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DISSERTATION

LEWIS ACID CATALYZED REGIO- AND STEREOSELECTIVE [1, 3] O TO C REARRANGEMENTS

Submitted by

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In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, CO

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY CHRISTOPHER GEORGE NASVESCHUK ENTITILED LEWIS ACID CATALYZED REGIO- AND STEREOSELECTIVE [1, 3] O TO C REARRANGEMENTS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

LEWIS ACID CATALYZED REGIO- AND STEREOSELECTIVE [1, 3] O TO C REARRANGEMENTS

A regioselective Lewis acid-mediated [1, 3] rearrangement of allyl vinyl ethers has been developed. The rearrangement involves Lewis acid coordination to the allyl vinyl ether oxygen, which upon ionization produces a metalloenolate and allyl cation that recombine in a regioselective manner. Substitution about the allyl vinyl ether can be used to control the regioselectivity of the reaction.

A diastereoselective [1, 3] ring contraction of 2,5-dihydrooxepins to provide densely functionalized cyclopentenes has been realized. A modular synthesis of the 2,5-dihydrooxepin skeleton combined with the Lewis acid-mediated ring contraction provides access to tri-, tetra- and pentasubstituted cyclopentenes. An enantioselective variant of the reaction has also been developed.

A mild and efficient diastereoselective Heck reaction of 1,3-dioxepins is described. The reaction scope is broad with respect to both sp^2 iodide and alkene coupling partners. The reaction is also chemoselective for the Z-alkene of the 1,3-dioxepin in the presence of other potentially reactive E-alkenes. The diastereoselectivity is influenced by substitution at the 2- and 4-positions of the 1,3-dioxepin.

A Lewis acid-mediated ring contraction of 1,3-dioxepins to provide 2,3,4- and 2,3,4,5-substituted tetrahydrofurans has been investigated. Rearrangement in the presence of TMSOTF-MeCN provides the 2,3-*cis*/3,4-*trans* diastereomer, while $SnCl_4$-CH_2Cl_2 provides the 2,3-*trans*/3,4-*cis* diastereomer in good yield and diastereoselectivity.

The reaction scope is broad and both conditions are tolerant of a range of functionality including other Lewis basic groups.

The utility of the union of the diastereoselective Heck reaction and the Lewis acid-mediated [1, 3] ring contraction of 1,3-dioxepins has been evaluated in the context of total synthesis. These two reactions formulate the core strategy used to accomplish the synthesis of (+/-)-sylvone and as an approach to the core of lophirone H.

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First and foremost I thank Professor Tomislav Rovis. Through your rigorous approach to science, your enthusiasm and tenacity about solving problems and asking deep and thoughtful questions you have made me a better man and scientist. Words do not do justice to the impact you have had on my life and I will honor your efforts every day.

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To Colorado: Thank you for the mountains, which provided a place to utilize and test my other skills, skiing and cycling. To Moots: Thank you for building the most fantastic bicycle/piece of exercise/entertainment equipment I have ever owned. To Rage against the Machine: Thank you for sympathizing. To Hops and Berries: Thank you for opening your business and providing me with the excellent past-time of brewing beer.

To my family, my core, Jen, Blane, Cindi, Pete, Angela, Matt, Paddington and Bailey: Life is about love and doing something meaningful with it. I dedicate this work to you. Thank you.

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LIST OF ABBREVIATIONS

DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EtCN	Propionitrile
DME	Dimethoxyethane
PMP	1,2,2,6,6-Pentamethylpiperidine
DMAP	4-Di(methylamino)pyridine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
LDA	Lithiumdiisopropylamide
AIBN	Azobisisobutyronitrile
p-TsOH	*p*-Toluenesulfonic Acid
AcOH	Acetic Acid
TFAA = Tf_2O	Trifluoroacetic Anhydride
TMSOTf	Trimethylsilyltrifluormethanesulfonate
NMO	4-Methylmorpholine N-oxide
dba	Dibenzylidineacetone
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
MAD	Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)

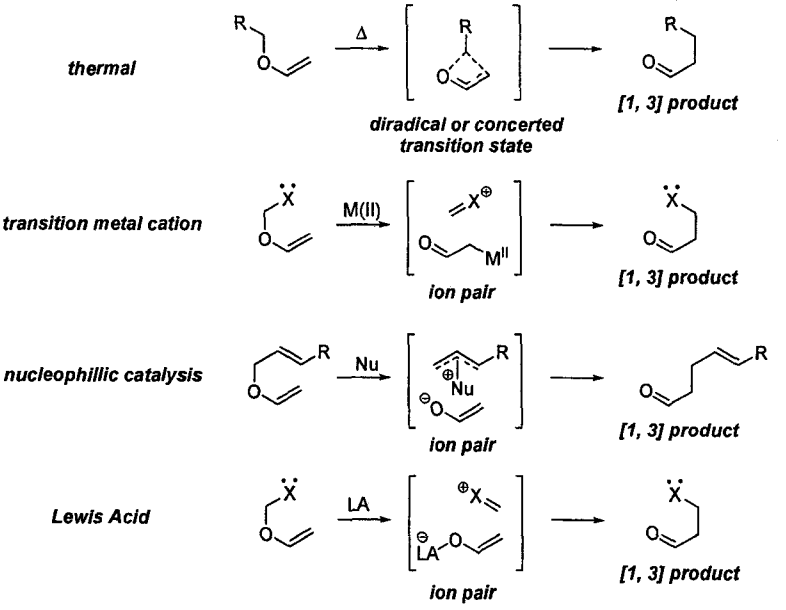
Chapter 1

[1, 3] O to C Rearrangements: A Review

1.1. Introduction.

Central to the synthesis of complex molecular targets are methodologies to construct carbon-carbon bonds. Rearrangement technology has been an area of intense research for decades providing convergent and efficient solutions to problems that are otherwise difficult using more traditional methods.[1] [1, 3] O to C rearrangements, relative to the Claisen rearrangement, are less well-known, yet have been the subject of an increasing number of studies in recent years. There are four general methods for the activation and [1, 3] rearrangement of vinyl ethers (Scheme 1). The oldest method, thermal activation, can furnish [1, 3] products through two different mechanisms: 1) a diradical, or 2) a concerted shift. [1, 3] Rearrangement by transition metal catalysis proceeds by electrophillic or nucleophillic activation. Nucleophillic catalysis may also be mediated by an organocatalyst. Lastly and most intensely studied are Lewis acid-mediated processes. The unifying theme among these diverse methods of activation is that an intermediate pair, whether it be radial or ionic in nature, is formed and control of these species leads to the formation of the desired products. The purpose of this review is to provide a compilation of the numerous reports of [1, 3] rearrangements and to provide a basis for further understanding of the various modes of activation that lead to these interesting rearrangement products.

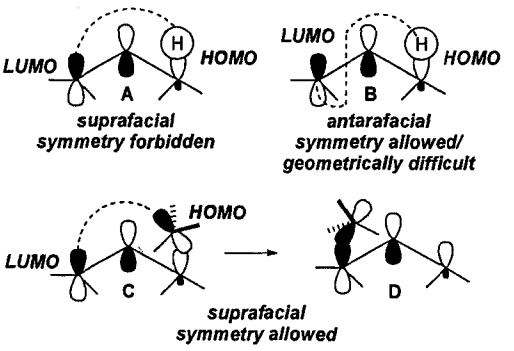
Scheme 1.



1.2. Orbital Symmetry of [1, 3] Rearrangements.

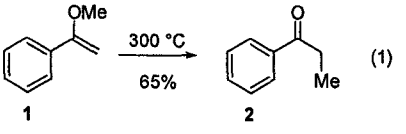
[1, 3] Sigmatropic shifts can be rationalized by frontier molecular orbital theory.[2] For a reaction to occur there must be symmetry within the system to allow for HOMO-LUMO orbital overlap between the reacting ends of the molecule. A [1, 3] suprafacial sigmatropic rearrangement is symmetry-forbidden (**A**, Fig. 1). However, the antarafacial shift is allowed (**B**, Fig. 1).[3] If the migrating group possesses a p-orbital, the suprafacial [1, 3] shift is symmetry-allowed and proceeds with inversion of stereochemistry at the migrating carbon (**C** to **D**, Fig 1).[4] The majority of migrating groups in O to C [1, 3] shifts are sp^3-hybridized, which places additional geometric constraints on the system.

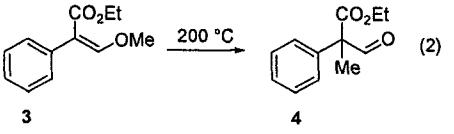
Figure 1.

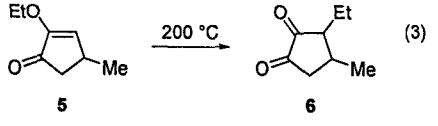


1.3. Early Examples.

The seminal report of a thermal [1, 3] rearrangement was presented by Claisen in 1896[5], prior to his discovery that O-allyl acetoacetate undergoes a [3, 3] sigmatropic rearrangement.[6] He stated, "on short superheating such as boiling for a few hours under two atmospheres' pressure" β-methoxystyrene provided propiophenone, the product of formal [1, 3] shift. A qualitative enhancement in reaction efficiency for [1, 3] alkyl shifts was reported to follow the general trend *n*-propyl > ethyl > methyl (Eq 1). Wislecenus and Schrotter (1921) illustrated that this methodology could be used to generate quaternary stereocenters (Eq. 2).[7] The thermal [1, 3] shift also proceeds efficiently with cyclic systems to provide substituted cyclopentanediones (Eq. 3).[8]



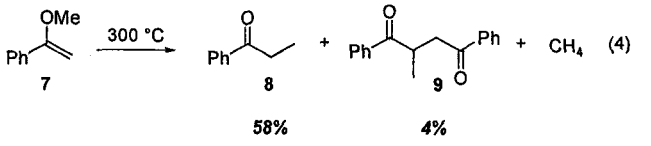




1.4. Thermal Reactions.

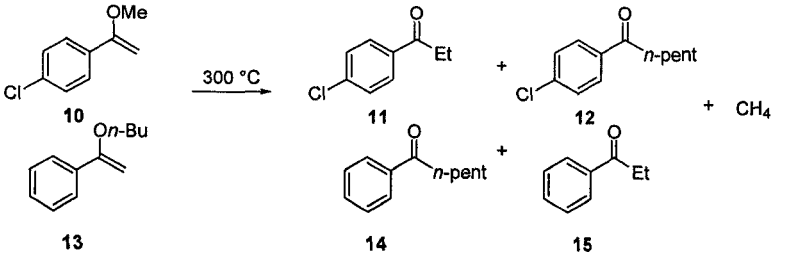
1.4.1. Thermal Reactions: Mechanism.

Although the early studies of the [1, 3] O to C rearrangement were primarily focused on identification and expansion of the substrate scope, the mechanism was not addressed until 1933.[9] In the thermal rearrangement of α-methoxystyrene the identification of 1,2-dibenzoylpropane and methane as byproducts led to a series of experiments that suggested the involvement of radical species (Eq. 4).



In an eloquent crossover experiment, Spielman and coworkers observed the formation of propiophenone (Scheme 2). Alone, this result suggests that there is an intermolecular component to the transformation, and leads to the hypothesis that radical intermediates are involved during the course of the reaction. This idea is further supported by the evolution of methane gas from the reaction mixture, presumably formed via hydrogen atom abstraction from the solvent or product.[10,11,12]

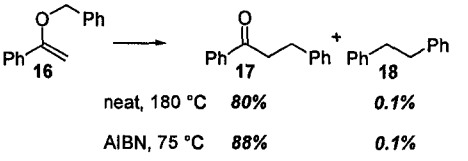
Scheme 2.



Kinetic evaluation of the rearrangement of α-methoxystyrene showed the process to be second order, supporting a radical mechanism.[13] Wiberg and coworkers provided further support for a radical mechanism in 1963.[14] AIBN was reported to catalyze a

radical chain mechanism for the rearrangement of α-benzyloxystyrene, for which the reaction was first order in substrate and half order in catalyst. The corresponding uncatalyzed, thermal reaction proceeds at 180 °C and also obeys second order kinetics, which further supports Spielman's findings. In support of a radical mechanism, dibenzyl was isolated as the main byproduct from both the catalyzed and uncatalyzed reactions.

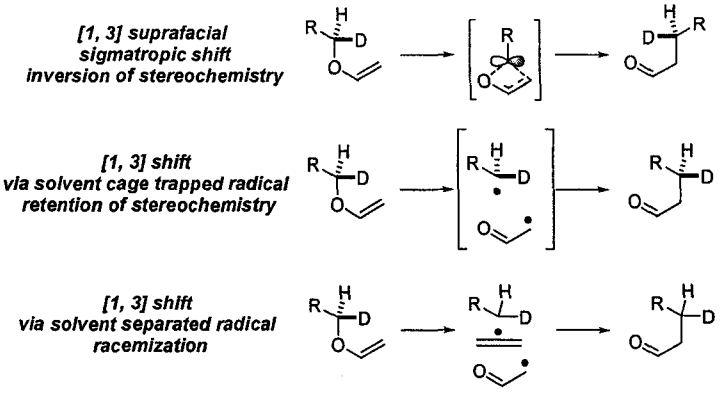
Scheme 3.



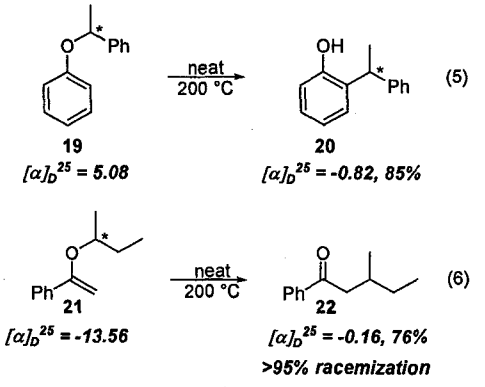
1.4.2. Thermal Reactions: Mechanism and Stereochemistry.

Consideration of stereochemistry in the context of thermal [1, 3] O to C rearrangements is a sensitive probe of mechanism. In the event that rearrangement proceeds with inversion of configuration at the migrating center, a concerted [1, 3]-sigmatropic shift is the operative mechanism.[15] On the other hand, if the rearrangement proceeds with retention of configuration at the migrating center, a fast intra-solvent cage radical-radical trapping mechanism can be invoked.[16] If racemization predominates, dissociation or rotation of a radical pair[17] can be invoked (*vide infra*, Scheme 4).

Scheme 4.

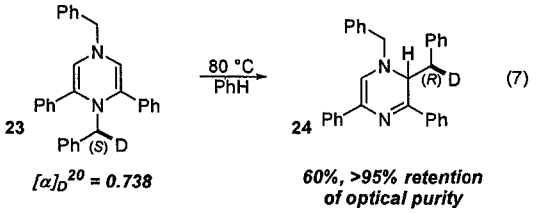


In 1954, a report by Hart and Eleuterio described the rearrangement of optically active phenethyl phenylether, which proceeded with approximately 20% retention of optical purity (Eq. 5).[18] The argument was advanced that there is an intramolecular component to the reaction. This type of stereochemical test was shown to be substrate dependent by Wiberg and Rowland, in a process in which optically active α-2-butoxystyrene was racemized upon heating, thus suggesting radical pair dissociation (Eq. 6).[19]



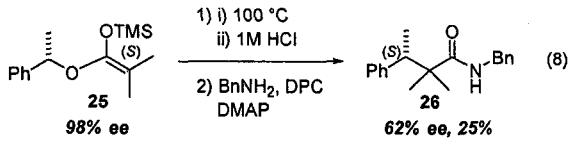
A [1, 3]-*sigmatropic* N to C rearrangement has been accomplished by Lown, Akhtar, and McDaniel (Eq. 7). Deuterium labeled 1,4-dibenzyl-1,4-dihydropyrazine **23** was thermally rearranged in the presence of radical inhibitor butane thiol[20] to provide **24** in >95% stereopecificity and with inversion at the migrating benzyl carbon. The reaction

follows first-order kinetics, which implies that it proceeds through a concerted process and not a radical mechanism.[21]



(7)

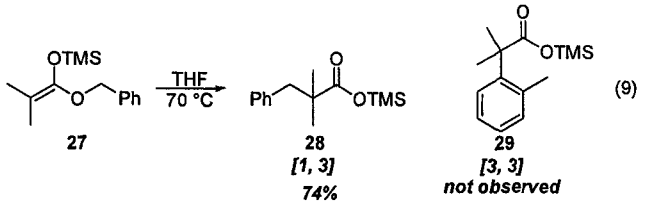
In an interesting report by Shiina and Nagasue a "[1, 3] sigmatropic rearrangment" proceeding with *retention* of configuration at the migrating phenethyl group was described (Eq. 8).[22] In light of the above mechanistic discussion, it seems more likely that this particular example proceeds via the radical pair mechanism.



(8)

1.4.3. Thermal Rearrangements: Examples.

The concept of [1, 3] rearrangement via migration of an alkyl group, specifically $-CH_2Ar$, found broad success under the thermal reaction manifold. Presumably, this functionality could stabilize either radical intermediates or charge build-up in the transition state for the concerted mechanism. Arnold and Kulenovic showed that silylenolethers derived from benzyl acetate would rearrange upon heating to provide [1, 3] adducts in good chemical yield (Eq. 9). In all cases, no [3, 3] product was observed.[23]

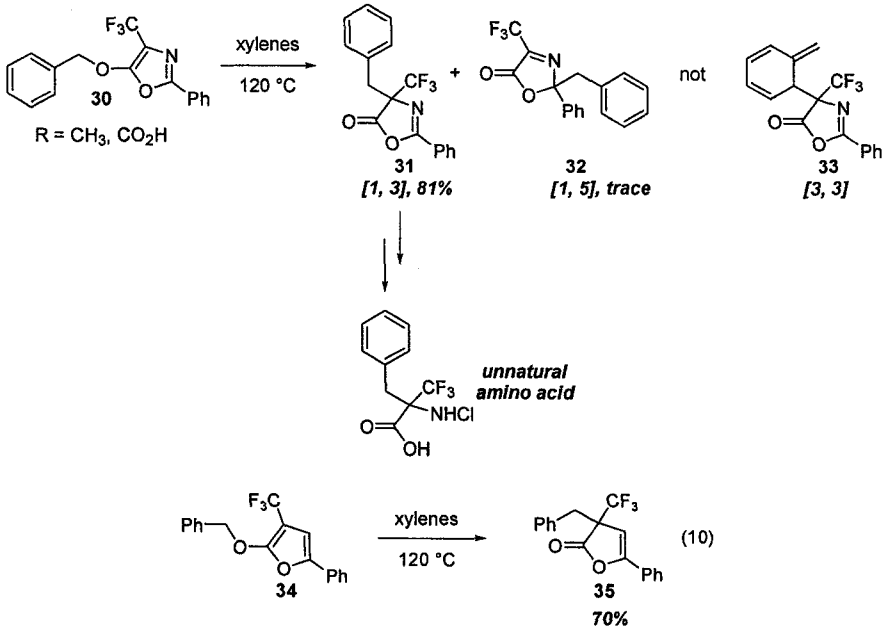


(9)

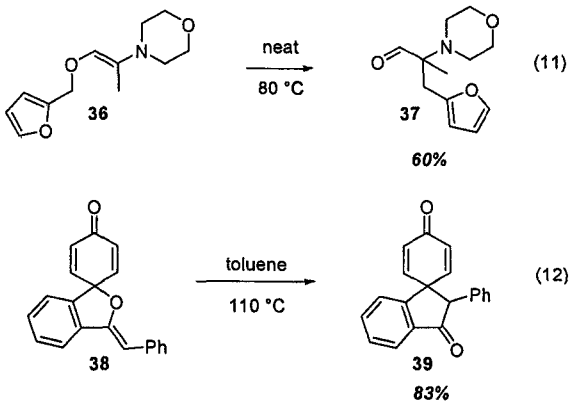
Heteroaromatics also participate as the vinyl ether component en route to unnatural amino acids (Scheme 5)[24] and functionalized butenolides (Eq. 10).[25] It is important to

note that the major competing process in this system is not the [3, 3] rearrangement **33**, but rather the corresponding [1, 5] shift **32**.

Scheme 5.

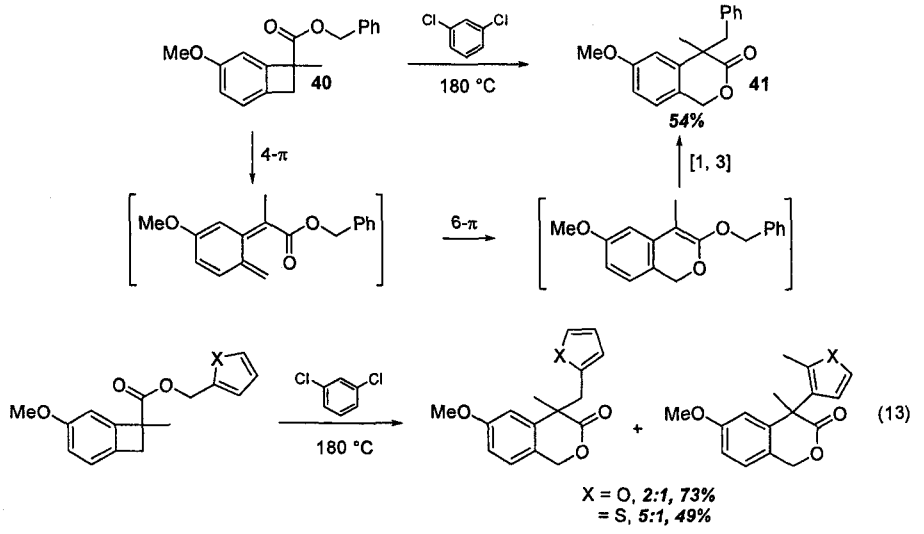


During their studies of aminomercuration of alkynes, Barluenga and coworkers found that with furanyl substitution, β–oxy enamine products would undergo a subsequent [1, 3] rearrangement in 60% yield (Eq. 11).[26] Deuterium labeling experiments revealed a secondary kinetic isotope effect of 1.83, which suggests complete C-O bond cleavage in the transition state and that the reaction may proceed via a radical pair mechanism. The thermally initiated [1, 3] O to C rearrangement can also be used to synthesize spirocyclic systems as described by Swenton (Eq 12).[27]



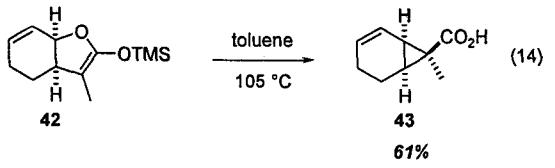
[1, 3] Benzyl group migrations have been used as the termination step in a domino reaction (Scheme 6).[28] Benzocyclobutane **40** rearranges via a 4-π electrocyclic ring opening followed by a 6-π electrocyclic ring closing and [1, 3] benzyl shift, to provide isochromene **41**. However, when heteroaromatics such as furyl or thiophenyl are employed the [3, 3] termination process is competitive (Eq. 13).

Scheme 6.



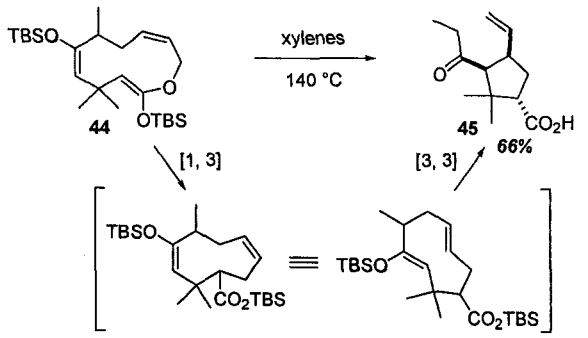
A thermal [1, 3] rearrangement of allyl vinyl ethers has been noted in two instances. In both cases the [3, 3] process is prohibited by a significant kinetic barrier due to strain in the transition state and thus the [1, 3] rearrangement predominates.

Danishefsky reported an unusual ring contraction of lactone enolates of type **42** (Eq. 14).[29]



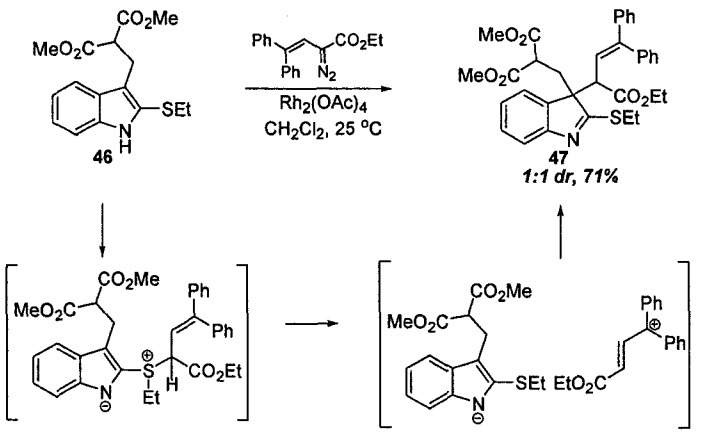
Knight showed that silylenolether **44** resists rearrangement until it is heated in refluxing xylenes (Scheme 7).[30] The structure of cyclopentane **45** was confirmed by x-ray analysis and is proposed to arise from initial [1, 3] shift followed by a Cope rearrangement.

Scheme 7.



Rainier and coworkers reported an interesting [1, 3] rearrangement of an allyl vinyl thioether (Scheme 8).[31] The reaction proceeds through rhodium-mediated coupling of a thioether and a vinyl diazoacetate to provide an ylide, which typically rearranges in a [3, 3] manner. However, if the allyl moiety is sufficiently sterically encumbered ionization predominates and [1, 3] products are formed.

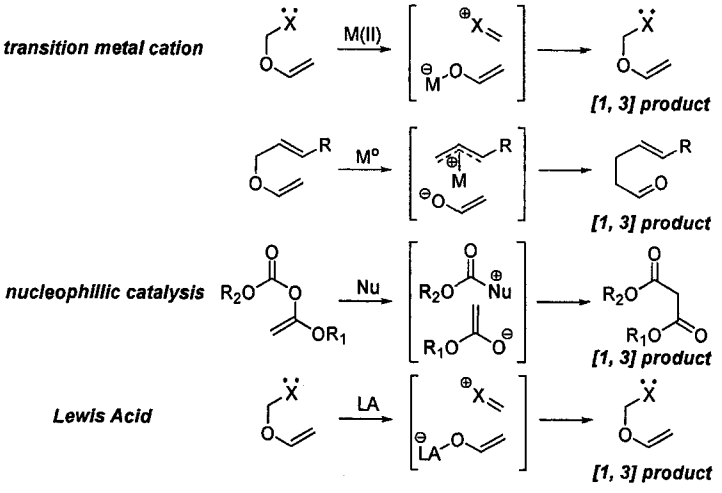
Scheme 8.



1.5. [1, 3] Rearrangements Proceeding through an Ion Pair.

To this point, this review has focused on examples of thermal cleavage of vinyl ethers to provide [1, 3] shift products; however, the majority of the work in this field has used other methods for the activation of vinyl ethers. Transition metal or Lewis acid activation of a vinyl ether provides an ion pair, a metalloenolate and carbocation, which collapse in a [1, 3] sense to form a new carbon-carbon bond (Scheme 9).

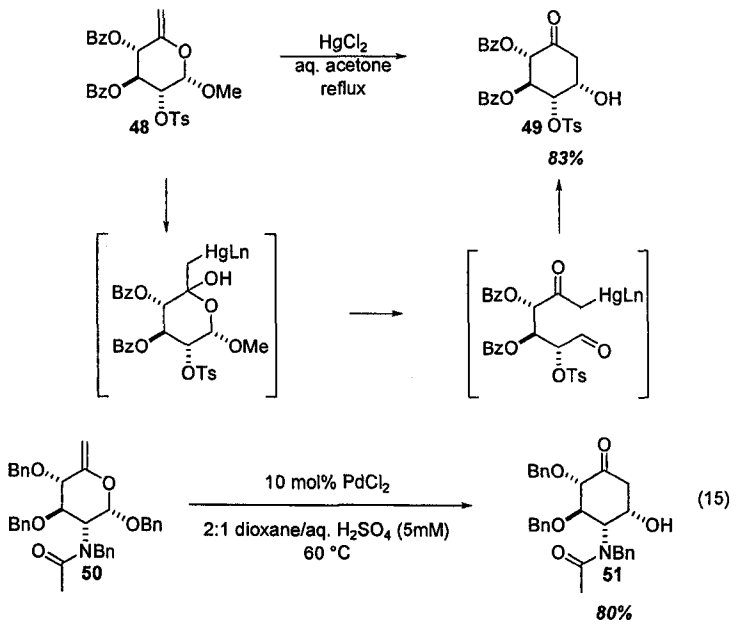
Scheme 9.



1.5.1. Transition Metal (II)-Mediated Reactions.

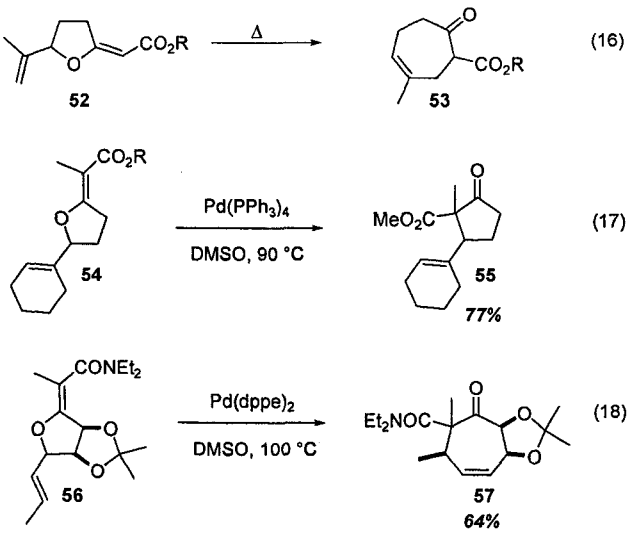
In 1979, Ferrier reported that $HgCl_2$ mediates a [1, 3] rearrangement of hexose **48** to cyclohexanone **49**, a reaction that now bears his name. The mechanism of the reaction is thought to proceed via oxymercuration of the olefin, followed by fragmentation and subsequent aldehyde alkylation with the mercury enolate (Scheme 10). This type of carbocyclization is now known as the Ferrier reaction.[32,33] Palladium (II) also catalyzes a similar carbocycliztion, presumably through electrophillic-Pd activation of the vinyl ether (Eq. 15).[34,35]

Scheme 10.



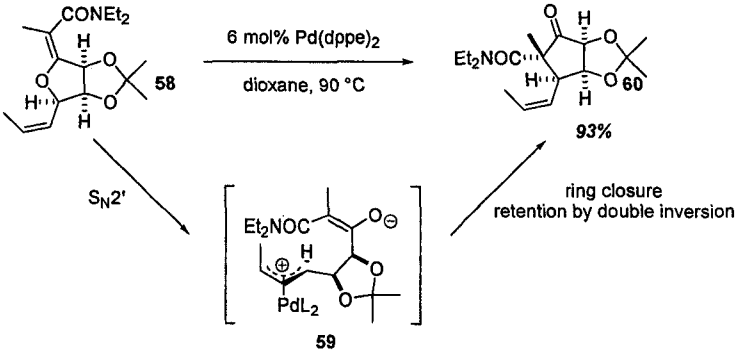
1.5.2. Transition Metal (0)-Mediated Reactions.

Alkylidenetetrahydrofurans of type **52** are known to undergo a thermal [3, 3] rearrangement to produce cycloheptanones (Eq 16).[36] In 1980, Trost and coworkers described a Pd(0) catalyst system that rearranges **54** in a [1, 3] sense to produce cyclopentanone **55** (Eq. 17).[37] It was later found that a complementary Pd-ligand combination would provide the cycloheptanone product (Eq. 18).[38]



The mechanism by which cyclopentanone **60** is created presumably proceeds by coordination of Pd(0) to the 1,1-disubstituted olefin of **58** followed by an S_N2' attack to create the zwitterionic intermediate **59**, which subsequently collapses in regioselective fashion.[39] The reaction proceeds with overall retention of configuration by double inversion (Scheme 11).[40]

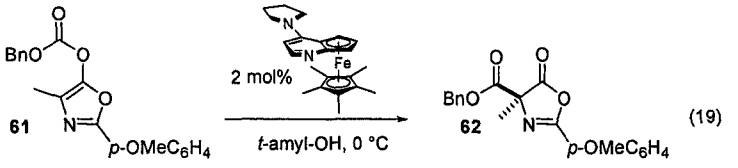
Scheme 11.



1.5.3. Other Nucleophillic Catalyst-Mediated Reactions.

[1, 3] Rearrangements may also be catalyzed by nucleophillic small molecules or organocatalysts as first demonstrated by Höfle and Steglich in 1970.[41] The reaction proceeds by nucleophillic addition of the catalyst to the carbonate moiety, which then fragments to create an ion pair intermediate, followed by C-alkylation and formation of

the product. Eloquent work by Fu (Eq. 19) and Vedejs (Eq. 20) showed that chiral DMAP catalysts may render the reaction asymmetric.[42] The reaction will also proceed in the presence of an N-heterocyclic carbene (Eq. 21).[43]



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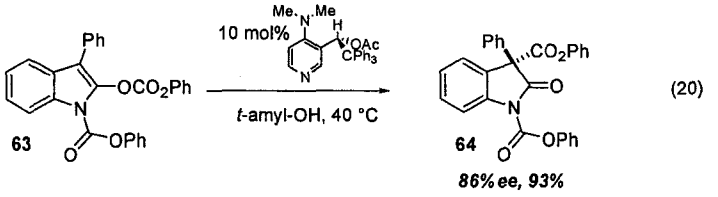

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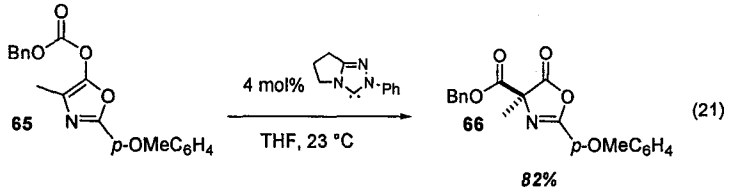


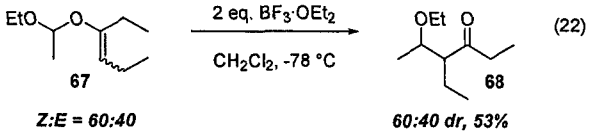
(21)

1.5.4. Lewis Acid-Mediated Reactions.

1.5.4.1. Lewis Acid-Mediated [1, 3] Rearrangement of Acyclic Systems.

Another convenient way to access ion pair intermediates that facilitate [1, 3] rearrangement is treatment of a suitably functionalized substrate with a Lewis acid. The overall process is of considerable utility owing to the often convergent and rapid assembly of starting materials and the ability to control the stereochemical course of the reaction through judicious choice of rearrangement parameters. Originally developed as a route to cross-aldol products, β-hydroxy ketones,[44] Lewis acid-mediated [1, 3] rearrangement of vinyl acetals showed early promise. Vinyl acetal **67**, bearing a trisubstituted alkene as a 60:40 mixture of geometrical isomers, rearranges in the

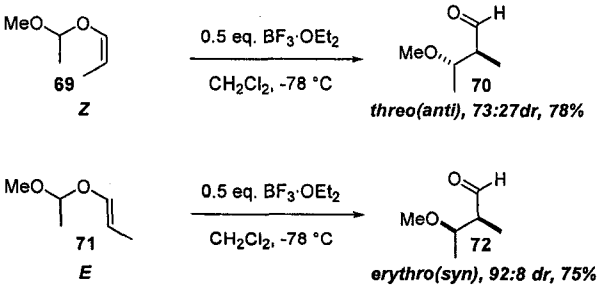
presence of superstoichiometric amounts of Lewis acid to produce protected β-hydroxy ketone **68** as a 60:40 mixture of diastereomers (Eq. 22).[45]



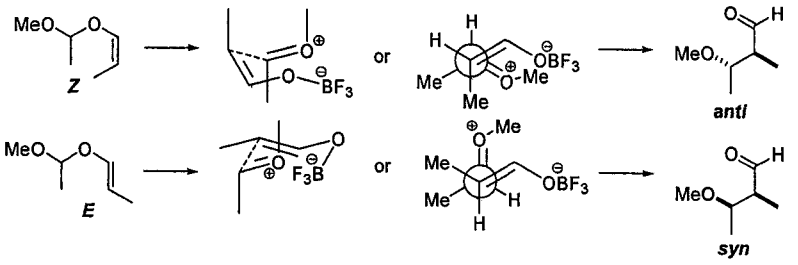
(22)

It was later shown that the [1, 3] O to C alkyl group migration could be rendered diastereoselective if a single alkene isomer was employed in the starting material (Scheme 12).[46] The authors rationalized the stereochemical outcome of the rearrangement as an "electrostatically stabilized chair transition state" in a Zimmerman-Traxler model (Scheme 13). A presumed electrostatic attraction between the boronate and the oxocarbenium ion holds the ion pair in the ordered transition state; however it may be more prudent to rationalize stereochemistry using a simple Newman projection viewing down the axis of the forming bond.

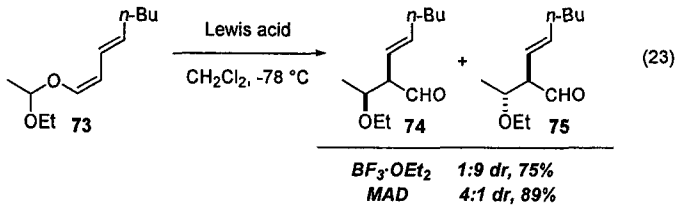
Scheme 12.

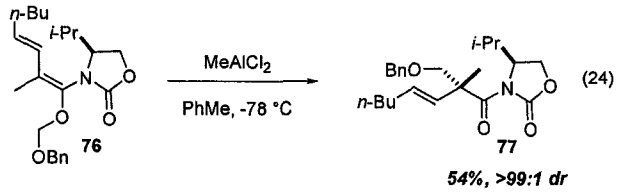


Scheme 13.



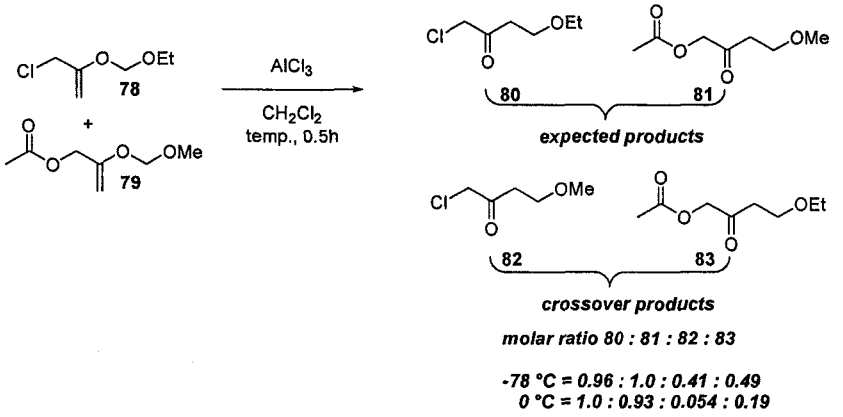
More recently, dienes have been shown to undergo a regio- and diastereoselective rearrangement (Eq. 23).[47] These results are consistent with the rearrangement of vinyl acetals shown in Scheme 12 and most likely proceed via a similar transition state. In the presence of a chiral auxiliary the [1, 3] rearrangement can be rendered highly diastereoselective and can produce all-carbon quaternary stereocenters (Eq. 24).[48]



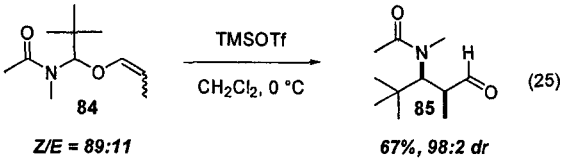


Okahara and coworkers provided early mechanistic insight for the [1, 3] rearrangement of vinyl acetals in a crossover study. At -78 °C the ratio was expected products: 0.96, 1.00, to crossover products 0.41,0.49 and at 0 °C the amount of crossover products decreased (Scheme 14).[49] The dependence of the degree of ion mixing on temperature suggests that the reaction proceeds through a contact ion pair.[50] Ion pairing has been implicated as a control element for the [1, 3] rearrangement of pyranyl vinyl acetals and will be discussed in depth in the following section.

Scheme 14.

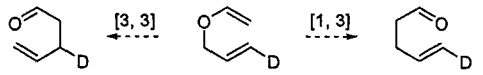


N,O-Vinyl acetals undergo facile Lewis acid-induced O to C migration, in which the corresponding ion pair consists of an N-acyliminium ion and a metalloenolate. The Lewis bacicity of the amine functionality necessitates its delocalization via a carbonyl or some π-withdrawing substituent for adequate reactivity. Frauenrath and coworkers were the first to report this reactivity and showed that sterics will override the stereochemical influence of enolate geometry (Eq. 25).[51]

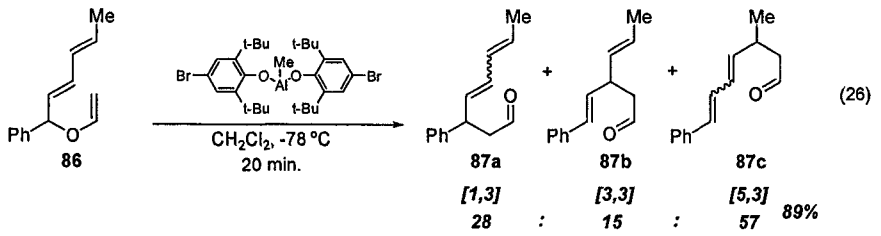


The allyl group also provides sufficient electron donation to fragment allyl vinyl ethers in the presence of a Lewis acid. The corresponding ion pair allows access to the [1, 3] product in the face of a possible [3, 3] rearrangement. The [1, 3] product is accessed under kinetic conditions, where product selectivity is governed by approach of the metalloenolate to the more exposed terminus of the corresponding allyl cation (Scheme 15).

Scheme 15.

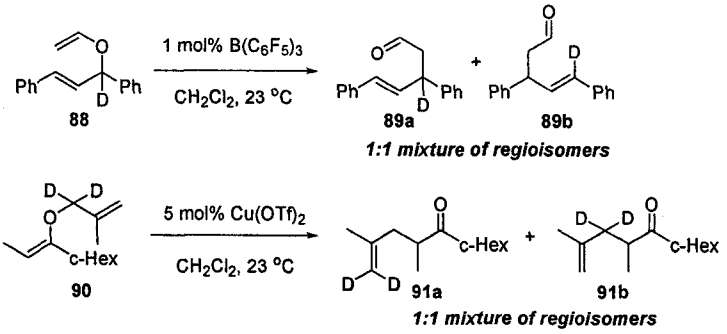


An early example by Yamamoto and coworkers showed that, under ionizing conditions, the [1, 3] product is accessible in acyclic systems (Eq. 26).[52] Rearrangement of pentadienyl vinyl ether **86** provides a mixture of products in which the [1, 3] product **87a** is a significant portion of the isolated material.

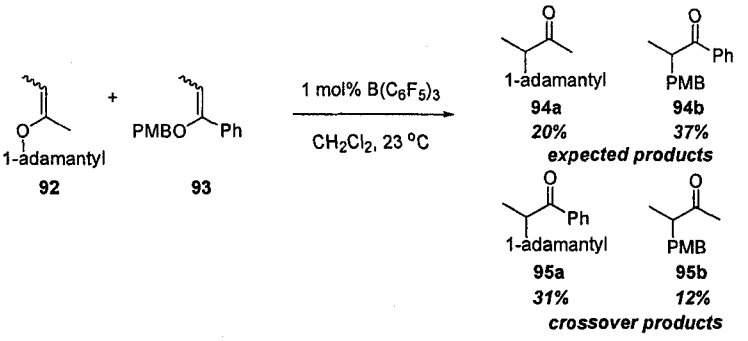


Gansauer showed that labeled symmetrical allyl vinyl ethers rearrange in the presence of catalytic Lewis acid to a 1:1 mixture of regioisomeric aldehydes through an unselective trapping of the symmetrical cation intermediate (Scheme 16).[53] A mixture of vinyl ethers **92** and **93** produces a significant quantity of ion-exchanged products (Scheme 17).

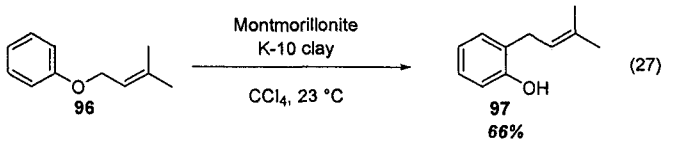
Scheme 16.



Scheme 17.



