 1H), 2.00 (d, *J* = 5.5 Hz, 1H), 1.72-1.50 (m, 3H), 1.51 (s, 3H), 1.26 (s, 3H), 0.38 (d, *J* = 6.5 Hz, 3H).

To a solution of the epoxide **5-7** (650 mg, 2.82 mmol) in 15 mL of CH_2Cl_2 at room temperature were added imidazole (768 mg, 11.28 mmol), TBSCl (851 mg, 5.64 mmol) and DMAP (5 mg). After 5 hours, the reaction mixture was poured into 10 mL of saturated $NaHCO_3$ aqueous solution and 50 mL of ether. The organic phase was washed successively with 1 M $CuSO_4$ aqueous solution, H_2O, brine, and then concentrated. The crude residual oil was purified by flash column chromatography (5% EtOAc/hexane) to give 1.0 g (>100%) of fragment **C** as a colorless oil always contaminated with some silyl residue.

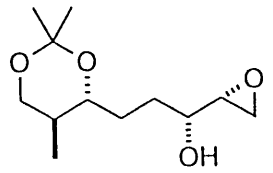
^{1}H NMR (500 MHz, C_6D_6) δ 3.57 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.33 (t, *J* = 10.0 Hz, 1H), 3.29 (d, *J* = 11.5 Hz, 1H), 3.22 (ddd, *J* = 4.0, 7.5, 7.5 Hz, 1H), 2.75 (ddd, *J* = 2.5, 4.0, 7.0 Hz, 1H), 2.30 (t, *J* = 4.5 Hz, 1H), 2.15 (dd, *J* = 2.5, 5.0 Hz, 1H), 1.79 (m, 1H), 1.71-1.52 (m, 3H), 1.52 (s, 3H), 1.30 (s, 3H), 1.06 (s, 9H), 0.45 (d, *J* = 7.0 Hz, 3H), 0.33 (s, 3H), 0.18 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 98.3, 74.8, 74.6, 66.3, 56.2, 45.2, 34.0, 30.0, 29.9, 28.3, 26.1, 19.3, 18.4, 12.9, -4.1, -4.8.

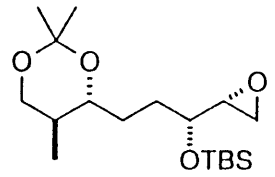
IR (neat) 2928, 2856, 2360, 1462, 1380, 1255, 1101 cm^{-1}

$[\alpha]_D^{24}$ =+23.8 (c=1.0, $CHCl_3$)

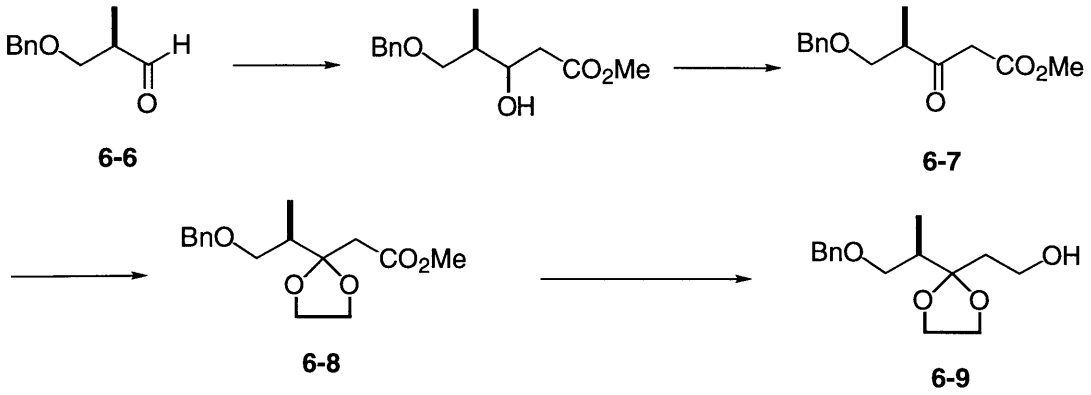
HRMS $C_{18}H_{36}O_4Si$: $[M-CH_3]^+$ calculated: 329.2148, found: 329.2147.



5-7



Fragment C



6-9: Aldehyde **6-6** was prepared from 12.3 g of the corresponding alcohol and used as crude in this reaction. To a solution of ethyl acetate (13.4 mL, 136.8 mmol) in THF (300 mL) at -78 ^{o}C was added LiHMDS (1.0 M in THF, 102.6 mL, 102.6 mmol). After half an hour, the aldehyde **6-6** in 30 mL of THF was cannulated into this enolate solution slowly. The reaction mixture was kept at -78 ^{o}C for 15 minutes before being poured into 400 mL of the 1:1 mixture of pH 7 buffer and saturated ammonium chloride aqueous solution. The aqueous layer was extracted with CH_2Cl_2 (150 mL each time) four times. The combined organics were dried over $MgSO_4$, concentrated to give an oil which was purified by column chromatography (25% to 33% ethyl acetate/hexane) to afford 15.7 g (86% for two steps) of the aldol product as a colorless oil.

The aldol product (15.7 g, 58.9 mmol) was dissolved in 250 mL of CH_2Cl_2 at room temperature. To this solution were added 4 Å molecular sieves (30 g) and PCC (15.3 g, 71.0 mmol). After 1.5 hours, 300 mL of ether was poured into the reaction flask and filtration through a pad of florisil furnished crude ketoester **6-7** as a yellow oil and used without further purification.

The crude ketoester **6-7** was dissolved in 200 mL of benzene. To this solution were added ethylene glycol (35 mL) and $TsOH{\cdot}H_2O$ (0.76 g, 4.0 mmol). The reaction mixture was heated under reflux with Dean-Stark trap to remove water for three hours. Then it was poured into 100 mL of saturated $NaHCO_3$ aqueous solution. The aqueous

layer was extracted with ether and the combined organics were dried over MgSO4 and concentrated to give an oil which was purified by column chromatography (20% ethyl acetate) to furnish compound **6-8** (8.1 g, 35% over four steps) as a clear oil.

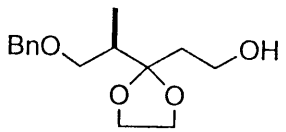
To a solution of **6-8** (8.1 g, 26.2 mmol) in ether (200 mL) at 0 ^{o}C was added LAH (2.0 g, 52.5 mmol) as a solid. The reaction mixture was allowed to warm up to room temperature over one hour. Then CH_2Cl_2 (200 mL) was poured into the reaction and the excess of LAH was quenched by adding THF/water (1:1, 20 mL) dropwise. The mixture was then stirred vigorously with celite. Filtration gave crude alcohol **6-9** (7.0 g, 100%) as a clear oil. An analytical sample was obtained by a column chromatography.

^{1}H NMR (300 MHz, C_6D_6) δ 7.30 (d, *J* = 7.8 Hz, 2H), 7.05-7.20 (m, 3H), 4.34 (d, *J* = 12.6 Hz, 1H), 4.28 (d, *J* = 12.0 Hz, 1H), 3.75 (q, *J* = 6.0 Hz, 2H), 3.60 (dd, *J* = 4.5, 9.3 Hz, 1H), 3.28-3.40 (m, 4H), 3.24 (dd, *J* = 8.1, 8.7 Hz, 1H), 2.44 (br t, *J* = 5.4 Hz, 1H), 2.14 (m, 1H), 1.83 (m, 2H), 1.11 (d, *J* = 6.9 Hz, 3H).

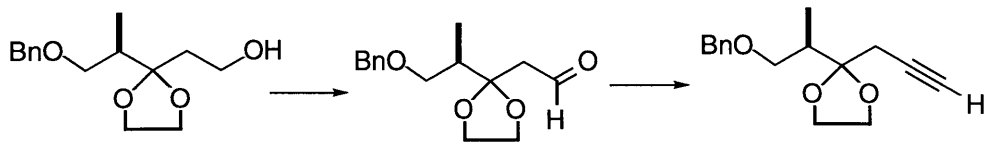
^{13}C NMR (75 MHz, C_6D_6) δ 139.7, 129.0, 128.1, 113.8, 73.7, 72.6, 65.2, 59.0, 41.2, 36.8, 13.5.

IR (neat) 3400, 2950 cm^{-1}

$[\alpha]_D^{24}$=+28.0 (c=0.69, CH_2Cl_2).



6-9



6-9 **6-1**

6-1: The alcohol was then converted into the aldehyde by a usual Swern oxidation.

CBr_4 (922 mg, 2.78 mmol) and Zn (182 mg, 2.78 mmol) were suspended in CH_2Cl_2 (14 mL) at 0 °C. To this suspension was added Ph_3P (728 mg, 2.78 mmol) in portions. The reaction mixture was stirred vigorously at 0 °C for 12 hours at which time the aldehyde in CH_2Cl_2 (5 mL) was added dropwise. The reaction flask was placed in the refrigerator overnight before the reaction mixture was diluted with hexane. Filtration gave a crude oil which was used immediately in the next step.

