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DISSERTATION

[1,3]-OXYGEN TO CARBON REARRANGEMENT FOR THE CONSTRUCTION OF CARBON-CARBON BONDS BETWEEN ADJACENT RINGS AND 1,3-DIOXEPINES IN SYNTHESIS

Submitted by

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In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JEFFREY DANIEL FREIN ENTITLED – [1,3]-OXYGEN TO CARBON REARRANGEMENT FOR THE CONSTRUCTION OF CARBON-CARBON BONDS BETWEEN ADJACENT RINGS AND 1,3-DIOXEPINES IN SYNTHESIS- BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Professor Oren Anderson

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Professor Julia Inamine

Advisor Professor Tomislav Rovis

Department Head Professor Anthony K. Rappé

ABSTRACT OF DISSERTATION

[1,3]-OXYGEN TO CARBON REARRANGEMENT FOR THE CONSTRUCTION OF CARBON-CARBON BONDS BETWEEN ADJACENT RINGS AND 1,3-DIOXEPINES IN SYNTHESIS

Several methods for the stereoselective formation of carbon–carbon bonds between contiguous rings where a stereogenic center is already present have been examined. The approaches investigated were: a [1,3]-oxygen to carbon rearrangement of cyclic vinyl acetals; an intermolecular enolsilane addition into an *in situ* generated oxocarbenium ion; an intramolecular conjugate addition of tethered alkoxy enones; and epimerization of several α-pyranyl cycloalkanones. These routes have been found to be complementary in several cases and have enabled formation of both the *trans:anti* and *cis:anti* stereoisomers in good to excellent yields and varying diastereoselectivities. The C2–C2' relative stereochemistry of the carbon-carbon bond between the adjacent rings was proven *via* a chemical correlation.

The versatility of 1,3-dioxepines as precursors to the formation of 1,4-diols and 1,2,4-triols has been examined. The rapid synthesis of unsymmetrical 1,3-dioxepines and the installation of a 4-acetoxy substituent as a synthetic handle for further functionalization has been realized. The Lewis acid mediated addition into *in situ* generated oxocarbenium ions has been developed for variety of different nucleophiles. Furthermore, a highly *trans*-diastereoselective Heck reaction has been performed on unsymmetrical 1,3-dioxepines and their synthetic utility as precursors to the formation of

2,3,4-alkyl substituted tetrahydrofurans and 2-methoxy-4,5-alkyl substituted tetrahydrofurans have been exploited.

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for your support and faith in me, I know this would have been impossible. We have had a lot of good times and some rough times, but through it all I still love you. And I dedicate to you:

A Wish

Never before have I been touched like this,
For you are all I have ever wished.
I love you more than you will know,
But how I wish I could show
My heart is not always so clear,
Oh but how I love you, my dear.

Don't know how to tell you I love you so,
For I am short of words to do so.
You make me feel like I'm high above,
Filled with your wonderful love.
I know we will pass the test of time,
For our love is one of a kind.

Nothing more I cherish than your kiss,
I always hoped it would be like this.
Everything you do fills me with enchanting desire,
For I am your true squire..
Never am I going to jeopardize this,
For you are all I have ever WISHED!

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LIST OF ABBREVIATIONS

AcBr	acetyl bromide
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobis(isobutyronitrile)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
n-BuLi	*n*-butyl lithium
t-BuOK	potassium *t*-butoxide
CSA	camphor sulphonic acid
m-CPBA	*meta*-chloroperbenzoic acid
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	di-*iso*-butylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMP	Dess-Martin periodinane
n-Hex	*n*-hexyl
HMPA	hexamethylphosphorictriamide
KHMDS	potassium hexamethyldisilazane
LA	Lewis acid
LAH	lithium aluminum hydride

LDA	lithuim di-*iso*-propylamine
LPDE	lithium perchlorate diethyl ether
MS	molecular sieves
MsCl	methanesulfonyl chloride
NR	no reaction
Nuc	nucleophile
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium flouride
TBS	*tert*-butyl dimethyl silyl
TBDMS	*tert*-butyl dimethyl silyl
TEA	triethyl amine
TfOH	triflic acid
TMS	trimethyl silyl
TMSCl	chloro trimethylsilane
TMSOTf	trimethylsilyl triflate
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonyl acid

Chapter 1

Rearrangements Involving Oxygen Atoms

1.1 Introduction

Over the past century organic chemistry has seen many advances in both the isolation of complex natural products and the development of powerful methodologies for their synthesis. Even though the organic chemist is well armed with a variety of powerful reactions for the creation of complex targets, there are still fundamental

Scheme 1.

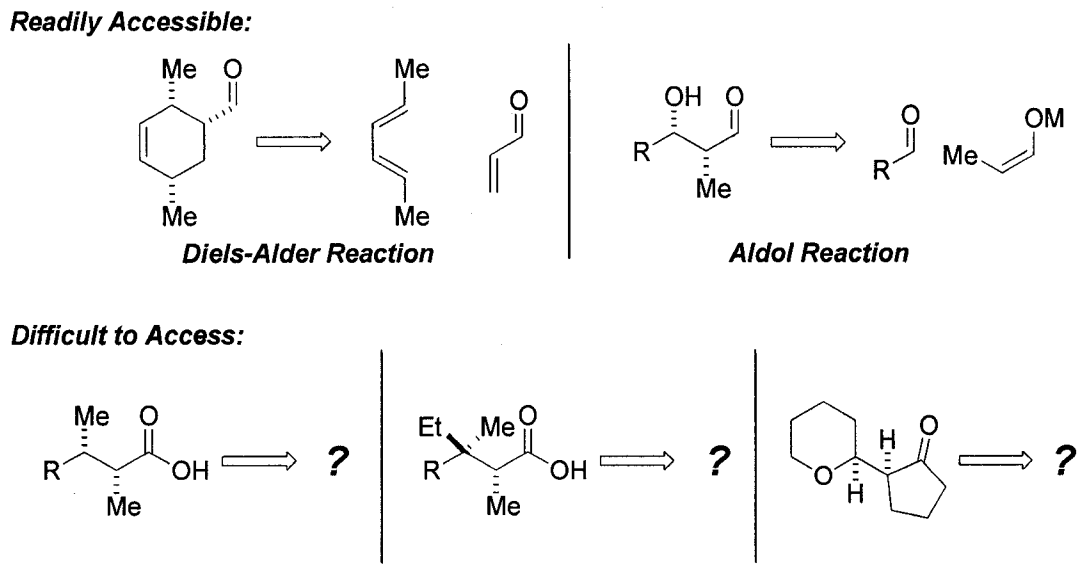
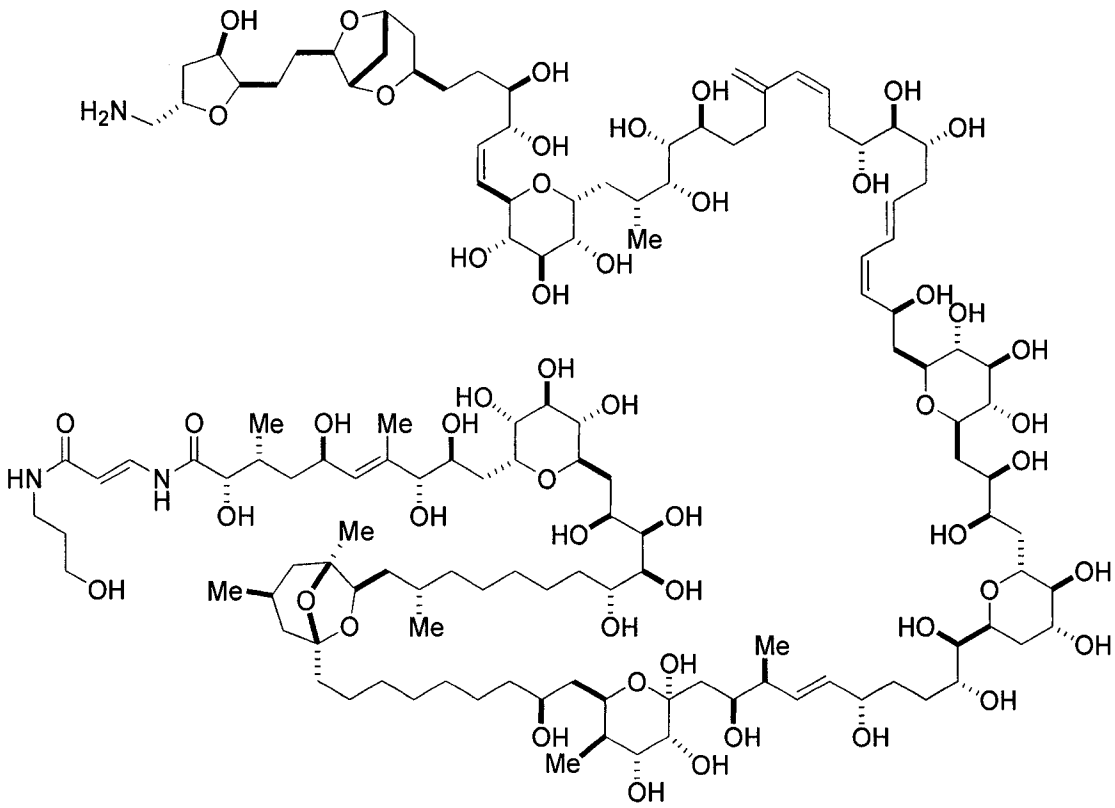


Figure 1.



Palytoxin

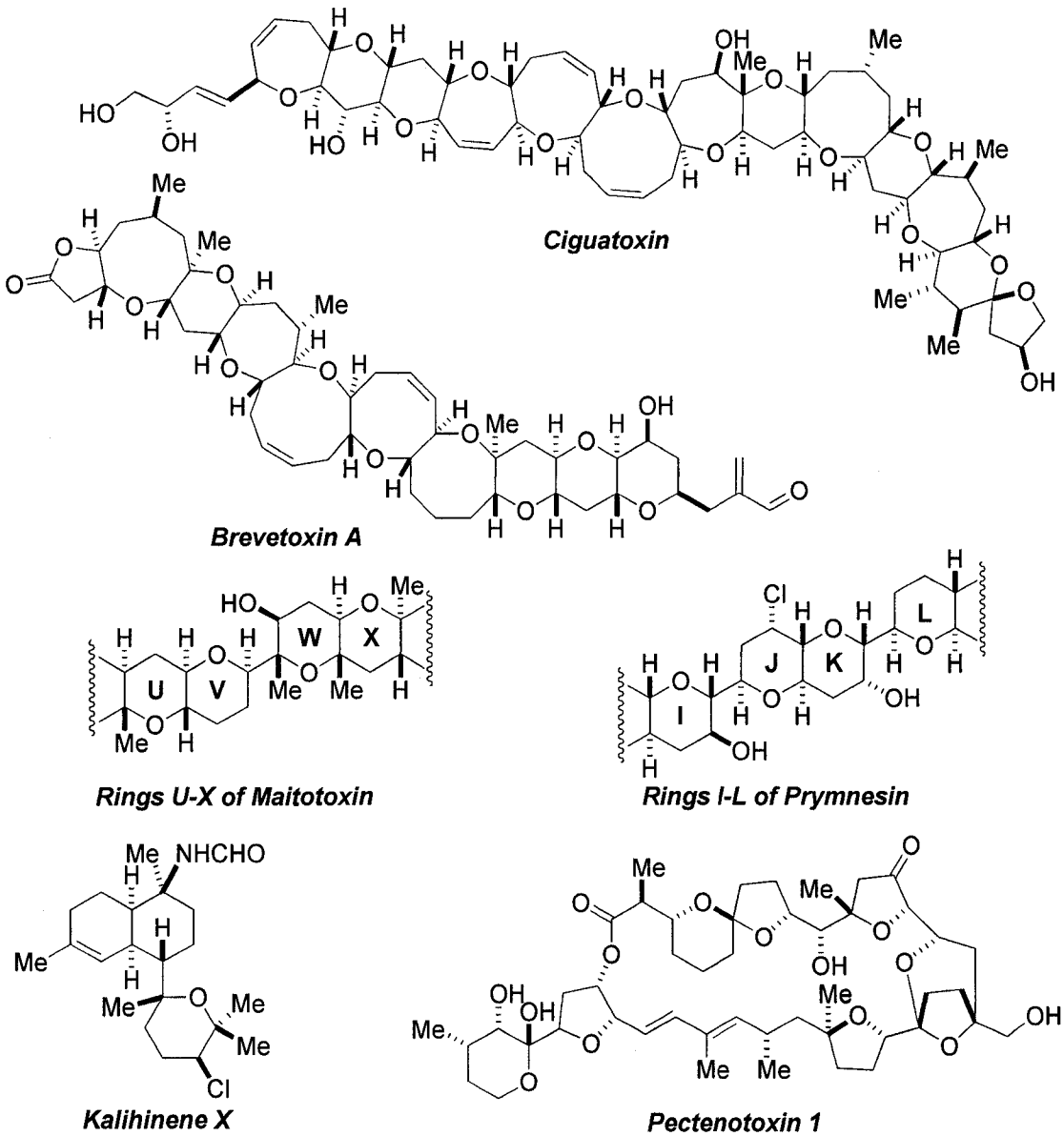
voids remaining in the capabilities of many of these transformations.

The stereoselective formation of carbon-carbon bonds is one such incomplete area. Scheme 1 illustrates a few common natural product motifs which are easily prepared by well-developed transformations, i.e. the Diels-Alder and aldol reactions, and other substructures which are not as trivial. The formation of these "difficult to access" carbon-carbon bonds in a rapid, efficient, and stereoselective manner still remains an important obstacle in synthetic method development.

Many of these "difficult to access" carbon-carbon linkages can be found in the polyketide class of natural products. One of the most well known complex natural

products is palytoxin (Figure 1), which has only been synthesized once since its isolation in 1971.[1]

Figure 2.



The syntheses of daedal compounds, such as palytoxin, ciguatoxin and brevetoxin A, demonstrate the formidable capabilities organic chemist have (Figure 2).[2,3] However, the

construction of these natural products usually proceed in a large number of steps (40-60) and in low overall yield. Even though the syntheses of these molecules are archetypes by which to compare the complexity of emerging total syntheses, they are not practical. As a result, the development of practical and convenient methods for the syntheses of complex sub-targets are constantly being pursued.

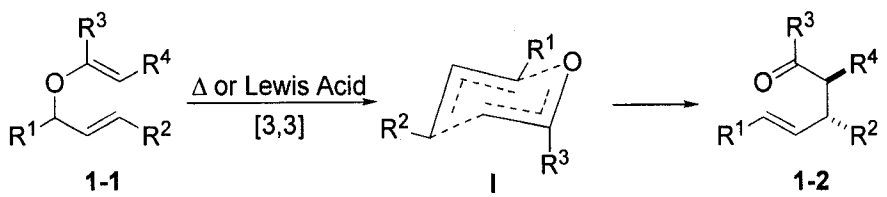
Many of the molecules illustarated in Figure 2, contain congested carbon-carbon bonds between adjacent ring systems, as well as highly substituted oxacycles. One potential solution for the concise formation of these complex motifs is by implementing a stereoselective [1,3]-oxygen to carbon rearrangement. Since there is a plethora of established routes for the stereoselective synthesis of carbon-oxygen bonds, the [1,3]-rearrangement, alluded to earlier, has the potential to be a linchpin coupling step in many total syntheses.

1.2 An Overview of Rearrangements Involving Oxygen Atoms

1.2.1 [3,3] Sigmatropic Rearrangements

Thermally or Lewis acid induced 3,3-sigmatropic rearrangements of allyl vinyl ethers **1-1** to γ,δ-unsaturated carbonyl compounds **1-2**, i.e. the Claisen rearrangement, are important reactions in synthetic organic chemistry (Scheme 2).

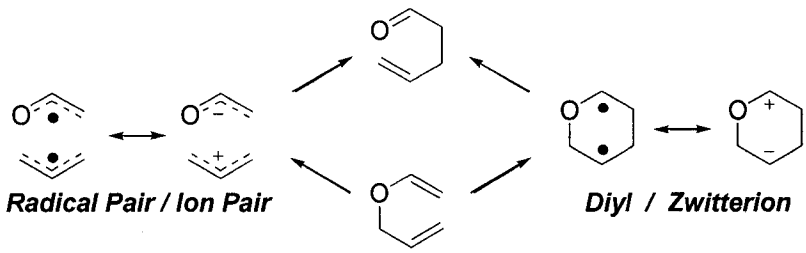
Scheme 2.



1-1 **I** **1-2**

The mechanism of this rearrangement has been the object of numerous experimental and theoretical studies.[4] The Claisen rearrangement is a unimolecular process with activation parameters that suggest a cyclic transition state **I**.[5] The transfer of stereochemical information from the olefins to the newly formed σ-bonds suggests an early chair-like transition state with delocalization of the six electrons of the original π-bonds and the carbon-oxygen σ-bond. This theoretical evidence is consistent with the Woodward-Hoffman rules for conservation of orbital symmetry.[6] There are several transition state extremes possible involving either an ion pair/radical pair or diyl/zwitterion (Scheme 3). The actual transition state depends on the nature of the substituents at the various positions of the starting allyl vinyl ether **1-1**. When comparing the bond strengths of the starting ally vinyl ether **1-1**, C-C_π (65 kcal mol^{-1}) and C-O_σ (85 kcal mol^{-1}), and the forming bonds **1-2**, C-O_π (85 kcal mol^{-1}) and C-C_σ (85 kcal mol^{-1}), there is a clear thermodynamic driving force for the reaction to occur ($\Delta H \sim 20$ kcal mol^{-1}).

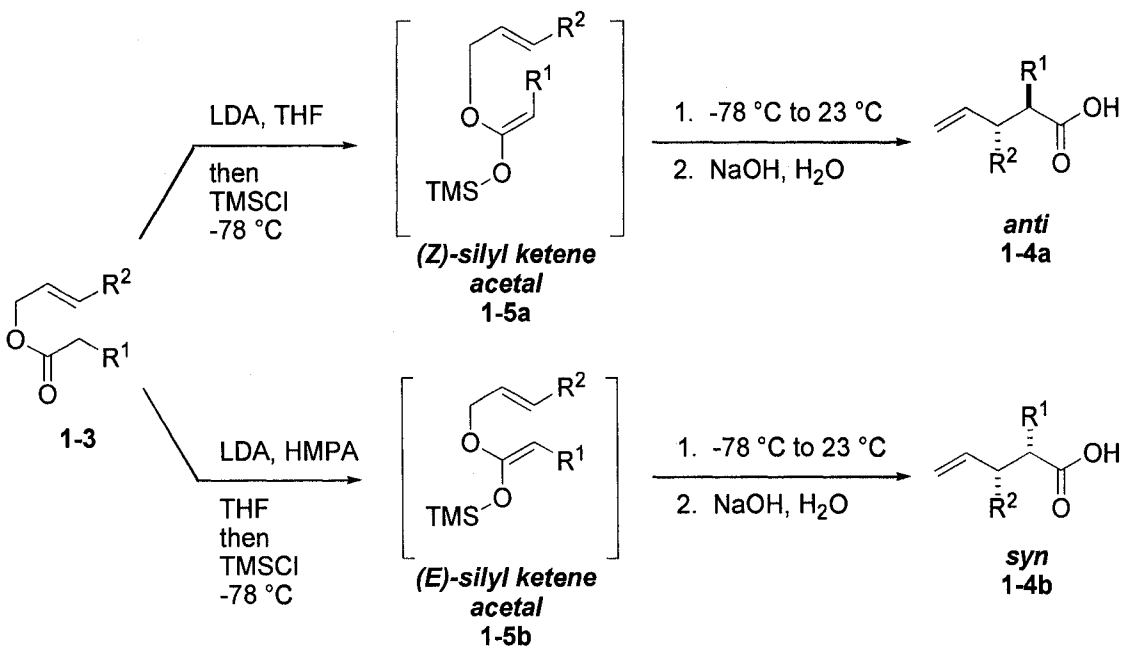
Scheme 3.



Due to the sovereignty of this 3,3-sigmatropic rearrangement, there have been many modifications. The 3,3-sigmatropic rearrangement of *O*-trialkylsilylketene acetals **1-5** to γ, δ-unsaturated carboxlic acids **1-4** is known as the Ireland-Claisen rearrangement.[7] The Ireland-Claisen rearrangement is performed under much milder

conditions than the Claisen rearrangement. The ease of the reaction is accredited to the highly nucleophilic enolate **1-5** that generally accelerates sigmatropic processes.[8] Due to the highly ordered cyclic transition state, high levels of stereocontrol can be achieved. When kinetic deprotonation (LDA) is used to form the (*Z*)-ester enolates **1-5a**, *anti*-γ,δ-unsaturated carboxlic acids **1-4a** can be formed selectively. Whereas when LDA is used in the presence of HMPA, the (*E*)-ester enolate **1-5b** is formed and thus *syn*-γ,δ-unsaturated carboxlic acids **1-4b** are formed (Scheme 4).[9,10] Overall, this reaction is very versatile and it allows for the formation of highly functionalized structures.

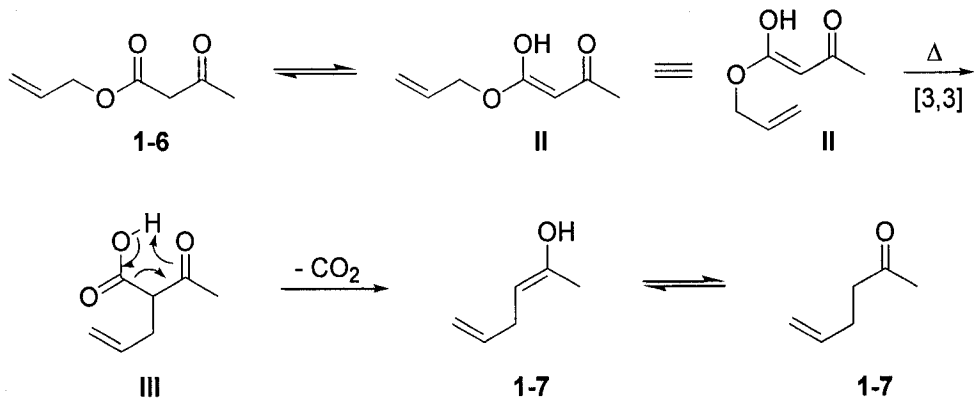
Scheme 4.



Another rearrangement very similar to the Ireland-Claisen is the Carroll rearrangement. The Carroll rearrangement is the [3,3]-sigmatropic rearrangement of allylic β-keto esters **1-6** to γ,δ-unsaturated ketones **1-7**.[11] In the Carroll rearrangement,

the enol tautomer form of β-keto allylic esters **II** undergo a [3,3]-sigmatropic rearrangement to yield an α-substituted keto acid **III**. Under the forcing conditions, the keto acid **III** decarboxylates to afford the γ,δ-unsaturated ketone **1-7** (Scheme 5). Until recently, this reaction has meet with limited use in synthetic applications due to the harsh conditions (130-220 °C) needed to induce the rearrangement. Recently, other surrogates of this transformation have been contributed by Tunge[12] and Stoltz[13], in which they use transition metals to decrease the severity of the reaction.

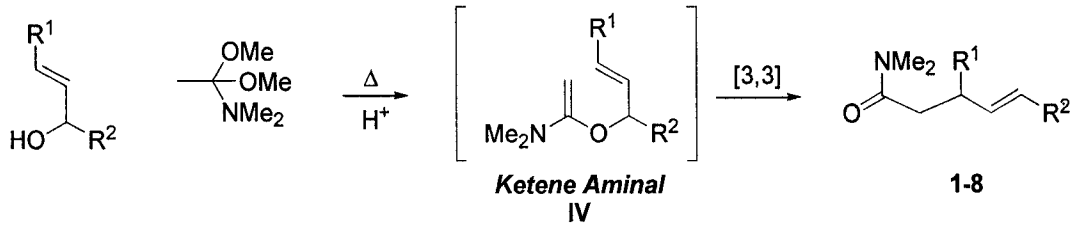
Scheme 5.



Further modifications of [3,3]-sigmatropic rearrangements came in two similar reactions, the Eschenmoser-Claisen and Johnson-Claisen rearrangements (Scheme 6).[14,15] Both rearrangements are the [3,3]-sigmatropic rearrangement of *in situ* generated mixed acetals. The Eschenmoser-Claisen rearrangement is the rearrangement of a ketene aminal **IV** to furnish an amide **1-8**, while the Johnson-Claisen rearrangement is the rearrangement of a ketene acetal **V** to an ester **1-9** (Scheme 6). The high temperature requirements of these rearrangements are their limiting factor.

Scheme 6.

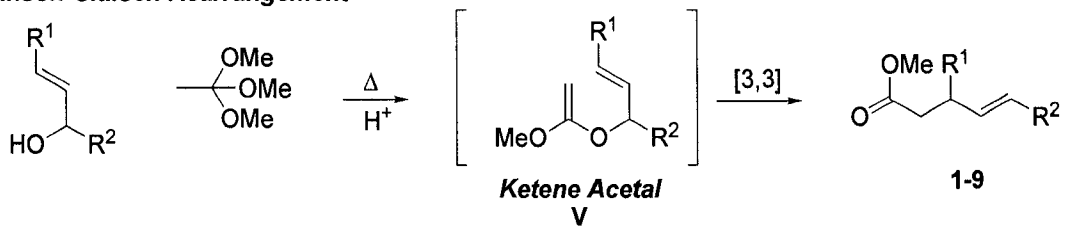
Eschenmoser-Claisen Rearrangement



Ketene Aminal
IV

1-8

Johnson-Claisen Rearrangement



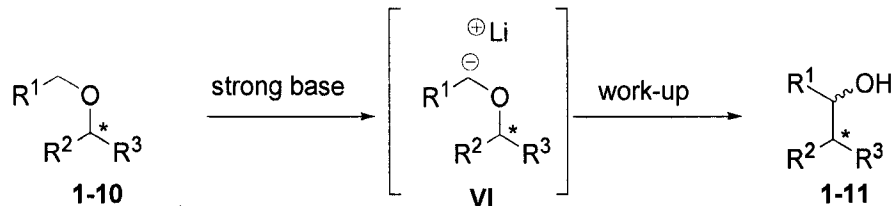
Ketene Acetal
V

1-9

1.2.2. [1,2] and [2,3] Wittig Rearrangements

In 1942, Wittig *et. al.* reported that the deprotonation of benzyl methyl ether **1-10** (when R^1 = Ph, R^2 = R^3 = H) with phenyllithium affords 1-phenylethanol **1-11**.[16] Subsequent studies showed this facile rearrangement was general for α-lithiated aryl alkyl ethers **VI** to afford lithio alkoxides in an overall [1,2]-alkyl shift (Scheme 7). The [1,2]-Wittig rearrangement proceeds via a radical pair dissociation-recombination mechanism. The most important feature of the [1,2]-Wittig rearrangement is that R^1 needs to be carbanion stabilizing (Scheme 7). However, the yields of the [1,2]-Wittig rearrangement are usually low, due to the harsh reactions conditions.

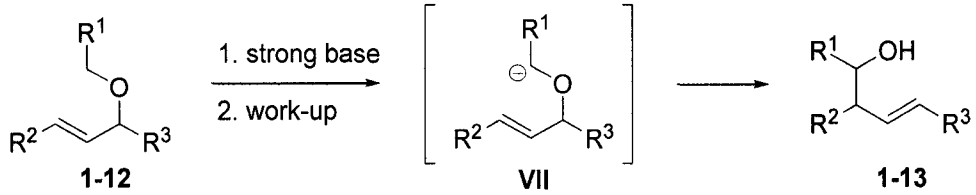
Scheme 7.



R^1 = aryl, alkenyl, alkynyl
R^{2-3} = H, alkyl

Wittig also showed that deprotonation of allylic ethers **1-12** mainly underwent a [2,3]-sigmatropic shift to afford homoallylic alcohols **1-13**. This rearrangement is now referred to as the [2,3]-Wittig rearrangement (Scheme 8). The [2,3]-Wittig rearrangement follows a concerted, thermally allowed sigmatropic process **VII** proceeding via an envelope-like transition state in which the substituents are pseudo-equatorial. Overall, the [2,3]-Wittig rearrangement proceeds under milder conditions and usually in higher yields than the [1,2]-Wittig rearrangement. The [2,3]-Wittig rearrangement is stereoselective in respect to the geometry of the new double bond and the two new stereocenters. In addition, five different enantioselective versions of the rearrangement have been identified.[17]

Scheme 8.



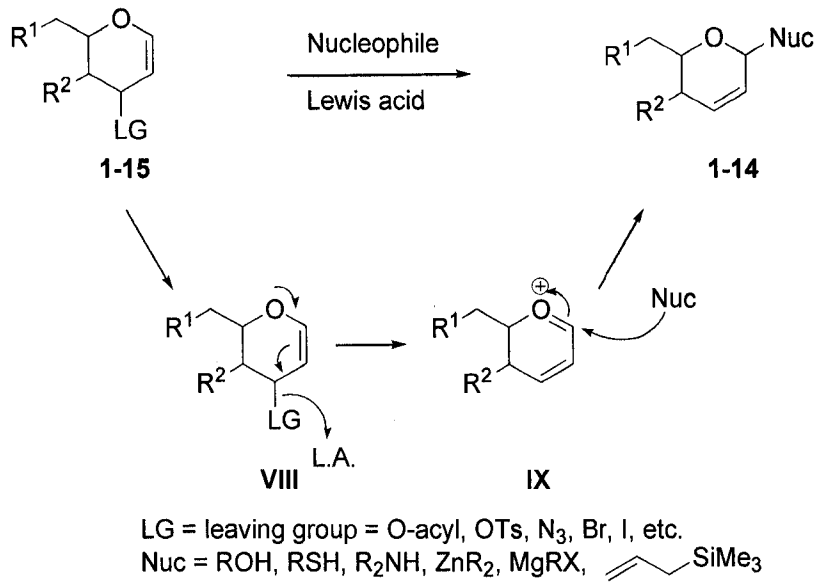
R^1 = carbanion stabilizing: aryl, alkenyl, alkynyl, COR, CN, CO_2R
R^{2-3} = H, alkyl

1.2.3 Ferrier Reaction and Rearrangement

In 1914, Fischer observed the allylic substitution of tri-*O*-acetyl-D-glycal to the corresponding 2,3-unsaturated acetal upon heating with water.[18] However, it wasn't until the 1960's that Ferrier found the synthetic utility of this transformation in the formation of *O*-, *S*-, and *N*-linked unsaturated glycosyl **1-14** compounds from 1,2-glycals **1-15** and nucleophiles in the presence of Lewis acids.[19-21] This reaction is the Type I Ferrier reaction (Scheme 9). The key aspects to its success involve the treatment of 1,2-glycals **1-15** with good leaving groups (LG) in the 4-position with a variety of nucleophiles in the presence of either heat or a Lewis acid. The first step in the mechanism is the donation of electrons from the oxygen to effect the departure of the leaving group at *C*-4* in an E2 fashion **VIII**. The allyloxocarbenium ion **IX** is then quenched by the addition of a nucleophile into the *C*-2 position. The stereochemistry of the final 2,3-glycal **1-14** at the anomeric center (*C*-2) depends on the relative stereochemistry of the groups at the *C*-5 and *C*-6 positions in the starting glycal, however if no stereoelectronic effects are present the α-anomer usually predominates. The resultant *C*-2 α-anomer is often accredited to the anomeric effect (Section 1.3.2.).

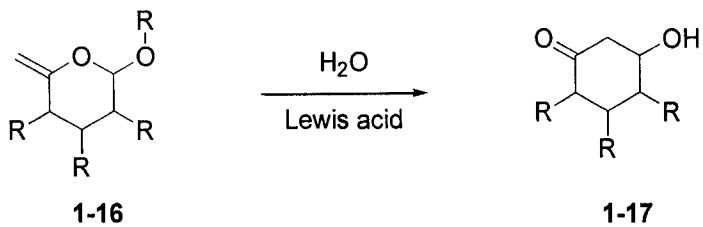
* Hetereocyclic numbering system used.

Scheme 9.



The other form of the Ferrier reaction is the Type II Ferrier rearrangement. The Type II Ferrier rearrangement was first reported in 1979 when exocyclic enol ethers **1-16** were converted to substituted cyclohexanones **1-17** upon treatment with mercury (II) salts.[22] The overall transformation is shown in Scheme 10.

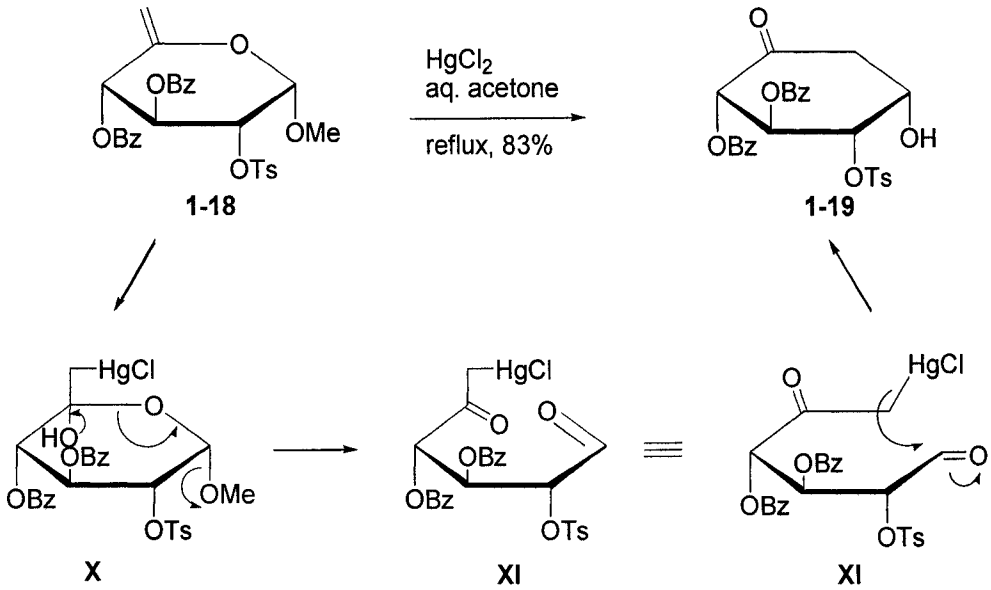
Scheme 10.



Ferrier initially observed that when glucose derivative **1-18** was treated in refluxing aqueous acetone with one equivalent of mercury (II) chloride the resultant cyclohexanone **1-19** was obtained in good yields. They proposed that during the course of the reaction, regioselective hydroxymercuration of the vinyl ether component occured to give the unstable hemiacetal **X**, which following loss of methanol affords the

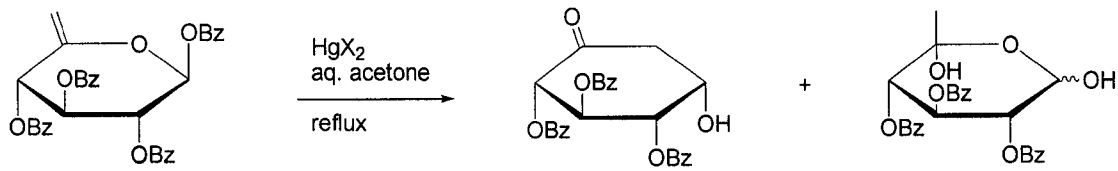
dicarbonyl intermediate **XI**. This then performs an aldol-like, intramolecular cyclization to give the cyclohexanone **1-19** as a single diastereomer (Scheme 11).

Scheme 11.



In a closer study of the reaction, the tetrabenzoate **1-20** in the presence of mercury (II) chloride gave the analogous ketone **1-21** together with the cyclic diol **1-22**, which was assumed to arise by hydrolysis of the mercury-containing analogue of the intermediate **X,** in 55 % yield (Entry 1, Scheme 12). Since such a hydrolysis would be subject to acid catalysis, it became desirable to carry out the reaction with a mercury salt that would not give rise to a strong acid as byproduct. As a result, when mercury (II) acetate was used in the same reaction, only the rearrangement product was observed in 93 % yield (Entry 2, Scheme 12).

Scheme 12.



1-20 1-21 1-22

Entry	X_2	21:22	Yield (%)
1	Cl	---	55
2	OAc	>99:1	93

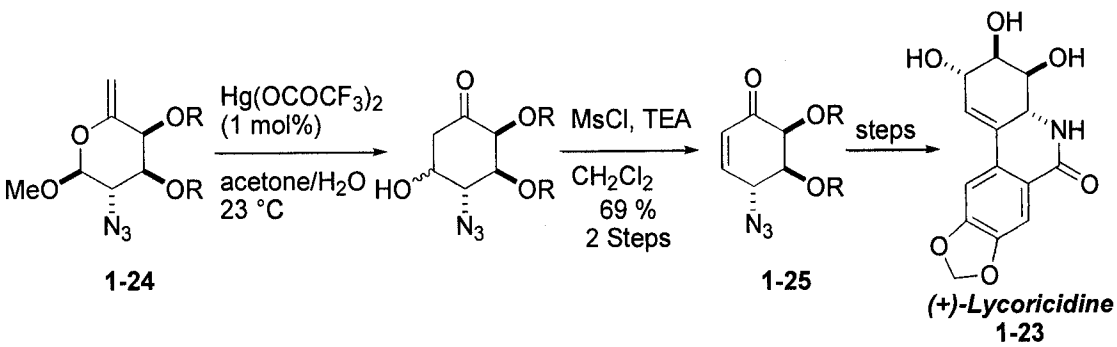
Ferrier later found mercury (II) trifluoroacetate proved more effective than mercury (II) chloride or mercury (II) acetate in the transformation. This is contrary to the previous belief that the salts of weak acids best facilitated the reaction. Furthermore, Ferrier also established that mercury (II) salts could be used in catalytic amounts (0.1 mol equivalents) to allow the reaction to proceed in good yields and with the minimization of undesired side products.

The Type II Ferrier rearrangement became synthetically significant due to multiple reasons. First, the precursors are readily synthesized from carbohydrates; therefore stereochemically defined, highly substituted cyclohexanones can be readily prepared. Second, the use of catalytic amounts of Lewis acid can be used; as a result, complex targets bearing acid sensitive functionalities are more tolerated.

Many groups have used the Type II Ferrier rearrangement in the construction of complex natural products. Ogawa and co-workers has used the reaction in the syntheses of two natural products. First, they used the catalytic version of the Type II Ferrier rearrangement in the synthesis of (+)-lycoricidine **1-23** as their key step.[23] The vinyl ether **1-24** was treated with catalytic mercury (II) trifluoroacetate and following

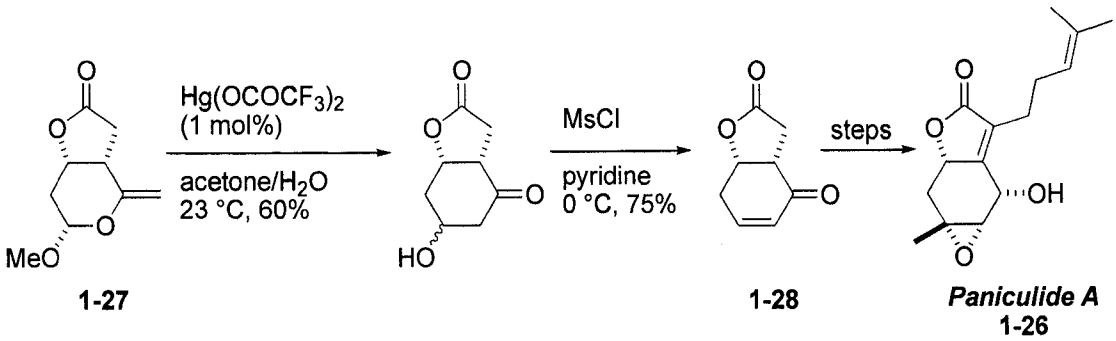
elimination of the hydroxyl group, they obtained the optically active cyclohexenone moiety **1-25**. Further manipulations yielded (+)-lycoricidine **1-23** (Scheme 13).

Scheme 13.



In addition, Ogawa has also used the rearrangement in the synthesis of the highly oxygenated sesquiterpene, paniculide A **1-26**.[24] Starting from the chiral D-glucose derivative **1-27**, the Type II rearrangement was used as their key step to construct the substituted cyclohexenone subunit **1-28** of paniculide A **1-26**. Further manipulations yielded the desired natural product (Scheme 14).

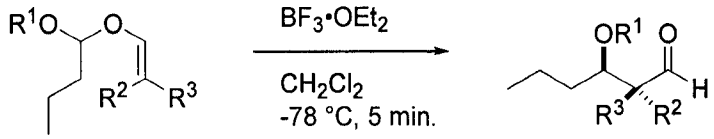
Scheme 14.



The first acyclic example of the Type II Ferrrier rearrangement was reported by Morooka and Suzuki in 1982. They reported a 1,3-alkyl migration of 1-alkenyl alkyl ketals **1-29** (Scheme 15).[25,26] These transformation were effectively catalyzed by

BF_3•OEt_2 to yield cross aldol type products **1-30** in a diastereoselective manner. The authors suggest that under kinetic control the (*E*)-1-alkenyl alkyl acetals are selectively converted to *syn*-products (Entries 1 and 3; Scheme 15), while the (*Z*)-1-alkenyl alkyl acetals lead to *anti*-products with loss of diastereoselectivity (Entries 2 and 4; Scheme 15).

Scheme 15.



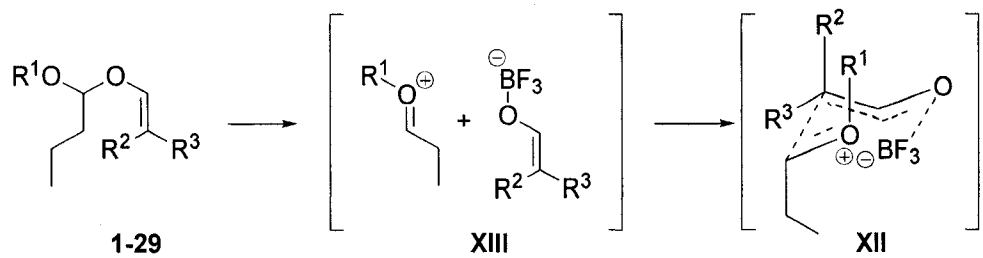
1-29 **1-30**

Entry	R^1	R^2	R^3	Yield (%)	syn:anti
1	Et	H	Me	82	94:6
2	Et	Me	H	79	30:70
3	Bz	H	Me	90	98:2
4	Bz	Me	H	92	40:60

Of note is that the diastereoselectivity attained in the present reaction is different from that observed in the aldol reaction, in which (*Z*)-lithium enolates give *syn*-aldol products and the (*E*)-lithium enolates give the *anti*-aldol products. The authors propose an electrostatically stabilized chair transition state **XII** to account for the observed diastereoselectivities. When the carbon-oxygen bond is cleaved, the induced ion-pair **XIII** of the (*E*)-oxocarbenium ion and vinyloxyborate complex would adopt a chair comformation as seen in Scheme 16. In both transition states, R^1 would adopt an axial position to help minimize interactions, which overall allows for a chair transition state. As a result, the *syn*-product would arise from an equatorial orientation of R^3 (in the case in R^2 = H, R^3 = Me) and affords high diastereoselectivity, while the diaxial

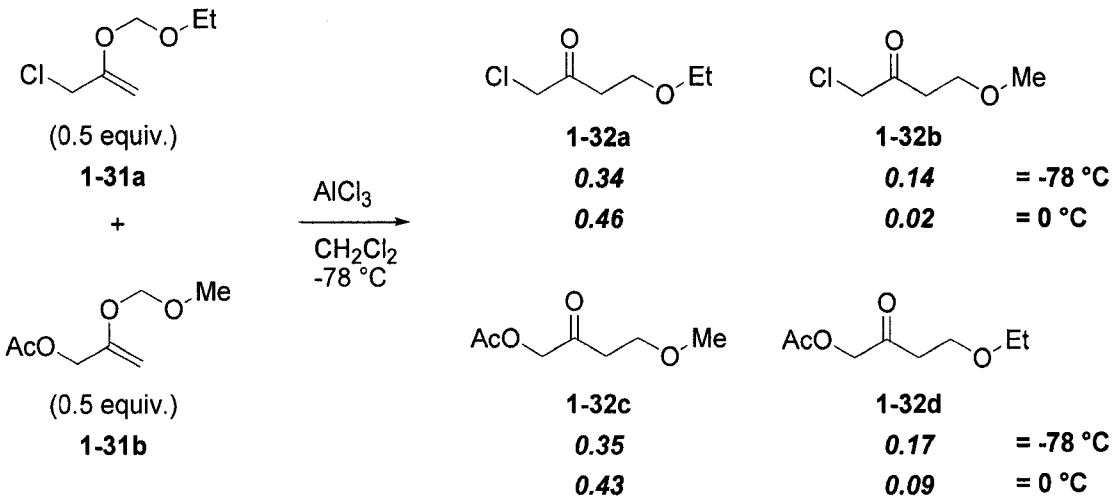
interaction of R^1 and R^2 (in the case when R^2 = Me, R^3 = H) could cause the lower observed selectivity for the *anti*-product (Scheme 16).

Scheme 16.



Okahara has shown that, when two distinct vinyl acetals **1-31a-b** are subjected to $AlCl_3$ at -78 °C and 0 °C, the two reactions form the four possible products **1-32a-d** in two different non-statistical ratios (Scheme 17).[27] The different ratios at different temperature suggest that there is a significant intramolecular component to the reaction. If the return of the nucleophile to its initial partner is due to solvent cage effects (i.e. contact ion pair and solvent separated ion pair), it is conceivable then that the oxocarbenium ion and Lewis acid complexed enolate are in considerable contact and not completely disassociated and thus resulting in the non-statistical ratio.

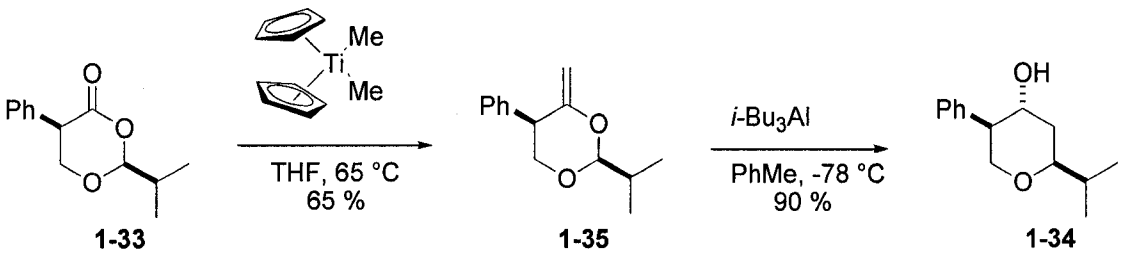
Scheme 17.



1.2.4 Petasis-Ferrier Rearrangement

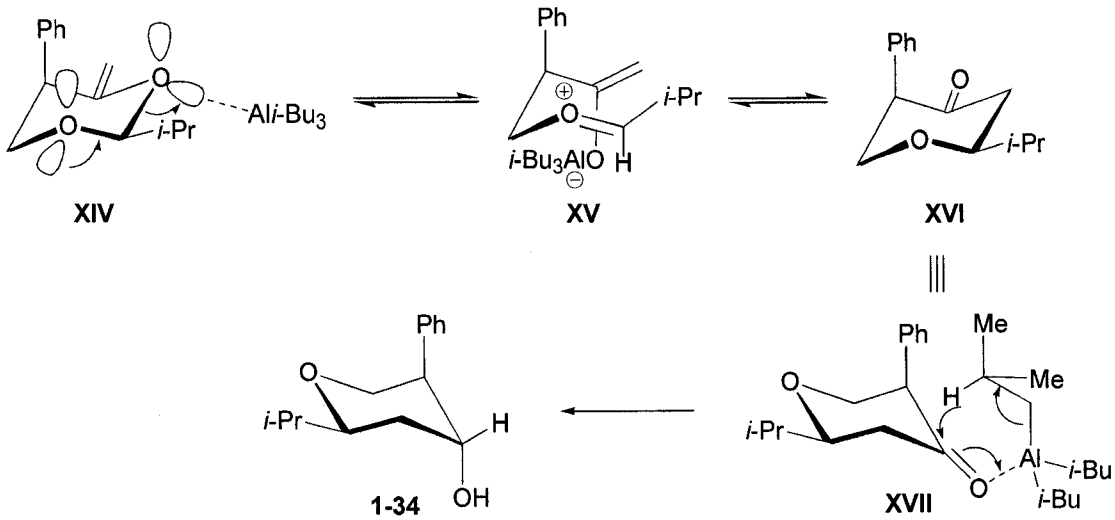
In 1995, Petasis reported the Lewis acid promoted rearrangement of five- and six-membered acetals to substituted tetrahydro-furans and –pyrans, respectively.[28,29] They demonstrated following methylation of the 1,3-dioxan-4-one **1-33** that subsequent treatment with triisobutylaluminum hydride at -78 °C induced the transposition of an oxygen atom with a carbon atom in the ring. In fact, the products **1-34** of the reaction were the epimeric alcohols formed from a Meerwein-Ponndorf-Verley type reduction of the resultant ketone (Scheme 18).

Scheme 18.



Petasis proposed that the aluminum-mediated [1,3]-sigmatropic rearrangement of enol acetal **1-35** proceeds stepwise. The first step is the coordination of the aluminum Lewis acid to the *O*-atom of the enol ether **XIV**. Coordination to the alternate ether *O*-atom is also possible, however this is reversible and non-productive. Cleavage of the adjacent *C-O* bond, assisted by the antiperiplanar lone pair of the ethereal *O*-atom, stereospecifically gives rise to an oxocarbenium enolate species **XV**, which cyclizes to the desired oxacycle **XVI**. Petasis has observed a rate difference in the formation of the 5- and 6-membered oxacycles. The rate difference can be attributed to the more facile 6-(enolendo)-endo-trig cyclization according to Baldwin's rules.[30,31] The last step is the intramolecular Meerwein-Pondorf-Verley type reduction **XVII** of the ketone **XVI** (Scheme 19).

Scheme 19.

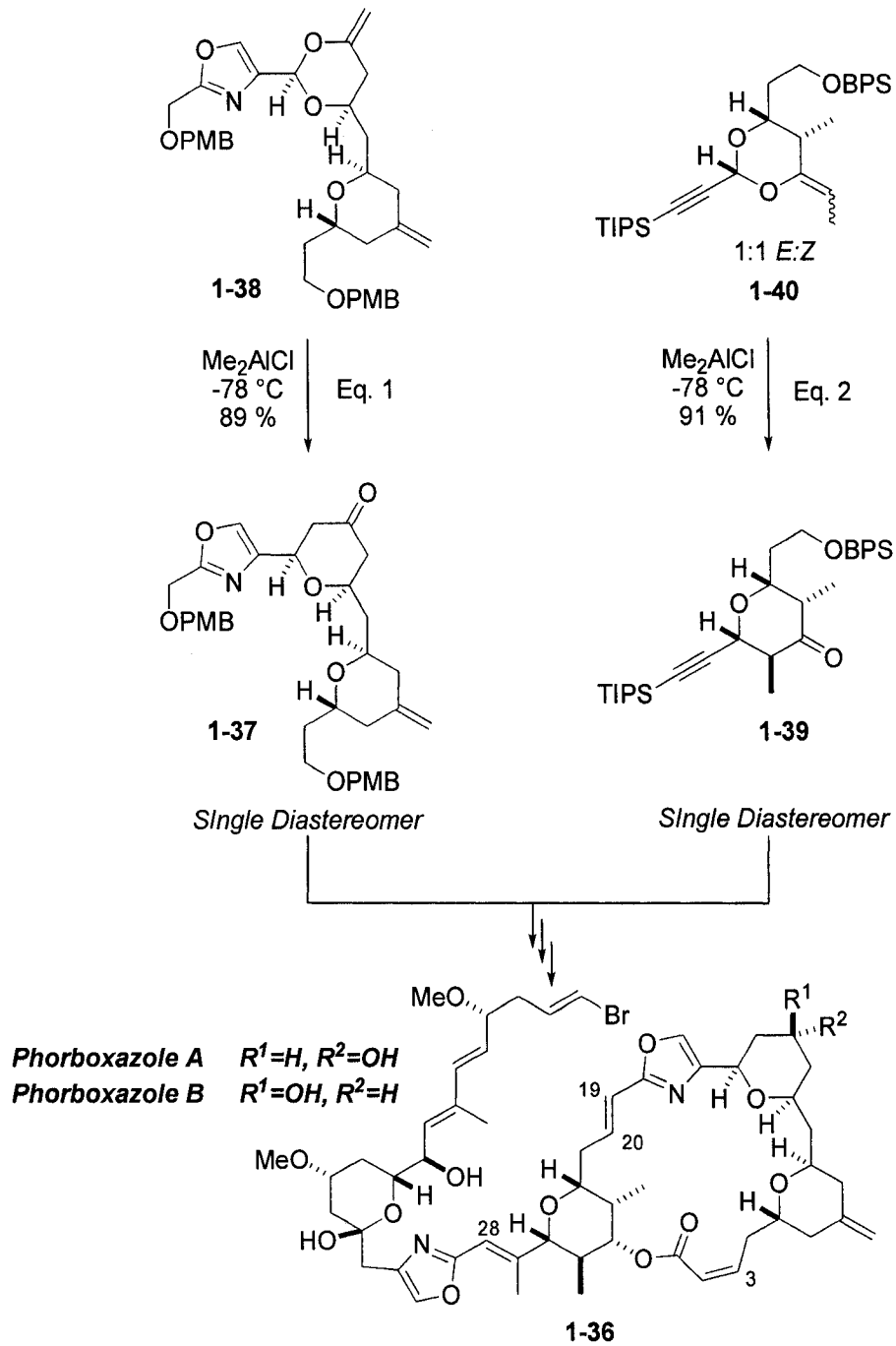


The Petasis-Ferrier rearrangement is very similar to the Type II Ferrier rearrangement. Both rearrangements involve the formation of an oxocarbenium ion intermediate and can form products stereoselectively. However, the Petasis-Ferrier

rearrangement is slightly more powerful due to the ease of constructing the substrate enol acetals. The enol acetals are usually derived from α- or β-hydroxy ketoacids, which can be made enantiomerically enriched.

It was not until 1999 that this rearrangement was modified and utilized for the total synthesis of natural products. In the synthesis of phorboxazole **1-36**, Smith demonstrated the power of the Petasis-Ferrier rearrangement in the construction of two subsections.[32,33] One example was the construction of the *C*-(3-19) subsection **1-37**. The vinyl ether **1-38** was treated with Me_2AlCl at -78 °C, which yielded the desired pyranone **1-37** as a single diastereomer in 89 % yield (Eq. 1, Scheme 20). The other example was the construction of the *C*-(20-28) subsection **1-39**. Treatment of the vinyl ether **1-40** with Me_2AlCl at -78 °C yielded the required pyranone **1-39** in 91 % yield as a single diastereomer (Eq. 2, Scheme 20). Further chemical manipulations afforded phorboxazole **1-36**.

Scheme 20.



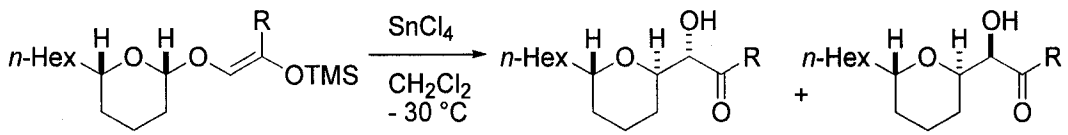
Smith has also applied this methodology in the total synthesis of (+)-zampanolide and (+)-dactylolide.[34,35] In summary, Smith has demonstrated the power of

the Petasis-Ferrier rearrangement in the total synthesis of highly functionalized pyran rings from relatively easily prepared starting materials with varied functionality.

1.2.5. Oxygen to Carbon Rearrangement of Linked Enol Ethers

In 1998, Ley and co-workers reported a diastereoselective anomeric oxygen to carbon rearrangement of silyl enol ether derivatives of lactols.[36] The reactivity of a silyl enol ether towards oxocarbenium ion intermediates combined with the potential for further elaboration has led to their use in the intermediate displacement of anomeric leaving groups in pyran ring systems. Ley showed that when the silyl enol ethers **1-41** were treated with $SnCl_4$, the α-hydroxy ketones **1-42a-b** were isolated in good yields and modest diastereoselectivity (Scheme 21).

Scheme 21.



cis
1-42a

trans:syn
1-42a

trans:anti
1-42b

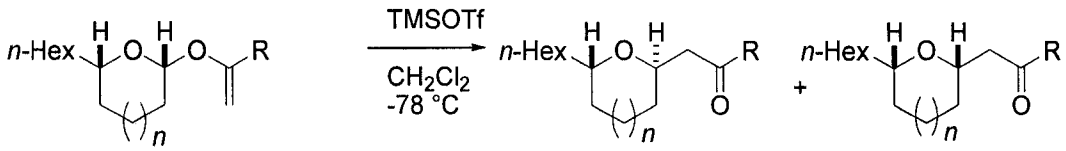
Entry	R	Yield (%)	*syn:anti*
1	Ph	86	3:1
2	Me	90	1:1
3	*t*-Bu	84	3:1

One thing to note about Ley's system is the stereochemistry of the initial pyran **1-41** is *cis*, while the stereochemistry of the product pyrans **1-42** are *trans*. This is a clear example of a solvent separated ion pair within the reaction intermediates to yield the non-

retentive and more favorable *trans*-pyran products. In a later publication, Ley used this methodology towards the total synthesis of (+)-goniodiol.[37]

The scope of the anomeric oxygen to carbon rearrangement was further extended when Ley demonstrated the rearrangement of 6-substituted tetrahydropyranyl enol ethers **1-43**.[38] Enol ether **1-43**, prepared in high diastereoselectivity (>20:1), was treated with catalytic amounts of TMSOTf in CH_2Cl_2 at -78 °C to afford the *trans*-6-substituted tetrahydropyranyl ketones **1-44a-b** in good yields and high diastereoselectivities (91:9 - >95:5)(Scheme 22).

Scheme 22.



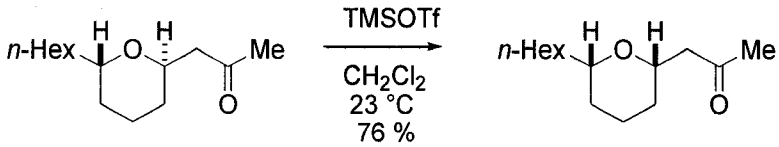
1-43 ***trans*** **1-44a** ***cis*** **1-44b**

Entry	*n*	R	Yield (%)	*trans:cis*
1	1	Me	72	94:6
2	1	Ph	82	87:13
3	1	Bu	87	97:3
4	0	Me	90	55:45

When a tetrahydrofuranyl system was used (Entry 3, Scheme 22), the diastereoselectivity was virtually non-existant. This is in accord with previous results, which Ley reported earlier.[39] Another important aspect of this research was the ability to epimerize the *trans*-pyran products **1-45** to the *cis*-pyran products **1-46** at higher temperatures and with stoichoimetric amounts of TMSOTf (Scheme 23). In the

epimerization pathway a reversible β-elimination occurs leading to an equilibrium where the thermodynamically favored *cis*-product predominates (Scheme 23).

Scheme 23.

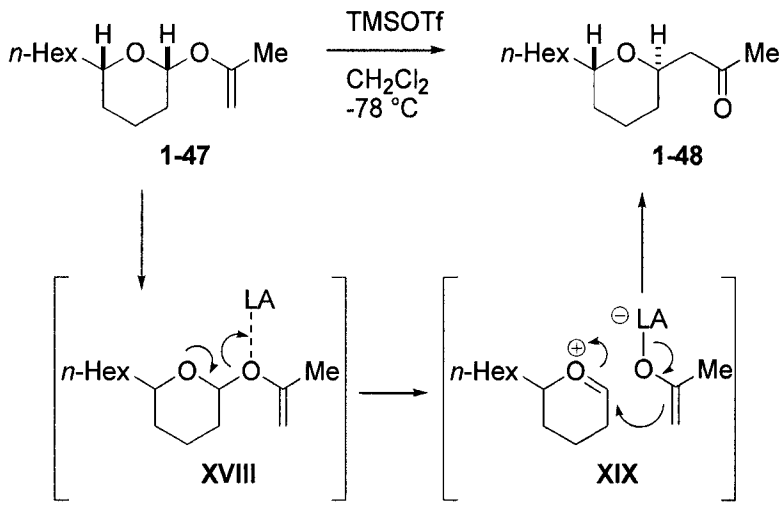


trans
1-45

cis
1-46
93:7 (*cis:trans*)

The accepted mechanism of the oxygen to carbon rearrangement, begins with initial coordination of the enol oxygen to the Lewis acid **XVIII**. Ionization then occurs to form a Lewis acid enol silane and an oxocarbenium ion **XIX**. These components then recombine with the concurrent loss of the Lewis acid to form the desired product **1-48** (Scheme 24).

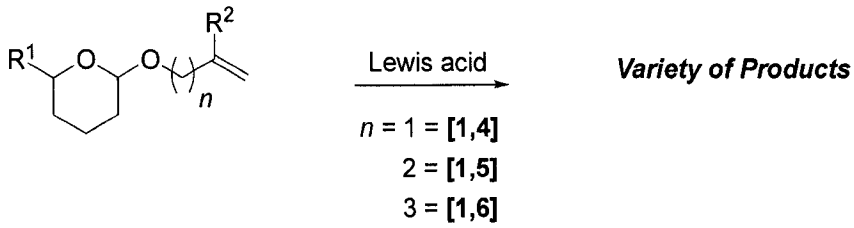
Scheme 24.



In consecutive publications, Ley reported this transformation can be applied to afford products of [1,4]-, [1,5]-, and [1,6]-rearrangement pathways, instead of just a

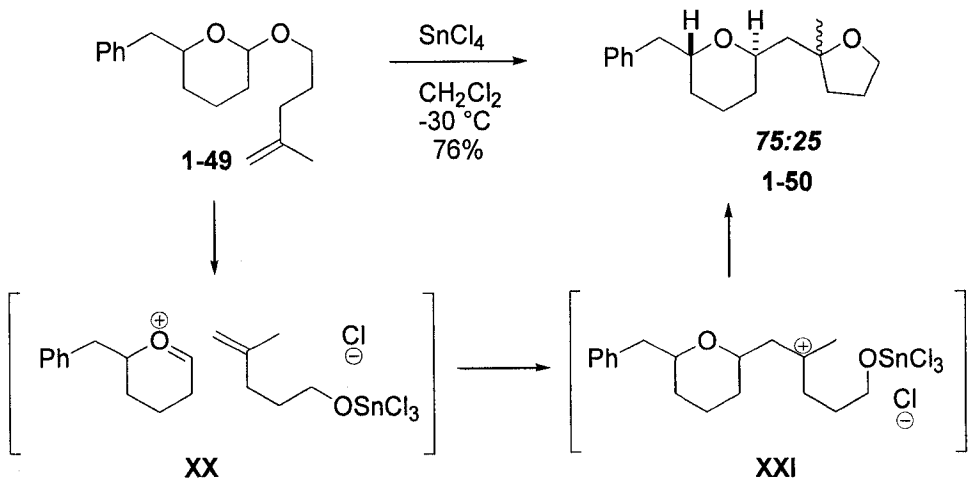
[1,3]-pathway (Figure 3). The first publication reported in the sequence describes the ability to extend the carbon linker to various lengths.[40] A [1,6]-

Figure 3.



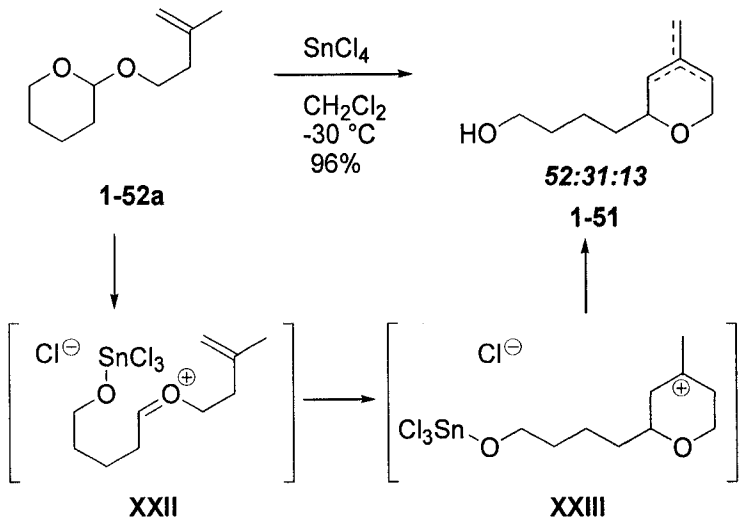
rearrangement was shown to be viable starting with anomeric ether **1-49** in the presence of $SnCl_4$ to furnish the bicycle **1-50** as a 3:1 mixture of diastereomers in 76 % yield (Scheme 25). Initial ionization yields the oxocarbenium ion and Lewis acid complexed enolate **XX**, in which the oxocarbenium ion is then trapped by the olefin (Prins-type reaction) yielding the tertiary carbocation **XXI**. The carbocation **XXI** is subsequently quenched by the Lewis acid complexed alkoxide. It is noteworthy to mention that the Lewis acid complexed alkoxide **XXI** is still sufficiently nucleophilic to undergo an intramolecular cyclization faster than the competing chloride trap or elimination pathway.

Scheme 25.



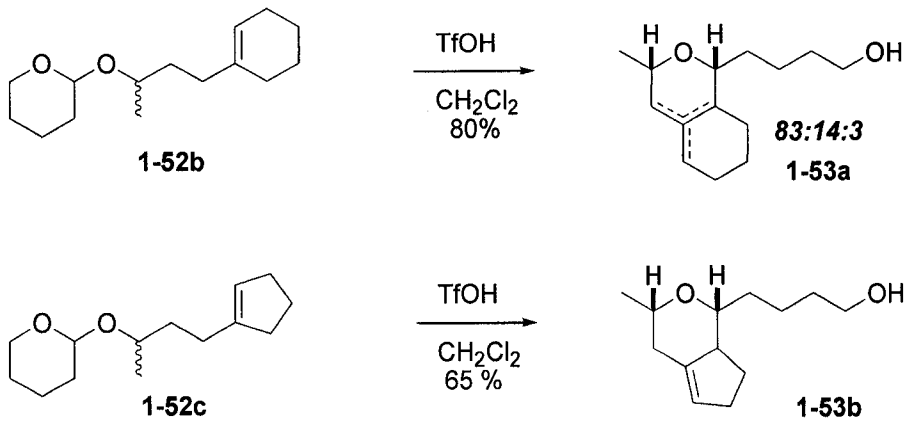
The subsequent report revealed the ability to form mono- (**1-51**) and bi-cyclic ethers (**1-53**) via an acid catalyzed ring-opening cyclization of tetrahydropyranyl ether derivatives **1-52a-c**.[41] This publication is unique because rather than the substrate undergoing an anomeric oxygen to carbon rearrangement, the regiomeric oxocarbenium ion **XXII** is formed followed by cyclization of the olefin onto resultant oxocarbenium ion **XXIII** and subsequent elimination to give a mixture of the three regioisomeric alkenols **1-51** in a 52:31:13 ratio in near quantitative yield (Scheme 26).

Scheme 26.



Furthermore, Ley demonstrated the ability to use this new rearrangement for the synthesis of fused bicyclic compounds **1-53**. Using equilmolar TfOH, [4.4.0]-bicycles **1-53a** can be formed as a 83:14:3 mixture of regioisomers and [4.3.0]-bicycles **1-53b** can also be synthesized as an exclusive regioisomer (Scheme 27).

Scheme 27.



1.2.6 Conclusion

Sigmatropic rearrangements containing oxygen atoms are important organic chemical transformations. The ability to form carbon-oxygen bonds stereoselectively, which may then be translated into the stereoselective synthesis of carbon-carbon bonds makes these sigmatropic rearrangements useful weapons in the organic chemists armory.

1.3 Dictating Effects in the Reactions of Cyclic Oxocarbenium Ions

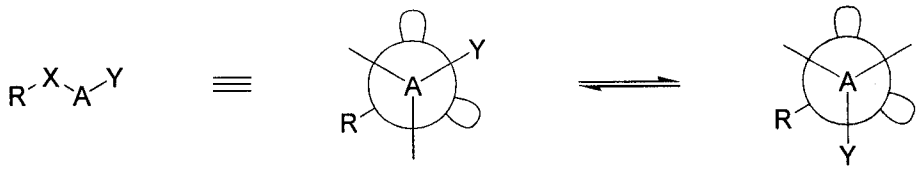
1.3.1 Introduction

The reactivity of oxocarbenium ions and in particular, the resulting stereochemistry can depend on many factors. Much work has been done on this subject, including discussions on the anomeric effect and substituent factors which help dictate system stereoselectivities.

1.3.2. Anomeric Effect

The anomeric effects origin began with an initial study by Edward in 1955.[42] He proposed that in a pyranose ring, axial alkoxy substituents at *C*-1 position are generally more stable than the equatorial ones. His interpretation of this observation is based on the antiperiplanar orientation of the unshared electrons of the ring oxygen to the alkoxy substituent and is the first example of determining conformational preferences with regards to stereoelectronic effects.[43] These initial observations were confirmed by Lemieux and his studies on the equilibrium of α↔β-anomers of *xylo*-configurated pyranose.[44] It was at this time that the term "anomeric effect" was coined. The initial definition of anomeric effect refers to the "tendency of an electronegative substituent at *C*-1 of a pyranoid ring to assume the axial rather than the equatorial orientation, in contrast to predictions based solely on steric grounds."[45] It soon became clear that this phenomenon is not just restricted to carbohydrates but to other five- and six-membered heterocycles as well. The generalized anomeric effect is now defined as "the preference of the synclinal (gauche) position **XXIV** over the antiperiplanar (anti) **XXV** in segments R-X-A-Y, where A is an element of intermediate electronegativity (i.e. C, P, S), Y denotes an atom more electronegative than A (i.e. O, N, or halogen), X denotes an element which possesses lone pairs, and R stands for H or C" (Figure 4).[44]

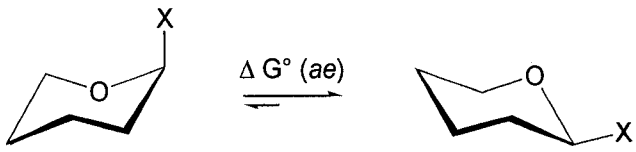
Figure 4.



anti **XXV** ***gauche*** **XXVI**

Further studies conducted by Tvaroski and Bleha have tried to quantitatively describe the anomeric effect by evaluating the conformational energy difference between a substituted pyran ring and a substituted cyclohexane ring (Table 1).[46] Their results establish that the anomeric effect decreases as the electron withdrawing ability of the substituent decreases : halogen > RO > RS > OH > NH_2. There is, however, a recognized problem with this analysis. The steric requirements of a substiteunt in the anomeric position of the pyran ring are different than those in the cyclohexane ring, which is attributed to the difference in bond lengths. The C-O bond (1.43 Å) in the pyran ring is shorter than a C-C bond (1.54 Å) in the cyclohexane ring and steric congestion of an axial 2-substituent should be greater on the pyran system than the cyclohexane system. As a result, the magnitude of the anomeric effect tends to be underestimated.

Table 1.

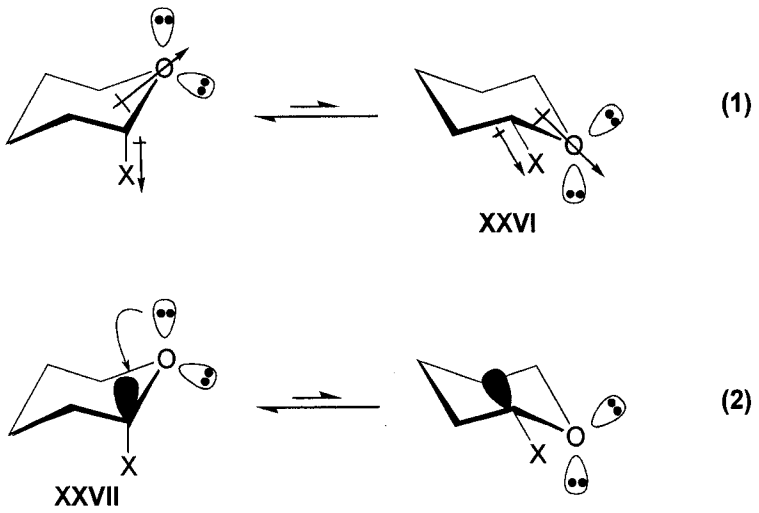


X	ΔG° (pyran)*	-	ΔG° (cyclohexane)*	=	ΔG° (*ae*)*
Cl	1.8		0.6		2.4
Br	1.8		0.5		2.3
OMe	0.9		0.8		1.7
OEt	0.8		0.8		1.6
SMe	0.5		1.0		1.5
OH	-0.1		0.9		0.8
NHMe	-0.9		1.3		0.4
CO_2Me	-1.4		1.3		-0.1

*All values represented in kcal mol^{-1}
ae = anomeric effect

Overall there are two underlying theories which described why there is an anomeric effect.[43] The first theory, involves an unfavorable dipole-dipole interaction between the carbon-heteroatom bonds on the ring and the bond from *C*-1 to the equatorial, electronegative *X*-substituent **XXVI** (Eq. 1, Scheme 28). The second theory involves the antiperiplanar interaction of the ring heteroatom lone pair electrons with an antibonding σ*-orbital (n→σ*) of the *C*-1 substituent which stabilizes the axial orientation of the *X*-substituent **XXVII** (Eq. 2, Scheme 28). Further experimental evidence has shown that both theories play an important role on the anomeric effect, as well as solvent. Typically, the more polar the solvent, the lessening of the anomeric effect is observed.[47]

Scheme 28.

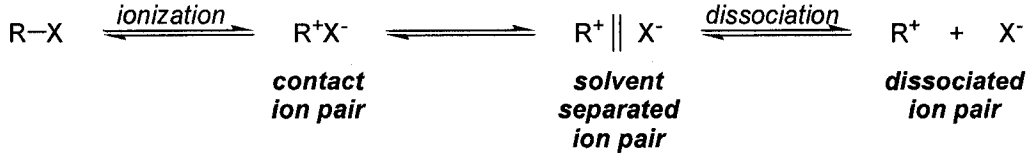


1.3.3. Ion Pairing

Whenever an oxocarbenium ion is invoked in a reaction mechanism, there exist an ion pair. Since the reactivity of an ion can be significantly affected by the presence of its nearby counter ion, the ion-pairing phenomenon plays an important role in the chemistry of ionic intermediates in solution.

Winstein has suggested that along the path to complete dissociation of a cation and anion there exists two distinct types of ion pairs: the contact ion pair, R^+X^-, in which a cation and anion have no solvent between them, and the solvent-separated ion pair, $R^+ \| X^-$, in which a molecule of solvent inserts between the two ions (Scheme 29).[48]

Scheme 29.



In the previous example of Ley's [1,3]-oxygen to carbon rearrangement (Scheme 21-22, 24-25), it is believed that initial ionization of the *cis*-tetrahydropyran **XVIII** occurs in a way that either solvent separated ion pairs or complete dissociation occurs. They observed formation of the *trans*-tetrahydropyran product **1-48** from the *cis* starting material **1-47**, which supports this hypothesis.[36-39,41] The separation of ions allows for the returning nucleophile to attack in the thermodynamically more favored manner and afford the *trans*-tetrahydropyran product **1-48**. Therefore, if the initial ionization and recombination of the enol ether occurs in a way that achieves only contact ion pairs, the stereochemistry of the initial *cis*-tetrahydropyran should be relayed into the final product to afford the *cis*-product. Overall this process would result in a net stereoretentive process.

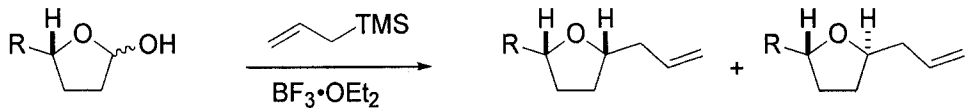
1.3.4. Stereoelectronic Effects

Over recent years, much effort has been put forth in the development and understanding of the reaction of oxocarbenium ions and nucleophiles. The ability to form these bonds stereoselectively is of paramount importance in the arena of synthesis and as a result many studies have been conducted on the stereoelectronic effects which dictate this selectivity.

Schmitt and Reissig found that the stereochemical outcome of allylations and alkylations to oxocarbenium ions derived from tetrahydrofuran lactols **1-54** varied dramatically depending on the nucleophile and the substituents on the ring.[49,50] When a

bulky C-5 substituent is employed, the *trans*-product **1-55b** is favored, while when the C-5 substituent is small, the *cis*-product **1-55a** dominates (Scheme 30).

Scheme 30.