O-allyl phenols undergo a [1, 3] rearrangement catalyzed by montmorillonite K-10 clay as originally reported by Dauben.[54] This reaction was later optimized by Dintzner and coworkers to produce the product of [1, 3] rearrangement (Eq. 27). It was noted that the activity of the catalyst diminished significantly in successive runs and became inactive after the third run.[55]

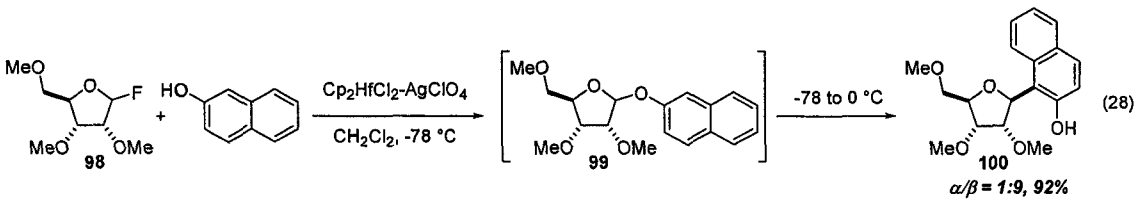


(27)

1.5.4.2. Lewis Acid-Mediated [1, 3] Rearrangement of Pendant Aryl and Vinyl Ethers.

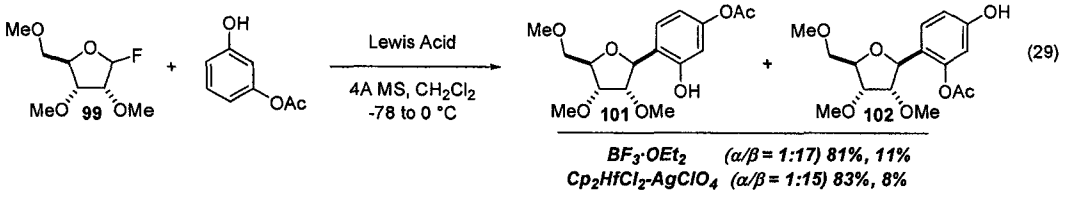
Development of the [1, 3] rearrangement of pendant aryl and vinyl ethers illustrated both the utility and convergence of this reaction manifold. At the heart of the stereochemical issues associated with this rearrangement are ion pairing and ring conformation. A variety of models can be used to rationalize the observed product ratios; however, the steric influence of substituents primarily dictates product stereochemistry. An early example of a [1, 3] O to C rearrangement was disclosed by Suzuki and coworkers. A mixture of anomeric fluorides and a phenol first formed an O-glycosidic linkage, which upon warming rearranged to its C-congener. Tin and boron Lewis acids

were effective for the formation of the α-product, while the Cp_2HfCl_2-$AgClO_4$ mixed Lewis acid provided the β-product (Eq. 28).[56]



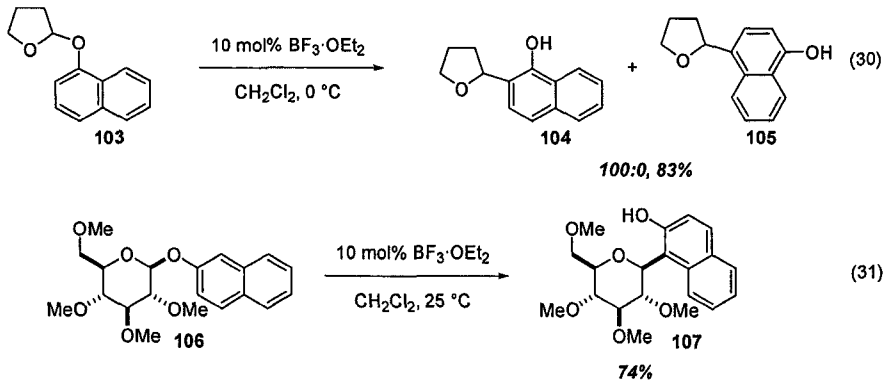
(28)

Resorcinol derivatives also perform well under these reaction conditions, favoring the β-product with good regioselectivity (Eq. 29).[57] This method has been expanded to incorporate O-acetyl glycosides as efficient glycoside donors[58] and as an approach toward the vineomycin skeleton.[59]

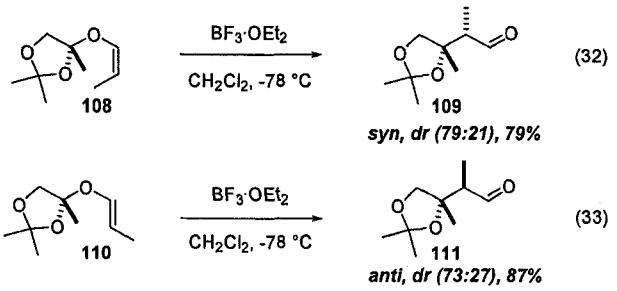


(29)

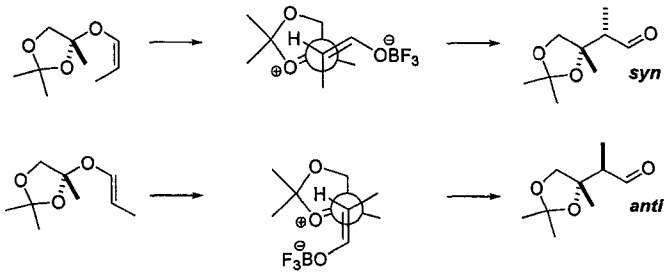
Preformed tetrahydrofuranyl O-aryl glycosides rearrange efficiently in the presence of catalytic Lewis acid as shown by Kometani and coworkers (Eq. 30).[60] In more complex sugar-derived systems the β-product was the favored product (Eq. 31).[61] The reaction was proposed by Suzuki to proceed through an ion pair; however, this series of communications did not describe any experiments designed to elucidate the mechanism (*vide infra*).



Frauenrath and Runsink described the stereoselective rearrangement of dioxolanylpropenyl ethers **108** and **110** to the corresponding aldehydes (Eq. 32 and 33).[62] Once again, double bond geometry affects the stereochemistry of the product: Z olefin configuration provides the syn product (dioxolane oxygen syn to methyl) and E olefin configuration gives the anti product, although neither proceeds with high selectivity (Scheme 18).

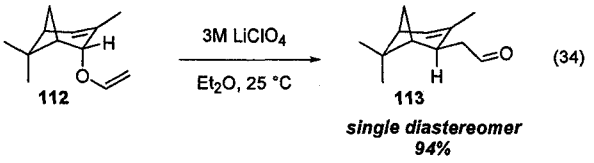


Scheme 18.



The steric environment about the allyl cation can also control facial selectivity in the recombination event. Grieco and coworkers developed a $LiClO_4$-Et_2O protocol for

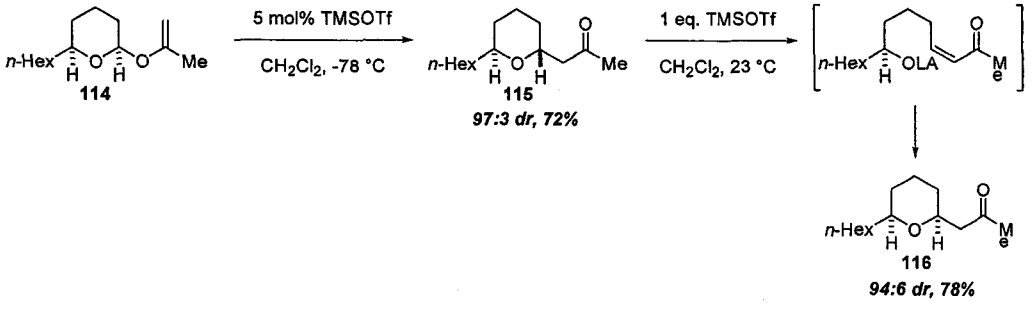
the [1, 3] rearrangement of aliphatic allyl vinyl ethers. In a particularly nice example, an allyl vinyl ether derived from verbenol **112** rearranges with complete inversion (Eq. 34). A crossover experiment revealed that these conditions were enabling the reaction to proceed through a dissociated ion pair, which mandates that product selectivity arises from recombination from the less hindered face of the ring system.[63]



(34)

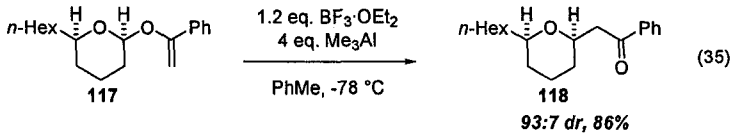
A sequence of papers by Ley and coworkers described the rearrangement of pyranyl vinyl acetals and related anomerically-linked nucleophiles.[64] Typically, products of 2,6-*trans* stereochemistry about the pyran ring are isolated. The *trans* products are essentially identical to those that can be accessed by intermolecular oxocarbenium ion alkylations. However, by simply increasing the amount of Lewis acid and reaction temperature, the *trans* product could be equilibrated to the *cis*-stereochemistry presumably through ring-opening of the pyran (Scheme 19).[65]

Scheme 19.



Using Okahara's insight into the nature of the ion pair intermediates formed by Lewis acid-mediated cleavage of vinyl acetals, Rovis and coworkers developed a stereoretentive rearrangement of pyranyl vinyl acetals. A mixture of Lewis acids (4:1

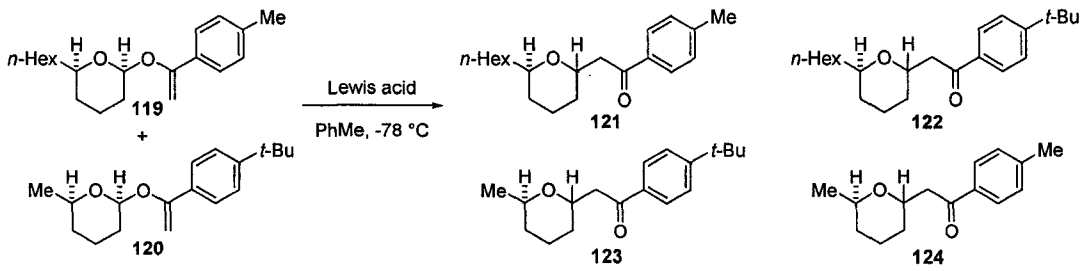
Me_3Al and $BF_3{\cdot}OEt_2$) produces a tight ion pair from the cleavage of vinyl acetal **117**, which leads to the formation of the 2,6-*cis* pyran stereochemistry (Eq. 35).[66] The reaction of **117** in presence of $BF_3{\cdot}OEt_2$ provides *trans*-**118** in >95:5 dr and 93% yield.



117 **118** ***93:7 dr, 86%*** (35)

It was hypothesized that a tight contact ion pair was responsible for the cis product stereochemistry. Indeed a crossover experiment revealed minimal amounts of products arising from ion scrambling while providing *cis* stereochemistry (Scheme 20). The crossover experiment, when performed in the presence of $BF_3{\cdot}OEt_2$, provides primarily the *trans* products with modest but significant amounts of crossover. This suggests that two different ionic species are involved: 1) a tight ion pair that provides the *cis* product ($Me_3Al/BF_3{\cdot}OEt_2$) and 2) a solvent-equilibrated ion pair ($BF_3{\cdot}OEt_2$) that emulates an intermolecular nucleophillic addition to an oxocarbenium ion, but does not fully dissociate.

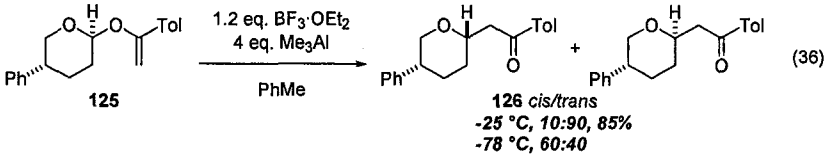
Scheme 20.



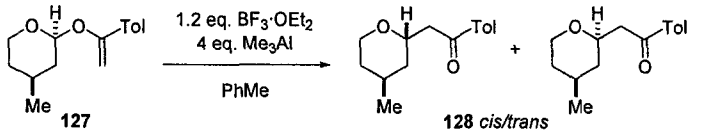
Lewis Acid	*cis*-121	*trans*-121	*cis*-123	*trans*-123	*cis*-122	*trans*-122	*cis*-124	*trans*-124
$BF_3{\cdot}OEt_2$	0.5	23.0	0.3	36.0	0.6	20.8	0.1	15.3
$Me_3Al/BF_3{\cdot}OEt_2$	48.8	1.4	42.8	6.8	0	0.3	0	<0.2

Another interesting observation that evolved from this report is an example of the isoinversion principle: lower temperatures provide lower selectivity, while higher

temperatures provide greater selectivity (Eq. 36 and 37), a situation easily explained when one considers the entropic factors involved in salvation two distinct ions.[67] This method also provides stereoselective access to 2,7-disubstituted oxepanes and 2,5-disubstituted tetrahydrofurans.

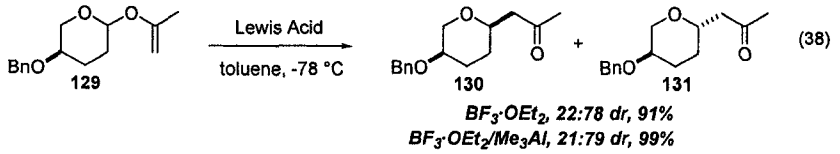


(36)



(37)

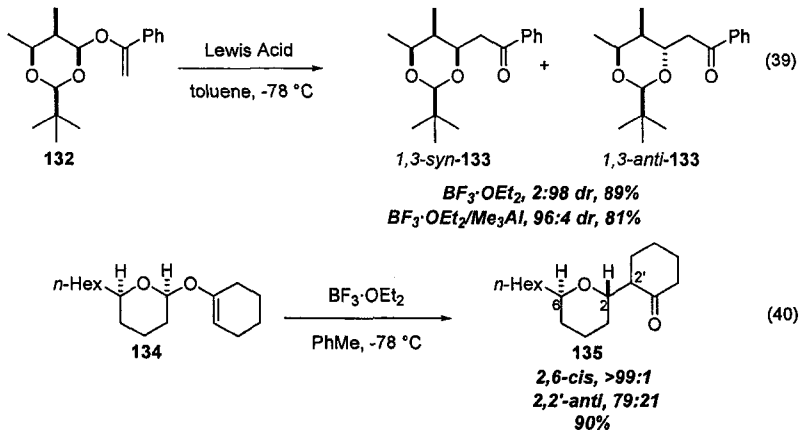
Woerpel and Shenoy showed that 5-benzyloxy pyranyl vinyl acetal **129** rearranges under the Rovis conditions for generating contact ion pairs and $BF_3{\cdot}OEt_2$ to provide the *trans* product stereochemistry in nearly identical yield and selectivity (Eq. 38).[68] They suggest that the reaction proceeds under both conditions via a solvent-equilibrated ion pair. In this case ion pairing does not explain their results, which remain consistent with their inside attack model.[69]



(38)

Rovis and coworkers also showed that this rearrangement technology could be applied to more complex systems. Rearrangement of vinyl acetal **132** can provide access to 1,3-polyol arrays through a stereoretentive process that provides *syn*-**133** or a solvent-equilibrated ion pair that provides *anti*-**133** (Eq. 39).[70] The rearrangement of pendant cyclic vinyl ethers also works well under the solvent-equilibrated ion pair conditions to

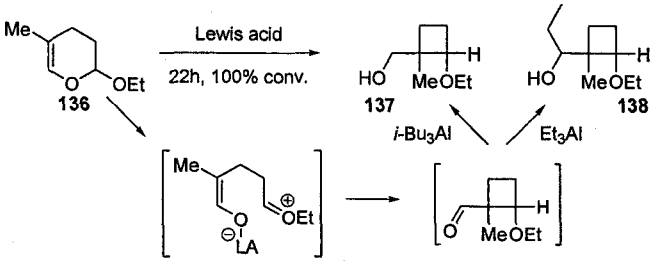
provide **135** with the simultaneous formation of two new contiguous stereocenters (Eq. 40).[71]



1.5.4.3. Lewis Acid-Mediated [1, 3] Rearrangement to make Hetero- and Carbocycles.

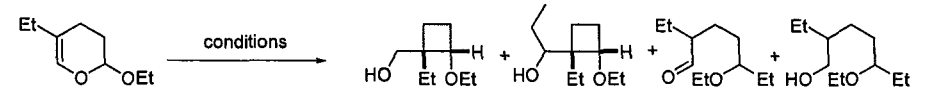
Lewis acid-mediated rearrangement of cyclic vinyl ethers to form either hetero- or carbocycles is fundamentally different from the rearrangement of pendant vinyl ethers because they lack a cyclic oxocarbenium ion that can be used as a control element. A correspondingly grater influence is derived by both the size of the Lewis acid employed and the nature of the substituents on the substrate in question. In an early report, Menicagli and coworkers showed that dihydro-2H-pyrans would undergo ring contraction to form the corresponding cyclobutanes (Scheme 21).[72]

Scheme 21.



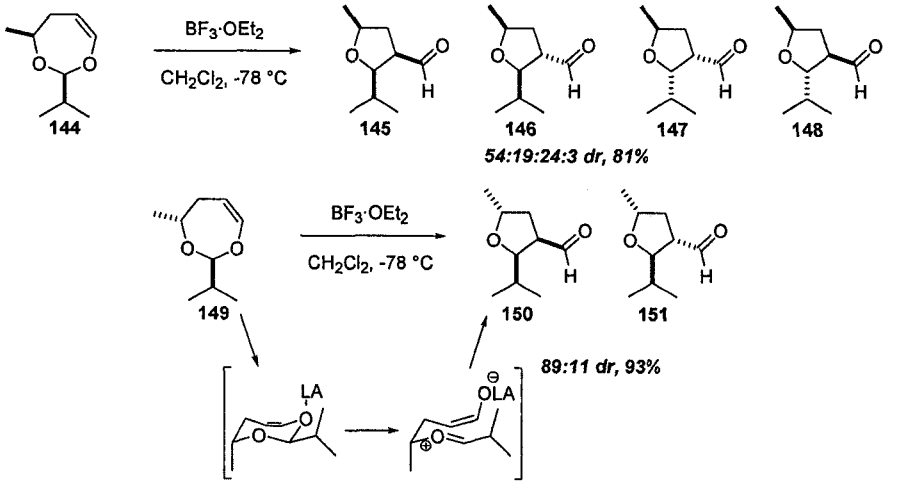
They later confirmed the stereochemistry about the cyclobutane ring to be *cis* (hydroxy methylene *cis* to ethoxy group). Interestingly, employment of an Al-etherate complex provides the product of alkyl group transfer (secondary OH) in preference to reduction (Scheme 22).[73]

Scheme 22.



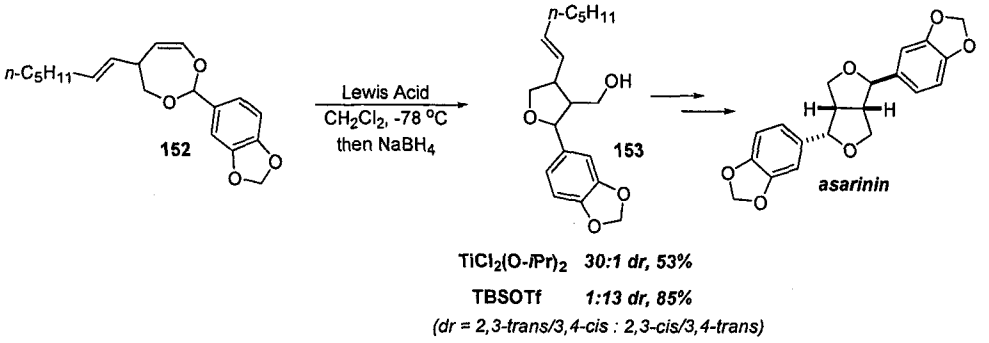
Seven-membered rings may be converted into their five-membered ring counterparts via Lewis acid activation. Frauenrath and coworkers described a ring-contraction of 2,4-disubstituted dioxepins; however, a surprising effect was noted. The cis 2,4-disubstituted dioxepin provides a mixture of the four possible diastereomeric tetrahydrofurans, while the trans disubstituted dioxepin provides only two tetrahydrofuran products with good selectivity for **150** (Scheme 23).[74]

Scheme 23.

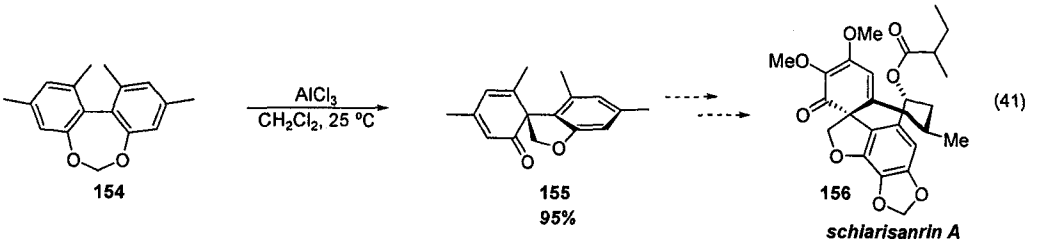


Takano and coworkers illustrated a diastereoselective ring contraction to produced a 2,3,4-trisubstituted tetrahydrofuran enroute to (+/-)-asarinin (Scheme 24). They showed that two different Lewis acids would provide two different diastereomeric tetrahydrofurans with good selectivity.[75]

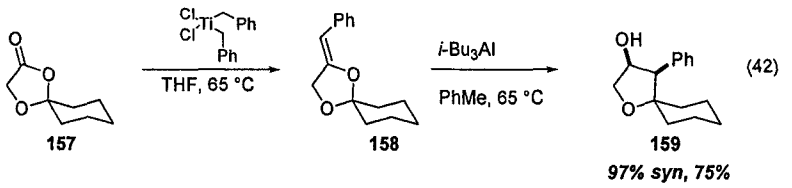
Scheme 24.



Coleman and coworkers described a similar ring contraction of dibenzodioxepins, as an approach to the spirobicyclic ring system of the schiarisanrin class of natural products (Eq. 41).[76]



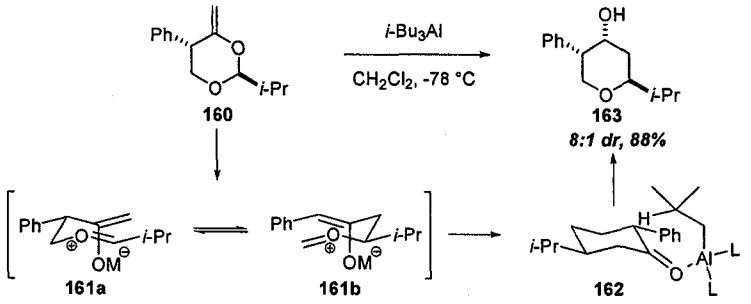
Another effective and convergent oxacycle synthesis evolved from the labs of Petasis.[77] Condensation between a hydroxy acid and a ketone provides spirocycles of type **157**. Carbonyl olefination with the Petasis reagent provides the desired vinyl acetal, and when treated with *i*-Bu_3Al, rearrangement followed by ketone reduction furnishes **159** with excellent cis diastereoselectivity (Eq. 42). Tertiary alcohols may be accessed using this method through the use of Me_3Al or Et_3Al as the Lewis acid/alkylation reagent.



(42)

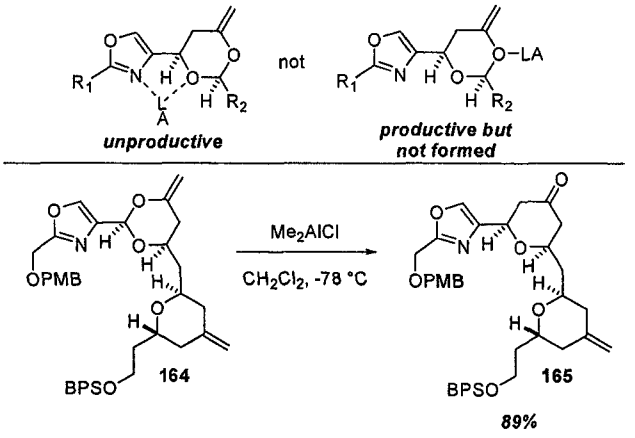
Pyrans may also be constructed using this method, for which the reduction to the secondary alcohol proceeds with good diastereoselectivity (Scheme 25).[78] In spite of the potential for an oxonia Cope rearrangement, the reaction still proceeds with excellent diastereoselectivity between the phenyl and isopropyl substituents in product **163**.

Scheme 25.



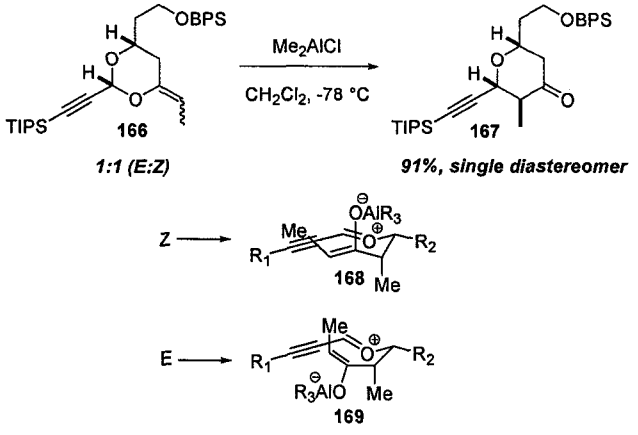
In the arena of natural product synthesis, the most spectacular examples of this type of transformation were accomplished by Smith and coworkers en route to (+)-phorboxazole A.[79,80] A first generation approach to the key dioxane revealed that the oxazole and ether oxygen could form a chelate with the Lewis acid, suppressing reactivity (Scheme 26). This problem was overcome through the synthesis of a regioisomeric dioxane, which rearranges in the presence of Me_2AlCl.

Scheme 26.



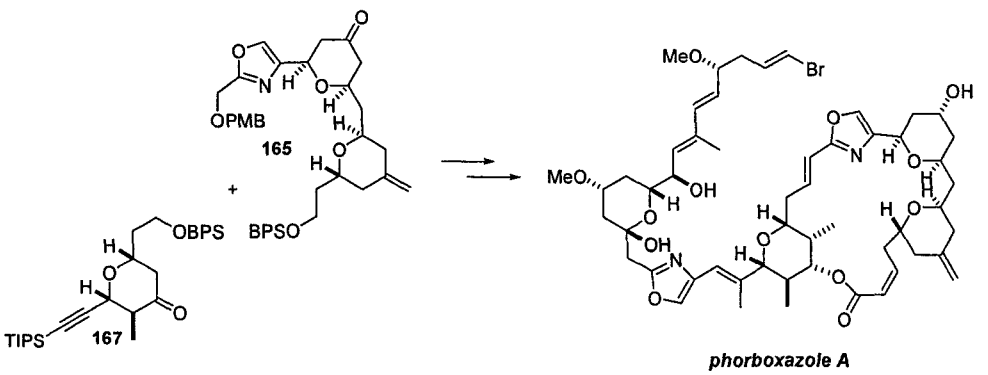
Stereoconvergent rearrangement of a 1:1 mixture of E and Z trisubstituted alkene isomers **166** provided **167** as a single diastereomer in good yield (Scheme 27). This surprising result was rationalized as follows: the Z isomer reacts via a preferred chair transition state **168** while the E isomer rearranges through a boat conformation **169**.

Scheme 27.

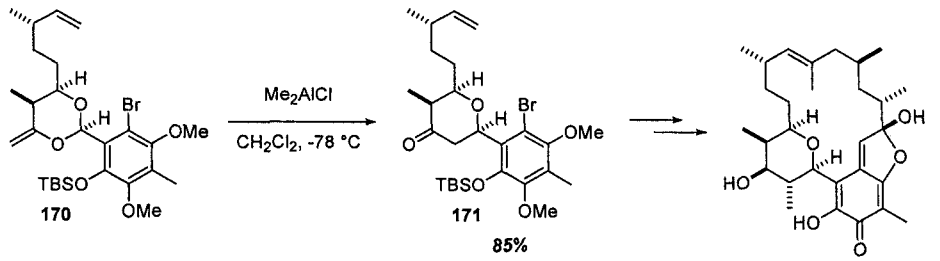


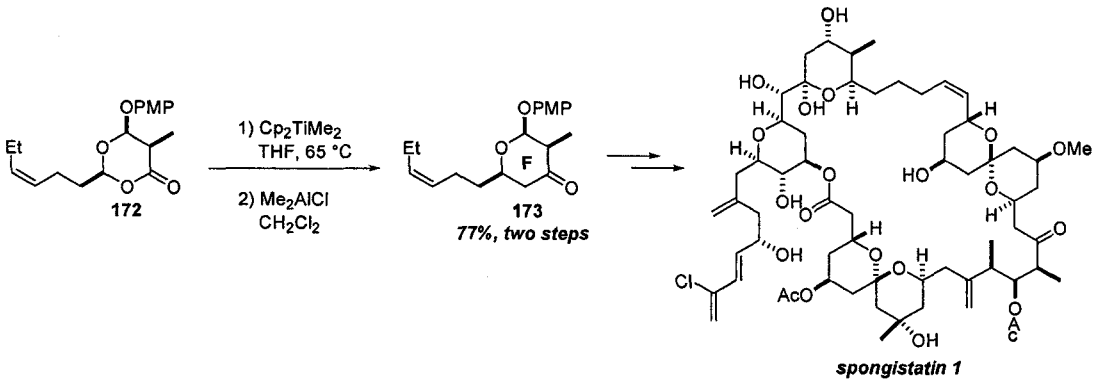
Both **165** and **167** were carried on to complete the total synthesis of (+)-phorboxazole A (Scheme 28). This carbocyclization has also been effectively used by Smith and coworkers enroute to (-)-kendomycin and the EF fragment of (+)-spongistatin 1 (Scheme 29).[81]

Scheme 28.

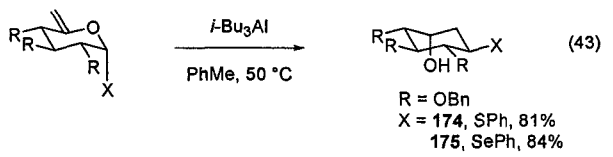


Scheme 29.



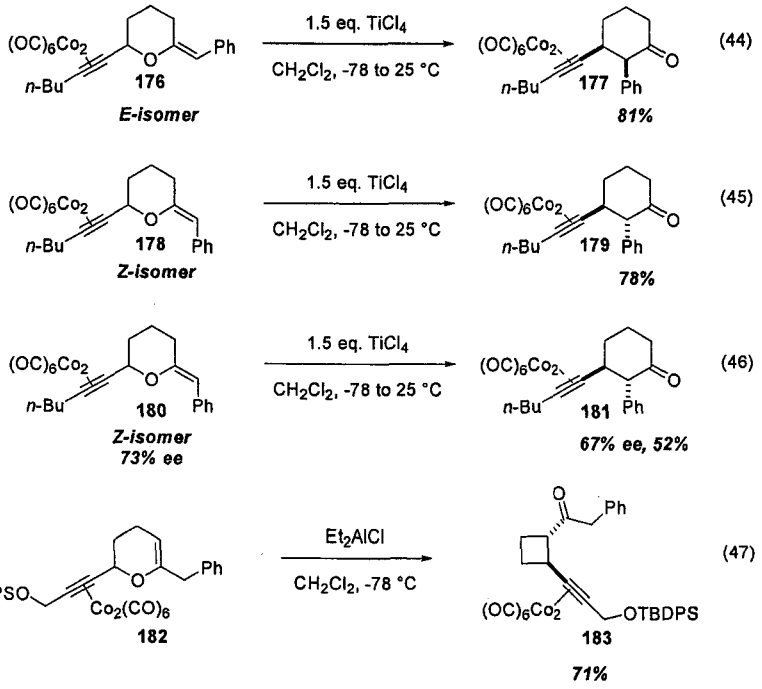


Electron-donating groups other than the ether functionality will sufficiently activate a vinyl ether towards [1, 3] rearrangement. Sinay and coworkers reported a Lewis acid-mediated Ferrier reaction for a variety of functionalized C-glycosides (Eq. 43).[82,83] The ketone intermediates, formed after the rearrangement, are further reduced by *i*-Bu_3Al as per the work of Petasis.



(43)

Dicobalt hexacarbonyl complexes of alkynes are known to stabilize propargylic cations[84] and thus have been used in the context of [1, 3] rearrangement of pyrans.[85] In contrast to the example by Smith (*vide supra*), Harrity and coworkers have illustrated that E and Z olefin isomers lead to different diastereomers (Eq. 44 and 45). Enantioenriched pyran **180** rearranges efficiently in the presence of $TiCl_4$ with minimal racemization (Eq. 46). This method may also be used in the diastereoselective ring contraction of dihydro-2H-pyrans to provide cyclobutanes (Eq. 47).[86]

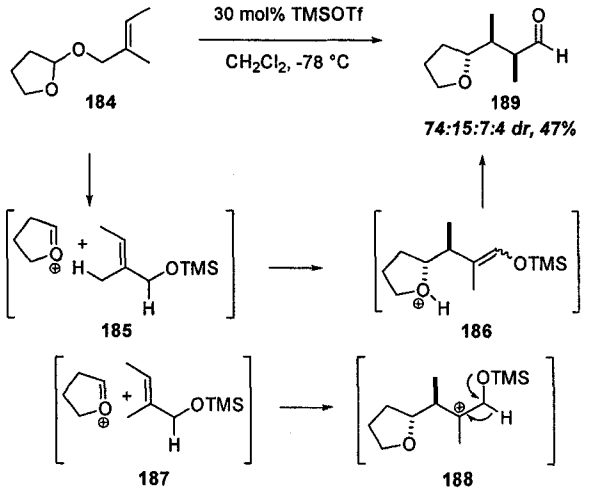


1.5.4.4. Related [1, 5], [1, 4] and [1, 2] Rearrangements.

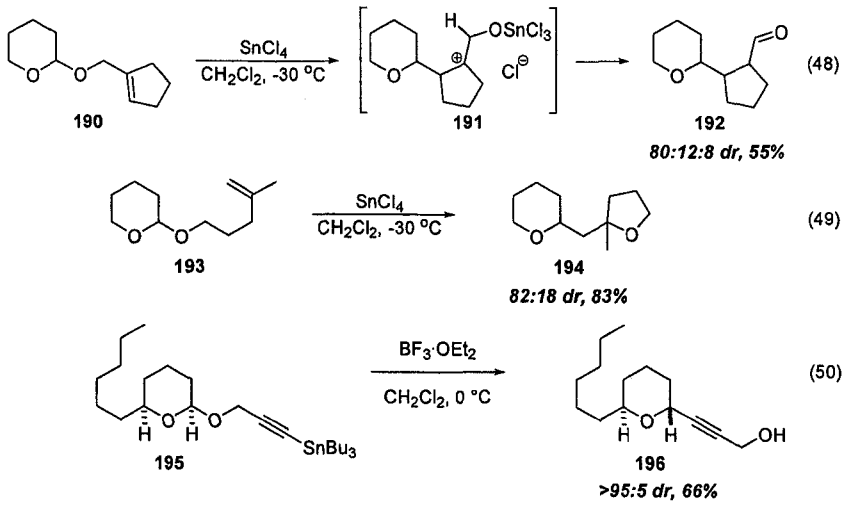
Related to the discussion of pendant vinyl and aryl ethers is the rearrangement of other anomerically-linked nucleophiles. Mikami and Kishino described an example of this type of reactivity via an "oxonium"-ene reaction, a formal [1, 4] rearrangement.[87]

Exposure of **184** to TMSOTf induces acetal cleavage to generate an oxocarbenium ion. The authors then propose a concerted ene reaction that forms the new C-C bond and transfers a proton to the tetrahydrofuran oxygen (**185** to **186**). The oxonium ion then quenches the newly formed silylenolether (Scheme 30). One may also envision that the ene-alkylation of the oxocarbenium ion does not transfer a proton and the resultant tertiary cation is quenched by a hydride shift **187** to **188**.

Scheme 30.

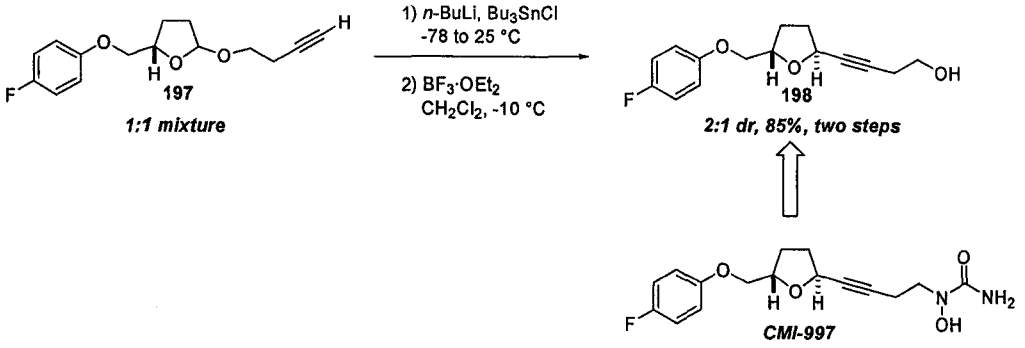


This method was expanded by Ley and coworkers, where the intermediate tertiary cation could be trapped by an exogenous nucleophile (Eq. 48).[88] In the case of **197**, an ene reaction generates a tertiary cation which is trapped in intramolecular fashion by the primary alcohol (Eq. 49). Ley also extended this method to incorporate alkynyl stannanes as the nucleophile component (Eq. 50).[89]



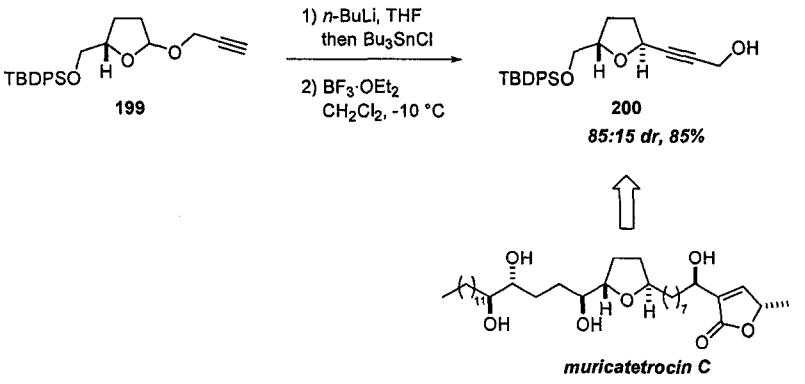
Although the rearrangement proceeds efficiently and with good diastereoselectivity with pyran systems, the analogous reaction with a tetrahydrofuran proceeds with only 2:1 selectivity. This material was used in the synthesis of CMI-997 (Scheme 31).[90]

Scheme 31.

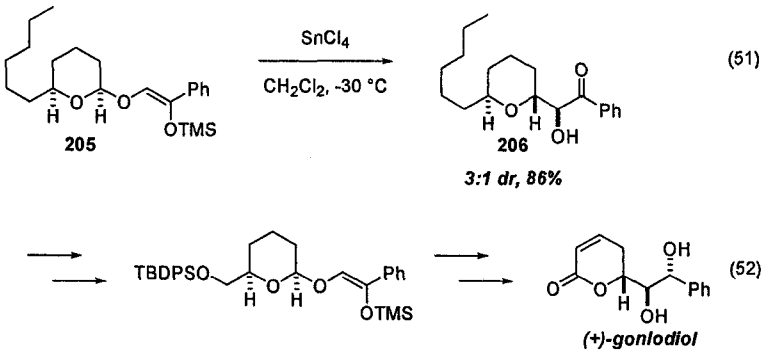


Later, in a synthesis of muricatetrocin C, it was shown that increasing the steric bulk at the 5-position of the tetrahydrofuran had a positive effect on the diastereoselectivity for the rearrangement (Scheme 32).[91]

Scheme 32.



Two contiguous stereocenters could be set in a single operation to provide α-hydroxy ketones (Eq. 51).[92] This method was utilized in the synthesis of (+)-goniodiol (Eq. 52).[93]



1.6. Conclusion.

This review has attempted to comprehensively survey the advances that have been made in the development of [1, 3] rearrangements. Although significant progress has been made in this area, there is room for improvement of existing methods and their application to more complex scenarios. In particular, the incorporation of nitrogen into rearrangement precursors would undoubtedly expand the utility of this class of reactions. Certainly, future research with an eye towards substituent effects and ion pairing will have a large impact on the general understanding and development of new [1, 3] rearrangements.

1.7. References.

[1] a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 223-247. b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 827-873. c) Blechert, S. *Synthesis* **1989**, 71-82. d) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43-50. e) Udo, N. *Synthesis* **2003**, 961-1008. f) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939-3002.

[2] a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970. b)Flemmin, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience, New York, 1976.

[3] There are few examples of [1, 3] antarafacial shifts. For an example see: Baldwin, J. E.; Flemming, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 2140-2142.

[4] Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406-414.

[5] Claisen, L. *Chem. Ber.* **1896**, *29*, 2931-2932.

[6] Claisen, L. *Chem. Ber.* **1912**, *45*, 3157-3166.

[7] Wislicenus, W.; Schrotter, R. *Ann. Chem.* **1921**, *424*, 215-232.

[8] Staudinger, H.; Ružicka, L. *Helv. Chim. Acta.* **1924**, *7*, 377-390.

[9] Lauer, W. M.; Spielman, M. A. *J. Am. Chem. Soc.* **1933**, *55*, 4923-4930.

[10] This is supported by prior work where heating of phenyl benzyl ether produced toluene as a product. a) Powell, S. G.; Adams, R. *J. Am. Chem. Soc.* **1920**, *36*, 646-658. b) Lauer, W. M.; Spielman, M. A. *J. Am. Chem. Soc.* **1920**, *36*, 1572-1574.

[11] Methane was also a product of the reaction between α-methoxystyrene and other hydrocarbons. a) Spielman, M. A.; Mortenson, C. W. *J. Am. Chem. Soc.* **1939**, *55*, 666-667.

[12] Other 1,3-shifts were shown to proceed via an intermolecular rearrangement: Wiberg, K. B.; Shryne, T. M.; Kintner, R. R. *J. Am. Chem. Soc.* **1957**, *79*, 3160-3164.

[13] MacDougall, F. H.; Lauer, W. M.; Spielman, M. A. *J. Am. Chem. Soc.* **1933**, *55*, 4089-4097.

[14] Wiberg, K. B.; Kintner, R. R.; Motell, E. L. *J. Am. Chem. Soc.* **1963**, *85*, 450-454.

[15] Woodward, R. B.; Hoffmann, R. *The conservation of Orbital Symmetry*; Verlag Chemie, Academic Press: New York, 1971.

[16] Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867-874.

[17] [1, 3] O to C rearrangements that proceed via an ion pair will be discussed in the next section.

[18] Hart, H.; Eleuterio, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 519-522.

[19] Wiberg, K. B.; Rowland, B. I. *J. Am. Chem. Soc.* **1955**, *77*, 1159-1163.

[20] Used as a radical trap for dissociated radicals produced under thermal rearrangement conditions, approximately 12% of the butanethiol adduct was isolated.

[21] Lown, J. W.; Akhtar, M. H.; McDaniel, R. S. *J. Org. Chem.* **1974**, *39*, 1998-2006.

[22] Shiina, I.; Nagasue, H. *Tetrahedron Lett.* **2002**, *43*, 5837-5840.

[23] Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1980**, *45*, 891-894.

[24] Burger, K.; Gaa, K.; Geith, K.; Schierlinger, C. *Synthesis*, **1989**, 850-855.

[25] Burger, K.; Fuchs, A.; Hennig, L.; Helmreich, B.; Greif, D. *Monatshefte fur Chemie*, **2001**, *132*, 929-945.

[26] a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc. Chem. Commun.* **1984**, 1427-1428. b) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Org. Chem.* **1987**, *52*, 5190-5194.

[27] a) Morrow, G. W.; Wang, S.; Swenton, J. S. *Tetrahedron Lett.* **1988**, *29*, 3441-3444. b) Wang, S.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364-5371.

[28] Shishido, K.; Shitara, E.; Fukumoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 5810-5812.

[29] Danishefsky, S.; Funk, R. L.; Kerwin Jr., J. F. *J. Am. Chem. Soc.* **1980**, *102*, 6891-6893.

[30] Kahn, K. M.; Knight, D. W. *J. Chem. Soc. Chem. Commun.* **1991**, 1699-1701.

[31] Novikov, A. V.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993-996.

[32] a) Ferrier, R. J. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1455-1458. b) Blattner, R.; Ferrier, R. J.; Haines, S. R. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 2413-2416.

[33] Other examples of Hg(II)-mediated carbocyclization: a) Barton, D. H. R.; Camara, J.; Dalko, P.; Gero, S. D.; Quiclet-Sire, B.; Stutz, P. *J. Org. Chem.* **1989**, *54*, 3764-3766. b) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumeny, J. M.; Gero, S. D.; Quiclet-Sire, B.; Stutz, P. *Tetrahedron*, **1990**, *46*, 215-230.

[34] Adam, S. *Tetrahedron Lett.* **1988**, *29*, 6589-6592.

[35] Other examples of Pd(II) catalysis: a) Laszlo, P.; Dudon, A. *J. Carbohydrate Chem.* **1992**, *11*, 587-593.
[36] a) Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 5813-5815. b) Demole, E.; Enggish, P. *Chem. Commun.* **1969**, 264-265.
[37] a) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.***1980**, *102*, 2840-2841. b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550-7559.
[38] Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2485-2487.
[39] Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559-7572.
[40] a) Trost, B. M. *Tetrahedron*, **1977**, *33*, 2615-2649. b) Trost, B. M. *Acc. Chem. Res.* **1980**, *12*, 385-393.
[41] Steglich, W., Höfle, G. *Tetrahedron Lett.* **1970**, *11*, 4727-4730.
[42] a) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533. b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368-13369. c) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925-934.
[43] Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785-3788.
[44] Takahashi, M.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Chem. Lett.* **1981**, 1435-1438.
[45] Takahashi, M.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 1079-1082.
[46] Takahashi, M.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 4031-4039.
[47] Tayama, E.; Isaka, W. *Org. Lett.* **2006**, *8*, 5437-5439.
[48] Suzuki, T.; Inui, M.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 3713-3716.
[49] Gu, X. P.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1988**, *53*, 2737-2740.
[50] For further reading about contact ion pairs see: a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1965**, *87*, 669-670. b) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307-318. c) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 318-324.
[51] Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 83-85.
[52] Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316-322.
[53] a) Gansäuer, A; Fielenbach, D.; Stock, C. *Adv. Synth. Catal.* **2002**, *344*, 845-848. b) Gansäuer, A; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *Adv. Synth. Catal.* **2003**, *345*, 1017-1030.
[54] Dauaben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241-3244.
[55] Dintzner, M. R.; Morse, K. M.; McClelland, K. M.; Coligado, D. M. *Tetrahedron Lett.* **2004**, *45*, 79-81.
[56] Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935-6938.
[57] Matsumoto, T.; Hosoya, T.; Suzuki, K. *Synlett*, **1991**, 709-711.
[58] Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 4629-4632.
[59] a) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K *Tetrahedron Lett.* **1989**, *30*, 6185-6188. b) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 2175-2178.
[60] Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis*, **1988**, 1005-1007.
[61] A similar rearrangement in the presence of stoichiometric Lewis acid was reported: Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1992**, *33*, 3061-3064.
[62] Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1988**, *53*, 1860-1862.
[63] Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489.
[64] See miscellaneous section for discussion of anomerically linked nucleophiles.
[65] Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2385-2394.
[66] Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720-9721.
[67] For a review on inverse Eyring relationships see: Bushmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477-515.
[68] Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157-1160.
[69] a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169. b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528.
[70] Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979-8987.
[71] Frein, J. D.; Rovis, T. *Tetrahedron* **2006**, *62*, 4573-4583.
[72] Menicagli, R.; Malanga, C.; Lardicci, L.; Tinucci, L. *Tetrahedron Lett.* **1980**, *21*, 4525-4528.
[73] Menicagli, R.; Malanga, C.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 2288-2291.
[74] a) Frauenrath, H.; Runsink, J.; Scharf, H.-D. *Chem. Ber.* **1982**, *115*, 2728-2729. b) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707-2712.
[75] Takano, S.; Samizu, K.; Ogasawara, K. *Synlett*, **1993**, 785-787.
[76] Coleman, R. S.; Guernon, J. M.; Roland, J. T. *Org. Lett.* **2000**, *2*, 277-280.

[77] Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394-6395.
[78] Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141-144.
[79] a) Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909-912. b) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913-916. c) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834-4836.
[80] Smith, A. B.; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637-3640.
[81] a) Smith, A. B.; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637-3640. b) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948-6949. c) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292-5299.
[82] Sollogoub, M.; Mallet, J.-M.; Sinay, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 362-364.
[83] For more varied examples see: a) Das, S. K.; Mallet, J.-M.; Sinay, P. *Angew. Chem. Int. Ed. Engl.* **1997**, *109*, 493-496. b) Sinay, P.; Dalko, P. *Angew. Chem Int. Ed.* **1999**, *111*, 819-823. c) Pearce, A. J.; Sollogoub, M.; Mallet, J.-M.; Sinay, P. *Eur. J. Org. Chem.* **1999**, 2103-2117.
[84] Nicholas, A. M. *Acc. Chem. Res.* **1987**, *20*, 207-214.
[85] a) Meek, S. J.; Pradaux, F.; Carbery, D. R.; Demont, E. H.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 10046-10056. b) Carbery, D. R.; Reignier, S.; Miller, N. D.; Adams, H.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4392-4399. c) Carbery, D. R.; Reignier, S.; Myatt, J. W.; Miller, N. D.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2584-2587.
[86] Meek, S. J.; Pradaux, F.; Demont, E. H.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 5597-5600.
[87] Mikami, K.; Kishino, H. *Tetrahedron Lett.* **1996**, *37*, 3705-3708.
[88] Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc. Perkin 1.* **2000**, 1815-1827.
[89] Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett*, **1998**, 1091-1092.
[90] Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Reynolds, D. J.; Storer, R. I. *Org. Biomol. Chem.* **2004**, *2*, 1145-1154.
[91] Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3622-3626.
[92] Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett*, **1998**, 1093-1095.
[93] Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 3125-3126.