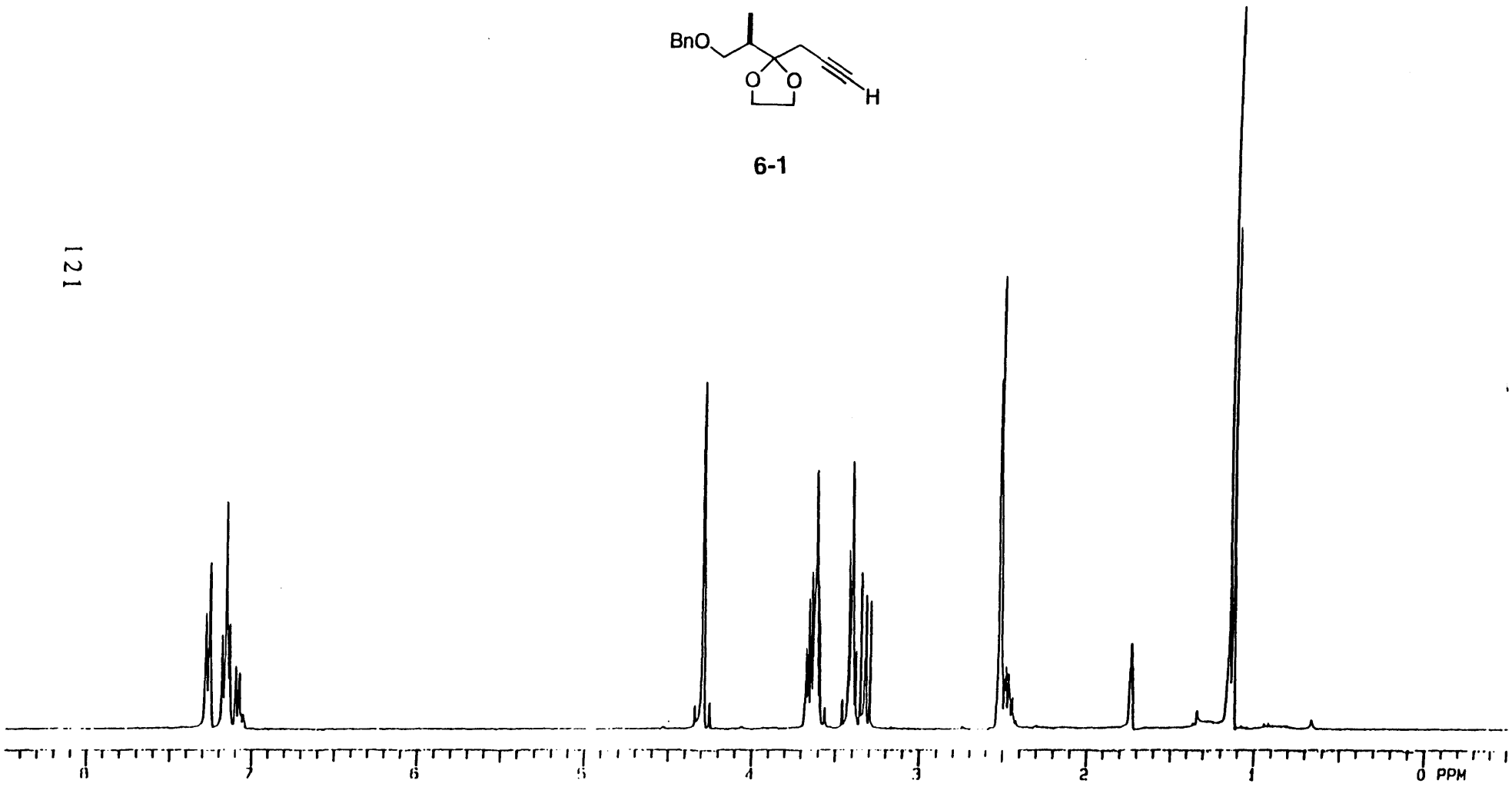
The crude product from above was dissolved in THF (8 mL) at -78 °C. To this solution was added *n*-BuLi (1.0 M in hexane, 7.0 mL, 7.0 mmol) dropwise. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated. The residual oil was purified by flash column chromatography (15% ethyl acetate/hexane) to furnish the alkyne **6-1** (658 mg, 91%) as a clear oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 7.5 Hz, 2H), 7.16 (m, 2H), 7.09 (m, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 3.68 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.62 (m, 3H), 3.41 (m, 2H), 3.34 (dd, *J* = 8.0, 9.5 Hz, 1H), 2.54 (d, *J* = 2.5 Hz, 2H), 2.51 (m, 1H), 1.73 (t, *J* = 2.5 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H).

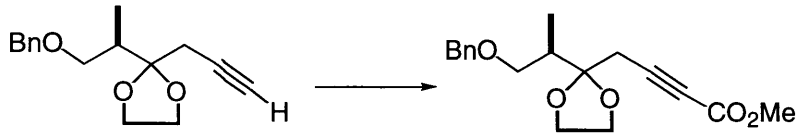
^{13}C NMR (75 MHz, C_6D_6) δ 139.8, 129.0, 128.1, 128.0, 111.8, 81.2, 73.6, 72.3, 70.8, 66.2, 66.0, 41.7, 27.7, 13.2.

IR (neat) 3280, 2972, 2886, 2121, 1454 cm^{-1}

$[\alpha]_D^{24}$=+26.3 (c=0.65, CH_2Cl_2).



6-1



6-1 **6-3**

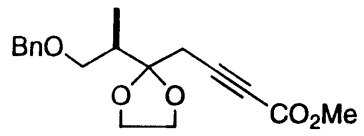
6-3: To a solution of the alkyne **6-1** (155 mg, 0.60 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (2.59 M in hexane, 0.28 mL, 0.71 mmol) dropwise. Five minutes later, methyl chloroformate (0.083 mL, 1.07 mmol) was added as neat slowly. The reaction mixture was allowed to warm up to room temperature gradually and then the reaction was quenched with the addition of 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over $MgSO_4$ and concentrated. The residual oil was purified by flash column chromatography (10%-15% ethyl acetate/hexane) to provide the acetylenic ester **6-3** (173 mg, 91%) as a pale yellow oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, J = 7.5 Hz, 2H), 7.18 (m, 2H), 7.01 (m, 1H), 4.27 (s, 2H), 3.68 (m, 2H), 3.53 (dd, J = 5.5, 9.5 Hz, 1H), 3.34 (m, 2H), 3.26 (dd, J = 6.5, 9.0 Hz, 1H), 3.24 (s, 3H), 2.58 (d, J = 17.5 Hz, 1H), 2.52 (d, J = 17.0 Hz, 1H), 2.24 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H).

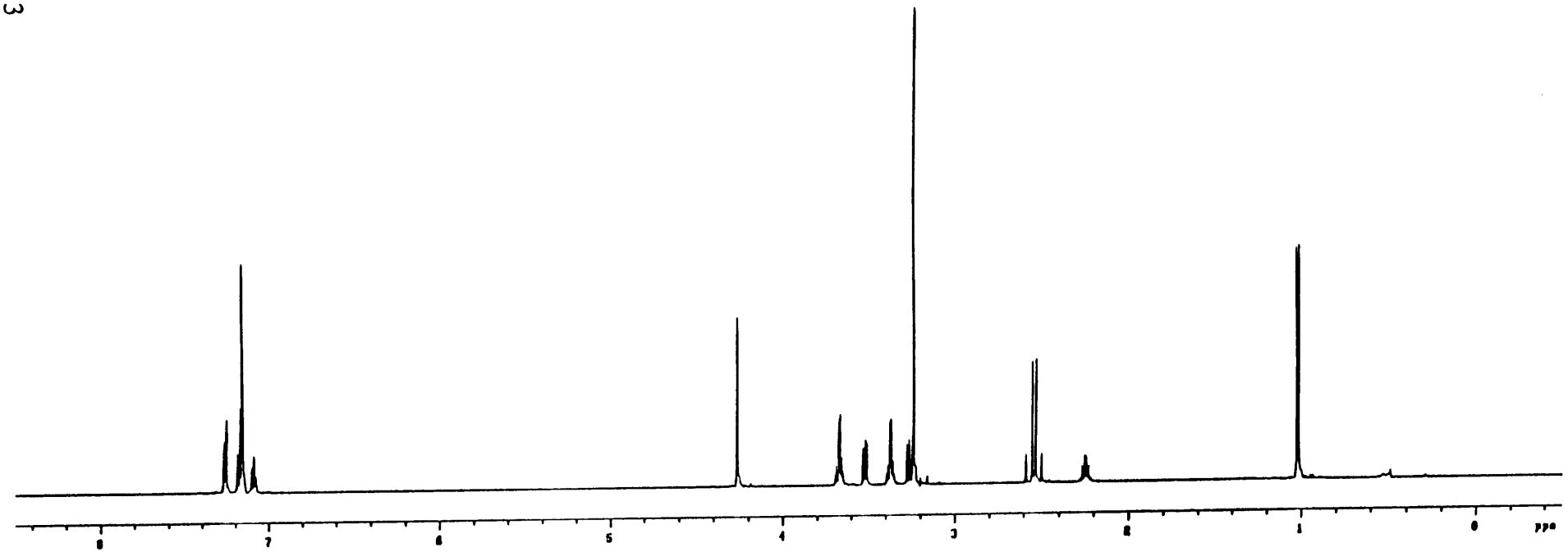
^{13}C NMR (125 MHz, C_6D_6) δ 154.5, 139.6, 129.0, 128.8, 111.4, 86.5, 75.5, 73.6, 72.1, 66.4, 66.3, 42.2, 28.2.2, 13.1.