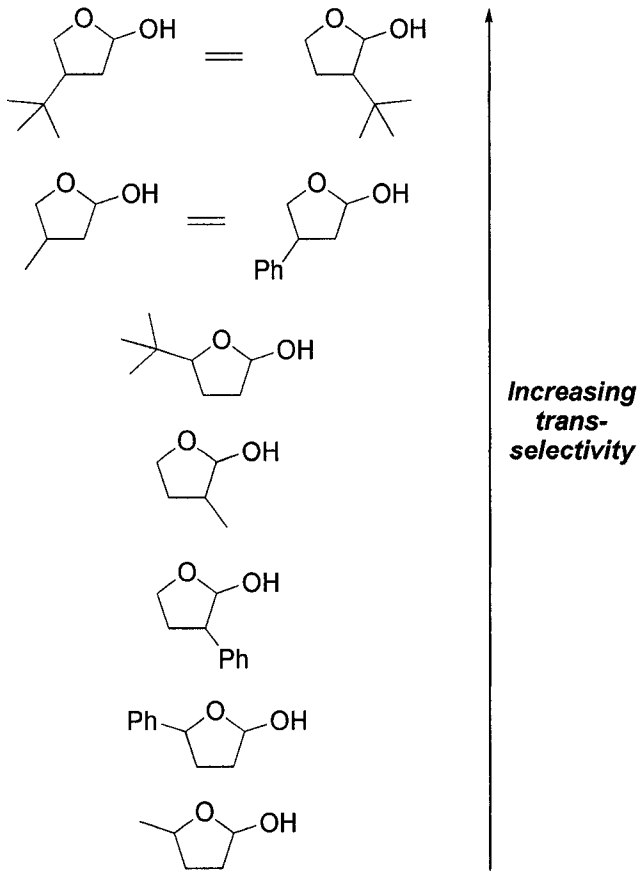


1-54 | ***cis*** **1-55a** | ***trans*** **1-55b**

Entry	R	*trans:cis*
1	Me	40:60
2	Ph	47:53
3	*t*-Bu	88:12

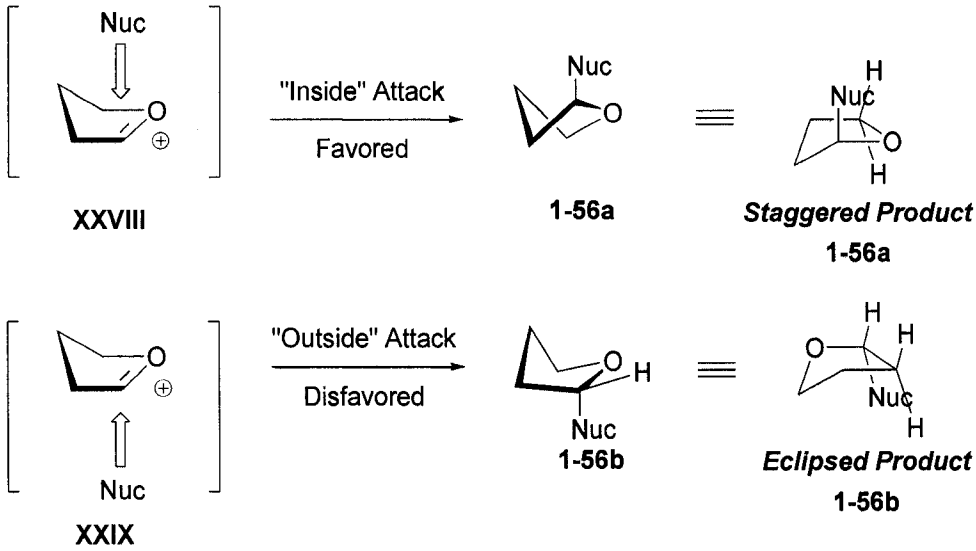
They also report that substituents at different positions on the tetrahydrofuran ring effectively direct which face nucleophilic attack will occur at. A series of results indicates which positions in the tetrahydrofuran ring impact selectivity the greatest. The general trend reveals that the *C*-5 substituents effect the stereoselectivity the least, followed by the *C*-3, then *C*-4 (Figure 5). In contrast, extremely bulky substituents located in any position along the tetrahydrofuran ring show a higher level of *trans*-selectivity.

Figure 5.



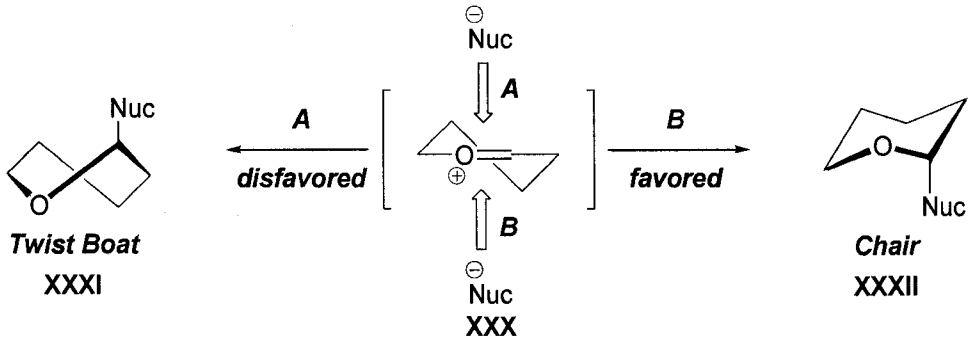
There are several models developed to explain these results. The "inside/outside" attack model has been developed by Woerpel.[51] Experimental results and theoretical calculations revealed that through the minimization of unfavorable interactions, the stereochemical outcome can be rationalized. The oxocarbenium ion can be attacked from either the "inside" or the "outside" face of the envelope by a nucleophile (Scheme 31).[51] "Inside" attack **XXVIII** leads to the all-staggered, favored conformer **1-56a**, while the "outside" attack **XXIX** leads to the eclipsed, disfavored conformer **1-56b**. As a result, the lower energy, staggered conformer is typically the favored product.

Scheme 31.



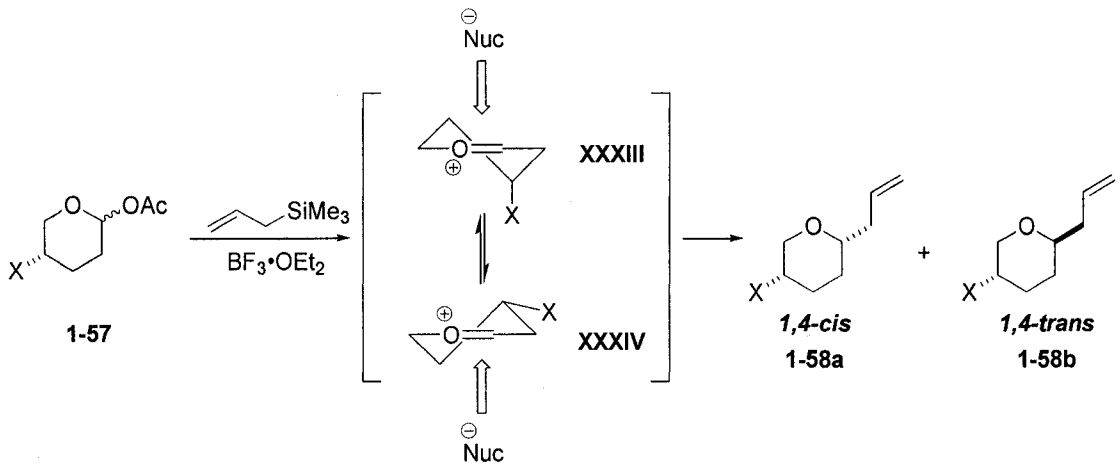
Similar results have been found on tetrahydropyran systems. Woerpel *et. al.* have shown that the electronic nature of a substituent on a tetrahydropyran oxocarbenium ion **XXX** can exert a profound difference on the selectivity of its reaction with nucleophiles.[52] An understanding of the obtained stereoselectivity of 6-membered oxocarbenium ions with nucleophiles can be achieved by considering its journey from an intermediate half chair conformation **XXX** to the final product conformation (Scheme 32). Attack of the nucleophile can occur from either face, however if the attack is from the top face, the ring must go through the disfavored twist-boat conformation **XXXI**. While if attack occurs from the lower face, the ring can transform into the favored chair conformation **XXXII**. Thus, nucleophilic attack on an oxocarbenium ion typically occurs in such a manner as to lead to the lowest energy conformer possible **XXXII**.

Scheme 32.



When substituents are varied around the tetrahydropyran ring, the observed stereochemical outcome can be altered. Alkyl substitution at the 4-position of the tetrahydropyran system **1-57** favors a pseudo-equitorial orientation **XXXIV** and thus results in the *cis*-product **1-58a** (Entries 1 and 3, Scheme 33), while 4-alkoxy tetrahydropyranyl substituents favor the pseudo-axial conformation **XXXIII** and affords the *trans*-product **1-58b** (Entry 2, Scheme 33).

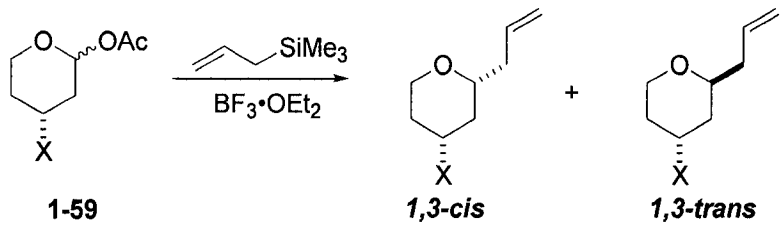
Scheme 33.



Entry	X	*cis:trans*	yield (%)
1	Me	94:6	74
2	OBn	1:99	75
3	CH_2Bn	93:7	77

The reversal of selectivity, as seen in the *C*-4 subsituted tetrahydropyranyl systems **1-57**, is also observed in *C*-3 substituted tetrahydropyranyl systems **1-59** (Scheme 34).

Scheme 34.

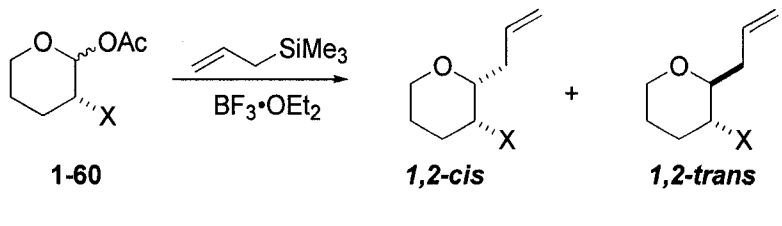


1-59 ***1,3-cis*** ***1,3-trans***

Entry	X	*cis:trans*	yield (%)
1	Me	<1:>99	69
2	OBn	89:11	94

Further examination revealed that alkyl *C*-2 substitution on a tetrahydropyran ring **1-60** minimally influenced the selectivity (Entry 1, Scheme 35), while the alkoxy *C*-2 substituent on a tetrahydropyran ring **1-60** still maintained some selectivity in the nucleophilic addition (Entry 2, Scheme 35).

Scheme 35.

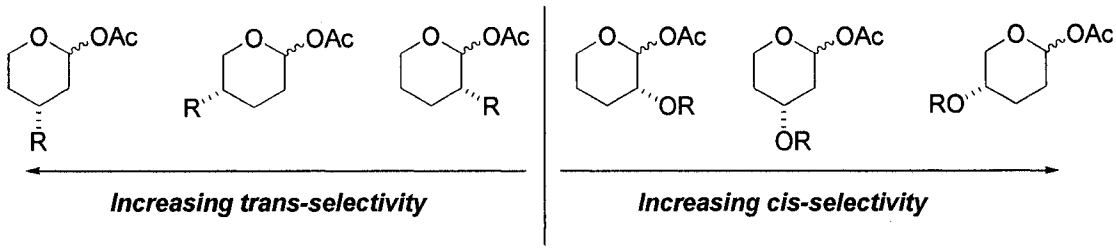


1-60 ***1,2-cis*** ***1,2-trans***

Entry	X	*cis:trans*	yield (%)
1	Me	52:48	57
2	OBn	83:17	84

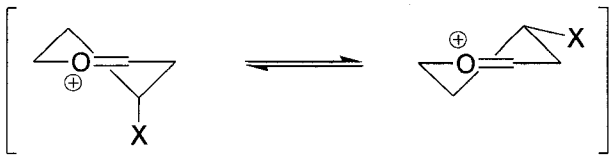
The general trend for the formation of *trans*-substituted tetrahydropyrans is as follows: *C*-2 alkyl < *C*-4 alkyl < *C*-3 alkyl; while the general trend for the formation of *cis*-substituted tetrahydropyrans is as follows: *C*-2 alkoxy < *C*-3 alkoxy < *C*-4 alkoxy (Figure 6).

Figure 6.



To account for the observed stereochemical outcome, Bowen as well as Deslongschamp and Miljkovic theoretically suggested in *C*-4 alkoxy substituted oxocarbenium ions that a through-space effect, but not anchimeric assistance, stabilizes the axial conformation **XXXV** by about 4 kcal mol^{-1} relative to the equatorial conformer **XXXVI** (Entry 1, Scheme 36). While the *C*-4 alkyl substituted oxocarbenium ion cannot be stabilized by this through-space interaction and as a result, it prefers the equitorial conformer **XXXVI** over the axial conformer **XXXV** by about 0.7 kcal mol^{-1} (Entry 2, Scheme 36).[53,54]

Scheme 36.



XXXV XXXVI

Entry	X	Δ G° (kcal/mol)
1	OH	+4.7
2	Me	-0.7

1.4 Conclusion

The ability to use oxygen containing sigmatropic rearrangements in the formation of stereoselective products is a powerful tool to organic chemist, in particular the [1,3]-sigmatropic rearrangement. When considering all of the factors which dictate the stereochemical outcome, the ability to perform this reaction in a stereoretentive manner is a great challenge and of utmost significance. Within this dissertation, the ability to perform the stereoretentive [1,3]-oxygen to carbon rearrangement to form congested carbon-carbon bonds will be investigated, as well as a survey of other methods for the construction of these same types of bonds. In addition, further studies on the stereoselective formation of highly substituted oxacycles will be investigated.

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Chapter 2

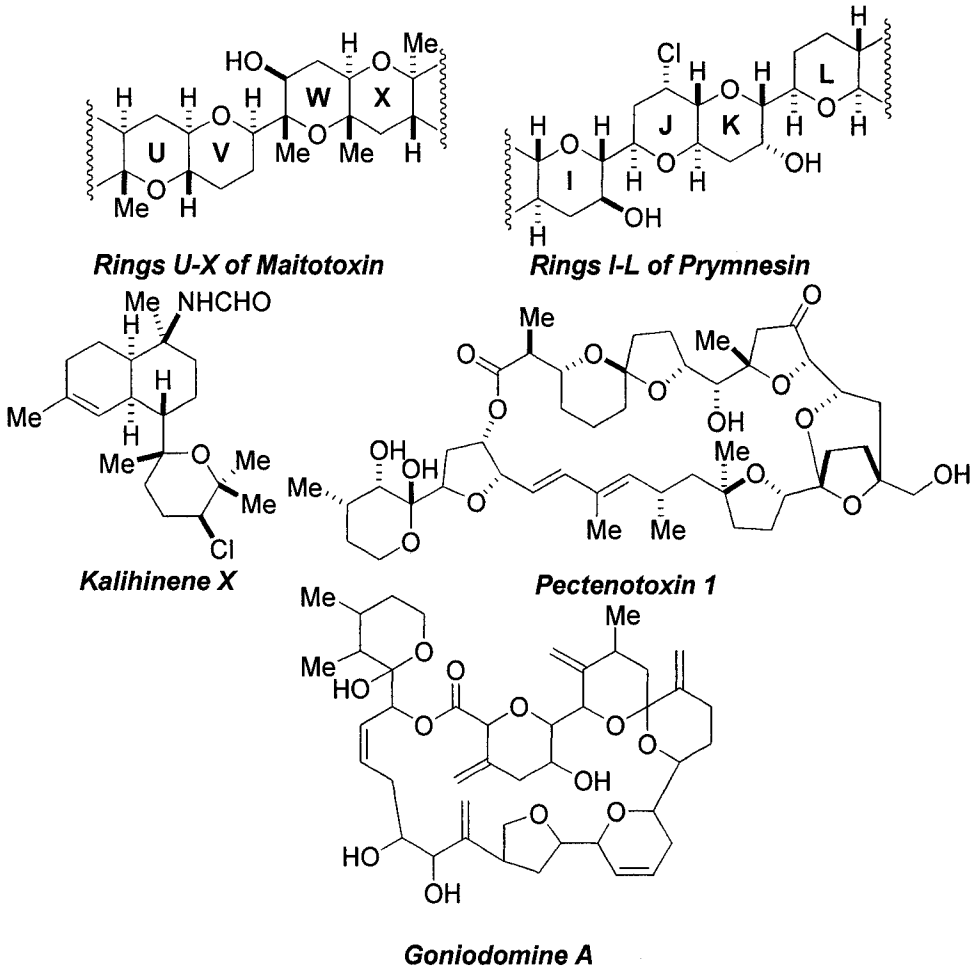
Surveying Approaches to the Formation of Carbon-Carbon Bonds Between a Pyran and an Adjacent Ring

2.1 Introduction

Among the largest and most complicated non-biopolymer molecules discovered to date are maitotoxin, prymnesin and ciguatoxin, along with other members of the polyether ladder toxin family.[1,2] These molecules are characterized by sections of fused oxacycles connected to each other by carbon linkers. Only a handful of total syntheses have emerged to date, including Nicolaou's synthesis of brevetoxin[3] and Hirama's recent synthesis of ciguatoxin.[4] No syntheses have yet appeared of the largest members of this family, maitotoxin and prymnesin. At least a part of the reason for this is the comparative complexity of subsections of maitotoxin, compelling and challenging targets in their own right. We became interested in the problem of how to connect subsections of these molecules once they are assembled. Arguably the most obvious bond disconnections involve the single C-C bonds that connect the fused oxacycle subsections to each other (Figure 1).[5-17] An approach to these types of bonds must

address the key issue of controlling stereochemistry at both ends, a problem that is shared by various other natural product targets as well.

Figure 1.



2.2 Synthetic Approaches to the Formation of Bonds Between Adjacent Rings

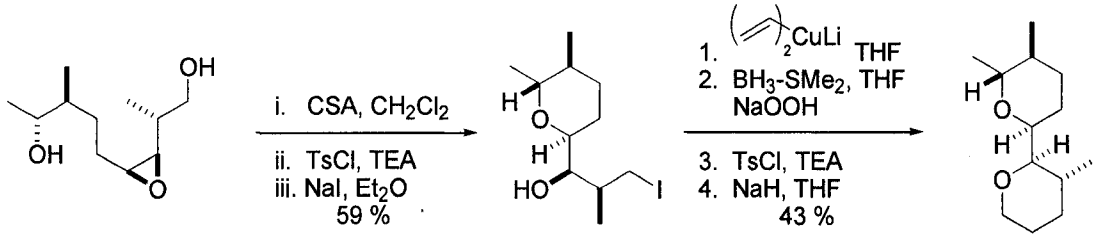
The frequency of carbon-carbon linkages between adjacent rings in natural products has lead to the development of various methods for their construction.

However, since this is still an under developed area of organic chemistry, there are continual reports published on this type of linkage.

2.2.1. Acidic Processes

In 1989, Still and Erickson developed a route for the synthesis of a carbon-carbon bond between two adjacent pyran rings.[18] In their synthesis, they utilized an epoxide ring opening of **2-1** to form the first pyran ring, **2-2**. Following the addition of a two carbon extension, the final ring **2-3** was formed by nucleophilic substitution reaction (Scheme 1).

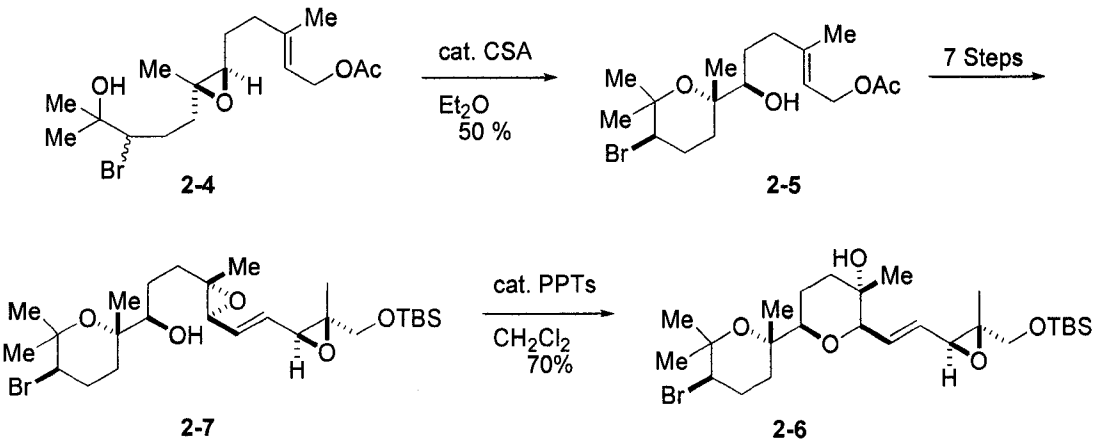
Scheme 1.



2-1 **2-2** **2-3**

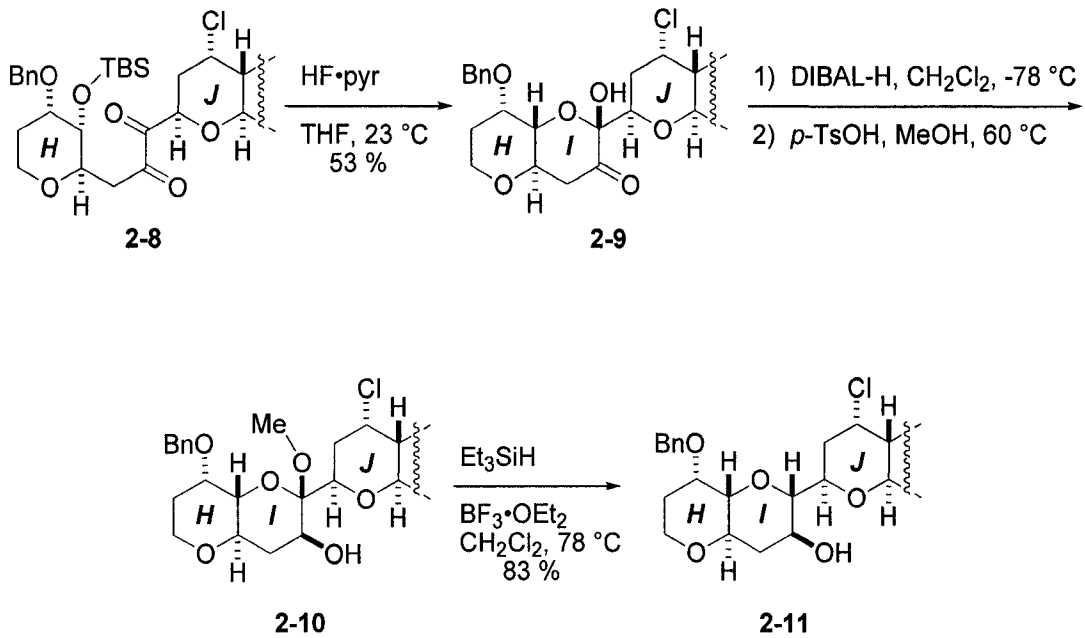
Further utilization of the epoxide ring opening method was contributed by McDonald.[19] When the epoxy alcohol **2-4** was treated with catalytic CSA, the reaction afforded 50% of the desired pyranol **2-5**. After further manipulations, the final pyran ring **2-6** is constructed by treatment of the epoxy alcohol **2-7** with catalytic amounts of PPTS (Scheme 2).

Scheme 2.



In 2001, Sasaki *et. al.* reported the synthesis of the HI-JK ring juncture of prymnesins (Scheme 3).[16] Following deprotection, the diketone **2-8** underwent cyclization to afford the hemi-acetal **2-9** as a single diastereomer in 53 % yield. The ketone **2-9** was reduced with DIBAL-*H* and converted to the corresponding methyl acetal **2-10**. Treatment of **2-10** with Et_3SiH and $BF_3 \cdot OEt_2$ affords the reduced tricycle ether core **2-11** found in prymnesin-1.

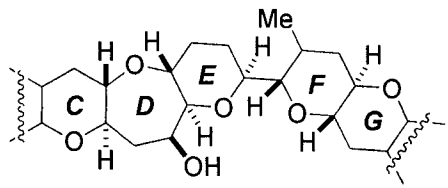
Scheme 3.



2-8 **2-9** **2-10** **2-11**

Sasaki *et. al.* have used a very similar route for the construction of the CDE-FG ring juncture of pyrmnesin (Figure 2).[20]

Figure 2.



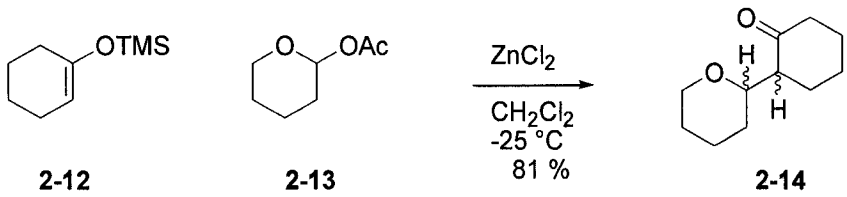
CDE-FG Rings of Prymnesin

2.2.2. Addition into Oxocarbenium Ion

In 1983, Reetz and Muller-Starke reported that cyclic enol silanes **2-12** were competent nucleophiles for the addition into oxocarbenium ions.[21] They showed that

when cyclic enol silane **2-12** was treated with $ZnCl_2$ in the presence of the anomeric acetate **2-13** that a carbon-carbon bond was formed between the resultant adjacent rings **2-14** in good yields (Scheme 4). Unfortunately, the diastereoselectivity of this reaction was not reported.

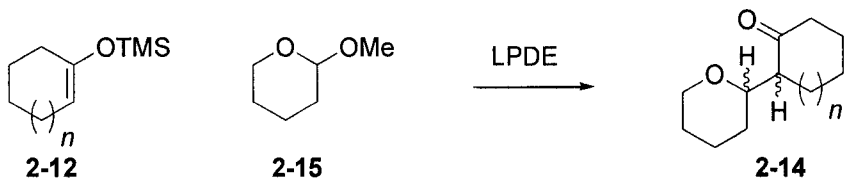
Scheme 4.



2-12 **2-13** **2-14**

In 1995, Sankararaman showed that this addition can be mediated by using lithium perchlorate-diethyl ether (LPDE) complex.[22] When cyclic enol silane **2-12** and anomeric ether **2-15** were treated with LPDE at room temperature, they isolated the desired bicycle **2-14** in 90 % yield as a mixture of unreported diastereomers (Entry 1, Scheme 5). Furthermore, when the cyclopentanone derived silyl enol ether **2-12** ($n = 0$) was used, no reaction (NR) took place (Entry 2, Scheme 5).

Scheme 5.



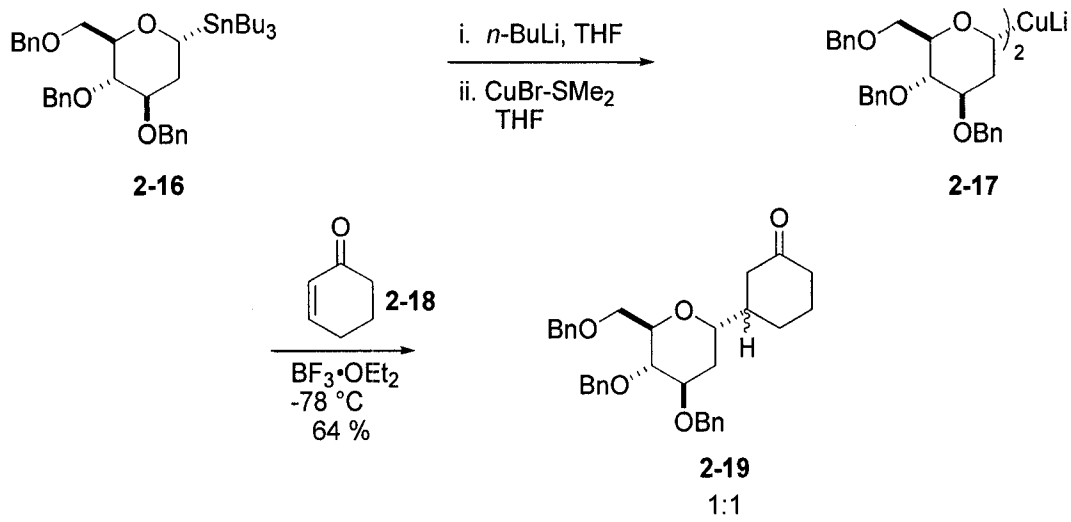
2-12 **2-15** **2-14**

Entry	*n* =	Yield (%)
1	0	NR
2	1	90

2.2.3. Anionic Approaches

The use of anionic pyran units for the construction of adjacent bicycles was first reported in 1987 by Fuchs and co-workers.[23] Following the transmetallation of the anomeric stannane **2-16** with *n*-BuLi and subsequent treatment with CuBr, the organocuprate **2-17** was treated with cyclohexenone **2-18** in the presence of $BF_3 \cdot OEt_2$ at -78 °C. The reaction afforded the bicyclic systems **2-19** as a 1:1 mixture of diastereomers (Scheme 6).

Scheme 6.

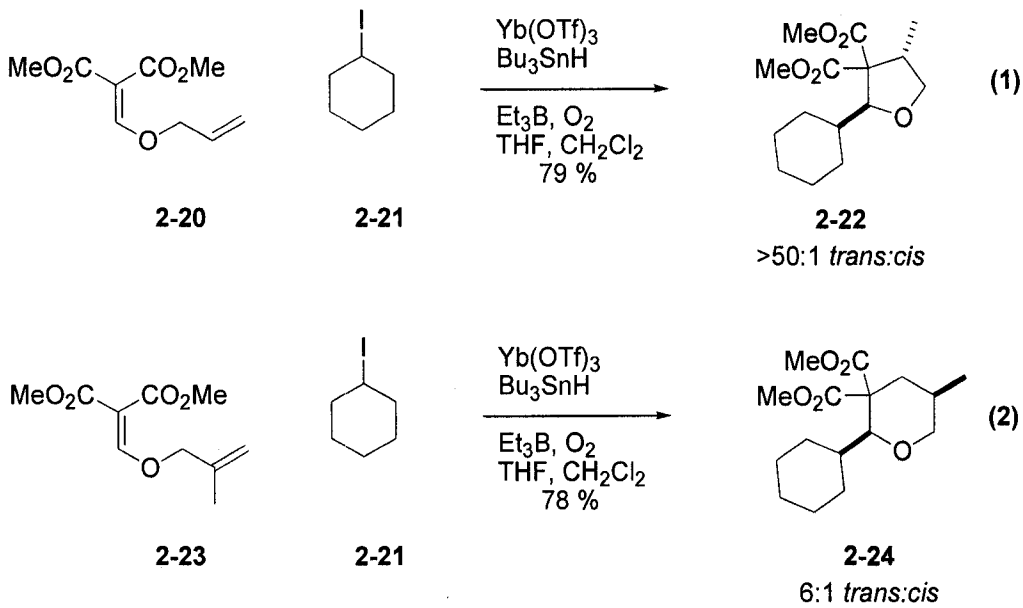


2.2.4. Radical Approaches

Another approach to these types of motifs involves a radical approach. Sibi and co-workers described the synthesis of oxacycles by a tandem radical addition-cyclization reactions.[24] Treatment of the allyl vinyl ether **2-20** with cyclohexyl iodide

2-21, Bu_3SnH, and a Lewis acid afforded a 5-*exo* cylization to furnish the furanyl bicycle **2-22** in a >50:1 ratio of *trans:cis* diastereomers (Eq. 1, Scheme 7). When the allyl vinyl ether was switched to **2-23**, the reaction afforded the 6-*endo* cyclization product **2-24** in 6:1 ratio of *cis:trans* isomers in 78 % yield (Eq. 2, Scheme 7).

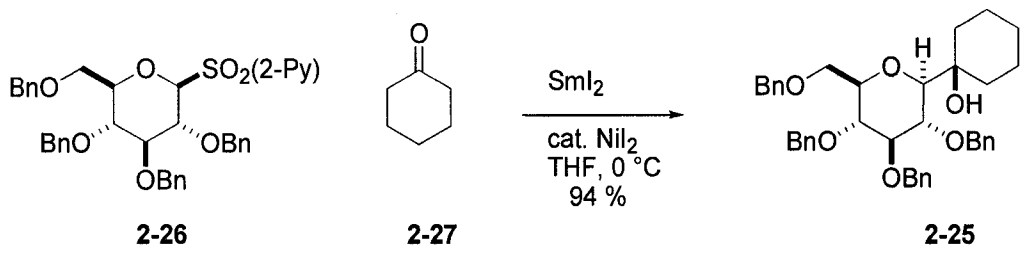
Scheme 7.



2.2.5. Utilization of Samarium Iodide

Beau and co-workers have demonstrated that SmI_2 is a useful reagent for the construction of 1,2-*trans*-*C*-glycosyl compounds **2-25**.[25] When anomeric sulphone **2-26** and ketone **2-27** were treated with SmI_2 in the presence of 1 mol% NiI_2, the reductive samariation product **2-25** was isolated as a single diastereomer in 94 % yield (Scheme 8). The practicability of this coupling makes it a useful tool, however it is limited to ketones as the reductive partner.

Scheme 8.



2-26 **2-27** **2-25**

2.3 Development of a Stereoretentive [1,3]-Oxygen to Carbon Rearrangement

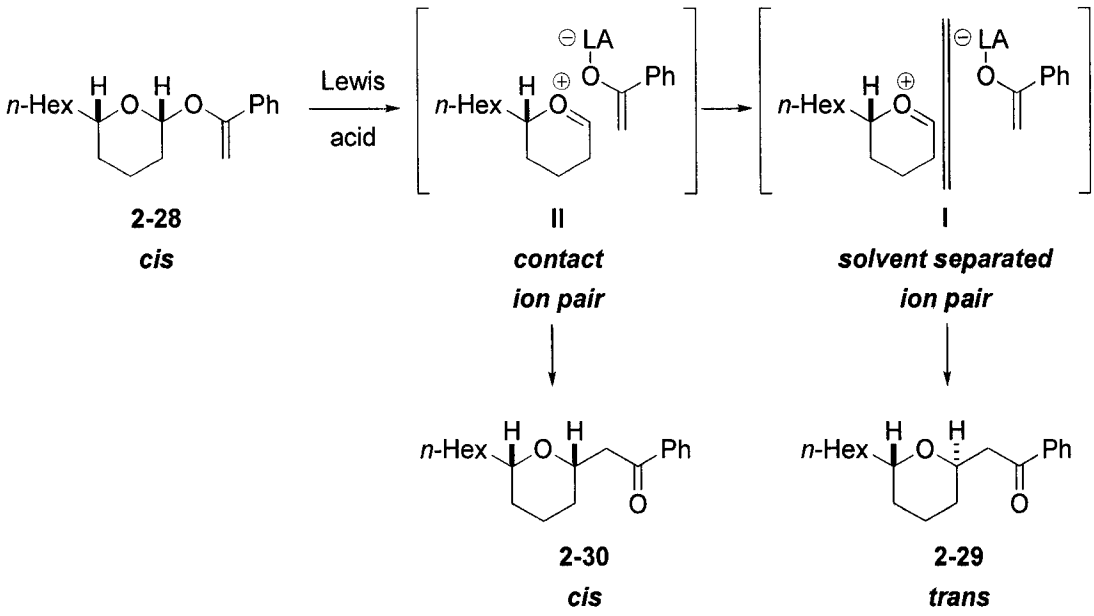
2.3.1 Initial Development

Recently, Rovis *et. al.* have shown the true potential of the [1,3]-oxygen to carbon rearrangement as a synthetic tool.[26] In their system, they were able to harness the stereoelectronic effects of oxocarbenium ion intermediates and the ability to use pre-existing stereocenters in the starting vinyl acetal to dictate the stereochemistry in the carbon-carbon bond forming event. Their ability to rearrange the vinyl acetal in a stereoretentive manner proceeding via a contact ion pairing is an important advance in the development of non-concerted oxygen containing rearrangements.

As a model system, they synthesized *cis*-6-substituted tetrahydropyran vinyl acetal **2-28**. When 6-substituted tetrahydropyran vinyl acetals **2-28** are used in the rearrangement, they proceed to yield *trans*-selective alkylation products **2-29**.[27-31] The *trans*-products **2-29** are afforded from the Lewis acid complexed enolate escaping the solvent cage prior to recombination **I** (Figure 3). Thus, when the Lewis acid complexed enolate recombines with the oxocarbenium ion, it attacks in the least hindered

orientation to yield the *trans*- products **2-29**. The initial screen of Lewis acids revealed a wide range of varying selectivities (Scheme 9).

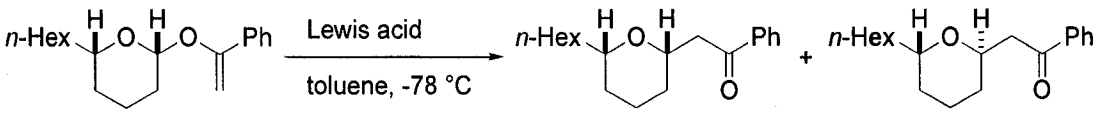
Figure 3.



Scheme 9 reveals the strong Lewis acids, $SnCl_4$ and $BF_3{\bullet}OEt_2$, cause the ions to dissociate and the *trans*-products **2-29** to prevail. However, switching to a milder Lewis acid, Et_2AlCl, allowed for the rearrangement to become more *cis*-selective **2-30** (55:45). When Et_3Al was used as the Lewis acid, the rearrangement proceeded in high *cis*-selectivity to form **2-30** (95:5), but the yield was poor (38 %). The proper mix of yield and diastereoselectivity was achieved when a mixture of four equivalents of Me_3Al and one equivalent of $BF_3{\bullet}OEt_2$ was used. These conditions yielded the desired *cis*-product **2-30** in 93:7 (*cis:trans*) diastereoselectivity and in good yields (86 %). It is believed that under these conditions, the generated Lewis acid complexed enolate remains as a contact ion pair with the oxocarbenium ion **II** and overall the

recombination of the two ions then becomes faster than dissociation (Figure 3), thus giving the stereoretentive *cis*-product **2-30**.

Scheme 9.

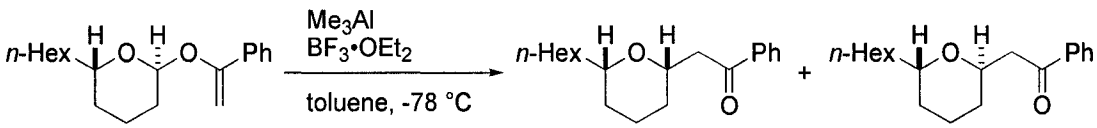


2-28 ***cis*** **2-30** ***cis*** **2-29** ***trans***

Lewis acid	*cis:trans*	Yield (%)
$SnCl_4$	5:95	75
$BF_3{\cdot}OEt_2$	5:95	93
Et_2AlCl	55:45	98
Et_3Al	95:5	38
Me_3Al / $BF_3{\cdot}OEt_2$	93:7	86

To examine if the *cis*-product **2-30** was a function of the Lewis acid or ion pairing, the *trans*-6-substituted tetrahydropyran **2-29** was subjected to the same reaction conditions (Scheme 10). As anticipated, the *trans*-product **2-29** predominated. Another control experiment revealed that the *trans*-product **2-29** does not epimerize to the *cis*-product **2-30** under the reaction conditions and no epimerization was observed.

Scheme 10.

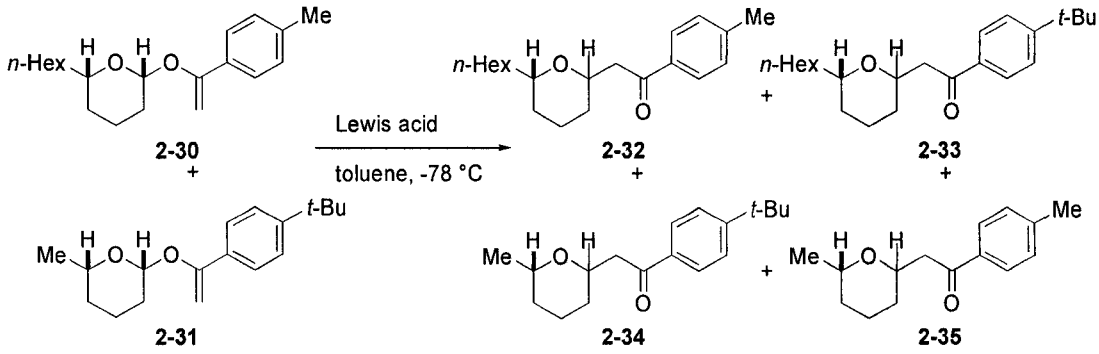


2-29 ***trans*** **2-30** ***cis*** ***8:92*** **2-29** ***trans***

To further investigate the ion pairing hypothesis, a cross over experiment was conducted by subjecting two distinct vinyl acetals (**2-30** and **2-31**) to the rearrangement

conditions (Scheme 11). If ion pairing is responsible for the observed diastereoselectivity, then the enolate generated from **2-30** should not recombine with the oxocarbenium ion of **2-31** (and vice versa) and therefore, no crossover product (**2-33** and **2-35**) should be observed. Fortunately, the crossover experiment supported the initial theory that contact ion pairing was the reason for the stereoretentive product. The two crossover products, **2-33** and **2-35**, were only seen in trace amounts (<0.3 % by GC-MS), while the contact ion pair stereoretentive products (**2-32** and **2-34**) were observed as the major products. Under the same crossover conditions, $BF_3 \cdot OEt_2$ was successful in causing ion dissociation and yielding all four *trans*-products (**2-32**)-(**2-35**), including cross-over products (Scheme 11).

Scheme 11.

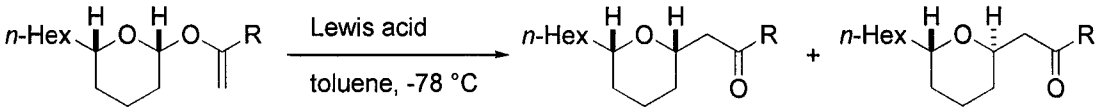


Lewis acid	*cis*-32	*trans*-32	*cis*-34	*trans*-34	*cis*-33	*trans*-33	*cis*-35	*trans*-35
$BF_3 \cdot OEt_2$	0.5	23.0	0.3	36.0	0.6	20.8	0.1	15.3
Me_3Al / $BF_3 \cdot OEt_2$	48.8	1.4	42.8	6.8	0	0.3	0	<0.2

Further investigations into the scope of the rearrangement revealed that the nucleophilicity of the developing enolate played an important role in the diastereoselectivities. Under the optimal stereoretentive conditions, the more nucleophilic enolate afforded a higher *cis*-selectivity **2-36** (Entry 2, Scheme 12), while

the less nucleophilic enolate afforded a lower *cis*-selectivity (Entry 3, Scheme 12). Another interesting note, which fits the observed trend, is the less nucleophilic methyl and cyclohexyl substituted vinyl acetals **2-37** yielded the stereoretentive products **2-36** in a diminished ratio (Entries 4 and 5, Scheme 12, respectively).

Scheme 12.

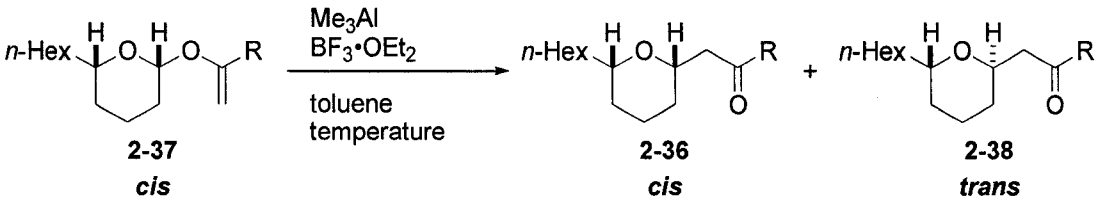


2-37 ***cis*** **2-36** ***cis*** **2-38** ***trans***

Entry	Lewis acid	R	*cis:trans*	Yield (%)
1	$BF_3{\cdot}OEt_2$	Ph	5:95	93
2		(4-Me)Ph	7:93	90
3		(4-Br)Ph	5:95	90
4		Me	5:95	88
5		*cy*-Hex	5:95	90
6	Me_3Al / $BF_3{\cdot}OEt_2$	Ph	93:7	86
7		(4-Me)Ph	96:4	92
8		(4-Br)Ph	90:10	80
9		Me	81:19	--
10		*cy*-Hex	50:50	--

To correct for the diminished selectivity in the less nucleophilic substrate series, a temperature study was performed. Interestingly, lowering the temperature diminished the selectivities (Entry 1, Scheme 13), while warming the reaction afforded the stereoretentive products **2-36** in improved selectivities, providing a partial solution (Entry 2, Scheme 13). A possible rationale for the observed selectivities may lie in the observation that contact ion pairs are disfavored relative to solvent separated ion pairs at lower temperatures.[32-35]

Scheme 13.

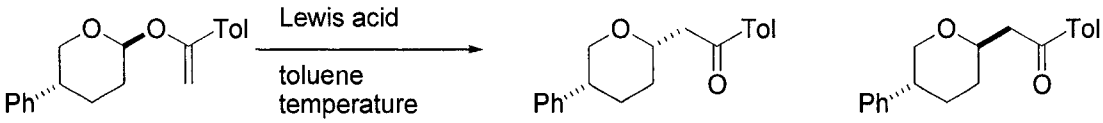


2-37 ***cis*** **2-36** ***cis*** **2-38** ***trans***

Entry	Temp (°C)	R	*cis:trans*	Yield (%)
1	-90	Me	55:45	---
2	-55	Me	89:11	82
3	-32	*cy*-Hex	90:10	83

Next, the substitution position was varied around the pyran ring. When a 5-phenyl substituted tetrahydropyran **2-39** was used, the BF_3•OEt_2 mediated rearrangement proceeded in excellent selectivities (95:5; *cis:trans*) (Entry1, Scheme 14). The stereoretentive rearrangement afforded the stereoretentive *trans*-product **2-40** in good yields, when conducted at higher temperatures (Entry 2, Scheme 14).

Scheme 14.



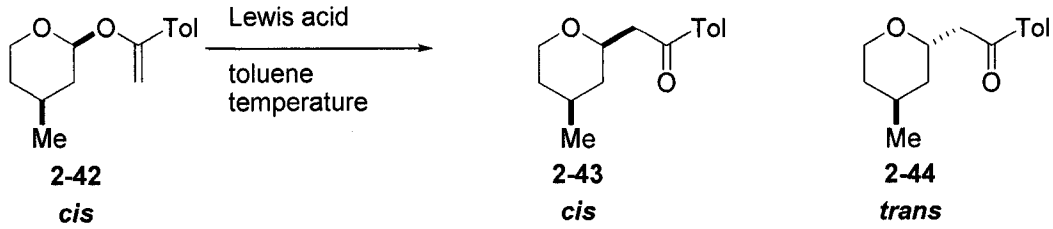
2-39 ***trans*** **2-41** ***cis*** **2-40** ***trans***

Entry	Lewis acid	Temp (°C)	*cis:trans*	Yield (%)
1	BF_3•OEt_2	-78	95:5	95
2	Me_3Al / BF_3•OEt_2	-25	10:90	85

The 4-methyl substituted tetrahydropyran **2-42** yielded very similar results. Under the BF_3•OEt_2 conditions, the reaction afforded a 5:95 (*cis:trans*) ratio of

diastereomers (Entry 1, Scheme 15), while the stereoretenctive conditions proved successful again. The $Me_3Al/BF_3{\cdot}OEt_2$ conditions yielded a 89:11 (*cis:trans*) ratio of diastereomers in 78 % yield when the reaction was run at -25 °C (Entry 2, Scheme 15).

Scheme 15.

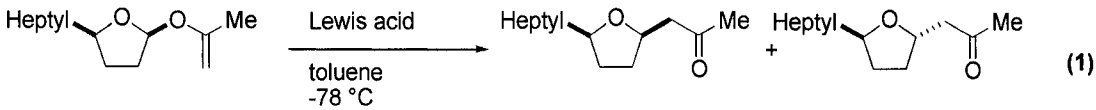


2-42 ***cis*** **2-43** ***cis*** **2-44** ***trans***

Entry	Lewis acid	Temp (°C)	*cis:trans*	Yield (%)
1	$BF_3{\cdot}OEt_2$	-78	5:95	92
2	Me_3Al / $BF_3{\cdot}OEt_2$	-25	89:11	78

Next, the ring size was examined to see if it played an important role on selectivity. They found that $BF_3{\cdot}OEt_2$ sufficiently rearranged the vinyl acetals, however the selectivities varied from good to modest for the tetrahydrofuran **2-45** (Entry 1, Eq. 1) and oxepane ring **2-46** (Entry 1, Eq. 2)(Scheme 16). The stereoretentive rearrangement conditions proved satisfactory, yielding the stereoretentive products in good diastereoselectivities for both the tetrahydrofuran **2-47** (Entry 2, Eq. 1) and oxepane **2-48** (Entry 2, Eq. 2) systems (Scheme 16).

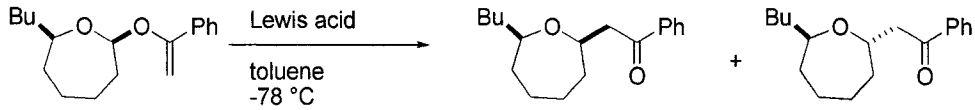
Scheme 16.



(1)

2-45 ***cis*** **2-47** ***cis*** **2-49** ***trans***

Entry	Lewis acid	*cis:trans*	Yield (%)
1	$BF_3 \cdot OEt_2$	67:33	92
2	Me_3Al / $BF_3 \cdot OEt_2$	92:8	85



(2)

2-46 ***cis*** **2-48** ***cis*** **2-50** ***trans***

Entry	Lewis acid	*cis:trans*	Yield (%)
1	$BF_3 \cdot OEt_2$	3:97	92
2	Me_3Al / $BF_3 \cdot OEt_2$	86:14	84

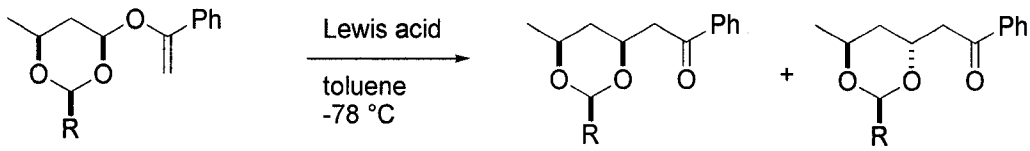
Overall conditions for a Lewis acid-mediated stereoretentive rearrangement of vinyl acetals have been developed, wherein the selectivity is controlled by contact ion pairing. They have shown how a chiral acetal may be rearranged to form either diastereomer by simple choice of Lewis acid and/or reaction temperatures.

2.3.2The Use of the [1,3]-Oxygen to Carbon Rearrangement for the Construction of 1,3-Polyol Sequences

The ability to form skipped polyol units remain an important challenge for organic chemist due to their abundance in natural products. One potential method for the construction of these polyol sequences is by implementing the recently developed [1,3]-stereoretentive oxygen to carbon rearrangement of vinyl acetals.[26]

Further research from the Rovis group has revealed that in the 1,3-dioxane moiety **2-51**, the substitution at the *C*-2 acetal position had the greatest impact on the rearrangement.[36] Under either the *syn*- or *anti*-selective reaction conditions, when the *C*-2 substituent was sterically small, i.e. methyl or phenyl, many products were isolated (Entries 1 and 2, respectively, Scheme 17). When the *C*-2 substituent was changed to a sterically larger, i.e. isopropyl or tertbutyl, the reaction proceeded with high diastereoselectivity for both reaction conditions (Entries 3 and 4, respectively, Scheme 17).

Scheme 17.



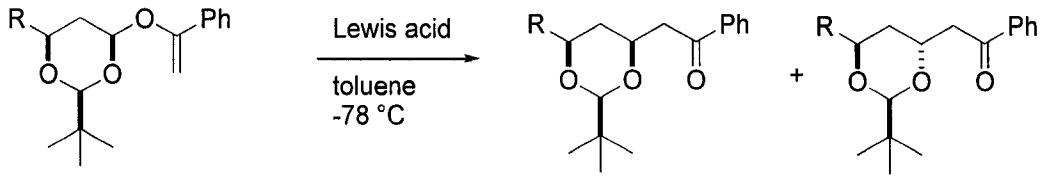
2-51
syn

syn ***anti***

Entry	R	*syn:anti* (Yield) $BF_3 \cdot OEt_2$	*syn:anti* (Yield) Me_3Al / $BF_3 \cdot OEt_2$
1	Me	Many Products	Many Products
2	Ph	Many Products	Many Products
3	*i*-Pr	3:97 (92 %)	90:10 (80 %)
4	*t*-Bu	2:98 (82 %)	96:4 (90 %)

Next using the *C*-2 *t*-butyl-substituted dioxane **2-52**, they examined what impact substituents at the *C*-6 position played on the diastereoselectivity. They determined that a variety of sterically and electronically dissimilar subsituents could be tolerated at this position. In all cases, excellent *syn*- (**2-53**) and *anti*- (**2-54**) selectivities were obtained in good yields (Scheme 18). Overall, the diastereoselective rearrangement could tolerate a wide range of sterically different groups at the *C*-2 position.

Scheme 18.

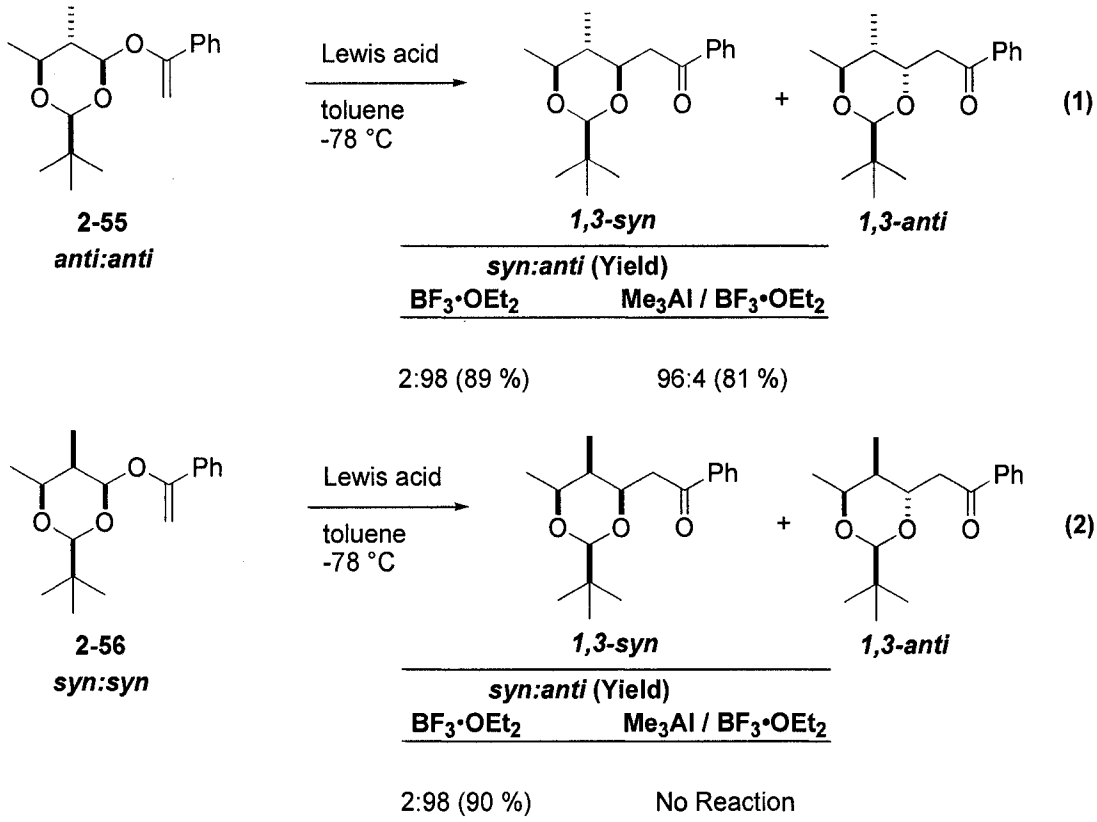


2-52 ***syn*** **2-53** ***syn*** **2-54** ***anti***

Entry	R	*syn:anti* (Yield) $BF_3 \cdot OEt_2$	Me_3Al / $BF_3 \cdot OEt_2$
1	Me	2:98 (82 %)	96:4 (90 %)
2	*n*-Hex	2:98 (87 %)	92:8 (90 %)
3	*cy*-Hex	2:98 (96 %)	93:7 (87 %)
4	*i*-Pr	2:98 (97 %)	93:7 (85 %)
5	Ph	2:98 (87 %)	92:8 (81 %)
6	CH_2CH_2Ph	2:98 (91 %)	98:2 (89 %)

To further extend this methodology, they demonstrated the stereoretentive rearrangement on *C*-5-methyl substituted moieties (**2-55** and **2-56**). These mixed propionate arrays are common units in important natural products and still remain an important challenge to chemists.[37-44] The rearrangement of the *anti:anti* series **2-55** proceeded in high diastereoselectivities for both the *syn*- and *anti*-selective conditions in good yields (Eq. 1, Scheme 19). Furthermore, the rearrangement of the *syn:syn* series **2-56** underwent the *anti*-selective rearrangement in excellent selectivities, however, the stereoretentive *syn*-rearrangement of **2-56** did not proceed at all, even at room temperature (Eq. 2, Scheme 19).

Scheme 19.



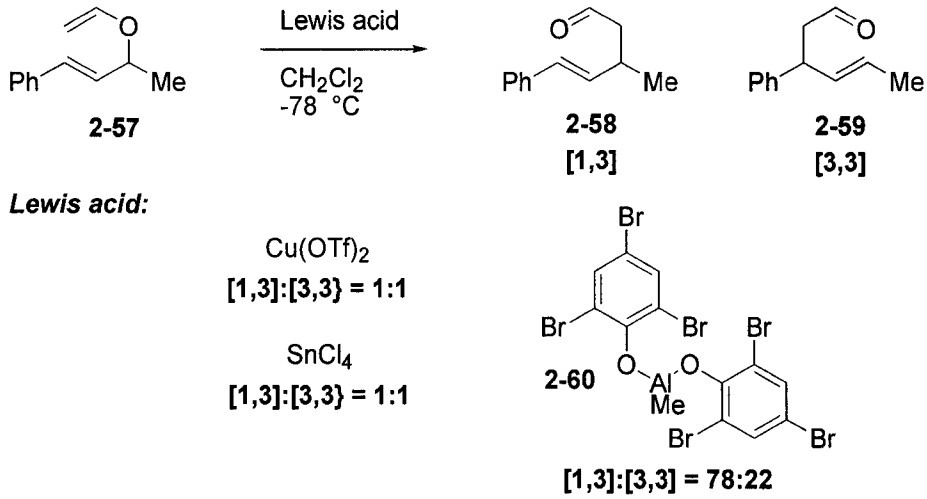
In conclusion, the Rovis group has developed a new process for the construction of highly diastereoselective *anti*- and *syn*-3,5-dihydroxy ketone units via a stereoretentive [1,3]-oxygen to carbon rearrangement. This new methodology continues to further expand the scope of the oxygen to carbon rearrangement of vinyl acetals.

2.3.3. Regioselective [1,3]-Oxygen to Carbon Rearrangement of Allylvinyl Ethers

Research conducted alongside with my studies by Rovis and Nasveschuk was aimed at developing a stereoselective [1,3]-rearrangement of allyl vinyl ethers **2-57**. Due to observations made by other groups,[45-48] in which [1,3]-rearrangement products **2-58** were isolated from allylvinyl ethers **2-57**, they wanted to harness the reactivity of this [1,3]-rearrangement and elucidate the factors which govern its selectivity.[49]

After initial screening, they found the best conditions involved CH_2Cl_2 or toluene as solvent and a bisphenoxy aluminum Lewis acid **2-60** provided the best regiocontrol (Scheme 20).

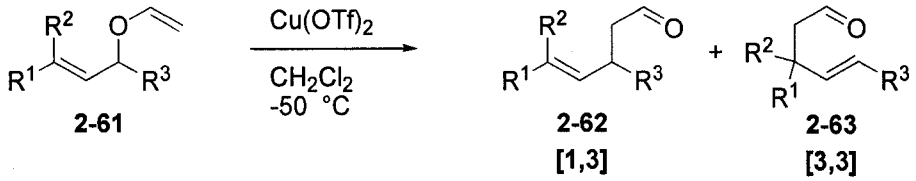
Scheme 20.



Due to the modest selectivities achieved, they wanted to explore the possibility of tri-subsituted allylvinyl ethers **2-61**. They anticipated the tri-substituted allylvinyl ethers **2-61** would prefer to undergo a [1,3]-rearrangement **2-62** rather than a [3,3]-rearangement **2-63**, since Claisen rearrangements of tri-substituted allylvinyl

ethers **2-61** usually occur at elevated temperatures due to the demands of forming a quaternary stereocenter **2-63**. The use of a variety of Lewis acids [$Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, Me_2AlCl, $EtAlCl_2$, and $MeAl(OAr)_2$] all afforded the [1,3]-rearrangement products **2-62** in regioselectivities ranging from 80:20 to >95:5 ([1,3]:[3,3]). $Cu(OTf)_2$ proved the best overall mix for selectivity (>95:5) and yield (81 %). The extended scope of the new conditions are shown in Scheme 21. As can be seen, the introduction of the trisubstituted allylvinyl ether **2-61** proved to be the key for the desired [1,3]-regiocontrol in the rearrangement.

Scheme 21.



Entry	R^1	R^2	R^3	[1,3]:[3,3]	Yield (%)
1	Ph	Me	Me	>95:5	81
2	Ph	Me	Et	>95:5	70
3	Ph	Me	*i*-Pr	>95:5	53
4	Ph	Me	*t*-Bu	85:15	63
5	Ph	Et	Me	>95:5	64
6	*n*-Bu	Me	Me	80:20	50
7	*n*-Bu	Me	CH_2CH_2Ph	69:31	84

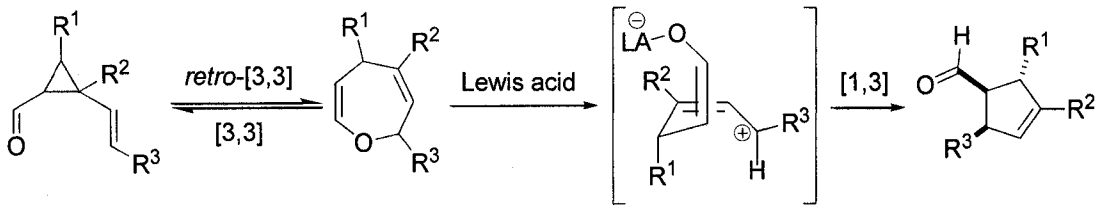
In conclusion, they have shown that under strong Lewis acidic conditions, the Claisen rearrangement ([3,3]) does not proceed via a concerted mechanism, but proceeds via an ionization pathway. This ionization then allows for the fragments to

recombine in either a net overall [1,3] or [3,3] pathway, in which the [1,3] is preferred when tri-substituted allylvinyl ethers are used as the starting materials.

2.3.4. [1,3]-Oxygen to Carbon Rearrangement for the Construction of Polysubstituted Cyclopentenes

Most of the previous examples for the construction of cyclopentenes involve only mono- and di-substitution patterns, while the synthesis of poly-substituted cyclopentene systems are rare.[50] As a result, Rovis and Nasveschuk began to explore using the [1,3]-oxygen to carbon rearrangement for the construction of substituted cyclopentenes **2-64**. They reported the successful implementation of a retro [3,3]-rearrangement of cyclopropyl aldehydes **2-65** to construct 2,5-dihydrodioxepines **2-66**, which was followed by the [1,3]-ring contraction **III** to afford the substituted cyclopentenes **2-64** (Scheme 22).[51]

Scheme 22.

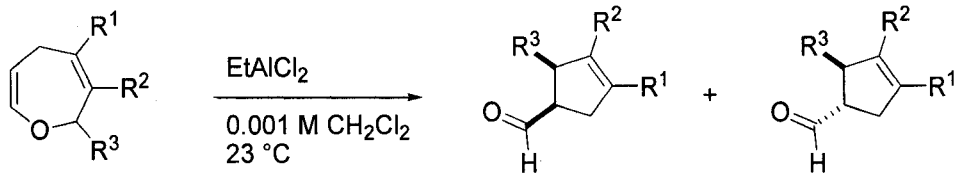


2-65 **2-66** **III** **2-64**

When optimizing the ring contraction conditions, a variety of Lewis acids were screened [$Cu(OTf)_2$, $TiCl_4$, $SnCl_4$, $EtAlCl_2$]. They concluded the optimized conditions for highest diastereoselectivity and highest yields were under high dilution

(0.001 M) with $EtAlCl_2$ as the Lewis acid. The scope of the reaction is shown in Scheme 23. Overall, they found that electron-donating or –withdrawing groups in the *para*-position of the phenyl ring are easily tolerated (Entries 2 and 3, respectively, Scheme 23), as well as additional substituents on the dihydrooxepine ring **2-67** (Entry 4, Scheme 23). All of the systems analyzed yielded the cyclopentenes **2-68** and **2-69** in good to excellent diastereoselectivities and in modest to high yields (Scheme 23).

Scheme 23.

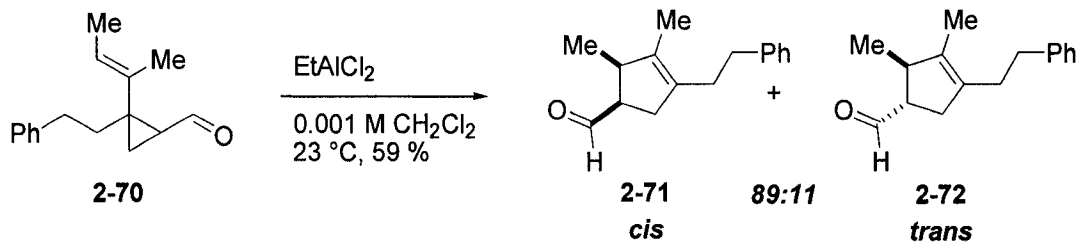


2-67 **2-68** ***cis*** **2-69** ***trans***

Entry	R^1	R^2	R^3	*cis:trans*	Yield (%)
1	Ph	H	Me	90:10	89
2	*p*-Tol	H	Me	93:7	85
3	*p*-$C_6H_4CF_3$	H	Me	87:13	75
4	Ph	Me	Me	88:12	58
5	Ph	H	CH_2CH_2Ph	85:15	73
6	Ph	H	$CH_2CH_2OTBDMS$	85:15	52

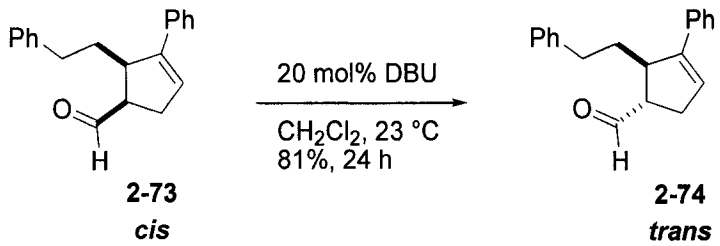
Further experiments revealed the cyclopropane aldehyde **2-70** can directly be treated with a Lewis acid to form the cyclopentene products **2-71** and **2-72**, thus highlighting that the formation of the 2,5-dihydrooxepine **2-67** is not necessary (Scheme 24). It is assumed that the Lewis acid initiates the retro-Claisen to form the 2,5-dihydrodioxepine *in situ*, which subsequently undergoes the [1,3]-rearrangement.

Scheme 24.



The versatility of this ring contraction approach was achieved by subjecting the cyclopentenes to epimerization conditions. They showed that when the *cis*-cyclopentene product **2-73** was treated with catalytic amounts of DBU, the *trans*-cyclopentene products **2-74** were isolated in excellent diastereoselectivity (Scheme 25). The ability to epimerize the products of the ring contraction to their complementary diastereomer allows for the construction of either *cis*- or *trans*-substituted cyclopentenes and therefore broadening the scope of this transformation.

Scheme 25.



In summary, the Rovis group has shown the [1,3]-oxygen to carbon rearrangement can be implemented in the construction of either *cis*- or *trans*-polysubstituted cyclopentenes. The ease in the formation of the starting 2,5-dihydrodioxepines allows for the formation of highly subsitituted cyclopentene rings,

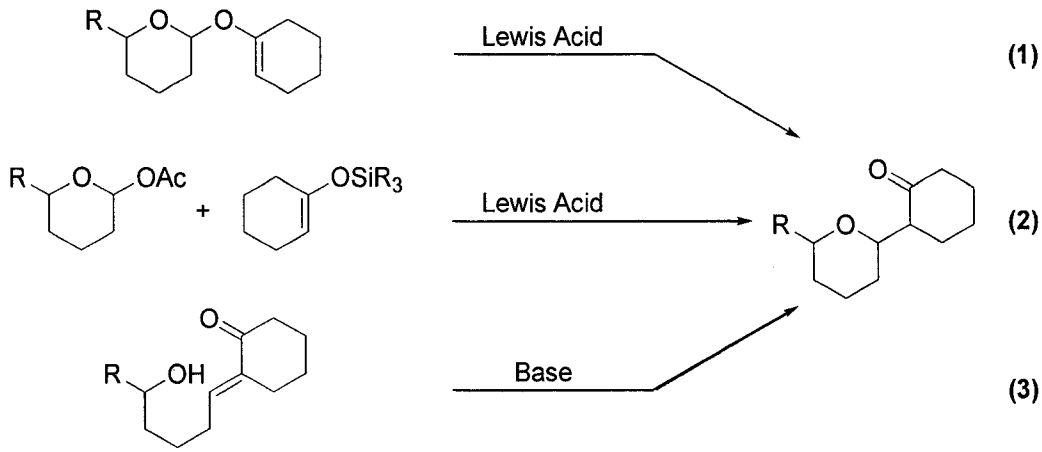
which can further be modified to install other functionality by use of the inherent olefin and aldehyde functionality.

2.4. Results

Due to these recent successes the Rovis group has pursued in the advancement of the stereoretentive [1,3]-oxygen to carbon rearrangement.[26,36,49,51] We believed that we could apply this methodology to the construction of complex, congested carbon-carbon bonds. We chose to conduct an in-depth study of various approaches to this type of ring juncture. Prime amoung these was our intention to apply our recently developed stereoretentive [1,3]-oxygen to carbon rearrangement to this problem (Eq.1, Scheme 26). In doing so, we hoped to take advantage of the relative facility of controlling stereochemistry in the formation of a C-O bond and induce it to rearrange to a C-C bond, having already paid the entropic price of bringing two fragments together in the formation of the C-O bond. The question that we needed to address was our ability to control the second stereocenter in the rearrangement. Second, we hoped to contrast these results with selectivities obtained in the more classical Lewis acid induced intermolecular enolsilane addition to an *in situ* generated oxocarbenium ion (Eq. 2, Scheme 26). This method is comparable to the rearrangement method without having to address the issue of creating the oxocarbenium ion and enolate via an intramolecular event, although it lacks the possibility of providing the *cis*-adduct via a

stereoretentive process. Last, we wanted to exploit an intramolecular conjugate addition of an alkoxide into an α,β-unsaturated ketone (Eq. 3, Scheme 26).

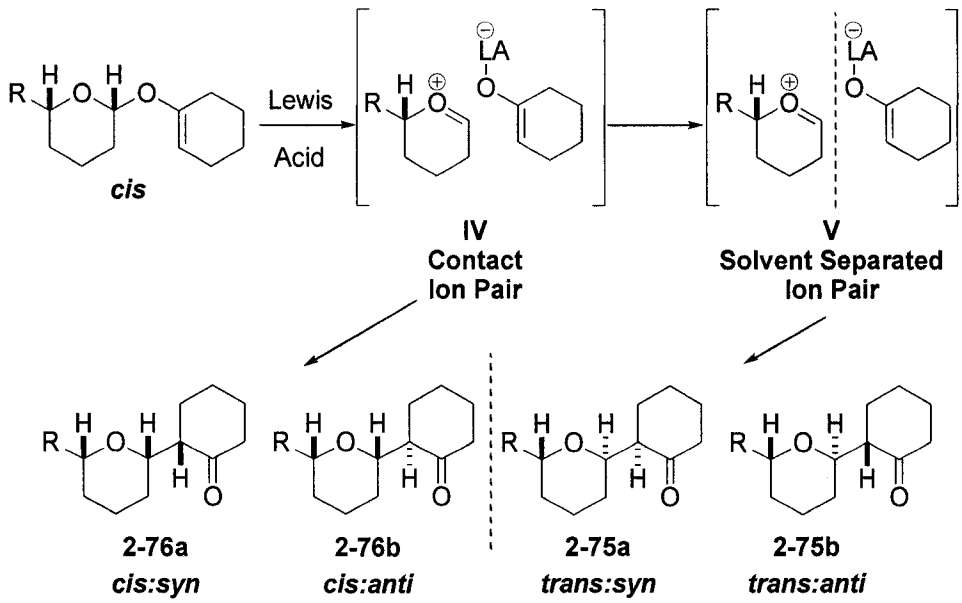
Scheme 26.



2.4.1. [1,3]-Oxygen to Carbon Rearrangement

Using the recently developed [1,3]-oxygen to carbon rearrangement,[26] we believed that selectivity could be controlled by contact ion pairing of the resulting oxocarbenium ion and Lewis acid complexed enolate **IV**. Should the generated ions escape the solvent cage prior to recombination **V**, the *trans*-product **2-75** will predominate. However, if recombination occurs faster than dissociation, the *cis*-product **2-76** will result. We believed that the chosen Lewis acid used to mediate the rearrangement would have the ability to control the recombination of the intermediates and possibly form one of the four possible diastereomers in a highly selective manner (Figure 4).

Figure 4.



We chose to begin our investigations with simple enolates and oxocarbenium ions devoid of electronic or steric features, which might dictate selectivity in the bond forming event.

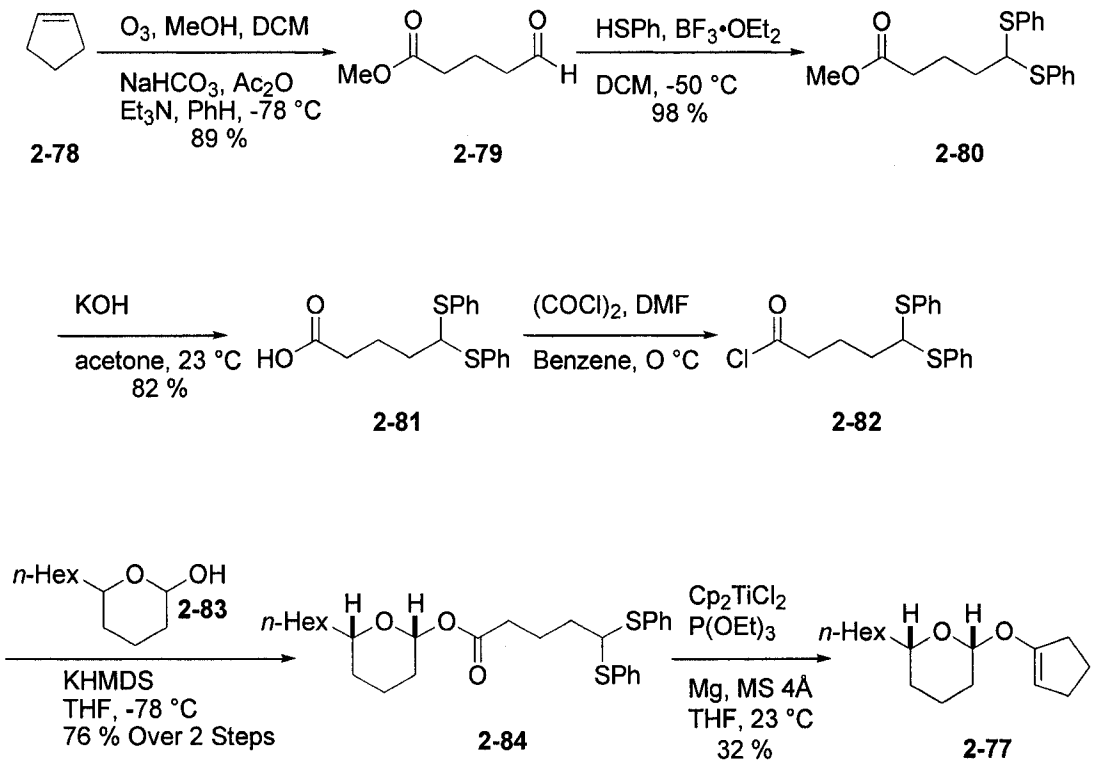
2.4.1.1 (2-Cyclopent-1-enyloxy)-Tetrahydropyran

2.4.1.1.1. Substrate Synthesis

The synthesis of the requisite (*cis*)-2-(cyclopent-1-enyloxy)-6-hexyl-tetrahydropyran **2-77** began using Schrieber's modification for the ozonolytic cleavage of cycloalkenes to terminally differentiated products (Scheme 27).[52] Treatment of cyclopentene **2-78** with ozone in CH_2Cl_2, followed by acetic anhydride and Et_3N afforded the terminally differentiated methyl ester-aldehyde **2-79** in 89 %. Subsequent

treatment of **2-79** with thiophenol and $BF_3 \cdot OEt_2$ yielded the thioacetal-methyl ester **2-80** in near quantitative yield. The thioacetal-methyl ester **2-80** was then hydrolyzed with KOH to the thioacetal-carboxylic acid **2-81** and subsequent treatement with oxalyl chloride in the presenece of catalytic DMF furnished the thioacetal-acyl chloride **2-82**.

Scheme 27.

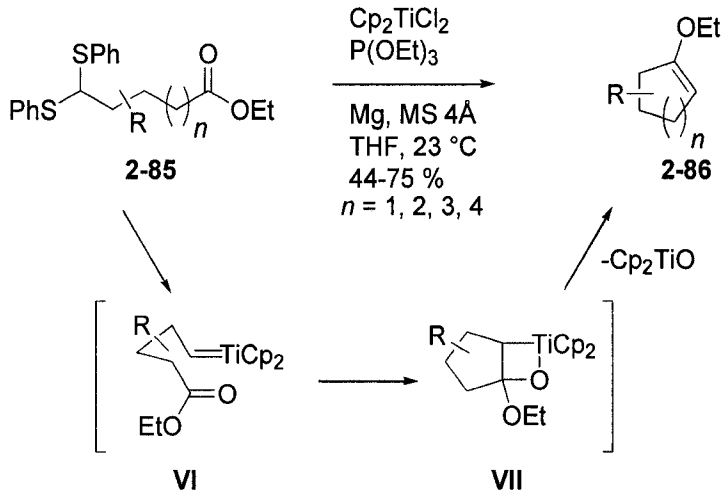


When the lactol **2-83**, prepared via the DIBAL-*H* reduction of the corresponding lactone, was treated with KHMDS followed by **2-82**, under the procedure developed by Ley, *cis*-anomeric ester **2-84** was isolated in >95:5 (*cis:trans*) diastereoselectivity.[31]

From here, we wished to implement Takeda's recently developed intramolecular carbonyl olefination of esters **2-85** with thioacetals to form the desired

cyclic vinyl ether **2-86** (Scheme 27).[53] The reaction is believed to proceed via the titanium-alkylidene complex **VI**, which then undergoes a net [2+2] to afford the oxatitanacyclo-butane **VII**. The metallocycle then undergoes a net retro [2+2] to furnish the cyclic vinyl ether **2-86** and titanocene oxide (Scheme 28).

