NAZAROV REACTION: DEVELOPMENT TOWARDS ASYMMETRIC CYCLOPENTANNELATION USING CHIRAL AUXILIARIES AND METAL CATALYSIS

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAII IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

AUGUST 2008

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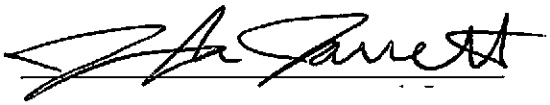

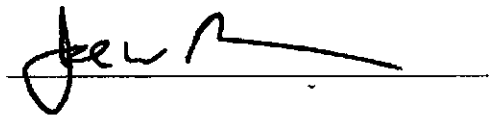

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Professor Marcus A. Tius for giving me the privilege and opportunity to work in his group. His patience, encouragement and guidance helped me pull through the most challenging problems. I will carry all that I have learned from him throughout the years to come.

I would like to thank all Tius group members, past and present (especially Brad Tokeshi, Elizabeth Uhrich, Gideon Berger and Danielle McAtee whom I interacted with the most), for their friendship, insight and support. All members have made the long days and weeks in lab tolerable and worthwhile. Each member has made a special impact in my life and their friendships will all be cherished. Special thanks go to Dr. Gideon Berger who has been an extremely wonderful mentor and friend. I truly appreciate all his advice and the fun times.

Thank you to all my committee members, Professor Thomas Hemscheidt, Professor Philip Williams, Professor Joseph Jarrett and Professor Joseph Ramos for their time and wisdom. Thank you to Wesley Yoshida and Mike Burger for their help in acquiring data.

Special thanks go to my family for their encouragement and support from miles away. Without their moral and financial support, my struggle throughout this journey would have been several times more magnified. I am also very grateful for the Thai family who has given me support and encouragement throughout my years in graduate school.

Last but not least, to Stephen Thai, I realize how much frustration and hardship I subjected him to. He has tolerated my frequent absence as well as my short-temper and negativism at the peak of my stress. He has sacrificed and had set aside many aspirations so that I can pursue mine. I am forever grateful for his patience, unconditional support and companionship throughout this endeavor.

ABSTRACT

Five-membered rings are common structural motifs in many important natural products. In general, the synthesis of highly functionalized five-membered rings, particularly with stereocontrol, is not as highly developed as that for six-membered rings. Thus, the pursuit of new methodologies towards this end is of great importance in synthetic chemistry. While there are several strategies for making five-membered rings, the Nazarov reaction is one that is particularly efficient in installing multiple stereogenic centers through a single operation. This thesis describes some recent progress for this reaction.

In Chapter 1, the Nazarov reaction is introduced. A mechanism of the reaction is first described and a discussion of recent advances follows. The recent advances are discussed in the context of new variations of the reaction and the pioneering work towards asymmetric cyclopentannelation.

In Chapter 2, we discuss how the synthesis and screening of a number of sugar-derived auxiliaries have paved the way to two superior chiral auxiliaries for the allene and the optimization of the reaction conditions for the Nazarov cyclization. The scope of each sugar-derived allene under the optimized conditions has been demonstrated through their reactions with a variety of morpholino enamides and in one case, an α,β-unsaturated butyrolactone. Additionally, we report a more detailed, well-substantiated mechanistic hypothesis for the asymmetric allenyl ether Nazarov reaction that rationalizes the stereochemical outcome of our products. This model will aid in the design of simpler chiral allenyl ethers with non-sugar based scaffolds.

In Chapter 3, we describe a triply-convergent cyclopentannelation reaction. This work is an extension of an existing methodology developed by our group that expands the scope and versatility of our allenyl ether Nazarov reaction.

Lastly, in Chapter 4 we discuss ongoing work towards the development of a catalytic asymmetric Nazarov cyclization. Two approaches are described using α-alkoxy-substituted divinyl ketones. In the first approach, asymmetry is introduced through the use of chiral oxophilic Lewis acids. In the second approach, chiral ligands are employed as a means for transferring chiral information in our unique palladium(II)-catalyzed Nazarov reaction.

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LIST OF ABBREVIATIONS

[α]	absolute optical rotation
Å	angstrom
Ac	acetyl
app.	apparent (spectral)
aq	aqueous
ar	aryl
(*R*)-BINAP	(*R*)-(+)-(1,1'-Binaphthalene-2,2' diyl)bis(diphenylphosphine)
br	broad (spectral)
box	bis(oxazoline)
BPS	*tert*-butyldiphenylsilyl
BuLi	butyllithium
^{13}C NMR	carbon nuclear magnetic resonance
°C	degrees Celsius
calcd	calculated
CD	circular dichroism
cm^{-1}	reciprocal centimeter
δ	chemical shift
d	days(s); doublet (spectral)
DCM	dichloromethane
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets (spectral)

dm	doublet of multiplets (spectral)
ddd	doublet of doublet of doublets (spectral)
ddt	doublet of doublet of triplets (spectral)
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodane
DMS	dimethyl sulfide
DMF	dimethyl formamide
dt	double of triplets (spectral)
EDCI	3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EIMS	electron impact mass spectrometry
ESI	electron spray ionization
er	enantiomeric ratio
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
^{19}F NMR	fluorine nuclear magnetic resonance
g	gram
h	hour
HFIP	hexafluoroisopropanol
^{1}H NMR	proton nuclear magnetic resonance
HMPA	hexamethylphosphoramide

HPLC	high performance liquid chromatography
HREIMS	high resolution electron impact mass spectrometry
HRESIMS	high resolution electrospray ionization mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
m	multiplet (spectral)
M	moles per liter
M^+	molecular ion
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
mL	milliliter
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
m/z	mass to charge ratio (mass spectrometry)
N	normal
Nf	nonaflyl fluoride
Ph	phenyl

ppm	parts per million (spectral)
pyr	pyridine
q	quartet (spectral)
quint	quintet (spectral)
R	rectus
$\mathbf{R_f}$	retention factor (chromatography)
rt	room temperature
s	singlet (spectral)
sp	sparteine
S	sinister
sec	seconds
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl

TBSCl	*tert*-butyldimethylsilyl chloride
TESCl	triethylsilyl chloride
TIPSCl	triisopropylsilyl chloride
TMSBr	trimethylsilyl bromide
TsCl	toluenesulfonyl chloride
UV	ultraviolet
y	yield
Z	zusammen

CHAPTER 1: Introduction of the Nazarov Reaction

1. Introduction

Electrocyclizations are highly efficient processes, characterized by the simultaneous breaking and forming of bonds, and are recognized as convenient, invaluable tools for total synthesis.[1] The Nazarov reaction represents a 4π electrocyclic conrotatory process for the conversion of divinyl ketones to cyclopentenones upon exposure to either a Lewis or protic acid. Although shortcomings of the classic Nazarov reaction had previously limited its utility, numerous improved variants of this reaction have emerged in recent years, making it possible for cyclopentenones of varying complexity to be synthesized efficiently.[2,3] Figure 1.1 highlights a few interesting examples of targets derived from variations of the Nazarov reaction.

In 2001, Tius and coworkers reported the first total asymmetric synthesis of roseophilin using a camphor-derived chiral allenyl ether and a morpholino enamide (equation [1]). The cross-conjugated cyclopentenone formed is characteristic of products generated through this class of Nazarov cyclizations.[4]

Recently in 2007, an extremely efficient catalytic Nazarov reaction was used in the synthesis of racemic merrilactone (equation [2]). In this report, a highly substituted, sterically encumbered divinyl ketone was efficiently transformed to a bicyclic system bearing two adjacent quaternary carbon atoms in excellent yield. Since this motif is generally difficult to access by other means, this example illustrates the attractiveness of this electrocyclic process.[5]

The ability to access multicyclic systems in the course of a Nazarov reaction was also demonstrated by the work of Trauner and Denmark (equations [3] and [4]).[6] Both reactions

led to their corresponding multicyclic products in excellent yields. During the synthesis of taiwaniaquinol D, Trauner showcased this methodology as a key step towards its tricyclic skeleton. Lastly, West and coworkers used the Nazarov reaction to initiate a cationic olefin cascade for the synthesis of a steroid-like compound. The synthesis represents a unique application of the Nazarov reaction and the degree of molecular complexity that results when it is combined with other carbon-carbon bond forming processes (equation [5]).[7]

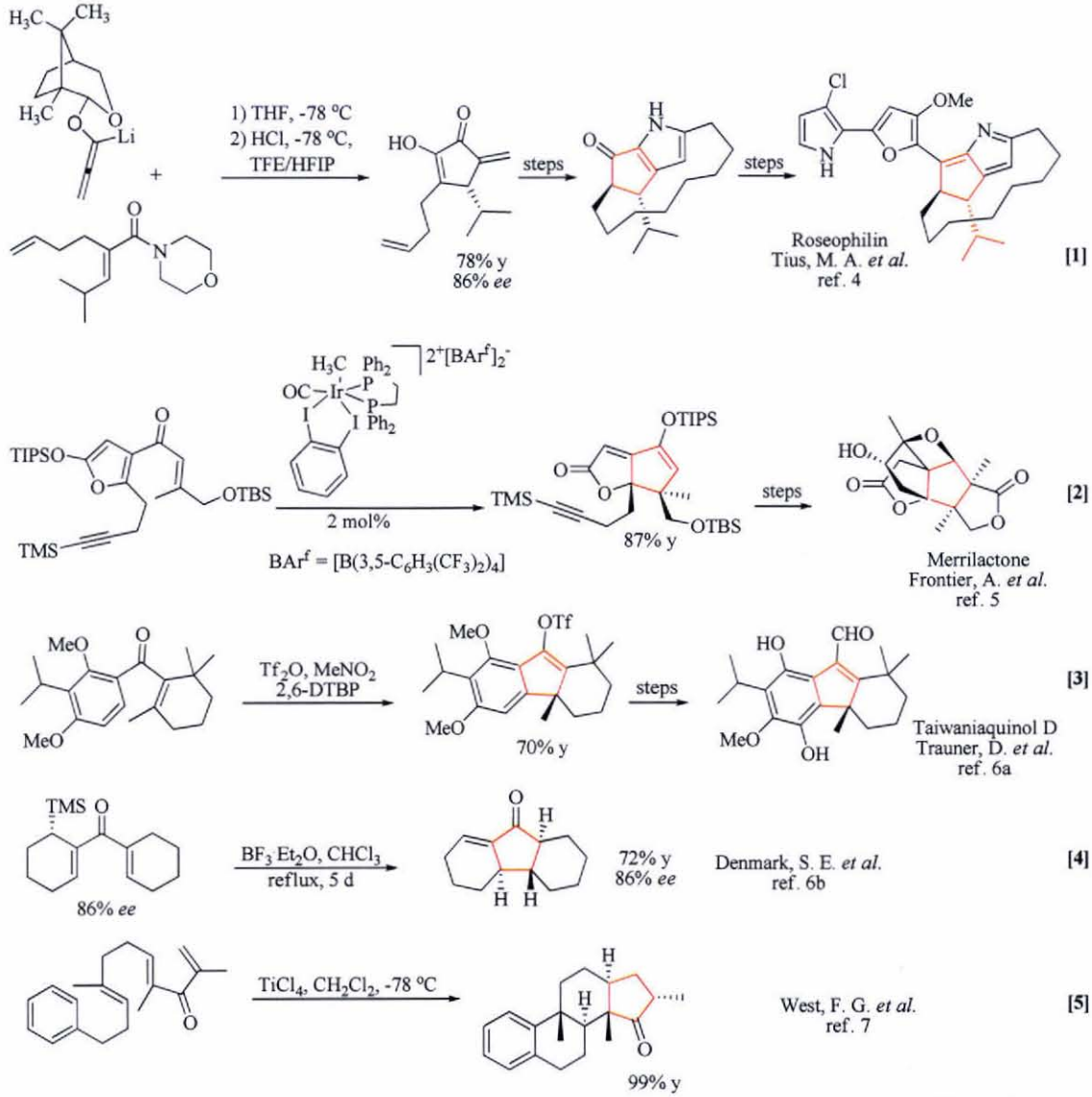
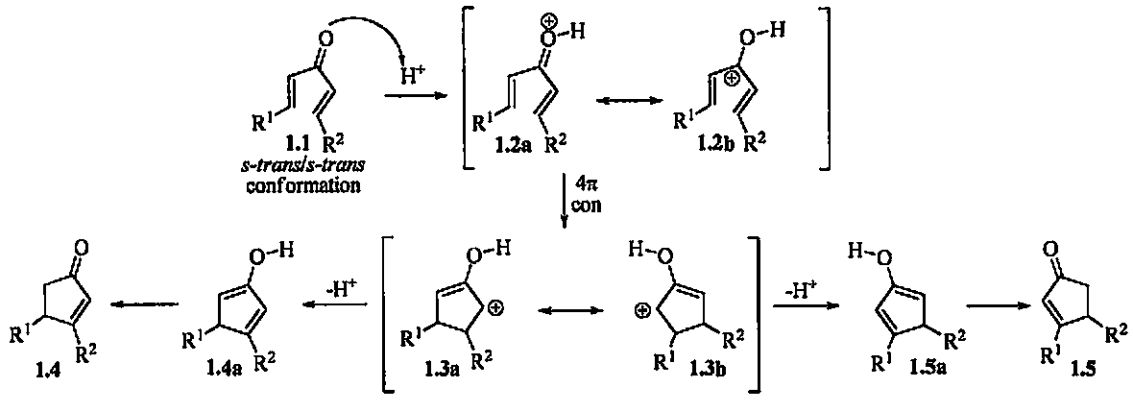


Figure 1.1. Examples of Interesting Transformations from the Nazarov Reaction

2. Classical Nazarov Reaction Mechanism[8]

The classical Nazarov reaction is defined as the conversion of a divinyl ketone to a cyclopentenone by exposure to either a Lewis or Brønsted acid (Scheme 1.1). Complexation of divinyl ketone **1.1** to the Lewis acid or protonation by the Brønsted acid promotes the formation of pentadienyl cation **1.2** that undergoes thermally allowed, 4π conrotatory ring closure to furnish oxyallyl cation **1.3**. The reaction is then terminated by proton loss and subsequent tautomerization to afford cyclopentenones **1.4** or **1.5**.[1,3]



Scheme 1.1

Like all concerted electrocyclic processes, the key advantage of this reaction is that there is control of stereochemistry. This is best understood through the pentadienyl cation **1.6** depicted in Figure 1.2. According to the conservation of orbital symmetry rules, cyclization of pentadienyl cation **1.6** is only possible through thermally allowed 4π conrotation. Although the direction of conrotation can either proceed clockwise or counter-clockwise, "torquoselectivity," the preference for the least sterically encumbered sense of conrotation, may allow cyclization to proceed favorably in one direction over the other.[9,10] In cases in

which remote stereocenters are present in the divinyl ketone, cyclization results in a diastereomerically enriched product mixture. On the other hand, when either a chiral, non-racemic external source (for example, Lewis acid M in Figure 1.2) is used or the divinyl ketone bears a chiral, non-racemic function that is cleaved during cyclization, an enantiomerically enriched product mixture is obtained.[1,3]

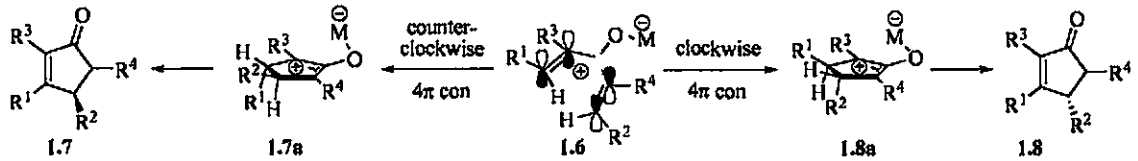


Figure 1.2. Stereochemical Outcome of the Nazarov Reaction Predicted by Molecular Orbital Symmetry Rules

3. Challenges and Considerations

There are challenges in the Nazarov reaction that can limit its synthetic utility. For instance, forcing conditions, such as high temperatures and excesses of strong acids, are often required to initiate the reaction. Additionally, alternative products are often formed from competing pathways. This includes retro-Nazarov ring-cleavage products,[11] or products derived from migrations[12] or non-regioselective proton losses. Low product yields, formation of side-products and recovery of starting material underscore the ongoing challenges of the Nazarov cyclization, all of which relate to reactivity and regioselectivity issues.[3c] New developments have offered methods for circumventing these challenges and are described within this section.

3.1. Reactivity

In recent years, various factors that influence reactivity have been identified. First is the steric influence of the α-substituent of the divinyl ketone (Figure 1.3). It is suspected that α-substituents (R^1 and R^2) enforce the favored *s-trans/s-trans* conformation of the divinyl ketone intermediates, thereby allowing for good π orbital alignment and concomitant cyclization.[13] A second factor known to influence reactivity is the electronic nature of the substituents that are α and β to the carbonyl.[14,12b] As shown by the asterisks on the pentadienyl cation and oxyallyl cation in Figure 1.3, the distribution of positive charge changes from C1, C3 and C5 in the pentadienyl cation to C2 and C4 in the oxyallyl cation. Thus, cation-stabilizing substituents can either promote or inhibit cyclization depending on their position. Cation-stabilizing β substituents (R^3, R^4 = electron donating) are suspected to stabilize the *pentadienyl cation*, raising the activation barrier for cyclization unfavorably.[15] Contrastingly, cation-stabilizing α-substituents (R^1, R^2 = electron donating) stabilize the *oxyallyl cation* product and promote cyclization even under mild conditions and with catalytic quantities of the promoter.

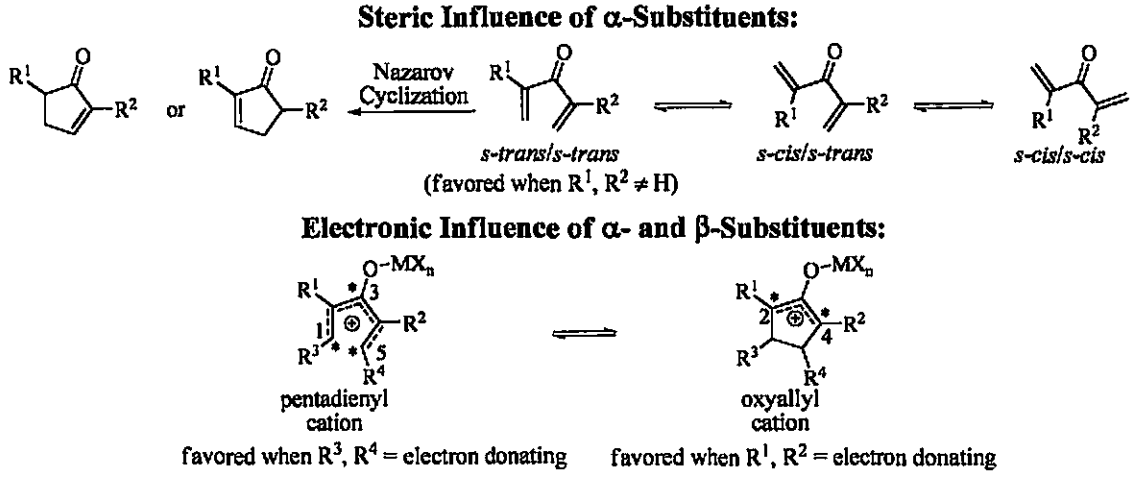
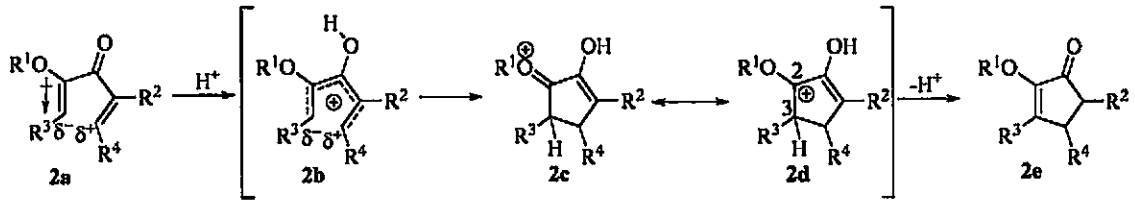


Figure 1.3. Steric and Electronic Influences of α- and β-Substituents

A marked increase in reactivity of α-substituted substrates is observed when one of the α-substituents is heteroatomic (Scheme 1.2). This is thought to result from the increased electron density at one terminus, as shown for α-alkoxy divinyl ketone **2a**, which lowers the activation barrier towards cyclization. Following cyclization, the resultant oxyallyl cation is stabilized through electron donation by the heteroatom as shown for resonance structures **2c** and **2d** in Scheme 1.2.[10a]



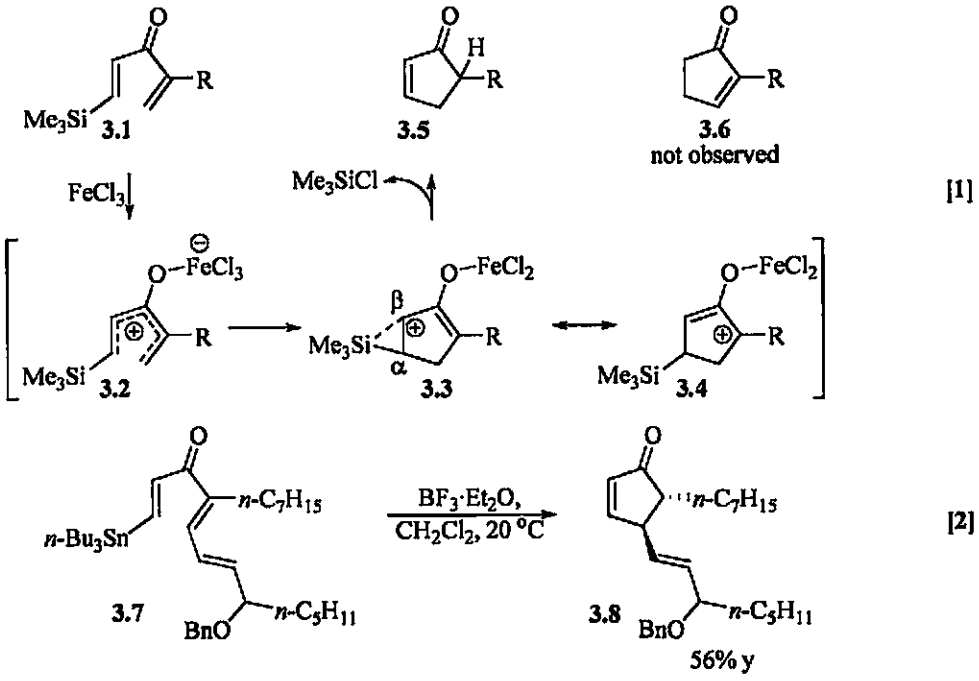
Scheme 1.2

3.2. Regioselectivity

In many cases, termination of the reaction process occurs through deprotonation of one tautomer such as **2d** (Scheme 1.2). An effective means for selective deprotonation and placement of the double bond has been through the use of a strategically placed heteroatom, such as the oxygen atom in substrate **2a**. As noted in Section 3.1, the role of this heteroatom is to increase the electron density at one terminus. However, it is also known that the heteroatom localizes the positive charge of the resultant oxyallyl cation at C2 (see tautomer **2d**, Scheme 1.2), which consequently promotes deprotonation of the adjacent hydrogen at C3 (see conversion of tautomer **2d** to product **2e**). Alternative heteroatoms, such as fluorine atoms in the α position of divinyl ketone **2a** have had a similar effect.[16]

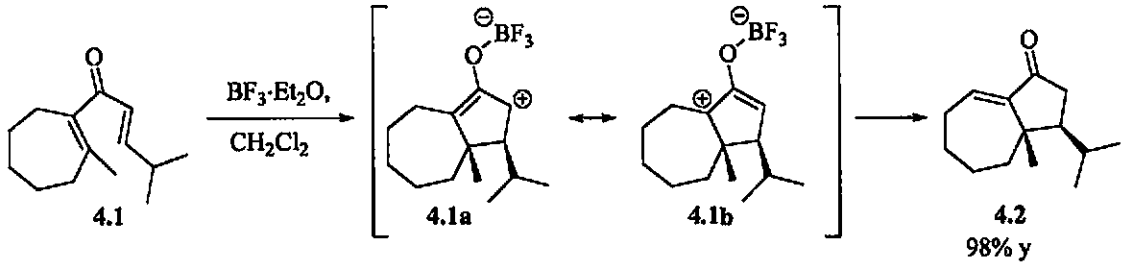
Heteroatoms at the β-position may also be used to control the location of the double bond.[17] Such is the case when β-silicon substituents are used. For example, in Denmark's study of substrates such as **3.1** (equation [1], Scheme 1.3), it was demonstrated that the use of a β-trimethylsilyl group localized the positive charge β to the silicon group (see oxyallyl cation **3.3**). Thus, upon exposure of divinyl ketone **3.1** to ferric(III) chloride, cyclization and subsequent regioselective loss of the trialkylsilyl group from tautomer **3.3** took place to provide cyclopentenone isomer **3.5** exclusively.[18,6b]

Years later, this method was applied in Johnson's prostaglandin synthesis (equation [2], Scheme 1.3).[19] However, rather than using a trialkylsilyl substituent, he instead employed a β-trialkylstannyl group. As shown by prostaglandin precursor **3.8**, formation of the desired kinetic product (*i.e.* the cyclopentenone with the least substituted carbon-carbon double bond) was accomplished in 56% yield by loss of the β-tri-*n*-butylstannyl substitutent.



Scheme 1.3

In the absence of the heteroatom to direct the placement of the double bond, the thermodynamic product is often formed (Scheme 1.4). An example of this phenomenon was seen in the preparation of guanacastepene. Divinyl ketone **4.1** was treated with boron trifluoride diethyl etherate to provide bicyclic enone **4.2** nearly quantitatively. The exocyclic double bond of enone **4.2** originates from the tautomer that places the cation on the tertiary carbon atom (tautomer **4.1b**), which subsequently loses a proton from the adjacent cycloheptane carbon atom.[20]



4.1 **4.1a** **4.1b** **4.2** 98% y

Scheme 1.4

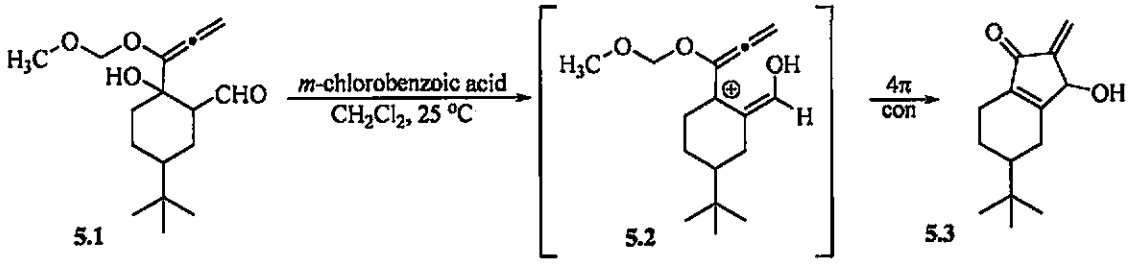
4. Non-Classical Nazarov Reactions

Many of these recent discoveries have led to numerous modifications of the classical Nazarov reaction. The key details of a few variations will be highlighted in the following discussion.

4.1. Allenyl Ether Variant of the Nazarov Reaction

Over two decades ago, the allenyl ether cyclopentannelation reaction was discovered accidentally by the Tius group in an effort to prepare an *ortho*-quinone from tertiary alcohol **5.1** (Scheme 1.5).[21] Interestingly, upon exposure to *m*-chloroperoxybenzoic acid (*m*-CPBA),

hydroxycyclopentenone **5.3** was instead formed through an unanticipated Nazarov process catalyzed by the trace amounts of *m*-chlorobenzoic acid present in the untreated stock bottle of *m*-CPBA.[i] However, rather than proceeding through the classical divinyl ketone, the reaction proceeded through allenyl vinyl cation **5.2**. The high reactivity of allene **5.2** towards cyclization is attributed to the relief of strain of the allene function and facile approach of the allenic sp and vinyl sp^2 carbon atoms.[4a]

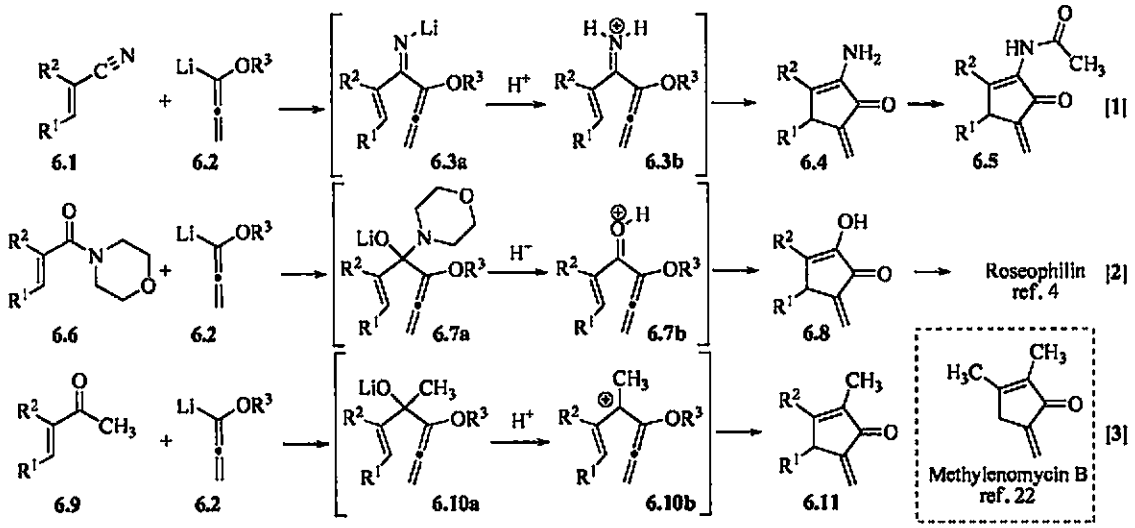


Scheme 1.5

The discovery of this reaction paved the way to variations of the allenyl ether Nazarov reaction (Scheme 1.6). Three classes of this reaction involve the methoxymethyl lithioallenyl ether addition to a tri- or tetrasubstituted α,β-unsaturated nitrile,[22] amide[23] or ketone (equations [1], [2] and [3]) to give rise to the intermediates **6.3a**, **6.7a** and **6.10a**, respectively. Quenching these intermediates with acid resulted in formation of their corresponding α-amino- , α-hydroxy-, or α-alkyl cyclopentenones (cyclopentenones **6.4**, **6.8**, and **6.11**, respectively). It should be noted that α-aminocyclopentenones were susceptible to polymerization due to intermolecular conjugate addition by the α-amino function. For this reason, α-aminocyclopentenones were isolated as their protected derivatives **6.5**. The use of

[i] An alternative mechanism is the Prins reaction.

enones *via* equation [3] was found as a useful means towards the synthesis of achiral target, methylenomycin B (R^1 = H).[24] Of the three variants, the morpholino enamide version has been most thoroughly investigated and has also been applied to the total synthesis of roseophilin.[4]

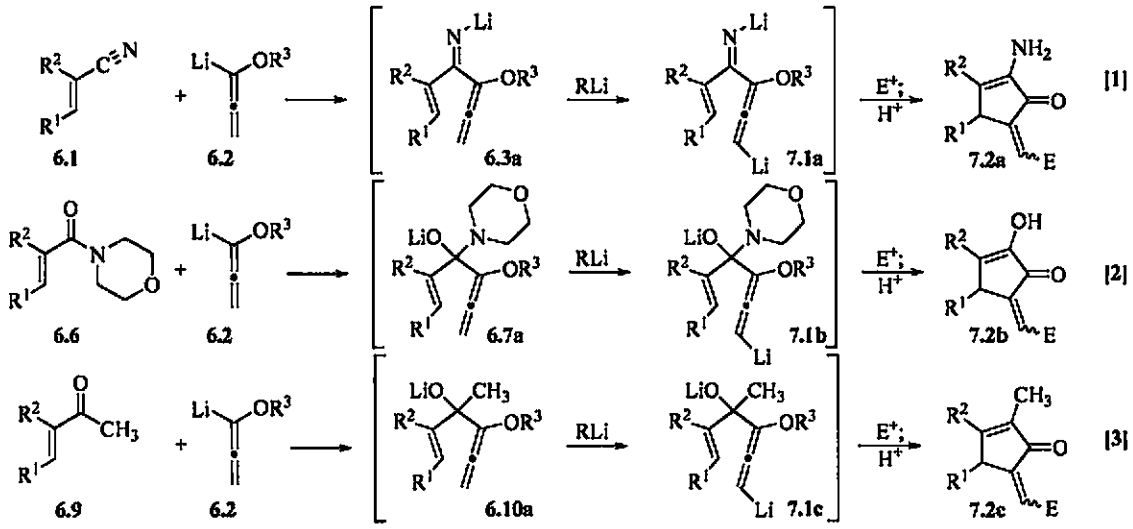


Scheme 1.6

It was later envisioned that this methodology could be elaborated further to synthesize densely functionalized cyclopentenone products, particularly with substitution on the exocyclic double bond, through a triply convergent process (Scheme 1.7).[25] Gratifyingly, treatment of the tetrahedral intermediates **6.3a**, **6.7a** and **6.10a** with an equivalent of organolithium to form intermediates **7.1a-c** followed by trapping of an electrophile and subsequent cyclization led to products **7.2a-c** efficiently.[ii] The process offers the key

[ii] It is usually necessary to protect the α amino function in equation [1] in Scheme 1.7 to prevent polymerization from occurring. When a large E^+ is used, polymerization through Michael addition to the exocyclic double bond by the amino function is inhibited due to the additional sterics of E. Therefore, protection may not be needed.

advantage of creating a large degree of molecular complexity in a single operation, making it highly amenable to natural products synthesis and to the synthesis of small molecule libraries.

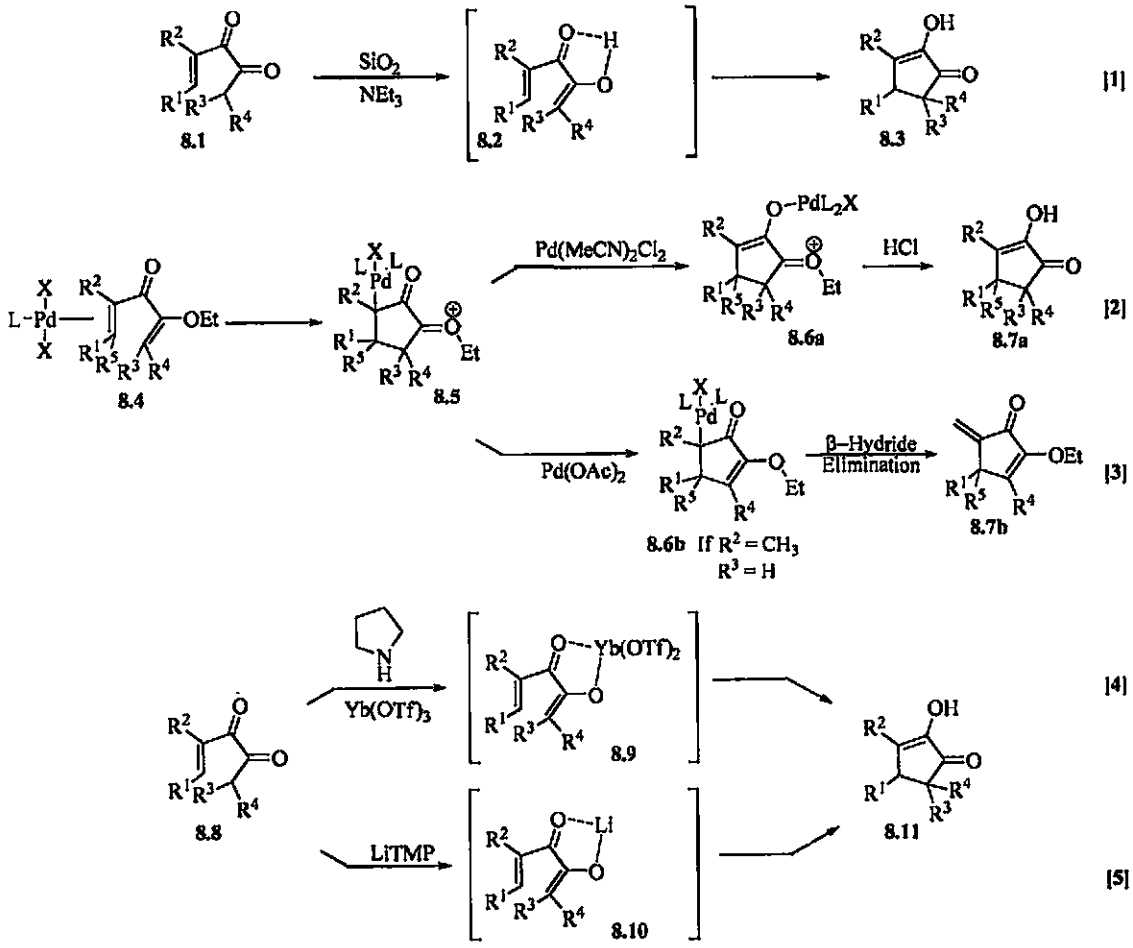


Scheme 1.7

4.2. Unique Nazarov Substrates and Processes

More recently, the Tius group has investigated additional variants to the Nazarov reaction using α-diketones and derivatives thereof. Three classes of cyclopentannelation reactions have been developed thus far: Lewis acid-catalyzed,[26] transition-metal catalyzed[27] and base-promoted cyclopentannelation (Scheme 1.8).[28] α-Diketones cyclize to form α-hydroxycyclopentenones in the presence of silica gel and triethylamine through the intermediacy of an enol tautomer (equation [1]). For Nazarov reactions mediated by transition metals, two different cyclopentenone products are formed under mild conditions depending on the choice of Pd(II) catalyst (equations [2] and [3] and Chapter 4). Of the two

processes the one that forms compounds such as **8.7a** is particularly interesting as it allows access to two contiguous quaternary carbon centers. Lastly, for the base-promoted cyclopentannelation reactions, metalloenolates derived from α,β-unsaturated α-diketones undergo cyclization to α-hydroxycyclopentenones. These reactions are the first Nazarov reactions to be described for enolates (equations [4] and [5]).

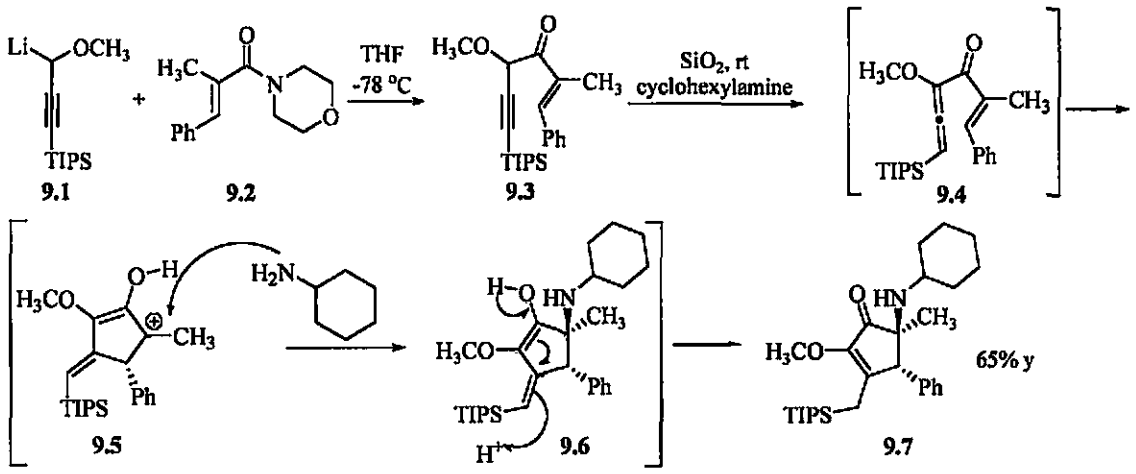


Scheme 1.8

4.3. Interrupted Nazarov Reaction

Although the examples thus far described have involved the termination of the Nazarov reaction through proton loss, in some cases termination of the Nazarov reaction occurs through other processes. For example, an alternative fate of oxyallyl cation **2d** (Scheme 1.2) is exemplified by West's exceptional cascade synthesis of the steroid-like compound that had been previously shown in equation [5], Figure 1.1. The reaction is described as "interrupted" due to the fact that the Nazarov process is terminated by the attack of a nucleophile as opposed to proton loss. Although the example illustrates an intramolecular process with carbon nucleophiles, heteroatomic nucleophiles and intermolecular processes have also been disclosed.[29]

Another reaction that makes use of an interrupted Nazarov reaction is the unique cascade isomerization-cyclization-trapping process, reported by Tius and Dhoro (Scheme 1.9).[30] The precursor to the tandem process is formed by the addition of propargyllithium **9.1** to morpholino enamide **9.2**. The cascade process is subsequently accomplished by exposure of the isolated propargyl vinyl ketone **9.3** to a premixed slurry of dry activated silica gel and cyclohexylamine to form α-aminocyclopentenone **9.7** in 65% yield. Mechanistically, the reaction occurs by an initial isomerization of the propargyl vinyl ketone **9.3** to form reactive intermediate allenyl vinyl ketone **9.4**. The presence of the weakly acidic silica is sufficient to promote cyclization to oxyallyl cation **9.5**, which is intercepted by cyclohexylamine, tautomerized and rearranged to provide the observed cyclic product **9.7**. This process will be revisited in Section 5.2 but will be discussed in the context of its asymmetric variant.



Scheme 1.9

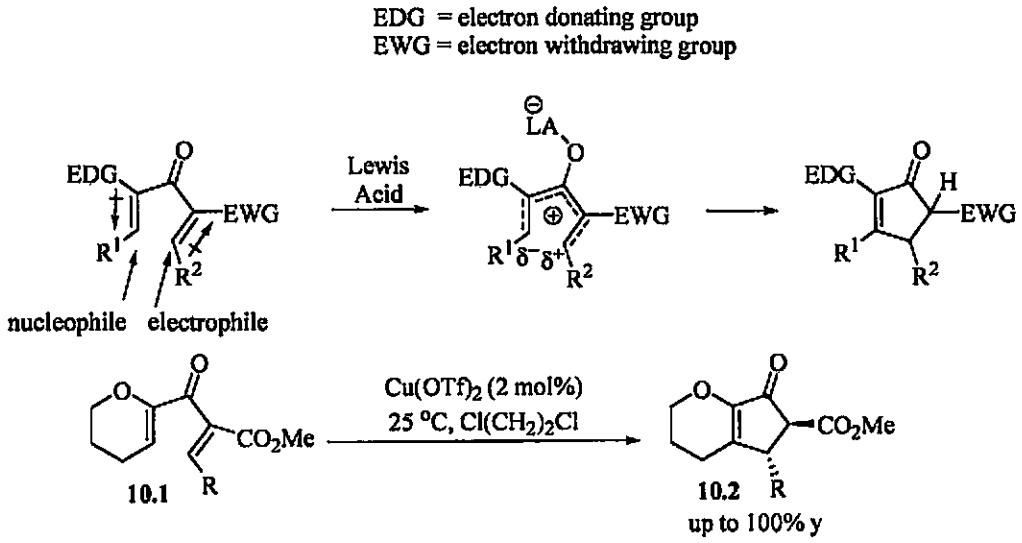
4.4. Lewis Acid-Catalyzed Nazarov Reaction

As earlier discussed, one of the ongoing challenges of the Nazarov reaction is the low reactivity of divinyl ketones (refer to Section 3.1). Whereas cyclization of allenyl vinyl ketones occurs spontaneously upon exposure to mild acids and at low temperature, divinyl ketones have usually required several equivalents of a promoter (a strong Lewis or Brønsted acid) under harsher reaction conditions. Extensive work has been invested by several research groups, including ours, towards a catalytic cyclopentannelation process.[6a,9,31] Both substrate and promoter have been thoroughly examined.

Since the Nazarov reaction takes place through the "u"-shaped (*s-trans/s-trans*) conformer of the pentadienyl cation, one strategy used to increase the population of this conformation is by the use of Lewis acid coordination to α-alkoxy or α-carboxy substituents. Additionally, since the electronic nature and position of substituents has been shown to significantly alter the reactivity of the divinyl ketones, an approach to promoting cyclization

is through strategic placement of substituents with complementary electronic properties. Both strategies were examined in the pioneering work of Frontier.[6]

In 2003, Frontier and coworkers investigated the synergistic effects of various combinations of polar substituents at different positions on the divinyl ketones (Scheme 1.10). By installing both electron donating and withdrawing groups on the divinyl ketone, Frontier was able observe quantitative yields of cyclopentenone **10.2** with completely regioselective placement of the double bond using a very mild Lewis acid catalyst, copper(II) triflate.



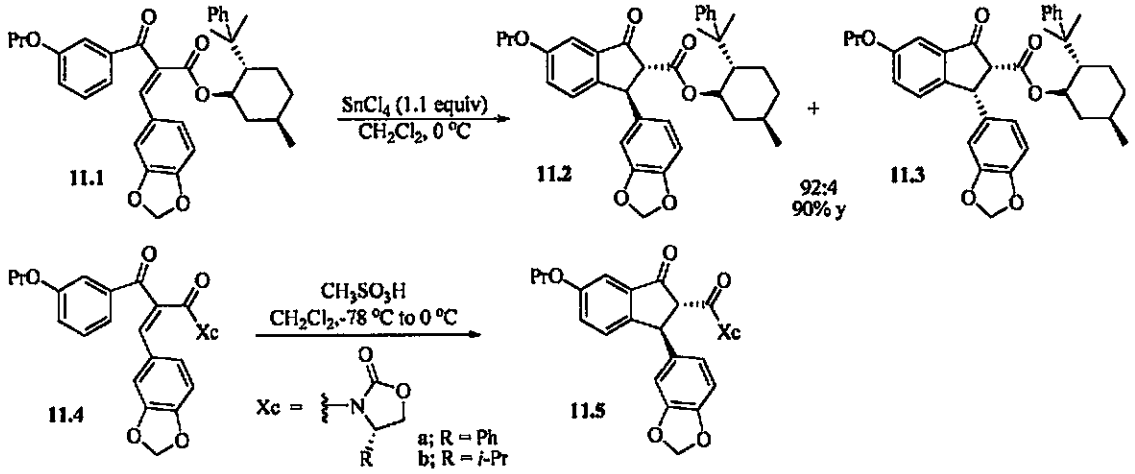
Scheme 1.10

Although Frontier was able to establish efficient catalytic conditions for the formation of racemic cyclopentenones, an asymmetric variant of this catalytic Nazarov reaction had not been disclosed at this time. As will be discussed in Section 5.3, catalytic asymmetric processes followed within the same year and were reported independently by Trauner and Aggarwal.

5. Asymmetric Nazarov Reactions

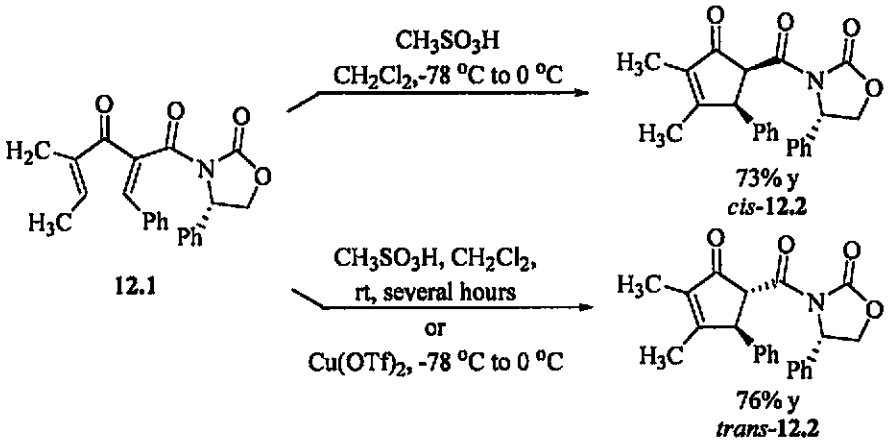
5.1. Chiral Auxiliaries in Nazarov Reactions

The use of chiral auxiliaries was demonstrated as an effective means for controlling asymmetry in the course of cyclopentannelation reactions. The first asymmetric Nazarov reaction utilizing a chiral auxiliary was reported in 1999 by Pridgen and coworkers (Scheme 1.11).[32] By using a chiral auxiliary, Pridgen was able to observe high diastereoselectivity for *trans* cyclopentenone **11.2** upon exposure of substrate **11.1** to tin(IV) tetrachloride. Additionally, protic acid catalyzed cyclization of the oxazolidinone analog **11.4** also provided *trans* cyclopentenone **11.5** with good diastereoselectivity. The latter result was particularly surprising as it indicated that the conformational restriction through bidentate chelation to a metal promoter was not a prerequisite for performing stereoselective cyclization in these types of substrates.



Scheme 1.11

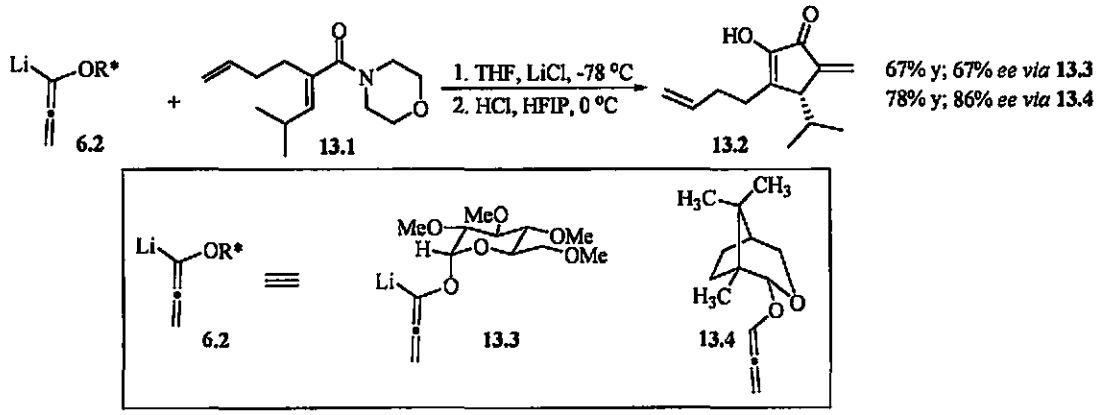
On the other hand, high diastereoselectivity for the formation of *cis* cyclopentenone **12.2** (Scheme 1.12) was observed by Flynn and coworkers by treating divinyl ketone **12.1**, which was derived from an Evans oxazolidinone, with methanesulfonic acid at low temperature.[33] Prolonged exposure to acid at room temperature was observed to promote epimerization of *cis* **12.2** to the more thermodynamically favored *trans* isomer. Thus, through the appropriate reaction conditions and oxazolidinone enantiomer, any one of the four possible stereoisomers of the cyclopentenone can be selectively synthesized.



Scheme 1.12

In Pridgen and Flynn's methodologies, it has not yet been established whether high diastereomeric excesses are also obtained from divinyl ketones such as **11.1**, **11.4** and **12.1** with substituents other than a β aryl group. On the other hand, Tius's asymmetric allenyl ether Nazarov reaction, which also makes use of a chiral auxiliary, is general for a wide array of substrates. Moreover, the chiral auxiliary in the Tius allenyl ether Nazarov reaction is conveniently removed simultaneously with cyclization, providing enantioenriched cross-

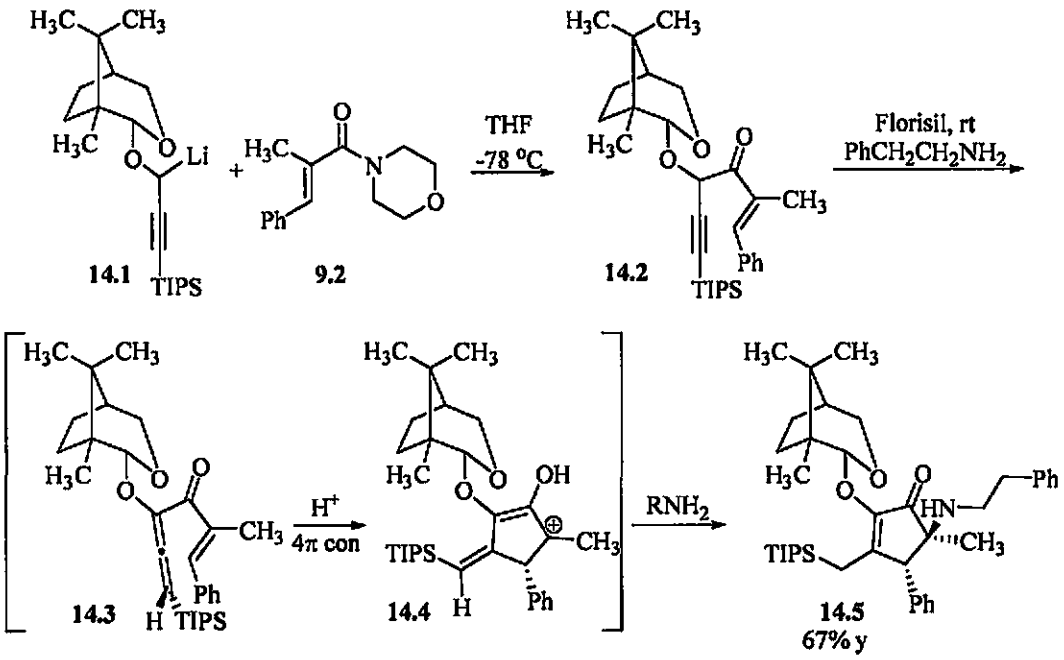
conjugated α-hydroxycyclopentenones in moderate to excellent yields.[4a,34] As illustrated in Scheme 1.13, when lithioallenyl ether **13.3** was treated with morpholino enamide **13.1** in the presence of lithium chloride, cyclopentenone **13.2** was formed in 67% yield and 67% enantiomeric excess. Although these results were remarkable for a 1st generation chiral auxiliary, reactivity and enantioselectivity were severely reduced upon scaling up the synthesis of cyclopentenone **13.2**. In searching for an alternative, Tius and coworkers developed camphor-derived auxiliary **13.4** that was just as easily prepared but was superior in both reactivity and enantioselectivity (78% y, 86% *ee*).



Scheme 1.13

The efficiency of the camphor-derived auxiliary later encouraged Tius and coworkers to explore its application in asymmetric amine-intercepted Nazarov cyclizations (Scheme 1.14). In light of the methodology detailed in Section 4.3, it was envisioned that cyclization of camphor-derived propargyl vinyl ketone **14.2** and interception of resultant cation **14.4** would provide cyclopentenone **14.5** with high diastereoselectivity. Addition of propargyllithium **14.1** to morpholino enamide **9.2** led to propargyl vinyl ketone **14.2**. Upon exposure to a

mixture of dry, activated Florisil and phenylethylamine diastereomerically pure cyclopentenone **14.5** was formed in 67% yield. This reaction worked both intra- and intermolecularly and represents the first asymmetric interrupted Nazarov process.

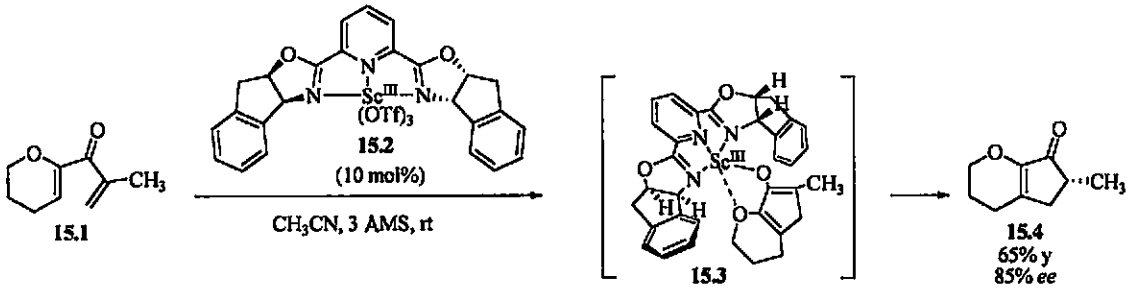


Scheme 1.14

5.2. Chiral Lewis Acid-Catalyzed Nazarov Reactions

As mentioned in Section 4.4, α-alkoxy and α-carboxy substituents of divinyl ketones were recognized as convenient bidentate ligands for Lewis acid catalysis. Dihydropyranyl-derived substrates bearing adjacent oxygen atoms such as **15.1** in Scheme 1.15 possessed this motif and were efficiently cyclized from exposure to aluminum(III) trichloride in either dichloromethane or acetonitrile.[35] The asymmetric version of the reaction was published using chiral scandium(III) complexes soon thereafter. As an example of the asymmetric

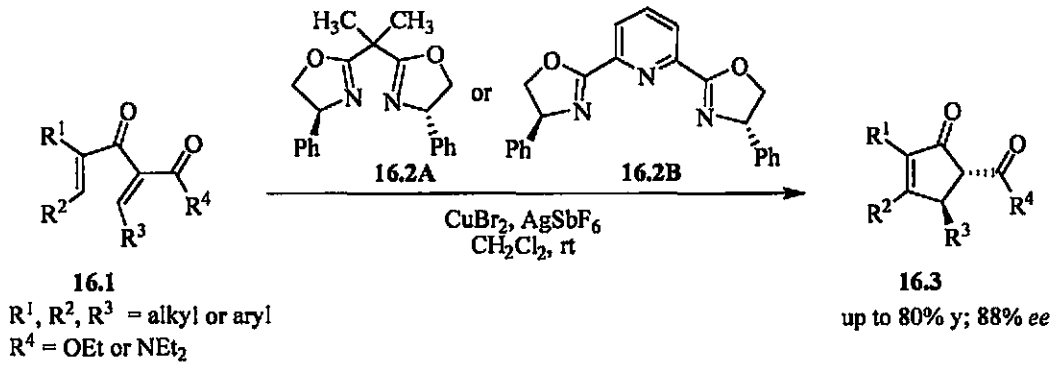
process, exposure of alkoxydienone **15.1** to 10 mol% of chiral scandium(III) triflate pybox complex **15.2** in acetonitrile provided enantiomerically enriched bicycle **15.4** in 65% yield and in 85% *ee*. It is important to note that in this particular reaction the chiral complex does *not* control the absolute sense of conrotation. Instead, the product stereochemistry is determined by the proton transfer to metalloenolate **15.3**. Pybox scandium(III) triflate complex **15.2** presumably shields one of the diastereotopic faces of metalloenolate **15.3**, thereby directing protonation towards the less hindered face during the termination step. This methodology was applied towards the enantioselective synthesis of numerous dihydropyranyl cyclopentenones and marked the first reported successful catalytic asymmetric Nazarov reaction.[36]



Scheme 1.15

Immediately following Trauner's communication, Aggarwal and coworkers reported the enantioselective formation of α-carboxy cyclopentenones **16.3** (Scheme 1.16).[30] Literature precedence had indicated that complexes of (bisoxazoline)Cu(II) with alkylidene malonates resulted in a boat-like conformation.[37] In light of this, Aggarwal postulated a similar boat-like conformation for complexes of (bisoxazoline)Cu(II) with α-carboxy divinyl ketones during an asymmetric Nazarov reaction. The puckered conformation would presumably

shield one face of the α-carboxy divinyl ketone, allowing the sense of conrotation to take place so as to move the β-vinyl substituents away from the bulk of the phenyls of the chiral ligand. The reactions of various α-carboxy divinyl ketones were evaluated on the basis of this prediction. As shown through numerous examples, highly enantioenriched cyclopentenones were obtained, providing strong support for Aggarwal's predicted stereochemistry-determining transition state.



16.1
R^1, R^2, R^3 = alkyl or aryl
R^4 = OEt or NEt_2

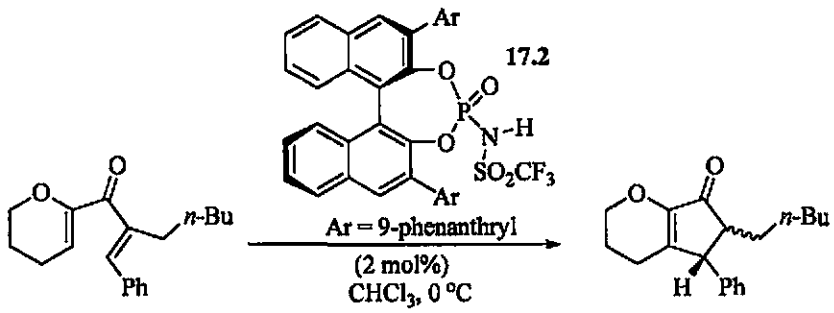
16.3
up to 80% y; 88% *ee*

Scheme 1.16

5.3. Chiral Brønsted Acid-Catalyzed Nazarov Reactions

Recently, Reuping and coworkers described the first organocatalytic Nazarov reaction of a wide array of substrates (Scheme 1.17). Enantioselectivity as high as 95% *ee* was obtained under very mild reaction conditions and low catalyst loading. Although *cis*-cyclopentenones were formed selectively, isomerization to the corresponding *trans*-cyclopentenone was readily achieved by exposure to basic alumina without loss of enantiopurity.[38] The high enantioselectivity, reactivity under mild conditions and low catalyst loading coupled with the

accessibility to both *cis* and *trans*-cyclopentenones has made this reaction one of the more attractive methods for asymmetric cylopentannelation to date.



17.1

17.3
86% y *cis:trans* 2:1
cis: 89% *ee*, *trans:* 95% *ee*

Scheme 1.17

6. Progress for the Nazarov Reaction in the Tius Group

This thesis describes our successful design, synthesis and use of improved chiral auxiliaries for the allenyl ether Nazarov reaction (Chapter 2). A thorough screening of numerous chiral auxiliaries has led to two superior sugar-derived allenes, along with the optimization of reaction conditions and a more detailed, well-substantiated mechanistic hypothesis for the reaction. In Chapter 3, a triply convergent cyclopentannelation reaction is described. This work is an extension of an existing method developed by our group that expands the scope and versatility of our allenyl ether Nazarov reactions. Lastly, Chapter 4 describes effort toward catalytic asymmetric cyclopentannelation using chiral Lewis acids and chiral palladium(II). The work reported in Chapter 4 is an extension of unpublished discoveries relating to the formation of enantioenriched cyclopentenones using chiral Lewis acids as well as a method published earlier in our group, in which racemic cyclopentenones were prepared from divinyl ketones using palladium(II) catalysis.

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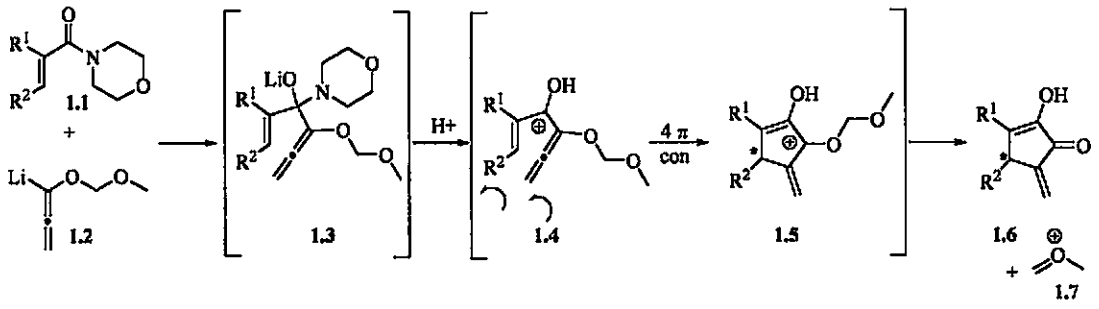
CHAPTER 2: Asymmetric Allenyl Ether Nazarov Reaction: Improved Sugar-Derived Auxiliaries

1. Background and Objective

1.1. Allenyl Ether Nazarov Reaction Mechanism

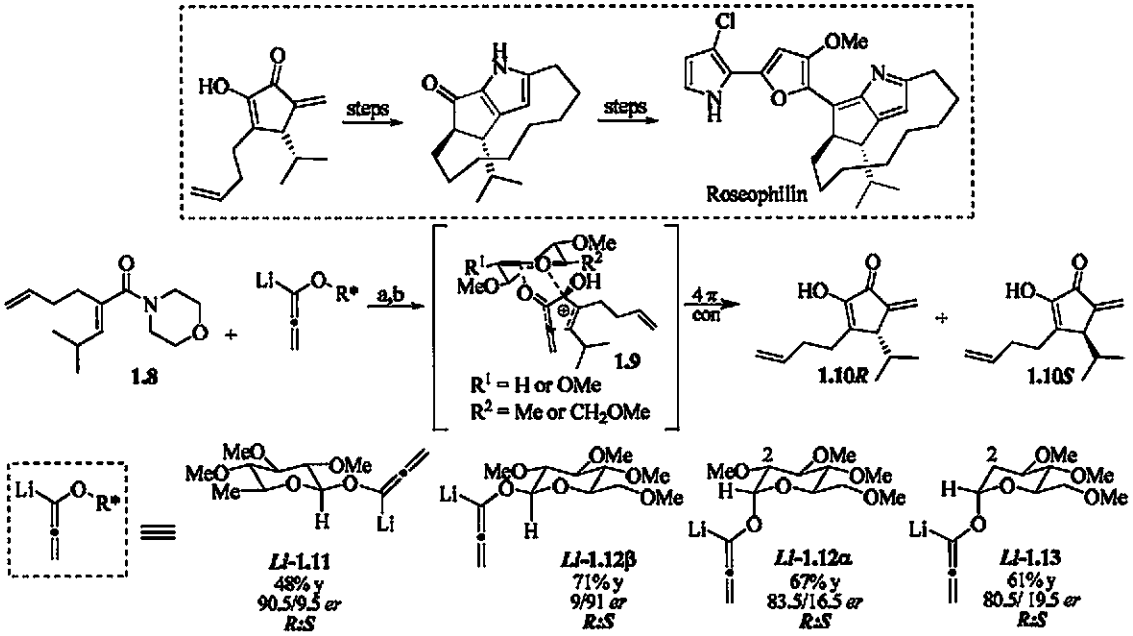
Asymmetric cyclopentannelation has been an ongoing area of research in our group.[1] Our most highly developed method is a variant of the Nazarov reaction involving addition of a lithioallenyl ether such as **1.2** to a morpholino enamide such as **1.1** (Scheme 2.1). Upon exposure to acid, the resultant tetrahedral intermediate **1.3** collapses to allenylvinyl cation **1.4** which subsequently undergoes thermally allowed 4π conrotation to cation **1.5**. Irreversible loss of **1.7** terminates the reaction, furnishing the cross-conjugated cyclopentenone **1.6** in moderate to excellent yields. The conversion of allenylvinyl cation **1.4** to cyclopentenone **1.6** is rapid and irreversible due to the relief of strain of the allene function, the small steric requirement for the approach of the terminal sp^2 and sp carbon atoms and the polarization of the enol ether function.