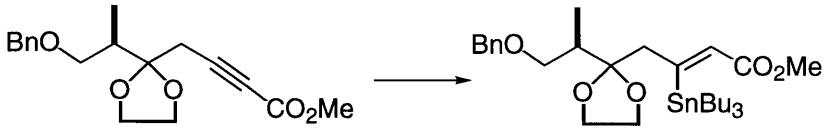
IR (neat) 2891, 2239, 1714, 1262, 1078 cm^{-1}

$[\alpha]_D^{24}$=+23.4 (c=0.58, CH_2Cl_2)



6-3





6-3 **6-5**

6-5: To a suspension of CuCN (66 mg, 0.73 mmol) in THF (5.5 mL) at -78 °C was added *n*-BuLi (2.59 M in hexane, 0.57 mL, 1.47 mmol). The reaction mixture was briefly warmed to get a clear solution and recooled to -78 °C. Then Bu_3SnH (0.40 mL, 1.47 mmol) was added dropwise via syringe. After 15 minutes at -78 °C, the ester **6-3** (94 mg, 0.29 mmol) in 1 mL THF was cannulated into this solution. The reaction mixture was kept at -40 °C for half an hour before the reaction was quenched with a few drops of MeOH and 5 mL of saturated ammonium chloride aqueous solution. Extraction with ether, drying over $MgSO_4$ and removal of solvents gave a crude oil which was purified by flash column chromatography (2% ethyl acetate/hexane) to give compound **6-5** (130 mg, 70%) as a clear oil.

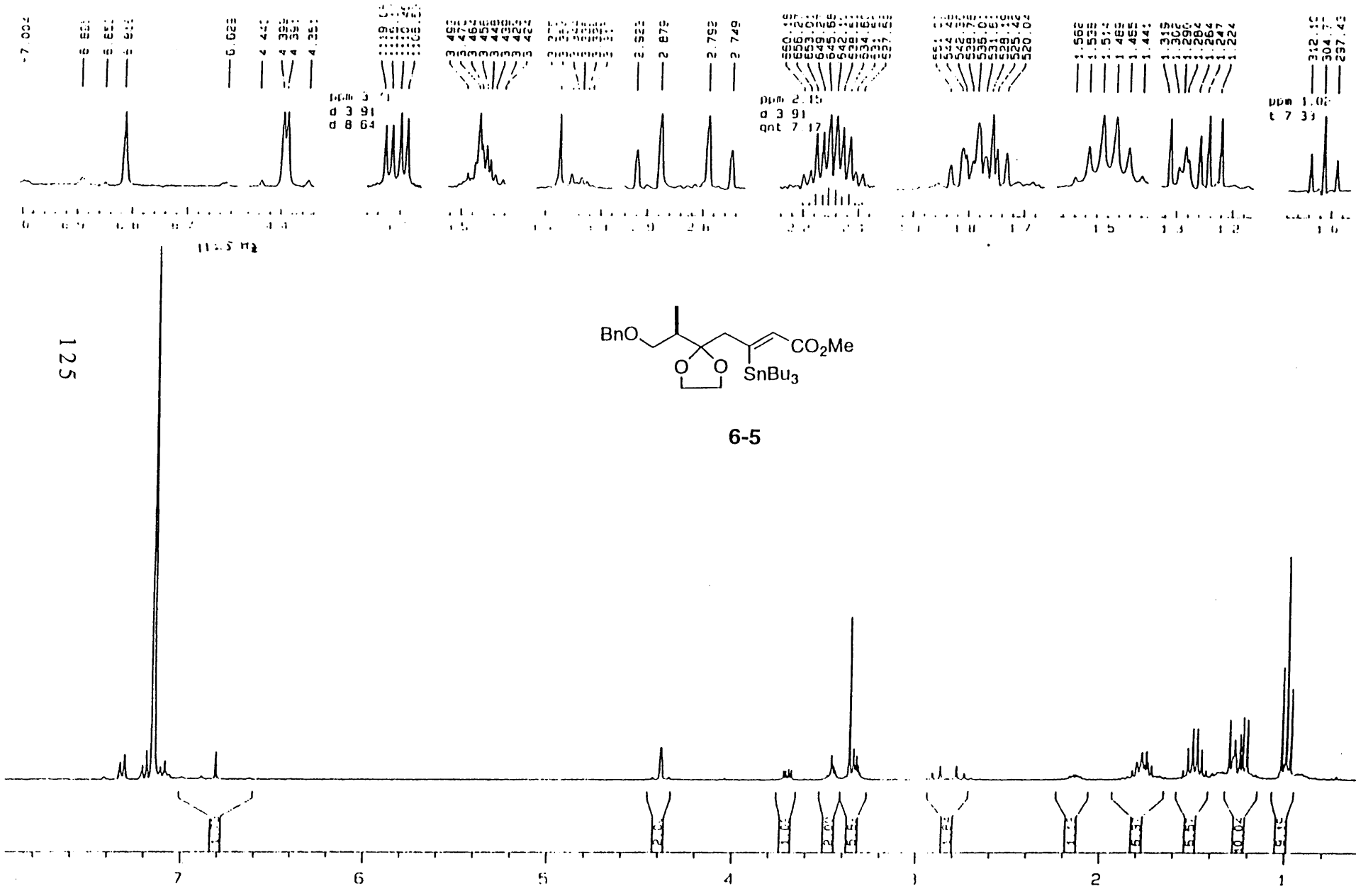
^{1}H NMR (300 MHz, C_6D_6) δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.03-7.22 (m, 3H), 6.28 (s, 1H, *J*(Sn) = 112.5 Hz) 4.42 (d, *J* = 12.3 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 3.71 (dd, *J* = 3.9, 8.6 Hz, 1H), 3.45 (m, 2H), 3.38 (s, 3H), 3.33 (m, 2H), 2.90 (d, *J* = 13.2 Hz, 1H), 2.77 (d, *J* = 12.9 Hz, 1H), 2.15 (dq, *J* = 3.9, 7.2 Hz, 1H), 1.80 (m, 6H), 1.50 (m, 6H), 1.22 (m, 6H), 1.02 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (75 MHz, C_6D_6) δ 171.6, 168.8, 139.8, 133.2, 129.0, 113.6, 73.9, 72.8, 66.0, 51.7, 43.9, 43.3, 30.5, 28.8, 14.8, 14.1, 12.8.

IR (neat) 2956, 1710, 1596, 1454, 1330, 1197, 1094, 1040 cm^{-1}

$[\alpha]_D^{24}$=+18.0 (c=2.0, CH_2Cl_2)

HRMS $C_{30}H_{50}O_5Sn$ $[M-Bu]^+$ calculated: 553.1976, found: 553.1978.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O
O
SnBu3
6-5
125
7
6
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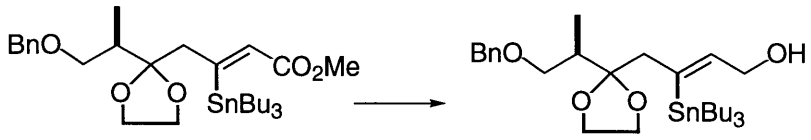
3
2
1
ppm



6-5 **6-11**

6-11: To a solution of the ester **6-5** (737 mg, 1.21 mmol) in 25 mL of ether at -78 °C was added DIBAL (1.0 M in hexane, 3.36 mL, 3.63 mmol). After 10 minutes, the reaction was quenched with the additions of a few drops of MeOH and 5 mL of saturated ammonium chloride aqueous solution. The reaction mixture was warmed up to room temperature. Then 5 mL of sodium potassium tartrate (1 M aqueous solution) was added and the mixture was stirred vigorously for 2 hours. Extraction with ether, drying over $MgSO_4$ and removal of solvents gave a crude oil which was purified by flash column chromatography (10%-15% ethyl acetate/hexane) to afford the allylic alcohol **6-11** (519 mg, 74%) as a clear oil.