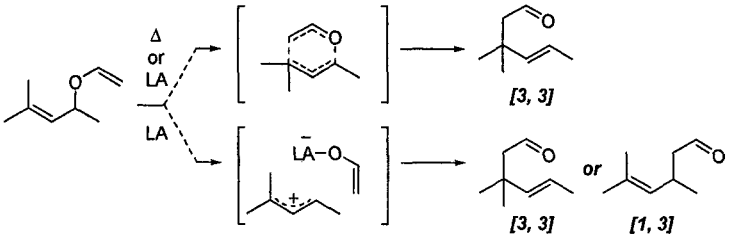
Chapter 2

Regioselective Lewis Acid-Mediated [1, 3] Rearrangement of Allylvinyl Ethers

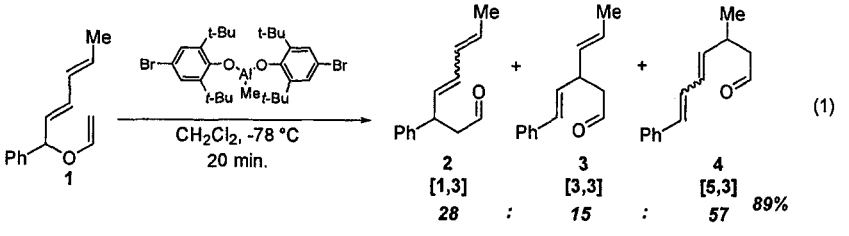
2.1. Introduction.

The formation of sterically-congested carbon-carbon bonds with control of stereochemistry represents a formidable challenge in organic synthesis. One tool that has met this challenge is the Claisen rearrangement, a [3, 3] rearrangement of allylvinyl ethers.[1] This thermal sigmatropic rearrangement relays stereochemical information from the cleaving C-O bond to the forming C-C bond via a concerted transition state.[2] More recently, the use of Lewis acids has provided rate acceleration for the Claisen rearrangement.[1] However, under the Lewis acid manifold, ionic intermediates have been proposed, a divergence from the generally-accepted concerted mechanism.[3] If true ionic intermediates do exist, then other regioisomeric products should be observed (Scheme 1).

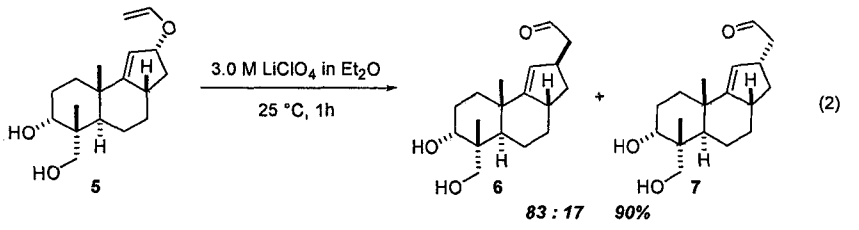
Scheme 1.



Yamamoto and coworkers reported that pentadienyl vinyl ether **1** undergoes rearrangement to produce a mixture of [1, 3], [3, 3], and [5, 3] regioisomers in the presence of bulky aluminum bisphenoxy Lewis acid (Eq. 1).[3]

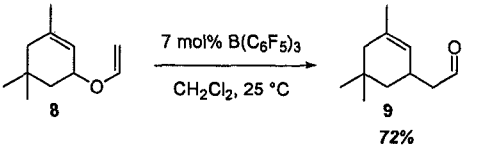


Grieco and coworkers, under strongly ionizing conditions, were able to selectively produce [1, 3] rearrangement products from sterically-hindered allylvinyl ether **5** (Eq. 2).[4]



(2)

Gansauer has also illustrated a $Cu(OTf)_2$- and $B(C_6F_5)_3$-catalyzed regioselective [1, 3] rearrangement of *tert*-butyl alcohol, benzyl alcohol, and isophorone-derived vinyl ethers (Eq. 3).[5,6]



(3)

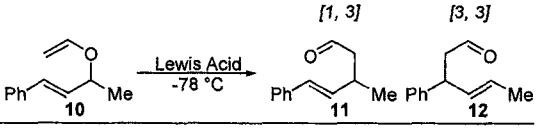
In these cases, the Lewis acid-mediated [1, 3] rearrangement of allylvinyl ethers necessarily proceeds through an allyl cation and metallo-enolate ion pair. As part of our efforts aimed at developing stereoselective [1, 3] rearrangements,[7,8] we initiated a study to elucidate the factors that govern regioselectivity, harness this reactivity, and explore the scope of the [1, 3] rearrangement of allylvinyl ethers.

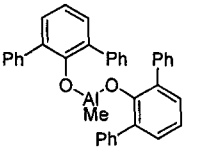
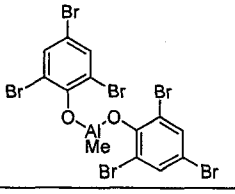
2.2. Initial Studies.

Experimentation began with a brief screen of Lewis acids using cinnamyl vinyl ether **1** as a substrate. Cu(II), Sn(IV), and Ti(IV) Lewis acids provided mixtures of [1, 3] and [3, 3] adducts (entries 1-3, Table 1). The reaction worked equally well in CH_2Cl_2 or toluene. Lewis basic solvents were inferior. Bisphenoxy Al complexes are better suited for this study due to the electronic and steric perturbations that could be achieved through substitution of the phenol ring.[9] We identified two different Lewis acids that gave complementary regioselectivity for the rearrangement of cinnamaldehyde-derived

allylvinyl ether **1** (entries 4 and 5, Table 1). Steric bulk about the Al-metal center proved to be optimal for the [3, 3] product (entry 4), while halide substitution produced a stronger Lewis acid that is moderately [1, 3] selective (entry 5). Although this dichotomy is not easy to rationalize, it is evident that there is a fine line between accelerating the concerted [3, 3] rearrangement versus generating an ionic intermediate. An increase in the strength of the Lewis acid or in the stability of the allyl cation should result in greater degree of C-O bond ionization and hence, increased [1, 3] selectivity.

Table 1. Initial Lewis Acid Screen.



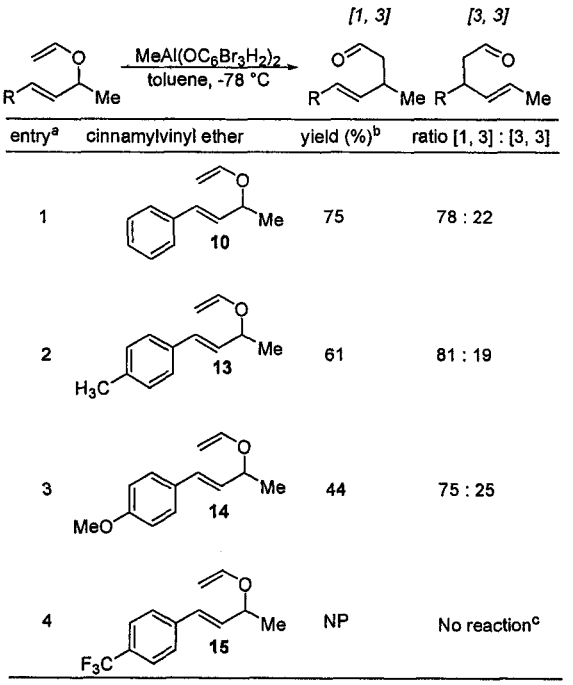
entry[a]	Lewis Acid	ratio [1, 3] : [3, 3]
1	$Cu(OTf)_2$[b]	50 : 50
2	$SnCl_4$	50 : 50
3	$TiCl_4$	67 : 33
4		5 : 95
5		78 : 22 (75%)[c]

a) Reactions conducted in toluene or CH_2Cl_2 using 1.05 eq. of Lewis acid. b) Reaction performed at -50 °C. c) Combined isolated yield.

We next sought better [1, 3] selectivity through electronic variation at the 4-phenyl position of the model substrate. As expected, on the basis of the above rationale, 4-methyl substitution **13** increased the [1, 3] selectivity to 81:19 (entry 2, Table 2). However, 4-methoxy substitution **14** resulted in decreased regioselectivity (entry 3), a situation we ascribe to secondary Lewis acid coordination to the methoxy group.

Electron-withdrawing substitution about the ring **15** resulted in recovered starting material, even after warming the reaction mixture from -78 °C to ambient temperature, presumably due to destabilization of the forming cation (entry 4).

Table 2. Effect of 4-Substituent on Regioselectivity.

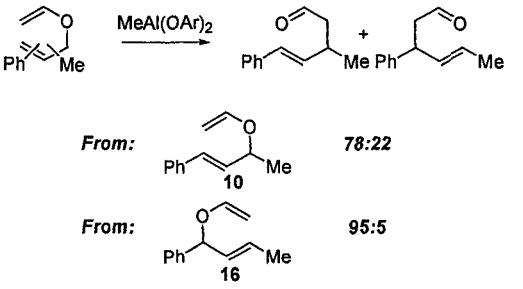


a) Reactions conducted using 1.05 eq. of Lewis acid. b) Combined yield.
c) Reaction was warmed to 23 °C and starting material was isolated.

2.3. Control Experiments.

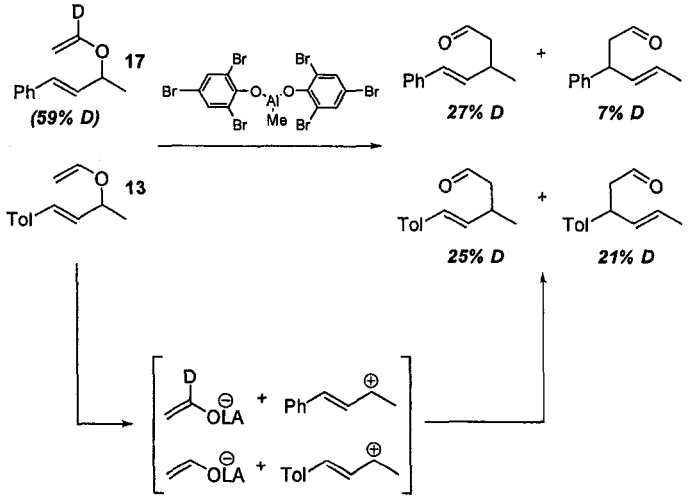
To further explore why electronic variation of the substrate did not afford significant improvements in [1, 3] regioselectivity, a control experiment was designed (Scheme 2). The regioisomeric allylvinyl ether **7** was synthesized and subjected to the optimized conditions. Both regioisomeric allylvinyl ethers provide the same major product, suggesting that the largest coefficient in the LUMO of the cation (ie. most reactive carbon) is furthest away from phenyl group stabilization. Interestingly, the regioselectivity ratio does not match between the two substrates which may be due to a partitioning between ionic [1, 3], ionic [3, 3] and concerted [3, 3] mechanisms.

Scheme 2.



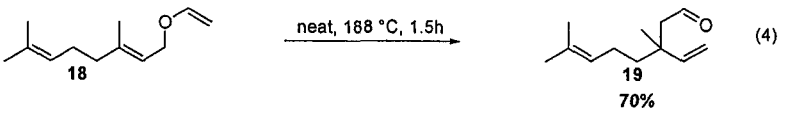
We hypothesize that if an ionic mechanism is operating, the allyl cation determines the observed regioselectivity.[10] Indeed, a crossover experiment using deuterium-labeled vinyl ether illustrates nearly complete scrambling of the label (Scheme 3).

Scheme 3.



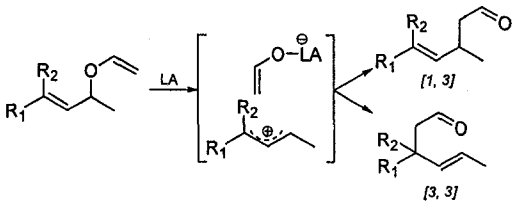
2.4. Regiocontrol and Reaction Scope.

In an attempt to further control regioselectivity, we turned our attention to allyl systems bearing trisubstituted alkenes. It is known that elevated temperatures are required in systems that undergo [3, 3] rearrangement to form quaternary carbon centers (Eq. 4).[11]



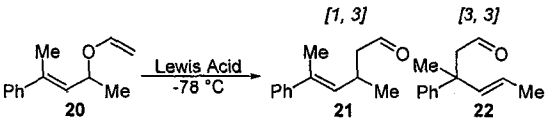
We thought to apply this apparent characteristic of the Claisen rearrangement to our methodology: under ionic conditions, [3, 3] recombination of the metallo-enolate and allyl cation to form a quaternary carbon center at the tertiary cation should be slow relative to [1, 3] recombination at the less hindered secondary cation (Scheme 4).

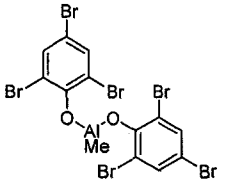
Scheme 4.



Trisubstituted allylvinyl ethers are easily prepared by carboalumination of commercially available alkynes,[12] trapping with aldehydes, and Hg(II)-catalyzed transvinylation.[13] A variety of Lewis acids afford the [1, 3] adduct in moderate to good yield and excellent regioselectivity (Table 3).

Table 3. Lewis Acid Scope.

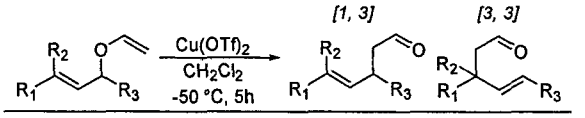


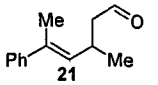
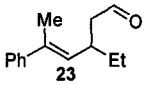
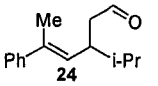
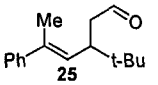
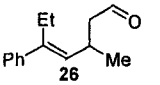
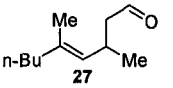
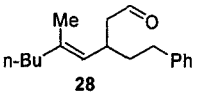
entry[a]	Lewis Acid	yield (%)	ratio [1, 3] : [3, 3]
1	$Cu(OTf)_2$[b]	81	>95 : 5
2	$SnCl_4$	40	80 : 20
3	$TiCl_4$	44	>95 : 5
4	Me_2AlCl	73	>95 : 5
5	$EtAlCl_2$	55	>95 : 5
6		44	>95 : 5

a) Reactions conducted in toluene or CH_2Cl_2 using 1.05 eq. of Lewis acid. b) Reaction performed using 10 mol% Lewis acid.

A broad range of trisubstituted allylvinyl ethers undergo [1, 3] rearrangement with exceptionally high selectivity (Table 4). The reaction seems to be somewhat insulated from electronic issues; the yield and the selectivity decrease slightly by switching from aromatic to alkyl substitution of the double bond (entries 6 and 7). We observe diminished selectivities when a *tert*-butyl group **25** is present at the 1-position and the enolate must attack either the tertiary position ([3, 3]) or the neopentyl position ([1, 3]) (entry 4).

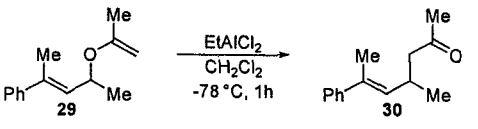
Table 4. Substrate Scope.



entry[a]	product	yield (%)	ratio [1, 3] : [3, 3]
1	 **21**	81	>95 : 5
2	 **23**	70	>95 : 5
3	 **24**	53	>95 : 5
4	 **25**	63	85 : 15
5	 **26**	64	>95 : 5
6[b]	 **27**	50	80 : 20
7[b]	 **28**	84	69 : 31

a) Reactions conducted using 5 mol% Lewis acid at -50 °C for 5h.
b) Reaction conducted at -30 °C for 48h.

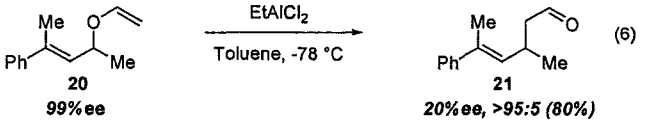
Rearrangement of an isopropenyl vinyl ether produced a 50:50 mixture of regioisomers when using $Cu(OTf)_2$ as the Lewis acid. Increasing the strength of the Lewis acid by using $EtAlCl_2$ restored the regioselectivity (Eq. 5). This is consistent with the hypothesis that a weaker Lewis acid is capable of accelerating the Claisen via a concerted pathway, while the stronger Lewis acid results in bond ionization.



(5)

The nature of the intermediate ion pair was evaluated by rearrangement of enantioenriched allyl vinyl ether **20** (Eq. 6). The [1, 3] product was isolated in good yield, with >95:5 regioselectivity and 20% ee. Based on the discussion in the preceding chapter

there are two distinct ionic species formed under these conditions: 1) a tight ion pair and 2) a dissociated ion pair. The tight ion pair leads to enantioenriched product, while the dissociated ion pair is responsible for racemization. Attempts to improve the degree of stereoretention failed.



2.5. Conclusion.

In conclusion, this section has illustrated a regioselective [1, 3] rearrangement of allylvinyl ethers. Both Lewis acidity of the catalyst and electronic variation of the cation can be used to exert a measure of control on the rearrangement. These results suggest that there is a partitioning between the ionic [1, 3], ionic [3, 3] and concerted [3, 3] pathways that leads to the observed levels of regioselectivity. Substrate structure, for trisubstituted alkenes, can be used to direct the recombination event between the allyl cation and metallo-enolate.

2.6. References.

[1] (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 223-247. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 827-873. (c) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939-3002.

[2] For a mechanistic discussion, see: Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219-225.

[3] Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316-322.

[4] Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489.

[5] (a) Gansauer, A.; Fielenbach, D.; Stock, C. *AdV. Synth. Catal.* **2002**, *344*, 845-848. (b) Gansauer, A.; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *AdV. Synth. Catal.* **2003**, *345*, 1017-1030.

[6] Other examples of [1,3] rearrangements include: (a) Shi, G.; Cai, W. *J. Org. Chem.* **1995**, *60*, 6289-6295. (b) Sperling, D.; Reissig, H.-U.; Fabian, J. *Eur. J. Org. Chem.* **1999**, 1107-1114. (c) Shiina, I.; Nagasue, H. *Tetrahedron Lett.* **2002**, *43*, 5837-5840. (d) Novikov, A. V.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993-996. (e) Suzuki, T.; Inui, M.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 3713-3716. (f) Cai, Y.; Roberts, B. P. *Tetrahedron Lett.* **2003**, *44*, 4645-4648.

[7] Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720-9721.

[8] Nasveschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3264-3267.

[9] (a) Yamamoto, H.; Maruoka, K. *Pure Appl. Chem.* **1988**, *60*, 21-26. (b) Yamamoto, H.; Yanagisawa, A.; Ishihara, K.; Saito, S. *Pure Appl. Chem.* **1998**, *70*, 1507-1512.

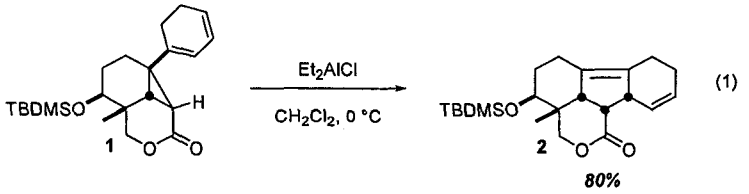
[10] Jia, Z. S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* **2002**, *67*, 182-187.
[11] Julia, S.; Julia, M.; Linares, H.; Blondel, J. C. *Bull. Chim. Soc. Fr.* **1962**, 1947-1952.
[12] Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068-1071.
[13] Maruoka, K.; Banno, H.; Yamamoto, H. *Tetrahedron: Asymmetry* **1991**, *2*, 647-662.

Chapter 3

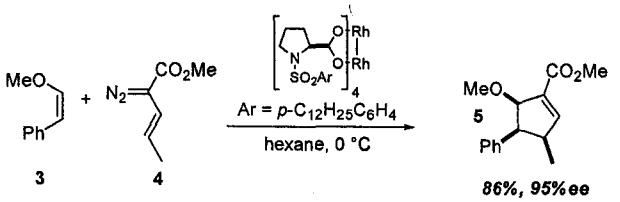
Stereoselective Lewis Acid-Mediated [1, 3] Ring Contraction of 2,5-Dihydrooxepines as a Route to Polysubstituted Cyclopentenes

3.1. Introduction.

The Diels–Alder reaction is a cornerstone of organic synthesis, and its ability to enable the production of cyclohexanes in a stereocontrolled manner is unparalleled. In contrast, no method exists for the synthesis of cyclopentanes that matches the scope and power of the Diels–Alder reaction in spite of the prevalence of these ring systems in natural products. Among numerous methods that have been used to target these cores, vinylcyclopropane ring-expansion strategies have been intensively investigated and have provided some spectacular successes.[1,2] Corey showed that vinyl cyclopropane ring expansions under Lewis acidic conditions are a viable approach to tetracyclic systems enroute to (+/-)-antheridium (Eq. 1).[3] Davies demonstrated an eloquent and convergent approach to tetrasubstituted cyclopentenes through employment of his Rh_2(*S*-DOSP)$_4$ catalyst (Eq. 2).[4]



(1)

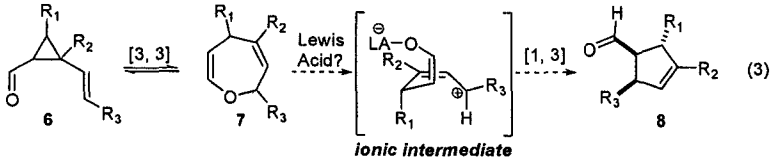


(2)

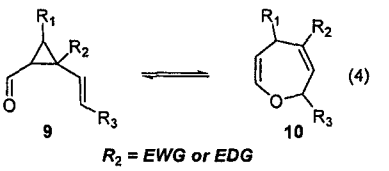
Nevertheless, most reports result in mono- or disubstituted cyclopentanes or cyclopentenes, while approaches to polysubstituted systems are rare. We were interested

in addressing this deficiency and developing a diastereoselective approach to tri-, tetra-, and pentasubstituted cyclopentanes from readily available precursors.

Our group has previously reported the [1, 3] rearrangement of vinyl acetals which proceeds through a metalloenolate and oxocarbenium ion pair.[5] To extend this concept to other stabilized cations, we initiated a program to study the [1, 3] rearrangement of allylvinyl ethers that would form a metalloenolate and an allylic cation ion pair under Lewis acidic conditions. However, we were mindful that these substrates could also undergo a Lewis acid (LA) accelerated Claisen rearrangement which, if concerted, would form the [3, 3] rearrangement product exclusively.[6] A number of workers have documented that the Lewis acid mediated Claisen rearrangement proceeds stepwise[7] and occasionally provides the [1, 3] adduct with some selectivity.[8] To favor the [1, 3] over the [3, 3] product, we envisioned that a cyclic allylvinyl ether or 2,5-dihydrooxepin could provide access to densely functionalized cyclopentenes under ionizing conditions as the [3, 3] rearrangement should be disfavored because of ring strain in the cyclopropane product (Eq. 3).

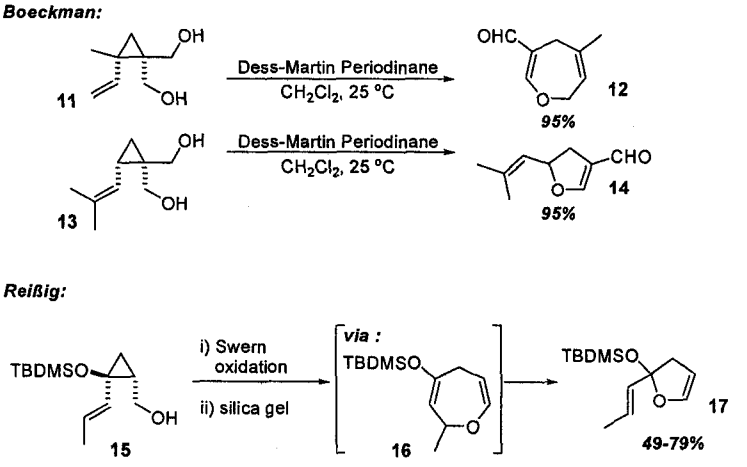


Despite their apparent complexity, 2,5-dihydrooxepins are readily prepared by a retro-Claisen reaction of the corresponding cyclopropane carboxaldehyde **9**, itself available by a modular approach using established methods (see next section).[9,10] An equilibrium between **9** and **10** has been predicted computationally,[11] and it may be shifted towards the 2,5-dihydrooxepin with π-stabilizing substituents (Eq. 4).[10]



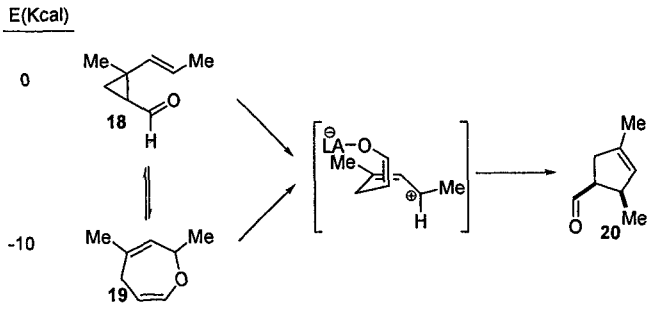
[1, 3] Rearrangments of 2,5-dihydrooxepines have been previously reported[9,10]; however, the rearrangement proceeds to form dihydrofurans in the opposite sense of the desired process (Scheme 1).

Scheme 1.



Our own PM3 semi-emperical calculations supported previous reports by Reißig that 2,5-dihydrooxepines were accessible by a retro-Claisen rearrangement of the corresponding cyclopropane carboxaldehydes (Scheme 2). Intuition suggested that an appropriate Lewis acid should to ionize the allyl C-O bond, which in principle could lead to the desired [1, 3] rearrangement. This chapter will discuss the successful implementation of this strategy, in which a unique Lewis acid promoted ring contraction of 2,5-dihydrooxepines to cyclopentenes was developed.

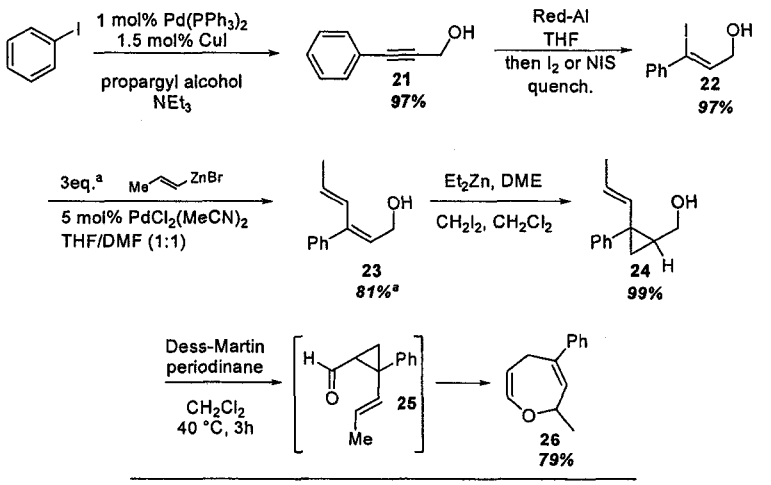
Scheme 2.



3.2. Substrate Synthesis.

We began our investigations by developing a highly modular approach to the 2,5-dihydrooxepin skeleton. A representative synthesis is illustrated in Scheme 3. A Sonogashira cross-coupling between propargyl alcohol and aryl halides provided **21**.[12] Selective formation of the (Z)-vinyl iodide **22** was effected with Red-Al/I_2,[13] and a Negishi coupling was then employed to insert an additional alkene.[14] A directed Simmons-Smith cyclopropanation afforded **24** in near quantitative yield as a single regioisomer.[15] We felt that **24** could be converted into **26** in a one-pot oxidation/retro-Claisen sequence and, after some optimization, it was found that 1.5 equivalents of the Dess-Martin periodinane in CH_2Cl_2 at 40 °C provided the desired 2,5-dihydrooxepin. Depending on the nature of the equilibrium, some unrearranged aldehyde **25** could be isolated and subsequently converted into **26** by heating overnight in toluene at 110 °C.

Scheme 3.

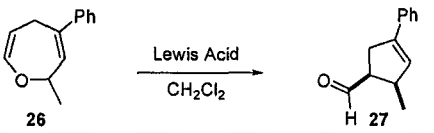


a) Reaction performed using vinyl zinc bromides derived from the corresponding lithium reagent.

3.3. Reaction Optimization.

With a convergent approach to the requisite 2,5-dihydrooxepins in hand, we began our studies on the stereoselective [1, 3] ring contraction by conducting a brief screen of Lewis acids. $Cu(OTf)_2$, $TiCl_4$, and $SnCl_4$ yielded no product under a variety of conditions (Table 1, entries 1-3). In the presence of $EtAlCl_2$ (entries 4-6), the starting material was consumed with the formation of uncharacterized oligomeric products. This could happen in one of two ways: 1) vinyl ether **26** could polymerize before ionization of the C-O bond or 2) the zwitterionic intermediate generated from the ionization of C-O is stable enough that intramolecular ring closure is slower than the bimolecular reaction. Thus, cyclopentene **27** was isolated in 89% yield with 90:10 (cis/trans) selectivity (entry 7) when **26** was subjected to dilute Lewis acid at ambient temperature. Slow addition of dilute 2,5-dihydrooxepin to the Lewis acid generally provides an incremental increase in selectivity (entry 8).

Table 1. Lewis Acid Screen.



26 27

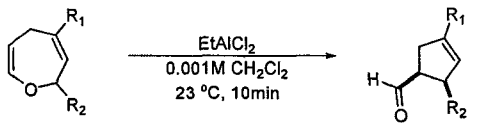
Entry	Lewis Acid	Conditions	Product (*cis/trans*)
1	$Cu(OTf)_2$	various	***NP***[a]
2	$TiCl_4$	various	***NP***[a]
3	$SnCl_4$	various	***NP***[a]
4	$EtAlCl_2$	0.1M, -78 °C 0.5h	***NP***[a]
5	$EtAlCl_2$	0.1M, 23 °C 0.5h	***NP***[a]
6	$EtAlCl_2$	0.001M, -78 °C, 1h	***NP***[a]
7	$EtAlCl_2$	0.001M, 23 °C, 5 min	***89% (90:10)***
8[b]	$EtAlCl_2$	0.02M, 23 °C, 5 min	***53%(93:7)***

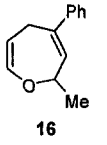
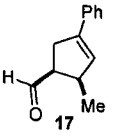
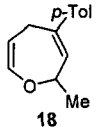
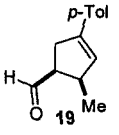
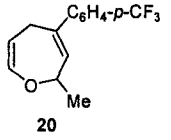
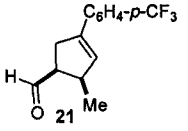
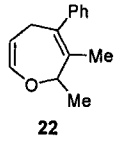
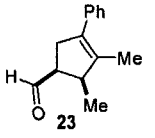
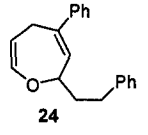
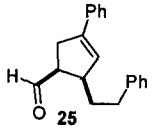
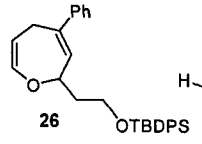
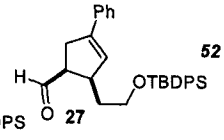
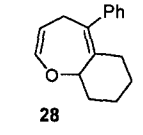
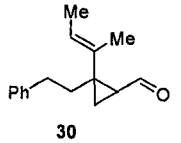
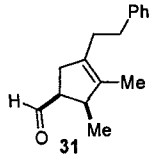
a) Starting material consumed. b) Slow addition of substrate to dilute Lewis acid.

3.4. Reaction Scope.

We then evaluated the scope of the [1, 3] ring contraction of the 2,5-dihydrooxepins. Electron-donating and electron-withdrawing groups in the para position of the aromatic ring are tolerated and give products in comparable yield and selectivity (Table 2, entries 1-3). Additional substitution on the dihydrooxepin unit is well-tolerated, with substrate **32** furnishing tetrasubstituted cyclopentene **33** with good selectivity. An increase in the steric bulk of the substituent from a methyl group (**16**) to a phenethyl group (**34**) or protected alcohol (**36**) results in a slight decrease in the yield and selectivity, but still provides synthetically useful amounts of product. Bicyclic [4.3.0] systems can be accessed using this method, although the yield in this case is unoptimized (entry 7). Lastly, the use of aldehyde **40** as a substrate indicates that formation of the dihydrooxepin is not necessary to achieve reaction. Furthermore, this substrate lacks the aryl stabilization evident in the other substrates, thus suggesting that aliphatic stabilization is sufficient in some cases.

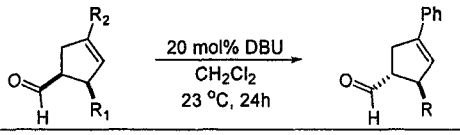
Table 2. Reaction Scope.

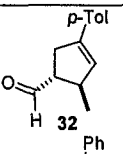
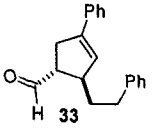


Entry	Substrate	Product	Yield%	*cis/trans*
1	 **16**	 **17**	***89***	***90 : 10***
2	 **18**	 **19**	***85***	***93 : 7***
3	 **20**	 **21**	***75***	***87 : 13***
4	 **22**	 **23**	***58***	***88 : 12***
5	 **24**	 **25**	***73***	***85 : 15***
6	 **26**	 **27**	***52***	***85 : 15***
7	 **28**	 **29**	***38***	***92 : 8***
8	 **30**	 **31**	***59***	***89 : 11***

These disubstituted cyclopentene carboxaldehydes are readily epimerized[15] to form the *trans* diastereomer upon treatment with DBU (Table 3, entries 1 and 2).

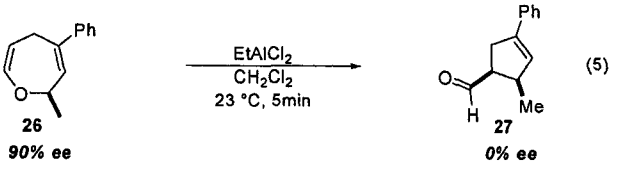
Table 3. Aldehyde Epimerization.



Entry	R_1, R_2	Product	Yield%	*trans/cis*
1	Me, *p*-Tol **19**	 **32**	*68*	*88 : 12*
2	-CH_2CH_2Ph, Ph **25**	 **33**	*81*	*97 : 3*

3.5. Enantioenriched Cyclopentene Synthesis.

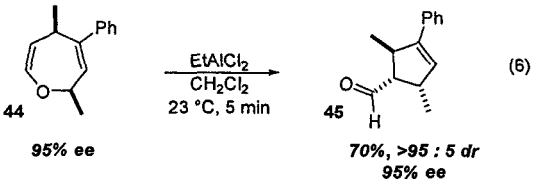
A considerable advantage of this method is the ability to introduce substitution at every position of the dihydrooxepin ring and, when desired, enantioenrichment during the cyclopropanation step. With this approach in mind, we sought to apply the protocol of Charette et al.[15] as a means of introducing asymmetry and additional substitutents onto the cyclopropane. 2,5-Dihydrooxepin **26** was synthesized in enantioenriched form using the Charette-Simmons-Smith protocol in 56% yield. When reacted under the optimized conditions, the corresponding cyclopentene was isolated in 0 %ee (Eq. 5).



26
90% ee

27
0% ee

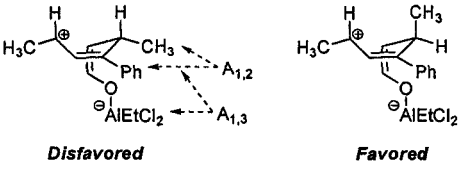
Clearly, racemization is due to ionization of the allyl C-O bond to the flat allyl cation. To access enantioenriched cyclopentenes using this methodology 2,4,5-trisubsituted dihydrooxepine **44**, which possesses a stereocenter that cannot be epimerized was constructed. When **44** was subjected to the optimized reaction conditions, **45** was isolated in 70 % yield and 95 %ee (Eq. 6).



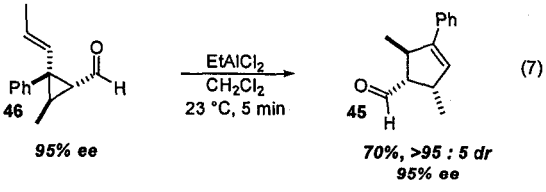
(6)

The pre-existing stereocenter controls the diastereoselective course of the reaction, and the observed selectivity can be rationalized by our proposed model (Figure 1). There is an interplay of minimization between the $A_{1,2}$ strain, between the phenyl group on the allyl cation and the adjacent methyl, and the $A_{1,3}$ strain, between the alkoxide of the enolate and the methyl group, that presumably leads to the observed levels of diastereoselectivity.

Figure 1.



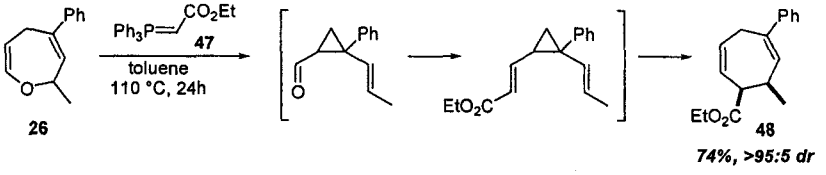
As noted above, we may also use the aldehydes as precursors for the rearrangement (Table 2, entry 8; Eq. 7). This may be rationalized in two ways: 1) initial Lewis acid catalyzed retro-Claisen rearrangement provides the 2,5-dihydrooxepin prior to [1, 3] bond migration or 2) the Lewis acid accelerates the Claisen/retro-Claisen equilibrium so that a Curtin–Hammett situation is present where the cyclopentene product is siphoned off from either the 2,5-dihydrooxepin or the cyclopropane carboxaldehyde. Although the exact mechanism at this stage remains unclear, this observation makes the overall procedure operationally simpler.



(7)

3.6. Substrate and Product Utility.

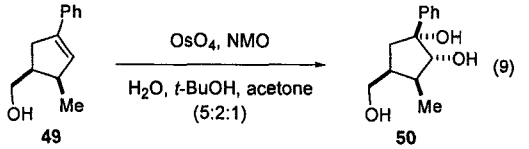
To show that an equilibrium between the 2,5-dihydrooxepine and cyclopropane carboxaldehyde exists, **26** was heated in the presence of phosphorane **47** (Eq. 8). Cycloheptadiene **48**, the product of initial Claisen rearrangement followed by Wittig reaction and then Cope rearrangement, was isolated in good yield and excellent diastereoselectivity.



26 **48** (8)

74%, >95:5 dr

The presence of the olefin in the cyclopentene allows for further diastereoselective functionalization. For example, diastereoselective dihydroxylation produces a pentasubstituted cyclopentane **40** in modest yield but excellent selectivity (Eq. 9).[16]



49 **50** (9)

60%, 91 : 9 ds

3.7. Conclusion.

In summary, we have developed a novel room-temperature Lewis acid-mediated diastereoselective [1, 3] ring contraction of 2,5-dihydrooxepins. A modular approach to these seven-membered heterocycles allows for the installation of a variety of groups at every position. The rearrangement provides access to *cis* and *trans* cyclopentene carboxaldehydes with good selectivities, and can lead to tetrasubstituted cyclopentenes in high enantiomeric excess and diastereoselectivity.

3.8. References.

[1] a) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247-335; b) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467-1486. c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165-198. d) Hudlicky, T.; Reed, J. W. *Comprehensive Organic Synthesis, Vol. 5* (Eds. Trost, B.; Fleming, I.; Paquette, L. A.), Pergamon, Oxford, **1991**, pp. 899-970. e) Reißig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151-1196.

[2] a) Larsen, S. D.; Fisher, P. V.; Libby, B. E.; Jensen, R. M.; Mizsak, S. A.; Watt, W.; Ronk, W. R.; Hill, S. T. *J. Org. Chem.* **1996**, *61*, 4725-4738. b) Zuo, G.; Louie, J. *Angew. Chem.* **2004**, *116*, 2327-2329; *Angew. Chem. Int. Ed.* **2004**, *43*, 2277-2279.

[3] Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574-5576.

[4] Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461-7462.

[5] Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720-9721.

[6] Examples of [1, 3] rearrangements of allyl vinyl ethers: a) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1988**, *53*, 1860-1862. b) K. Nonoshita, H. Banno, K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 316-322. c) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489. d) Gänsauer, A.; Fielenbach, D; Stock, C. *Adv. Synth. Catal.* **2002**, *344*, 845-848. e) Gänsauer, A.; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *Adv. Synth. Catal.* **2003**, *345*, 1017-1030.

[7] Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316-322.

[8] Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489.

[9] a) Hofmann, B.; Reißig, H.-U. *Synlett* **1993**, 27-29. b) Hofmann, B.; Reißig, H.-U. *Chem. Ber.* **1994**, *127*, 2327-2335.

[10] Boeckman, Jr., R. K.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295-1297.

[11] Sperling, D.; Reißig, H.-U.; Fabian, J. *Liebigs Ann.* **1997**, 2443-2449.

[12] Scott, E. E.; Donnelly, E. T.; Welker, M. E. *J. Organomet. Chem.* **2003**, *673*, 67-76.

[13] Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863-872.

[14] Abarbri, M.; Thibonnet, J.; Parrain, J.-L.; Duchêne, A. *Synthesis* **2002**, 543-551.

[15] Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943-11952.

[16] Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111-2119.

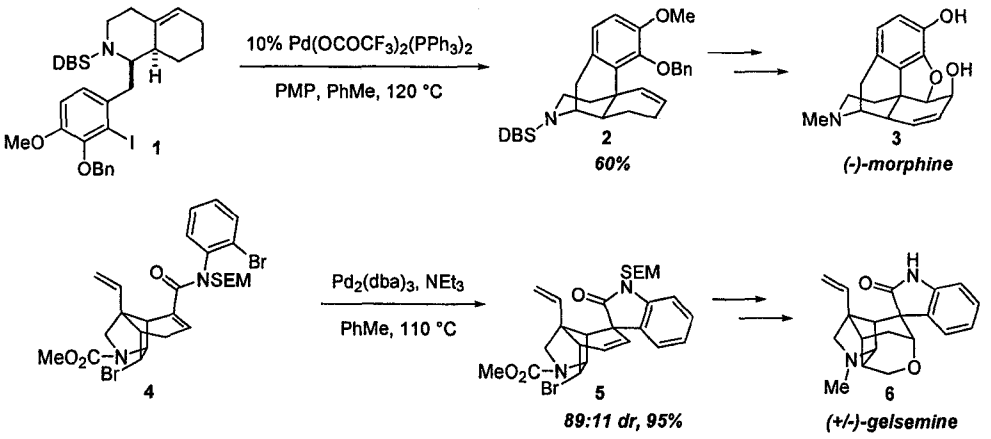
Chapter 4

A Diastereoselective Intermolecular Heck Reaction of 1,3-Dioxepins

4.1. Introduction.

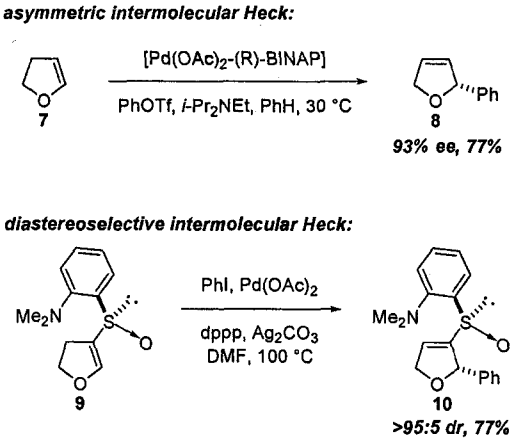
Essential to the organic chemist are the tools for the formation of new carbon-carbon bonds. Transition metal-catalyzed processes that accomplish this goal[1] have received increasing attention in recent years due to the mild nature of the reaction conditions used and functional group compatibility. One such method is the Heck reaction, which traditionally involves the coupling of an alkene and an organic halide in the presence of a palladium-derived catalyst. The intramolecular Heck reaction has been extensively investigated and as a result has played a crucial role in the successful synthesis of complex molecules (Scheme 1).[2,3]

Scheme 1.



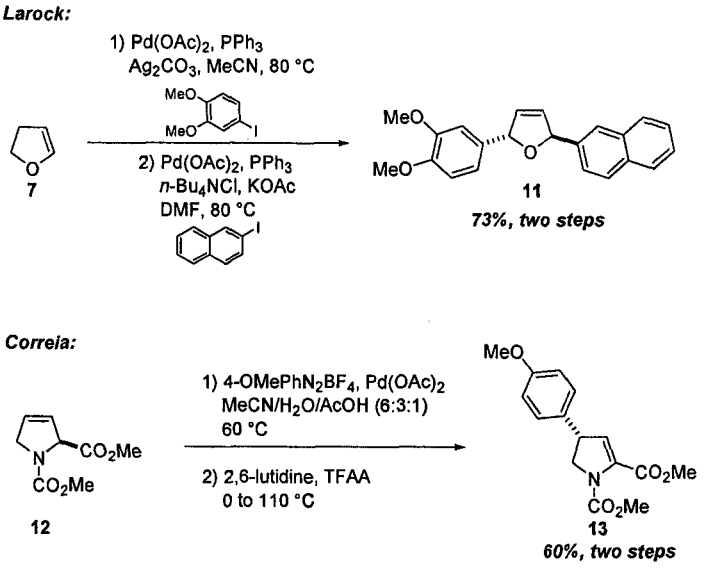
Despite the myriad of different catalyst systems, the intermolecular Heck reaction is less well-understood. Perhaps most illustrative of this issue is that only the simplest cyclic olefins participate well in the asymmetric intermolecular Heck reaction.[4] Only recently has the diastereoselective intermolecular Heck reaction been explored, in which diastereoselectivity is produced by chelation of an auxiliary (Scheme 2).[5,6]

Scheme 2.



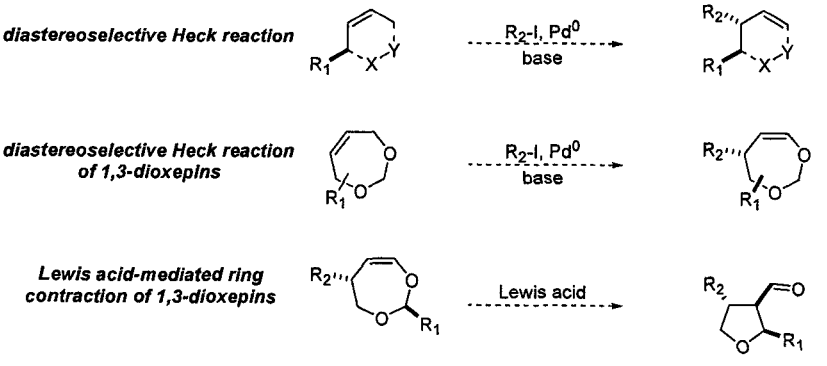
In the absence of the directing influence of an auxiliary, the reaction would take place through diasteromeric transition states and the level of diasteroselection should be dictated by sterics alone. There are a limited number of examples of this type of diastereoselective Heck reaction; however, no general protocol exists. Larock and coworkers illustrated a diastereoselective Heck reaction that provides *trans*-2,5-diaryltetrahydrofurans en route to platelet-activating factor antagonists.[7] More recently Correia and coworkers described a diastereoselective Heck reaction of substituted pyrrolines with arenediazonium salts as an approach to aryl kainoids (Scheme 3).[8]

Scheme 3.