Scheme 2.1

1.2. Asymmetric Cyclopentannelation

The process depicted in Scheme 2.1 results in the formation of a chiral center. When α-(methoxy)methoxy-α-lithioallene **1.2** was used, cyclopentenone **1.6** was formed as a racemic mixture. However, replacing the methoxymethyl group with a chiral auxiliary resulted in the formation of enantiomerically enriched products. This method was seen as a convenient approach for the construction of cyclopentenone **1.10*R***, a precursor to natural roseophilin, which prompted the group to develop numerous chiral auxiliaries (Figure 2.1). Good enantioselectivity and yield of cyclopentenone **1.10*R*** was achievable when the chiral auxiliary fulfilled the following criteria: first, the chiral auxiliary was capable of imposing a clockwise or counterclockwise bias on the sense of conrotation that controlled the tetrahedral asymmetry of the ring carbon atom in product **1.6** and second, the chiral auxiliary was capable of leading to a stable α-oxo carbocation following its cleavage from the allylic cyclic cation (Figure 2.1).[2]



(a) morpholino enamide **1.8**, lithioallene, LiCl (4 equiv), -78 °C to -30 °C, 1 h; (b) HCl, HFIP/TFE (1/1) or EtOH, -78 °C.

Figure 2.1. Nazarov Reaction of Morpholino Enamide 1.8 with First Generation Sugar-Derived Auxiliaries

1.2.A. First Generation Sugar-Derived Auxiliaries

Carbohydrates and their derivatives are commonly used as chiral auxiliaries.[1,3] They were viewed as suitable sources of chirality since they are cheap, commercially available and as is the case with **1.2**, the ether fragment can be lost from the Nazarov product as a stable oxonium ion (refer to conversion of **1.5** to **1.6**, Scheme 2.1). The first chiral auxiliary synthesized for the lithioallene was ***Li*-1.12α**.[2a] Treatment of ***Li*-1.12α** with morpholino enamide **1.8** followed by cyclization using the conditions summarized in Figure 2.1 furnished cyclopentenone **1.10*R***. Shortly thereafter, permethylated glucose-derived lithioallenes ***Li*-1.11**, ***Li*-1.12β**, and ***Li*-1.13** were prepared and subjected to the identical cyclization

conditions to afford either cyclopentenone **1.10*S*** or **1.10*R*** (Figure 2.1).[i] Put together, these preliminary results revealed important aspects of the reactivity of the chiral allenes.[1,2a]

The first important aspect was that the absolute stereochemistry of the products correlated with the absolute stereochemistry of the anomeric carbon atom of the chiral auxiliary. When lithioallenyl α-D-glycopyranoside ***Li*-1.12α** was treated with morpholino enamide **1.8**, cyclopentenone **1.10*R*** was formed in 67% yield with 83.5/16.5 *er*. However, when lithioallenyl β-D-glycopyranoside ***Li*-1.12β** was used, asymmetric induction was not only improved (9/91 *er*) but the absolute stereochemistry of **1.10** was reversed, favoring the *S* enantiomer rather than the *R*. Since L-glucose is rare and therefore highly expensive (about $65.00/g), these results indicated that the cheap and readily available enantiomeric form of the sugar (*i.e.* D-glucose) alone could be used to generate both enantiomeric series of chiral cyclopentenones. Moreover, what this suggested to us was that the interaction involving the pyranose oxygen atom of the chiral auxiliary was critical for determining the product stereochemistry. It was hypothesized that the pyranose oxygen atom had two functions during the course of cyclization: first, to stabilize the pentadienyl cation **1.9** through lone electron pair donation and second, to stabilize the developing oxonium cation of the chiral auxiliary during its cleavage (Figure 2.1).

The results also indicated that not all substituents of the sugar-derived auxiliary were essential for good asymmetric induction. One example of this was illustrated by comparing two sugar-derived allenes, one with a C2 substituent and one without. Permethylated α-D-glucose-derived lithioallene ***Li*-1.12α** provided cyclopentenone **1.10*R*** with a moderate *er* of

[i] The enantiomeric ratios were determined by HPLC; co-injection of each cyclopentenone product with racemic **1.10** confirmed the peak assignment in the chromatogram. The absolute stereochemistry of cyclopentenones **1.10*R*** and **1.10*S*** was later determined through conversion of **1.10*R*** to natural roseophilin whose absolute stereochemistry was confirmed by CD spectroscopic analysis.

83.5/16.5. In the absence of the C2 alkoxy group (see 2-deoxy-α-D-glucose analog ***Li*-1.13**), an *er* of 80.5/19.5 was observed, implying that the C2 substituent was not actually required for optimal asymmetric induction. In another example, reactions with lithioallene ***Li*-1.11** (the C6-deoxy pseudoenantiomer of lithioallene ***Li*-1.12β**) led to **1.10*R*** in 48% yield and with 90.5/9.5 *er*. The fact that this enantiomeric ratio was comparable to that of ***Li*-1.12β** (9/91 *er*) indicated that the C6 methoxy substituent was also not essential for good asymmetric induction. The results from reactions with ***Li*-1.11** and ***Li*-1.13** were highly unexpected, since both C2 and C6 alkoxy groups were closest to the allene function and were therefore anticipated to exert a dominant influence on the direction of conrotation.

Although the first generation sugar auxiliaries showed promising results, there were two major shortcomings associated with all three. First, because the nucleophilicity of these allenes was limited (presumably due to aggregation of the lithioallene),[4] several equivalents of LiCl were necessary for addition to morpholino enamides to take place.[5] Second, whereas the enantiomeric excess of cyclopentenone **1.10** was good on a modest scale, a notable erosion was observed upon scaling up the reaction.

1.2.B. Camphor-Derived Auxiliary

As an equally cheap and easily accessible alternative, the group turned to camphor-derived auxiliary **1.14** (Figure 2.2).[2b,c] Treatment of allene ***Li*-1.14** with morpholino enamide **1.8** followed by cyclization using the conditions that are summarized in Figure 2.2 led to cyclopentenone **1.10*R*** in 78% yield and with 93/7 *er*, a marked improvement over the sugar-derived allenes. Interestingly, LiCl was not required in this case, suggesting that aggregation of the lithioallene was minimal (refer to Section 1.2.C for a further discussion of this effect).

Furthermore, no complications were encountered upon scale-up. The chiral auxiliary was consequently used for the total asymmetric synthesis of roseophilin and its scope and utility was later demonstrated through its application in other asymmetric Nazarov reactions (Figure 2.2).[2b,c,6] The absolute stereochemistry of the resultant cyclopentenone products was determined through chemical correlation with cyclopentenone **1.24*R*** whose absolute stereochemistry was determined crystallographically[7] as well as with cyclopentenone **1.10*R***[2a] whose absolute stereochemistry was later determined after further elaboration to natural roseophilin.[ii,8] As with cyclopentenone **1.10*R*** and **1.24*R*** the major enantiomer of the cyclopentenones **1.18**, **1.20** and **1.22** was the less mobile of the two on HPLC analysis using a Chiralcel-OD column. It should be emphasized that until all other stereochemical assignments are confirmed through additional methods they should be considered tentative.

[ii] Our stereochemical assignment of natural roseophilin was confirmed by Boger's synthesis of the enantiomer (see reference 8).

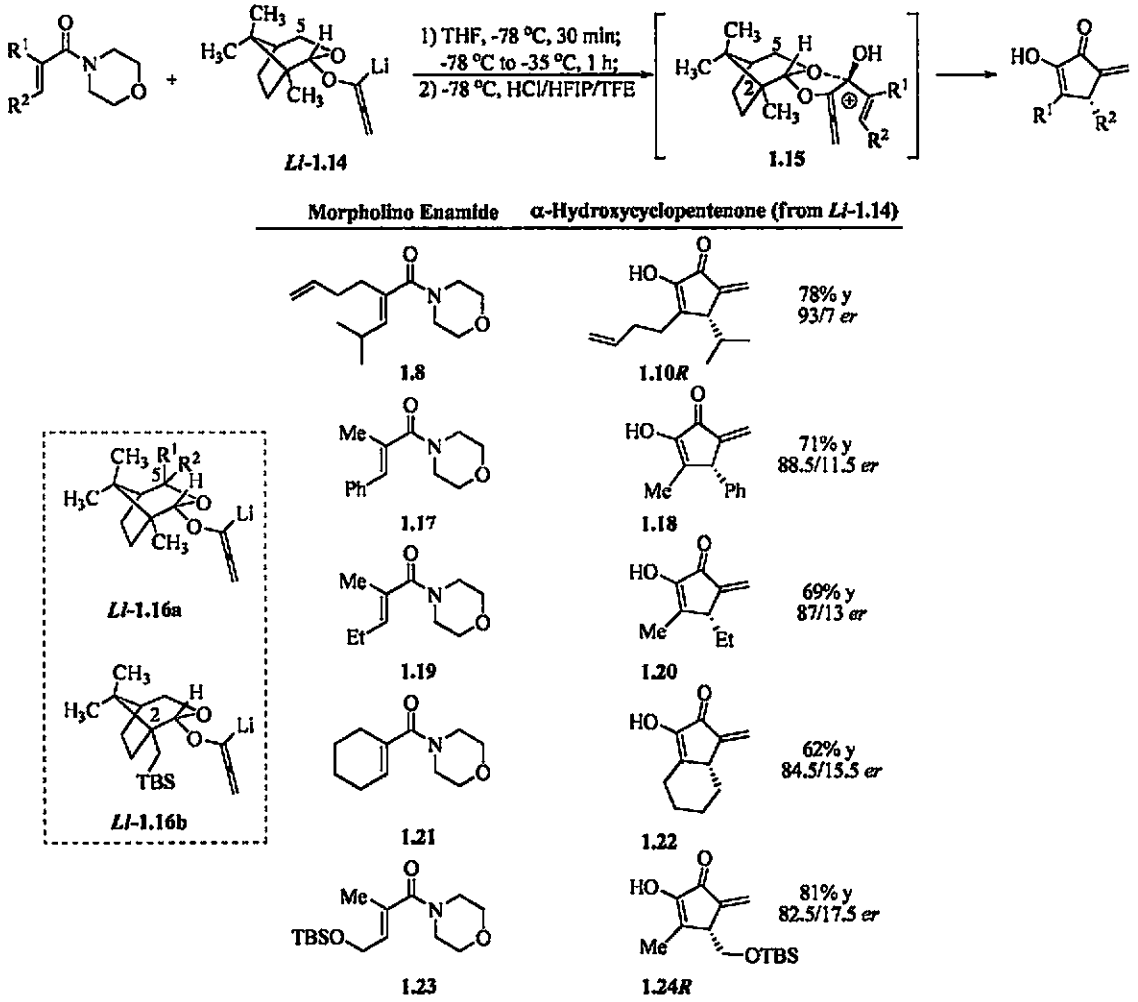


Figure 2.2. Enantiomerically Enriched Cyclopentenones from Camphor-Derived Allene 1.14

In order to optimize the chiral auxiliary, the group proposed stereochemistry-determining intermediate **1.15** (Figure 2.2). It was believed that the C5 or C2 groups on the camphor auxiliary controlled the direction of conrotation due to the close proximity of these two carbon atoms to the allene function. Analogs ***Li*-1.16a** and ***Li*-1.16b** (Figure 2.2) were prepared on the basis of this hypothesis and were evaluated through their reactions with morpholino enamide **1.17**.[9] Surprisingly, all reactions led to cyclopentenone **1.18** with poorer

enantioselectivity. Unfortunately, the modification of other positions of camphor was not straightforward and precluded further improvement of this chiral auxiliary. The group consequently took a second look at sugar-derived auxiliaries for optimization of the methodology. Unlike camphor, sugars have multiple sites that can be easily derivatized. This allowed us to probe how the location and size of the substitituents on the chiral auxiliary affected the stereochemical outcome of the cyclization.

1.2.C. Second Generation Sugar-Derived Auxiliary

As mentioned in Section 1.2.A, the major disadvantage to using the sugar-derived lithioallenes was that they were poor nucleophiles and their addition to enamides required the presence of several equivalents of LiCl for optimal yields. The role of the additive was presumably to coordinate the many oxygen substituents, thereby disrupting aggregation of the lithioallenyl ether and leading to a more reactive nucleophile.[10] A related solution for overcoming the reactivity issue of the sugars was to replace the methyl groups with trialkylsilyl substituents. In doing so it was believed that the trialkylsilyl substituents would sterically suppress aggregation of the allenyllithium and lead to a more reactive nucleophile. Persilylated glucose-derived lithioallene ***Li*-1.25α** was thus synthesized and evaluated by former group member, Derrick delos Santos (Figure 2.3).[11] Gratifyingly, treatment of persilylated glucose-derived lithioallene ***Li*-1.25α** with morpholino enamide **1.17** led to cyclopentenone **1.18** in 84% yield, a substantial improvement in yield over lithioallene ***Li*-1.14**. However, more interestingly, reactions using lithioallene ***Li*-1.25α** still required the same amount of LiCl and yet led to a marked improvement in the enantioselectivity for a number cyclopentenones relative to all previous chiral auxiliaries.

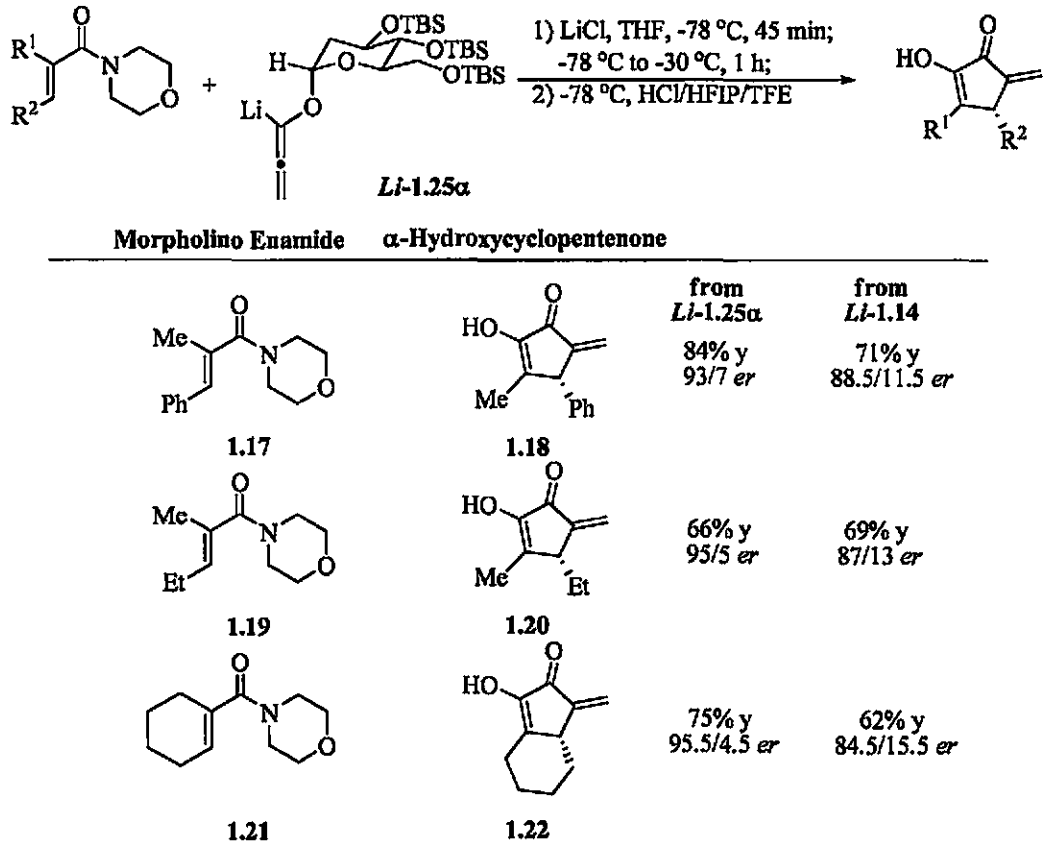


Figure 2.3. Enantiomerically Enriched Cyclopentenones Derived from Allene 1.25α

The fact that enantioselectivity significantly improved with the silyloxy groups implicated a steric influence of substituents of the chiral auxiliary. However, it should be noted that while reactivity of the chiral auxiliary with silyloxy substituents also improved, LiCl was still necessary for optimal yields.

1.2.D. Key Observations from Early Generation Chiral Auxiliaries

Extensive effort was invested towards the development of the asymmetric allenyl ether Nazarov reaction. From the preliminary work that has been thus far described using chiral auxiliaries derived from permethylated D-glucose (*Li*-1.11 through *Li*-1.13), camphor and

persilylated D-glucose (chiral auxiliaries ***Li*-1.14** and ***Li*-1.25α**, respectively) several important observations were made. First, each enantiomer of cyclopentenones bearing a chiral center β to the carbonyl can be selectively synthesized using D-glucose-derived allenes depending on the anomer (α or β) that is used. This suggested that an interaction involving the pyranose oxygen atom of the chiral auxiliary was critical for determining the product stereochemistry. Secondly, aggregation of the allenyl anions attenuated the nucleophilicity of auxiliaries having methoxy substituents. As was demonstrated in the case of chiral auxiliary **1.25α**, the use of larger silyloxy substituents was shown to override this effect and led to improved reactivity and enantioselectivity. These observations offered guidance for the present work that is described in what follows.

1.3. Project Objective

As a primary focus of my thesis work, a number sugar-derived auxiliaries were prepared and evaluated. The purpose of this work was two fold. First, we sought to elucidate exactly what structural features were important for the control of stereochemistry. Second, in the process we wanted to understand the mechanism by which the chiral auxiliaries exerted their control.[12] We have since examined how both the position and size of the C3, C4 and C6 substituents on the pyran affected the stereochemical outcome of the Nazarov reaction. Through these studies the synthesis and screening of numerous chiral auxiliaries have paved the way to two superior sugar-derived allenes and the optimization of reaction conditions for the Nazarov cyclization. The scope of each chiral auxiliary under these optimized conditions has been demonstrated through its reactions with a variety of morpholino enamides and in one case, an α,β-unsaturated butyrolactone. Additionally, we report a more detailed, well-

substantiated mechanistic hypothesis that rationalizes the stereochemical outcome of our products. This model will aid in the design of simpler allenyl ethers bearing chiral auxiliaries with non-sugar derived scaffolds.

2. Results and Discussion

2.1. Effects of the C3 and C6 Substituents of Glucose-Derived Auxiliaries on the Enantioselectivity of the Nazarov Reaction

Prior studies (refer to Section 1.2.A) had indicated that not all alkoxy substituents on the sugar-derived auxiliary were important for asymmetric induction in the Nazarov reaction. We hoped to more thoroughly identify which of the substituents were the critical ones. Numerous sugar-derived analogs were therefore synthesized and evaluated through their reactions with morpholino enamide **1.17**.

2.1.A. Equatorial C3 Substituent

Since it had been demonstrated that the effect of the C2 substituent (compare lithioallenes ***Li*-1.12α** and ***Li*-1.13**, Figure 2.4) on enantioselectivity was negligible, we next decided to examine the effect of the C3 substituent of the improved lithioallene, ***Li*-1.25α** (Figure 2.4).

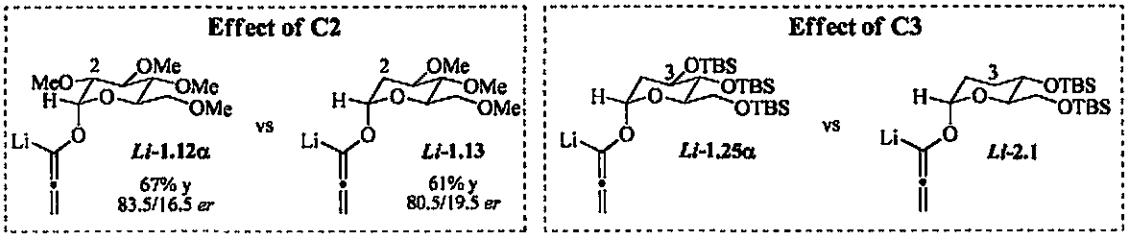
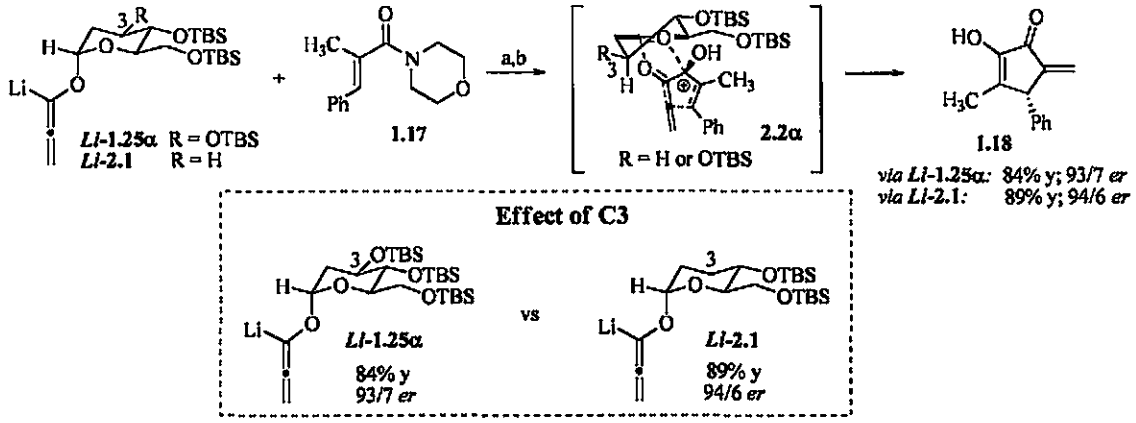


Figure 2.4. The Effects of C2 and C3 Equatorial Substituents of Sugar-Derived Auxiliaries on the Enantioselectivity of Nazarov Reactions

D-Glucose-derived lithioallene *Li*-**2.1** was treated with morpholino enamide **1.17** using the conditions detailed in Scheme 2.2. Cyclization led to cyclopentenone **1.18** in 89% yield and in a 94/6 enantiomeric ratio, nearly identical to the results observed from reactions with D-glucose-derived lithioallene *Li*-**1.25α** (84% yield, 93/7 *er*). We therefore concluded that, like the C2 substituent, the equatorial C3 substituent of the pyanose was also not required for good asymmetric induction. This was not surprising when considering the distance between the equatorial C3 substituent and the allene moiety in the proposed stereochemistry-determining transition state **2.2α** (Scheme 2.2). According to the model, the equatorial C3 substituent in **2.2α** is too far from the pentadienyl cation to have significant control on the direction of conrotation. On the other hand, this is not true for the C6 substituent (nor the axial C3 position of conformationally locked auxiliaries, refer to Section 2.3). The effects of the C6 substituents will be discussed in Section 2.1.B.



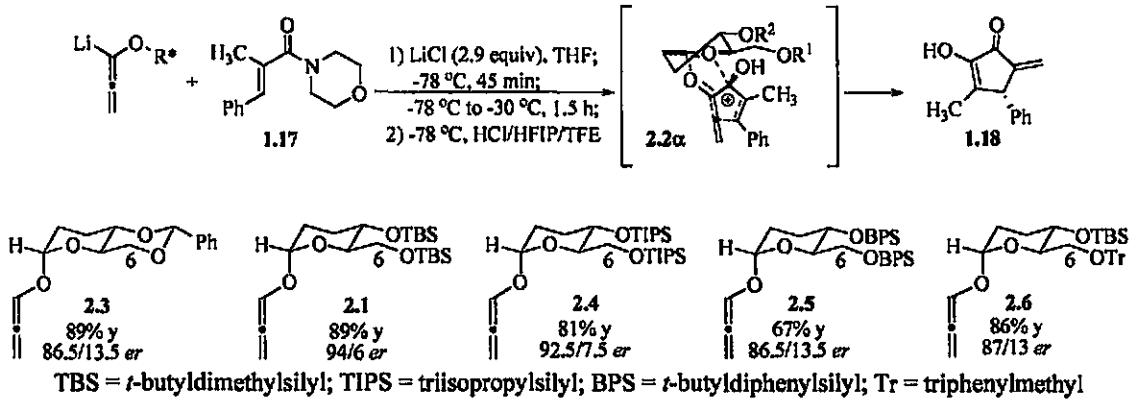
Scheme 2.2 (a) (i) allene *Li*-**2.1** (2.0 equiv), LiCl (2.9 equiv), THF, -78 °C, 45 min; (ii) amide **1.17** (1.0 equiv), THF, -78 °C; warm to -30 °C, 1.5 h; (b) HCl (33 equiv), HFIP/TFE (1/1), 2 min, -78 °C.

2.1.B. Equatorial C6 Substituent

It was first predicted that as the steric bulk of the C6 substituent on the chiral auxiliary increased, the enantiomeric excess of the Nazarov product would increase. A series of α- and β-glycosides were synthesized and evaluated through their reaction with morpholino enamide **1.17** using the conditions shown in Figure 2.5 and 2.6. The effects of varying the C6 substituent on both the α- and β- series of auxiliaries were examined and rationalized according to stereochemistry-determining transition state **2.2α** (Figure 2.5) and **2.2β** (Figure 2.6).

α-Series

The size of the C6 substituent was varied by choice of protecting group. This group was largest when the C6 hydroxyl was protected as a trityl ether and smallest in the case of a benzylidene (Figure 2.5, sugar-derived allenes **2.6** and **2.3**, respectively). The auxiliaries are listed from left to right in the order of the increasing size of the C6 substituent. While it was apparent that the enantioselectivity was influenced by the C6 substituent, no direct relationship between the size of the C6 substituent and the degree of asymmetric induction could be seen. Sugar-derived allene **2.1**, only having the second smallest C6 group, was optimal among all the auxiliaries. Moreover, what was more perplexing was that the conformationally locked auxiliary **2.3** having the smallest C6 substituent size was in fact comparable in enantioselectivity to auxiliaries **2.5** and **2.6** having the largest C6 substituents. Thus, contrary to what we expected, increasing the size of the C6 substituent did not lead to improved enantioselectivity. As will be discussed, this also proved to be the case for the β-series of auxiliaries.



TBS = *t*-butyldimethylsilyl; TIPS = triisopropylsilyl; BPS = *t*-butyldiphenylsilyl; Tr = triphenylmethyl

Figure 2.5. Effect of the C6 Equatorial Substituents of the α-Series of Auxiliaries on Enantioselectivity of Cyclopentenone 1.18

β-Series

Since prior work (refer to Section 1.2.A) had shown that permethylated β-glucose-derived lithioallene ***Li*-1.12β** provided cyclopentenones with the opposite absolute stereochemistry as those derived from permethylated α-glucose-derived lithioallene ***Li*-1.12α**,[2a] we were curious to learn whether this was also true for persilylated β-glucosides. Gratifyingly, cyclization using persilylated β-glucose-derived lithioallene ***Li*-1.25β** with morpholino enamide **1.17** provided cyclopentenone **1.18** with 11/89 *er* with preference for the opposite absolute stereochemistry as the α-series of auxiliaries, which was consistent with previous results (Figure 2.6). However, by comparing lithioallenes ***Li*-1.25β** and ***Li*-1.12β** it was apparent again, contrary to our prediction, that larger C6 substituents did not substantially improve enantioselectivity.

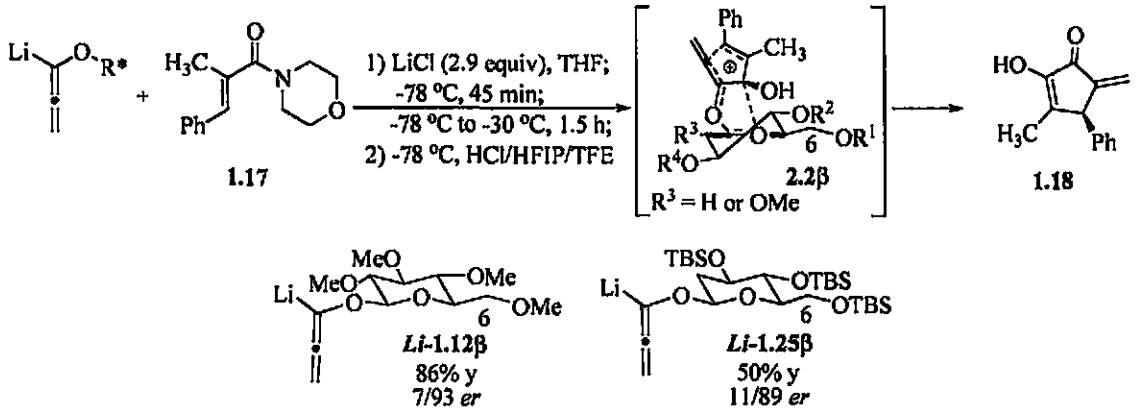


Figure 2.6. Effect of the C6 Equatorial Substituents of the β-Series of Auxiliaries on Enantioselectivity of Cyclopentenone 1.18

Taken together, it was concluded that enantioselectivity was not completely independent of substituent size for certain positions on the chiral auxiliary. However, at the time a clear trend could not be established based on the current model and consequently an alternative stereochemistry-determining transition state model was considered (see discussion in Section 2.2.).

2.2. Mechanistic Rationale

While there are a number of possible ring conformations, pyrans predominantly adopt the chair (Figure 2.7). In the case of α-D-glucose, the two chair conformers can be labeled $^4C_1$, in which the substituents at the C2, C3, C4 and C5 are equatorial and the $^1C_4$ chair, in which they are all axial. Of the two, the $^4C_1$ conformation is most energetically favored since it is destabilized by 1,3-diaxial interactions to a lesser extent.[13]

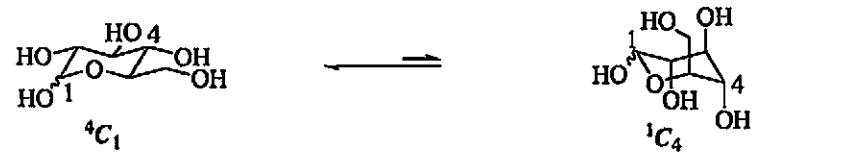


Figure 2.7. Chair Conformations of α-D-Glucose

Up to this point we had assumed that the pyran did not interconvert between conformations $^4C_1$ and $^1C_4$ during the course of the reaction and had therefore rationalized the stereochemical outcome based solely on intermediate **2.7** (Figure 2.8). However, because the current data did not support this proposed model, ring-inverted intermediate **2.8** had to be considered.

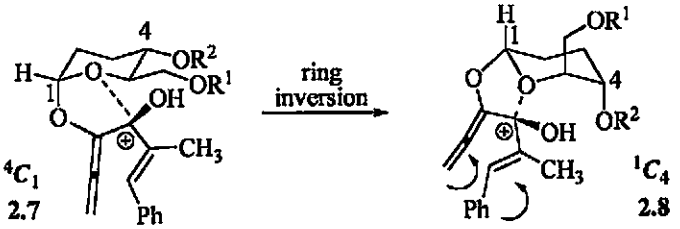


Figure 2.8. Postulated Stereochemistry-Determining Intermediates for Cyclizations Using Sugar-Derived Allenes

2.2.A. Literature Precedence for Conformational Inversions of Pyrans

There is precedent that supports the fact that in some cases the conformation of a pyran with the larger number of axial substituents is paradoxically lower in energy than the one with the larger number of equatorial substituents. Here we wish to define "non-inverted chair" as the conformation of a pyran with the largest number of equatorial substituents ($^4C_1$) and "ring-inverted chair" as the one with the largest number of axial substituents ($^1C_4$). In

1994, our own group isolated persilylated *C* glycoside **2.9** in the inverted chair conformation shown in Figure 2.9. The conformation was verified from the small coupling constants between the equatorial ring hydrogens in the 500 MHz ^{1}H NMR spectrum.[14] Two years later, Suzuki and co-workers also observed inverted conformations for related pyrans **2.10** and **2.11**.[15] Glycoside **2.11** is especially noteworthy since it demonstrated that the anomeric effect that usually provides further stabilization for the non-inverted conformer in *O*-glycosides was essentially overridden by a steric effect; the large *tert*-butyldiphenylsilyloxy (OBPS) groups are unexpectedly less sterically encumbered in the axial position and as result this pushes the equilibrium between the two conformations (inverted and non-inverted) in favor of the inverted chair. This phenomenon was investigated more thoroughly by Yamada and coworkers in 2004.[16] In the case of pyran **2.12**, which contains two adjacent OTBS groups, the non-inverted conformation was observed. However, when the groups were exchanged for large silyloxy substituents (OBPS), the *trans* equatorial steric repulsion between the adjacent silyloxy substituents in the non-inverted conformation became so overwhelming that the inverted chair shown in **2.13** was favored instead. This trend was also observed with the corresponding thioglycoside **2.14**.

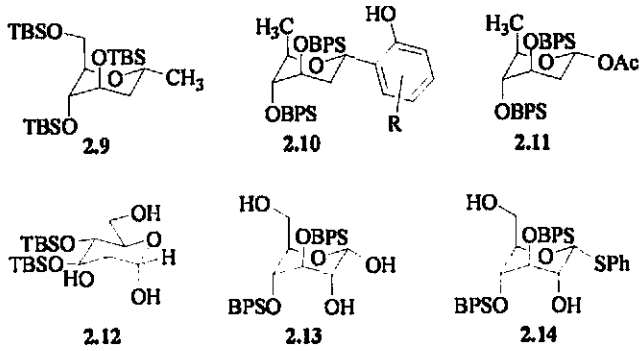
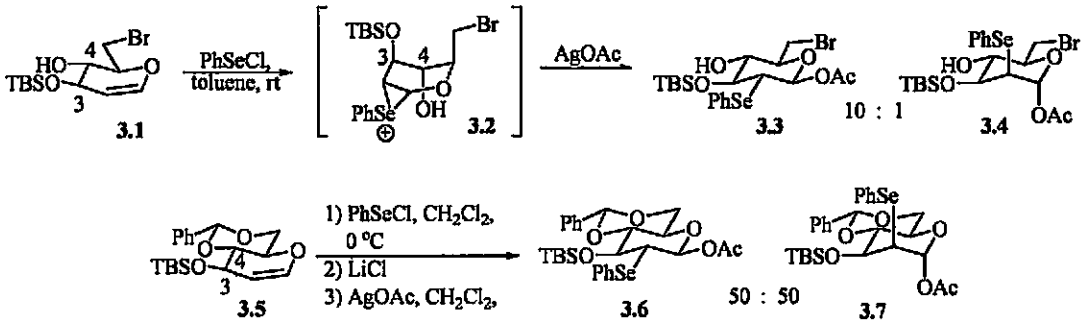


Figure 2.9. Ring-Inverted Pyranoses

In 1997, Roush and coworkers observed excellent selectivity for β-glucoside **3.3** over α-mannoside **3.4** from treatment of glucal **3.1** with phenylselenium chloride followed by silver acetate (Scheme 2.3). The selectivity was rationalized by implicating the ring-inverted intermediate **3.2** which formed after addition of phenylselenium chloride. Following this step, S_N2 nucleophilic attack on intermediate **3.2** by the acetate took place on the top face of the ring, providing the observed products **3.3** and **3.4** in a high diastereomeric ratio of 10:1. The postulated structure of intermediate **3.2** was supported by the fact that the reaction of conformationally locked glucal **3.5** under the same reaction conditions was nonselective.[17]

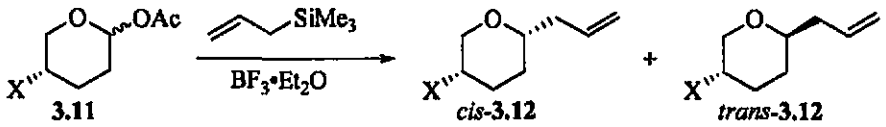


Scheme 2.3

Lastly, the most supportive literature examples for proposed transition state **2.8** (Figure 2.8) come from the work of the Bowen and Woerpel groups. In the early 90's, Bowen applied molecular mechanics calculations in his study of oxocarbenium ions (Figure 2.10)[18]. What he found was that the conformational preferences of the ions were highly dependent on the electronic nature of the pyran substituents. When substituents were alkyl, the ring adopted conformer **3.8** in which the alkyl groups were pseudo equatorial. Conversely, when the substituents were either hydroxy or alkoxy the ring assumed conformer **3.9**, in which case the hydroxy or alkoxy groups were pseudo axial.

Figure 2.10. Bowen's Ring-Inverted Intermediate

In 2006, Woerpel's studies of nucleophilic substitutions on pyran **3.11** proved to be consistent with these calculations (Figure 2.11). The product ratios of three analogous alkyl- and alkoxy- substituted acetals were compared. The results shown in the table were consistent with what one should expect based on the intermediates **3.8** or **3.9** proposed by Bowen. For example, the *cis* selectivity of the methyl and benzyl-substituted tetrahydropyrans resulted from nucleophilic attack on the bottom face of intermediate **3.8**. Conversely, the *trans* selectivity of the *O*-benzyl-substituted tetrahydropyran resulted from nucleophilic attack on the top face of intermediate **3.9**. Woerpel hypothesized that when the substituents are heteroatomic, as is the case for intermediate **3.9**, the unusual inverted conformer is favored due to electrostatic attraction between the lone electron pair of the C4 heteroatom and the oxocarbenium ion (see cation **3.10**).[19]



compound	X	*cis* : *trans*	yield%
a	Me	94 : 6	74
b	OBn	1 : 99	75
c	CH_2Bn	93 : 7	77

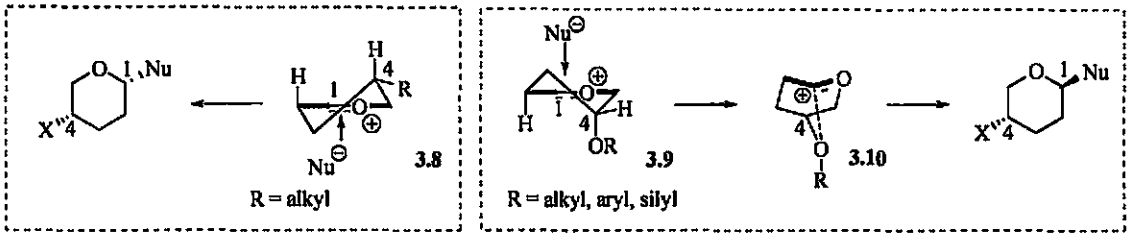
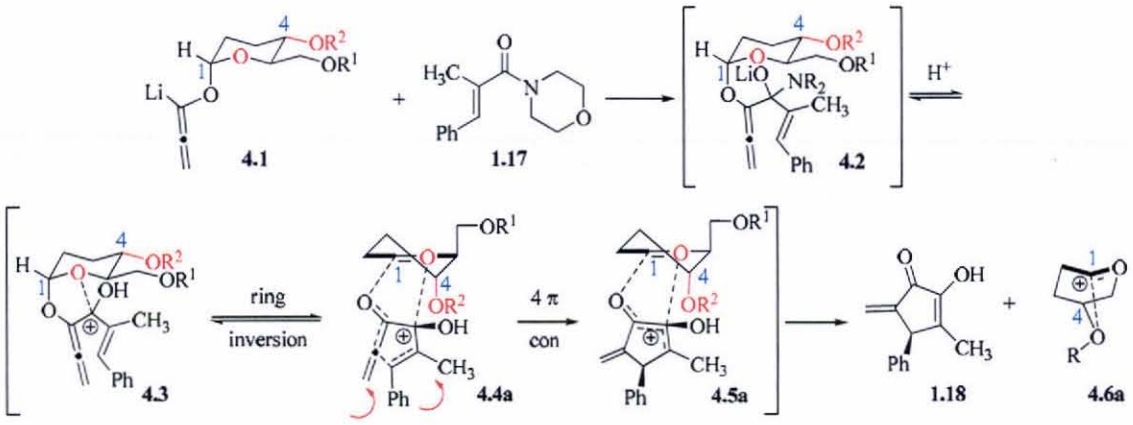


Figure 2.11. Woerpel's Ring-Inverted Intermediate

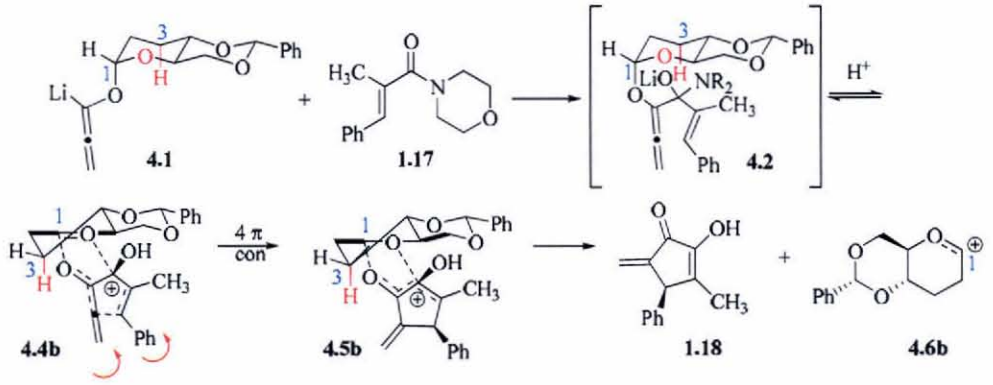
2.2.B. Mechanistic Hypothesis

In light of these literature precedents, the following mechanism was proposed. Treatment of lithioallenyl ether **4.1** with morpholino enamide **1.17** provides tetrahedral intermediate **4.2** (Scheme 2.4). Upon exposure to the polar acidic quench conditions, a conformational inversion is induced, allowing newly formed pentadienyl cation (see **4.3**) to be stabilized by the non-bonding electron pair of the pyranose oxygen atom. This restricts the conformational mobility of the pentadienyl cation and orients the C4 group directly behind it (see **4.4a**). As a consequence, conrotation is directed away from the C4 substituent. According to Woerpel ring inversion in transition state **4.4a** is presumably induced by the electrostatic interactions between the C4 silyloxy substituent and the developing oxocarbenium ion at C1 of the pyran.[17,18]



Scheme 2.4

In the case of conformationally locked auxiliaries (*e.g.* allene **2.3**, Figure 2.5), ring inversion of intermediate of **4.3** to transition state **4.4a** cannot occur. Consequently, the direction of conrotation in these auxiliaries is instead controlled by interactions between the axial C3 hydrogen atom of the chiral auxiliary and the pentadienyl cation, as shown by transition state **4.4b** (Scheme 2.5).



Scheme 2.5

Termination of the reaction for either pathway (*via* **4.4a** or **4.4b**) is accomplished by cleavage of a highly resonance-stabilized oxocarbenium ion **4.6** and formation of the cross-conjugated cyclopentenone **1.18**.

There are three aspects of this mechanism that deserve emphasis. First, asymmetric induction is optimal when the conformational mobility of the pentadienyl cation is restricted. Second, regardless of whether ring inversion takes place during the stereochemistry-determining step, the sense of conrotation is ultimately controlled by the shielding axial (or pseudo axial) substituent of the chiral auxiliary which directly blocks one face of the pentadienyl moiety (refer to transition states **4.4a** and **4.4b**). Third, ring inversion **4.3** to **4.4a** presumably results from the electrostatic interactions between the lone electron pair of the shielding alkoxy substituent and the developing cation at the anomeric carbon atom (C1) of the chiral auxiliary as suggested through Woerpel's work.

2.3. Confirming Studies: Evaluating the Effects of Suspected Important Structural Elements of the Chiral Auxiliary

Based on the mechanism proposed in Scheme 2.4 and 2.5, the following predictions were made:

(1) Role of the Pyranose Oxygen Atom of the Chiral Auxiliaries: If the role of the pyranose oxygen atom of the chiral auxiliary is to restrict conformational mobility of the pentadienyl cation, then removing it should result in undesired free rotation of the pentadienyl moiety and consequently poor transfer of stereochemical information (Figure 2.12). Additionally, it is also believed that the pyranose oxygen stabilizes the oxopyrylium ion that is formed upon

fragmentation of the pentadienyl cation. Therefore, deleting the pyranose oxygen atom should also lead to diminished yields.

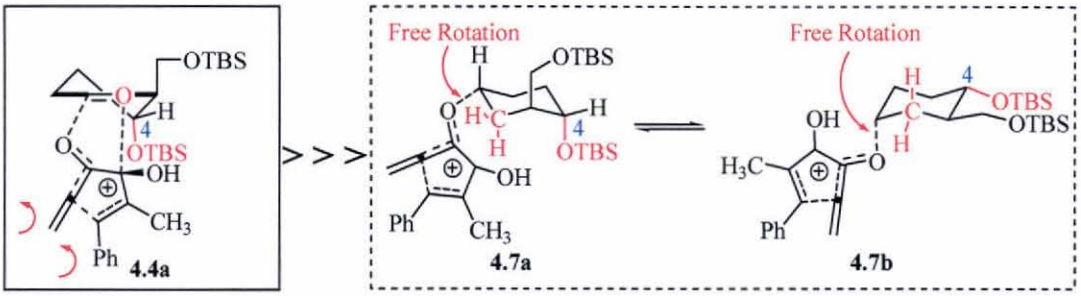
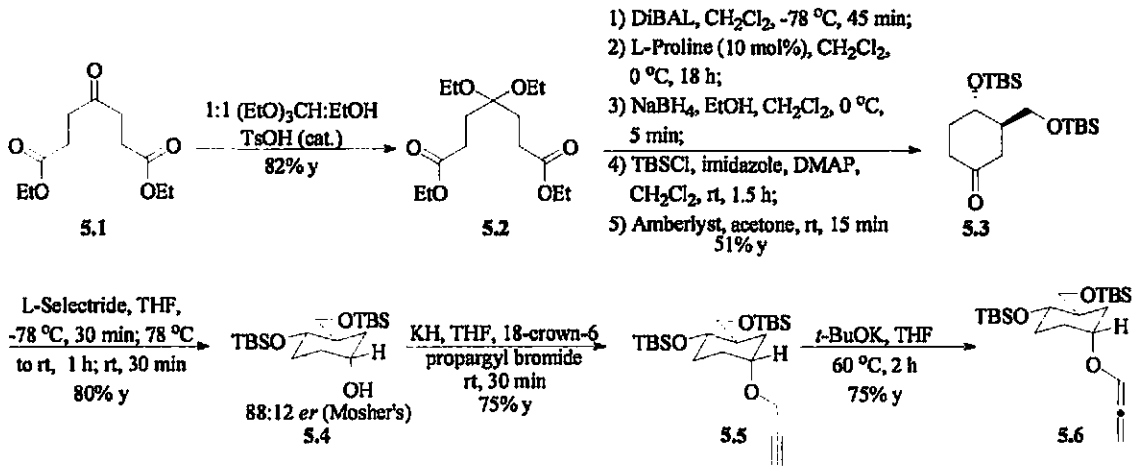


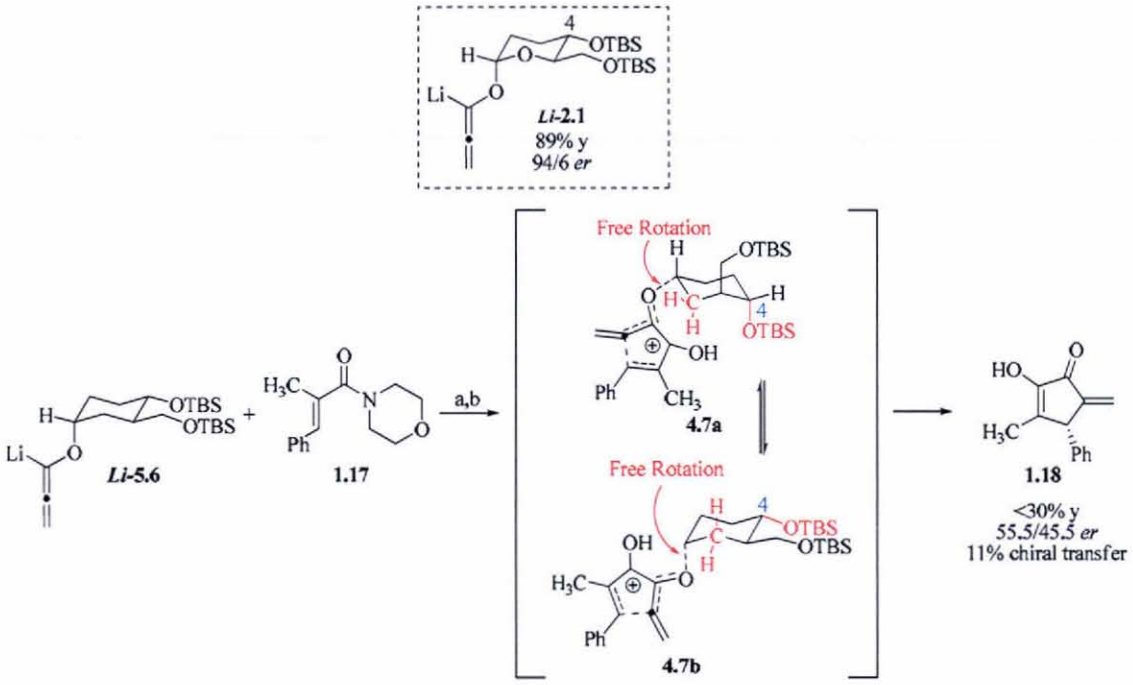
Figure 2.12. Predicted Role of the Pyranose Oxygen

Allene **5.6** was prepared in 88/12 *er* according to the procedure summarized in Scheme 2.6. Diethylacetal **5.2** was formed from commercially available 4-oxopimelate **5.1** by standard methods. DIBALH reduction of **5.2** led to an unstable dialdehyde which was immediately subjected to List's asymmetric aldol condensation condition using L-proline.[20] Standard reduction of the resultant unstable dialdehyde using $NaBH_4$ followed by silylation and deprotection of the ketone afforded compound **5.3** in an overall yield of 51%. Selective formation of axial alcohol **5.4** (broad s at 3.99 ppm on the 300 MHz NMR) was accomplished in 80% yield using L-Selectride. The optical purity of **5.4** was determined to be 88/12 *er* based on its Mosher's ester. Treatment of alcohol **5.4** with potassium hydride followed by propargyl bromide provided alkyne **5.5** which was subsequently isomerized to allene **5.6** according to Brandsma's method.[21]



Scheme 2.6

Lithioallene ***Li*-5.6** was added to morpholino enamide **1.17** and the reaction was allowed to warm from -78 °C to -30 °C for 1 h. The resultant tetrahedral intermediate was then cooled to -78 °C and cyclized by rapid addition *via* cannula into a solution of anhydrous HCl in HFIP and TFE at -78 °C. The isolated crude material consisted of a number of uncharacterized materials and minimal amounts of the desired Nazarov product with 11% chirality transfer (Scheme 2.7). The low conversion and asymmetric induction supported the hypothesis that the role of the pyranose oxygen was two-fold: first it restricted the conformational mobility of the pentadienyl cation and second it facilitated clean cleavage of the chiral auxiliary during the cyclization.



Scheme 2.7 (a) (i) allene ***Li*-5.6** (2.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (ii) amide **1.17** (1.0 equiv), THF, -78 °C; -78 °C to -30 °C, 1 h; (b) (i) HCl/HFIP/TFE, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

(2) Importance of the C4 Substituent of Ring-Inverted Chiral Auxiliaries on Asymmetric Induction: Since the pseudo axial C4 silyloxy substituent in a ring-inverted chiral auxiliary presumably controls the sense of conrotation, deleting this group should likewise result in poorer enantioselectivity (see **4.8**, Figure 2.13).

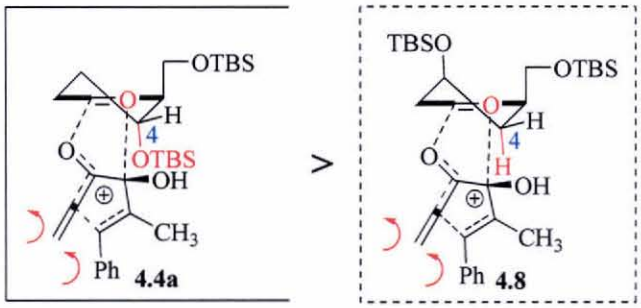
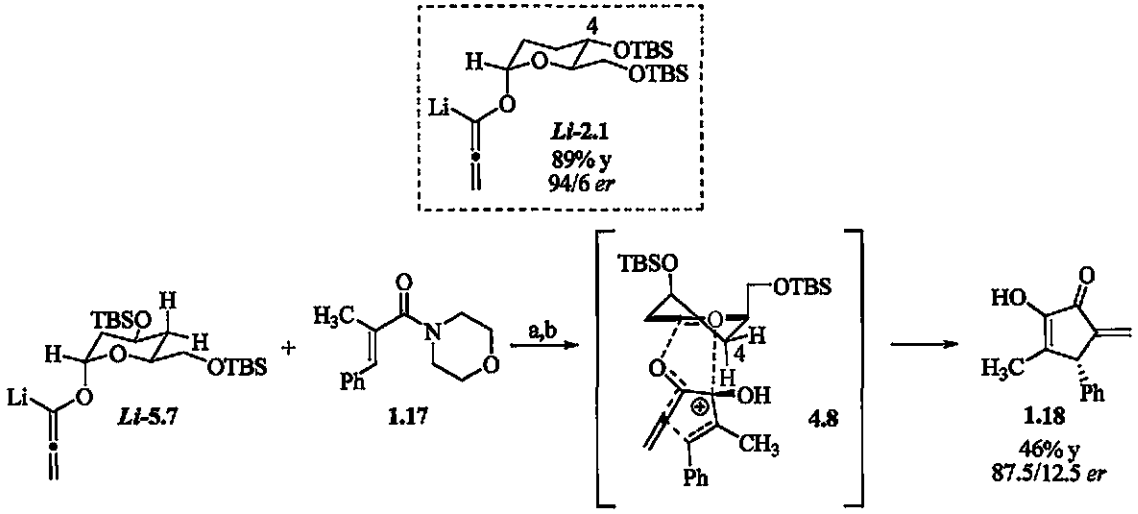


Figure 2.13. Predicted Importance of the Pseudo Axial C4 Substituent of Ring-Inverted Pyrans on Asymmetric Induction

Under the reaction conditions detailed in Scheme 2.8, lithioallene ***Li*-5.7** was added to morpholino enamide **1.17** and the resultant addition product was cyclized to provide cyclopentenone **1.18** with enantioselectivity (87.5/12.5 *er*) which was notably lower than that from lithioallene ***Li*-2.1** (96/4 *er*). Considering that lithioallene ***Li*-5.7** only differs from lithioallene ***Li*-2.1** by the absence of an equatorial C4 substituent, it can be concluded that the C4 substituent is indeed critical for good enantioselectivity. Moreover, when the size of this equatorial substituent is decreased, enantioselectivity decreases.



Scheme 2.8 (a) (i) allene ***Li*-5.7** (2.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (ii) amide **1.17** (1.0 equiv), THF, -78 °C; -78 °C to -30 °C, 1 h; (b) (i) HCl/HFIP/TFE, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

(3) Importance of C3 Substituents of Conformationally Locked Chiral Auxiliaries: If an *axial* C3 substituent on a conformationally locked chiral auxiliary directs the sense of conrotation by shielding one face of the pentadienyl cation, then a large C3 *axial* silyloxy substituent on chiral auxiliary **2.3** should improve asymmetric induction (transition state **4.9**, Figure 2.14). On the other hand, an *equatorial* C3 silyloxy substituent of any size should neither improve

nor erode enantioselectivity since it projects away from the pentadienyl cation and is too far to have any influence (transition state **4.10**, Figure 2.14).

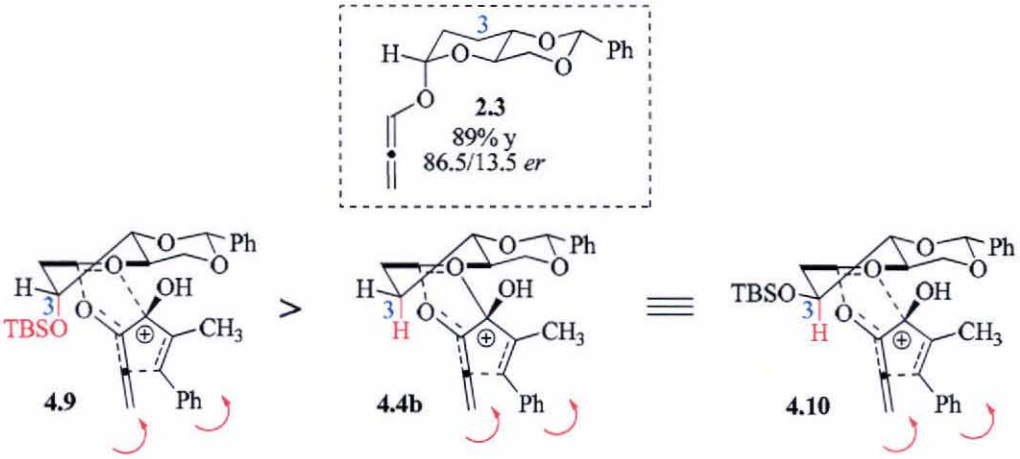
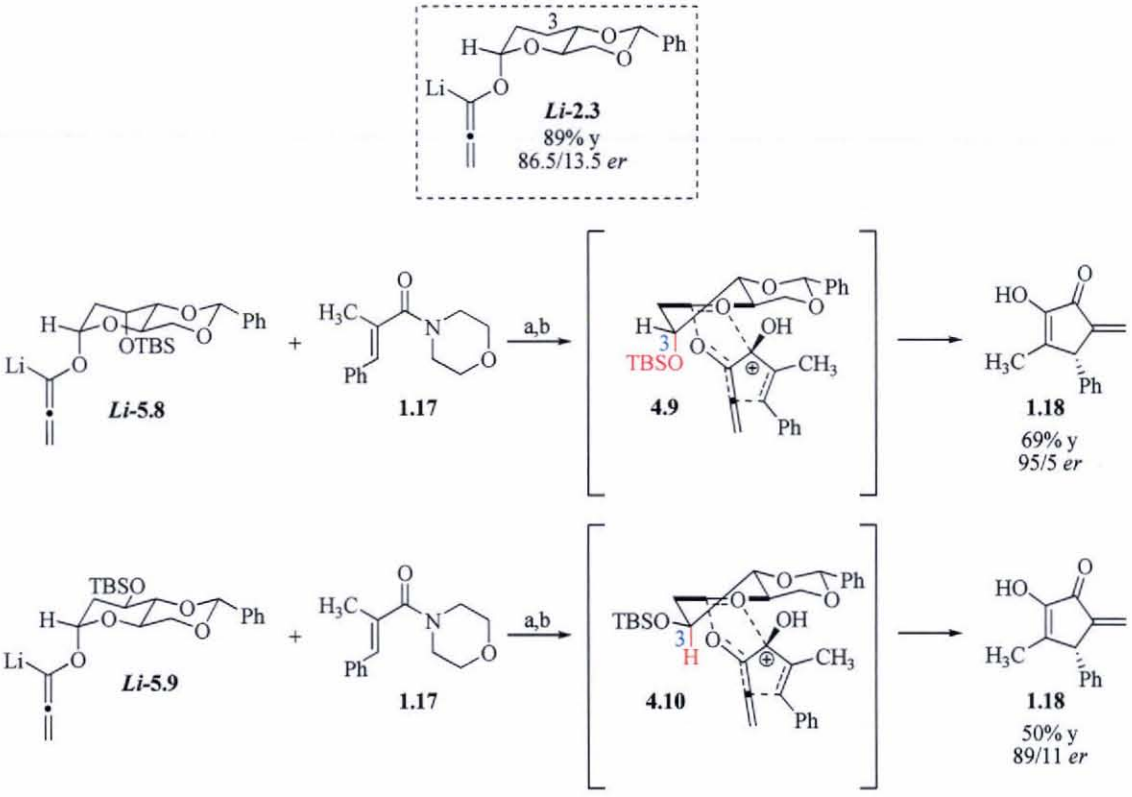


Figure 2.14. Predicted Importance of the C3 Substituents of Conformationally Locked Chiral Auxiliaries

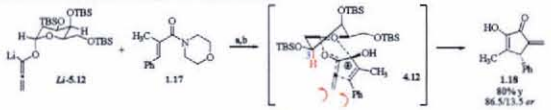
Treatment of lithioallene ***Li*-5.8** with morpholino enamide **1.17** followed by cyclization using the conditions described in Scheme 2.9 provided cyclopentenone **1.18** in 69% yield and with 95/5 *er*, a notable improvement compared to chiral auxiliary **2.3** (86.5/13.5 *er*). In contrast, reactions with lithioallene ***Li*-5.9** and morpholino enamide **1.17** led to cyclopentenone product **1.18** in 50% yield and with 89/11 *er*, nearly the same as the results obtained from using chiral auxiliary **2.3** (86.5/13.5 *er*). It can thus be concluded that, unlike the equatorial C3 substituent, the C3 axial substituent is critical for optimal asymmetric induction for this class of chiral auxiliaries.



Scheme 2.9 (a) (i) allene ***Li*-5.8** or ***Li*-5.9** (2.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (ii) amide **1.17** (1.0 equiv), THF, -78 °C; -78 °C to -30 °C, 1 h; (b) (i) HCl/HFIP/TFE, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

(4) Predicted Stereochemistry-Determining Transition States of β-Galactosides: Since the axial C4 substituent in β-galactosides **5.10** and **5.11** (Figure 2.15) is already predisposed to stabilize the developing oxocarbenium ion in the stereochemistry-determining transition state (refer to discussion of Woerpel's results, Figure 2.11), the stereochemistry-determining transition states of allenes **5.10** and **5.11** should not involve ring inversion.[iii] Their postulated

[iii] This would also be the case for persilylated α-D-galactoside **5.12**. The stereochemistry-determining transition state of this auxiliary would be thus be analogous to the conformationally locked auxiliaries **2.3**, **5.8** and **5.9** in which the axial C3 controls the direction of conrotation.



stereochemistry-determining transition state is shown in Figure 2.15. Furthermore, a large C4 substituent on the chiral auxiliary such as a silyloxy group should result in a better enantiomeric ratio for the product compared to a chiral auxiliary bearing a small C4 substituent such as methoxy group.

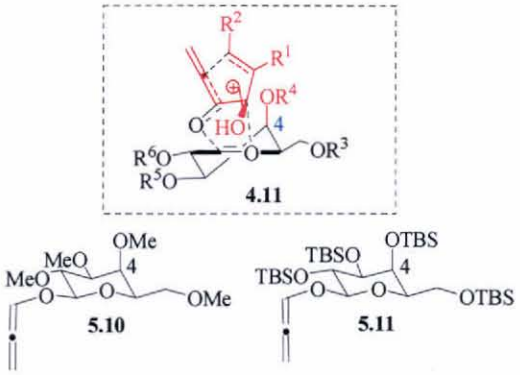


Figure 2.15. β-Galactoside-Derived Auxiliaries and their Predicted Transition States

Using a published procedure[2a] D-galactose was converted to allene **5.10** (Figure 2.15). Treatment of lithioallene ***Li*-5.10** with morpholino enamide **1.17** followed by cyclization using the conditions in Scheme 2.10 provided cyclopentenone **1.18** with 7/93 *er*.