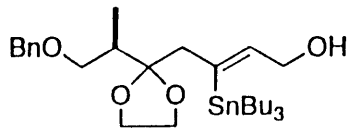
^{1}H NMR (300 MHz, C_6D_6) δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.02-7.18 (m, 3H), 6.36 (t, *J* = 6.3 Hz, 1H, *J*(Sn-H) = 133.8 Hz), 4.38 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.3 Hz, 1H), 3.94 (br d, *J* = 4.5 Hz, 1H), 3.72 (dd, *J* = 3.6, 8.7 Hz, 1H), 3.51 (m, 2H), 3.37 (m, 2H), 3.34 (dd, *J* = 8.7, 8.7 Hz, 1H), 2.68 (d, *J* = 12.6 Hz, 1H), 2.56 (d, *J* = 13.0 Hz, 1H), 2.21 (m, 1H), 1.60 (m, 6H), 1.40 (m, 6H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.03 (m, 6H), 0.95 (t, *J* = 7.2 Hz, 9H).

^{13}C NMR (75 MHz, C_6D_6) δ 145.0, 142.0, 140.0, 129.0, 128.1, 113.5, 74.0, 72.8, 66.1, 65.5, 45.1, 42.6, 30.4, 28.7, 14.7, 14.0, 12.2.

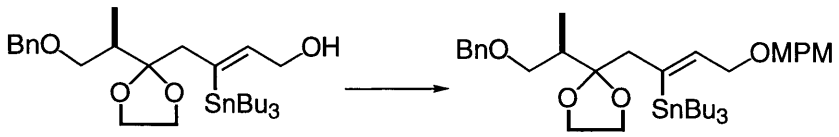
IR (neat) 3394, 2954, 2922, 1454, 1374, 1136, 1074, 1028 cm^{-1}

$[\alpha]_D^{24}$=+17.9 (c=0.76, $CHCl_3$)

HRMS $C_{29}H_{50}O_4Sn$ $[M\text{-}Bu]^+$ calculated: 525.2027 , found: 525.2028.



6-11



6-11 **6-12**

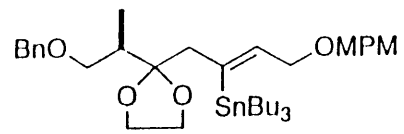
6-12: To a solution of the alcohol **6-11** (100 mg, 0.17 mmol) in 3 mL of DMF at room temperature was added sodium hydride (14 mg, 60% suspension in mineral oil, 0.35 mmol) followed by MPMCl (35 μL, 0.26 mmol). After 1 hour, the reaction was quenched by adding 10 mL of water slowly into the reaction mixture. Extraction with ether, drying over $MgSO_4$ and removal of solvents gave a crude oil which was purified by flash column chromatography (5% ethyl acetate/hexane) to afford compound **6-12** (110 mg, 91%) as a clear oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.09 (m, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.63 (t, *J* = 6.0 Hz, *J*(Sn-H) = 125 Hz, 1H), 4.45 (s, 2H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 2H), 3.79 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.61 (m, 2H), 3.43 (m, 2H), 3.39 (t, *J* = 9.0 Hz, 1H), 3.30 (s, 3H), 2.76 (d, *J* = 13.5 Hz, 1H), 2.64 (d, *J* = 13.5 Hz, 1H), 2.29 (m, 1H), 1.67 (m, 6H), 1.45 (m, 6H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.10 (m, 6H), 1.00 (t, *J* = 6.0 Hz, 9H).

^{13}C NMR (125 MHz, C_6D_6) δ 160.2, 142.9, 139.9, 131.5, 130.1, 129.0, 128.1, 128.0, 114.5, 113.5, 73.8, 72.9, 72.8, 72.7, 66.0, 55.2, 45.1, 42.6, 30.3, 30.2, 30.1, 28.6, 14.5, 13.8, 11.9.

IR (neat) 2955, 1613, 1514, 1454, 1362, 1302, 1248 cm^{-1}

$[\alpha]_D^{24}$= +18.0 (c=0.55, CH_2Cl_2)



6-12

6-12 **fragment D**

Fragment D: To a solution of vinyl tin **6-12** (78 mg, 0.11 mmol) in 4 mL of CH_2Cl_2 at 0 °C was cannulated a solution of I_2 (57 mg, 0.22 mmol) in 1 mL of CH_2Cl_2 carefully. The reaction mixture was gradually warmed up to room temperature for 15 minutes. The reaction was quenched by adding 1 M Na_2SO_3 aqueous solution. The aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$ and concentrated. The crude oil was purified by column chromatography (7% ethyl acetate/hexane) to afford the vinyl iodide (fragment **D**) as a colorless oil (53 mg, 90%).

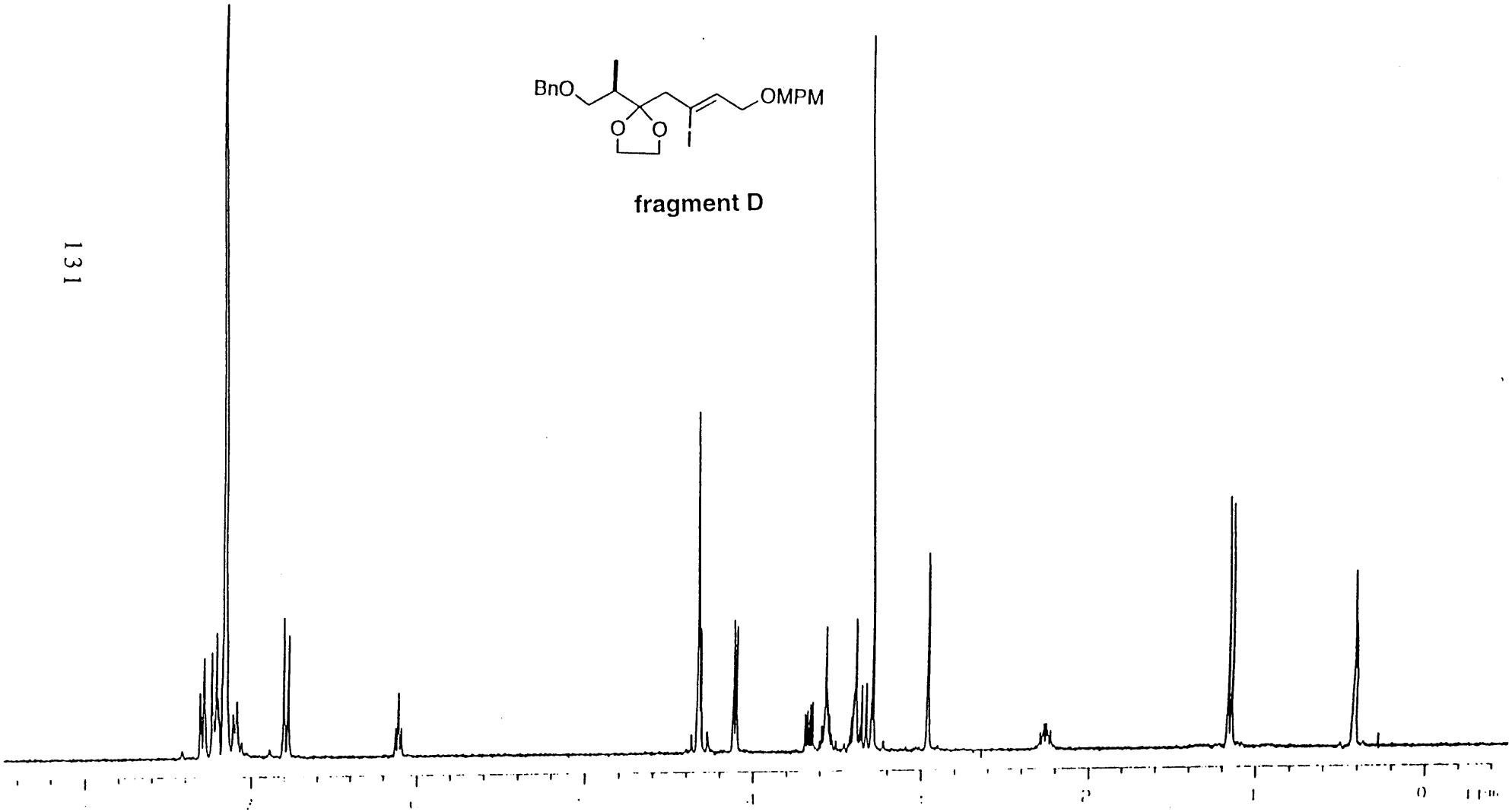
^{1}H NMR (300 MHz, C_6D_6) δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.22 (m, 3H), 7.10 (m, 2H), 6.80 (d, *J* = 7.8 Hz, 2H), 6.12 (t, *J* = 5.4 Hz, 1H), 4.34 (m, 4H), 4.11 (d, *J* = 5.4 Hz, 2H), 3.67 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.57 (m, 2H), 3.40 (m, 2H), 3.33 (dd, *J* = 7.8, 8.7 Hz, 1H), 3.29 (s, 3H), 2.97 (s, 2H), 2.26 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 160.2, 140.0, 138.8, 131.3, 130.0, 129.0, 128.1, 114.5, 112.8, 105.1, 99.3, 94.3, 75.8, 73.7, 72.8, 72.4, 65.9, 65.8, 55.2, 50.2, 42.3, 13.4.