We became interested in a Heck reaction of 1,3-dioxepins as a framework to evaluate the diastereoselective intermolecular Heck reaction because these compounds are readily synthesized with substitution at the 2- and 4-positions. The Heck products themselves are also of use in the study of diastereoselective [1, 3] ring contractions. This reaction, when combined with the overall sequence to the dioxepin framework, provides a general and modular approach to substituted tetrahydrofurans (Scheme 4).

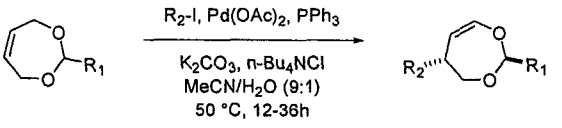
Scheme 4.

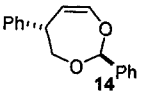
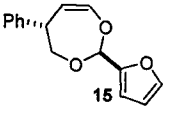
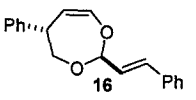
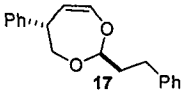
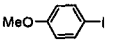
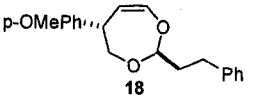
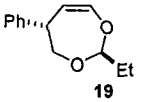
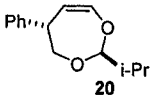
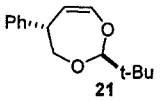
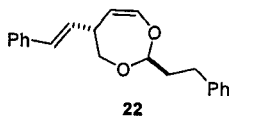
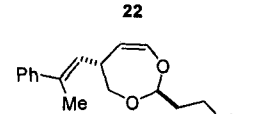
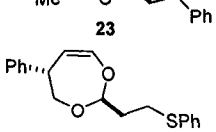


4.2. Early Results.

The Heck reaction of unsubstituted 1,3-dioxepins is known and a number of different catalyst systems have been communicated.[9] Unfortunately, the reported Heck conditions do not translate well to reactions with 2-substituted dioxepins. These reactions tended to be messy, and were plagued by prohibitively long reaction times and low conversions. However, a survey of other Heck conditions revealed that modification of Jeffery's conditions[10] produced the desired 1,3-dioxepin Heck adducts in good yield and diasteroselectivity.[11] The scope of the reaction is broad. Iodobenzene and electron-rich aromatic as well as 1,2-disubstituted and trisubstituted alkenes couple efficiently (entries 5, 9 and 10, Table 1). The reaction is also chemoselective for coupling at the Z-double bond in the presence of potentially reactive E olefins (entry 3). The diastereoselectivity appears to be independent of the substitution at the 2-position of the dioxepin and the reaction proceeds even in the presence of a thioether (entry 11).

Table 1. Scope of the Intermolecular Heck Reaction.

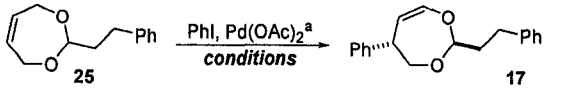


Entry	R_2-I	Product	dr	Yield %
1		 **14**	***87 : 13***	***75***
2		 **15**	***87 : 13***	***65***
3		 **16**	***83 : 17***	***71***
4		 **17**	***85 : 15***	***65***
5		 **18**	***85 : 15***	***59***
6		 **19**	***85 : 15***	***64***
7		 **20**	***85 : 15***	***67***
8		 **21**	***83 : 17***	***68***
9		 **22**	***79 : 21***	***42***
10		 **23**	***78 : 22***	***71***
11		 **24**	***83 : 17***	***59***

4.3. Reaction Optimization.

Although these modified Jeffery conditions provided material for initial [1, 3] ring contraction studies, we endeavored improve the diastereoselectivity and expand the scope of this useful reaction. Control experiments found the diastereoselectivity to be dependent on the nature of the base employed (entries 1 and 2, Table 2). We hypothesized that a more organic-soluble base would serve to increase the rate of X-Pd-H decomposition, thus suppressing the undesired Pd-H-mediated epimerization of the desired *trans* diastereomer. The reaction, when conducted using our optimized modified Jeffery conditions,[12,13] provides the desired dioxepin in excellent yield and selectivity (entry 4). The concentration of base also plays a role under the optimized conditions albeit the effect is not as pronounced (95:5 *vs* >95:5, entries 4 and 5). It is worthy to note that both of the described Heck conditions require an induction period of 10 minutes prior to the addition of substrate, which is critical for obtaining a solution that contains active catalyst. During the "aging" period there is a color change of the solution from orange to red-brown.[14,15]

Table 2. Base Study and Reaction Optimization.

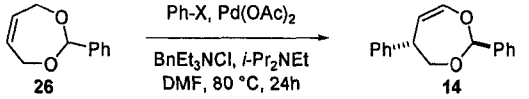


Entry	Conditions	dr (*trans:cis*)
1	K_2CO_3, *n*-Bu_4NCl 0.1M $MeCN/H_2O$ (9:1), 50 °C	***33:67***
2	K_2CO_3, *n*-Bu_4NCl 1M $MeCN/H_2O$ (9:1), 50 °C	***85:15***
4	1 eq. *i*-Pr_2NEt, $BnEt_3NCl$ DMF, 80 °C	***95:5***
5	3 eq. *i*-Pr_2NEt, $BnEt_3NCl$ DMF, 80 °C	***>95:5***[b]

a) Reactions were performed with 8 mol% $Pd(OAc)_2$. b) The minor diastereomer was not observed by ^1H NMR.

The halide scope of the reaction was evaluated (Table 3). Iodobenzene is a competent coupling partner, while the reaction falters in the presence of bromobenzene (entries 1 and 2). Aryl trifylates and acid chlorides do not participate in the reaction under these condtions (entries 3 and 4).

Table 3. Halide Scope.



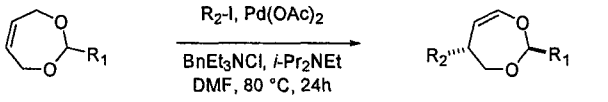
26 14

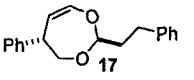
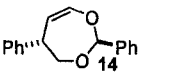
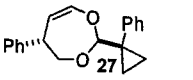
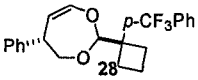
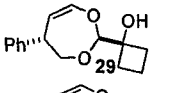
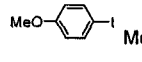
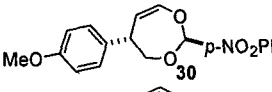
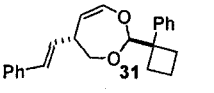
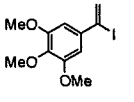
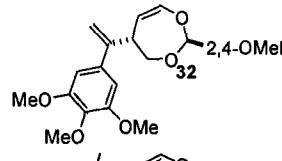
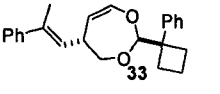
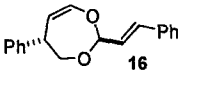
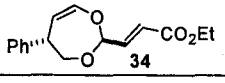
Entry	Ph-X	dr	Yield %
1	Ph-I	*>95:5*	*85*
2	Ph-Br	*>95:5*	*32*
3	Ph-OTf	*ND*	*<5*
4	PhCO-Cl	*ND*	*NR*

4.4. Reaction Scope.

The scope of the desymmetrizing Heck reaction of 1,3-dioxepins with respect to substitution at the acetal position is broad. Simple alkyl, and electron-rich and election-deficient aromatic substitution is well-tolerated (entries 1, 2, 6 and 8, Table 4). The sterochemistry of the Heck adducts was *trans* by nOe experiments and single crystal X-ray diffraction anaysis of **30**. Pendant and strained cyclopropane and cyclobutane substituents remain intact under the reaction conditions (entries 3-5, 7 and 9). Chemoselectivity for the dioxepin olefin is exclusive in the presence of other potentially reactive E-olefins (entries 10 and 11). Unprotected alcohols are also tolerated and exhibit no deleterious effects on the reaction (entry 5). The coupling partner scope is also quite broad, where electron-rich aryl, 1,2-disubstituted, 1,1-disubstituted and trisubstituted alkenyl iodides provide dioxepin products with good diastereoselectivity and respectable yields (entries 6-9).

Table 4. Reaction Scope of 2-Substituted Dioxepins.

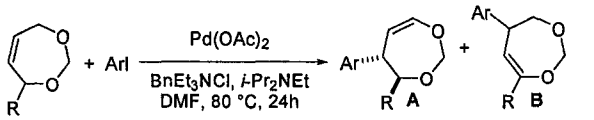


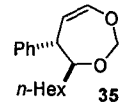
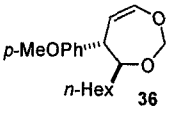
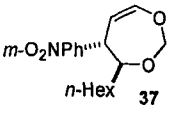
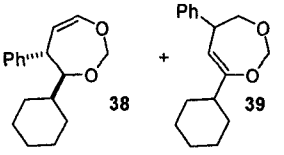
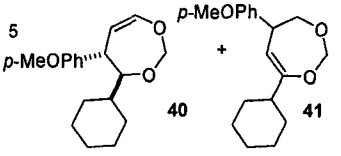
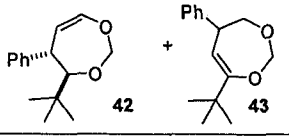
Entry	R_2-I	Product	dr	Yield %
1		 **17**	>95 : 5	87
2		 **14**	>95 : 5	85
3		 **27**	>95 : 5	80
4		 **28**	>95 : 5	80
5		 **29**	>95 : 5	72
6		 **30**	>95 : 5	67
7		 **31**	>95 : 5	50
8		 **32**	>95 : 5	45
9		 **33**	>95 : 5	36
10		 **16**	>95 : 5	77
11		 **34**	>95 : 5	64

Dioxepins that contain a preexisting stereocenter at the 4-position are also competent olefins for the Heck reaction (Table 5).[16] Electron-rich, neutral and deficient aromatic iodides all couple with excellent diastereoselectivity and good yield to provide the *trans* dioxepin products (entries 1-3). Interestingly, when the size of the substitutent

at the dioxepin 4-position reaches a steric threshold, the reverse olefin insertion becomes competitive (entries 5 and 6) and in the extreme is the major product (entry 7).

Table 5. Reaction Scope of 4-Substituted 1,3-Dioxepins.

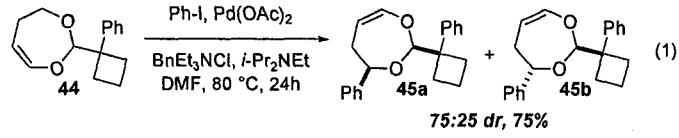


Entry	Products	Product Ratio (A:B)	Yield %, (A dr)
1	 35	*>95:5*	*83, >95:5*
2	 36	*>95:5*	*81, >95:5*
3	 37	*>95:5*	*56, >95:5*
4	 38 + 39	*64:36*	*84, >95:5*
5	 40 + 41	*78:22*	*84, >95:5*
6	 42 + 43	*38:62*	*61, >95:5*

4.5. Stereochemistry.

In order to rationalize the stereochemistry of the products we considered thermodynamic versus kinetic selectivity. It has been established that alkenes can "walk" under a variety of Heck conditions by Pd-H-mediated isomerization to the more thermodynamically favored position.[17] To determine if this mechanism was operative under our conditions 1,3-dioxepin **44** was subjected to the optimized Heck conditions and

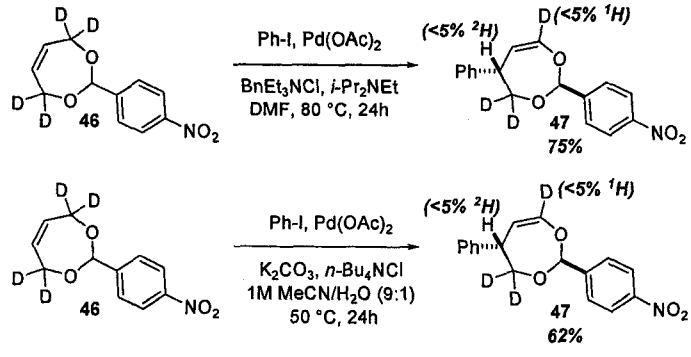
returned **45** in good yield and modest dr confirming that the vinyl ether is the thermodynamically favored position for the alkene (Eq. 1).



(1)

This result however, does not determine whether an epimerization event is responsible for the formation of the *trans*-dioxepin stereochemistry. To evaluate this possibility, 4,4,7,7-tetradeuteriodioxepin **46** was synthesized. If the *trans*-dioxepin is produced by thermodynamic selecitivity (isomerization/epimerization by Pd-H or Pd-D) the there should be ^{2}H enrichment at the 5-position and ^{1}H enrichment at the 7-position of the dioxepin. If kinetic selectivity predominates then no 5-^{2}H or 7-^{1}H enrichment should be observed. Exposure of **46** to both sets of modified Jeffery conditions showed no ^{2}H enrichment at the 5-position and no ^{1}H incorporation at the 7-position.[18] When combined, this data suggessts that the high levels of diastereoselection obtained under the optimized conditions are a result of *kinetic* selecitvity and not epimerization of the newly formed stereocenter by a long-lived Pd-H.

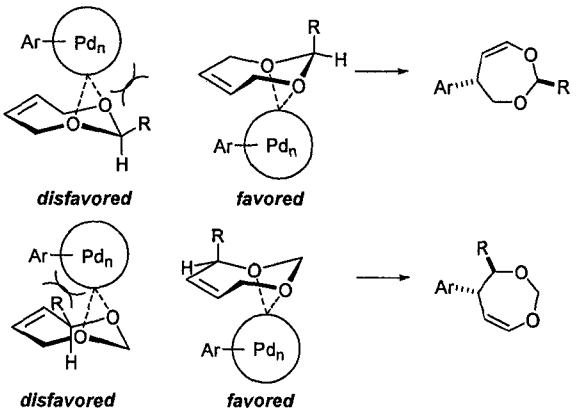
Scheme 5.



The relative stereochemistry can be rationalized by our proposed stereochemical model. Coordination of the Pd-alkyl species to the acetal oxygen-lone pairs brings the

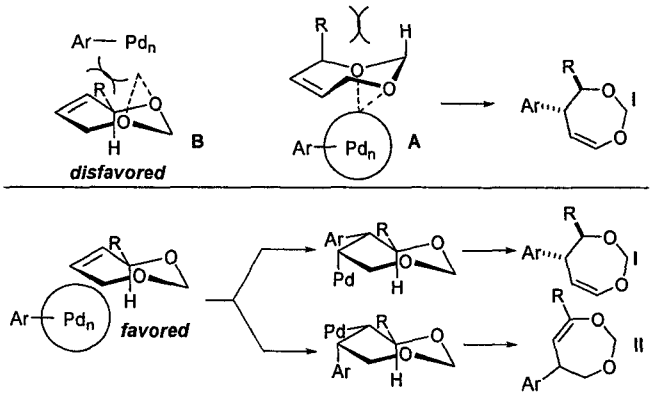
metal into steric contact with the substitutent at the 2- or 4-position of the dioxepin.[19] This steric clash forces a ring flip, placing the substituent in the axial position and *anti* to the Pd-alkyl species, which leads to the *trans* product (Figure 1).

Figure 1.

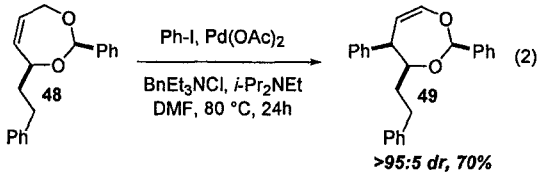


Recall that increasing steric bulk at the 4-position of the 1,3-dioxepin increases the amount of regioisomeric product was formed (entries 4-6, Table 5). This product arises from a different mode of olefin insertion (*vide infra*). To rationalize this result, it is necessary to consider the aforementioned stereochemical models. The reaction via structure **A** leads to the expected product **I** (Fig. 2). However, as the steric size increases there is a developing 1,3-diaxial interaction. This, combined with a preference for large substitutents to occupy equitorial positions leads to a chair-like conformation (Fig. 2, **B**). Delivery of the Pd-alkyl species by coordination of the acetal-oxygens in the chair-like conformation would lead to the *cis* product, which is not observed. Hence, the formation of **II** most likely arises from a true intermolecular reaction between the olefin of the 1,3-dioxepin and the Pd-alkyl species.

Figure 2.

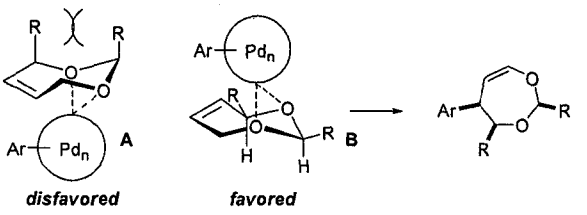


We next directed our attention towards determining the combined effect of substitution at the 2- and 4-positions of the dioxepin. Interestingly we found that when *cis*-2,4-disubstituted dioxepin **48** was subjected to optimized conditions, the all *cis*-2,4,5-trisubstituted dioxepin **49** was obtained in good yield and excellent diastereoselectivity (Eq. 2).[20]



To rationalize this surprising result we propose that the combined effect of the 2-phenyl and 4-phenethyl groups produces a chair-like ground state conformation of **48** in which the substituents occupy equitorial positions. Coordination of the Pd-alkyl species to the acetal-oxygens does not promote a ring flip due to a developing 1,3-diaxial interaction (Fig 3, **A**). Instead, acetal-oxygen coordination delivers the Pd-alkyl *syn* to the substitutents at the 2- and 4-positions of the dioxepin (Fig. 3, **B**).

Figure 3.



4.6. Conclusion.

In summary, we have developed a general and highly *trans*-diastereoselective intermolecular Heck reaction of 1,3-dioxepins. Sustitution at the 2- and 4-positions of 1,3-dioxepins both lead to the *trans*-dioxepin product. Labling studies that suggest that the selectivity is kinetic in origin and not a result of an initial unselective olefin insertion followed by an epimerization event. The overall synthetic sequence provides an efficient and modular approach to the versatile 1,3-dioxepin framework.

4.7. References.

[1] Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.

[2] See, for example: Morphine: Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028-11029. Gelsemine: Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054-18065.

[3] For some excellent reviews of the Heck reaction see: a) Daves Jr., G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433-1445. b) Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379-2411. c) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314-321. d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066. e) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963.

[4] a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417-1419. b) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227-1230. c) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200-202.

[5] a) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129-7130. b) de la Rosa, J. C.; Diaz, N.; Carretero, J. C. *Tetrahedron Lett.* **2000**, *41*, 4107-4111. c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430-3431.

[6] For a microreview on neighbouring-group effects in the Heck reaction see: Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783-792.

[7] Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407-408.

[8] da Silva, K. P.; Godoi, M. N.; Correia, C. R. D. *Org. Lett.* **2007**, *9*, 2815-2818.

[9] a) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227-1230. (b) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200-202. (c) Loiseleur, O.; Hayashi, M.; Schemees, N.; Pfaltz, A. *Synthesis* **1997**, 1338-1344. (d) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16-22. Other Asymmetric Heck Reactions of 1,3-dioxepins: (e) Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymm.* **2000**, *11*, 2205-2210. (f) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161-164. (g) Mata, Y.; Montserrat, D.; Pamies, O.; Claver, C. *Org. Lett.* **2005**, *7*, 5597.

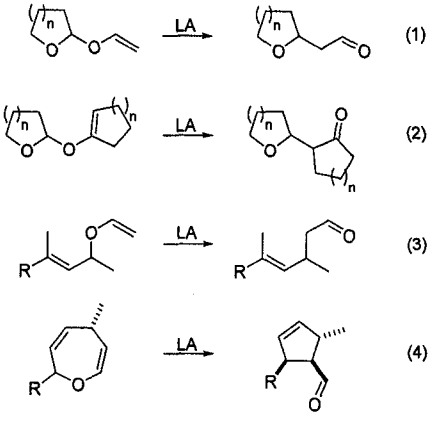
[10] a) Jeffery, T. *Tetrahedron*, **1996**, *52*, 10113-10130.
[11] For examples of modified Jeffery's conditions in the Heck reaction see: a) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett.* **1993**, 785-787. b) Ogasawara also reported a singular example: Samizu, K.; Ogasawara, K. *Chem. Lett.* **1995**, 543-544.
[12] A useful resource for conditions commonly used in Heck reactions: Heck, R. F. *Organic Reactions*, **1982**, *27*, 345-390.
[13] We optimized these conditions to be as follows: 1.05 eq. ArI, 1 eq. dioxepin, 8 mol% $Pd(OAc)_2$, 2 eq. $BnEt_3NCl$, 3 eq. *i*-Pr_2NEt, 0.4 M in DMF (with respect to the alkene) at 80 °C.
[14] This observation is consistent with the formation of Pd nanoparticles and/or colloids which have been implicated in the Heck reaction and other Pd-catalyzed reactions: a) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett.* **2003**, *5*, 983-986. b) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285-3288. c) Consorti, C. S.; Flores, F. R.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 12054-12065.
[15] For procedures and discussion about how to determine the "true" catalyst see: a) Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891-4910. b) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A-Chem.* **2003**, *198*, 317-341. c) Özkar, S.; Finke, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 5796-5810.
[16] The work on 4-substituted dioxepins was performed by Dr. Jeffrey D. Frein during the course of his doctorate studies and is included in this chapter order to tell a more complete story.
[17] See reference 3.
[18] Crossover experiments between **46** and **47**, and **46** and **25** using optimized modified Jeffery conditions also did not show any ^2H enrichment at the 5-position and no and ^1H enrichment at the 7-position in the dioxepin product.
[19] This type of interaction has been invoked to explain the stereochemical outcome of Fe-catalyzed [4+4] ene reactions of 1,3-dioxepins: Takacs, J. M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542-2544.
[20] Relative stereochemistry was determined by nOe experiments. See supporting information for details.

Chapter 5

A Diastereoselective Ring Contraction of 1,3-Dioxepins to 2,3,4-Trisubstituted and Tetrasubstituted Tetrahydrofurans

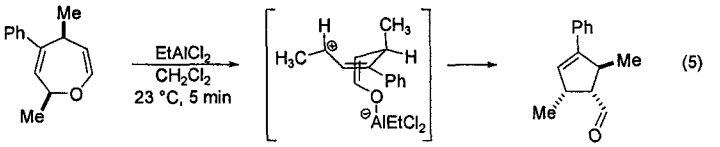
5.1. Introduction.

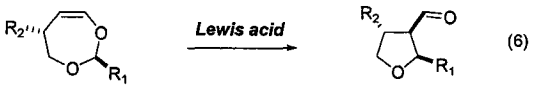
The transformation of a C-O bond to a C-C bond with control of configuration at the reactive carbon centers represents a significant challenge in synthesis. The Claisen reaction, a [3, 3] rearrangement of allyl vinyl ethers is one such strategy. Related to this process is the less well known [1, 3] O to C rearrangement of vinyl ethers, which can be initiated thermally or mediated by transition metals and Lewis acids.[1] Our group has been interested in the latter of these strategies, the Lewis acid-mediated [1, 3] rearrangement of vinyl ethers. Our program initially began with the stereoretentive rearrangement of vinyl acetals (Eq. 1 and 2) and more recently has expanded to incorporate the regio- and stereoselective rearrangement of allyl vinyl ether systems (Eq. 3 and 4).[2]



During our studies of 2,5-dihydrooxepins we found that a preexisting stereocenter exerts a positive influence on the diastereoselectivity of the reaction (Eq. 5). We hypothesized that this effect would be operative in other [1, 3] ring contractions, which

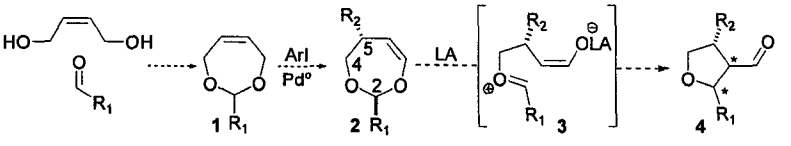
directed us towards 1,3-dioxepins as precursors to tetrahydrofurans (Eq. 6), an common motif in natural products.[3,4]





Linchpin strategies that rapidly assemble densely functionalized tetrahydrofurans are particularly attractive and some recent advances have emerged.[5] These include Pd-catalyzed oxy-arylation of alkenes, [3+2] annulation of aldehydes, and intramolecular oxocarbenium ion allylation.[6] We envisioned a complementary method in which *cis*-1,4-butenediol could be used as a platform for the construction of a tetrahydrofuran (Scheme 1). Functionalization of a 1,3-dioxepin could be coupled with an olefin migration to provide a vinyl acetal such as **2**. Subsequent Lewis acid-induced ring contraction of **2** should provide 2,3,4-trisubstituted tetrahydrofurans.

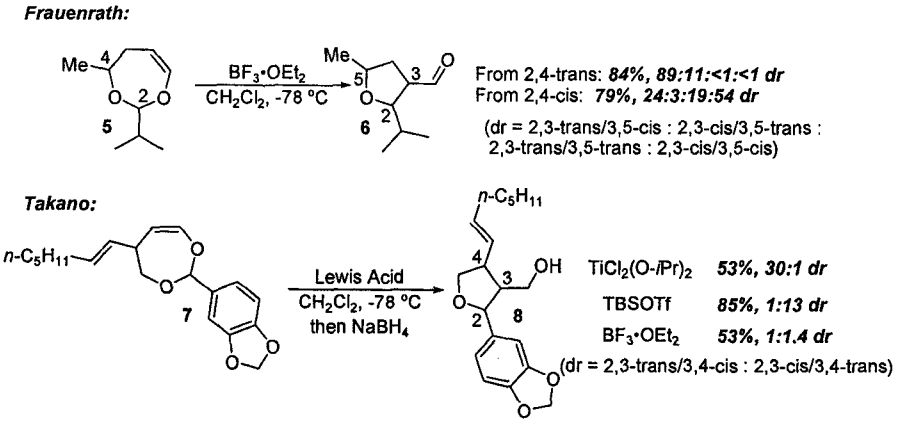
Scheme 1.



Some precedent in the literature suggested that this approach should be feasible. In the course of extensive contributions to the chemistry of vinyl acetals,[7] Frauenrath has shown that 2,4-disubstituted dioxepin **5** undergoes ring contraction in good yield with varying diastereoselectivity dependent on starting material stereochemistry.[8] Takano has illustrated an elegant approach to the furofuran lignan (+/-)-asarinin using a Heck reaction of a 1,3-dioxepin followed by ring contraction of **7** (Scheme 2).[9] To our

knowledge, substrates **5** and **7** are the only two examples of a [1, 3] ring contraction of a 1,3-dioxepin to produce trisubstituted tetrahydrofurans. In particular, we wondered whether there were structural parameters that would be key in determining the efficiency and selectivity that could be attained. We endeavored to expand the scope of this approach to the tetrahydrofuran framework and recently reported a general and modular approach for the synthesis to the 2,3-*cis*/3,4-*trans* tetrahydrofuran diastereomer.[10] Herein we report a full account of our research in this area.

Scheme 2.



5.2. Reaction Development.

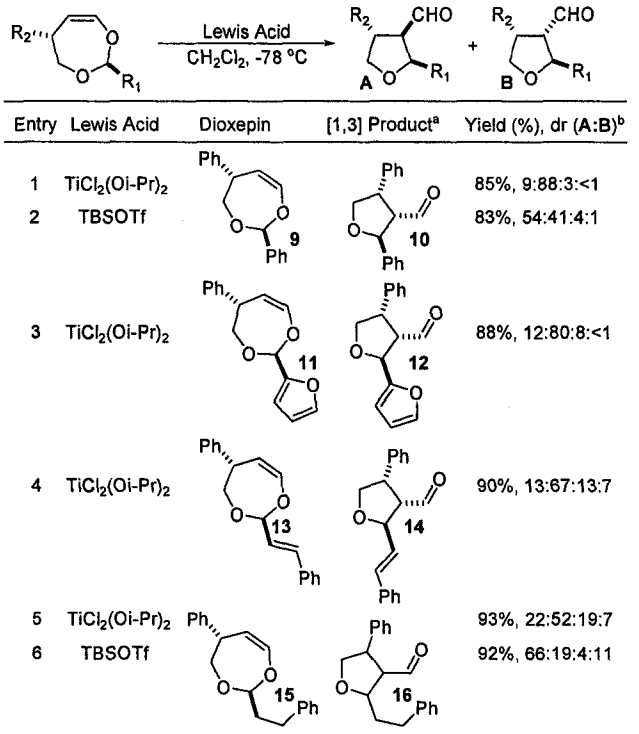
The [1, 3] ring contraction of 1,3-dioxepins has been proposed to proceed by initial coordination of the Lewis acid to the vinyl acetal oxygen, followed by ionization to produce a metalloenolate and oxocarbenium ion **3**, which then collapse to form the tetrahydrofuran product **4** (Scheme 1). In light of the mechanism there are two ways to approach the development of this reaction that should have a direct affect on the diastereoselectivity in the tetrahydrofuran product; 1) an analysis of the substitution at the 2-position of the1,3-dioxepin, which directly affects the stability and lifetime of the oxocarbenium ion intermediate and 2) changing the Lewis acid to alter the

nucleophilicity of the resultant metalloenolate. Frauenrath's work illustrated that simple alkyl substitution at the 2-postion of the dioxepin can lead to mixtures of all four tetrahydrofuran diastereomers. Takano's work showed that changing the Lewis acid had a pronounced effect on the diastereoselectivity of the reaction; $TiCl_2(O\text{-}iPr)_2$ produced the 2,3-*trans*/3,4-*cis* stereochemistry and TBSOTf gave the 2,3-*cis*/3,4-*trans* stereochemistry (Scheme 2).

In light of this precedent, we hypothesized that π-donation of a substituent at the 2-position of the 1,3-dioxepin would be key in obtaining synthetically useful diastereoselectivities and began our studies by evaluating the generality of Takano's conditions through manipulation of substitution at the 2-position of the dioxepin. To this end, **9**, **11**, and **13**, were subjected to Takano's conditions: stoichiometric $TiCl_2(O\text{-}iPr)_2$ in CH_2Cl_2 at -78 °C. As expected, the corresponding tetrahydrofurans were isolated in good yield and diastereoselectivity (Table 1, entries 1, 3 and 4). However, and consistent with our hypothesis, all four diastereomers are obtained in significant amounts when simple alkyl substitution is present at the acetal position (entry 5, **15**). The minor diastereomer produced from these reactions was the 2,3-*cis*/3,4-*trans* tetrahydrofuran.

Takano also reported that ring contraction in the presence of TBSOTf provides the 2,3-*cis*/3,4-*trans* diastereomeric tetrahydrofuran. This reaction, however, is very sensitive to the nature of the 2-substitutent. Treatment of **9** and **15** with TBSOTf provides **10** and **16** in poor diastereoselectivity (entries 2 and 6). These results suggest that the reported conditions are not general.

Table 1. Evaluation of Takano's Conditions.



Entry	Lewis Acid	Dioxepin	[1,3] Product[a]	Yield (%), dr (A:B)[b]
1	$TiCl_2(Oi\text{-}Pr)_2$	9	10	85%, 9:88:3:<1
2	TBSOTf			83%, 54:41:4:1
3	$TiCl_2(Oi\text{-}Pr)_2$	11	12	88%, 12:80:8:<1
4	$TiCl_2(Oi\text{-}Pr)_2$	13	14	90%, 13:67:13:7
5	$TiCl_2(Oi\text{-}Pr)_2$	15	16	93%, 22:52:19:7
6	TBSOTf			92%, 66:19:4:11

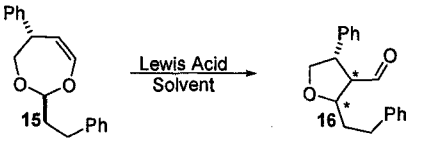
a) Relative stereochemistry was assigned by nOe experiments.
b) The 2,3-*cis*/3,4-*cis* and 2,3-*cis*/3,4-*trans* diastereomers are not shown.

Consistent with our initial hypothesis, the lifetime and inherent stability of the oxocarbenium intermediate appears to be the key in accessing synthetically useful levels of diastereoselection in the ring contraction of 1,3-dioxepins. With this in mind we decided to pursue a more general protocol. A brief Lewis acid screen for the conversion of **15** to **16** was conducted in CH_2Cl_2 at -78 °C. Conventional conditions for the Lewis acid-mediated processes did produce tetrahydrofuran products albeit in poor diastereoselectivity (Table 2, entries 1-3).

It has been reported that oxocarbenium ion reactivity can be tuned by judicious choice of solvent.[11] We hypothesized that a polar aprotic solvent would stabilize the transient acyclic oxocarbenium ion generated upon Lewis acid ionization of the 1,3-dioxepin, and would serve to enhance the diastereoselectivity of this process. We found

that 10 mol% TMSOTf in MeCN at -40 °C provides the 2,3-*cis*/3,4-*trans* adduct **16** in good yield and excellent diastereoselectivity (Table 2, entry 4).[12]

Table 2. Lewis acid Screen.

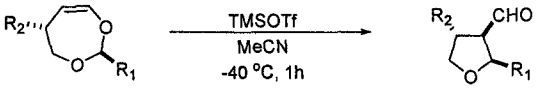


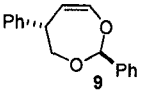
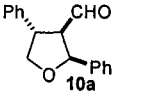
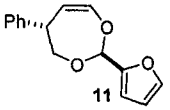
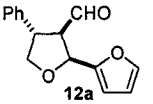
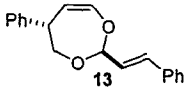
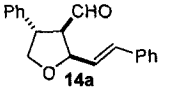
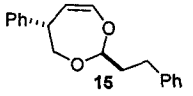
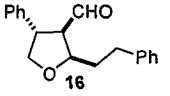
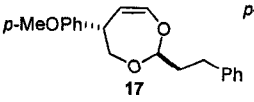
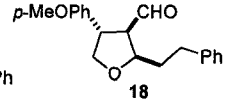
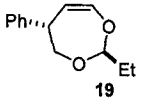
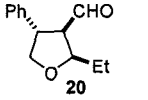
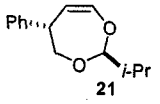
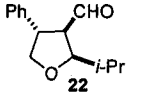
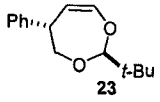
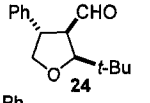
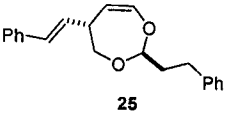
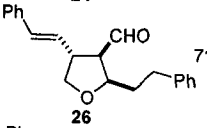
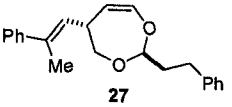
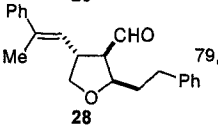
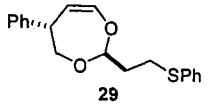
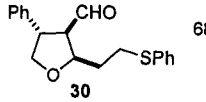
Entry	Lewis Acid	Eq.	Solvent	T (°C)	dr	Yield (%)
1	BF_3•OEt_2	0.1	CH_2Cl_2	-78	62 : 24 : 3 : 11	93
2	$TiCl_2(Oi\text{-}Pr)_2$	1.1	CH_2Cl_2	-78	52 : 22 : 19 : 7	93
3	TMSOTf	0.1	CH_2Cl_2	-78	55 : 33 : 6 : 8	80
4	TMSOTf	0.1	MeCN	-40	91 : 5 : 4 : <1	85

5.3. Reaction Scope for 2,3-*cis*/3,4-*trans* Tetrahydrofurans.

The substrate scope for the TMSOTf-MeCN conditions is broad and provides functionalized tetrahydrofurans in uniformly high diastereoselectivity. The highest levels of diastereoselection are observed for substrates that possess aromatic or alkene substitution at the 2-position (Table 3, entries 1-3). Branched 2-alkyl substitution results in diminishing diastereoselectivity with increasing steric bulk (entries 6-8). The reaction is also tolerant of Lewis basic functionality (entries 2 and 11). Di- and tri-substituted olefins at the dioxepin 5-position also provide tetrahydrofurans in good yield and selectivity (entries 9 and 10).

Table 3. Reaction Scope.

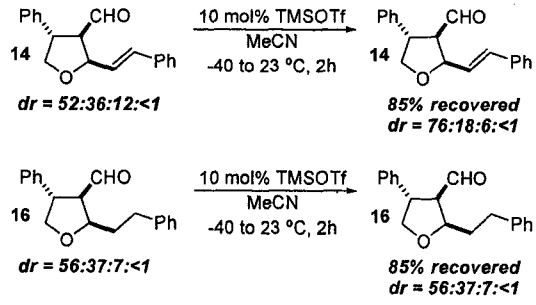


Entry	Dioxepin	[1,3] Product	Yield (%), dr
1	 9	 10a	70, 94:5:1:<1
2	 11	 12a	94, 95:5:<1:<1
3	 13	 14a	88, 96:3:1:<1
4	 15	 16	85, 96:3:1:<1
5	 17	 18	84, 91:6:2:1
6	 19	 20	97, 90:7:2:<1
7	 21	 22	83, 85:10:5:<1
8	 23	 24	55, 70:18:12:<1
9	 25	 26	71, 93:6:1:<1
10	 27	 28	79, 83:17:<1:<1
11	 29	 30	68, 83:13:4:<1

To further elucidate the contributing factors that determine the diastereoselectivity of this reaction, a control experiment was designed (Scheme 3). A mixture of diastereomers of **14**, formed via a different route, were subjected to the optimized

conditions and returned **14** with enhanced dr. This result suggests that ring opening/epimerization may be responsible for the high levels of diastereoselection found for substrates with π-donating substituents at the 2-position. Interestingly, the reaction conditions do not provide diastereomeric enrichment in the case of **16**, implying that its formation is not reversible and the selectivities for substrates with alkyl substitution are kinetic in origin.

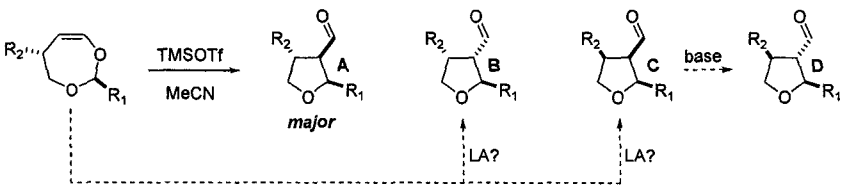
Scheme 3.



5.4. Reaction Development and Scope for 2,3-*trans*/3,4-*cis* Tetrahydrofurans.

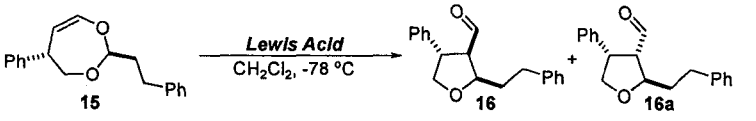
Having developed a general, catalytic and diastereoselective ring contraction of 1,3-dioxepin derivatives to the corresponding 2,3-*cis*/3,4-*trans* tetrahydrofurans (Scheme 4, **A**) we desired access to one of the other three possible diastereomers. Presumably, **B** or **C** could be produced by Lewis acid-mediated ring contraction and **D** could by made by epimerization of **C**. Stabilization of the oxocarbenium ion intermediate by solvent (MeCN) was crucial in providing access to **A**, we therefore hypothesized that **B** or **C** could be formed under conditions that provides a more reactive oxocarbenium-metalloenolate ion pair.

Scheme 4.



Using Takano's conditions as a starting point, a brief Lewis acid screen revealed that stoichiometric $SnCl_4$ promotes the rearrangement of **15** to **16a** in good yield and good 2,3-*trans*/3,4-*cis* diastereoselectivity (Scheme 5, entry 2).

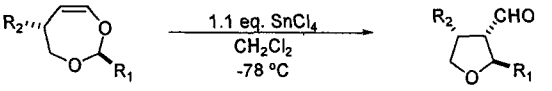
Scheme 5.

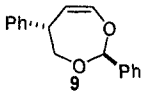
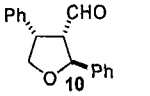
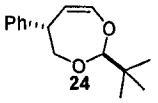
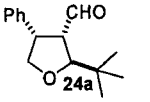
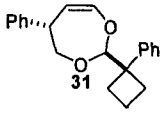
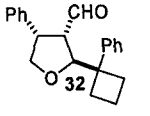
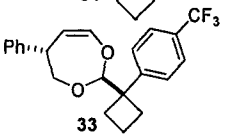
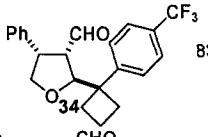
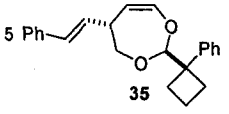
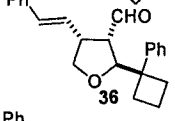
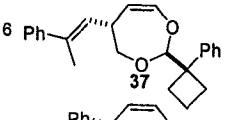
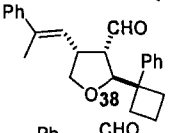
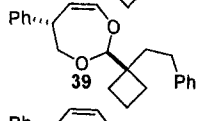
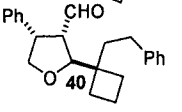
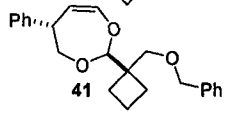
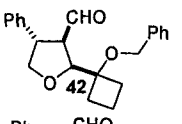
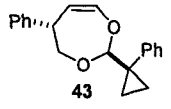
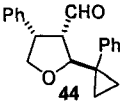
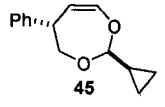
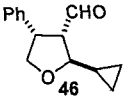
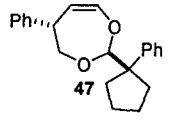
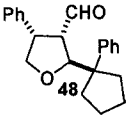


Entry	Lewis acid	Yield (%)	dr (16:16a:other isomers)
1	$TiCl_2(Oi\text{-}Pr)_2$	93	22:52:19:7
2	$SnCl_4$	89	10:81:9:<1

The substrate scope for these conditions is general and proceeds in excellent diastereoselectivity provided that there is an aromatic or branched alkyl group at the 2-position of the dioxepin (Table 4, entries 1 and 2). The reaction also proceeds with good chemo- and diastereoselectively in the face of a possible [1, 2] alkyl shift. Cyclobutanes (entries 3-8), cyclopropanes (entries 9 and 10) and cyclopentanes (entry 11) survive under the optimized conditions to provide 2-cycloalkyl tetrahydrofuran products in good yield and diastereoselectivity. In all cases the minor diastereomer formed was the 2,3-*cis*/3,4-*trans* tetrahydrofuran.

Table 4. Reaction Scope.

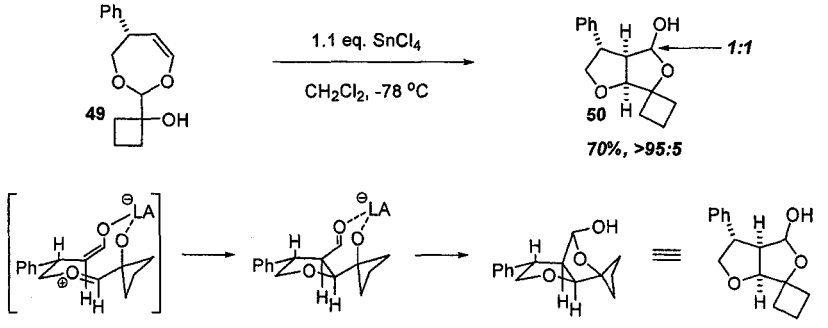


Entry	Dioxepin	[1,3] Product	Yield (%), dr
1			87, 95:5:<1:<1
2			89, 88:12:<1:<1
3			86, 92:8:<1:<1
4			83, 82:9:6:3
5			83, 95:5:<1:<1
6			80, 86:14:<1:<1
7			92, 84:16:<1:<1
8			65, 95:5:<1:<1
9			90, 89:11:<1:<1
10			87, 95:5:<1:<1
11			96, 91:9:<1:<1

In an attempt to promote the alkyl group shift, substrate **49** was prepared and subjected to the optimized $SnCl_4$ reaction conditions. Tetrahydrofuran-lactol **50** was

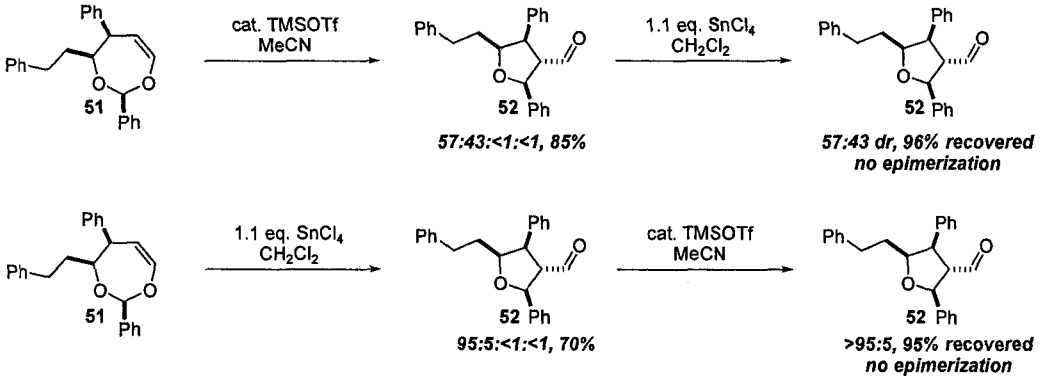
isolated as the 2,3-*cis*/3,4-*trans* product (Scheme 6). One can envision this product arising from initial Lewis acid chelation between the free hydroxyl group and the vinyl ether oxygen. After ionization, the Lewis acid remains chelated, which orients the and oxocarbenium ion appropriately to furnish the *cis* stereochemistry. Presumably, this chelation mechanism also promotes the formation of 2,3-*cis*/3,4-*trans* tetrahydrofuran **42**.

Scheme 6.



Tetrasubstituted tetrahydrofuran scaffolds can also be accessed using this methodology. Ring contraction of **51** in the presence of catalytic amounts of TMSOTf in MeCN produces the desired tetrahydrofuran in good yield and poor diastereoselectivity (Scheme 7). However, rearrangement of **51** in the presence of $SnCl_4$ provided tetrasubstituted tetrahydrofuran **52** in excellent yield and exceptional diastereoselectivity. No diastereomeric enrichment or epimerization was observed when **52** was exposed to $SnCl_4$ in CH_2Cl_2. The same was true for the TMSOTf-MeCN conditions, showing that the selectivities obtained under both reaction conditions are kinetic and do not arise from initial unselective alkylation followed by an epimerization event. These results also suggest that the reversibility previously discussed is a function of the substitution present on the tetrahydrofuran (Scheme 3).

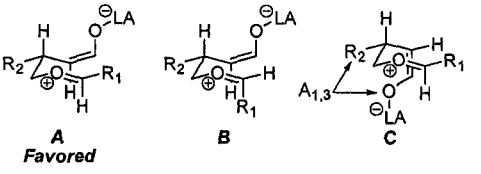
Scheme 7.



5.5. Stereochemistry.

We have shown that solvent and electronic stabilization of the oxocarbenium ion independently increase the selectivity of the [1, 3] ring contraction. These effects proved to be synergistic, leading to exceptional levels of diastereoselection for the 2,3-*cis*/3,4-*trans* tetrahydrofuran in the presence of TMSOTf in MeCN.

Figure 1.