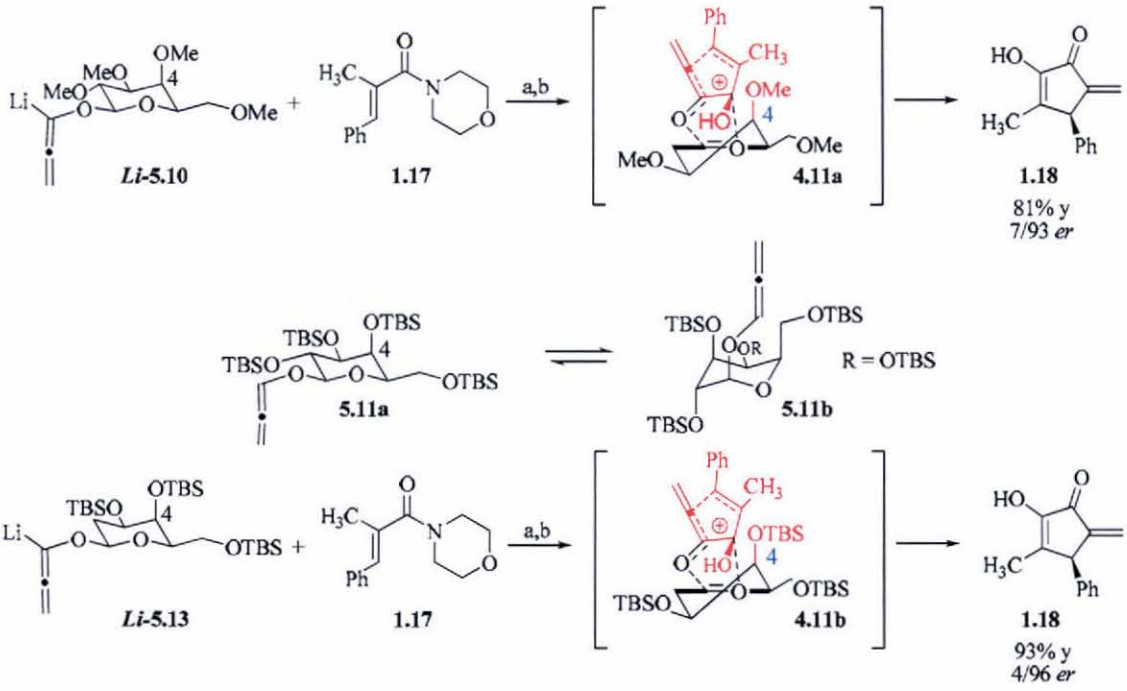
Persilylated analog **5.11** was also prepared from D-galactose according to a similar procedure. Interestingly, a sample of the product at room temperature led to complex 300 MHz ^{1}H NMR spectrum which we assumed to be due to an equilibrium mixture of both conformations **5.11a** and **5.11b** (Scheme 2.10). This was noteworthy in the sense that when four methoxy substituents of allene **5.10** were exchanged for large silyloxy substituents the difference in stability between inverted and non-inverted conformations (at room temperature) was actually minimal. While we were in the process of confirming the identity of product **5.11** using low temperature ^{1}H NMR studies, we proceeded to evaluate

persilylated 2-deoxy-β-D-galactose-derived lithioallene ***Li*-5.13** (Scheme 2.10). In the absence of the C2 silyloxy substituent only the non-inverted conformer of **5.13** was observed (Scheme 2.10). Treatment of lithioallene ***Li*-5.13** with morpholino enamide **1.17** followed by cyclization led to cyclopentenone **1.18** in 93% yield and with 4/96 *er*, thus far the highest enantioselectivity observed within the β-series of auxiliaries. Although a more direct comparison between **5.10** and **5.11** would be ideal, interpretation of the results from the reaction with **5.11** should be done with caution. As previously noted, room temperature ^{1}H NMR analysis on the 300 MHz NMR of **5.11** suggested that the allene existed as an equilibrium of non-inverted conformer **5.11a** and inverted conformer **5.11b**.[iv] Low temperature ^{1}H NMR studies of the same product sample (-50 °C, 500 MHz NMR) suggested that this was the case and that at -50 °C the major conformation observed on the 500 MHz NMR was **5.11a** based on the chemical shift and multiplicity of the anomeric proton (4.38 ppm, d, J = 4.5 Hz). However, a ratio of conformer **5.11a** to **5.11b** in the sample could not be obtained. It can be expected that at -78 °C, the temperature at which the Nazarov reaction is conducted, allene **5.11** exists mostly as conformation **5.11a**. However, without certain knowledge of this it must be assumed that the stereochemistry-determining transition state of **5.11** would also consist of a mixture of inverted and non-inverted conformations and the results from its Nazarov reaction may not accurately reflect the effect of the C4 silyloxy substituent.

In short, for the β-series of D-galactose-derived auxiliaries we predicted that the enantioselectivity of the Nazarov reactions increases by increasing the size of the axial C4 substituent. From allene **5.10** with allene **5.13** it is shown that increasing the size of the axial

[iv] A twist conformation is also a possibility.

C4 substituent from a methoxy to a silyloxy group only leads to a marginal improvement in enantiomeric ratio. It is expected that further optimization in enantioselectivity may be achievable through the use of C4 substituents larger than TBS (*e.g.* TIPS or BPS).



Scheme 2.10 (a) (i) allene ***Li*-5.10** or ***Li*-5.13** (2.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (ii) amide **1.17** (1.0 equiv), THF, -78 °C; -78 °C to -30 °C, 1 h; (b) (i) HCl/HFIP/TFE, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

2.4. Structural Homology of Stereochemistry-Determining Intermediates of the Sugar- and Camphor-Derived Auxiliaries

The accuracy of our predictions allowed us to recognize the structural homology between the stereochemistry-determining transition states of the sugar- and camphor-derived auxiliaries. This in turn allowed us to rationalize trends in earlier data. For example, it was pointed out that derivatization of the C5 group of the camphor-derived allene **1.14** and the C6

group of the sugar-derived allenes did not improve enantioselectivity. According to models **2.8** and **1.15**, the reason for this has become clear (Figure 2.16). In both systems it is shown that these groups project slightly away from the pentadienyl moiety and therefore have little control over the direction of conrotation. However, Figure 2.16 also suggests that one face of the pentadienyl cation is entirely shielded by the axial C4 substituent in both of the chiral auxiliaries. By this model the equatorial C4 substituents in the inverted stereochemistry-determining transition state of the α-series of sugar-derivatives function similarly as the C4 methylene group of the camphor-derived auxiliary.

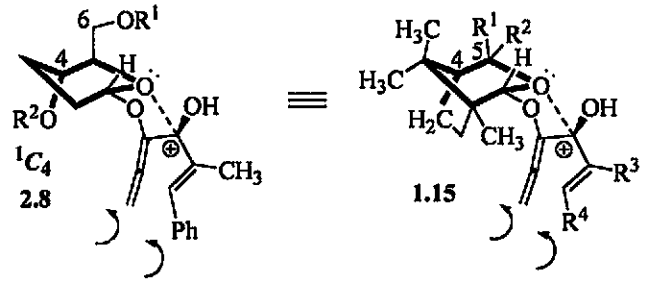


Figure 2.16. Structural Homology of Postulated Stereochemistry-Determining Intermediate Using Sugar- and Camphor-Derived Allenes

2.5. Optimal Chiral Auxiliaries

The results of the test studies described in Section 2.3 support the mechanism proposed in Section 2.2.B. These findings are briefly summarized as follows. First, it was shown that a pyranose oxygen atom is needed to restrict the conformational mobility of the pentadienyl cation. Second, regardless of whether ring inversion takes place during the stereochemistry-determining step, in both the α- and β-series of auxiliaries the sense of conrotation is controlled by the shielding axial (or pseudo axial) substituent of the chiral auxiliary which

directly blocks one face of the pentadienyl moiety. Third, while ring inversion is believed to be unnecessary for galactosides, in the case of some α-glucosides it is presumed to take place due to the electrostatic interactions between the lone electron pair of the shielding alkoxy substituent and the developing cation at the anomeric carbon atom of the chiral auxiliary.

On the basis of our predictions, two optimal chiral auxiliaries, α-allene **5.8** and β-allene **5.13**, have been designed and synthesized (Figure 2.17). Evaluation of these auxiliaries with additional substrates is discussed in Section 2.6. The stereochemistry-determining transition state model of each will aid in the design of simpler chiral allenyl ethers with non-sugar scaffolds.

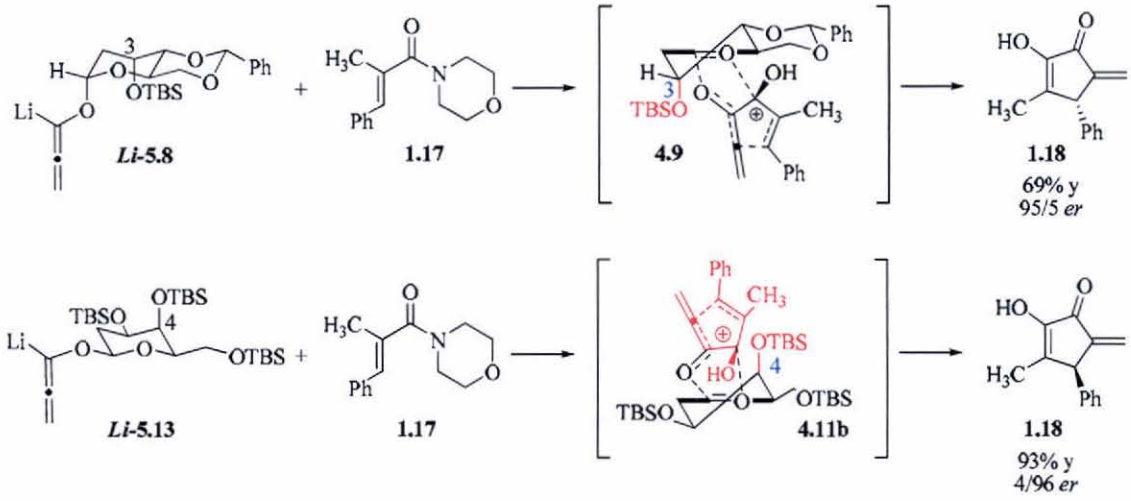


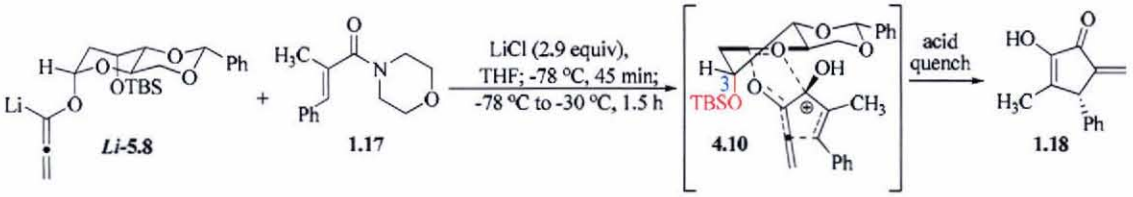
Figure 2.17. Optimal α- and β-Auxiliaries

2.6. Optimization of Reaction Conditions

2.6.A. Optimization of Cyclization Conditions

The rationale for using strong acid and a highly polar solvent system was to ensure rapid cyclization so as to prevent potential loss of stereochemical information through cationic

rearrangements. For the permethylated and persilylated chiral auxiliaries, the standard conditions (33 equivalents of anhydrous HCl in HFIP/TFE) led to reproducible yields and enantioselectivity. On the other hand, these same conditions led to significant variability in yields and *er*s with chiral auxiliary **5.8**. This was attributed to the viscosity of the quench solution at -78 °C, which presumably led to the acid-catalyzed decomposition of the benzylidene group at a rate competitive with the cyclization. Consequently, we explored alternative quench conditions that maintained homogeneity at cold temperatures and preserved the integrity of the benzylidene (Figure 2.18). Conveniently, the weaker and inexpensive acid, acetic acid in dichloromethane was optimal, leading to reproducible *er*s of 96/4. Additionally, because hydrolysis of the silyloxy or acetal groups on the chiral auxiliary did not occur, the chiral auxiliary can be recovered intact and can therefore be recycled.



Trial	Acid (equiv)	Solvent	T(°C)	Time (min)	*Er*s
1	HCl (33)	HFIP:TFE (1:1)	-78	2	95/5
2	HCl (33)	HFIP:TFE (1:1)	-78	2	86.5/13.5
3	HCl (33)	HFIP:TFE (1:1)	-78	2	75/25
4	HCl (33)	HFIP:TFE (1:1)	-78	2	70/30
5	HCl (6)	HFIP:TFE (1:1)	-78	2	66.5/33.5
6	$ClCH_2CO_2H$ (33)	HFIP:TFE (1:1)	-78	2	87/13
7	AcOH (33)	THF	-78	2	90.5/9.5
8	AcOH (33)	Et_2O	-78	2	90.5/9.5
9	AcOH (33)	toluene	-78	2	90.5/9.5
10	AcOH (33)	*t*-BME	-78	2	92.5/7.5
11	AcOH (33)	CH_2Cl_2	-78	2	96/4

Figure 2.18. Screen of Acid Quench Conditions for Cyclization Reactions of Allene 5.8 and Morpholino Enamide 1.17

2.6.B. Optimization of Addition Reaction

Earlier studies had suggested that the stereochemistry of the tetrahedral intermediate that is formed from addition of the lithioallene to enones influenced the stereochemical outcome of the Nazarov reaction. As shown in Figure 2.19, the enantioselectivity from cyclopentannelation reactions in which enones were used as electrophiles were significantly lower than that of reactions in which morpholino enamides were used, indicating that the formation of the carbon-carbon bond took place at least in part before the ionization of the tertiary, bis-allylic alcohol **6.2** had occurred.[2b] This raised concern whether the diastereoselectivity of the addition to enamides also affected the overall enantioselectivity of the cyclopentenone product. If this was the case, we might expect to observe variable *er*s over a range of addition temperatures and from reactions with enamides derived from different secondary amines.

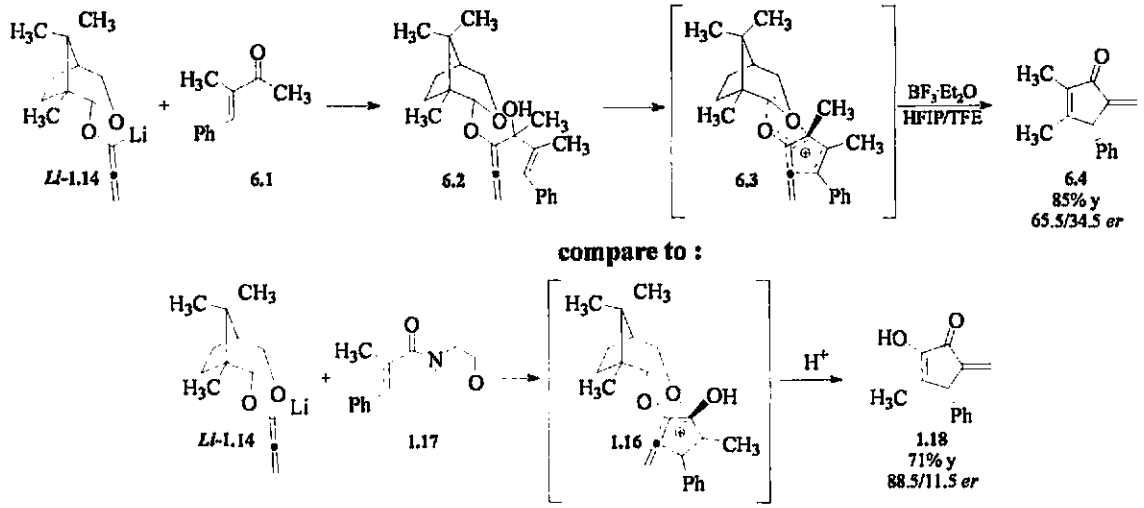
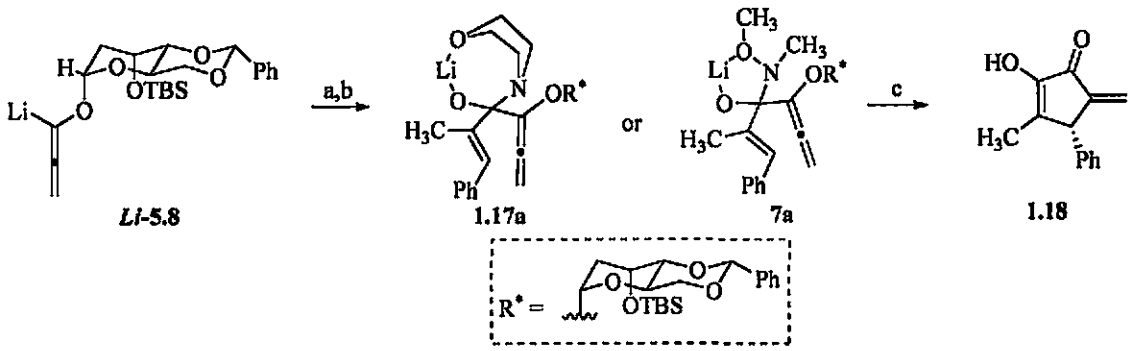


Figure 2.19. Nazarov Reaction Using Enone 6.1 and Morpholino Enamide 1.17

Using the morpholino and Weinreb enamides of *E*-2-methylcinnamic acid at three temperatures, we have demonstrated that the diastereoselectivity of the addition did indeed have some influence on the enantioselectivity of cyclization. As shown in Figure 2.20, asymmetric induction from both enamides eroded as the addition temperature was raised. This effect was significantly more pronounced with morpholino enamides. Although the reason for this is not entirely understood, it may be attributed to the stability of the tetrahedral intermediate. For example, addition of lithioallene ***Li*-5.8** to morpholino enamide **1.17** results in the formation of a 7-membered ring chelate which is less stable than the 5-membered ring chelate formed from addition to Weinreb enamide **7** (compare **1.17a** and **7a**). Thus, as the temperature of the reaction is raised collapse of tetrahedral intermediate **1.17a** takes place to a larger extent than that of tetrahedral intermediate **7a**. At -20 °C intermediate **1.17a** completely collapses, allowing the resultant allenylvinyl ketone to freely rotate and then cyclize non-stereoselectively upon exposure to acid. This process is prevented when the addition of the electrophile is performed at -78 °C and the reaction mixture is kept at that temperature for 3.5 h then quenched rapidly *via* cannula into a solution of acetic acid in dichloromethane at -78 °C.



Li-5.8 1.17a 7a 1.18

Trial	T (°C)	Time (min)	*er*
1	-78	210	97/3
2	-40	150	91/9
3	-20	30	50/50
1	-78	210	94/6
2	-40	150	90/10
3	-20	30	84/16

1.17

7

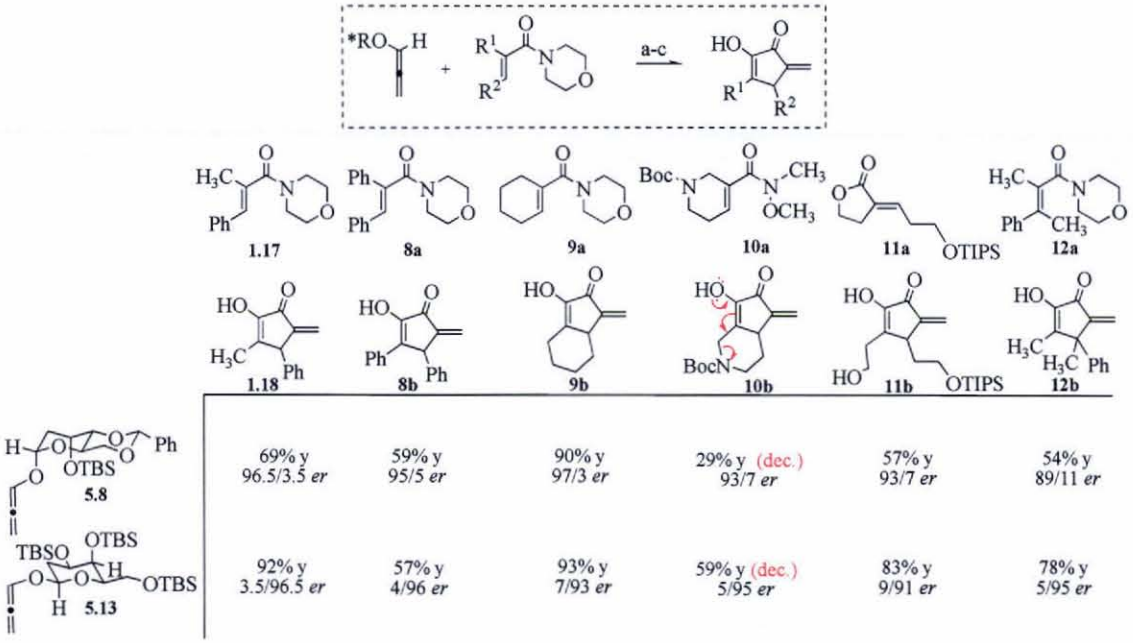
(a) allene ***Li*-5.8** (1.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (b) amide **1.17** or **7** (2.0 equiv); (c) (i) AcOH (30 equiv), CH_2Cl_2, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

Figure 2.20. Effects of Variable Temperatures of the Addition Reaction on the Enantioselectivity of Cyclization Using Allene 5.8 Morpholino Enamides 1.17 and 7

2.7. Substrate Scope

To evaluate the scope of sugar-derived lithioallenes ***Li*-5.8** and ***Li*-5.13**, each was reacted with electrophiles **8a** through **12a** under the optimized reaction conditions depicted in Figure 2.21 to provide cyclopentenones **8b** through **12b**, respectively. In all cases starting material was fully consumed and product was formed in moderate to excellent yield and with excellent enantioselectivity. In the case of cyclopentenone **12b** addition of the lithioallenes to the tetrasubstituted morpholino enamide **12a** required warming to 0 °C. After the reaction mixture had been stirred at 0 °C for 2 h, full consumption of the allenes that were used as the

limiting reagent was observed. The optimized yield from allene **5.8** was 54%, whereas from allene **5.13** the yield of **12b** was 78%. Cyclopentenone **8b** was formed from allene **5.8** in 59% yield and with 95/5 *er* and from **5.13** in 57% yield and with 4/96 *er*. Cyclopentenone **9b** was formed in excellent yield of 90% (97/3 *er*) and 93% (7/93 *er*) from allene **5.8** and **5.13**, respectively. Lactone **11a** was unique among the electrophiles we surveyed. As shown in Figure 2.21, cyclization of lactones is also accomplished in good enantioselectivity with both chiral allenes. Lastly, of the electrophiles, morpholino enamide **10a** led to cyclized product **10b** with good enantioselectivity, but low to moderate yields due to rapid decomposition by the retro-Michael elimination reaction indicated by the arrows in Figure 2.21. The yields reported are not optimal and might be improved by different purification methods. Nevertheless, cyclopentenone **10b**, as well as cyclopentenone **11b** are especially important targets, as they serve as precursors to natural products, nakadomarin A and terpestacin,[22] respectively. Cyclopentenone **11b** represents the formal asymmetric synthesis of terpestacin which had been recently completed racemically by Dr. Gideon Berger of our group.



(a) allene (1.0 equiv), *n*-BuLi (2.0 equiv), LiCl (2.9 equiv), -78 °C, 45 min; (b) electrophile (2.0 equiv), THF, -78 °C, 2.5 h; (c) (i) AcOH (30 equiv), CH_2Cl_2, 2 min, -78 °C; (ii) saturated $NaHCO_3/CH_2Cl_2$ (1/1); warm to rt.

Figure 2.21. Cyclopentenones Derived from Nazarov Reactions of Allenes 5.8 and 5.13

2.8. Conclusion

The asymmetric allenyl ether Nazarov reaction has been an ongoing focus of research in our group. Prior work had shown that, unlike some of the substituents of the chiral auxiliary, the pyranose oxygen atoms play a pivotal role in the stereochemical outcome of the reaction. The objective of my thesis work was to identify more precisely the role of the pyranose oxygen atoms and to determine which among the many substituents on the pyran is critical for optimal asymmetric induction. In the process, we hoped to develop a model that rationalizes the stereochemical outcome of our Nazarov reactions.

Several noteworthy observations were made in the course of this present study. For example, two classes of auxiliaries have been identified, ones that undergo conformational

inversion and ones that are conformationally locked. Ring inversion is presumably induced by the electrostatic interactions between the developing oxopyrylium ion of the chiral auxiliary and the lone electron pair of the shielding axial substituent in the stereochemistry-determining transition state. However, regardless of whether a ring inversion takes place, there is strong evidence suggesting that the pyranose oxygen atom restricts the conformational mobility of the pentadienyl cation and is necessary for both enantioselectivity and yield. Although the substituent that controls the direction of conrotation depends on the class of chiral auxiliary (inverted or non-inverted) it is shown to be the axial or pseudo axial substituent that directly shields one face of the pentadienyl cation.

On the basis of these results, we have designed two auxiliaries, a conformationally locked α-D-glucose- as well as a β-D-galactose-derived allenyl ether, which each lead to opposite enantiomers of cross-conjugated cyclopentenone products bearing chiral centers β to the carbonyl with high optical purity. Additionally, the reaction conditions for this particular Nazarov reaction have been improved. Enantioselectivity is optimal when the addition of the lithioallene to the morpholino enamide is performed at low temperature and the cyclization is initiated rapidly with mildly acidic, homogenous solvent mixtures at -78 °C. The scope of each chiral auxiliary under these optimized conditions has been demonstrated through reactions with a variety of morpholino enamides and in one case, an α,β-unsaturated butyrolactone. Of these examples, two suggest potential applications of the auxiliaries toward the total asymmetric synthesis of terpestacin and nakadomarin.

In summary, we have postulated a transition state that rationalizes the stereochemical outcome of our Nazarov reactions. While it is not the only possible model, the transition state explains the data of all chiral auxiliaries prepared by our group thus far and it has been used

to make several successful predictions. From these predictions, we have confirmed the role of the pyranose oxygen atom, identified the key substituents that control the direction of conrotation, optimized the reaction conditions and in the process we have developed a well-substantiated mechanistic hypothesis for the asymmetric allenyl ether Nazarov reaction. We have since prepared two improved sugar-derived allenyl ethers which reproducibly formed cyclopentenone products in high optical purity under our optimized reaction conditions. Future effort will be directed towards the synthesis of even more efficient chiral auxiliaries.

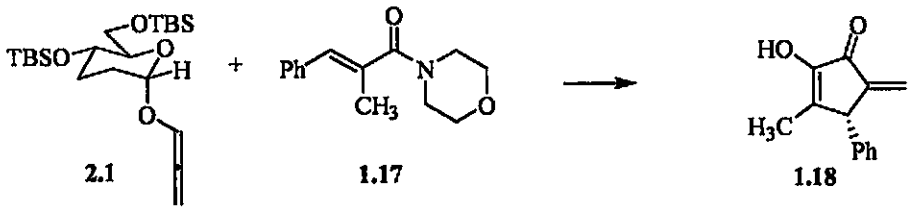
3. Experimental for Sugar-Derived Auxiliaries

3.1. General Experimental Detail

^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Mercury Plus 300 NMR spectrometer operating at either 300 MHz (^{1}H) or 75 MHz (^{13}C) or on a Varian Unity Inova 500 operating at 500 MHz (^{1}H) or 126 MHz (^{13}C). Chemical shifts are reported in δ units and are referenced to the solvent, *i.e.* 7.26/77.0 for $CDCl_3$, 7.15/128.0 for C_6D_6 or 2.04/206.0, 29.8 for acetone-d_6. Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Thermo Nicolet Avatar 360 FT-IR spectrometer. Enantiomeric ratios were determined using Beckman Coulter System Gold HPLC (diode array UV detector with a 125 solvent module or a variable wavelength UV detector with a 126 solvent module) with a Diacel Chem. Ind., Ltd. Chiralcel OD-H column (0.46 cm x 25 cm). Electron impact mass spectra were obtained from a VG-70SE mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter using the sodium (589 nm, D line) lamp and are reported as follows: $[\alpha]_D^{T\,°C}$ (c = g/mL, solvent). Thin-layer chromatography (TLC) was performed on Sigma-Aldrich TLC plates, 250 μm, particle size 5 to 15 μm, pore size, 60 Å. Flash column chromatography was performed on Natland International Corporation silica gel, 200-400 mesh. Tetrahydrofuran was used directly from Glass contour (www.glasscontour.com) purification system. All other reagents were used as received. All moisture sensitive reactions were performed under a static nitrogen atmosphere in oven- or flame-dried glassware. Some synthetic intermediates were present as anomeric mixtures. Data are reported for the major anomers shown in each reaction scheme. The

mixtures were carried through and the anomers were separated at the allene stage. Only anomerically pure chiral allenes were used for the Nazarov cyclizations.

3.2. General Procedure for Nazarov Cyclization

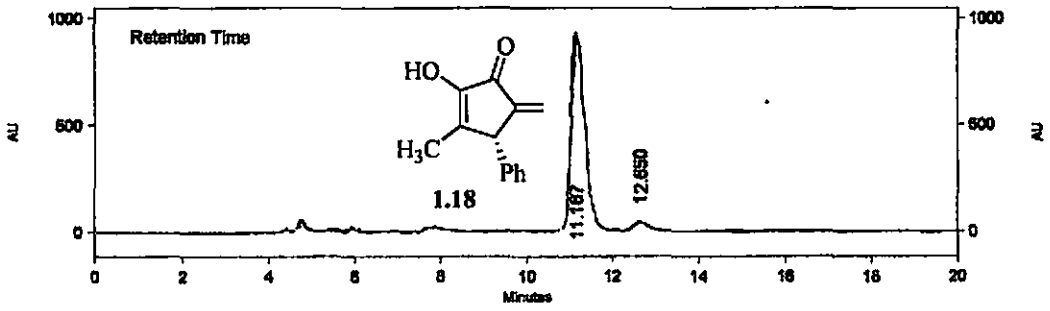


2.1 **1.17** **1.18**

Lithium chloride (16 mg, 0.377 mmol) was added to a 10 mL round-bottom flask equipped with a small stir bar and was flame-dried under vacuum. (*E*)-2-Methyl-1-morpholino-3-phenylprop-2-en-1-one **1.17** (60 mg, 0.259 mmol) and allene **2.1** (53 mg, 0.128 mmol) were added into separate 5 mL round-bottom flasks then were individually dried by azeotropic distillation of toluene and purged with nitrogen (3x). Allene **2.1** was dissolved into 2 mL of THF, was dried over 4 Å MS and the solution was transferred *via* cannula into the 10 mL flask containing the 16 mg of LiCl. A small crystal of 1,10-phenanthroline was added and the solution was cooled to -78 °C. Residual water in the solution of allene was quenched using *n*-BuLi (1.62 M in hexanes), turning the mixture from a lemon-yellow color to the endpoint, a dark brown color. The brownish mixture was then treated with *n*-BuLi (160 µL, 0.259 mmol, 1.62 M in hexanes) and was stirred at -78 °C for 45 min. The solution of enamide **1.17** in 2 mL of THF was dried over 4 Å MS, was cooled to -78 °C and was transferred at a rate of one drop per three seconds to the solution of lithioallene *via* cannula.[v] The mixture was maintained at -78 °C for 2 h and was transferred

[v] It is critical that the solution of the lithioallene and the enamide both be at -78 °C and that the transfer of enamide to lithioallene be conducted *slowly* in order for optimal *ers* to be obtained.

rapidly *via* cannula to a solution of 20 mL anhydrous CH_2Cl_2 and 220 μL of AcOH (3.90 mmol) at -78 °C.[vi] After stirring for 5 min at -78 °C, the mixture was poured into 20 mL of a 1:1 two-phase solution of saturated aqueous $NaHCO_3$:CH_2Cl_2 and the mixture was gradually warmed to 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, were dried over $MgSO_4$ and were concentrated. Purification *via* flash column chromatography on silica gel (20% EtOAc in hexanes) provided 18 mg (0.090 mmol, 69% yield, 95/5 *er*) of cyclopentenone **1.18**.[vii] The HPLC solvent used for measuring the optical purity was 2% *iso*propanol in hexanes at a rate of 0.75 mL/min (t_R = 11.2 (major) and t_R = 12.7 min (minor) on a Chiralcel OD-H column (0.46 cm x 25 cm)).



Det 168-254nm
Results

Time	Area	Area %	Height	Height %
11.167	20499404	95.34	927795	95.65
12.650	1002403	4.66	42202	4.35

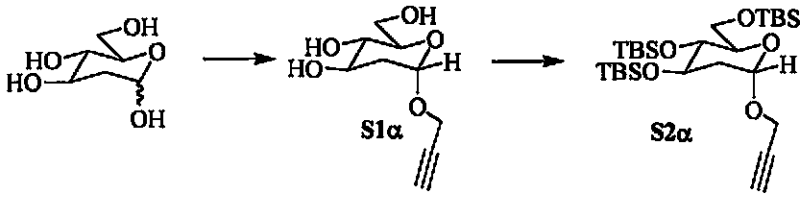
Figure 2.22. HPLC Trace of 2-Hydroxy-3-Methyl-5-Methylene-4-Phenylcyclopent-2-Enone 1.18 Derived from the Convergent Nazarov Cyclization of Chiral Lithioallene 2.1 and (*E*)-2-Methyl-1-Morpholino-3-Phenylprop-2-En-1-One 1.17.

[vi] It is imperative that the solution of AcOH and CH_2Cl_2 be completely homogenous and that the solution containing the tetrahedral intermediate be transferred *rapidly* so as to achieve optimal *er*s.

[vii] For characterization of cyclopentenone **1.18** refer to: Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091-10100.

3.3. Synthesis of Sugar-Derived Auxiliaries

Propargyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S2α**

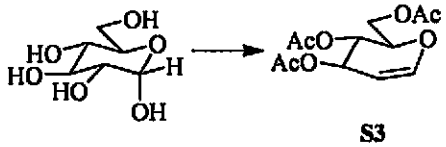


A mixture of 2-deoxy-D-glucose (1.00 g, 6.09 mmol) in 7.1 mL of propargyl alcohol (122 mmol) was cooled to 0 °C and was treated with $BF_3{\cdot}Et_2O$ (1 mL, 8.10 mmol) dropwise. Once the entire portion of $BF_3{\cdot}Et_2O$ had been added, the temperature was allowed to gradually rise to rt. The mixture was stirred for 16 h at rt after which it was cooled to 0 °C and was treated with NEt_3 (3.4 mL, 24.4 mmol). After 15 min of stirring at 0 °C, the mixture was gradually warmed to rt and was stirred for an additional 15 min. The brownish solution was filtered through a short plug of basic alumina, was absorbed onto silica gel and was added onto a column packed with silica gel. A quick elution using 5% MeOH in EtOAc provided 1.10 g (5.44 mmol, 90% yield) of a 13:1 α:β mixture of propargyl 2-deoxy-α-D-glucopyranoside **S1α**.

To 500 mg of propargyl 2-deoxy-α-D-glucopyranoside **S1α** (2.47 mmol) in 3 mL of DMF was added pyridine (1 mL, 12.4 mmol). The solution was cooled to 0 °C and was treated with TBSOTf (2 mL, 8.71 mmol). The mixture was stirred for 1 h at 0 °C then was diluted with 10 mL of CH_2Cl_2 and was quenched with 3 mL of ice-cold saturated $NaHCO_3$. The organic layer was separated, was washed with 5 mL of ice-cold H_2O (5x) followed by 5 mL of brine then was dried over $MgSO_4$ and was concentrated. Purification *via* flash column chromatography on silica gel (12% CH_2Cl_2 in hexanes) provided 1.20 g (2.20 mmol, 89%

yield) of title compound **S2α** as a clear viscous oil; R_f = 0.27 (20% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.06-5.00 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.20 (d, *J* = 2.3 Hz, 1H), 4.15 (d, *J* = 2.3 Hz, 1H), 3.95 (ddd, *J* = 10.5, 7.6, 4.7 Hz, 1H), 3.86 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.65 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.50 (ddd, *J* = 8.9, 6.6, 2.3 Hz, 1H), 3.36 (dd, *J* = 8.9, 7.6 Hz, 1H), 2.38 (t, *J* = 2.3 Hz, 1H), 2.07 (ddd, *J* = 13.6, 4.7, 2.0 Hz, 1H), 1.66 (ddd, *J* = 13.6, 10.5, 3.5 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 18H), 0.10 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.8, 79.5, 74.3, 74.0, 73.0, 71.0, 63.0, 53.2, 38.4, 26.3, 26.1, 25.9, 18.3(2), 18.0, -3.1(2), -4.2, -4.5, -5.1, -5.3; IR (neat) 3054, 2987, 2306, 1265 cm^{-1}; EIMS *m/z* (%) 73 (100), 97 (70), 147 (48), 489 (24); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2700.

3,4,6-Tri-*O*-acetyl-D-glucal **S3**[viii]



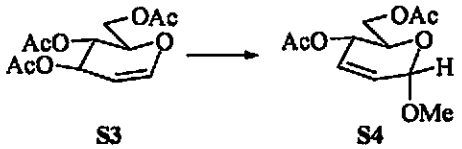
S3

To a suspension of D-glucose monohydrate (20.0 g, 111 mmol) in acetic anhydride (63 mL, 666 mmol) was added 31% HBr/AcOH (42.0 g, 161 mmol) at rt. The reaction mixture was stirred for 2.5 h during which time the suspended solid went into solution. This solution was then treated with an additional 120 g (460 mmol) of 31% HBr/AcOH and the resulting solution was stirred overnight. Anhydrous NaOAc (36.5 g, 444 mmol) was then added to neutralize the excess HBr, and this mixture was added to a suspension of NaOAc (18.9 g, 230 mmol), pulverized $CuSO_4 \cdot H_2O$ (5.74 g, 32.3 mmol) and Zn (116 g, 1.77 mol) in a solution of water (20 mL) and AcOH (30 mL). The slurry was stirred vigorously for 3.5 h.

[viii] Koreeda, M.; Shull, B. K.; Wu, Z. J. *Carbohydrate Chem.* **1996**, *15*, 955-964.

The solid was then removed by filtration and the filtrate was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with ice-cold water (5 x 50 mL) followed by 50 mL of saturated aqueous $NaHCO_3$ (3x) then with 50 mL brine and were dried over $MgSO_4$. The solvent was removed under reduced pressure to provide 30.0 g (110 mmol, 100% yield) of 3,4,6-tri-*O*-acetyl-D-glucal **S3** as a white solid.

Methyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-*erythro*-hex-2-enopyranose **S4**

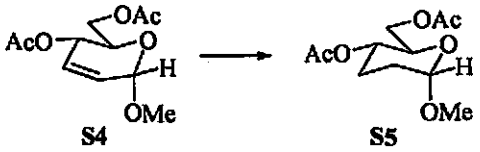


S3 **S4**

3,4,6-Tri-*O*-acetyl-D-glucal **S3** (8.00 g, 29.4 mmol) and (1.3 mL, 32.1 mmol) MeOH were dissolved in 150 mL of dry CH_2Cl_2 and were stirred under N_2 at rt. $BF_3{\cdot}Et_2O$ (1.6 mL, 13.0 mmol) was added to the solution and the mixture was stirred overnight (16 h). The mixture was then neutralized by the addition of 15 mL saturated aqueous $NaHCO_3$ and the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with 15 mL brine, were dried over $MgSO_4$ and were concentrated in vacuo to yield 7.00 g (28.7 mmol, 98% yield) of title compound **S4** as a pale yellow, odorless oil; R_f = 0.19 (25% EtOAc in hexanes).[ix]

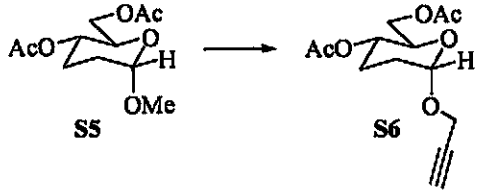
[ix] Cottier, L.; Freitas Filho, J. R.; Descotes, G.; Soro, Y.; Srivastava, R. M. *J. Carbohydrate Chem.* **2001**, *20*, 561-568.

Methyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S5**



EtOH (7 mL) was first added into a 25 mL round-bottom flask, the system was flushed with H_2 gas and then charged with 10% palladium (113 mg, 0.106 mmol) over carbon. A solution of methyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-*erythro*-hex-2-enopyranose **S4** (1.73 g, 7.08 mmol) in 7 mL EtOH (previously flushed with H_2 gas) was then added *via* cannula and the mixture was allowed to stir at rt for 1 h. The mixture was then filtered through a short plug of Celite to afford 1.14 g (4.63 mmol) of title compound **S5** (65% yield);[x] R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78-4.66 (m, 1H), 4.67 (br d, J = 1.2 Hz, 1H), 4.21 (dd, J = 12.1, 5.3 Hz, 1H), 4.06 (dd, J = 12.1, 2.1 Hz, 1H), 3.85 (ddd, J = 9.9, 5.3, 2.1 Hz, 1H), 3.26 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.98-1.92 (m, 1H), 1.82-1.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.9, 97.4, 68.4, 67.7, 63.1, 54.5, 28.5, 23.8, 20.9, 20.7; IR (neat) 2955, 2830, 1744, 1372, 1235, 1048 cm^{-1}; EIMS *m/z* (%) 84 (100), 101 (75), 144 (80), 215 (59); HREIMS *m/z* exact mass calcd for $C_{10}H_{15}O_5$ (M^+ - OCH_3) 215.0919, found 215.0930.

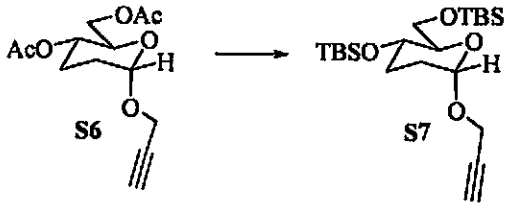
Propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6**



[x] Jessup, P. J.; Overman, L. E. *J. Am. Chem. Soc.* **1978**, *100*, 5179-5185.

Methyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S5** (3.00 g, 11.1 mmol) and propargyl alcohol (4.3 mL, 73.9 mmol) were dissolved in dry 152 mL of CH_2Cl_2 at 0 °C and the mixture was stirred under N_2 at rt. $BF_3{\cdot}Et_2O$ (2.3 mL, 18.6 mmol) was added dropwise and the mixture was slowly heated to 45 °C. After 1 h at 45 °C the reaction mixture was cooled to 0 °C and NEt_3 (3.4 mL, 24.4 mmol) was added. The solution was stirred at 0 °C for 15 min then was concentrated and filtered through a plug of silica gel to provide title compound **S6** (3.10 g, 11.5 mmol, 94% yield) as a clear, odorless oil; R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.75-4.59 (m, 1H), 4.30-4.14 (m, 1H), 4.17 (t, *J* = 2.2 Hz, 2H), 4.03 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.87 (ddd, *J* = 10.0, 5.1, 2.2 Hz, 1H), 2.41 (t, *J* = 2.2 Hz, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.86-1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 95.0, 74.6, 74.4, 68.8, 67.4, 62.8, 54.0, 28.3, 23.6, 20.9, 20.6; IR (neat) 3272, 2957, 2118, 1743, 1370, 1245, 1043, 999 cm^{-1}; EIMS *m/z* (%) 71 (100), 82 (94), 114 (49), 125 (36), 215 (43); HREIMS *m/z* exact mass calcd for $C_{10}H_{15}O_5$ (M^+ - OCH_2CCH) 215.0919, found 215.0910.

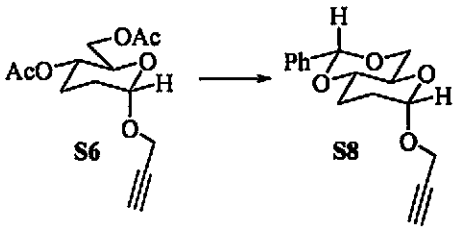
Propargyl 2,3-dideoxy-4,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside S7



Crude propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6** (400 mg, 1.48 mmol) was dissolved in 5.9 mL of MeOH. To a separate flask containing 1 mL MeOH was added 60% NaH (20 mg, 0.500 mmol) and the mixture was transferred *via* cannula to the

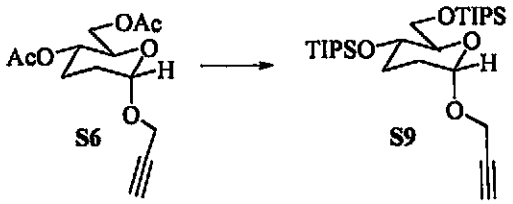
solution of glucoside **S6** at rt. After 1 h, the solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was stirred for 2 min, after which it was filtered through a short plug of silica gel and concentrated. This unpurified material was dissolved in 3 mL CH_2Cl_2 at rt and was treated with TBSCl (91 mg, 0.604 mmol), imidazole (64 mg, 0.940 mmol) and DMAP (cat.). After 3 h, 10 mL saturated aqueous $NaHCO_3$ was added and the aqueous layer was separated and extracted with 10 mL CH_2Cl_2 (3x). The combined organic extracts were washed with 10 mL brine, were dried over $MgSO_4$ and were concentrated. Purification *via* flash column chromatography on silica gel provided title compound **S7** (349 mg, 0.844 mmol, 57% yield) as a clear, viscous oil; R_f = 0.36 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (br d, J = 2.2 Hz, 1H), 4.26 (dd, J = 15.7, 2.4 Hz, 1H), 4.17 (dd, J = 15.7, 2.4 Hz, 1H), 3.85 (d, J = 11.0 Hz, 1H), 3.68 (dd, J = 11.0, 5.0 Hz, 1H), 3.47 (br d, J = 5.0 Hz, 2H), 2.40 (d, J = 2.4 Hz, 1H), 1.88-1.68 (m, 4H), 0.89 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.3, 79.7, 74.9, 73.9, 66.8, 63.0, 53.2, 28.8, 27.9, 25.9, 25.7, 18.4, 17.9, -4.2, -4.9, -5.1, -5.3; IR (neat) 2955, 2930, 2120, 1253, 1101, 1047 cm^{-1}; EIMS *m/z* (%) 73 (100), 143 (37), 225 (22), 301 (38), 357 (40); HREIMS *m/z* exact mass calcd for $C_{17}H_{33}O_4Si_2$ (M^+ - $C(CH_3)_3$) 357.1917, found 357.1922.

(2*R*,4a*R*,6*S*,8a*S*)-2-Phenyl-6-(prop-2-ynyloxy)hexahydropyrano[3,2-*d*][1,3]dioxine **S8**



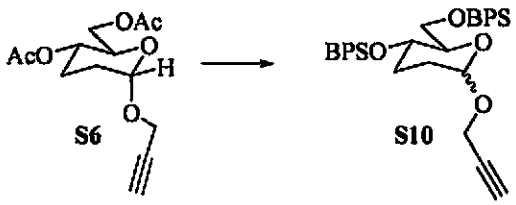
Crude propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6** (483 mg, 1.79 mmol) was dissolved in 5.9 mL MeOH. To a separate flask containing 1 mL of MeOH was added 60% NaH (20 mg, 0.500 mmol) and the mixture was transferred *via* cannula to the solution of glucoside at rt. After 1 h, the solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was stirred for 2 min, after which it was filtered through a short plug of silica gel and concentrated. To a stirred solution of this crude material in about 2 mL of DMF was added benzaldehyde diethyl acetal (450 μL, 2.53 mmol) and TsOH (20 mg, 0.116 mmol). The resulting solution was heated at 80 to 85 °C under reduced pressure (about 26 mm Hg) for 2 hr then was cooled to rt and was poured into 7 mL saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with 3 mL CH_2Cl_2 (3x). The combined organic phases were washed with 5 mL brine, were dried over $MgSO_4$ and were concentrated to a highly viscous oil that was purified by flash column chromatography on silica (50% CH_2Cl_2 in hexanes) to provide 256 mg (0.933 mmol, 52% yield) of an 4:1 α:β mixture of title compound **S8**; R_f = 0.20 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.40-7.26 (m, 3H), 5.58 (s, 1H), 5.00 (d, *J* = 3.0 Hz, 1H), 4.35-4.15 (m, 1H), 4.32 (d, *J* = 2.4 Hz, 1H), 4.25 (d, *J* = 2.4 Hz, 1H), 3.90-3.75 (m, 2H), 3.61 (td, *J* = 10.2, 3.9 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H), 2.05-1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.0, 128.4, 128.3, 126.2, 101.9, 95.4, 79.3, 78.1, 69.3, 65.3, 55.0, 54.1, 29.2, 23.8; IR (neat) 2986, 2306, 1264, 1110 cm^{-1}; EIMS *m/z* (%) 105 (38), 125 (100), 149 (61), 219 (1), 274 (12); HREIMS *m/z* exact mass calcd for $C_{16}H_{18}O_4$ (M^+) 274.1205, found 274.1216.

Propargyl 2,3-dideoxy-4,6-di-*O*-triisopropylsilyl-α-D-glucopyranoside **S9**



Crude propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6** (400 mg, 1.48 mmol) was dissolved in 5.9 mL MeOH. To a separate flask containing 1 mL MeOH was added 60% NaH (20 mg, 0.500 mmol) and the mixture was transferred *via* cannula to the solution of glucoside **S6** at rt. After 1 h, the solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was allowed to stir for 2 min after which it was filtered through a short plug of silica gel and concentrated. This unpurified material was dissolved in 3 mL CH_2Cl_2 at rt and was treated with TIPSCl (700 μL, 3.27 mmol), imidazole (302 mg, 4.44 mmol) and DMAP (cat.). After 3 h, 10 mL saturated aqueous $NaHCO_3$ was added and the aqueous layer was separated and extracted with 10 mL CH_2Cl_2 (3x). The combined organic extracts were washed with 10 mL brine, were dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel provided title compound **S9** (465 mg, 0.932 mmol, 63% yield) as a clear, viscous oil; R_f = 0.48 (2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.29 (d, J = 15.5 Hz, 1H), 4.20 (d, J = 15.5 Hz, 1H), 4.08 (d, J = 10.3 Hz, 1H), 3.80-3.50 (m, 3H), 2.39 (s, 1H), 1.92-1.64 (m, 4H), 1.07 (s, 21H), 1.05 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.1, 79.7, 75.5, 73.9, 67.7, 63.7, 51.3, 28.8, 28.3, 18.1(2), 17.9, 12.7, 11.9; IR (neat) 3313, 2944, 2867, 2120, 1900, 1464, 1108, 1046, 883 cm^{-1}; EIMS *m/z* (%) 75 (27), 91 (44), 115 (63), 145 (47), 157 (100), 199 (47), 207 (56), 399 (93), 455 (17); HREIMS *m/z* exact mass calcd for $C_{24}H_{47}O_4Si_2$ (M^+ - $CH(CH_3)_2$) 455. 3013, found 455. 3032.

Propargyl 2,3-dideoxy-4,6-di-*O*-*t*-butyldiphenylsilyl-α-D-glucopyranoside **S10**

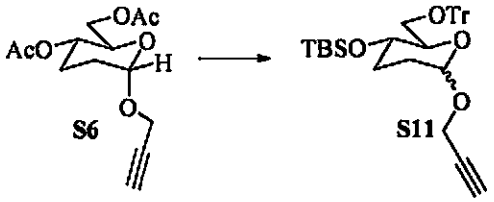


Crude propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6** (400 mg, 1.48 mmol) was dissolved into 5.9 mL MeOH. To a separate flask containing 1 mL of MeOH was added 60% NaH (20 mg, 0.500 mmol) and the mixture was transferred *via* cannula to the solution of glucoside **S6** at rt. After 1 h, the solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was allowed to stir for 2 min after which it was filtered through a short plug of silica gel and concentrated. This unpurified material was dissolved in anhydrous DMF and was treated with imidazole (160 mg, 2.36 mmol), 189 mg (1.55 mmol) DMAP and *t*-butyldiphenylsilyl chloride (850 μL, 3.27 mmol) under N_2 at 50 °C. The mixture stirred for 16 h then was diluted with 2 mL of H_2O and 2 mL of CH_2Cl_2. The organic layer was separated and washed with saturated 2 mL of $NaHCO_3$ (3x) then 2 mL of brine and was dried over $MgSO_4$. Purification *via* flash column chromatography on silica gel (0 to 30% CH_2Cl_2 in hexanes) provided 576 mg (0.871 mmol, 59% yield) of an 11:1 α:β mixture of title compound **S10** as a clear, viscous oil; R_f = 0.34 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.65 (m, 4H), 7.62-7.54 (m, 4H), 7.42-7.23 (m, 12H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.32 (dd, *J* = 15.7, 2.5 Hz, 1H), 4.24 (dd, *J* = 15.7, 2.5 Hz, 1H), 4.20 (dd, *J* = 10.7, 1.8 Hz, 1H), 3.75 (ddd, *J* = 9.2, 7.0, 1.8 Hz, 1H), 3.61 (dd, *J* = 10.7, 7.0 Hz, 1H), 3.55 (dd, *J* = 9.2, 1.6 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H), 1.89-1.63 (m, 2H), 1.58-1.40 (m, 2H), 1.09 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 135.8(2), 129.5(4), 127.5(3), 94.0, 76.6, 74.9, 74.0, 68.3, 64.0, 53.2, 28.6, 27.9, 26.9, 26.8, 19.3(2); IR (neat)

3054, 2987, 2305, 896 cm^{-1}; EIMS *m/z* (%) 97 (32), 135 (86), 199 (100), 267 (27), 319 (33), 330 (10), 549 (25), 662 (8); HRESIMS *m/z* exact mass calcd for $C_{41}H_{50}O_4Si_2Na^+$ (MNa^+) 685.3145, found 685.3145.

Propargyl 2,3-dideoxy-4-*O*-*t*-butyldimethylsilyl-6-*O*-triphenylmethyl-α-D-glucopyranoside

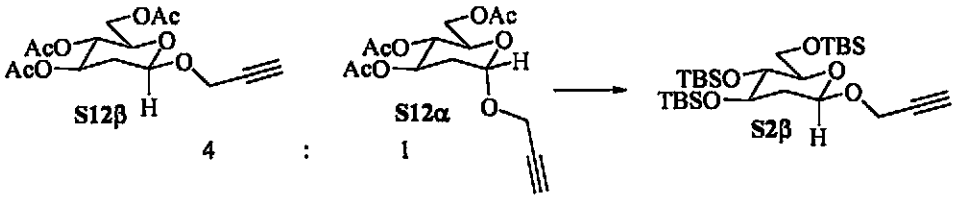
S11



Crude propargyl 2,3-dideoxy-4,6-di-*O*-acetyl-α-D-glucopyranoside **S6** (400 mg, 1.48 mmol) was dissolved into 5.9 mL MeOH. A separate flask containing 60% NaH (20 mg, 0.500 mmol) was added to 1 mL MeOH and the mixture was transferred *via* cannula to the solution of glucoside **S6** at rt. After 1 h, the solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H^+. The mixture was allowed to stir for 2 min after which it was filtered through a short plug of silica gel and concentrated. This unpurified material was dissolved in 1 mL CH_2Cl_2 and was treated with DMAP (8 mg, 65 μmol) and Hünig's base 590 μL (3.39 mmol). Trityl chloride (453 mg, 1.62 mmol) was added and the mixture was sitrred at 60 °C for 3 hr. The mixture was then cooled to 0 °C and was treated with TBSOTf (370 μL, 1.61 mmol), was stirred at 0 °C for 30 min and was quenched with 3 mL saturated $NaHCO_3$. Extractive isolation with CH_2Cl_2 (3 x 5 mL) followed by purification *via* flash column chromatography (4% EtOAc in hexanes) provided 522 mg (0.962 mol, 65% yield) of title compound **S11** as a 10:1 α:β anomeric mixture; R_f = 0.26 (25% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 6H), 7.34-7.14 (m, 9H), 5.09 (s, 1H), 4.51 (d,

J = 15.5 Hz, 1H), 4.42 (d, J = 15.5 Hz, 1H), 3.85 (t, J = 8.5 Hz, 1H), 3.37 (d, J = 9.2 Hz, 2H), 3.09 (t, J = 8.5 Hz, 1H), 2.46 (s, 1H), 1.94-1.70 (m, 4H), 0.68 (s, 9H), -0.07 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.7, 128.3, 127.7, 126.8, 94.1, 79.6, 74.1, 73.6, 67.4, 64.3, 53.3, 28.7, 28.2, 25.5, 17.6, -4.3, -5.3; IR (neat) 3059, 2954, 2929, 2856, 2120, 1900, 1448, 1252, 1097, 1045, 836 cm^{-1}; EIMS *m/z* (%) 119 (3), 152 (6), 164 (23), 165 (100), 228 (14), 241 (88), 243 (30); HRESIMS *m/z* exact mass calcd for $C_{34}H_{42}O_4SiNa^+$ (MNa^+) 565.2742, found 565.2753.

Propargyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-β-D-glucopyranoside **S2β**

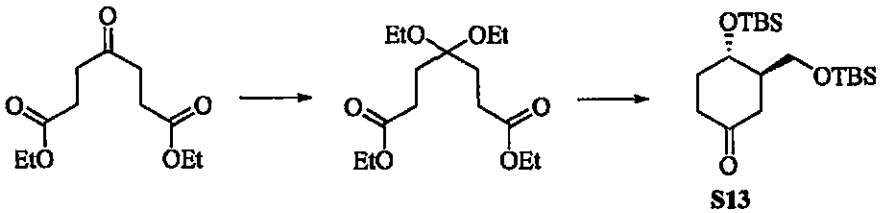


A solution of propargyl 2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranoside **S12** (300 mg, 0.914 mmol) was dissolved in 2 mL of MeOH and the solution was cooled to 0 °C. To a separate flask containing 5 mL of MeOH was added 60% NaH (15 mg, 0.375 mmol) and the mixture was transferred *via* cannula into the solution of propargyl glucoside **S12**. The mixture was then warmed to rt and after 1 h was cooled 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. After stirring for 15 min, the mixture was filtered through a short plug of silica gel and concentrated. Recrystallization of the mixture using 2 mL of 1:5 MeOH:toluene afforded 120 mg (0.593 mmol, 65% yield) of propargyl 2-deoxy-β-D-glucopyranoside as white, needle-like crystals; mp = 166-172 °C; R_f = 0.50 (5% MeOH in EtOAc). The crystals were dried by azeotropic distillation of toluene, were dissolved in 2 mL

DMF and were treated with Hunig's base (800 μL, 4.59 mmol). After cooling to 0 °C, TBSOTf was (670 μL, 2.92 mmol) added and the mixture was stirred at 0 °C for 1.5 h. Ice-cold saturated aqueous $NaHCO_3$ (3 mL) and CH_2Cl_2 (10 mL) were added and the organic layer was separated and was washed with 2 mL of H_2O (3x) followed by 2 mL brine. The organic layer was then dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (20% CH_2Cl_2 in hexanes) provided title compound **S2β** (323 mg, 0.593 mmol, 100% yield) as a viscous, colorless oil; R_f = 0.24 (30% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (dd, J = 9.4, 2.2 Hz, 1H), 4.37 (dd, J = 18.5, 2.5 Hz, 1H), 4.29 (dd, J = 18.5, 2.5 Hz, 1H), 3.88 (dd, J = 11.1, 2.5 Hz, 1H), 3.78-3.65 (m including dd at 3.75, J = 11.1, 5.5 Hz, 2H), 3.39 (t, J = 8.2 Hz, 1H), 3.17 (ddd, J = 8.2, 5.5, 2.5 Hz, 1H), 2.42 (t, J = 2.5 Hz, 1H), 2.16 (ddd, J = 12.9, 4.9, 2.2 Hz, 1H), 1.62-1.50 (m, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 6H), 0.09 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.7, 79.2, 77.0, 74.5, 73.1, 72.4, 62.7, 54.9, 39.9, 26.3, 26.1, 25.9, 18.4(2), 18.0, -3.0(2), -4.0, -4.6, -5.0, -5.3; IR (neat) 3313, 2930, 2858, 2361, 2120, 1472, 1254, 1006, 778 cm^{-1}; EIMS *m/z* (%) 73 (100), 89 (36), 117 (38), 147 (30), 171 (16), 299 (13), 357 (16); HRESIMS *m/z* exact mass calcd for $C_{27}H_{56}O_5Si_3Na^+$ (MNa^+) 567.3334, found 567.3340.

(3*R*,4*S*)-4-(*t*-Butyldimethylsilyloxy)-3-((*t*-butyldimethylsilyloxy)methyl)cyclohexanone[xi]

S13



S13

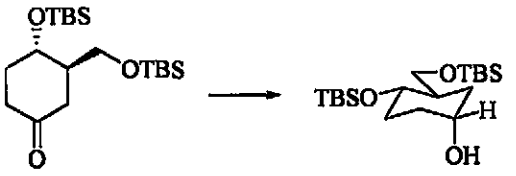
[xi] List, B. *Acc. Chem. Res.* **2004**, *37*, 548-557.

To a solution of diethyl 4-oxopimelate (3.03 g, 13.0 mmol) in 7 mL of a 1:1 mixture of triethylorthoformate:EtOH was added TsOH (120 mg, 0.697 mmol). The reaction was refluxed for 4 h then was cooled to 0 °C and was treated with 20 mL of ice-cold saturated $NaHCO_3$ and 20 mL of Et_2O. The aqueous layer was separated, extracted with 6 mL of Et_2O (3x) and the combined organic layers were washed with brine, were dried over $MgSO_4$ and were concentrated to provide 3.00 g (9.86 mmol, 76% yield) of crude diethyl ketal. This unpurified material was dissolved in 20 mL CH_2Cl_2, was dried over 4 Å MS, transferred *via* cannula to a 250 mL round-bottom flask and diluted with 80 mL CH_2Cl_2. The solution was cooled to -78 °C, treated with DIBALH (4 mL, 22.4 mmol) dropwise over 15 min and was vigorously stirred for 45 min. Acetone (1.7 mL, 23.2 mmol) was introduced dropwise and the mixture was removed from the dry-ice bath, was treated with 50 mL of saturated potassium sodium tartrate and was vigorously stirred at 0 °C. After 30 min, the stirring was reduced to gentle stirring for 2 h during which the emulsion dissipated. The layers were separated and the aqueous layer was extracted with 20 mL portions of CH_2Cl_2 (6x). The combined organic layers were washed with 30 mL of brine, were dried over $MgSO_4$ and were concentrated to a volume of 5 mL.[xii] The dialdehyde was diluted with 45 mL of CH_2Cl_2 (45 mL) and was dried over 4 Å MS. In a separate 250 mL round-bottom flask, a solution of L-proline (113 mg, 0.982 mmol) in 50 mL of CH_2Cl_2 was prepared by sonication. After 1 h the suspension of L-proline was cooled to 0 °C and was treated with the dialdehyde solution (previously cooled to 0 °C for 15 min) *via* cannula. The mixture was allowed to stir at 0 °C for 18 h, after which 25 mL of EtOH was added and the resulting mixture was treated with 652 mg of $NaBH_4$. The mixture was stirred at 0 °C for 5 min and was quenched carefully with saturated KH_2PO_4.

[xii] Neat dialdehyde was unstable at 0 °C overnight (16 h).

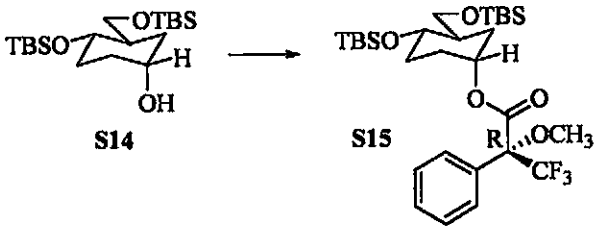
The aqueous layer was separated and was saturated with solid NaCl and was extracted with 20 mL EtOAc (6x). The combined organic layers were washed with 20 mL of brine then were dried over $MgSO_4$ and were concentrated. To the crude diol in 40 mL CH_2Cl_2 was added imidazole (3.36 g, 49.4 mmol) and DMAP (cat.) then TBSCl (4.46 g, 29.6 mmol). The mixture was stirred at rt for 1 h then was diluted with 10 mL of H_2O. The organic layer was separated, was washed with 10 mL of 1 N HCl (2x) followed by 20 mL of brine and was dried over $MgSO_4$ and was concentrated. The crude material was diluted with 10 mL of acetone, was treated with a spatula-tip of Amberlyst 15 resin at rt and was stirred for 30 min. The mixture was filtered, concentrated and was purified *via* flash column chromatography on silica gel (5% EtOAc in hexanes) to provide title compound **S13** in 1.88 g (5.04 mmol, 51% yield); R_f = 0.48 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01, (td, J = 7.0, 3.4 Hz, 1H), 3.68 (dd, J = 10.1, 4.5 Hz, 1H), 3.45 (dd, J = 10.1, 5.3 Hz, 1H), 2.53 (br dd, J = 13.2, 5.4 Hz, 1H), 2.49 (br dd, J = 13.2, 6.7 Hz, 1H), 2.27 (dd, J = 13.2, 8.2 Hz, 2H), 2.04 (m, 2H), 1.80 (td, J = 13.2, 8.2 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.028 (s, 3H), 0.019 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 67.9, 63.4, 46.9, 40.7, 37.7, 32.1, 25.8, 25.7, 18.2, 18.0, -4.5, -4.9, -5.4, -5.6; IR (neat) 2858, 2361, 1717, 1255, 1103 cm^{-1}; EIMS *m/z* (%) 73 (58), 147 (83), 183 (45), 315 (100); HREIMS *m/z* exact mass calcd for $C_{15}H_{31}O_3Si_2$ (M^+ - $C(CH_3)_3$) 315.1811, found 315.1825.