Scheme 28.



The titanocene mediated carbonyl olefination reaction proceeded on our system to afford the cyclic vinyl ether **2-77**, however, the yields were a very modest 32 %.

2.4.1.1.2. Rearrangement Results

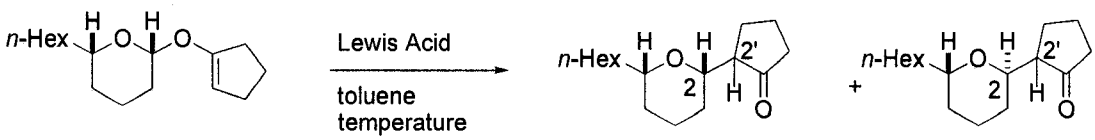
With the requisite cyclic vinyl ether **2-77** in hand, we began with the "standard" conditions that had worked on our previous systems.[26,36] Treatment of **2-77** with $BF_3 \cdot OEt_2$ at -78 °C in toluene yielded the *trans*-product **2-87** as a single *cis:trans*

diastereomer in good yield, 90% (Entry 1, Table 1). The C2-C2' *anti:syn* diastereomeric ratio was a modest 79:21 (*anti:syn*). Under the stereoretentive rearrangement conditions, $Me_3Al/BF_3{\bullet}OEt_2$ afforded a 40:60 ratio of *cis:trans* diastereomers (Entry 2, Table 1). The *cis*-product **2-88** was isolated as a 60:40 mixture of C2-C2' (*anti:syn*) diastereomers, while the *trans*-product **2-87** contained a 74:26 (*anti:syn*) mixture of C2-C2' diastereomers. Unfortunately, the stereoretentive rearrangement conditions did not prove capable for my system; we accredit this to the increased steric requirement of the trisubstituted olefin **2-77** when compared to the disubstituted olefins **2-37** found in the original system (Scheme 12).

Next, we focused our attention on finding other Lewis acids which were competent for the stereoretentive rearrangement. Adjustment of the Lewis acidity to Et_2AlCl provided a partial solution, potentially due to the slightly more reactive enolate intermediate. At -78 °C, the rearrangement presumably proceeds via tight ion pairing and results in modest *cis:trans* diastereoselectivity (Entry 7, Table 1). The C2-C2' *anti:syn* diastereoselectivity for the *cis*-diastereomer **2-88** afforded a 69:31 (*anti:syn*) ratio, while the *trans*-diastereomer **2-87** yielded a 77:23 (*anti:syn*) ratio of C2-C2' diastereomers. With this initial result and our previous knowledge that temperature plays an important role on ion pairing,[32-35] we next conducted the Et_2AlCl mediated rearrangement at -50 °C and 0 °C (Entries 8 and 9, respectively, Table 1). Unfortunately, the ratios of the product diastereomers did not improve by any appreciable amount. At 0 °C, the *cis:trans* ratio did improve slightly, but the C2-C2' ratios were diminished (Entry 9, Table 1).

We continued to investigate other Lewis acids for the rearrangement and found the best stereoretentive conditions involved using 1.5 equivalents of Et_2AlCl in the presence of 1.65 equivalents of PPh_3 (Entry 4, Table 1). These conditions yielded a 73:27 (*cis:trans*) ratio of diastereomers, with the *cis*-diastereomer **2-88** containing a 66:34 (*anti:syn*) ratio of C2-C2' diastereomers. Furthermore, $FeCl_3$ proved to be an efficient mediator for the *trans*-selective rearrangement **2-87**, affording a 16:84 (*cis:trans*) mixture of diastereomers (Entry 6, Table 1). The *trans*-C2-C2' diastereomeric ratio was also good (81:19; *anti:syn*) and the reaction afforded the products in a 87 % overall yield. Unfortunately, further modifications aimed at increasing the *cis-trans* and C2-C2' diastereoselectivities met with failure.

Table 1.



2-77 ***cis*** **2-88** ***cis*** **2-87** ***trans***

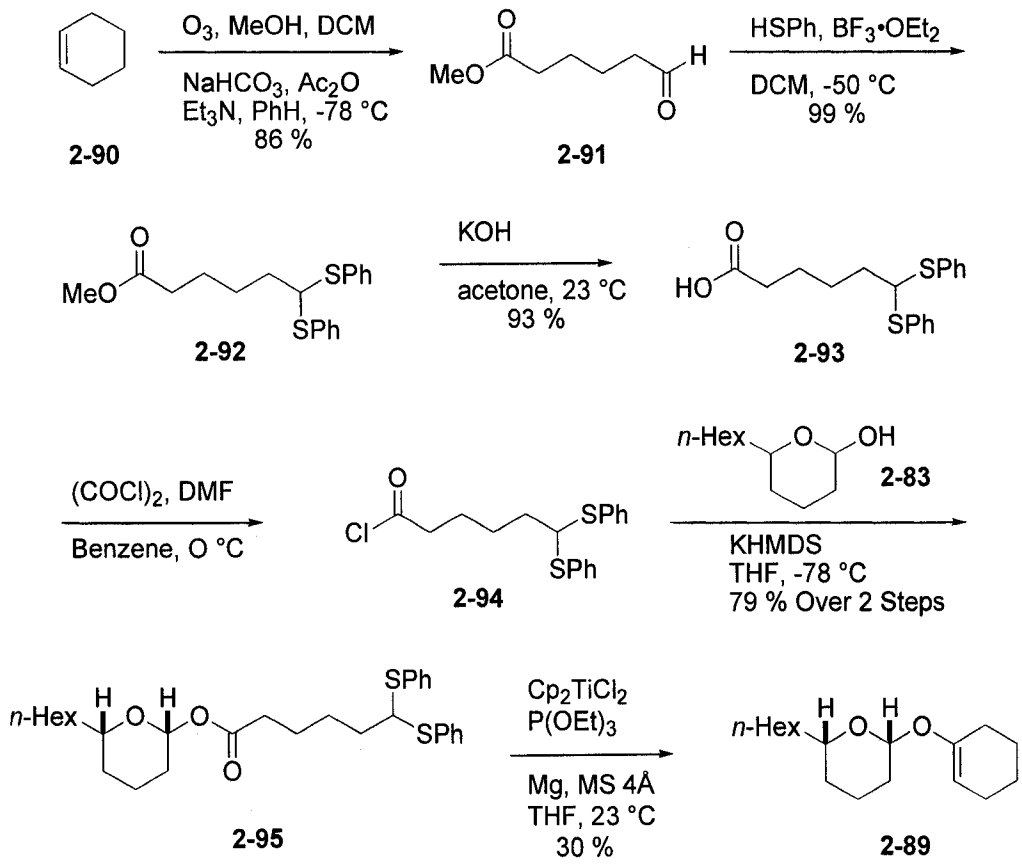
Entry	Lewis acid	Temp (°C)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	Yield (%)
1	$BF_3{\cdot}OEt_2$	-78	<1:>99	NA	79:21	90
2	Me_3Al / $BF_3{\cdot}OEt_2$	-78	40:60	60:40	74:26	75
3	$EtAlCl_2$	-78	36:64	62:38	80:20	67
4	PPh_3 / Et_2AlCl	-78	73:27	66:34	73:27	79
5	Me_2AlCl	-78	35:65	70:30	73:27	69
6	$FeCl_3$	-78	16:84	74:26	81:19	87
7	Et_2AlCl	-78	69:31	69:31	77:23	86
8	Et_2AlCl	-50	62:38	62:38	88:12	74
9	Et_2AlCl	0	72:28	58:42	81:19	68

2.4.1.2. (2-Cyclohex-1-enyloxy)-Tetrahydropyran

2.4.1.2.1. Substrate Synthesis

The synthesis of the requisite (*cis*)-2-(cyclohex-1-enyloxy)-6-hexyl-tetrahydropyrans **2-89** was performed in an analogous fashion to that of the cyclopentenyl analogue **2-77**. Cyclohexane **2-90** was transformed to **2-89** in 6 steps and in 19 % yield (Scheme 29).

Scheme 29.



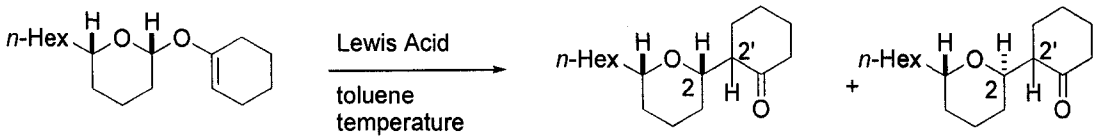
2.4.1.2.2. Rearrangement Results

When cyclic vinyl ether **2-89** was subjected to the BF_3•OEt_2 mediated rearrangement conditions, it furnished a 2:98 ratio of *cis:trans* diastereomers in an 88 % yield (Entry 1, Table 2). The *trans*-diastereomer **2-96** was isolated as a 84:16 (*anti:syn*) mixture of C2-C2' isomers. Under the stereoretentive rearrangement conditions, Me_3Al/BF_3•OEt_2 proved to be non-selective providing a nearly equal amount of *cis:trans* diastereomers (52:48) in 81 % yield (Entry 2, Table 2). The *cis*-isomer **2-97** was isolated as a 72:28 (*anti:syn*) mixture of C2-C2' diastereomers, while the *trans*-isomer **2-96** was afforded in a 62:38 (*anti:syn*) ratio of C2-C2' epimers. The stereoretentive conditions again proved unsuccessful for the rearrangement of these tri-substituted olefins.

Attempting to adjust the acidity of the Lewis acid shifted our attention to the use of Et_2AlCl. Under various reaction temperatures (-78, -50, and 0 °C), the rearrangement yielded ratios of 92:8, 83:17, and 85:15 (*cis:trans*), respectively, and all in good yields (Entries 7, 8, and 9, respectively, Table 2). Unfortunately, the C2-C2' ratios for either the *cis*- or *trans*-products were modest at best, usually affording the *anti:syn* diastereomers as roughly a 60:40 mixture. These results are interesting when compared to those obtained on cyclic vinyl ether **2-77** (Entry 9, Table 1). The 5-membered cyclic vinyl ether **2-77** at 0 °C gave the highest *cis:trans* diastereoselectivities, while the 6-membered cyclic vinyl ether **2-89** afforded the highest *cis:trans* diastereoselectivities at -78 °C (Entry 7, Table 2).

With Et_2AlCl, the *cis:trans* diastereoselectivities were reasonable, but it lacked stereoselectivity at the C2-C2' stereocenters (Entry 7, Table 2). As a result, other Lewis acids were screened in hope that the C2-C2' stereoselectivity would increase. The use of $EtAlCl_2$, a mixture of PPh_3 and Et_2AlCl, and $FeCl_3$ all afforded the *trans*-product **2-96** as the major isomer in modest selectivities (Entries 3, 4, and 6; respectively, Table 2). However, when Me_2AlCl was used the C2-C2' diastereoselectivity was improved (Entry 5, Table 2). In entry 5, the *cis:trans* selectivity was modest (78:22), but the 78:22 (*anti:syn*) ratio for the *cis*-C2-C2' diastereomers was the highest isolated in this system thus far.

Table 2.



2-89 ***cis*** **2-97** ***cis*** **2-96** ***trans***

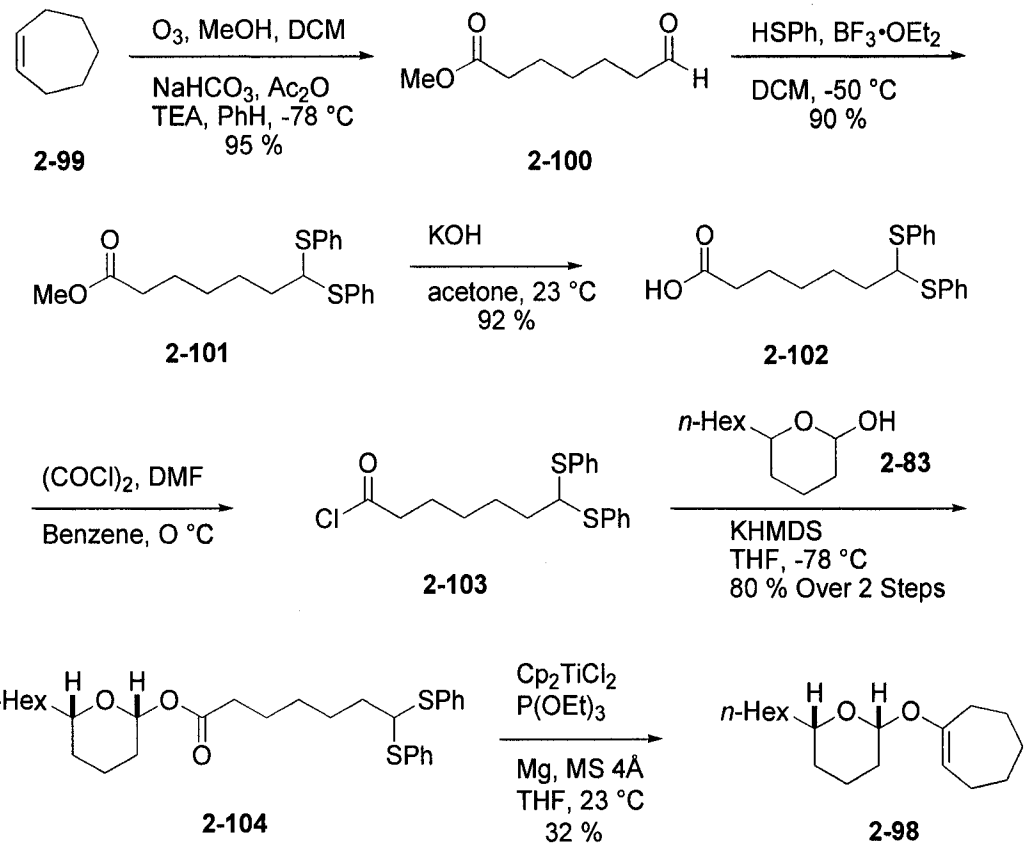
Entry	Lewis acid	Temp (°C)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	Yield (%)
1	$BF_3{\cdot}OEt_2$	-78	2:98	NA	84:16	88
2	Me_3Al / $BF_3{\cdot}OEt_2$	-78	52:48	72:28	62:38	81
3	$EtAlCl_2$	-78	43:57	60:40	66:34	64
4	PPh_3 / Et_2AlCl	-78	35:65	74:26	73:27	79
5	Me_2AlCl	-78	78:22	79:21	75:25	75
6	$FeCl_3$	-78	25:75	60:40	74:26	95
7	Et_2AlCl	-78	92:8	63:37	86:14	84
8	Et_2AlCl	-50	83:17	66:34	57:43	81
9	Et_2AlCl	0	85:15	57:43	71:29	88

2.4.1.3. (2-Cyclohept-1-enyloxy)-Tetrahydropyran

2.4.1.3.1. Substrate Synthesis

The synthesis of the requisite (*cis*)-2-(cyclohept-1-enyloxy)-6-hexyl-tetrahydropyrans **2-98** was performed in an anolgous fashion to that of the cyclopentenyl analogue **2-77**. Cycloheptane **2-99** was transformed to **2-98** in 6 steps and in 20 % yield (Scheme 30).

Scheme 30.

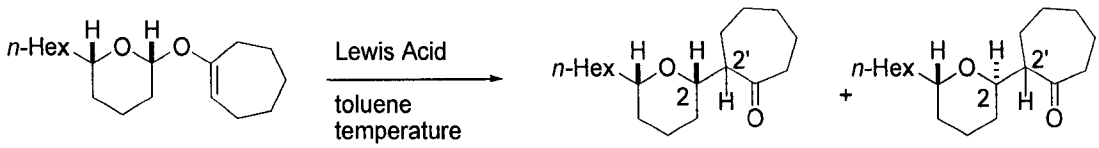


2.4.1.3.2. Rearrangement Results

When cyclic vinyl ether **2-98** was treated with BF_3•OEt_2 at -78 °C in toluene, the rearrangement furnished a 2:98 (*cis:trans*) ratio of diastereomers in 92 % yield (Entry 1, Table 3). Unfortunaetly, the observed 52:48 (*anti:syn*) *trans*-C2-C2' diastereoselectivity was non-existent. Under the stereoretentive rearrangement conditions, Me_3Al/BF_3•OEt_2 yielded a 40:60 (*cis:trans*) ratio of diastereomers (Entry 2, Table 3). These results are interesting when comparing it to the 5- and 6-membered cyclic vinyl ethers **2-77** and **2-89** (respectively) (Entry 2, Table 1 and 2, respectively), which afforded *cis*-selective products **2-88** and **2-97** (respectively), albeit in poor ratios, but the 7-membered cyclic vinyl ether **2-98** afforded the *trans*-product **2-105** as the major diastereomer . Further attempts at using Et_2AlCl and adjusting the temperature, also proved unsuccessful. The *cis:trans* diastereomers where isolated in modest ratios and with absolutely no stereoselectivity at the C2-C2' stereosequence (Entries 7, 8, and 9, Table 3). Further adjustment to the more Lewis acidic $EtAlCl_2$ afforded a 16:84 (*cis:trans*) ratio of *trans*-selective diastereomers **2-105**, which exhibited no stereoselectivity across the C2-C2' bond (Entry 3, Table 3). When using a mixture of PPh_3 and Et_2AlCl, the reaction became *cis*-selective furnishing the *cis:trans* diastereomers in a 89:11 ratio (Entry 4, Table 3). This is another interesting result when comparing it to the previous examples. These conditions proved *trans*-selective for the 6-membered cyclic vinyl ether system **2-89**, while the 5- and 7-membered cyclic vinyl ether systems (**2-77** and **2-98**, respectively) afforded the *cis*-diastereomer (**2-88** and **2-106**, respectively) as the major diastereomer. Further efforts at increasing the C2-C2'

diastereoselectivities all met with failure, possibly due to the flexibility associated with 7-membered rings.

Table 3.



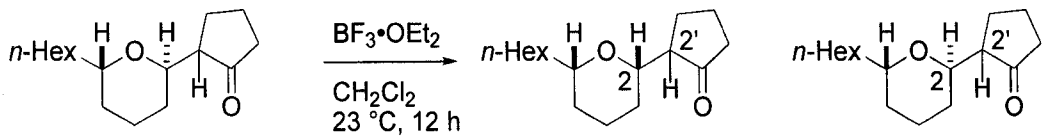
2-98 ***cis*** **2-106** ***cis*** **2-105** ***trans***

Entry	Lewis acid	Temp (°C)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	Yield (%)
1	$BF_3{\cdot}OEt_2$	-78	2:98	52:48	52:48	92
2	Me_3Al / $BF_3{\cdot}OEt_2$	-78	40:60	69:31	52:48	68
3	$EtAlCl_2$	-78	16:84	52:48	57:43	69
4	PPh_3 / Et_2AlCl	-78	89:11	55:45	52:48	88
5	Me_2AlCl	-78	43:57	54:46	57:43	63
6	$FeCl_3$	-78	6:94	52:48	57:43	82
7	Et_2AlCl	-78	72:28	58:42	57:43	90
8	Et_2AlCl	-50	71:29	56:44	57:43	71
9	Et_2AlCl	0	62:38	52:48	55:45	75

2.4.2. Epimerization Studies

Previous work had established that the *cis*-isomer is the lowest energy ring system, due to reduced di-axial interactions relative to the *trans*-diastereomer, a feature which has long been utilized in the synthesis of *cis*-tetrahydropyrans.[54] Ley has previously exploited this aspect to access the *cis*-isomer by epimerization of the *trans*-isomer with TMSOTf at 23 °C (Section 1.2.5.).[29,31]

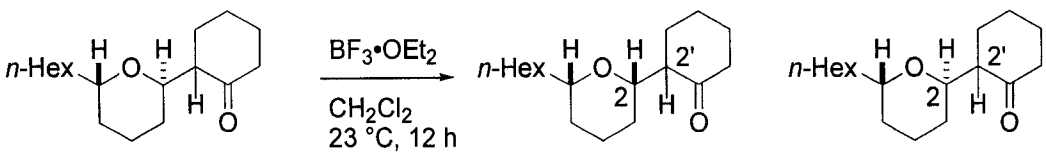
Scheme 31.



2-87		**2-88**	**2-87**
trans		***cis***	***trans***
		93	7
64:36	C2-C2' (*anti:syn*):	80:20	92:8

In our system, when the *trans*-cyclopentenyl ketone **2-87** was subjected to BF_3•OEt_2 at room temperature for 12 hours, the *cis*-cyclopentenyl ketone **2-88** was isolated as a 93:7 (*cis:trans*) ratio of diastereomers in nearly quantitative yield (Scheme 31). The 80:20 (*anti:syn*) ratio of C2-C2' isomers for the *cis*-adduct **2-88** was slightly elevated when compared to the results obtained under the rearrangement conditions (Table 1). This can be attributed to the thermodynamic ratios which are induced in the epimerization reaction conditions and not under the rearrangement conditions.

Scheme 32.

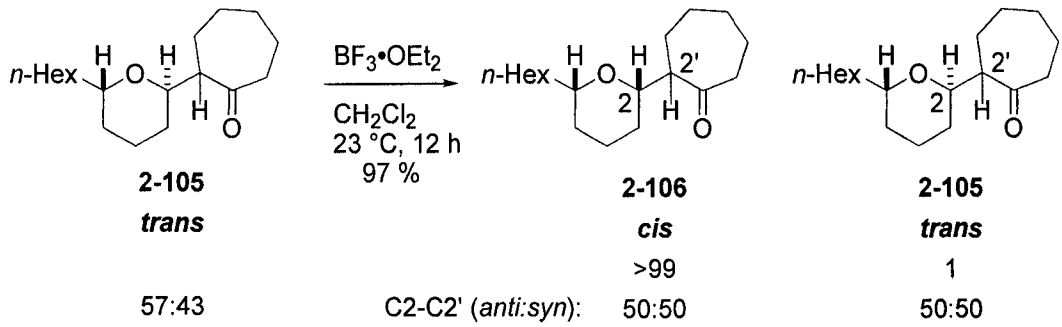


2-96		**2-97**	**2-96**
trans		***cis***	***trans***
		97	3
77:23	C2-C2' (*anti:syn*):	50:50	79:21

Similar observations were made for the *trans*-cyclohexenyl ketone **2-96**, in which after treatment with BF_3•OEt_2 at room temperature for 12 hours the *cis*-tetrahydropyran ring **2-97** was afforded as a 97:3 (*cis:trans*) mixture of diastereomers in

96 % yield (Scheme 32). Unfortunately, the epimerization conditions exhibited no selectivity over the C2-C2' bond linkage.

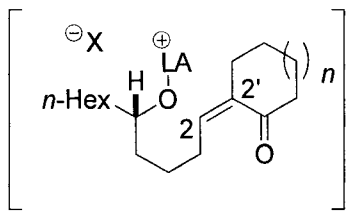
Scheme 33.



2-105		**2-106**	**2-105**
trans		***cis***	***trans***
		>99	1
57:43	C2-C2' (*anti:syn*):	50:50	50:50

In addition, when the *trans*-cycloheptenyl ketone **2-105** was treated under the same conditions, the *cis*-tetrahydropyran **2-106** was yielded as a single *cis:trans* diastereomer (Scheme 33). Also, there was no observed control of the C2-C2' stereochemistry in this system either.

Figure 5.



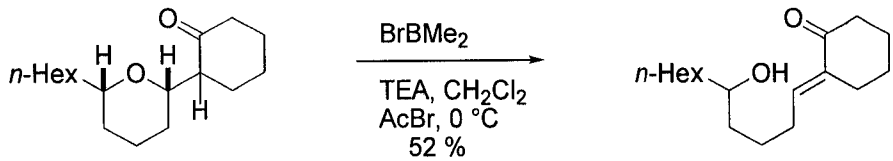
VIII

n = 0, 1, 2

The epimerization pathway is believed to occur at higher temperatures via a β-elimination-recombination pathway **VIII** (Figure 5). In order to determine if this was a viable pathway, we subjected the ketone **2-97** to conditions developed by Giese

(Scheme 34).[55] Upon workup, the reaction afforded the elimination product **2-107** in good yields, thus validating the previous claim. The ratios obtained under the epimerization conditions are imposed completely by the thermodynamic equilibrium. Since some of the rearrangement products offer different C2-C2' ratios than what is observed under the epimerization conditions, the power of ion pairing becomes experimentally apparent.

Scheme 34.

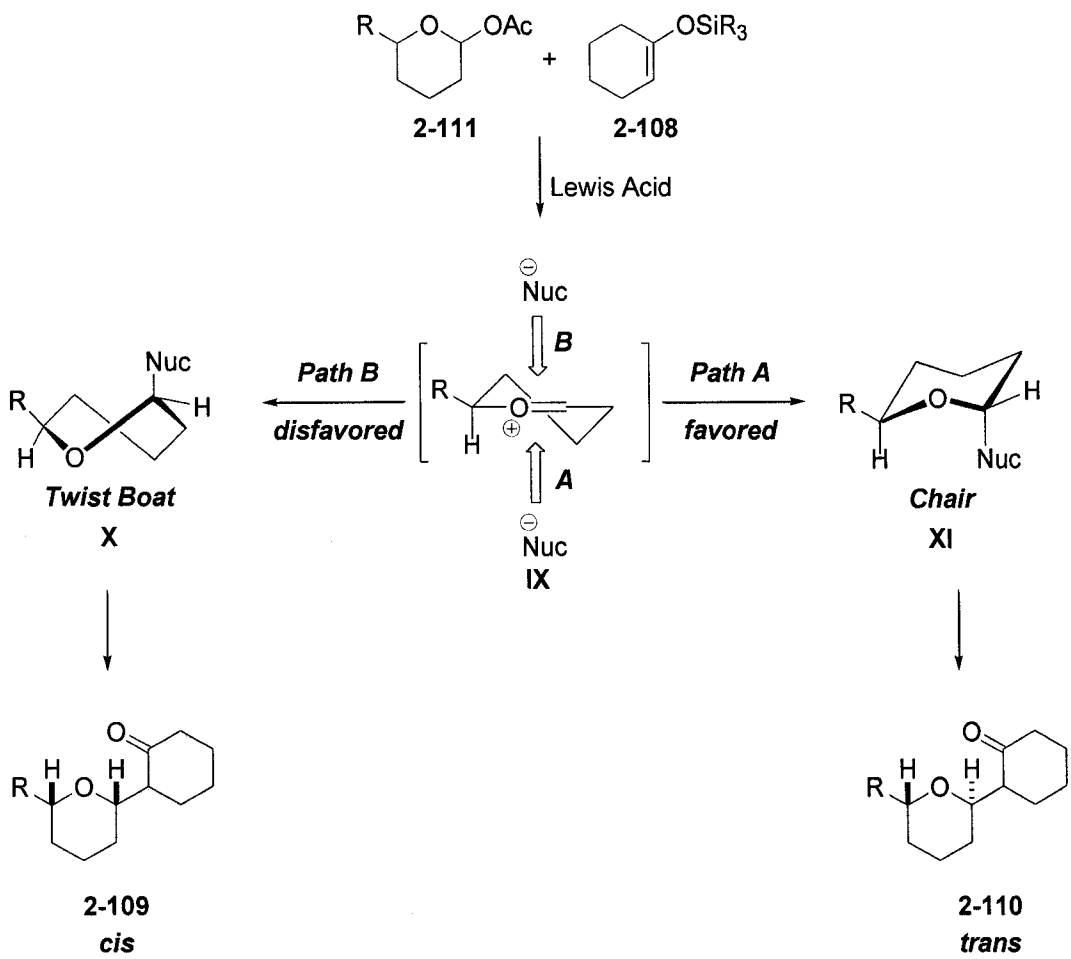


2-97 **2-107**

2.4.3. Intermolecular Enol Silane Addition

Another possible route to the formation of bonds between adjacent rings can arise from the intermolecular addition of enol silanes **2-108** into *in situ* generated oxocarbenium ions **IX** (Scheme 35). Following the proposed mechanism of Deslongchamps, attack on an oxocarbenium ion **IX** will occur *trans* (Path A) to a *C*-6 substituent as a result of the greater stability of the chair-like transition state **X** that is formed, where as the *cis*-isomer **2-109** is formed *via* an unfavorable attack (Path B) to lead to the higher energy boat-like transition state **XI** (Scheme 35).[56] As a result, the formation of *trans*-tetrahydropyrans **2-110** should dominate at low temperatures, while if β-elimination ensues (Figure 5) an equilibrium should be reached and the *cis*-tetrahydropyran **2-109** will be formed.

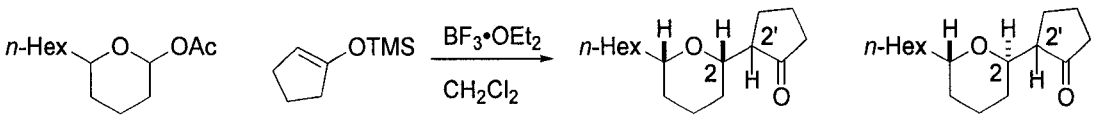
Scheme 35.



When anomeric acetate **2-112** and enolsilane **2-113** were treated with BF_3•OEt_2 at -78 °C for 1 h, the kinetic *trans*-product **2-87** was isolated as a 4:96 (*cis:trans*) mixture of isomers (Entry 1, Scheme 36). The C2-C2' diastereoselectivity of the *trans*-isomer **2-87** was a modest 64:36 (*anti:syn*). To our delight, when anomeric acetate **2-112** and enolsilane **2-113** were treated with BF_3•OEt_2 at room temperature for

12 h, the *cis*-isomer **2-88** was isolated in 96:4 (*cis:trans*) (Entry 2, Scheme 36). The C2-C2' selectivity for the *cis*-diastereomer **2-88** was slightly diminished when compared to the epimerization conditions. Under both conditions, the products were obtained in excellent yields.

Scheme 36.

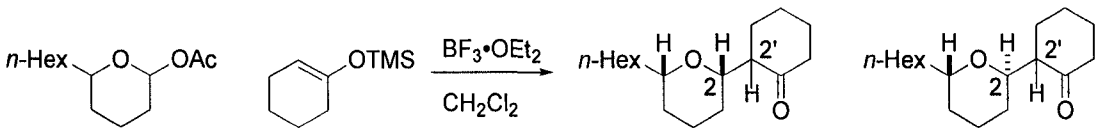


2-112 **2-113** **2-88** ***cis*** **2-87** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	4:96	64:36	64:36	90
2	23	12	98:2	76:24	64:36	86

At low temperatures, the cyclohexanone derived enol silane **2-114** and anomeric acetate **2-112** afforded the *trans*-diastereomer **2-96** as a 3:97 (*cis:trans*) ratio in 94 % yield (Entry 1, Scheme 37). The C2-C2' diastereoselectivity was comparable to the results obtained under the rearrangement conditions (Table 2). When the reaction was performed at room temperature, the *cis*-isomer **2-97** was isolated in a 98:2 (*cis:trans*) mixture of diastereomers (Entry 2, Scheme 37). Unfortunately, there was no selectivity over the forming C2-C2' bond under either set of reaction conditions.

Scheme 37.

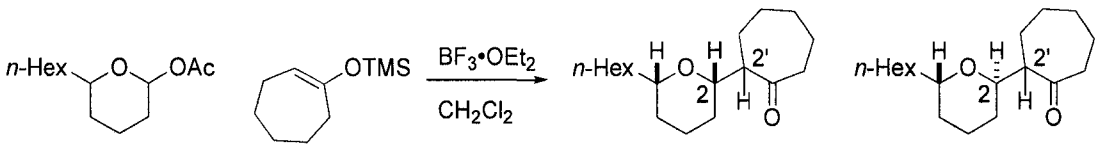


2-112 **2-114** **2-97** ***cis*** **2-96** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	3:97	70:30	77:23	94
2	23	12	98:2	52:48	66:34	87

When the cycloheptanone derived enol silane **2-115** was used, the nucleophilic addition at -78 °C yielded the *trans*-diastereomer **2-105** in a <1:>99 (*cis:trans*) mixture of isomers (Entry 1, Scheme 38), while at room temperature, the *cis*-diastereomer **2-106** was isolated as a mixture of 99:1 *cis:trans*-isomers (Entry 2, Scheme 38). Again neither condition proved effective at the selective formation of the resultant C2-C2' bond, affording the *anti:syn*-isomers as a nearly equal mixture.

Scheme 38.

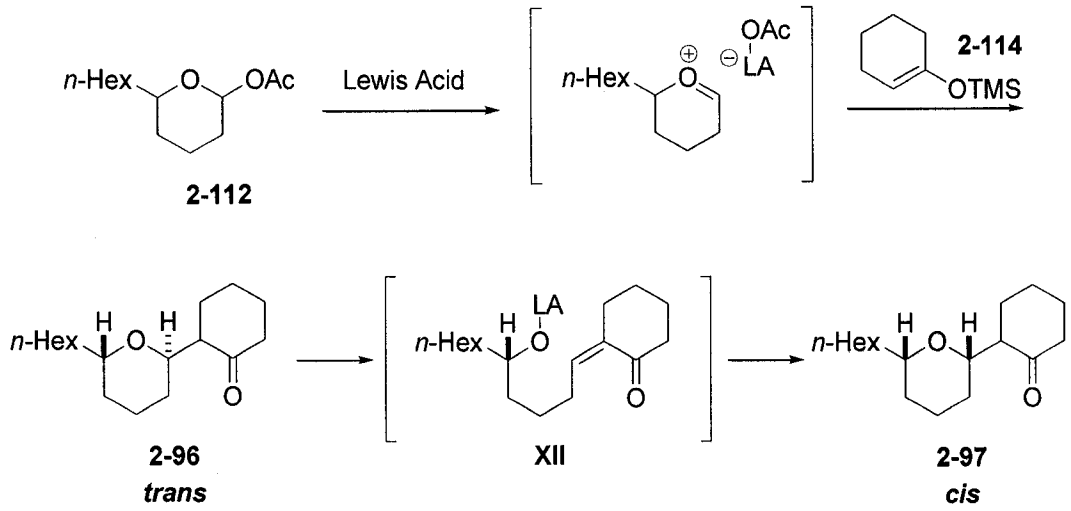


2-112 **2-115** **2-106** ***cis*** **2-105** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	<1:>99	37:63	57:43	92
2	23	12	99:1	52:48	66:34	92

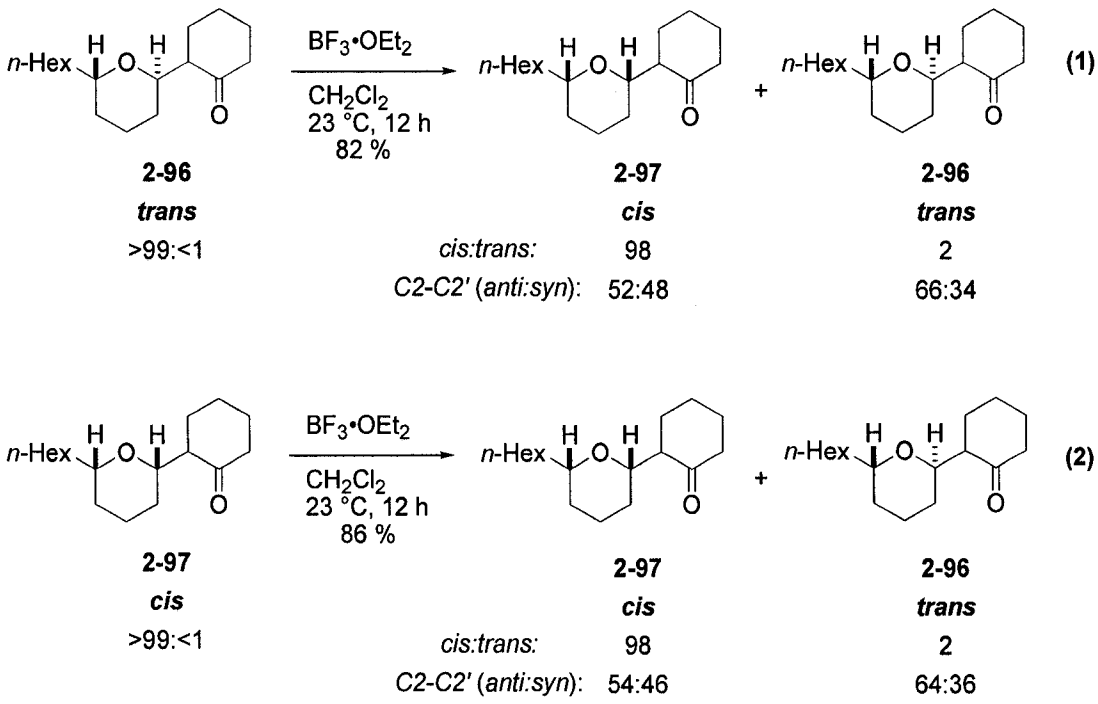
This powerful control of selectivity by a simple modification of the reaction conditions is the result of two factors. At low temperatures, an initial highly diastereoselective reaction occurs under kinetic control, directed by the alkyl chain in the *C*-6 position, to afford *trans*-products **2-96**. At higher temperatures a reversible β-elimination ensues **XII**, leading to an equilibrium where the thermodynamically favored *cis*-product **2-97** predominates (Scheme 39).

Scheme 39.



This mechanism is supported by the observation that the pure *cis*-isomer **2-97** (Eq. 1) or pure *trans*-isomer **2-96** (Eq. 2) both gave relatively identical *cis:trans* mixtures on treatment with one equivalent of $BF_3 \cdot OEt_2$ at room temperature in CH_2Cl_2 (Scheme 40).

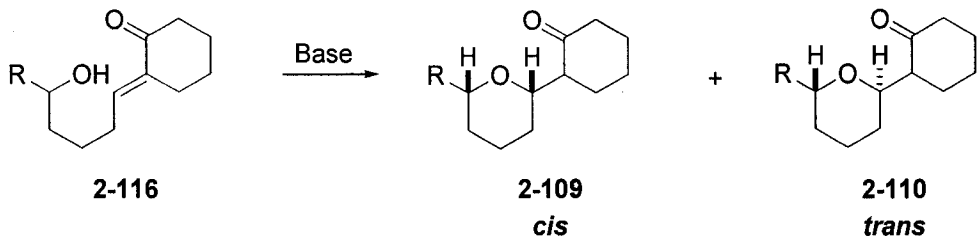
Scheme 40.



2.4.4. Intramolecular Conjugate Addition

Lastly, we envisioned an intramolecular alkoxide conjugate addition into a α, β-unsaturated ketone **2-116** would be a viable route to the required carbon-carbon linkage **2-109** and **2-110** (Scheme 41).

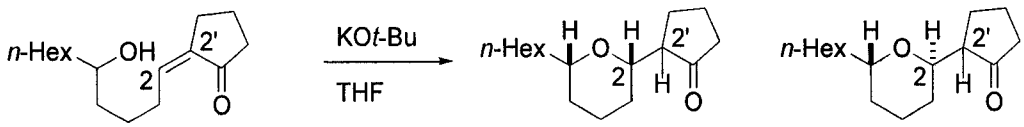
Scheme 41.



Other groups have used this disconnection point in their syntheses of substituted tetrahydropyran ring systems.[57-61] De Brabander has shown that treatment of the 7-hydroxy-α,β-unsaturated ketone with catalytic amounts of KO*t*-Bu at -78 °C in THF afforded the *trans*-tetrahydropyran product **2-110** in 90:10 (*trans:cis*) ratio.[57] While treatment with catalytic amounts of KO*t*-Bu at 0 °C in THF afforded the *cis*-tetrahydropyran product **2-109** in 1:>99 (*trans:cis*) ratio. In the system used by Evans and co-workers, they were unable to selectively form the *trans*-tetrahydropyran product **2-110** in any substantial amount and instead where continually isolating the *cis*-product **2-109**.[58,59]

On our cyclopentenyl system **2-117**, the *trans*-product **2-87** was isolated as a 16:84 (*cis:trans*) ratio when the reaction was performed at -78 °C (Entry 1, Scheme 42). The resultant C2-C2' diastereoselectivity was comparable to the results previously obtained. The *cis:trans* selectivity was diminished when compared to the other methods for their syntheses, this illustrates how the ability to form the *trans*-tetrahydropyran product **2-87** is more difficult and system dependent, as mentioned previously. We expected the treatment of the α,β-unsaturated ketone with catalytic amounts of KO*t*-Bu at 0 °C to afford the thermodynamic *cis*-product **2-88** in excellent diastereoselectivity (Entry 2, Scheme 42). Again, the C2-C2' diastereoselectivities were in accordance with the previously obtained ratios.

Scheme 42.

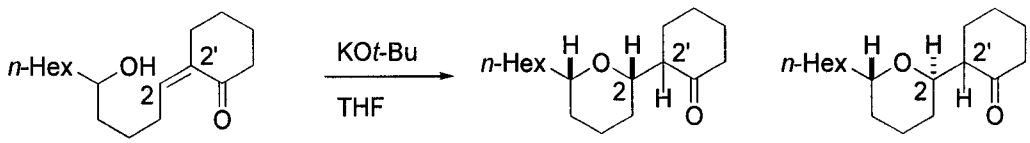


2-117 **2-88** ***cis*** **2-87** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	16:84	74:26	81:19	83
2	0	12	96:4	77:23	94:6	88

Similar selectivities were obtained when the cyclohexenyl system **2-107** was used. At -78 °C, the *trans*-isomer **2-96** was obtained, again in diminished selectivities, as a 18:82 (*cis:trans*) mixture of stereoisomers (Entry 1, Scheme 43). While at 0 °C, the reaction yielded a 98:2 (*cis:trans*) diastereomers in good yields (Entry 2, Scheme 43). The observed C2-C2' diastereoselectivities were in accordance with the prior results obtained.

Scheme 43.

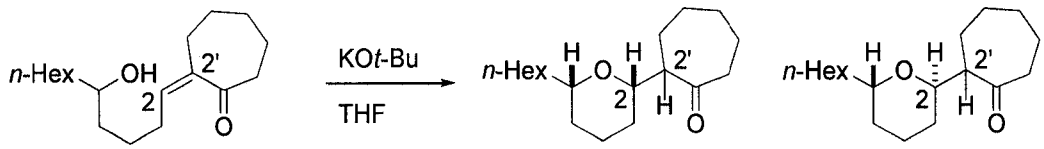


2-107 **2-97** ***cis*** **2-96** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	18:82	60:40	74:26	84
2	0	12	98:2	55:45	60:40	86

Interestingly when the cycloheptenyl derivative **2-118** was used, the reaction yielded a 48:52 (*cis:trans*) mixture of isomers when performed at -78 °C (Entry 1, Scheme 44). The decreased diastereoselectivity was most evident in this system and further attempts to isolate the *trans*-product **2-105** in higher ratios met with failure. The formation of the *cis*-tetrahydropyran ring **2-106** went smoothly at 0 °C affording a 89:11 (*cis:trans*) ratio of diastereomers (Entry 2, Scheme 44). Again, the diastereoselectivity of the C2-C2' isomers proceeded with no selectivity yielding the products in typically around a 1:1 (*anti:syn*) ratio of isomers.

Scheme 44.



2-118 **2-106** ***cis*** **2-105** ***trans***

Entry	Temp (°C)	Time (h)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	1	48:52	55:45	62:38	85
2	0	12	89:11	52:48	55:45	90

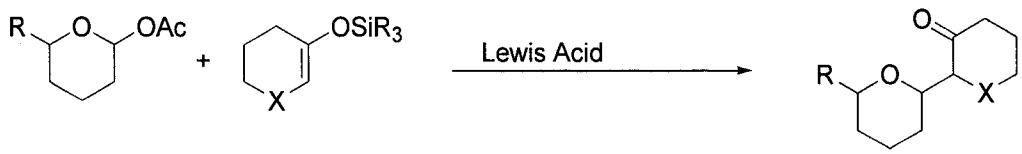
The conjugate addition technique proved to be a viable route to the formation of *cis*-tetrahydropyrans, however selectivity of the *trans*-product formation was modest to good at best. This route also proves to be inefficient for the selective formation of the C2-C2' carbon-carbon bond. We assumed that this method would give rise to the highest C2-C2' diastereoselectivities since it is a completely intramolecular process. However after obtaining the results, one can rationalize while the protonation

of the enolate intermediate is a non-selective event resulting in modest *anti:syn* C2-C2' diastereoselectivities.

2.4.5. Heteroatom Incorporation

After completing the previously described studies, we wanted to apply this to a system containing a heteroatom in both ring fragments **2-119**. Furthermore, we decided to use the intermolecular enol silane addition reaction conditions, since it contains the more easily accessible starting materials (Scheme 45).

Scheme 45.



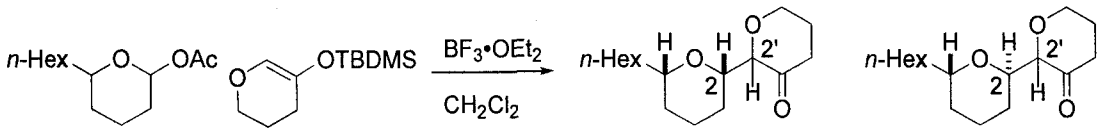
2-119

The starting tetrahydropyranone derived enol silane **2-120** was obtained by a non-trivial route developed by Gallagher.[62]

When anomeric acetate **2-112** and enol silane **2-120** in CH_2Cl_2 were treated with $BF_3 \cdot OEt_2$ at -78 °C, the *trans*-tetrahydropyran **2-121** was isolated as a single *cis:trans*- diastereomer and the C2-C2' diastereoselectivity was also impressive (Entry 1, Scheme 46). To our surprise, when the reaction was performed at room temperature, the *cis*-product **2-122** was not formed in any appreciable quantity (Entry 2, Scheme 46). The reaction afforded the *trans*-diastereomer **2-121** again as a single isomer in 89 %

yield, but the C2-C2' diastereoselectivity diminished to 75:25 (*anti:syn*). Further efforts aimed at epimerizing the *trans*-isomer **2-121** to the *cis*-isomer **2-122** under the previously reported conditions were also ineffective.

Scheme 46.



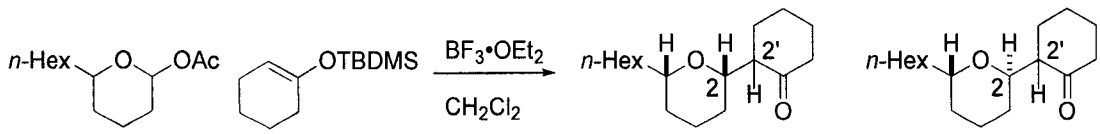
2-112 **2-120** **2-122** ***cis*** **2-121** ***trans***

Entry	Temp (°C)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	<1:>99	NA	85:15	94
2	23	<1:>99	NA	75:25	89

In order to explain this result, we wanted to verify that the interesting selectivity obtained was not dependant on the type of enol silane used (TMS vs. TBS). As a result, we synthesized the TBDMS protected enol silane **2-123** of cyclohexanone. When enol silane **2-123** and anomeric acetate **2-112** were treated at -78 °C with BF_3•OEt_2, the reaction afforded a 4:96 (*cis:trans*) ratio of diastereomers (Entry 1, Scheme 47). The *trans*-C2-C2' isomer **2-96** was obtained as a 80:20 mixture of *anti:syn* isomers. As anticipated, when the reaction was performed at room temperature, a 97:3 mixture of *cis:trans* diastereomers were obtained (Entry 2, Scheme 47). The *cis*-C2-C2' **2-97** *anti:syn* isomers were obtained as a 1:1 mixture. The ratios obtained using the TBS protected silyl enol ether **2-123** [(3:97) and (2:98) (*cis:trans*)] and TMS protected silyl enol ether **2-114** [(4:96) and (97:3) (*cis:trans*)] are in accord

with each other (Scheme 47 and 37, respectively), thus revealing that the observed diastereoselectivity differences is not related to the size of the silyl group used, but potentially more a result of the electronic differences between the two systems (Scheme 46 and 37 or 47, respectively). With these results, we can conclude that during the addition into the oxocarbenium ion, the incorporation of an oxygen atom into both ring systems plays a crucial role on the stereochemical outcome.

Scheme 47.



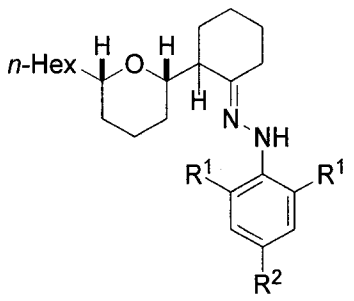
2-112 **2-123** **2-97** ***cis*** **2-96** ***trans***

Entry	Temp (°C)	*cis:trans*	*cis* C2-C2' (*anti:syn*)	*trans* C2-C2' (*anti:syn*)	yield (%)
1	-78	4:96	88:12	80:20	94
2	23	97:3	52:48	57:43	89

2.4.6. Determination of Stereochemistry

With all of the results obtained, the ability to discern the two C2-C2' diastereomers need to be achieved. Initially, our attempts were aimed at obtaining a x-ray crystal structure of the readily prepared hydrazone derivatives **2-125**. Unfortunately, we were unable to induce crystallization of these hydrazones, probably a result of the lipophilic *n*-hexyl side chain within the system (Figure 6).

Figure 6.

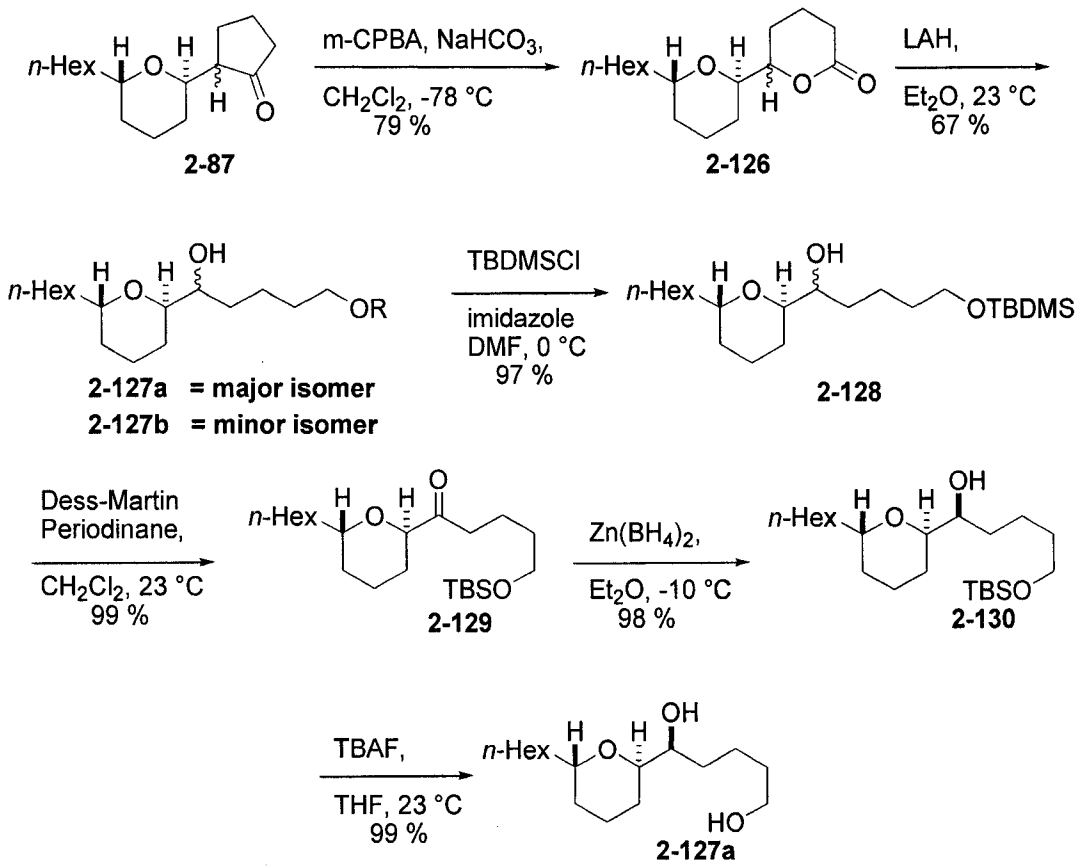


2-125a $R^1 = H$; $R^2 = Me$

2-125b $R^1 = R^2 = i\text{-Pr}$

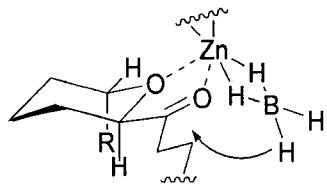
As a result of our inability to induce crystallization, we needed to use a chemical correlation route to determine the C2-C2' stereochemistry (Scheme 48). When the pure *trans*-ketone **2-87** was treated with *m*-CPBA, a Baeyer-Villiger rearrangement ensued which afforded the lactone **2-126** in 79 % yield. A global reduction of the lactone was achieved by treatment with $LiAlH_4$ at room temperature and the resultant diols **2-127a** and **2-127b** were easily separated at this stage. The primary alcohol

Scheme 48.



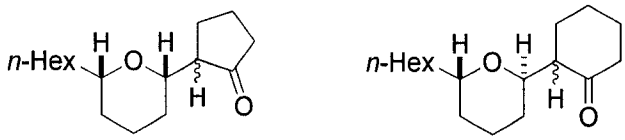
of the major isomer **2-127a** was mono-protected as the TBS ether **2-128** and subsequent oxidation of the secondary alcohol with Dess-Martin periodinane afforded the ketone **2-129** in quantitative yield. Next, a stereoselective reduction of the ketone was performed using $Zn(BH_4)_2$ in Et_2O at -10 °C. According to a report by Nakata, $Zn(BH_4)_2$ stereoselectively delivers the hydride via an α-chelation to afford an overall *syn*-relationship between the C2-C2' stereocenters (Figure 7).[63]

Figure 7.



To our delight, the chelation controlled reduction afforded the alcohol as a single diastereomer **2-130**. Following the deprotection of the alcohol with TBAF and comparison of spectroscopic data, it was established that the major isomer was that shown as **2-127a**, corresponding to the rearrangement product *anti* **2-87**. This route was also performed on substrates **2-98** and **2-96** (Figure 8).

Figure 8.



2-88
cis

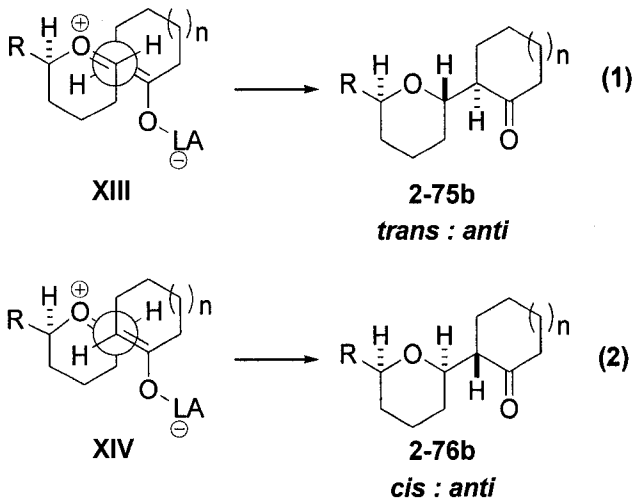
2-96
trans

The assignment of stereochemistry in **2-97**, **2-105**, **2-106**, **2-121** and **2-122** was based on analogies derived from predictable GC retention times of the product diastereomers. The GC chromatograms would always detect the *cis:anti*-product (major) first, followed by the *cis:syn*-product (minor). These peaks were then followed by the *trans:anti*-product (major) and the *trans:syn*-product (minor). Thus, all reactions resulted in the C2-C2' *anti* isomer as the major product C2-C2' diastereomeric sequence.

2.4.7. Discussion

We propose that the C2-C2' *anti* selectivity is a result of the recombination of the oxocarbenium ion and Lewis acid complexed enolate in the lowest energy staggered conformation when the two hydrogen atoms are *anti*-periplanar **XIII** and **XIV** (Figure 9). The *cis:trans* selectivity in the rearrangement is a result of the recombination from either a contact (*cis*) **2-76b** or solvent separated (*trans*) **2-75b** ion pair. The *cis:trans* selectivity in the intermolecular oxocarbenium ion/enolsilane addition and alkoxy conjugate addition conditions reflect thermodynamic/kinetic control, whereas kinetic control furnishes the *trans*-products. While under thermodynamic control, the reaction probably proceeds through the kinetic *trans*-product first, then epimerization

Figure 9.



allows for the thermodynamic *cis*-products result. Furthermore, the epimerization studies also reflect this thermodynamic (*cis*) stability.

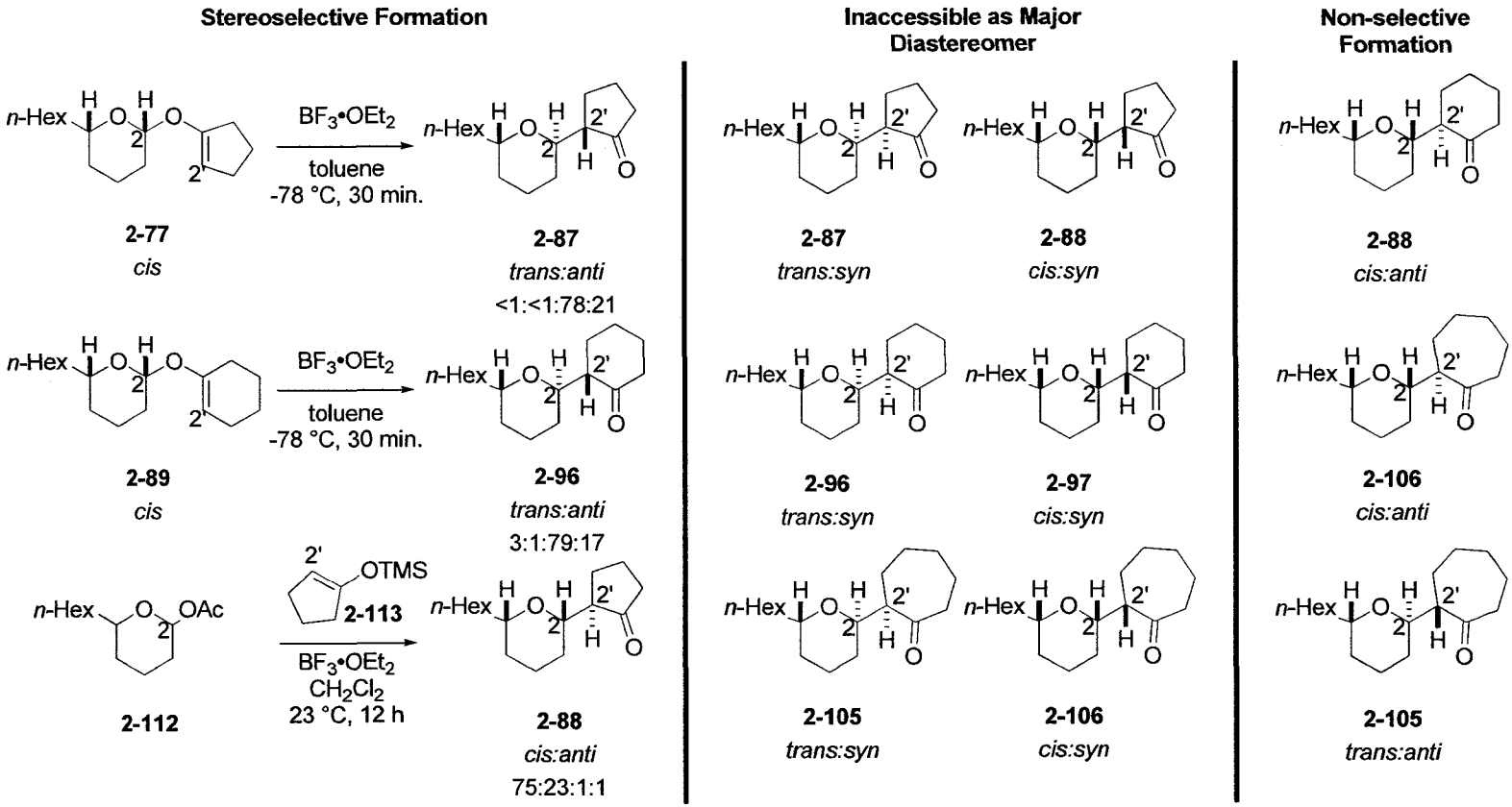
2.4.8. Conclusions

In summary, we have investigated the formation of carbon-carbon bonds between adjacent rings via a stereoretentive [1,3]-oxygen to carbon rearrangement of cyclic vinyl acetals, an intermolecular addition of an enolsilane into an *in situ* generated oxocarbenium ions, and an intramolecular conjugate addition of an ω-hydroxy-α,β-unsaturated ketones. Furthermore, we have shown that the product ratios obtained from the epimerization studies are indeed at their thermodynamic equilibrium positions, as justified by the similar results shown in Scheme 32 and 40.

The [1,3]-oxygen to carbon rearrangement proved the best route for synthesizing the *trans:anti* diastereomer for substrates **2-87** and **2-96** in 70 % yield for each of the desired diastereomers (Figure 10). The enolsilane addition into an *in situ* generated oxocarbenium ion afforded the *cis:anti* diastereomer in 65 % yield for substrate **2-88** (Figure 10). The synthesis of substrates **2-88** (*cis:anti*), **2-106** (*cis:anti*), and **2-105** (*trans:anti*) proceeded in a non-selective manner and unfortunately, the synthesis of the C2-C2' *syn*-diastereomers in all cases proved to be stereoselectively inaccessible by these approaches.

The most promising result that we have identified is the selective assembly of the *trans*-bis-tetrahydropyrans such as **2-121**, of particular relevance to key subsections of the polyether ladder toxin family of natural products.

Figure 10.



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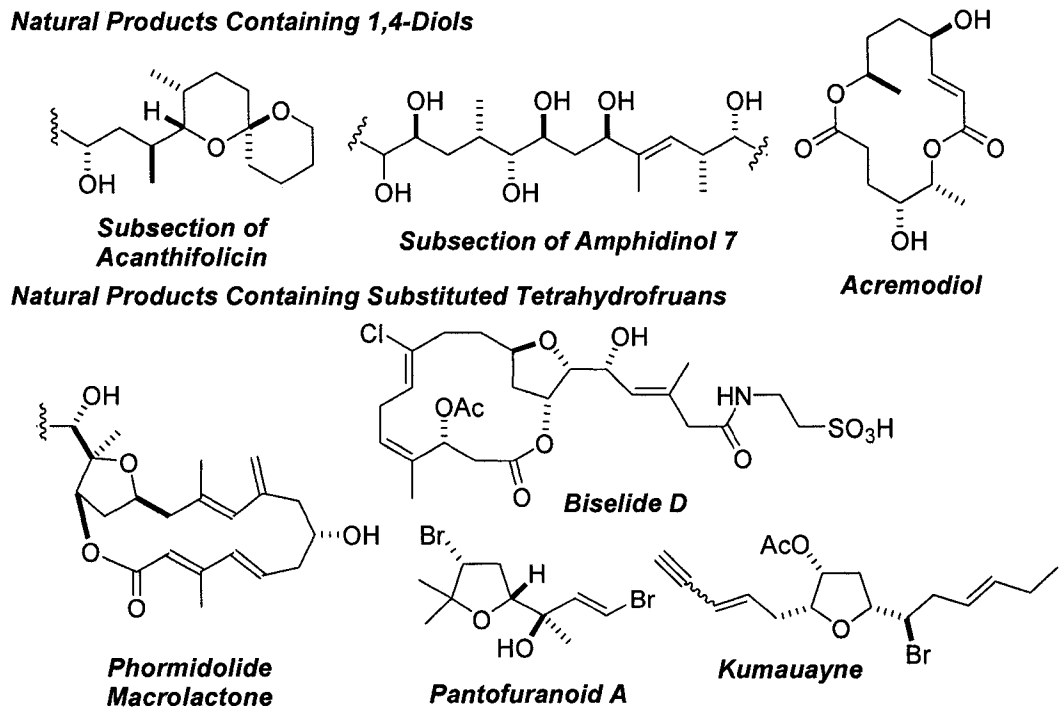
Chapter 3

The Chemistry of 1,3-Dioxepines

3.1.Introduction

Substituted tetrahydrofuran rings and 1,4-diols are a few common motifs found in a variety of natural products (Figure 1). As a result, the synthetic chemist needs to have versatile and efficient routes for their construction.

Figure 1.



3.2 Heck Reaction

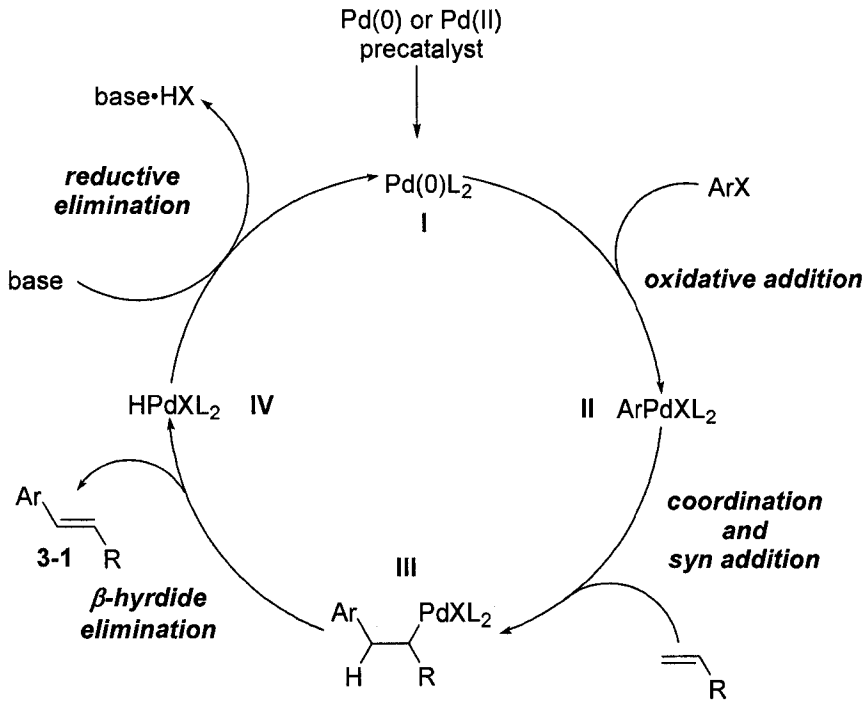
3.2.1. Introduction

The sp^2-sp^2 coupling of carbon-carbon bonds has become a powerful weapon in the arsenal of an organic chemist. Today there are a variety of methods for this transformation, including the Heck, Stille, Suzuki, and Negishi cross-coupling reactions. The Heck reaction will be utilized in this chapter and therefore, a brief introduction of the reaction will be presented.

3.2.2. Mechanism

Simultaneously reported in the early 1970's by Heck[1] and Mizoroki[2], the Pd(0)-mediated coupling of an aryl or vinyl halides or triflates with alkenes is known today as the Heck reaction. The general description for the catalytic cycle of the Heck reaction is shown in Scheme 1.

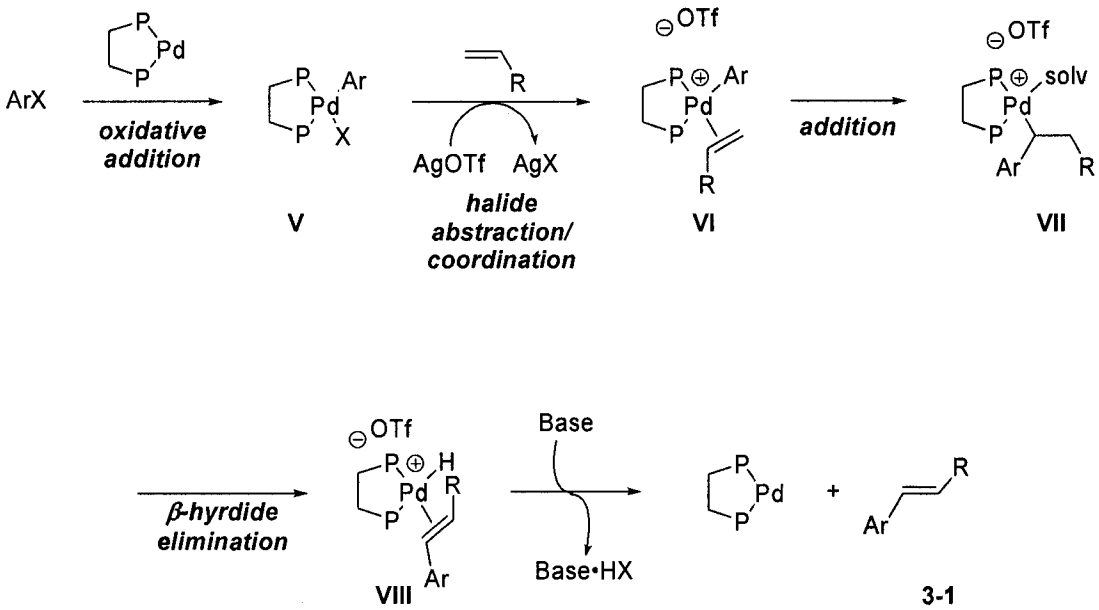
Scheme 1.



In the proposed catalytic cycle, the active Pd(0) **I** catalyst oxidatively inserts into the ArX bond to afford the tetra-coordinate Pd(II) **II** species. The Pd(II) complex then creates a vacant site by loss of a neutral ligand to accommodate the coordination of the incoming olefin. After coordination, the alkene undergoes carbopalladation to form the σ-bonded palladium-carbon species **III**, which following rotation may undergo β-hydride elimination **IV**. The palladium (II) complex **IV**, with the aid of base, reductively eliminates HX to regenerate the active Pd(0) species **I**. Although this is the generally accepted mechanism, numerous mechanistic studies into the catalytic pathway have revealed that it represents a vast over simplification of the actual mechanism.[3,4] One major problem is this mechanism does not rationalize why the addition of certain additives have accelerating effects on the reaction.

This issue was first addressed by Cabri[5] and Hayashi,[6] when they first proposed a cationic pathway to describe the reaction of aryl triflates in the presence of palladium-diphosphine catalysts. Generally, the cationic pathway is now accepted as the mechanism where the addition of Ag(I) or Tl(III) salts is involved (Scheme 2). Typically after oxidative addition **V**, the halide is abstracted by the Ag(I) salts, thus vacating a coordination site on the Pd(II) complex **VI**. The olefin now coordinates to the metal in the newly created vacant site, which promotes the carbo-palladation **VII**. The organopalladium species **VII** then undergoes β-hydride elimination **VIII** and base propagates the catalytic cycle.

Scheme 2.

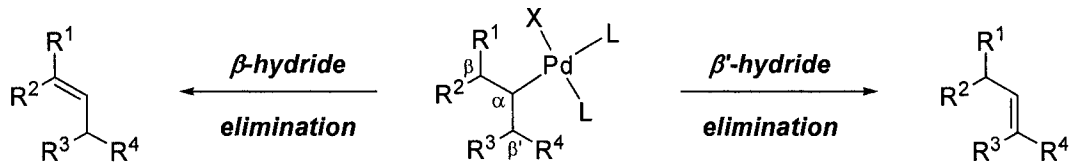


3.2.3. Factors Governing Regioselectivity

The Heck reaction displays many advantages usually associated with Pd-mediated reactions (ease of scale up and tolerance of water and/or other functional

groups),[7] however problems in the regiocontrol of unsymmetrical alkene substrates have proved to be its huckleberry. For example, if the organopalladium species **XI** contains two β-hydrides, then competing β- and β'-hydride elimination further complicates the regioselectivity of the transformation (Scheme 3). As a result, many systems are carefully chosen to ensure there is only one β-hydride available in the substrate, thus resulting in complete regiocontrol of the product.

Scheme 3.



IX

In light of this, many people choose simple acrylate ester substrates, which undergoes a highly regioselective Heck reaction, since the steric and electronic envoriments are highly biased.

Another problem lies in the reversibility of the process, which can result from the reinsertion of the alkene **3-1** into the Pd-H bond in **IV** to regenerate the σ-bonded palladium-carbon species **III** or another regioisomer of the palladium addition. If any of the substituents on the palladium species contain a suitably placed β-hydrogen, β-hydride elimination will ensue. This reversibility will result in the formation of isomerization products. Fortunately, methods have been developed to suppress this side reaction, typically involving the addition of Ag(I)[8,9] or Tl(III)[10] salts.

Recently there have been further advances on the asymmetric Heck reaction and these developments will not be discussed, since they are not pertinent to this research and because they have been presented in two outstanding reviews.[11,12]

3.2.4. Precatalyst, Ligands, Solvent and Base

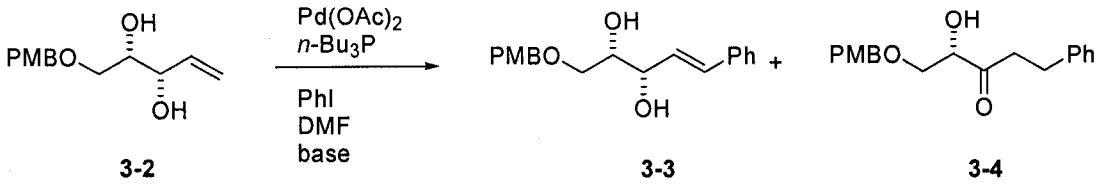
A variety of Pd(0) and Pd(II) complexes are efficient precursors to the active Pd(0) species. The most commonly used precatalysts are $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ and their loading is typically 5-10 mol%. Also, other metals have been found to catalyze this transformation, including Co, Rh, Ru, Mo, Ni and Ir.[13-15]

The choice of ligand is another important issue influencing the Heck reaction. PPh_3 has been employed most often, however in reactions run at high temperatures (>100 °C), the cleavage of a phenyl group from the phosphine and subsequent coupling to the alkene is seen. This phenyl exchange results in product contamination and catalyst decomposition.[16,17] Even under milder conditions, palladium complexes have been known to undergo aryl exchange.[11,18] This type of by-product can be a significant obstacle when using PPh_3, as a result ligand development is constantly being pursued. Another ligand, P(*o*-tolyl)$_3$, has long been a viable alternative choice, due to its slower cleavage.[4]

Typically only polar, aprotic solvents such as DMF, NMP, and MeCN are used in the reaction, but recently the presence of water has been found to accelerate certain Heck reactions.[19]

The type of base employed can also have a significant impact on the outcome of the reaction. As illustrated in Scheme 4, when Et_3N or K_2CO_3 is used as the base, the reaction yields two distinct products (Entries 1 and 2, respectively).[20] Generally, the weaker bases (*i.e.*-hydrocarbonates and acetates) perform better under anhydrous conditions, while the stronger bases (*i.e.*-alkali metal carbonates) work the best when around 10 vol% of water is added to the reaction.[11]

Scheme 4.



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

Entry	Base	3:4	Yield (%)
1	K_2CO_3	>99:1	93
2	Et_3N	1:>99	85

3.2.5. Additives

As mentioned earlier, the addition of Ag(I) and Tl(III) salts to the Heck reaction greatly impacts the rate and the reaction outcome. The regioselectivity of the forming carbon-carbon σ-sigma bond in the intermolecular Heck reaction has always been a major concern, as well as the nature of the steric and electronic environments provided by the unsymmetrical olefin. Table 1 illustrates how the mechanism pathway can influence the regioselectivity of the Heck products. Some selected examples

indicate that regioselectivity is related only in the coordination/insertion pathway, in which the steric factors always favor the migration of the R group to the less substituted carbon with formation of linear products (Entry 1 and 3, Table 1). However in the cationic pathway, electronic parameters predominate. The coordination of the π-system in a cationic complex will increase the amount of polarization and therefore, selective migration of the aryl moiety onto the carbon with the lower charge density will occur.[21,22]

Table 1.

Entry	Base	Temp (°C)	Time (h)	5:6	Yield (%)
1	Et_3N	100	18	67:33	63
2	TlOAc	80	1	>99:1	92
3	Et_3N	100	18	61:39	54
4	TlOAc	80	0.7	>99:1	97

In 1984, Jeffery first noted the beneficial effect of quaternary ammounium salts in the Heck reaction.[23-25] Under her conditions, she noticed the coupling reaction was significantly accelerated by the use phase transfer catalyst (PTC) and solid inorganic bases.[23,26] Even though the use of phase transfer catalysts allows for the coupling of iodoarenes and olefins at room temperature, which is a significant decrease from the previously harsh reactions conditions, it did not gain in popularity until the intramolecular work reported by Larock.[27] There are several explanations used for the

description of how PTC effect the Heck reaction. One theory states that the PTC can act as a solid-solid phase transfer agent when inorganic bases (*i.e.*-K_2CO_3, NaOAc) are used, since most are not soluble in standard Heck solvents. Another theory proposes that when the Heck reaction is performed under aqueous conditions, the PTC is believed to be a liquid-liquid phase transfer agent between the soluble inorganic base and insoluble organic product. A further report suggests that the reaction rate increase is based on the fact that palladium complexes can be stabilized by the coordination of halide ions, therefore the catalyst is less likely to decompose under the Jeffery reaction conditions.[3,28] In most Jeffery conditions, the exact nature of the PTC cannot be narrowed down to a single effect, but a combination of several.[29]

3.2.6. The Olefin and Leaving Groups

The Heck reaction has proven to work the best on mono- or 1,1- disubstituted alkenes, due to their increased reactivity, and has also been shown to work on certain tetra-substituted alkenes.[20]

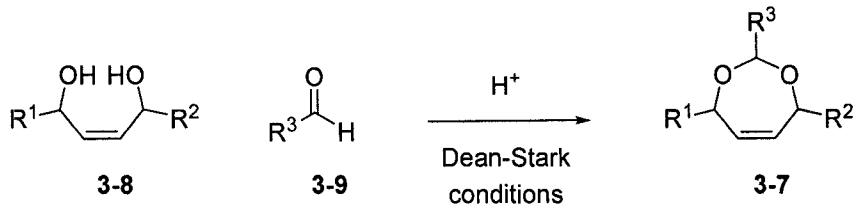
The Heck coupling can be used to couple alkenes to variety of other functional groups, including alkenyl, aryl, benzyl, methyl, and alkynyl halides, as well as many others. The substituent on the oxidative addition partner plays a major role in the Heck process and the general trend is that, I > OTf > Br >> Cl, for the rate of oxidative addition to occur. Also, there are a variety of other substituents which are not as commonly used, including: $SiMe_2OH$, diazonium salts, *N*-nitroso-*N*-aryl acetamides and hypervalent iodine compounds.[12,20,30]

3.3. Dioxepines as Versatile Building Blocks for Organic Chemistry

3.3.1. Introduction to Dioxepines

1,3-Dioxepines are typically used as a protecting group for 1,4-diols. However their usefulness does not stop there; they are versatile as intermediates in the construction of substituted tetrahydrofurans, as well as 1,3-dioxanes.[31-34] The most common method for the construction of 1,3-dioxepines **7** involves the condensation of a 1,4-diol **3-8** onto an aldehyde **3-9** or acetal (Scheme 5).[35,36]

Scheme 5.