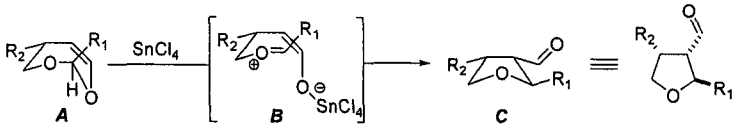


The relative configuration in the 2,3,4-trisubstituted tetrahydrofuran products can be rationalized with our proposed stereochemical model (Fig. 1). Although the stereochemical relationship is primarily controlled via the pre-existing stereocenter at the 5-position of the 1,3-dioxepin (A, Fig. 1), the stereochemical fidelity of the 1,3-ring contraction is influenced by the type of substitution and not the relative stereochemistry at the acetal position (A *vs* B, Fig. 1). Furthermore, there is an interplay of energy minimization brought about by the potential relief of $A_{1,3}$ strain between R_2 and the (Fig.

1, C) and the substituents R_1 and R_2 occupying pseudoequatorial positions (A *vs* B, Fig. 1).

The 2,3-*trans*/3,4-*cis* tetrahydrofurans, formed under the $SnCl_4$ conditions, can be rationalized by a different stereochemical model. Assuming that the E-oxocarbenium ion is formed by ionization of the acetal, a boat-like and starting material-like transition state leads to the observed stereochemistry in the tetrahydrofuran product (Fig. 2, B). The R_1 and R_2 substituents occupy equatorial positions, which minimize their steric interactions. The tin alkoxide occupies an axial position; however, the steric interaction with R_1 is minimal. This transition state structure may also benefit from an electrostatic stabilization between the tin alkoxide and the oxocarbenium ion, which could help to stabilize the boat-like transition state.

Figure 2.



5.6. Conclusion.

In summary, we have developed a modular and diastereodivergent [1, 3] ring contraction of 1,3-dioxepins. The diastereoselectivity of the [1, 3] rearrangement is controlled by the combination of Lewis acid and solvent. TMSOTf in MeCN leads to the formation of the 2,3-*cis*/3,4-*trans* diastereomer while $SnCl_4$ in CH_2Cl_2 provides the 2,3-*trans*/3,4-*cis* diastereomer. The application of this method to the synthesis of tetrahydrofuran-containing natural products is ongoing.

5.7. References.

[1] For some leading references of [1, 3] rearrangements see: a) Ferrier, R. J. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1455-1458. Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559-7572. Wang, S.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364-5371. Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489.

[2] (a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720-9721. (b) Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979. (c) Nasveschuk, C. G.; Rovis, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3264-3267. (d) Nasveschuk, C. G.; Rovis T. *Org. Lett.* **2005**, *7*, 2173-2176. (e) Frein, J. D.; Rovis, T. *Tetrahedron*, **2006**, *62*, 4573-4583.

[3] Reviews: (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2473. (b) Elliott, M. C. *J. Chem. Soc. Perkin Trans. 1*, **2002**, 2301-2323. For a review of lignan natural products see: c) Ward, R. S. *Nat. Prod. Rep.* **1997**, *16*, 75-96.

[4] For a review of synthetic methods for the synthesis of furofuran lignans see: Brown, R.; Swain, N. A. *Synthesis*, **2004**, 811-827.

[5] Oxidative Cyclization: (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371-3373. (b) Takacs, J. M.; Schroeder, S. D.; Han, J.; Gifford, M.; Jiang, X.; Saleh, T.; Vayalakkada, S.; Yap, A. *Org. Lett.* **2003**, *5*, 3595-3598. (c) Hartung, J.; Drees, S.; Greb, M. Schmidt, P.; Svoboda, I.; Feuss, H.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388-2408. Epoxide Ring Opening: (d) Makosza, M.; Barbasiewicz, M.; Krajewski, D. *Org. Lett.* **2005**, *7*, 2945-2948.

[6] Pd-catalyzed oxy-arylation of alkenes: a) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099-3107. [3+2] Annulation of aldehydes: b) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245-4248. Intramolecular oxocarbenium ion allylation: c) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett*, **1997**, 1411-1413.

[7] Frauenrath, H. *Synthesis* **1989**, 721-734.

[8] Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707-2712.

[9] Takano, S.; Samizu, K.; Ogasawara, K. *Synlett*, **1993**, 785-787.

[10] Nasveschuk, C. G.; Jui, N. T.; Rovis, T. *Chem. Commun.* **2006**, 3119-3121.

[11] (a) Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, *17*, 4073-4076. (b) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc. Perkin Trans. 1.* **1990**, 747-750. (c) Marra, A.; Esnault, J.; Veyrières, A.; Sinaÿ, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354-6360.

[12] See supporting information for stereochemical assignment by X-ray and nOe experiments.

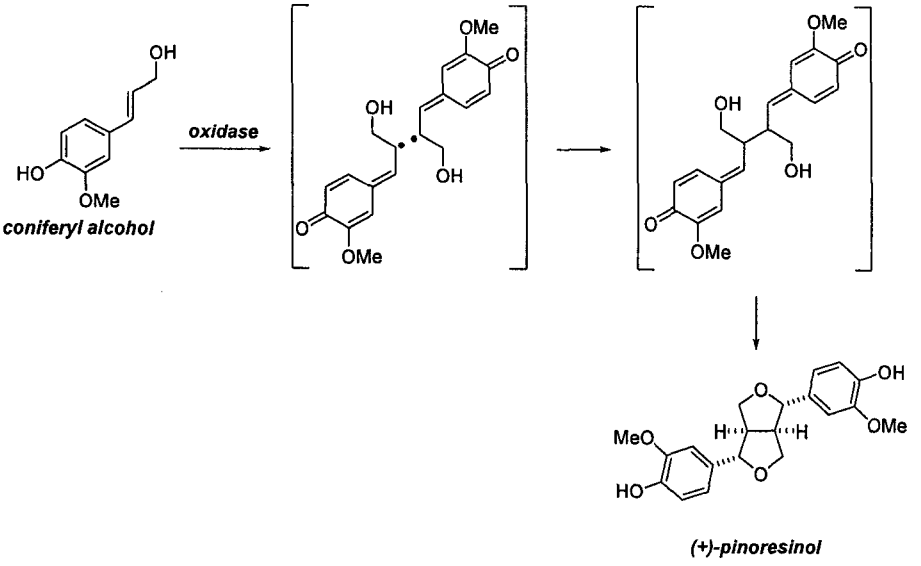
Chapter 6

[1, 3] Rearrangement of 1,3-Dioxepins: A Rapid Total Synthesis of (+/-)-Sylvone and an Approach to Lophirone H

6.1. Introduction.

Furofuran lignans are a large and diverse class of molecules that possess a tetrahydrofuran core and ornamental aromatic substitution. Typically isolated from plant materials, many of which are used in indigenous and traditional herbal medicines, furofurans display broad biological activity.[1] The biosynthesis of furofuran lignans occurs by phenoxy radical dimerization of coniferyl alcohol, catalyzed by an oxidase.[1] Subsequent internal trapping of the quinone methide intermediates completes the formation of the furofuran lignan core (Scheme 1). Although it was known for some time that various enzymes would catalyze this process unselectively, it was the exceptional work by Lewis and coworkers that identified an auxiliary protein that rendered the process regio- and enantioselective.[2]

Scheme 1.

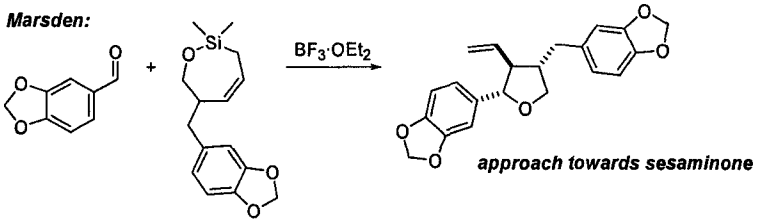


coniferyl alcohol

(+)-pinoresinol

New lignans continue to be isolated and have thus compelled the community to develop new synthetic methodology that provides access to the variety of different substitution patterns possessed by these molecules.[3,4] Of the currently existing strategies there are few that provide direct and efficient construction of 2,3,4-trisubstituted tetrahydrofurans.[5] Perhaps the most eloquent of these approaches was reported by Marsden and coworkers in which substituted tetrahydrofurans were constructed by condensation of an aldehyde and a [1,2]oxasilepine (Scheme 2).[6]

Scheme 2.

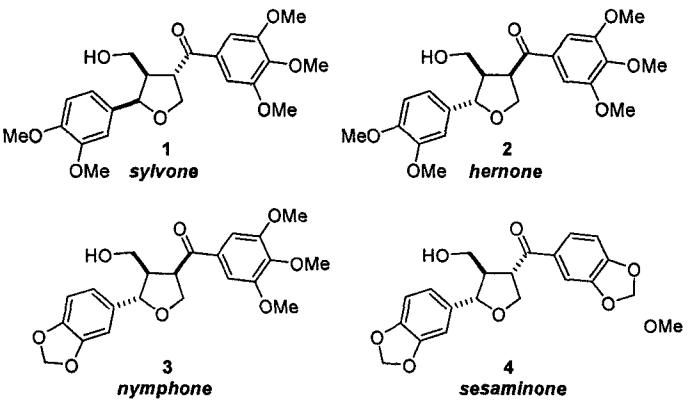


We have developed a complementary approach to the 2,3,4-trisubstituted tetrahydrofuran framework via a diasteroselective [1, 3] ring-contraction of 1,3-dioxepins.[7,8]

6.2. Synthesis of (+/-)-Sylvone.

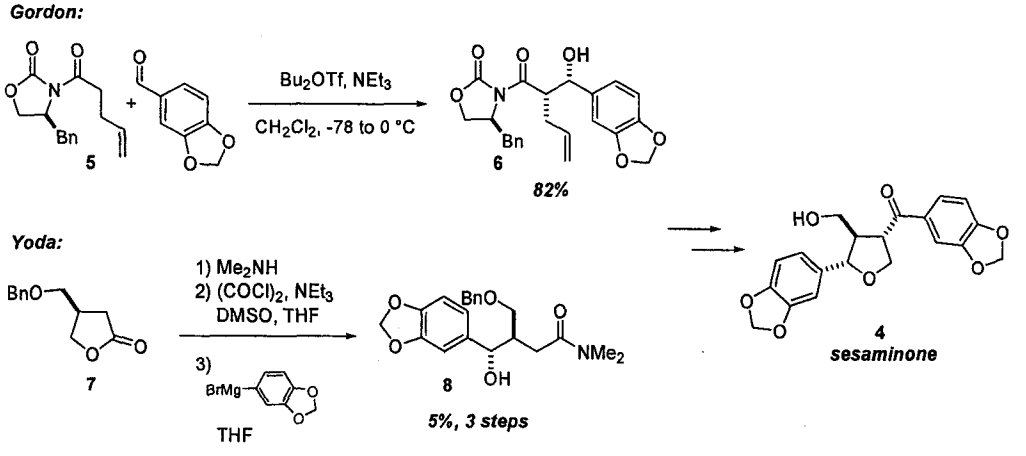
Sylvone (**1**) is a furofuran lignan isolated by Banerji and coworkers from the petrol extracts of seeds derived from *Piper sylvaticum* (Scheme 3).[9] Although the bioactivity profile of **1** is not known other members of its class display a range of activity including antitumor, antimitotic and antiviral characteristics.[10]

Scheme 3.



Of this small sub-class of furofuran lignans only sesaminone has been synthesized (Scheme 4).[11] Gordon's approach utilized a diastereoselective syn aldol reaction as the key step, which proceeded in 11 steps and 16% overall yield. Yoda's key step involved a fragmentation and diastereoselective alkylation of **7**. The overall sequence to sesaminone proceeded in 17 steps and 0.7% overall yield.

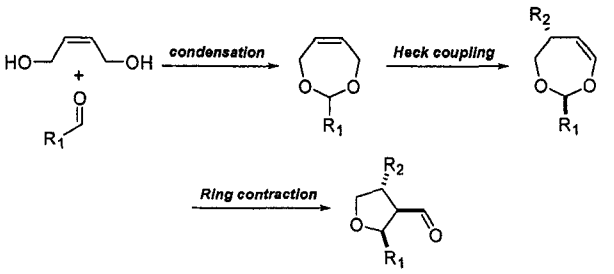
Scheme 4.



We envisioned the formation of the 2,3,4-trisubstituted tetrahydrofuran core of sylvone by a ring contraction of a 1,3-dioxepin. This strategy revolves around the use of *cis*-1,4-butene diol as a lynchpin (Scheme 5). The diol is functionalized with an aldehyde to provide a symmetric 1,3-dioxepin. The olefin is subsequently desymmetrized by a

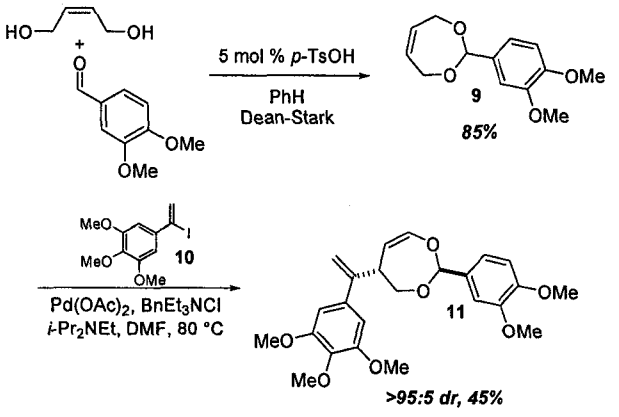
Heck reaction, which simultaneously adds a necessary aryl substituent and activates the system towards [1, 3] rearrangement.

Scheme 5.



The synthetic sequence commenced with condensation of *cis*-1,4-butenediol and veratraldehyde. An intermolecular Heck reaction between **9** and 1,1-disubstituted alkene **10**[12] proceeded in excellent diastereoselectivity and moderate yield (Scheme 6). Increasing the catalyst loading or extension of the reaction time did not increase the yield.

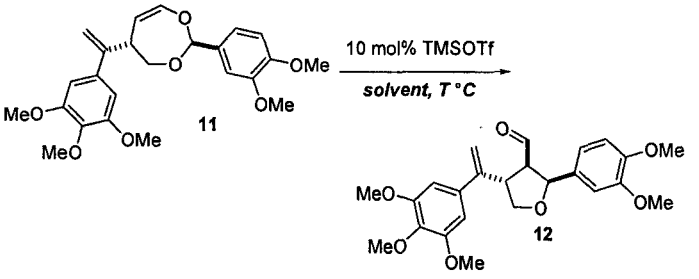
Scheme 6.



Ring contraction of key dioxepin **11** under our previously reported conditions led to complex mixtures of unidentifiable products (Table 1, entry 1). It was hypothesized that exposure to aqueous acid during workup facilitated product decomposition. This pitfall was overcome by the low temperature quench of the Lewis acid with NEt_3 followed by an aqueous $NaHCO_3$ work-up. Unfortunately, the TMSOTf-MeCN

conditions produced the desired tetrahydrofuran with modest diastereoselectivity. Only two of the four possible diastereomers were produced. The major diastereomer was the 2,3-*cis*/3,4-*trans* product and the minor diastereomer contained the 2,3-*trans*/3,4-*cis* relative configuration (entry 2). Diastereoselectivity was restored by changing the solvent to EtCN, which allowed access to lower temperatures (entry 3).

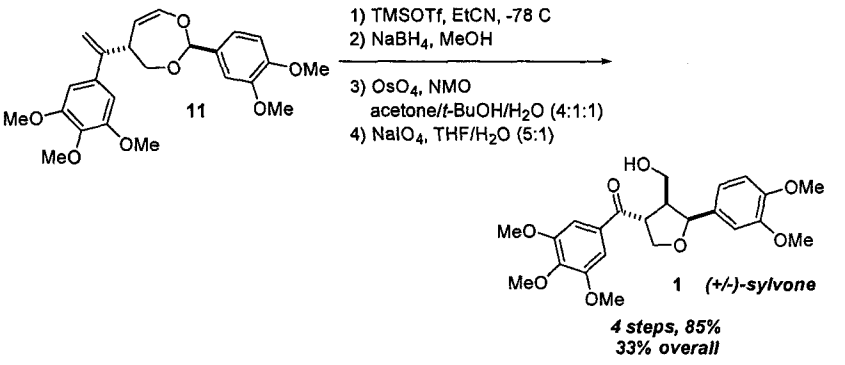
Table 1. *Optimization of Ring Contraction.*



Entry	solvent	temp. (°C)	dr
1	*MeCN*	*-40*	*ND*
2	*MeCN*	*-40*	*78:22*
3	*EtCN*	*-78*	*90:10*

The remainder of the synthesis proceeded without incident (Scheme 7). Reduction of the aldehyde with $NaBH_4$ was followed by dihydroxylation of the 1,1-disubstituted olefin. Finally, oxidative cleavage with $NaIO_4$ produced (+/-)-sylvone in 85% from **11**. Due to the acid-sensitive nature of tetrahydrofuran **12** and the complex diastereomeric mixture derived from facially-unselective dihydroxylation, this four reaction sequence was performed without intermediate purification. Upon work-up (+/-)-sylvone was isolated as a white solid whose physical data matched the reported literature values. The synthesis was completed in 33% overall yield for six linear steps from commercially available materials.

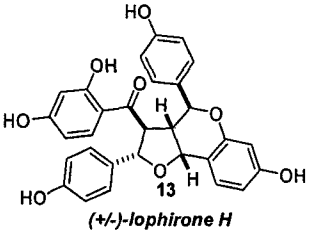
Scheme 7.



6.3. Studies Toward the Synthesis of (+/-)-Lophirone H.

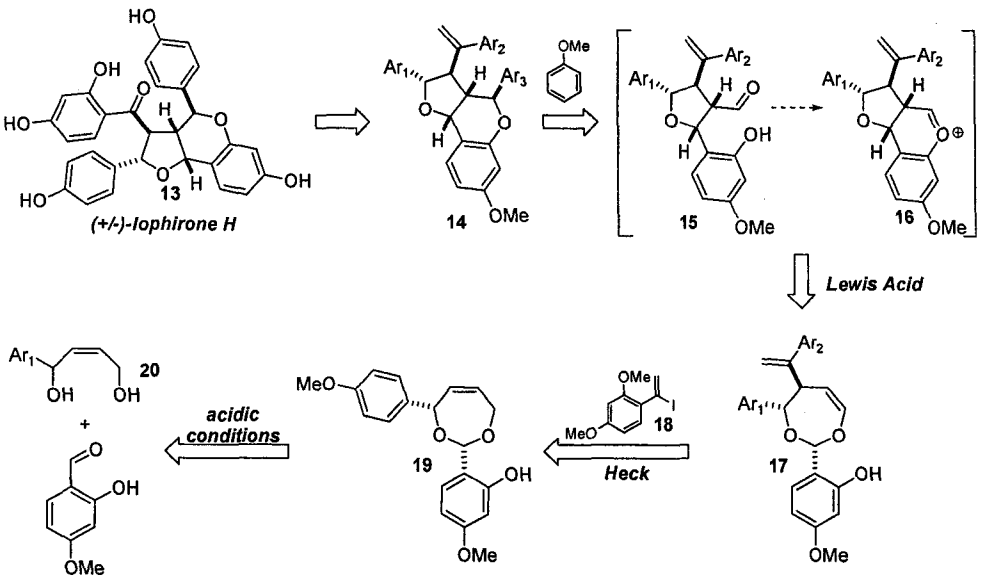
Lophirone H (**13**) is a biflavonoid that was isolated by Bodo and coworkers from the bark of *lophira lanceolata*.[13] Its tricyclic core is biosynthetically related to furofuran lignan natural products, which all possess a tetrahydrofuran as the central structural component (Figure 1). Synthetic pursuit of lophirone H was undertaken as a challenging test for the [1, 3] rearrangement of 1,3-dioxepins.

Figure 1.



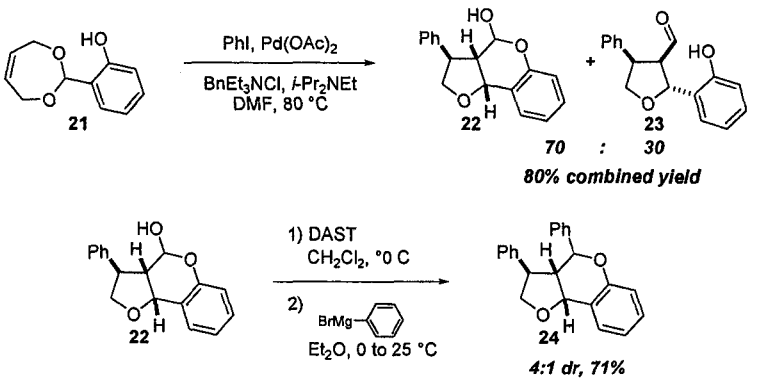
Retrosynthetic analysis of the core of lophirone H led to functionalized tetrahydrofuran **14**, which could be accessed by a tandem ring contraction and Friedel-Crafts alkylation of oxocarbenium derived from **17**. Key dioxepin **17** could be accessed by condensation of unsymmetrical diol **20** and 4-methoxysalicylaldehyde followed by a Heck reaction with vinyl iodide **18** (Scheme 8).

Scheme 8.



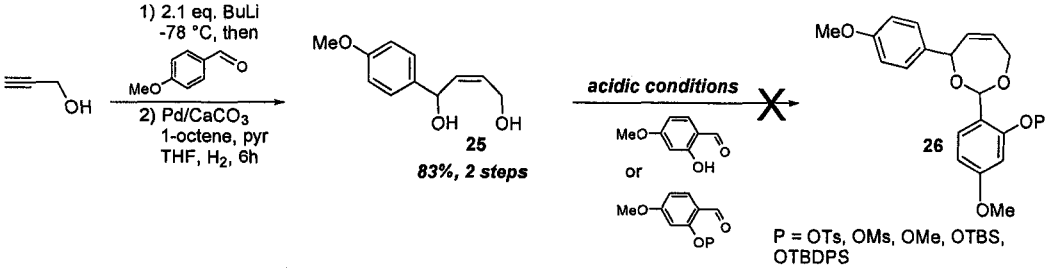
Synthetic studies commenced with a model study (Scheme 9). Dioxepin **21** was constructed using established methods. Heck reaction under previously optimized conditions in the presence of the free phenol provided tetrahydrofurans **22** and **23**. This unexpected result can be rationalized by first a Heck coupling of the dioxepin and iodobenzene followed by a diastereoselective ring contraction, where the 2,3-*cis* diastereomer (major) cyclizes to the tricyclic product **22**. The major diastereomer was converted into the anomeric fluoride, which was subsequently alkylated with phenyl magnesium bromide[14] to provide **24** in good yield and diastereoselectivity. The relative configuration of the major diastereomer was not determined. We also found that 1-aryl-1-iodoalkenes would participate in the Heck reaction of 1,3-dioxepins.[15]

Scheme 9.



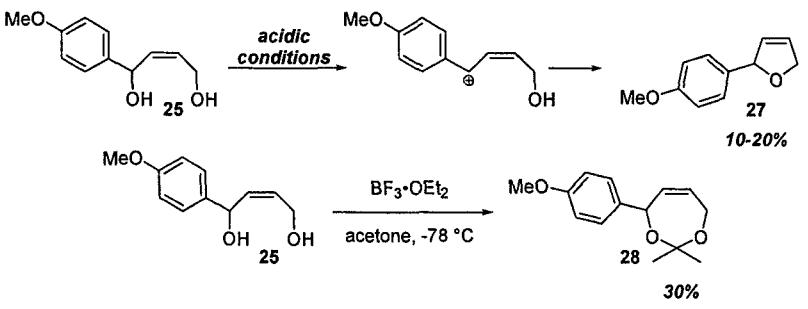
Functionalized diol **25** was prepared by C-alkylation of propargyl alcohol with anisaldehyde, followed by a Z-selective Lindlar reduction of the corresponding alkyne. All attempts to form 1,3-dioxpin **26** failed under acidic conditions (Scheme 10).

Scheme 10.

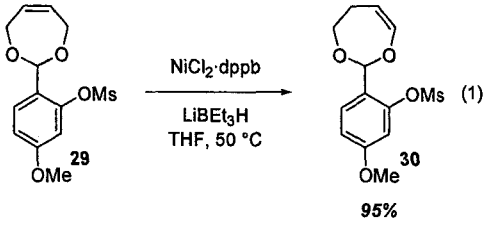


In all cases the major product isolated was 2,5-dihydrofuran **27**. The problem appears to involve ionization of the doubly-activated secondary alcohol and trapping of the allyl cation by the primary alcohol. When the reaction is conducted in acetone the reaction proceeds in moderate yield to provide isopropylidine acetal **28** (Scheme 11).[16]

Scheme 11.

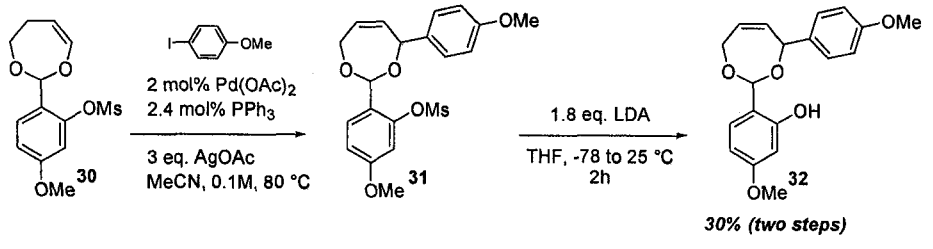


Clearly, access to the key dioxepin by standard chemistry is problematic; hence a more practical approach was adopted. Dioxepin **29** was synthesized using previously developed methods. Double bond isomerization to provide dioxepin **30** was accomplished using a Ni-H catalyst (Eq. 1).[17]



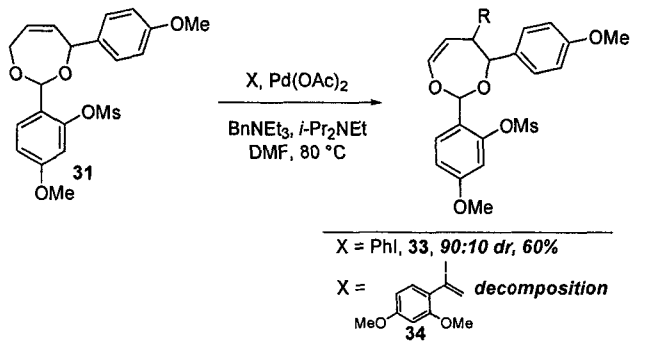
A Heck reaction in the presence of AgOAc followed by deprotection with LDA furnished the desired dioxepin **32** in 30% yield for two steps (Scheme 12).[18]

Scheme 12.



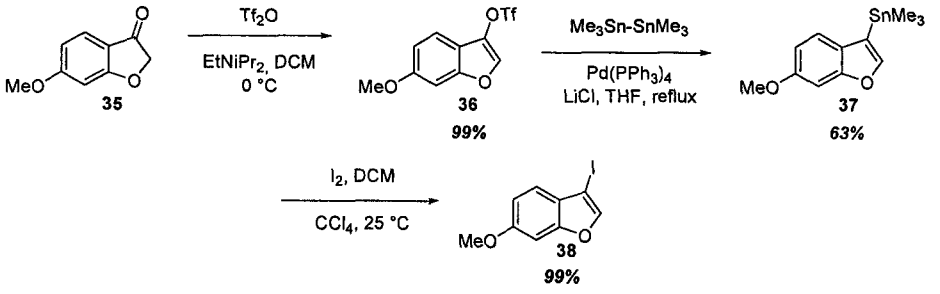
With key dioxepin **31** in hand, a second Heck reaction using iodobenzene provided **33** in good diastereoselectivity and yield. Unfortunately, 1-aryl-1-iodoalkene **34** decomposed under the reaction conditions (Scheme 13).

Scheme 13.



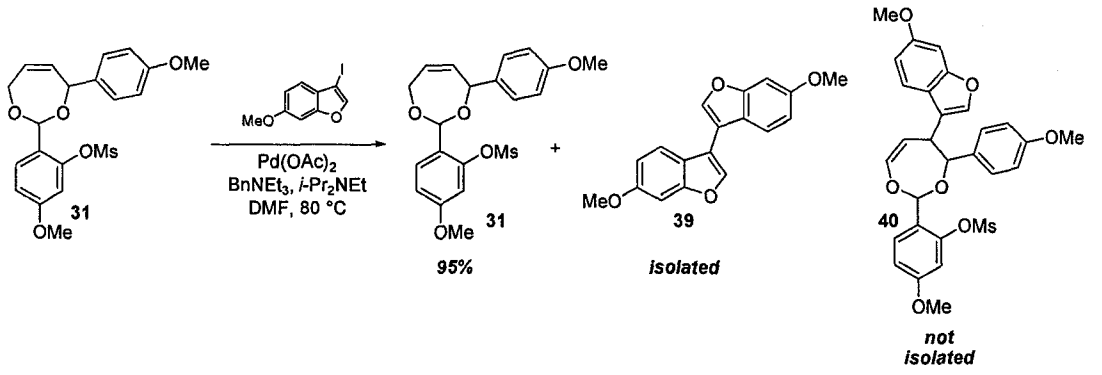
It was hypothesized that the 2-methoxyl group was responsible for the facile decomposition of vinyl iodide **34**. To test this and not significantly alter our synthetic plan to lophirone H, the 2-methoxyl group was incorporated into the aromatic ring system in the form of a benzofuran. Using published procedures, 3-iodobenzofuran **38** was prepared in 62% yield over three steps (Scheme 14).[19]

Scheme 14.



Unfortunately, 3-iodobenzofuran **38** was also not a competent coupling partner under the optimized Heck conditions (Scheme 15). It is worthy of note that the key 1,3-dioxepin **31** was recovered in near quantitative yield from the reaction, while **38** was consumed. The major product isolated from the reaction is the homo-coupling product of **38**, whose nominal mass spectrum matches **39**; however, the specific connectivity was not assigned.

Scheme 15.



6.4. Conclusion.

In conclusion, we have developed a diastereoselective Heck and [1, 3] ring contraction protocol that provides expedient access to stereodefined densely functionalized tetrahydrofurans. This modular and convergent methodology was successfully applied to the synthesis of (+/-)-sylvone. Additionally, the limitations of this method were identified in the formation of the Heck precursor and key Heck reaction in the attempted synthesis of lophirone H. A partial solution was described for the synthesis of the key dioxepin **31**, which was a competent coupling partner for a Heck reaction with iodobenzene. Problematic decomposition and homo-coupling of 1-(2-Methoxyaryl)-1-iodoalkene **34** and 3-iodobenzofuran **38** stifled this synthetic approach.

6.5. References.

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[1] For reviews concerning lignans see: a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207-1220. b) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499-525. c) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1-28. d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183-205. e) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43-74. f) Ward, R. S. *Nat. Prod. Rep.* **1997**, *16*, 75-96.

[2] a) Paré, P. W.; Wang, H.-B.; Davin, L. B.; Lewis, N. G. *Tetrahedron Lett.* **1994**, *35*, 4731-4734. b) Davin, L. B.; Wang, H.-B.; Crowell, A. L.; Bedgar, D. L.; Martin, D. M.; Sarkanen, S.; Lewis, N. G. *Science* **1997**, *275*, 362-366.

[3] For reviews concerning lignans see: a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207-1220. b) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499-525. c) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1-28. d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183-205. e) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43-74. f) Ward, R. S. *Nat. Prod. Rep.* **1997**, *16*, 75-96.

[4] For reviews on the strategies of oxacycle synthesis see: a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2473. b) Elliott, M. C. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2301-2323.

[5] For methods resulting in a total synthesis of a furofuran lignan see: a) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785-787. b) Akindele, T.; Marsden, S. P.; Cumming, J. G. *Org. Lett.* **2005**, *7*, 3685-3688. c) Wardrop, D. J.; Fritz, J. *Org. Lett.* **2006**, *8*, 3659-3662. d) And a review: Brown, R.; Swain, N. A. *Synthesis*, **2004**, 811-827.

[6] a) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411-1413. b) Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J. *J. Org. Chem.* **2004**, *69*, 6874-6882.

[7] a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720-9721. b) Zhang, Y.; Rovis, T. *Tetrahedron Lett.* **2003**, *59*, 8979-8987. c) Nasveschuk, C. G.; Rovis, T. *Org. Lett.* **2005**, *7*, 2173-2176. d) Nasveschuk, C. G.; Rovis, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3264-3267. e) Frein, J. D.; Rovis, T. *Tetrahedron* **2006**, *62*, 4573-4583.

[8] Nasveschuk, C. G.; Jui, N. T.; Rovis, T. *Chem. Commun.* **2006**, 3119-3121.

[9] a) Banerji, A.; Sarkar, M.; Ghosal, T.; Pal, S. C.; Shoolery, J. N. *Tetrahedron* **1984**, *40*, 5047-5052. b) Banerji, A.; Basu, S. *J. Indian Chem. Soc.* **1992**, *69*, 321-325.

[10] For reports that discuss the bioactivity of lignas see: a) Chen, I.-S.; Chen, J.-J.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1997**, *45*, 991-996. b) Parmar, V. S.; Jain, S. C.; Bisht, K. S.; Jain, R.; Taneja, P.; Jha, A.; Tyagi, O. D.; Prasad, A. K.; Wengel, J.; Olsen, C. E.; Boll, P. M. *Phytochemistry* **1997**, *46*, 597-673.

[11] First synthesis of sesaminone: a) Maioli, A. T.; Civiello, R. L.; Foxman, B. M.; Gordon, D. M. *J. Org. Chem.* **1997**, *62*, 7413-7417. Second synthesis of sesaminone: b) Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855-856. c) Yoda, H.; Mizutani, M.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 4701-4702. d) Yoda, H.; Kimura, K.; Takabe, K. *Synlett* **2001**, 400-402.

[12] For a procedure to prepare **10** see: Scannell, R. T.; Stevenson, R. *J. Heterocyclic Chem.* **1980**, *17*, 1727-1728.

[13] Tih, R. G.; Sondengam, B. L.; Martin, M. T.; Bodo, B. *Phytochemistry*, **1990**, *29*, 2289-2293.

[14] The procedure for this reaction was adapted from: Ringom, R; Benneche, T. *Acta Chemica Scaninavica*, **1999**, *53*, 41-47.

[15] See Chapter 4 about the Heck reaction of 1,3-dioxepins.

[16] This reaction was previously reported: Zweifel, G.; Leung, T.; Najafi, M. R.; Najdi, S. *J. Org. Chem.* **1985**, *50*, 2004-2006.

[17] Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis*, **1998**, 305-308.

[18] Leading reports documenting the effect of Ag(I) and Tl(1) salts: a) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1987**, *52*, 3529-3536. b) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603-2606. c) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464-2470. d) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687-690.

[19] Preparation of vinyl triflate: Morice, C.; Garrido, F.; Mann, A.; Suffert, J. *Synlett.* **2002**, 501-503. Vinyl Stannane and vinyl iodide: Paquette, L. A.; Hong, F.-T. *J. Org. Chem.* **2003**, *68*, 6905-6918.

Chapter 2 Experimental

Regioselective Lewis Acid-Mediated [1, 3] Rearrangement of Allylvinyl Ethers

General Methods. All reactions were performed under an inter atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane and toluene were degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, and aqueous ceric ammonium molybdate followed by heating.

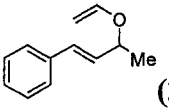
$CuOTf_2$ was purchased from Strem Chemical Co. All other Lewis acids used were purchased from Aldrich Chemical Co. and used without further purification. Et_2AlCl was purchased as a 1.8M solution in toluene. $EtAlCl_2$ was purchased as a 1.0M solution in hexane.

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 100 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.23 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated.

General Procedure for the Lewis acid-mediated [1,3] rearrangement of allylvinyl ethers. Reactions were performed on a 0.25 mmol scale in allylvinyl ether. A flame-dried round-bottom flask was charged with Lewis acid (1.05 eq.) under an inert atmosphere of argon and subsequently diluted with CH_2Cl_2 or toluene (2.5 mL, 0.1 M with respect to allylvinyl ether) and mixed for 10 min. at ambient temperature. The mixture was then cooled to the appropriate temperature, allylvinyl ether (1 eq.) was then added neat, drop wise via syringe (1 drop per 5 seconds) and the reaction was stirred for 1-5 h. The reaction mixture was quenched with 5 mL sat. aq. NH_4Cl and allowed to warm to ambient temperature. The biphasic mixture was poured onto 10 mL of H_2O, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, then concentrated *in vacuo*, and purified via silica gel column chromatography using 9:1 (Hex: EtOAc, 1% NEt_3) as eluent.

Yamamoto-type Lewis acids were formed in situ by dilution of the appropriate phenol (2eq.) in toluene, subsequently cooling the mixture to 0 °C, followed by drop wise addition of Me_3Al (1eq., 1 drop per 5 seconds) and mixing for 1h.

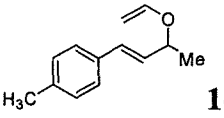
Mass spectrometry was attempted under TOF+, FAB+ and ES- ionization for allvinyl ethers **10**, **13**, **14**, **15**, **16**, **20**, **23sm**, **24sm**, **25sm**, **26sm**, **27sm**, **28sm**, and **29**; however, mass spectra were not obtained due to decomposition.



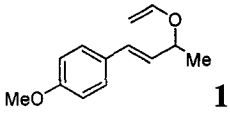
(3-Vinyloxy-but-1-enyl)-benzene (10).[1] ^{1}H NMR (400 MHz $CDCl_3$) δ 7.49-7.22 (5H, m), 6.56 (1H, d, J = 16.0 Hz), 6.38 (1H, dd, J = 14.1, 6.6 Hz), 6.17 (1H, dd, J = 16.0, 6.6 Hz), 4.51 (1H, dq, J = 6.5, 6.5 Hz), 4.36 (1H, dd, J = 14.3, 1.4 Hz), 4.03 (1H, dd,

[1] Cresson, P. *Bull Chim. Soc. Fr.* **1964**, *10*, 2629-2635.

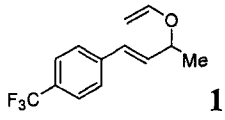
J = 6.6, 1.5 Hz), 1.41 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.7, 136.6, 131.3, 130.6, 128.8, 128.0, 126.7, 89.2, 76.6, 21.4; IR (NaCl dep from CH_2Cl_2) 2979, 1633, 1322, 1191, 967, 693 cm^{-1}.



1-Methyl-4-(3-vinyloxy-but-1-enyl)-benzene (13). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.30-7.11 (4H, m), 6.52 (1H, d, J = 16.0 Hz), 6.37 (1H, dd, J = 14.1, 6.6 Hz), 6.12 (1H, dd, J = 16.0, 6.8 Hz), 4.49 (1H, dq, J = 6.6, 6.6 Hz), 4.35 (1H, d, J = 14.1 Hz), 4.02 (1H, d, J = 6.6 Hz), 2.34 (3H, s) 1.41 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz CDCl3) δ 150.7, 137.9, 133.8, 131.3, 129.6, 129.5, 126.6, 89.2, 76.8, 21.4, 21.4; IR (NaCl dep from CH_2Cl_2) 2978, 1633, 1514, 1191, 1065, 800 cm^{-1}.

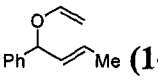


1-Methoxy-4-(3-vinyloxy-but-1-enyl)-benzene (14). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.35-6.83 (4H, m), 6.50 (1H, d, J = 16.0 Hz), 6.38 (1H, dd, J = 14.1, 6.6 Hz), 6.03 (1H, dd, J = 16.0, 6.8 Hz), 4.48 (1H, dq, J = 6.6, 6.6 Hz), 4.35 (1H, dd, J = 14.1, 1.3 Hz), 4.02 (1H, dd, J = 6.4, 1.1 Hz), 3.81 (3H, s) 1.40 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz CDCl3) δ 159.6, 150.7, 130.9, 129.3, 128.4, 127.9, 114.2, 89.1, 76.9, 55.5, 21.5; IR (NaCl dep from CH_2Cl_2) 2977, 1634, 1512, 1250, 1035, 820 cm^{-1}.

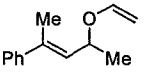


1-Trifluoromethyl-4-(3-vinyloxy-but-1-enyl)-benzene (15). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.59-7.45 (4H, m), 6.59 (1H, d, J = 16.2 Hz), 6.38 (1H, dd, J = 14.1, 6.6 Hz), 6.28 (1H, dd, J = 16.2, 6.4 Hz), 4.55 (1H, dq, J = 6.4, 6.4 Hz), 4.36 (1H, dd, J = 14.1, 1.5 Hz), 4.07 (1H, dd, J = 6.6, 1.5 Hz), 1.43 (3H, d, J = 6.4 Hz); ^{13}C NMR (100

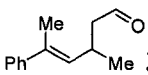
MHz $CDCl_3$) δ 150.5, 140.1, 133.3, 129.6, 126.9, 126.9, 125.8, 125.7, 89.4, 76.0, 21.2; IR (NaCl dep from CH_2Cl_2) 2982, 1616, 1415, 1326, 1124, 819 cm^{-1}.



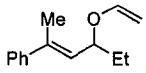
(1-Vinyloxy-but-2-enyl)-benzene (16). ^1H NMR (400 MHz $CDCl_3$) δ 7.41-7.27 (5H, m), 6.39 (1H, dd, J = 14.1, 6.6 Hz), 5.79-5.59 (2H, m), 5.17 (1H, d, J = 6.8 Hz), 4.34 (1H, d, J = 14.1 Hz), 4.03 (1H, d, J = 6.6 Hz), 1.72 (3H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.5, 140.8, 131.2, 129.3, 128.7, 127.9, 126.7, 89.8, 82.4, 18.0; IR (NaCl dep from CH_2Cl_2) 3030, 1635, 1452, 1318, 1175, 965, 698 cm^{-1}.



(1-Methyl-3-vinyloxy-but-1-enyl)-benzene (20). ^1H NMR (400 MHz $CDCl_3$) δ 7.44-7.23 (5H, m), 6.38 (1H, dd, J = 14.3, 6.6 Hz), 5.76 (1H, dd, J = 8.4, 1.1 Hz), 4.79 (1H, dq, J = 6.6, 6.6 Hz), 4.32 (1H, dd, J = 13.9, 1.1 Hz), 4.03 (1H, dd, J = 6.6, 1.1 Hz), 2.10 (3H, d, J = 1.1 Hz), 1.39 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.6, 142.8, 137.0, 129.8, 128.5, 127.5, 126.0, 88.8, 72.9, 21.1, 16.4; IR (NaCl dep from CH_2Cl_2) 2978, 1633, 1444, 1192, 821, 696 cm^{-1}.

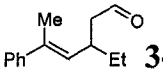


3-Methyl-5-phenyl-hex-4-enal (21). Isolated in 81% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.74 (1H, t, J = 2.13 Hz), 7.36-7.19 (5H, m), 5.55 (1H, d, J = 9.6 Hz), 3.14 (1H, m), 2.46 (2H, dd, J = 7.0, 2.1 Hz), 2.07 (3H, s), 1.11 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.5, 143.6, 134.9, 132.3, 128.4, 127.1, 125.9, 51.2, 28.6, 21.2, 16.3; IR (NaCl dep from CH_2Cl_2) 2961, 1724, 1445, 1026, 759, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{16}O$, 188.1201. Found 188.1193.

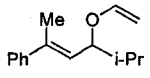


(1-Methyl-3-vinyloxy-pent-1-enyl)-benzene (23sm). ^1H NMR (400 MHz $CDCl_3$) δ 7.46-7.24 (5H, m), 6.40 (1H, dd, J = 13.9, 6.6 Hz), 5.73 (1H, d, J = 8.4 Hz), 4.56 (1H, dt, J = 6.6, 6.6 Hz), 4.30 (1H, dd, J = 14.3, 1.5 Hz), 4.01 (1H, dd, J = 6.6, 1.1

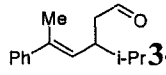
Hz), 2.12 (3H, s) 1.91-1.58 (2H, m) 0.99 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.9, 143.0, 137.9, 128.7, 128.5, 127.5, 126.0, 88.6, 78.2, 28.5, 16.7, 9.8; IR (NaCl dep from CH_2Cl_2) 2966, 1632, 1446, 1190, 757, 696 cm^{-1}.



3-Ethyl-5-phenyl-hex-4-enal (23). Isolated in 70% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.73 (1H, t, J = 2.3 Hz), 7.37-7.19 (5H, m), 5.49 (1H, dd, J = 10.0, 1.3 Hz), 2.93 (1H, m), 2.51 (1H, ddd, J = 16.0, 5.8, 2.3 Hz), 2.41 (1H, ddd, J = 16.0, 8.1, 2.3 Hz), 2.06 (3H, s), 1.55 (1H, m), 1.37 (1H, m), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.7, 143.8, 136.3, 131.1, 128.4, 127.1, 126.0, 49.7, 35.5, 28.9, 16.7, 11.9; IR (NaCl dep from CH_2Cl_2) 2961, 2721, 1724, 1494, 1027, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{18}O$, 202.1358. Found 202.1355.

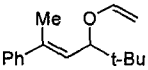


(1,4-Dimethyl-3-vinyloxy-pent-1-enyl)-benzene (24sm). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.43-7.22 (5H, m), 6.36 (1H, dd, J = 14.1, 6.4 Hz), 5.7 (1H, dd, J = 9.2, 1.3 Hz), 4.32 (1H, dd, J = 9.0, 6.4 Hz), 4.25 (1H, dd, J = 14.1, 1.5 Hz), 4.95 (1H, dd, J = 6.6, 1.3 Hz), 2.09 (3H, s), 1.99-1.90 (2H, m), 1.00 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 151.2, 143.1, 138.5, 128.4, 127.5, 127.3, 126.1, 88.4, 81.7, 33.5, 18.6, 18.2, 17.0; IR (NaCl dep from CH_2Cl_2) 2960, 1632, 1446, 1194, 1041, 696 cm^{-1}.

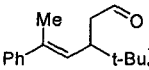


3-Isopropyl-5-phenyl-hex-4-enal (24). Isolated in 53% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.72 (1H, t, J = 2.4 Hz), 7.38-7.20 (5H, m), 5.57 (1H, d, J = 10.3 Hz), 2.87 (1H, ddt, J = 15.8, 10.3, 5.9 Hz), 2.63-2.37 (2H, m), 2.08 (3H, s), 1.74 (1H, dh, J = 13.6, 6.6 Hz), 0.97 (3H, d, J = 7.0 Hz), 0.94 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.0, 144.0, 136.8, 129.5, 128.4, 127.1, 126.1, 47.5, 40.0,

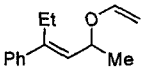
33.0, 20.7, 19.4, 16.9; IR (NaCl dep from CH_2Cl_2) 2959, 2720, 1724, 1494, 1027, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O$, 216.1514. Found 216.1513.



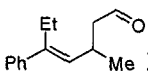
(1,4,4-Trimethyl-3-vinyloxy-pent-1-enyl)-benzene (25sm). ^1H NMR (400 MHz $CDCl_3$) δ 7.43-7.24 (5H, m), 6.36 (1H, dd, J = 14.3, 6.6 Hz), 5.72 (1H, dq, J = 9.6, 1.3 Hz), 4.26-4.21 (2H, m), 3.93 (1H, dd, J = 6.6, 1.3 Hz), 2.11 (3H, s), 0.98 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 151.7, 143.3, 138.9, 128.5, 127.5, 126.5, 126.1, 87.9, 84.1, 36.4, 26.1, 17.1; IR (NaCl dep from CH_2Cl_2) 2961, 1724, 1494, 1365, 1028, 698 cm^{-1}.