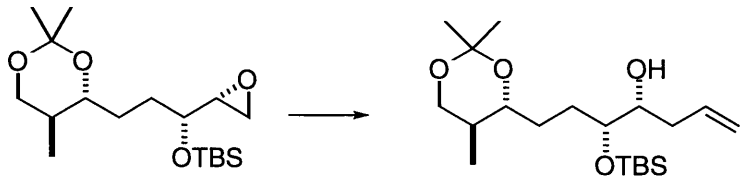
IR (neat) 2882, 1612, 1513, 1453, 1361, 1302, 1248, 1093, 1031 cm^{-1}

$[\alpha]_D^{24}$= +14.3, (c=0.10, CH_2Cl_2)

HRMS (FAB, 3-nitrobenzyl alcohol) $C_{25}H_{31}O_5I$ [M+H] calculated: 539.1201 , found: 539.1294



fragment D



fragment C **9-1**

9-1: To a suspension of CuI (75 mg, 0.4 mmol) in 15 mL of THF at -78 °C was added vinyl magnesium bromide (1.0 M in THF, 3.9 mL, 3.9 mmol). After 10 minutes, epoxide **C** (260 mg, 0.75 mmol) in 1 mL of THF was cannulated into this solution. The reaction mixture was allowed to warm to 0 °C over one hour. The reaction was then quenched with 10 mL of saturated NH_4Cl aqueous solution. Extraction with CH_2Cl_2, drying over Na_2SO_4 and concentration gave a crude oil which was purified by column chromatography to furnish the alcohol **9-1** (250 mg, 89%) as a pale yellow oil.

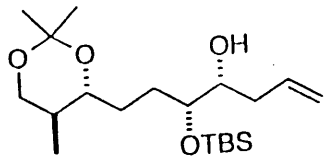
^{1}H NMR (500 MHz, C_6D_6) δ 5.96 (dddd, *J* = 7.0, 7.0, 10.0, 17.0 Hz, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 3.63 (m, 2H), 3.57 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.28 (t, *J* = 11.0 Hz, 1H), 2.29 (m, 1H), 2.05 (d, *J* = 6.5 Hz, 1H), 1.81 (m, 2H), 1.68 (m, 1H), 1.58 (m, 1H), 1.52 (s, 3H), 1.44 (m, 1H), 1.31 (s, 3H), 0.95 (s, 9H), 0.43 (d, *J* = 7.0 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 136.5, 128.8, 117.4, 98.7, 76.0, 75.5, 73.2, 66.5, 39.2, 34.8, 30.6, 29.7, 29.2, 26.6, 19.8, 18.8, 13.1, -3.6, -3.9.

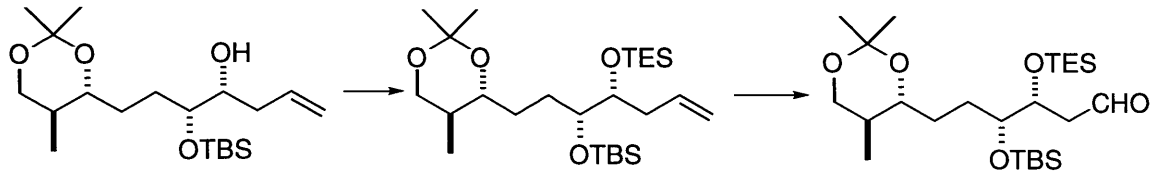
IR (neat) 3473, 3076, 2954, 2856, 1641, 1462, 1380, 1255, 1063, 836 cm^{-1}

$[\alpha]_D^{24}$= +22.4 (c=0.2, CH_2Cl_2)

HRMS $C_{20}H_{40}O_4Si$ $[M-CH_3]^+$ calculated: 357.2461, found: 357.2462.



9-1



9-1 **fragment C'**

Fragment C': To a solution of the alcohol **9-1** (173 mg, 0.46 mmol) in 6 mL of CH_2Cl_2 at -78 °C were added 2, 6-lutidine (0.11 mL, 0.98 mmol) and TESOTf (0.16 mL, 0.73 mmol). After 15 minutes, the reaction mixture was poured into 10 mL of water and 50 mL of ether. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$ and concentrated. The crude oil was purified by column chromatography (2% ethyl acetate/hexane) to give the protected compound (265 mg, 100%) as a clear oil.

^{1}H NMR (300 MHz, C_6D_6) δ 6.02 (dddd, J = 7.0, 7.5, 9.9, 17.4 Hz, 1H), 5.15 (d, J = 17.1 Hz, 1H), 5.08 (d, J = 9.9 Hz, 1H), 3.82 (m, 2H), 3.59 (dd, J = 5.1, 11.4 Hz, 1H), 3.43 (m, 1H), 3.31 (t, J = 11.4 Hz, 1H), 2.65 (dd, J = 6.0, 13.2 Hz, 1H), 2.30 (m, 1H), 2.05 (m, 1H), 1.74 (m, 4H), 1.53 (s, 3H), 1.33 (s, 3H), 1.04 (m, 9H), 1.00 (s, 9H), 0.67 (m, 6H), 0.49 (d, J = 6.6 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 137.7, 128.7, 117.0, 98.7, 76.7, 76.5, 75.6, 66.6, 36.6, 34.4, 31.1, 30.7, 26.6, 26.3, 19.7, 18.8, 13.1, 7.7, 7.6, 7.3, 6.1, -3.4, -3.8.

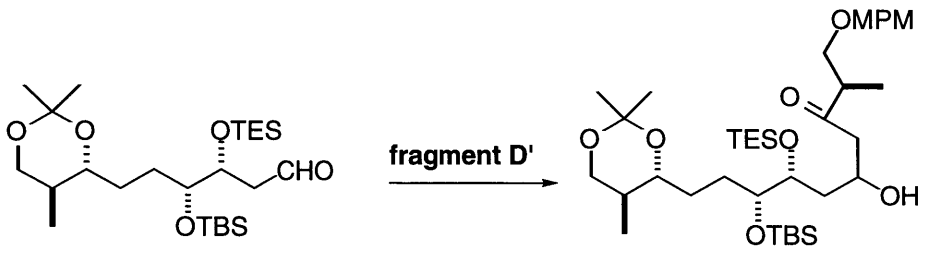
IR (neat) 3076, 2955, 2877, 1642, 1462, 1378, 1366, 1098, 1006 cm^{-1}

$[\alpha]_D^{24}$=+52.2 (c=0.23, CH_2Cl_2)

HRMS $C_{26}H_{54}O_4Si_2$ $[M-CH_3]^+$ calculated: 471.3326, found: 471.3324.

Fragment C': The alkene (45 mg, 0.92 mmol) was dissolved in CH_2Cl_2 (3 mL) and MeOH (0.75 mL) at -78 °C. A stream of ozone was bubbled through this solution until a light blue color was visible. The excessive ozone was purged with argon. Then Ph_3P (49

mg, 0.18 mmol) was added as a solid. The reaction mixture was allowed to warm up to room temperature over one hour. The solvents were removed and the residue was purified by column chromatography (5% ethyl acetate/hexane) to give the unstable aldehyde (fragment **C'**, 41 mg, 91%) which was used immediately in the next step.



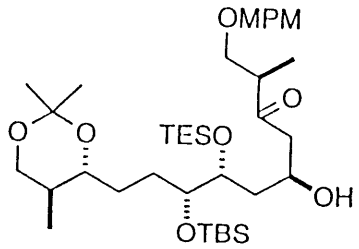
fragment C' **9-3**

Fragment D': Fragment **D'** was synthesized from the known aldehyde (*R*)-**8-7**.

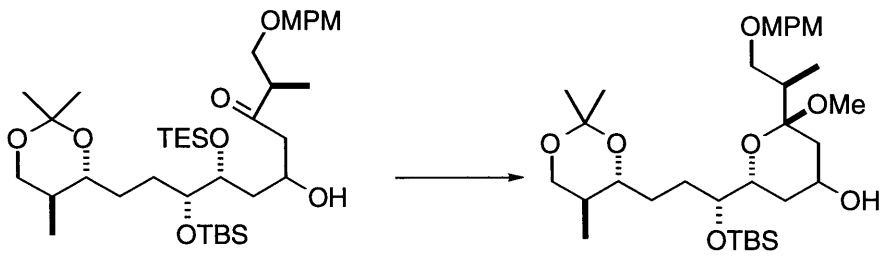
^{1}H NMR (500 MHz, C_6D_6) δ 7.14 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 4.24 (d, *J* = 11.5 Hz, 1H), 4.20 (d, *J* = 11.5 Hz, 1H), 3.42 (dd, *J* = 7.5, 9.0 Hz, 1H), 3.29 (s, 3H), 3.22 (dd, *J* = 5.5, 9.5 Hz, 1H), 2.50 (m, 1H), 1.82 (s, 3H), 0.88 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, C_6D_6) δ 209.3, 160.2, 131.2, 129.9, 122.8, 114.6, 73.5, 72.6, 55.2, 29.3, 13.9. **IR** (neat) 2935, 2859, 1714, 1612, 1514, 1462, 1248, 1093, 820.0 cm^{-1} $[\alpha]_D^{24}$= -14.0 (c=0.53, $CHCl_3$).