4-(*t*-Butyldimethylsilyloxy)-3-((*t*-butyldimethylsilyloxy)methyl)cyclohexanol **S14**



S13 **S14**

To a stirred solution of ketone **S13** (1.87 g, 5.02 mmol) in 50 mL of THF at -78 °C was added L-selectride (10 mL, 1.0 M in THF, 10.0 mmol). The reaction mixture was stirred at -78 °C for 1 h then was slowly warmed to rt over 1 h. After 30 min at rt, the reaction mixture was cooled to 0 °C and treated with 5 mL of 3 M NaOH followed by 5 mL of 30% H_2O_2 dropwise. After 15 min, 25 mL of brine was added. The layers were separated and the aqueous layer was extracted with 5 mL of Et_2O (3x). The combined organic layers were washed with 10 mL of KH_2PO_4 followed by brine then were dried over $MgSO_4$ and concentrated to provide 1.48 g (3.95 mmol, 79% yield) of alcohol **S14** as a clear, viscous oil; R_f = 0.21 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03-3.94 (m, 1H), 3.66 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.59 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.62-3.48 (m, 1H), 1.88-1.62 (m, 4H), 1.60-1.40 (m, 3H), 1.19 (s, 9H), 1.18 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.0, 66.0, 63.7, 42.0, 34.3, 31.0, 29.3, 26.0, 25.8, 18.3, 18.0, -4.2, -4.9, -5.3, -5.5; IR (neat) 3357 (br), 2928, 2856, 1473, 1256, 1005 cm^{-1}; EIMS *m/z* (%) 75 (87), 147 (100), 185 (40), 299 (26), 315 (100); HREIMS *m/z* exact mass calcd for $C_{15}H_{33}O_3Si_2$ (M^+ - $C(CH_3)_3$) 317.1968, found 317.1986.

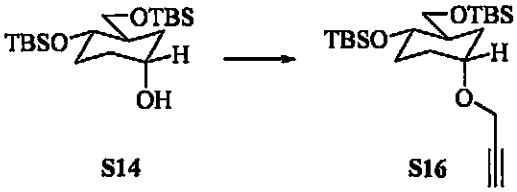


The optical purity of alcohol **S14** was determined by converting the alcohol to the (*R*)-Mosher's ester according to the following procedure. To a stirred solution of 10 mg (0.027 mmol) of alcohol **S14** in 2 mL of CH_2Cl_2 at 0 °C was added (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (15 μL, 0.080 mmol), NEt_3 (45 μL, 0.323 mmol) and a

small spatula-tip of DMAP. After 2 h at 0 °C, the reaction mixture was diluted with 2 mL of water. The layers were separated and the aqueous layer was extracted with 3 mL of CH_2Cl_2 (4x) and the combined organic layers were washed with 2 mL of 1 N HCl followed by 2 mL of saturated $NaHCO_3$ then brine. The organic layer was then dried over $MgSO_4$ and concentrated to provide 8 mg (0.014 mmol, 51% yield) of Mosher's ester **S15**. From integration of the fluorine NMR, enantiomeric purity of the Mosher's ester was determined to be 88:12 *er*. ^{19}F NMR (500 MHz, $CDCl_3$) δ -72.50 (major), -72.55 (minor).

t-Butyl((2-*t*-butyldimethylsilyloxy)-5-(prop-2-ynyloxy)cyclohexyl)methoxy) dimethylsilane

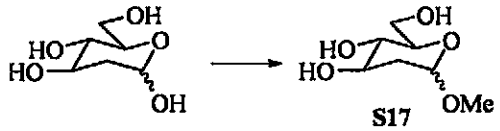
S16



To a solution of alcohol **S14** (1.00 g, 2.67 mmol) in 2.7 mL of THF at 0 °C was added a spatula-tip f 18-crown-6 followed by 762 mg (6.65 mmol) of 35% KH. The reaction mixture was stirred for 10 min (at which point the evolution of H_2 gas had ceased), was cooled to 0 °C and was treated with (80% w/v) propargyl bromide (2.4 mL, 16.0 mmol). The temperature of the reaction was allowed to warm slowly to rt, the mixture was stirred at rt for an additional 1 h then it was filtered through a short pad of Celite on a layer of sand. The filtrate was diluted with 3 mL of water. The layers were separated and the aqueous layer was extracted with 3 mL of Et_2O (3x). The combined organic layers were then washed with brine, dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (35% CH_2Cl_2 in hexanes) provided 613 mg (1.49 mmol, 56% yield) of title compound

S16 as a pail yellow oil and 487 mg of recovered alcohol **S14**; R_f = 0.81 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (d, *J* = 2.5 Hz, 2H), 3.80-3.74 (m, 1H), 3.66 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.60-3.44 (m, 2H), 2.38 (t, *J* = 2.5 Hz, 1H), 1.89-1.81 (m, 2H), 1.81-1.70 (m, 1H), 1.68-1.58 (m, 2H), 1.48-1.32 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.2, 73.6, 72.2, 70.1, 63.5, 54.9, 42.0, 30.9, 29.7, 27.9, 26.0, 25.8, 18.3, 18.0, -4.2, -4.9, -5.3, -5.5; IR (neat) 2929, 2857, 2361, 2339 cm^{-1}; EIMS *m/z* (%) 73 (47), 93 (38), 147 (100), 189 (12), 299 (75), 315 (16), 355 (14); HREIMS *m/z* exact mass calcd for $C_{18}H_{35}O_3Si_2$ (M^+ - $C(CH_3)_3$) 355.2124, found 355.2130.

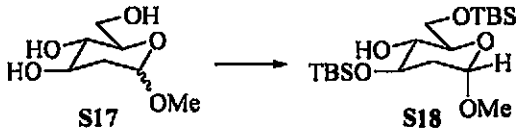
Methyl 2-deoxy-α-D-glucopyranoside **S17**



S17

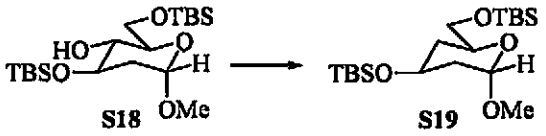
A mixture of 2-deoxy-D-glucose (2.00 g, 12.2 mmol) in 10 mL of MeOH was cooled to 0 °C and was treated with $BF_3{\cdot}Et_2O$ (2.3 mL, 18.6 mmol) dropwise. Once the entire portion of $BF_3{\cdot}Et_2O$ had been added, the temperature was allowed to gradually rise to rt. The mixture stirred for 16 h at rt, after which it was cooled to 0 °C and was treated with NEt_3 (6.8 mL, 48.8 mmol). After 15 min of stirring at 0 °C, the mixture was gradually warmed to rt and was stirred for an additional 15 min. The brownish solution was stirred with basic alumina then filtered and concentrated on silica gel. Purification *via* flash column chromatography on silica gel (5% to 10% MeOH in EtOAc) furnished 1.95 g (11.0 mmol, 90% yield) of title compound **S17** as a 13:1 α:β mixture.

Methyl 2-deoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S18**



Methyl 2-deoxy-α-D-glucopyranoside **S17** (2.17 g, 12.2 mmol) was dissolved in 50 mL of DMF and was treated with imidazole (2.07 g, 30.4 mmol) and a spatula-tip of DMAP. The solution was cooled to 0 °C and was treated with TBSCl (4.04 g, 26.8 mmol). After stirring at 0 °C for 1 h, ice-cold 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of CH_2Cl_2 was added. The organic layer was separated, washed with 5 mL of ice-cold H_2O (5x) followed by 5 mL of brine and was dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (10% CH_2Cl_2 in hexanes) provided a 6:1 α:β mixture of title compound **S18** as a clear, viscous oil (4.06 g, 9.98 mmol, 82% yield); R_f = 0.10 (50% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, J = 3.1 Hz, 1H), 3.92 (ddd, J = 11.3, 8.8, 5.1 Hz, 1H), 3.88 (dd, J = 11.0, 4.0 Hz, 1H), 3.82 (dd, J = 11.0, 5.1 Hz, 1H), 3.55 (ddd, J = 8.8, 5.1, 4.0 Hz, 1H), 3.36 (td, J = 8.8, 1.9 Hz, 1H), 3.30 (s, 3H), 2.50 (d, J = 1.9 Hz, 1H), 1.98 (dd, J = 13.0, 5.1 Hz, 1H), 1.64 (ddd, J = 13.0, 11.3, 3.1 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.8, 78.8, 76.8, 75.8, 69.3, 59.8, 43.6, 31.3, 31.1, 23.7, 23.4, 1.0, 0.8, 0.0(2); IR (neat) 3424 (br), 2955, 2930, 1253, 1131, 1101, 1054 cm^{-1}; EIMS *m/z* (%) 89 (95), 115 (62), 175 (155), 243 (40); HREIMS *m/z* exact mass calcd for $C_{15}H_{33}O_5Si_2$ (M^+ - $C(CH_3)_3$) 349.1869, found 349.1897.

Methyl 2,4-dideoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S19**[xiii]

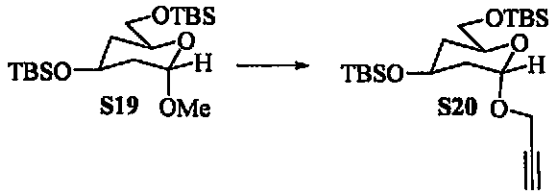


To methyl 2-deoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S18** (1.99 g, 4.89 mmol) in 9.8 mL DMF was added carbonyl diimidazole (2.62 g, 16.2 mmol) and DMAP (1.20 g, 9.82 mmol). After stirring at 65 °C for 30 h, the solution was diluted with water and Et_2O. The aqueous layer was separated and extracted with Et_2O (3x) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude mixture was dissolved in 30 mL DMF and treated with $(Bu_4N)_2S_2O_8$ (2.42 g, 3.57 mmol) and HCO_2Na (620 mg, 9.11 mmol). After 2 h at 65 °C the mixture was cooled to rt and poured into 20 mL of water. The aqueous layer was separated and extracted with 20 mL of CH_2Cl_2 (3x). The combined organic extracts were washed with 10 mL of brine then dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (50% CH_2Cl_2 in hexanes) provided 439 mg (1.12 mmol, 23% yield) of title compound **S19**; R_f = 0.20 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, J = 3.7 Hz, 1H), 4.07 (tt, J = 11.2, 4.8 Hz, 1H), 3.78-3.67 (m, 1H), 3.67 (dd, J = 10.1, 5.1 Hz, 1H), 3.55 (dd, J = 10.1, 5.1 Hz, 1H), 3.30 (s, 3H), 1.95 (br dd, J = 12.9, 4.8 Hz, 1H), 1.85 (br dd, J = 11.2, 4.8 Hz, 1H), 1.52 (ddd, J = 12.9, 11.2, 3.7 Hz, 1H), 1.25 (q, J = 11.2 Hz, 1H), 0.89 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.3, 68.7, 66.4, 64.5, 54.4, 39.8, 37.9, 25.9, 25.8, 18.3, 18.1, -4.6, -5.3; IR (neat) 2955, 2930, 1385, 1361, 1255, 1127, 1107, 1051 cm^{-1}; EIMS *m/z* (%) 73 (69), 117 (100), 147 (24), 201 (27); HREIMS *m/z*

[xiii] Park, H. S.; Lee, H. Y.; Kim, Y. H. *Org. Lett.* **2005**, *7*, 3187-3190.

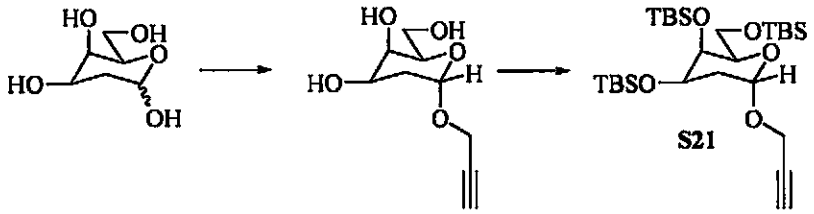
exact mass calcd for $C_{15}H_{33}O_4Si_2$ (M^+ - $C(CH_3)_3$) 333.1917, found 333.1945.

Propargyl 2,4-dideoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S20**



Methyl 2,4-dideoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S19** (3.00 g, 7.68 mmol) and propargyl alcohol (4.3 mL, 73.9 mmol) were dissolved in dry 152 mL of CH_2Cl_2 at 0 °C and the mixture was stirred under N_2 at rt. $BF_3{\cdot}Et_2O$ (2.3 mL, 18.6 mmol) was added dropwise at 0 °C and the mixture was warmed slowly to 45 °C. After 1 h at 45 °C the reaction mixture was cooled to 0 °C and NEt_3 (3.4 mL, 24.4 mmol) was added. The mixture was then concentrated and filtered through a plug of silica to provide title compound **S20** (3.10 g, 7.47 mmol, 97% yield) as a clear, odorless oil; R_f = 0.40 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (d, *J* = 3.5 Hz, 1H), 4.18 (t, *J* = 2.3 Hz, 2H), 4.08 (tt, *J* = 11.0, 4.7 Hz, 1H), 3.78-3.65 (m, 1H), 3.65 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.54 (dd, *J* = 10.3, 4.7 Hz, 1H), 2.39 (t, *J* = 2.3 Hz, 1H), 1.98 (br dd, *J* = 13.0, 4.7 Hz, 1H), 1.85 (br dd, *J* = 11.0, 4.7 Hz, 1H), 1.55 (ddd, *J* = 13.0, 11.0, 3.5 Hz, 1H), 1.25 (q, *J* = 11.0 Hz, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.6, 79.6, 74.0, 69.3, 66.2, 64.3, 54.5, 39.4, 37.6, 25.9, 25.8, 18.3, 18.0, -4.5, -4.6, -5.3(2); IR (neat) 3052, 2976, 2300, 1420, 1262, 1120 cm^{-1}; EIMS *m/z* (%) 73 (55), 117 (100), 201 (27), 225 (34), 301 (38); HREIMS *m/z* exact mass calcd for $C_{17}H_{33}O_4Si_2$ (M^+ - $C(CH_3)_3$) 357.1911, found 357.1917.

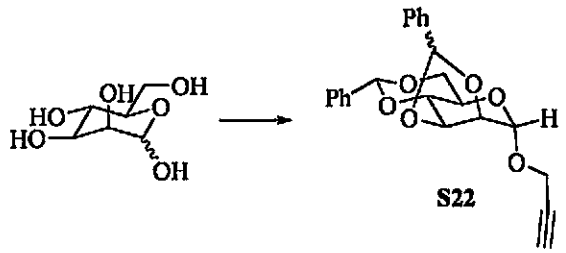
Propargyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-α-D-galactopyranoside **S21**



2-Deoxy-D-galactose (1.00 g, 6.09 mmol) in 7.1 mL of propargyl alcohol (122 mmol) was treated with 300 mg of DOWEX-50H$^+$ and the mixture was heated to 60 °C for 20 h. The dark-brownish solution was adsorbed onto silica gel, added onto a column packed with silica gel and was quickly eluted using 5% MeOH in EtOAc to remove base-line material. The crude material was then was dissolved in 5 mL of DMF. Pyridine (2.5 mL, 30.1 mmol) was added and the solution was cooled to 0 °C then was treated with TBSOTf (4.9 mL, 21.3 mmol). The mixture was allowed to stir at 0 °C for 1 h after which 7 mL ice-cold saturated $NaHCO_3$ was added. The mixture was diluted with 10 mL of CH_2Cl_2 and the organic layer was separated, was washed with 20 mL of ice-cold H_2O (5x) followed by 5 mL of brine and was dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (2.5% EtOAc in hexanes) provided 3.31 g (6.07 mmol, 100% yield) of title compound **S21** as a clear viscous oil; R_f = 0.17 (2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (d, J = 3.5 Hz, 1H), 4.18 (t, J = 2.3 Hz, 2H), 4.00 (ddd, J = 11.7, 4.4, 2.3 Hz, 1H), 3.81 (br s, 1H), 3.69-3.57 (m, 3H), 2.36 (t, J = 2.3 Hz, 1H), 2.12 (ddd, J = 12.6, 11.7, 3.5 Hz, 1H), 1.64 (dd, J = 12.6, 4.4 Hz, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.4, 79.8, 73.8, 73.2, 70.0, 68.2, 62.7, 53.6, 33.2, 26.2, 26.1, 25.8, 18.6, 18.5, 18.2, -3.9, -4.4, -4.7, -5.0, -5.3, -5.4; IR (neat) 3054, 2987, 2306, 1265 cm^{-1}; EIMS *m/z* (%) 73

(55), 117 (100), 225 (34); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2717.

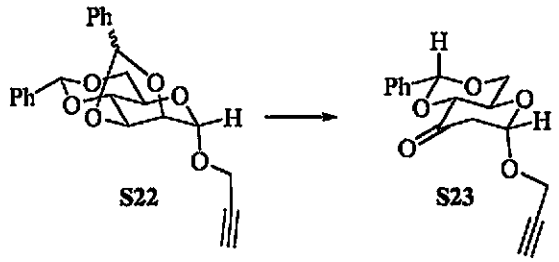
Tetrahydro-2-phenyl-6-(prop-2-ynyloxy)pyrano[3,2-d][1,3]dioxin-8(8a*H*)-one **S22**



S22

A mixture of D-mannose (4.50 g, 25.0 mmol) and DOWEX-50H$^+$ (1.00 g) in 30 mL of propargyl alcohol was stirred at 80 °C for 48 h. The mixture was then cooled to rt and was filtered. The propargyl alcohol was evaporated off and the crude material was dissolved in 25 mL of DMF and treated with benzaldehyde dimethyl acetal (8.2 mL, 55.0 mmol) and TsOH (1.25 g, 7.26 mmol). The mixture was stirred at 80 °C under reduced pressure (25 mm Hg) while bubbling through a gentle stream of N_2. After 3 h, the mixture was poured into ice-cold saturated aqueous $NaHCO_3$ and the resulting precipitate was filtered off, resuspended in ice-cold water and filtered off again. The brownish solid was absorbed onto Celite, added onto a column packed with silica gel and eluted using 20% EtOAc in hexanes to provide a diastereomeric mixture of propargyl title compound **S22** as a white, amorphous solid (5.63 g, 14.3 mmol, 57% yield); R_f = 0.34 (25% EtOAc in hexanes); IR (neat) 3283, 2360, 1217, 1090, 1074, 1025, 697 cm^{-1}; EIMS *m/z* (%) 91 (73), 105 (100), 144 (23), 233 (5); HREIMS *m/z* exact mass calcd for $C_{23}H_{22}O_6$ (M^+) 394.1416, found 394.1390.

(2*R*,4a*R*,6*S*,8a*R*)-2-Phenyl-6-(prop-2-ynyloxy)tetrahydropyrano[3,2-*d*][1,3]dioxin-8(8a*H*)-one **S23**[xiv]

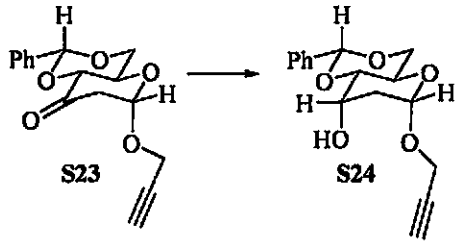


Propargyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside **S22** (100 mg, 0.254 mmol) in 1.8 mL of THF was cooled to -40 °C and then treated with *n*-BuLi (1.5 mL, 0.630 mmol, 2.38 M in hexanes). The temperature was kept between -40 °C to -30 °C for 1 h and the reaction mixture was poured directly into saturated NH_4Cl at 0 °C. After stirring for 5 min, the solvent was removed *via* rotoevaporation. The remaining aqueous solution was cooled to 0 °C at which point yellowish solids precipitated. The solids were filtered and rinsed with three 5 mL portions of hot hexane to provide 46 mg (0.160 mmol, 63% yield) of title compound **S23** as a pale yellow, amorphous solid; R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.44 (m, 2H), 7.42-7.31 (m, 3H), 5.59 (s, 1H), 5.49 (d, *J* = 4.7 Hz, 1H), 4.37 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.33 (d, *J* = 10.0 Hz, 1H), 4.25 (d, *J* = 2.0 Hz, 2H), 4.21 (td, *J* = 10.0, 4.7 Hz, 1H), 3.92 (t, *J* = 10.0 Hz, 1H), 2.88 (dd, *J* = 14.7, 4.7 Hz, 1H), 2.70 (d, *J* = 14.7 Hz, 1H), 2.47 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 137.2, 129.4, 128.7, 127.2, 102.3, 97.4, 84.7, 75.8, 69.3, 64.2, 60.5, 54.6, 32.2; IR (neat) 3067, 2925, 2360, 2342, 1691, 1591, 1250, 1139, 1096, 700 cm^{-1}; EIMS *m/z* (%) 91 (56), 105 (72), 127 (4), 143 (4); HREIMS *m/z* exact mass calcd for $C_{13}H_{13}O_4$ (M^+ - OCH_2CCH) 233.0814, found 233.0831.

[xiv] Horton, D.; Weckerle, *Carbohydrate Res.* **1995**, *44*, 227-240.

(2*R*,4a*R*,6*S*,8*S*,8a*S*)-2-Phenyl-6-(prop-2-ynyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-8-ol

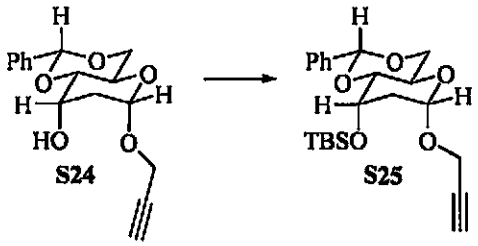
S24



A solution of DIBALH (400 μL, 2.24 mmol) in 5 mL of THF at 0 °C was treated with *t*-BuLi (3.9 mL, 2.26 mmol, 0.58 M in pentane). The mixture was stirred for 10 min then was cooled to -78 °C and was stirred for an additional 10 min. The solution was added to a mixture of propargyl 2-deoxy-4,6-*O*-benzylidene-α-D-*erythro*-hexopyranosid-3-ulose **S23** (500 mg, 1.73 mmol) in 24 mL of THF at -78 °C *via* cannula. The reaction mixture was stirred at -78 °C for 1.5 h then was treated with saturated aqueous Na_2SO_4 dropwise until a white, needle-like precipitate emerged. The precipitate was filtered off and rinsed with 5 mL of EtOAc. The filtrate was combined with the EtOAc rinse and was stirred with 25 mL of saturated aqueous Na_2SO_4 for 30 min. The organic layer was separated and washed with 20 mL of brine, then was dried over $MgSO_4$ and was concentrated. Purification *via* flash column chromatography on silica gel (30% EtOAc in hexanes, 1% NEt_3) provided title compound **S24** (411 mg, 1.42 mmol, 82% yield) as a white plate-like solid; mp = 118-120 °C; R_f = 0.29 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.36 (m, 2H), 7.33-7.22 (m, 3H), 5.57 (s, 1H), 5.03 (d, J = 4.0 Hz, 1H), 4.27-4.07 (m, 5H), 3.67 (br t, J = 9.6 Hz, 1H), 3.53 (br d, J = 9.6 Hz, 1H), 2.74 (d, J = 5.6 Hz, 1H), 2.35 (br d, J = 2.4 Hz, 1H), 2.12 (br d, J = 15.1 Hz, 1H), 1.80 (br d, J = 15.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 129.1, 128.2, 126.2, 102.0, 93.7, 79.4, 78.7, 74.9, 69.1, 64.6, 58.5, 54.6, 35.2; IR (neat) 3525 (br),

3284, 2933, 2117, 1383, 1101, 1030, 864, 701 cm^{-1}; EIMS *m/z* (%) 77 (51), 91 (26), 106 (10), 107 (100); HRESIMS *m/z* exact mass calcd for $C_{16}H_{19}O_5$ (MH^+) 291.1232, found 291.1232.

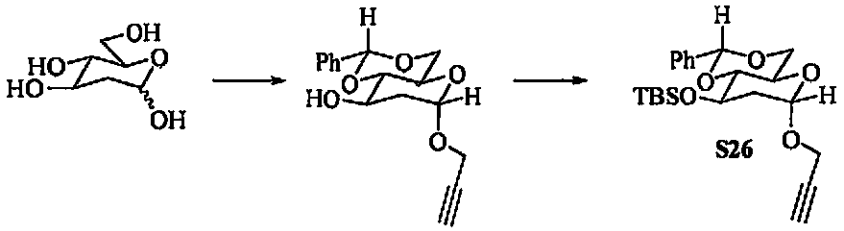
t-Butyldimethyl((2*R*,4a*R*,6*S*,8*S*,8a*R*)-2-phenyl-6-(prop-2-ynyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)silane **S25**



To a solution of propargyl 2-deoxy-4,6-*O*-benzylidene-α-D-allopyranoside **S24** (451 mg, 1.55 mmol) and pyridine (251 μL, 3.10 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added TBSOTf (430 μL, 1.87 mmol) dropwise. The solution was stirred at 0 °C for 35 min and was diluted with 2 mL of CH_2Cl_2 and 4 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and was extracted with 2 mL of CH_2Cl_2 (4x). The combined organic layers were washed with 3 mL of brine then was dried over $MgSO_4$ and was concentrated. Purification *via* flash column chromatography on silica gel (7% EtOAc in hexanes, 1% NEt_3) provided title compound **S25** (414 mg, 1.02 mmol 66% yield); R_f = 0.32 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.45 (m, 2H), 7.40-7.32 (m, 3H), 5.56 (s, 1H), 5.03 (d, *J* = 3.1 Hz, 1H), 4.38 (td, *J* = 10.0, 5.4 Hz, 1H), 4.28 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.26-4.17 (m, including d at 4.21, *J* = 2.2 Hz, 3H), 3.70 (t, *J* = 10.0 Hz, 1H), 3.55 (dd, *J* = 10.0, 2.4 Hz, 1H), 2.39 (t, *J* = 2.2 Hz, 1H), 2.08-1.92 (m, 2H), 0.93 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.9, 128.1, 126.3, 101.9, 95.2, 79.6, 73.9,

69.3, 64.8, 58.1, 54.1, 37.0, 25.7, 25.6, 18.1, -4.6, -5.1; IR (neat) 3305, 2928, 2855, 2119, 1253, 1106, 834, 777, 698 cm^{-1}; EIMS *m/z* (%) 75 (25), 105 (17), 145 (100), 171 (30); HRESIMS *m/z* exact mass calcd for $C_{22}H_{32}O_5SiNa^+$ (MNa^+) 427.1916, found 427.1916.

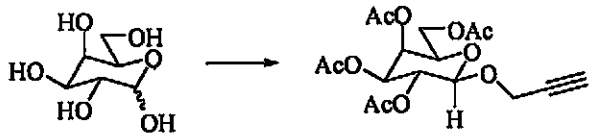
t-Butyldimethyl((2*R*,4a*R*,6*S*,8*R*,8a*R*)-2-phenyl-6-(prop-2-ynyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)silane **S26**



A mixture of 2-deoxy-D-glucose (1.00 g, 6.09 mmol) in 7.1 mL of propargyl alcohol (122 mmol) was cooled to 0 °C and was treated with $BF_3{\cdot}Et_2O$ (1 mL, 8.10 mmol) dropwise. Once the entire portion of $BF_3{\cdot}Et_2O$ had been added, the temperature was allowed to gradually rise to rt. The mixture was allowed to stir for 16 h at rt after which it was cooled to 0 °C and was treated with NEt_3 (3.4 mL, 24.4 mmol). After 15 min of stirring at 0 °C, the mixture was gradually warmed to rt and was stirred for an additional 15 min. The brownish solution was filtered through a short plug of basic alumina, was absorbed onto silica gel, was added onto a column packed with silica gel and was quickly eluted using 5% MeOH in EtOAc to remove baseline material. To a stirred solution of this crude material in 5 mL of DMF was added benzaldehyde diethyl acetal (450 µL, 3.00 mmol) and TsOH (20 mg, 0.116 mmol). The resulting solution was heated at 80 to 85 °C under reduced pressure (about 26 mm Hg) for 2 hr. After cooling to rt, the reaction mixture was poured into 7 mL saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with 10 mL CH_2Cl_2

(5x). The combined organic phases were washed with 5 mL brine, were dried over $MgSO_4$ and were concentrated to a highly viscous oil that was purified by flash column chromatography on silica (10% EtOAc in hexanes) to provide a 4:1 α:β mixture of hexahydro-2-phenyl-6-(prop-2-ynyloxy)pyrano[3,2-d][1,3]dioxine (436 mg, 1.50 mmol, 25% yield). This unpurified material was dissolved in 3 mL CH_2Cl_2 and was treated with TBSCl (359 mg, 2.38 mmol), imidazole (280 mg, 3.66 mmol) and DMAP (cat.) at rt. After 3 h, 5 mL saturated aqueous $NaHCO_3$ was added and the aqueous layer was separated and extracted with 10 mL CH_2Cl_2 (3x). The combined organic extracts were washed with 10 mL brine, were dried over $MgSO_4$ and were concentrated. Purification *via* flash column chromatography on silica gel provided title compound **S26** (518 mg, 1.28 mmol, 85% yield) as a clear, viscous oil; R_f = 0.47 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.48 (d, J = 8.4 Hz, 2H), 7.40-7.32 (m, 3H), 5.56 (s, 1H), 5.09 (d, J = 3.6 Hz, 1H), 4.20 (td, J = 11.0, 5.4 Hz, 1H), 4.03 (dd, J = 10.1, 5.0 Hz, 1H), 3.86-3.71 (m, including d at 3.77, J = 2.3 Hz, 3H), 3.43 (t, J = 10.1 Hz, 1H), 3.23 (t, J = 10.1 Hz, 1H), 1.98 (dd, J = 13.5, 5.4 Hz, 1H), 1.92-1.88 (m, 1H), 1.61 (ddd, J = 13.5, 11.0, 3.6 Hz, 1H), 0.86 (s, 9H), 0.07 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 138.6, 128.9, 128.2, 126.7, 102.1, 96.8, 84.0, 79.5, 74.7, 69.0, 67.1, 63.9, 54.1, 39.2, 26.0, 18.4, -4.2, -4.9; IR (neat) 3290, 2930, 2630, 2120, 1102 cm^{-1}; EIMS *m/z* (%) 143 (60), 149 (100), 219 (27), 265 (36), 291 (28); HREIMS *m/z* exact mass calcd for $C_{18}H_{23}O_5Si$ (M^+ - $C(CH_3)_3$) 347.1315, found 347.1279.

Propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **S27**

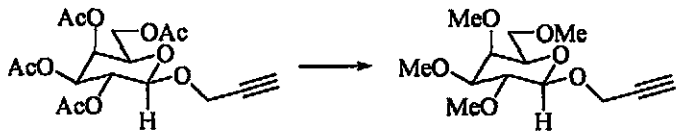


S27

To a suspension of D-galactose (2.00 g, 11.1 mmol) in acetic anhydride (6.3 mL, 66.6 mmol) was added 31% HBr/AcOH (4.20 g, 16.1 mmol) at rt. The temperature of the reaction mixture was maintained at rt for 16 h during which time the suspended solid went into solution. The solution was then treated with an additional portion of 31% HBr/AcOH (12.0 g, 46.0 mmol) and the mixture was stirred for 3 h. The mixture was poured into a solution of 25 mL CH_2Cl_2 and ice-cold water and the organic layer was separated, washed with ice-cold water (5x), saturated $NaHCO_3$ (3x) and brine then was dried over $MgSO_4$ and was concentrated. The crude material was dissolved in 15 mL of CH_2Cl_2 and was transferred to a solution of 50 mL CH_2Cl_2, propargyl alcohol (540 μL, 9.28 mmol), Ag_2CO_3 (5.10 g, 18.5 mmol) and powdered $CaSO_4$ (3.78 g, 27.8 mmol) *via* cannula. After 40 h of stirring at rt, the mixture was filtered through a short plug of Celite and was concentrated. Purification *via* flash column chromatography on silica gel (25% EtOAc in hexanes) provided title compound **S27** (1.70 g, 4.40 mmol, 40% yield) as pale-yellow, viscous oil; R_f = 0.28 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dd, J = 3.4, 1.0 Hz, 1H), 5.24 (dd, J = 10.4, 7.9 Hz, 1H), 5.06 (dd, J = 10.4, 3.4 Hz, 1H), 4.73 (d, J = 7.9 Hz, 1H), 4.38 (d, J = 2.3 Hz, 2H), 4.19 (dd, J = 11.3, 6.7 Hz, 1H), 4.12 (dd, J = 11.3, 6.7 Hz, 1H), 3.94 (td, J = 6.7, 1.0 Hz, 1H), 2.47 (t, J = 2.3 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.5, 98.6, 78.2, 75.3, 70.8(2), 68.5, 66.9, 61.2,

55.9, 20.8, 20.6(2), 20.5; IR (neat) 3277, 2982, 2120, 1748, 1371, 1225, 1079 cm^{-1}; EIMS *m/z* (%) 82 (83), 95 (80), 102 (72), 111 (58), 124 (199), 153 (68), 166 (92), 195 (33), 324 (10), 325 (19); HREIMS *m/z* exact mass calcd for $C_{15}H_{19}O_8$ (M^+ - $OCOCH_3$) 327.1080, found 327.1052.

Propargyl 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranoside **S28**

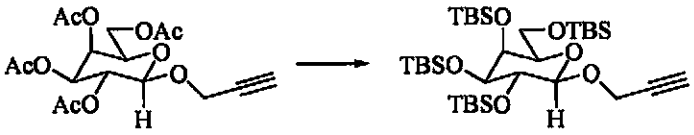


S27 **S28**

Propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **S27** (1.90 g, 4.92 mmol) was dissolved into 10 mL of MeOH and the solution was cooled to 0 °C. A separate flask containing 5 mL of MeOH was treated with 60% NaH (77 mg, 1.93 mmol) and the solution was transferred *via* cannula into the solution of propargyl galactoside **S27**. The mixture was warmed to rt and was stirred for 1 h. The solution was cooled to 0 °C and was treated with a small spatula tip of DOWEX-50H^+. The mixture was allowed to stir for 15 min after which it was filtered through a short plug of silica gel and was concentrated. The crude material and 250 mg of 18-crown-6 in 20 mL of THF and 3 mL of DMF was cooled to 0 °C and was treated with 5.50 g (98.0 mmol) of KOH. MeI (5 mL, 80.3 mmol) was added and the mixture was gradually warmed to rt. After stirring for 20 h, the mixture was filtered and diluted with 20 mL H_2O and 20 mL of EtOAc. The organic layer was separated and was washed with 20 mL portions of H_2O (3x) and 20 mL of brine. After drying over $MgSO_4$, the organic extract was concentrated and was purified *via* flash column chromatography on silica gel (50% EtOAc in hexanes) to provide title compound **S28** (282 mg, 1.03 mmol, 21% yield) as white

plate-like crystals; mp = 78-82 °C; R_f = 0.35 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (d, *J* = 7.6 Hz, 1H), 4.37 (d, *J* = 2.3 Hz, 2H), 3.68-3.45 (m, including s at 3.60, s at 3.59, s at 3.52 and s at 3.39, 17H), 3.16 (dd, *J* = 9.7, 3.1 Hz, 1H), 2.42 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.0, 83.7, 80.2, 79.1, 78.7, 74.7, 73.0, 70.6, 61.3, 60.8, 59.2, 58.4, 55.4; IR (neat) 3225, 2927, 2813, 2125, 1097 cm^{-1}; EIMS *m/z* (%) 73 (12), 75 (10), 88 (100), 89 (7), 99 (47), 101 (92), 102 (5); HREIMS *m/z* exact mass calcd for $C_{10}H_{19}O_5$ (M^+ - OCH_2CCH) 219.1232, found 219.1216.

Propargyl 2,3,4,6-tetra-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside **S29**

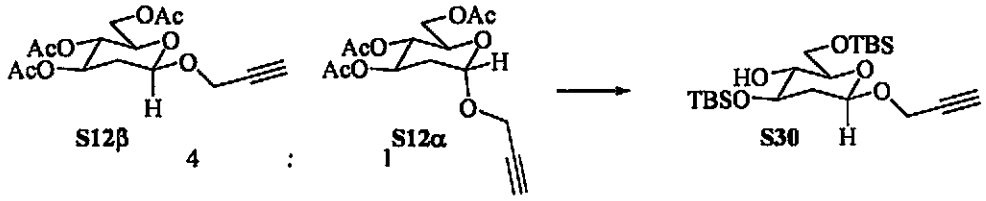


S27 **S29**

Propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **S27** (636 mg, 1.65 mmol) was dissolved into 5 mL of MeOH and the solution was cooled to 0 °C. A separate flask containing 5 mL of MeOH was treated with 60% NaH (26.0 mg, 0.658 mmol) and the mixture was transferred *via* cannula into the solution of propargyl galactoside **S27**. The mixture was then warmed to rt. After 1 h, the solution was recooled to 0 °C and was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was allowed to stir for 15 min after which it was filtered through a short plug of silica gel and was concentrated. The crude material was dissolved in 2 mL of DMF and 5 mL of CH_2Cl_2 then was cooled to 0 °C and was treated with imidazole (784 mg, 11.5 mmol), DMAP (402 mg, 3.29 mmol) and TBSCl (1.24 g, 8.23 mmol). The mixture was allowed to gradually warm to rt. After stirring for 20 h, the mixture was filtered and was diluted with 20 mL H_2O and 20 mL of EtOAc. The

organic layer was separated and was washed with 20 mL portions of H_2O (3x) and 20 mL of brine. After drying over $MgSO_4$, the organic extract was concentrated. The crude material was redissolved into 10 mL CH_2Cl_2 then was cooled to 0 °C and treated with 2,6-lutidine (290 μL, 2.49 mmol) followed by TBSOTf (380 μL, 1.65 mmol). The reaction mixture was stirred at 0 °C for 1.5 h then was diluted with saturated $NaHCO_3$ (10 mL). Extractive isolation using 5 mL CH_2Cl_2 (3x) followed by purification *via* flash column chromatography on silica gel (2.5% EtOAc in hexanes) provided title compound **S29** (550 mg, 0.815 mmol, 49% yield) as a clear, viscous oil; R_f = 0.21 (2.5% EtOAc in hexanes); IR (neat) 3225, 2927, 2813, 2125, 1097 cm^{-1}; HRESIMS *m/z* exact mass calcd for $C_{33}H_{70}O_6Si_4Na^+$ (MNa^+) 697.4145, found 697.4146.

Propargyl 2-deoxy-3,6-di-*O*-*t*-butyldimethylsilyl-β-D-glucopyranoside **S30**

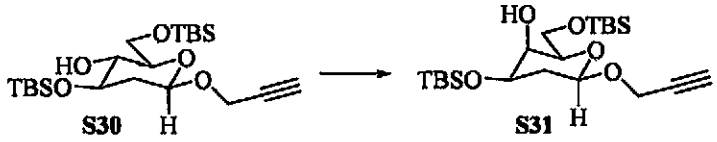


Propargyl 2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranoside **S12** (6.70 g, 20.4 mmol) was dissolved in 25 mL MeOH. To a separate flask containing 1 mL of MeOH was added 60% NaH (346 mg, 8.65 mmol) and the mixture was transferred *via* cannula to the solution of glucoside **S12** at rt. After 1 h, the solution was cooled to 0 °C then was treated with a small spatula tip of DOWEX-50H$^+$. The mixture was stirred for 2 min, after which it was filtered through a short plug of silica gel and was concentrated. The crude material was added onto a column packed with silica gel (5% MeOH in EtOAc) and eluted using a gradient of 5% to

7% to 10% MeOH in EtOAc. The resulting needle-like solids were dissolved in 5 mL of MeOH, were diluted with 15 mL of toluene and the resulting solution was evaporated to a volume of 6 mL. The mixture was slowly cooled and was allowed to crystallize at 0 °C. After 1 d at 0 °C, no more crystals emerged. The mother liquor was removed *via* pipette and the solids were rinsed with two 1 mL portions of an ice-cold solution of 1:5 mixture of MeOH:toluene to yield propargyl 2-deoxy-β-D-glucopyranoside (571 mg, 2.82 mmol, 14% yield). A mixture of propargyl 2-deoxy-β-D-glucopyranoside (571 mg, 2.82 mmol), imidazole (577 mg, 8.48 mmol) and catalytic DMAP was dissolved in 5.7 mL of DMF and was cooled to 0 °C. TBSCl (936 mg, 6.21 mmol) was added and the solution was allowed to gradually warm to rt overnight (16 h) and was diluted with 20 mL ice-cold saturated aqueous $NaHCO_3$ and 20 mL of CH_2Cl_2. The aqueous layer was separated, was extracted with 5 mL of CH_2Cl_2 and the combined organic layers were washed with 5 mL H_2O (4x) followed by 5 mL brine and was dried over $MgSO_4$. The pale yellowish solution was concentrated and then purified *via* flash column chromatography on silica gel (0% to 5% to 10% EtOAc in hexanes) to provide title compound **S30** as white, plate-like crystals (733 mg, 1.70 mmol, 60% yield); mp = 54-56 °C; R_f = 0.25 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 9.8, 1.8 Hz, 1H), 4.37 (d, J = 2.4 Hz, 1H), 4.31 (d, J = 2.4 Hz, 1H), 3.88 (d, J = 4.7 Hz, 1H), 3.87 (d, J = 4.7 Hz, 1H), 3.65 (ddd, J = 11.7, 9.4, 5.0 Hz, 1H), 3.35 (br t, J = 9.4 Hz, 1H), 3.27 (dt, J = 9.4, 4.7 Hz, 1H), 2.70 (d, J = 1.6 Hz, 1H), 2.44 (t, J = 2.4 Hz, 1H), 2.08 (ddd, J = 12.6, 5.0, 1.8 Hz, 1H), 1.61 (ddd, J = 12.6, 11.7, 9.8 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.2, 79.0, 75.1, 74.6, 73.8, 72.8, 64.3, 55.2, 39.5, 25.9, 25.8, 18.0(2), -4.5(2), -5.3, -5.4; IR (neat) 3515 (br), 2955, 2858, 2119, 1446, 1255, 1108, 1076, 836, 778 cm^{-1}; EIMS *m/z* (%) 185

(100), 201 (17), 273 (27), 317 (57); HRESIMS *m/z* exact mass calcd for $C_{21}H_{42}O_5Si_2K^+$ (MK^+) 469.2208, found 469.2184.

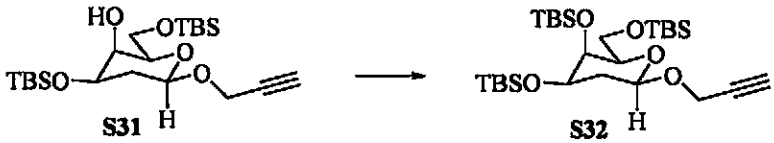
Propargyl 2-deoxy-3,6-di-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside **S31**



A solution of propargyl 2-deoxy-3,6-di-*O*-*t*-butydimethylsilyl-β-D-glucopyranoside **S30** (478 mg, 1.11 mmol) and DMP (519 mg, 1.22 mmol) in 11 mL of CH_2Cl_2 was stirred at 35 °C for 2 d. The mixture was then diluted with 5 mL of CH_2Cl_2, 5 mL of saturated aqueous $NaHCO_3$ and saturated sodium thiosulfate. After stirring for 10 min, the layers were separated. The organic layer was washed with 5 mL of H_2O followed by 5 mL of brine then was dried over $MgSO_4$ and concentrated. A solution of DIBALH (190 μL, 1.07 mmol) in 3 mL of THF at 0 °C was treated with *t*-BuLi (1.8 mL, 1.07 mmol, 0.58 M in pentane), was stirred for 10 min then was cooled to -78 °C and stirred for an additional 10 min. This mixture was subsequently added to a solution of the pyranoside in 3.1 mL THF at -78 °C *via* cannula. After stirring at -78 °C for 1.5 h, the mixture was treated with saturated aqueous Na_2SO_4 dropwise until a white, needle-like precipitate emerged. The precipitate was filtered off and rinsed with 5 mL of EtOAc. The filtrate was combined with the EtOAc rinse and was stirred in 10 mL of saturated aqueous Na_2SO_4 for 30 min. The organic layer was separated and was washed with 10 mL of brine, then dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (20% EtOAc in hexanes) provided title compound **S31** as a clear oil (127 mg, 0.290 mmol, 27% yield); R_f = 0.11 (10% EtOAc in

hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (dd, J = 9.5, 2.4 Hz, 1H), 4.39 (dd, J = 15.8, 2.5 Hz, 1H), 4.32 (dd, J = 15.8, 2.5 Hz, 1H), 3.86 (d, J = 2.4 Hz, 1H), 3.74-3.58 (m, including dd at 3.71, J = 7.1, 2.4 Hz, 4H), 3.32 (t, J = 7.1 Hz, 1H), 2.42 (t, J = 2.5 Hz, 1H), 1.93 (ddd, J = 11.9, 4.0, 2.4 Hz, 1H), 1.76 (td, J = 11.9, 9.5 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.8, 79.2, 76.0, 74.5, 69.6, 68.2, 61.7, 55.1, 35.4, 26.1, 25.8, 18.4, 18.2, -4.4(2), -5.3(2); IR (neat) 3497 (br), 2955, 2930, 2885, 2857, 2360, 2120, 1472, 1254, 1099, 1027, 827, 777 cm^{-1}; EIMS *m/z* (%) 73 (83), 117 (100), 185 (36), 317 (42); HRESIMS *m/z* exact mass calcd for $C_{21}H_{42}O_5Si_2Na^+$ (MNa^+) 453.2468, found 453.2466.

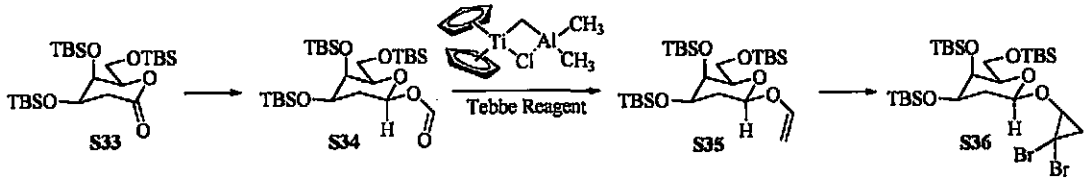
Propargyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside **S32**



To a solution of propargyl 2-deoxy-3,6-di-*O*-*t*-butydimethylsilyl-β-D-galactopyranoside **S31** (127 mg, 0.295 mmol) and pyridine (50 μL, 0.618 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added TBSOTf (100 μL, 0.435 mmol) dropwise. The solution was stirred at 0 °C for 35 min and was diluted with 2 mL of CH_2Cl_2 and 4 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with 2 mL of CH_2Cl_2 (4x). The combined organic layers were washed with 3 mL of brine and were dried over $MgSO_4$ then were concentrated. Purification *via* flash column chromatography on silica gel (50% CH_2Cl_2 in hexanes) provided title compound **S32** (127 mg, 0.233 mmol 79% yield); R_f = 0.21 (50% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (dd, J = 9.7, 2.0 Hz, 1H), 4.57 (dd, J = 15.7,

1.9 Hz, 1H), 4.31 (dd, J = 15.7, 1.9 Hz, 1H), 3.79-3.62 (m, 4H), 3.27 (t, J = 6.5 Hz, 1H), 2.41 (t, J = 1.9 Hz, 1H), 2.10 (dd, J = 12.0, 9.7 Hz, 1H), 1.71 (br d, J = 12.0 Hz, 1H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.9, 79.4, 77.4(2), 71.3, 69.0, 62.2, 55.0, 35.0, 26.2, 26.1, 25.8, 18.5(2), 18.1, -4.0, -4.4, -4.7, -4.9, -5.3(2); IR (neat) 3313, 2956, 2857, 2119, 1472, 1390, 1255, 1173, 1104, 1033, 836, 777 cm^{-1}; EIMS *m/z* (%) 73 (100), 147 (64), 313 (48), 355 (28); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2759.

(2-((*t*-Butyldimethylsilyloxy)methyl)-6-(2,2-dibromocyclopropoxy)-tetrahydro-2*H*-pyran-3,4-diyl)bis(oxy)bis(*t*-butyldimethylsilane) **S36**



To a stirred solution of ketone **S33** (1.00 g, 1.98 mmol) in 30 mL of CH_2Cl_2 at -78 °C was added DIBALH (1.8 mL, 1.21 M in toluene, 2.18 mmol) dropwise. The reaction mixture was stirred for 2 h at -78 °C then was treated with pyridine (1.3 mL, 16.1 mmol) followed by a solution of DMAP (270 mg, 2.21 mmol) and freshly prepared formic acetic anhydride (2.09 g, 23.7 mmol) in 20 mL of CH_2Cl_2 that had been allowed to dry over 4 Å MS.[xv] The reaction mixture was allowed to slowly warm to -20 °C over 2.5 h and was treated with 10 mL of saturated NH_4Cl and 10 mL of saturated Rochelle's salt. The aqueous layer was separated and extracted with 20 mL of CH_2Cl_2 (3x). The combined organic layers were washed with 20 mL of KH_2PO_4 followed by brine then were dried over $MgSO_4$ and were concentrated to

[xv] Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191-198.

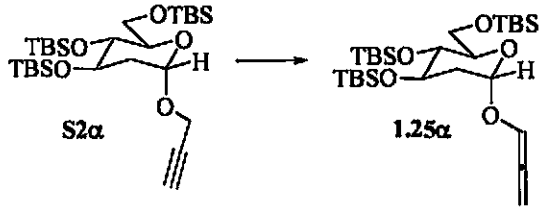
provide 1.05 g (1.97 mmol, 100% yield) of formic ester **S34**; R_f = 0.21 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 5.76 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.84 (s, 1H), 3.80-3.60 (m, 3H), 3.40 (t, *J* = 6.4 Hz, 1H), 2.10 (q, *J* = 10.0 Hz, 1H), 1.75 (dm, *J* = 10.0 Hz, 1H), 0.91 (s, 18H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H), 0.05 (s, 6H). To a stirred solution of the formic ester (1.00 g, 1.87 mmol) in 20 mL of THF and 4 mL of pyridine at -78 °C was added Tebbe reagent (12.5 mL, 0.24 M in toluene, 3.00 mmol).[xvi] The reaction mixture was stirred for 15 min at -78 °C and was slowly warmed to rt. After 16 h at rt, the reaction mixture was cooled to 0 °C and was treated with 15% aqueous solution of KOH dropwise. After the evolution of gas had ceased, the resulting brownish-green material was filtered through a layer of sand. The solids were rinsed with 10 mL CH_2Cl_2 (3x) and the filtrate was washed with 10 mL of 1 N HCl (2x) followed by 10 mL of saturated $NaHCO_3$ then brine. The material was then dried over $MgSO_4$, was concentrated and was purified *via* flash column chromatography on silica gel (10% to 25% CH_2Cl_2 in hexanes) to provide 571 mg (1.07 mmol, 57% yield) of vinyl ether **S35**; R_f = 0.31 (2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 6.54 (dd, *J* = 13.8, 6.3 Hz, 1H), 4.67 (dd, *J* = 13.8, 1.2 Hz, 1H), 4.52 (dd, *J* = 9.6, 2.1 Hz, 1H), 4.14 (dd, *J* = 6.3, 1.2 Hz, 1H), 3.85 (d, *J* = 1.0 Hz, 1H), 3.83 (br s, 1H), 3.80 (br s, 1H), 3.53 (ddd, *J* = 12.0, 3.9, 2.1 Hz, 1H), 3.23 (t, *J* = 3.9 Hz, 1H), 2.36 (td, *J* = 12.0, 9.6 Hz, 1H), 1.78 (dt, *J* = 12.0, 2.1 Hz, 1H), 1.02 (s, 9H), 0.99 (s, 9H), 0.91 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H), 0.09 (s, 6H), 0.02 (s, 3H), 0.001 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 99.1, 91.5, 76.9, 71.8, 69.5, 62.8, 35.1, 26.3(2), 26.1, 18.8, 18.7, 18.4, -3.5, -4.4, -4.6, -5.1, -5.2. Vinyl ether **S35** was immediately converted to dibromocyclopropane **S36** according to the procedure detailed below. To a solution of vinyl ether **S35** (660 mg,

[xvi] Yuan, J.; Lindner, K.; Frauenrath, H. *J. Org. Chem.* **2006**, *71*, 5457-5467.

1.24 mmol) in 12 mL of CH_2Cl_2 at 0 °C was added powdered KOH (1.00 g, 17.8 mmol), Bu_4NHSO_4 (258 mg, 0.381 mmol) and $CHBr_3$ (1 mL, 11.4 mmol). The reaction mixture was removed from the ice bath and was allowed to warm to rt over 16 h. The reaction mixture was then poured through a filter of cotton and sand and the filtrate was washed with 10 mL of water. The layers were separated and the aqueous layer was extracted with 10 mL Et_2O (3x). The combined organic layers were washed with brine, were dried over $MgSO_4$, were concentrated and wree flushed through a plug of silica gel to provide 868 mg (1.23 mmol, 100% yield) of diasteromeric mixture of dibromocyclopropane **S36** as an orange-tinted oil; R_f = 0.31, 0.34 (2.5% EtOAc in hexanes); IR (neat) 2857, 1789, 1463, 1255, 1101, 1063, 836 cm^{-1}.

3.4. General Isomerization Procedure

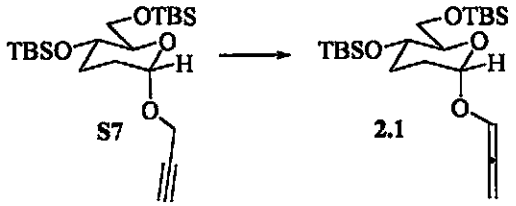
Allenyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **1.25α**



A mixture of propargyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **S2α** (500 mg, 0.917 mmol) in 500 μL of THF was heated to 60 °C and was treated with a spatula-tip of freshly sublimed *t*-BuOK. The mixture was stirred at 60 °C for 1 h then was cooled to rt and diluted with Et_2O. The solution was washed with 5 mL of saturated $NaHCO_3$ followed by 5 mL of brine and was dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (12% CH_2Cl_2 in hexanes, 1% NEt_3) provided 375

mg (0.688 mmol, 75% isolated yield) of title compound **1.25α** and 50 mg (0.092 mmol) of recovered alkyne **S2α**; R_f = 0.30 (20% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (t, *J* = 6.1 Hz, 1H), 5.39 (dd, *J* = 8.4, 6.1 Hz, 1H), 5.34 (dd, *J* = 8.4, 6.1 Hz, 1H), 5.09 (br s, 1H), 4.00 (ddd, *J* = 11.0, 7.6, 4.7 Hz, 1H), 3.82 (dd, *J* = 11.3, 2.6 Hz, 1H), 3.74 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.55 (ddd, *J* = 8.6, 4.7, 2.6 Hz, 1H), 3.48 (dd, *J* = 8.6, 7.6 Hz, 1H), 2.16 (ddd, *J* = 13.4, 4.7, 2.1 Hz, 1H), 1.64 (ddd, *J* = 13.4, 11.0, 3.5 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 18H), 0.10 (s, 6H), 0.09 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 117.5, 96.3, 89.1, 74.6, 72.4, 70.8, 62.4, 38.1, 26.3, 26.1, 25.9, 18.4, 18.3, 18.1, -3.1(2), -4.1, -4.7, -4.9, -5.3; IR (neat) 2930, 2857, 1957, 1427, 1253, 1104, 1013 cm^{-1}; EIMS *m/z* (%) 73 (100), 147 (50), 171 (16), 431 (32), 481 (100); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2776; $[\alpha]^{22}_D$ +61.1° (c = 0.002, CH_2Cl_2).

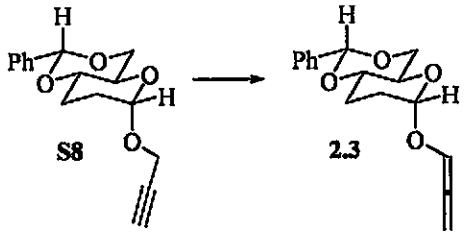
Allenyl 2,3-dideoxy-4,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **2.1**



75% yield; R_f = 0.35 (30% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (t, *J* = 6.0 Hz, 1H), 5.41 (dd, *J* = 8.7, 6.0 Hz, 1H), 5.35 (dd, *J* = 8.7, 6.0 Hz, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 3.80 (br d, *J* = 11.1 Hz, 1H), 3.73 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.57 (td, *J* = 9.0, 4.8 Hz, 1H), 3.53 (br dd, *J* = 9.0, 4.8 Hz, 1H), 1.95-1.70 (m, 4H), 0.90 (s, 18H), 0.30 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 117.3, 95.7, 88.7, 75.0, 66.2, 62.7, 28.7, 27.6, 25.9, 25.7, 18.4, 17.9, -4.2, -5.0(2), -5.4; IR (neat) 2930, 2857, 1957, 1462, 1253, 1100, 952, 836,

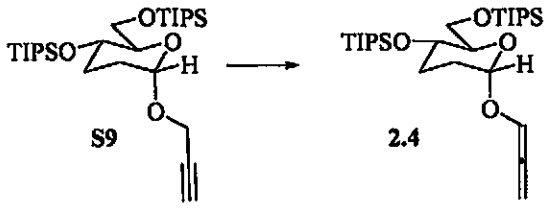
776 cm^{-1}; EIMS *m/z* (%) 73 (100), 75 (32), 143 (41); HREIMS *m/z* exact mass calcd for $C_{17}H_{33}O_4Si_2$ (M^+ - ($C(CH_3)_3$) 357.1917, found 357.1928; $[\alpha]^{22}_D$ +92.6° (c = 0.004, CH_2Cl_2).

(2*R*,4a*R*,6*S*,8a*S*)-2-Phenyl-6-(propa-1,2-dienyloxy)hexahydropyrano[3,2-*d*][1,3]dioxine **2.3**



54% yield; mp = 91-96 °C; R_f = 0.73 (30% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 7.45-7.39 (m, 2H), 7.34-7.25 (m, 3H), 6.56 (t, *J* = 6.0 Hz, 1H), 5.50 (s, 1H), 5.36 (dd, *J* = 8.9, 6.0 Hz, 1H), 5.30 (dd, *J* = 8.9, 6.0 Hz, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 4.14 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.84 (td, *J* = 10.0, 4.7 Hz, 1H), 3.63 (t, *J* = 10.0 Hz, 1H), 3.55 (td, *J* = 10.0, 4.7 Hz, 1H), 2.03-1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 137.5, 128.9, 128.2, 126.1, 117.3, 101.8, 95.7, 89.3, 77.9, 69.3, 65.4, 28.9, 23.7; IR (neat) 2930, 1957, 1448, 1096, 836 cm^{-1}; EIMS *m/z* (%) 87 (51), 107 (100), 113 (80); HREIMS *m/z* exact mass calcd for $C_{13}H_{15}O_3$ (M^+ - $OCHCCH_2$) 219.1021, found 219.1034; $[\alpha]^{22}_D$ +108.3° (c = 0.009, CH_2Cl_2).

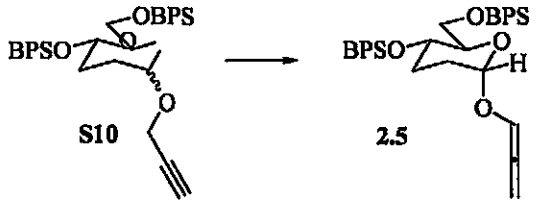
Allenyl 2,3-dideoxy-4,6-di-*O*-triisopropylsilyl-α-D-glucopyranoside **2.4**



67% yield; R_f = 0.51 (2.5% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (t, *J* = 6.0 Hz, 1H), 5.37 (dd, *J* = 8.7, 6.0 Hz, 1H), 5.32 (dd, *J* = 8.7, 6.0 Hz, 1H), 5.02 (d, *J* = 2.8

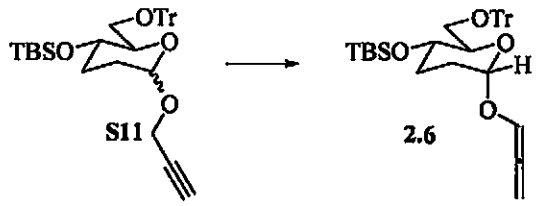
Hz, 1H), 4.01 (dd, J = 10.8, 2.1 Hz, 1H), 3.84 (dd, J = 10.8, 5.7 Hz, 1H), 3.75 (td, J = 8.8, 6.4 Hz, 1H), 3.61 (ddd, J = 8.8, 5.7, 2.1 Hz, 1H), 1.95-1.82 (m, 3H), 1.79-1.63 (m, 1H), 1.07 (s, 21H), 1.06 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 117.4, 95.5, 88.8, 75.6, 67.0, 63.3, 28.7, 28.0, 18.2, 18.0, 12.7, 12.0; IR (neat) 2891, 2867, 1957, 1463, 1127 cm^{-1}; EIMS *m/z* (%) 87 (25), 115 (49), 157 (69), 199 (43), 255 (30), 399 (100); HREIMS *m/z* exact mass calcd for $C_{24}H_{47}O_4Si_2$ (M^+ - $CH(CH_3)_2$) 455.3013, found 455.3026; $[\alpha]^{22}_D$ +86.0° (c = 0.005, CH_2Cl_2).

Allenyl 2,3-dideoxy-4,6-di-*O*-*t*-butyldiphenylsilyl-α-D-glucopyranoside **2.5**



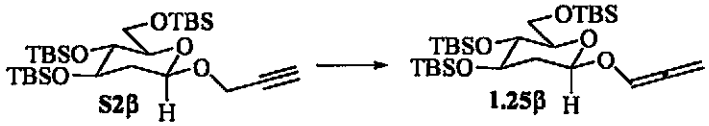
51% yield; R_f = 0.63 (30% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.42 (m, 8H), 7.30-7.08 (m, 12H), 6.55 (t, J = 6.0 Hz, 1H), 5.21 (dd, J = 8.6, 6.0 Hz, 1H), 5.16 (dd, J = 8.6, 6.0 Hz, 1H), 4.80 (d, J = 2.6 Hz, 1H), 3.86 (dd, J = 10.8, 1.6 Hz, 1H), 3.70 (ddd, J = 9.2, 6.0, 1.6 Hz, 1H), 3.59 (dd, J = 10.8, 5.8 Hz, 1H), 3.51 (td, J = 9.2, 4.2 Hz, 1H), 1.78-1.54 (m, 2H), 1.46-1.24 (m, 2H), 0.90 (s, 9H), 0.80 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 134.3, 134.0, 133.8, 133.4, 129.6, 129.5, 129.4(2), 127.6, 127.5(2), 127.4, 117.4, 95.5, 89.0, 75.1, 68.0, 63.9, 28.5, 27.6, 26.9, 26.8, 19.3, 19.2; IR (neat) 2931, 2857, 1952, 1427, 1111, 702 cm^{-1}; EIMS *m/z* (%) 131 (60), 135 (100), 199 (42), 267 (28), 319 (20), 549 (20); HREIMS *m/z* exact mass calcd for $C_{37}H_{41}O_4Si_2$ (M^+ - $C(CH_3)_3$) 605.2543, found 605.2563; $[\alpha]^{22}_D$ +58.0° (c = 0.001, CH_2Cl_2).

Allenyl 2,3-dideoxy-4-*O*-*t*-butyldimethylsilyl-6-*O*-triphenylmethyl-α-D-glucopyranoside **2.6**



65% yield; mp = 81-85 °C; R_f = 0.12 (2% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.47 (m, 6H), 7.35-7.20 (m, 9H), 6.84 (t, *J* = 6.0 Hz, 1H), 5.58 (dd, *J* = 8.8, 6.0 Hz, 1H), 5.33 (dd, *J* = 8.8, 6.0 Hz, 1H), 5.17 (s, 1H), 3.83 (dd, *J* = 9.5, 7.8 Hz, 1H), 3.33 (br td, *J* = 9.5, 4.9 Hz, 1H), 3.23 (br d, *J* = 9.5 Hz, 1H), 2.99 (dd, *J* = 9.5, 7.8 Hz, 1H), 2.00-1.65 (m, 4H), 1.49 (s, 9H), -0.17 (s, 3H), -0.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 144.3, 128.8, 127.7, 126.7, 117.4, 95.2, 89.1, 86.1, 73.9, 67.2, 64.0, 28.7, 28.1, 25.6, 17.7, -4.2, -5.1; IR (neat) 2925, 1449, 1382, 1171, 1052, 943, 746 cm^{-1}; EIMS *m/z* (%) 231 (79), 236 (8), 243 (100), 250 (4); HRESIMS *m/z* exact mass calcd for $C_{34}H_{42}O_4SiNa^+$ (MNa^+) 565.2742, found 565.2753; $[\alpha]^{22}_D$+11.0° (c = 0.007, CH_2Cl_2).