3-tert-Butyl-5-phenyl-hex-4-enal (25). Isolated as a separable mixture of regioisomers in 63% combined yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.65 (1H, t, J = 3.0), 7.35-7.29 (5H, m), 5.57 (1H, d, J = 11.1 Hz), 2.82 (1H, dt, 10.9, 3.4 Hz), 2.60 (1H, m), 2.35 (1H, m), 2.06 (3H, s), 0.94 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.3, 144.1, 137.1, 129.0, 128.4, 127.1, 126.1, 45.2, 43.5, 34.4, 27.6, 17.0; IR (NaCl dep from CH_2Cl_2) 2961, 1724, 1494, 1365, 1028, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}O$, 230.1671. Found 2230.1679.

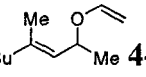


(1-Ethyl-3-vinyloxy-but-1-enyl)-benzene (26sm). ^1H NMR (400 MHz $CDCl_3$) δ 7.39-7.23 (5H, m), 6.37 (1H, dd, J = 14.3, 6.6 Hz), 5.6 (1H, d, J = 8.5 Hz), 4.78 (1H, m), 4.32 (1H, dd, J = 14.1, 1.3 Hz), 4.02 (1H, dd, J = 6.8, 1.5 Hz), 2.61-2.51 (2H, m), 1.39 (3H, d, J = 6.4 Hz), 0.98 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.6, 144.0, 141.8, 128.5, 128.3, 128.1, 126.7, 89.0, 72.8, 23.5, 21.7, 13.8; IR (NaCl dep from CH_2Cl_2) 2973, 1633, 1191, 1063, 762, 698 cm^{-1}.

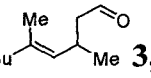


3-Methyl-5-phenyl-hept-4-enal (26). Isolated in 64% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.74 (1H, t, J = 2.4 Hz), 7.32-7.19 (5H, m), 5.39 (1H, d, J

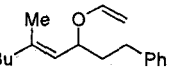
= 9.8 Hz), 3.14 (1H, m), 2.53 (2H, ddd, J = 21.1, 14.3, 7.3 Hz), 2.44 (2H, dd, J = 7.0, 2.4 Hz), 1.11 (3H, d, J = 6.6 Hz), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.5, 142.7, 141.8, 132.0, 128.4, 127.1, 126.7, 51.4, 28.4, 23.4, 21.7, 14.0; IR (NaCl dep from CH_2Cl_2) 2966, 1725, 1454, 1075, 763, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{18}O$, 202.1358. Found 202.1358.



4-Methyl-2-vinyloxy-oct-3-ene (27sm). ^{1}H NMR (400 MHz $CDCl_3$) δ 6.31 (1H, dd, J = 14.1, 6.6 Hz), 5.14 (1H, d, J = 8.5 Hz), 4.60 (1H, dq, J = 13.4, 6.6 Hz), 4.25 (1H, d, J = 14.3 Hz), 3.96 (1H, d, J = 6.6 Hz), 2.00 (2H, d, J = 7.2 Hz), 1.66 (3H, s), 1.44-1.28 (4H, m), 1.26 (3H, d, J = 6.2 Hz), 0.89 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.7, 138.9, 126.3, 88.4, 72.8, 39.3, 30.0, 22.5, 21.3, 16.7, 14.2; IR (NaCl dep from CH_2Cl_2) 2930, 1633, 1456, 1194, 1065, 811 cm^{-1}.

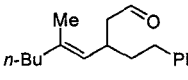


3,5-Dimethyl-non-4-enal (27). Isolated as a separable mixture of regioisomers in 50% combined yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.68 (1H, t, J = 2.6 Hz), 4.94 (1H, d, J = 9.4 Hz), 3.01-2.89 (1H, m), 2.37- 2.29 (2H, m), 1.94 (3H, t, J = 7.0 Hz), 1.62 (3H, s), 1.39-1.18 (4H, m), 1.01 (3H, d, J = 6.8 Hz), 0.88 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.3, 135.7, 128.7, 51.5, 39.5, 30.3, 26.3, 23.0, 21.5, 16.4, 14.3; IR (NaCl dep from CH_2Cl_2) 2958, 2872, 2716, 1727, 1456, 1380 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{20}O$, 168.1592. Found 168.1591.

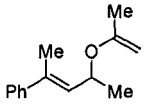


(5-Methyl-3-vinyloxy-non-4-enyl)-benzene (28sm). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.31-7.16 (5H, m), 6.31 (1H, dd, J = 14.3, 6.6 Hz), 5.14 (1H, dd, J = 8.7, 1.1 Hz), 4.41 (1H, dt, J = 8.7, 6.6 Hz), 4.24 (1H, dd, J = 14.1, 1.3 Hz), 3.96 (1H, dd, J = 6.6, 1.3 Hz), 2.71-2.64 (2H, m), 2.08-1.98 (3H, m), 1.83-1.72 (1H, m), 1.61 (3H, s), 1.44-

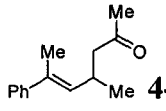
1.24 (4H, m), 0.90 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 150.8, 142.0, 140.1, 128.6, 128.6, 126.0, 125.1, 88.5, 75.9, 39.4, 37.1, 31.6, 30.1, 22.5, 16.9, 14.2; IR (NaCl dep from CH_2Cl_2) 2929, 1632, 1455, 1193, 822, 699 cm^{-1}.



5-Methyl-3-phenethyl-non-4-enal (28). Isolated as a separable mixture of regioisomers in 84% combined yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.65 (1H, t, J = 2.3 Hz), 7.30-7.13 (5H, m), 4.94 (1H, d, J = 10.0 Hz), 2.90-2.79 (1H, m), 2.72-2.60 (2H, m), 2.43-2.28 (2H, m), 2.01 (2H, t, J = 7.0 Hz), 1.60 (3H, s), 1.45-1.1 (6H, m), 0.91 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.1, 142.4, 138.1, 128.7, 128.6, 128.5, 126.0, 50.1, 39.7, 37.9, 33.7, 33.0, 30.4, 22.5, 16.8, 14.3; IR (NaCl dep from CH_2Cl_2) 2929, 2857, 1724, 1454, 1031, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{26}O$, 258.1984. Found 258.1971.

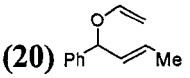


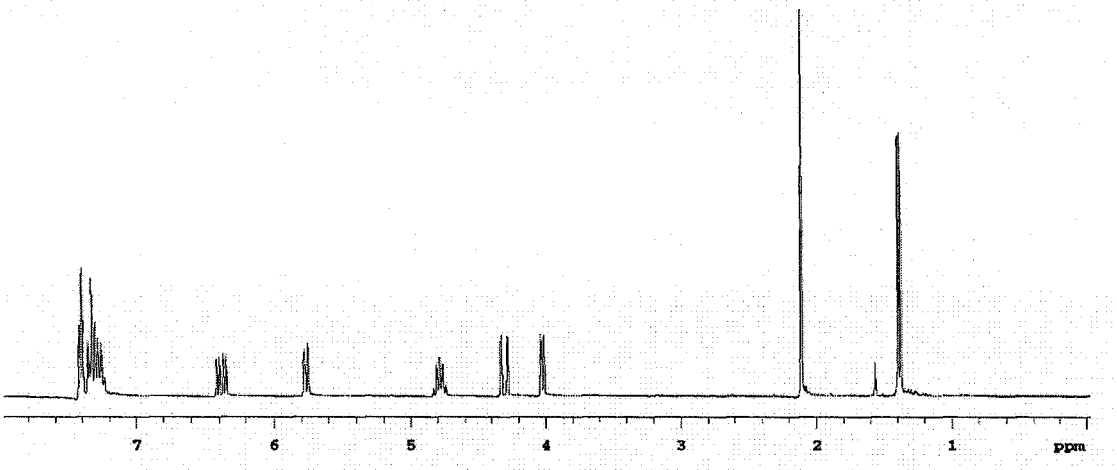
(3-Isopropenyloxy-1-methyl-but-1-enyl)-benzene (29). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.45-7.21 (5H, m), 5.77 (1H, dd, J = 7.7, 1.1 Hz), 4.88 (1H, dq, J = 12.8, 6.6 Hz), 3.87 (2H, d, J = 13.9 Hz), 2.09 (3H, s), 1.83 (3H, s), 1.39 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 158.5, 142.9, 135.5, 130.9, 128.4, 127.3, 125.9, 82.8, 70.8, 21.7, 20.9, 16.3; IR (NaCl dep from CH_2Cl_2) 2978, 1655, 1445, 1275, 1079, 696 cm^{-1}.

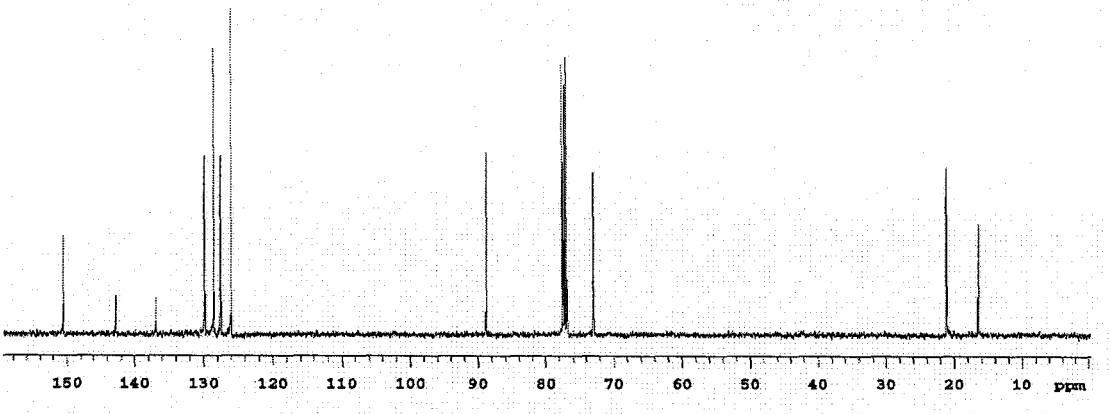


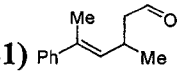
4-Methyl-6-phenyl-hept-5-en-2-one (30). Isolated in 69% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.38-7.18 (5H, m), 5.54 (1H, dd, J = 9.5, 1.1 Hz), 3.19-3.03 (1H, m), 2.48 (2H, dd, J = 6.6, 3.3 Hz), 2.14 (3H, s), 2.07 (3H, s), 1.07 (3H, d, J = 6.6 Hz);); ^{13}C NMR (100 MHz $CDCl_3$) δ 208.5, 143.8, 134.5, 132.9, 128.4,

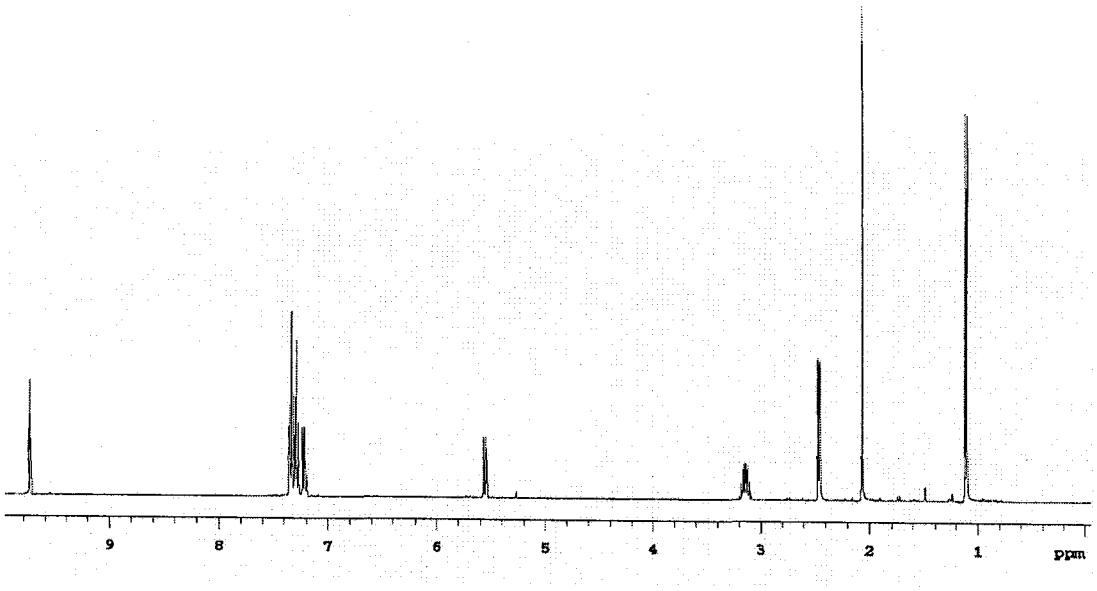
127.0, 125.9, 51.3, 30.8. 29.8, 21.1, 16.2; IR (NaCl dep from CH_2Cl_2) 2960, 1716, 1445, 1358, 1165, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{18}O$, 202.1358. Found 202.1357.

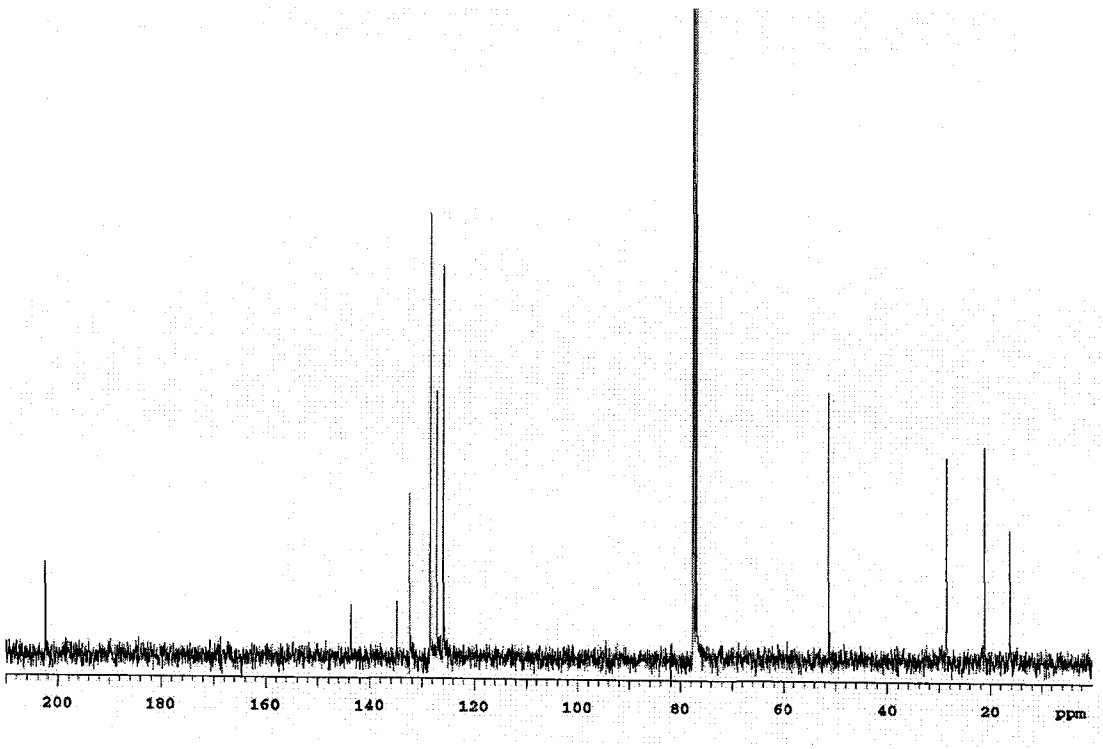
(20) 





(21) 





Chapter 3 Experimental

Stereoselective Lewis Acid-Mediated [1, 3] Ring Contraction of 2,5-Dihydrooxepines as a Route to Polysubstituted Cyclopentenes

General Methods: All reactions were performed under an inert atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, and aqueous ceric ammonium molybdate followed by heating.

All Lewis acids used were purchased from Aldrich Chemical Co. and used without further purification. $EtAlCl_2$ was purchased as a 1.0M solution in hexane.

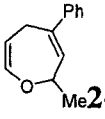
Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H and spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 100 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.23 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

General Procedure for the preparation of 2,5-dihydrooxepins. A flame-dried round-bottom flask was charged with 2.5 mmol of **24**, and diluted with CH_2Cl_2 (17 mL). 1.1 Eq. of Dess-Martin periodinane was then added and the reaction was fitted with a reflux condenser, purged with argon and heated at 40 °C. The reaction was monitored by TLC and upon disappearance of the starting material (typically 3h) the reaction was cooled to ambient temperature and the solvents were removed in *vacuo*. The residue was purified by column chromatography over NEt_3-treated silica gel using 9:1 (Hex:EtOAc, 1% NEt_3) as eluent. When left as a neat oil at ambient temperature, 2,5-dihydrooxepins decomposed slowly. The lifetime of these compounds may be increased by storing as a 0.2 M solution in toluene, under argon with refrigeration.

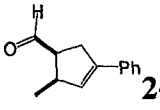
General Procedure (A) for the Lewis acid-mediated ring contraction of 2,5-dihydrooxepins. All ring contractions were performed on a 0.05 mmol scale. A flame-dried round-bottom flask was charged with $EtAlCl_2$ (1.05 eq.) under an inert atmosphere of argon and subsequently diluted with CH_2Cl_2 (50 mL) and mixed for 10 min at ambient temperature. 2,5-Dihydrooxepin in toluene (0.2 M in toluene, 1.0 eq.) was added via syringe (1 drop per second) and the reaction was stirred for 5-15 minutes at ambient temperature. The reaction mixture was quenched with 5 mL sat. aq. NH_4Cl, separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, then concentrated in *vacuo*, and purified via column chromatography over NEt_3-treated silica gel using 9:1 or 6:1 (Hex:EtOAc, 1% NEt_3).

General Procedure (B) for the Lewis acid-mediated ring contraction of 2,5-dihydrooxepins. All ring contractions were performed on a 0.05 mmol scale. A flame-

dried round-bottom flask was charged with $EtAlCl_2$ (1.05 eq.) under an inert atmosphere of argon and subsequently diluted with 1 mL CH_2Cl_2 and mixed for 10 min at ambient temperature. A separate flame-dried round bottom flask was charged with 2,5-dihydrooxepin (0.2 M in toluene, 1.0 eq.) and diluted with 1 mL CH_2Cl_2 and transferred slowly (0.5 mL/min), via cannula to the Lewis acid solution. Upon complete addition of the substrate the reaction was allowed to stir for 5 minutes and was subsequently quenched by addition of 5 mL sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, then concentrated in *vacuo*, and purified via column chromatography over NEt_3-treated silica gel using 9:1 or 6:1 (Hex:EtOAc, 1% NEt_3).

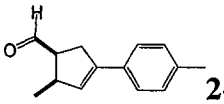


2-Methyl-4-phenyl-2,5-dihydro-oxepine (26). Isolated in 79% yield as a clear yellow oil. ^1H NMR (400 MHz $CDCl_3$) δ 7.42-7.21 (5H, m), 6.22 (1H, dd, J = 7.7, 2.7 Hz), 5.86 (1H, dd, J = 6.6, 2.9 Hz), 5.30 (1H, ddd, 12.8, 7.0, 6.2 Hz), 4.44 (1H, ddd, J = 5.1, 5.1, 2.9 Hz), 3.82 (1H, dq, J = 18.7, 2.9 Hz), 2.84 (1H, dd, J = 19.1, 8.1 Hz), 1.41 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 147.1, 146.7, 142.3, 129.3, 128.6, 127.7, 126.1, 100.1, 71.8, 29.3, 21.6; IR (NaCl dep from CH_2Cl_2) 3043, 2975, 1649, 1275, 1102, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{14}O$, 187.1123. Found 187.1116.

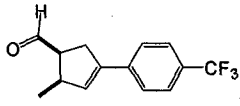


2-Methyl-4-phenyl-cyclopent-3-enecarbaldehyde (27). Isolated in 89% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.83 (1H, d, J = 2.5 Hz), 7.44-7.21 (5H, m), 6.05 (1H, d, 1.5 Hz), 3.38 (1H, m), 3.28-3.14 (2H, m), 2.77 (1H, dd, J = 15.6, 7.9 Hz), 1.08 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 204.2, 140.2, 135.8, 130.2, 128.6, 127.7, 125.8, 53.4, 42.3, 32.0, 16.5; IR (NaCl dep from CH_2Cl_2) 2959,

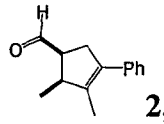
2726, 1720, 1494, 1447, 756, 693 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{14}O$, 186.1045. Found 186.1041.



2-Methyl-4-p-tolyl-cyclopent-3-enecarbaldehyde (29). Isolated in 85% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.81 (1H, d, J = 2.6 Hz), 7.30-7.08 (4H, m), 5.99 (1H, d, J = 1.9 Hz), 3.72 (1H, m), 3.24-3.11 (2H, m), 2.76 (1H, dd, J = 15.8, 8.1 Hz), 2.32 (3H, s), 1.08 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 211.1, 203.6, 139.4, 136.8, 128.6, 128.5, 125.0, 52.7, 41.6, 31.4, 20.7, 15.8; IR (NaCl dep from CH_2Cl_2) 2922, 2362, 1720, 1645, 1513, 809 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O$, 200.1201. Found 200.1198.

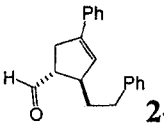


2-Methyl-4-(4-trifluoromethyl-phenyl)-cyclopent-3-enecarbaldehyde (31). Isolated in 75% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.86 (1H, d, J = 2.4 Hz), 7.60-7.48 (4H, m), 6.17 (1H, d, J = 1.9 Hz), 3.44 (1H, m), 3.34-3.18 (2H, m), 2.78 (1H, dd, J = 17.0, 9.6 Hz), 1.13 (3H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.6, 139.3, 132.7, 126.0, 125.6, 125.5, 53.2, 42.4, 31.9, 16.4; IR (NaCl dep from CH_2Cl_2) 2962, 1721, 1615, 1326, 1123, 827 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{13}F_3O$, 254.0929. Found 254.0919.

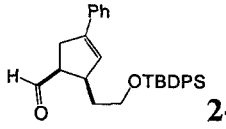


2,3-Dimethyl-4-phenyl-cyclopent-3-enecarbaldehyde (33). Isolated in 58% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.81 (1H, d, J = 2.3 Hz), 7.36-7.19 (5H, m), 3.18-3.06 (3H, m), 2.76 (1H, m), 1.81 (3H, s), 1.11 (3H, d, 6.8 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 204.8, 138.1, 137.8, 133.3, 128.4, 127.9, 126.8, 52.9, 47.0, 35.1,

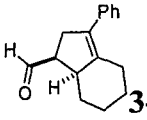
14.7, 13.6; IR (NaCl dep from CH_2Cl_2) 2961, 2722, 1720, 1446, 762, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O$, 200.1201. Found 200.1199.



2-Phenethyl-4-phenyl-cyclopent-3-enecarbaldehyde (35). Isolated in 73% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.82 (1H, d, J = 3.2 Hz), 7.46-7.14 (10H, m), 6.21 (1H, d, J = 1.9 Hz), 3.35-3.21 (2H, m), 3.14 (1H, m), 2.84 (1H, dd, J = 16.1, 8.0 Hz), 2.75-2.61 (2H, m), 1.92-1.68 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.9, 141.8, 141.3, 135.8, 128.7, 128.7, 128.6, 128.1, 127.9, 126.2, 125.9, 53.4, 47.7, 34.4, 33.5, 32.8; IR (NaCl dep from CH_2Cl_2) 2920, 2852, 1718, 1494, 695 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{20}O$, 276.1514. Found 276.1508.

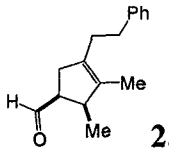


2-[2-(tert-Butyl-diphenyl-silanyloxy)-ethyl]-4-phenyl-cyclopent-3-enecarbaldehyde (37). Isolated in 52% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.76 (1H, d, J = 3.0 Hz), 7.68-7.65 (5H, m), 7.42-7.23 (10H, m), 6.10 (1H, s), 3.80-3.73 (2H, m), 3.49 (1H, m), 3.23 (1H, m), 3.10 (1H, m), 2.81 (1H, dd, J = 16.2, 8.5 Hz), 1.86 (1H, m), 1.59 (1H, m), 1.07 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 204.0, 140.9, 135.8, 133.9, 129.9, 128.6, 128.4, 127.9, 127.7, 125.8, 62.5, 53.3, 44.7, 34.0, 32.5, 27.1, 19.4; IR (NaCl dep from CH_2Cl_2) 3070, 2930, 2856, 1721, 1428, 1112, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{30}H_{34}O_2Si$, 454.2328. Found 454.2308.

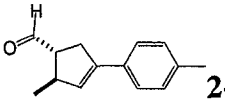


3-Phenyl-2,4,5,6,7,7a-hexahydro-1H-indene-1-carbaldehyde (39). Isolated in 38% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.82 (1H, d, J = 2.8 Hz), 7.42-7.17 (5H, m), 3.32-3.10 (3H, m), 2.87-2.71 (2H, m), 2.06-1.93 (1H, m), 1.89-1.72

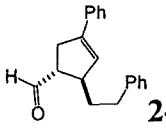
(2H, m), 1.47-1.10 (4H, m); HRMS (FAB+) calcd for $C_{16}H_{18}O$, 226.1358. Found 226.1356.



2,3-Dimethyl-4-phenethyl-cyclopent-3-enecarbaldehyde (41). Isolated in 59% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.71 (1H, d, J = 3.0 Hz), 7.28-7.17 (5H, m), 3.03-2.88 (2H, m), 2.76-2.62 (3H, m), 2.44-2.29 (3H, m), 1.42 (3H, s), 0.95 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 205.3, 142.1, 135.8, 132.6, 128.6, 128.4, 126.0, 52.9, 46.0, 34.3, 33.9, 30.5, 14.9, 11.7; IR (NaCl dep from CH_2Cl_2) 3026, 2928, 2854, 1721, 1453, 699 cm^{-1}.

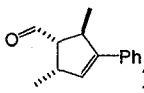


2-Methyl-4-p-tolyl-cyclopent-3-enecarbaldehyde (42). Isolated in 68% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.76 (1H, d, J = 2.4 Hz), 7.35-7.12 (4H, m), 5.97 (1H, d, J = 1.9 Hz), 3.23 (1H, m), 3.08-2.92 (2H, m), 2.78 (1H, m), 2.34 (3H, s), 1.24 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.1, 139.7, 137.5, 132.9, 129.3, 128.8, 125.7, 58.2, 41.8, 33.1, 21.4, 20.8; IR (NaCl dep from CH_2Cl_2) 2957, 2867, 2712, 1723, 1513, 809 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O$, 200.1201. Found 200.1204.

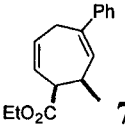


2-Phenethyl-4-phenyl-cyclopent-3-enecarbaldehyde (43). Isolated in 81% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.73 (1H, d, J = 2.1 Hz), 7.45-7.18 (10H, m), 6.11 (1H, d, J = 1.7 Hz), 3.20 (1H, m), 3.11-2.89 (3H, m), 2.74 (2H, t, J = 8.0 Hz), 1.97-1.82 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.8, 141.9, 140.7, 135.6, 128.7, 128.6, 127.8, 127.7, 126.2, 125.9, 56.0, 46.8, 37.5, 34.1, 33.0; IR (NaCl dep from CH_2Cl_2)

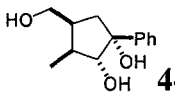
3026, 2921, 2712, 1721, 1447, 695 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{20}O$, 276.1514. Found 276.1502.



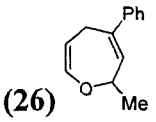
2,5-Dimethyl-3-phenyl-cyclopent-3-enecarbaldehyde (45). Isolated in 70% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.82 (1H, d, J = 3.2 Hz), 7.42-7.23 (5H, m), 5.89 (1H, s), 3.63 (1H, m), 3.38 (1H, m), 2.79 (1H, ddd, J = 8.3, 4.7, 3.4 Hz), 1.15 (3H, d, J = 6.8 Hz), 1.12 (3H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 204.3, 145.9, 135.6, 130.5, 128.7, 127.6, 126.5, 62.4, 40.5, 39.4, 18.8, 16.5; IR (NaCl dep from CH_2Cl_2) 3031, 2960, 2928, 1720, 1457, 761, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O$, 200.1201. Found 200.1202; $[\alpha]_D^{23}$ = -13.7° (c = 0.075 in CH_2Cl_2); HPLC analysis (Chiracel OD-H, 95:5 hex/*i*-PrOH, 1.0 mL/min, 254 nm; tr(minor) = 5.9 min., tr(major) = 12.7 min.) gave the isomeric composition of the product: 95% ee.

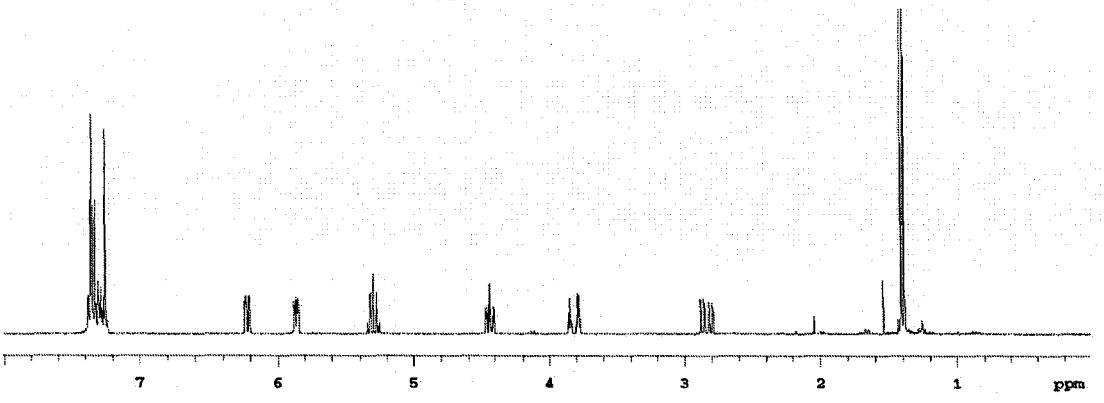


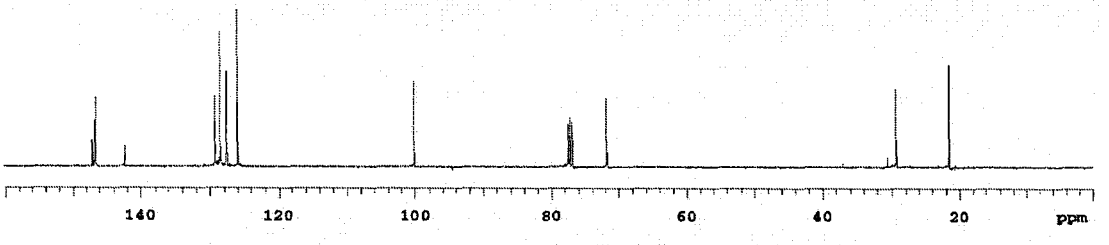
7-Methyl-5-phenyl-cyclohepta-2,5-dienecarboxylic acid ethyl ester (48). Isolated in 74% yield as a white solid. ^1H NMR (400 MHz $CDCl_3$) δ 7.26-7.12 (5H, m), 5.91-5.82 (2H, m), 5.77 (1H, dd, J = 6.2, 2.1 Hz), 4.10 (2H, q, J = 7.3 Hz), 3.54 (1H, d, J = 2.8 Hz), 3.45 (1H, d, J = 18.1 Hz), 3.09-2.99 (1H, m), 2.97-2.89(1H, m), 1.19 (3H, t, J = 7.2 Hz), 1.07 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 173.0, 144.9, 138.8, 133.8, 129.3, 128.4, 128.2, 126.7, 126.2, 60.7, 48.4, 34.6, 31.6, 18.1, 14.5; IR (NaCl dep from CH_2Cl_2) 2975, 1735, 1598, 1444, 1178, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{20}O_2$, 257.1463. Found 257.1531.

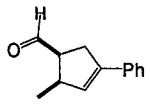


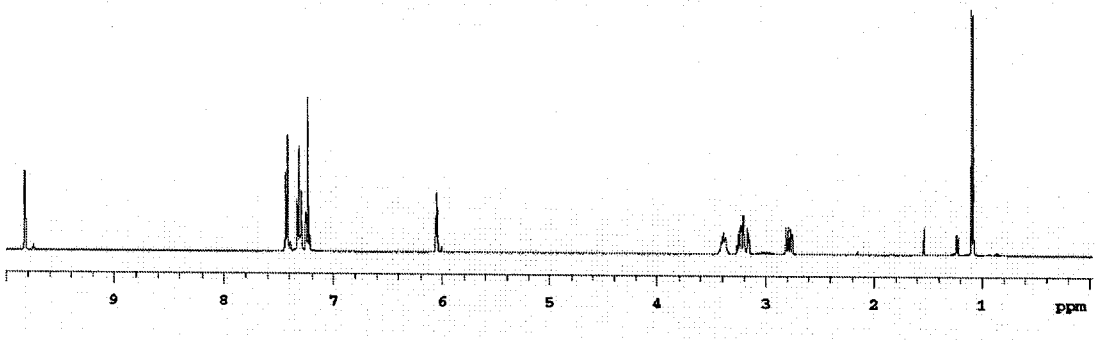
4-Hydroxymethyl-3-methyl-1-phenyl-cyclopentane-1,2-diol (50). Isolated in 60% yield as a white solid. ^1H NMR (400 MHz $CDCl_3$) δ 7.55-7.23 (5H, m), 3.98 (1H,

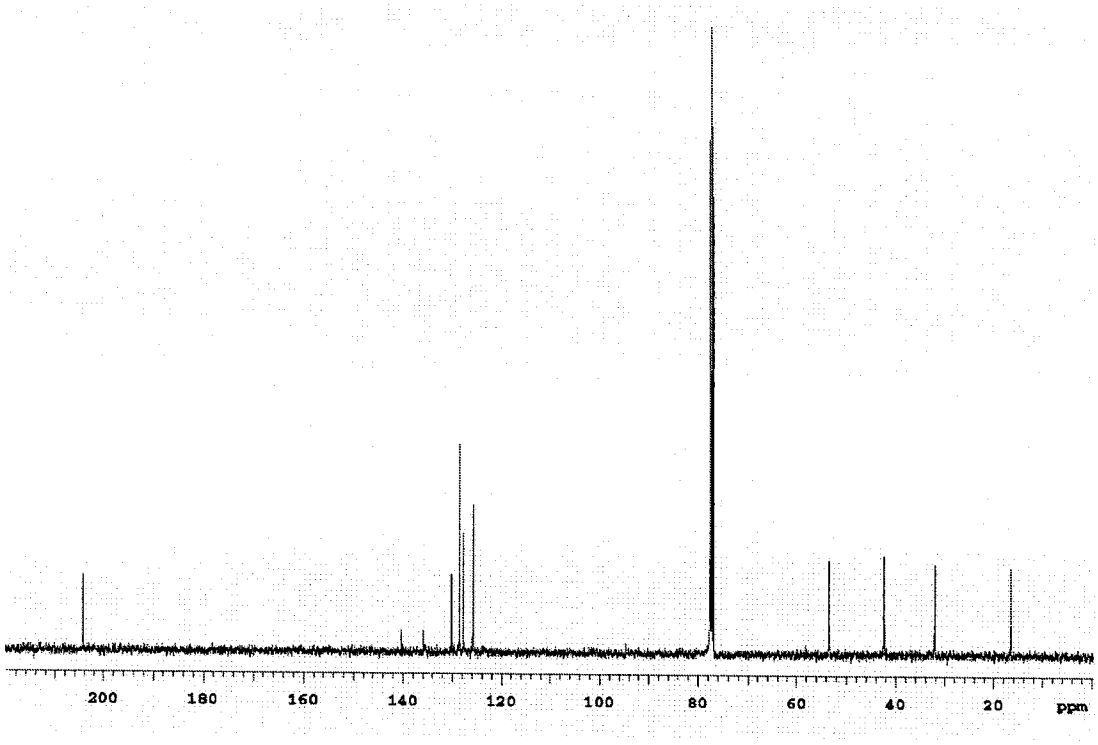
(26) 





(27) 





Chapter 4 Experimental

A Diastereoselective Intermolecular Heck Reaction of 1,3-Dioxepins

General Methods: All reactions were performed under an inert atmosphere of argon in flame-dried glassware with magnetic stirring. Acetonitrile (ACS grade) was purchased from Fisher Scientific and distilled from CaH_2 before use. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate followed by heating.

$Pd(OAc)_2$ was purchased from Fluka. All other chemicals were purchased from Aldrich Chemical Co. and used without further purification.

^1H NMR spectra are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.23 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 Chromopack Cp-Sil 8 CB (15 M X 0.25 mm) capillary column. Microwave reactions were conducted in a CEM Discovery microwave reactor.

General Procedure A for the preparation of symmetric 1,3-dioxepins. Note: This procedure is used for low molecular weight and thermally unstable aldehydes and can be conducted on a 15 mmol scale. A round-bottom flask was charged with aldehyde (1 eq.), *cis*-1,4-butenediol (1.8 eq.) and *p*-TsOH (0.1 eq.). The mixture was diluted with Et_2O (25

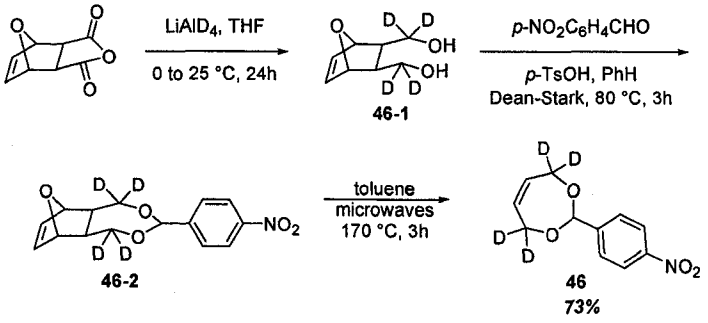
mL/ g of diol) and mixed at 25 °C for 15 min. or until the solution became cloudy. $MgSO_4$ was then added (1g/ g of aldehyde) and the mixture was monitored by TLC. Upon disappearance of the aldehyde more $MgSO_4$ was added (1g/ g of aldehyde). The solution was filtered through a pad of celite, the cake was washed with anhydrous Et_2O and the solvent was removed in *vacuo*. The residue was purified by silica gel column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure B for the preparation of symmetric 1,3-dioxepins. This reaction can be conducted on a 15 mmol scale. A round-bottom flask was charged with aldehyde (1 eq.), *cis*-1,4-butenediol (1.8 eq.) and *p*-TsOH (0.1 eq.). The mixture was diluted with benzene (25 mL/ g of diol) and mixed at 25 °C for 15 min. or until the solution became cloudy. The solution was then heated under Dean-Stark conditions (bath temperature typically 90 °C). Upon disappearance of the aldehyde by TLC, the crude reaction mixture was cooled to ambient temperature and the solvent was removed in *vacuo*. The residue was purified by silica gel column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure A for the Heck Reaction of 1,3-Dioxepins. This reaction can be conducted on a 5 mmol scale. A round-bottom flask was charged with $Pd(OAc)_2$ (0.05 eq.), PPh_3 (0.10 eq.), K_2CO_3 (1.78 eq.), and *n*-$Bu_4NCl{\cdot}H_2O$ (1 eq.). The flask was purged with argon and a 9:1 mixture of acetonitrile and deionized water were added (0.5M with respect to 1,3-dioxepin). After mixing for 0.25h at 50 °C 1,3-dioxepin (1 eq.) and sp^2-iodide (1.05 eq.) were added. The reaction was allowed to stir for 12-36h. Standard work-up proceeded with the addition of $MgSO_4$ (1g/0.5 mL H_2O) and dilution with Et_2O (6 mL/1 mL of reaction mixture) and mixed for 15 min. This solution was flushed

through a small pad of celite (1 cm) on top of a small pad of silica gel (1 cm) and eluted with Et_2O. To this solution was added $MgSO_4$ and activated charcoal, the mixture was allowed to stir at ambient temperature for 1h and then filtered through a pad of celite. The solvents were removed in *vacuo* and the residue was purified by column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure B for the Heck Reaction of 1,3-Dioxepins. This reaction may be conducted on an 8 mmol scale. A round-bottom flask was charged with $Pd(OAc)_2$ (0.08 eq.) and $BnNEt_3$ (2 eq.). The flask was purged with argon and DMF was added (0.4M with respect to 1,3-dioxepin). *i*-Pr_2NEt was added and the mixture was heated at 80 °C for 10 min. 1,3-dioxepin (1 eq.) and sp^2-iodide (1 eq.) were added and the reaction was allowed to stir for 12h. The reaction was then cooled to ambient temperature and diluted with Et_2O. The organic layer was washed 4 x H_2O and 1 x brine. The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

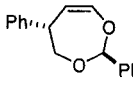


Synthesis of 2-(4-Nitro-phenyl)-4,4,7,7-tetradeuterio-4,7-dihydro-[1,3]dioxepine (46). *Exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride was reduced to **46-1** in the presence of $LiAlD_4$ according to a literature procedure.[1] The crude diol **46-1** was then condensed with *p*-nitrobenzaldehyde in the presence of 0.1 eq. *p*-TsOH under Dean-Stark conditions

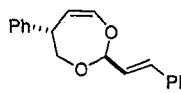
[1] For a procedure see: Das, J.; Vu, T.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1988**, *31*, 930-935.

to provide **46-2**. **46-2** was thermally decomposed to **46** by exposure to microwaves (250 W) in toluene at 170 °C for 3h.

Mass spectrometry was attempted under TOF+, FAB+ and ES- ionization for 1,3-dioxepins **16**, **20**, **21**, **22**, **27**, **28**, **29**, **30**, **31**, **34**, **45**, **47**, and **49**; however, mass spectra were not obtained due to decomposition.

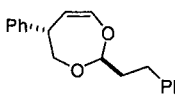


2,5-Diphenyl-4,5-dihydro-[1,3]dioxepine (14).[2] Isolated in 85% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.54-7.21 (10H, m), 6.53 (1H, dd, J = 7.5, 3.0 Hz), 5.57 (1H, s), 5.00 (1H, d, J = 7.3 Hz), 4.19 (1H, dd, J = 11.5, 5.1 Hz), 3.97 (1H, ddd, J = 7.9, 5.3, 2.8 Hz), 3.42 (1H, dd, J = 11.5, 11.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.4, 140.7, 138.9, 129.1, 129.0, 128.6, 128.2, 127.3, 126.2, 113.3, 106.7, 76.3, 48.5; IR (NaCl dep from CH_2Cl_2) 3031, 2868, 1647, 1453, 1029, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{16}O_2$, 253.1229. Found 253.1222.

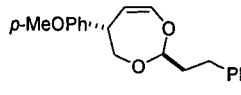


5-Phenyl-2-styryl-4,5-dihydro-[1,3]dioxepine (16). Isolated in 77% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.44-7.16 (10H, m), 6.83 (1H, d, J = 16.2 Hz), 6.49 (1H, dd, J = 6.8, 3.2 Hz), 6.30 (1H, dd, J = 16.0, 3.4 Hz), 5.22 (1H, s), 4.97 (1H, d, J = 7.2 Hz), 4.18-4.11 (1H, m), 3.94-3.91 (1H, m), 3.35 (1H, dd, J = 11.5, 11.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.2, 140.7, 133.2, 129.2, 129.0, 128.8, 128.4, 128.1, 127.3, 127.1, 125.9, 113.2, 105.9, 76.1, 48.5; IR (NaCl dep from CH_2Cl_2) 3028, 2867, 1645, 1492, 1146, 700 cm^{-1}

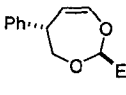
[2] The starting material for **14**, 4,7-dihydro-2-phenyl-1,3-dioxepin, may be purchased from Aldrich CAS# 2568-24-3.



2-Phenethyl-6-phenyl-4,5-dihydro-[1,3]dioxepine (17). Isolated in 87% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.37-7.18 (10H, m), 6.43 (1H, dd, J = 7.5, 3.0 Hz), 4.89 (1H, d, J = 7.5 Hz), 4.59 (1H, dd, J = 5.3, 5.3 Hz), 4.09 (1H, dd, J = 11.5, 5.1 Hz), 3.89 (1H, dddd, J = 10.7, 7.7, 5.1, 2.6 Hz), 3.20 (1H, dd, J = 11.4, 11.4 Hz), 2.81 (2H, t, J = 2.8 Hz), 2.18-2.06 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.3, 141.7, 140.9, 128.9, 128.7, 128.7, 128.1, 127.2, 126.1, 112.5, 106.9, 76.2, 48.4, 37.3, 30.8; IR (NaCl dep from CH_2Cl_2) 3027, 2867, 1647, 1453, 1145, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{20}O_2$, 280.1463. Found 280.1471.

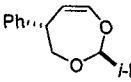


6-(4-Methoxy-phenyl)-2-phenethyl-4,5-dihydro-[1,3]dioxepine (18). Isolated in 67% yield as a yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.38-7.18 (7H, m), 6.94-6.88 (2H, m), 6.45 (1H, dd, J = 7.5, 3.0 Hz), 4.90 (1H, ddd, J = 7.5, 1.9, 1.3 Hz), 4.62 (1H, dd, J = 5.5, 5.5 Hz), 4.10 (1H, ddd, J = 11.7, 5.3, 1.3 Hz), 3.91-3.82 (4H, m), 3.20 (1H, dd, J = 11.5, 11.5 Hz), 2.84 (2H, t, J = 7.5 Hz), 2.22-2.08 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 158.8, 145.1, 141.7, 132.9, 129.4, 128.7, 128.6, 126.1, 114.2, 112.9, 106.9, 76.3, 55.5, 47.6, 37.3, 30.8; IR (NaCl dep from CH_2Cl_2) 2956, 1646, 1512, 1250, 1036, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{22}O_3$, 311.1647. Found 311.311.1635.

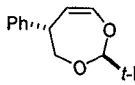


2-Ethyl-6-phenyl-4,5-dihydro-[1,3]dioxepine (19). Isolated in 64% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.34-7.21 (5H, m), 6.40 (1H, dd, J = 7.3, 3.0 Hz), 4.85 (1H, ddd, J = 7.5, 1.3, 1.3 Hz), 4.55 (1H, dd, J = 5.3, 5.3 Hz), 4.06 (1H, ddd, J = 11.7, 5.3, 1.1 Hz), 3.85 (1H, dddd, J = 11.3, 8.0, 5.3, 2.8 Hz), 3.21 (1H, dd, J = 11.3, 11.3 Hz), 1.85-1.72 (2H, m), 0.99 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ

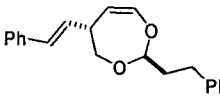
145.3, 141.0, 128.9, 128.1, 127.2, 112.3, 108.9, 76.2, 48.5, 29.1, 8.9; IR (NaCl dep from CH_2Cl_2) 2879, 1650, 1493, 1279, 1097, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{16}O_2$, 204.1150. Found 204.1142.



2-Isopropyl-6-phenyl-4,5-dihydro-[1,3]dioxepine (20). Isolated in 67% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 7.34-7.19 (5H, m), 6.40 (1H, dd, *J* = 7.5, 2.9 Hz), 4.81 (1H, ddd, *J* = 7.5, 1.3, 1.3 Hz), 4.35 (1H, d, *J* = 4.7 Hz), 4.07 (1H, ddd, *J* = 11.5, 5.3, 0.9 Hz), 3.85 (1H, dddd, *J* = 10.9, 8.1, 5.3, 2.8 Hz), 3.17 (1H, dd, *J* = 11.4, 11.4 Hz), 2.02-1.89 (1H, m), 0.98 (3H, d, *J* = 3.0 Hz), 0.97 (3H, d, *J* = 3.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.4, 141.0, 128.9, 128.1, 127.2, 111.8, 111.5, 76.4, 48.5, 33.7, 17.5, 17.3; IR (NaCl dep from CH_2Cl_2) 2961, 2872, 1645, 1454, 1104, 701 cm^{-1}.