9-3: To a solution of fragment **D'** (764 mg, 3.44 mmol) in CH_2Cl_2 (20 mL) at -78 °C were added Bu_2BOTf (1.0 M in CH_2Cl_2, 4.13 mL, 4.13 mmol) and TEA (1.20 mL, 8.6 mmol). The reaction mixture was kept at -78 °C for half an hour and 0 °C for half an hour and recooled to -78 °C. Then the aldehyde (660 mg, 1.34 mmol) dissolved in CH_2Cl_2 (2 mL) was cannulated into the enolate solution. The reaction was kept in the freezer (at about -65 °C) overnight. Usual workup gave the aldol product which was used as crude. Alternatively it can be purified by column chromatography (20% ethyl acetate/hexane).

^{1}H NMR (500 MHz, C_6D_6) δ 7.12 (d, *J* = 7.0 Hz, 2H), 6.81 (d, *J* = 7.1 Hz, 2H), 4.46 (br.s, 1H), 4.38 (br ddd, *J* = 2.5, 4.5, 10.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 3.90 (m, 1H), 3.61 (dd, *J* = 5.0, 11.5 Hz, 1H), 3.51 (m, 2H), 3.39 (t, *J* = 8.5 Hz, 1H), 3.34 (s, 3H), 3.33 (t, *J* = 11.5 Hz, 1H), 3.15 (dd, *J* = 5.0, 9.0 Hz, 1H), 2.49 (m, 1H), 2.31 (m, 2H), 2.14 (t, *J* = 12.5 Hz, 1H), 1.73-2.01 (m, 5H), 1.56 (s, 3H), 1.47 (t, *J* = 10.0 Hz, 1H), 1.36 (s, 3H), 1.11 (m, 9H), 1.07 (s, 9H), 0.78 (m, 9H), 0.52 (d, *J* = 7.0 Hz, 3H), 0.29 (s, 3H), 0.21 (s, 3H).



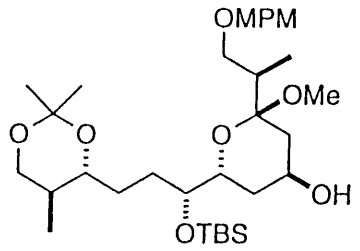
9-3



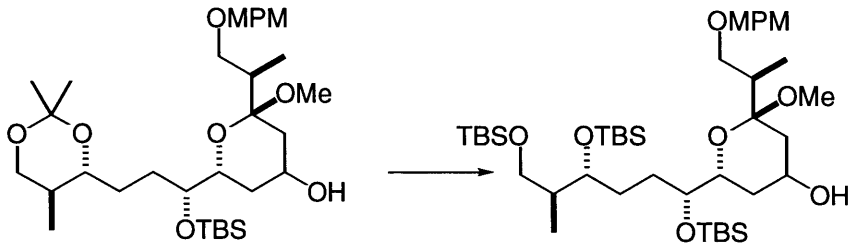
9-3 **9-4**

9-4: The crude or the purified aldol product (about 1.34 mmol) was dissolved in MeOH (3 mL). To this solution was added PPTS (catalytic amount, 10 mg). After 10 minutes, the reaction was quenched with the addition of saturated $NaHCO_3$ aqueous solution and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, concentrated to give an oil which was purified by column chromatography (15% ethyl acetate/hexane) to afford compound **9-4** as an oil (104 mg, 80% for two steps).

^{1}H NMR (500 MHz, C_6D_6) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.36 (s, 2H), 4.06 (m, 1H), 3.76 (m, 1H), 3.65 (ddd, *J* = 2.0, 6.0, 12.0 Hz, 1H), 3.59 (m, 2H), 3.37 (t, *J* = 10.0 Hz, 1H), 3.30 (t, *J* = 11.5 Hz, 1H), 3.30 (s, 3H), 3.03 (t, *J* = 8.5 Hz, 1H), 3.13 (s, 3H), 2.49 (m, 1H), 1.95 (m, 1H), 1.76-1.86 (m, 2H), 1.66 (m, 1H), 1.58 (m, 1H), 1.54 (s, 3H), 1.34 (dd, *J* = 11.0, 12.5 Hz, 1H), 1.33 (s, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.14 (q, *J* = 11.5 Hz, 1H), 1.02 (s, 9H), 0.77 (br s, 1H), 0.48 (d, *J* = 7.0 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H).



9-4



9-4 **9-12**

9-12: To a solution of **9-4** (485 mg, 0.79 mmol) in CH_2Cl_2 (15 mL) were added pyridine (0.26 mL, 3.18 mmol), acetic anhydride (0.15 mL, 1.59 mmol) and a catalytic amount of DMAP. After 2 hours, the reaction mixture was poured into water and the aqueous layer was extracted with ether. The combined organics were dried over Na_2SO_4 and concentrated to give an oil which was used as crude.

The crude acetate was taken in MeOH (15 mL) at 0 ^oC and a catalytic amount of CSA (about 10 mg) was added. After 2 hours, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and concentrated to give an oil which was purified by column chromatography (15% ethyl acetate/hexane) to afford the diol **9-11** as a colorless oil (414 mg, 85% for two steps)

The diol **9-11** (360 mg, 0.59 mmol) was dissolved in CH_2Cl_2 (10 mL) at -78 ^oC. To this solution were added 2, 6-lutidine (0.41 mL, 3.54 mmol) and TBSOTf (0.40 mL, 1.76 mmol). The reaction mixture was warmed up gradually to room temperature and the reaction was quenched with water. The aqueous layer was extracted with ether and the combined organics were washed with saturated $NaHCO_3$ aqueous solution and brine and dried over Na_2SO_4. Removal of the solvents gave a crude oil which was used as crude.

The crude product from above was dissolved in MeOH (10 mL) and to this solution was added K_2CO_3 (200 mg). The stirring was continued for two hours and the reaction was quenched with water. Extraction with CH_2Cl_2, drying over $MgSO_4$ and concentration

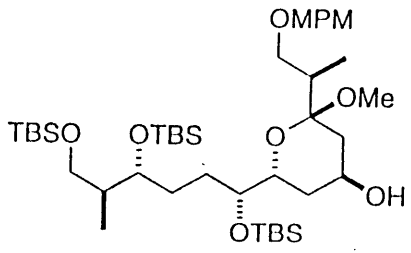
gave an oil which was purified by column chromatography (17% ethyl acetate/hexane) to afford compound **9-12** as a colorless oil (445 mg, 95% for two steps).

^{1}H NMR (500 MHz, C_6D_6) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.08 (m, 1H), 3.89 (br q, *J* = 3.5 Hz, 1H), 3.76 (m, 1H), 3.68 (m, 2H), 3.57 (m, 2H), 3.70 (s, 3H), 3.23 (t, *J* = 8.5 Hz, 1H), 3.12 (s, 3H), 2.50 (m, 1H), 2.04 (m, 1H), 1.80 (m, 2H), 1.62 (m , 1H), 1.36 (dd, *J* = 11.0, 12.5 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.23 (q, *J* = 12.0 Hz, 1H), 1.04 (s, 9H), 1.03 (s, 9H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 6H), 0.10 (s, 6H).

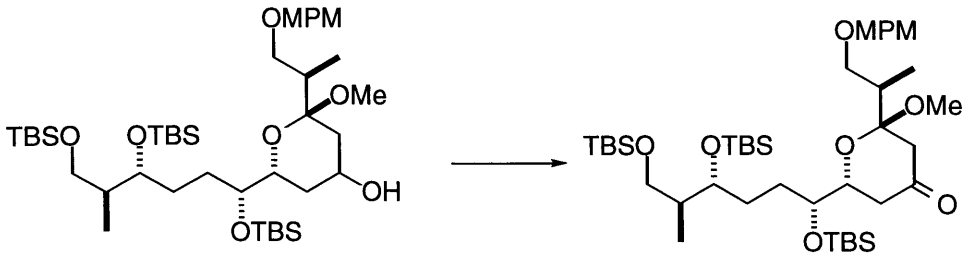
^{13}C NMR (125 MHz, C_6D_6) δ 160.2, 129.8, 114.6, 107.6, 103.4, 75.4, 74.3, 73.6, 72.9, 71.8, 61.1, 65.6, 55.2, 47.2, 42.2, 38.9, 38.4, 35.9, 29.8, 29.2, 19.0, 18.9, 18.8, 14.2, 13.0, -3.5, -3.6, -3.80, -3.84, -4.70, -4.74.