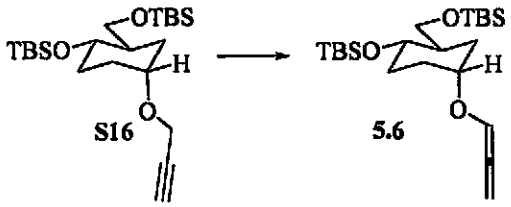
Allenyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-β-D-glucopyranoside **1.25β**



55% yield; R_f = 0.30 (20% CH_2Cl_2 in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (t, *J* = 6.1 Hz, 1H), 5.39 (dd, *J* = 8.6, 6.1 Hz, 1H), 5.31 (dd, *J* = 8.6, 6.1 Hz, 1H), 4.74 (dd, *J* = 9.1, 2.3 Hz, 1H), 3.90 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.74 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.70 (ddd, *J* = 9.1, 7.9, 4.7 Hz, 1H), 3.45 (t, *J* = 7.9 Hz, 1H), 3.20 (ddd, *J* = 7.9, 5.1, 3.2 Hz, 1H), 2.21 (ddd, *J* = 12.7, 4.7, 2.3 Hz, 1H), 1.66 (dt, *J* = 12.7, 9.1 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s,

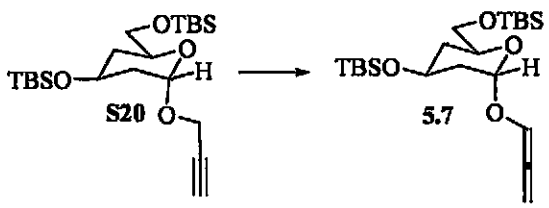
9H), 0.09 (s, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 118.7, 97.2, 89.5, 77.9, 72.6, 71.8, 62.7, 39.0, 26.3, 26.1, 25.9, 18.3, 18.4, 18.1, -3.2(2), -4.1, -4.6, -5.0, -5.4; IR (neat) 2931, 2857, 2362, 1470, 1390, 1254, 1200 cm^{-1}; EIMS *m/z* (%) 73 (100), 147 (45), 171 (32); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2769; $[\alpha]^{22}_D$ -2.9° (c = 0.001, CH_2Cl_2).

<u>*t*-Butyl((2-*t*-butyldimethylsilyloxy)-5-(allenyl)cyclohexyl)methoxy) dimethylsilane **5.6**</u>



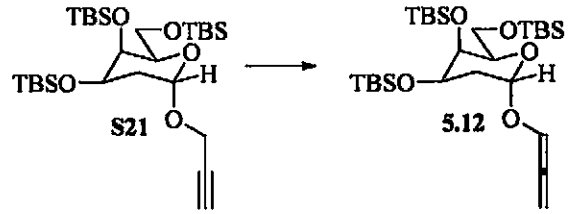
63% yield; R_f = 0.23 (5% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (t, *J* = 6.0 Hz, 1H), 5.36 (d, *J* = 6.0 Hz, 2H), 3.95-3.86 (m, 1H), 3.68 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.58 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.52 (dd, *J* = 8.5, 6.4 Hz, 1H), 2.40-1.88 (m, 2H), 1.85-1.71 (m, 1H), 1.70-1.60 (m, 2H), 1.47-1.30 (m, 2H), 0.87 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 119.8, 89.5, 72.6, 70.1, 63.6, 42.0, 31.2, 29.8, 28.0, 25.9, 25.8, 18.3, 18.0, -4.1, -4.9, -5.3, -5.5; IR (neat) 2929, 2361, 1557, 1087 cm^{-1}; EIMS *m/z* (%) 77 (29), 93 (13), 147 (100), 185 (27), 299 (42), 315 (16), 355 (16); HREIMS *m/z* exact mass calcd for $C_{18}H_{35}O_3Si_2$ (M^+ - $C(CH_3)_3$) 355.2125, found 355.2120.

Allenyl 2,4-dideoxy-3,6-di-*O*-*t*-butyldimethylsilyl-α-D-glucopyranoside **5.7**



75% yield; R_f = 0.46 (50% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (t, *J* = 6.2 Hz, 1H), 5.37 (dd, *J* = 8.8, 6.2 Hz, 1H), 5.44 (dd, *J* = 8.8, 6.2 Hz, 1H), 5.19 (d, *J* = 2.2 Hz, 1H), 4.12 (tt, *J* = 11.7, 4.6 Hz, 1H), 3.85-3.74 (m, 1H), 3.67 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.56 (dd, *J* = 10.5, 5.3 Hz, 1H), 2.06 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.90 (br d, *J* = 11.7 Hz, 1H), 1.55 (br t, *J* = 13.0 Hz, 1H), 1.31 (q, *J* = 11.7 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 117.5, 97.9, 88.9, 69.5, 66.1, 64.6, 39.2, 37.7, 25.9, 25.8, 18.3, 18.0, -4.6, -5.3; IR (neat) 2932, 2845, 2344, 1959, 1469, 1382, 1251, 1104, 1058, 837, 772 cm^{-1}; EIMS *m/z* (%) 73 (36), 117 (48), 145 (100), 231 (59); HREIMS *m/z* exact mass calcd for $C_{17}H_{33}O_4Si_2$ (M^+ - $C(CH_3)_3$) 357.1917, found 357.1928; $[\alpha]^{22}_D$ +55.3° (c = 0.017, CH_2Cl_2).

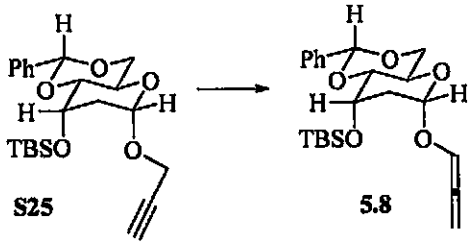
Allenyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-α-D-galactopyranoside **5.12**



75% yield; R_f = 0.38 (50% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (t, *J* = 6.1 Hz, 1H), 5.35 (dd, *J* = 8.9, 6.1 Hz, 1H), 5.33 (dd, *J* = 8.9, 6.1 Hz, 1H), 5.13 (br d, *J* = 3.3 Hz, 1H), 4.05 (br d, *J* = 12.5 Hz, 1H), 3.87 (br s, 1H), 3.70-3.58 (m, 3H), 2.14 (td, *J* = 12.5,

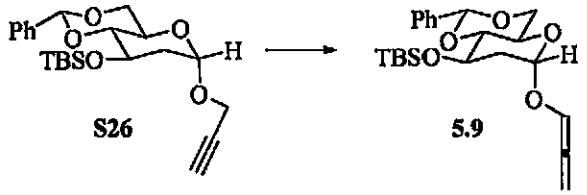
3.3 Hz, 1H), 1.72 (dd, J = 12.5, 4.4 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 117.5, 97.6, 88.7, 73.2, 69.8, 68.0, 62.1, 33.0, 26.2, 26.1, 25.8, 18.6, 18.5, 18.2, -3.9, -4.4, -4.7, -4.9, -5.3, -5.4; IR (neat) 2987, 2254, 1265, 1092, 1016 cm^{-1}; EIMS *m/z* (%) 73 (100), 147 (48), 245 (22), 301 (100); HREIMS *m/z* exact mass calcd for $C_{23}H_{47}O_5Si_3$ (M^+ - $C(CH_3)_3$) 487.2731, found 487.2757; $[\alpha]^{22}_D$ +38.5° (c = 0.001, CH_2Cl_2).

t-Butyldimethyl((2*R*,4a*R*,6*S*,8*S*,8a*R*)-2-phenyl-6-(propa-1,2-dienyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)silane **5.8**



73% yield; R_f = 0.38 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.46 (m, 2H), 7.37-7.36 (m, 3H), 6.60 (t, J = 6.2 Hz, 1H), 5.56 (s, 1H), 5.37 (dd, J = 8.8, 6.2 Hz, 1H), 5.35 (dd, J = 8.8, 6.2 Hz, 1H), 5.08 (d, J = 4.5 Hz, 1H), 4.42 (td, J = 10.0, 5.3 Hz, 1H), 4.27 (dd, J = 10.0, 5.3 Hz, 1H), 4.21 (q, J = 2.9 Hz, 1H), 3.68 (t, J = 10.0 Hz, 1H), 3.55 (dd, J = 10.0, 2.9 Hz, 1H), 2.18 (ddd, J = 14.8, 2.9, 0.9 Hz, 1H), 1.96 (ddd, J = 14.8, 4.5, 2.9 Hz, 1H), 0.92 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 137.8, 128.9, 128.1, 126.3, 118.1, 110.0, 101.9, 95.6, 89.1, 69.4, 64.8, 58.6, 36.7, 25.6, 18.1, -4.6, -4.1; IR (neat) 2928, 1955, 1105, 1015 cm^{-1}; EIMS *m/z* (%) 75 (88), 91 (32), 105 (26), 117 (89), 129 (98), 245 (100); HRESIMS *m/z* exact mass calcd for $C_{22}H_{32}O_5SiNa^+$ (MNa^+) 427.1916, found 427.1904; $[\alpha]^{22}_D$ +63.6° (c = 0.012, CH_2Cl_2).

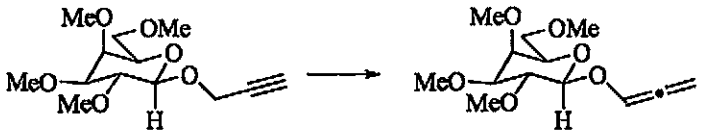
t-Butyldimethyl((2*R*,4a*R*,6*S*,8*R*,8a*R*)-2-phenyl-6-(propa-1,2-dienyloxy)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)silane **5.9**



S26 **5.9**

65% yield; R_f = 0.49 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.62 (d, *J* = 7.3 Hz, 2H), 7.25-7.06 (m, 3H), 6.47 (t, *J* = 6.0 Hz, 1H), 5.33 (s, 1H), 5.18 (dd, *J* = 8.9, 6.0 Hz, 1H), 5.10 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.90 (d, *J* = 3.5 Hz, 1H), 4.33 (ddd, *J* = 11.0, 9.6, 5.3 Hz, 1H), 4.15 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.00 (td, *J* = 9.6, 4.8 Hz, 1H), 3.50 (t, *J* = 9.6 Hz, 1H), 3.36 (t, *J* = 9.6 Hz, 1H), 2.08 (ddd, *J* = 13.6, 5.3, 1.0 Hz, 1H), 1.66 (ddd, *J* = 13.6, 11.0, 3.5 Hz, 1H), 0.95 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 201.8, 138.5, 128.9, 128.5, 128.2, 126.8, 102.1(2), 97.4(2), 89.3, 83.9, 69.1, 67.0, 64.3, 39.3, 26.0, 18.4, -4.2, -4.9; IR (neat) 2360, 1957, 1125, 1116 cm^{-1}; EIMS *m/z* (%) 75 (93), 91 (100), 129 (58), 185 (29), 291 (90); HREIMS *m/z* exact mass calcd for $C_{22}H_{32}O_5Si$ (M^+) 404.2019, found 404.2035; $[\alpha]^{22}_D$ +78.8° (c = 0.004, CH_2Cl_2).

Allenyl 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranoside **5.10**

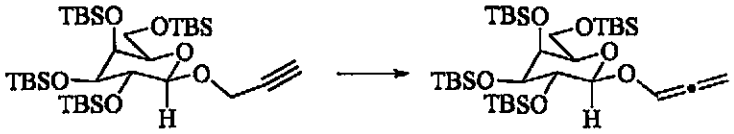


S28 **5.10**

100% yield; mp = 40-52 °C; R_f = 0.44 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (t, *J* = 6.1 Hz, 1H), 5.42 (dd, *J* = 8.8, 6.1 Hz, 1H), 5.38 (dd, *J* = 8.8, 6.1 Hz, 1H), 4.47 (d, *J* = 7.8 Hz, 1H), 3.62-3.40 (m, including s at 3.58, s at 3.55 and s at 3.52, 14H),

3.38 (s, 3H), 3.15 (dd, J = 9.7, 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 119.3, 101.4, 90.2, 83.8, 80.0, 74.5, 73.2, 70.4, 61.2, 60.8, 59.2, 58.3; IR (neat) 2931, 2826, 1963, 1457, 1194, 1014 cm^{-1}; EIMS *m/z* (%) 88 (57), 101 (100), 111 (62), 187 (82), 219 (100); HREIMS *m/z* exact mass calcd for $C_{10}H_{19}O_5$ (M^+ - $OCHCCH_2$) 219.1232, found 219.1216; $[\alpha]^{22}_D$ +2.6° (c = 0.004, CH_2Cl_2).

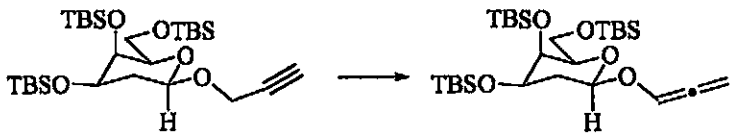
Allenyl 2,3,4,6-tetra-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside **5.11**



S29 **5.11**

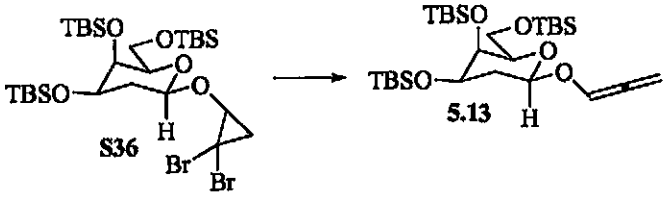
100% yield; R_f = 0.11 (10% CH_2Cl_2 in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, -50 °C) δ 6.61 (t, J = 6.0 Hz, 1H), 5.56 (dd, J = 8.5, 6.0 Hz, 1H), 5.40 (dd, J = 8.5, 6.0 Hz, 1H), 4.38 (d, J = 4.5 Hz, 1H), 3.98 (d, J = 0.9 Hz, 1H), 3.90 (dd, J = 5.7, 4.5 Hz, 1H), 3.64 (t, J = 5.7 Hz, 1H), 3.55 (dd, J = 5.7, 3.5 Hz, 1H), 3.44 (dd, J = 5.7, 0.9 Hz, 1H), 3.30 (dd, J = 5.7, 3.5 Hz, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.84 (s, 9H), 0.83 (s, 9H), 0.11 (s, 3H), 0.88 (s, 3H), 0.06 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.003 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$, -50 °C) δ 200.1, 120.0, 101.7, 90.8, 75.6, 74.8, 70.9, 70.5, 60.0, 26.6, 26.1, 25.9, 25.5, 18.9, 18.5, 18.1, 17.8, -2.8, -4.2, -4.3, -4.5(2), -4.6, -5.5, -5.5; IR (neat) 2930, 1963, 1472, 1522, 1102 cm^{-1}; HRESIMS *m/z* exact mass calcd for $C_{33}H_{70}O_6Si_4Na^+$ (MNa^+) 697.4145, found 697.4146.

Allenyl 2-deoxy-3,4,6-tri-*O*-*t*-butyldimethylsilyl-β-D-galactopyranoside **5.13**



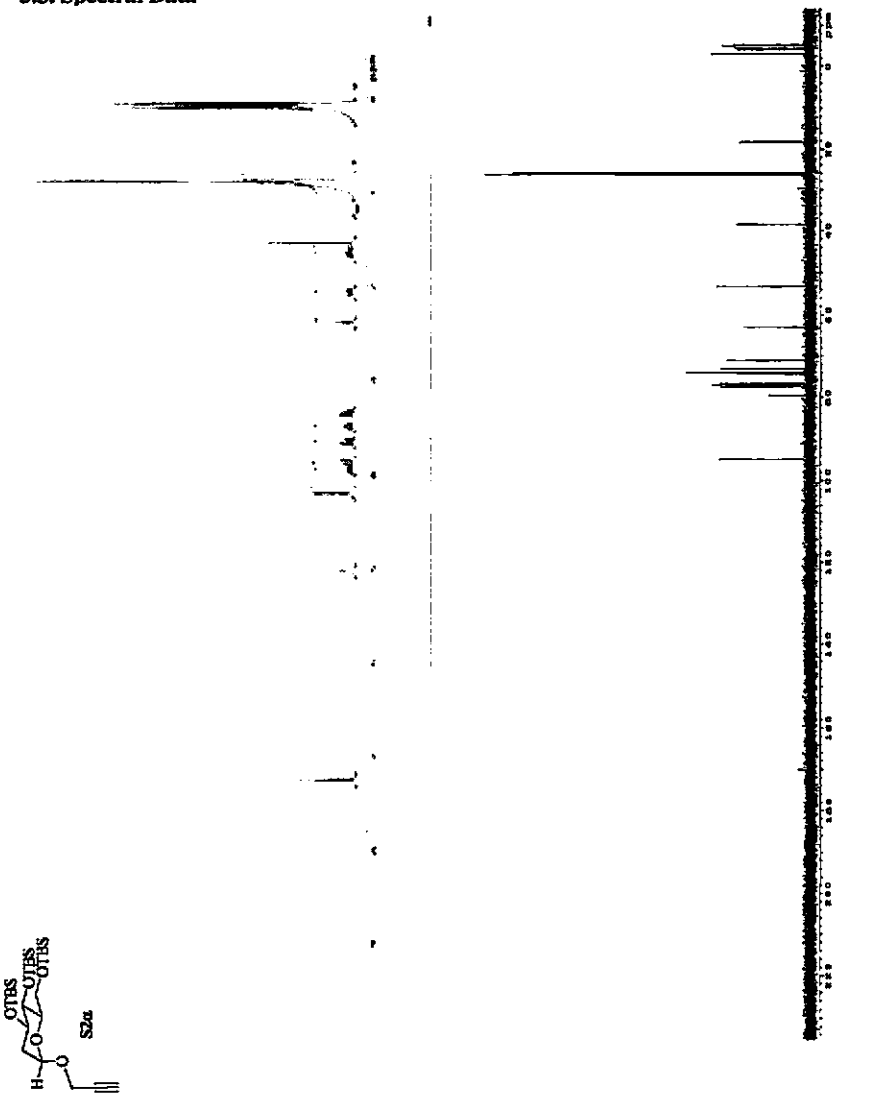
S32 **5.13**

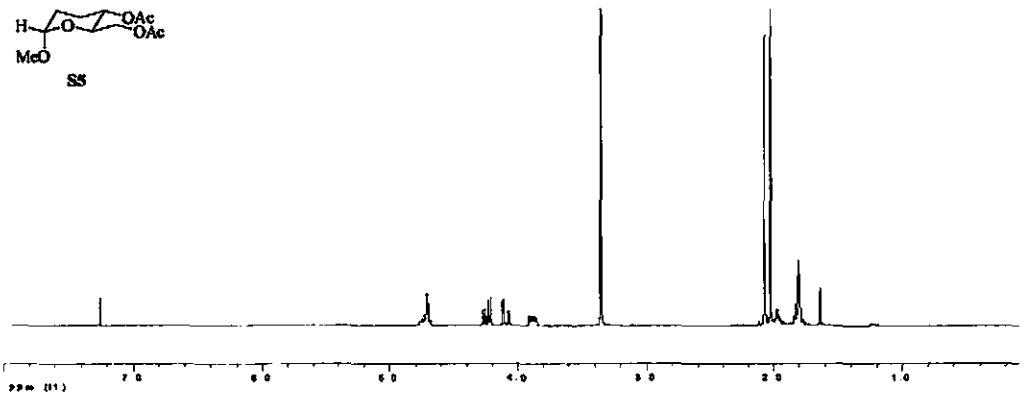
69% yield; R_f = 0.26 (50% CH_2Cl_2 in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.71 (t, *J* = 6.0 Hz, 1H), 5.42 (dd, *J* = 8.6, 6.0 Hz, 1H), 5.37 (dd, *J* = 8.6, 6.0 Hz, 1H), 4.67 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.79 (br s, 1H), 3.76 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.72-3.62 (m, including dd at 3.66, *J* = 10.0, 7.2 Hz, 2H), 3.26 (t, *J* = 7.2 Hz, 1H), 2.11 (q, *J* = 10.0 Hz, 1H), 1.79 (br d, *J* = 10.0 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 118.9, 110.6, 98.6, 89.8, 74.4, 68.7, 61.8, 34.6, 26.2, 26.1, 25.1, 18.6, 18.2, 15.5, -4.0, -4.3, -4.7, -4.8, -5.5(2); IR (neat) 2955, 2930, 2885, 2857, 2360, 1905, 1472, 1254, 1102, 1058, 835, 777 cm^{-1}; EIMS *m/z* (%) 73 (100), 147 (71), 245 (100), 357 (82); HRESIMS *m/z* exact mass calcd for $C_{27}H_{57}O_5Si_3$ (MH^+) 545.3514, found 545.3516; $[\alpha]^{22}_D$ -0.5° (c = 0.022, CH_2Cl_2).



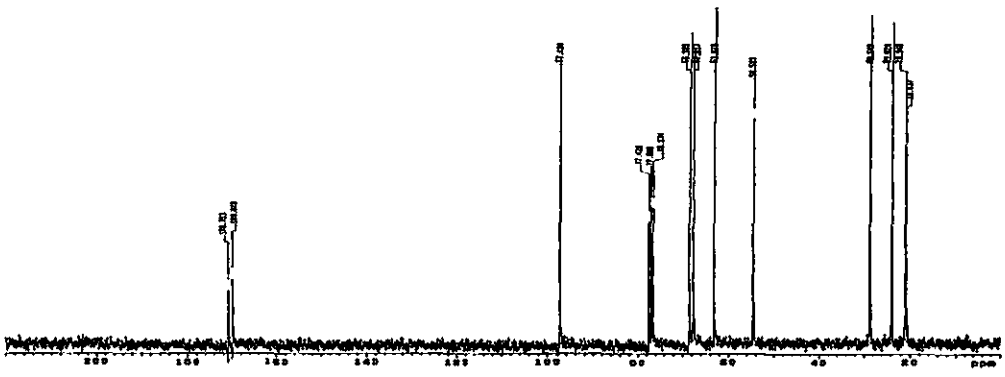
Dibromocyclopropane (868 mg, 1.23 mmol) in 20 mL Et_2O was cooled to -50 °C, treated with 1.6 mL MeLi (1.64 M, 2.62 mmol) dropwise and the reaction was slowly cooled to -20 °C over 1.5 h. The reaction was then quenched with slow addition of 10 mL of saturated NH_4Cl and the layers were separated. The aqueous layer was extracted with 5 mL Et_2O (3x) and the combined organic layers were washed with 5 mL brine and was dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography on silica gel (2% EtOAc in hexanes) provided 400 mg (0.734 mmol, 60% yield) of allene as a clear viscous oil.

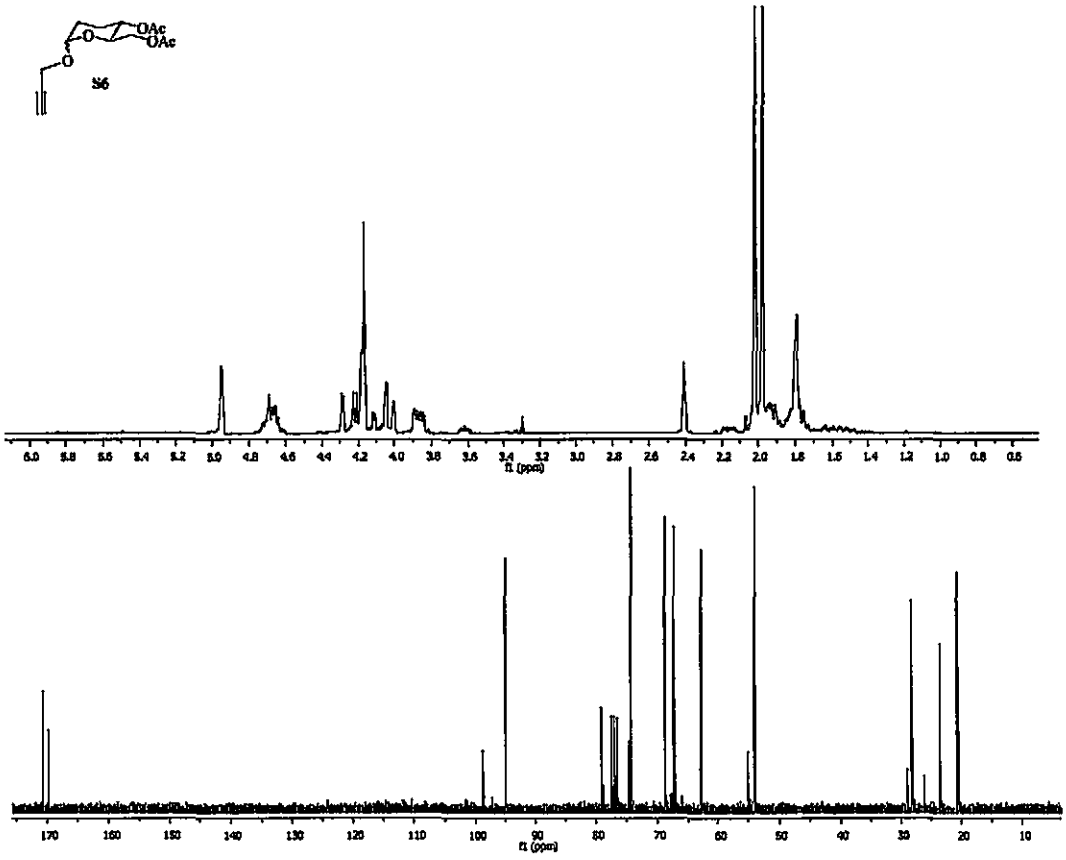
3.5. Spectral Data

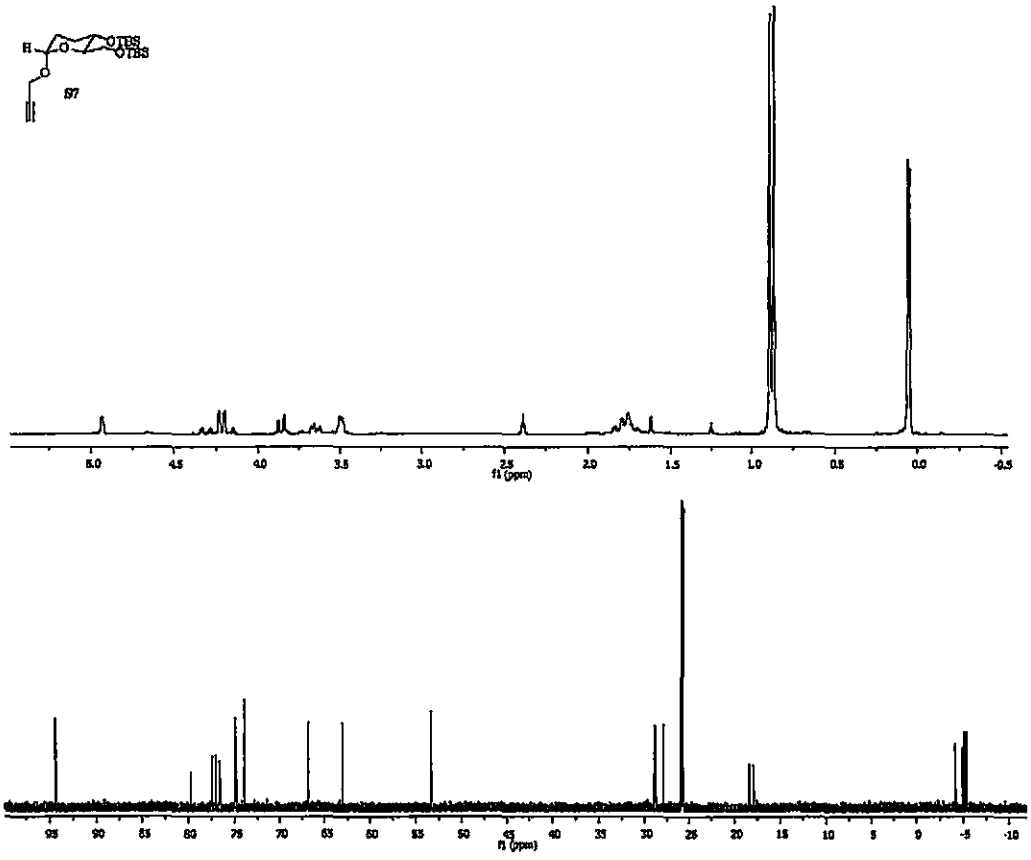


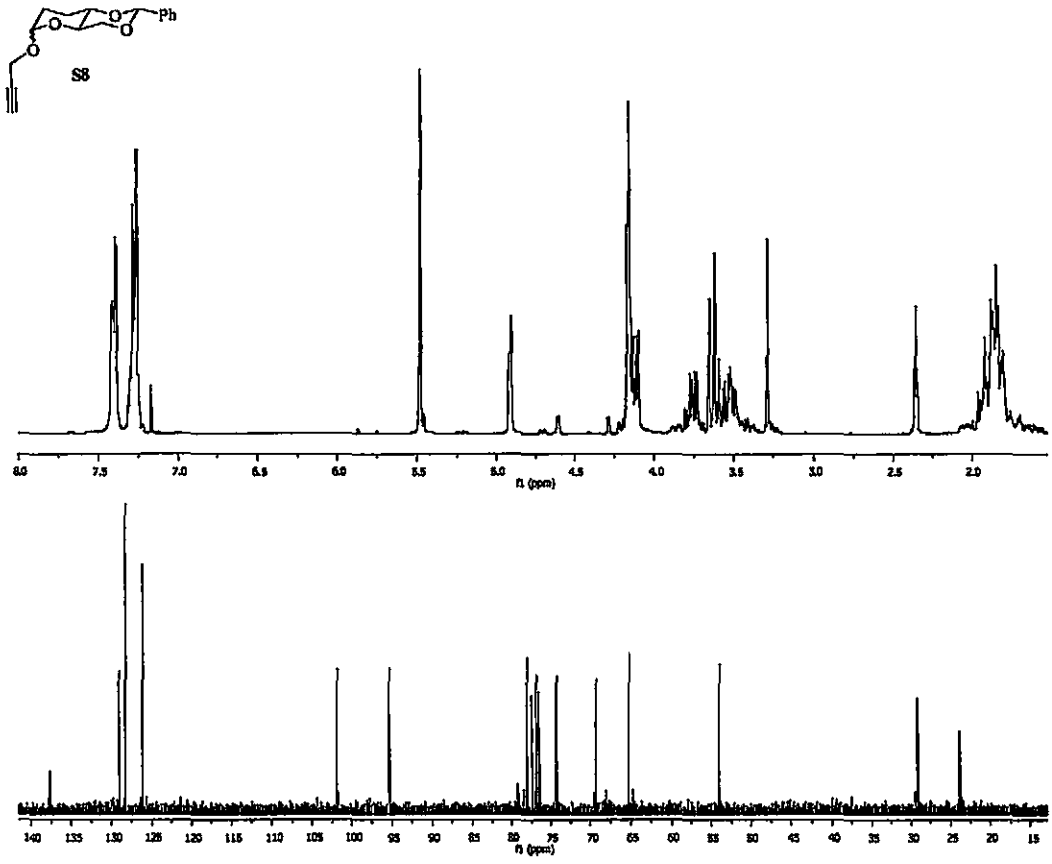


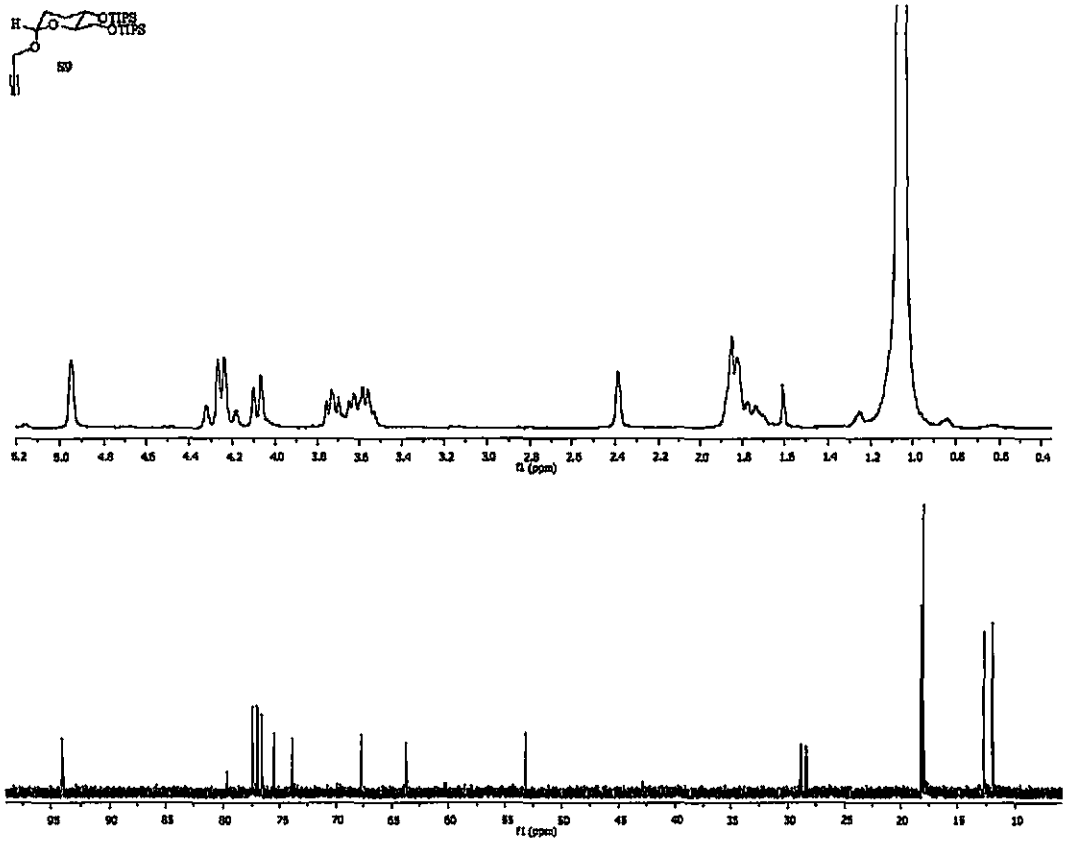
S5

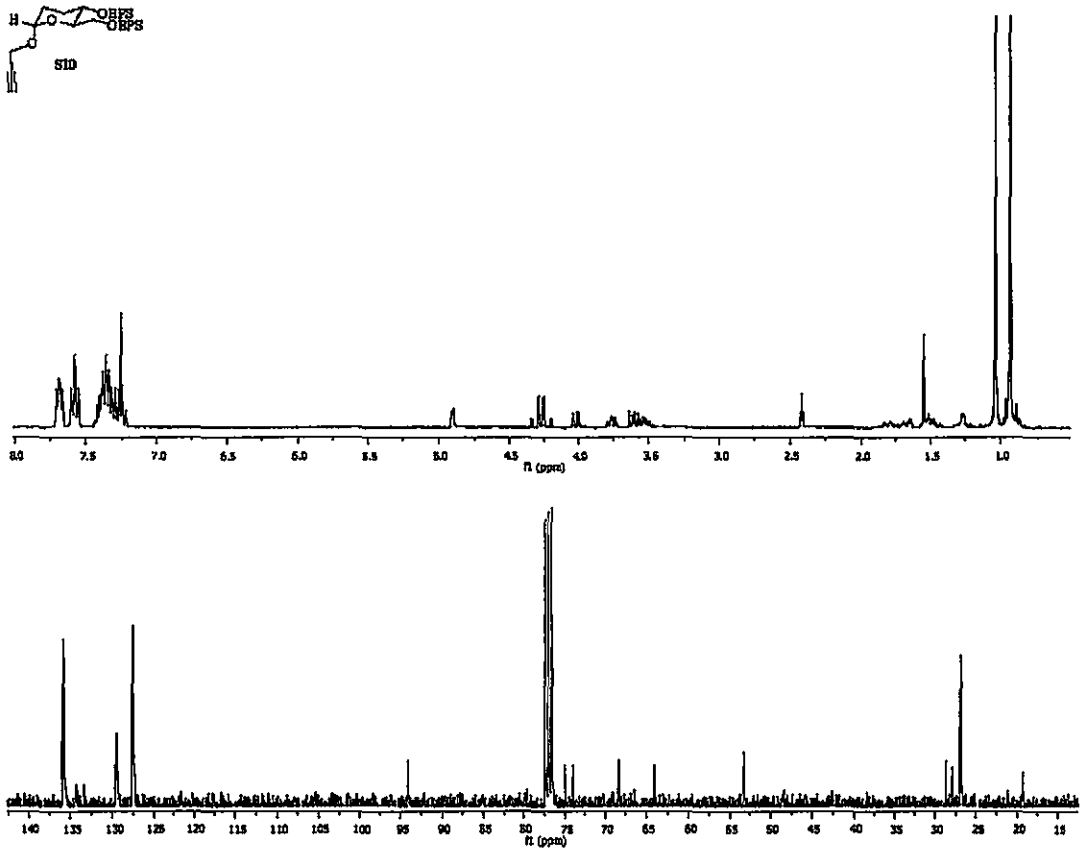


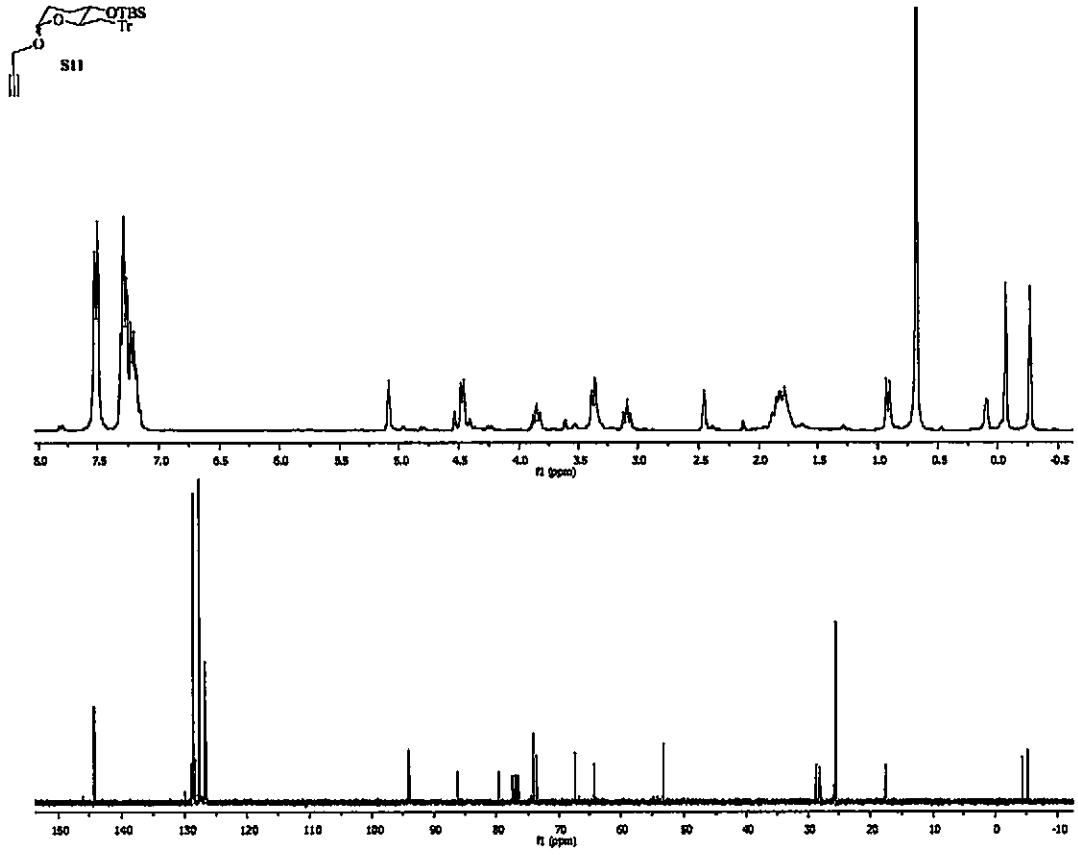

OAc
OAc
O
O
S6
f1 (ppm)
f1 (ppm)

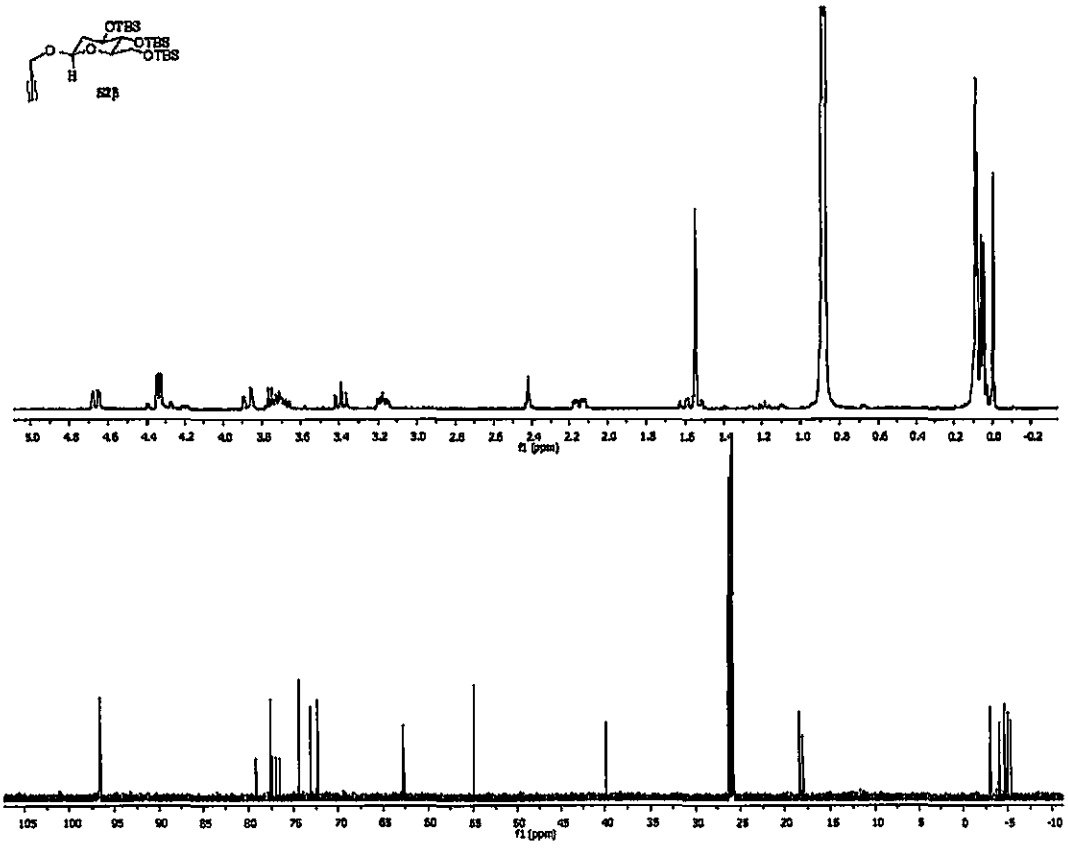

H
O
OTBS
OTBS
O
97
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)

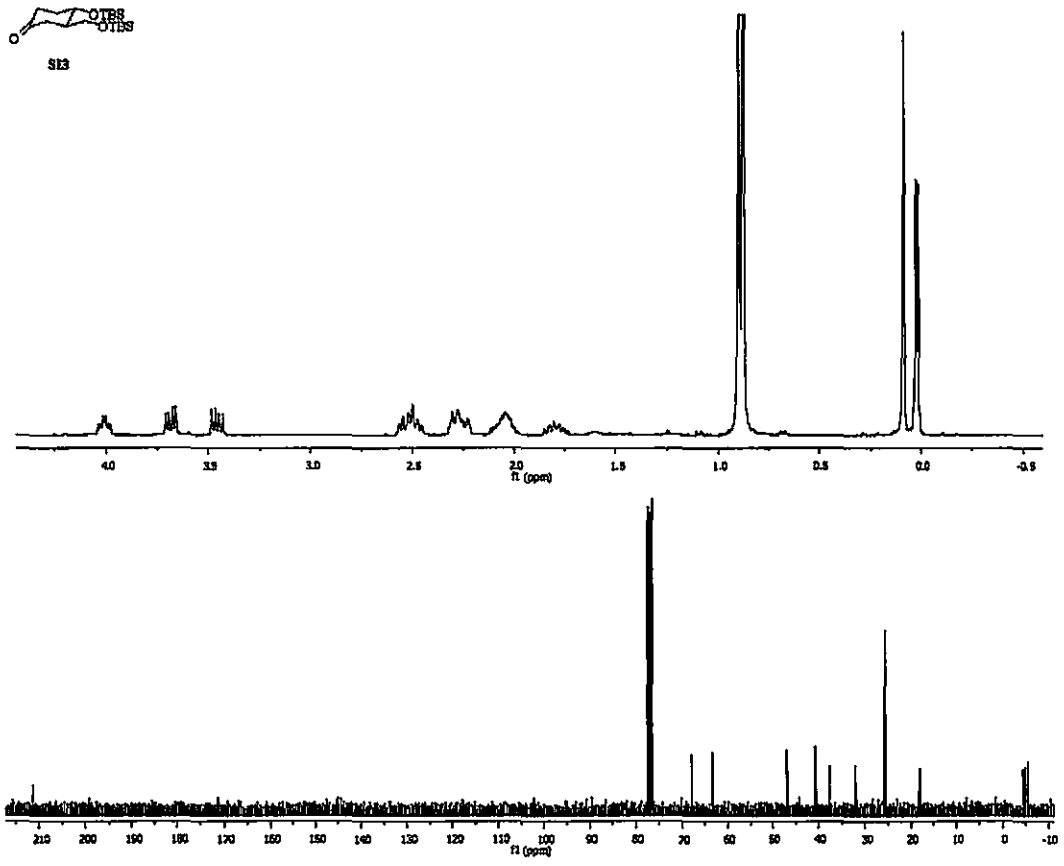

Ph
S8
f1 (ppm)
f1 (ppm)

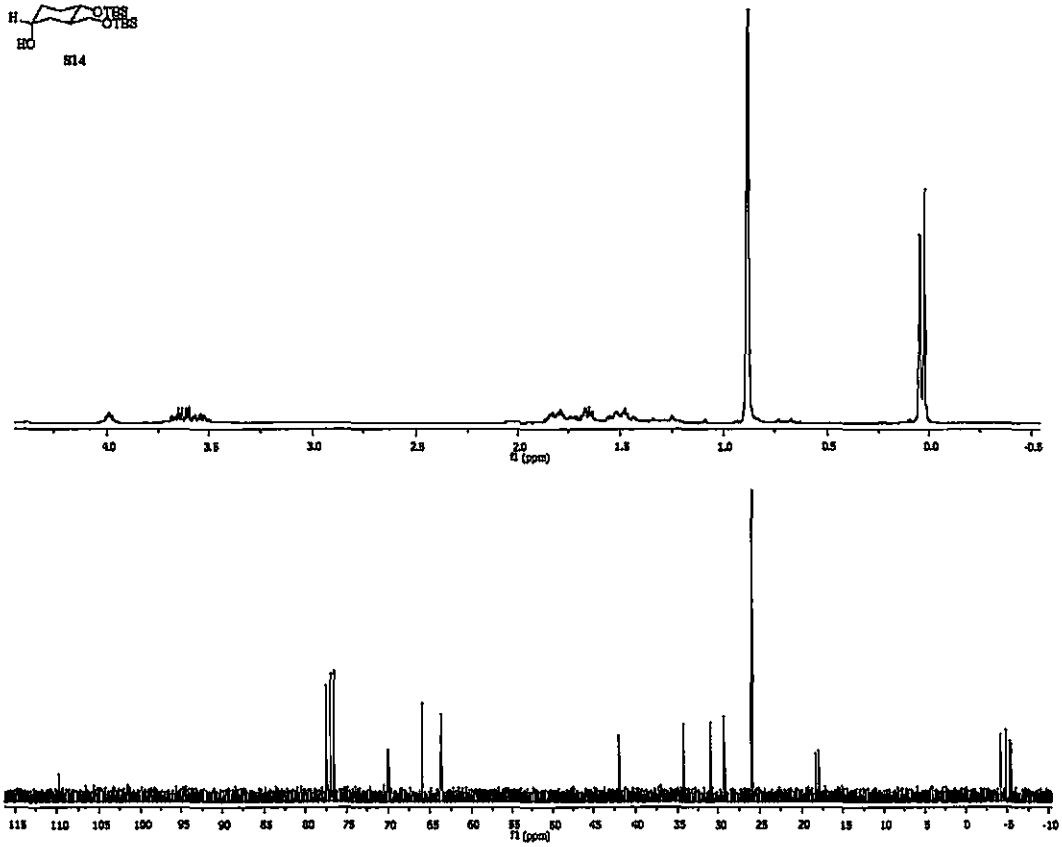

H
OTIPS
OTIPS
59
f1 (ppm)
f1 (ppm)

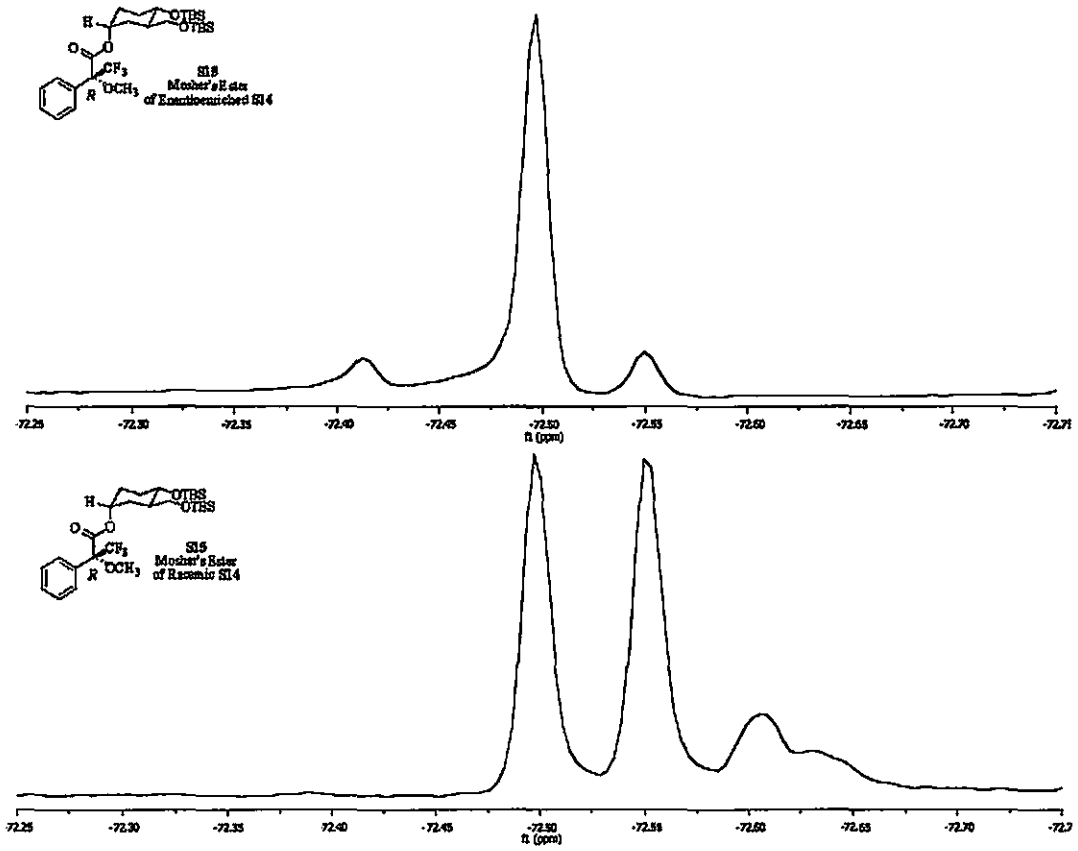

H
O
OHPS
OBPS
S1D
f1 (ppm)
f1 (ppm)

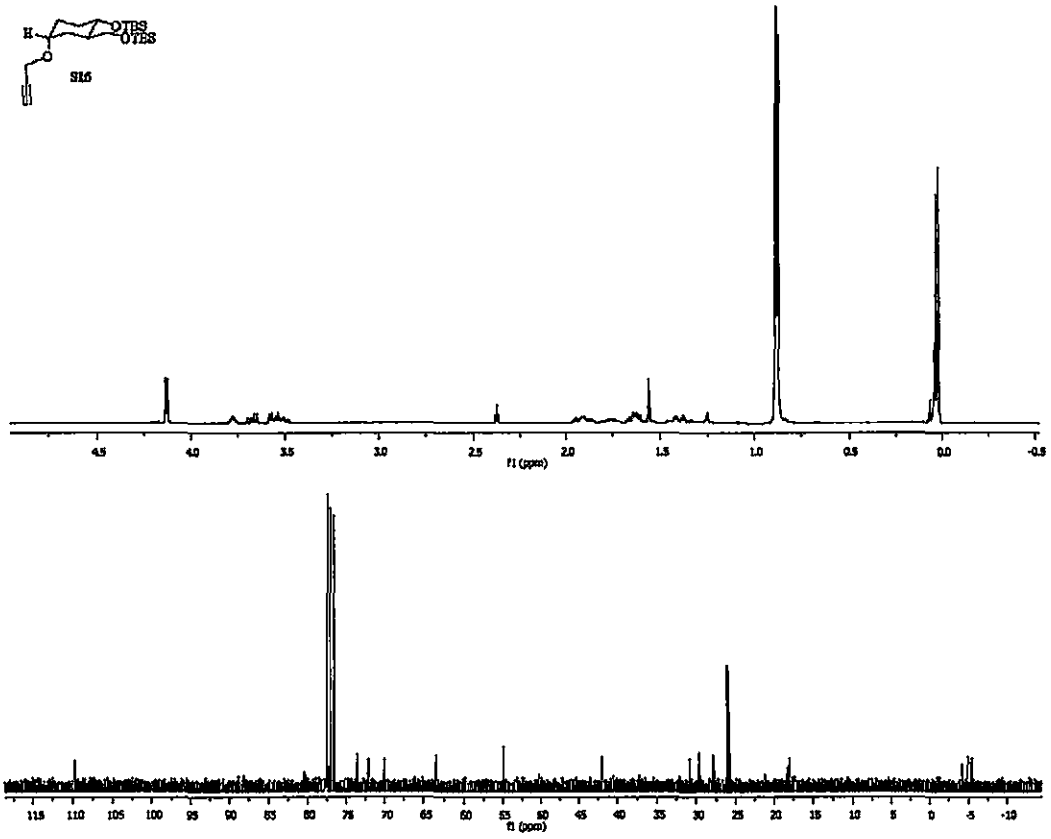

OTBS
Tr
O
O
S11
f1 (ppm)
f1 (ppm)

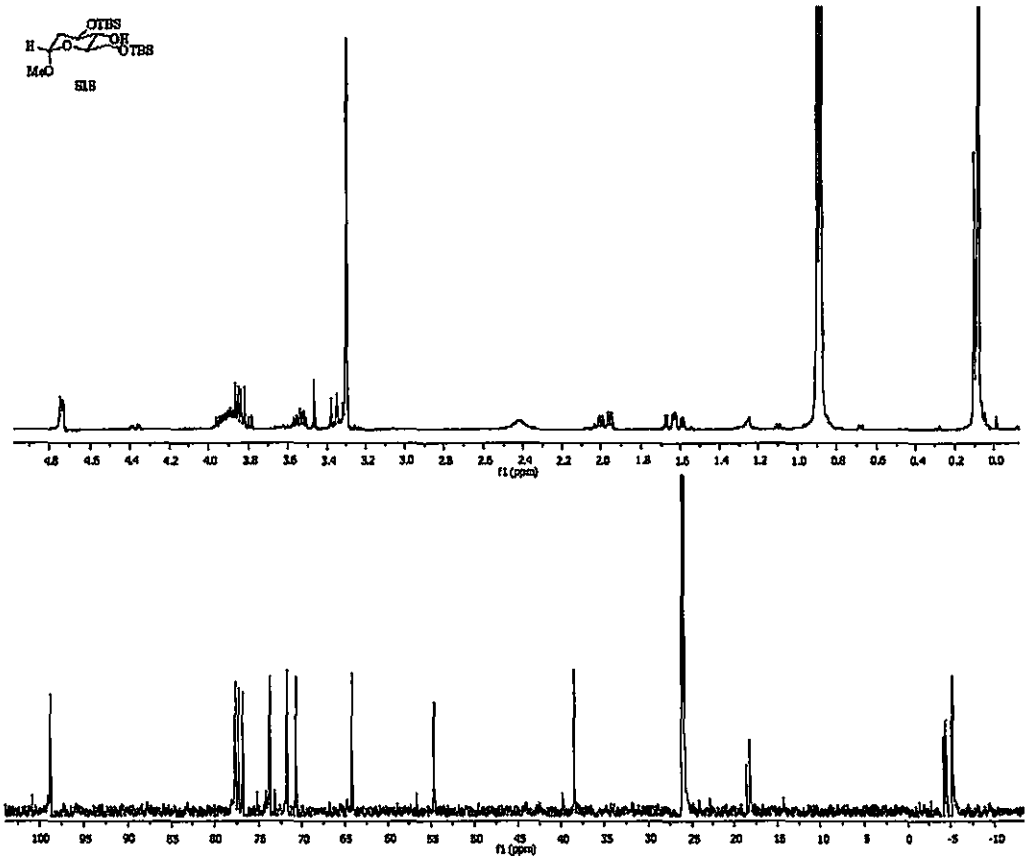

OTBS
OTBS
OTBS
H
82β
f1 (ppm)
f1 (ppm)

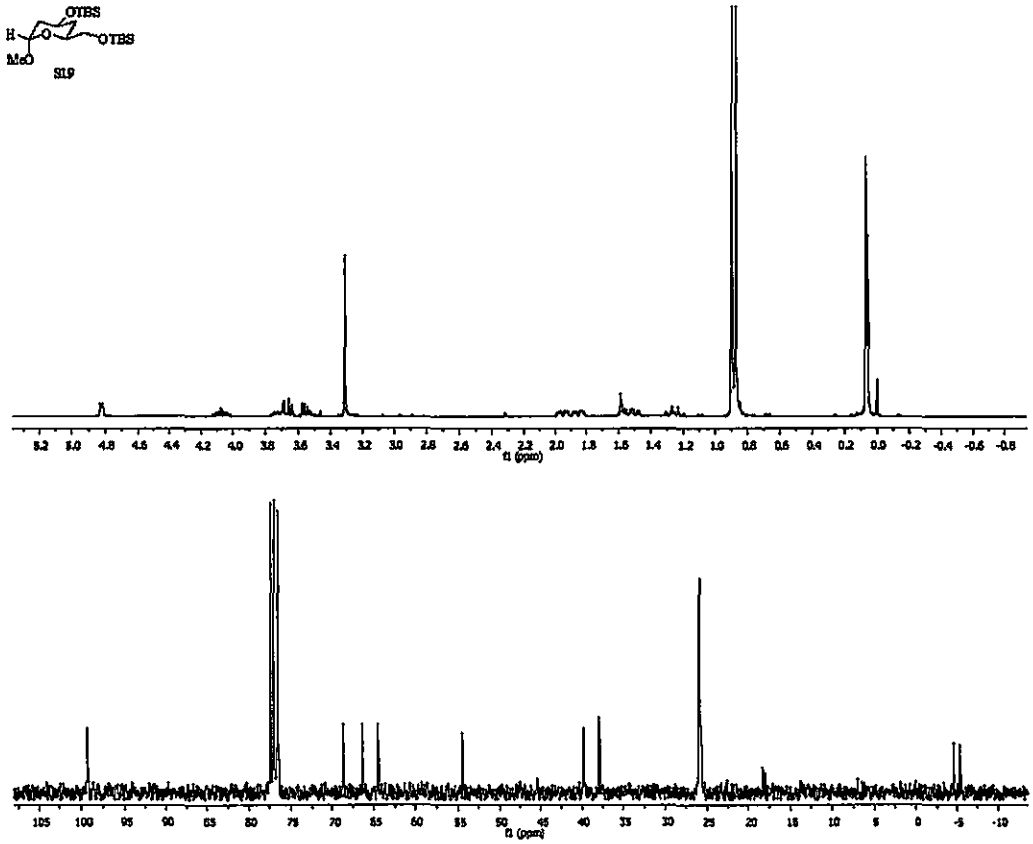

OTBS
OTBS
S13
f1 (ppm)
f1 (ppm)

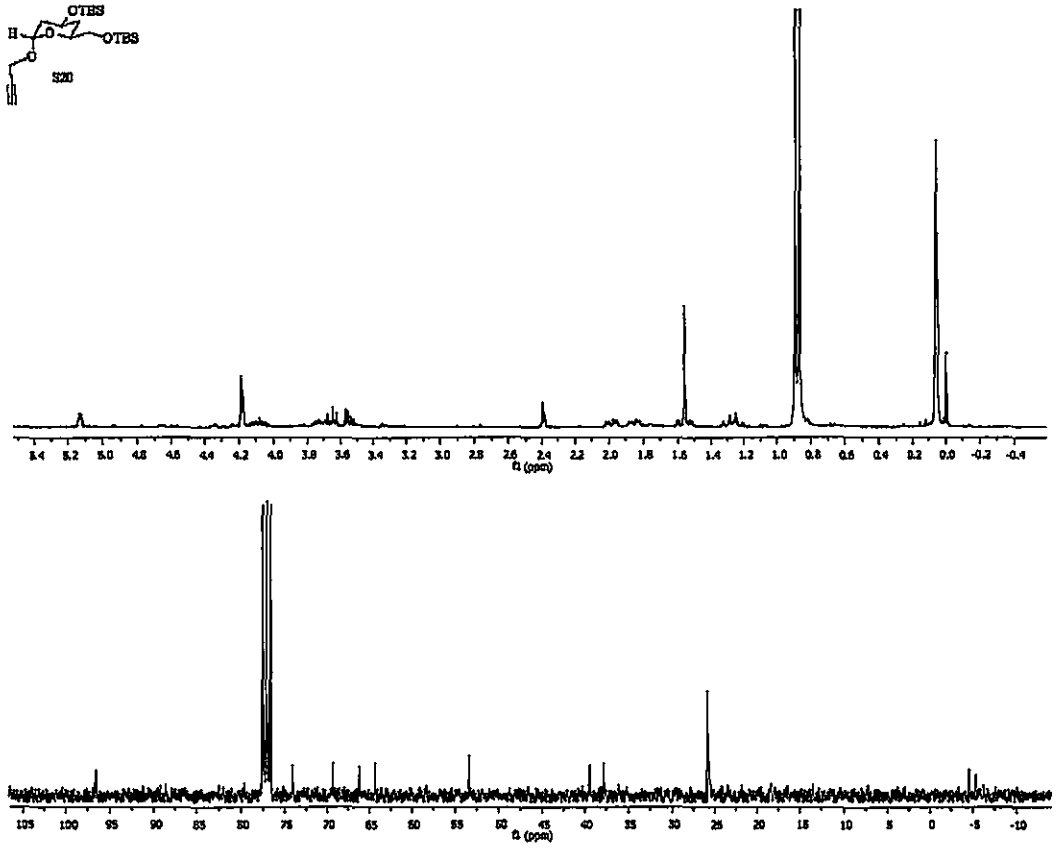

H
OTBS
OTBS
HO
SI14
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)

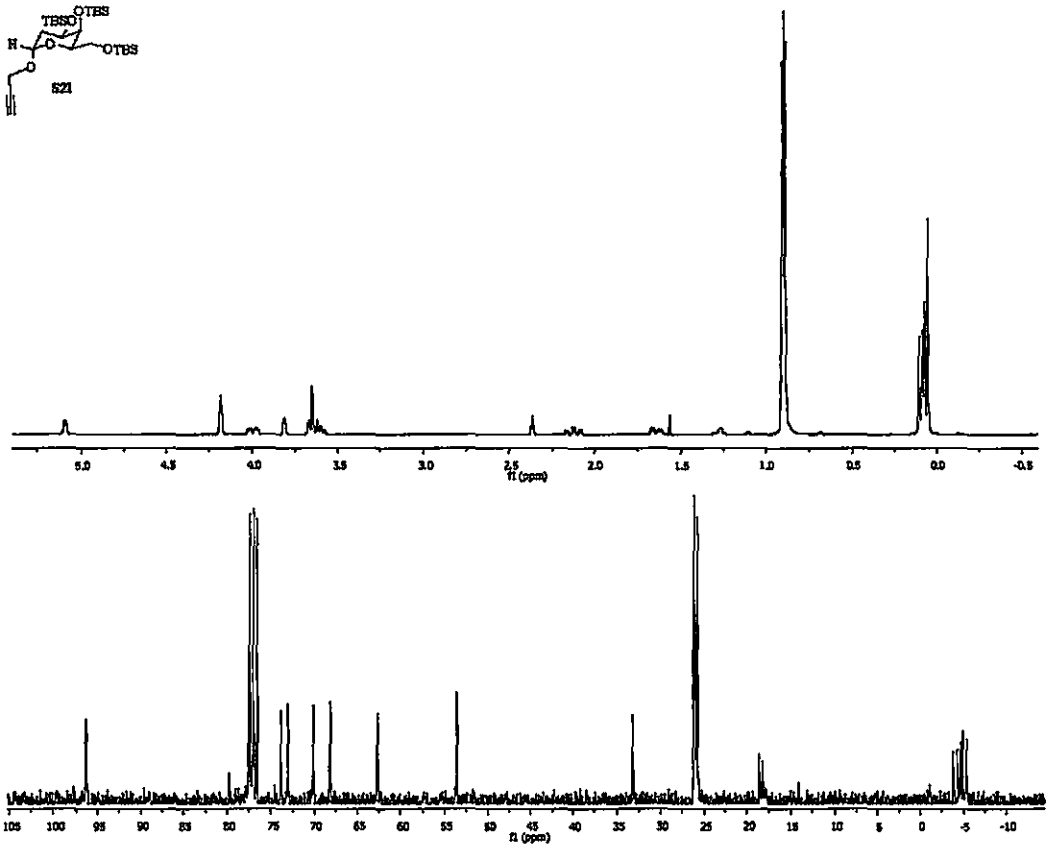

OTBS
OTBS
O
O
CF3
OCH3
R
SI8
Mosher's Ester
of Enantioenriched SI4
-72.25
-72.30
-72.35
-72.40
-72.45
-72.50
-72.55
-72.60
-72.65
-72.70
f1 (ppm)
OTBS
OTBS
O
O
CF3
OCH3
R
SI5
Mosher's Ester
of Racemic SI4
-72.25
-72.30
-72.35
-72.40
-72.45
-72.50
-72.55
-72.60
-72.65
-72.70
f1 (ppm)