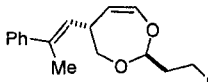


2-*tert*-Butyl-6-phenyl-4,5-dihydro-[1,3]dioxepine (21). Isolated in 68% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 7.37-7.24 (5H, m), 6.44 (1H, dd, *J* = 7.7, 3.2 Hz), 4.83 (1H, ddd, *J* = 3.4, 2.3, 1.5 Hz), 4.23 (1H, s), 4.12 (1H, ddd, *J* = 11.7, 5.5, 1.3 Hz), 3.89 (1H, m), 3.18 (1H, dd, *J* = 11.4, 11.4 Hz), 1.00 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.5, 141.1, 128.9, 128.2, 127.2, 113.7, 111.4, 76.4, 48.5, 36.1, 25.1; IR (NaCl dep from CH_2Cl_2) 2957, 2869, 1647, 1363, 1142, 700 cm^{-1}.



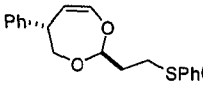
2-Phenethyl-6-styryl-4,5-dihydro-[1,3]dioxepine (22). Isolated in 50% yield as a yellow oil. ^1H NMR (400 MHz $CDCl_3$) δ 7.35-7.15 (10H, m), 6.49 (1H, d, *J* = 16.0 Hz), 6.33 (1H, dd, *J* = 3.8 Hz), 6.03 (1H, dd, *J* = 15.8, 8.1 Hz), 4.74 (1H, ddd, *J* = 7.5, 2.4, 1.1 Hz), 4.47 (1H, dd, *J* = 5.6, 5.6 Hz), 4.07 (1H, ddd, *J* = 11.5, 5.1, 0.9 Hz), 3.58-3.38 (1H, m), 3.12 (1H, dd, *J* = 11.3, 11.3 Hz), 2.76 (2H, t, *J* = 7.7 Hz), 2.12-1.98

(2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.0, 141.6, 137.1, 132.0, 128.8, 128.7, 128.7, 128.2, 127.8, 126.4, 126.1, 111.4, 106.7, 74.0, 44.9, 37.2, 30.8; IR (NaCl dep from CH_2Cl_2) 3026, 2958, 1650, 1455, 1131, 698 cm^{-1}.



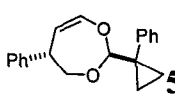
2-Phenethyl-6-(2-phenyl-propenyl)-4,5-dihydro-[1,3]dioxepine (23).

Isolated in 71% yield as a yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.40-7.16 (10H, m), 6.33 (1H, dd, J = 7.3, 2.8 Hz), 5.51 (1H, d, J = 9.6 Hz), 4.68 (1H, d, J = 7.2 Hz), 4.45 (1H, dd, J = 5.3, 5.3 Hz), 3.99 (1H, dd, J = 11.5, 5.1 Hz), 3.72-3.62 (1H, m), 3.08 (1H, dd, J = 11.3, 11.3 Hz), 2.77 (2H, t, J = 7.9 Hz), 2.12-2.00 (5H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 144.9, 143.3, 141.7, 137.7, 128.7, 128.6, 128.5, 127.4, 126.1, 125.9, 125.8, 113.0, 106.7, 73.1, 41.5, 37.3, 30.9, 16.3; IR (NaCl dep from CH_2Cl_2) 3026, 2863, 1645, 1455, 1145, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{24}O_2$, 321.1855. Found 321.1841.



6-Phenyl-2-(2-phenylsulfanyl-ethyl)-4,5-dihydro-[1,3]dioxepine (24).

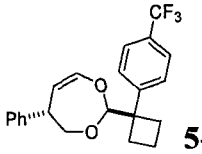
Isolated in 59% yield as a yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.39-7.16 (10H, m), 6.40 (1H, dd, J = 7.5, 3.0 Hz), 4.90 (1H, ddd, J = 7.5, 1.9, 1.5 Hz), 4.80 (1H, dd, J = 5.3, 5.3 Hz), 4.05 (1H, ddd, J = 11.5, 5.1, 1.1 Hz), 3.86 (1H, dddd, J = 11.1, 7.9, 5.1, 2.8 Hz), 3.21 (1H, dd, J = 11.5, 11.5 Hz), 3.09 (2H, t, J = 7.3 Hz), 2.18-2.06 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.2, 140.8, 136.4, 129.5, 129.2, 128.9, 128.1, 127.3, 126.2, 112.8, 106.0, 76.2, 48.4, 35.4, 28.8; IR (NaCl dep from CH_2Cl_2) 3028, 2869, 1646, 1438, 1144, 701cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{20}O_2S$, 313.1262. Found 313.1270.



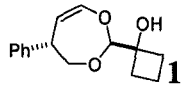
5-Phenyl-2-(1-phenyl-cyclopropyl)-4,5-dihydro-[1,3]dioxepine (27).

Isolated in 80% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.46-7.12 (10H,

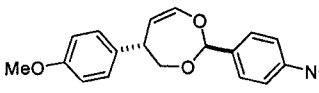
m), 6.34 (1H, dd, J = 7.7, 3.0 Hz), 4.79 (1H, d, J = 7.5 Hz), 4.61 (1H, s), 4.02 (1H, ddd, J = 11.7, 5.5, 1.3 Hz), 3.85-3.76 (1H, m), 3.13 (1H, dd, J = 11.5, 11.5 Hz), 1.17-1.07 (2H, m), 0.88-0.79 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.2, 141.9, 140.8, 130.7, 128.8, 128.5, 128.2, 128.1, 127.2, 126.9, 111.9, 109.8, 76.3, 48.3, 29.9, 10.2, 9.8; IR (NaCl dep from CH_2Cl_2) 3027, 2867, 1646, 1494, 1142, 700 cm^{-1}.



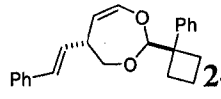
5-Phenyl-2-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-4,5-dihydro-[1,3]dioxepine (28). Isolated in 80% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.59-7.13 (9H, m), 6.39 (1H, dd, J = 7.5, 3.0 Hz), 4.82 (1H, s), 4.79 (1H, s), 4.08 (1H, dd, J = 11.7, 5.5 Hz), 3.82-3.75 (1H, m), 3.19 (1H, dd, J = 11.3, 11.3 Hz), 2.71-2.49 (2H, m), 2.47-2.35 (2H, m), 2.20-2.06 (1H, m), 1.93-1.82 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 149.8, 145.5, 140.8, 128.9, 128.7, 128.3, 128.1, 127.2, 124.6, 111.8, 110.8, 76.7, 50.4, 48.2, 30.5, 30.2, 16.2; IR (NaCl dep from CH_2Cl_2) 2947, 2866, 1647, 1327, 1163, 700 cm^{-1}.



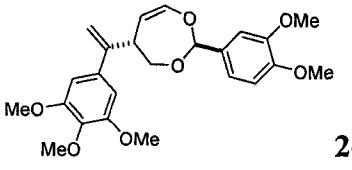
1-(5-Phenyl-4,5-dihydro-[1,3]dioxepin-2-yl)-cyclobutanol (29). Isolated in 72% yield as a pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.38-7.20 (5H, m), 6.45 (1H, dd, J = 7.5, 3.0 Hz), 4.90 (1H, ddd, J = 7.3, 1.1, 0.8 Hz), 4.54 (1H, s), 4.13 (1H, ddd, J = 11.7, 5.3, 1.1 Hz), 3.93-3.86 (1H, m), 3.27 (1H, dd, J = 11.5, 11.5 Hz), 2.51 (1H, s), 2.37-2.25 (2H, m), 2.11-2.01 (2H, m), 1.89-1.78 (1H, m), 1.72-1.58 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.1, 140.5, 129.0, 128.1, 127.4, 112.6, 108.8, 76.3, 75.8, 48.3, 31.2, 31.1, 12.5; IR (NaCl dep from CH_2Cl_2) 3419, 2948, 1646, 1453, 1139, 701 cm^{-1}.



5-(4-Methoxy-phenyl)-2-(4-nitro-phenyl)-4,5-dihydro-[1,3]dioxepine (30). Isolated in 67% yield as a white solid and was recrystallized from EtOAc and Hexanes using vapor diffusion to yield white needles. ^{1}H NMR (400 MHz $CDCl_3$) δ 8.23 (2H, d, J = 9.0 Hz), 7.72 (2H, d, J = 9.0 Hz), 7.18 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.53 (1H, dd, J = 7.3, 2.6 Hz), 5.63 (1H, s), 5.04 (1H, d, J = 7.2 Hz), 4.20 (1H, dd, J = 11.7, 5.1 Hz), 3.97-3.89 (1H, m), 3.80 (3H, s), 3.42 (1H, dd, J = 11.72, 11.72 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 159.0, 148.4, 145.3, 144.9, 132.3, 129.1, 127.5, 123.7, 114.4, 104.8, 76.5, 55.5, 47.5; IR (NaCl dep from CH_2Cl_2) 2958, 2866, 1645, 1516, 1028, 700 cm^{-1}.

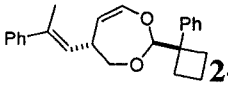


2-(1-Phenyl-cyclobutyl)-5-styryl-4,5-dihydro-[1,3]dioxepine (31). Isolated in 50% yield as a pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.39-7.20 (10H, m), 6.50 (1H, d, J = 15.8 Hz), 6.37 (1H, ddd, J = 7.3, 2.6, 2.6 Hz), 6.06 (1H, ddd, J = 15.8, 7.9, 1.7 Hz), 4.73 (1H, s), 4.71 (1H, s), 4.12 (1H, dd, J = 11.5, 5.3 Hz), 3.46-3.36 (1H, m), 3.18 (1H, dd, J = 11.5, 11.5 Hz), 2.68-2.54 (2H, m), 2.50-2.38 (2H, m), 2.19-2.06 (1H, m), 1.95-1.83 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 145.9, 145.3, 137.1, 131.8, 128.8, 128.3, 127.7, 127.6, 126.4, 126.3, 126.0, 111.1, 110.4, 74.3, 50.2, 44.8, 30.2, 30.0, 16.2; IR (NaCl dep from CH_2Cl_2) 2984, 2945, 1643, 1292, 1139, 699 cm^{-1}.

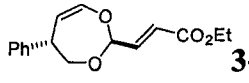


2-(3,4-Dimethoxy-phenyl)-5-[1-(3,4,5-trimethoxy-phenyl)-vinyl]-4,5-dihydro-[1,3]dioxepine (32). Isolated in 81% yield as a viscous pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.08-7.02 (2H, m), 6.84 (1H, d, J = 8.3 Hz), 6.62 (2H,

s), 6.53 (1H, dd, J = 7.5, 3.0 Hz), 5.49 (1H, s), 5.38 (1H, s), 5.19 (1H, s), 5.01 (1H, d, J = 7.3 Hz), 4.23 (1H, d, J = 11.5, 4.5), 3.94-3.82 (16H, m), 3.38 (1H, dd, J = 11.1, 11.1 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 153.3, 149.6, 149.1, 148.4, 145.3, 138.2, 136.9, 131.6, 118.7, 114.2, 113.3, 110.9, 109.0, 106.4, 103.9, 74.4, 61.1, 56.4, 56.2, 56.1, 46.9; IR (NaCl dep from CH_2Cl_2) 2937, 2836, 1645, 1411, 1128, 732 cm^{-1}; HRMS (+TOF MS) calcd for $C_{24}H_{28}O_7$, 428.4700. Found 429.1893.

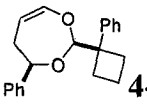


2-(1-Phenyl-cyclobutyl)-5-(2-phenyl-propenyl)-4,5-dihydro-[1,3]dioxepine (33). Isolated in 36% yield as a pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.36-7.15 (10H, m), 6.30 (1H, dd, J = 7.2, 3.0 Hz), 5.48 (1H, dd, J = 9.6, 1.1 Hz), 4.62 (1H, s), 4.58 (1H, dd, J = 7.5, 1.1 Hz), 3.98 (1H, dd, J = 11.7, 6.4 Hz), 3.65-3.55 (1H, m), 3.06 (1H, dd, J = 11.3, 11.3), 2.63-2.49 (2H, m), 2.44-2.32 (2H, m), 2.14-2.00 (4H, m), 1.89-1.77 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 146.0, 145.1, 143.4, 137.5, 128.4, 127.8, 127.7, 127.3, 126.2, 136.0, 125.9, 111.8, 111.3, 73.5, 50.2, 41.4, 30.2, 30.0, 16.3, 16.2; IR (NaCl dep from CH_2Cl_2) 2945, 2861, 1645, 1494, 1139, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{20}O_2S$, 313.1262. Found 313.1270.

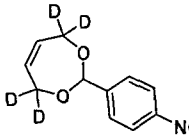


3-(5-Phenyl-4,5-dihydro-[1,3]dioxepin-2-yl)-acrylic acid ethyl ester (34). Isolated in 64% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.36-7.19 (5H, m), 6.87 (1H, dd, J = 16.0, 3.8 Hz), 6.44 (1H, dd, J = 7.2, 2.8 Hz), 6.22 (1H, d, J = 15.8 Hz), 5.16 (1H, d, J = 3.6 Hz), 4.97 (1H, dd, J = 7.5, 1.1 Hz), 4.21 (2H, q, J = 7.1 Hz), 4.11 (1H, dd, J = 11.5, 5.1 Hz), 3.93-3.85 (1H, m), 3.29 (1H, dd, J = 11.7, 11.7 Hz), 1.28 (3H, t, J = 7.03); ^{13}C NMR (100 MHz $CDCl_3$) δ 166.1, 145.0, 142.0, 140.4, 129.0, 128.1,

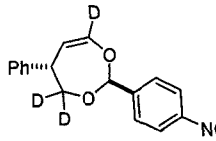
127.4, 124.3, 113.6, 103.5, 76.0, 60.9, 48.4, 14.4; IR (NaCl dep from CH_2Cl_2) 2981, 2870, 1724, 1647, 1146, 702 cm^{-1}.



4-Phenyl-2-(1-phenyl-cyclobutyl)-4,5-dihydro-[1,3]dioxepine (45). Isolated in 75% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 7.28-7.04 (10H, m), 6.38 (1H, dd, J = 6.6, 1.5 Hz), 5.66 (1H, s), 5.31 (1H, dd, J = 10.9, 2.6 Hz), 4.78 (1H, ddd, J = 7.3, 7.3, 2.8 Hz), 2.80 (1H, dddd, J = 17.5, 10.9, 2.6, 2.6 Hz), 2.65-2.54 (1H, m), 2.47-2.31 (1H, m), 2.21 (1H, dddd, J = 17.7, 7.5, 2.8, 1.5 Hz), 2.14-2.01 (1H, m), 1.89-1.77 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 148.0, 146.3, 142.8, 128.4, 127.8, 127.7, 127.4, 126.3, 125.9, 105.0, 104.8, 79.8, 50.0, 33.7, 30.3, 29.1, 16.4; IR (NaCl dep from CH_2Cl_2) 2986, 2941, 1650, 1494, 1111, 699 cm^{-1}.

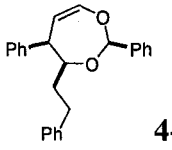


2-(4-Nitro-phenyl)-4,4,7,7-tetradeuterio-4,7-dihydro-[1,3]dioxepine (46). Isolated in 73% yield as a white solid. ^1H NMR (400 MHz $CDCl_3$) δ 8.23 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz), 5.88 (1H, s), 5.78 (2H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 146.0, 129.9, 127.9, 123.6, 101.1; IR (NaCl dep from CH_2Cl_2) 2875, 2213, 2099, 1513, 1348, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_7D_4NO_4$, 226.1017. Found 226.1011.



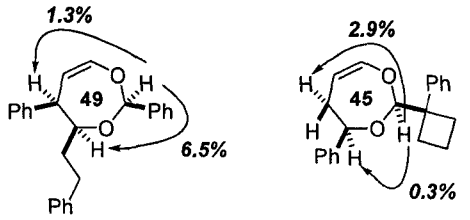
2-(4-Nitro-phenyl)-5-phenyl-4,4,5-trideuterio-4,5-dihydro-[1,3]dioxepine (47). Isolated in 75% yield as a white solid. ^1H NMR (400 MHz $CDCl_3$) δ 8.23 (2H, dd, J = 8.7, 2.4 Hz), 7.71 (2H, dd, J = 8.7, 2.1 Hz), 5.63 (1H, d, J = 2.1 Hz),

5.06 (1H, s), 3.97 (1H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 148.4, 145.2, 140.3, 129.1, 128.1, 127.5, 123.7, 113.8, 104.7, 48.2; IR (NaCl dep from CH_2Cl_2) 3081, 2873, 1635, 1345, 1128, 697 cm^{-1}.

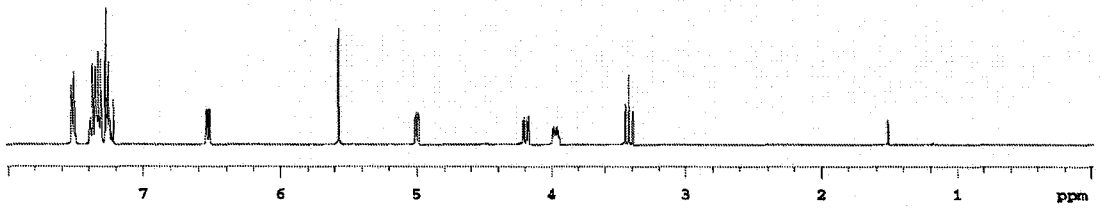


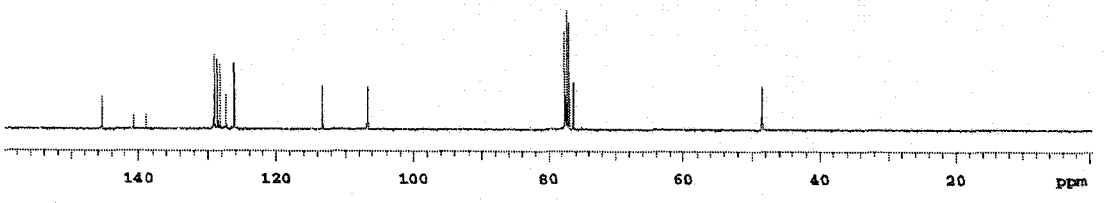
4-Phenethyl-2,5-diphenyl-4,5-dihydro-[1,3]dioxepine (49). Isolated in 70% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.62-6.92 (15H, m), 6.41 (1H, dd, J = 7.9, 3.0 Hz), 5.66 (1H, s), 4.76 (1H, dd, J = 7.7, 2.1 Hz), 3.65 (1H, dd, J = 10, 2.7 Hz), 3.57 (1H, ddd, J = 9.7, 9.7, 1.8 Hz), 2.92-2.82 (1H, m), 2.60-2.50 (1H, m), 1.89-1.78 (1H, m), 1.74-1.63 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.0, 143.96, 142.3, 141.8, 139.1, 129.0, 128.8, 128.6, 128.5, 128.4, 127.2, 126.2, 125.9, 112.1, 105.6, 85.1, 53.9, 35.3, 32.3; IR (NaCl dep from CH_2Cl_2) 3061, 2920, 1647, 1453, 1140, 698 cm^{-1}.

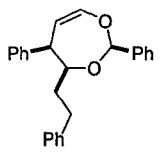
Stereochemical Assignment (nOe Experiments):



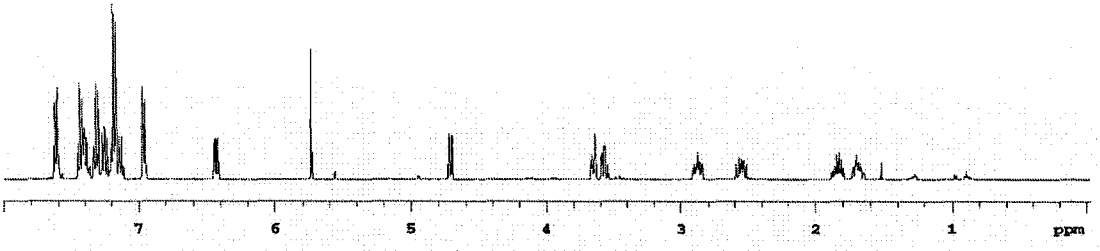
(14)

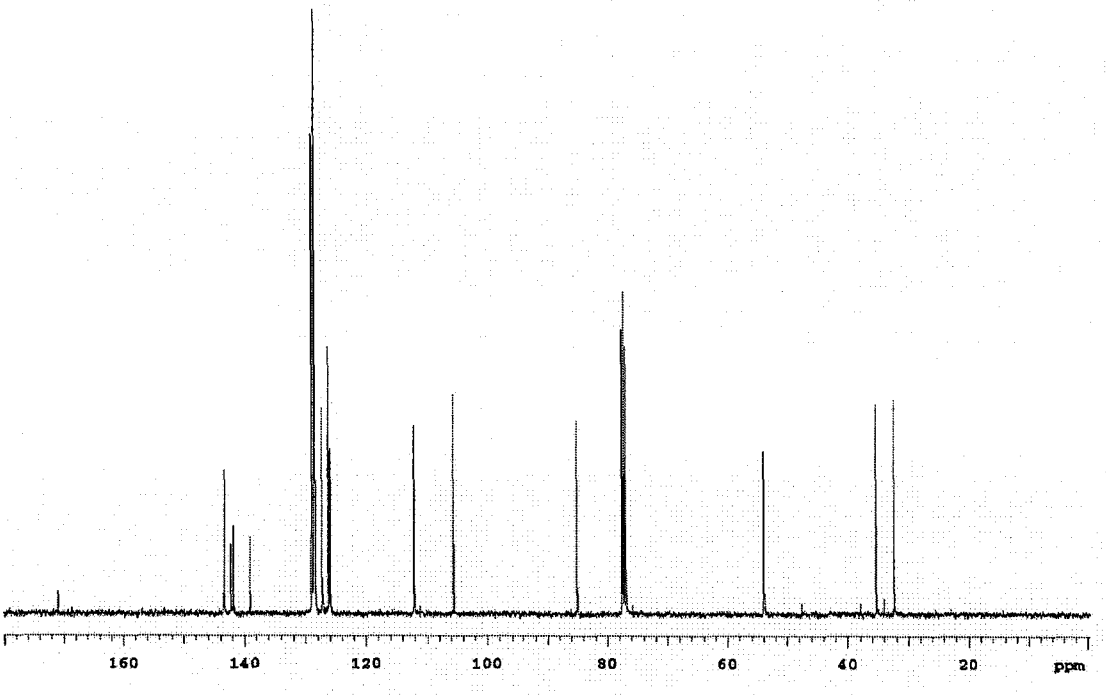






(49)





X-Ray Crystal Structure: Chapter 4, Compound 30.

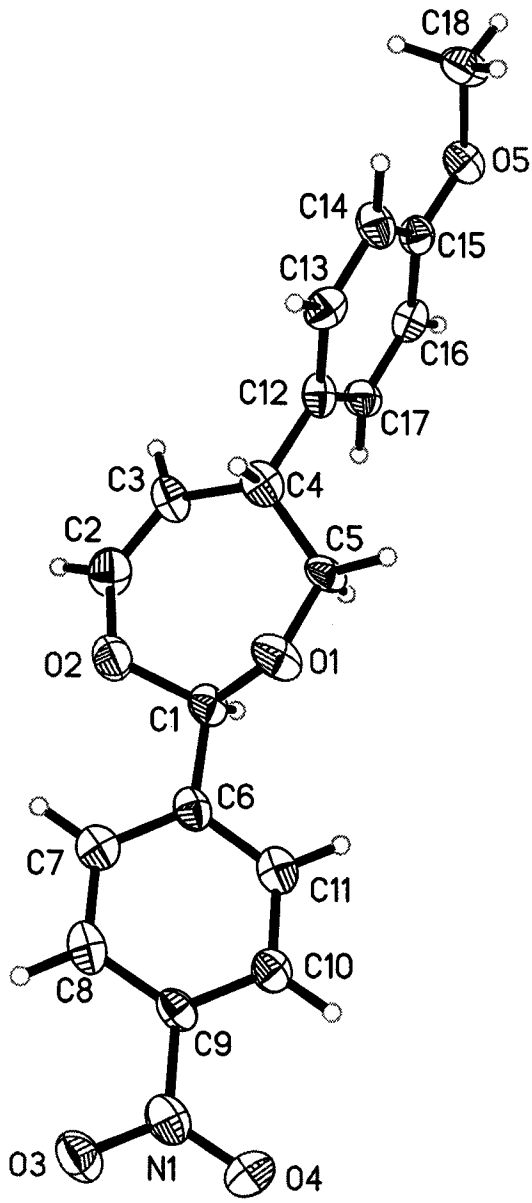


Table 1. Crystal data and structure refinement for rovis26_0m.

Identification code	rovis26_0m	
Empirical formula	C18 H17 N O5	
Formula weight	327.33	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.3133(8) Å	□= 90°.
	b = 8.0571(11) Å	□= 90°.
	c = 36.533(5) Å	□ = 90°.
Volume	1564.0(4) $Å^3$	
Z	4	
Density (calculated)	1.390 Mg/m^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	688	
Crystal size	0.59 x 0.11 x 0.03 mm^3	
Theta range for data collection	2.23 to 28.62°.	
Index ranges	-7<=h<=7, -10<=k<=10, -47<=l<=48	
Reflections collected	21496	
Independent reflections	3898 [R(int) = 0.2521]	
Completeness to theta = 28.62°	98.6 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9969 and 0.9418	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3898 / 0 / 218	
Goodness-of-fit on F^2	0.937	
Final R indices [I>2sigma(I)]	R1 = 0.0861, wR2 = 0.1656	
R indices (all data)	R1 = 0.2461, wR2 = 0.2244	
Absolute structure parameter	-2(3)	
Extinction coefficient	0.028(4)	
Largest diff. peak and hole	0.371 and -0.353 $e.Å^{-3}$	

Comment: Due to poor crystal quality the R1 and wR2 values are high. The crystal was a very small thin plate.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rovis26_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	9497(11)	7388(6)	3253(1)	36(1)
O(1)	6334(9)	8786(4)	1637(1)	38(1)
O(2)	4199(8)	6221(5)	1711(1)	38(1)
O(3)	8192(9)	6705(5)	3490(1)	43(1)
O(4)	11477(9)	8138(6)	3327(1)	44(1)
O(5)	4612(8)	10513(5)	-461(1)	33(1)
C(1)	6497(12)	7139(7)	1747(2)	29(1)
C(2)	3500(13)	5819(8)	1357(2)	39(2)
C(3)	3495(12)	6792(7)	1068(2)	31(2)
C(4)	4239(12)	8607(7)	1040(2)	33(2)
C(5)	6539(12)	9060(7)	1248(1)	29(2)
C(6)	7173(12)	7163(7)	2149(2)	29(2)
C(7)	5724(12)	6410(7)	2420(2)	31(2)
C(8)	6443(12)	6484(7)	2783(2)	33(2)
C(9)	8680(13)	7321(7)	2872(1)	28(1)
C(10)	10117(12)	8083(7)	2610(2)	30(2)
C(11)	9367(11)	7977(8)	2247(2)	30(2)
C(12)	4326(11)	9178(7)	643(2)	27(1)
C(13)	2565(12)	10275(7)	508(2)	31(2)
C(14)	2588(12)	10772(7)	138(2)	32(2)
C(15)	4411(12)	10146(7)	-89(2)	28(2)
C(16)	6189(12)	9062(7)	43(1)	29(2)
C(17)	6149(12)	8574(7)	408(2)	30(2)
C(18)	2611(13)	11531(8)	-612(2)	41(2)

Table 3. Bond lengths [Å] and angles [°] for rovis26_0m.

N(1)-O(3)	1.238(6)
N(1)-O(4)	1.243(6)
N(1)-C(9)	1.457(7)
O(1)-C(1)	1.389(6)
O(1)-C(5)	1.442(6)
O(2)-C(2)	1.383(7)
O(2)-C(1)	1.434(7)
O(5)-C(15)	1.396(6)
O(5)-C(18)	1.452(7)
C(1)-C(6)	1.512(7)
C(2)-C(3)	1.316(7)
C(3)-C(4)	1.519(8)
C(4)-C(5)	1.485(8)
C(4)-C(12)	1.522(8)
C(6)-C(11)	1.386(8)
C(6)-C(7)	1.392(8)
C(7)-C(8)	1.385(8)
C(8)-C(9)	1.405(8)
C(9)-C(10)	1.369(8)
C(10)-C(11)	1.387(7)
C(12)-C(13)	1.379(8)
C(12)-C(17)	1.383(8)
C(13)-C(14)	1.411(7)
C(14)-C(15)	1.370(8)
C(15)-C(16)	1.374(8)
C(16)-C(17)	1.389(7)
O(3)-N(1)-O(4)	122.5(5)
O(3)-N(1)-C(9)	118.9(6)
O(4)-N(1)-C(9)	118.5(5)
C(1)-O(1)-C(5)	115.2(4)
C(2)-O(2)-C(1)	115.9(4)
C(15)-O(5)-C(18)	115.7(5)
O(1)-C(1)-O(2)	114.4(5)

O(1)-C(1)-C(6)	106.5(4)
O(2)-C(1)-C(6)	107.4(5)
C(3)-C(2)-O(2)	127.7(6)
C(2)-C(3)-C(4)	128.9(6)
C(5)-C(4)-C(3)	114.6(5)
C(5)-C(4)-C(12)	112.9(5)
C(3)-C(4)-C(12)	111.3(5)
O(1)-C(5)-C(4)	113.9(5)
C(11)-C(6)-C(7)	119.2(5)
C(11)-C(6)-C(1)	117.3(5)
C(7)-C(6)-C(1)	123.6(6)
C(8)-C(7)-C(6)	120.7(6)
C(7)-C(8)-C(9)	118.4(5)
C(10)-C(9)-C(8)	121.7(5)
C(10)-C(9)-N(1)	119.0(6)
C(8)-C(9)-N(1)	119.3(5)
C(9)-C(10)-C(11)	118.7(6)
C(6)-C(11)-C(10)	121.3(6)
C(13)-C(12)-C(17)	118.6(5)
C(13)-C(12)-C(4)	121.0(5)
C(17)-C(12)-C(4)	120.5(5)
C(12)-C(13)-C(14)	121.3(6)
C(15)-C(14)-C(13)	118.8(6)
C(14)-C(15)-C(16)	120.5(5)
C(14)-C(15)-O(5)	124.4(6)
C(16)-C(15)-O(5)	115.1(5)
C(15)-C(16)-C(17)	120.4(6)
C(12)-C(17)-C(16)	120.5(6)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for rovis26_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	44(4)	21(3)	42(3)	6(2)	5(3)	4(3)
O(1)	64(3)	14(2)	35(2)	0(2)	-3(2)	5(2)
O(2)	42(3)	39(3)	33(2)	4(2)	3(2)	-8(2)
O(3)	61(3)	33(3)	36(2)	5(2)	5(2)	-9(3)
O(4)	42(3)	46(3)	42(3)	-5(2)	-9(2)	-8(3)
O(5)	42(3)	27(2)	31(2)	-1(2)	3(2)	2(2)
C(1)	35(4)	17(3)	36(3)	3(3)	0(3)	3(3)
C(2)	46(5)	39(4)	33(4)	-10(3)	4(3)	-9(4)
C(3)	41(4)	23(3)	28(3)	-1(3)	10(3)	0(3)
C(4)	40(4)	25(3)	34(4)	-1(3)	5(3)	4(3)
C(5)	42(4)	16(3)	28(3)	6(2)	-4(3)	2(3)
C(6)	28(4)	23(3)	35(3)	5(3)	5(3)	5(3)
C(7)	34(4)	25(3)	34(4)	-2(3)	3(3)	6(3)
C(8)	34(4)	23(3)	41(4)	2(3)	13(3)	4(3)
C(9)	37(4)	22(3)	25(3)	2(2)	5(3)	2(3)
C(10)	35(4)	18(3)	36(4)	3(3)	-1(3)	1(3)
C(11)	28(4)	26(3)	37(4)	1(3)	10(3)	8(3)
C(12)	27(4)	19(3)	36(3)	-2(3)	8(3)	0(3)
C(13)	31(4)	26(3)	36(4)	-9(3)	-3(3)	1(3)
C(14)	37(4)	22(3)	38(4)	2(3)	7(3)	3(3)
C(15)	30(4)	22(3)	32(4)	0(3)	-1(3)	-3(3)
C(16)	24(3)	27(3)	36(4)	-8(3)	4(3)	-1(3)
C(17)	36(4)	21(3)	31(3)	1(3)	-5(3)	-2(3)
C(18)	53(4)	33(4)	36(4)	6(3)	-8(3)	4(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for rovis26_0m.

	x	y	z	U(eq)
H(1A)	7861	6571	1606	35
H(2A)	2959	4709	1318	47
H(3A)	2953	6290	846	37
H(4A)	2834	9244	1156	40
H(5A)	7971	8403	1153	35
H(5B)	6918	10247	1204	35
H(7A)	4226	5840	2354	37
H(8A)	5448	5980	2969	39
H(10A)	11599	8672	2676	36
H(11A)	10378	8472	2063	36
H(13A)	1311	10705	667	37
H(14A)	1364	11526	47	39
H(16A)	7455	8644	-116	35
H(17A)	7381	7820	496	35
H(18A)	2920	11718	-873	61
H(18B)	2567	12600	-484	61
H(18C)	994	10964	-581	61

Chapter 5 Experimental

A Diastereoselective Ring Contraction of 1,3-Dioxepins to 2,3,4-Trisubstituted and Tetrasubstituted Tetrahydrofurans

General Methods: All reactions were performed under an inert atmosphere of argon in flame-dried glassware with magnetic stirring. Acetonitrile (ACS grade) was purchased from Fisher Scientific and distilled from CaH_2 before use. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate followed by heating.

TMSOTf was purchased from Fluka and was used as a 0.2M stock solution in acetonitrile and used within five days. All other chemicals were purchased from Aldrich Chemical Co. and used without further purification.

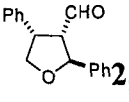
^1H NMR spectra are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.23 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 Chromopack Cp-Sil 8 CB (15 M X 0.25 mm) capillary column.

General Procedure A for the [1, 3] Ring Contraction of 1,3-Dioxepins. Reactions were performed on a 0.5 mmol scale. A flame-dried round-bottom flask was charged with 1,3-dioxepin (1 eq.) and freshly distilled MeCN (0.05M with respect to 1,3-dioxepin)

and cooled to -40 °C. TMSOTf (0.1 eq., 0.2M solution in MeCN) was added dropwise and the reaction was monitored by TLC. Upon disappearance of 1,3-dioxepin (typically 1h) the reaction was quenched with 0.5 mL of sat. aq. NH_4Cl and then diluted with ether. $MgSO_4$ was added and the reaction was mixed for 15 min., then filtered through a pad of celite and the solvent was removed in *vacuo*. The product was purified by silica gel column chromatography using 9:1-3:1 Hex:EtOAc as eluent.

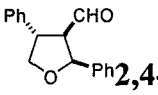
General Procedure B for the [1, 3] Ring Contraction of 1,3-Dioxepins. Reactions were performed on a 0.25 mmol scale. A flame-dried round-bottom flask was charged with CH_2Cl_2 (0.05M with respect to 1,3-dioxepin), 1.1 eq. of $SnCl_4$ and cooled to -78 °C. The 1,3-dioxepin was then added dropwise and the reaction was monitored by TLC. Upon disappearance of the 1,3-dioxepin (Typically 15 min.) the reaction was quenched with 0.5 mL of sat. aq. NH_4Cl and then diluted with ether. The organic layer was washed 2 x H_2O and 1 x brine and then dried over $MgSO_4$. After filtration, the solvents were removed in *vacuo*. The product was purified by silica gel column chromatography using 9:1-3:1, Hex:EtOAc as eluent.

Mass spectrometry was attempted under TOF+, FAB+ and ES- ionization for tetrahydrofurans **16a**, **19**, **22**, **24**, **24a**, **32**, **40**, **44**, **46**, **50**, and **52**, however, mass spectra were not obtained due to decomposition.

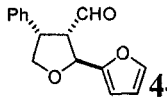


2,4-Diphenyl-tetrahydro-furan-3-carbaldehyde (10). Isolated in 87% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.39 (1H, d, J = 1.9 Hz), 7.40-7.22 (10H, m), 5.56 (1H, d, J = 7.0 Hz), 4.51 (1H, dd, J = 8.8, 6.5 Hz), 4.24 (1H, dd, J = 8.8, 5.9 Hz), 3.99 (1H, m), 3.33 (1H, ddd, J = 8.9, 6.8, 1.9 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 200.7, 141.9, 137.8, 129.3, 129.0, 128.3, 127.9, 126.3, 125.7, 79.5, 74.3, 64.3, 48.0; IR (NaCl

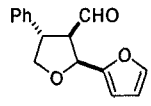
dep from CH_2Cl_2) 3030, 2863, 1720, 1494, 1068, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{16}O_2$, 253.1229. Found 253.1227.



2,4-Diphenyl-tetrahydro-furan-3-carbaldehyde (10a). Isolated in 70% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.01 (1H, d, J = 3.0 Hz), 7.31-7.14 (10H, m), 5.47 (1H, d, J = 8.5 Hz), 4.65-4.58 (1H, m), 3.95-3.87 (1H, m), 3.32 (1H, dddd, J = 11.5, 8.6, 5.8, 3.1 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 200.7, 139.7, 137.5, 129.2, 129.0, 128.4, 127.9, 127.5, 126.3, 82.6, 75.1, 63.6, 45.4; IR (NaCl dep from CH_2Cl_2) 3030, 2857, 1720, 1495, 1067, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{16}O_2$, 253.1229. Found 253.1227.



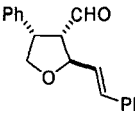
4-Phenyl-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carbaldehyde (12). Isolated in 88% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.32 (1H, d, J = 1.5 Hz), 7.41-7.21 (6H, m), 6.37-6.30 (2H, m), 5.55 (1H, d, J = 6.4 Hz), 4.41 (1H, dd, J = 8.7, 6.4 Hz), 4.18-4.02 (2H, m), 3.68 (1H, ddd, J = 8.5, 6.4, 1.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 200.0, 143.1, 137.7, 129.3, 129.2, 128.3, 127.8, 110.6, 108.4, 73.9, 73.0, 59.9, 48.0; IR (NaCl dep from CH_2Cl_2) 2868, 1721, 1495, 1068, 703 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{14}O_2$, 242.0943. Found 242.0939.



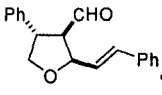
4-Phenyl-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carbaldehyde (12a).

Isolated in 94% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.35 (1H, d, J = 2.8 Hz), 7.42-7.22 (6H, m), 6.38-6.32 (2H, m), 5.46 (1H, d, J = 8.7 Hz), 4.54 (1H, dd, J = 8.2, 8.2 Hz), 4.12 (1H, dd, J = 16.6, 8.2 Hz), 3.94 (1H, dd, J = 8.6, 8.6 Hz), 3.41 (1H, dt, J = 8.7, 3.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 199.2, 151.2, 143.3, 139.4, 129.2, 127.8,

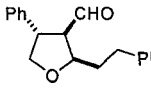
127.5, 110.7, 109.4, 75.7, 75.1, 62.9, 45.5; IR (NaCl dep from CH_2Cl_2) 2865, 1721, 1496, 1149, 1066, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{14}O_2$, 242.0943. Found 242.0939.



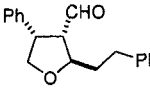
4-Phenyl-2-styryl-tetrahydro-furan-3-carbaldehyde (14). Isolated in 90% combined yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.34 (1H, d, J = 2.1 Hz), 7.42-7.20 (10H, m), 6.71 (1H, d, J = 15.8 Hz), 6.22 (1H, dd, J = 15.8, 6.2 Hz), 5.12 (1H, dd, J = 6.6, 6.6 Hz), 4.40 (1H, dd, J = 9.0, 6.6 Hz), 4.16 (1H, dd, J = 9.0, 5.8 Hz), 3.99-3.90 (1H, m); 3.22 (1H, ddd, J = 9.0, 7.0, 2.1 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 200.7, 137.8, 136.5, 131.7, 129.3, 129.1, 128.7, 128.1, 127.7, 127.6, 126.8, 78.8, 73.8, 61.9, 47.8; IR (NaCl dep from CH_2Cl_2) 3028, 2862, 1721, 1494, 1072, 696 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{18}O_2$, 279.1385. Found 279.1398.



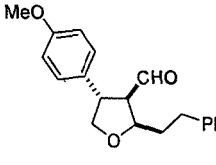
4-Phenyl-2-styryl-tetrahydro-furan-3-carbaldehyde (14a). Isolated in 88% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.70 (1H, d, J = 2.8 Hz), 7.38-7.22 (10H, m), 6.76 (1H, d, J = 16.0 Hz), 6.21 (1H, dd, J = 15.8, 7.0 Hz), 5.07 (1H, dd, J = 7.3, 7.3 Hz), 4.49 (1H, dd, J = 7.5, 7.5 Hz), 4.02-3.88 (2H, m), 3.36 (1H, ddd, J = 15.4, 8.3, 3.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 200.6, 139.8, 136.1, 133.3, 129.2, 128.9, 128.4, 127.8, 127.5, 127.0, 125.0, 81.5, 74.8, 63.5, 45.5; IR (NaCl dep from CH_2Cl_2) 3028, 2854, 1720, 1494, 1044, 695 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{18}O_2$, 279.1385. Found 279.1398; Gas chromatography analysis- gas flow 3mL/min with constant 150 °C oven temperature. Major diastereomer: 46.9 min, minor diastereomer: 61.5 min.



2-Phenethly-4-phenyl-tetrahydro-furan-3-carbaldehyde (16). Isolated in 85% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.76 (1H, d, J = 3.2 Hz), 7.34-7.18 (10H, m), 4.44 (1H, dd, J = 8.1, 8.1), 4.34 (1H, ddd, J = 8.1, 4.3, 4.1 Hz), 3.88 (1H, dd, J = 7.7, 7.7 Hz), 3.80 (1H, dd, J = 8.6, 8.6), 3.15 (1H, ddd, J = 7.9, 6.6, 3.4 Hz), 2.94-2.76 (2H, m), 2.05-1.84 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.3, 141.3, 140.3, 129.0, 128.7, 127.7, 127.3, 126.3, 81.0, 74.6, 62.5, 45.8, 33.6, 32.9; IR (NaCl dep from CH_2Cl_2) 3028, 2859, 1721, 1454, 1066, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{20}O_2$, 280.1463. Found 280.1475; Gas chromatography analysis- gas flow 3mL/min with constant 150 °C oven temperature. Minor diastereomer: 42.7 min, minor diastereomer: 49.1 min, major diastereomer: 53.2 min.

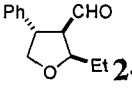


2-Phenethyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (16a). Isolated in 89% combined yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.24 (1H, d, J = 2.6 Hz), 7.35-7.15 (10H, m), 4.48 (1H, ddd, J = 7.3, 7.3, 7.0 Hz), 4.31 (1H, dd, J = 9.0, 6.6 Hz), 4.08 (1H, dd, J = 9.0, 6.6 Hz), 3.90-3.82 (1H, m), 3.01 (1H, ddd, J = 9.6, 4.2, 2.8 Hz), 2.89-2.79 (1H, m), 2.75-2.66 (1H, m), 1.99-1.87 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.4, 141.7, 138.0, 129.2, 128.7, 128.6, 128.3, 127.6, 127.5, 126.2, 78.1, 73.5, 61.3, 48.0, 37.4, 32.6; IR (NaCl dep from CH_2Cl_2) 3027, 2935, 1720, 1495, 1081, 701 cm^{-1}.

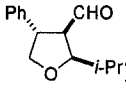


4-(4-Methoxy-phenyl)-2-phenethyl-tetrahydro-furan-3-carbaldehyde (18). Isolated in 84% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$)

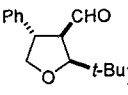
δ 9.77 (1H, d, J = 3.6 Hz), 7.35-7.14 (7H, m), 6.90-6.84 (2H, m), 4.44 (1H, dd, J = 8.1, 8.1 Hz), 4.35 (1H, ddd, J = 9.6, 8.1, 4.3 Hz), 3.94-3.76 (5H, m), 3.12 (1H, ddd, J = 8.1, 6.6, 3.6 Hz), 2.96-2.68 (2H, m), 2.06-1.84 (2H, m), 2.76 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.5, 141.3, 132.1, 128.8, 128.7, 126.3, 114.4, 80.9, 74.8, 62.6, 55.5, 45.2, 33.6, 32.9; IR (NaCl dep from CH_2Cl_2) 2935, 2837, 1719, 1514, 1034, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{22}O_3$, 311.1647. Found 311.1633.



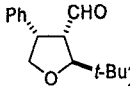
2-Ethyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (19). Isolated in 97% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.80 (1H, d, J = 3.6 Hz), 7.36-7.22 (5H, m), 4.43 (1H, dd, J = 7.9, 7.9 Hz), 4.28 (1H, ddd, J = 8.1, 8.1, 5.8 Hz), 3.91-3.78 (2H, m), 3.16 (1H, ddd, J = 7.8, 6.0, 3.4 Hz), 1.77-1.65 (2H, m), 1.06 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.5, 140.5, 129.1, 127.8, 127.3, 83.6, 74.6, 62.5, 45.8, 24.9, 11.2; IR (NaCl dep from CH_2Cl_2) 2967, 2876, 1721, 1455, 1075, 701 cm^{-1}.



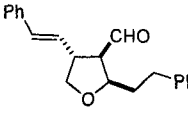
2-Isopropyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (22). Isolated in 83% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.80 (1H, d, J = 4.3 Hz), 7.34-7.19 (5H, m), 4.51 (1H, dd, J = 8.0, 8.0 Hz), 3.87-3.70 (3H, m), 3.05 (1H, ddd, J = 8.3, 6.8, 4.3 Hz), 1.99-1.88 (1H, m), 1.07 (3H, d, J = 6.4 Hz), 0.95 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.4, 141.0, 129.1, 127.7, 127.3, 88.8, 74.8, 61.8, 46.4, 29.5, 20.6, 19.3; IR (NaCl dep from CH_2Cl_2) 2961, 2873, 1720, 1470, 1073, 700 cm^{-1}; Gas chromatography analysis- gas flow 3mL/min with constant 130 °C oven temperature. Minor diastereomer: 3.4 min, minor diastereomer: 7.1 min, major diastereomer: 8.2 min.



2-*tert*-Butyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (24). Isolated in 55% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.88 (1H, d, J = 4.7 Hz), 7.34-7.20 (5H, m), 4.48 (1H, dd, J = 8.3, 8.3 Hz), 3.92 (1H, d J = 6.8 Hz), 3.85 (1H, dd, J = 8.5, 7.9 Hz), 3.80-3.70 (1H, m), 1.02 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.3, 140.9, 129.1, 127.8, 127.3, 92.0, 74.4, 63.1, 46.1, 34.3, 27.5; IR (NaCl dep from CH_2Cl_2) 2958, 2871, 1716, 1077, 1055, 700 cm^{-1}; Gas chromatography analysis- gas flow 3mL/min with constant 130 °C oven temperature. Minor diastereomer: 3.4 min, minor diastereomer: 3.8 min, major diastereomer: 19.2 min.