IR (neat) 3444, 2955, 2856, 1614, 1514, 1472, 1361, 1251, 1087, 835 cm^{-1}

$[\alpha]_D^{24}$=-6.7 (c=0.15, CH_2Cl_2)



9-12



9-12 **9-13**

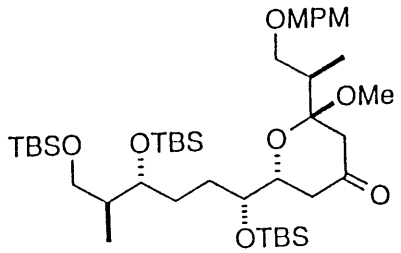
9-13: To a solution of $(COCl)_2$ (0.19 mL, 2.2 mmol) in CH_2Cl_2 (15 mL) at -78 ^oC was added DMSO (0.24 mL, 3.3 mmol) carefully. After 10 minutes, the alcohol **9-12** (440 mg, 0.55 mmol) dissolved in CH_2Cl_2 (2 mL) was cannulated into the reaction mixture. Two hours later, TEA (0.80 mL, 5.5 mmol) was added. The reaction mixture was kept at -78 ^oC for an hour before being warmed up to room temperature. Usual workup gave a crude oil which was purified by column chromatography (7% ethyl acetate/hexane) to give the ketone **9-13** (419 mg, 95%) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.28 (s, 2H), 3.93 (m, 1H), 3.87 (m, 1H), 3.67 (m, 1H), 3.64 (dd, *J* = 7.0, 10.0 Hz, 1H), 3.54 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.30 (s, 3H), 3.09 (dd, *J* = 7.5, 9.0 Hz, 1H), 3.04 (s, 3H), 2.49 (d, *J* = 14.0 Hz, 1H), 2.44 (m, 1H), 2.43 (d, *J* = 14.5 Hz, 1H), 2.28 (d, *J* = 14.5 Hz, 1H), 2.16 (t, *J* = 12.5 Hz, 1H), 2.01 (m, 1H), 1.72 (m, 3H), 1.57 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.091 (s, 3H), 0.06 (s, 3H).

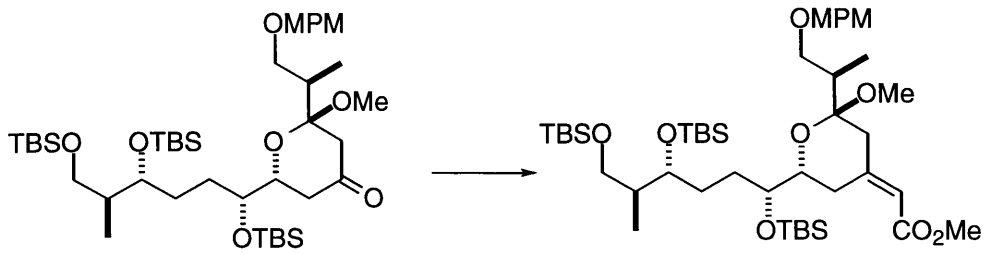
^{13}C NMR (125 MHz, C_6D_6) δ 204.1, 106.6, 106.3, 144.0, 131.5, 129.8, 114.6, 105.2, 94.4, 75.1, 74.1, 73.7, 73.1, 70.9, 66.1, 55.3, 47.7, 46.4, 42.5, 42.2, 38.4, 29.4, 29.1, 26.6, 19.0, 18.8, 18.7, 14.1, 12.8, -3.6, -3.62, -3.76, -3.81, -4.71, -4.76.

IR (neat) 2929, 2857, 1728, 1514, 1472, 1251, 1090, 1041, 836, 774 cm^{-1}

$[\alpha]_D^{24}$=-5.8 (c=0.48, CH_2Cl_2)



9-13



9-13 (*E*)-**9-14**

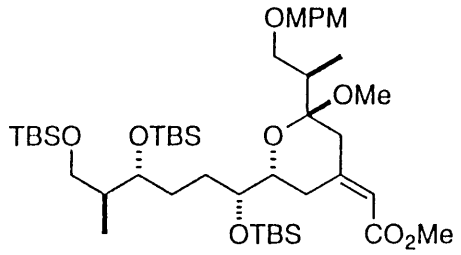
(*E*)-**9-14**: Methyl trimethylsilylacetate (80 mg, 0.55 mmol) was dissolved in THF (3 mL) at -78 °C. To this solution was added LiHMDS (1.0 M in THF, 0.44 mL, 0.44 mmol). After 0.5 hour, ketone **9-13** (44 mg, 0.055 mmol) dissolved in THF (1 mL) was cannulated into this enolate solution slowly. Five minutes later the reaction was quenched by the addition of 5 mL of saturated NH_4Cl aqueous solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over $MgSO_4$, concentrated. The crude oil was purified by column chromatography (3% ethyl acetate/hexane) to give the desired enoate (*E*)-**9-14** as a clear oil (30 mg, 65%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.84 (s, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 12.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.91 (m, 1H), 3.82 (ddd, *J* = 2.5, 5.0, 11.5 Hz, 1H), 3.78 (br q, *J* = 5.0 Hz, 1H), 3.68 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.50 (dd, *J* = 4.0, 9.0 Hz, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 3.20 (t, *J* = 8.5 Hz, 1H), 3.09 (s, 3H), 2.45 (m, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 2.04 (d, *J* = 13.5 Hz, 1H), 1.98 (t, *J* = 12.5 Hz, 1H), 1.86 (br s, 2H), 1.61 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 1.06 (s, 9H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.167 (s, 3H), 0.10 (s, 6H).

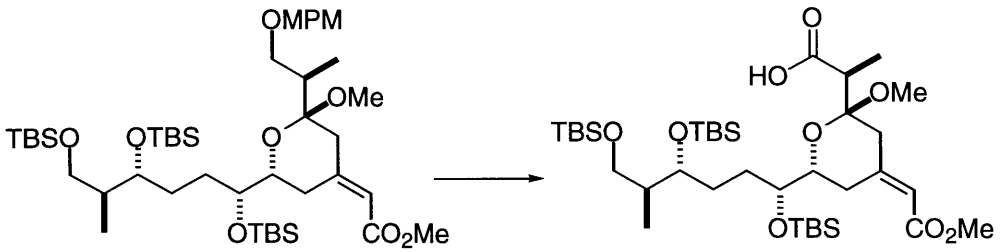
^{13}C NMR (125 MHz, C_6D_6) δ 166.8, 160.3, 156.6, 131.7, 129.8, 117.3, 114.6, 103.6, 75.5, 74.3, 73.6, 71.3, 66.1, 55.3, 50.9, 47.5, 42.2, 41.0, 38.6, 30.7, 29.8, 29.3, 26.7, 26.6, 19.0, 18.9, 14.2, 13.1, -3.5, -3.52, -3.8, -4.7, -4.74.

IR (neat) 2928, 2856, 1721, 1514, 1463, 1250, 1150, 1089 cm^{-1}

$[\alpha]_D^{24}$=+22.9 (c=0.14, CH_2Cl_2)



(*E*)-9-14



(*E*)-**9-14** **9-16**

9-16: To a solution of compound (*E*)-**9-14** (38 mg, 0.045 mmol) in CH_2Cl_2 (2.0 mL) were added 0.5 ml of water and DDQ (41 mg, 0.18 mmol). After vigorous stirring at room temperature for 15 minutes, the reaction was quenched with saturated $NaHCO_3$ aqueous solution. Extraction with CH_2Cl_2 and concentration gave a light orange oil which was purified by column chromatography (15% ethyl acetate/hexane) to afford the alcohol **9-15** as a colorless oil (28 mg, 84%). This compound tends to decompose as neat at room temperature. So it was used immediately in the next step.

The alcohol **9-15** was converted into the corresponding aldehyde using the standard Swern oxidation procedure. Crude aldehyde was used without further purification.

To a solution of the aldehyde in *t*-BuOH (2.0 mL) was added 2-methyl-2-butene (0.5 mL). In a separate vessel $NaClO_2$ (43 mg) and NaH_2PO_4 (53 mg) were dissolved in water (2 mL) and then transferred to the reaction flask. After half an hour, the reaction mixture was poured into 10 mL of the saturated NH_4Cl aqueous solution and the aqueous layer was extracted with ether. The combined organics were dried over Na_2SO_4, concentrated and the residual oil was purified by column chromatography to give the acid **9-16** as a light yellow oil (23 mg, 81% for two steps).