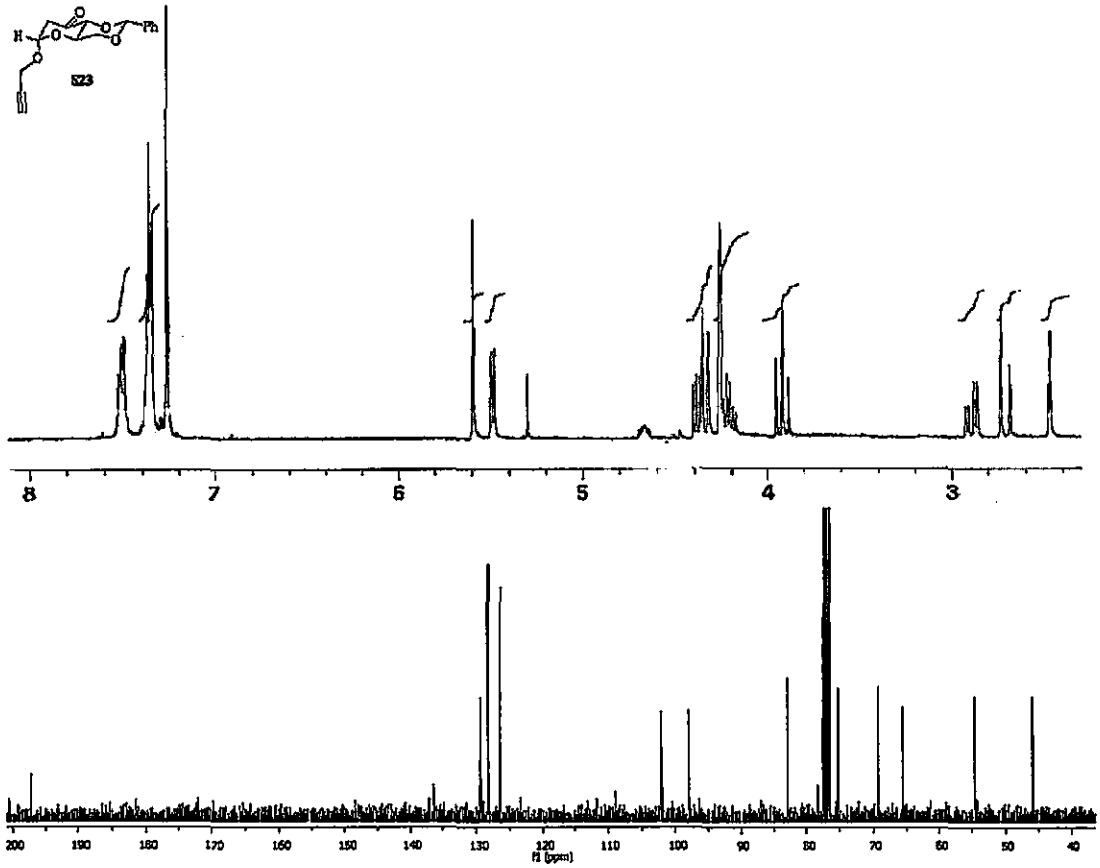

H
OTBS
OTES
SI15
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)

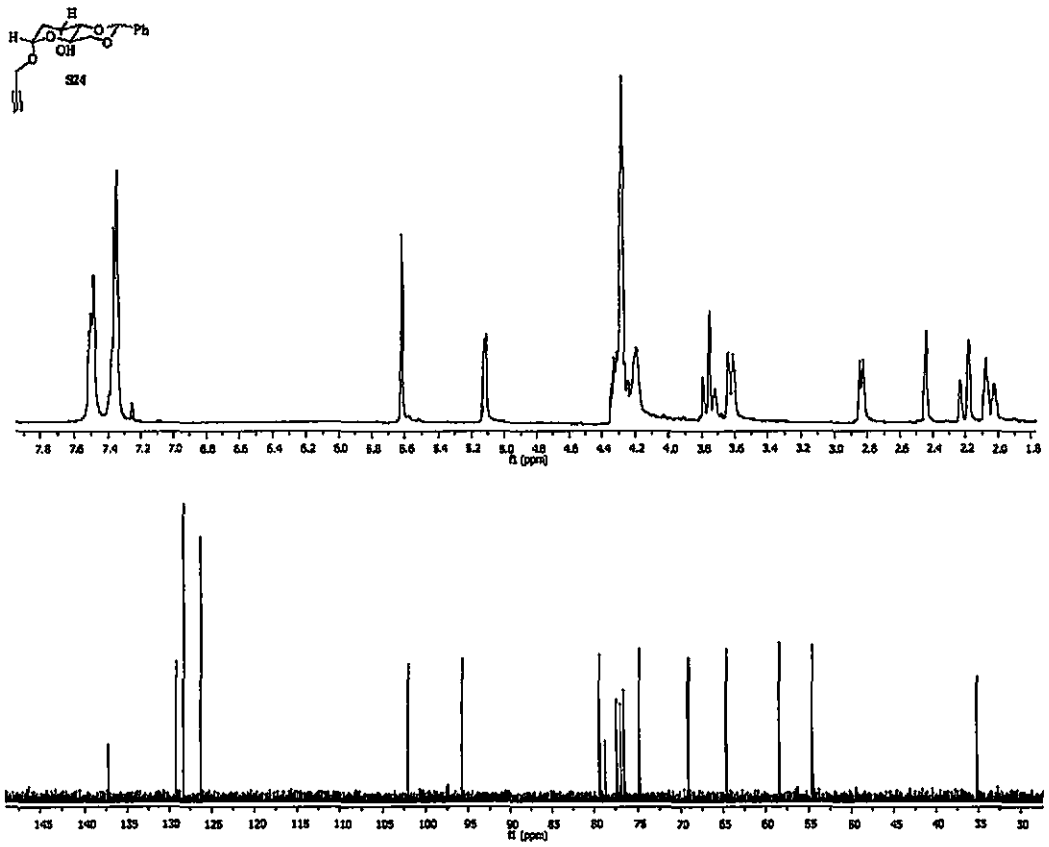

OTBS
H
O
OH
OTBS
MeO
SI8
f1 (ppm)
f1 (ppm)

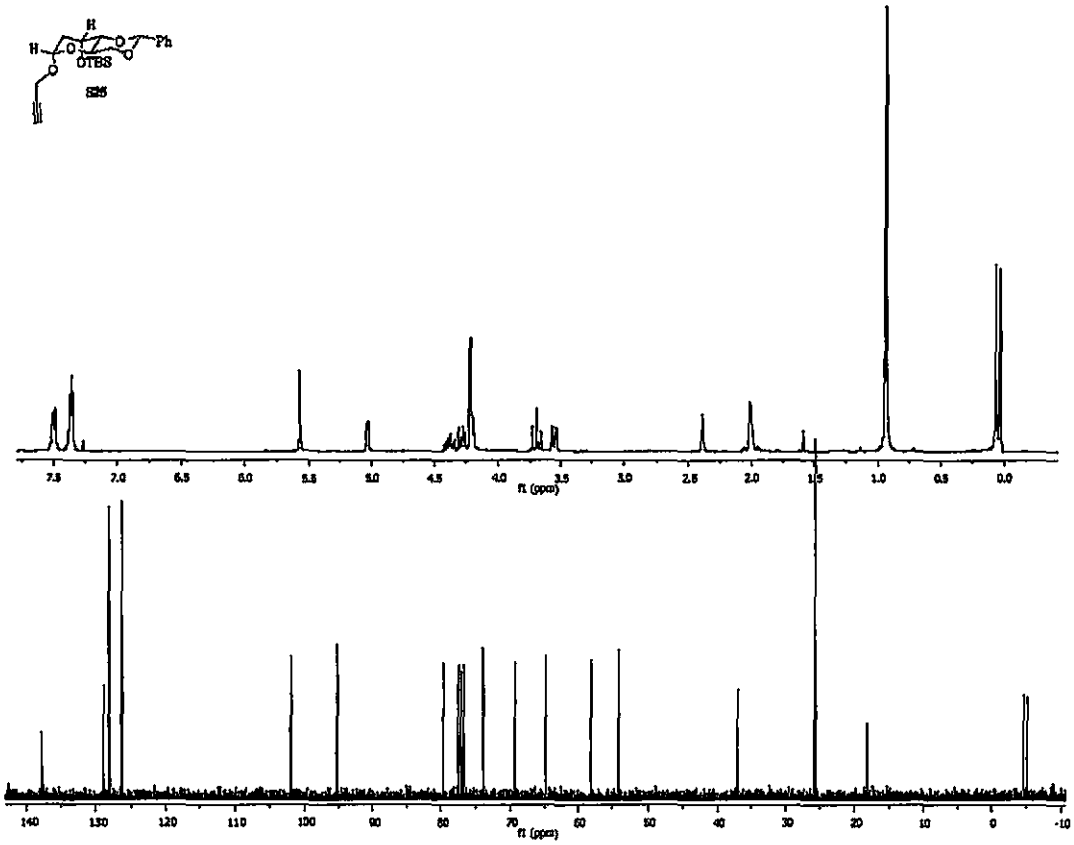

OTBS
H
O
OTBS
MeO
S19
f1 (ppm)

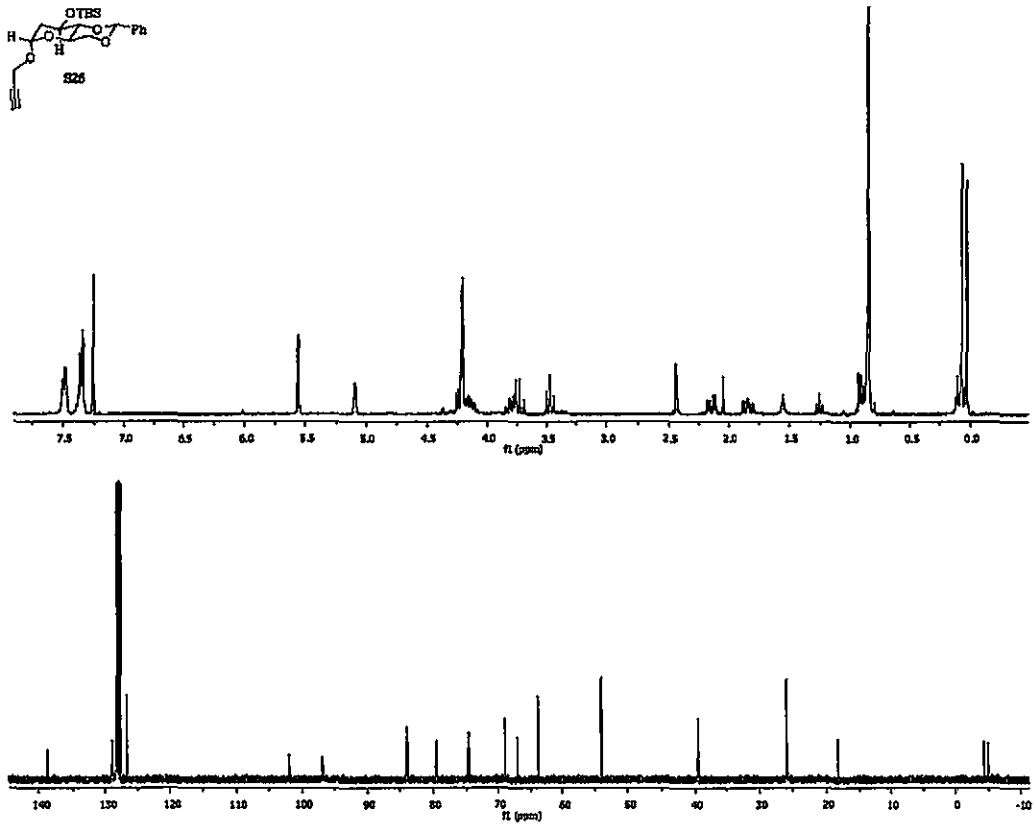

OTBS
H
O
OTBS
O
S20
f1 (ppm)
f1 (ppm)

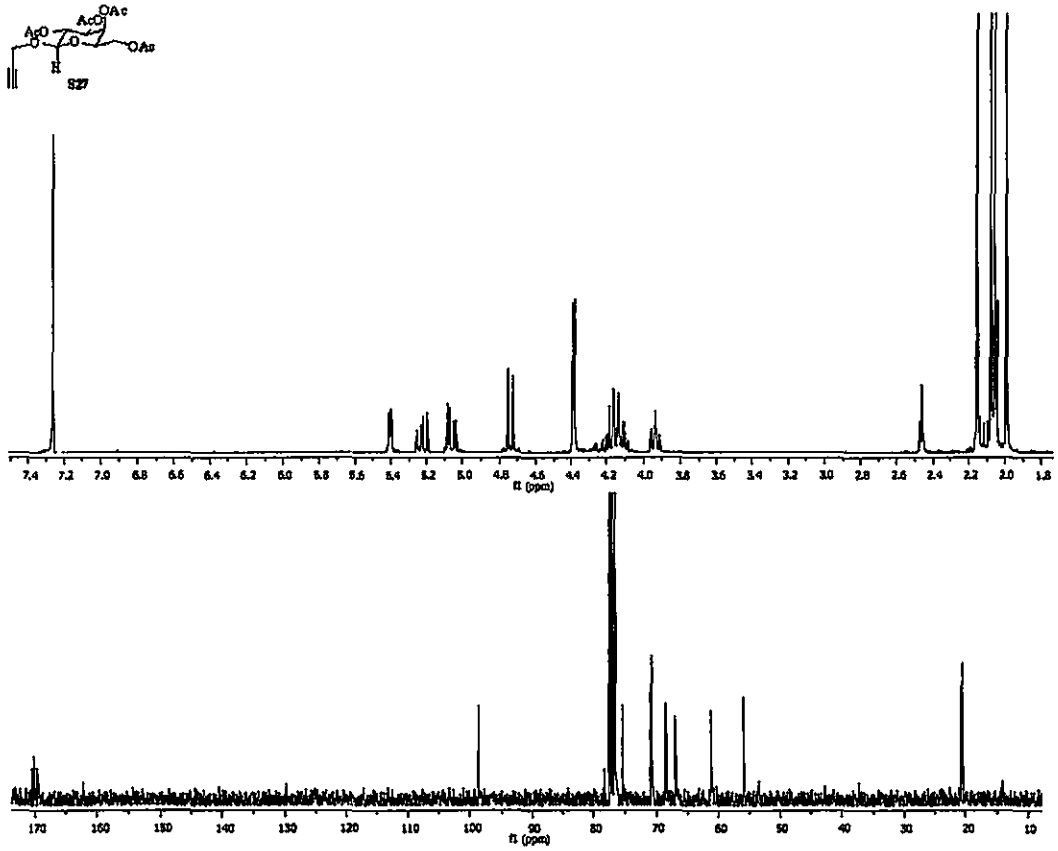

OTBS
TBSO
H
O
OTBS
O
S21
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)

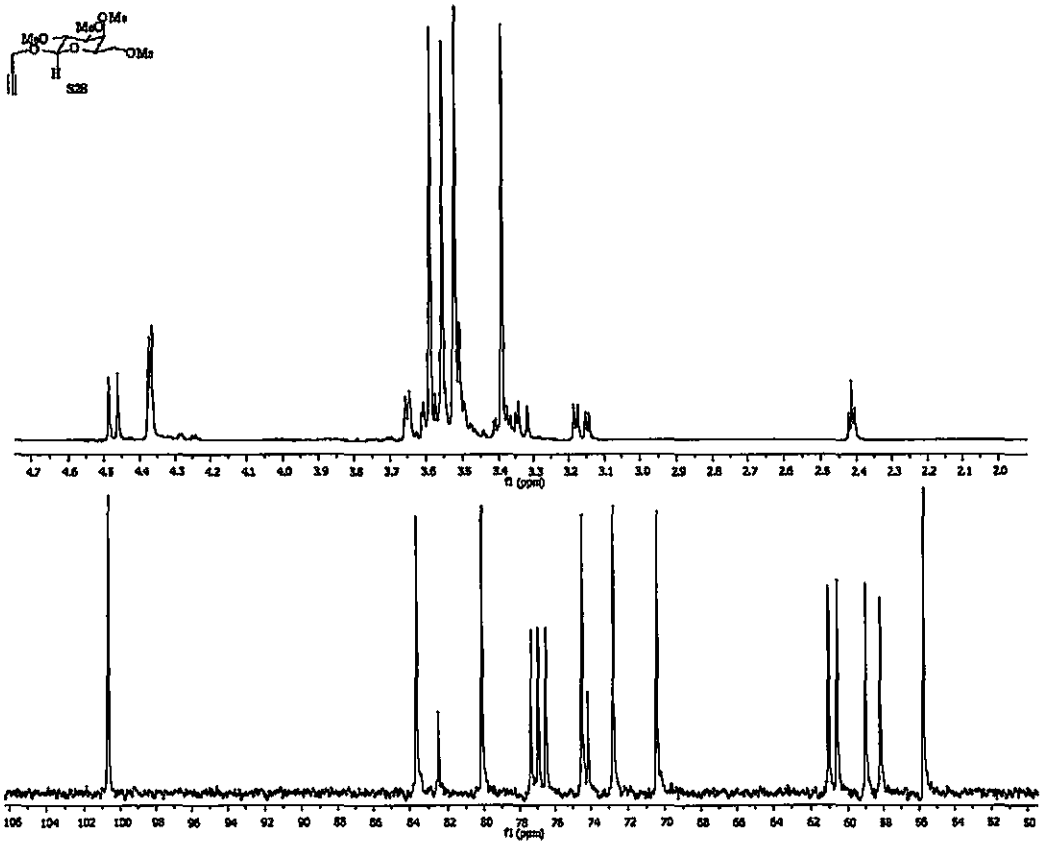

Ph
523
8
7
6
5
4
3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)

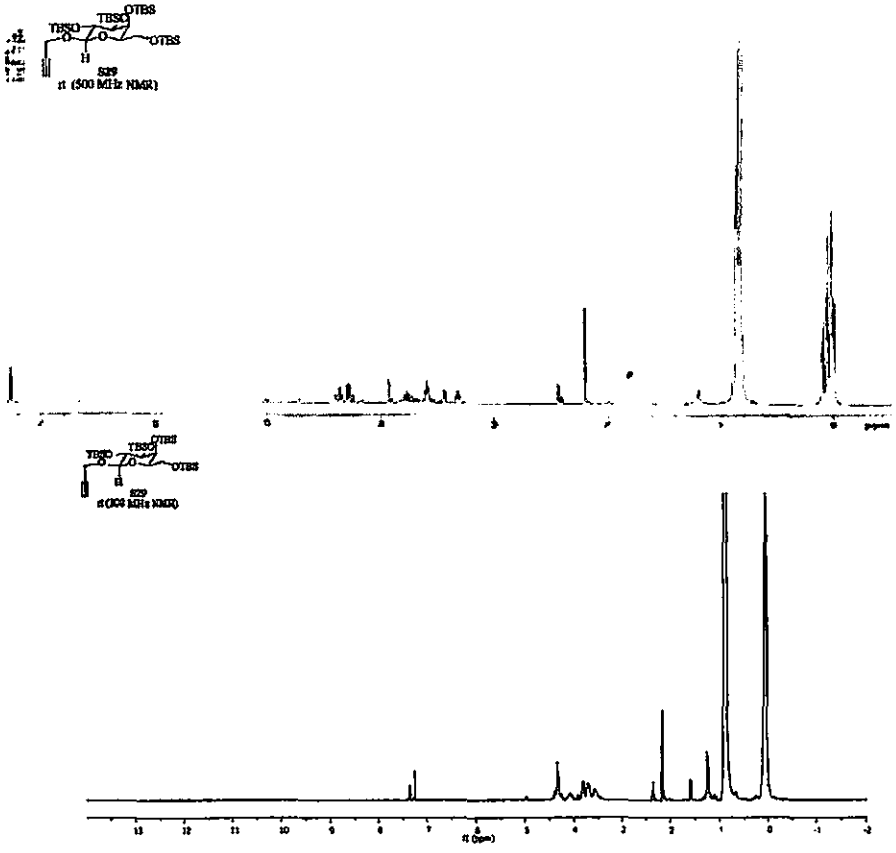

H
H
O
O
Ph
OH
O
O
S24
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)

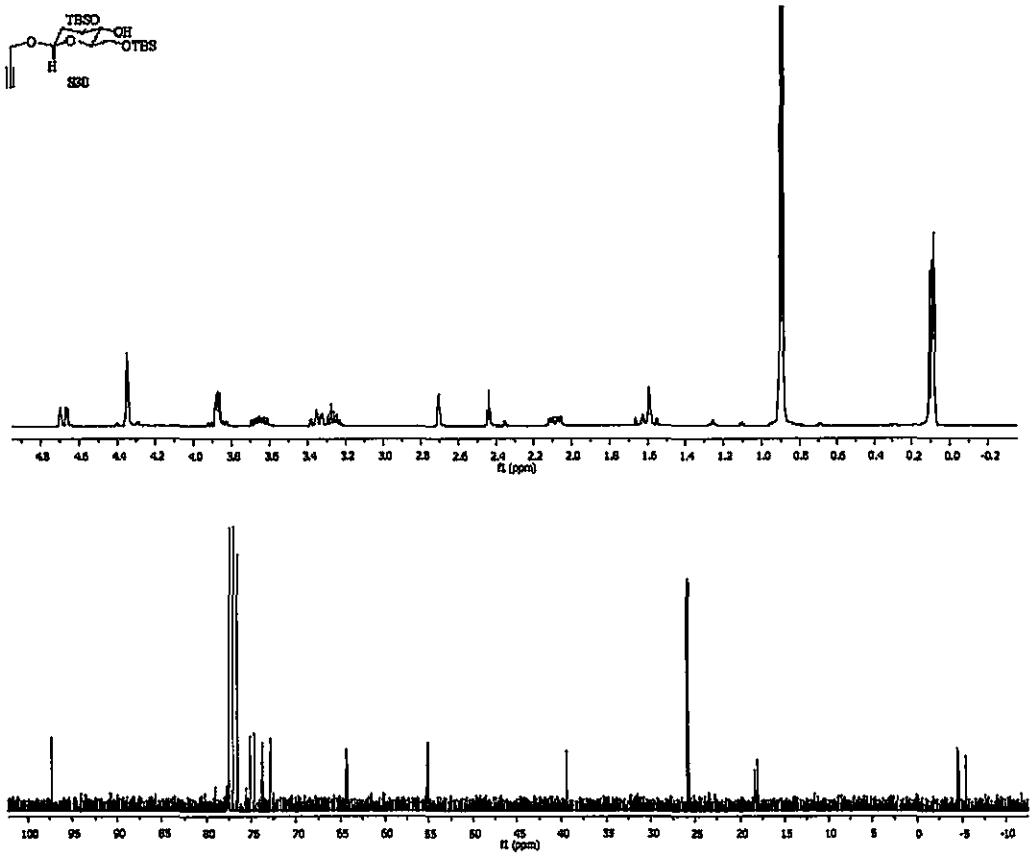

H
H
O
O
Ph
OTBS
S25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

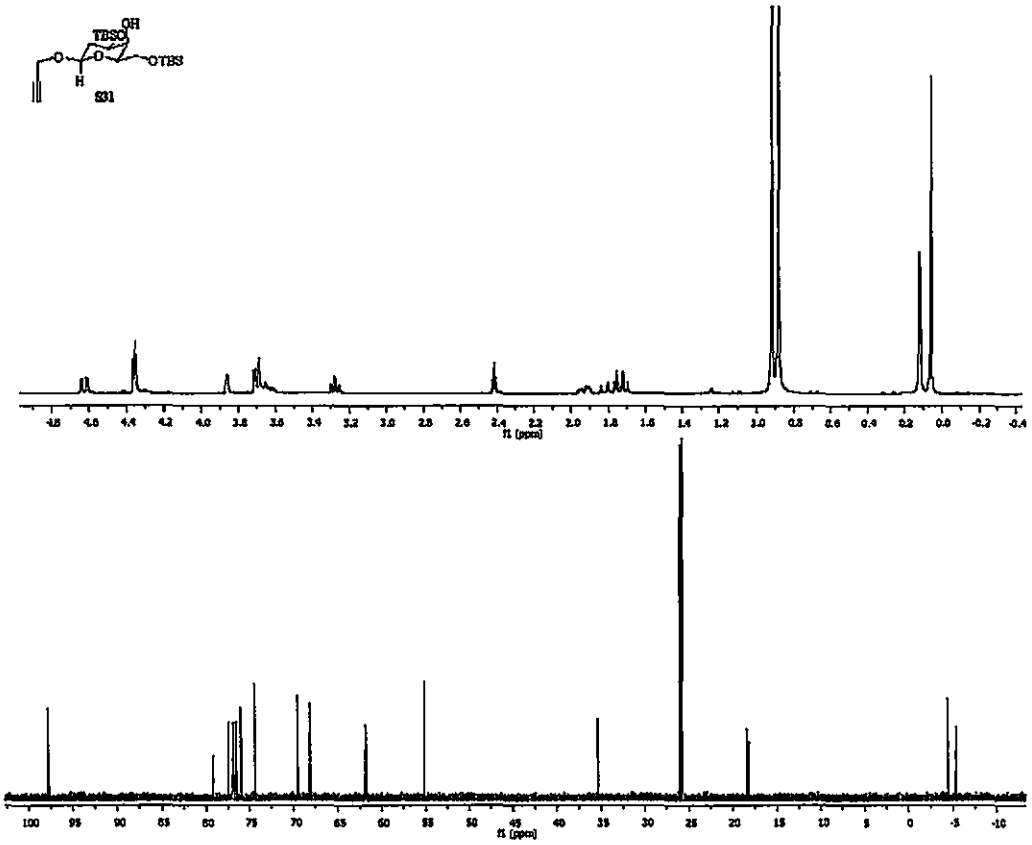

OTBS
H
O
O
O
Ph
H
O
S25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

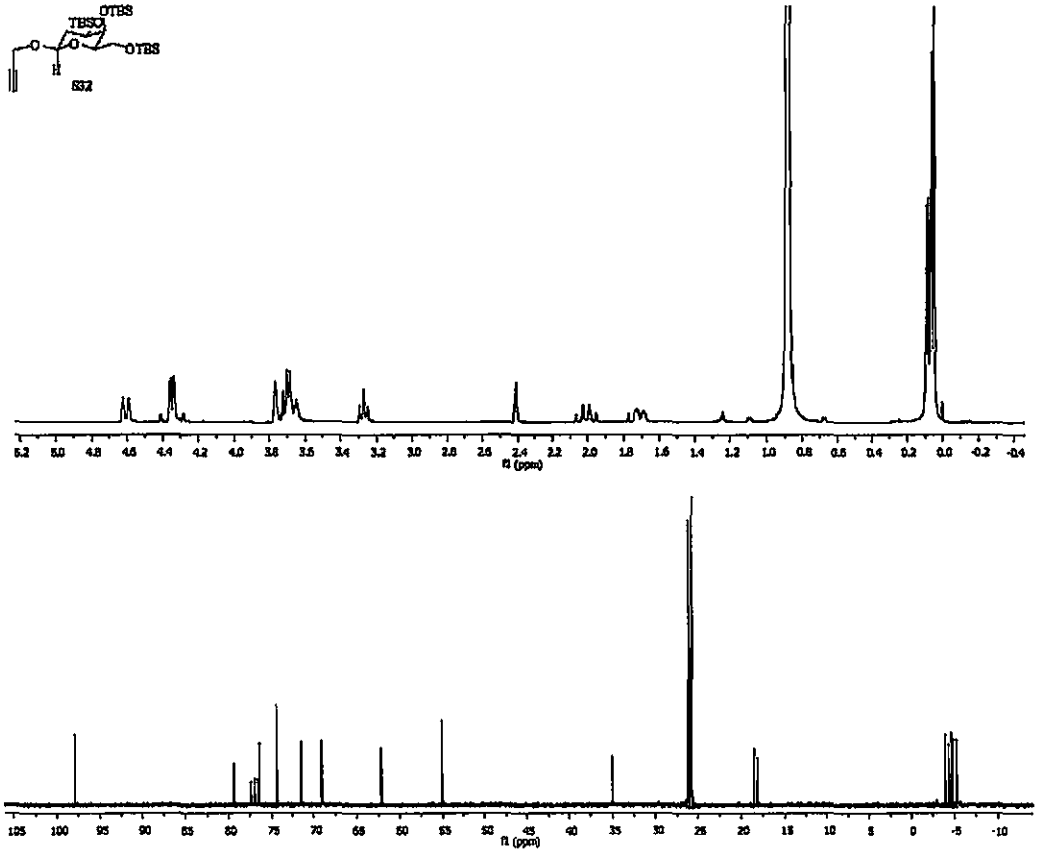

S27
f1 (ppm)
f1 (ppm)

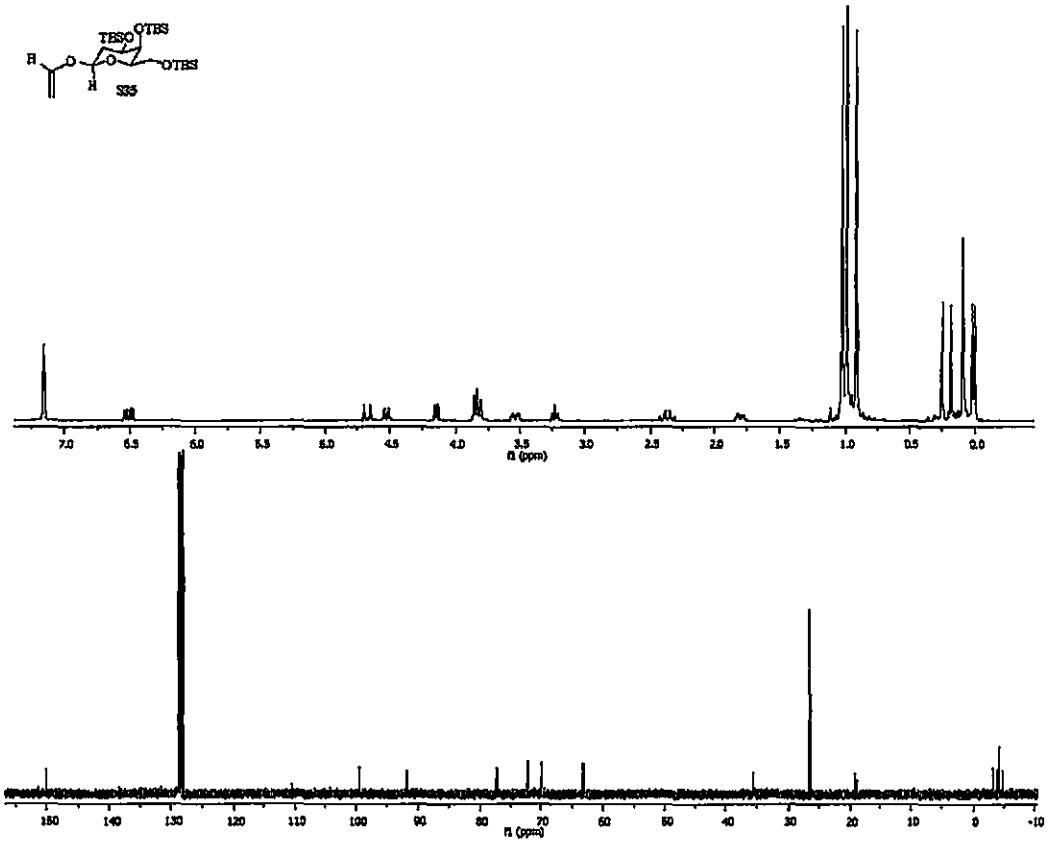

OMe
MeO
MeO
OMe
H
S28
f1 (ppm)
f1 (ppm)

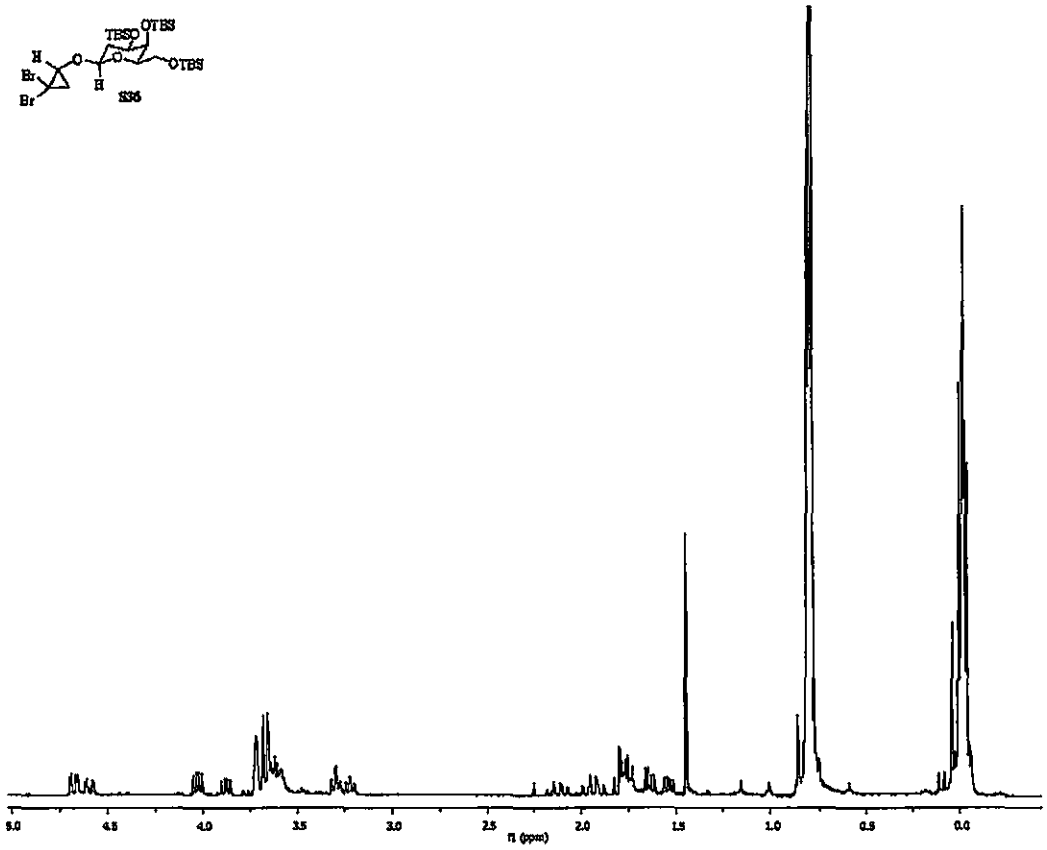


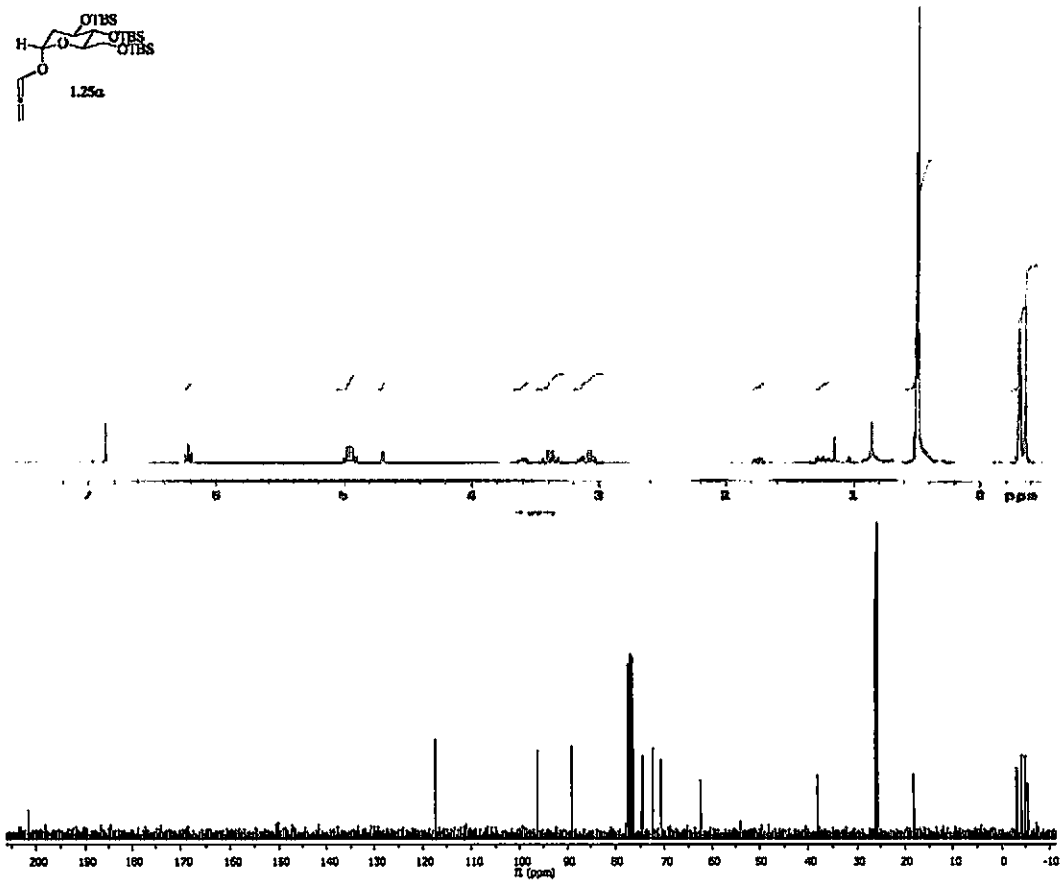

TBSO
OH
O
OTBS
H
SSO
f1 (ppm)
f1 (ppm)

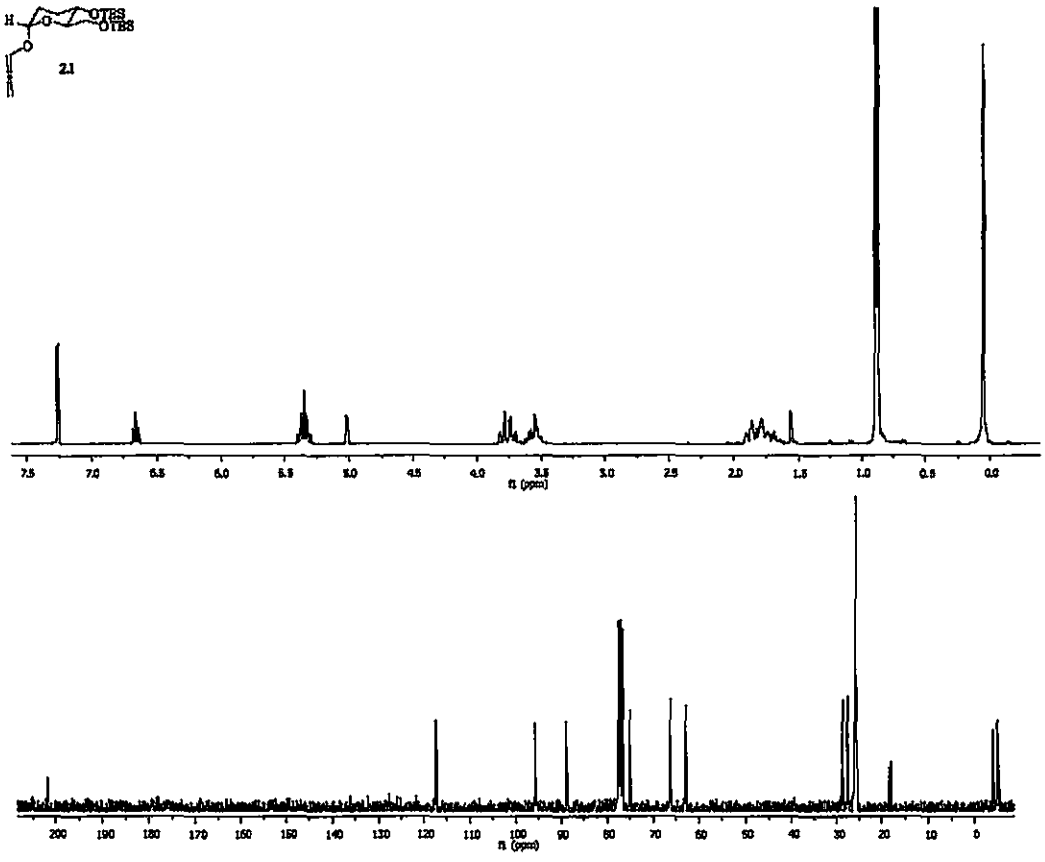

OH
TBSO
O
O
OTBS
H
831
f1 (ppm)
f1 (ppm)

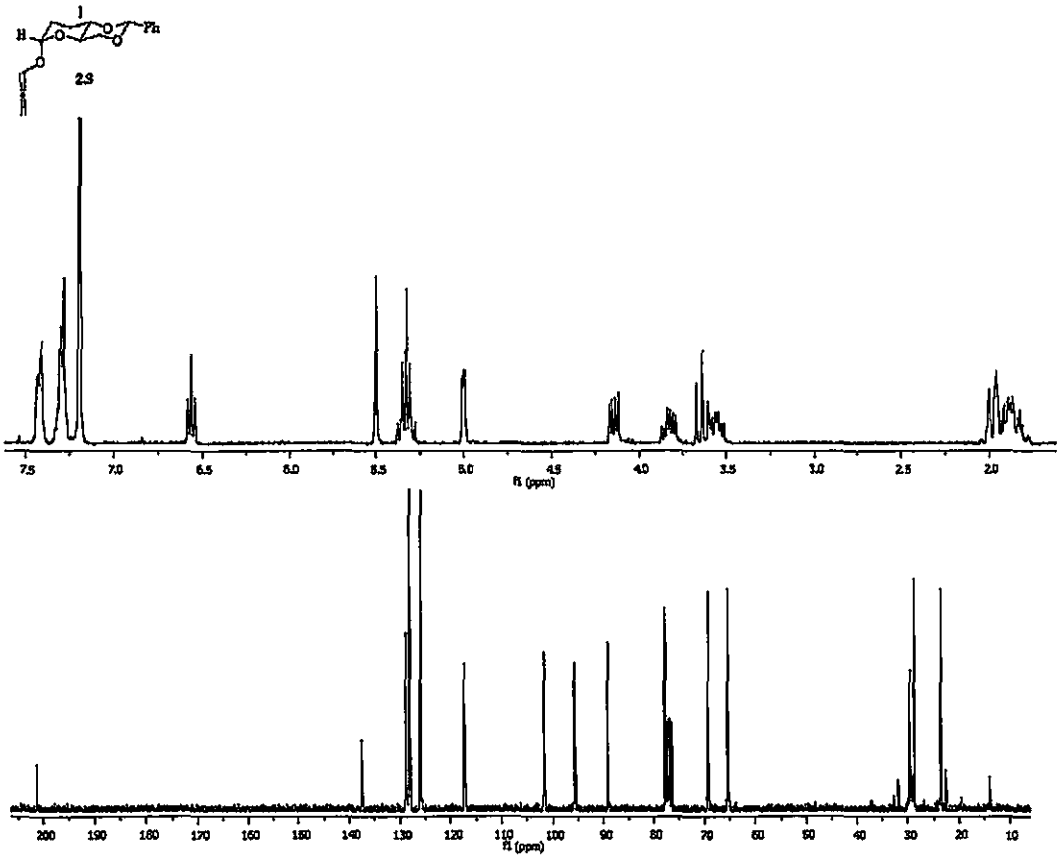

OTBS
TBSO
O
OTBS
H
532
f1 (ppm)
f1 (ppm)

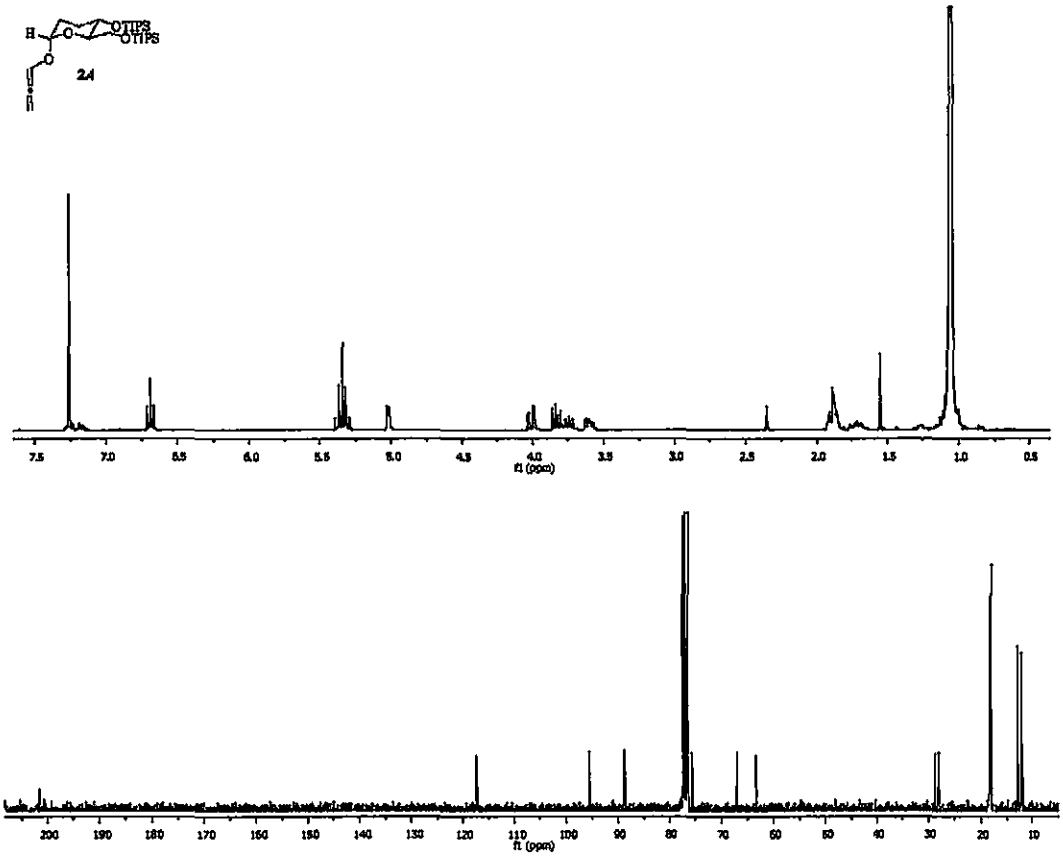

TESO
OTBS
OTBS
H
O
O
H
S35
f1 (ppm)
f1 (ppm)

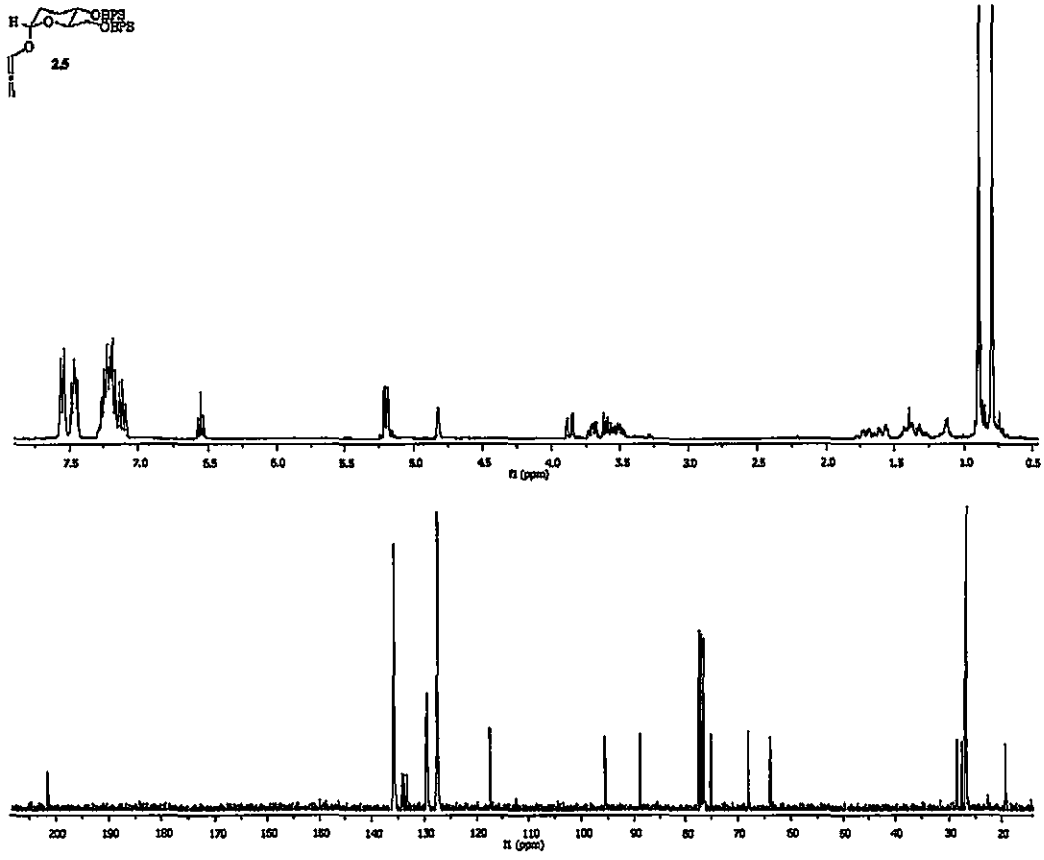

TBSO
OTBS
OTBS
H
O
O
H
Br
Br
S36
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

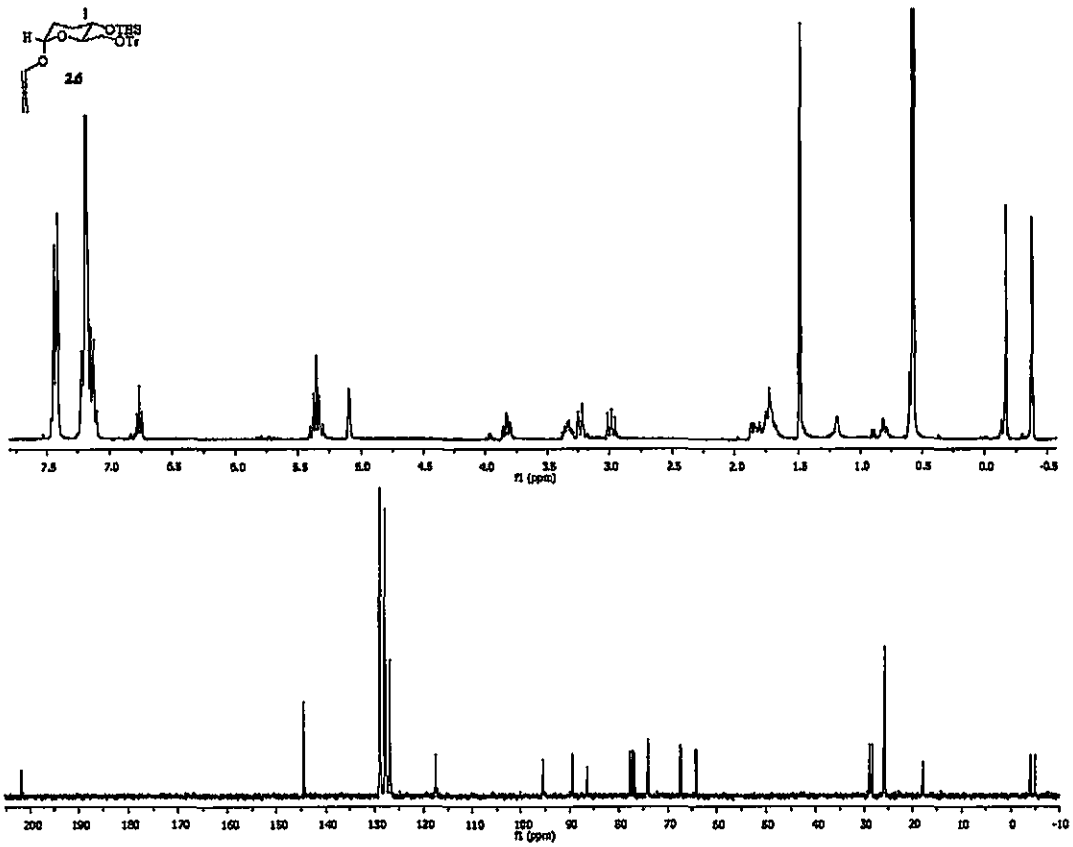

OTBS
OTBS
OTBS
H
O
O
1.25a
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f2 (ppm)

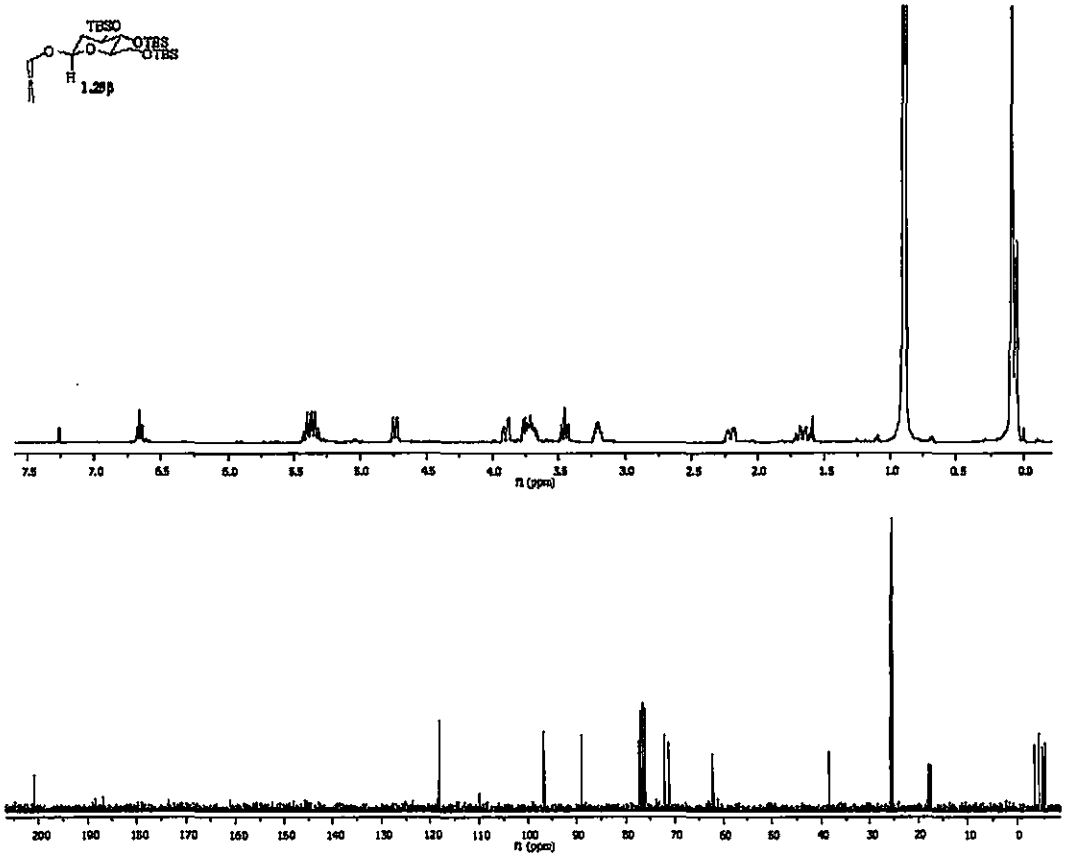

H
O
OTES
OTBS
2.1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

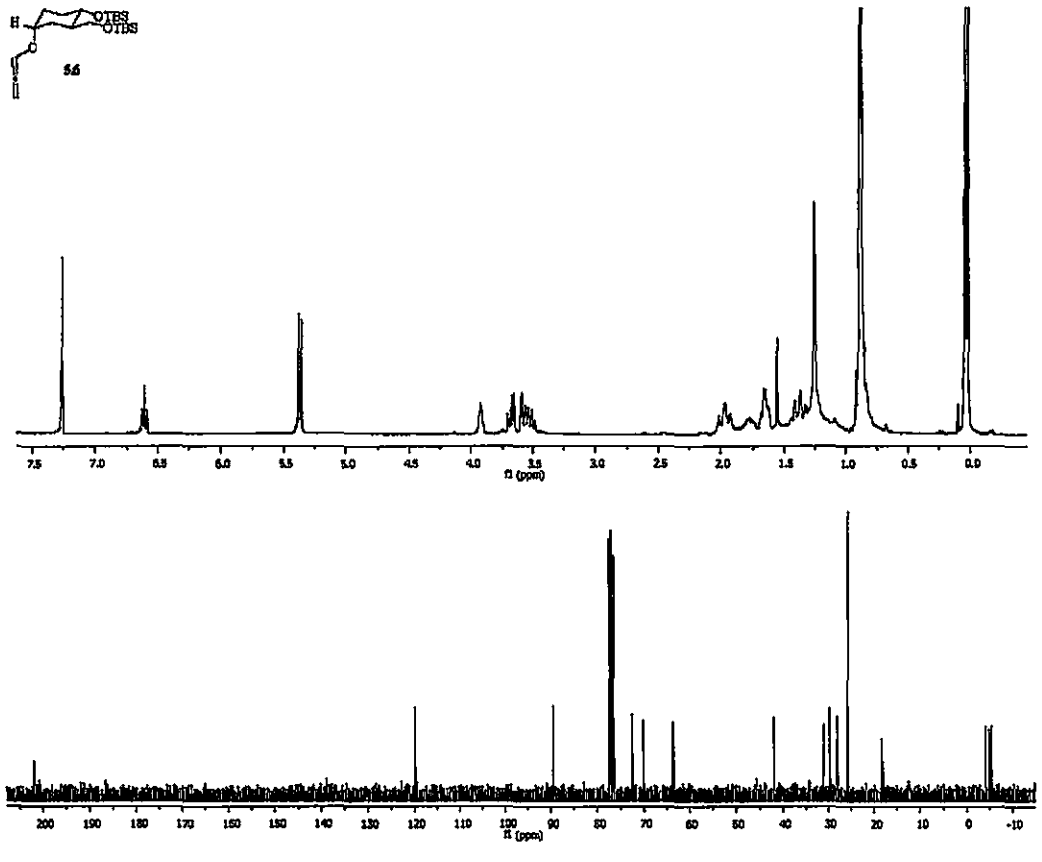

1
H
Ph
O
O
O
2.3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

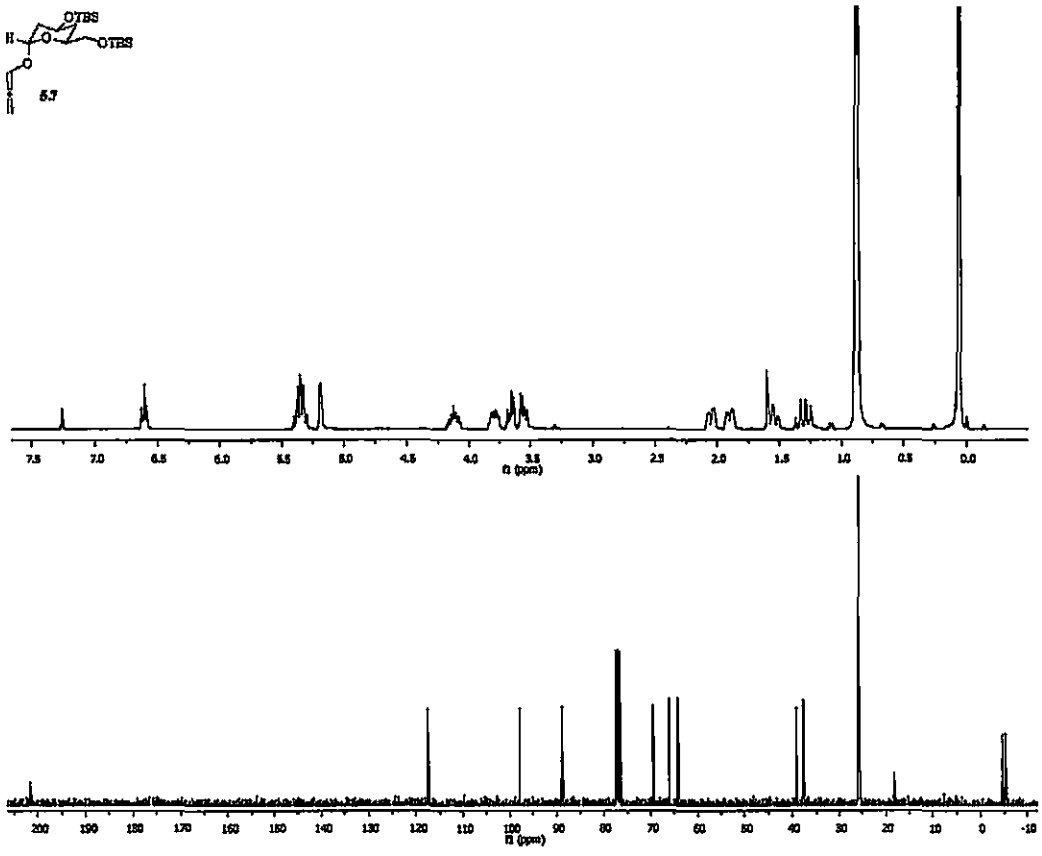

OTIPS
OTIPS
24
f1 (ppm)
f1 (ppm)

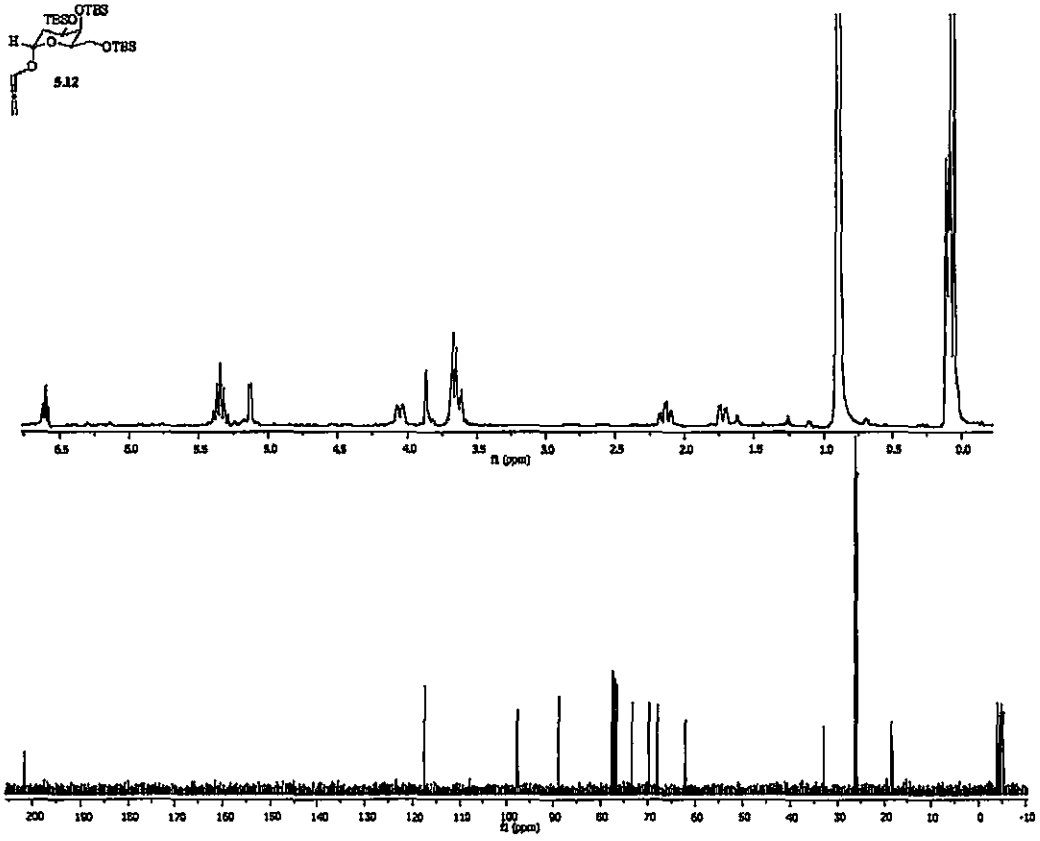

OBPS
OBPS
OBPS
2.5
f2 (ppm)
f1 (ppm)