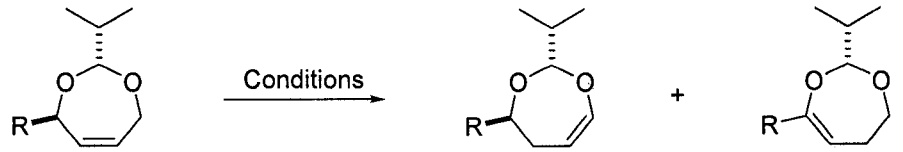


3.3.2. Dioxepines and the Heck Reaction

In 1982, Frauenrath and Runsink demonstrated that 1,3-dioxepines could be used for the stereoselective synthesis of 2,3,5-trisubstituted tetrahydrofurans.[31,32] The easily prepared 4,7-dihydro-1,3-dioxepines **3-10** were isomerized by two different routes to afford the 4,5-dihydro-1,3-dioxepines **3-11** and **3-12** (Scheme 6). The first route involves a KO*t*-Bu mediated isomerization of the olefin at room temperature, while the second route involves the use of catalytic amounts of $RuCl_2(PPh_3)_3$ and $NaBH_4$. Interestingly, when R=Me both methods led to the desired isomerization

product and only contained minimal amounts of the other regioisomeric olefin (Entry 3 and 4, Scheme 6).

Scheme 6.

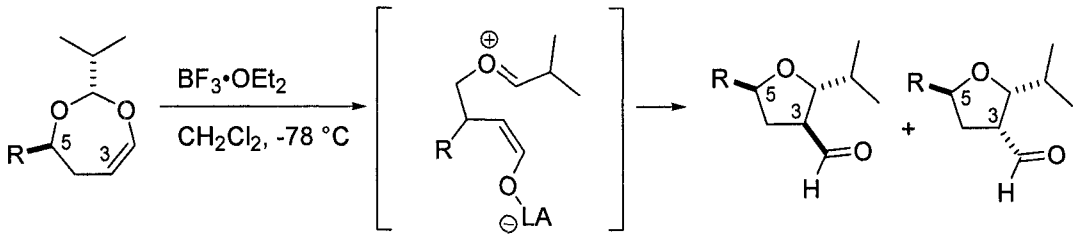


3-10 **3-11** **3-12**

Entry	R	Conditions	Yield of 11 (%)	Yield of 12 (%)
1	H	$RuCl_2(PPh_3)_3$, $NaBH_4$, MeOH	90	---
2	H	KO*t*-Bu, DMSO	78	---
3	Me	$RuCl_2(PPh_3)_3$, $NaBH_4$, MeOH	92	5
4	Me	KO*t*-Bu, DMSO	78	7

Treatment of the desired 4,5-dihydro-1,3-dioxepines **3-11** with BF_3•OEt_2 at -78 °C results in rearrangement to form 2,3,5-trisubstituted tetrahydrofurans **3-13** and **3-14** in good yields (Scheme 7).

Scheme 7.

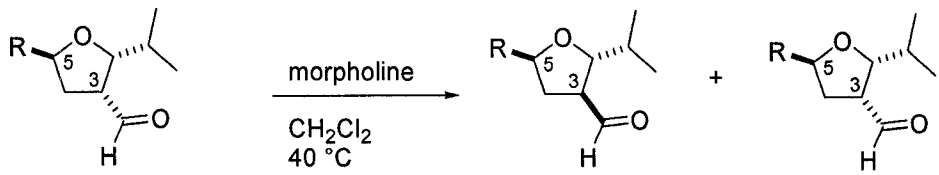


3-11 **X** **3-13** ***3,5-cis*** **3-14** ***3,5-trans***

Entry	R	*cis:trans*	yield (%)
1	H	34:66	93
2	Me	11:89	84

The unsymmetrical 1,3-dioxepine rearranged to a 11:89 mixture of *cis:trans* diastereomers across the *C*-2 and *C*-3 stereosequence (Entry 2). Fauenrath also showed that the *trans*-2,3-tetrahydrofuran **3-14** can epimerize nearly to the *cis*-substituted product **3-13** (98:2) by refluxing in CH_2Cl_2 in the presence of morpholine (Scheme 8).

Scheme 8.

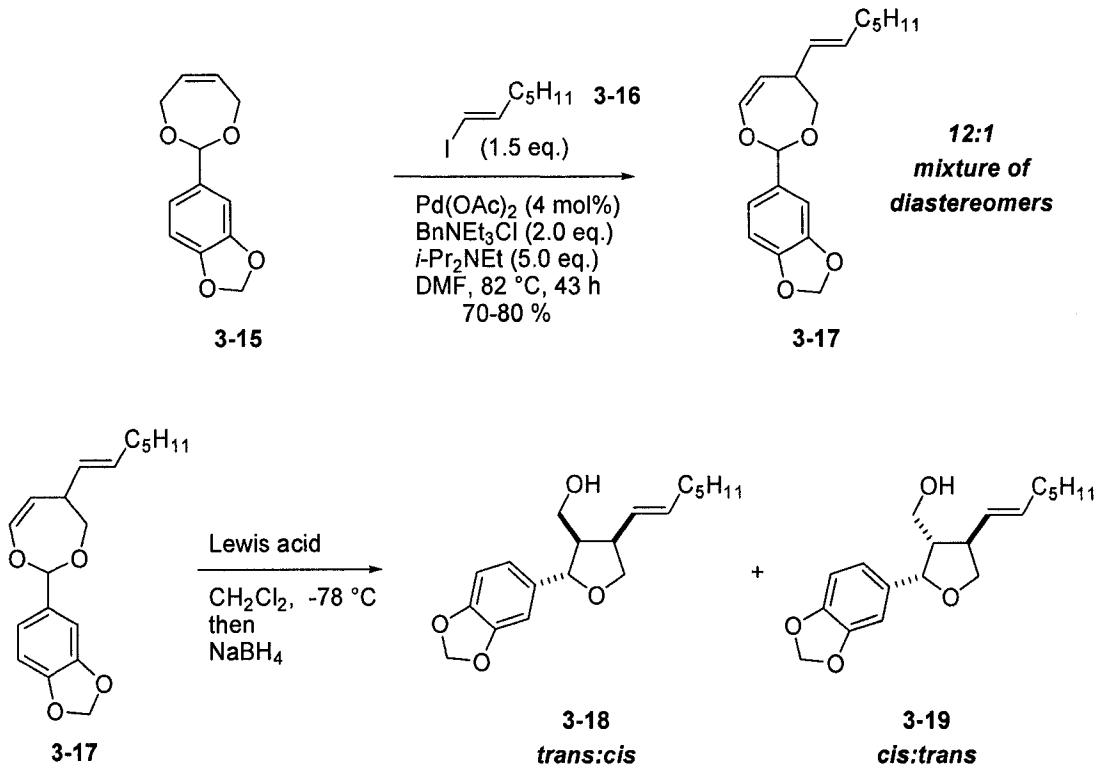


3-13 ***3,5-trans*** **3-14** ***3,5-cis*** **3-13** ***3,5-trans***

Entry	R	*cis:trans*	yield (%)
1	H	98:2	82
2	Me	98:2	95

In 1992, Takano and co-workers reported the synthesis of asarinin using the ring contraction of a 2,5-disubstituted-4,5-dihydro-1,3-dioxepine as their key step.[34] When the *meso*-dioxepine **3-15** and iodoalkene **3-16** were treated under Heck conditions, the reaction afforded the disubstituted dioxepine **3-17** as a 12:1 mixture of diastereomers (Scheme 9), which was unstable to isolation and subsequently treated with Lewis acid to form the tetrahydrofurans **3-18** and **3-19**. Interestingly, when **3-17** was treated with $Ti(O\textit{i}\text{-}Pr)_2Cl_2$, the reaction yielded the *trans:cis*-diastereomer **3-18** (Entry 1, Scheme 9), while treatment with TBSOTf afforded the *cis:trans* diastereomer **3-19** (Entry 2, Scheme 9).

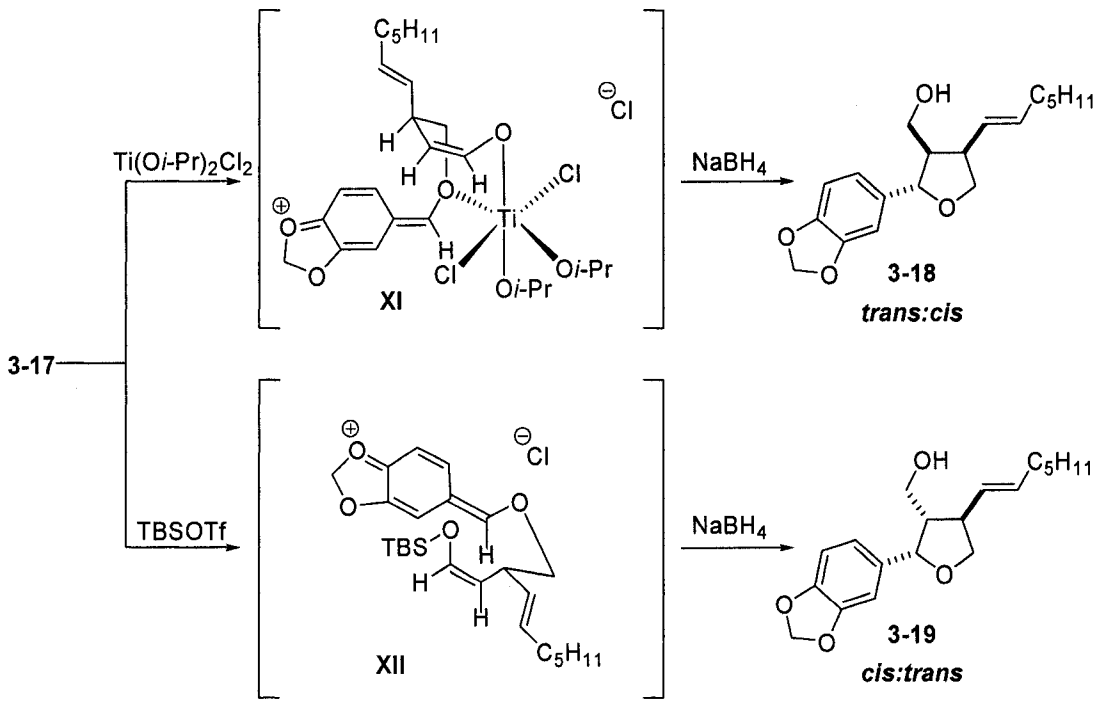
Scheme 9.



Entry	Lewis acid	18:19	Yield (%)
1	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	98:2	53
2	TBSOTf	7:93	85

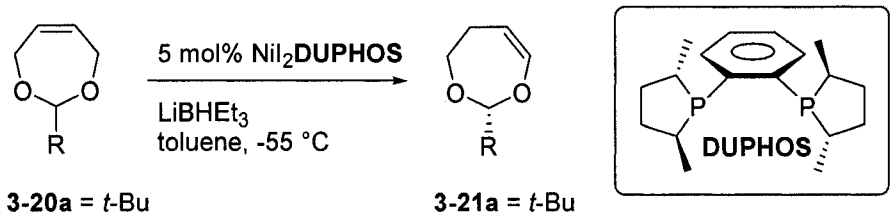
The authors propose this difference can be interpreted in terms of a Ti-chelating complex **XI** to account for the *trans:cis*-isomer **3-18** and a non-chelating species **XII** to explain the *cis:trans*-diastereomer **3-19** (Scheme 10).

Scheme 10.



Frauenrath *et. al.* continued their research in dioxepanes and in 2001, they reported an asymmetric isomerization of 1,3-dioxepines.[37] When the dioxepine **3-20** was treated with [NiI_2((-)-Me-DuPHOS)] and $LiBHEt_3$, the isomerized dioxepine **3-21** was isolated in excellent enantioselectivity (Scheme 11).

Scheme 11.



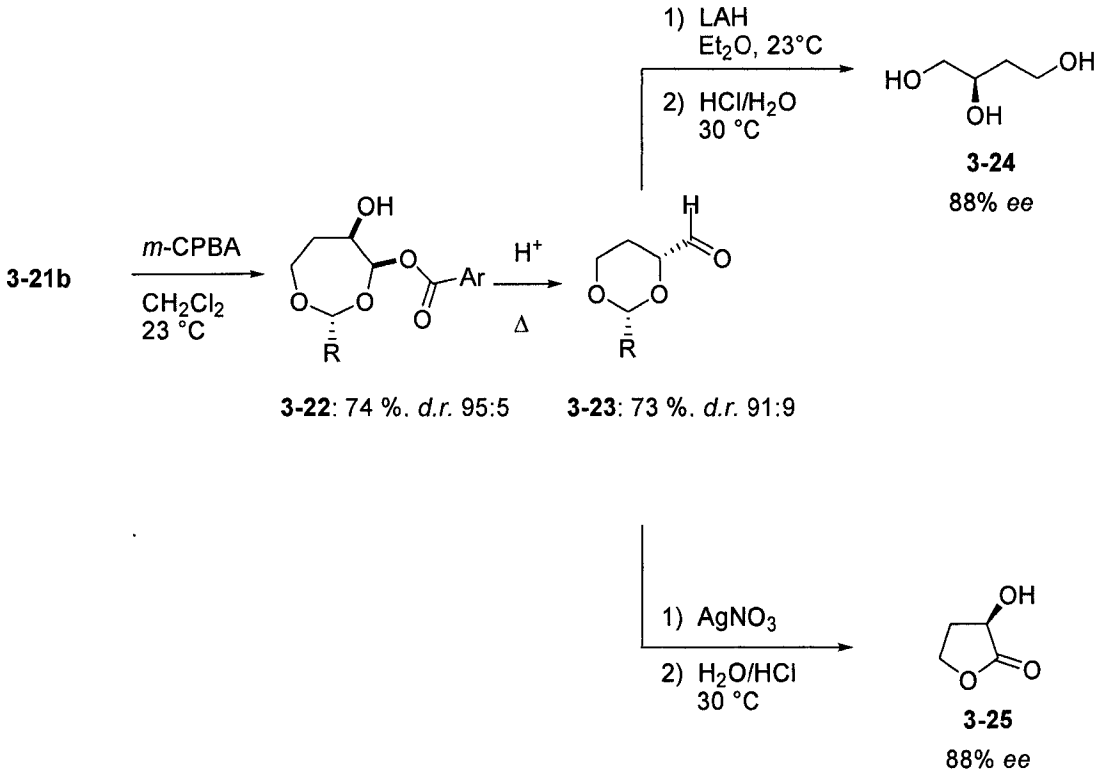
3-20a = *t*-Bu
3-20b = *i*-Pr
3-20c = *n*-Bu

3-21a = *t*-Bu
3-21b = *i*-Pr
3-21c = *n*-Bu

Entry	ee (%)	Yield (%)
1	98	74
2	90	75
3	90	75

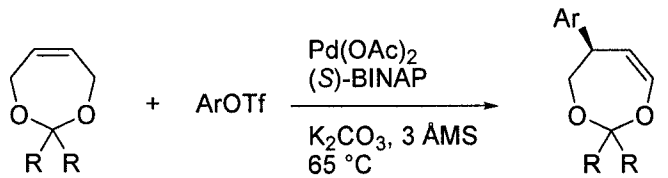
The isomerized dioxepanes **3-21** were then treated with *m*-CPBA and purified by distilling from an acidic medium to afford the highly diastereoselective 1,3-dioxanes **3-23** (Scheme 12). The dioxanes **3-23** were then further manipulated to form useful chiral building blocks in high enantioselectivities (Scheme 12).

Scheme 12.



Shibasaki and co-workers reported one of the first asymmetric Heck reactions on 4,7-dihydro-1,3-dioxepines.[38] The prochiral substrates **3-26** were cross coupled with aryl triflates in the presence of Pd(II)-BINAP complex to afford the chiral dioxepanes **3-27** in poor to moderate enantiomeric excess (Scheme 13). Their developed asymmetric Heck reaction works well for electron-rich, -neutral, and –poor aryl groups (Entries 2, 1, 4, respectively, Scheme 13).

Scheme 13.

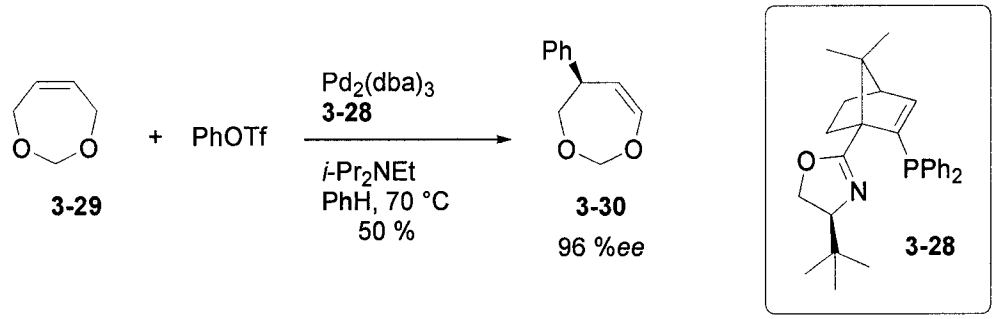


3-26 **3-27**

Entry	R	Ar	ee (%)	Yield (%)
1	Me	Ph	47	44
2	H	Ph	72	84
3	H	*p*-Cl-Ph	75	81
4	H	*p*-Me-Ph	70	86
5	H	*p*-OMe-Ph	67	48

Further improvements on the asymmetric Heck were achieved by Gilbertson and Fu in 2001.[39] Under their Heck conditions using a ligand **3-28** they recently developed, the dioxepine **3-30** was formed in high enantiomeric excess (96 % *ee*) (Scheme 14).

Scheme 14.

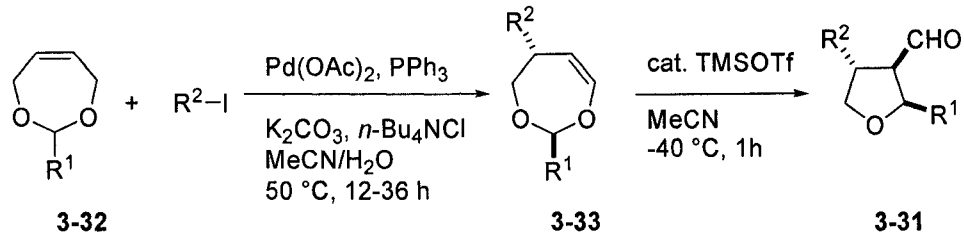


3-29 **3-30** 96 %*ee* **3-28**

Nasveschuk, Jui, and Rovis revealed a new development in the marriage of 1,3-dioxepines and the Heck reaction. They reported the modular approach to the synthesis of 2, 3, 4-trisubstituted tetrahydrofurans **3-31**.[33] When the achiral 1,3-

dioxepines **3-32** were subjected to Jeffery's conditions,[40] the Heck reaction proceeded under good diastereoselective control to afford the di-substituted dioxepines **3-33** (Scheme 15). Further treatment with catalytic TMSOTf at -40 °C resulted in the ring contraction products **3-31** in good diastereoselectivities (Scheme 15).

Scheme 15.



3-32 **3-33** **3-31**

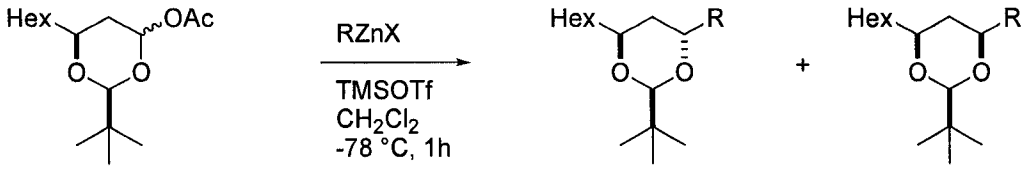
Entry	R^1	R^2	*d.r.* 33	Yield 33 (%)	*d.r.* 31	Yield 31 (%)
1	Ph	Ph	87:13	75	94:5:1:<1	70
2	2-furyl	Ph	87:13	65	>95:5:<1:<1	94
3	CH_2CH_2Ph	Ph	85:15	65	96:3:1:<1	85
4	CH_2CH_2Ph	*p*-OMePh	85:15	59	91:6:2:1	84
5	Et	Ph	85:15	64	90:7:2:<1	97
6	*t*-Bu	Ph	83:17	68	70:18:12:<1	55
7	CH_2CH_2Ph	CH_2CH_2Ph	79:21	42	93:6:1:<1	71

3.4. Nucleophilic Additions into Oxocarbenium Ions

3.4.1. 1,3-Dioxanes

Rychnovsky *et. al.* have reported the use of 1,3-dioxanes as useful building blocks for the contruction of *anti*-1,3-polyol chains.[41-44] They reported that treatment of 4-acetoxy-1,3-dioxanes **3-34** with dialkylzinc reagents in the presence of $BF_3 \cdot OEt_2$ at -78 °C afforded the *anti*-1,3-dioxane **3-35** products in high diastereoselectivities (Scheme 16).[41]

Scheme 16.

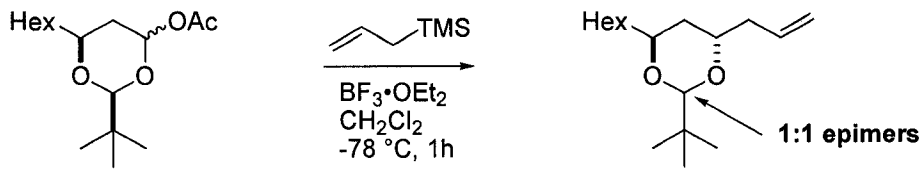


3-34 **3-35** ***anti*** **3-36** ***syn***

Entry	R	*anti:syn*	Yield(%)
1	Me	100:0	90
2	$Cl(CH_2)_4$	100:0	82
3	$EtO_2C(CH_2)_3$	100:0	77
4	$PhS(CH_2)_3$	89:11	36

Furthermore, they have shown that the Sakurai reaction of **3-34** with allyltrimethylsilane in the presence of BF_3•OEt_2 was highly diastereoselective for a single *anti*-1,3-dioxane **3-37**, but contained a 1:1 mixture of acetal epimers (Scheme 17).[44]

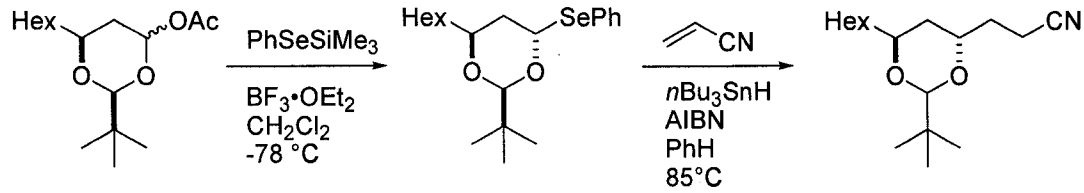
Scheme 17.



3-34 **3-37**
single *anti*-isomer

They also reported high diastereoselectivity, when the coupling reaction was performed under radical conditions.[44] Following conversion of the anomeric acetate **3-34** to the selenide **3-38**, the subsequent treatment with of AIBN, *n*-Bu_3SnH, and acrylonitrile afforded the *anti*-product **3-39** as a single diastereomer in good yield (Scheme 18).

Scheme 18.



3-34 **3-38** **3-39**

single *anti*-isomer

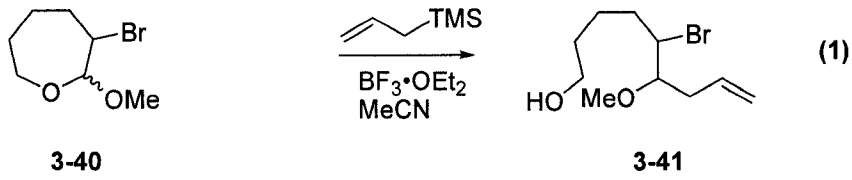
41 % Overall

In conclusion, they have shown that alkyl zincs and allyltrimethylsilane are sufficient nucleophiles for the cationic coupling with 4-acetoxy-1,3-dioxanes, as well as the radical reaction with acrylonitrile, for the construction of *anti*-1,3-diols.

3.4.2. Seven-Membered Rings

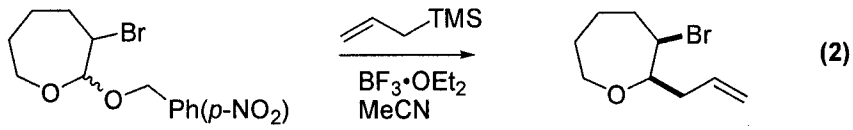
Much work has been done on the nucleophilic addition into 6-membered oxocarbenium ions (Section 1.3.4), but the addition into 7-membered oxocarbenium ions still remains an underdeveloped area. The first reported nucleophilic addition into an oxepane ring was reported by Rousseau in 1998.[45,46] When 3-bromo-2-methoxy-oxepane **3-40** was treated with strong Lewis acids (TMSOTf, SnF_2, and BF_3•OEt_2) and allyltrimethylsilane, only the ring cleavage product **3-41** was obtained in moderate yields (Eq. 1, Scheme 19). However, transformation to the 3-bromo-(4-nitro)-benzyloxy-oxepane **3-42** resulted in exclusive formation of the *cis*-diastereomer **3-43** (Eq. 2, Scheme 19).

Scheme 19.



(1)

3-40 **3-41**



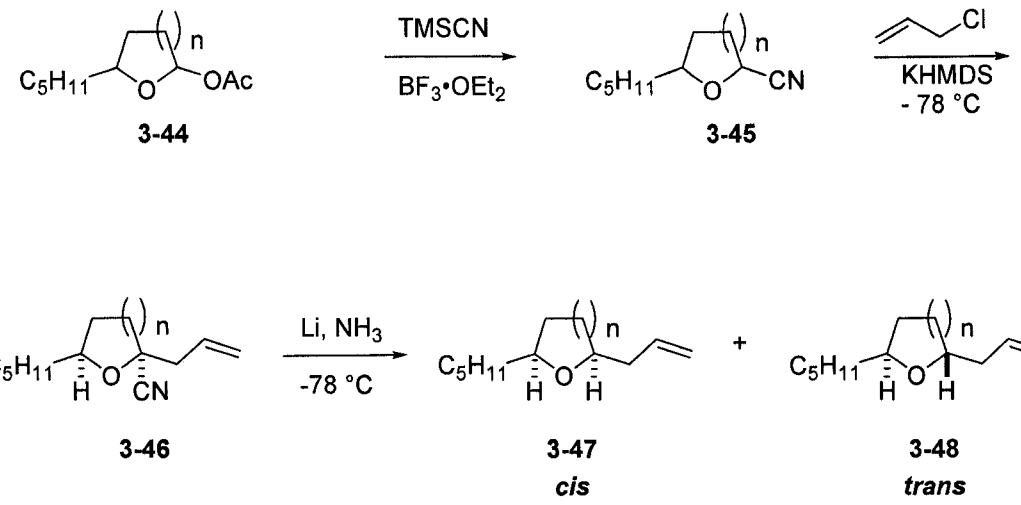
(2)

3-42 **3-43**

exclusive *cis*

In 1996, Rychnovsky and co-workers published a report on the selectivities of the cationic coupling between allyltrimethylsilane and various sized lactol ring acetates **3-44**.[47] Five through eight membered cyanohydrins **3-45** were synthesized and followed by deprotonation with KHMDS and treatment with allylchloride to afford the tertiary cyanohydrins **3-46**. Reduction of the cyano group afforded the di-substituted cyclic ethers **3-47** and **3-48** in ranging selectivities (Scheme 20).

Scheme 20.

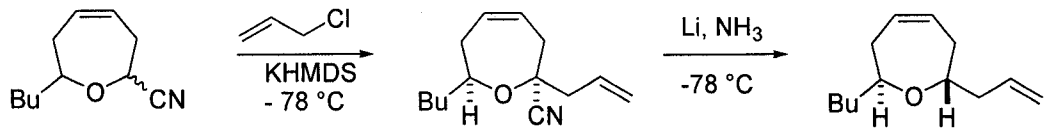


3-44 **3-45** **3-46** **3-47** ***cis*** **3-48** ***trans***

Entry	n	46 (*cis:trans*)	46 Yield (%)	47:48	47 + 48 Yield (%)
1	1	27:73	36	50:50	80
2	2	5:>95	82	>95:5	95
3	3	18:82	82	52:48	93
4	4	5:95	74	92:8	89

These results illustrate that oxocarbenium ions within 6- and 8-membered rings react in a highly *cis* selective fashion (>95:5 and 92:8, respectively), while the addition into 5- and 7-membered rings is problematic (50:50 and 52:48, respectively). This is in accordance with observations reported by Woerpel and Chamberland, in which they noticed that remote stereocenters in 8-membered ring oxocarbenium ions exhibit a strong influence over the diastereoselectivity.[48] When Rychnovsky treated the more rigid oxepine ring **3-49** under the same conditions, they assumed the unsaturated system **3-49** would adopt a more chair like conformation and would possibly result in increased diastereoselectivity. This did prove a partial solution, the disubstituted oxepine **3-51** was isolated as a 24:76 (*cis:trans*) mixture of isomers (Scheme 21).

Scheme 21.



3-49

3-50
22:78
cis:trans

3-51
24:76
cis:trans

When comparing the results obtained by Rousseau and Rychnovsky, the stereoselectivity of the nucleophilic addition into 7-membered oxocarbenium ions seems to be dictated by the substituents around the ring. Rousseau illustrated that good control could be achieved when a bromine atom is placed in the 3-position, while Rychnovsky illustrated that a substituent in the 7-position is incapable of dictating the incoming attack unless the system is made more rigid by the introduction of an olefin into the ring.

In this chapter, we propose to use nucleophilic addition into oxocarbenium ions generated from 1,3-dioxepanes for the construction of 1,4-polyol motifs and as a possible building block for some of the more common stereochemically congested sequences found in natural products. Furthermore, the use of 1,3-dioxepines in the synthesis of substituted tetrahydropyran rings will also be investigated.

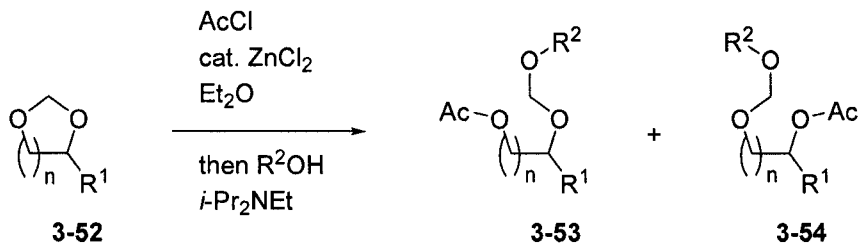
3.5. Results

3.5.1. Introduction

Bailey *et. al.* have shown regioselective acylative cleavage of cyclic formals **3-52** (Scheme 22),[49,50] wherein treatment of **3-52** with AcCl and catalytic $ZnCl_2$ yields

the cleavage products **3-53** and **3-54**. As a result, we believed this method could be implemented in the formation of differentially protected 1,4-diols.

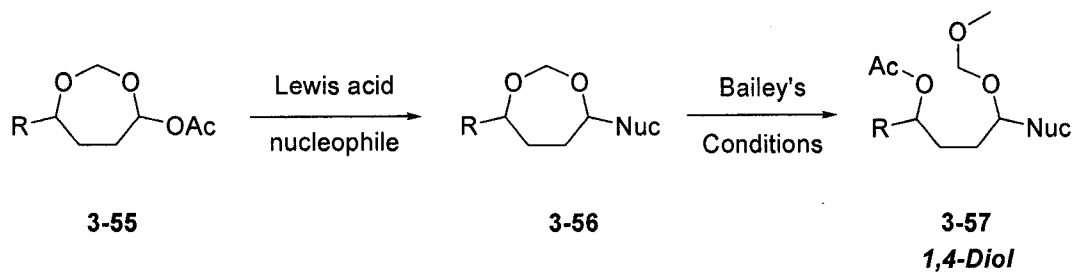
Scheme 22.



Entry	n	R^1	R^2OH	53:54	Yield (%)
1	1	Me	MeOH	75:25	92
2	2	Me	BnOH	>99:1	75
3	2	*i*-Pr	MeOH	>99:1	95

We envisioned that when a 7-substituted-4-acetoxy-1,3-dioxpine **3-55** is treated with a Lewis acid and a nucleophile that a cationic coupling will afford the 4,7-disubstituted-1,3-dioxepine **3-56**. The dioxepine **3-56** can then be treated under Bailey's conditions and the sterics of the system will bias the acetal cleavage to yield differentially protected 1,4-diol **3-57** (Scheme 23).

Scheme 23.

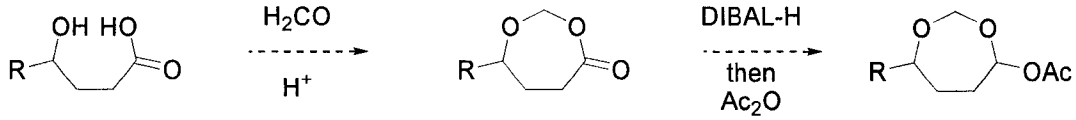


3.5.2. Substrate Synthesis

3.5.2.1. Synthesis of 4-Acetoxy Derivatized Substrates

The construction of 4-acetoxy-1,3-dioxanes **3-34** are well established,[41-43] however there is no literature precedent for the construction of 4-acetoxy-1,3-dioxepines **3-55**. As a result, we initially began our synthesis of these dioxepines implementing the analogous route used for the construction of the 1,3-dioxanes (Scheme 24). When the

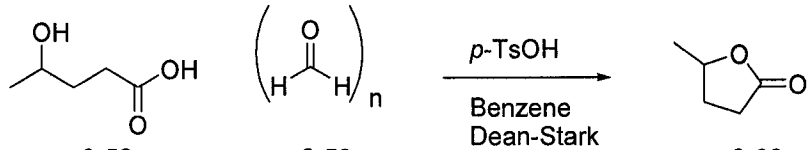
Scheme 24.



3-55

γ-hydroxy-butyric acid **3-58** was treated with paraformaldehyde **3-59** in the presence of catalytic acid, the reaction yielded the lactone **3-60** as the only product (Scheme 25). This was somewhat expected since under acidic medium, the intramolecular 5-*exo-trig*-cyclization pathway is probably more favorable than the intermolecular 7-*exo-tet*-cyclization process.[51]

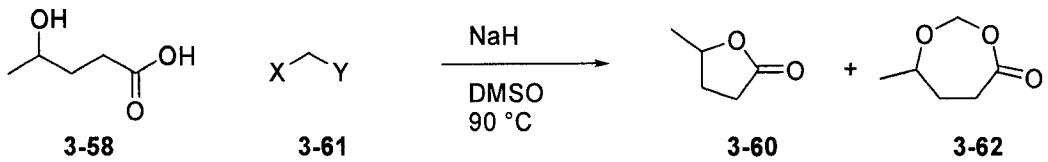
Scheme 25.



3-58 **3-59** **3-60**

Since the formation of the 1,3-dioxepine did not occur under acidic conditions, we next tried the reaction under basic conditions with halogenated methylene derivatives. Unfortunately, when the hydroxy acid **3-58** was treated with NaH and a variety of electrophiles **3-61**, the only isolable product was the lactone **3-60** (Scheme 26).

Scheme 26.

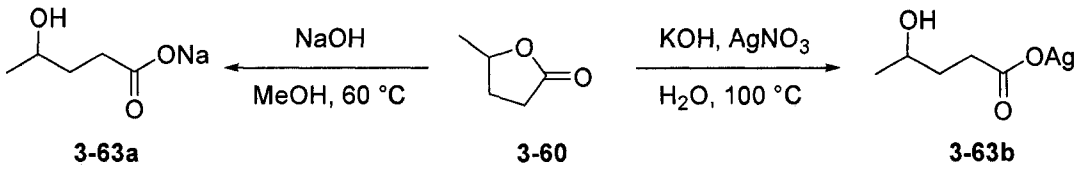


3-58 3-61 3-60 3-62

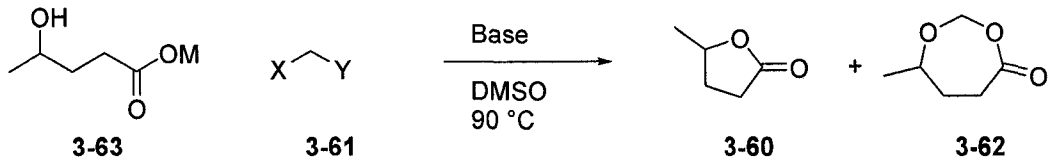
Entry	X	Y	61:62	Yield (%)
1	Cl	I	>99:1	90
2	I	I	>99:1	97

Undaunted, we next focused our attention on making the carboxylate salt **3-63** of the hydroxy acid. We assumed that the carboxylate anion of the salt would not allow the formation of the lactone **3-60** and should therefore result in the dioxepane **3-62**. The carboxylate salts **3-63** were prepared by treatment of the lactone with either KOH and $AgNO_3$ or NaOH and were formed as amorphous solids in good yields (Scheme 27). Each salt **3-63** was then treated with a variety of electrophiles **3-61** under different conditions (Scheme 27). Under the conditions examined, all of the carboxylate salts **3-63** yielded the lactone **3-60** as the major product. We envisioned the lactone **3-60** was being formed by hydrolysis of the carboxylate salt **3-63**, so steps were taken in order to assure the reaction was being performed under complete anhydrous conditions (*i.e.* using freshly dried solvent, addition of $MgSO_4$ or molecular sieves).

Scheme 27.



3-63a **3-60** **3-63b**



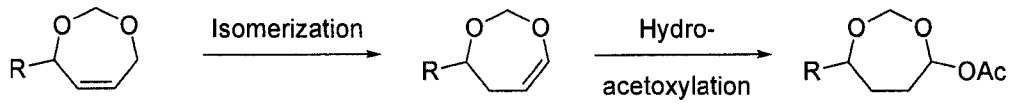
3-63 **3-61** **3-60** **3-62**

Entry	M	X	Y	Base	60:62	Yield (%)
1	Ag	Cl	I	NaH	>99:1	90
2	Ag	I	I	NaH	>99:1	97
3	Ag	Cl	I	KH	>99:1	88
4	Ag	I	I	KH	>99:1	82
5	Na	Cl	I	NaH	>99:1	64
6	Na	I	I	NaH	>99:1	87
7	Na	Cl	I	KH	>99:1	69
8	Na	I	I	KH	>99:1	79

Even under the anhydrous conditions, the lactone **3-60** was still formed in significant quantities.

This route proved to be inefficient for the construction of the desired dioxepanes and as a result a new route was devised. We postulated that if the unsymmetrical dioxepine could be formed, that isomerization and hydroacetoxylation would yield the desired substrate **3-66** (Scheme 28).

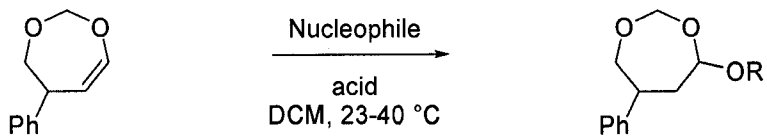
Scheme 28.



3-64 **3-65** **3-66**

We began this new route using the readily prepared dioxepine **3-67**,[38] from the Heck reaction of phenyl iodide and 4,7-dihydro-1,3-dioxepine, shown in Scheme 30. We assumed the dioxepine **3-67** would react very similar to dihydropyran and as a result we began our studies using methods which mirror a THP protection. When the dioxepine **3-67** was treated with catalytic amounts of acid and a nucleophile at a variety of temperatures, the starting dioxepine **3-67** was never consumed and was isolated in nearly quantitative yield (Scheme 29). In order to ensure that the use of the weakly nucleophilic AcOH was not the root of the problem, we subjected MeOH to the same reaction conditions and no reaction occurred either (Entry 6, Scheme 29).

Scheme 29.

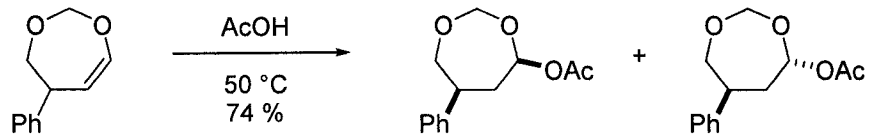


3-67

Entry	Nucleophile	Acid	Outcome
1	AcOH	TfOH	**67**
2	AcOH	$MeSO_3H$	**67**
3	AcOH	*p*-TsOH	**67**
4	AcOH	PPTS	**67**
5	AcOH	amberlyst H-15	**67**
6	MeOH	*p*-TsOH	**67**

Undaunted, one last attempt was made at synthesizing the desired dioxepine **3-68** and **3-69** via this route. To our gratification, when the dioxepine **3-67** and AcOH were heated to at least 50 °C, the reaction yielded a 74:26 (*cis:trans*) mixture of diastereomers (Scheme 30). Interestingly, when the reaction was attempted below 50 °C, the reaction did not take place. The *cis:trans* relationship was confirmed by nOe studies.

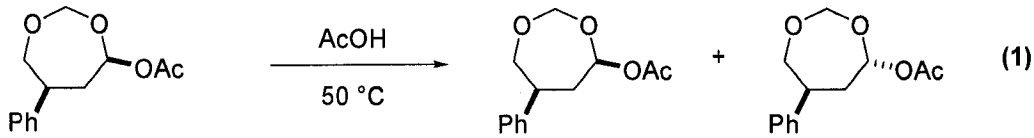
Scheme 30.



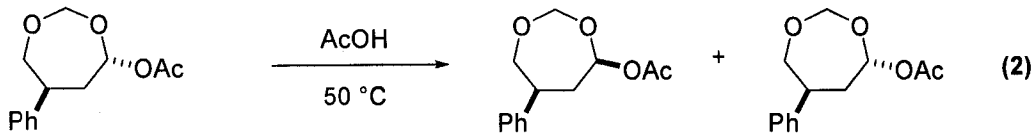
3-67 **3-68** ***cis*** **74:26** **3-69** ***trans***

We believed the obtained ratio was in thermodynamic equilibrium and to test this hypothesis we subjected the pure *cis*-dioxepane **3-68** (Eq. 1) and pure *trans*-dioxepane **3-69** (Eq. 2) to the same reaction conditions (Scheme 31). In both reactions, a 75:25 ratio of *cis:trans*-diastereomers were obtained.

Scheme 31.



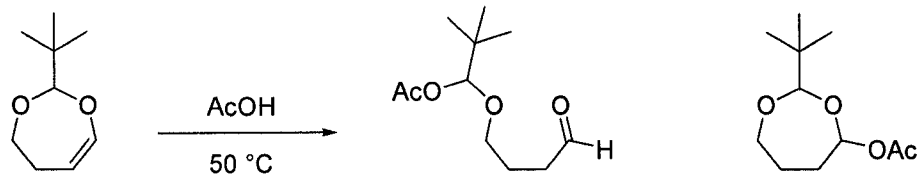
3-68 ***cis*** **3-68** ***cis*** **74:26** **3-69** ***trans***



3-69 ***trans*** **3-68** ***cis*** **75:25** **3-69** ***trans***

In order to test whether this method can be generally used on all dioxepines, we synthesized the 2-*t*-butyl-1,3-dioxepine **3-70**, prepared from the condensation of *cis*-1,4-butenediol and pivaldehyde, and subjected it to the reaction conditions (Scheme 32). To our surprise, the desired product **3-71** was not obtained but instead the ring cleavage product **3-72** was isolated in good yield.

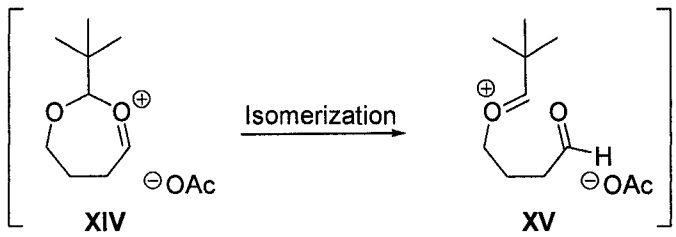
Scheme 32.



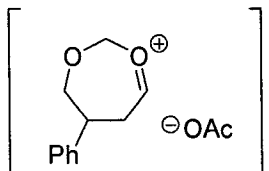
3-70 **3-72** **3-71** ***not observed***

In order to account for this unexpected result, we rationalized that the initial oxocarbenium ion **XIV** formed in the *t*-butyl substituted acetal is less stabilized than it's isomerized oxocarbenium ion **XV**. The isomerized oxocarbenium ion **XV** is subsequently trapped by the nucleophile, while with the methylene acetal the initial oxocarbenium ion **XVI** is long lived enough to allow for trapping by the nucleophile (Figure 2). As a result, this method only seems to be a viable route for methylene acetals.

Figure 2.



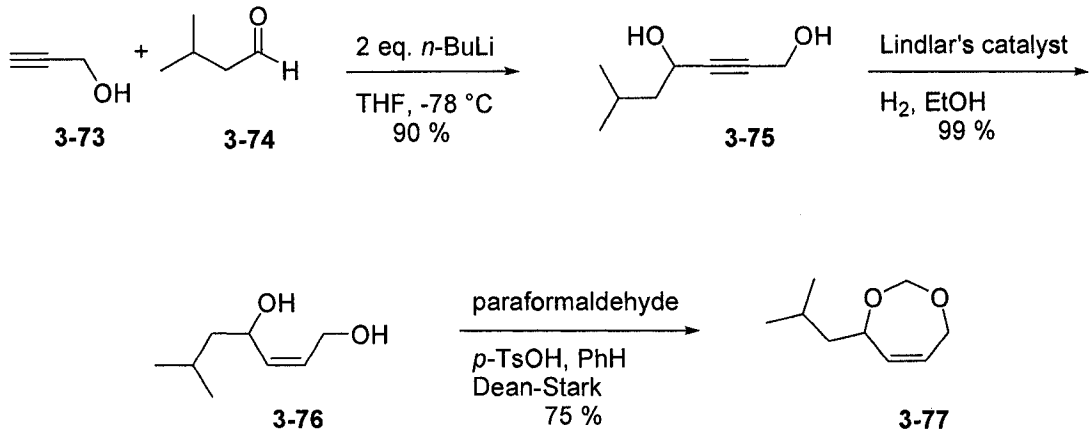
XIV XV



XVI

With a route to installing the desired 4-acetoxy functionality, we wanted to synthesize 7-substituted dioxepanes. The 7-substituted dioxepanes are not as readily prepared as the 6-substituted dioxepanes. Treatment of propargyl alcohol **3-73** with 2 equivalents of *n*-BuLi at -78 °C followed by addition of the aldehyde **3-74** and warming to ambient temperature affords the bis-propargyl alcohol **3-75** in good yields (Scheme 33). Lindlar reduction of the alkyne **3-75** and subsequent condensation of the diol with paraformaldehyde using catalytic acid under Dean-Stark conditions yielded the desired unsymmetrical 1,3-dioxepine **3-77**.

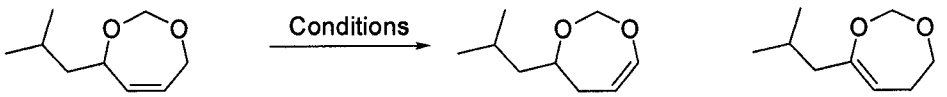
Scheme 33.



3-73 3-74 3-75 3-76 3-77

Isomerization of the 4-substituted-4,7-dihydro-1,3-dioxepine **3-77** to the 4-substituted-4,5-dihydro-1,3-dioxepine **3-78** can be accomplished via two routes. First, isomerization can be accomplished using a Ru catalyst and $NaBH_4$, while the second option involves basic isomerization using KO*t*-Bu. The unsymmetrical dioxepine **3-77** was isomerized under both conditions and the results are shown in Scheme 34.

Scheme 34.



3-77 **3-78** **3-79** ***not observed***

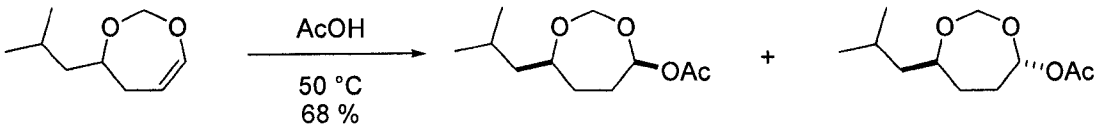
Entry	Conditions	Yield (%)
1	$RuCl_2(PPh_3)_3$, $NaBH_4$, MeOH	33
2	KO*t*-Bu, DMSO	81

To our delight, the desired product **3-78** was obtained and the other regioisomer **3-79** was never observed. Overall, in our hands when the Ru mediated isomerization was

employed, the reaction proceeded albeit in low yields; therefore, we typically performed the isomerization under basic conditions.

With the desired isomerized dioxepine **3-78** in hand, we treated it with our hydroacetoxylation reaction conditions. The presence of a substituent had no effect on the outcome of the reaction and the acetoxy dioxepanes **3-80** and **3-81** were isolated as a 70:30 (*cis:trans*) mixture of diastereomers (Scheme 35).

Scheme 35.



3-78 **3-80** ***cis*** **70:30** **3-81** ***trans***

Using conditions analogous to those shown in Scheme 33, 34 and 35, we prepared the following 7-alkyl-4-acetoxy-1,3-dioxepanes for use in our studies (Figure 3).

Figure 3.

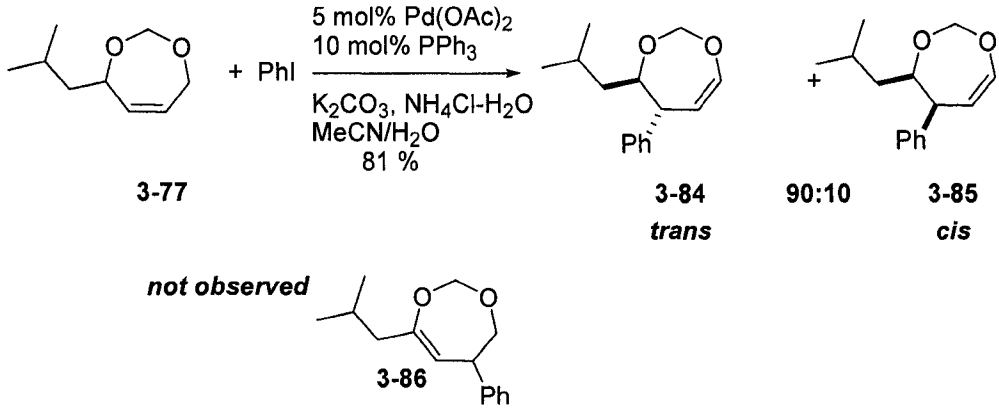
3-82 **3-83**

3.5.2.2. Synthesis of Poly-Substituted Substrates

As stated earlier, the Heck reaction and dioxepines have a long history together, however there was little work reported on the Heck reaction with unsymmetrical dioxepines. As a result, investigations into this transformation were initiated. When the unsymmetrical dioxepine **3-77**, prepared in a route similar to

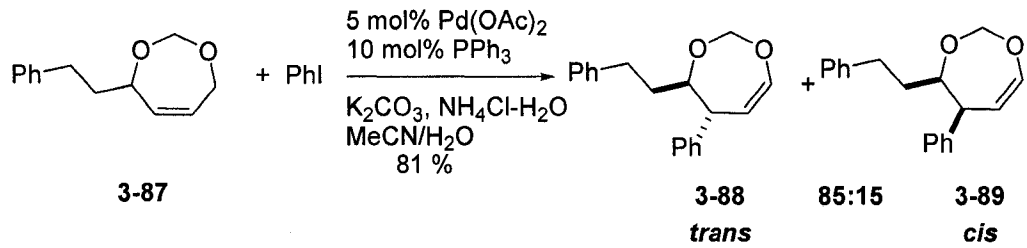
Scheme 34, was treated with Jeffery's conditions, the desired products **3-84** and **3-85** were obtained as a single regioisomer in a 90:10 mixture of *trans:cis* diastereomers (Scheme 36).[23-25,40]

Scheme 36.



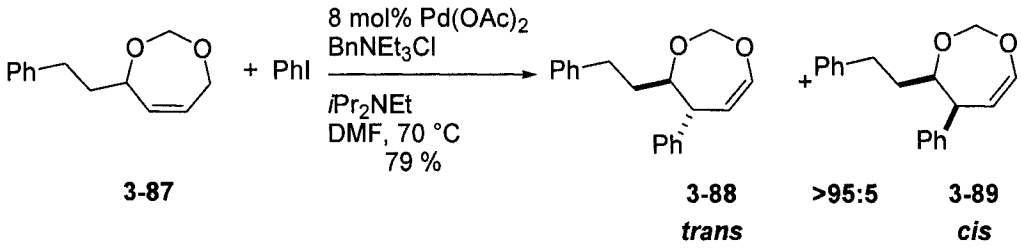
With the anticipation of broadening the scope of this transformation, treatment of **3-87** under the same set of conditions yielded 85:15 (*trans:cis*) ratio of diastereomers and again with no detectable amount of the regioisomer (Scheme 37).

Scheme 37.



Due to the lower diastereoselectivity of the previous example, other Heck conditions were screened. To our delight, the implementation of Takano's conditions on the phenethyl derived dioxepine **3-87** provided a >95:5 (*trans:cis*) ratio of diastereomers as a single regioisomer (Scheme 38).[34]

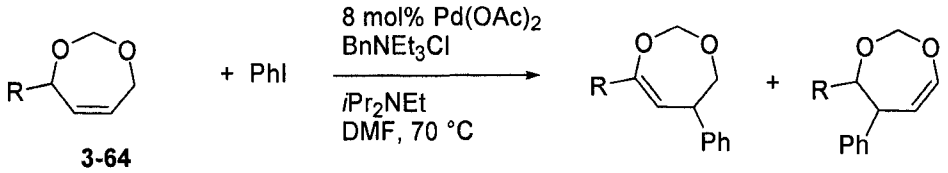
Scheme 38.

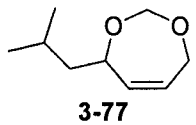
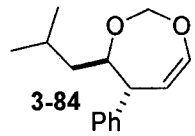
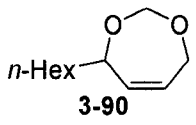
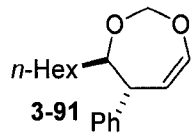
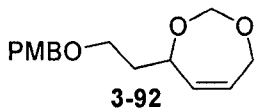
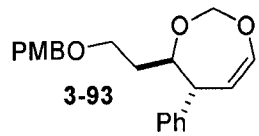
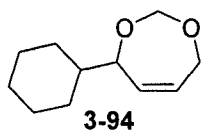
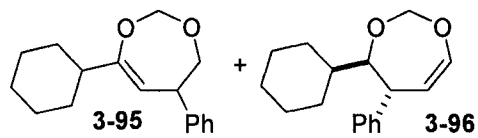
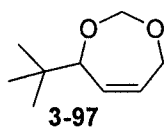
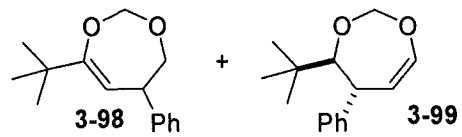


3-87 **3-88** ***trans*** **>95:5** **3-89** ***cis***

Scheme 39 illustrates the substrate scope under the new conditions. In all of the examples, when the desired regioisomer was obtained, it was in a >95:5 (*trans:cis*) ratio. Interestingly, as the size of the alkyl substituent increases, for example from *n*-hexyl to *cy*-hexyl to *t*-butyl, the amount of the other regioisomer also increases (Entries 2, 4, and 5, respectively, Scheme 39). In conclusion, a highly diastereoselective transformation and a basic understanding of how sterics impacts the selectivity of this Heck reaction has been achieved.

Scheme 39.



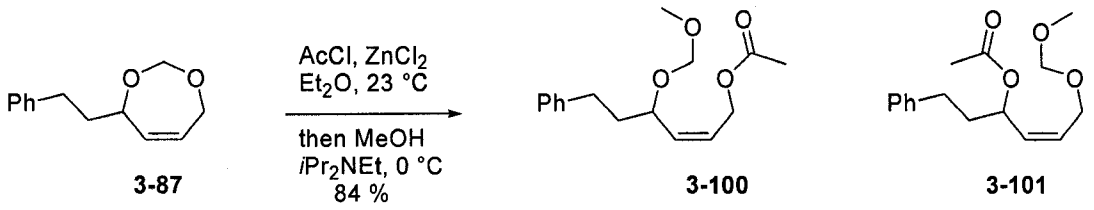
Entry	Substrate	Products	Ratio	Yield (%)
1	 3-77	 3-84	---	81
2	 3-90	 3-91	---	79
3	 3-92	 3-93	---	56
4	 3-94	 3-95 3-96	36:74	77
5	 3-97	 3-98 3-99	62:38	61

3.5.3. Methylene Acetal Ring Cleavage

In order to insure that 1,3-dioxepines can undergo selective methylene acetal cleavage, we subjected the dioxepine **3-87** to Bailey's conditions.[49,50] Treatment of **3-**

87 with AcCl in the presence of catalytic $ZnCl_2$ followed by subsequent treatment with Hunig's base and MeOH afforded a single regioisomer **3-100** in good yields (Scheme 40).

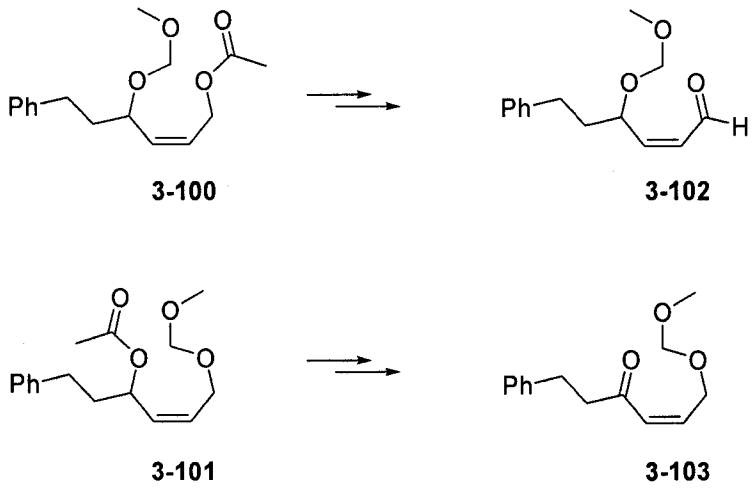
Scheme 40.



3-87 **3-100** **3-101** ***not observed***

Based on the previous results by Bailey,[49,50] we believed the primary *O*-acetate was the observed product **3-100**, however absolute verification was needed. As a result, we decided to cleave the acetate group and oxidize the resultant alcohol. If **3-100** was formed, then the oxidation will yield an aldehyde **3-102**, while if **3-101** was formed the oxidation will yield a ketone **3-103** (Figure 4).

Figure 4.

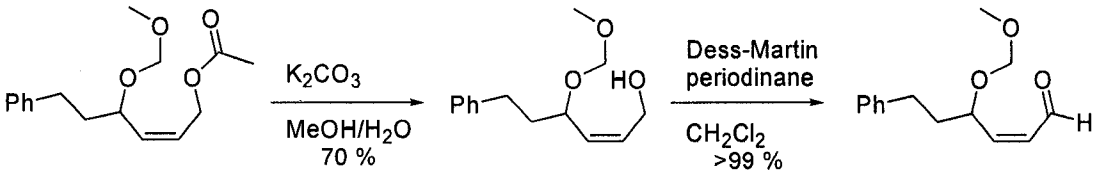


3-100 **3-102**

3-101 **3-103**

The acetate cleavage of our product was induced upon treatment of **3-100** with K_2CO_3 in $MeOH/H_2O$ and the free alcohol **3-104** was isolated in 70 % yield. The alcohol **3-104** was oxidized with Dess-Martin periodinane and supporting our hypothesis, an aldehyde proton signal was observed in ^1H NMR (9.8 ppm)(Scheme 41).

Scheme 41.



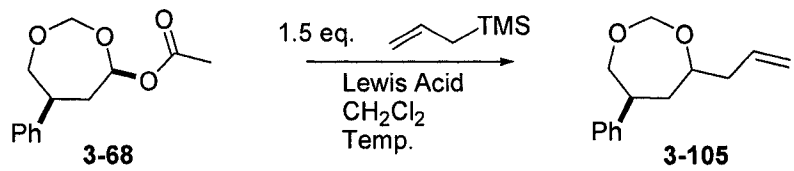
3-100 **3-104** **3-102**

By gaining the ability to synthesize the desired 7-alkyl-4-acetoxy-1,3-dioxepanes and the preliminary selective methylene acetal cleavage result, we believed the stage was set to further pursue using this system for the construction of 1,4-diols.

3.5.4. Generation of 1,4-Diols

Since there were no reports of the cationic coupling reactions of 1,3-dioxepanes, our initial efforts paralleled those reported for 1,3-dioxanes.[41-43] We began with a simple screen of Lewis acids. The dioxepane **3-68** and 1.5 equivalents of allylTMS in CH_2Cl_2 were treated with TMSOTf, $MgBr_s$, and $Yb(OTf)_3$ (Scheme 42).

Scheme 42.

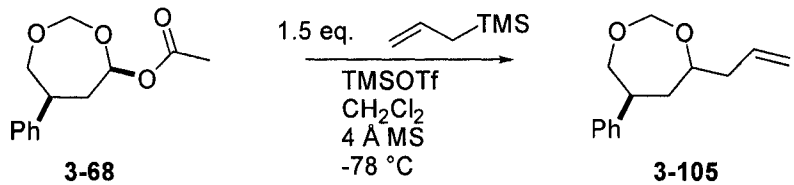


3-68 **3-105**

Entry	Lewis Acid	Temp. (°C)	Yield (%)
1	TMSOTf (1.05 eq.)	-78	---
2	TMSOTf (0.2 eq.)	-78	---
3	$MgBr_2$ (1.05 eq.)	-78	SM
4	$Yb(OTf)_3$ (0.2 eq.)	23	SM

When the stronger Lewis acid (TMSOTf) was used in either stoichmetric or catalytic amounts, the reaction afforded no isolable products (Entries 1 and 2, respectively, Scheme 42), while the milder Lewis acids ($MgBr_2$ and $Yb(OTf)_3$) returned unreacted starting material **3-68** (Entries 3 and 4, respectively, Scheme 42). In order to determine if residual water was playing havoc on the TMSOTf mediated reactions, we performed the reaction under the same conditions, but with the addition of activated 4 Å MS (Scheme 43).

Scheme 43.

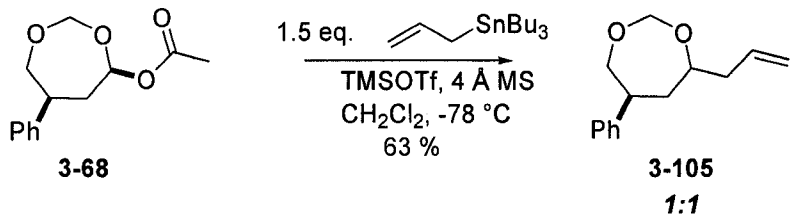


3-68 **3-105**
trace amounts

Under these new conditions, the crude reaction mixture contained trace amounts of the desired product **3-105**, however no other appreciable product could be isolated.

After analyzing the previous data, we believed that if the nucleophilicity of the allylic nucleophile could be increased then the oxocarbenium ion could potentially be trapped faster and possibly cease the background reactions. As a result, we began to investigate the use of allyltributyltin as the nucleophile. Treatment of the dioxepane **3-68** with allyltributyltin and TMSOTf resulted in formation of the desired dioxepane **3-105** in 63 % yield as a 1:1 mixture of diastereomers (Scheme 44).

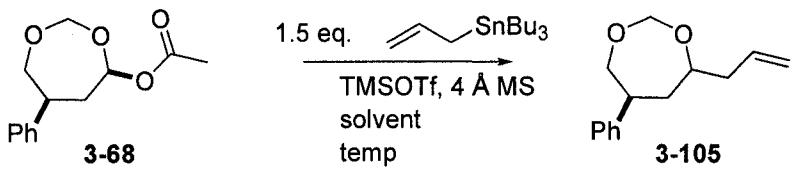
Scheme 44.



3-68 **3-105** ***1:1***

After our initial result, we performed a simple screen of solvents to see if there is any impact on selectivity. Under the reaction conditions, CH_2Cl_2 and toluene successfully afforded the desired products **3-105** (Entries 1 and 2, respectively, Scheme 45), albeit in 1:1 diastereoselectivity, while MeCN was non-productive (Entry 3, Scheme 45).

Scheme 45.

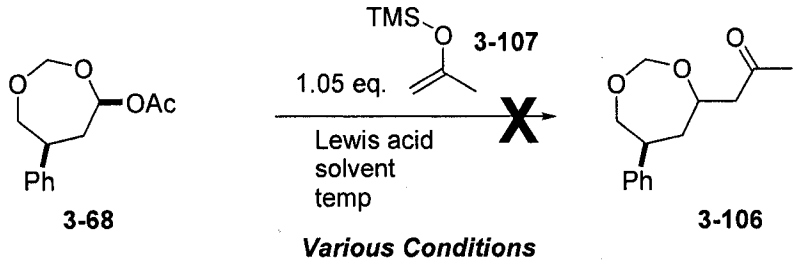


3-68 **3-105**

Entry	Solvent	Temp. (°C)	*cis:trans*	Yield (%)
1	CH_2Cl_2	-78	1:1	63
2	toluene	-78	1:1	18
3	MeCN	-50	---	---

Due to the lack of stereoselectivity and from our previous results (Chapter 2), we began to investigate the use of enol silanes as nucleophiles in this reaction. The initial results of treating the dioxepine **3-68** with 1.05 eq. of the enol silane **3-107** and various Lewis acids are shown in Scheme 46. A few generalizations can be made from Scheme 46; first, when catalytic or stoichometric $BF_3 \cdot OEt_2$ was used as the Lewis acid at low or high temperatures, decomposition products were obtained. Second, the use of catalytic amounts of TMSOTf (0.2 eq.) proved to be more efficient at the transformation than stoichometric amounts. At all temperatures, the TMSOTf mediated reaction proceeded to yield products, however using catalytic TMSOTf at -78 °C afforded the product **3-106** in the best yields (~25 %) with the least amount of decomposition products. Third, the choice of solvent was critical in this reaction,

Scheme 46.

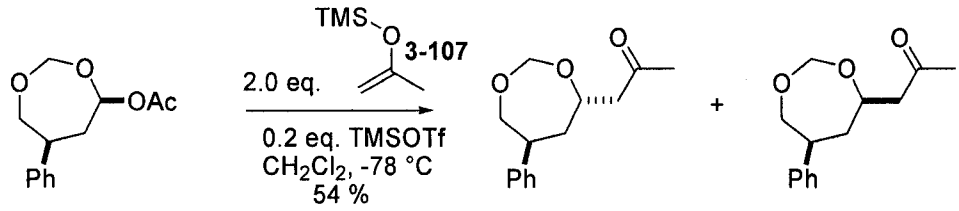


in which CH_2Cl_2 afforded product but toluene did not. As a result, further optimization conditions were aimed at utilizing catalytic amounts of TMSOTf in CH_2Cl_2 at -78 °C.

We next focused on the amount of enol silane **3-107** required for this transformation. As shown previously, 1.05 eq. of enol silane **3-107** afforded the product, albeit in low yields. As a result, we decided to increase the amount of enol silane **3-107** to 2 equivalents. When the dioxepane **3-68** and 2 equivalents of enol

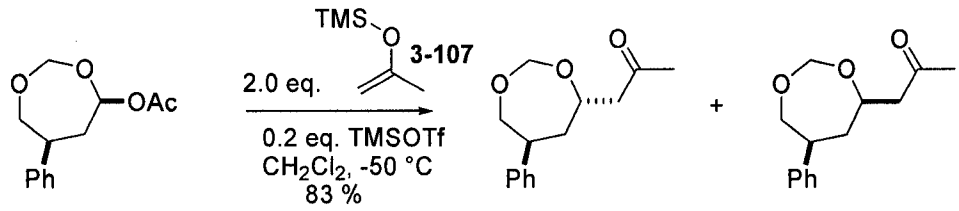
silane **3-107** in CH_2Cl_2 at -78 °C were treated with catalytic amounts of TMSOTf, the reaction proceeded over 8 h to yield the desired products **3-107** and **3-108** as a 73:27 (*trans:cis*) mixture of diastereomers in moderate yields (54 %) and with remaining material being decomposition products (Scheme 47).

Scheme 47.



We believed the decomposition products could result from the long reaction time (8 h), as a result the temperature was raised to -50 °C and the same conditions were re-run. To our delight, at -50 °C the reaction afforded the desired products **3-107** and **3-108** in 2 h as a 75:25 (*trans:cis*) mixture of isomers in good yields (83 %) and with little decomposition products (Scheme 48).

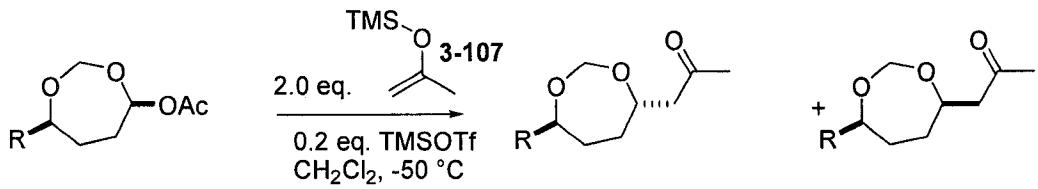
Scheme 48.



With these conditions in hand, we set out to examine the scope of this reaction. When the 7-alkyl-4-acetoxy-1,3-dioxepines **3-109** were treated under these

conditions, the reaction afforded the desired products **3-110** and **3-111** in good yields, however the selectivity was modest at best (Scheme 49).

Scheme 49.

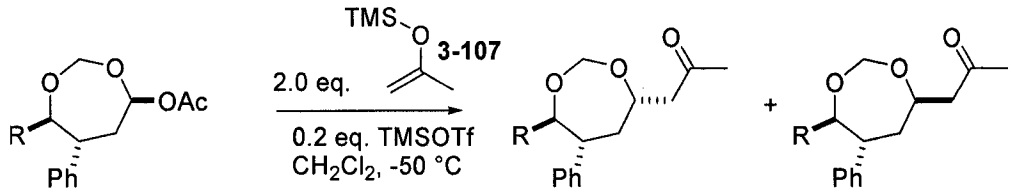


3-109 **3-110** ***trans*** **3-111** ***cis***

Entry	R	*trans:cis*	Yield (%)
1	CH_2CH_2Ph	76:24	78
2	*i*-Bu	72:28	81

From here, we had multiple avenues to explore in order to envision their impact on the selectivity. First, due to Rychnovsky's report that the more rigid the 7-membered ring, the higher the selectivity,[47] we wanted to try our more rigid tri-substituted dioxepanes **3-112**. Under the optimized conditions, the tri-substituted dioxepanes **3-112** smoothly underwent the reaction to yield the desired products **3-113** and **3-114** in good yields, however the selectivity was again modest (Scheme 50).

Scheme 50.

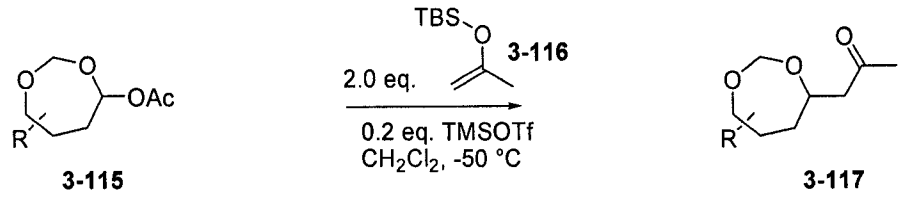


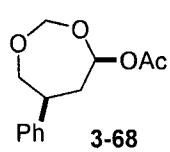
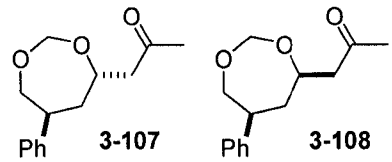
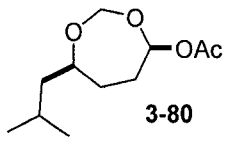
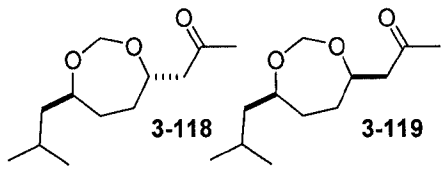
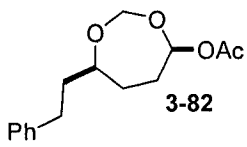
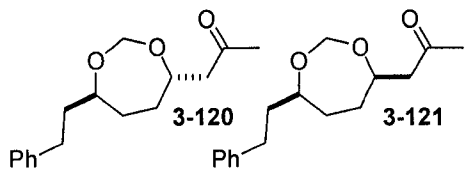
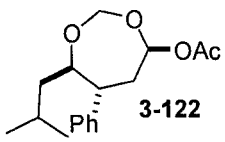
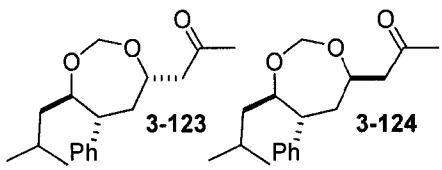
3-112 **3-113** ***trans:cis*** **3-114** ***trans:trans***

Entry	R	113:114	Yield (%)
1	CH_2CH_2Ph	75:25	78
2	*i*-Bu	74:26	81

Undaunted, we next examined if the size of the silyl protecting group on the enol silane impacted the diastereomeric ratio. As a result, the TBS protected enol silane **3-116** was chosen due to it's increased steric size. Treatment of the requisite dioxepanes **3-115** with the TBS-protected enol silane **3-116** under the optimized conditions afforded the desired products **3-117** in good yields (Scheme 51). Unfortunately, increasing the steric size of the silyl protecting group exhibited zero enhancement on the product ratios.

Scheme 51.

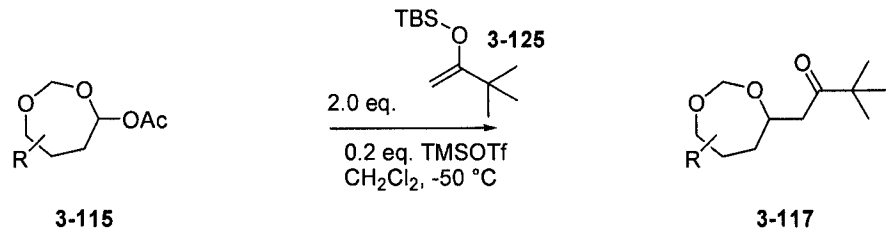


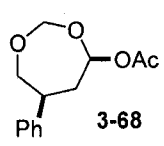
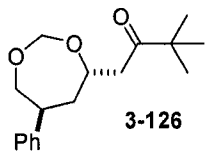
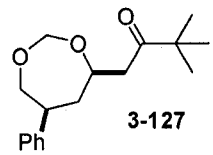
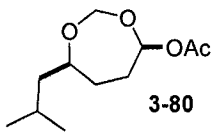
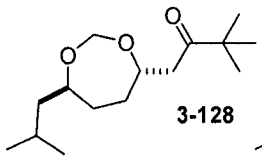
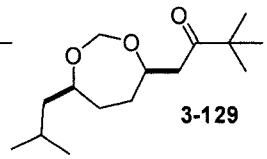
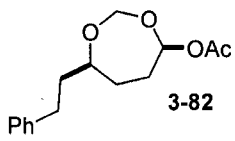
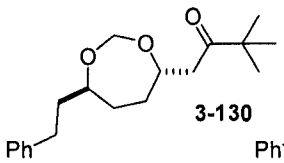
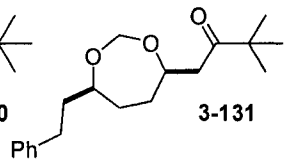
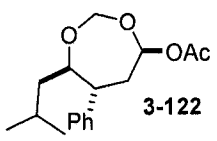
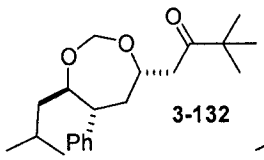
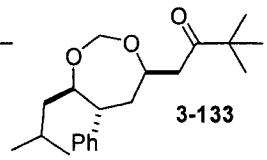
Entry	Substrate	Product	Ratio	Yield (%)
1	 3-68	 3-107 3-108	74:26	74
2	 3-80	 3-118 3-119	75:25	78
4	 3-82	 3-120 3-121	73:27	70
5	 3-122	 3-123 3-124	75:25	67

Since increasing the steric size of the silyl protecting group had no effect on increasing the diastereoselectivity, we further explored the possibility of increasing steric size on the incoming nucleophile. As a result, we synthesized the TBS-protected

enol silane **3-125** derived from pinacolone. The results obtained under the standard conditions with the sterically larger enol silane are shown in Scheme 52.

Scheme 52.

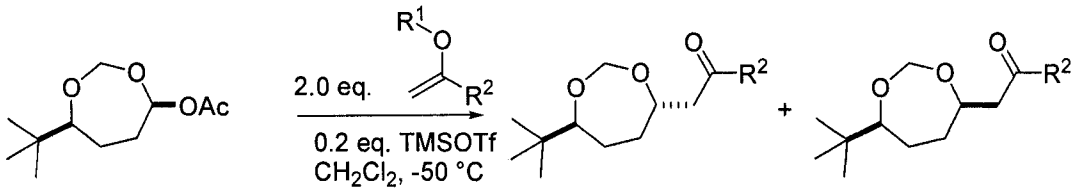


Entry	Substrate	Product	Ratio	Yield (%)
1	 3-68	 3-126  3-127	78:22	62
2	 3-80	 3-128  3-129	73:27	68
4	 3-82	 3-130  3-131	75:25	67
5	 3-122	 3-132  3-133	77:23	63

Increasing the steric size of the silyl protecting group or the incoming nucleophile exhibited similar control over the resulting stereocenters, as a result we decided to investigate increasing the steric size on the dioxepane ring itself. The 7-*t*-butyl-4-

acetoxy-1,3-dioxepane **3-83** was synthesized via the previously reported route and subjected to the standard reaction conditions (Scheme 53).