^{1}H NMR (500 MHz, C_6D_6) δ 5.84 (s, 1H), 4.29 (d, *J* = 14.0 Hz, 1H), 3.90 (br s, 1H), 3.77 (d, *J* = 11.0 Hz, 1H), 3.67 (m, 2H), 3.56 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.37 (s, 3H), 3.25 (s, 3H), 3.13 (q, *J* = 7.0 Hz, 1H), 2.58 (d, *J* = 14.5 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 2.04 (m, 1H), 1.98 (t, *J* = 13.0 Hz, 1H), 1.78 (m, 3H), 1.58 (m, 1H),

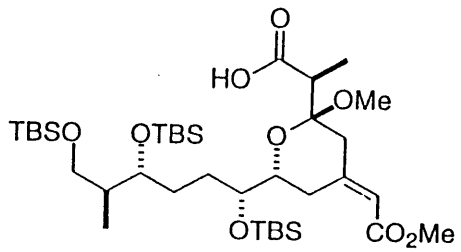
1.26 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 1.048 (s, 9H), 1.03 (d, J = 7.0 Hz, 3H), 1.01 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.137 (s, 3H), 0.10 (s, 3H), 0.099 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 179.4, 166.8, 155.3, 122.8, 117.8, 102.6, 83.1, 75.3, 74.5, 74.2, 66.1, 51.0, 48.4, 45.6, 42.2, 40.8, 30.5, 29.7, 29.4, 26.7, 19.0, 18.9, 18.8, 18.4, 13.9, 13.0, -3.53, -3.56, -3.76, -4.71, -4.76.

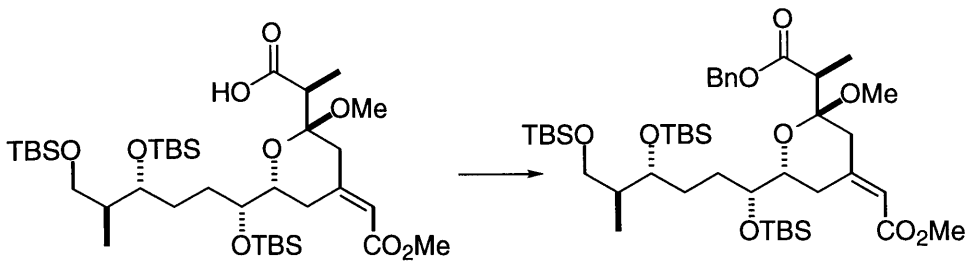
IR (neat) 3600-2900 (br), 2928, 1719, 1655, 1460, 1256, 1093, 836, 741 cm^{-1}

$[\alpha]_D^{24}$=+11.0 (c=0.4, CH_2Cl_2)

HRMS (FAB, 3-nitrobenzyl alcohol) $C_{37}H_{74}O_9Si_3$ $[M\text{-}OCH_3]^+$ calculated: 715.4457, found: 715.4457.



9-16

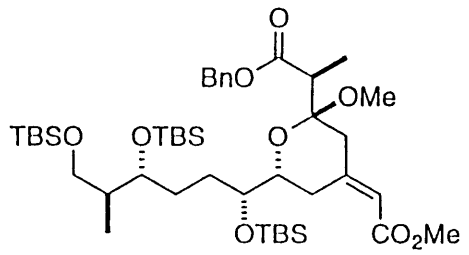


9-16 **9-17**

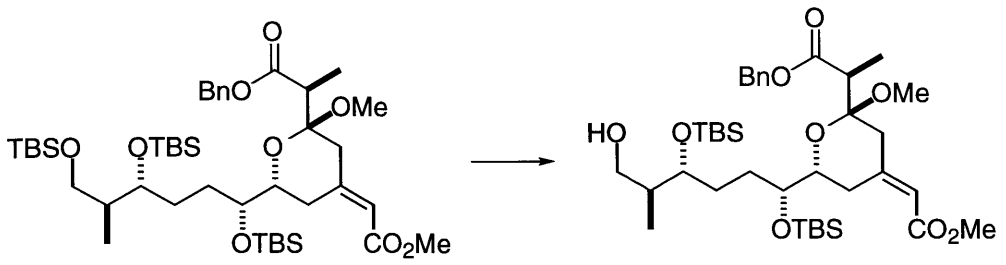
<u>**9-17**</u>: To a solution of the acid **9-16** (23 mg, 0.031 mmol) in CH_2Cl_2/DMF (1 mL +1 mL) were added Cs_2CO_3 (101 mg, 0.31 mmol) and BnBr (8 μL, 0.062 mmol) The reaction was stirred for 15 minutes before being poured into 10 mL of water. Extraction with ether, drying over $MgSO_4$ and concentration gave a yellow oil which was then purified by column chromatography (4% ethyl acetate/hexane) to furnish the benzyl ester **9-17** as a colorless oil (22 mg, 84%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.20 (d, *J* = 8.5 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 2H), 7.05 (m, 1H), 5.85 (s, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 13.5 Hz, 1H), 3.90 (br q, *J* = 6.5 Hz, 1H), 3.76 (ddd, *J* = 2.5, 5.0, 12.0 Hz, 1H), 3.72 (br q, *J* = 4.0 Hz, 1H), 3.67 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.56 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.35 (s, 3H), 3.27 (s, 3H), 3.25 (q, *J* = 7.0 Hz, 1H), 2.60 (d, *J* = 13.5 Hz, 1H), 2.49 (d, *J* = 13.5 Hz, 1H), 2.04 (quint, *J* = 6.5 Hz, 1H), 1.94 (t, *J* = 13.0 Hz, 1H), 1.85-1.77 (m, 3H), 1.58 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 1.048 (s, 9H), 1.03 (d, *J* = 7.5 Hz, 3H), 1.00 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), 0.14 (s, 6H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (125 MHz, C_6D_6) δ 172.6, 166.7, 155.8, 137.0, 129.2, 128.9, 128.8, 117.7, 102.7, 75.3, 74.4, 74.1, 61.9, 66.0, 50.9, 48.2, 45.4, 42.1, 40.8, 30.4, 29.6, 29.2, 26.7, 19.0, 18.9, 18.8, 14.1, 13.0, -3.50, -3.56, -3.77, -4.70, -4.75. **IR** (neat) 2954, 2856, 1732, 1660, 1462, 1386, 1336, 1256 cm $^{-1}$ $[\alpha]_D^{24}$= +15.2 (c=0.6, CH_2Cl_2)

HRMS (FAB, 3-nitrobenzyl alcohol) $C_{44}H_{80}O_9Si_3$ $[M\text{-}OCH_3]^+$ calculated: 805.4926, found: 805.4926.



9-17



9-17 **9-18**

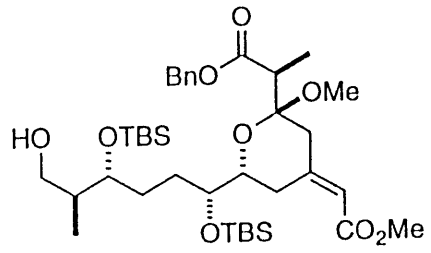
9-18: To a solution of compound **9-17** (22 mg, 0.026 mmol) in THF (1.5 mL) was added (HF-pyridine, pyridine) stock solution (0.8 mL). The reaction mixture was stirred for 3.5 hours before the reaction was quenched with the saturated $NaHCO_3$ aqueous solution. Extraction with CH_2Cl_2, drying over $MgSO_4$ and concentration gave a yellow oil which was then purified by column chromatography (20% ethyl acetate/hexane) to furnish the primary alcohol **9-18** as a colorless oil (17 mg, 92%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.20 (d, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 2H), 7.06 (m, 1H), 5.84 (s, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.96 (d, *J* = 12.5 Hz, 1H), 4.30 (d, *J* = 14.0 Hz, 1H), 3.79-3.73 (m, 2H), 3.65 (m, 2H), 3.53 (m, 1H), 3.34 (s, 3H), 3.26 (s, 3H), 3.22 (q, *J* = 7.0 Hz, 1H), 2.60 (d, *J* = 14.0 Hz, 1H), 2.48 (d, *J* = 14.0 Hz, 1H), 2.86 (t, *J* = 12.5 Hz, 1H), 1.86 (t, *J* = 12.5 Hz, 1H), 1.80 (m, 2H), 1.69 (m, 3H), 1.60 (m, 1H), 1.30 (d, *J* = 7.5 Hz, 3H), 1.04 (s, 9H), 1.01 (s, 9H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.12 (s, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 172.7, 166.9, 155.9, 137.0, 130.0, 117.7, 102.7, 76.3, 75.3, 74.5, 66.9, 65.5, 50.9, 48.3, 45.4, 40.8, 40.5, 30.9, 30.5, 29.4, 26.6, 18.8, 14.2, 14.0, -3.53, -3.63, -3.83. **IR** (neat) 3516, 2951, 2856, 1720, 1658, 1462, 1255, 1150, 1088, 1040, 836 cm^{-1} $[\alpha]_D^{24}$= +12.5 (c=0.2, CH_2Cl_2)

HRMS (FAB, 3-nitrobenzyl alcohol) $C_{38}H_{66}O_9Si_2$ $[M\text{-}OCH_3]^+$ calculated: 691.4062, found: 691.4062.

9-19: Alcohol **9-18** was then converted into the aldehyde **9-19** by a standard Swern oxidation.



9-18

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