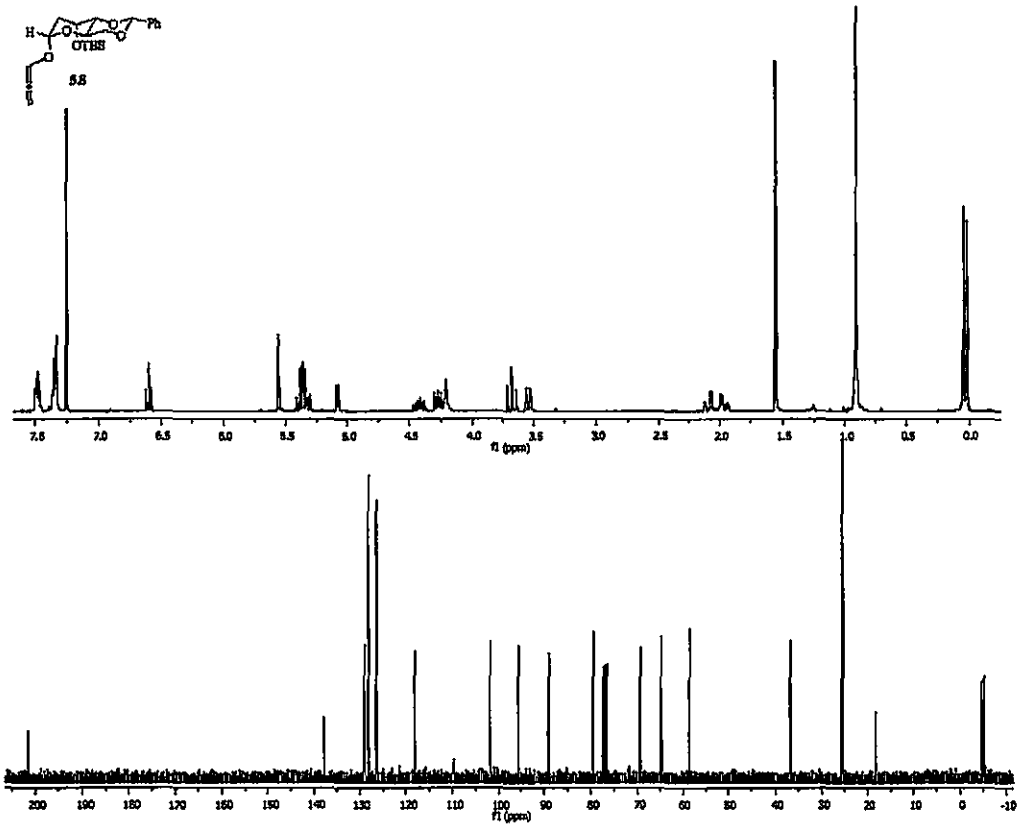

OTBS
OTr
26
f1 (ppm)
f1 (ppm)

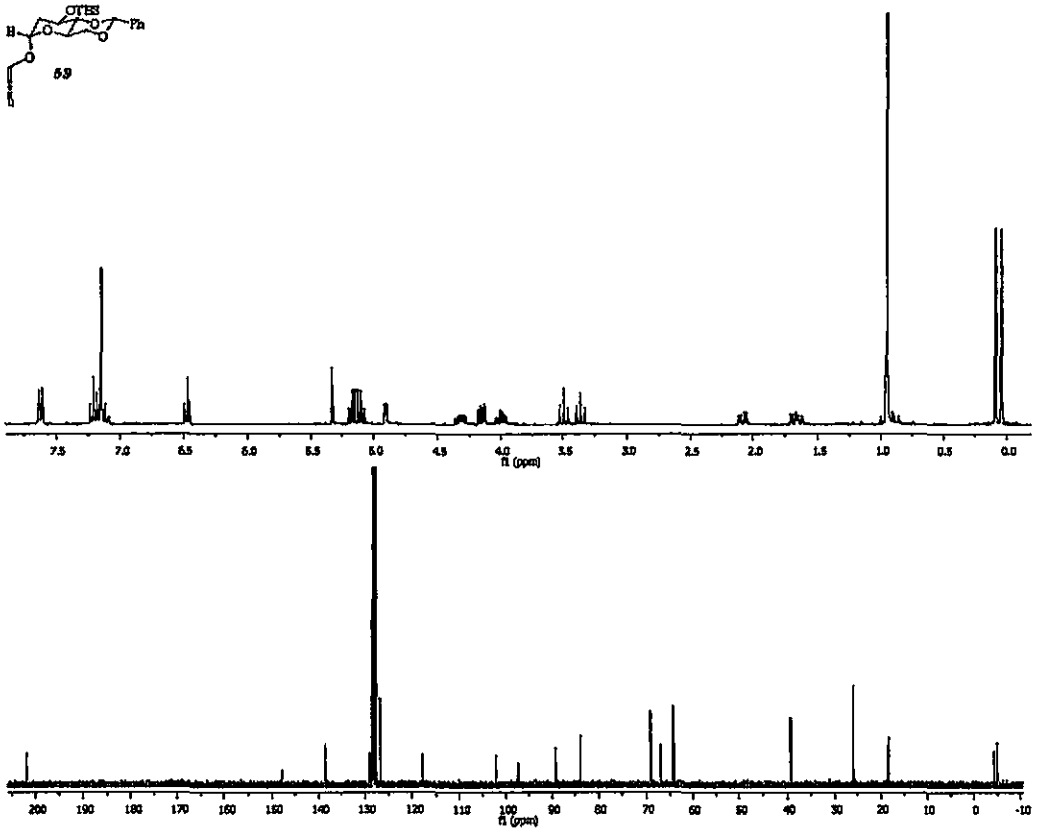

TBSO
OTBS
OTBS
1.25β
f1 (ppm)
f1 (ppm)

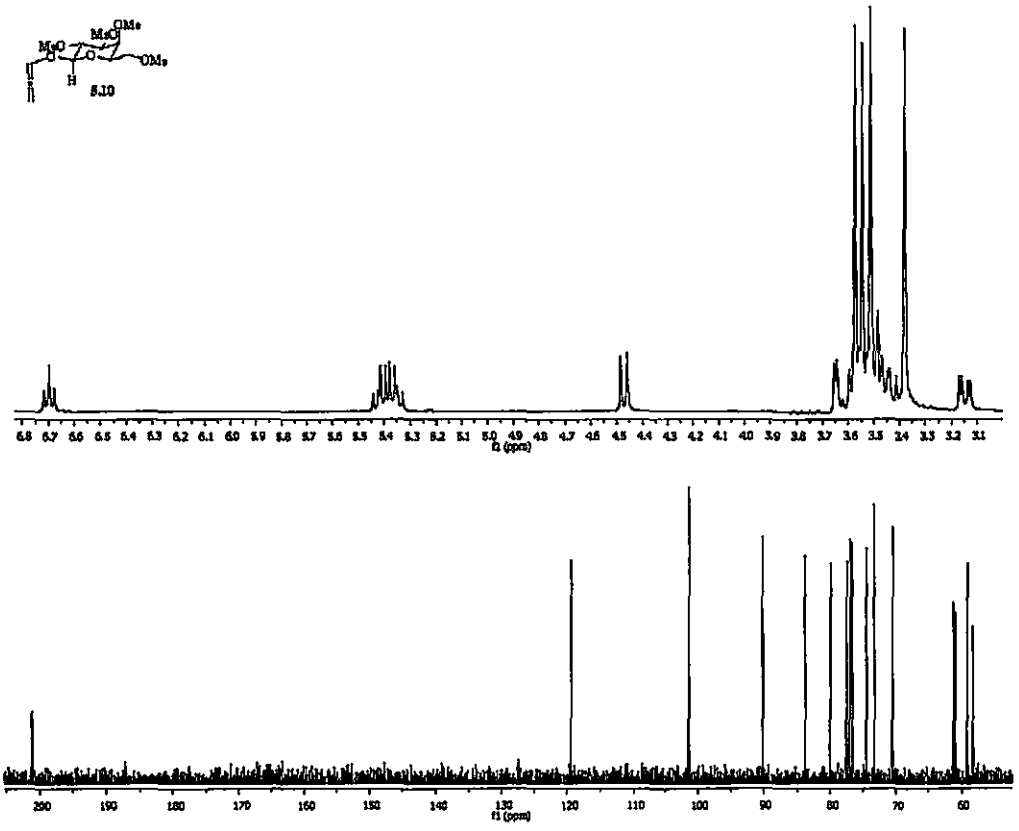

H
OTBS
OTBS
O
56
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

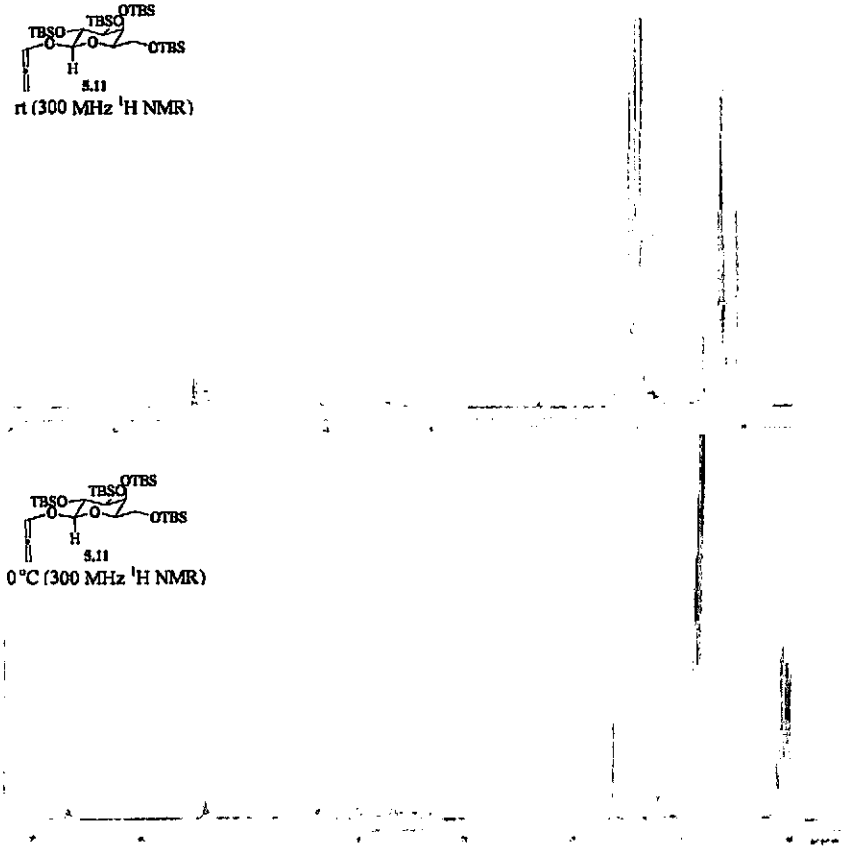

OTBS
OTBS
5.7
f1 (ppm)
f1 (ppm)

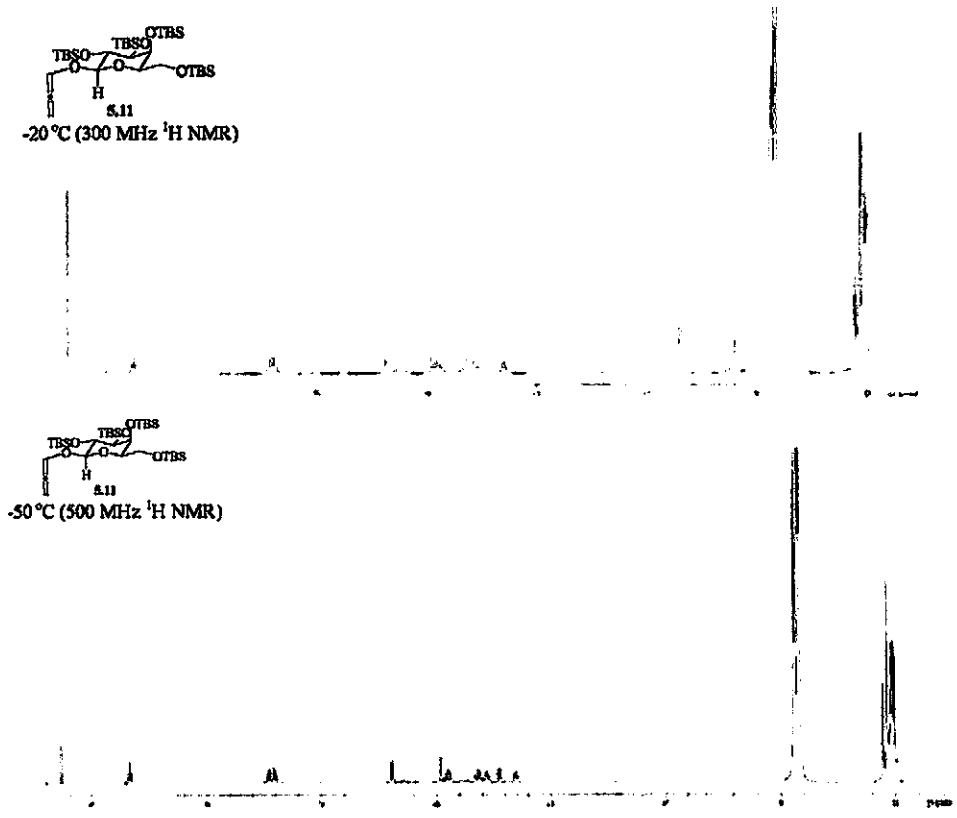

OTBS
TESO
H
O
OTBS
5.12
f1 (ppm)
f1 (ppm)

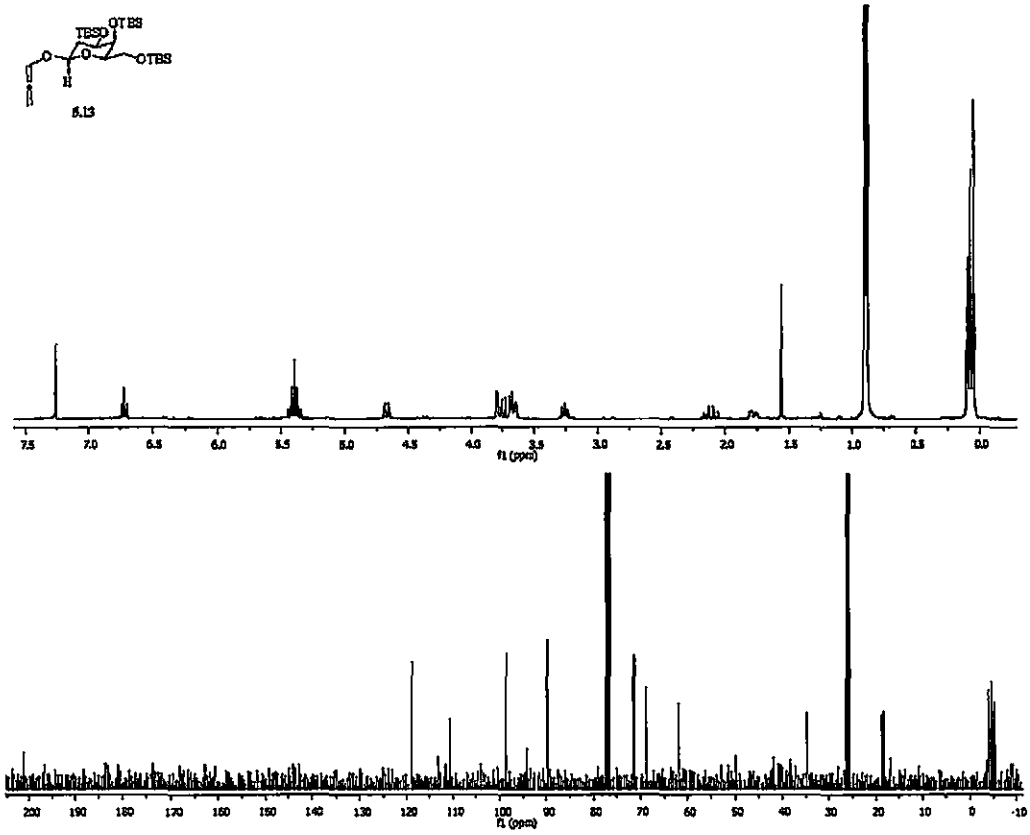

OTBS
5S
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OTES
Ph
59
f1 (ppm)
f1 (ppm)


OMe
MeO
MeO
O
O
OMe
H
5.10
f2 (ppm)
f1 (ppm)


OTBS
TBSO
TBSO
OTBS
H
5.11
rt (300 MHz ¹H NMR)
OTBS
TBSO
TBSO
OTBS
H
5.11
0 °C (300 MHz ¹H NMR)


OTBS
TBSO
TBSO
OTBS
H
5.11
-20 °C (300 MHz ¹H NMR)
OTBS
TBSO
TBSO
OTBS
H
5.11
-50 °C (500 MHz ¹H NMR)


OTBS
TBSO
OTBS
H
5.13
f1 (ppm)
f1 (ppm)

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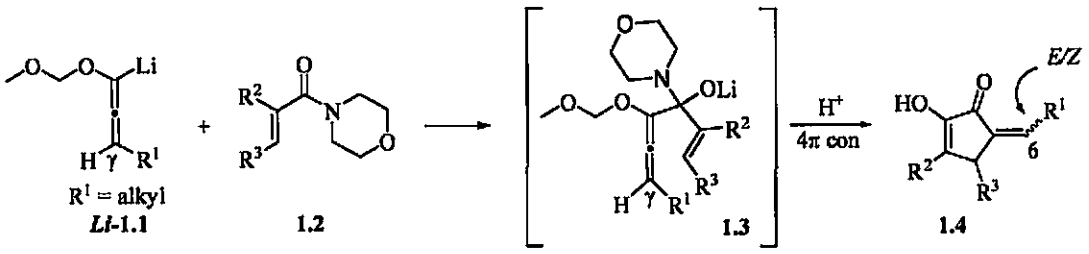
CHAPTER 3: Triply Convergent Cyclopentannelation: An Extension of an Existing Method

1. Introduction

1.1. Background

Several years ago, our group developed a convergent method for the synthesis of C6-substituted cross-conjugated cyclopentenones using the allenyl ether Nazarov reaction summarized in Scheme 3.1.[1,2] Addition of γ-substituted lithioallene *Li*-**1.1** to morpholino enamide **1.2** provided tetrahedral intermediate **1.3**, which subsequently cyclized upon exposure to acid *via* thermally allowed 4π conrotation to form *E* and *Z* isomers of cyclopentenone **1.4**.



Scheme 3.1

Preparation of a library of C6-substituted cross-conjugated cyclopentenones was possible by varying the morpholino enamides and γ-substituted lithioallenes. While most morpholino enamides were easily prepared from their corresponding α,β-unsaturated carboxylic acids, the synthesis of various γ-substituted lithioallenes was not as direct and presented some problems. A few of the earlier approaches towards the synthesis of γ-substituted allenyl ethers are discussed in what follows.

In the first approach, treatment of terminally-substituted alkyne **1.5** with *n*-BuLi using Brandsma's method resulted in incomplete isomerization to allene **1.1** (Figure 3.1).[3]

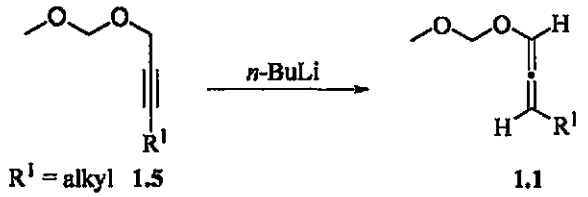


Figure 3.1. Preparation of γ-Substituted Allenes by the Isomerization of Terminally-Substituted Alkynes

The second approach involved the multi-step sequence outlined in Figure 3.2. Exposure of alkyne **1.6** to *t*-BuOK led to complete isomerization to allene **1.7**. α-Lithiation of **1.7** followed by trapping with TMSCl provided allene **1.8**, which was subsequently deprotonated and quenched with a suitable electrophile to furnish trisubstituted allene **1.9**. Lastly, desilylation was accomplished by exposure to TBAF to afford γ-substituted allene **1.1** as the sole reaction product. However, because this approach involved a few additional steps it was not completely satisfactory.

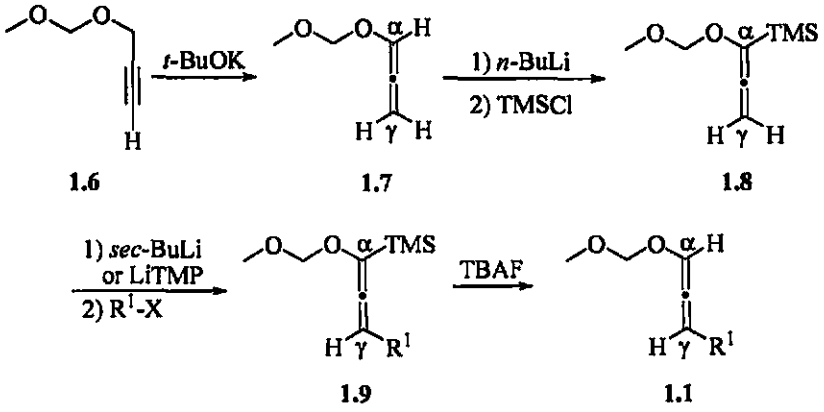


Figure 3.2. Preparation of γ-Substituted Allenes through a Multi-Step Sequence

Since both terminal carbon atoms of the allene can be deprotonated, a more direct approach towards allene **1.1** would be through α,γ-dilithioallene **1.11** (Figure 3.3) followed by the addition of a suitable electrophile. Since the γ-anion forms last, addition to the electrophile would be expected to take place selectively at this more reactive site. However, preparation of α,γ-dilithioallene **1.11** proved to be infeasible. Examples of related *C,C*-dianions from the literature indicate that stabilizing substituents such as SiR_3, SPh or Ph are needed at both ends of the allene to be able to effect deprotonation of both α and γ carbons atoms.[4]

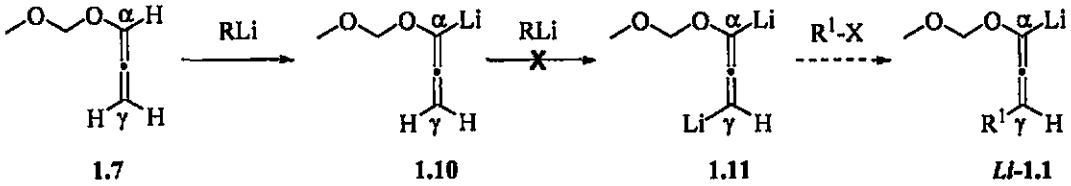
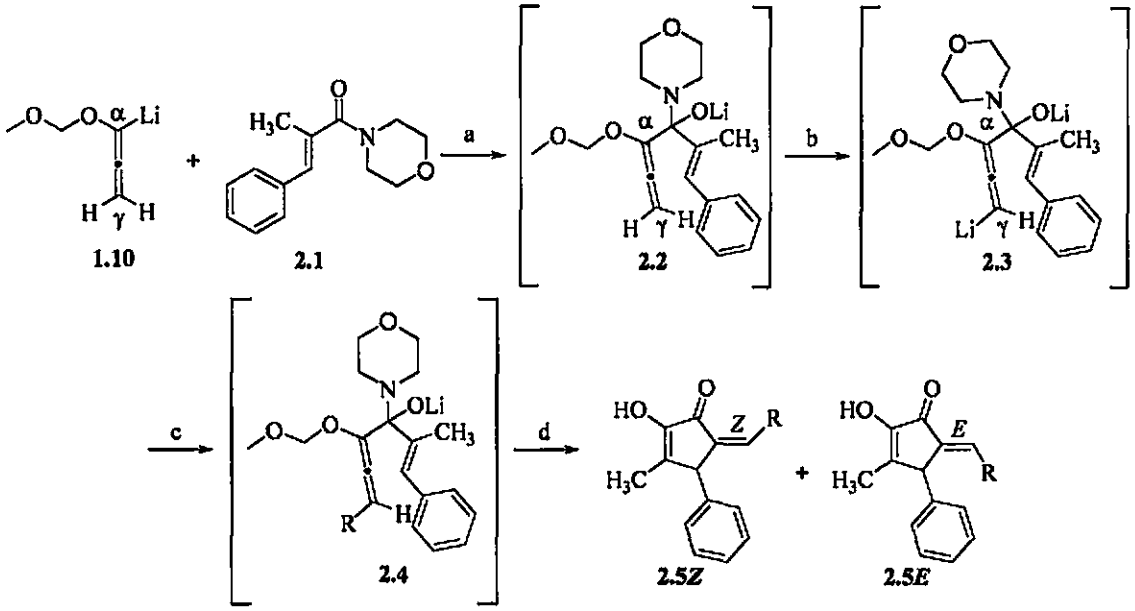


Figure 3.3. Preparation of γ-Substituted Allenes through a *C,C* Dianion

The search for an alternative approach for the synthesis of γ-substituted allenes culminated in the triply convergent process that is described in Scheme 3.2.[5]



Scheme 3.2 (a) lithioallene **1.10** (1.2 equiv), amide **2.1** (1.0 equiv), THF, -78 °C, 30 min; (b) *sec*-BuLi (1.7 equiv), -78 °C, 20 min; (c) R = electrophile (3.0 equiv), -78 °C for 30 min and then -40 °C for 30 min; (d) 5% HCl in EtOH.

Addition of lithioallenyl ether **1.10** to morpholino enamide **2.1** provides tetrahedral intermediate **2.2**. Upon addition of *sec*-butyllithium, *O,C*-dianion intermediate **2.3** is produced and the γ-carbanion is subsequently trapped with a suitable electrophile (R) to give intermediate **2.4**. Exposure to acid promotes cyclization of **2.4** to provide cross-conjugated cyclopentenones **2.5*Z*** and **2.5*E***.[i] It should be noted that although this approach also proceeds through a dianion, *O,C*-dianion **2.3** is low in energy since the two negative charges are

[i] The stereochemistry of the exocyclic bonds was determined by ^{1}H NMR; the proton chemical shift of the vinyl proton of (*E*)-hydroxycyclopentenones was approximately 1.2 ppm downfield relative to that of (*Z*)-hydroxycyclopentenones.

further apart. Moreover, unlike the *C,C* dianion **1.11** shown in Figure 3.3, dianion **2.3** involves an oxygen anion which is more capable of stabilizing the negative charge.

When alkyl halides are used as electrophiles, cyclization of intermediates **2.4** with KH_2PO_4 provides a mixture of cross-conjugated cyclopentenone isomers **2.5*Z*** and **2.5*E*** (Figure 3.4). It had been shown that isomerization of **2.5*Z*** to **2.5*E*** takes place upon treatment with strong acid (equation [1], Figure 3.4). Thus, exposure of a mixture of **2.5*Z*** and **2.5*E*** with 5% HCl in ethanol leads exclusively to (*E*)-hydroxycyclopentenone **2.5*E***.

On the other hand, when ketones are used as electrophiles, only (*Z*)-hydroxycyclopentenone **2.6*Z*** is observed from treatment with KH_2PO_4. Interestingly, these products do not isomerize to the (*E*)-hydroxycyclopentenone after exposure to HCl (equation [2], Figure 3.4). It was postulated that the rate of isomerization of this type of cyclopentenone is reduced due to electronic deactivation by the allylic hydroxyl group and the destabilizing interactions between the phenyl and the C6 substituent in the *E* isomer.

When trialkylsilyl halides are used as electrophiles, (*Z*)-hydroxycyclopentenone **2.7*Z*** is also isolated as the sole product after exposure to KH_2PO_4 (equation [3], Figure 3.4). Mild acid such as KH_2PO_4 is required when this class of electrophiles is used in order to preserve the trialkylsilyl substituent in the product.

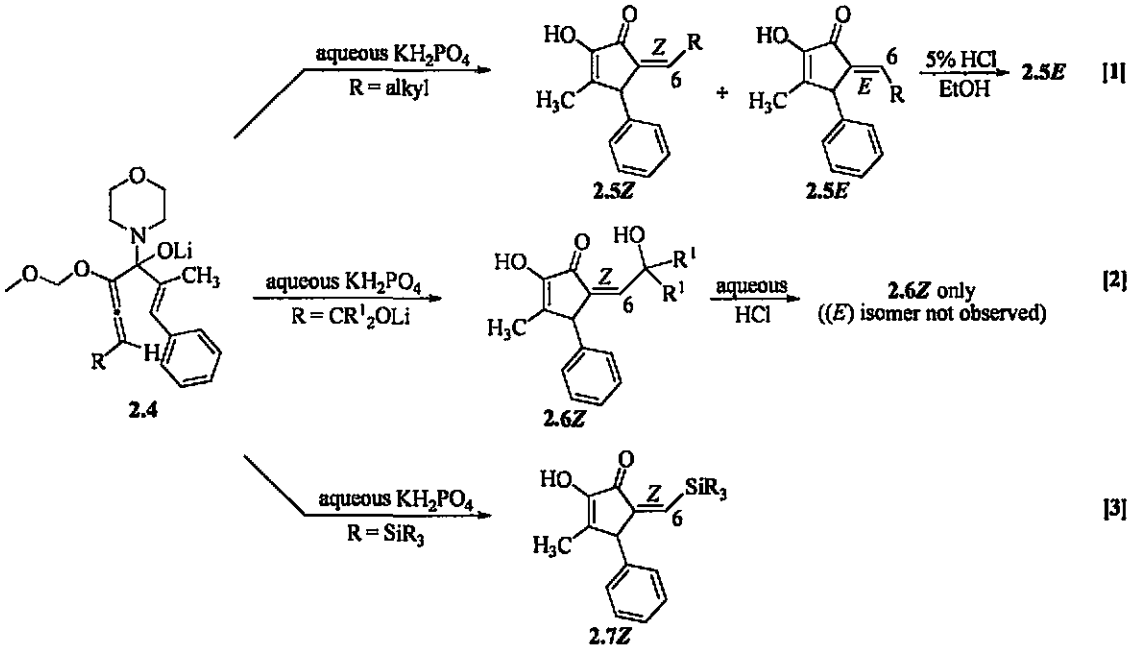


Figure 3.4. Stereochemical Outcome of Representative Cyclizations Using KH_2PO_4 and HCl.

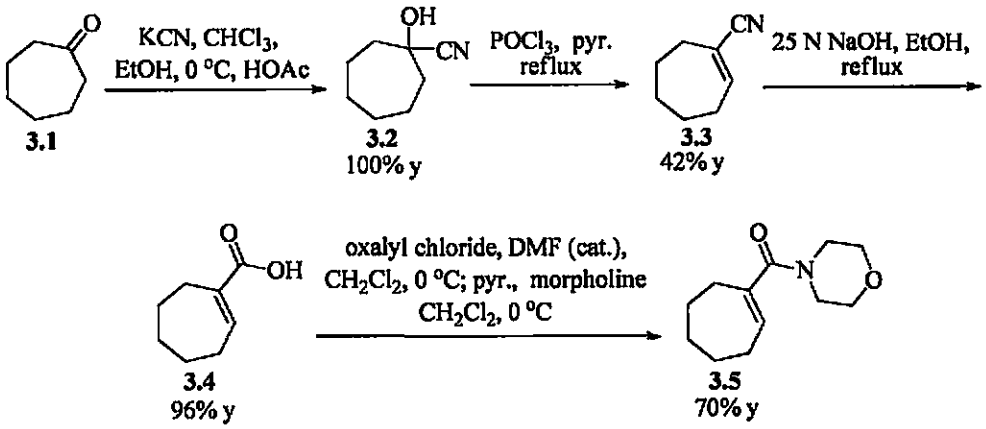
1.2. Objective

These studies led to the development of a successful method for the formation of C6-substituted cross-conjugated cyclopentenones. The method is a triply convergent process that combines an α-lithioallene, morpholino enamide and an electrophile. In this present work, which was done as a collaborative effort with other group members, optimum reaction conditions were defined and the reactions of several enamides and electrophiles were examined.

2. Preparation of Morpholino Enamide 3.5

While most morpholino enamides were directly synthesized from the commercially available α,β-carboxylic acids, some were obtained through elaboration of known ketones. A

representative example is illustrated for morpholino enamide **3.5** (Scheme 3.3). Treatment of cycloheptanone **3.1** with potassium cyanide and acetic acid provided cyanohydrin **3.2**. Exposure of **3.2** to phosphorous oxychloride in refluxing pyridine gave vinyl nitrile **3.3**, which was subsequently converted to carboxylic acid **3.4** by hydrolysis. The synthesis of morpholino enamide **3.5** was accomplished with catalytic DMF and oxalyl chloride followed by pyridine and morpholine.



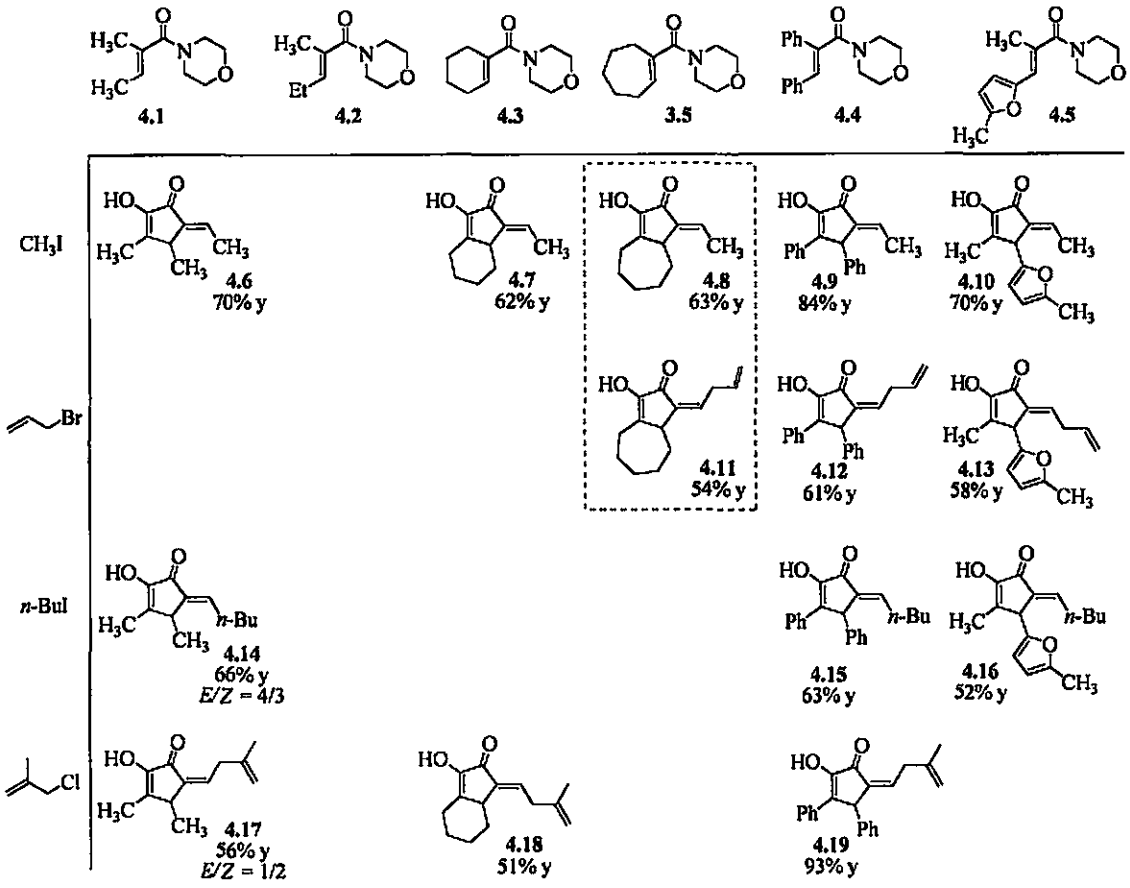
Scheme 3.3

3. Cyclization

Freshly distilled alkyl halide electrophiles were passed through a short column of basic alumina prior to addition. All ketone electrophiles were distilled from CaH_2 and stored over activated 4Å molecular sieves prior to use. TBSCl was sublimed immediately before use and a fresh bottle TIPSCl was required for the success of the reaction. The tandem alkylation-cyclization reactions using these electrophiles were performed as described in Scheme 3.2. The library of cyclopentenone products is shown in Tables 3.1 through 3.3 along with the morpholino enamides and electrophiles from which they were derived.[6,7]

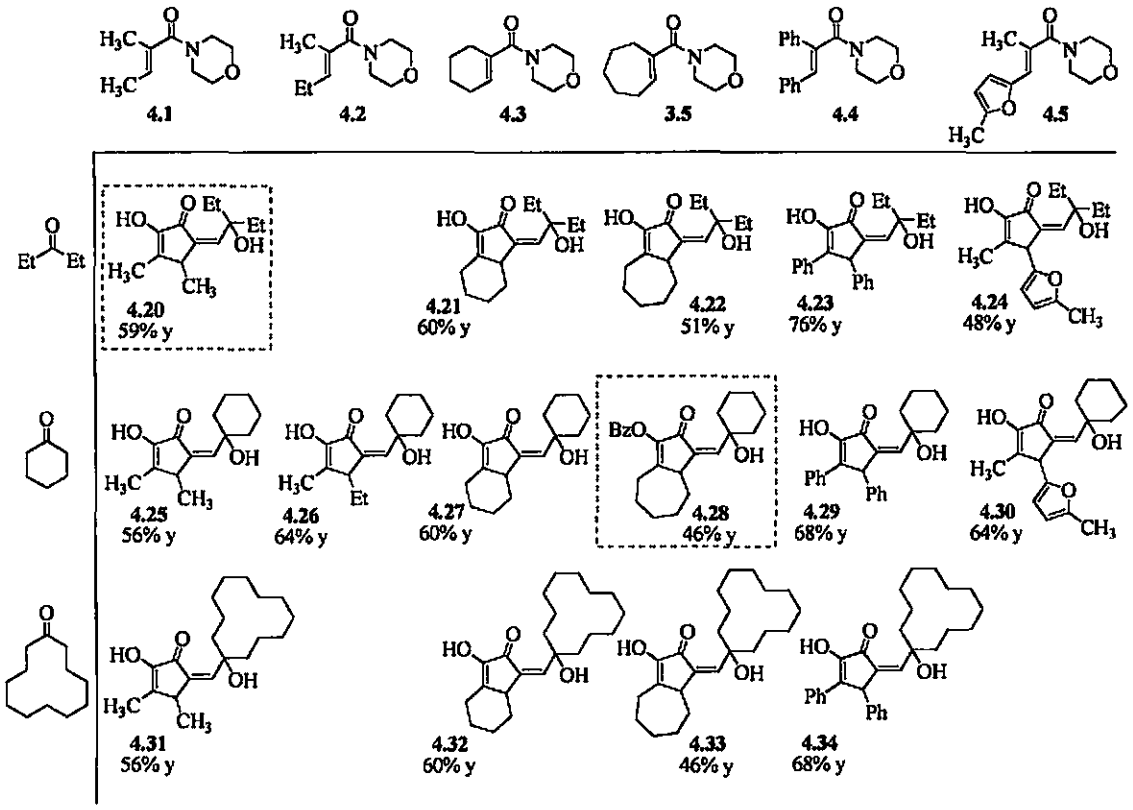
As shown in Table 3.1, *E* and *Z* product isomers are observed in some cases due to the length of exposure to acid in the quench; short contact time with HCl led to geometric isomers whilst prolonged exposure to acid led to exclusive isolation of (*E*)-hydroxycyclopentenones. In cases where allyl bromide and *n*-butyl iodide were used, addition of these electrophiles were sluggish and required warming to -30 °C. The use of HMPA was also necessary to accelerate the reaction.

Table 3.1. Morpholino Enamides and Alkyl Halides Used in Our Triply-Convergent Cyclopentannelation Reaction



All reactions with ketones led exclusively to the corresponding *(Z)*-hydroxycyclopentenones. As previously noted, the preference for *Z* geometry originates from both steric and electronic influences; isomerization to the *E* isomer is prevented from taking place both by the destabilizing interactions between the C6 substituent and the group on the tertiary ring carbon atom, as well as by electronic deactivation by the allylic hydroxyl group.

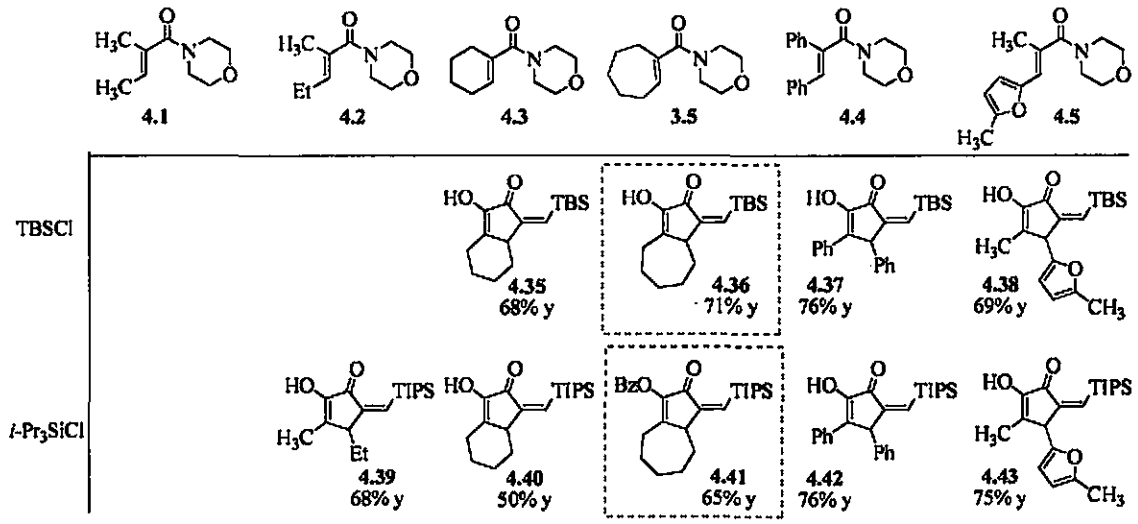
Table 3.2. Morpholino Enamides and Ketones Used in Our Triply-Convergent Cyclopentannelation Reaction



As was the case for reactions with ketone electrophiles, all cyclizations in which trialkylsilyl chlorides were used as electrophiles led exclusively to the (*Z*)-hydroxycyclopentenones. This was consistent with our previous work. Reactions in which

trialkylsilyl chlorides were used as electrophiles required mild acid (KH_2PO_4) to preserve the exocyclic silyl group.

Table 3.3. Morpholino Enamides and Trialkylsilyl Chlorides Used in Our Triply-Convergent Cyclopentannelation Reaction



4. Results and Discussion

As shown in Tables 3.1 through 3.3, the product yields varied from moderate to good for reactions of a number of morpholino enamides with ketones, methyl iodide and silylating reagents. For reasons previously discussed, the kinetic products of cyclization were the *Z* isomers at the exocyclic double bond. In the case where alkyl halides were used as electrophiles, longer contact times with acid during cyclization led to isomerization to the *E* isomer.

There are two noteworthy points regarding the execution of this reaction. First, as with all tandem processes it was important that each step proceed to completion. Second, it was critical to take pains to exclude adventitious proton sources. The lack of attentiveness to these precautions inevitably led to formation of undesired unsubstituted cyclopentenones (*i.e.* product **2.5** where R = hydrogen). During the course of this work, we have developed a detailed protocol that mitigates these problems and reproducibly leads to C6-substituted cyclopentenones. According to this protocol, all morpholino enamides and electrophiles were previously dried by azeotropic distillation of toluene or benzene and then dissolved in THF and dried further over 4 Å molecular sieves prior to use. Additionally, only fresh solutions of newly titrated *n*- and *sec*-butyllithium (in hexanes and cyclohexane, respectively) were used. Alkyllithium solutions with concentrations no less than 1 M were typically employed to minimize the proportion of hydrocarbons that was suspected to impede the addition of the electrophile to intermediate **2.3**.

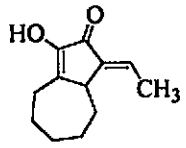
5. Conclusion

The triply convergent cyclopentannelation reaction is a convenient method that allows direct access to a wide range of small molecules. Through this study we have defined optimal reaction parameters for a broad range of morpholino enamides and electrophiles. The process offers the key advantage of creating a large degree of molecular complexity in a single operation, making it highly amenable to natural products synthesis and the preparation of small molecule libraries.[2] The evaluation of the sugar-derived allenes for an asymmetric version of this methodology may also be investigated in due course.

6. Experimental

6.1 General Procedure for the Cyclization to α-Hydroxycyclopentanones:

(3*E*)-3-Ethylidene-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one **4.8**

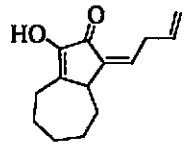


4.8

To a solution of methoxymethyl allene ether **1.1** (80 mg, 0.800 mmol) in 2 mL of THF at -78 °C was added *n*-BuLi (360 μL, 2.49 M in hexanes, 0.896 mmol). After 30 min, a solution of cycloheptenamide **3.5** (105 mg, 0.502 mmol) in 2 mL THF was introduced at -78 °C *via* cannula and the reaction mixture was allowed to warm from -78 °C to -30 °C over 1 h. The reaction mixture was cooled to -78 °C, treated with *sec*-BuLi (950 μL, 1.68 M in cyclohexane, 1.60 mmol) and was stirred at -78 °C for 30 min. MeI (150 μL, 2.40 mmol) in 1 mL THF was added at -78 °C *via* cannula and the reaction was allowed to warm from -78 °C to -30 °C over 1 h after which it was quenched with 5% HCl in EtOH, was allowed to warm to rt over 20 to 30 min and was neutralized with pH 7 buffer. The mixture was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography on silica gel (0 to 5 to 10% EtOAc in hexanes) yielded **4.8** as a white crystalline solid (61 mg, 0.317 mmol, 63% yield); decomposition at 78 °C; R_f = 0.38 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 7.45 (br s, 1H), 6.59 (q, J = 7.3 Hz, 1H), 2.76 (d, J = 9.9 Hz, 1H), 2.70-2.44 (m, 2H), 1.83 (dm, J = 13.8 Hz, 1H), 1.60-1.44 (m, 3H), 1.35 (d, J = 7.3 Hz, 3H), 1.30-0.76 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 188.9, 150.5, 147.2, 139.3, 128.6, 41.4, 34.3, 30.3, 29.5, 28.1, 25.5, 14.0; IR (film) 3292 (br), 2927, 1671, 1626, 1404, 953 cm^{-1}; EIMS *m/z* (%) 107 (20), 135

(20), 149 (85), 164 (10), 174 (20), 192 (100); HREIMS *m/z* exact mass calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1166.

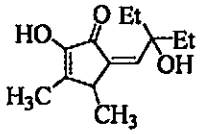
(3*Z*)-3-(But-3-enylidene)-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one **4.11**



4.11

Isolated as a white amorphous solid (75 mg, 0.344 mmol, 54% yield); R_f = 0.21 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.53 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H), 5.33 (t, *J* = 7.6 Hz, 1H), 4.80 (dm, *J* = 17.0 Hz, 1H), 4.71 (d, *J* = 10.1 Hz, 1H), 3.48 (dd, *J* = 18.0, 9.0 Hz, 1H), 3.37 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.36 (d, *J* = 10.1 Hz, 1H), 2.18-2.10 (m, 2H), 1.45-1.34 (m, 1H), 1.34-1.10 (m, 3H), 0.96-0.55 (m, 5H); ^{13}C NMR (75 MHz, C_6D_6) δ 190.1, 151.3, 146.2, 137.2, 136.2, 136.2, 115.9, 43.8, 35.1, 32.0, 30.7, 29.8, 28.1, 25.9; IR (neat) 3584, 3383 (br), 2924, 1670, 1613, 1407, 1078 cm^{-1}; EIMS *m/z* (%) 70 (10), 84 (100), 91 (10), 105 (10), 218 (25); HREIMS *m/z* exact mass calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1297.

(5*Z*)-2-Hydroxy-5-(2-hydroxy-2-ethylbutylidene)-3,4-dimethylcyclopent-2-enone **4.20**

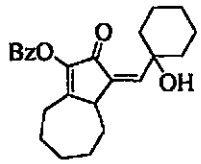


4.20

Isolated as a pale yellow oil (70 mg, 0.312 mmol, 59% yield); R_f = 0.19 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 6.97 (s, 1H), 5.71 (s, 1H), 5.65 (br s, 1H), 2.36 (q, *J* =

6.0 Hz, 1H), 1.80 (dq, J = 6.0, 3.0 Hz, 1H), 1.75 (dq, J = 6.0, 3.0 Hz, 1H), 1.62 (q, J = 6.0 Hz, 1H), 1.57 (q, J = 6.0 Hz, 1H), 1.50 (s, 3H), 1.06 (t, J = 6.0 Hz, 3H), 1.03 (t, J = 6.0 Hz, 3H), 0.67 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 190.8, 151.7, 147.6, 143.5, 138.0, 77.0, 38.9, 34.4, 17.5, 11.5, 8.7; IR (film) 3306 (br), 2966, 1661, 1616, 797 cm^{-1}; EIMS *m/z* (%) 125 (39), 167 (37), 196 (100), 206 (7), 224 (3); HREIMS *m/z* exact mass calcd for $C_{13}H_{20}O_3$ (M^+) 224.2961, found 224.1416.

(Z)-3-((1-Hydroxycyclohexyl)methylene)-2-oxo-2,3,3a,4,5,6,7,8-octahydroazulen-1-yl benzoate **4.28**

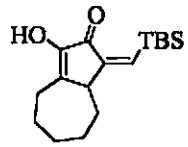


4.28

To a solution of methoxymethyl allene ether **1.1** (80 mg, 0.800 mmol) in 2 mL of THF at -78 °C was added *n*-BuLi (330 μL, 2.49 M in hexanes, 0.820 mmol). After 30 min, a solution of cycloheptenamide **3.5** (105 mg, 0.500 mmol) in 2 mL THF was introduced at -78 °C *via* cannula and the reaction mixture was allowed to warm from -78 °C to -30 °C over 1 h. The reaction mixture was treated with *sec*-BuLi (600 μL, 1.68 M in cyclohexane, 1.00 mmol) and was stirred at -78 °C for an additional 30 min. Cyclohexanone (180 μL, 1.51 mmol) in 1 mL THF was added at -78 °C *via* cannula and the reaction was allowed to warm from -78 °C to -30 °C over 1 h, was quenched with 5% HCl in EtOH, was allowed to warm to rt over 20 to 30 min and was neutralized with pH 7 buffer. The mixture was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and

concentrated to yield 110 mg of crude material. The crude material was then dissolved into 2 mL of DCM and was treated with Hünig's base (270 μL, 1.50 mmol). The mixture was cooled to 0 °C, treated with benzoyl chloride (60 μL, 0.520 mmol) dropwise and was stirred at rt. After 1 h the reaction was quenched with $NaHCO_3$ (aq). The organic layer was separated and washed with brine then was isolated *via* flash column chromatography on silica gel (0 to 5 to 10% EtOAc in hexanes) to yield a clear oil (88 mg, 0.231 mmol, 46% yield); R_f = 0.19 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 8.19 (d, J = 6.9 Hz, 2H), 7.30-6.95 (m, 3H), 6.70 (br s, 1H), 6.20 (s, 1H), 2.67 (d, J = 7.5 Hz, 1H), 2.37-2.16 (m, 2H), 2.10-1.90 (m, 4H), 1.74-0.80 (m, 14H); ^{13}C NMR (75 MHz, C_6D_6) δ 188.8, 164.5, 163.0, 150.8, 147.4, 139.6, 136.2, 133.6, 132.9, 130.2, 128.5, 126.0, 71.3, 45.1, 38.1, 37.9, 34.6, 30.2, 29.5, 28.4, 25.9, 25.2, 22.2, 20.5; IR (film) 3442 (br), 2931, 1745, 1681, 1633, 707; EIMS *m/z* (%) 77 (25), 105 (100), 258 (20), 362 (15), 380 (4); HREIMS *m/z* exact mass calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.1961.

(3*Z*)-3-((*tert*-Butyldimethylsilyl)methylene)-3a,4,5,6,7,8-hexahydro-1-hydroxyazulen-2(1*H*)-one **4.36**



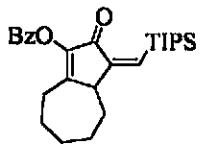
4.36

Isolated as a white crystalline solid (86 mg, 0.294 mmol, 71% yield); mp 128 °C-133 °C; R_f = 0.29 (3% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 6.83 (s, 1H), 6.14 (s, 1H), 2.68 (dm, J = 10.5 Hz, 1H), 2.54-2.49 (m, 2H), 1.86 (dm, J = 13.0 Hz, 1H), 1.62-1.40 (m, 3H), 1.24-1.10 (m, 2H), 1.12 (s, 9H), 1.00-0.80 (m, 2H), 0.51 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (75

MHz, C_6D_6) δ 189.6, 154.3, 151.9, 148.7, 134.9, 45.5, 35.1, 30.7, 30.1, 28.4, 26.7(3), 25.8, 17.4, -5.3 (2); IR (film) 3339, 2923, 1671, 1601, 1407, 825 cm^{-1}; EIMS *m/z* (%) 75 (35), 149 (3), 236 (19); HREIMS *m/z* exact mass calcd for $C_{17}H_{28}O_2Si$ (M^+) 292.18586, found 292.1875.

(1*Z*)-1,2,4,5,6,7,8,8a-Octahydro-1-((triisopropylsilyl)methylene)-2-oxoazulen-3-yl benzoate

4.41

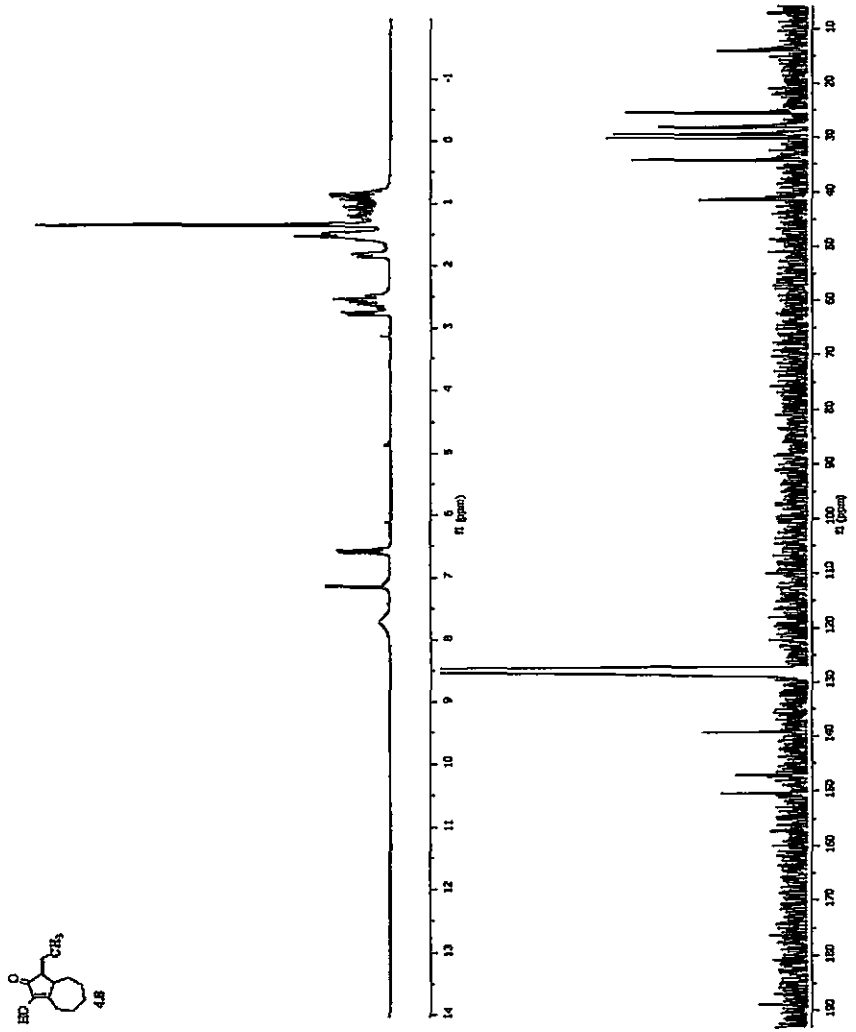


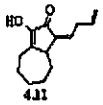
4.41

To a solution of methoxymethyl allene ether **1.1** (76 mg, 0.760 mmol) in 2 mL of THF at -78 °C was added *n*-BuLi (310 μL, 2.49 M in hexanes, 0.780 mmol). After 30 min, a solution of cycloheptenamide **3.5** (99 mg, 0.470 mmol) in 2 mL THF was added at –78 °C *via* cannula and the reaction mixture was allowed to warm from –78 °C to –30 °C over 1 h. The reaction was treated with *sec*-BuLi (570 μL, 1.68 M in cyclohexane, 0.950 mmol) and was stirred at –78 °C for an additional 30 min. TIPSCl (300 μL, 1.40 mmol) in 1 mL THF was added at –78 °C *via* cannula and the reaction was allowed to warm from –78 °C to –30 °C over 1 h. The mixture was quenched with 5% HCl in EtOH and was allowed to warm to rt over 20 to 30 min then was neutralized with pH 7 buffer. The mixture was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude mixture was dissolved into 2 mL of DCM and was the mixture was treated with Hünig's base (250 μL, 1.42 mmol). The mixture was cooled to 0 °C, treated with

benzoyl chloride (60 μL, 0.520 mmol) dropwise, stirred at rt for 1 h and was quenched with $NaHCO_3$ (aq). The organic layer was separated and washed with brine then isolated *via* flash column chromatography on silica gel (1% EtOAc in hexanes) to yield a pale yellow oil (112 mg, 0.345 mmol, 65% yield); R_f = 0.39 (3% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 8.13 (d, J = 8.1 Hz, 2H), 7.10 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 7.1 Hz, 1H), 6.80 (d, J = 7.1 Hz, 1H), 6.10 (s, 1H), 2.88 (br d, J = 9.0 Hz, 1H), 2.36-2.28 (m, 2H), 1.99-1.89 (m, 1H), 1.70-1.23 (m, 6H), 1.23-1.14 (m, 20H), 1.14-0.84 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 186.7, 163.0, 162.0, 154.6, 148.2, 133.4, 133.3, 130.5, 129.3, 128.6, 46.7, 35.1, 30.4, 29.7, 28.3, 25.5, 19.5, 12.6; IR (film) 2929, 1747, 1702, 1608, 1257, 882, 706 cm^{-1}; EIMS *m/z* (%) 105 (98), 135 (4), 173 (2), 395 (100); HREIMS *m/z* exact mass calcd for $C_{27}H_{38}O_3Si$ (M^+ - $CH(CH_3)_2$) 395.2042, found 395.20.