Scheme 53.



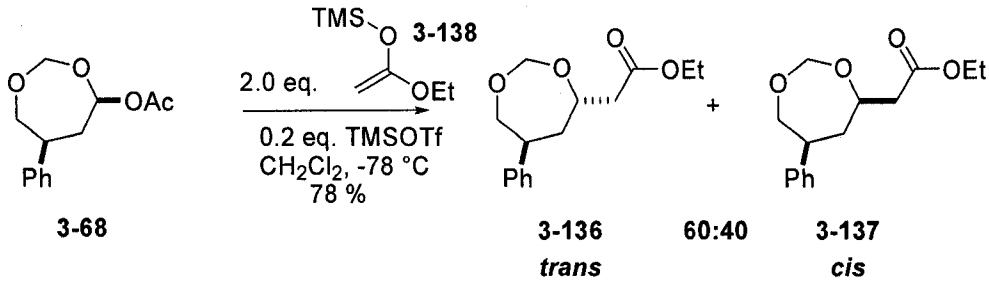
3-83 **3-134** ***trans*** **3-135** ***cis***

Entry	R^1	R^2	*trans:cis*	Yield (%)
1	TMS	Me	81:19	81
2	TBS	Me	80:20	79
3	TBS	*t*-Bu	82:18	70

When the *t*-butyl substituted dioxepane **3-83** was reacted with the TMS-protected enol silane **3-107** (Entry 1, Scheme 53), there was an observed enhancement of diastereoselectivity, unfortunately only a slight increase to 81:19 (*trans:cis*). Further efforts aimed at increasing the steric size around the reacting center also afforded the products in similar diastereoselectivities (Entries 2 and 3, Scheme 53).

Previously, we desribed how increasing the nucleophilicity of the incoming nucleophile had an impact on the rate of the reation. As a result, we believed that switching from a silyl enol ether to a silyl ketene acetal may have a significant impact on the outcome of the reaction. When the dioxepane **3-68** was treated with silyl ketene acetal **3-138** under the standard reaction conditions, no enhancement of stereoselectivity was seen, in fact the diastereoselectivity was eroded to 60:40 (*trans:cis*)(Scheme 54).

Scheme 54.



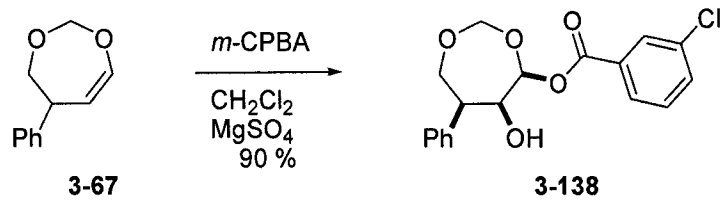
3-68 **3-136** ***trans*** **60:40** **3-137** ***cis***

In conclusion, the diastereoselectivity observed under these conditions were modest, yet not suprising given the previous results utilizing oxepane rings[47] and the lack of reports on substitution of 1,3-dioxepane rings. Since the ratios obtained under our conditions are slightly elevated when compared to the ratios obtained by Rychnovsky,[47] we can conclude that the addition of another oxygen atom into the 7-membered ring has a slight rigidifying effect on the ring system. As a result, the diastereoselectivity is increased, however the effects on the 7-membered ring system are not comparable with the observed effects on 6-membered ring systems (Chapter 2) and therefore, the enhancement in diastereoselectivity is modest.

3.5.5. Poly-Substituted Systems

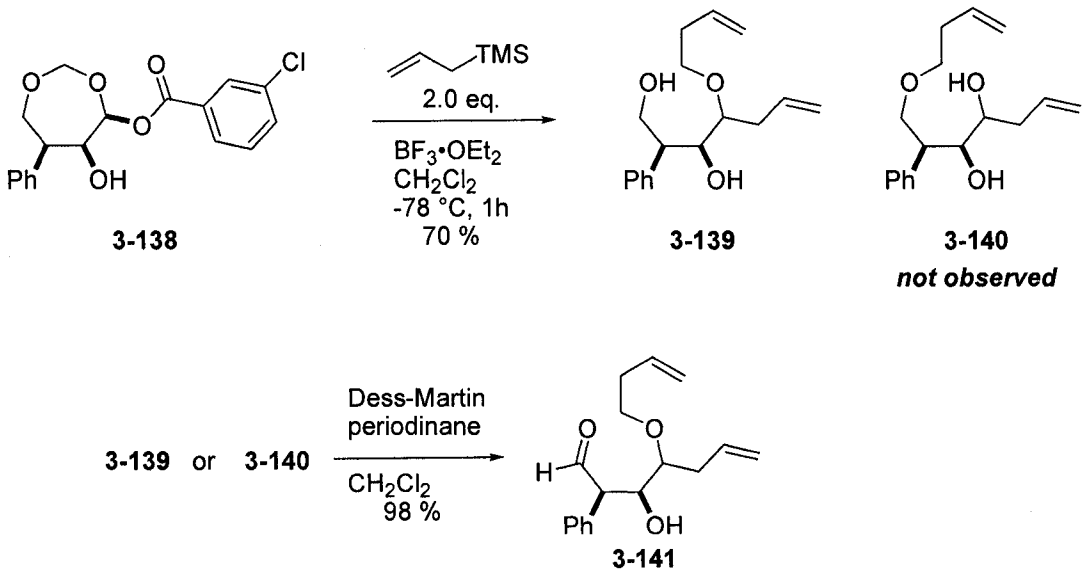
After analyzing the previous results and comparing them to the results obtained by Rychnovsky[47] and Rousseau,[45,46] we believed that increasing the rigidity of the 1,3-dioxepane ring may have an influential effect on the diastereomeric outcome of the cationic coupling reaction. As a result, we synthesized a trisubstituted dioxepane **3-138** by treatment of the dioxepine **3-67** with *m*-CPBA (Scheme 55).

Scheme 55.



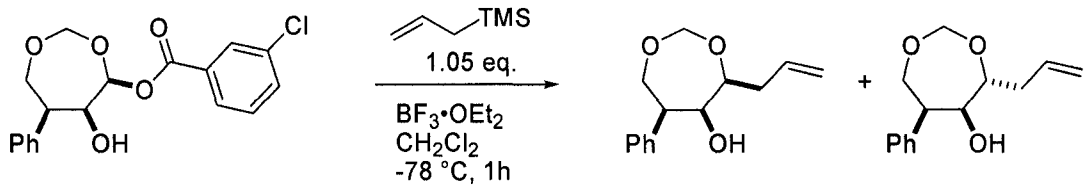
Upon treatment of the cyclic alcohol **3-138** with 2 equivalents of allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$, a product containing a terminal olefin was isolated (Scheme 56). Further analysis revealed that in fact two terminal olefins were present in the final product and we speculated that it was one of two products **3-139** and **3-140**. In order to differentiate the two products, a Dess-Martin oxidation was performed. Upon workup, an aldehyde hydrogen was seen via ^1H NMR and the structure was concluded to be the 1,3-diol product **3-139** and not the 1,2-diol product **3-140**.

Scheme 56.



When the amount of allyltrimethyl silane was decreased to 1.05 equivalents in order to potentially retard the double addition product, the reaction afforded the desired allylation product **3-142** and **3-143** as a 1:1 mixture of diastereomers, in 23% yield using 0.2 equivalents of Lewis acid (Entry 1, Scheme 57). Further experiments revealed that increasing the amount of Lewis acid had a direct relationship with the yield (Entries 2-4, Scheme 57).

Scheme 57.



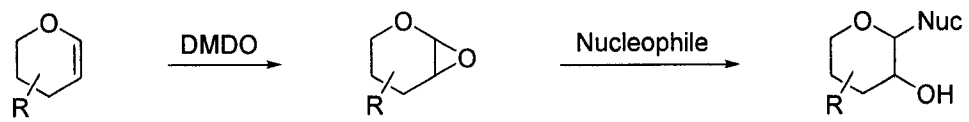
3-138 → **3-142** *cis:cis* + **3-143** *cis:trans*

Entry	Eq. of BF_3•OEt_2	[*cis:cis*]:[*cis:trans*]	Yield (%)
1	0.2	52:48	23
2	0.4	50:50	39
3	1.1	51:49	82
4	2.2	55:45	84

Due to the lack of selectivity in the previous example, we believed that one potential solution to this would be a one pot epoxidation/nucleophilic ring opening reaction. Since there were no reports on this type of reaction on 1,3-dioxepine systems, we began our attempts using the previously reported methods involving dihydropyran compounds.[52-56] The reported procedures involve treatment of a 1,2-glycal **3-144** with DMDO to form the unstable epoxide **3-145** followed by subsequent addition of a

nucleophile affords the desired pyranols **3-146** in a wide range of selectivities (Scheme 58).

Scheme 58.

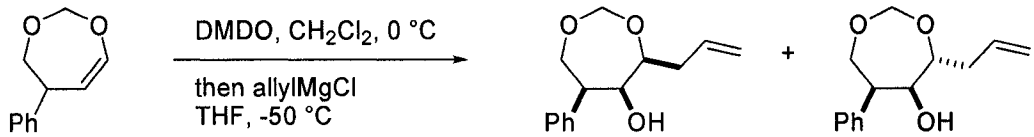


3-144 | **3-145** ***unstable epoxide*** | **3-146** (66:34) - (>95:5)

Typically, the substituents on the tetrahydropyran ring **3-144** bias the resultant diastereoselectivity.

Treatment of the 1,3-dioxepine **3-67** with a freshly prepared solution DMDO[57] at 0 °C followed by concentration *in vacuo*, dilution with THF, and subsequent addition of allylMgCl afforded the desired allylation products **3-142** and **3-143** as a 1:1 mixture of diastereomers (Scheme 59).

Scheme 59.

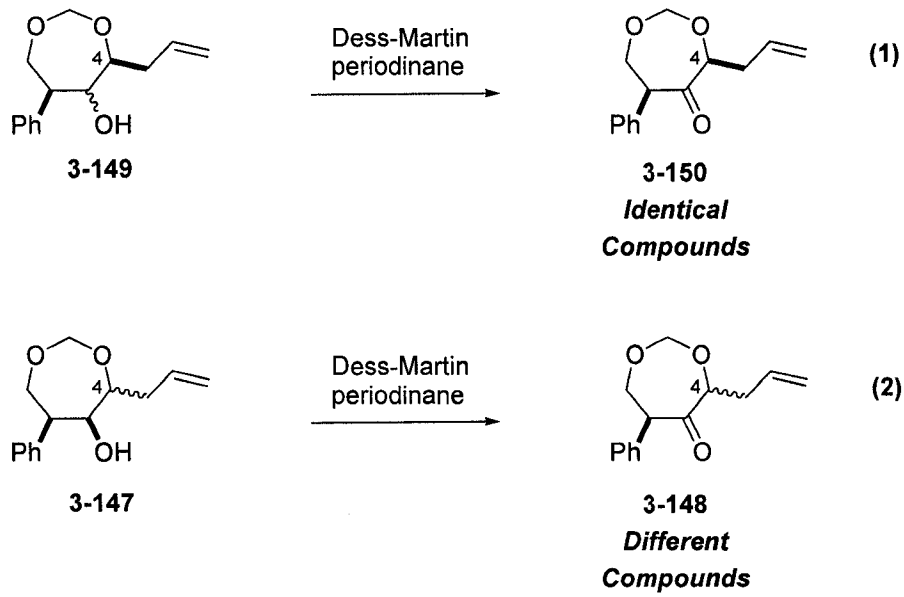


3-67 | **3-142** ***cis:cis*** | **52:48** | **3-143** ***cis:trans***

In order to determine if the isomers were epimeric at the *C*-4 or *C*-5 positions, we subjected the products **3-142** and **3-143** to a Dess-Martin oxidation. Upon oxidation, if the isomers are epimeric at the *C*-4 position **3-147**, the two obtained products **3-148** should be different (Eq.1, Scheme 60). However, if the epimers are about the *C*-5

position **3-149**, then the two oxidation products **3-150** should appear identical (Eq. 2, Scheme 60).

Scheme 60.

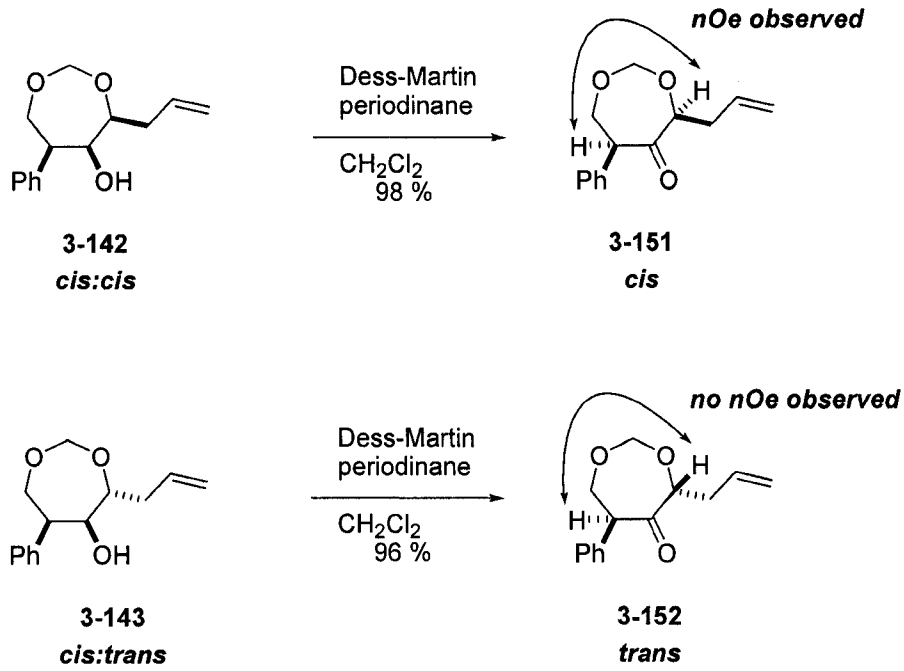


3-149 **3-150** ***Identical Compounds***

3-147 **3-148** ***Different Compounds***

Following treatment of our allylation products **3-142** and **3-143** with DMP, two distinct compounds **3-151** and **3-152** were obtained (Scheme 61). Therefore, the two allylation diastereomers **3-142** and **3-143** must be epimeric at the *C*-4 position. The *C*-5 and *C*-6 stereogenic relationship was determined to by nOe correlations and was found be *cis*.

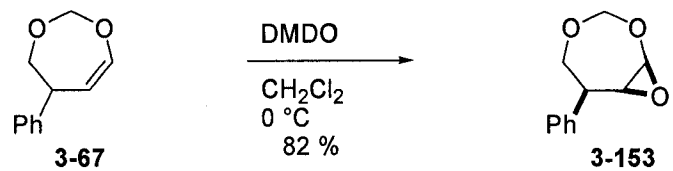
Scheme 61.



A small solvent screen (MeCN, toluene, hexanes, Et_2O) was conducted and no increase in diastereoselectivity was observed. Unfortunately, the implementation of the one pot reaction sequence exhibited no gain in diastereoselectivity, when compared to the two step sequence.

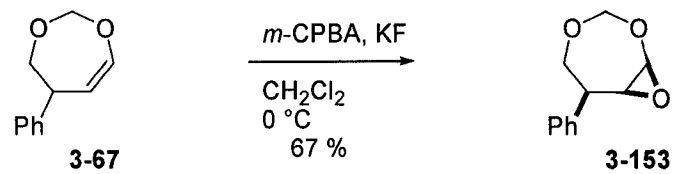
Interestingly, we found that the epoxides **3-153** generated from 1,3-dioxepines **3-67** are relatively stable (Scheme 62). Unlike their pyran counterparts **3-145**, which are not stable to any Lewis basic or acidic functionality, these dioxepine epoxides **3-153** are stable to aqueous workup and column chromatography on silica gel.

Scheme 62.



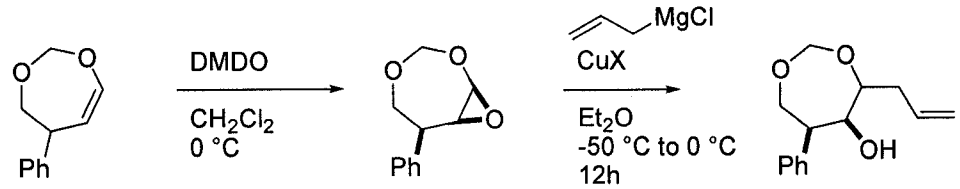
Furthermore when the epoxidation is preformed under the conditions shown in Scheme 56, the epoxide **3-153** is subsequently opened by the residue *m*-chlorobenzoic acid and the hydroxyl-ester **3-138** is formed. However, Camp's conditions[58,59] can be used to form only the epoxide **3-153** (Scheme 63). Camp's conditions involve pre-mixing the *m*-CPBA and KF together before addition of the olefin **3-67**. Since the fluoride ion has a strong affinity towards compounds with acidic hydrogens,[60-64] the insoluble *m*-CPBA-KF and *m*-chlorobenzoic acid/KF complexes can easily be removed upon filtration. As a result of the residual acid not being in solution, no further reaction with the epoxide **3-153** takes place.

Scheme 63.



Since the addition of Grignard reagents to the epoxide **3-153** did not yield any synthetically useful diastereoselectivities and since we know that the epoxide **3-153** is more stable than initially thought, we decided to subjected the epoxides **3-153** to organo-cuprate compounds. It is well established that organo-cuprates can be employed in the opening of epoxides.[65-67] After a quick screen of conditions (Scheme 64), we discovered that the reaction proceeded in the highest yields using 0.2 equivalents of CuI, 1.4 equivalents of Grignard reagent and with the addition of THF as co-solvent and $ZnCl_2$ as a catalyst (Entry 4, Scheme 64). Unfortunately, the use of organo-cuprates did not have any effect on the diastereoselectivity when the nucleophile was an allyl group.

Scheme 64.

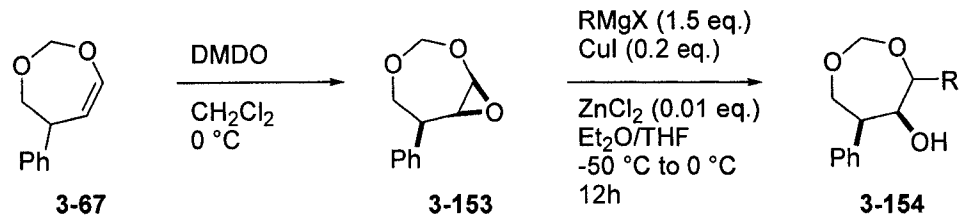


3-67 **3-153** **3-142 & 3-143**

Entry	CuX	Grignard Eq.	Additive	Ratio	Yield (%)
1	CuI (0.2 eq.)	4.0	---	52:48	35
2	CuI (0.2 eq.)	2.7	---	50:50	44
3	CuI (0.2 eq.)	1.5	$ZnCl_2$	50:50	50
4	CuI (0.2 eq.)	1.5	$ZnCl_2$/THF	52:48	82
5	CuCN (6 eq.)	12	THF	51:49	49
6	CuBr-SMe_2 (0.1 eq.)	1.5	THF	50:50	27

In order to ensure that the poor observed diastereoselectivity was not a function of the Grignard chosen, we repeated the reaction under the optimized conditions using a variety of other Grignard reagents (Scheme 65). Unfortunately, the Grignard reagent was not the origin of the poor diastereoselectivity and as a result, all of the new Grignard reagents yielded products in a 1:1 ratio.

Scheme 65.



3-67 **3-153** **3-154**

Entry	R	Ratio	Yield (%)
1	vinyl	52:48	77
2	Ph	50:50	72
3	Bn	50:50	79

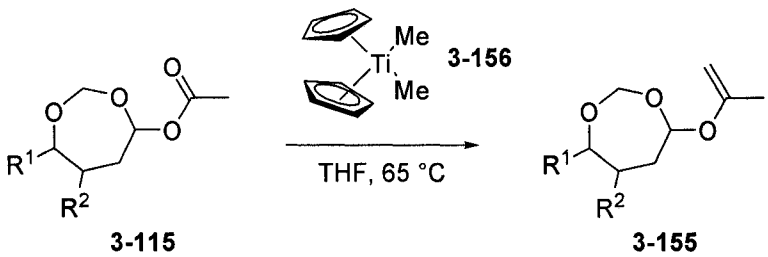
In conclusion, the observed ratios obtained under almost all of the cationic coupling conditions screened resulted in similar diastereoselectivities to those reported for oxepane rings.[47] However, there was an enhancement of diastereoselectivity in the cationic coupling reaction of the 4-acetoxy-1,3-dioxepine with enol silane nucleophiles. Eventhough, the ratios were modest (75:25 to 80:20), they were still higher than the previously reported ratio (52:48).[47] The lack of rigidity and the inability of 7-membered rings to adopt a stable chair-like conformation, like 6-membered rings, can be accredited for the lack of stereoselectivity in the bond forming event.

3.5.6. [1,3]-Oxygen to Carbon Rearrangement of Substituted 1,3-Dioxepanes

Due to our previous work involving the [1,3]-oxygen to carbon rearrangement of vinyl ethers derived from 1,3-dioxanes,[68] we wanted see if this methodology could be applied to the vinyl ethers derived from 1,3-dioxepanes. As a

result, the substituted 4-acetoxy-1,3-dioxepanes **3-115** were olefinated with the Petasis reagent **3-156** (Scheme 66).[69]

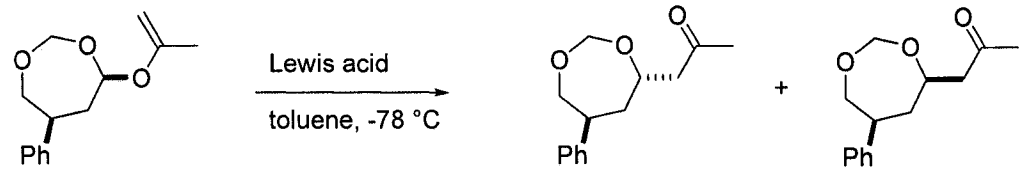
Scheme 66.



Entry	R^1	R^2	Yield (%)
1	H	Ph (*cis*)	52
2	H	Ph (*trans*)	48
3	CH_2CH_2Ph (*cis*)	H	47

Treatment of the *cis*-1,3-dioxepane under the stereoretentive rearrangement conditions afforded complete decomposition products (Entry 1, Scheme 67), however treatment with BF_3•OEt_2 afforded the rearranged product in a 67:33 (*trans:cis*) ratio of diastereomers (Entry 2, Scheme 67).

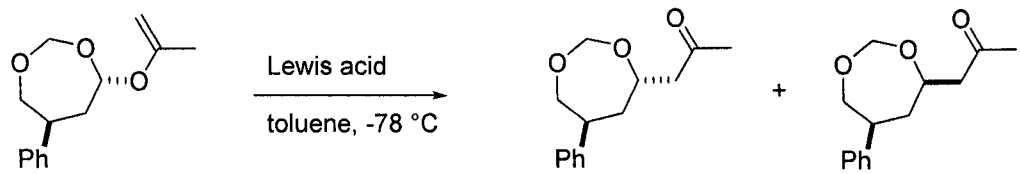
Scheme 67.



Entry	Lewis acid	*trans:cis*	Yield (%)
1	Me_3Al/BF_3•OEt_2	---	decomposition
2	BF_3•OEt_2	67:33	79

Similar results were obtained for the *trans*-1,3-dioxepane **3-157**, in which the $Me_3Al/BF_3{\bullet}OEt_2$ conditions afforded decomposition products while $BF_3{\bullet}OEt_2$ alone yielded a 70:30 (*trans:cis*) ratio of diastereomers (Entries 1 and 2, respectively, Scheme 68).

Scheme 68.

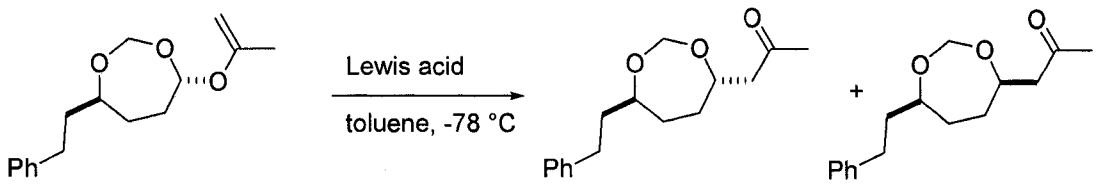


3-157 ***trans*** **3-107** ***trans*** **3-108** ***cis***

Entry	Lewis acid	*trans:cis*	Yield (%)
1	$Me_3Al/BF_3{\bullet}OEt_2$	---	decomposition
2	$BF_3{\bullet}OEt_2$	70:30	83

When the *cis*-7-substituted vinyl ether **3-158** was employed, the stereoretentive conditions yielded a 55:45 (*trans:cis*) mixture of diastereomers in a 39 % yield (Entry 1, Scheme 69). While treatment of **3-158** with $BF_3{\bullet}OEt_2$ afforded a 74:26 (*trans:cis*) ratio of isomers in 83 % yield (Entry 2, Scheme 69).

Scheme 69.



3-158 ***cis*** **3-120** ***trans*** **3-121** ***cis***

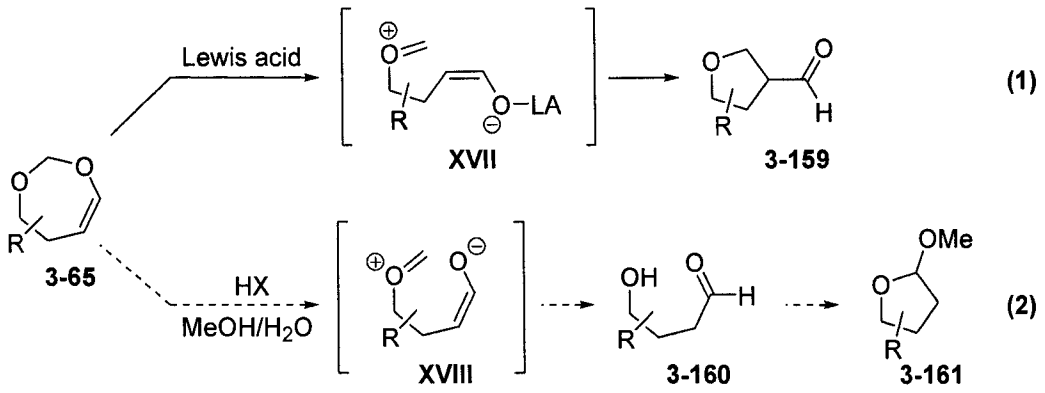
Entry	Lewis acid	*trans:cis*	Yield (%)
1	$Me_3Al/BF_3{\bullet}OEt_2$	55:45	39
2	$BF_3{\bullet}OEt_2$	75:25	83

Unfortunately as seen earlier, 1,3-dioxepanes are incapable of discriminating facial attack and as a result, the [1,3]-oxygen to carbon rearrangements of these vinyl ethers afford ratios which are very similar to those obtained under all the previously explored avenues.

3.5.7. Formation of Substituted Tetrahydrofurans from 1,3-Dioxepines

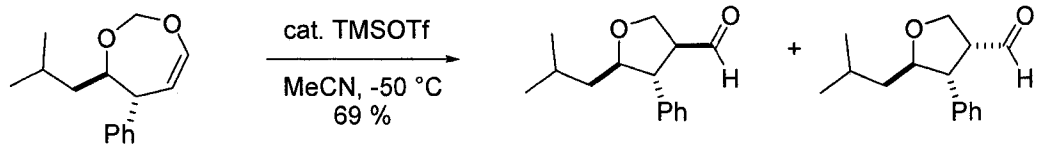
As mentioned earlier, 1,3-dioxepines are useful building blocks for the construction of substituted tetrahydrofurans.[31-34] The treatment of 1,3-dioxepines **3-65** with a Lewis acid results in poly-substituted tetrahydrofurans **3-159** containing an aldehyde functionality (Eq. 1, Scheme 70), however we wanted to explore what would happen if the 1,3-dioxepines **3-65** were treated under acetal hydrolysis conditions (Eq. 2, Scheme 70).

Scheme 70.



To our satifaction, treatment of **3-84** under methods previously developed in our laboratories,[33] furnished the substituted tetrahydrofurans **3-162** and **3-163** as a 74:26 mixture of diastereomers in 69 % yield (Scheme 71). This reaction shows how the *C*-2 stereocenter impacts the rearrangement more than any other stereocenter in the system, as evidence by the erosion of the diastereoselectivity when compared to the previous group results.[33]

Scheme 71.

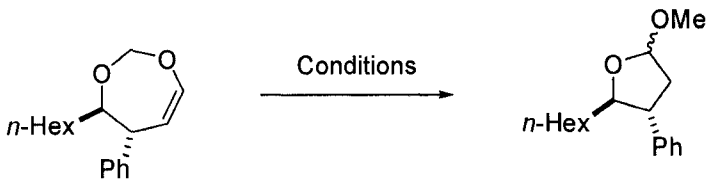


3-84 ***trans***

3-162 ***trans:trans*** **74:26** **3-163** ***trans:cis***

Our initial efforts at the acidic hydrolysis of the dioxepine rings began with two separate procedures. To our delight, treatment of **3-91** under either harsh or mild acidic conditions furnished the desired substituted tetrahydrofuran **3-164** in good yields as a 1:1 mixture of anomeric isomers (Entries 1 and 2, respectively, Scheme 72).

Scheme 72.

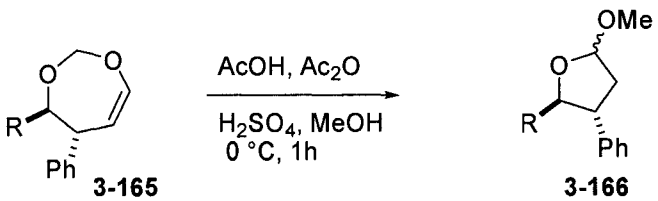


3-91 3-164

Entry	Conditions	Ratio	Yield (%)
1	AcOH, Ac_2O, H_2SO_4, MeOH, 0 °C, 1h	50:50	73
2	cat. *p*-TsOH, MeOH, H_2O, 50 °C, 12h	50:50	56

The catalytic *p*-TsOH reaction conditions furnished the product along with recovered starting material only at elevated temperatures for an extended amount of time, while the AcOH conditions yielded only product in a fraction of the time. As a result, the AcOH method was used to further extend the scope. Two other substrates **3-88** and **3-96** were tested under these conditions and each furnished the desired substituted tetrahydrofurans **3-166** as a 1:1 mixture of anomeric isomers in good yields (Scheme 73).

Scheme 73.



3-165 3-166

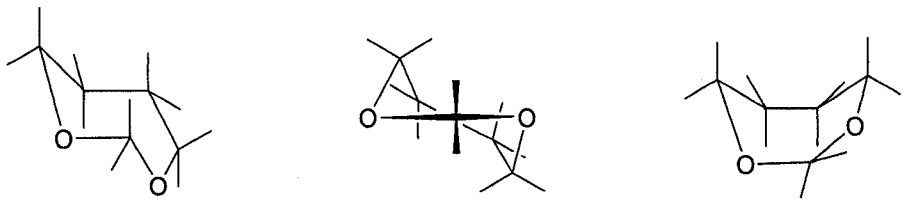
Entry	R	Ratio	Yield (%)
1	*cy*-Hexyl (**3-167**)	50:50	79
2	CH_2CH_2Ph (**3-168**)	50:50	82

In conclusion, we have demonstrated that 1,3-dioxepines are successful precursors to substituted tetrahydrofurans and anomeric acetals. Depending on the method chosen, two distinctly different substituted tetrahydrofuran products can be obtained.

3.6. Conclusion

In conclusion, the obtained diastereoselectivities were not in accordance with what we initially expected. As a result, a plausible explanation for the "lack" of stereocontrol needs to be explored. Even though there is not much precedent with 1,3-dioxepanes, there are still a number of publications involving theoretical calculations.[70-74] Grindley *et. al.* have theoretically shown that symmetric 1,3-dioxepanes have 3 possible conformations, the chair **XIX**, twist chair **XX**, and boat **XXI**, of which the twist chair **XX** is preferred (Figure 5).[72,73]

Figure 5.

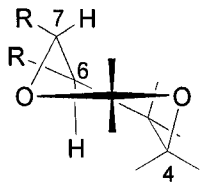


XIX ***Chair*** **XX** ***Twist-Chair*** **XXI** ***Boat***

They conclude that the shorter *C-O* bond distances in the 1,3-dioxepane ring should make the large transannular *H-H* repulsive interactions, that are present in cycloheptanes, more severe in 1,3-dioxepanes.[72,73] As a result, the 1,3-dioxepanes

prefer the twist chair conformation **XX** over the chair **XIX**, unlike its cycloheptane analogue.[72,73] If we apply these theoretical calculations to our present system, a *C*-7 subsituent could potentially impact the stereoselectivity in the cationic coupling better than a *C*-6 substituent, which is slightly farther away from of the reactive *C*-4 carbon (Figure 6).

Figure 6.

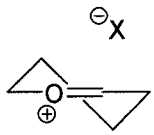


XX

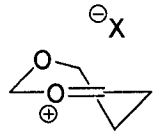
Twist-Chair

This justification may be valid, however it still contains one fundamental flaw. The reactive *C*-4 position is not sp^3 hybridized, but since it is an oxocarbenium ion, it is more sp^2 hybridized. As a result, another analogy must be used in order to accurately warrant the observed diastereoselectivity. Oxocarbenium ions found in 6-membered rings are known to react *via* a half-chair intermediate **XXII**,[75] therefore if we relate this into our 1,3-dioxepane system we obtain a conformer **XXIII** similar to that shown in Figure 7.

Figure 7.



XXII
6-Membered Oxocarbenium Ion Half-Chair Conformer

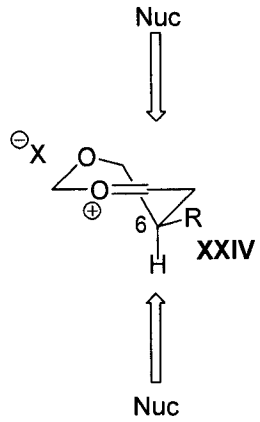


XXIII
1,3-Dioxepane Oxocarbenium Ion Half-Chair Conformer

If we install the desired *C*-6 and *C*-7 substituents in the preferred pseudo-equatorial positions and analyze the possible facial discrimination of the incoming nucleophile (Figure 8), we can conclude that neither substituent is in proximity to significantly impact the facial selectivity **XXIV** and **XXV**. As a result, the diastereoselectivity of the cationic coupling reactions typically led to a 1:1 ratio of isomers when organometallic nucleophiles (allylTMS, Grignard reagents, and organocuprates) were implemented.

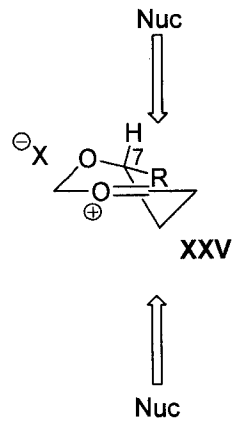
Figure 8.

C-6 Substituted 1,3-Dioxepane



XXIV

C-7 Substituted 1,3-Dioxepane

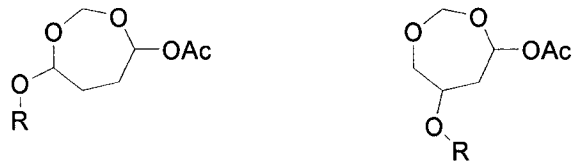


XXV

Since the cationic coupling reactions involving enol silanes show somewhat enhanced levels of diastereoselectivity (from 1:1 to 3-4:1), the models in Figure 8 are not fully representative of all of the effects which govern this transformation. Insight into this

phenomenon may come from the implementation of substrates similar to those used by Woerpel (Chapter 1), in which the substrates contain heteroatoms in the various locations (Figure 9). If the ratios obtained from heteroatom incorporation are different from those with carbon substituents, then there must be some sort under appreciated stereoelectronic effect present in the system which could potentially be harnessed to access the products in high diastereoselectivities.

Figure 9.



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Chapter 2 Experimental

Surveying Approaches to the Formation of Carbon-Carbon Bonds Between a Pyran and an Adjacent Ring

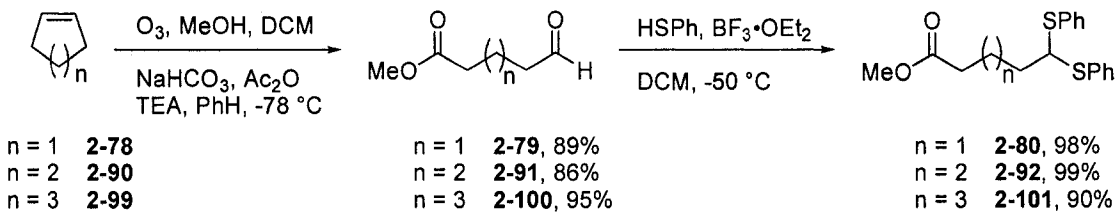
General Methods. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel (230-400 mesh). Thin layer chromatography was performed on EM Science silica gel 60 (230-400 mesh). Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, I_2, vanillin, or anisaldehyde dips followed by heating.

All chemicals were purchased from Aldrich, Alfa Aesar, Strem, or Fluka and used as received.

Infared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data recorded as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS)] or deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer at 75 MHz or 100 MHz at ambient temperature. Chemical shifts are

reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Gas chromatography was performed on a Varian CP 3800 gas chromatograph equipped with a flame ionization detector using a Chrompack CP-Sil8CB (15 M x 0.25 mm) capillary column.

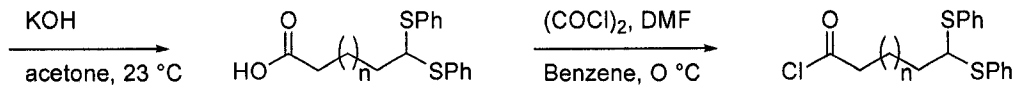
Synthesis of Starting Materials:



n = 1 **2-78**
n = 2 **2-90**
n = 3 **2-99**

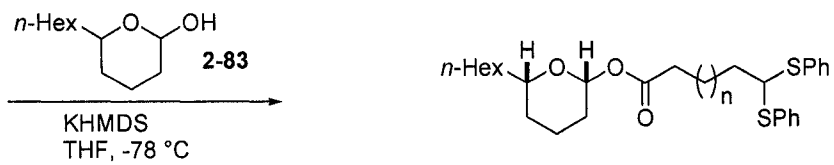
n = 1 **2-79**, 89%
n = 2 **2-91**, 86%
n = 3 **2-100**, 95%

n = 1 **2-80**, 98%
n = 2 **2-92**, 99%
n = 3 **2-101**, 90%

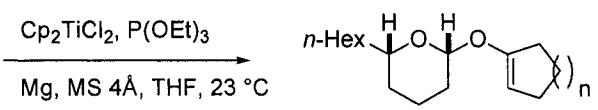


n = 1 **2-81**, 82%
n = 2 **2-93**, 93%
n = 3 **2-102**, 92%

n = 1 **2-82**
n = 2 **2-94**
n = 3 **2-103**



n = 1 **2-84**, 76%
n = 2 **2-95**, 79%
n = 3 **2-104**, 80%



n = 1 **2-77**, 32%
n = 2 **2-89**, 30%
n = 3 **2-98**, 32%

General Procedure for the Synthesis of Cyclic Vinyl Acetals.

A 500 mL, three necked, round bottomed flask with a glass tube to admit ozone, a calcium chloride drying tube, and a glass stopper is charged with 5.109 g (75.0 mmol) of cyclopentene **2-78**, 250 mL of CH_2Cl_2, 50 mL of MeOH, and 2.0 g of anhydrous $NaHCO_3$. After the apparatus is cooled to ca. -78 °C, ozone is bubbled

through the solution as it is stirred. Ozone addition is stopped when the solution turns blue. Argon is passed through until the blue color is discharged and then the cold bath is removed. The solution is filtered into a 1-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation. After dilution with 225 mL of CH_2Cl_2 the flask is cooled to 0 °C and 16 mL (113 mmol) of TEA and 21.24 mL (225 mmol) of Ac_2O are added via syringe, and the solution is stirred under an argon atmosphere at 0 °C for 15 min. The ice bath is removed and stirring is continued for 4 h. The solution is washed with 150 mL portions of aq. 0.1 N HCl, 10% aq. NaOH, and H_2O. The organic layer is dried over $MgSO_4$, filtered, and concentrated to provide 9.85 g (89%) of aldehyde-methyl ester **2-79** as colorless oil.

A 250 mL round bottomed flask was charged with 1.68 g (12.9 mmol) of **2-79** and 40 mL of CH_2Cl_2 then cooled to -50 °C. Next, 2.91 g (26.45 mmol) of PhSH and 4.58 g (32.25 mmol) of BF_3•OEt_2 were added successively. The mixture was stirred at -50 °C for 30 min., then poured into a little ice-water and extracted with CH_2Cl_2. The organic layer was washed successively with 30 mL portions of 7% aq. KOH, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield 4.22 g (98%) of thioacetal-methyl ester **2-80** as a yellow oil.

A 50 mL round bottomed flask was charged with thioacetal-methyl ester **2-80** (4.22 g, 12.69 mmol), 3.56 g (63.46 mmol) of KOH, and 40 mL of acetone. The mixture was stirred overnight and then acidified with conc. HCl to pH 4. The reaction mixture was extracted with EtOAc (3 x 50 mL) and washed with 100 mL H_2O. The combined

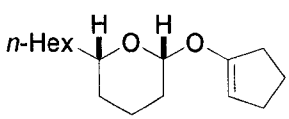
organic layers were dried over $MgSO_4$, filtered and concentrated to yield a black oil. The crude product was purified by standard acid/base workup to yield 3.6 g (89%) of thioacetal-acid **2-81**.

A 25 mL round bottomed flask was charged with 1.0 g (3.14 mmol) of thioacetal-acid **2-81**, 5 drops of dry DMF, and 10.0 mL of benzene, then cooled to 0 °C and 1.24 g (9.73 mmol) of $(COCl)_2$ was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Excess reagents and solvent were removed by rotary evaporation and the residue was twice treated with 10 mL of benzene and concentrated by rotary evaporation. The reaction yielded 1.04 g (98%) of thioacetal-acyl chloride **2-82** as a yellow oil.

To a stirred solution of lactol **2-83** (0.547 g, 2.94 mmol) in 10 mL THF at -78 °C was added a solution of KHMDS in toluene (0.5 M, 5.94 mL, 2.97 mmol) dropwise, and the reaction mixture was warmed to 0 °C over 5 min. before cooling to -78 °C. A solution of thioacetal-acyl chloride **2-82** (1.04 g, 3.09 mmol) in 5 mL THF was added dropwise, and the reaction mixture was stirred for 2 h at -78 °C before quenching with sat. aq. NH_4Cl (20 mL). Next, distilled water (20 mL) was added and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Purification by flash column chromatography, eluting with 15% EtOAc in hexanes with 1% TEA, provided 1.10 g (76 %) of ester **2-84** as a yellow oil in >95:5 *cis:trans* diastereoselectivity.

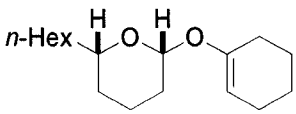
Finely powdered 4 Å MS (400 mg), Mg turnings (120 mg, 4.94 mmol), and Cp_2TiCl_2 (1.03 g, 4.12 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2-3 mmHg). During this procedure care was taken not to sublime Cp_2TiCl_2. After cooling, THF (5 mL) and $P(OEt)_3$ (1.37 g, 8.24 mmol) were added successively with stirring at room temperature under argon. Within 15 min., the reaction mixture turned dark green and then dark brown with slight evolution of heat. After 3 h, the ester **2-84** (0.5 g, 1.03 mmol) in 10 mL THF was added to the reaction mixture dropwise over 20 min. After stirring for 3h, the reaction was quenched by addition of aq. 1 M NaOH (20 mL) and then the insoluble materials were filtered off through Celite and washed with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with aq. 1 M NaOH, stirred with deactivated charcoal, and dried over $MgSO_4$. The slurry was then filtered and concentrated. The residue was purified by flash column chromatography, eluting with 25 % EtOAc in hexanes containing 1% TEA, to afford 138 mg (32 %) of cyclic vinyl acetal **2-77** as a colorless oil.

Characterization of Cyclic Vinyl Acetals (3a-c).

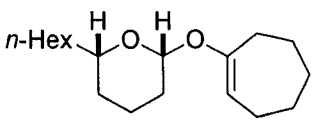


(2R, 6S*)-2-(Cyclopent-1-enyloxy)-6-hexyl-tetrahydro-pyran* (**2-77**). Following the general procedure afforded **2-77** as a yellow oil in 17.4 % overall yield: $R_f = 0.309$ (25 % EtOAc/Hex. with 1 % TEA); ^1H NMR (400 MHz, $CDCl_3$) δ4.66 (1H, d, $J = 9.4$), 3.89 (1H, m), 3.37 (1H, m), 1.06-1.88

(22H, m), 0.84 (3H, t, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.6, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) Calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2176.

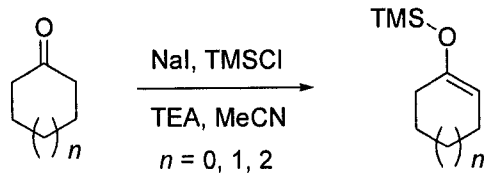


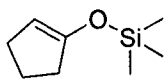
(2R, 6S*)-2-(Cyclohex-1-enyloxy)-6-hexyl-tetrahydro-pyran* (**2-89**). Following the general procedure afforded **2-89** as a yellow oil in 18.8 % overall yield: R_f = 0.283 (25 % EtOAc/Hex. with 1 % TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, d, J = 9.2), 3.89 (1H, m), 3.37 (1H, m), 1.05-1.89 (24H, m), 0.84 (3H, t, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.7, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) Calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2329.



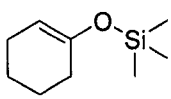
(2R, 6S*)-2-(Cyclohept-1-enyloxy)-6-hexyl-tetrahydro-pyran* (**2-98**). Following the general procedure afforded **2-98** as a yellow oil in 20.1 % overall yield: R_f = 0.278 (25 % EtOAc/Hex. with 1 % TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, m), 3.88 (1H, m), 3.37 (1H, m), 1.05-1.89 (26H, m), 0.84 (3H, t, J = 6.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.4, 30.6, 30.0, 29.6, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2931, 2858 cm^{-1}; HRMS (FAB+) Calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2489.

Synthesis of Enol Silanes:



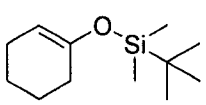


(Cyclopent-1-enyloxy)-trimethyl-silane (**2-113**): To a round bottom flask was added 2.21 mL (25.0 mmol) of cyclopentanone, 4.684 g (31.25 mmol) of NaI, 4.36 mL (31.25 mmol) of TEA, and 40 mL of MeCN. To this solution was added dropwise 3.97 mL (31.25 mmol) of TMSCl. The reaction was left to stir at room temperature for 12h, then quenched with 50.0 mL of cold pentane and 50.0 mL of cold H_2O. The layers were separated and the aqueous layer was extracted (3 x 50 mL) with cold pentane. The organic layers were combined then washed (2x 50 mL) with H_2O. The organic layer was then dried over $NaSO_4$, filtered and concentrated to yield 3.32 g (85 %) of the known enol silane, which matched all spectral data.[1]

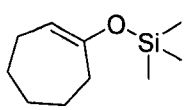


(Cyclohex-1-enyloxy)-trimethyl-silane (**2-114**): To a round bottom flask was added 2.60 mL (25.0 mmol) of cyclohexanone, 4.684 g (31.25 mmol) of NaI, 4.36 mL (31.25 mmol) of TEA, and 40 mL of MeCN. To this solution was added dropwise 3.97 mL (31.25 mmol) of TMSCl. The reaction was left to stir at room temperature for 12h, then quenched with 50.0 mL of cold pentane and then 50.0 mL of cold H_2O. The layers were separated and the aqueous layer was extracted (3x 50 mL)

with cold pentane. The organic layers were combined then washed (2x 50 mL) with H_2O. The organic layer was then dried over $NaSO_4$, filtered and concentrated to yield 4.19 g (98 %) of the known enol silane, which matched all spectral data.[1]



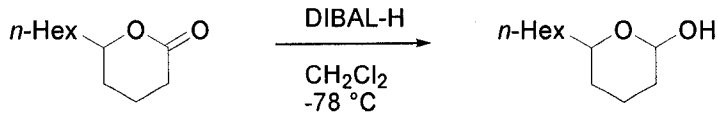
tert-Butyl-(cyclohex-1-enyloxy)-dimethyl-silane (**2-123**): To a round bottom flask was added 2.0 mL (19.3 mmol) of cyclohexanone, 3.63 g (24.13 mmol) of NaI, 3.4 mL (24.13 mmol) of TEA, and 22 mL of MeCN. To this solution was added dropwise a solution of 3.64 g (24.13 mmol) of TBDMSCl in 15.0 mL of MeCN. The reaction was left to stir at room temperature for 12h, then quenched with 50.0 mL of cold pentane and then 50.0 mL of cold H_2O. The layers were separated and the aqueous layer was extracted (3x 50 mL) with cold pentane. The organic layers were combined then washed (2x 50 mL) with H_2O. The organic layer was then dried over $NaSO_4$, filtered and concentrated to yield 3.65 g (89 %) of the known enol silane, which matched all spectral data.[2]



(Cyclohept-1-enyloxy)-trimethyl-silane (**2-115**): To a round bottom flask was added 2.95 mL (25.0 mmol) of cycloheptanone, 4.684 g (31.25 mmol) of NaI, 4.36 mL (31.25 mmol) of TEA, and 40 mL of MeCN. To this solution was added dropwise 3.97 mL (31.25 mmol) of TMSCl. The reaction was left to stir at room temperature for 12h, then quenched with 50.0 mL of cold pentane and then 50.0 mL of cold H_2O. The layers were separated and the aqueous layer was extracted (3x

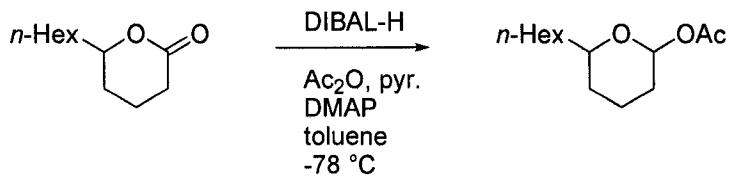
50 mL) with cold pentane. The organic layers were combined then washed (2x 50 mL) with H_2O. The organic layer was then dried over $NaSO_4$, filtered and concentrated to yield 3.73 g (81 %) of the known enol silane, which matched all spectral data.[1]

Synthesis of Lactol:



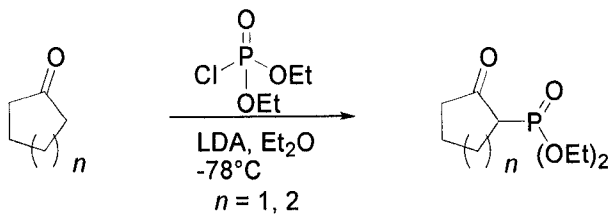
6-Hexyl-tetrahydro-pyran-2-ol **(2-83):** To a round bottom flask was added 10.0 mL (56.00 mmol) of undecanoic δ-lactone and 50.0 mL of CH_2Cl_2. The solution was cooled to -78 °C and 62.0 mL of DIBAL-H (1.0M in heptane) was added dropwise in a manner to not raise the internal temperature above -60 °C. After the addition was complete, the reaction was left to stir at -78 °C for 4h. The reaction was then carefully quenched at -78 °C by the dropwise addition of MeOH (careful extremely exothermic!!). After quenching, the reaction was warmed to room temperature then diluted with 100 mL of aqueous solution of Rochelle's salt and 50 mL of CH_2Cl_2 and left to stir for 4h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined and washed with brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 9.82 g (94 %) of the desired known lactol, which matched all spectral data.[3]

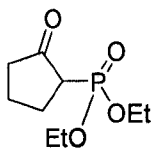
Synthesis of Anomeric Acetate:



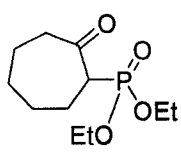
Acetic acid 6-hexyl-tetrahydro-pyran-2-yl ester **(2-112):** To a round bottom flask was added 2.85 mL (15.0 mmol) of undecanoic δ-lactone and 100.0 mL of toluene. The solution was cooled to -78 °C and 4.05 mL (22.75 mmol) of DIBAL-H was added dropwise in a manner to not raise the internal temperature above -60 °C. After the addition was complete, the reaction was left to stir at -78 °C for 4h. Next, 3.64 mL (45.0 mmol) of pyridine and 5.66 mL (60.0 mmol) of acetic anhydride followed by a solution of 2.56 g (21.0 mmol) of DMAP in 50.0 mL of toluene was added. The reaction was left to stir and gradually warm to room temperature overnight. The reaction was then carefully quenched by the dropwise addition of MeOH (careful extremely exothermic!!). After quenching, the reaction was diluted with 100 mL of aqueous solution of Rochelle's salt and 50 mL of CH_2Cl_2 and left to stir for 4h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined and washed with brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 9.82 g (94 %) of the desired known anomeric acetate, which matched all spectral data.[3]

Synthesis of HWE Reagents:





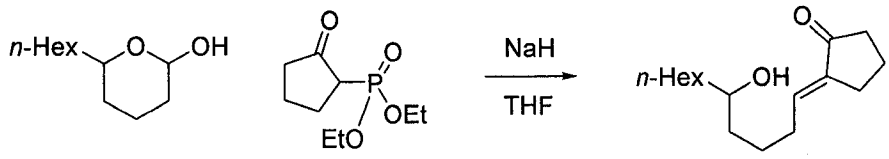
(2-Oxo-cyclopentyl)-phosphonic acid diethyl ester **(E1):** A solution of cyclopentanone (0.21 mg, 2.5 mmol) in ether (0.5 mL) was added dropwise via syringe to a stirred solution of LDA (2.75 mmol, prepared from in situ diisopropylamine (0.38 mL) and *n*-BuLi (1.90 mL, 1.6 M in hexanes)) in diethyl ether (6 mL) at -78 °C. After 40 min., diethyl phosphorochloridite (0.39 mL, 2.75 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to room temperature over 2h. The reaction was quenched by slow addition of acetic acid in ether (1N, 3 mL) and the mixture was filtered through a Florisil pad (60-120 mesh). After concentration in vacou, the resulting crude oil was magnetically stirred in a round bottom flask open to air overnight, and then purified by column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 435 mg (79 %) of the known desired phosphonate, which matched all spectral data.[4]



(2-Oxo-cycloheptenyl)-phosphonic acid diethyl ester **(E2):** A solution of cycloheptanone (0.280 mg, 2.5 mmol) in ether (0.5 mL) was added

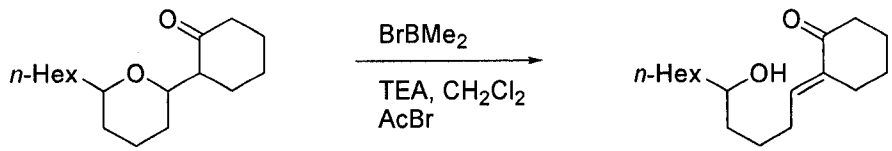
dropwise via syringe to a stirred solution of LDA (2.75 mmol, prepared from in situ diisopropylamine (0.38 mL) and *n*-BuLi (1.90 mL, 1.6 M in hexanes)) in diethyl ether (6 mL) at -78 °C. After 40 min., diethyl phosphorochloridite (0.39 mL, 2.75 mmol) was added dropwise to the resulting enolate, and the reaction mixture was allowed to warm to room temperature over 2h. The reaction was quenched by slow addition of acetic acid in ether (1N, 3 mL) and the mixture was filtered through a Florisil pad (60-120 mesh). After concentration in vacou, the resulting crude oil was magnetically stirred in a round bottom flask open to air overnight, and then purified by column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 348 mg (56 %) of the known desired phosphonate, which matched all spectral data.[4]

Synthesis of Hydroxy Ketones:



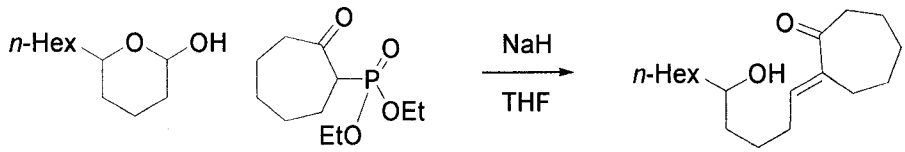
2-(5-Hydroxy-undecylidene)-cyclopentanone (**2-117**). To a solution of 44 mg (1.82 mmol) of NaH (60 % in oil) in 18 mL of THF at 0 °C was added dropwise a solution of 400 mg (1.82 mmol) of HWE reagent **E1** in 5 mL of THF over 10 min.. After the addition was complete, the reaction was warmed to room temperature and a solution of 283 mg (1.52 mmol) of lactol **2-83** in 5 mL of THF was added. The reaction was heated to 50 °C. The reaction was stirred for 8h then cooled to room temperature and quenched

with 20 mL sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (3x 30 mL). The organic layers were combined and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude reaction was purified by silica gel column chromatography (25 % EtOAc/Hexane) to yield 128 mg (33%) of hyrdoxy ketone **2-117** as a yellow oil: $R_f = 0.138$ (25% EtOAc/Hex.); ^1H NMR (400 MHz, $CDCl_3$) δ 6.5 (1H, dddd, $J = 2.8, 2.8, 7.5, 10.2$), 3.55 (1H, m), 2.54 (2H, t, $J = 7.0$), 2.29 (2H, t, $J = 7.7$), 2.13 (2H, q, $J = 7.0$), 1.90 (2H, quint., $J = 7.7$), 1.19-1.67 (15H, m), 0.84 (3H, t, $J = 6.4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 137.7, 136.1, 71.9, 38.8, 37.8, 37.2, 32.0, 29.8, 29.5, 26.9, 25.8, 24.7, 22.8, 20.0, 14.3; IR (NaCl, neat) 3430, 2929, 2857, 1718, 1647 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{28}O_2$, 252.2089. Found 252.2084.



2-(5-Hydroxy-undecylidene)-cyclohexanone (**2-107**). To a solution of 20 mg (0.075 mmol) of ketone **2-97** and 0.0045 mL (0.033 mmol) of TEA in 0.5 mL of CH_2Cl_2 at 0 °C was added dropwise 0.037 mL (0.375 mmol) of $BrBMe_2$. After 30 min., 0.055 mL (0.750 mmol) of AcBr was added and the solution was stirred for 2h at room temperature. Addition of 5 mL of H_2O at 0 °C and extracted with CH_2Cl_2. The organic layer was dried

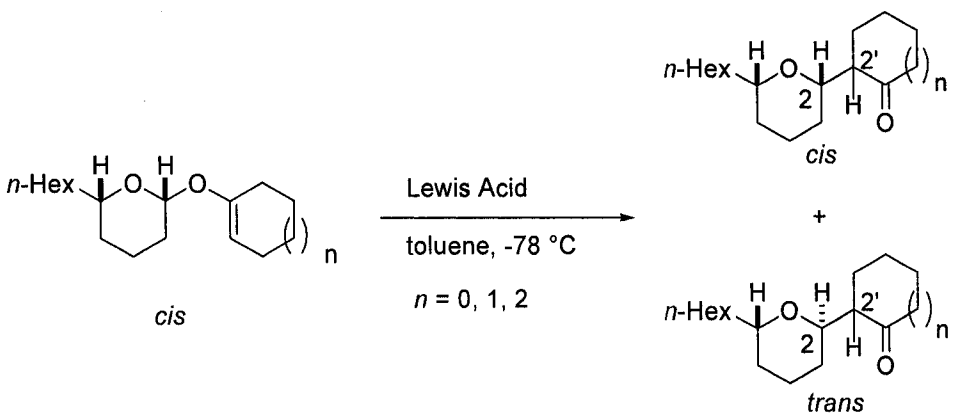
over $MgSO_4$, filtered, and concentrated. Column chromatography (25 % EtOAc/Hexane) afforded the 10.4 mg (52 %) of the hydroxyl ketone **2-107** as a yellow oil: $R_f = 0.142$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, $J = 4.3$), 3.55 (1H, m), 2.39 (2H, m), 2.32 (2H, m), 2.15 (2H, m), 1.94 (2H, m), 1.25-1.65 (15H, m), 0.86 (3H, t, $J = 5.5$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 145.3, 140.0, 72.1, 38.8, 37.7, 37.4, 32.0, 29.7, 29.6, 28.9, 26.2, 25.8, 25.6, 23.4, 22.8, 14.3; IR (NaCl, neat) 3431, 2928, 2856, 1666 cm^{-1}. HRMS (EI+) Calcd for $C_{17}H_{30}O_2$, 266.2246. Found 266.2248.



2-(5-Hydroxy-undecylidene)-cycloheptanone (**2-118**). To a solution of 34 mg (1.4 mmol) of NaH (60 % in oil) in 15 mL of THF at 0 °C was added dropwise a solution of 400 mg (1.61 mmol) of HWE reagent **E2** in 5 mL of THF over 10 min.. After the addition was complete, the reaction was warmed to room temperature and a solution of 250 mg (1.34 mmol) of lactol **2-83** in 5 mL of THF was added. The reaction was heated to 50 °C. The reaction was stirred for 8h then cooled to room temperature and quenched with 20 mL sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (3x 30 mL). The organic layers were combined and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude reaction was

purified by silica gel column chromatography (25 % EtOAc/Hexane) to yield 146 mg (39 %) of hyrdoxy ketone **2-118** as a yellow oil: R_f = 0.150 (25% EtOAc/Hex.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, t, *J* = 7.46), 3.55 (1H, m), 2.56 (2H, m), 2.39 (2H, m), 2.13 (2H, m), 1.20-1.76 (21H, m), 0.85 (3H, t, *J* = 6.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 140.9, 139.0, 71.9, 43.5, 37.7, 37.3, 32.0, 31.6, 30.0, 29.5, 28.1, 27.3, 25.8, 25.4, 25.1, 22.8, 14.3; IR (NaCl, neat) 3433, 2927, 2855, 1686, 1616 cm^{-1}; HRMS (FAB+) Calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2482.

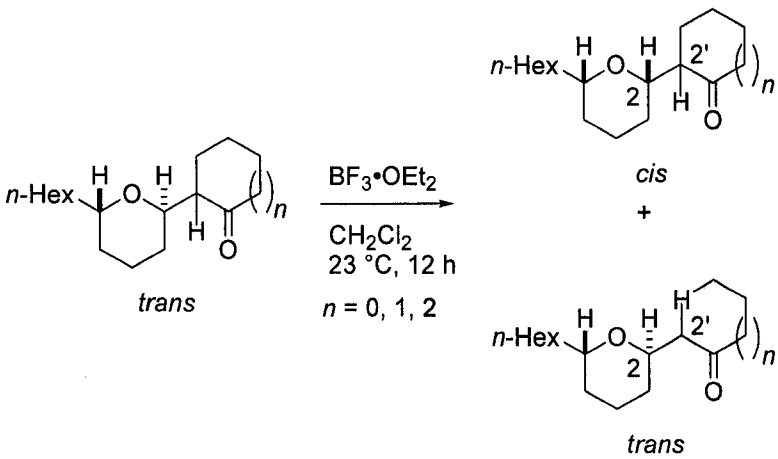
General Procedure A for Rearrangement of Cyclic Vinyl Ethers.



To a flame dried 5 mL round bottomed flask was added 5.0 mg (0.019 mmol) of cyclic vinyl ether **2-89** and 1.0 mL of toluene. The reaction mixture was cooled to -78 °C and BF_3•OEt_2 (2.7 μL, 0.021 mmol) was added dropwise. The reaction was allowed to stir until **2-89** was completely consumed as seen by TLC, then quenched with 2 mL of

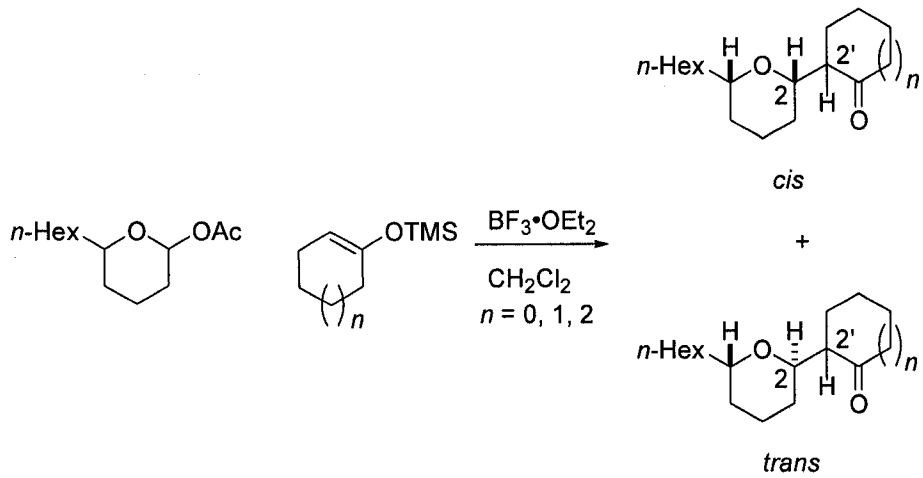
sat. aq. Na_2CO_3 and the layers were then separated. The aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.4 mg (88 %) of a 2:98 (*cis:trans*) mixture of ketones **2-97** and **2-96.**

General Procedure B for the epimerization of trans-ketone to cis-ketone.



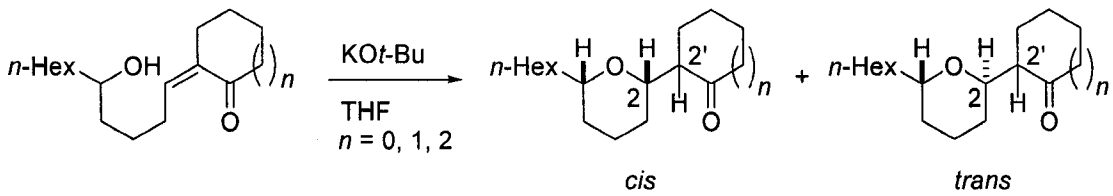
To a flame dried 5 mL round bottomed flask containing 100 mg (0.438 mmol) of ketone **2-96** and 5.0 mL of CH_2Cl_2 was added dropwise at room temperature 124 mg (0.876 mmol) of BF_3•OEt_2. The mixture was stirred for 12 h and quenched with 7.0 mL of sat. aq. Na_2CO_3. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 96 mg (96 %) of a 98:2 (*cis:trans*) mixture of ketones **2-96** and **2-97.**

General Procedure C for the Intermolecular Enolsilane Addition Reaction.



To a flame dried 5 mL round bottomed flask was added 22.8 mg (0.10 mmol) of lactol **2-112**, 25.5 mg (0.15 mmol) of silyl enol ether **2-114**, and 1.0 mL of CH_2Cl_2. The reaction was then cooled to -78 °C and 19 μL (0.15 mmol) of BF_3•OEt_2 was added dropwise. After 1 h at -78 °C, the reaction was quenched by the addition of 1.0 mL sat. aq. Na_2CO_3 and extracted with Et_2O (3 x 10 mL). The organics were combined and washed with H_2O, then sat. aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 21.2 mg (94 %) of 98:2 (*cis:trans*) mixture of ketones **2-97** and **2-96**.

General Procedure D for the Conjugate Addition.



To a flame dried 5 mL round bottomed flask was added 10.0 mg (0.036 mmol) of hydroxy-ketone **2-117** and 0.5 mL of THF. The reaction was cooled to 0 °C and 1.0 mg (0.0072 mmol) of KO*t*Bu was added. After 10 min., the reaction was quenched with 0.5 mL of sat. aq. NH_4Cl and extracted with Et_2O (3 x 10 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated to afford 8.8 mg (88 %) of 96:4 (*cis:trans*) mixture of ketones **2-88** and **2-87**.

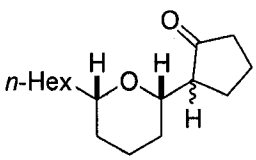
α-Pyranyl-Cycloalkonones.

(2'S,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone* (**2-88**). Following general procedure **A**: 10mg (0.04 mmol) of **77** in 0.25 mL of toluene was treated with 23 μL (0.042 mmol) of Et_2AlCl at -78 °C for 1.5 h. After workup, 8.6 mg (86 %) of **2-88** and **2-87**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **B**: 40 mg (0.1585 mmol) of **2-87** in 4 mL of CH_2Cl_2 was treated with 40 μL (0.317 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 39.2 mg (98 %) of **2-88** and **2-87**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.5 g (2.19 mmol) of **2-112**, 0.685 g (4.38 mmol) of **2-113**, and 5.0 mL of CH_2Cl_2 were treated with 0.555 mL (4.38 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 0.476 g (86 %) of **2-87** and **2-88**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **D**: 10.0 mg (0.040 mmol) of **2-117** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at 0 °C for 4 h. After workup, 8.8 mg (88 %) of **2-88** and **2-87**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.



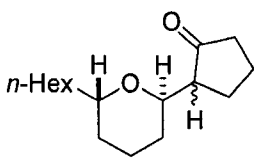
2-88: R_f= 0.429 (15% EtOAc/Hex.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, d, J = 11.3 Hz), 3.56 (1H, ddd, J = 10.9, 3.4, 1.9 Hz), 3.19 (2H, m), 0.95-2.33 (46H, m), 0.84 (3H, t, J = 7.0 Hz), 0.84 (3H, t, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 219.9, 78.5, 78.2, 77.9, 76.8, 53.8, 53.3, 39.6, 39.5, 36.6, 32.0, 31.6, 31.5, 29.9, 29.5, 29.4, 27.7, 26.4, 25.6, 25.5, 24.4,

23.8, 22.8, 21.3, 21.2, 14.3; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) Calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177. The crude product was diluted with toluene for dr determination. GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 30 min run time): t_r (*anti*) = 15.5 min., t_r (*syn*) = 16.9 min.

(2'R,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone* (**2-87**). Following general procedure **A**: 10mg (0.04 mmol) of **2-77** in 0.25 mL of toluene was treated with 5.3 μL (0.042 mmol) of BF_3•OEt_2 at -78 °C for 1.5 h. After workup, 9.0 mg (90 %) of **2-87** and **2-88**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.5 g (2.19 mmol) of **2-112**, 0.685 g (4.38 mmol) of **2-113**, and 5.0 mL of CH_2Cl_2 were treated with 0.555 mL (4.38 mmol) of BF_3•OEt_2 at -78 °C for 1h. Following workup afforded 0.497 g (90 %) of **2-87** and **2-88**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **D**: 10.0 mg (0.040 mmol) of **2-117** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at -78 °C for 5h. After workup, 8.3 mg (83 %) of **2-87** and **2-88**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.



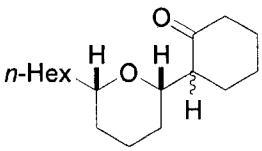
2-87: R_f = 0.365 (15% EtOAc/Hex.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78-3.94 (2H, m), 3.56-3.67 (1H, m), 1.10-2.38 (47H, m), 0.82-0.94 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 219.4, 73.3, 72.4, 69.9, 69.6, 52.8, 51.9, 39.5, 32.7, 32.2, 31.1, 29.7, 29.0, 28.9, 27.7, 26.4, 26.3, 26.0, 25.3, 23.0, 21.2, 21.0, 19.0, 14.5; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) Calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177; GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 30 min run time): t_r (*anti*) = 19.9 min., t_r (*syn*) = 22.6 min.

(2'S,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone* (**2-97**). Following general procedure **A**: 10mg (0.038 mmol) of **2-89** in 0.25 mL of toluene was treated with 22 μL (0.040 mmol) of Et_2AlCl at -78 °C for 1.5 h. After workup, 8.4 mg (84 %) of **2-97** and **2-96**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **B**: 100 mg (0.438 mmol) of **2-96** in 5 mL of CH_2Cl_2 was treated with 111 μL (0.876 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 96.0 mg (96 %) of **2-97** and **2-96**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.040 g (0.1752 mmol) of **2-112**, 0.060 g (0.3504 mmol) of **2-114**, and 5.0 mL of CH_2Cl_2 were treated with 0.044 mL (0.3504 mmol) of $BF_3 \cdot OEt_2$ at ambient temperature for 12h. Following workup afforded 0.0406 g (87 %) of **2-97** and **2-96**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **D**: 10.0 mg (0.038 mmol) of **2-107** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at 0 °C for 4 h. After workup, 8.8 mg (88 %) of **2-97** and **2-96**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

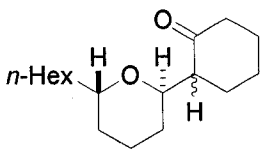


2-97: R_f = 0.429 (15% EtOAc/Hex.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (1H, ddd, *J* = 11.2, 6.2, 1.5 Hz); 3.51 (1H, ddd, *J* = 10.2, 9.0, 1.3 Hz), 3.22 (2H, m), 2.20-2.49 (6H, m), 0.95-2.40 (44H, m), 0.80-0.90 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 212.1, 78.5, 78.3, 76.5, 76.0, 56.7, 56.1, 42.9, 42.0, 36.8, 36.6, 32.1, 31.7, 30.5, 30.0, 29.5, 29.4, 29.2, 28.5, 28.2, 28.0, 25.8, 25.6, 24.4, 24.0, 23.8, 22.8, 14.3; IR (NaCl, neat) 2931, 2858, 1711 cm^{-1}; HRMS (FAB+) Calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331; GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 40 min run time): t_r (*anti*) = 26.9 min., t_r (*syn*) = 30.4 min.

(2'R,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone* (**2-96**). Following general procedure **A**: 10mg (0.038 mmol) of **2-89** in 0.25 mL of toluene was treated with 22 μL (0.040 mmol) BF_3•OEt_2 at -78 °C for 1.5 h. After workup, 8.4 mg (84 %) of **2-97** and **2-96**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.040 g (0.1752 mmol) of **2-112**, 0.060 g (0.3504 mmol) of **2-114**, and 5.0 mL of CH_2Cl_2 were treated with 0.044 mL (0.3504 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 0.0406 g (87 %) of **2-97** and **2-96**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **D**: 10.0 mg (0.038 mmol) of **2-107** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at 0 °C for 4 h. After workup, 8.6 mg (86 %) of **2-97** and **2-96**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.



2-96: R_f = 0.341 (15% EtOAc/Hex.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (1H, ddd, *J* = 10.6, 8.1, 3.3 Hz), 3.92 (1H, ddd, *J* = 9.9, 5.9, 4.0 Hz), 3.69 (1H, m), 3.51 (1H, m), 2.53-2.66 (2H, m), 2.37-2.49 (1H, m), 2.20-2.32 (4H, m), 2.07-2.20 (1H, m), 1.45-2.00 (20H, m), 1.13-1.40 (22H, m), 0.77-0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 212.1, 72.4, 71.8, 69.1, 69.0,

54.2, 53.0, 42.9, 41.5, 33.8, 32.8, 30.4, 30.2, 29.8, 29.7, 29.7, 29.4, 28.9, 27.3, 26.1, 24.4, 23.3, 23.0, 19.0, 18.8, 14.4; IR (NaCl, neat) 2931, 2858, 1710 cm^{-1}; HRMS (FAB+) Calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331; GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 40 min run time): t_r (*anti*) = 34.2 min., t_r (*syn*) = 37.8 min.

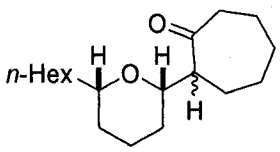
(2'S,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone* (**2-106**). Following general procedure **A**: 10mg (0.036 mmol) of **2-98** in 0.25 mL of toluene was treated with 31 μL (0.056 mmol) of Et_2AlCl and 16 mg (0.061 mmol) of PPh_3 at -78 °C for 1.5 h. After workup, 8.8 mg (88 %) of **2-106** and **2-105**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **B**: 40 mg (0.1426 mmol) of **2-105** in 4 mL of CH_2Cl_2 was treated with 36 μL (0.2852 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 38.8 mg (97 %) of **2-106** and **2-105**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.5 g (2.19 mmol) of **2-112**, 0.807 g (4.38 mmol) of **2-115**, and 5.0 mL of CH_2Cl_2 were treated with 0.555 mL (4.38 mmol) of BF_3•OEt_2 at ambient temperature for 12h. Following workup afforded 0.565 g (92 %) of

2-106 and **2-105**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **D**: 10.0 mg (0.036 mmol) of **2-118** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at 0 °C for 4 h. After workup, 9.0 mg (90 %) of **2-106** and **2-105**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.



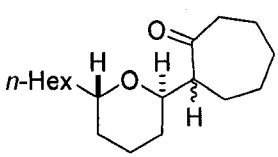
2-106: R_f = 0.455 (15% EtOAc/Hex.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (1H, ddd, *J* = 12.7, 6.1, 1.6 Hz), 3.18 (1H, m), 2.30-2.62 (3H, m), 2.16-2.19 (1H, m), 1.00-1.98 (23H, m), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 215.4, 79.3, 79.0, 78.3, 58.5, 58.4, 44.4, 44.4, 36.7, 36.5, 32.1, 31.9, 31.7, 30.0, 29.7, 29.6, 29.5, 28.8, 28.5, 28.1, 27.4, 26.2, 25.7, 25.6, 25.4, 24.9, 23.9, 22.8, 14.3; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}. HRMS (FAB+) Calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2486; GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 70 min run time): t_r (*anti*) = 45.1 min., t_r (*syn*) = 45.9 min.