6.2. Spectral Data





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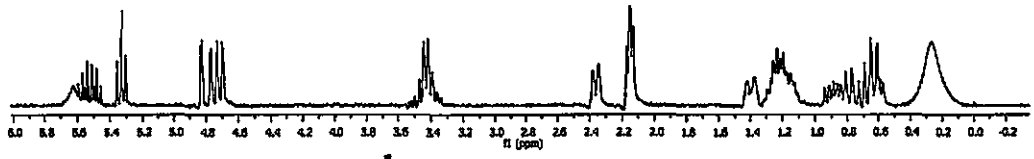
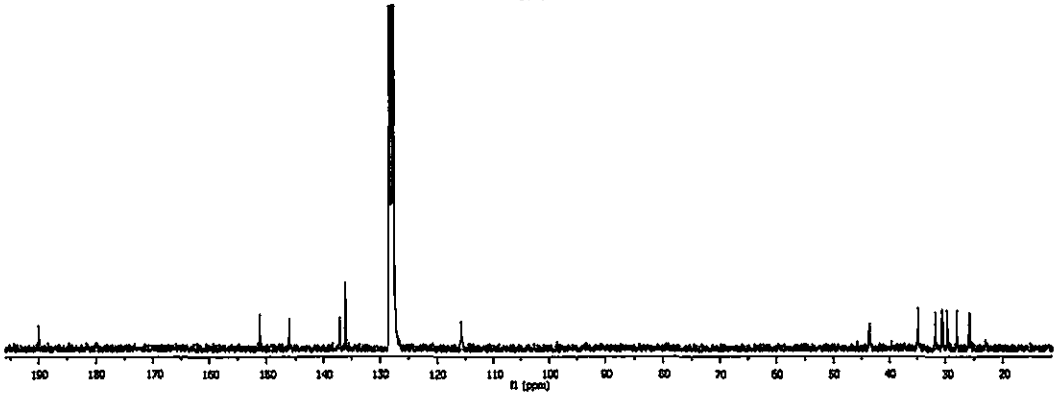
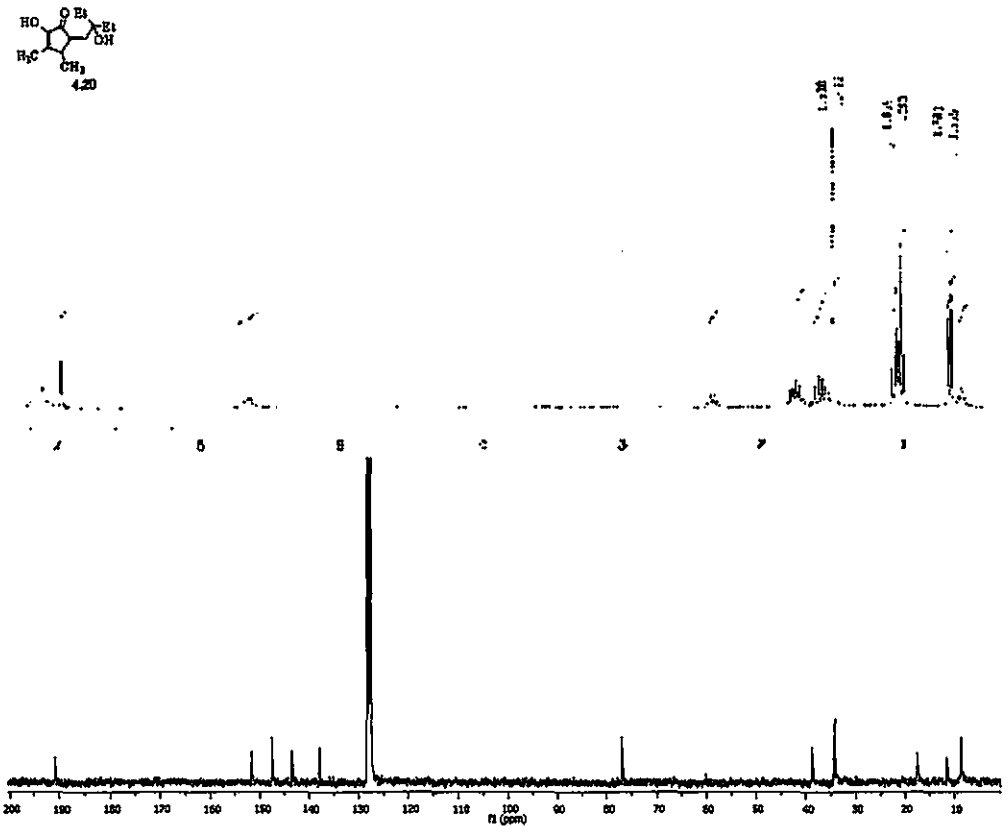
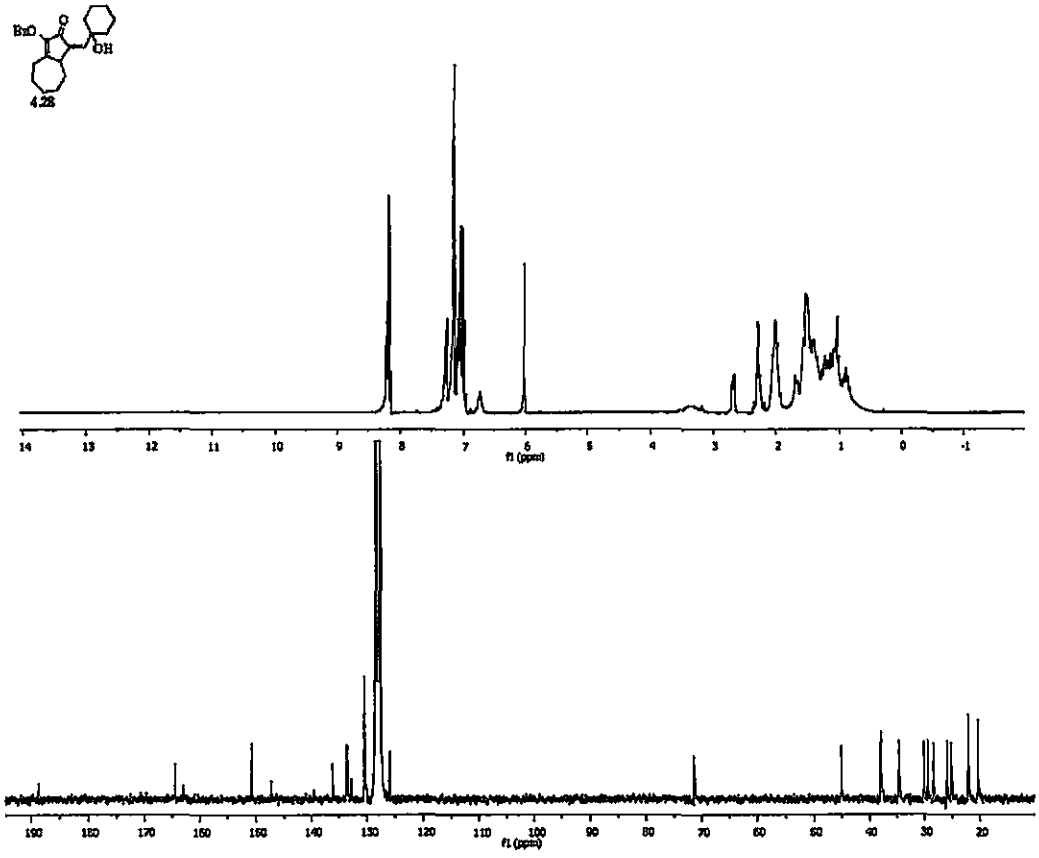
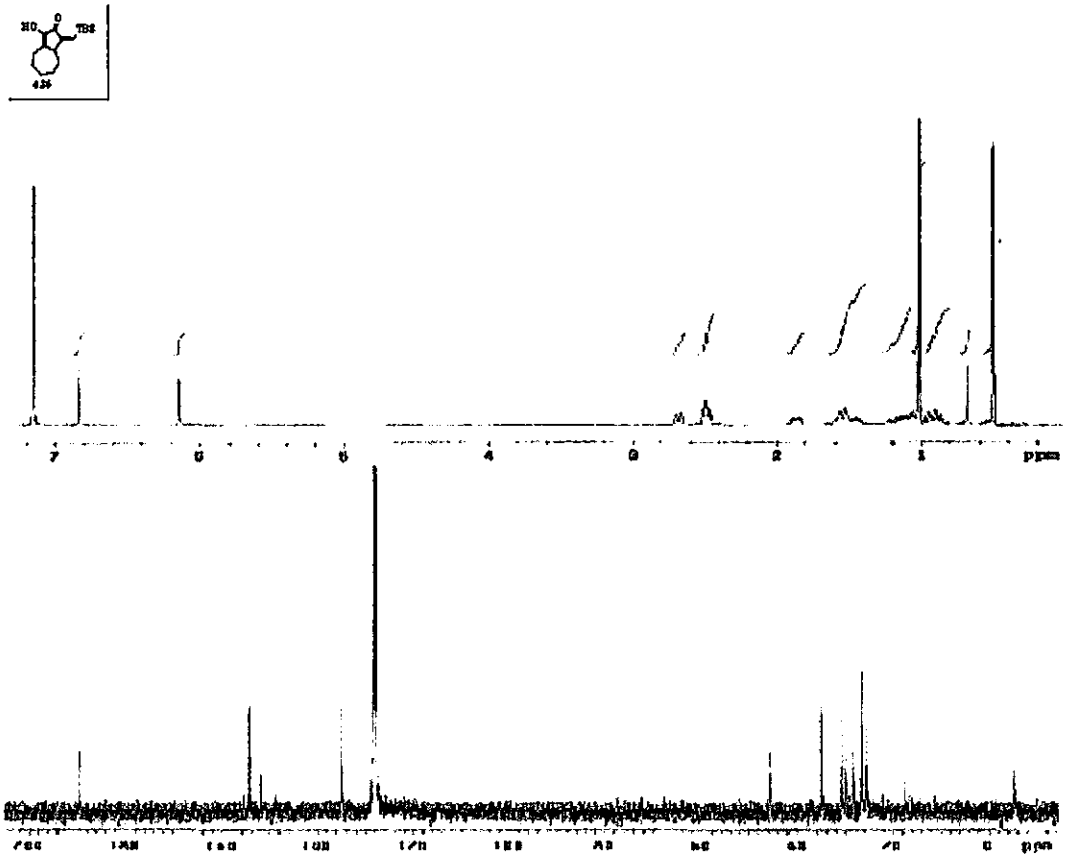
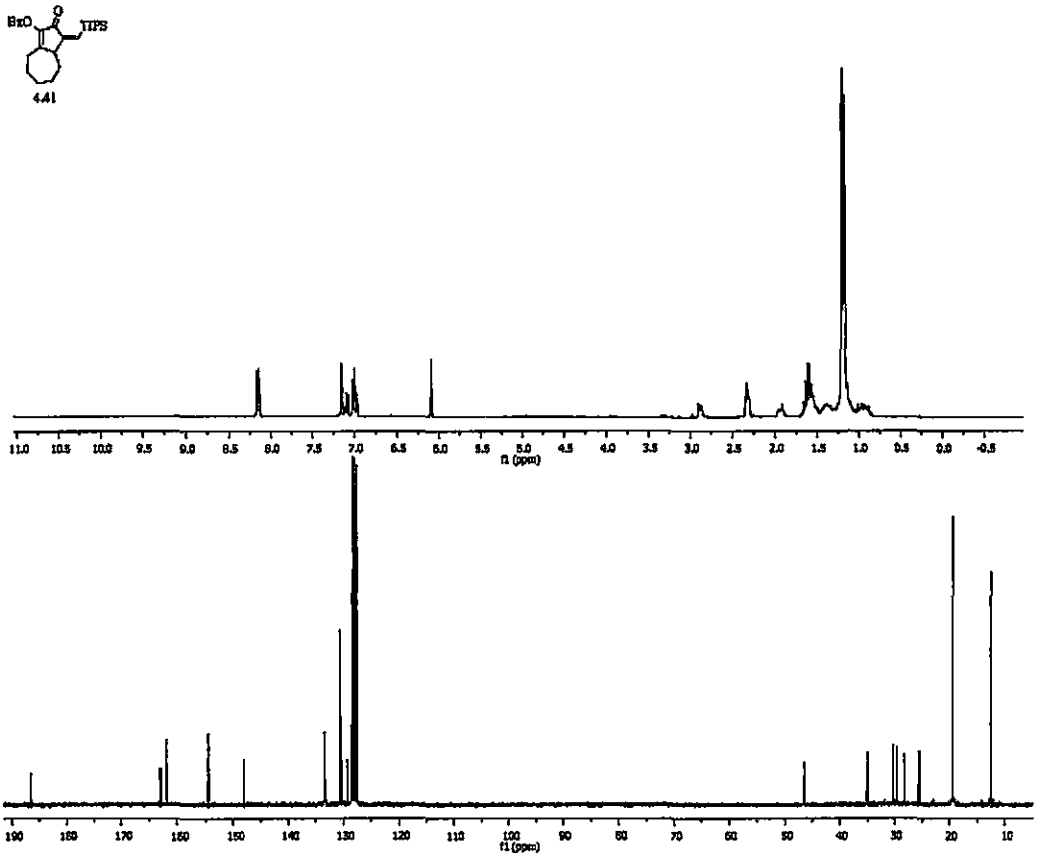





HO
O
Et
Et
OH
H3C
CH3
4.20
f1 (ppm)


BnO
O
OH
4.22
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


HO
O
TBS
4.5%
7
6
5
4
3
2
1
ppm


BnO
O
TIPS
4.41
f1 (ppm)
f1 (ppm)

7. References Cited

[1] For an overview of our work, see: Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284-290.

[1] (a) Tius, M. A.; Zhou, X. *Tetrahedron Lett.* **1989**, *30*, 4629-4632. (b) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219-4222. (c) Jang, W. B.; Hu, H.; Lieberman, M. M.; Morgan, J. A.; Stergiades, I. A.; Clark, D. S.; Tius, M. A. *J. Comb. Chem.* **2001**,*3* , 346-353.

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[1] Bee, C.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1681-1684.

[1] Banaag, A. R.; Berger, G. O.; Dhoro, F.; delos Santos, D. B.; Dixon, D. D.; Mitchell, J. P.; Tokeshi, B. K.; Tius, M. A. *Tetrahedron* **2005**, *61*, 3419-3428.

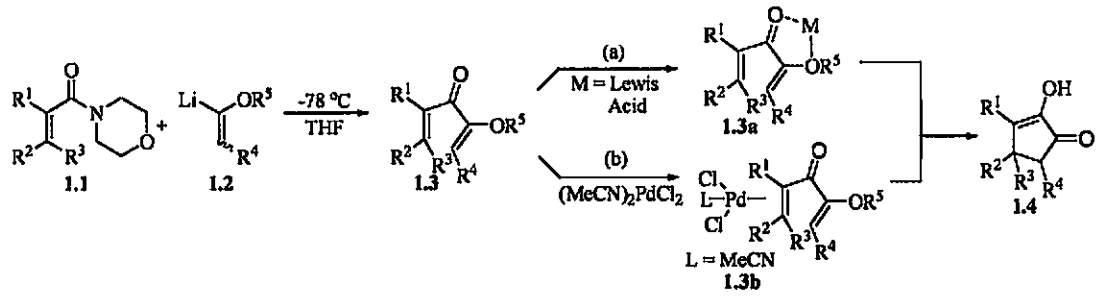
[1] The boxed cyclopentenone products highlight those that I had synthesized.

CHAPTER 4: Metal-Catalyzed Asymmetric Cyclopentannelation

1. Introduction

1.1. Project Objective

In Chapters 2 and 3, we have described a method for preparing cross-conjugated cyclopentenones *via* an allenyl ether Nazarov reaction. In this chapter, we discuss our ongoing studies toward the development of a catalytic, asymmetric Nazarov reaction for the synthesis of a more general class of cyclopentenones using α-alkoxy-substituted divinyl ketones. α-Alkoxy-substituted divinyl ketones may function as bidentate ligands for Lewis acids[1] and are reactive (due to the polarizing effects of the α-oxygen atom, refer to Chapter 1, Section 3.1) under mild reaction conditions. Thus, one possible means for introducing asymmetry in the Nazarov reaction is by using chiral oxophilic metals (see path (a), Scheme 4.1).[2] Alternatively, α-alkoxy-substituted divinyl ketones have also been shown to undergo a unique and versatile palladium(II)-catalyzed Nazarov reaction (see path (b), Scheme 4.1).[3] We hoped to develop an asymmetric variant of this method using chiral palladium(II) complexes.



Scheme 4.1

1.2. Literature Precedence

Thus far there are only three reported types of catalytic asymmetric Nazarov reactions. The first, reported by Trauner and Liang, involved cyclization of cyclopentenyl(3,4-dihydro-2*H*-pyran-6-yl)methanone **1.5** with enantioselectivity of 61% *ee* using chiral (pybox)scandium(III) triflate **1.6** (equation [1], Figure 4.1).[4] Shortly thereafter, Aggarwal and Belfield disclosed the efficient (box)copper(II)-catalyzed cyclization of divinyl ketoester **1.8** to obtain α-carboxycyclopentenone **1.11** with enantioselectivities of up to 88% *ee* (equation [2], Figure 4.1).[5] Recently, Reuping *et al.* described the first asymmetric organocatalytic Nazarov reaction with enantioselectivity as high as 95% *ee* using a unique BINOL-derived Brønsted acid **1.13** (equation [3], Figure 4.1).[6]

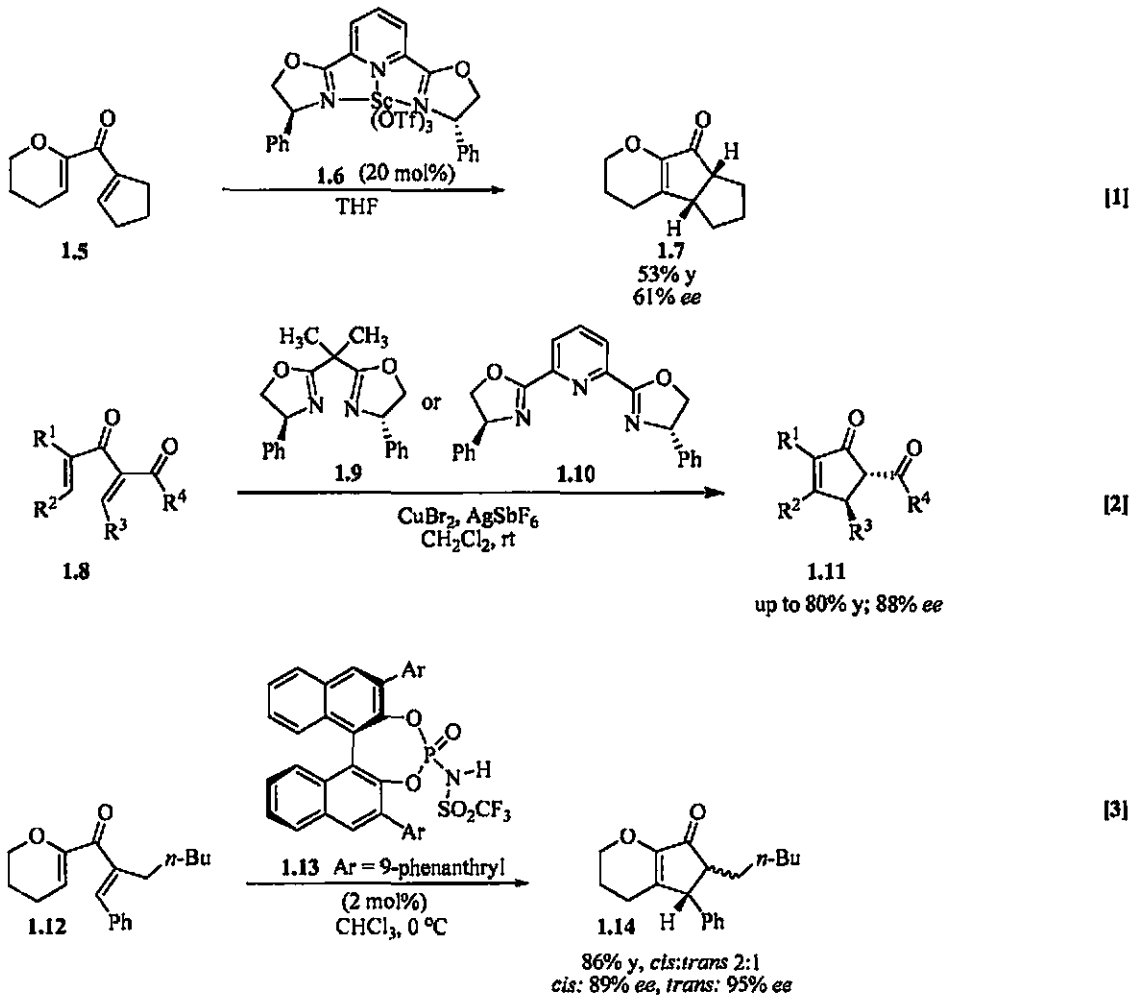


Figure 4.1. Recent Examples of Catalytic Asymmetric Nazarov Reactions

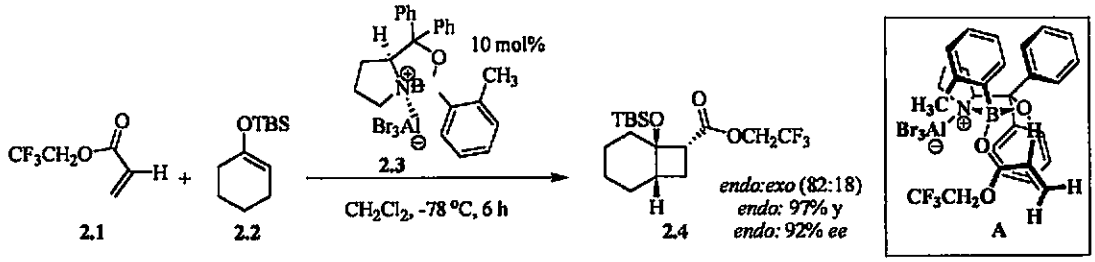
2. Catalytic Asymmetric Nazarov Reactions *via* Oxophilic Metals

Present work within the Tius laboratory is aimed towards developing a method for synthesizing cyclopentenone 1.4 (Scheme 4.1) catalytically and asymmetrically using chiral oxophilic metal catalysts.

2.1. Corey-Bakshi-Shibata (CBS)-Catalyzed Nazarov Reaction

2.1.A. Rationale

In 2007, Corey and Canales disclosed a highly enantioselective [2+2] cycloaddition reaction catalyzed by chiral aluminum bromide complex **2.3** (Scheme 4.2).[7] Numerous enol ethers were treated with trifluorethyl acrylate **2.1** in the presence of catalyst **2.3** to form cyclobutanes in excellent yields and optical purity. The stereochemistry of the products was rationalized by pre-transition state assembly **A** in which the chiral catalyst **2.3** is associated with trifluorethyl acrylate **2.1** through two interactions: (1) coordination of the boron atom of catalyst **2.3** to the carbonyl of **2.1** (2) interactions between the oxygen atom of catalyst **2.3** and the hydrogen atom that is α to the carbonyl of **2.1**.



Scheme 4.2

We were drawn to this method particularly since similar interactions as those in pre-transition state assembly **A** were shown to be critical for optimal enantioselectivity in our allenyl ether Nazarov reaction (Figure 4.2).[8] As described in Chapter 2, these interactions had the effect of both minimizing conformational mobility and allowing for the sterics of a shielding substituent (*e.g.* C4 substituent on **2.5**) on the auxiliary to control the direction of conrotatory ring closure.

Figure 4.2. Proposed Stereochemistry-Determining Transition State of the Asymmetric Allenyl Ether Nazarov Reaction

It was believed that if a pre-transition state similar to complex **A** were to form in the CBS-catalyzed Nazarov reaction of divinyl ketone **2.8** (Figure 4.3) then the two key interactions would likewise have the effect of minimizing the free rotation of the divinyl ketone. In this case, the key interactions would be the coordination of the carbonyl oxygen atom of divinyl ketone **2.8** to the boron atom of catalyst **2.3** as well as the electrostatic interactions between the catalyst's oxygen atom lone electron pair to the developing carbocation of the divinyl ketone **2.8** (see complex **B**, Figure 4.3). As with the allenyl ether Nazarov reaction, the resultant pentadienyl cation would be immobilized in such a way that allows the phenyl substituents of the catalyst to shield the back face of the pentadienyl cation and thus control the direction of conrotation in a counter-clockwise sense (as viewed by the reader).

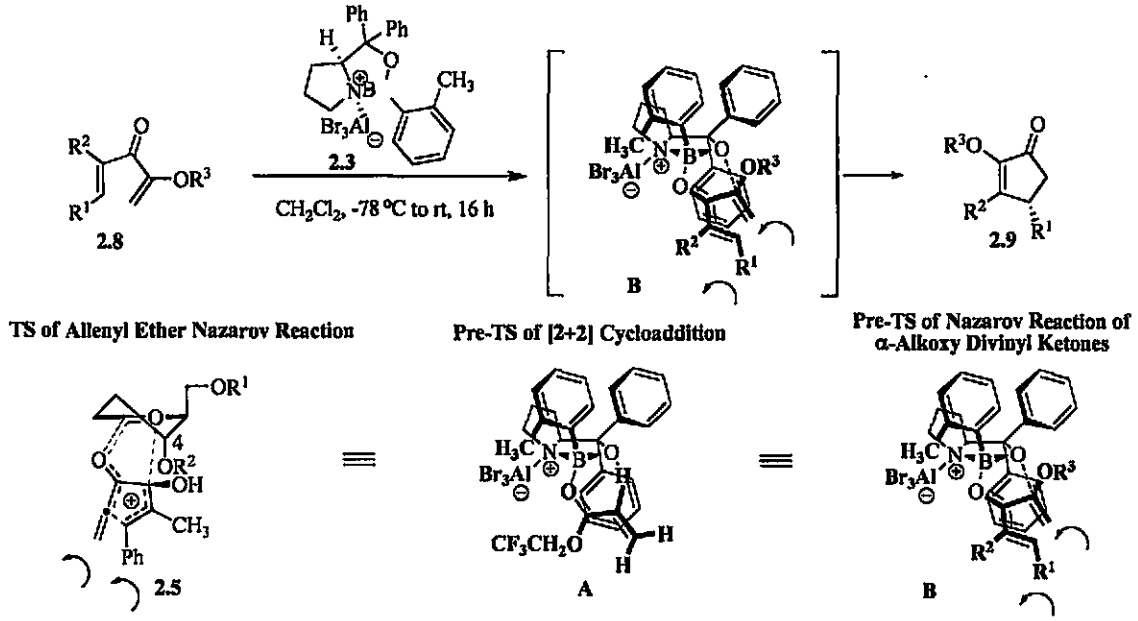
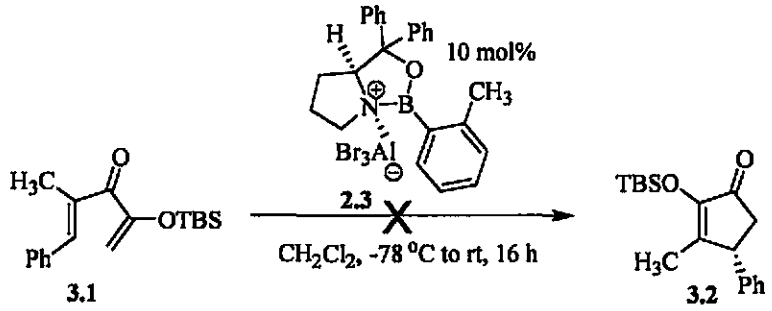


Figure 4.3. Proposed Pre-Transition State Assembly of CBS-Catalyzed Nazarov Reaction of Divinyl Ketone 2.8 and its Structural Homology with Stereochemistry-Determining Complexes of Nazarov Reactions from Chiral Allenes and [2+2] Cycloadditions Using CBS Catalyst

2.1.B. Present Work with CBS-Catalyzed Nazarov Reaction

Cyclizations of silyl enol ether **3.1** were performed using the conditions described for Corey's [2+2] cycloaddition reactions (Scheme 4.3).[7] Catalyst **2.3** was prepared fresh and was introduced to a solution of silyl enol ether **3.1** in dichloromethane at -78 °C. The reaction was gradually warmed and monitored periodically as the temperature of the reaction was allowed to rise. However, after 16 h at room temperature only unreacted silyl enol ether **3.1** was observed.



Scheme 4.3

The fact that divinyl ketone **3.1** failed to cyclize was suspected to be due to the poor reactivity of the divinyl ketone. As will be discussed shortly, problems with reactivity using divinyl ketone **3.1** were also encountered using ytterbium(III) triflate (see Section 2.2.).

2.2. Chiral $Yb(OTf)_3$-Catalyzed Nazarov Reaction

2.2.A. Prior Work Towards a Chiral $Yb(OTf)_3$-Catalyzed Nazarov Reaction

Earlier in the Tius laboratory Dr. Eric Leclerc had shown that a variety of metals (ytterbium(III), scandium(III), copper(II), zinc(II)) could cyclize substrate **3.3** to cyclopentenone **3.6** in moderate to good yields under mild reaction conditions (Figure 4.4).[2]

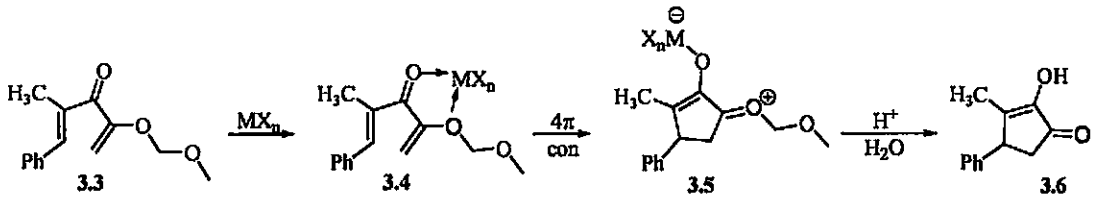
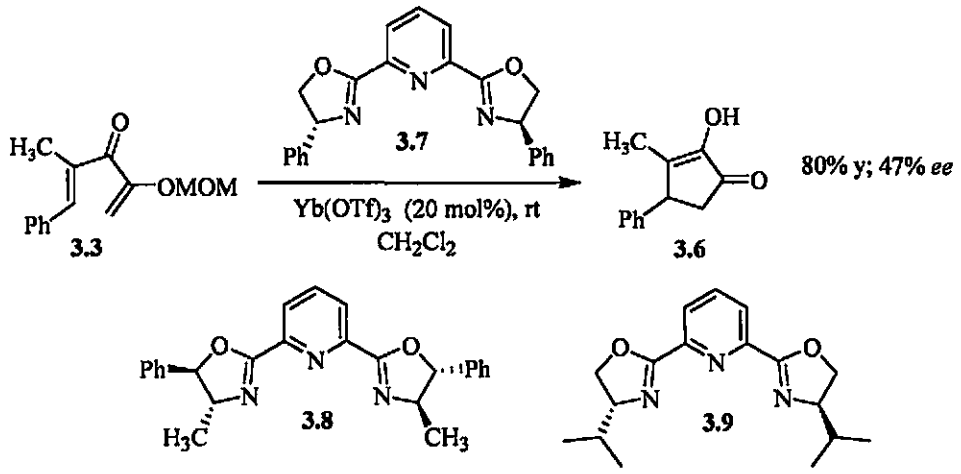


Figure 4.4. Mechanism of the Oxophilic Metal-Catalyzed Nazarov Reaction Using Divinyl Ketone 3.3

A number of asymmetric catalysts were prepared from these metals and were evaluated from their reactions with divinyl ketone **3.3**. Among the catalysts, ((*R*)-Ph-pybox)ytterbium(III) triflate (in dichloromethane) was demonstrated to be most efficient in reactivity and enantioselectivity (47% *ee*). Attempts to optimize enantioselectivity further using several solvents, ligands and additives with ytterbium(III) led to the results shown in Figure 4.5. Solvents other than dichloromethane (entries 1 through 3) led to poorer asymmetric induction. Entries 4 through 6 show that the reaction was completely inhibited by protic additives. Reactions in which ytterbium(III) trichloride was used also led to the recovery of unreacted starting divinyl ketone **3.3** (entry 7). On the other hand, while cyclization was observed from reactions with $[((R)\text{-Ph-pybox})Yb]^{3+}[SbF_6^-]_3$, the product formed was racemic (entry 8). Chiral complexes of ytterbium(III) with pybox ligands **3.8** and **3.9** were also evaluated but were no better than chiral complexes with ligand **3.7** (entries 9 and 10).



Entry	Ligand	Metal	Additive	Solvent	Yield(%)	*ee*(%)
1	**3.7**	$Yb(OTf)_3$	none	$CHCl_3$	64	26
2	**3.7**	$Yb(OTf)_3$	none	CH_3NO_2	69	-31
3	**3.7**	$Yb(OTf)_3$	none	THF	64	-24
4	**3.7**	$Yb(OTf)_3$	*i*-PrOH	toluene	-	-
5	**3.7**	$Yb(OTf)_3$	0.5% H_2O	CH_2Cl_2	-	-
6	**3.7**	$Yb(OTf)_3$	2,4,6-tri-*t*-butylphenol	CH_2Cl_2	-	-
7	**3.7**	$YbCl_3$	none	CH_2Cl_2	-	-
8	**3.7**	$YbCl_3$	$AgSbF_6$	CH_2Cl_2	54	-
9	**3.8**	$Yb(OTf)_3$	none	CH_2Cl_2	74	-22
10	**3.9**	$Yb(OTf)_3$	none	CH_2Cl_2	16	0

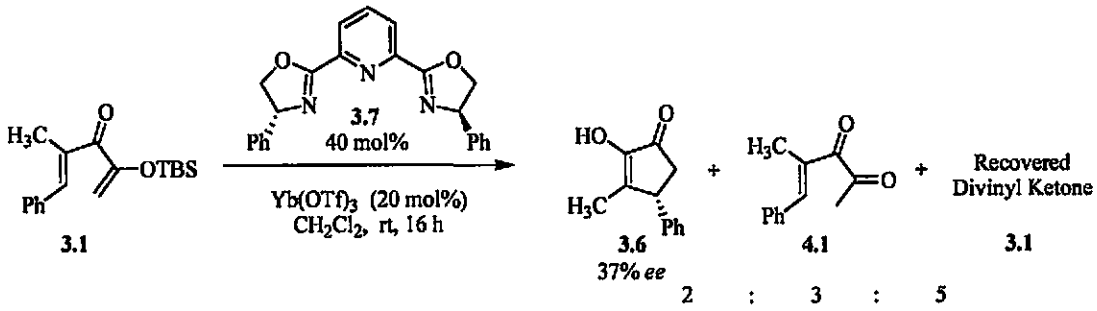
[a]All chiral complexes were prepared by pre-complexing the anhydrous Lewis acid to the chiral ligand at rt for at least 1.5 h in the corresponding solvents prior to use.

Figure 4.5. Conditions Screened for the Catalytic Asymmetric Nazarov Reactions Using (pybox)Yb(III) and Divinyl Ketone 3.3

2.2.B. Present Work Towards a Chiral $Yb(OTf)_3$-Catalyzed Nazarov Reaction

As an extension of this work, we decided to evaluate silyl enol ether **3.1** (Scheme 4.4), predicting that the large, more labile silyl group would improve reactivity and discrimination of the two enantiotopic faces of the divinyl ketone. Silyl enol ether **3.1** was treated with 20 mol% of ((*R*)-Ph-pybox)ytterbium(III) triflate in dichloromethane at room temperature (the optimized conditions shown in Figure 4.5). After 16 h the reaction progressed no further and only led to compounds **3.6**, **4.1** and **3.1** in a 2:3:5 ratio based on ^1H NMR estimation of the

crude material. Although cyclopentenone **3.6** was of slightly lower enantiomeric excess (37% *ee*) in this reaction compared to the product derived from divinyl ketone **3.3** (47% *ee*) the difference was not significant enough to draw any conclusions about the relevance of the size of the α substituent on the divinyl ketone on the enantioselectivity of the reaction. A screen of additional divinyl ketones bearing larger silyl groups, such as TIPS or *t*-$BuPh_2Si$ will be performed in due course in the hope that they will reveal a more obvious trend.



Scheme 4.4

2.3. Conclusions and Future Work Towards a Chiral Oxophilic Acid-Catalyzed Nazarov Reaction

Attempts to promote cyclization of silyl enol ether using CBS catalyst **2.3** (Scheme 4.3) only led to recovered starting material. On the other hand, while cyclization of silyl enol ether **3.1** using ytterbium(III) triflate was observed, the reaction was significantly slower than cyclizations using divinyl ketone **3.3** (Figure 4.5). Whereas reactions with divinyl ketone **3.3** were complete after 16 h, reactions with silyl enol ether **3.1** led to only minimal amounts of cyclic product **3.6** in addition to hydrolyzed silyl enol ether **4.1** and a significant amount of recovered starting material **3.1**. It is conceivable that additives, such as molecular sieves,

triphenylphosphine oxide (Ph_3PO) and TMSCl may improve catalytic efficiency (Figure 4.6). The addition of triphenylphosphine oxide would presumably promote desilylation of divinyl ketone **4.2** to give enolate **4.3**.[9] Following conrotatory ring closure, the presence of TMSCl would allow the conversion of intermediate **4.4** to cyclopentenone **3.6** to take place faster and regenerate the catalyst. Lastly, molecular sieves would scavenge residual Brønsted acid and suppress formation of diketone **4.1** and other potential background reactions. We hope to explore these options and evaluate additional chiral ligands (*e.g.* additional box ligands, pybox, BINAP ligands) in our future investigations.

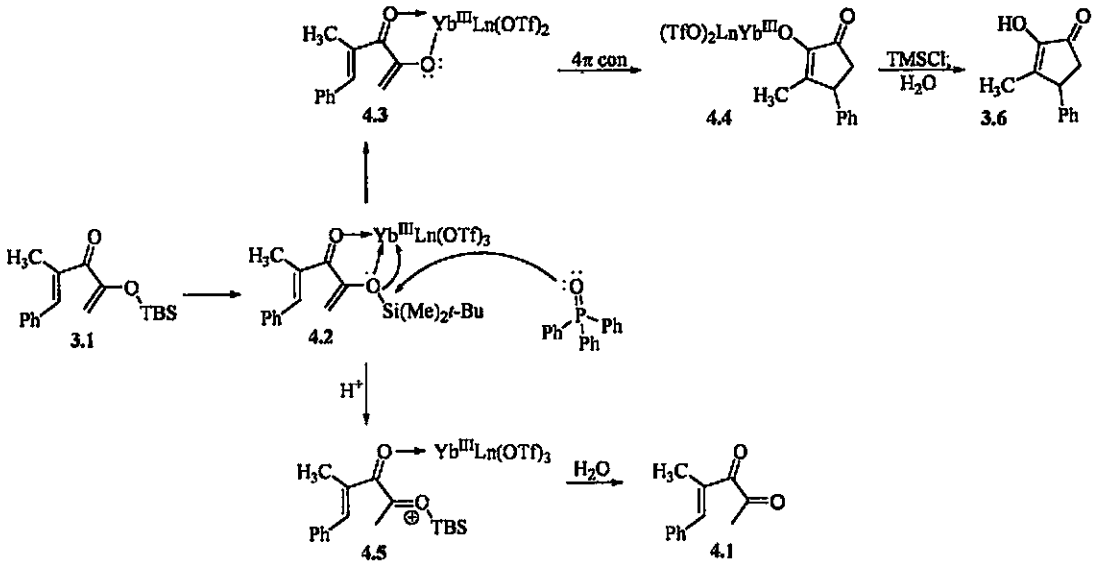


Figure 4.6. Mechanism of the Catalytic Asymmetric Nazarov Reactions Using (pybox)Yb(III) and Silyl Enol Ether 3.1 with Ph_3PO, TMSCl and Molecular Sieves

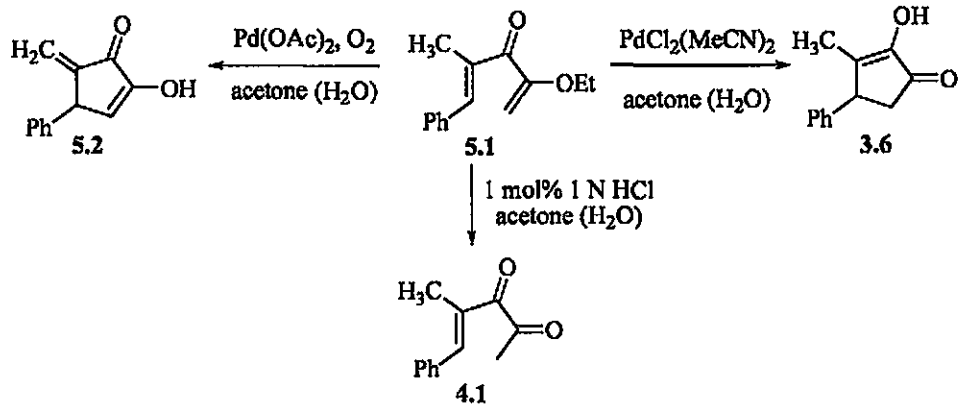
3. Palladium(II)-Catalyzed Nazarov Reaction

With little success from oxophilic metal-catalyzed cyclizations of α-alkoxy-substituted divinyl ketones, we shifted our efforts toward palladium(II)-catalyzed cyclizations. The results of these preliminary investigations are discussed in what follows.

3.1. Background for the Palladium(II)-Catalyzed Nazarov Reaction

During the course of surveying Lewis acid catalysts for the cyclization of divinyl ketone **5.1**, Dr. Eric Leclerc had observed two distinct reactions to take place depending on the source of palladium(II) used (Scheme 4.5).[3] Further studies to evaluate the scope of each reaction and to determine the mechanism by which each reaction proceeded was later performed by former group member of the Tius laboratory, Dr. Cisco Bee shortly thereafter. From these subsequent investigations it was shown that treatment of substrate **5.1** with $PdCl_2(MeCN)_2$ provided the expected cyclopentenone **3.6**, whereas treatment with $Pd(OAc)_2$ provided cross-conjugated cyclopentenone **5.2** exclusively. As will be discussed, reactions with $Pd(OAc)_2$ resulted in a net oxidation of **5.1** and a reduction of Pd(II) to Pd(0). Therefore, in order to regenerate Pd(II) and restore the catalytic cycle reactions had to be performed under an oxygen atmosphere.

Formation of cyclized product **3.6** from adventitious HCl was ruled out by the control experiment summarized in Scheme 4.5. As shown, exposure of **5.1** to 1 mol% of 1 N HCl in aqueous acetone provided only diketone **4.1** quantitatively after three days.



Scheme 4.5

3.2. Mechanism for the Palladium(II)-Catalyzed Nazarov Reaction

Since palladium(II) chloride is known to have a high affinity for π electrons,[10] it was postulated that formation of α-hydroxycyclopentenones **5.2** and **3.6** from divinyl ketone **5.1** involved an initial π-palladium(II) complex. The mechanism proposed for the formation of α -hydroxycyclopentenones is detailed in Figure 4.7.

Although complexation to the electron-rich enol ether (see **5.3**, Figure 4.7) is preferred, this cannot lead to the formation of α-hydroxycyclopentenones **3.6** and **5.2**. Formation of complex **5.3** is believed to be reversible and can either result in hydrolysis to diketone **4.1** or equilibrate to the productive intermediate **5.4**, in which case the olefin is activated towards intramolecular attack from the enol ether. The resultant palladium enolate **5.5** has one of two possible fates depending on the counteranion. When X=Cl, migration and subsequent hydrolysis (by the strong acid) furnishes cyclopentenone **3.6**. On the other hand, when X=OAc, intermediate **5.5** undergoes deprotonation from the more basic acetate anion (compared to the chloride anion) and subsequent β-elimination to provide cross-conjugated

cyclopentenone **5.2**. The pathway towards formation of **5.2** is not catalytic as a net oxidation of divinyl ketone **5.1** takes place concurrently with the reduction of Pd(II) to Pd(0). To make the process catalytic Pd(0) must be reoxidized back to Pd(II). Among a number of oxidants that were evaluated, the most effective was found to be atmospheric oxygen in DMSO.

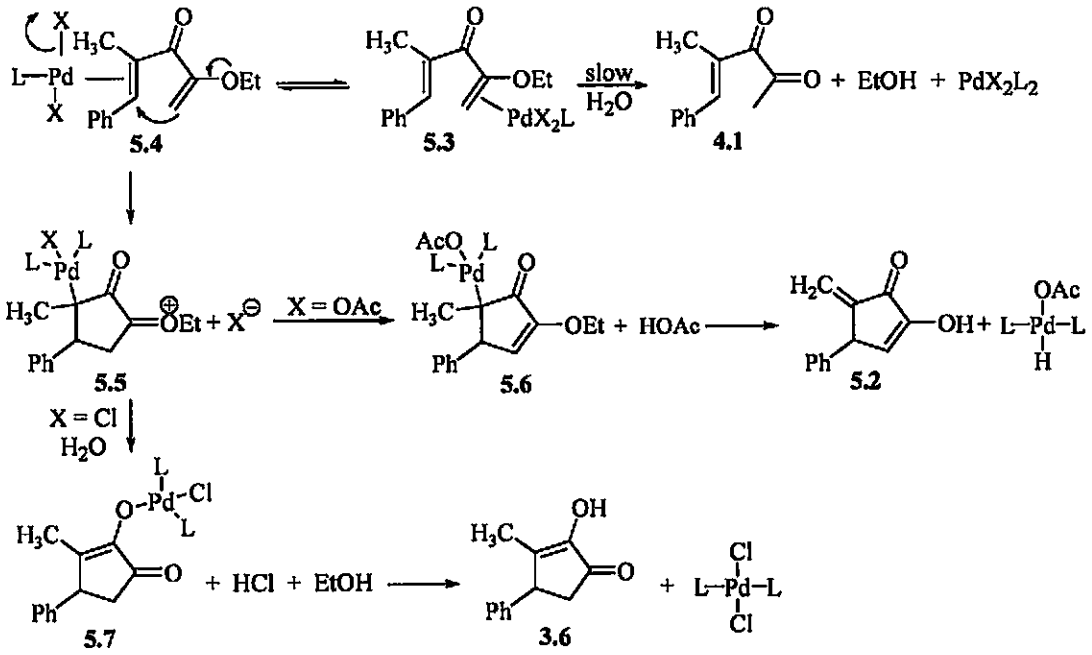
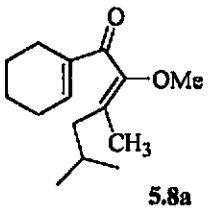
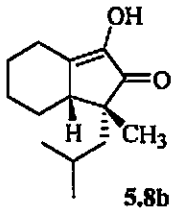
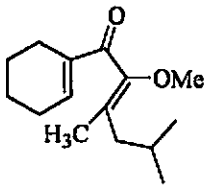
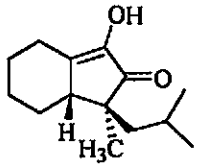
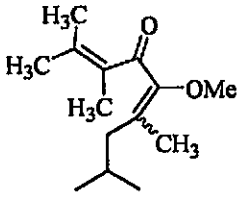
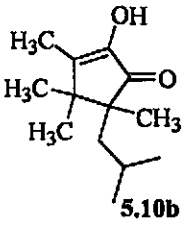
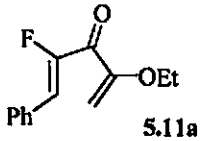
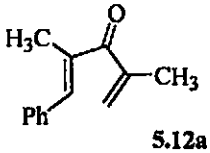


Figure 4.7. Mechanism of the Palladium(II)-Catalyzed Nazarov Reaction

Of the two pathways, the $PdCl_2(MeCN)_2$-catalyzed process was of more interest since it was a highly efficient approach towards the synthesis of cyclopentenones bearing adjacent quaternary carbon centers (see **5.10b**, Table 4.1). Additionally, there are few noteworthy examples of this reaction that lend support for the proposed π-palladium(II)-activated Nazarov mechanism (Table 4.1). First, complete transfer of stereochemistry in divinyl ketones **5.8a** and **5.9a** to α-hydroxycyclopentenones **5.8b** and **5.9b**, respectively, was

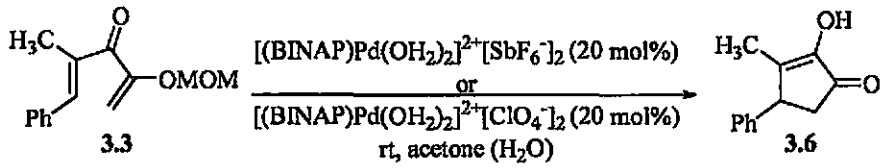
suggestive of an electrocyclic Nazarov reaction. Second, the fact that the deactivated α-fluoro divinyl ketone **5.11a** failed to react suggests that the catalytic cycle must be initiated upon formation of complex **5.4**. Last, divinyl ketone **5.12a** also did not undergo cyclization, which underscored the role of the enol ether.

Table 4.1. α-Hydroxycyclopentenones Formed from $PdCl_2(MeCN)_2$-Catalyzed Nazarov Reactions

Divihy Ketone	α-Hydroxycyclopentenone	
 **5.8a**	 **5.8b**	90% y
 **5.9a**	 **5.9b**	74% y
 **5.10a**	 **5.10b**	79% y
 **5.11a**		No Reaction
 **5.12a**		No Reaction

3.3. Work Towards an Asymmetric Palladium(II)-Catalyzed Nazarov Reaction

The palladium(II)-catalyzed Nazarov offers opportunities for asymmetric catalysis through the use of chiral ligands. The work reported herein consists of the preliminary screens of chiral ligands and reaction conditions during the development of an asymmetric version of the palladium(II)-catalyzed Nazarov reaction. Axially chiral bidentate phosphine ligands were first evaluated by Dr. Eric Leclerc in our group using divinyl ketone **3.3** in aqueous acetone (Scheme 4.6).



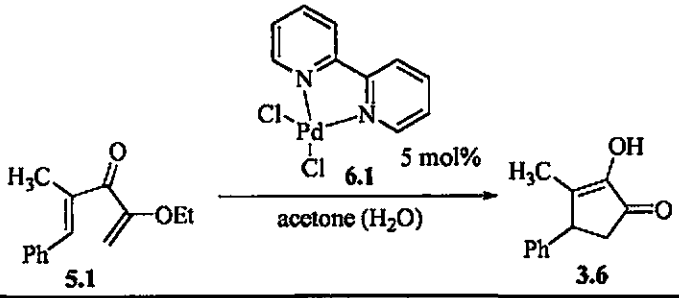
Scheme 4.6

Neutral binaphthyl palladium(II) complexes were unreactive and were therefore converted to dicationic $[(BINAP)Pd(II)]^{2+}$ with two equivalents of silver hexafluoroantimonate ($AgSbF_6$) or silver perchlorate ($AgClO_4$). Although cyclization was observed for each dicationic complex, the products obtained were both racemic. Two obvious concerns were racemization of the product and the possibility of a silver-catalyzed reaction. As a control study, substrate **3.3** was submitted to catalytic $AgSbF_6$ in aqueous acetone at room temperature. After a period of one day, no cyclization was observed. To address whether racemization was occurring, optically enriched cyclopentenone **3.6** (19% *ee*) was resubmitted to the initial reaction conditions. After 12 h, no significant erosion (17% *ee*) in enantiomeric excess was detected. Clearly, racemization was not occurring and the dicationic binaphthyl palladium(II) complex was indeed the active catalyst.

The objective of the present study was first, to probe the reactivity of general divinyl ketones using catalysts of variable reactivity and second, to evaluate the enantioselectivity from a range of structurally diverse chiral ligands.

3.3.A. Nitrogen,Nitrogen (N,N) Ligands[11]

Of all possible ligands, bipyridine (bipy) was first evaluated since it was moderately basic and was therefore not expected to deactivate palladium(II) (Figure 4.8). Divinyl ketone **5.1** was treated with (bipy)palladium(II) chloride **6.1** at room temperature in aqueous acetone. Cyclization was neither observed after 48 h at room temperature nor after 2 h at 50 °C. The reaction was repeated using $[(bipy)PdCl]^{+}SbF_6^{-}$. After 5 h at room temperature cyclization was complete, indicating that at a minimum a monocationic palladium(II) catalyst was required for cyclization of divinyl ketone **5.1**. Thus, for all subsequent screens only cationic chiral palladium(II) complexes were investigated.



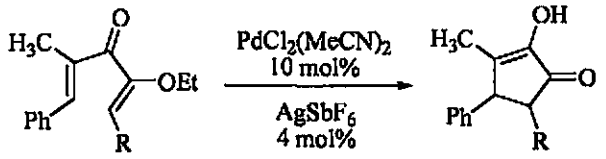
Entry	Additive (equiv)	T(° C)	Time(h)	Conversion(%)
1	none	rt	48	0
2	none	50	2	0
3 [a]	$AgSbF_6$ (0.04)	rt	5	100

[a] The cationic catalyst was freshly prepared prior to use by mixing (bipy)$PdCl_2$ and $AgSbF_6$ in wet acetone at rt for 1 h.

Figure 4.8. Conditions Screened for the Catalytic Nazarov Reactions Using (bipy)Palladium(II) Complex 6.1 and Divinyl Ketone 5.1

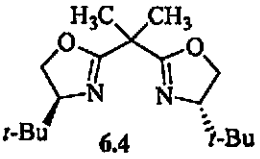
To our knowledge there are currently no commercially available optically pure bipyridine ligands. Although the syntheses of many bipyridine ligands have been reported, they involve many steps.[12] On the other hand, since a wide array of chiral bis(oxazoline) ligands are commercially available[13] and have led to high enantioselectivity in copper-catalyzed Nazarov cyclizations[3] we considered them appropriate alternatives for our screens. Two divinyl ketones were evaluated in combination with chiral (box)palladium(II) complexes.

The experiments summarized in Figure 4.9 were conducted using (box)palladium(II) complexes **6.4** and **6.5** in aqueous acetone. In all experiments, the catalytic complexes were pre-formed by mixing ligand **6.4** or **6.5** with $PdCl_2(MeCN)_2$ in the respective solvent one hour prior to use. The divinyl ketones **5.1** and **6.2** were individually dissolved with the same solvents as those of the catalysts and each divinyl ketone solution was treated with its corresponding catalyst solution at 0 °C. With the exception of entries 1, 3 and 9, all reactions were warmed to room temperature. Although cyclization was observed under all conditions, excluding those of entries 6 and 8, all cyclopentenone products were racemic. Despite the lack of enantioselectivity, two interesting observations were made. First, the catalyst complex from **6.4** exhibited higher catalytic efficiency compared to the catalyst complex from **6.5**. Second, divinyl ketone **6.2** was more reactive compared to divinyl ketone **5.1**.

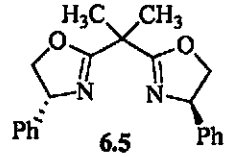


5.1 R = H
6.2 R = $(CH_2)_2Ph$

3.6 R = H
6.3 R = $(CH_2)_2Ph$



6.4



6.5

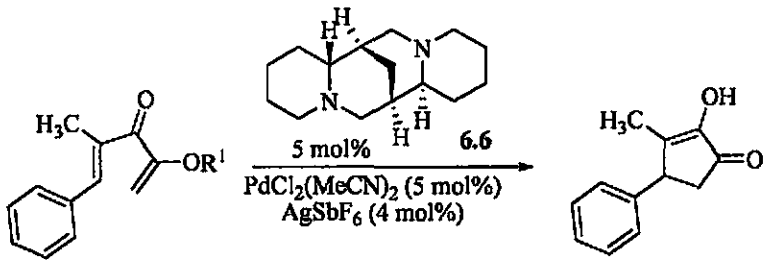
Entry	Ligand	Substrate	Solvent	T(° C)	Time(h)	Conversion(%)	*ee*(%)
1	**6.4**	**6.2**	Acetone (H_2O)	0	16	50	0
2	**6.5**	**5.1**	Acetone (H_2O)	rt	14	50	0
3	**6.4**	**6.2**	Acetone (H_2O)	0	3	60	0
4	**6.5**	**5.1**	Acetone (H_2O)	rt	2	40	0
5	**6.4**	**5.1**	THF (H_2O)	rt	120	95	0
6	**6.4**	**5.1**	CH_3CN (H_2O)	rt	120	<5	-
7	**6.4**	**5.1**	CH_3NO_2 (H_2O)	rt	120	90	0
8	**6.4**	**5.1**	DMSO (H_2O)	rt	44	streaking	-
9	**6.4**	**5.1**	HFIP	0	120	40	0

[a] The chiral catalysts were freshly prepared prior to use by mixing $PdCl_2(MeCN)_2$ with ligand **6.4** or **6.5** in the corresponding solvent at rt. After 1 h, $AgSbF_6$ was added and the mixture was stirred for 30 min at rt.

Figure 4.9. Conditions Screened for the Catalytic Nazarov Reactions Using Palladium(II), Bisoxazoline 6.4 and 6.5 and Divinyl Ketones 5.1 and 6.2

Since related bis(oxazoline)-palladium(II) complexes are known to undergo decomplexation,[14] it was conceivable that the reactions shown in Figure 4.9 were actually catalyzed by ligand-free palladium(II). We therefore shifted our attention to an alternative N,N ligand, sparteine (sp) **6.6** (Figure 4.10), expecting that the more basic tertiary amine would form a more stable complex with palladium(II). Anticipating that the more basic tertiary amine would concomitantly deactivate the catalyst, we performed the screens using a known reactive monocationic complex, $[pyr(sp)Pd(II)Cl]^+SbF_6^-$.[15] The catalyst was introduced to individual solutions of divinyl ketones **3.1** and **5.1** using the conditions detailed in Figure 4.10. Reactions with substrate **3.1** in wet acetone at room temperature for one day led to full recovery of starting material. Similarly, reactions with divinyl ketone and **5.1** also

led to the recovery of starting material under same reaction conditions, as well as in dimethylsulfoxide and refluxing dichloromethane. This led us to suspect that tertiary amine ligands would not be suitable since they nullified the reactivity of palladium(II).



3.1 R^1 = TBS
5.1 R^1 = Et

3.6

Entry	Substrate	Solvent	T(°C)	Time(h)	Conversion(%)	*ee*(%)
1	**3.1**	Acetone (H_2O)	rt	24	0	-
2	**5.1**	Acetone (H_2O)	rt	24	0	-
3	**5.1**	CH_2Cl_2	reflux	10	0	-
4	**5.1**	DMSO (H_2O)	100	10	0	-

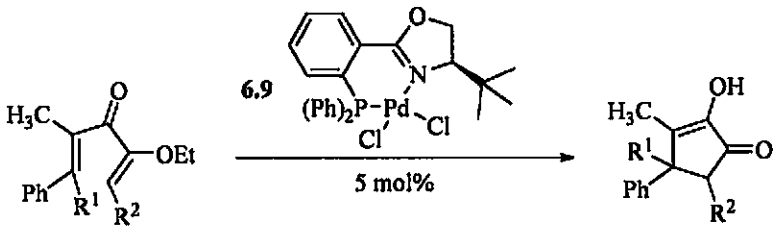
Figure 4.10. Conditions Screened for the Catalytic Nazarov Reactions Using Palladium(II), (-)Sparteine and Divinyl Ketones 3.1 and 5.1

Taken together, the preliminary studies from this present work and the work from former group members have shown that neutral or monocationic palladium(II) complexes with strongly coordinating ligands such as those containing bidentate phosphine or tertiary nitrogen atoms are unreactive catalysts. Conversely, while monocationic palladium(II) complexes consisting of bipyridine or bis(oxazolines) ligands have been able to promote cyclization, all reactions led to racemic products. Since related bis(oxazoline)-palladium(II) complexes are known to undergo decomplexation,[15] it is conceivable that the reactions shown in Figure 4.9 may have actually been catalyzed by ligand-free palladium(II).

To circumvent these problems, we turned to a P,N ligand in the hope that a bidentate ligand with only one phosphorous atom would ensure that palladium(II) remains ligated and reactive. Substrates **5.1** and **6.2** were each evaluated so that the effects variable substitution motifs of the divinyl ketone on the kinetics and enantioselectivity of the cyclization could also be probed.

3.3.B. Phosphine,Nitrogen (P,N) Ligands

Divinyl ketones **5.1**, **6.7** and **6.2** were individually treated with mono- and dicationic complexes of catalyst **6.9** using the conditions listed in Figure 4.11. As shown, divinyl ketone **6.2** was most reactive and had cyclized at room temperature and with a monocationic catalyst (entry 3). Substrate **5.1** also reacted with a monocationic catalyst but required elevated temperature (entry 1). Of the three substrates, divinyl ketone **6.7** was the least reactive and only cyclized upon treatment with dicationic catalyst (entry 5). Moreover, with the exception of benzene, cyclization was observed in all the solvents listed in Figure 4.11. As with all previous cyclizations, all the reactions led to racemic products. At this time the reason behind the lack of enantioselectivity of this reaction remains unclear.



5.1 $R^1 = R^2 = H$
6.7 $R^1 = CH_3$; $R^2 = H$
6.2 $R^1 = H$; $R^2 = (CH_2)_2Ph$

3.6 $R^1 = R^2 = H$
6.8 $R^1 = CH_3$; $R^2 = H$
6.3 $R^1 = H$; $R^2 = (CH_2)_2Ph$

Entry	Substrate	$AgSbF_6$ (equiv)	Solvent	T(° C)	Time(h)	Conversion(%)	*ee*(%)
1	**5.1**	0.04	Acetone (H_2O)	50	27	60	0
2	**6.7**	0.04	Acetone (H_2O)	50	27	0	-
3	**6.2**	0.04	Acetone (H_2O)	rt	19	70	0
4	**5.1**	0.08	Acetone (H_2O)	rt	6	60	0
5	**6.7**	0.08	Acetone (H_2O)	rt	45	60	0
6	**5.1**	0.08	CH_3CN	45	48	40	0
7	**5.1**	0.08	CH_3NO_2	45	48	95	0
8	**5.1**	0.08	CH_2Cl_2	0	5.5	90	0
9	**5.1**	0.08	benzene	45	48	0	-
10	**6.7**	0.08	CH_2Cl_2	0	1.2	5	0

[a] The cationic catalyst was freshly prepared prior to use by mixing $PdCl_2(MeCN)_2$ with ligand **6.9** and in the corresponding solvents at rt. After 1 h, $AgSbF_6$ was added and the mixture was stirred for 30 min at rt.

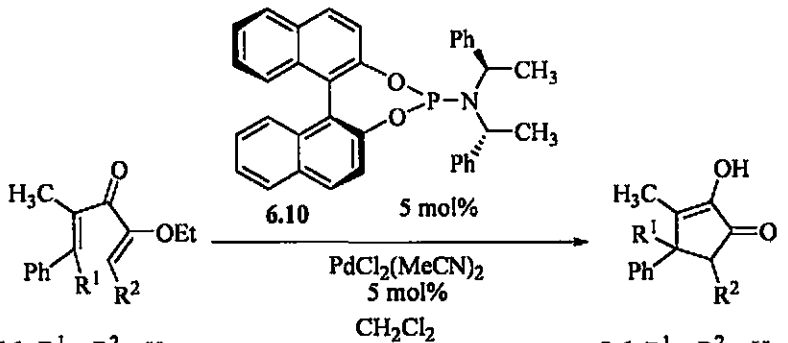
Figure 4.11. Conditions Screened for the Catalytic Nazarov Reactions Using Palladium(II) Complex 6.9 and Divinyl Ketones 5.1, 6.7 and 6.2

3.3.C. Phosphoramidite Ligand

Despite the lack of asymmetric induction, entries 1 and 3 of Figure 4.11 showed that a monocationic phosphine-based palladium(II) complex was capable of initiating cyclization for substrates **5.1** and **6.2**. We therefore evaluated a monocationic complex of palladium(II) with monodentate, phosphine-based ligand **6.10** (Figure 4.12).[16]

Pre-complexation of the catalyst was accomplished by mixing together the phosphoramidite ligand and $PdCl_2(MeCN)_2$ in a 1:1 ratio (Figure 4.12). After one hour, divinyl ketones **5.1, 6.7** and **6.2** were individually treated with 5 mol% of the resultant

phosphoramidite-palladium(II) complex in the previously established optimal solvent, dichloromethane (see Section 3.3.A). For all divinyl ketones, neutral, mono- and dicationic phosphoramidite palladium(II) were evaluated. However, in each case no reaction took place.



5.1 $R^1 = R^2 = H$
6.7 $R^1 = CH_3$; $R^2 = H$
6.2 $R^1 = H$; $R^2 = (CH_2)_2Ph$

3.6 $R^1 = R^2 = H$
6.8 $R^1 = CH_3$; $R^2 = H$
6.3 $R^1 = H$; $R^2 = (CH_2)_2Ph$

Entry	Substrate	$AgSbF_6$ (equiv)	T(° C)	Time(h)	Conversion(%)	*ee*(%)
1	**5.1**	0.00	rt	14	0	-
2	**6.7**	0.00	rt	14	0	-
3	**6.2**	0.00	rt	14	0	-
4	**5.1**	0.04	rt	3	0	-
5	**6.7**	0.04	rt	3	0	-
6	**6.2**	0.04	rt	3	0	-
7	**5.1**	0.08	rt	3	0	-
8	**6.7**	0.08	rt	3	0	-
9	**6.2**	0.08	rt	3	0	-

[a] The cationic catalyst was freshly prepared prior to use by mixing $PdCl_2(MeCN)_2$ with ligand **6.10** in CH_2Cl_2 at rt. After 1 h $AgSbF_6$ was added and the mixture was stirred for 30 min at rt.

Figure 4.12. Conditions Screened for the Catalytic Nazarov Reactions Using Palladium(II), Ligand 6.10 and Divinyl Ketones 5.1, 6.7 and 6.2

4. Conclusions and Future Work

Preliminary work towards an asymmetric metal-catalyzed Nazarov reaction has been described. We have examined a number of chiral metal catalysts, divinyl ketones and solvent systems. The key observations are discussed in what follows.

Three divinyl ketones have demonstrated marked differences in reactivity. Monosubstitution on the enol terminus is shown to promote cyclization whereas disubstitution on the electron poor olefin of the divinyl ketone is shown to suppress it. Future screening of a broader range of substrates will be performed in due course in order to identify additional trends.

In past and present studies, asymmetric induction was observed using (box)ytterbium(III) triflate for two similar divinyl ketones, one bearing a methoxymethyl enol ether and the other a silyl enol ether. Optimization of reactivity and enantioselectivity is clearly needed in both cases and is hoped to be achievable through the use of additives and alternative ligands (*e.g.* alternative box ligands or BINAP derivatives).

For palladium(II)-catalyzed Nazarov reactions there were problems with both reactivity and enantioselectivity. For instance, neutral palladium complexes with bidentate phosphine-phosphine, phosphine-nitrogen and nitrogen-nitrogen ligands were demonstrated to be too strong of sigma donors which thereby reduced the ability of the palladium(II) species to activate the olefin to nucleophilic attack by the enol ether. Only when these catalyst complexes had non-coordinating anions, such as SbF_6^- was an appreciable amount of cyclization observed. However, the products obtained from these reactions were all racemic. Plausible explanations for the lack of enantioselectivity may be that either racemization of the product is occurring or that either adventitious Brønsted acid or ligand-free metal (or a

combination of both) is actually catalyzing the cyclization. Product racemization and Brønsted acid-catalyzed cyclization were each ruled out by the two control experiments performed by Dr. Eric Leclerc summarized earlier. In one example, when an enantiomerically enriched cyclopentenone sample was resubmitted to the reaction conditions, no erosion in enantioselectivity was observed. In another case, when divinyl ketone **5.1** was treated with a strong Brønsted acid (aqueous HCl) only diketone **4.1** was observed. This present work as well as recent work from group member Danielle McAtee suggests the possibility that the lack of asymmetric induction may likely result from either ligand-free metal catalysis or perhaps a background catalytic process that is initiated upon both coordination of a ligand-free metal to the electron poor olefin of the divinyl ketone as well as interactions between the two oxygen atoms of the divinyl ketone and either a proton or metal (palladium(II) or silver(I)) which enforces the requisite *s-cis/s-cis* conformation of the divinyl ketone (for example, refer to **6.12**, Figure 4.13).

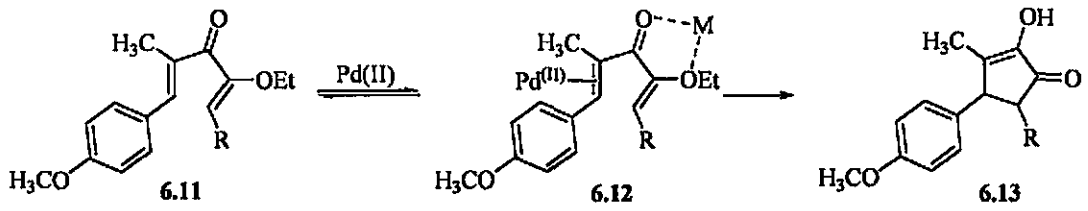


Figure 4.13. Suspected Interactions Required for the Initiation of the Catalytic Cyclization of Divinyl Ketone 6.11

If catalyst decomposition is in fact taking place and the interactions shown in **6.12** are required for cyclization then one means for ensuring both cyclization and asymmetric induction is by performing the test study that is summarized in what follows. First is to use reactive, robust chiral non-racemic catalyst, such as dicationic catalytic complexes of

palladium(II) and bidentate phosphine ligands. Second is to use divinyl ketones with increased electron density at the electron poor olefin, such as divinyl ketone **6.11** shown in Figure 4.13, to ensure that the equilibrium between complexed and decomplexed divinyl ketone (Figure 4.13, **6.11** and **6.12**, respectively) is pushed in favor or **6.12**. Last, since the rate of cyclization is enhanced with substitution on the enol ether terminus and by enforcement the *s-cis/s-cis* conformation through use of a metal or proton, it is hoped that installing alkyl groups on the enol terminus and introducing an additional metal or mild protic acid into the reaction mixture will also promote cyclization.

It is hoped that the combined observations from our group's past and present studies will offer guidance in further investigations. Future effort will be directed towards optimizing the reaction and evaluating the scope of the method using a broad range of substrates.

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CONCLUSION

The work reported herein includes my contributions towards the progress of the asymmetric Nazarov reaction. In the allenyl ether variant, a number of sugar-derived auxiliaries have been synthesized and screened against a small panel of electrophiles. The results from the cyclization reaction of each auxiliary have led to a more detailed, well-substantiated mechanism and the optimization of reaction conditions. Two optimal chiral auxiliaries, each providing one enantiomeric series of cyclopentenones, have been designed and synthesized on its basis. Thus, both enantiomeric series of cyclopentenones are accessible in high optical purity. Additionally, a triply convergent cyclopentannelation reaction has been discussed. The method involves the merging of three components, a lithioallene, a morpholino enamide and electrophiles. Through this study we have defined optimal reaction parameters for a broad range of morpholino enamides and electrophiles. The process offers the advantage of creating a large degree of molecular complexity in a single operation which lends itself useful towards the preparation of natural products and small molecule libraries. Finally, there is significant interest towards catalytic asymmetric cyclopentannelation. Our preliminary work within this area has also been reported. It is clear from the evaluation of several catalysts using a small panel of divinyl ketones that the challenges which involve the poor reactivity of the divinyl ketones and enantioselectivity of these reactions remain unmet. Efforts towards this end are currently in progress.