(2'R,6'S*)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone* (**2-105**). Following general procedure **A**: 10mg (0.036 mmol) of **2-98** in 0.25 mL of toluene was treated with 4.8 μL (0.038 mmol) of BF_3•OEt_2 at -78 °C for 1.5 h. After workup, 9.2 mg (92 %) of **2-**

106 and **2-105**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

Following general procedure **C**: 0.5 g (2.19 mmol) of **2-112**, 0.807 g (4.38 mmol) of **2-115**, and 5.0 mL of CH_2Cl_2 were treated with 0.555 mL (4.38 mmol) of $BF_3{\bullet}OEt_2$ at -78 °C for 4h. Following workup afforded 0.565 g (92 %) of **2-106** and **2-105**, a yellow oil, as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.

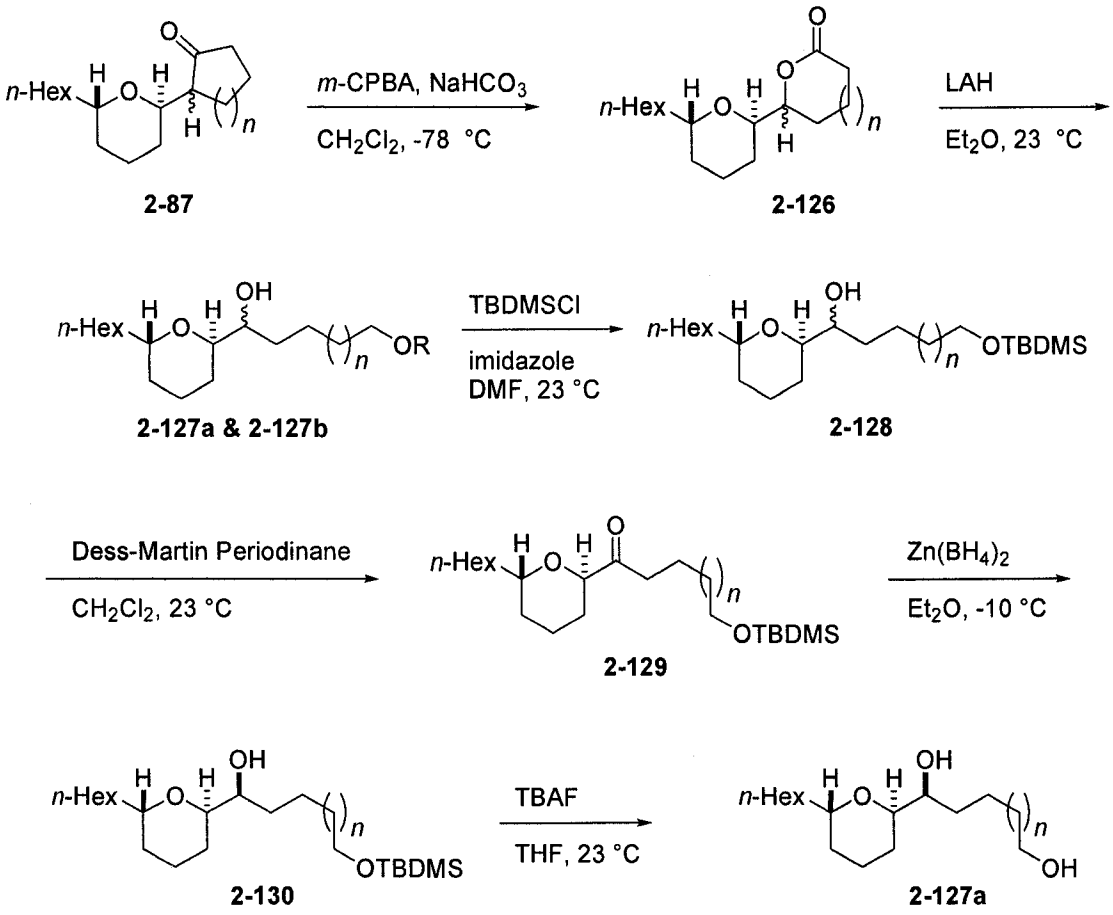
Following general procedure **D**: 10.0 mg (0.036 mmol) of **2-118** in 1.0 mL of THF was treated with 1.0 mg (0.008 mmol) of KO*t*-Bu at 0 °C for 4 h. After workup, 8.5 mg (85 %) of **2-106** and **2-105**, a yellow oil, was isolated as a mixture of diastereomers which were separable on column chromatography using 15% EtOAc/Hexanes as eluent.



2-105: R_f = 0.417 (15% EtOAc/Hex.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, ddd, *J* = 15.0, 6.7, 2.6 Hz), 3.72 (1H, m), 3.61 (1H, m), 2.68-2.81 (2H, m), 2.20-2.65 (7H, m), 2.06-2.18 (1H, m), 1.12-1.98 (44H, m), 0.80-0.92 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 214.5, 72.4, 72.2, 72.0, 71.4, 56.5, 55.5, 44.1, 42.2, 33.1, 32.9, 32.2, 32.2, 30.3, 30.1, 29.9, 29.7, 29.6, 28.8, 27.7, 27.6, 26.9, 26.0, 25.0, 24.7, 23.0, 19.1, 18.8, 14.5; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}; HRMS (FAB+) Calcd for $C_{18}H_{33}O_2$, 281.2481. Found

281.2486; GC analysis (Chrompack CP-Sil8CB, oven temperature = 130 °C, 3.0 mL/min flow rate, and 70 min run time): t_r (*anti*) = 55.6 min., t_r (*syn*) = 59.2 min.

Synthetic Route for Determination of Stereochemistry:



General Procedure for the Determination of C2-C2' Stereochemistry.

A 25 mL round bottomed flask was charged with 370 mg (1.63 mmol) of ketone **2-87**, 3.3 mL of aq. 0.5M $NaHCO_3$ (1.63 mmol), and 6.0 mL of CH_2Cl_2. *m*-CPBA (564 mg, 3.27 mmol, purity 77 % max) was added portionwise at room temperature and

the reaction was allowed to stir overnight. The reaction was quenched by addition of 15 % aq. Na_2SO_3 (5 mL) and stirred at room temperature for 1 h. The layers were separated and the organic layer was washed with 5 mL portions of H_2O, 5 % aq. $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 255 mg (55 %) of lactone **2-126**.

To a 125 mL round bottomed flask charged with 255 mg (0.908 mmol) of lactone **2-126** and 30.0 mL of Et_2O was added portionwise 111 mg (2.937 mmol) of LAH. The reaction was stirred for 12 h, then cooled to 0 °C and added to the reaction flask 0.111 mL of H_2O, 0.111 mL of 15 % aq. NaOH, and 0.333 mL of H_2O (Fieser Workup[5]). The reaction was allowed to stir until the grey solution turned clear. The precipitate was filtered off and the filtered solution was then concentrated to afford a crude oil. The crude oil was purified by flash column chromatography using 90 % EtOAc in hexanes as eluant to yield 146 mg (56 %) of diol **2-127a** and 50.6 mg (19 %) of diol **2-127b**.

A 25 mL round bottomed flask was charged with 40 mg (0.140 mmol) of diol **2-127a** and 2.0 mL of dry DMF. The reaction was cooled to 0 °C and then successively added 11.4 mg (0.168 mmol) of imidazole and 21.9 mg (0.145 mmol) of TBDMSCl. After 15 min., the reaction was diluted with 5.0 mL of Et_2O and 5.0 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 50 mg (89%) of alcohol **2-128**.

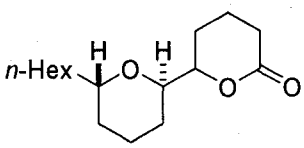
A 5 mL round bottomed flask was charged with 50 mg (0.125 mmol) of alcohol **2-128**, trace amount of $NaHCO_3$, 84.4 mg (0.200 mmol) of Dess-Martin periodinane, and 1.0 mL of DCM and stirred for 12h at room temperature. The reaction mixture was diluted with 2.0 mL sat. aq. $NaHCO_3$ and 2.0 mL of sat. aq. $Na_2S_2O_3$, then extracted with Et_2O (3 x 5 mL). The combined organics were washed with 5 mL portions of H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 48 mg (96 %) of ketone **2-129**.

To a stirred solution of 20.0 mg (0.0502 mmol) of ketone **2-129** in ether (1.0 mL) was added dropwise a 0.14 M solution of $Zn(BH_4)_2$ in ether at -10 °C, and the mixture was stirred at the same temperature for 0.5 h. After quenching with sat. aq. NH_4Cl (2.0 mL), the resulting mixture was dried over $MgSO_4$, filtered through a pad of Celite, and concentrated to yield 19 mg (94 %) of alcohol **2-130**.

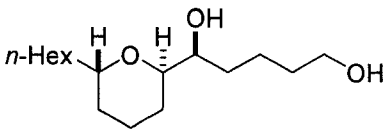
Preparation of $Zn(BH_4)_2$: In a round bottom flask was added 10 g of anhydrous $ZnCl_2$ and 100 mL of Et_2O. The mixture was then refluxed for 2h under argon and allowed to stand at room temperature. The supernatant sat. solution of $ZnCl_2$ in ether was added to a stirred suspension of 4 g (106 mmol) of $NaBH_4$ in 300 mL Et_2O. The mixture was stirred for 2 d and stored under argon at room temperature. The solution was used as is for the reduction. Concentration of the $Zn(BH_4)_2$ solution was determined by back titration with 0.1M HCl.

A 5 mL round bottomed flask was charged with 20 mg (0.050 mmol) of alcohol **2-130**, a solution of TBAF in THF (1.0 M, 0.10 mmol, 0.1 mL), and 0.5 mL of THF. The reaction was allowed to stir at room temperature for 12 h, then quenched with 1.0 mL sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with 10.0 mL brine, and dried over $MgSO_4$. The slurry was filtered and concentrated to afford 14.0 mg (97 %) of diol **2-127a**.

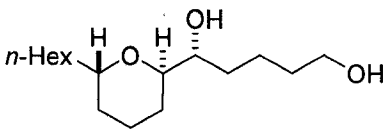
Characterization of the Determination of Stereochemistry Products:



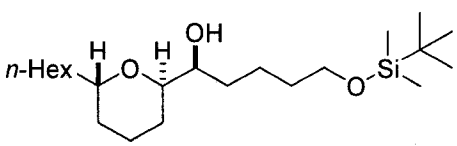
(2'R,6'S*)-6'-Hexyl-octahydro-[2,2']-bipyranyl-6-one* **(2-126).** Following the general procedure **2-126** was isolated as a yellow oil: R_f= 0.179 (25% EtOAc/hex) major isomer, R_f= 0.120 (25% EtOAc/hex) minor isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (1.5H, ddd, *J*=3.5, 8.0, 11.11 Hz), 4.19–4.25 (1.25H, m), 3.87 (1H, m), 3.55–3.67 (4H, m), 2.50–2.61 (2.75H, m), 2.36–2.48 (2.75H, m), 1.18–2.11 (60H, m), 0.85 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 82.8, 80.6, 73.2, 72.8, 72.4, 70.7, 32.9, 32.0, 31.0, 30.0, 29.9, 29.7, 29.5, 28.7, 26.4, 26.1, 26.0, 24.6, 23.8, 22.8, 18.7, 18.6, 18.4, 14.3; IR (NaCl, neat) 2931, 2857, 1736, 1241, 1049 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.



1-(S)-(6-(S*)-Hexyl-tetrahydro-pyran-2-(R*)-yl)-pentane-1,5-diol* **(2-127a).** Following the general procedure **2-127a** was isolated as a clear oil: R_f = 0.242 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.55–3.64 (3H, m), 3.42 (1H, dddd, *J*=4.1, 4.1, 8.8, 13.3 Hz), 2.25 (1H, s), 1.82 (1H, s), 1.18–1.79 (22H, m), 0.85 (3H, t, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 73.0, 72.4, 62.9, 32.8, 32.0, 31.9, 31.2, 29.5, 29.1, 26.2, 24.9, 22.8, 22.3, 18.3, 14.3; IR (NaCl, neat) 3344, 2930, 2858, 1077, 1037 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2427.

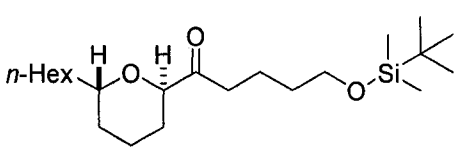


1-(R)-(6-(S*)-Hexyl-tetrahydro-pyran-2-(R*)-yl)-pentane-1,5-diol* **(2-127b).** Following the general procedure **2-127b** was isolated as a clear oil: R_f = 0.328 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, ddd, *J*=4.3, 4.3, 8.8 Hz), 3.61 (2H, t, *J*=6.0 Hz), 3.54 (1H, ddd, *J*=2.5, 8.4, 10.3 Hz), 3.34 (1H, ddd, *J*=2.7, 7.8, 10.7 Hz), 2.77 (1H, s), 1.83 (1H, s), 1.18–1.75 (22H, m), 0.84 (3H, t, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.7, 72.4, 72.0, 62.9, 32.9, 32.6, 32.4, 32.0, 29.5, 29.4, 26.7, 26.0, 22.8, 21.9, 18.6, 14.3; IR (NaCl, neat) 3402, 2932, 2858, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2441.

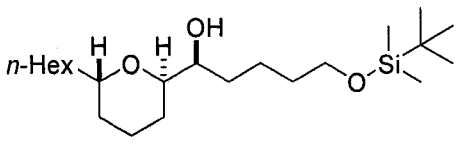


5-(t-Butyl-dimethyl-silanyloxy)-1-(S)-(6-(S*)-hexyl-tetrahydro-pyran-2-(R*)-yl)-pentan-1-ol* **(2-128).** Following the general procedure **2-128** was

isolated as a clear oil: R_f = 0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, *J*=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, *J*=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, *J*=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, -5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.



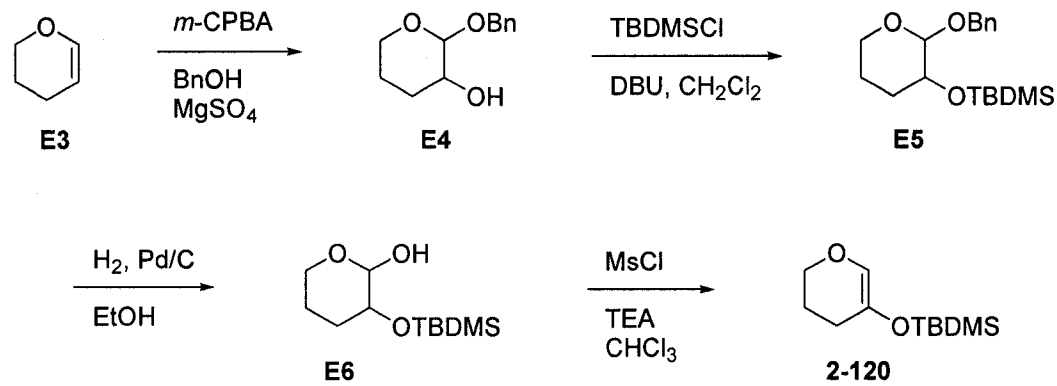
5-(t-Butyl-dimethyl-silanyloxy)-1-(6-(S)-hexyl-tetrahydro-pyran-2-(R*)-yl)-pentan-1-one* **(2-129).** Following the general procedure **2-129** was isolated as a clear oil: R_f = 0.282 (10% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, dd, *J*=4.3, 4.3 Hz), 3.58 (2H, t, *J*= 6.4 Hz), 3.42 (1H, m), 2.59 (1H, ddd, *J*=1.8, 1.8, 6.2 Hz), 2.53 (1H, ddd, *J*=1.8, 1.8, 6.2 Hz), 1.92 (1H, m), 1.20–1.67 (19H, m), 0.86 (9H, s), 0.85 (3H, t, *J*=6.0 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 78.5, 74.4, 63.1, 38.4, 35.3, 32.6, 32.0, 30.7, 29.6, 26.2, 25.8, 25.2, 22.8, 20.2, 19.7, 18.5, 14.3, -5.1; IR (NaCl, neat) 2930, 2857, 1717, 1101 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{45}O_3Si$, 385.3138. Found 385.3128.



5-(t-Butyl-dimethyl-silanyloxy)-1-(S)-(6-(S*)-hexyl-tetrahydro-pyran-2-(R*)-yl)-pentan-1-ol* **(2-130).** Following the general procedure **2-130** was isolated as a clear oil: R_f = 0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77

(1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, *J*=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, *J*=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, *J*=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, -5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.

Synthesis of tert-Butyl-(5,6-dihydro-4H-pyran-3-yloxy)-dimethyl-silane:



tert-Butyl-(5,6-dihydro-4H-pyran-3-yloxy)-dimethyl-silane **(2-120):** To a round bottom flask was added 5.0 mL (54.8 mmol) of dihydropyran **E3**, 5.0 g of $MgSO_4$, 50.0 mL of BnOH, and 17.2 g (76.72 mmol) of *m*-CPBA (77 % max). The reaction was left to stir at room temperature overnight. The reaction was filtered, then excess BnOH and dihydropyran were distilled off. To the residue was added 40 mL of 2M NaOH and the solution was left to stir for 0.5 h. The solution was then extracted with CH_2Cl_2 (3x 50

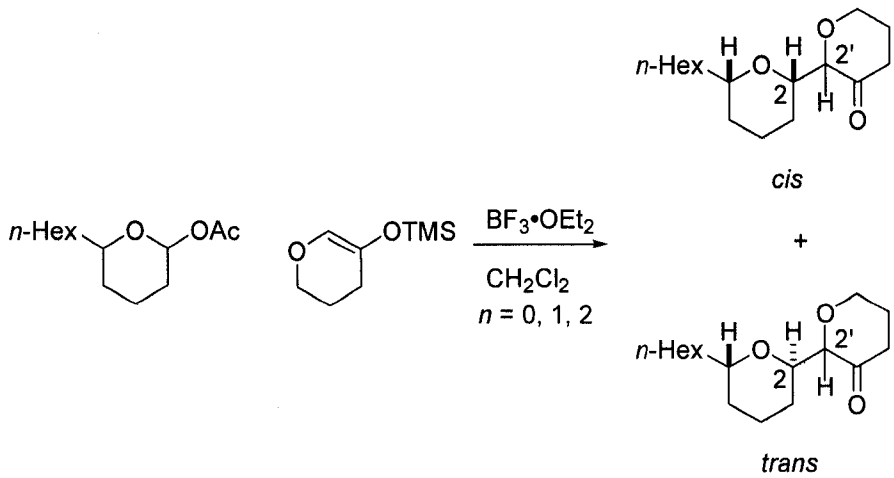
mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated. The alcohol was purified on column chromatography (25 % EtOAc/Hex) to yield 9.4 g (82 %) of **E4**.

To a round bottom flask was added 3.144 g (20.86 mmol) of TBDMSCl, 3.12 mL (20.86 mmol) of DBU, and 100.0 mL of CH_2Cl_2. To this solution was added a solution of 3.62 g (17.38 mmol) of the alcohol **E4** in 50 mL of CH_2Cl_2. The reaction was stirred at room temperature for 12h, then diluted with H_2O. The layers were separated and the organic layer was washed with 2M HCl then sat. aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 5.50 g (98 %) of the silyl ether **E5**.

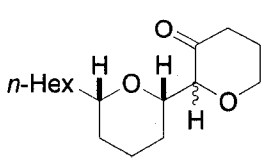
To a round bottom flask was added 5.5 g (17.05 mmol) of silyl ether **E5**, 0.7 g of 10% Pd/C, and 25.0 mL of EtOH. Argon was passed throught the solution for 20 min., then a balloon of H_2 was placed into the reaction vessel. After the reduction was complete, as monitored by TLC, the solution was passed through a plug of Celite and eluted with Et_2O. The solution was concentrated to afford 3.9 g (98 %) of the alcohol **E6**.

To a round bottom flask was added 6.0 g (25.82 mmol) of alcohol **E6**, 16.2 mL (116.19 mmol) of TEA, and 60 mL of $CHCl_3$. The reaction was cooled to 0 °C and 4 mL (51.64 mmol) of MsCl was added dropwise. After addition, the reaction was refluxed for 12h, then cooled to room temperature. The reaction was quenched with 100 mL of H_2O and the layers were separated. The organic layer was washed with 2M HCl, then dried over $MgSO_4$, filtered, and concentrated to afford 4.6 g (83 %) of the known silyl enol ether **2-120**, which matched all spectral data.[6]

General Procedure for the Pyran Derived Enol Silane Addition:



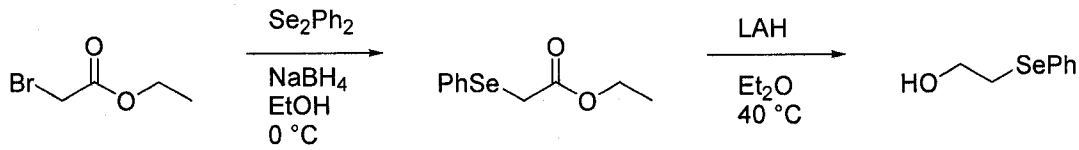
(2'R, 6'S*)-6'-Hexylhexahydro-2H, 2'H-2,2'-bipyran-3(4H)-one* (**2-122**). To a flame dried 5 mL round bottomed flask was added 10.0 mg (0.0438 mmol) of lactol **2-112**, 14.1 mg (0.0657 mmol) of silyl enol ether **2-120**, and 1.0 mL of CH_2Cl_2. The reaction was then cooled to -78 °C and 8.5 μL (0.0657 mmol) of BF_3•OEt_2 was added dropwise. After 1 h at -78 °C, the reaction was quenched by the addition of 1.0 mL sat. aq. Na_2CO_3 and extracted with Et_2O (3 x 10 mL). The organics were combined and washed with H_2O, then sat. aq. $NaHCO_3$. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to yield 15.2 mg (94 %) of <1:>99 (*cis:trans*) mixture of ketones **2-122** and **2-121** as a yellow oil



2-122: R_f = 0.175 (15% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, ddd, *J* = 11.7, 5.5, 5.5, major), 4.09 (1H, m,

minor), 4.01 (1H, m, major), 3.91 (d, 1H, J = 3.6, minor), 3.78-3.85 (2H, m), 3.70 (1H, d, J = 3.2, major), 3.62 (1H, ddd, J = 11.6, 8.1, 5.1, major), 2.50-2.64 (1H, m), 2.35-2.46 (1H, m), 2.02-2.27 (1H, m), 1.86-2.00 (1H, m), 1.52-1.80 (7H, m), 1.38-1.50 (1H, m), 1.06-1.38 (13H, m), 0.84 (3H, t, J = 6.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 208.1, 85.1, 85.0, 73.3, 73.1, 69.6, 69.1, 64.4, 64.8, 37.9, 37.2, 31.8, 30.9, 30.4, 29.2, 29.1, 28.2, 28.4, 26.9, 25.9, 25.6, 25.5, 25.2, 23.8, 22.6, 18.6, 18.2, 14.1; IR (NaCl, neat) 2930, 2857, 1723 cm^{-1}; HRMS (FAB+) Calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.

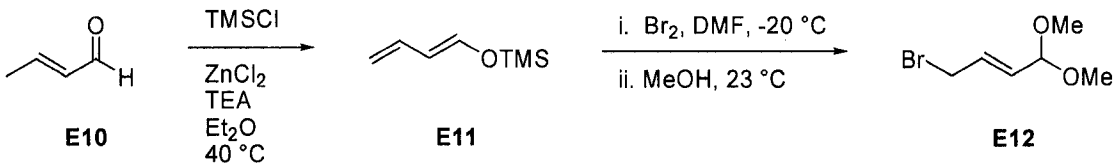
Synthesis of Tandem Ferrier/Diels-Alder Substrates:



E7 **E8** **E9**

2-Phenylselanyl-ethanol (**E9**): To a round bottom flask was added 3.5 g (11.2 mmol) of Se_2Ph_2 and 60 mL of EtOH. The reaction was cooled to 0 °C and 0.85 g (22.2 mmol) of $NaBH_4$ was added portionwise. After addition was complete, 2.5 mL (22.2 mmol) of **E7** in 30 mL of EtOH was added dropwise and the reaction was left to stir at 0 °C for 1h. Once the reaction was warmed to room temperature, it was quenched carefully with H_2O and diluted with CH_2Cl_2. The layers were separated and the organic layer was washed with brine. After the layers were separated, the organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 5.3 g (98 %) of **E8**, as a yellow oil.

To a round bottom flask was added 5.3 g (21.8 mmol) of **E8** and 100 mL of Et_2O. The reaction was cooled to 0 °C and 1.2 g (32.7 mmol) of LAH was added in small protions. After addition was complete, the reaction was refluxed for 12h. The reaction was then cooled and quenched using the Fieser method. Purification on column chromatography (silica gel, 10 % EtOAc/Hexanes) afforded 4.14 g (94 %) of **E9**, as a yellow oil.

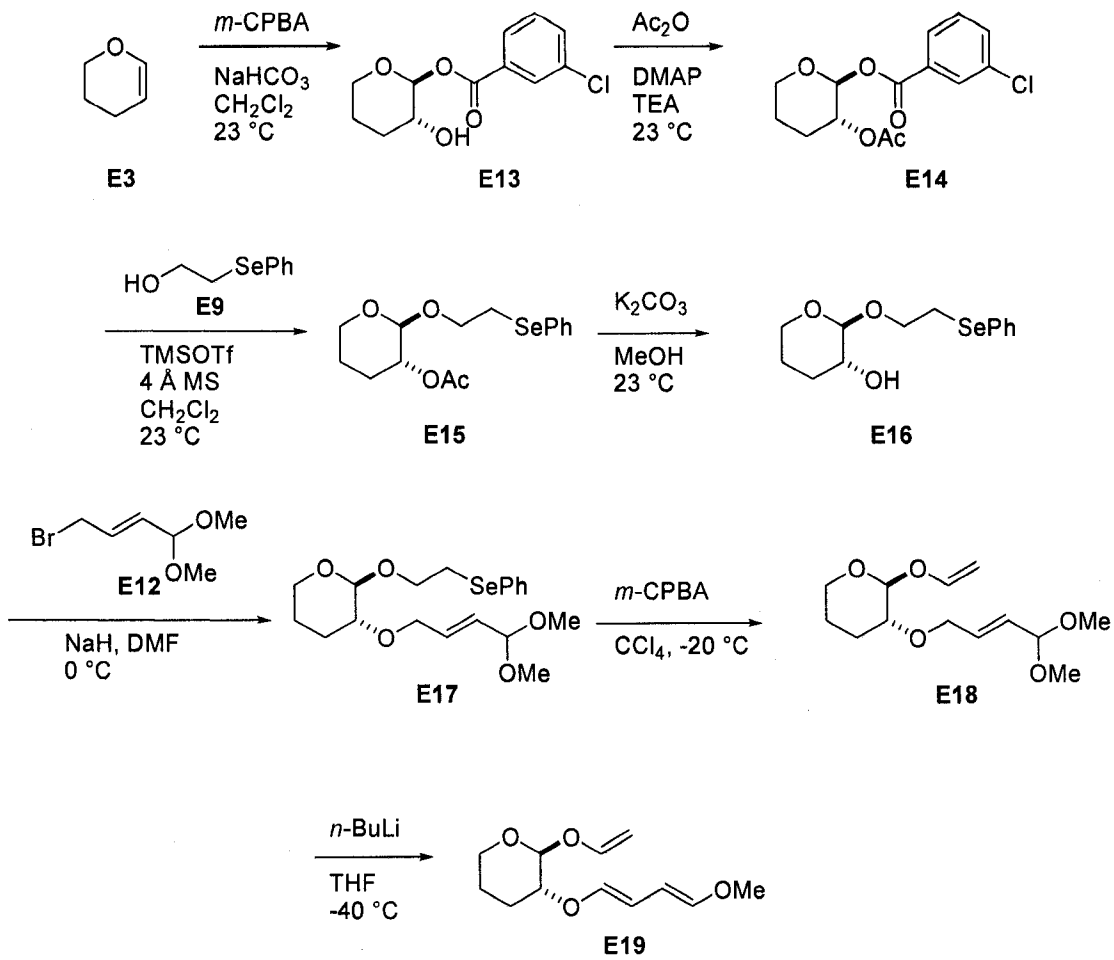


E10 **E11** **E12**

4-Bromo-1,1-dimethoxy-but-2-ene (**E12**): To a solution of 10 g (140 mmol) of crotonaldehyde **E10**, 26 g (260 mmol) of TEA, 180 mg (1.4 mmol) of $ZnCl_2$ in 24 mL of Et_2O was added dropwise (neat) 16.2 g (150 mmol) of TMSCl. The mixture was refluxed for 25h. After cooling to room temperature, 100 mL of pentane was added and left to stir for 1h. The solution was then filtered through a pad of Celite and fractional distillation afforded 12.4 g (62 %) of **E11**.

To a round bottom flask was added 12.4 g (87 mmol) of **E11** in 87 mL of dry DMF, then the reaction was cooled to -20 °C and 4.7 mL (87 mmol) of Br_2 was added dropwise. After 10 min., 87 mL of absolute MeOH was added and the mixture was stirred for 1.3h at this temperature. The reaction was quenched with H_2O and extracted 3 times (3 x 100 mL) with Et_2O. The organic layers were combined and washed 3 times (3

x 100 mL) with H_2O. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified by solumn chromatography (silica gel, 25 % EtOAc/Hexanes) to afford (76 %) of **E12** as a orange oil.



Synthesis of Triene:

To a round bottom flask was added 5.0 g (59.44 mmol) of dihydropyran **E3**, 200 mL of 10 % aqueous solution of $NaHCO_3$, and 200 mL of CH_2Cl_2. To this solution was added 14.0 g (81.13 mmol) of *m*-CPBA (77 % max) portionwise and the reaction was left to stir at ambient temperature for 12h. The reaction was quenched with 100 mL of saturated aqueous Na_2SO_4. The layers were separated and the organic layer was washed with brine. After separation, the organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 12.9 g (84 %) of the desired alcohol **E13**.

To a round bottom flask containing 6.45 g (25.12 mmol) of alcohol **E13**, 154 mg (1.26 mmol) of DMAP, and 4.2 mL (30.14 mmol) of TEA was added dropwise 2.61 mL (27.63 mmol) of neat Ac_2O. After 1h, the reaction became homogenous and was diluted with EtOAc and saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ and then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude slurry was purified on silica gel (25 % EtOAc/Hexanes) to afford 7.4 g (98 %) of the acetic acid ester **E14**, as a clear oil.

To a round bottom flask was added 1.0 g (3.35 mmol) of acetic acid ester **E14**, 0.708 g (3.52 mmol) of selenide **E9**, 0.950 g of 4 Å MS and 15 mL of CH_2Cl_2. To this solution was added dropwise 0.675 mL (3.69 mmol) of neat TMSOTf and the reaction was stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was passed through a pad of Celite using EtOAc as eluent. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The slurry was purified on silica gel (25 % EtOAc/Hexanes) to afford 788 mg (70 %) of selenide **E15**, as a yellow oil.

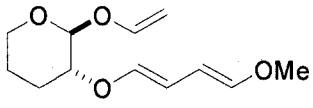
To a round bottom flask was added 788 mg (2.3 mmol) of selenide **E15**, 1.6 g (11.5 mmol) of K_2CO_3 and 15 mL of MeOH at 0 °C. After 1h, the reaction mixture was diluted with H_2O and extracted with EtOAc (3 x 25 mL). The organic layers were combined and washed with 30 mL portions of H_2O and brine, then dried over $MgSO_4$.

The slurry was filtered, concentrated and purified on silica gel (25 % EtOAc/Hexanes) to afford 640 mg (92 %) of the alcohol **E16**, as a yellow oil.

To a round bottom flask was added 60 mg (2.49 mmol) of NaH (60 % in minerial oil) and 10 mL of dry DMF. The reaction was cooled to 0 °C and a solution of 300 mg (0.996 mmol) of alcohol **E16** in 5 mL of dry DMF was added dropwise. The reaction was stirred for 20 min., then a solution of 223 mg (1.145 mmol) of bromide **E12** in 5 mL of dry DMF was added dropwise and the solution was stirred for 1h. The reaction was quenched with H_2O and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined and washed with H_2O and dried over $MgSO_4$. The slurry was filtered, concentrated to which it afforded 412 mg (99 %) of the desired dimethyl acetal **E17**, as a yellow oil.

A round bottom flask was charged with 245 mg (0.5898 mmol) of dimethyl acetal **E17** in 5 mL of CCl_4 and was cooled to -20 °C. To the chilled solution was added 153 mg (0.8847 mmol) of *m*-CPBA (77 % max) and the reaction was stirred at this temperature for 1h. Then 0.650 mL (8.85 mmol) of SMe_2 and 0.164 mL (1.18 mmol) of TEA were added and the resulting solution was refluxed for 5h. The reaction was then partitioned between H_2O and EtOAc after cooling to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were washed with H_2O and dried over $MgSO_4$. The slurry was filtered, concentrated, and purified on silica gel (15 % EtOAc/Hexanes) to afford 140 mg (92 %) of vinyl ether **E18**, as a clear oil.

To a round bottom flask was added 140 mg (0.542 mmol) of vinyl ether **E18** in 4 mL of THF and the solution was cooled to -40 °C. At this temperature was added 0.410 mL (0.650 mmol) of *n*-BuLi (1.6 M in Hexanes) dropwise and the reaction was stirred for 30 min. The reaction was quenched with H_2O and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combied organic layers were washed with H_2O and dried over $MgSO_4$. The slurry was filtered, concentrated, and purified on silica gel (10 % EtOAc/Hexanes) to afford 124 mg (84 %) of the desired triene **E19**, as a clear oil.



(2S, 3R*)-3-(4-Methoxy-buta-1,3-dienyloxy)-2-vinyloxy-tetrahydro-pyran* (**E19**): R_f = 0.464 (25% EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, d, *J* = 12.9), 6.43 (1H, dd, *J* = 6.6, 13.8), 5.79-5.96 (m, 2H), 5.02 (1H, dd, *J* = 6.2, 10.6), 4.91 (1H, d, *J* = 2.9), 4.55 (1H, dd, *J* = 1.5, 13.9), 4.19 (1H, dd, *J* = 1.8, 6.6), 3.83 (m, 1H), 3.55-3.68 (m, 3H), 1.74-2.07 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.8, 141.1, 104.8, 98.8, 98.2, 92.0, 75.6, 61.7, 56.4, 24.8, 20.9; IR (NaCl, neat) 2931, 1642, 1611 cm^{-1}; HRMS (FAB+) Calcd for $C_{12}H_{17}O_4$, 22.51127. Found 225.1130.

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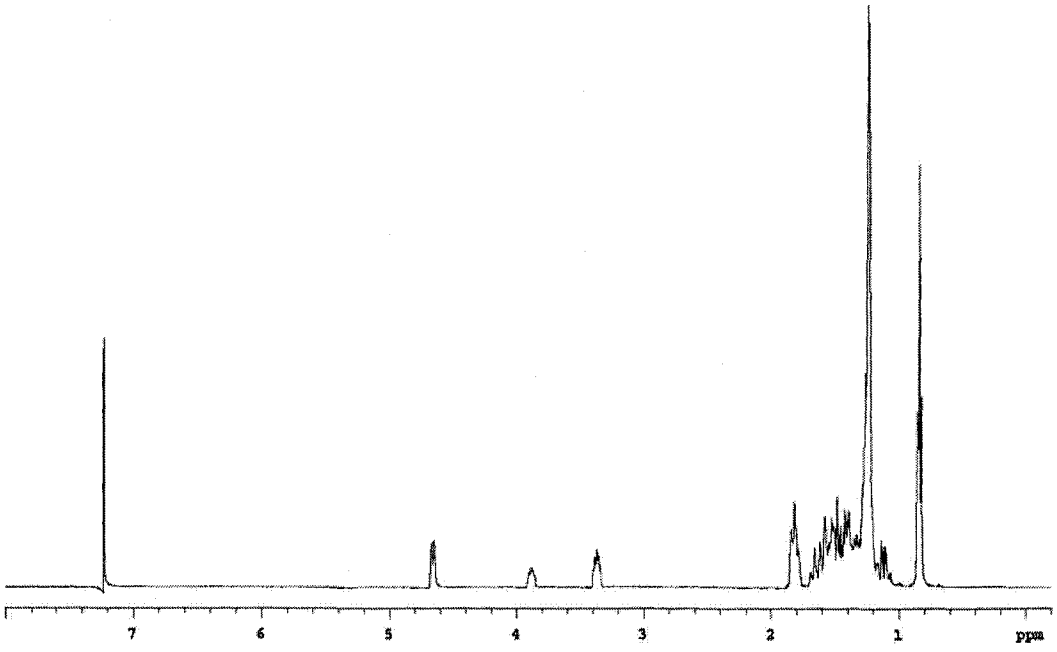
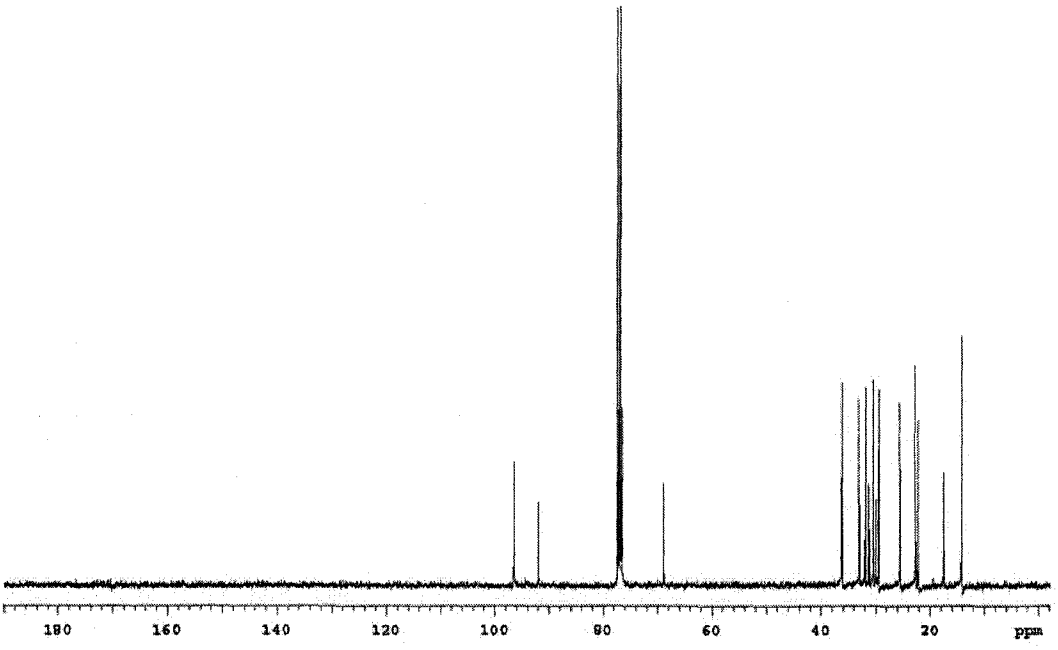
^{1}H and ^{13}C spectra for **2-77**:





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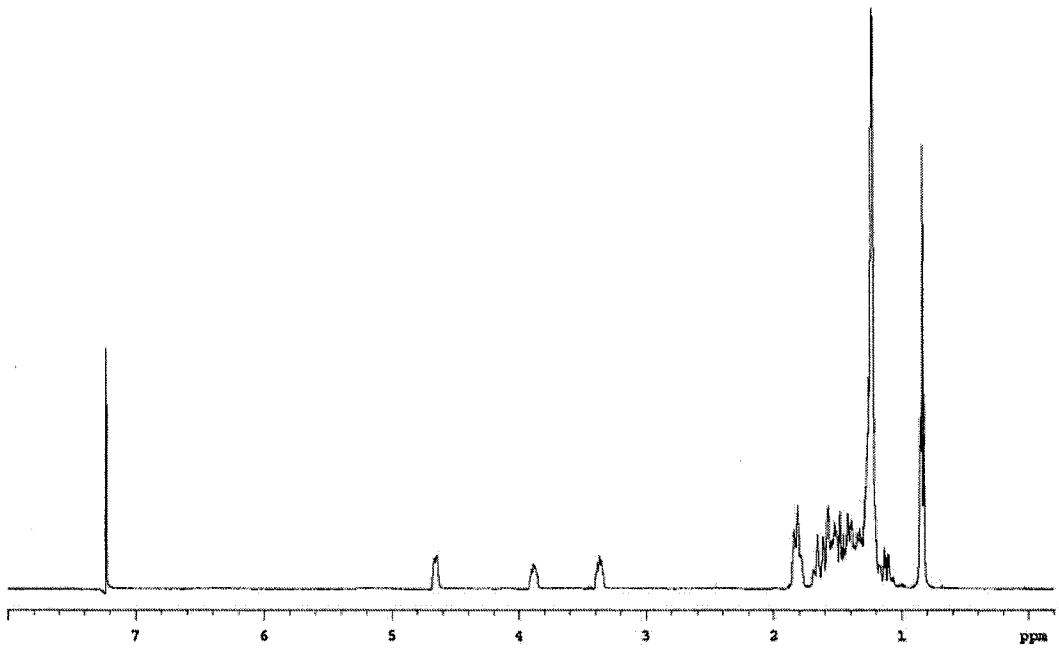

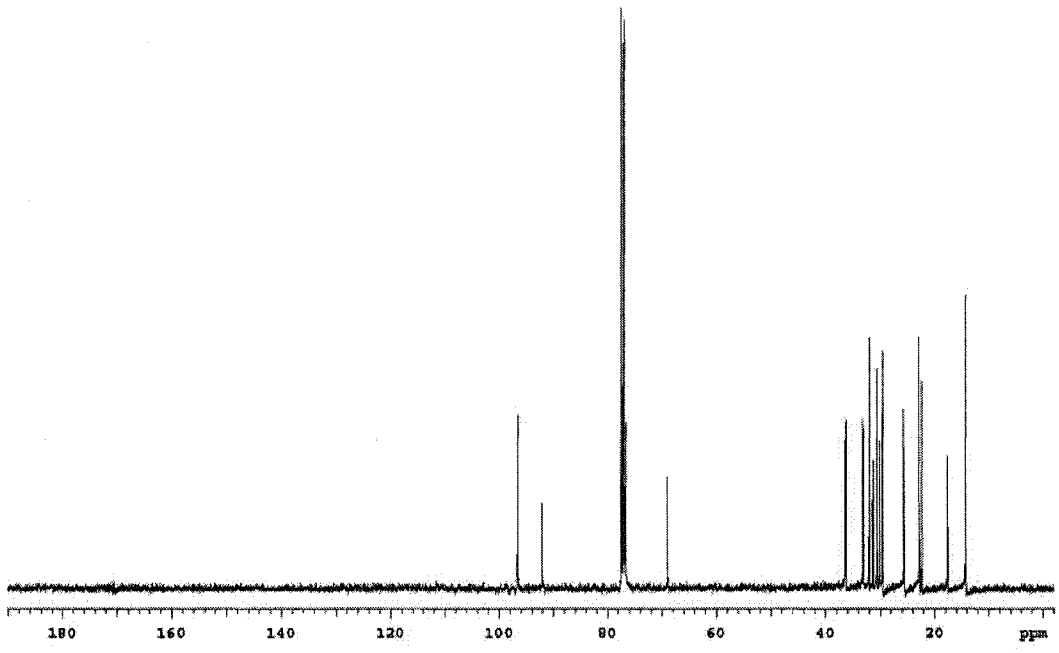

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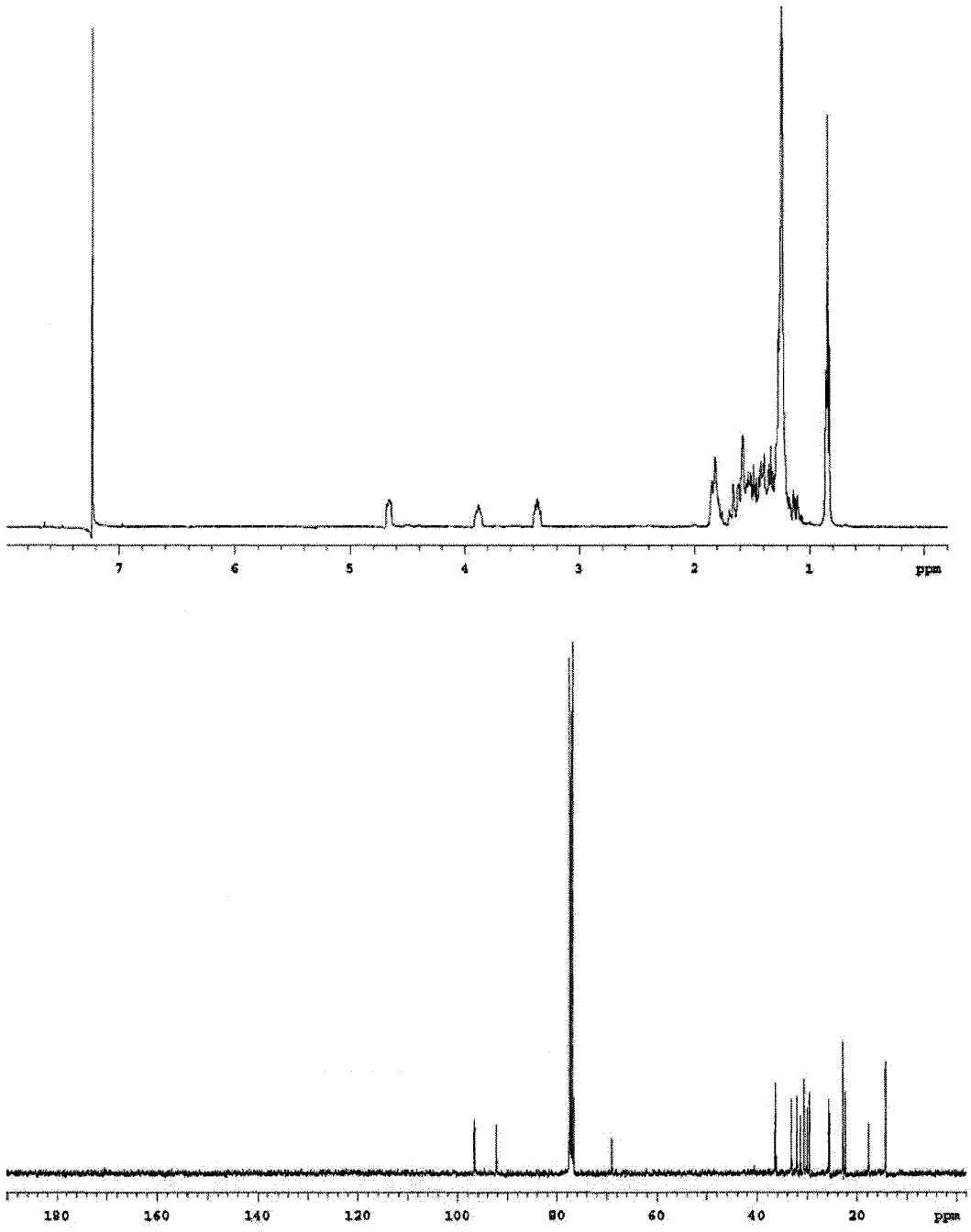

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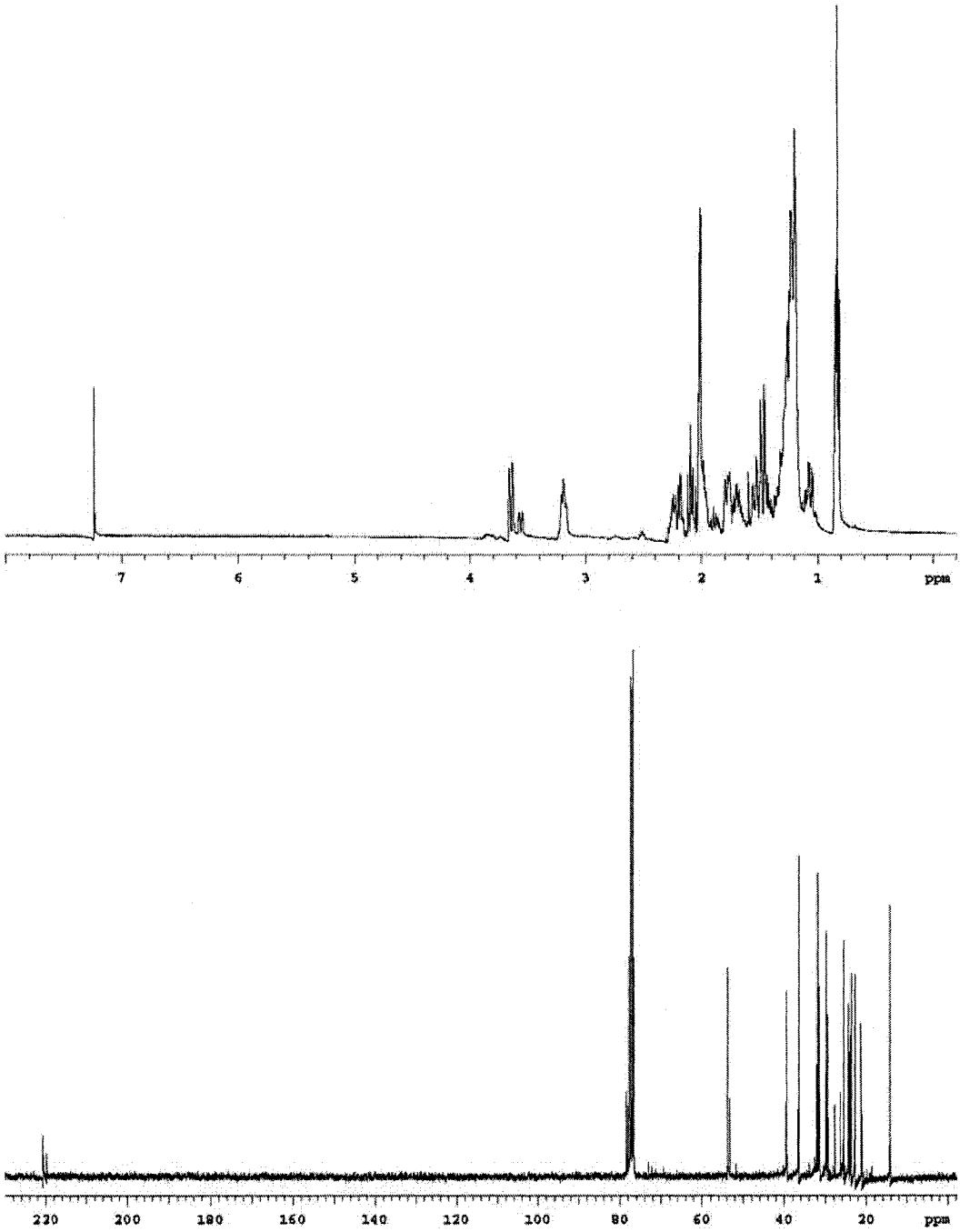

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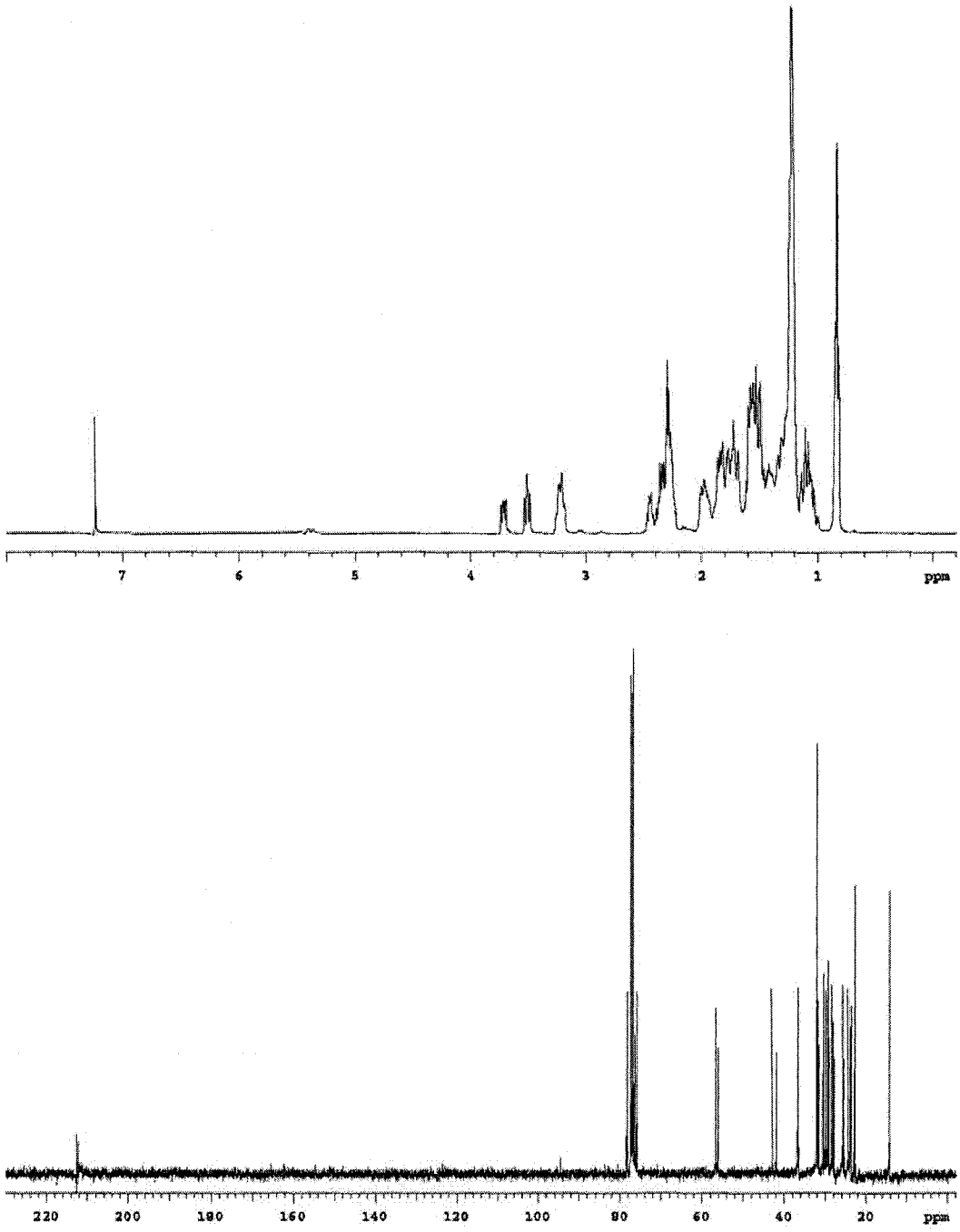

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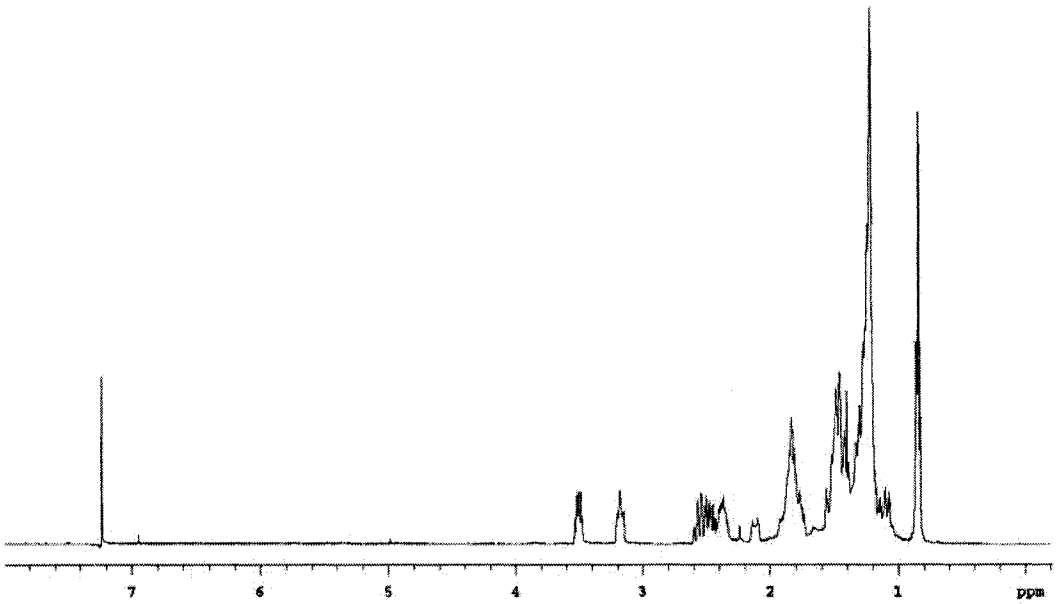

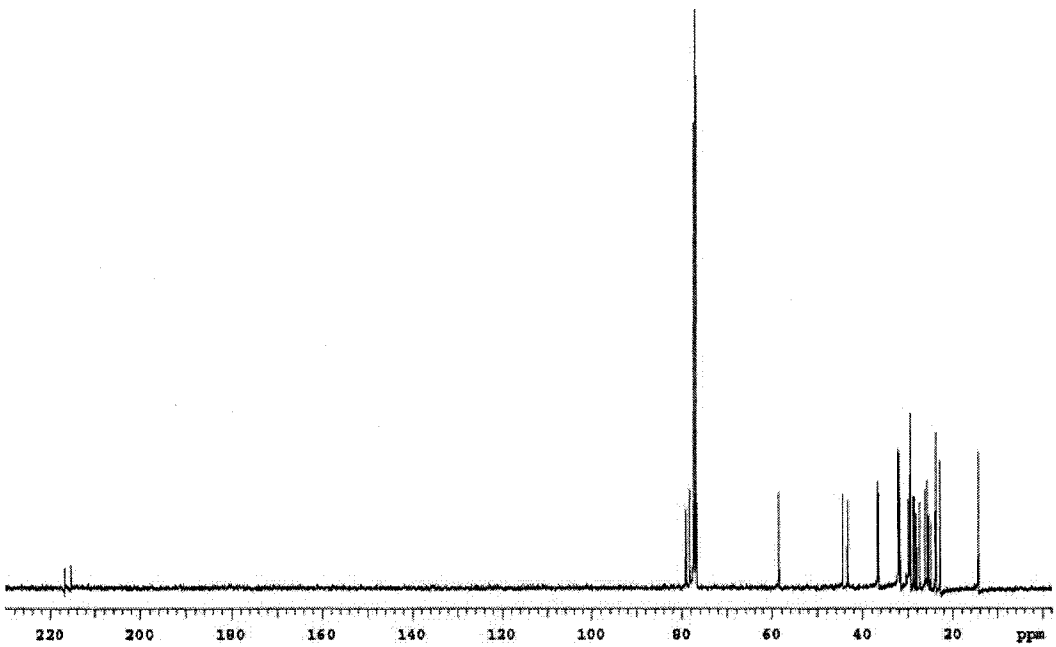

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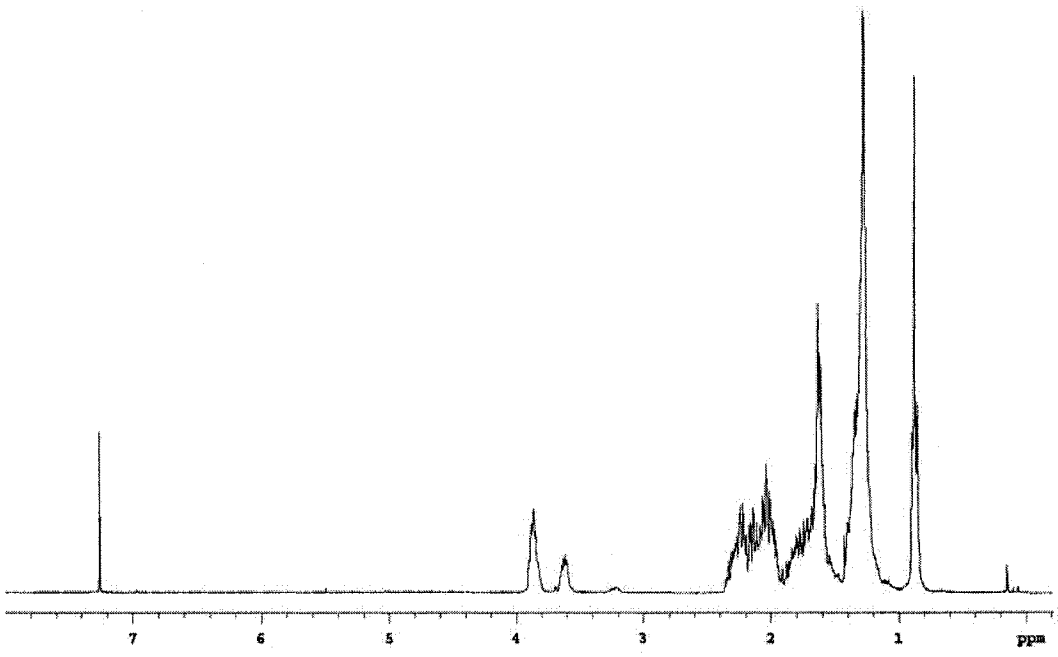

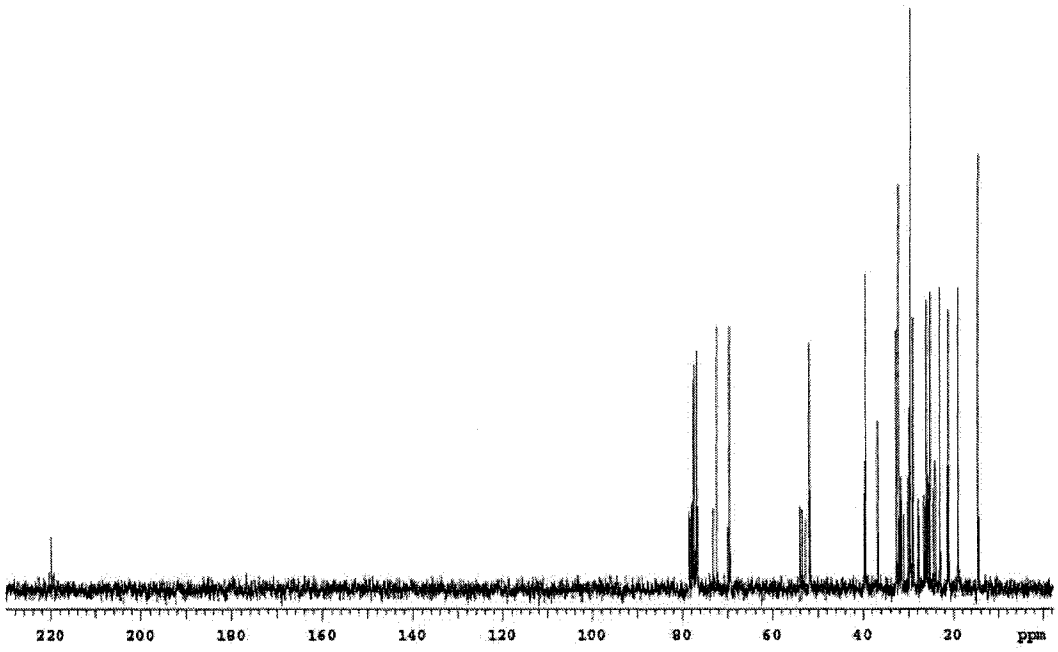

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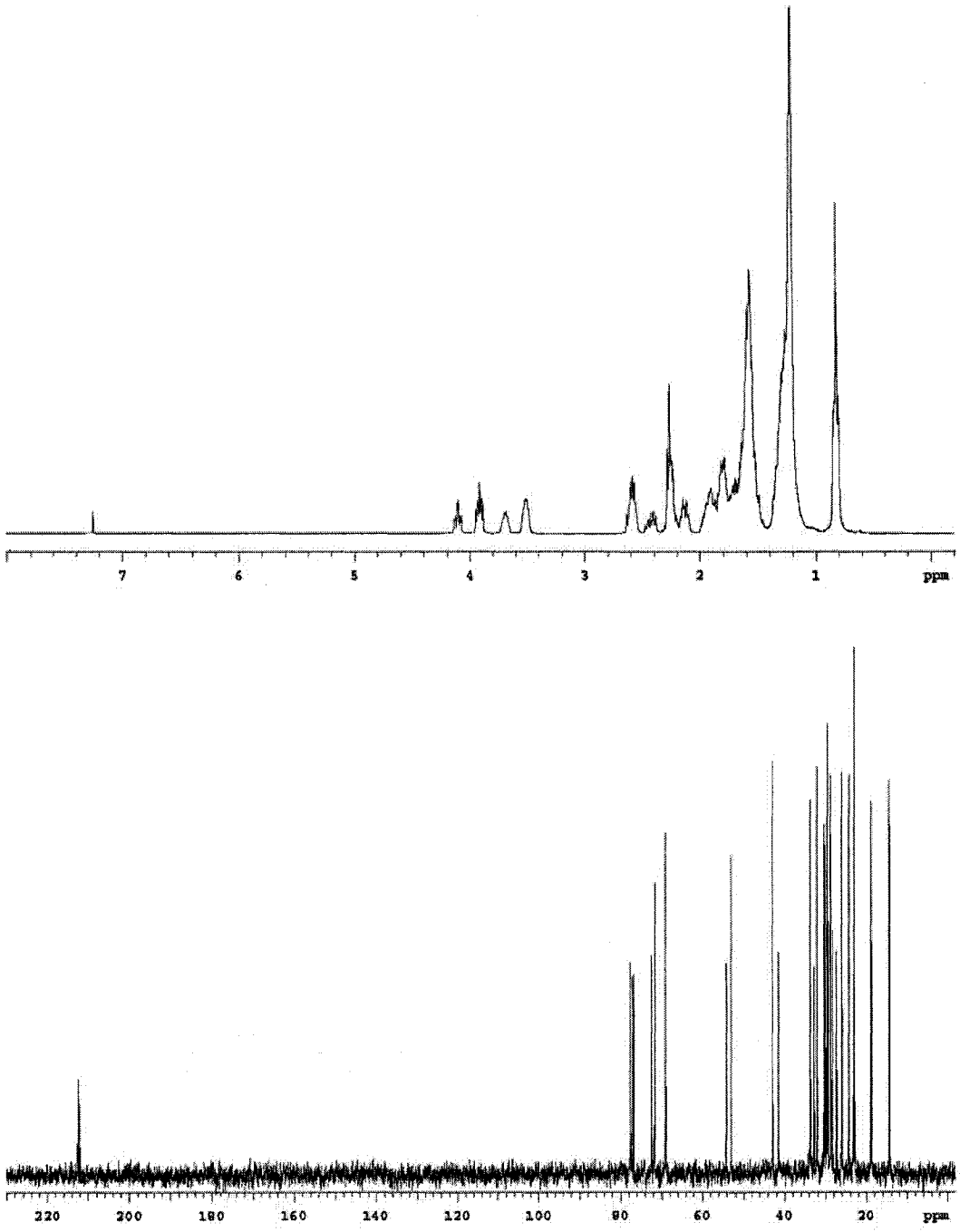

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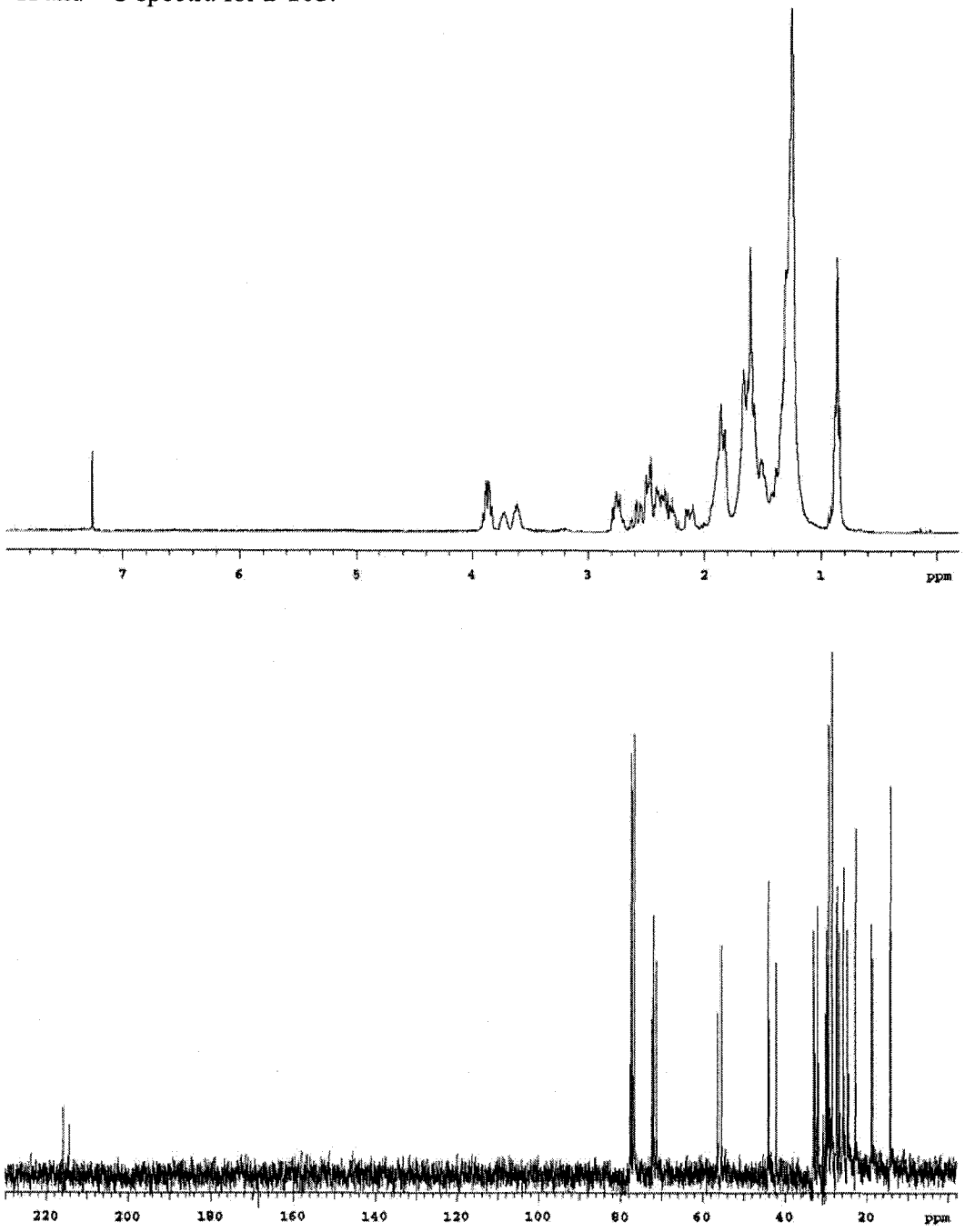

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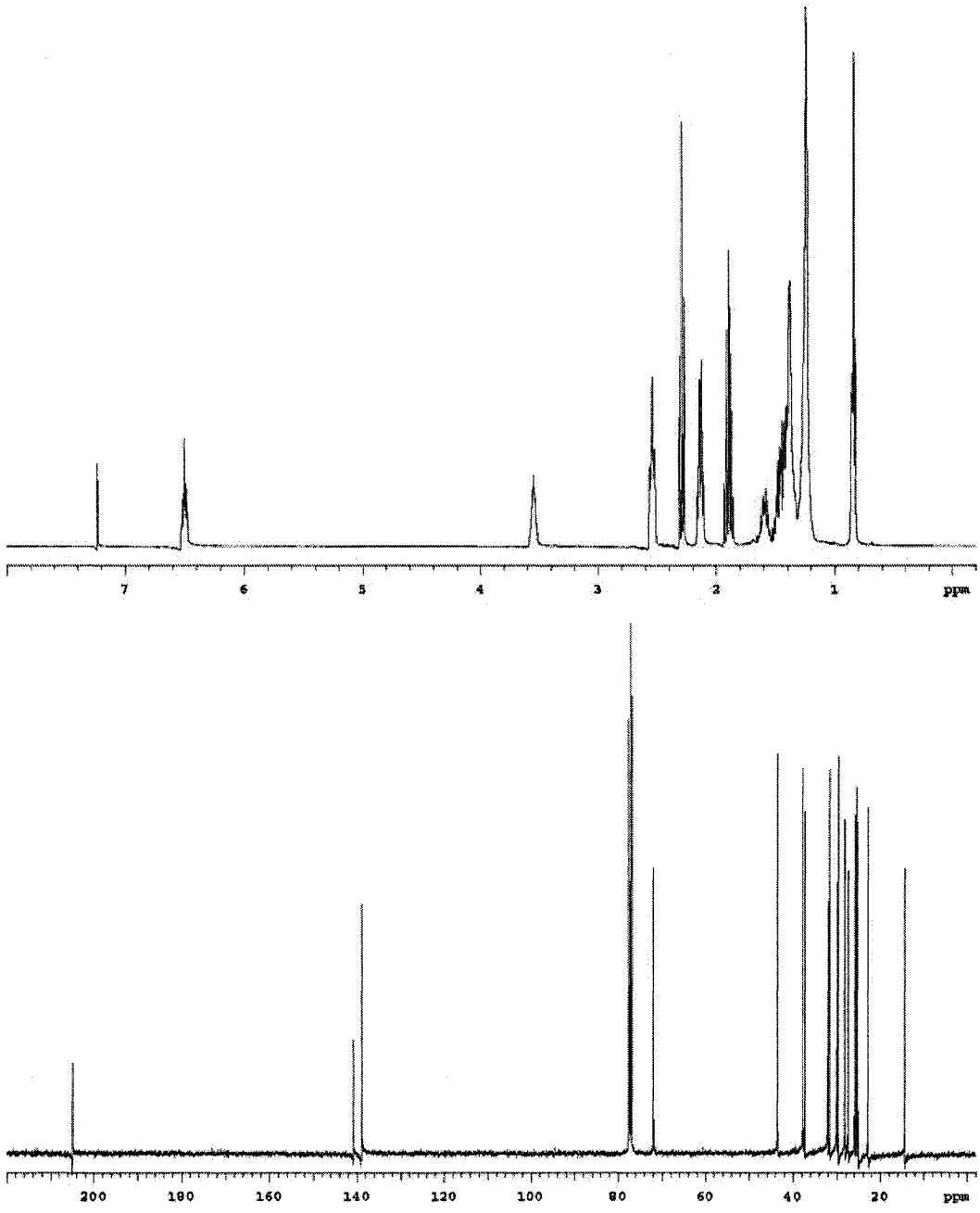

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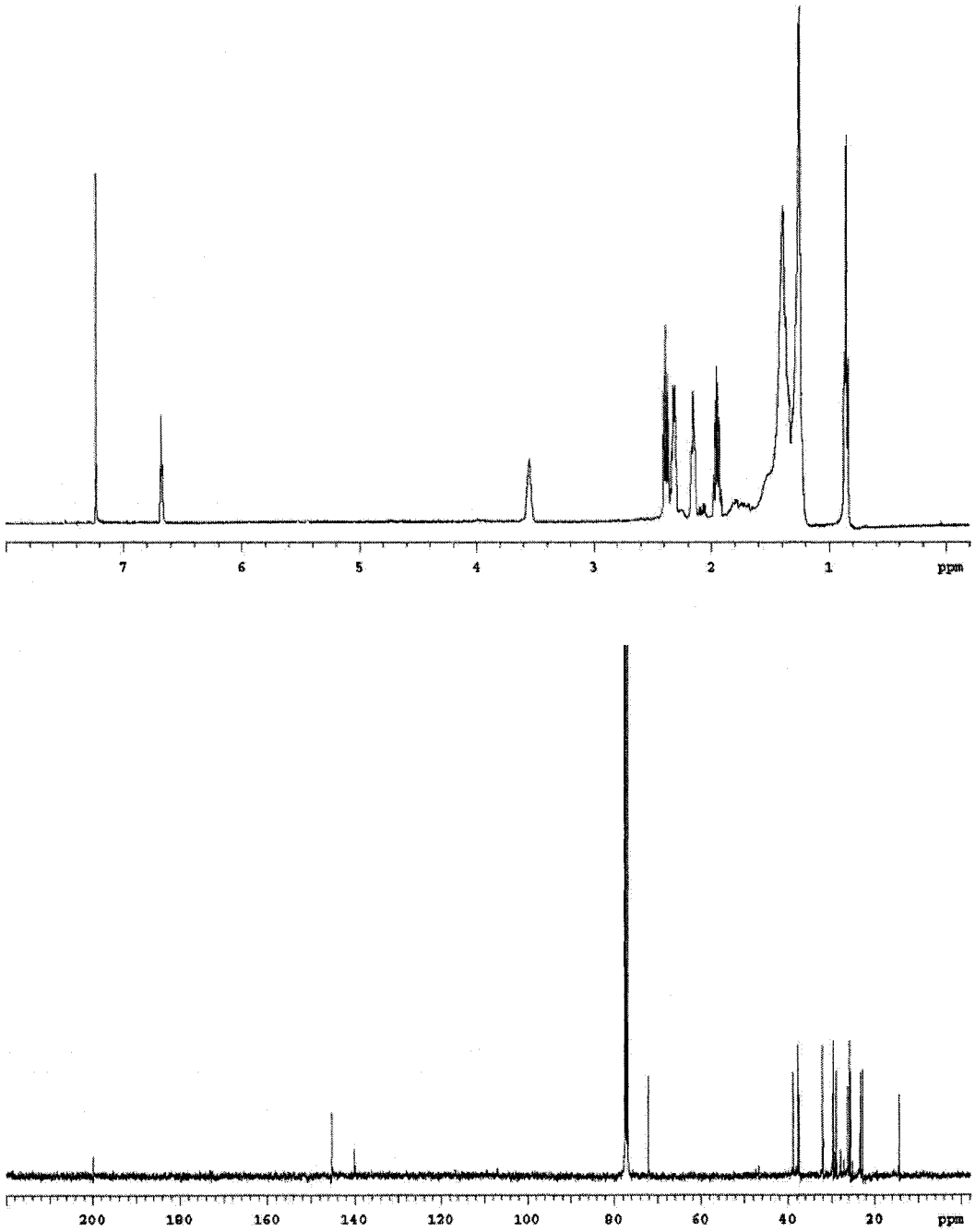

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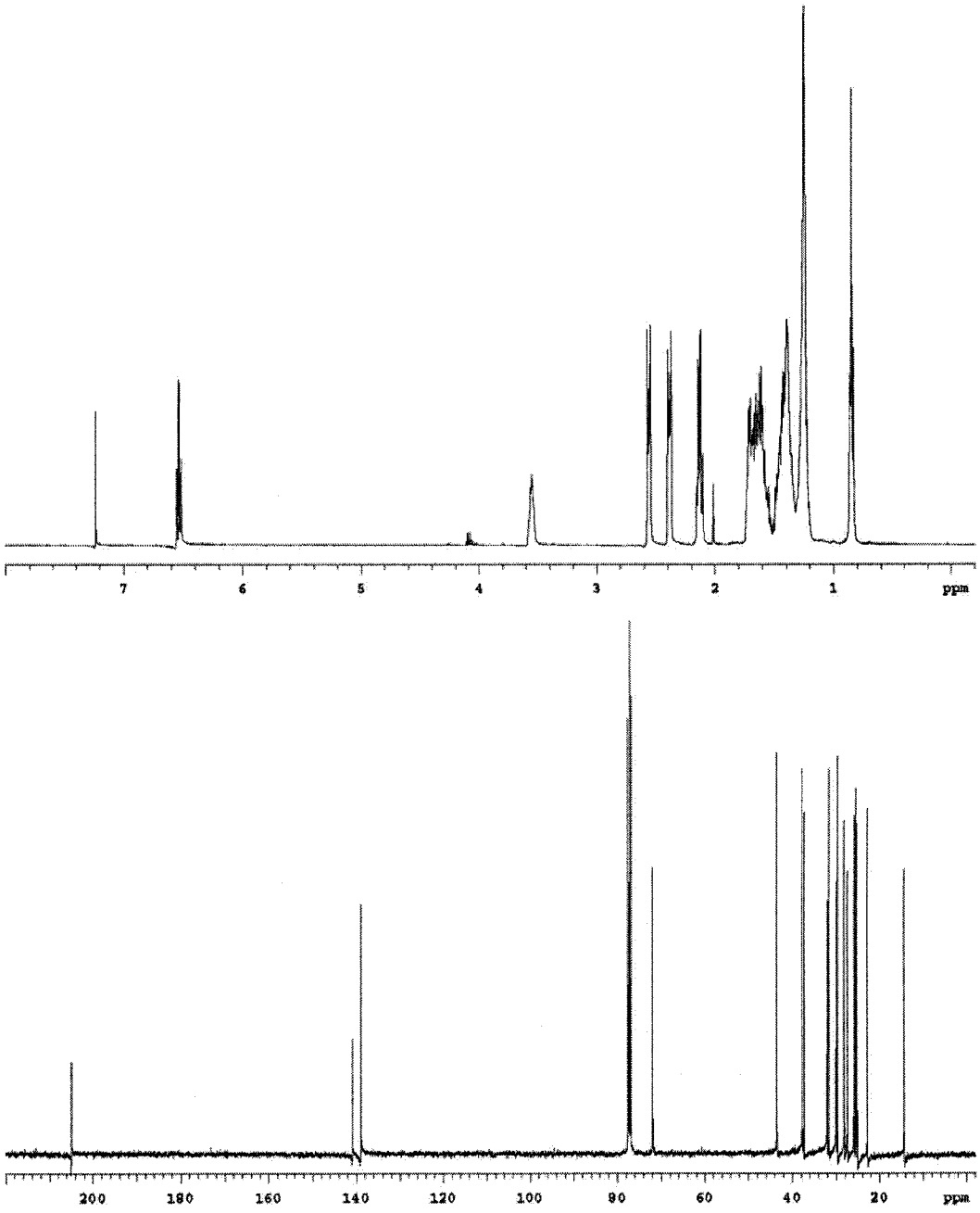

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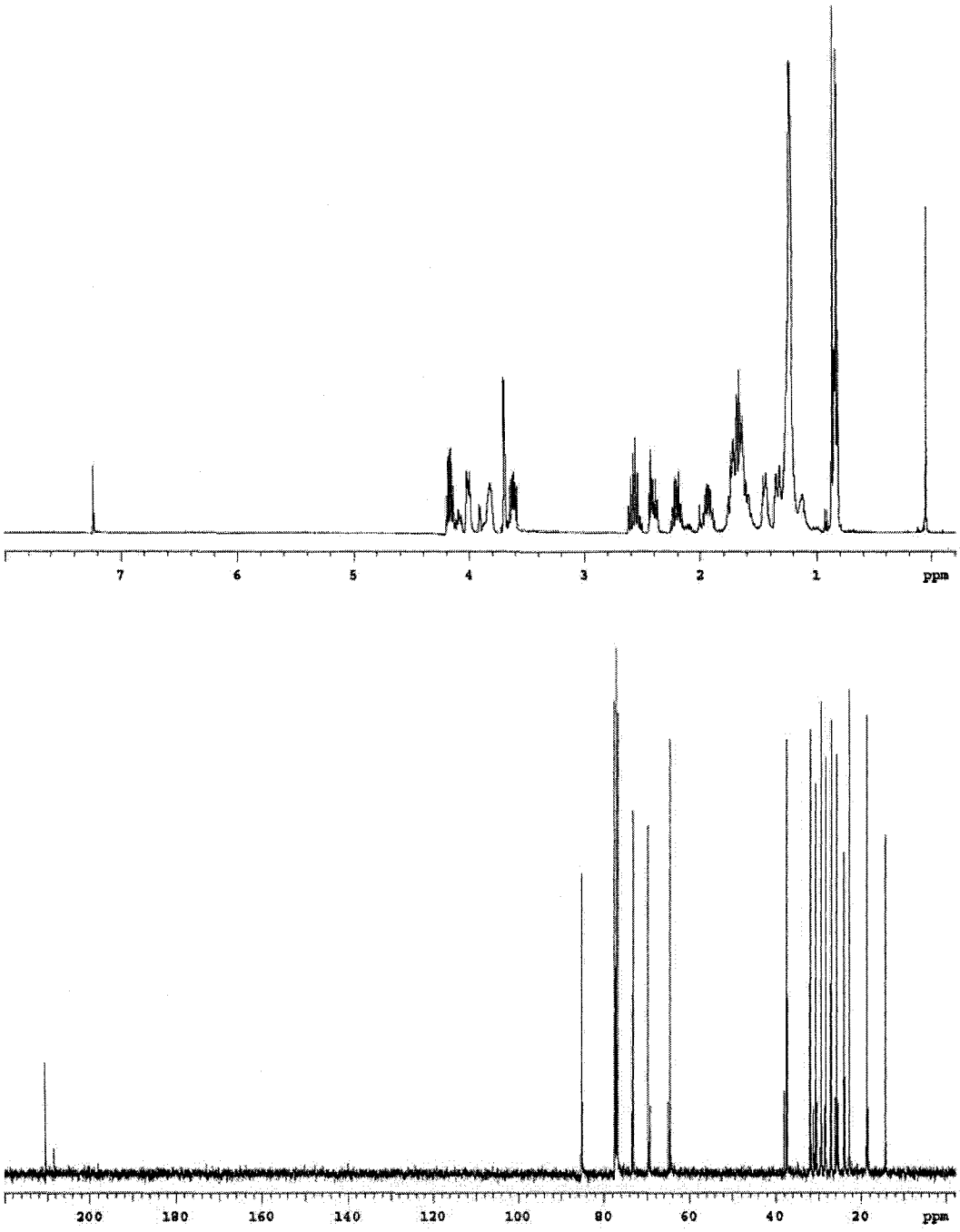

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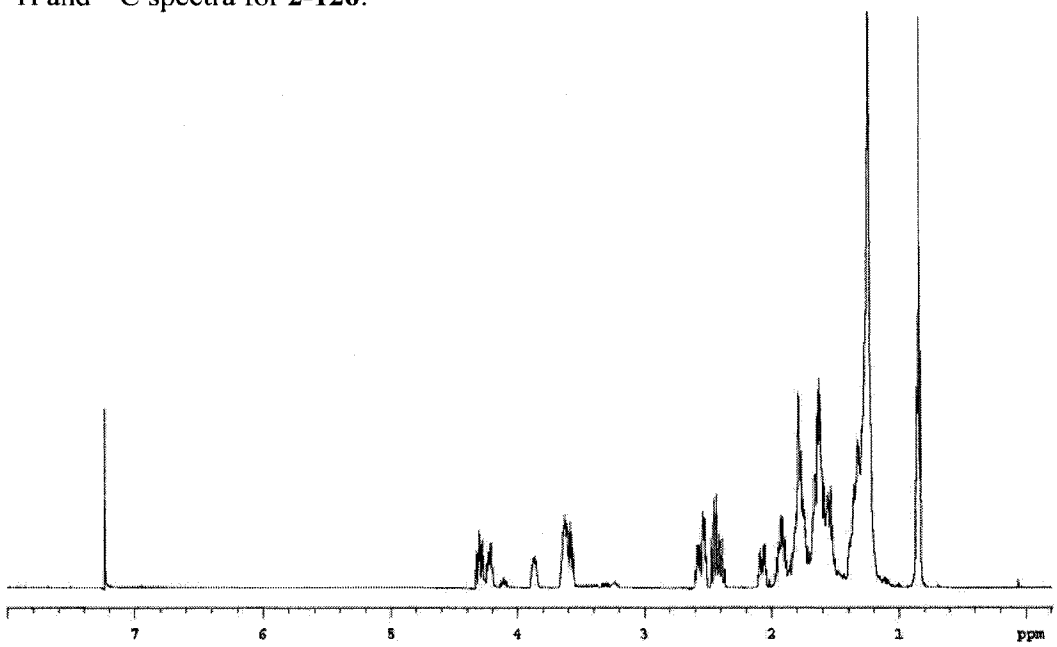

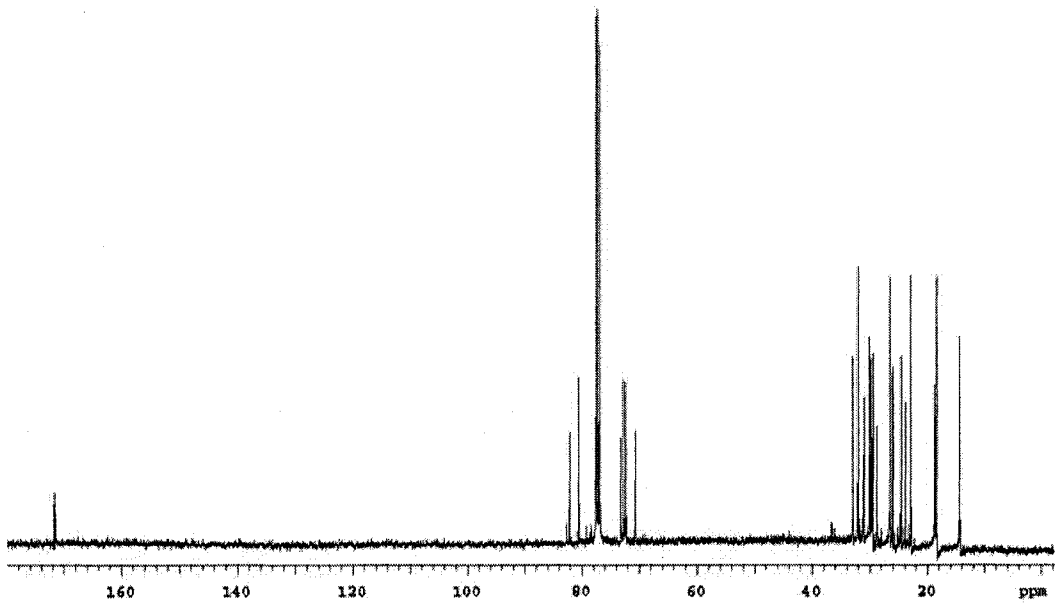

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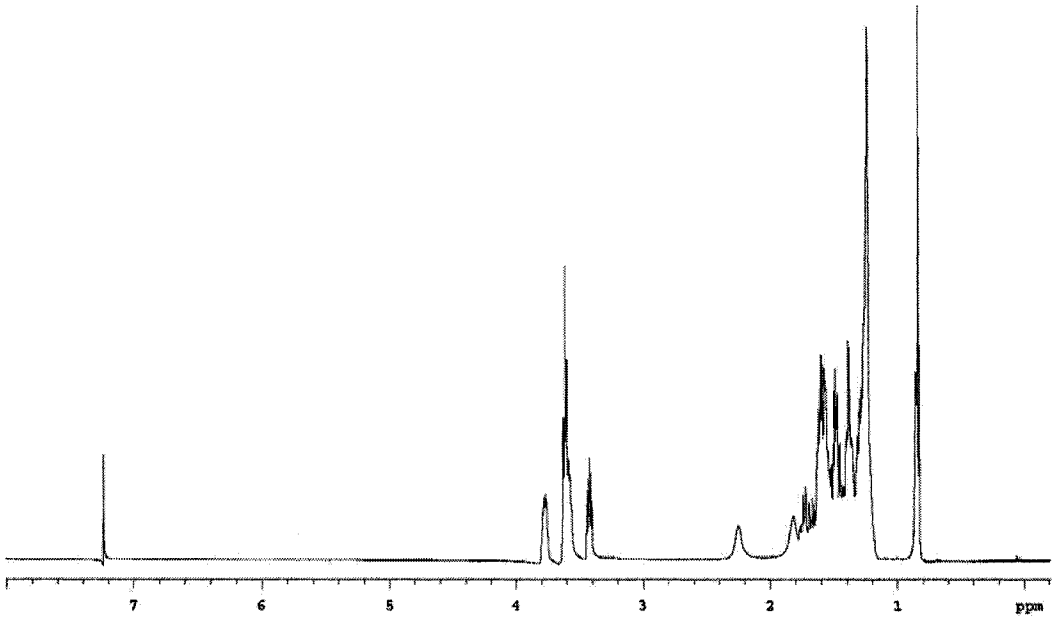

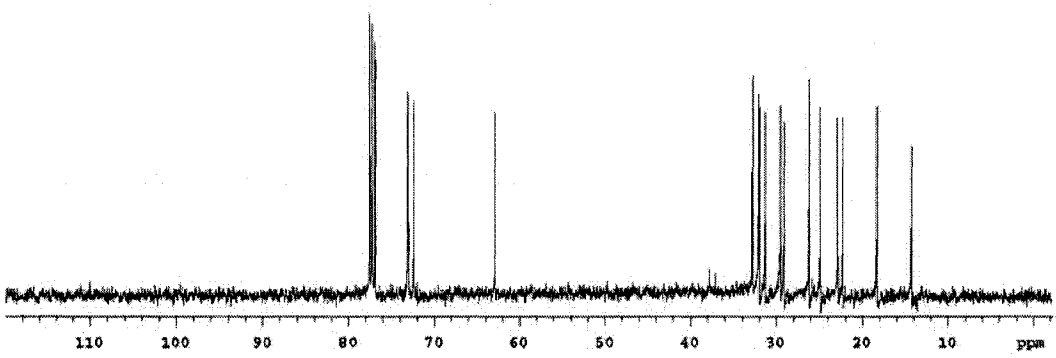

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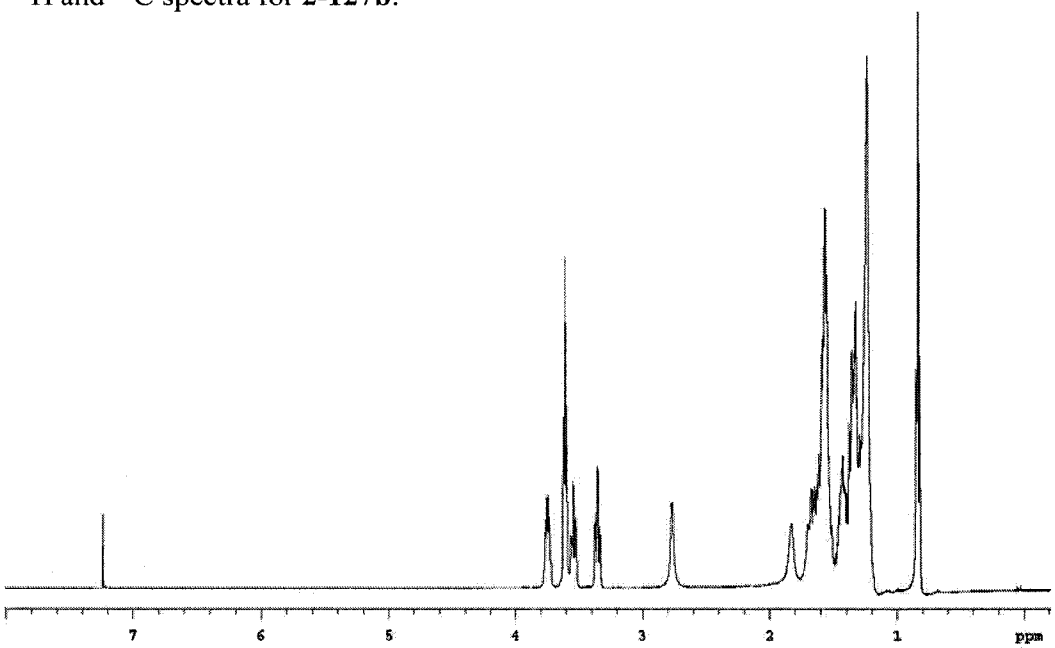

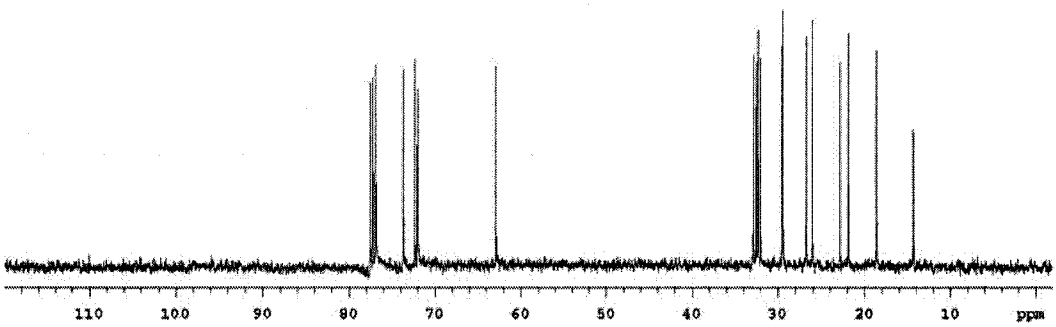

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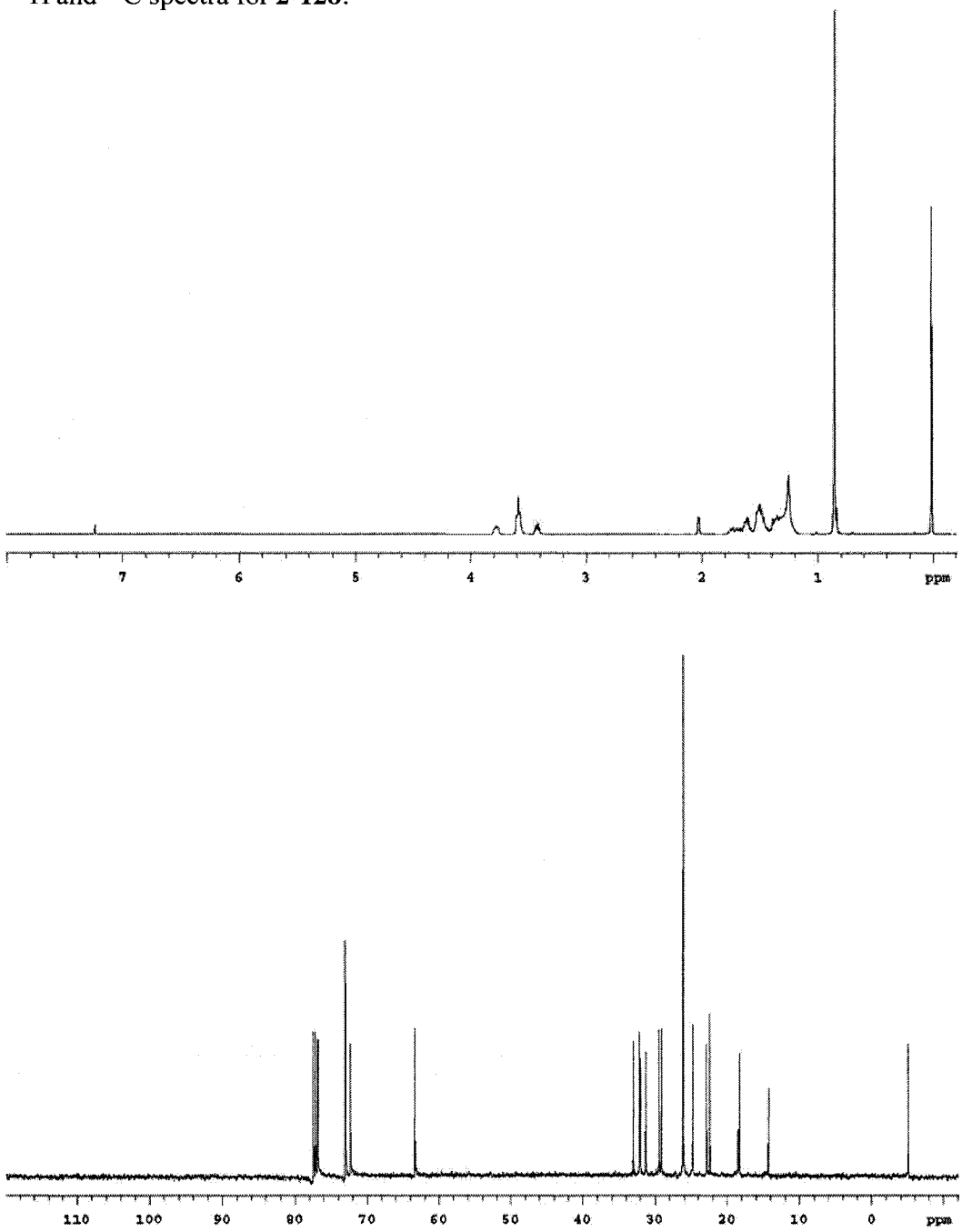

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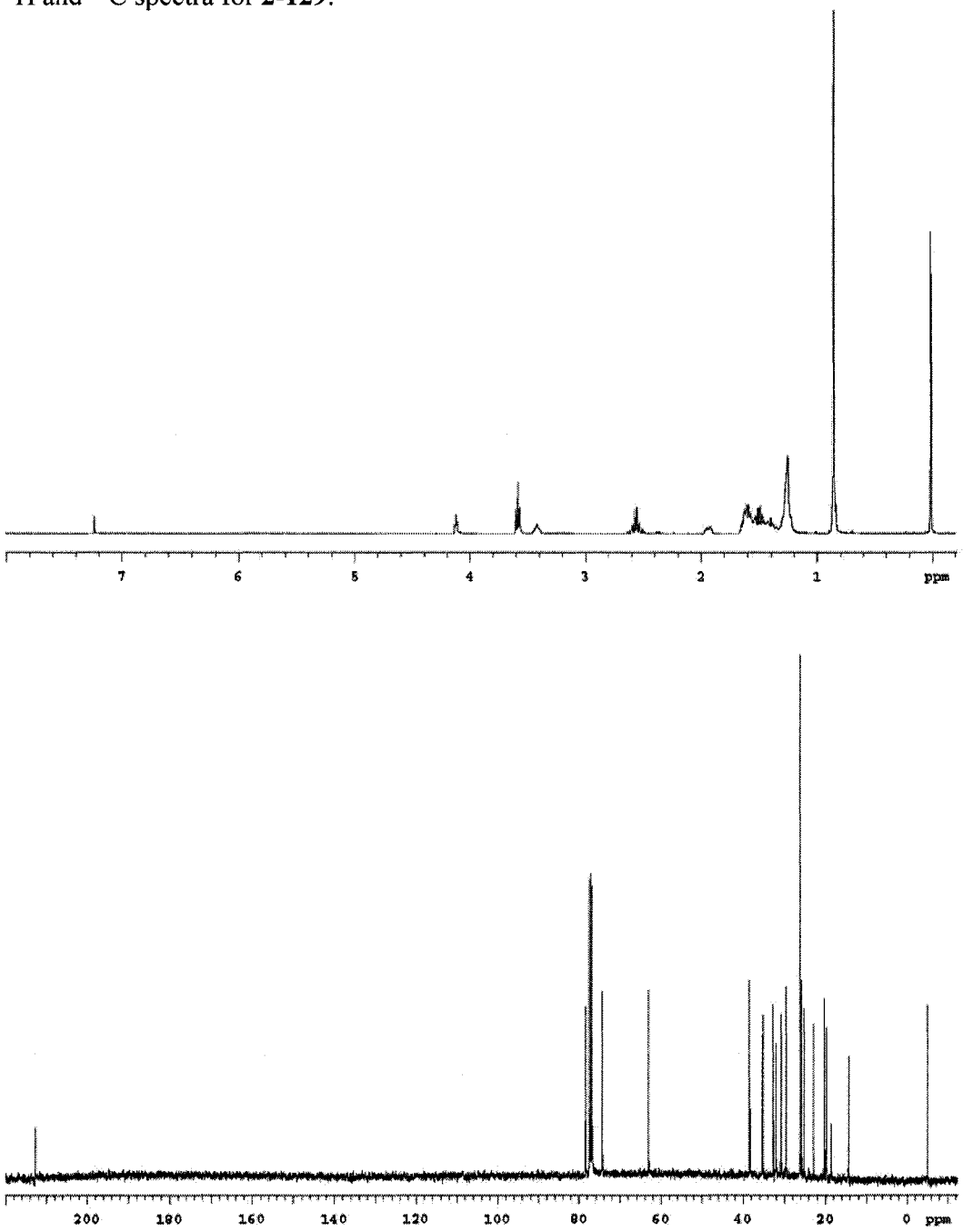

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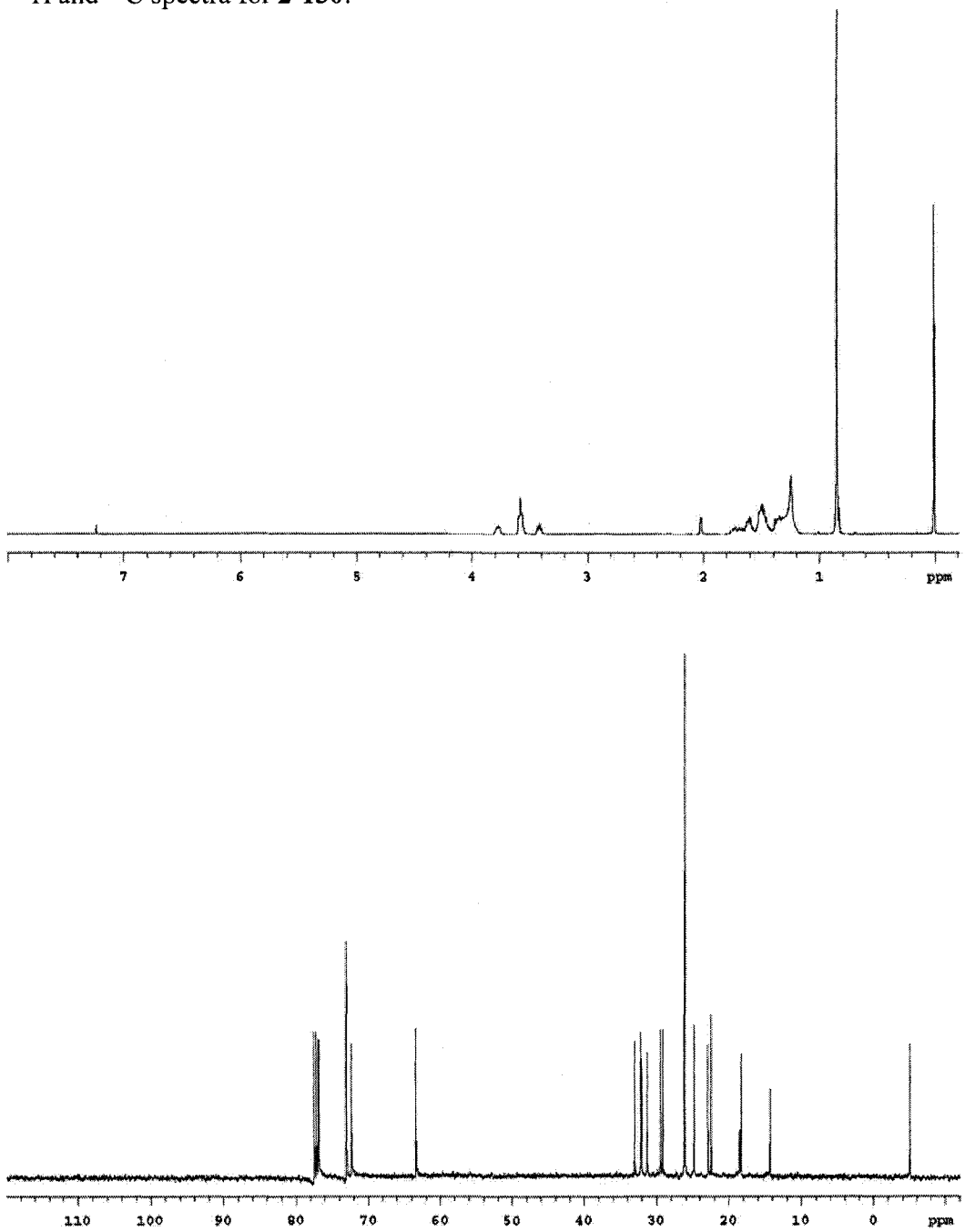

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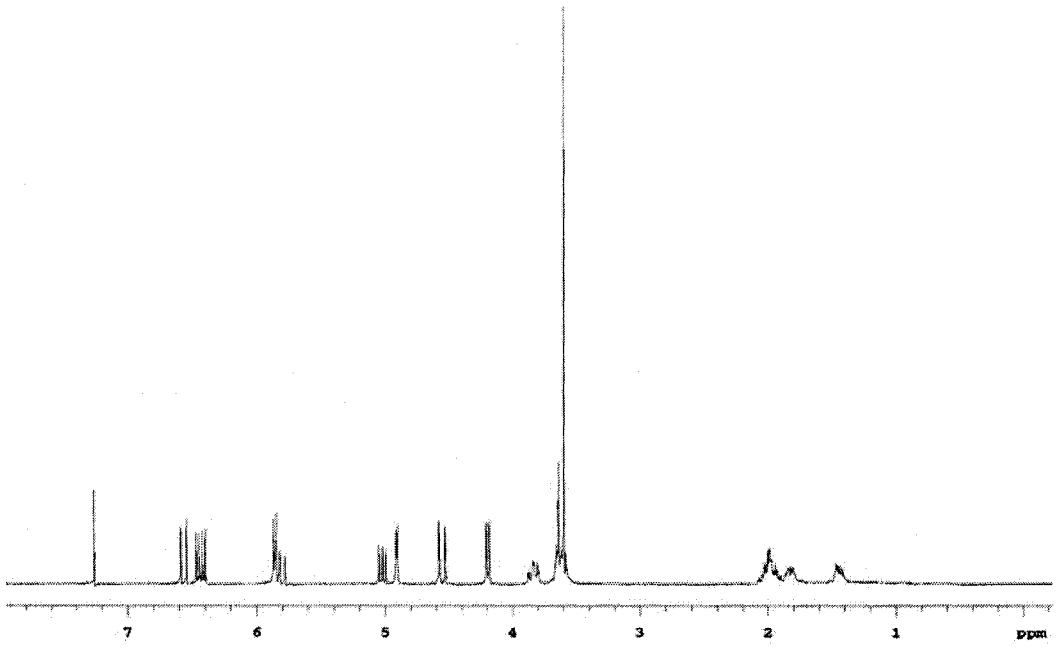
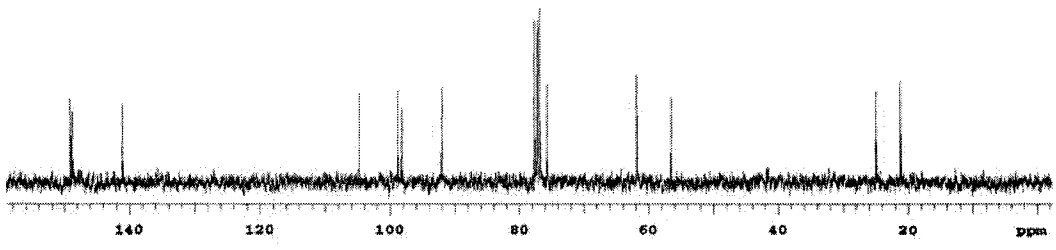




Chapter 3 Experimental

The Chemistry of 1,3-Dioxepines

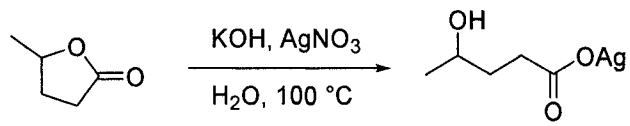
General Methods. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel (230-400 mesh). Thin layer chromatography was performed on EM Science silica gel 60 (230-400 mesh). Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, I_2, vanillin, or anisaldehyde dips followed by heating.

All chemicals were purchased from Aldrich, Alfa Aesar, Strem, or Fluka and used as received.

Infared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data recorded as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS)] or deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer at 75 MHz or 100 MHz at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons

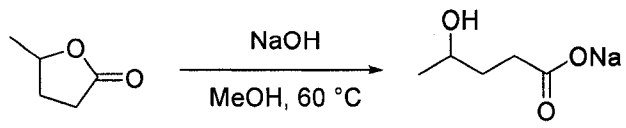
VG Autospec. Gas chromatography was performed on a Varian CP 3800 gas chromatograph equipped with a flame ionization detector using a Chrompack CP-Sil8CB (15 M x 0.25 mm) capillary column.

Synthesis of the Carboxylate Salts:



3-60 **3-63b**

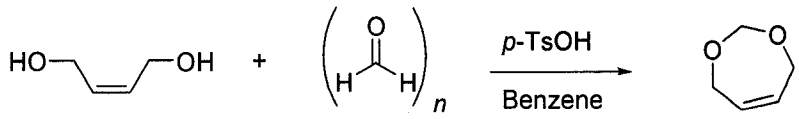
4-Hydroxy-pentanoic acid silver salt (**3-63b**): To a round bottom flask was added 1.8 g (18.83 mmol) of **3-60**, 1.05 g (18.83 mmol) of KOH and 6 mL of H_2O. The mixture was heated to 100 °C for 1h and then cooled to ambient temperature. The reaction was neutralized by adding 6N HNO_3 dropwise until pH = 8 and then 3.19 g (18.83 mmol) of $AgNO_3$ in 4 mL of H_2O was added. The reaction was cooled to 0 °C at which the Ag salt began to crash out of solution. The reaction was filtered and the salt was rinsed consecutively with MeOH then Et_2O to afford a white solid which was dried over P_2O_5 in the dark under vacuum for 24 h. The dried salt was kept at room temperature in an aluminum foil covered vial.



3-60 **3-63a**

4-Hydroxy-pentanoic acid sodium salt (**3-63a**): To a round bottom flask was added 0.28 g (2.81 mmol) of **3-60**, 0.118 g (2.95 mmol) of NaOH and 5 mL of MeOH. The reaction was refluxed for 12h and then cooled to room temperature. The solvent was removed *in vacou* to afford the desired sodium salt **3-63a**. The salt was dried over P_2O_5 for 12h under vacuum to yield 350 mg (89 %) of the dried sodium salt **3-63a**.

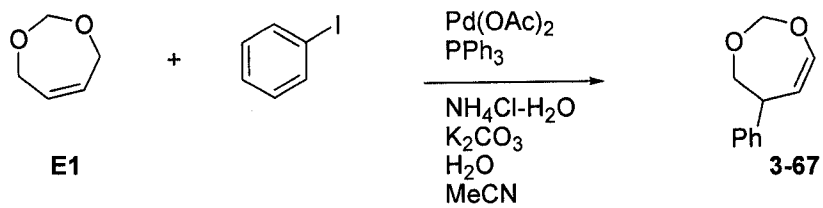
Synthesis of 6-Substituted Dioxepine:



E1

4,7-Dihydro-[1,3]-dioxepine (**E1**): A flame dried round bottom flask fitted with a Dean-Stark trap and reflux condenser was charged with 5.0 mL (60.83 mmol) of *cis*-2-buten-1,4-diol, 1.82 g (60.83 mmol) of paraformaldehyde, 115 mg (0.6 mmol) of *p*-TsOH and 10 mL of benzene. The reaction was heated to reflux and stirred until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was cooled and concentrated. The crude oil was purified by distillation (127 °C, 760 mm of Hg) to

afford 5.81 g (95 %) of the known dioxepine **E1**, which matched all reported spectral data.[1]



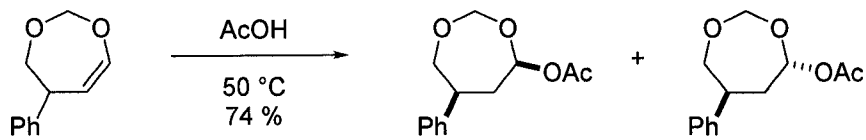
E1 **3-67**

Jeffery Conditions: 5-Phenyl-4,5-dihydro-[1,3]dioxepine (**3-67**): To a round bottom flask was added 28 mg (0.125 mmol) of $Pd(OAc)_2$, 66 mg (0.25 mmol) of PPh_3, 614 mg (6.25 mmol) of K_2CO_3, and 682 mg (2.5 mmol) of NH_4Cl-H_2O. The flask was then flushed with Ar (3x) and diluted with 0.5 mL of H_2O and 4.5 mL of MeCN. The slurry was stirred for 15 min., then 0.25 g (2.5 mmol) of **E1** and 0.28 mL (2.5 mmol) of PhI were added simultaneously and the reaction was stirred at room temperature for 12 h. After 12 h, 1g of $MgSO_4$ was added to the reaction and the reaction was diluted with 20mL of a 10% EtOAc/Hexanes solution. The reaction was stirred for 1h, then filtered through a pad of silica gel and Celite using 10% EtOAc/Hexanes as eluent. Activated charcoal and $MgSO_4$ were added to the collected filtrate and the slurry was stirred for 1h. The slurry was filtered through a pad of Celite and concentrated. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 356 mg (81 %) of the known dioxepine **3-67**, which matched all reported spectral data.[2]

E1 **3-67**

Takano Conditions: 5-Phenyl-4,5-dihydro-[1,3]dioxepine (**3-67**): To a round bottom flask was added 360 mg (1.6 mmol) of $Pd(OAc)_2$, 9.1 g (39.96 mmol) of $BnNEt_3Cl$, 17.4 mL (100 mmol) of *i*-Pr_2NEt and 30 mL of DMF. The reaction was heated to 70 °C for 30 min. then 2.0 g (19.98 mmol) of **E1** and 2.25 mL (19.98 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 50 mL). The organic layers were combined and washed with H_2O (3 x 50mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The product was purified by Kugelruhr distillation (120 °C, 5 mm of Hg) to afford 2.92 g (83 %) of the known dioxepine **3-67**, which matched all reported spectral data.[2]

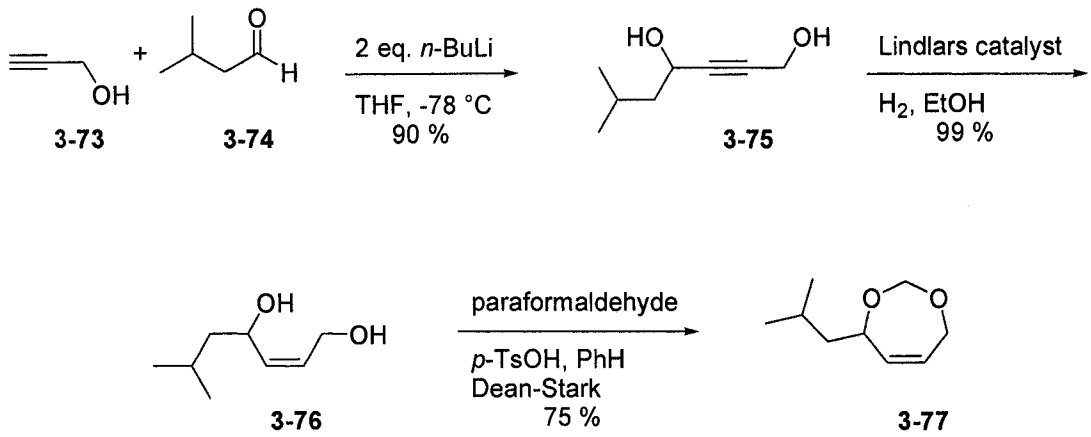
General Route for the Synthesis of 4-Acetoxy Dioxepines:



3-67 **3-68** ***cis*** **74:26** **3-69** ***trans***

Acetic acid 6-phenyl-[1,3]dioxepan-4-yl ester (**3-68** and **3-69**): A round bottom flask was charged with 1.0 g (5.68 mmol) of **3-67** and 4.0 mL of AcOH and subsequently heated to 50 °C for 12h. After 12h, the AcOH was removed by distillation and the crude oil was purified on silica gel using 10 % EtOAc/Hexanes as eluent. Purification afforded 744 mg of **3-68** and 247 mg of **3-69** in 74 % overall yield.

Synthesis of 7-Substituted Dioxepines:

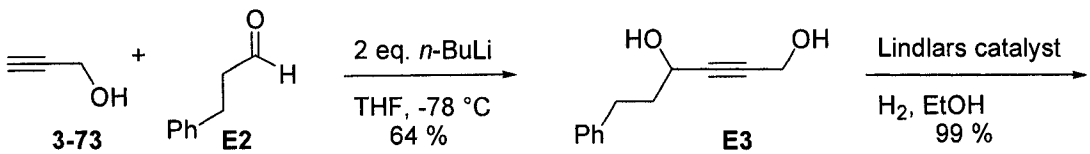


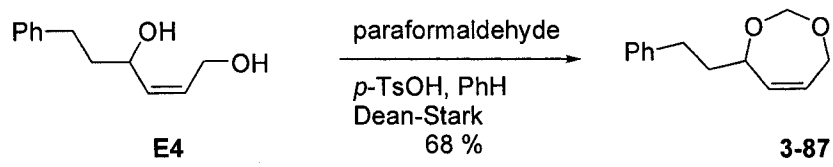
4-Isobutyl-4,7-dihydro-[1,3]-dioxepine (**3-77**): To a round bottom flask was added 2.08 mL (17.18 mmol) of **3-73** and 20 mL of THF. The reaction was cooled to -78 °C and 22.4 mL (35.73 mmol) of a 1.6 M *n*-BuLi solution in hexanes was added dropwise. After the addition, the reaction was left to stir for 1h and then 1.85 mL (17.18 mmol) of **3-74** was added all at once. The reaction was allowed to warm to room temperature over 4h and then quenched by addition of 20 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed consecutively with 30 mL of H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 2.2 g (90 %) of **3-75**.

A round bottom flask was charged with 2.2 g (15.4 mmol) of **3-75**, 0.25 g of Lindlars catalyst, 0.3 mL of quinoline, 12 mL of 1-octene, and 40 mL of EtOH. Argon was bubbled through the solution for 30 min., then a balloon of H_2 was introduced to the reaction vessel. The reaction was monitored by TLC until complete and then was filtered

through a pad of Celite. The filtrate was concentrated and then subsequently diluted with 100 mL of Et_2O. The solution was washed with a saturated aqueous solution of $CuSO_4$ and 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 2.22 g (99 %) of **3-76**.

A round bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 2.22 g (15.5 mmol) of **3-76**, 0.465 g (15.5 mmol) of paraformaldehyde, 100 mg of *p*-TsOH and 30 mL of benzene. The reaction was refluxed until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was concentrated and purified *via* Kugelruhr distillation (70 °C at 5 mm of Hg) afforded 1.8 g (75 %) of **3-77**.



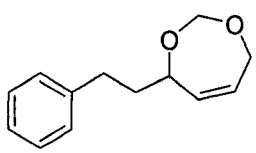


4-Phenethyl-4,7-dihydro-[1,3]-dioxepine (**3-87**): To a round bottom flask was added 2.25 mL (37.82 mmol) of **3-73** and 40 mL of THF. The reaction was cooled to -78 °C and 49.6 mL (79.42 mmol) of a 1.6 M *n*-BuLi solution in hexanes was added dropwise.

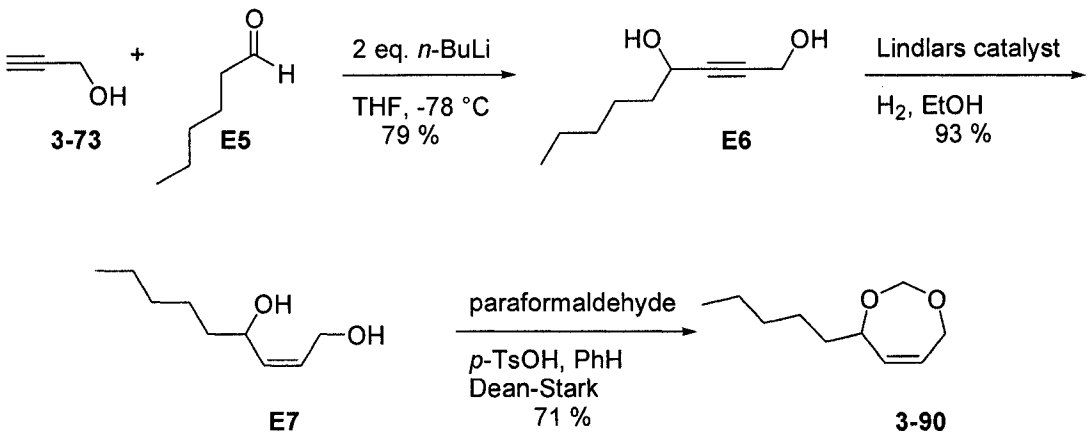
After the addition, the reaction was left to stir for 1h and then 5.0 mL (37.82 mmol) of **E2** was added all at once. The reaction was allowed to warm to room temperature over 4h and then was quenched by addition of 30 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 35 mL). The organic layers were combined and washed consecutively with 50 mL of H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 4.5 g (64 %) of **E3**.

A round bottom flask was charged with 4.50 g (23.65 mmol) of **E3**, 0.45 g of Lindlars catalyst, 0.5 mL of quinoline, 20 mL of 1-octene, and 60 mL of EtOH. Argon was bubbled through the solution for 30 min., then a balloon of H_2 was introduced to the reaction vessel. The reaction was monitored by TLC until complete and then was filtered through a pad of Celite. The filtrate was concentrated and subsequently diluted with 100 mL of Et_2O. The solution was then washed with a saturated aqueous solution of $CuSO_4$ and 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 4.7 g (99 %) of **E4**.

A round bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 4.7 g (24.45 mmol) of **E4**, 0.771 g (25.67 mmol) of paraformaldehyde, 200 mg of *p*-TsOH and 50 mL of benzene. The reaction was refluxed until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was concentrated and purified *via* Kugelruhr distillation (90 °C at 5 mm of Hg) afforded 3.4 g (68 %) of **3-87**.



4-Phenethyl-4,7-dihydro-[1,3]-dioxepine (**3-87**): R_f = 0.43 (25% EtOAc/Hexanes); IR (Thin Film) ν 3062, 3026, 2924, 2876, 2785, 1497, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.28 (2H, m), 7.14-7.19 (3H, m), 5.67 (1H, m), 5.56 (1H, m), 4.95 (1H, dd, *J* = 1.6, 5.2 Hz), 4.81 (1H, dd, *J* = 1.2, 4.8 Hz), 4.19-4.35 (3H, m), 2.79 (1H, ddd, *J* = 5.2, 9.6, 14.0 Hz), 2.67 (1H, m), 1.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 134.3, 130.2, 128.7, 128.6, 126.0, 95.7, 75.7, 67.0, 37.4, 31.9; HRMS (ESI) *m/e* calcd ($C_{13}H_{16}O_2$) 204.1106, found 204.1102.

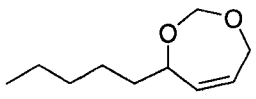


4-Pentyl-4,7-dihydro-[1,3]-dioxepine (**3-90**): To a round bottom flask was added 2.37 mL (40.64 mmol) of **3-73** and 40 mL of THF. The reaction was cooled to -78 °C and 52.1 mL (83.3 mmol) of a 1.6 M *n*-BuLi solution in hexanes was added dropwise. After the addition, the reaction was left to stir for 1h and then 5.0 mL (40.64 mmol) of **E5** was added all at once. The reaction was allowed to warm to room temperature over 4h and

then was quenched by addition of 30 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 35 mL). The organic layers were combined and washed consecutively with 50 mL of H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 5.0 g (79 %) of **E6**.

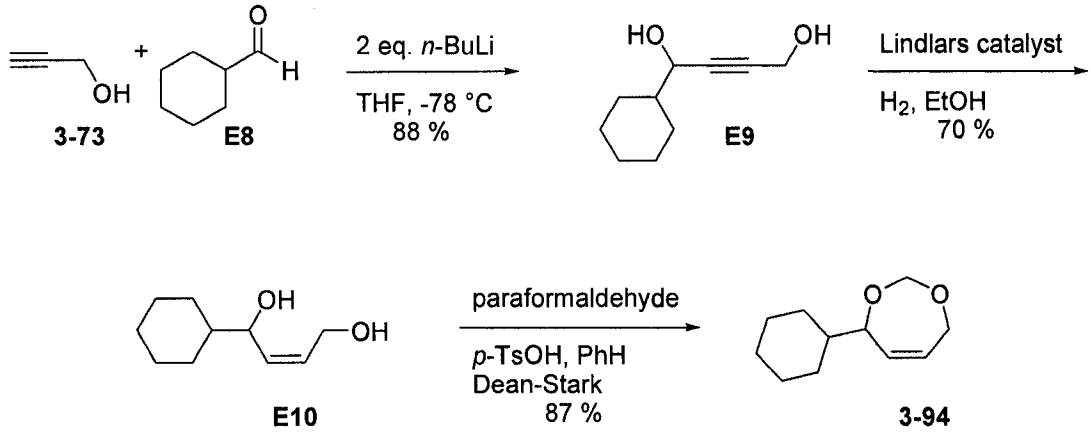
A round bottom flask was charged with 5.0 g (32.0 mmol) of **E6**, 0.45 g of Lindlars catalyst, 0.5 mL of quinoline, 20 mL of 1-octene, and 60 mL of EtOH. Argon was bubbled through the solution for 30 min., then a balloon of H_2 was introduced to the reaction vessel. The reaction was monitored by TLC until complete and then was filtered through a pad of Celite. The filtrate was concentrated and subsequently diluted with 100 mL of Et_2O. The solution was then washed with a saturated aqueous solution of $CuSO_4$ and 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 4.7 g (93 %) of **E7**.

A round bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 4.7 g (29.7 mmol) of **E7**, 0.940 g (31.19 mmol) of paraformaldehyde, 200 mg of *p*-TsOH and 50 mL of benzene. The reaction was refluxed until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was concentrated and purified *via* Kugelruhr distillation (80 °C at 5 mm of Hg) afforded 3.6 g (71 %) of **3-90**.



4-Pentyl-4,7-dihydro-[1,3]-dioxepine (**3-90**): R_f = 0.43 (25% EtOAc/Hexanes); IR (Thin Film) ν 2927, 2855, 1123, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60-5.68 (1H, m), 5.54-5.59 (1H, m), 4.91 (1H, d, J = 5.2

Hz), 4.86 (1H, d, J = 4.8 Hz), 4.17-4.32 (3H, m), 1.20-1.68 (8H, m), 0.86 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 129.9, 95.7, 76.8, 66.9, 35.6, 31.9, 25.4, 22.8, 14.3; HRMS (ESI) *m/e* calcd ($C_{10}H_{18}O_2$) 170.1307, found 170.1306.

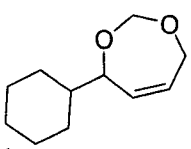


4-Cyclohexyl-4,7-dihydro-[1,3]-dioxepine (**3-94**): To a round bottom flask was added 2.08 mL (17.18 mmol) of **73** and 20 mL of THF. The reaction was cooled to -78 °C and 22.4 mL (35.73 mmol) of a 1.6 M *n*-BuLi solution in hexanes was added dropwise. After the addition, the reaction was left to stir for 1h and then 1.0 mL (17.18 mmol) of **E8** was added all at once. The reaction was allowed to warm to room temperature over 4h and then was quenched by addition of 20 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed consecutively with 30 mL of H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 2.54 g (88 %) of **E9**.

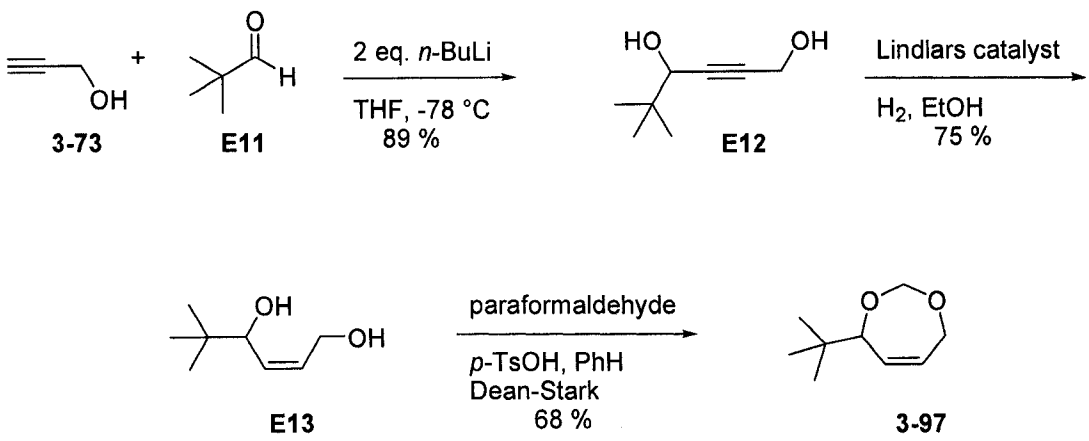
A round bottom flask was charged with 2.54 g (15.1 mmol) of **E9**, 0.25 g of Lindlars catalyst, 0.3 mL of quinoline, 12 mL of 1-octene, and 40 mL of EtOH. Argon

was bubbled through the solution for 30 min., then a balloon of H_2 was introduced to the reaction vessel. The reaction was monitored by TLC until complete and then was filtered through a pad of Celite. The filtrate was concentrated and subsequently diluted with 100 mL of Et_2O. The solution was then washed with a saturated aqueous solution of $CuSO_4$ and 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 1.81 g (70 %) of **E10**.

A round bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 1.81 g (10.65 mmol) of **E10**, 0.336 g (11.18 mmol) of paraformaldehyde, 100 mg of *p*-TsOH and 30 mL of benzene. The reaction was refluxed until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was concentrated and purified *via* Kugelruhr distillation (90 °C at 5 mm of Hg) afforded 1.7 g (87 %) of **3-94**.



4-Cyclohexyl-4,7-dihydro-[1,3]-dioxepine (**3-94**): R_f = 0.54 (25% EtOAc/Hexanes); IR (Thin Film) ν 2925, 2852, 1449, 1122, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63-5.72 (2H, m), 4.91 (1H, d, J = 4.8 Hz), 4.76 (1H, d, J = 4.8 Hz), 4.15-4.31 (2H, m), 4.05 (1H, m), 1.6-1.8 (4H, m), 1.44-1.54 (1H, m), 1.00-1.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 130.5, 95.9, 80.7, 66.9, 42.8, 29.3, 28.0, 26.6, 26.4; HRMS (ESI) *m/e* calcd ($C_{11}H_{18}O_2$) 182.1306, found 182.1303.

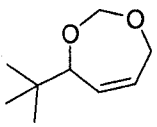


4-tert-Butyl-4,7-dihydro-[1,3]-dioxepine (**3-97**): To a round bottom flask was added 0.536 mL (9.21 mmol) of **73** and 20 mL of THF. The reaction was cooled to -78 °C and 12.1 mL (19.34 mmol) of a 1.6 M *n*-BuLi solution in hexanes was added dropwise. After the addition, the reaction was left to stir for 1h and then 1.0 mL (9.21 mmol) of **E11** was added all at once. The reaction was allowed to warm to room temperature over 4h and then was quenched by addition of 20 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed consecutively with 30 mL of H_2O then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 1.16 g (89 %) of **E12**.

A round bottom flask was charged with 1.16 g (15.1 mmol) of **E12**, 0.08 g of Lindlars catalyst, 0.1 mL of quinoline, 7 mL of 1-octene, and 20 mL of EtOH. Argon was bubbled through the solution for 30 min., then a balloon of H_2 was introduced to the reaction vessel. The reaction was monitored by TLC until complete and then was filtered through a pad of Celite. The filtrate was concentrated and subsequently diluted with 100 mL of Et_2O. The solution was then washed with a saturated aqueous solution of $CuSO_4$

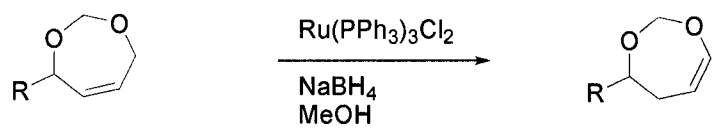
and 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 0.881 g (75 %) of **E13**.

A round bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 0.881 g (6.11 mmol) of **E13**, 0.193 g (6.42 mmol) of paraformaldehyde, 100 mg of *p*-TsOH and 30 mL of benzene. The reaction was refluxed until the theoretical amount of water was collected in the Dean-Stark trap. The reaction was concentrated and purified *via* Kugelruhr distillation (75 °C at 5 mm of Hg) afforded 0.65 g (68 %) of **3-97**.



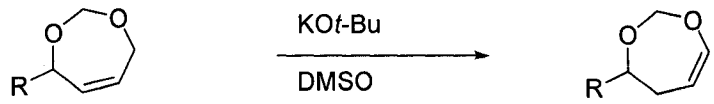
4-tert-Butyl-4,7-dihydro-[1,3]-dioxepine (**3-97**): R_f = 0.44 (10% EtOAc/Hexanes); IR (Thin Film) ν 3036, 2957, 2909, 2872, 2781, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, m), 5.70 (1H, m), 4.90 (1H, d, *J* = 4.8 Hz), 4.75 (1H, d, *J* = 4.8 Hz), 4.25 (2H, m), 3.87 (1H, m), 0.96 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 131.2, 96.2, 83.8, 66.7, 34.5, 26.0; HRMS (ESI) *m/e* calcd ($C_9H_{16}O_2$) 126.1956, found 126.1950.

General Procedure for the Synthesis of the Isomerized Products:



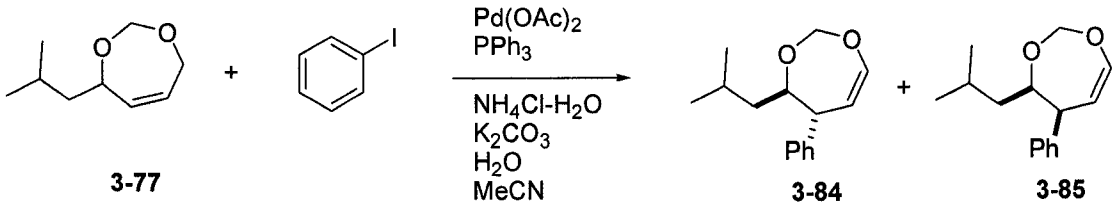
A round bottom flask was charged with 26 mg (0.166 mmol) of **3-77**, 1.0 mg (0.00033 mmol) of $Ru(PPh_3)_3Cl_2$ and 2.0 mL of dry MeOH. The reaction was refluxed

for 1h, then 1.0 mg (0.0083 mmol) of $NaBH_4$ was added and the reaction was left to stir for 6h. After 6h, the reaction was cooled and diluted with water and Et_2O. The layers were separated and the organic layer was dried over $MgSO_4$. The slurry was filtered and concentrated to afford 8.5 mg (33 %) of **3-78**.



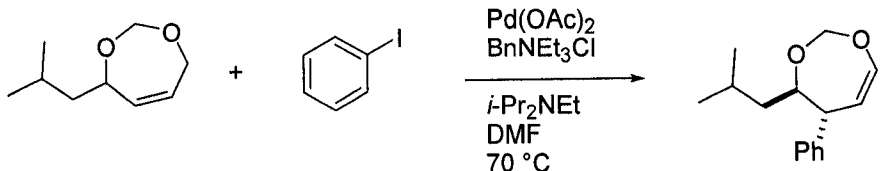
To a round bottom flask was added 26 mg (0.166 mmol) of **3-77** and 2.0 mL of dry DMSO. Next, 19 mg (0.17 mmol) of freshly sublimed KO*t*-Bu was added portionwise to the flask and the reaction was left to stir at room temperature for 6h. After 6h, the reaction was diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 5 mL). The organic layers were combined and washed with water (3 x 5 mL). After separation of the layers, the organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel (5 % EtOAc/Hexanes as eluent) to afford 21 mg (81 %) of the isomerized dioxepine **3-78**.

General Procedure for the Heck Reaction on Unsymmetrical Dioxepines:



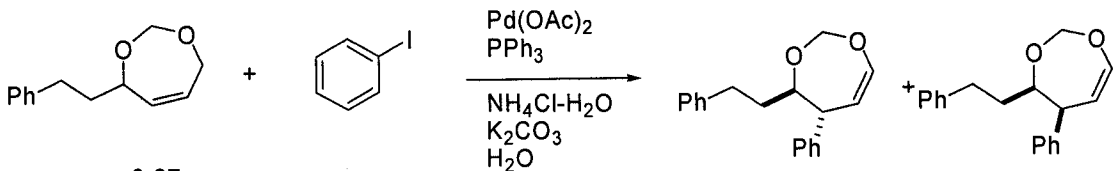
3-77 **3-84** **3-85**

Jeffery Conditions: 4-Isobutyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (**3-84**): To a round bottom flask was added 4 mg (0.016 mmol) of $Pd(OAc)_2$, 8.5 mg (0.032 mmol) of PPh_3, 79 mg (0.8 mmol) of K_2CO_3, and 87.3 mg (0.32 mmol) of NH_4Cl-H_2O. The flask was flushed with Ar (3x) and diluted with 0.25 mL of H_2O and 1.0 mL of MeCN. The slurry was stirred for 15 min., then 0.050 g (0.32 mmol) of **3-77** and 0.036 mL (0.32 mmol) of PhI were added simultaneously and the reaction was stirred at room temperature for 12 h. Next, 0.5 g of $MgSO_4$ was added to the reaction and the reaction was diluted with 10 mL of a 10% EtOAc/Hexanes solution. The reaction was stirred for 1h, then filtered through a pad of silica gel and Celite using 10% EtOAc/Hexanes as eluent. Activated charcoal and $MgSO_4$ were added to the collected filtrate and the slurry was stirred for 1h. The slurry was then filtered through a pad of Celite and concentrated. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 60 mg (81 %) of the dioxepines **3-84** and **3-85**, as a 90:10 mixture.



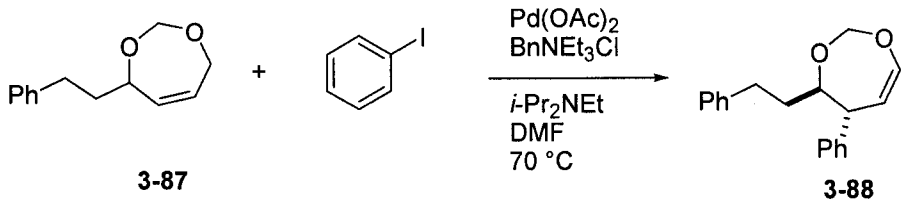
3-77 **3-84**

Takano Conditions: 4-Isobutyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (**3-84**): To a round bottom flask was added 4 mg (0.016 mmol) of $Pd(OAc)_2$, 0.146 g (0.64 mmol) of $BnNEt_3Cl$, 0.28 mL (1.6 mmol) of *i*-Pr_2NEt and 1.0 mL of DMF. The reaction was heated to 70 °C for 30 min. then 0.050 g (0.32 mmol) of **3-77** and 0.036 mL (0.32 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 50 mL). The organic layers were combined and washed with H_2O (3 x 50mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 60 mg (81 %) of the dioxepine, **3-84**.



3-87 **3-88** **3-89**

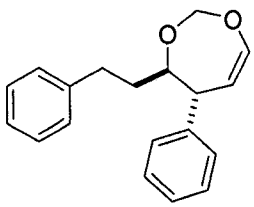
Jeffery Conditions: 4-Phenethyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (**3-88**): To a round bottom flask was added 60 mg (0.25 mmol) of $Pd(OAc)_2$, 130 mg (0.49 mmol) of PPh_3, 1.2080 g (12.3 mmol) of K_2CO_3, and 1.3363 g (4.9 mmol) of NH_4Cl-H_2O. The flask was then flushed with Ar (3x) and diluted with 1.0 mL of H_2O and 10.0 mL of MeCN. The slurry was stirred for 15 min., then 1.0 g (4.9 mmol) of **3-87** and 0.55 mL (4.9 mmol) of PhI were added simultaneously and the reaction was stirred at room temperature for 12 h. Next, 2.0 g of $MgSO_4$ was added to the reaction and the reaction was diluted with 40 mL of a 10% EtOAc/Hexanes solution. The reaction was stirred for 1h, then filtered through a pad of silica gel and Celite using 10% EtOAc/Hexanes as eluent. Activated charcoal and $MgSO_4$ were added to the collected filtrate and the slurry was stirred for 1h. The slurry was then filtered through a pad of Celite and concentrated. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 1.1 g (81 %) of the dioxepines **3-88** and **3-89**, as an 85:15 mixture.



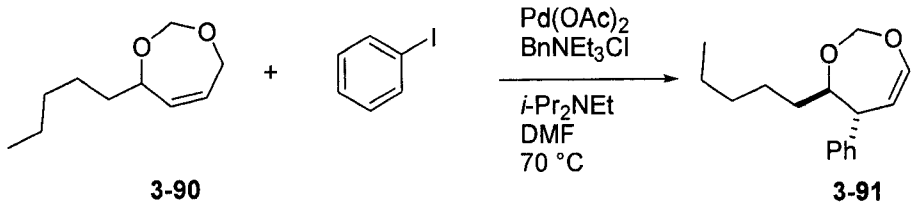
3-87 **3-88**

Takano Conditions: 4-Phenethyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (**3-88**): To a round bottom flask was added 9 mg (0.04 mmol) of $Pd(OAc)_2$, 0.223 g (0.98 mmol) of $BnNEt_3Cl$, 0.427 mL (2.45 mmol) of *i*-Pr_2NEt and 1.0 mL of DMF. The reaction was

heated to 70 °C for 30 min. then 0.10 g (0.49 mmol) of **3-87** and 0.055 mL (0.49 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The organic layers were combined and washed with H_2O (3 x 20mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 108 mg (79 %) of the dioxepine, **3-84**.

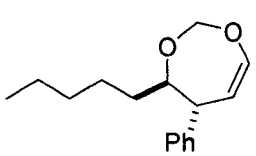


(4R, 5R*)-4-Phenethyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-84**): R_f = 0.56 (25% EtOAc/Hexanes); IR (Thin Film) ν 3026, 2923, 2872, 1649, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06-7.30 (8H, m), 6.95-7.00 (2H, m), 6.30 (1H, dd, *J* = 2.8, 7.6 Hz), 5.45 (1H, d, *J* = 7.2 Hz), 4.71 (1H, d, *J* = 6.8 Hz), 4.58 (1H, dd, *J* = 2.0, 7.6 Hz), 3.52 (1H, ddd, *J* = 2.4, 2.4, 9.6 Hz), 3.24 (1H, ddd, *J* = 2.4, 10.0, 10.0 Hz), 2.79 (1H, ddd, *J* = 4.8, 10.0, 14.0 Hz), 2.48 (1H, ddd, *J* = 8.8, 8.8, 17.2 Hz), 1.55-1.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 142.2, 142.0, 128.9, 128.5, 128.4, 127.1, 125.9, 112.0, 97.4, 85.7, 54.0, 35.2, 32.0; HRMS (ESI) *m/e* calcd ($C_{19}H_{20}O_2$) 280.1463, found 280.1460.



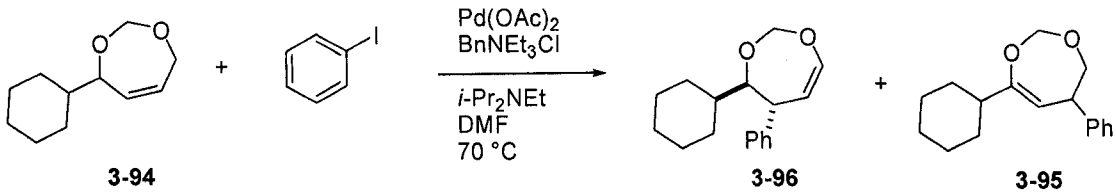
3-90 **3-91**

Takano Conditions: (4R, 5R*)-4-Pentyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-91**): To a round bottom flask was added 5.2 mg (0.023 mmol) of $Pd(OAc)_2$, 0.134 g (0.588 mmol) of $BnNEt_3Cl$, 0.256 mL (1.47 mmol) of *i*-Pr_2NEt and 1.0 mL of DMF. The reaction was heated to 70 °C for 30 min. then 0.050 g (0.294 mmol) of **3-90** and 0.033 mL (0.294 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The organic layers were combined and washed with H_2O (3 x 20mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 57 mg (79 %) of the dioxepine, **3-91**.



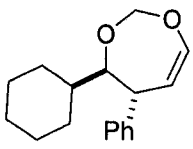
(4R, 5R*)-4-Pentyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-91**): R_f = 0.57 (10% EtOAc/Hexanes); IR (Thin Film) ν 3062, 3028, 2926, 2870, 2800, 1647, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13-7.32 (5H, m), 5.42 (1H, dd, *J* = 1.6, 6.8 Hz), 4.70 (1H, dd, *J* = 1.2, 6.8 Hz), 4.58 (1H, ddd, *J* = 1.6, 1.6, 7.6 Hz), 3.49 (1H, m), 3.27 (1H, m), 1.02-1.50 (8H, m), 0.79 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 128.8, 128.6, 127.0, 111.9, 97.4,

86.9, 54.1, 33.7, 31.8, 25.6, 22.7, 14.2; HRMS (ESI) *m/e* calcd ($C_{16}H_{22}O_2$) 246.1620, found 246.1616.

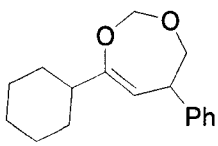


3-94 **3-96** **3-95**

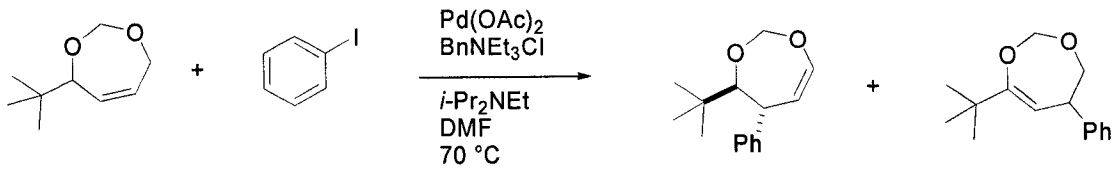
Takano Conditions: (4R, 5R*)-4-Pentyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-96**) *and 7-Cyclohexyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-95**): To a round bottom flask was added 5.2 mg (0.023 mmol) of $Pd(OAc)_2$, 0.134 g (0.588 mmol) of $BnNEt_3Cl$, 0.256 mL (1.47 mmol) of *i*-Pr_2NEt and 1.0 mL of DMF. The reaction was heated to 70 °C for 30 min. then 0.054 g (0.294 mmol) of **3-94** and 0.033 mL (0.294 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The organic layers were combined and washed with H_2O (3 x 20mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 58 mg (77 %) of a 74:36 mixture of regiosiomers, **3-96** and **3-95**, respectively.



(4R, 5R*)-4-Cyclohexyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* **(3-96)**: R_f = 0.60 (10% EtOAc/Hexanes); IR (Thin Film) ν 3061, 3027, 2921, 2853, 1647, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-7.32 (5H, m), 6.27 (1H, dd, *J* = 3.2, 8.0 Hz), 5.41 (1H, d, *J* = 6.8 Hz), 4.72 (1H, d, *J* = 6.8 Hz), 4.57 (1H, dd, *J* = 2.4, 7.6 Hz), 3.76 (1H, ddd, *J* = 2.8, 2.8, 10.4 Hz), 3.16 (1H, d, *J* = 10.4 Hz), 1.75 (2H, m), 1.57 (2H, m), 1.39 (1H, m), 1.17-1.31 (2H, m), 0.92-1.13 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 128.9, 128.3, 127.4, 126.9, 112.1, 97.6, 91.3, 50.0, 39.0, 31.4, 26.6, 26.6, 26.4, 25.7; HRMS (ESI) *m/e* calcd ($C_{17}H_{22}O_2$) 258.1620, found 258.1624.



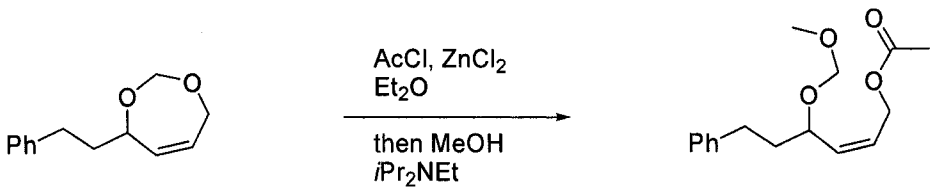
7-Cyclohexyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine **(3-95)**: R_f = 0.51 (10% EtOAc/Hexanes); IR (Thin Film) ν 3061, 3027, 2926, 2853, 2802, 1664, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.32 (5H, m), 5.17 (1H, d, *J* = 6.8 Hz), 4.89 (1H, d, *J* = 4.0 Hz), 4.73 (1H, d, *J* = 6.8 Hz), 3.86 (1H, dd, *J* = 3.6, 11.2 Hz), 3.75 (1H, ddd, *J* = 4.0, 4.0, 8.4 Hz), 3.43 (1H, dd, *J* = 8.8, 11.2 Hz), 1.96 (1H, m), 1.70-1.85 (4H, m), 1.63 (1H, m), 1.10-1.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 142.2, 128.8, 128.1, 127.0, 107.8, 97.5, 76.0, 47.5, 44.1, 31.2, 31.1, 26.5, 26.4, 26.4; HRMS (ESI) *m/e* calcd ($C_{17}H_{22}O_2$) 258.1620, found 258.1623.



3-97 **3-99** **3-98**

Takano Conditions: (4R, 5R*)-4-Pentyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-99**) *and 7-tert-Butyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine* (**3-98**): To a round bottom flask was added 6.0 mg (0.030 mmol) of $Pd(OAc)_2$, 0.146 g (0.640 mmol) of $BnNEt_3Cl$, 0.280 mL (1.60 mmol) of *i*-Pr_2NEt and 1.0 mL of DMF. The reaction was heated to 70 °C for 30 min. then 0.050 g (0.320 mmol) of **3-97** and 0.036 mL (0.320 mmol) of PhI were added simultaneously and the reaction was stirred for 12h. After 12h, the reaction was cooled to room temperature and diluted with water and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The organic layers were combined and washed with H_2O (3 x 20mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The concentrate was purified on silica gel using 10% EtOAc/Hexanes as eluent to afford 45 mg (61 %) of a 38:62 mixture of regiosiomers, **3-99** and **3-98**, respectively.

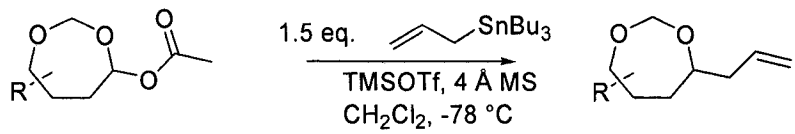
General Procedure for Methylene Acetal Cleavage:



3-87 **3-100**

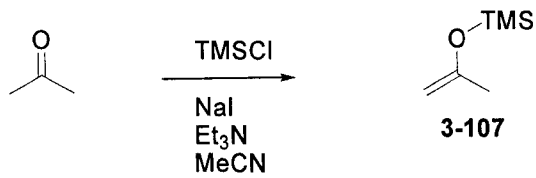
To a round bottom flask was added 0.100 g (0.49 mmol) of **3-87**, 2 drops of a 1.0 M $ZnCl_2$ solution in Et_2O and 3 mL of Et_2O. A solution of freshly distilled AcCl (0.042 mL in 1.0 mL of Et_2O; 0.59 mmol) was added dropwise to the reaction and the reaction was left to stir for 1h. In a separate round bottom flask was added 0.103 mL (0.59 mmol) of *i*-Pr_2NEt, 0.120 mL (2.96 mmol) of dry MeOH and 2.0 mL of Et_2O. This flask was cooled to 0 °C and the other flask, after 1h, was added dropwise *via* cannula. During the addition, copious amounts of ammonium salts were formed. After complete addition, the cooling bath was removed and the reaction mixture was stirred for 1h at room temperature. The reaction mixture was then concentrated at reduced pressure, pentane was added to the residue, and the flask was cooled to induce crystallization of the ammonium salts. The supernatant was passed through a short column of neutral alumina using pentane as the eluent. Removal of the solvent by rotary evaporation afforded 115 mg (84 %) of essentially pure alkoxymethyl ether acetate **3-100**.

General Procedure for the Allylation of 4-Acetoxy Dioxepanes:



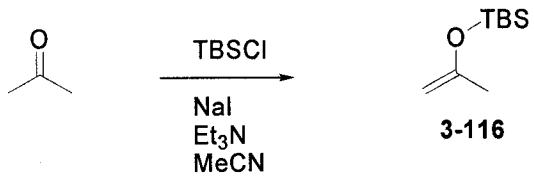
To a round bottom flask was added 10 mg (0.042 mmol) of **3-68**, 20 mg of 4 Å MS and 0.5 mL of CH_2Cl_2. After cooling to -78 °C, 0.020 mL (0.063 mmol) of allyltributyl tin and 0.01 mL (0.044 mmol) of TMSOTf were added and the reaction was stirred for 4h. After 4h, the reaction was quenched by addition of H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and washed with 10 mL of brine. Following separation, the organic layer was dried over $MgSO_4$, filtered and concentrated to afford the crude residue. The residue was purified on silica gel (10 % EtOAc/Hexanes) to afford 5.7 mg (63 %) of a 1:1 mixture of allylated products, **3-105**.

Synthesis of Required Enol Silanes and Silyl Ketene Acetals:

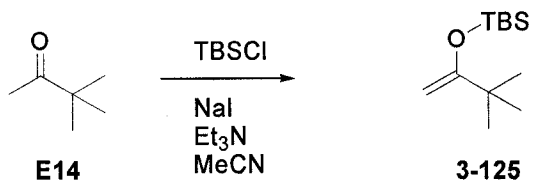


A round bottom flask was charged with 3.67 mL (50.0 mmol) of acetone, 8.65 mL (62.0 mmol) of Et_3N, 7.86 mL (62.0 mmol) of TMSCl and 50 mL of MeCN. To this reaction was added 9.3 g (62.0 mmol) of NaI over 15 min. and the reaction was left to stir for 30 min. The reaction was quenched by addition of 50 mL of pentane and 50 mL of H_2O.

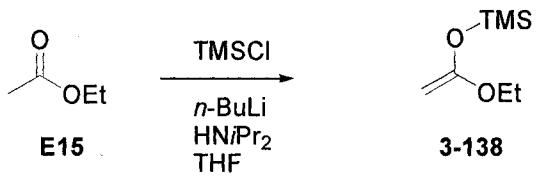
The layers were separated and the aqueous layer was further extracted with pentane (2 x 50 mL). The organic layers were combined, washed with ice water (2 x 50 mL) and then separated. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by distillation to afford 4.0 g (61 %) of the desired enol silane **3-107**, which matched all reported spectral data.[3]



A round bottom flask was charged with 2.0 mL (27.24 mmol) of acetone, 4.75 mL (34.0 mmol) of Et_3N, 5.13 g (34.0 mmol) of TBSCl and 35 mL of MeCN. To this reaction was added 5.1 g (34.0 mmol) of NaI over 15 min. and the reaction was left to stir for 30 min. The reaction was quenched by addition of 50 mL of pentane and 50 mL of H_2O. The layers were separated and the aqueous layer was further extracted with pentane (2 x 50 mL). The organic layers were combined, washed with ice water (2 x 50 mL) and then separated. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by distillation to afford 3.7 g (79 %) of the desired enol silane **3-116**, which matched all reported spectral data.[4]



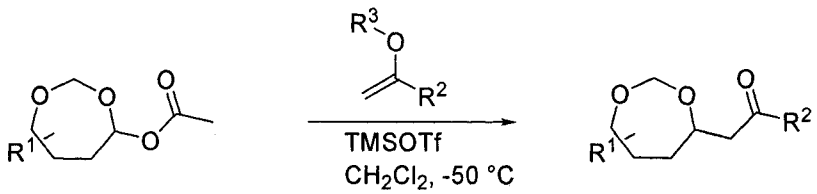
A round bottom flask was charged with 5.0 mL (40.2 mmol) of **E14**, 7.0 mL (50.25 mmol) of Et_3N, 7.6 g (50.25 mmol) of TBSCl and 50 mL of MeCN. To this reaction was added 7.53 g (50.25 mmol) of NaI over 15 min. and the reaction was left to stir for 30 min. The reaction was quenched by addition of 50 mL of pentane and 50 mL of H_2O. The layers were separated and the aqueous layer was further extracted with pentane (2 x 50 mL). The organic layers were combined, washed with ice water (2 x 50 mL) and then separated. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by distillation to afford 4.6 g (66 %) of the desired enol silane **3-125**, which matched all reported spectral data.[5]



A round bottom flask was charged with 10.0 mL (102.4 mmol) of **E15** and 150 mL of THF. To this flask was added a freshly prepared solution of LDA [70.4 mL (112.6 mmol) of a 1.6 M solution of *n*-BuLi in hexanes and 17.2 mL (122.9 mmol) of $HNiPr_2$] at 0 °C and the reaction was stirred at this temperature for 4h. After 2 h, 15.7 mL (123.9 mmol) of TMSCl was added dropwise over 30 min and the reaction was left to warm to room temperature over 2h. After warming, the reaction was quenched by addition of 50 mL of pentane and 50 mL of H_2O. The layers were separated and the aqueous layer was further extracted with pentane (2 x 50 mL). The organic layers were combined, washed with ice water (2 x 50 mL) and then separated. The organic layer was dried over Na_2SO_4,

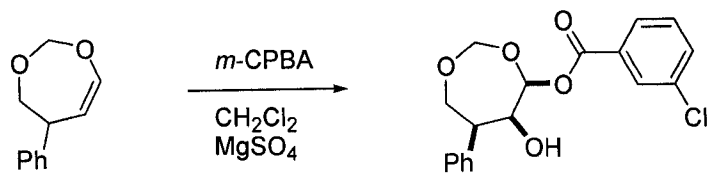
filtered and concentrated. The residue was purified by distillation to afford 12.2 g (74 %) of the desired silyl ketene acetal **3-138**, which matched all reported spectral data.[6]

General Procedure for the Addition of Enol Silanes and Silyl Ketene Acetals:



A round bottom flask was charged with 20 mg (0.086 mmol) of **3-68**, 0.030 mL (0.172 mmol) of **3-107** and 1.0 mL of CH_2Cl_2. The reaction was cooled to -50 °C and 3.3 μL (0.018 mmol) of TMSOTf was added. The reaction was left to stir for 2h and then was quenched with 1.0 mL of water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$. The slurry was filtered and concentrated to yield the crude residue. The residue was purified on silica gel (10 % EtOAc/Hexanes) to afford 16.6 mg (83 %) of a 75:25 mixture of the desired diastereomers.

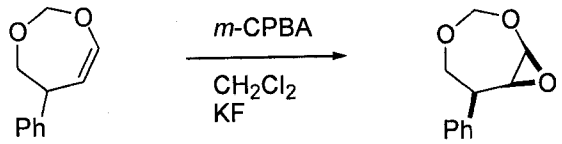
General Procedure for the Epoxidation/Acetate Opening of a 1,3-Dioxepine:



3-67 **3-138**

To a round bottom flask was added 0.25 g (1.42 mmol) of **3-67**, 0.25 g of $MgSO_4$ and 15 mL of CH_2Cl_2. To this mixture was added 0.5 g (2.84 mmol) of *m*-CPBA and the reaction was left to stir at room temperature for 12h. After 12h, the reaction was quenched by addition of 10 mL of a 1:1 solution of saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was dried over $MgSO_4$. The slurry was filtered and concentrated. The concentrate was purified on silica gel (25 % EtOAc/Hexanes) to afford 445 mg (90 %) of **3-138** as a white solid.

General Procedure for the Epoxidation of 1,3-Dioxepines with Camp's Reagent:



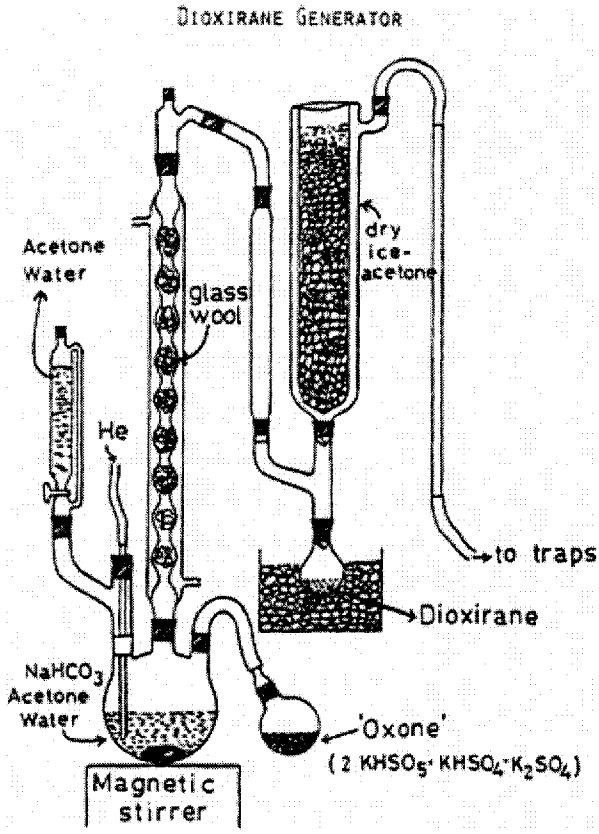
3-67 **3-153**

A round bottom flask was charged with 0.245 g (1.42 mmol) of *m*-CPBA and 10 mL of CH_2Cl_2. The mixture was stirred until the solution became homogenous and then 0.165 g (2.84 mmol) of KF was added all at once. The solution became cloudy and was stirred for 1h. A solution of 0.10 g (0.568 mmol) of **3-67** in 5 mL of CH_2Cl_2 was added to the reaction and the reaction was stirred for 6h. After 6h, the reaction was filtered through a

pad of Celite, eluting with CH_2Cl_2. The filtrate was then concentrated to afford 73 mg (67 %) of the epoxide **3-153**.

Procedure for Generation of DMDO solution:

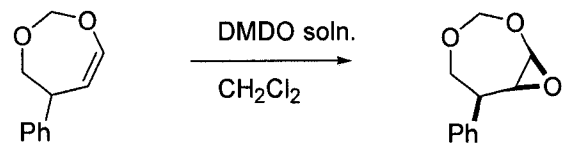
Figure 1.



A 1L, three necked, round bottom flask containing a mixture of water (80 mL), acetone (50 mL) and $NaHCO_3$ (96 g) is equipped with a magnetic stirring bar and a pressure equalizing addition funnel containing water (60 mL) and acetone (60 mL). A solid addition flask containing Oxone (180 g) is attached to the reaction vessel via a rubber

tube. An air condenser loosely packed with glass wool is attached to the reaction vessel. The outlet of the air condenser is connected to a Dewar condenser filled with dry ice-acetone that is connected to a receiving flask cooled in a dry ice-acetone bath. The receiving flask is connected to a drying tube and aspirator. A gas inlet tube is connected to the reaction flask and a stream of Ar is bubbled through the reaction mixture (Figure 1). The Oxone is added in portions while the acetone-water mixture is simultaneously added dropwise. The reaction mixture is stirred vigorously throughout the addition of reagents. A yellow solution of DMDO in acetone collects in the receiving flask. Vigorous stirring is continued for an additional 15 min. while a slight vacuum (~30 mm of Hg, water aspirator) is applied to the cold trap. The collected yellow DMDO solution (60 – 80 mL) is dried over Na_2SO_4, filtered and stored in the freezer over Na_2SO_4. The DMDO content of the solution is assayed using a reported technique.[7] The DMDO content of the solution is generally in the range of 0.05-0.07 M.

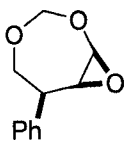
General Procedure for Epoxidation with DMDO:



3-67 **3-153**

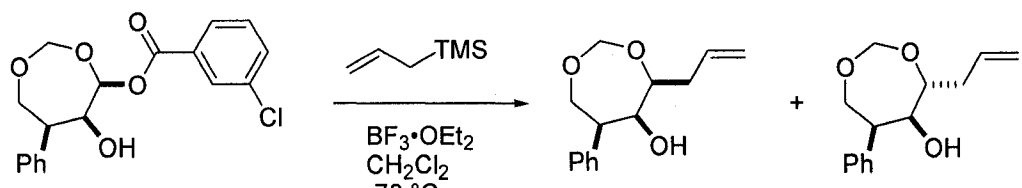
A round bottom flask is charged with 100 mg (0.568 mmol) of **3-67** and 2 mL of CH_2Cl_2 and is subsequently cooled to 0 °C. To the cooled solution is added ~2 mL of a DMDO solution in acetone *via* cannula. After the addition, the reaction is stirred for 30 min. then

warmed to room temperature and concentrated *in vacou* to afford 89 mg (82 %) of the desired epoxide **3-153**.



6-Phenyl-2,4,8-trioxa-bicyclo[5.1.0]-octane (**3-153**): R_f = 0.464 (25 % EtOAc/Hexanes); IR (Thin Film) ν 2906, 1171, 1090, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.41 (5H, m), 5.11 (1H, d, *J* = 2.4), 4.93 (1H, d, *J* = 7.2), 4.80 (1H, d, *J* = 7.2), 3.95 (2H, d, *J* = 2.1), 3.66 (1H, ddd, *J* = 2.1, 2.1, 4.2), 3.23 (1H, dd, *J* = 2.1, 4.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.4, 128.8, 127.8, 91.4, 81.7, 73.1, 61.0, 47.7.

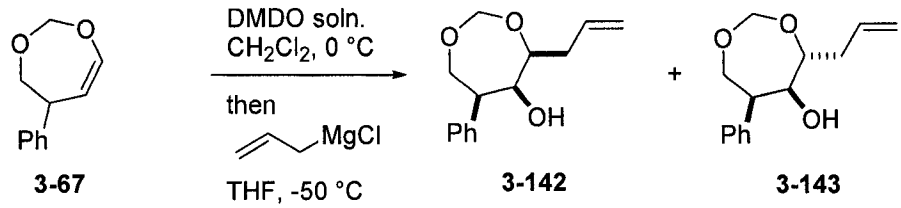
General Procedure for the Allylation of Tri-substituted Dioxepanes:



3-138 **3-142** **3-143**

A round bottom flask is charged with 30 mg (0.086 mmol) of **3-138**, 0.0145 mL (0.0172 mmol) of allyltrimethyl silane and 1.5 mL of CH_2Cl_2. The flask was cooled to -78 °C and 12.0 μL (0.095 mmol) of $BF_3•OEt_2$ was added dropwise. The reaction was left to stir at this temperature for 3h. After 3h, the reaction was quenched by the addition of 1.0 mL of H_2O. The layers were separated and the organic layer was dried over $MgSO_4$. The slurry was filtered and concentrated to afford the crude product. The crude product was purified on silica gel (25 % EtOAc/Hexanes) to afford 16.4 (82 %) of **3-142** and **3-143** as a 1:1 mixture of isomers.

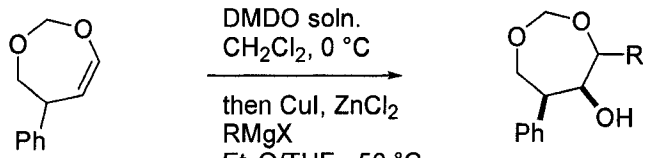
General Procedure for the One-Pot Epoxidation/Grignard Addition Reaction:



3-67 **3-142** **3-143**

A round bottom flask is charged with 25 mg (0.142 mmol) of **3-67** and 1 mL of CH_2Cl_2 and is subsequently cooled to 0 °C. To the cooled solution is added ~2 mL of a DMDO solution in acetone *via* cannula. After the addition, the reaction is stirred for 30 min. then warmed to room temperature and concentrated *in vacou* to afford the epoxide **3-153**. The epoxide **3-153** was diluted with 1 mL of THF and cooled to -50 °C. After cooling, 0.106 mL (0.213 mmol) of a 2.0 M solution of allyl magnesium chloride in THF was added dropwise. After the addition, the reaction was stirred at this temperature for 6h then diluted with 2 mL of H_2O and 4 mL of Et_2O. The layers were separated and the organic layer was dried over $MgSO_4$. The slurry was filtered, concentrated and purified on silica gel (25 % EtOAc/Hexanes) to afford 22 mg (67 %) of **3-142** and **3-143** as a 1:1 mixture of diastereomers.

General Procedure for the One-Pot Epoxidation/Cuprate Addition Reaction:

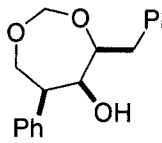


3-67 **3-154**

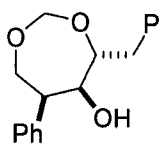
A round bottom flask is charged with 25 mg (0.142 mmol) of **3-67** and 1 mL of CH_2Cl_2 and is subsequently cooled to 0 °C. To the cooled solution is added ~2 mL of a DMDO solution in acetone *via* cannula. After the addition, the reaction is stirred for 30 min. then warmed to room temperature and concentrated *in vacou* to afford the epoxide **3-153**. The epoxide **3-153** was then diluted with 1 mL of Et_2O and 5 drops of a 1.0 M $ZnCl_2$ solution in Et_2O.

In a separate flask was added 8.1 mg (0.0426 mmol) of CuI, 0.210 mL of Et_2O and 0.040 mL of THF. The flask was cooled to 0 °C and 0.426 mL (0.426 mmol) of a 1.0 M solution of BnMgCl in Et_2O was added dropwise. The reaction was stirred at this temperature for 1h, then was introduced *via* cannula into the other reaction vessel dropwise while maintaining the temperature at -50 °C. The reaction was left to stir at this temperature for 12h, then was warmed to room temperature. The reaction was quenched with 2 mL of H_2O and then diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with 10 mL of H_2O. The layers were separated and the organic layer was

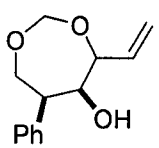
dried over $MgSO_4$. The slurry was filtered, concentrated and purified on silica gel (15 % EtOAc/Hexanes) to afford 32 mg (79 %) of the trisubstituted dioxepane **3-154**.



(4S, 5S*, 6S*)-4-Benzyl-6-phenyl-[1,3]-dioxepan-5-ol* (**E14**): R_f = 0.189 (10 % EtOAc/Hexanes); IR (Thin Film) ν 3445, 3028, 2885, 1135, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (10H, m), 4.72 (1H, d, *J* = 4.5), 4.50 (1H, d, *J* = 4.4), 3.92 (1H, ddd, *J* = 2.7, 9.3, 9.3), 3.78 (2H, m), 3.63 (1H, dd, *J* = 3.3, 9.3), 3.29 (1H, dd, *J* = 2.7, 14.1), 2.86 (1H, ddd, *J* = 4.2, 10.8, 10.8), 2.72 (1H, dd, *J* = 9.6, 14.1), 1.63 (1H, d, *J* = 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 138.8, 129.8, 129.3, 128.5, 128.4, 127.8, 126.3, 93.8, 79.3, 77.5, 66.5, 55.6, 38.7.



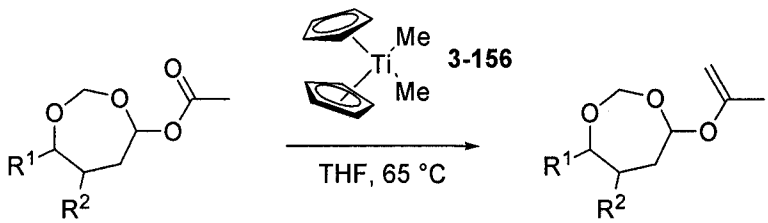
(4R, 5S*, 6S*)-4-Benzyl-6-phenyl-[1,3]-dioxepan-5-ol* (**E15**): R_f = 0.205 (10 % EtOAc/Hexanes); IR (Thin Film) ν 3414, 2921, 2883, 1453, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (10H, m), 5.07 (1H, d, *J* = 6.6), 4.73 (1H, d, *J* = 6.6), 4.22 (1H, dd, *J* = 9.3, 12.3), 4.02 (2H, m), 3.91 (1H, m), 3.45 (1H, ddd, *J* = 3.3, 3.3, 6.9), 2.99 (1H, dd, *J* = 3.0, 5.4), 2.05 (1H, d, *J* = 3.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.4, 129.6, 129.0, 128.8, 128.6, 127.3, 127.2, 126.6, 96.3, 85.3, 68.7, 49.7, 40.1.



4-Vinyl-6-phenyl-[1,3]-dioxepan-5-ol (**E16**): R_f = 0.180 (10 % EtOAc/Hexanes); IR (Thin Film) ν 3440, 3028, 2885, 1130, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.40 (10H, m), 5.95-6.10 (2H, m), 5.27-5.48 (4H, m),

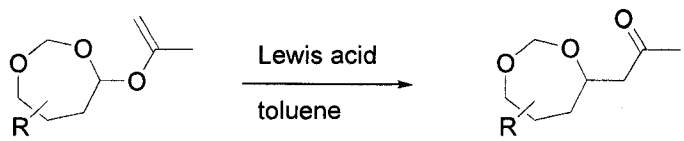
5.09 (1H, d, J = 6.6), 4.94 (1H, d, J = 6.3), 4.91 (1H, d, J = 4.5), 4.86 (1H, d, J = 4.5), 4.41 (1H, m), 4.20 (2H, m), 3.72-4.02 (4H, m), 3.63 (1H, ddd, J = 2.1, 8.7, 8.7), 3.41 (1H, m), 2.90 (1H, ddd, J = 4.2, 10.5, 10.5), 2.38 (1H, d, J = 6.0), 1.62 (1H, d, J = 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.8, 136.2, 135.3, 129.2, 129.0, 128.6, 128.4, 127.7, 127.3, 118.2, 117.7, 94.0, 93.4, 83.4, 79.4, 77.5, 77.1, 68.6, 66.9, 54.7, 48.5.

General Procedure for the Petasis Olefination of 4-Acetoxy Dioxepanes:



To a round bottom flask was added 0.180 g (0.68 mmol) of **3-82** and 6.0 mL (1.63 mmol) of a 0.27 M solution of **3-156**[8,9] in toluene and THF. The mixture was heated to 75 °C for 12 h in the dark and then was cooled to room temperature. The cooled solution was diluted with 10 mL of hexanes and the orange precipitate was filtered off through a plug of Celite. The filtrate was concentrated and purified on silica gel (10 % EtOAc/Hexanes) to afford 83 mg (47 %) of the vinyl ether.

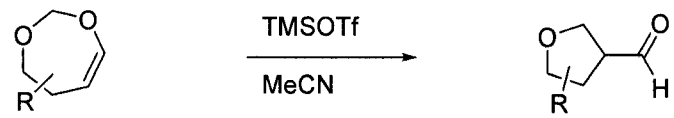
General Procedure for the [1,3]-Rearrangement Vinyl Ethers:



BF_3•OEt_2 Mediated Rearrangement Procedure: A round bottom flask was charged with 10 mg (0.0381 mmol) of **3-158** and 0.5 mL of toluene. The flask was cooled to -78 °C and 5.0 μL (0.04 mmol) of BF_3•OEt_2 was added dropwise. The reaction was stirred for 1h, then quenched with 1 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with 10 mL of brine. After the layers were separated, the organic layer was dried over $MgSO_4$. The slurry was filtered, concentrated and purified on silica gel (10 % EtOAc/Hexanes) to afford 8.3 mg (83 %) of **3-121** as a 75:25 mixture of diastereomers.

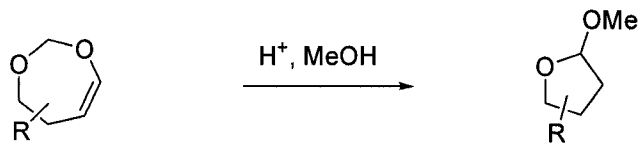
Stereoretentive Rearrangement Procedure: A round bottom flask was charged with 10 mg (0.0381 mmol) of **3-158** and 0.5 mL of toluene. The flask was cooled to -78 °C and 0.076 mL (0.152 mmol) of a 2.0 M solution of $AlMe_3$ in toluene was added. The reaction was stirred for 2 min., then 5.0 μL (0.04 mmol) of BF_3•OEt_2 was added dropwise. The reaction was stirred for 1h, then quenched with 1 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with 10 mL of brine. After the layers were separated, the organic layer was dried over $MgSO_4$. The slurry was filtered, concentrated and purified on silica gel (10 % EtOAc/Hexanes) to afford 3.9 mg (39 %) of **3-121** as a 55:45 mixture of diastereomers.

General Procedure for the Ring Contraction of 1,3-Dioxepines:



A round bottom flask was charged with 0.100 mg (0.430 mmol) of **3-84** and 2.0 mL of dry MeCN. The reaction was cooled to -50 °C and 8.0 μL (0.043 mmol) of TMSOTf was added dropwise. The reaction was stirred at this temperature for 1h then quenched with 2 mL of H_2O and diluted with 5 mL of Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with 10 mL of brine. After separation, the organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel (10 % EtOAc/Hexanes) to afford 69 mg (69 %) of **3-162** and **3-163**, as a 74:26 mixture, respectively.

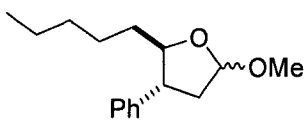
General Procedure for the Hydrolysis of the Methylene Acetal:



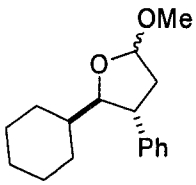
p-TsOH Mediated Acetal Cleavage: To a round bottom flask was added 25 mg (0.10 mmol) of **3-91**, 5 mg of *p*-TsOH, 3.0 mL of MeOH and 1.0 mL of H_2O. The reaction was heated to 50 °C for 12h and then was diluted with 10 mL of Et_2O and 5 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The

concentrate was purified on silica gel (25 % EtOAc/Hexanes) to afford 14 mg (56 %) of **3-164** as a 1:1 mixture of anomeric isomers.

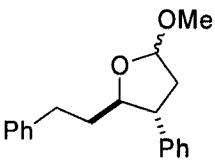
AcOH Mediated Acetal Cleavage: A round bottom flask was charged with 25 mg (0.10 mmol) of **3-91**, 0.1 mL of AcOH, 0.11 mL of Ac_2O, 1 drop of H_2SO_4 and 0.2 mL of MeOH at 0 °C. The reaction was stirred for 1h and then was diluted with 2 mL Et_2O and 2 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The concentrate was purified on silica gel (25 % EtOAc/Hexanes) to afford 14 mg (56 %) of **3-164** as a 1:1 mixture of anomeric isomers.



(2R, 3S*)-5-Methoxy-2-pentyl-3-phenyl-tetrahydro-furan* (**3-164**): R_f = 0.39 (25% EtOAc/Hexanes); IR (Thin Film) ν 3029, 2953, 2930, 2859, 2828, 1455, 1103, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23-7.4 (10H, m), 5.17 (1H, dd, *J* = 2.4, 5.7 Hz), 5.13 (1H, dd, *J* = 4.8 Hz), 3.95-4.15 (2H, m), 3.49 (3H, s), 3.44 (3H, s), 3.25-3.34 (2H, m), 2.89 (1H, m), 2.71 (1H, ddd, *J* = 5.7, 10.5, 13.5 Hz), 2.37 (1H, dd, *J* = 3.0, 12.9 Hz), 2.27 (1H, dd, *J* = 4.8, 12.0 Hz), 2.05 (1H, ddd, *J* = 2.4, 7.8, 13.5 Hz), 1.22-1.70 (17H, m), 0.91 (3H, t, *J* = 6.9 Hz), 0.89 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.5, 128.8, 128.7, 128.2, 127.8, 126.8, 126.7, 104.8, 104.6, 87.5, 84.6, 54.9, 54.4, 50.8, 49.1, 42.7, 36.3, 33.5, 32.1, 32.0, 26.3, 26.2, 22.7, 14.2, 14.1; HRMS (FAB+) *m/e* calcd (M^+ - OMe)($C_{15}H_{21}O$) 217.1592, found 217.1520.



2-Cyclohexyl-5-methoxy-3-phenyl-tetrahydro-furan (**3-167**): R_f = 0.635 (25 % EtOAc/Hexanes); IR (Thin Film) ν 2924, 2852, 1449, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-7.33 (10H, m), 5.05 (1H, dd, *J* = 1.5, 4.2), 5.02 (1H, d, *J* = 3.6), 3.86 (2H, dd, *J* = 6.0, 8.8), 3.40 (3H, s), 3.36 (3H, s), 3.35 (1H, m), 3.02 (1H, dd, *J* = 9.2, 17.6), 2.59 (1H, ddd, *J* = 5.6, 10.8, 13.6), 2.29 (1H, dd, *J* = 7.2, 12.8), 2.08 (1H, ddd, *J* = 4.8, 12.0, 12.0), 1.86-2.00 (2H, m), 1.82 (1H, m), 1.64-1.74 (2H, m), 1.38-1.64 (8H, m), 0.80-1.22 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.7, 128.8, 128.7, 128.4, 128.0, 126.7, 126.5, 104.7, 104.4, 91.4, 88.6, 54.8, 54.6, 47.3, 46.6, 44.2, 43.8, 43.6, 41.4, 30.0, 30.0, 29.5, 28.7, 26.7, 26.4, 26.3, 26.2; HRMS (FAB+) *m/e* calcd (M^+ - OMe)($C_{16}H_{21}O$) 229.1592, found 229.1588.



5-Methoxy-2-phenethyl-3-phenyl-tetrahydro-furan (**3-168**): R_f = 0.530 (25 % EtOAc/Hexanes); IR (Thin Film) ν 3027, 2927, 1495, 1454, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07-7.31 (20H, m), 5.12 (1H, dd, *J* = 2.4, 5.6), 5.09 (1H, d, *J* = 4.8), 4.04 (1H, ddd, *J* = 4.8, 8.4, 8.4), 3.96 (1H, ddd, *J* = 4.0, 8.8, 8.8), 3.44 (3H, s), 3.41 (3H, s), 3.26 (1H, ddd, *J* = 8.0, 8.0, 16.0), 2.74-2.90 (2H, m), 2.51-2.70 (4H, m), 2.32 (1H, dd, *J* = 7.2, 12.8), 2.20 (1H, dd, *J* = 5.2, 12.4), 1.99 (1H, ddd, *J* = 2.4, 8.4, 13.6), 1.76-1.96 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 142.3, 141.5, 141.3, 128.9, 128.8, 128.5, 128.4, 128.3, 127.9, 127.0, 126.9, 126.0, 105.0, 104.7, 86.8, 83.9, 77.4, 55.1, 54.6, 50.9, 49.1, 42.8, 42.7, 38.3, 35.6, 32.9; HRMS (FAB+) *m/e* calcd (M^+ - OMe)($C_{18}H_{19}O$) 251.1436, found 251.1431.

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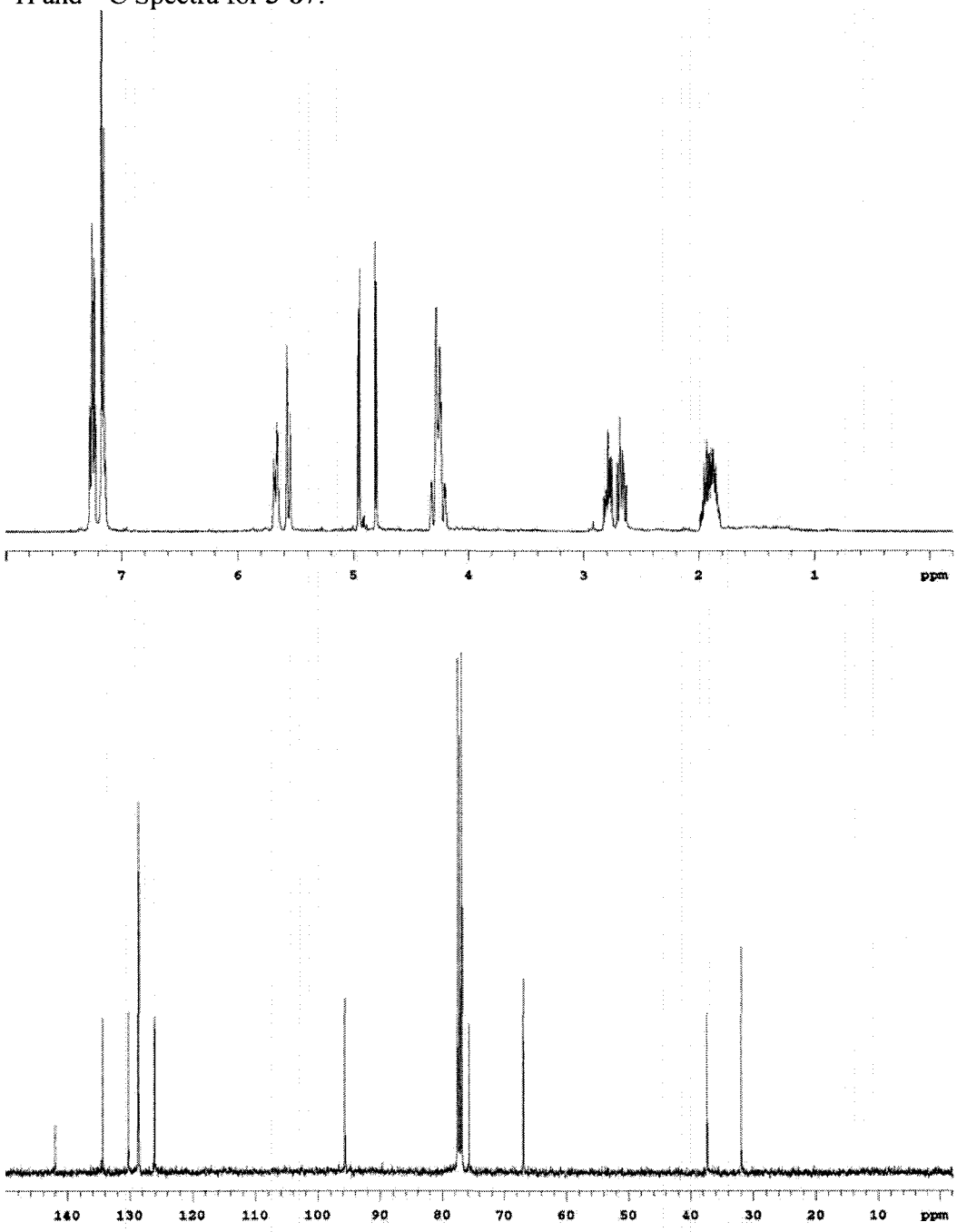
(9) Petasis, N. A.; Bzowej, E. I. *Journal of the American Chemical Society* **1990**, *112*, 6392-6394.

^{1}H and ^{13}C Spectra for **3-87**:



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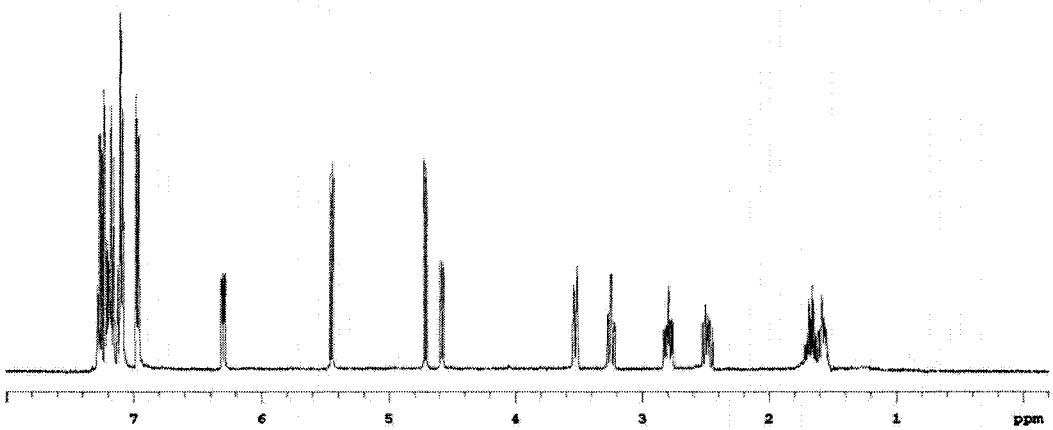

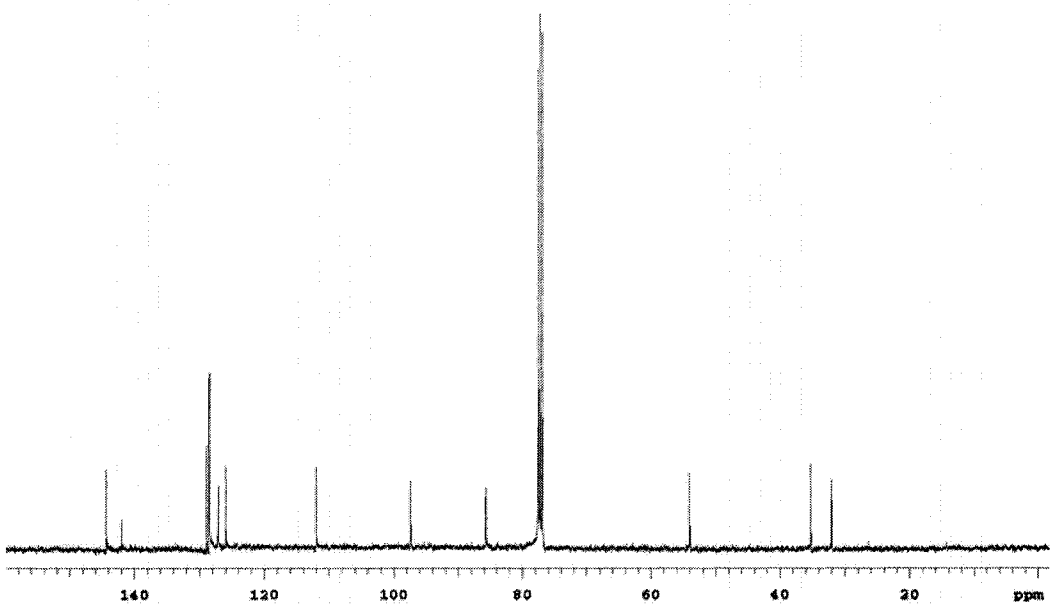

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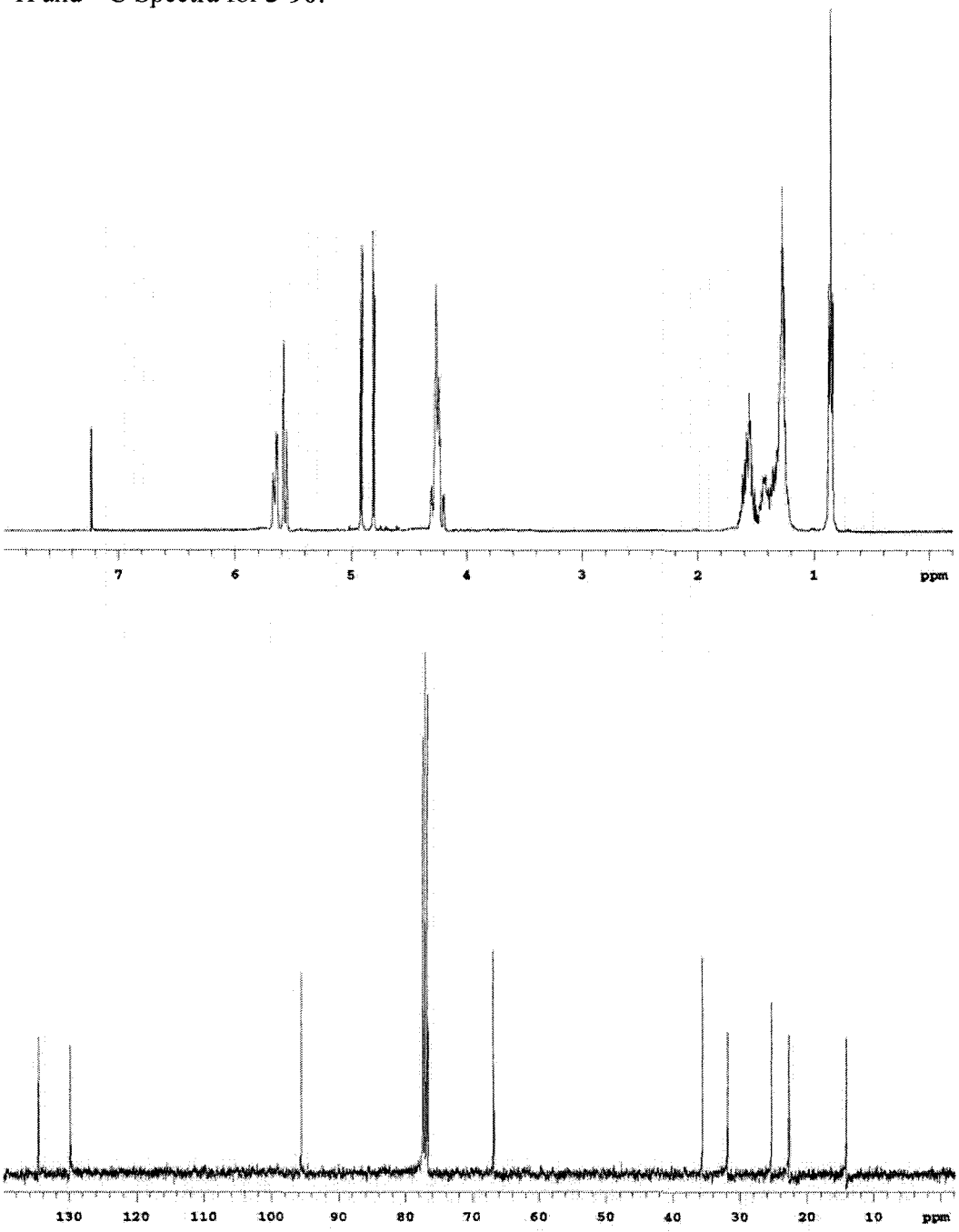

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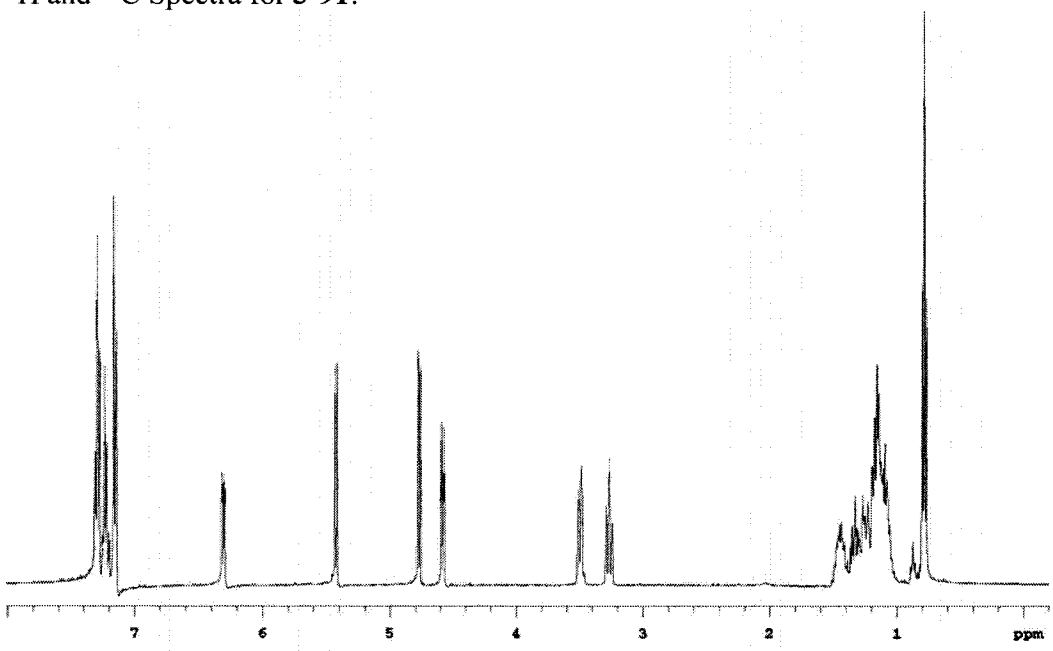

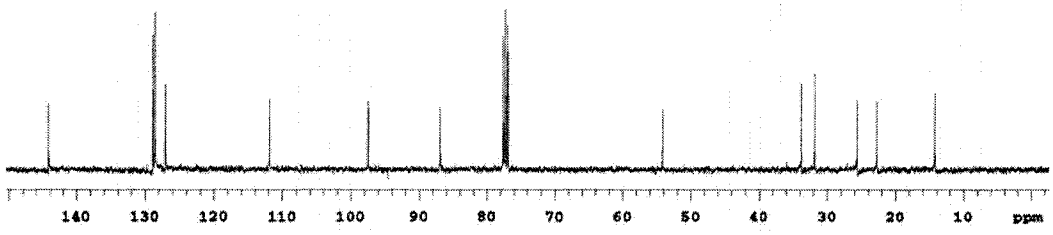

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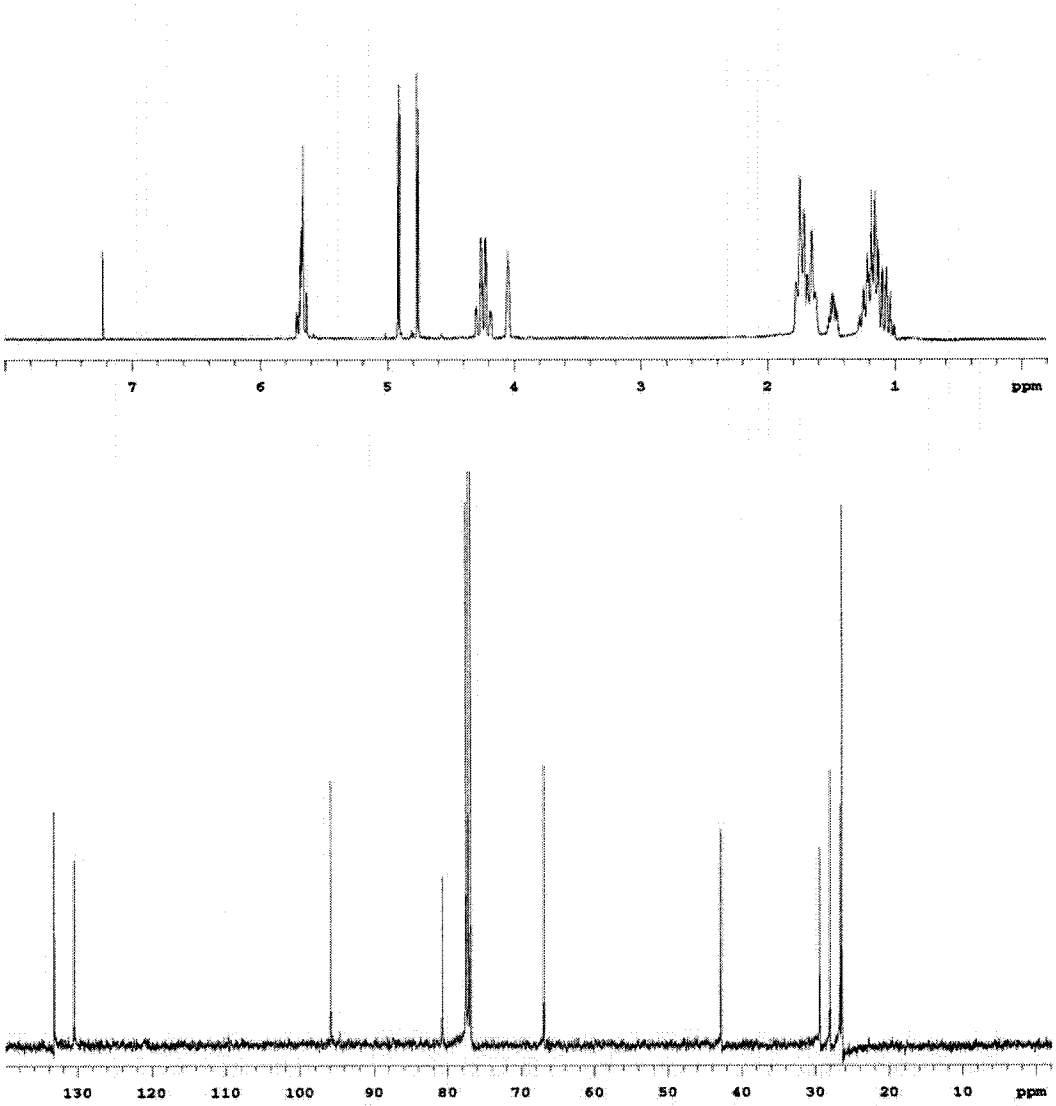

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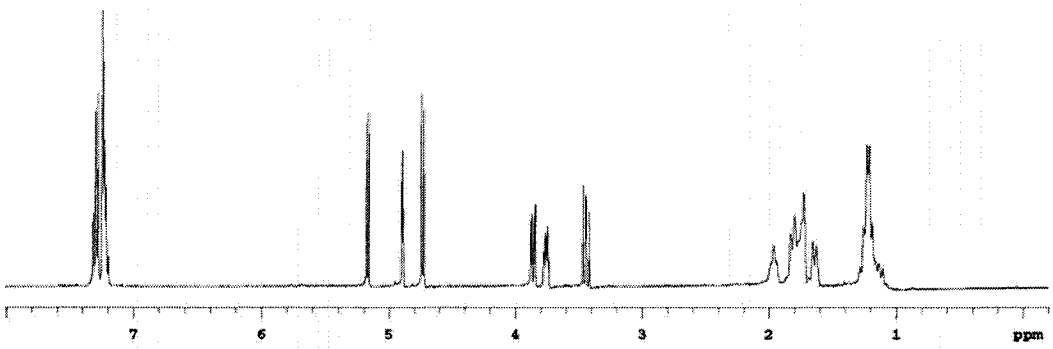

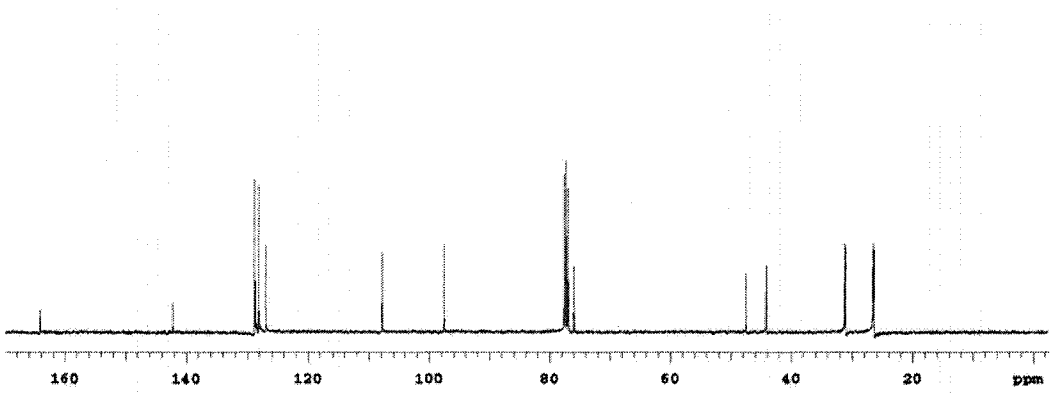

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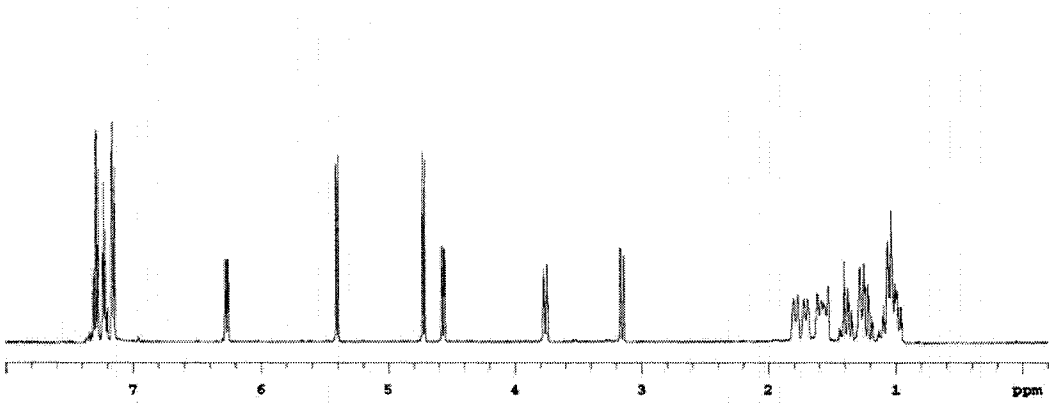

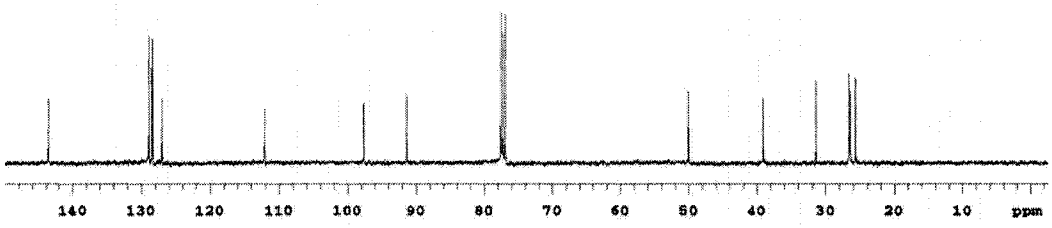

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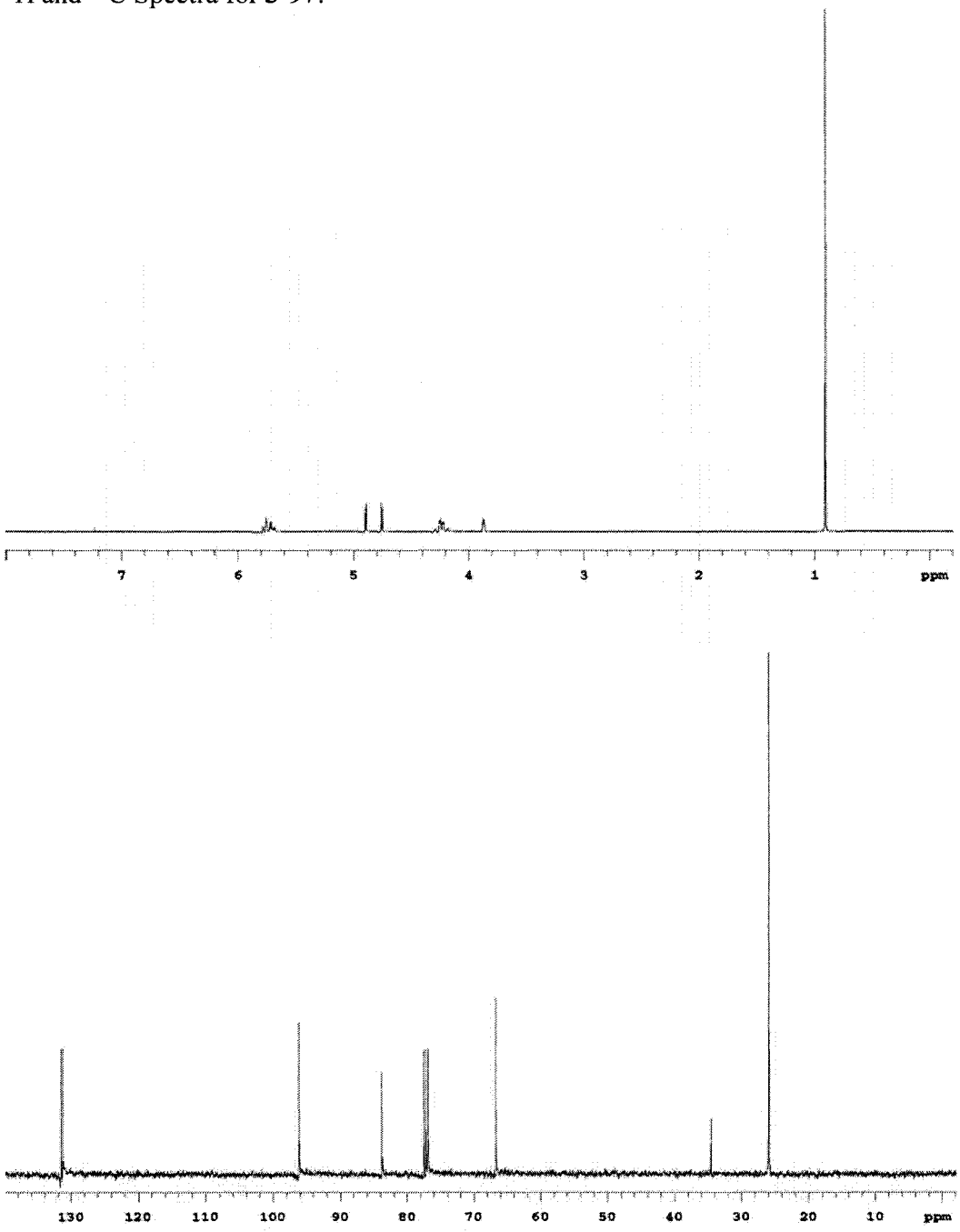

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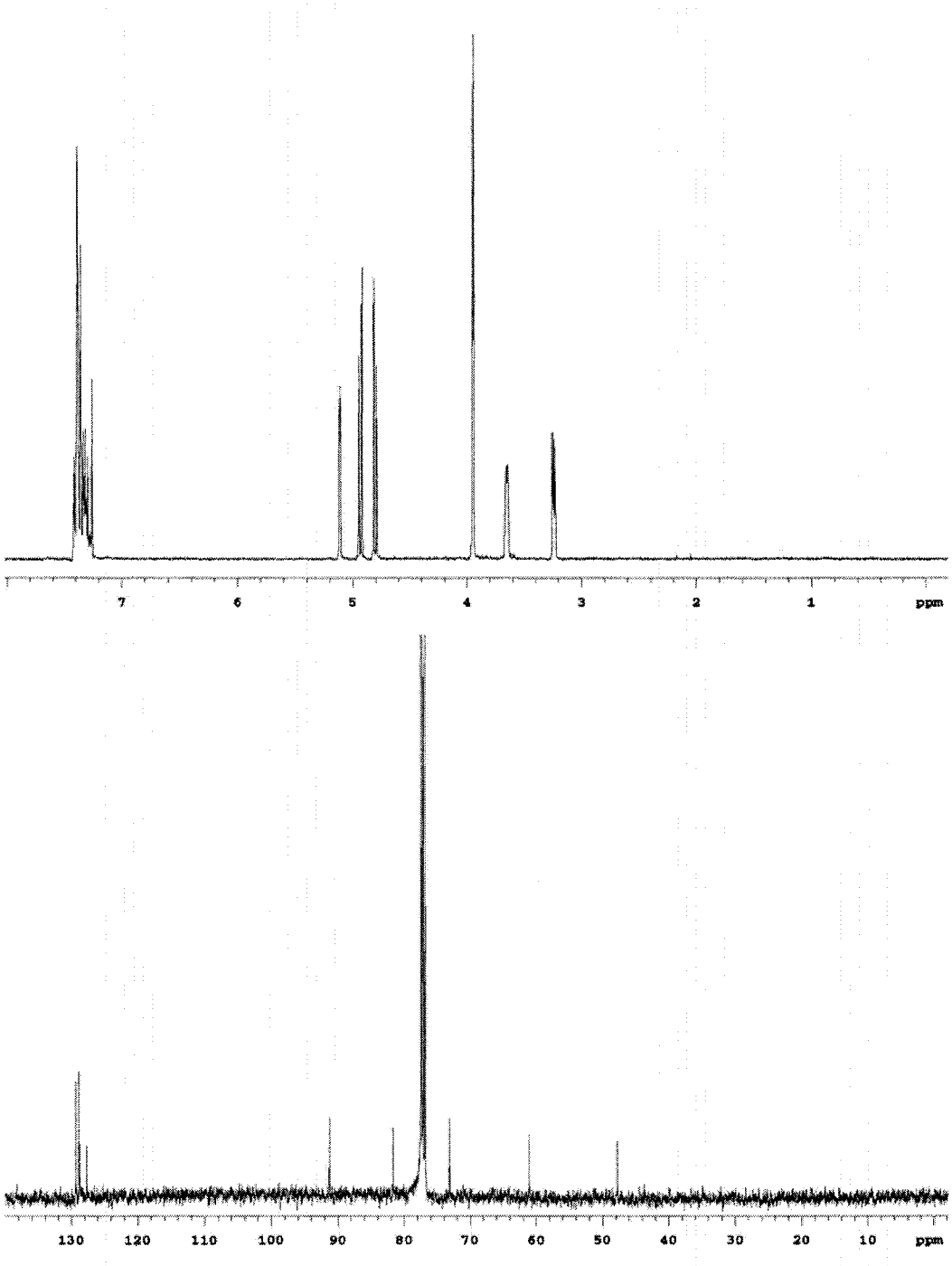

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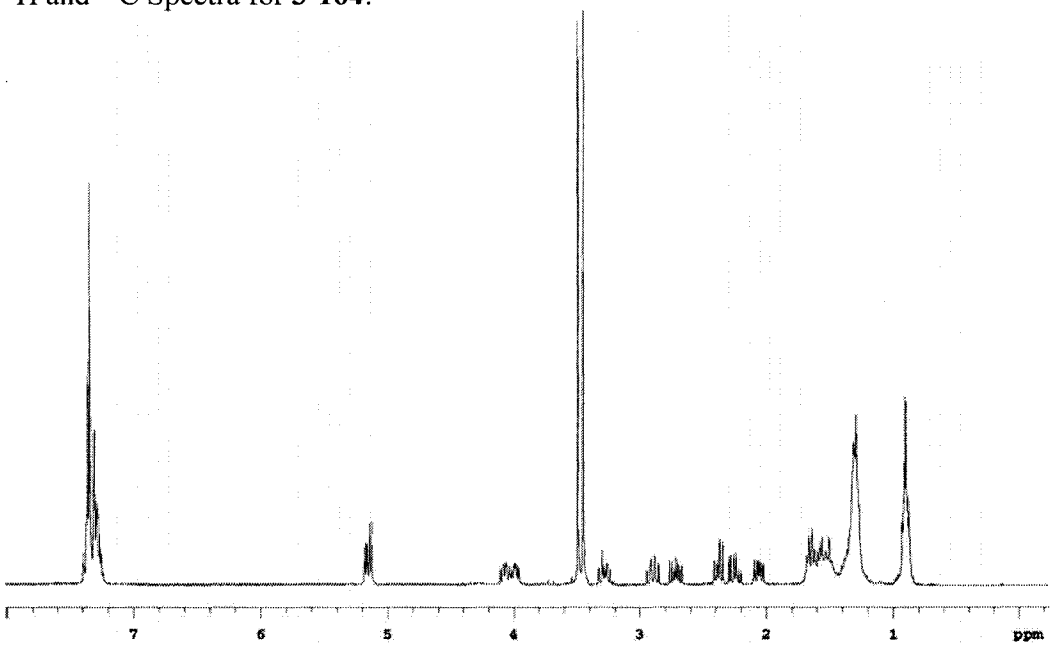

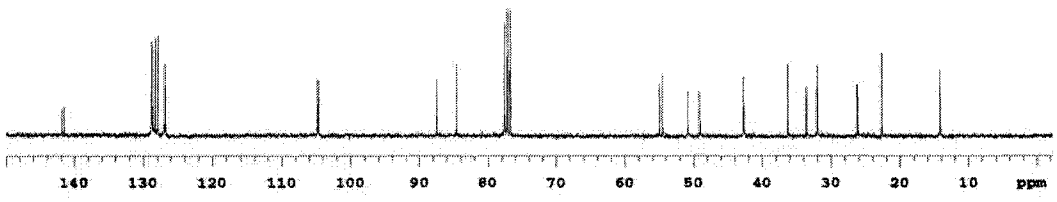

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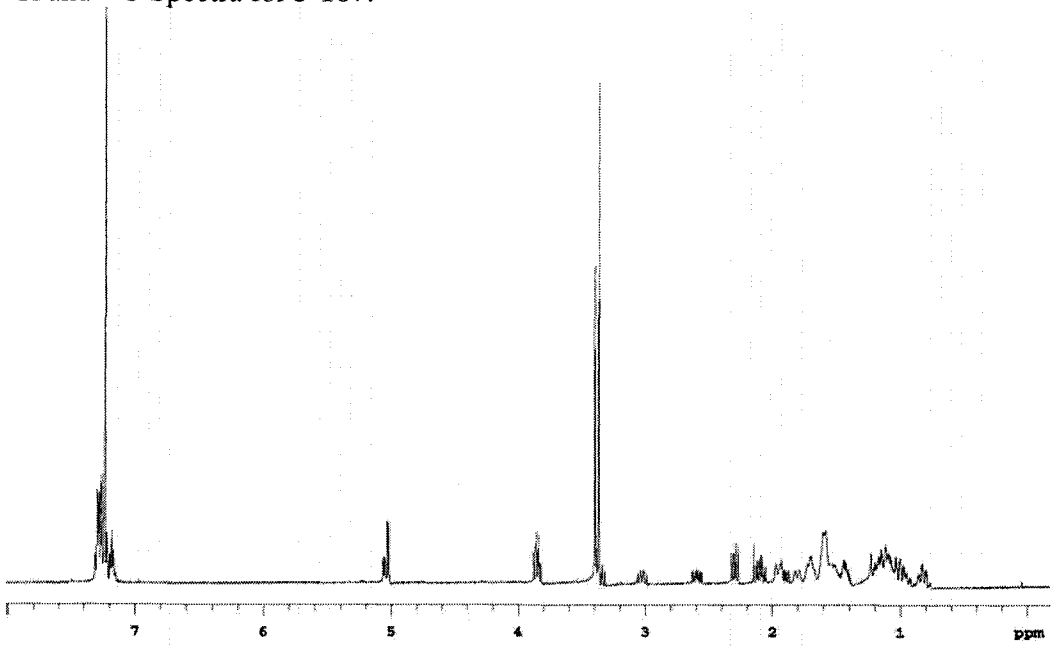

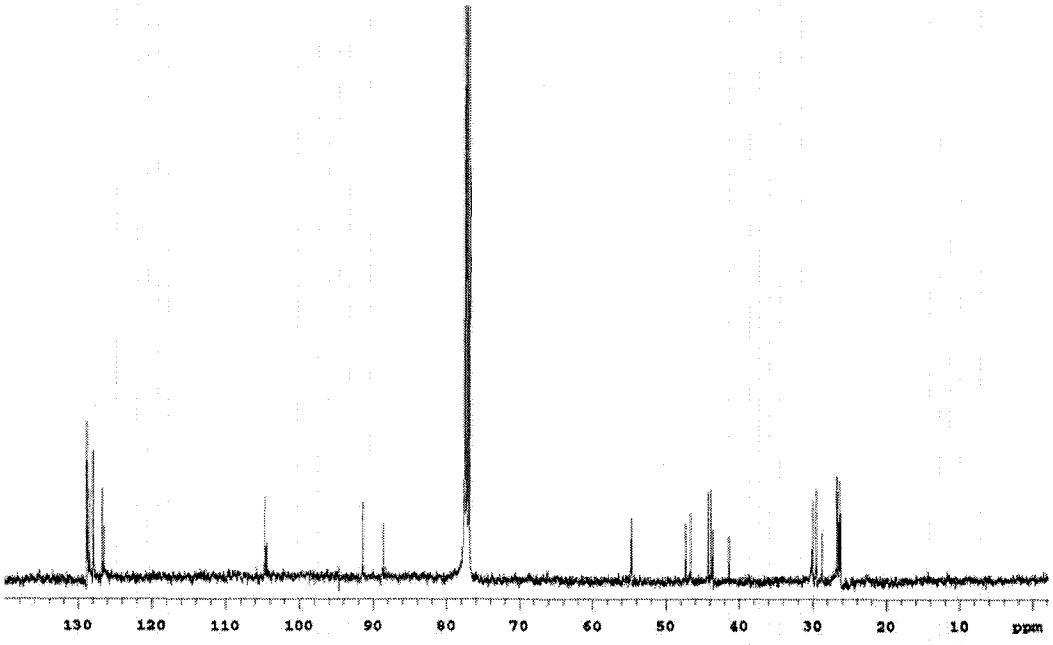

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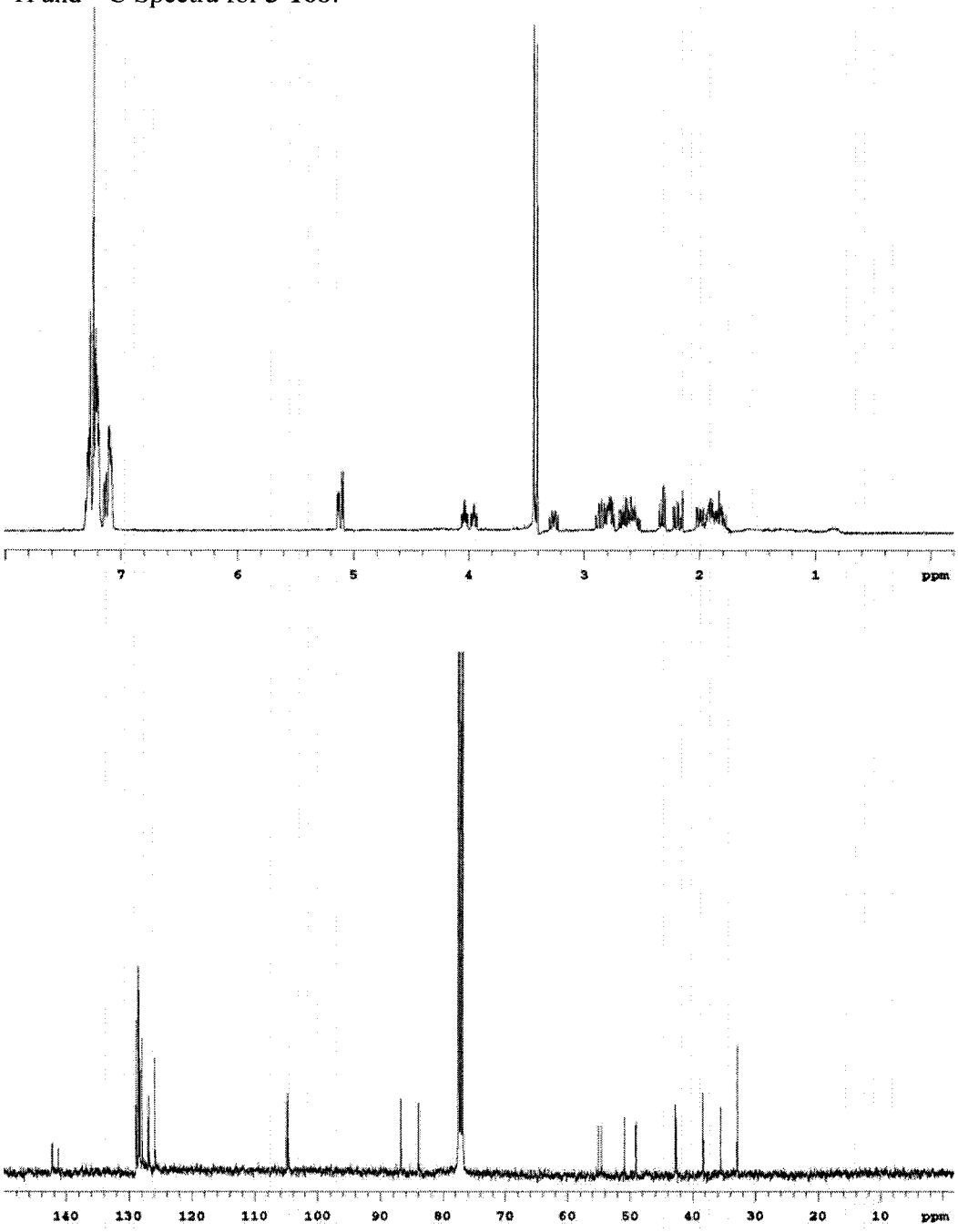

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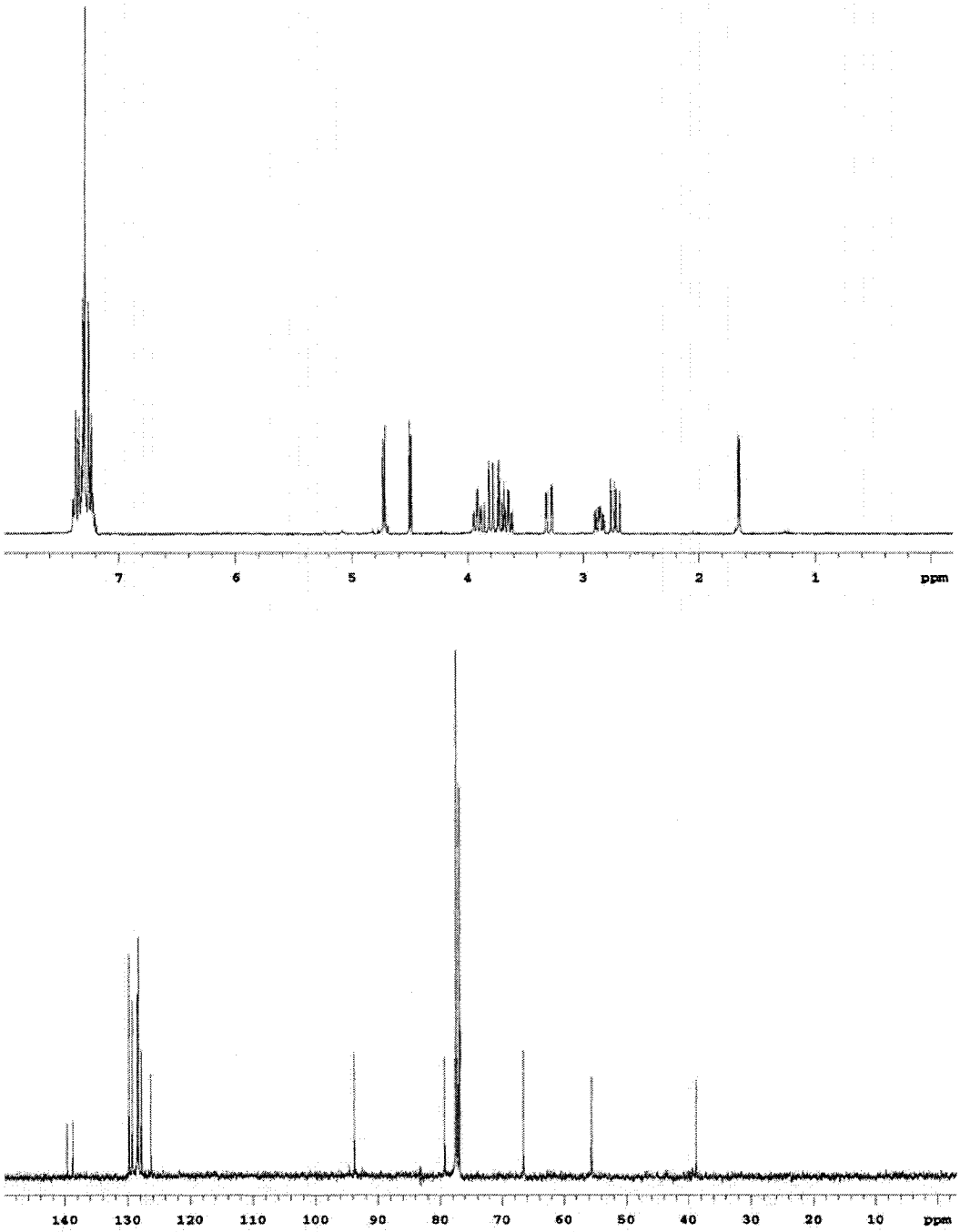

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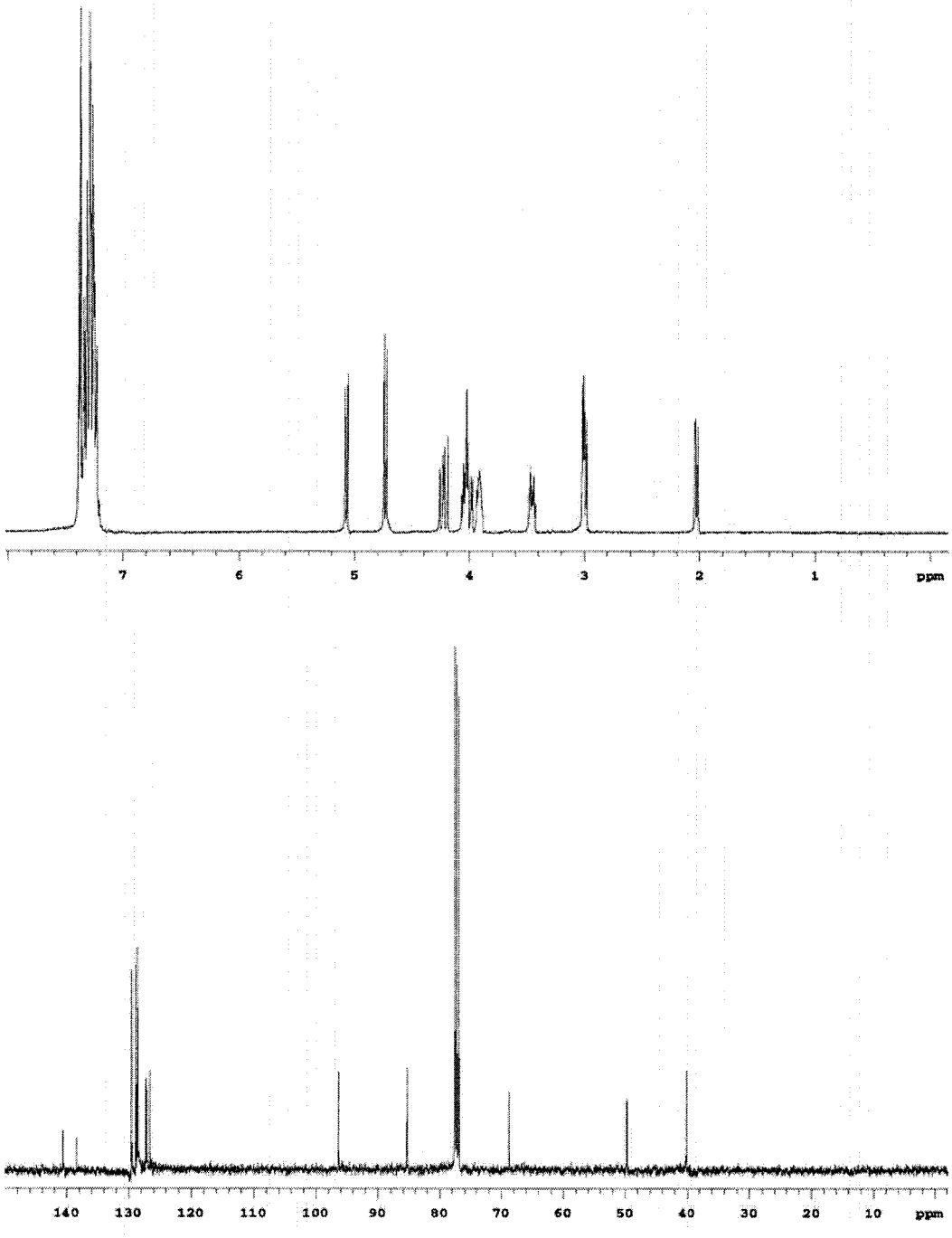

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