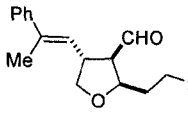


2-tert-Butyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (24a). Isolated in 89% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.19 (1H, d, J = 3.6 Hz), 7.33-7.19 (5H, m), 4.23-4.16 (2H, m), 4.09 (1H, dd, J = 8.7, 6.2 Hz), 3.72 (1H, ddd, J = 9.2, 6.1, 6.1 Hz), 3.14 (1H, ddd, J = 9.2, 7.3, 3.6 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.3, 137.6, 129.2, 128.4, 127.6, 86.2, 73.5, 56.8, 49.3, 34.8, 26.0; IR (NaCl dep from CH_2Cl_2) 2957, 2868, 1721, 1364, 1078, 702 cm^{-1}.

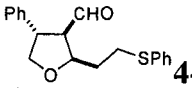


2-Phenethly-4-styryl-tetrahydro-furan-3-carbaldehyde (26). Isolated in 71% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.72 (1H, d, J = 3.6 Hz), 7.35-7.13 (10H, m), 6.46 (1H, d, J = 15.8 Hz), 6.04 (1H, dd, J = 15.8, 8.5 Hz), 4.28 (1H, dd, J = 8.3, 8.3 Hz), 4.22-4.14 (1H, m), 3.59 (1H, dd, J = 8.3, 8.3 Hz), 3.52-3.41 (1H, m), 2.99-2.74 (2H, m), 2.74-2.62 (1H, m), 2.00-1.80 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.2, 141.3, 136.7, 132.4, 128.8, 128.7, 127.9, 126.4, 126.3, 80.5, 72.8, 60.7, 44.1,

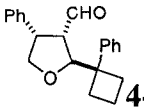
33.5, 32.9; IR (NaCl dep from CH_2Cl_2) 2934, 2857, 1720, 1495, 1049, 696 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{22}O_2$, 307.1698. Found 307.1709.



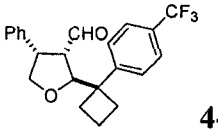
2-Phenethly-4-(2-phenyl-propenyl)-tetrahydro-furan-3-carbaldehyde (28). Isolated in 79% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.75 (1H, d, J = 3.6 Hz), 7.34-7.14 (10H, m), 5.59 (1H, d, J = 9.4 Hz), 4.30 (1H, dd, J = 8.2, 8.2 Hz), 4.16 (1H, ddd, J = 11.7, 9.4, 4.5 Hz), 3.74-3.64 (1H, m), 3.50 (1H, dd, J = 8.4, 8.4 Hz), 2.90-2.82 (2H, m), 2.72-2.62 (1H, m), 2.12-1.82 (6H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.6, 143.1, 141.3, 138.2, 128.7, 128.6, 128.5, 127.4, 126.7, 126.3, 125.9, 80.6, 73.2, 61.7, 40.1, 33.5, 33.0, 16.7; IR (NaCl dep from CH_2Cl_2) 2934, 2858, 1719, 1494, 1060, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{24}O_2$, 321.1855. Found 321.1848; Gas chromatography analysis- gas flow 3mL/min with constant 130 °C oven temperature. Minor diastereomer: 6.3 min, minor diastereomer: 7.1 min, major diastereomer: 7.4 min.



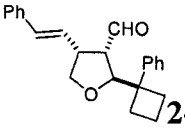
4-Phenyl-2-(2-phenylsulfanyl-ethyl)-tetrahydro-furan-3-carbaldehyde (30). Isolated in 68% yield as a pale yellow oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.70 (1H, d, J = 3.2 Hz), 7.35-7.14 (10H, m), 4.50 (1H, ddd, J = 10.2, 8.1, 3.8 Hz), 4.34 (1H, dd, J = 7.9, 7.9 Hz), 3.84 (1H, dd, J = 15.3, 8.1 Hz), 3.77 (1H, dd, J = 8.5, 8.5 Hz), 3.21-3.12 (1H, m), 3.04-2.95 (1H, m), 2.04-1.82 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.0, 140.2, 136.1, 129.4, 129.2, 129.1, 127.7, 127.4, 126.3, 80.0, 74.6, 62.4, 45.7, 31.5, 30.7; IR (NaCl dep from CH_2Cl_2) 2937, 2856, 1720, 1439, 1071, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{20}O_2S$, 313.1262. Found 313.1252.



4-Phenyl-2-(1-phenyl-cyclobutyl)-tetrahydro-furan-3-carbaldehyde (32). Isolated in 87% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 8.89 (1H, d, J = 3.2 Hz), 7.33-7.06 (10H, m), 4.82 (1H, d, J = 6.6 Hz), 4.04 (1H, dd, J = 8.7, 5.5 Hz), 3.91 (1H, dd, J = 8.6, 6.1 Hz), 3.13 (1H, ddd, J = 8.7, 5.8, 5.8 Hz), 3.96-2.89 (1H, m), 2.59-2.51 (1H, m), 2.47-2.31 (2H, m), 2.29-2.21 (1H, m), 2.17-2.04 (1H, m), 1.91-1.79 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.4, 145.6, 137.7, 129.0, 128.2, 128.2, 127.4, 126.5, 84.0, 73.6, 57.1, 49.7, 48.4, 30.7, 30.4, 15.9; IR (NaCl dep from CH_2Cl_2) 3028, 2941, 1722, 1494, 1076, 702 cm^{-1}.

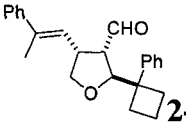


4-Phenyl-2-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-tetrahydro-furan-3-carbaldehyde (34). Isolated in 83% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.02 (1H, d, J = 3.0 Hz), 7.62-7.06 (9H, m), 4.88 (1H, d, J = 6.8 Hz), 4.00 (1H, dd, J = 8.7, 5.8 Hz), 3.84 (1H, dd, J = 8.7, 6.2 Hz), 3.17 (1H, ddd, J = 8.7, 6.0, 6.0 Hz), 2.88 (1H, ddd, J = 9.8, 6.8, 3.0 Hz), 2.65-2.55 (1H, m), 2.45-2.28 (2H, m), 2.26-2.08 (2H, m), 1.92-1.80 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.3, 149.9, 137.4, 129.1, 128.2, 128.0, 127.6, 125.0, 125.0, 83.2, 73.5, 57.1, 49.7, 48.4, 31.3, 30.3, 16.0; IR (NaCl dep from CH_2Cl_2) 2943, 2864, 1723, 1327, 1120, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{21}F_3O_2$, 373.1415. Found 373.1398.

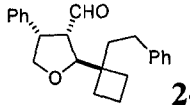


2-(1-Phenyl-cyclobutyl)-4-styryl-tetrahydro-furan-3-carbaldehyde (36). Isolated in 83% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.39 (1H, d, J = 3.2 Hz), 7.34-7.14 (10H, m), 6.31 (1H, d, J = 15.8 Hz), 6.04 (1H, dd, J = 15.8, 9.2 Hz),

4.75 (1H, d, J = 6.4 Hz), 3.80 (1H, dd, J = 8.5, 6.2 Hz), 3.71 (1H, dd, J = 8.3, 6.6 Hz), 2.84 (1H, ddd, J = 11.7, 6.6, 3.2 Hz), 2.77-2.67 (1H, m), 2.55-2.46 (1H, m), 2.44-2.31 (2H, m), 2.29-2.21 (1H, m), 2.16-2.02 (1H, m), 1.90-1.78 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.4, 145.7, 136.5, 133.3, 128.8, 128.2, 128.0, 127.3, 126.5, 125.2, 84.4, 73.3, 57.1, 49.5, 47.1, 30.7, 30.1, 15.9; IR (NaCl dep from CH_2Cl_2) 2980, 2858, 1721, 1494, 1088, 703 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{24}O_2$, 333.1855. Found 333.1850.

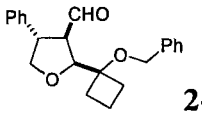


2-(1-Phenyl-cyclobutyl)-4-(2-phenyl-propenyl)-tetrahydro-furan-3-carbaldehyde (38). Isolated in 80% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.44 (1H, d, J = 3.2 Hz), 7.38-7.15 (10H, m), 5.56 (1H, d, J = 9.8 Hz), 4.77 (1H, d, J = 5.5 Hz), 3.81 (1H, dd, J = 7.7, 7.7 Hz), 3.63 (1H, dd, J = 7.57, 7.5 Hz), 2.86-2.79 (1H, m), 2.77-2.67 (1H, m), 2.57-2.48 (1H, m), 2.44-2.33 (2H, m), 2.23-2.05 (2H, m), 1.91-1.78 (4H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.5, 145.8, 143.0, 139.3, 128.4, 128.2, 127.5, 127.3, 126.5, 125.9, 122.7, 84.3, 73.7, 56.9, 49.5, 42.7, 30.5, 30.5, 16.6, 15.8; IR (NaCl dep from CH_2Cl_2) 2980, 2858, 1721, 1494, 1091, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{26}O_2$, 346.1933. Found 346.1930.

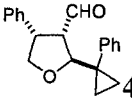


2-(1-Phenethyl-cyclobutyl)-4-phenyl-tetrahydro-furan-3-carbaldehyde (40). Isolated in 92% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.26 (1H, d, J = 3.6 Hz), 7.35-7.12 (10H, m), 4.52 (1H, d, J = 7.0 Hz), 4.31 (1H, dd, J = 9.0, 6.4 Hz), 4.13 (1H, dd, J = 8.5, 7.0 Hz), 3.78 (1H, ddd, J = 9.4, 6.6, 6.6 Hz), 3.09 (1H, ddd, J = 9.8, 7.0, 3.6 Hz), 2.70-2.52 (2H, m), 2.24-2.12 (1H, m), 2.08-1.98 (1H, m), 1.96-1.80 (4H, m), 1.78-1.68 (1H, m), 1.64-1.52 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.2, 142.9,

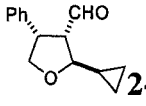
137.3, 129.2, 128.6, 128.6, 128.4, 127.6, 125.9, 82.2, 73.3, 56.9, 49.4, 44.9, 39.5, 30.6, 27.2, 26.9, 15.1; IR (NaCl dep from CH_2Cl_2) 2935, 2857, 1721, 1496, 1075, 700 cm^{-1}.



2-(1-Benzyloxy-cyclobutyl)-4-phenyl-tetrahydro-furan-3-carbaldehyde (42). Isolated in 65% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.74 (1H, d, J = 2.8 Hz), 7.32-7.18 (10H, m), 4.50 (2H, d, J = 6.2 Hz), 4.43 (1H, dd, J = 7.9, 7.9 Hz), 4.12 (1H, d, J = 6.8 Hz), 3.86 (1H, ddd, J = 7.2, 7.2, 3.8 Hz), 3.80 (1H, dd, 7.8, 7.8 Hz), 3.64 (1H, d, J = 9.6 Hz), 3.57 (1H, d, J = 9.6 Hz), 2.98 (1H, m), 2.42-2.32 (1H, m), 2.23-2.13 (1H, m), 1.92-1.68 (3H, m), 1.60-1.51 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.7, 141.9, 138.3, 129.0, 128.7, 128.0, 127.8, 127.1, 85.7, 74.8, 74.2, 73.7, 62.4, 45.4, 44.4, 27.3, 25.5, 15.3; IR (NaCl dep from CH_2Cl_2) 2938, 2858, 1716, 1495, 1075, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{24}O_3$, 351.1960. Found 351.1956.

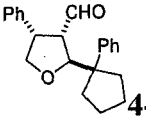


4-Phenyl-2-(1-phenyl-cyclopropyl)-tetrahydro-furan-3-carbaldehyde (44). Isolated in 90% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.13 (1H, d, J = 2.8 Hz), 7.43-7.09 (10H, m), 4.08 (1H, d, J = 7.5 Hz), 3.97 (1H, dd, J = 8.7, 4.9 Hz), 3.92 (1H, dd, J = 8.7, 6.1 Hz), 3.44-3.37 (1H, m), 3.17 (1H, ddd, J = 8.7, 8.7, 2.7 Hz), 1.06-0.99 (1H, m), 0.93-0.78 (3H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.2, 141.0, 138.2, 131.6, 129.1, 128.3, 128.2, 127.5, 127.3, 84.8, 73.7, 59.1, 48.1, 28.8, 11.9, 9.5; IR (NaCl dep from CH_2Cl_2) 3027, 2862, 1721, 1495, 1075, 702 cm^{-1}.



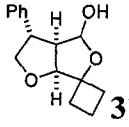
2-Cyclopropyl-4-phenyl-tetrahydro-furan-3-carbaldehyde (46). Isolated in 87% yield as a colorless oil. ^1H NMR (400 MHz $CDCl_3$) δ 9.25 (1H, d, J = 2.8 Hz),

7.34-7.18 (5H, m), 4.30 (1H, dd, J = 9.0, 6.4 Hz), 4.05 (1H, dd, J = 9.0, 5.5 Hz), 3.92-3.82 (2H, m), 3.23 (1H, ddd, J = 9.4, 7.0, 2.6 Hz), 1.04-0.94 (1H, m), 0.66-0.57 (1H, m), 0.51-0.41 (2H, m), 0.31-0.22 (1H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.3, 138.2, 129.2, 128.3, 127.6, 82.7, 73.6, 61.8, 48.2, 15.4, 3.7, 1.8; IR (NaCl dep from CH_2Cl_2) 3006, 2861, 1721, 1495, 1070, 703 cm^{-1}.



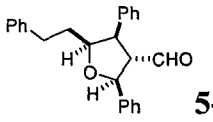
4-Phenyl-2-(1-phenyl-cyclopentyl)-tetrahydro-furan-3-carbaldehyde (48).

Isolated in 96% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 8.95 (1H, d, J = 3.4 Hz), 7.44-7.03 (10H, m), 4.60 (1H, d, J = 6.6 Hz), 3.96 (1H, dd, J = 8.5, 5.8 Hz), 3.81 (1H, dd, J = 8.7, 6.0 Hz), 3.09-3.02 (1H, m), 2.98-2.91 (1H, m), 2.30-2.21 (1H, m), 2.13-1.93 (2H, m), 1.86-1.53 (5H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.7, 143.8, 137.6, 129.0, 128.5, 128.2, 128.1, 127.4, 126.7, 83.7, 73.3, 58.0, 55.1, 48.4, 35.2, 35.0, 23.5, 23.5; IR (NaCl dep from CH_2Cl_2) 2958, 2870, 1722, 1495, 1079, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{24}O_2$, 321.1855. Found 321.1846.



3'-Phenylhexahydrospiro[cyclobutane-1,6'-cyclopenta[*b*]furan]-4'-ol (50).

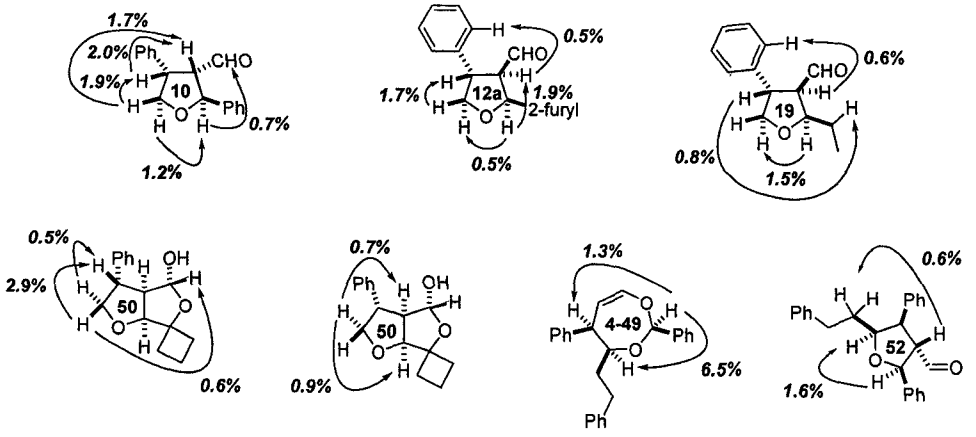
Isolated in 70% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.32-7.18 (5H, m), 5.29 (1H, s), 4.59 (1H, d, J = 6.8 Hz), 4.06 (1H, dd, J = 8.5, 6.5 Hz), 3.77 (1H, dd, J = 8.5, 6.2 Hz), 3.22 (1H, ddd, J = 6.1, 6.1, 5.4 Hz), 2.82 (1H, dd, J = 5.8, 5.8 Hz), 2.45-2.36 (1H, m), 2,23 (1H, ddd, J = 11.3, 10.2, 10.2 Hz), 1.88-1.76 (2H, m), 1.70-1.49 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 141.9, 129.0, 127.3, 127.0, 103.7, 87.4, 86.6, 74.8, 58.8, 50.4, 36.5, 29.0, 13.5; IR (NaCl dep from CH_2Cl_2) 2935, 1496, 1243, 1127, 1078, 698 cm^{-1}.

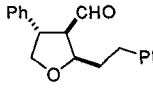


5-Phenethyl-2,4-diphenyl-tetrahydro-furan-3-carbaldehyde (52).

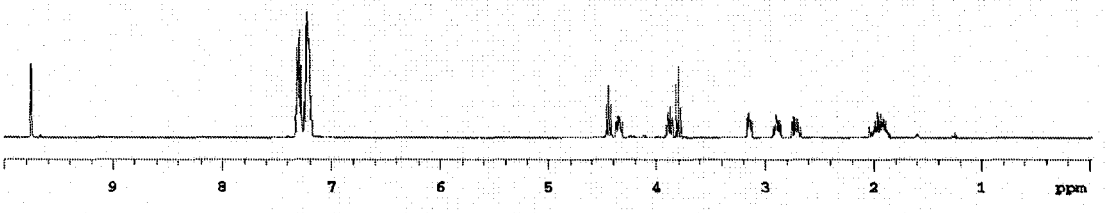
Isolated in 70% yield as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.32 (1H, d, J = 1.9 Hz), 7.44-7.11 (15H, m), 5.56 (1H, d, J = 7.3 Hz), 4.30 (1H, ddd, J = 7.9, 7.9, 4.3 Hz), 3.57 (1H, dd, J = 10.4, 8.1 Hz), 3.30 (1H, ddd, J = 10.7, 7.3, 1.7 Hz), 2.94-2.86 (1H, m), 2.76-2.67 (1H, m), 2.07-1.91 (2H, m); ^{13}C NMR (100 MHz $CDCl_3$) δ 201.4, 141.9, 141.6, 137.0, 129.3, 128.8, 128.8, 128.6, 128.0, 127.8, 126.2, 126.1, 84.2, 79.4, 64.4, 53.5, 36.3, 32.6; IR (NaCl dep from CH_2Cl_2) 3028, 2928, 1718, 1495, 1060, 700 cm^{-1}.

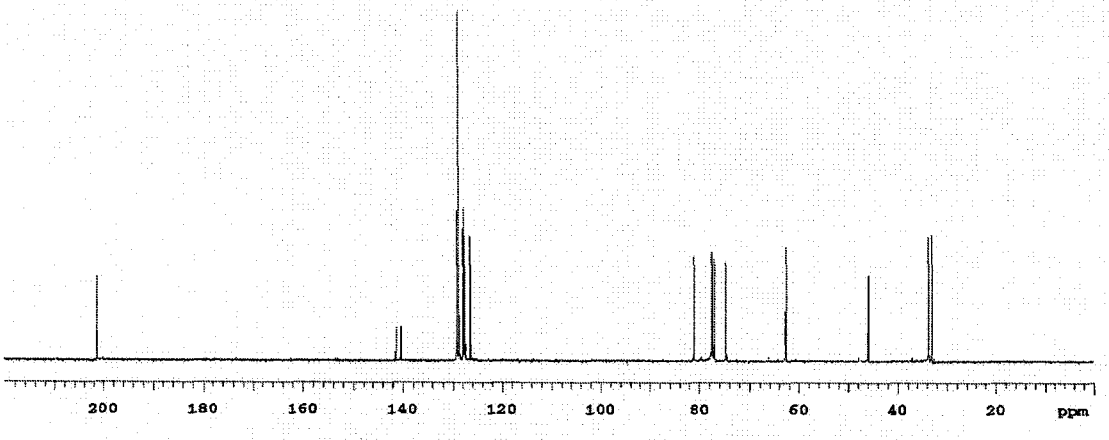
Stereochemical Assignment (nOe Experiments):

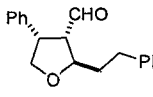




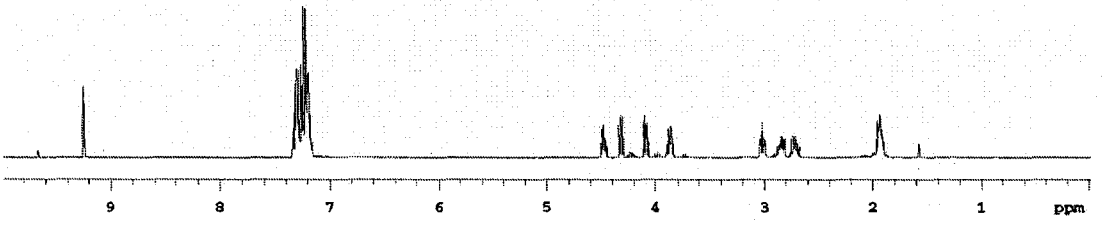
(16).

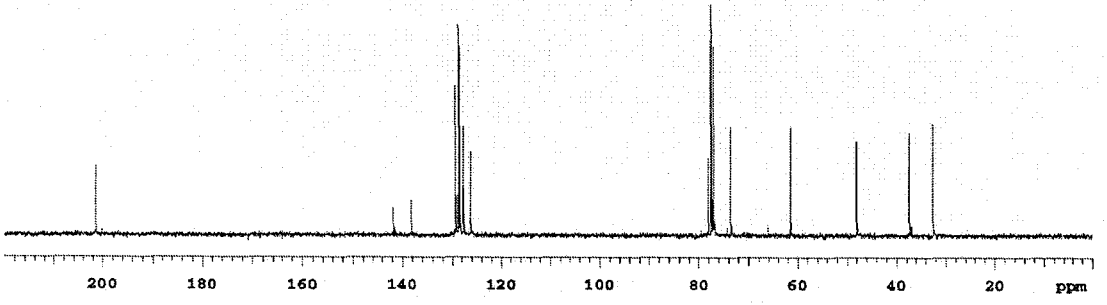


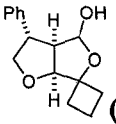




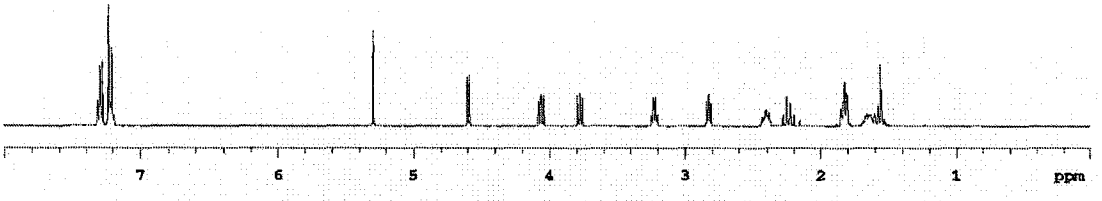
(16a).

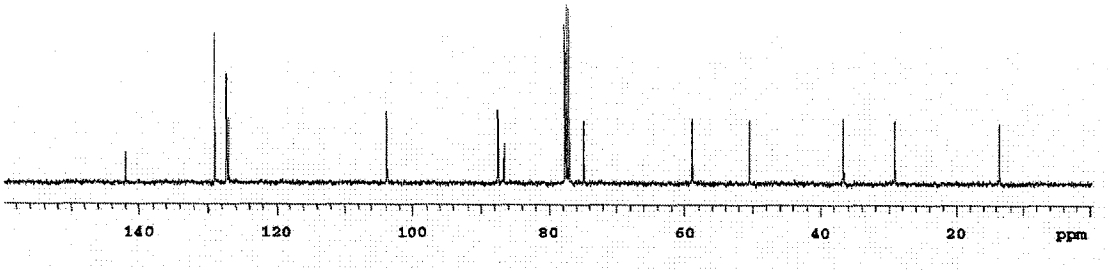


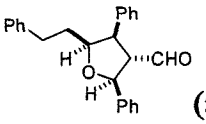




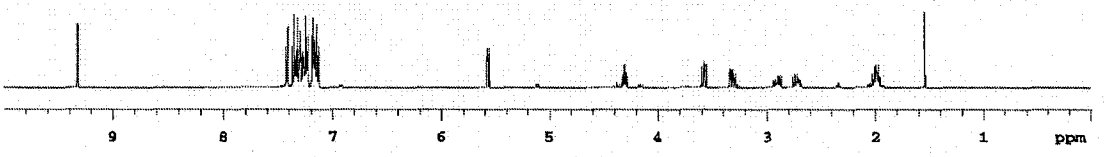
(50).

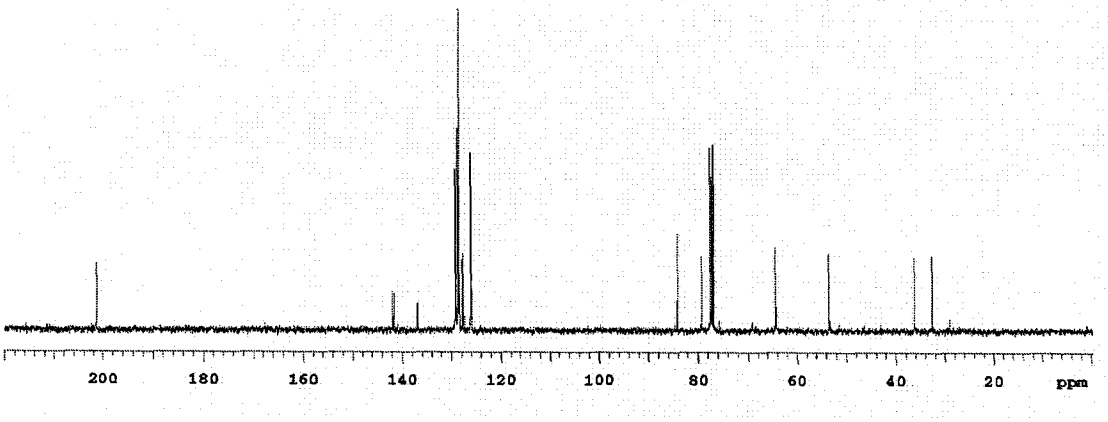






(52).





X-Ray Crystal Structure: Chapter 5, Tosylhydrazone of Compound 32.

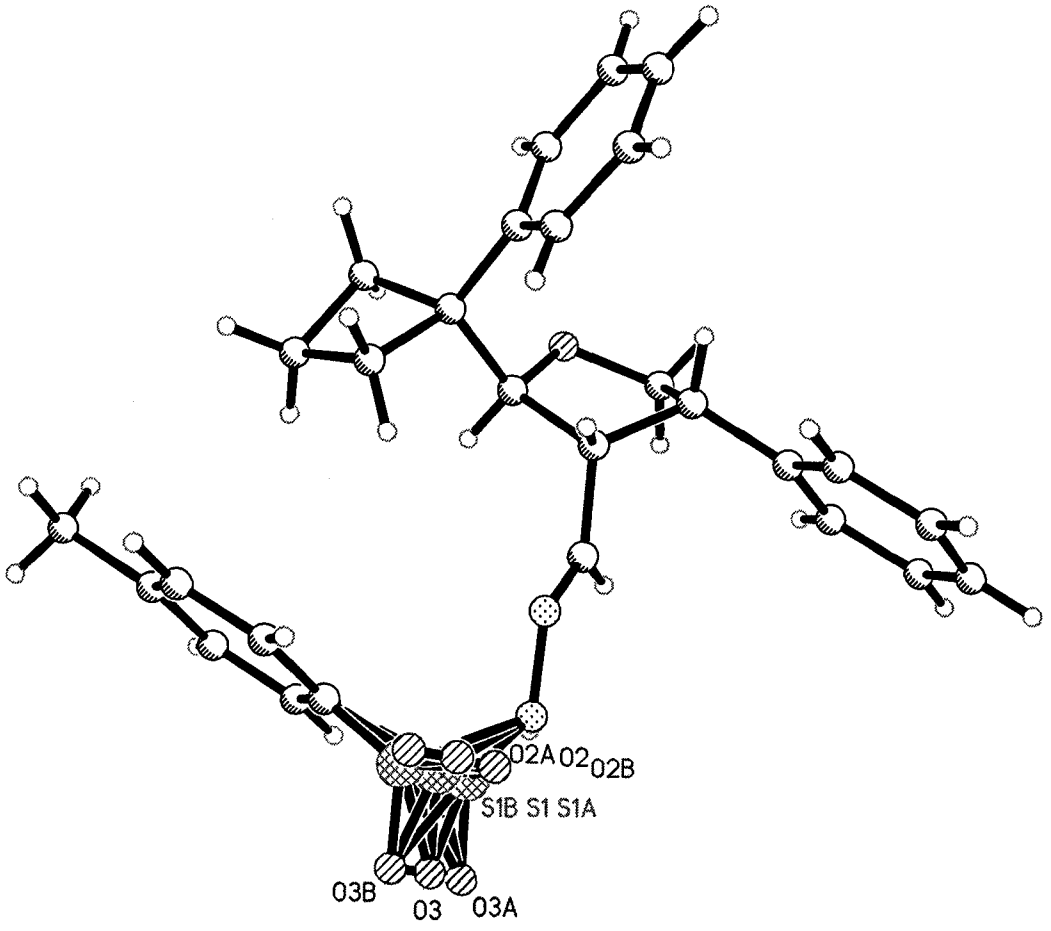


Table 1. Crystal data and structure refinement for rovis21.

Identification code	rovis21	
Empirical formula	C28 H30 N2 O3 S	
Formula weight	474.60	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 18.3685(6) Å	□= 90°.
	b = 6.0035(2) Å	□= 103.078(2)°.
	c = 22.7956(8) Å	□ = 90°.

Volume	2448.59(14) $Å^3$
Z	4
Density (calculated)	1.287 Mg/m^3
Absorption coefficient	0.165 mm^{-1}
F(000)	1008
Crystal size	0.46 x 0.10 x 0.06 mm^3
Theta range for data collection	1.83 to 30.60°.
Index ranges	-25<=h<=26, -8<=k<=8, -29<=l<=32
Reflections collected	34627
Independent reflections	7524 [R(int) = 0.0628]
Completeness to theta = 30.60°	99.7 %
Absorption correction	multi-scan
Max. and min. transmission	0.9897 and 0.9280
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7524 / 0 / 320
Goodness-of-fit on F^2	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0641, wR2 = 0.1405
R indices (all data)	R1 = 0.1192, wR2 = 0.1651
Largest diff. peak and hole	0.446 and -0.937 $e.Å^{-3}r$

Disorder of S, O2 O3 in three positions each. Refined isotropically.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rovis21. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	833(1)	7338(2)	4918(1)	20(1)
S(1A)	695(1)	7474(3)	4768(1)	11(1)
S(1B)	991(1)	7054(3)	5106(1)	12(1)
O(1)	2965(1)	15074(2)	4034(1)	25(1)
O(2)	1052(2)	5305(6)	4680(2)	31(1)
O(2A)	1246(3)	4989(8)	4918(2)	13(1)
O(2B)	882(3)	5472(8)	4492(2)	9(1)
O(3)	128(2)	7529(6)	5087(2)	24(1)
O(3A)	-18(3)	7694(10)	4922(3)	14(1)
O(3B)	291(3)	7205(9)	5289(2)	12(1)

N(1)	1476(1)	9400(3)	4222(1)	33(1)
N(2)	795(1)	9245(4)	4405(1)	41(1)
C(1)	2890(1)	12968(3)	4318(1)	20(1)
C(2)	2353(1)	11519(3)	3843(1)	20(1)
C(3)	2307(1)	12841(3)	3254(1)	23(1)
C(4)	2394(1)	15219(4)	3490(1)	30(1)
C(5)	3669(1)	11941(3)	4558(1)	19(1)
C(6)	4106(1)	13292(4)	5111(1)	25(1)
C(7)	3816(1)	11661(4)	5527(1)	31(1)
C(8)	3616(1)	10006(3)	4996(1)	27(1)
C(9)	4061(1)	11517(3)	4053(1)	18(1)
C(10)	4009(1)	9469(3)	3760(1)	24(1)
C(11)	4331(1)	9149(4)	3272(1)	32(1)
C(12)	4727(1)	10854(4)	3076(1)	33(1)
C(13)	4809(1)	12873(4)	3378(1)	29(1)
C(14)	4473(1)	13210(3)	3860(1)	23(1)
C(15)	1641(1)	12298(4)	2747(1)	27(1)
C(16)	1636(1)	10292(4)	2438(1)	36(1)
C(17)	1046(1)	9725(4)	1961(1)	39(1)
C(18)	452(1)	11164(4)	1784(1)	36(1)
C(19)	444(1)	13150(4)	2086(1)	37(1)
C(20)	1033(1)	13717(4)	2567(1)	32(1)
C(21)	1617(1)	11252(4)	4012(1)	28(1)
C(22)	1547(1)	8110(4)	5535(1)	45(1)
C(23)	1472(1)	10083(4)	5835(1)	41(1)
C(24)	2031(1)	10754(6)	6314(1)	51(1)
C(25)	2675(2)	9453(7)	6501(1)	71(1)
C(26)	2737(2)	7505(8)	6195(2)	93(2)
C(27)	2188(2)	6835(6)	5718(2)	76(1)
C(28)	3284(2)	10280(10)	7021(1)	118(2)

Table 3. Bond lengths [Å] and angles [°] for rovis21.

S(1)-O(2)	1.429(4)
S(1)-O(3)	1.436(4)
S(1)-O(3B)	1.447(5)

S(1)-O(2B)	1.498(5)
S(1)-O(3A)	1.580(6)
S(1)-O(2A)	1.601(5)
S(1)-N(2)	1.627(3)
S(1)-C(22)	1.754(3)
S(1A)-S(1B)	0.874(3)
S(1A)-N(2)	1.385(3)
S(1A)-O(3)	1.398(4)
S(1A)-O(2B)	1.434(5)
S(1A)-O(3A)	1.437(6)
S(1A)-O(2)	1.492(4)
S(1A)-O(3B)	1.545(5)
S(1A)-O(2A)	1.792(6)
S(1A)-C(22)	2.101(4)
S(1B)-C(22)	1.395(3)
S(1B)-O(2A)	1.425(5)
S(1B)-O(3B)	1.441(5)
S(1B)-O(2)	1.452(4)
S(1B)-O(3)	1.601(4)
S(1B)-O(2B)	1.666(5)
S(1B)-O(3A)	1.846(6)
S(1B)-N(2)	2.039(3)
O(1)-C(4)	1.434(2)
O(1)-C(1)	1.440(2)
O(2)-O(2A)	0.608(5)
O(2A)-O(2B)	1.088(7)
O(3)-O(3B)	0.527(5)
O(3A)-O(3B)	0.945(8)
N(1)-C(21)	1.260(3)
N(1)-N(2)	1.409(2)
C(1)-C(5)	1.542(2)
C(1)-C(2)	1.554(3)
C(2)-C(21)	1.497(2)
C(2)-C(3)	1.545(3)
C(3)-C(15)	1.516(3)
C(3)-C(4)	1.521(3)

C(5)-C(9)	1.512(3)
C(5)-C(8)	1.549(3)
C(5)-C(6)	1.559(3)
C(6)-C(7)	1.539(3)
C(7)-C(8)	1.545(3)
C(9)-C(10)	1.392(3)
C(9)-C(14)	1.397(3)
C(10)-C(11)	1.387(3)
C(11)-C(12)	1.387(3)
C(12)-C(13)	1.386(3)
C(13)-C(14)	1.391(3)
C(15)-C(20)	1.391(3)
C(15)-C(16)	1.393(3)
C(16)-C(17)	1.393(3)
C(17)-C(18)	1.379(3)
C(18)-C(19)	1.378(3)
C(19)-C(20)	1.397(3)
C(22)-C(27)	1.387(4)
C(22)-C(23)	1.391(3)
C(23)-C(24)	1.379(4)
C(24)-C(25)	1.401(4)
C(25)-C(26)	1.379(6)
C(25)-C(28)	1.517(5)
C(26)-C(27)	1.367(6)

O(2)-S(1)-O(3)	121.2(2)
O(2)-S(1)-O(3B)	117.7(3)
O(3)-S(1)-O(3B)	21.1(2)
O(2)-S(1)-O(2B)	18.7(2)
O(3)-S(1)-O(2B)	115.0(3)
O(3B)-S(1)-O(2B)	119.2(3)
O(2)-S(1)-O(3A)	118.8(3)
O(3)-S(1)-O(3A)	15.1(2)
O(3B)-S(1)-O(3A)	36.1(3)
O(2B)-S(1)-O(3A)	108.0(3)
O(2)-S(1)-O(2A)	22.25(18)

O(3)-S(1)-O(2A)	121.7(2)
O(3B)-S(1)-O(2A)	109.9(3)
O(2B)-S(1)-O(2A)	40.9(3)
O(3A)-S(1)-O(2A)	126.1(3)
O(2)-S(1)-N(2)	107.36(19)
O(3)-S(1)-N(2)	104.0(2)
O(3B)-S(1)-N(2)	122.4(2)
O(2B)-S(1)-N(2)	93.4(2)
O(3A)-S(1)-N(2)	91.6(2)
O(2A)-S(1)-N(2)	124.3(2)
O(2)-S(1)-C(22)	107.8(2)
O(3)-S(1)-C(22)	108.64(19)
O(3B)-S(1)-C(22)	91.9(2)
O(2B)-S(1)-C(22)	125.0(2)
O(3A)-S(1)-C(22)	121.4(2)
O(2A)-S(1)-C(22)	87.9(2)
N(2)-S(1)-C(22)	107.06(12)
S(1B)-S(1A)-N(2)	127.5(2)
S(1B)-S(1A)-O(3)	86.3(2)
N(2)-S(1A)-O(3)	120.5(2)
S(1B)-S(1A)-O(2B)	89.0(3)
N(2)-S(1A)-O(2B)	107.7(2)
O(3)-S(1A)-O(2B)	121.9(3)
S(1B)-S(1A)-O(3A)	103.3(3)
N(2)-S(1A)-O(3A)	109.1(3)
O(3)-S(1A)-O(3A)	17.0(2)
O(2B)-S(1A)-O(3A)	120.4(3)
S(1B)-S(1A)-O(2)	70.2(2)
N(2)-S(1A)-O(2)	117.9(2)
O(3)-S(1A)-O(2)	119.5(2)
O(2B)-S(1A)-O(2)	18.8(2)
O(3A)-S(1A)-O(2)	124.5(3)
S(1B)-S(1A)-O(3B)	66.6(2)
N(2)-S(1A)-O(3B)	133.8(3)
O(3)-S(1A)-O(3B)	19.8(2)
O(2B)-S(1A)-O(3B)	117.0(3)

O(3A)-S(1A)-O(3B)	36.7(3)
O(2)-S(1A)-O(3B)	108.3(3)
S(1B)-S(1A)-O(2A)	51.6(2)
N(2)-S(1A)-O(2A)	127.4(2)
O(3)-S(1A)-O(2A)	112.0(3)
O(2B)-S(1A)-O(2A)	37.4(3)
O(3A)-S(1A)-O(2A)	122.4(3)
O(2)-S(1A)-O(2A)	18.62(18)
O(3B)-S(1A)-O(2A)	96.6(3)
S(1B)-S(1A)-C(22)	28.43(15)
N(2)-S(1A)-C(22)	100.59(14)
O(3)-S(1A)-C(22)	93.7(2)
O(2B)-S(1A)-C(22)	108.1(2)
O(3A)-S(1A)-C(22)	109.2(3)
O(2)-S(1A)-C(22)	90.1(2)
O(3B)-S(1A)-C(22)	77.0(2)
O(2A)-S(1A)-C(22)	73.10(19)
S(1A)-S(1B)-C(22)	134.2(2)
S(1A)-S(1B)-O(2A)	99.6(3)
C(22)-S(1B)-O(2A)	111.5(3)
S(1A)-S(1B)-O(3B)	79.6(3)
C(22)-S(1B)-O(3B)	109.2(2)
O(2A)-S(1B)-O(3B)	121.1(3)
S(1A)-S(1B)-O(2)	75.2(2)
C(22)-S(1B)-O(2)	129.9(2)
O(2A)-S(1B)-O(2)	24.40(19)
O(3B)-S(1B)-O(2)	116.6(3)
S(1A)-S(1B)-O(3)	60.6(2)
C(22)-S(1B)-O(3)	120.1(2)
O(2A)-S(1B)-O(3)	122.5(3)
O(3B)-S(1B)-O(3)	19.0(2)
O(2)-S(1B)-O(3)	109.6(2)
S(1A)-S(1B)-O(2B)	59.4(2)
C(22)-S(1B)-O(2B)	141.0(2)
O(2A)-S(1B)-O(2B)	40.3(3)
O(3B)-S(1B)-O(2B)	109.5(3)

O(2)-S(1B)-O(2B)	15.9(2)
O(3)-S(1B)-O(2B)	98.5(2)
S(1A)-S(1B)-O(3A)	49.3(2)
C(22)-S(1B)-O(3A)	127.1(2)
O(2A)-S(1B)-O(3A)	119.6(3)
O(3B)-S(1B)-O(3A)	30.4(3)
O(2)-S(1B)-O(3A)	103.0(3)
O(3)-S(1B)-O(3A)	11.4(2)
O(2B)-S(1B)-O(3A)	90.2(3)
S(1A)-S(1B)-N(2)	32.61(15)
C(22)-S(1B)-N(2)	103.17(15)
O(2A)-S(1B)-N(2)	109.7(2)
O(3B)-S(1B)-N(2)	100.1(2)
O(2)-S(1B)-N(2)	88.20(19)
O(3)-S(1B)-N(2)	82.25(17)
O(2B)-S(1B)-N(2)	75.1(2)
O(3A)-S(1B)-N(2)	72.4(2)
C(4)-O(1)-C(1)	108.40(14)
O(2A)-O(2)-S(1)	95.0(7)
O(2A)-O(2)-S(1B)	75.4(6)
S(1)-O(2)-S(1B)	19.62(9)
O(2A)-O(2)-S(1A)	109.9(7)
S(1)-O(2)-S(1A)	14.97(10)
S(1B)-O(2)-S(1A)	34.53(14)
O(2)-O(2A)-O(2B)	3.1(6)
O(2)-O(2A)-S(1B)	80.2(7)
O(2B)-O(2A)-S(1B)	81.9(4)
O(2)-O(2A)-S(1)	62.8(6)
O(2B)-O(2A)-S(1)	64.4(4)
S(1B)-O(2A)-S(1)	17.46(10)
O(2)-O(2A)-S(1A)	51.5(6)
O(2B)-O(2A)-S(1A)	53.1(3)
S(1B)-O(2A)-S(1A)	28.75(14)
S(1)-O(2A)-S(1A)	11.35(9)
O(2A)-O(2B)-S(1A)	89.5(4)
O(2A)-O(2B)-S(1)	74.6(4)

S(1A)-O(2B)-S(1)	14.90(10)
O(2A)-O(2B)-S(1B)	57.9(3)
S(1A)-O(2B)-S(1B)	31.65(15)
S(1)-O(2B)-S(1B)	16.80(9)
O(3B)-O(3)-S(1A)	96.0(8)
O(3B)-O(3)-S(1)	80.7(8)
S(1A)-O(3)-S(1)	15.56(10)
O(3B)-O(3)-S(1B)	63.1(7)
S(1A)-O(3)-S(1B)	33.03(14)
S(1)-O(3)-S(1B)	17.56(9)
O(3B)-O(3A)-S(1A)	77.9(4)
O(3B)-O(3A)-S(1)	64.3(4)
S(1A)-O(3A)-S(1)	13.65(11)
O(3B)-O(3A)-S(1B)	50.4(4)
S(1A)-O(3A)-S(1B)	27.45(15)
S(1)-O(3A)-S(1B)	13.89(9)
O(3)-O(3B)-O(3A)	3.8(8)
O(3)-O(3B)-S(1B)	97.8(8)
O(3A)-O(3B)-S(1B)	99.2(5)
O(3)-O(3B)-S(1)	78.2(8)
O(3A)-O(3B)-S(1)	79.6(4)
S(1B)-O(3B)-S(1)	19.58(10)
O(3)-O(3B)-S(1A)	64.1(7)
O(3A)-O(3B)-S(1A)	65.4(4)
S(1B)-O(3B)-S(1A)	33.82(16)
S(1)-O(3B)-S(1A)	14.32(10)
C(21)-N(1)-N(2)	116.31(19)
S(1A)-N(2)-N(1)	118.3(2)
S(1A)-N(2)-S(1)	11.47(10)
N(1)-N(2)-S(1)	111.22(18)
S(1A)-N(2)-S(1B)	19.89(10)
N(1)-N(2)-S(1B)	105.23(16)
S(1)-N(2)-S(1B)	8.44(8)
O(1)-C(1)-C(5)	109.57(14)
O(1)-C(1)-C(2)	106.80(14)
C(5)-C(1)-C(2)	114.56(16)

C(21)-C(2)-C(3)	113.79(16)
C(21)-C(2)-C(1)	110.35(15)
C(3)-C(2)-C(1)	102.68(15)
C(15)-C(3)-C(4)	118.30(16)
C(15)-C(3)-C(2)	115.43(16)
C(4)-C(3)-C(2)	101.18(15)
O(1)-C(4)-C(3)	104.30(15)
C(9)-C(5)-C(1)	111.11(14)
C(9)-C(5)-C(8)	118.36(16)
C(1)-C(5)-C(8)	109.90(15)
C(9)-C(5)-C(6)	117.20(14)
C(1)-C(5)-C(6)	110.25(16)
C(8)-C(5)-C(6)	88.01(14)
C(7)-C(6)-C(5)	88.92(14)
C(6)-C(7)-C(8)	88.86(14)
C(7)-C(8)-C(5)	89.10(15)
C(10)-C(9)-C(14)	118.33(17)
C(10)-C(9)-C(5)	121.42(17)
C(14)-C(9)-C(5)	120.23(17)
C(11)-C(10)-C(9)	120.78(19)
C(12)-C(11)-C(10)	120.4(2)
C(13)-C(12)-C(11)	119.45(19)
C(12)-C(13)-C(14)	120.1(2)
C(13)-C(14)-C(9)	120.83(19)
C(20)-C(15)-C(16)	117.86(18)
C(20)-C(15)-C(3)	123.25(19)
C(16)-C(15)-C(3)	118.88(18)
C(15)-C(16)-C(17)	121.4(2)
C(18)-C(17)-C(16)	119.9(2)
C(19)-C(18)-C(17)	119.6(2)
C(18)-C(19)-C(20)	120.6(2)
C(15)-C(20)-C(19)	120.7(2)
N(1)-C(21)-C(2)	117.90(19)
C(27)-C(22)-C(23)	119.6(3)
C(27)-C(22)-S(1B)	113.4(3)
C(23)-C(22)-S(1B)	126.4(2)

C(27)-C(22)-S(1)	121.7(3)
C(23)-C(22)-S(1)	118.70(19)
S(1B)-C(22)-S(1)	12.30(10)
C(27)-C(22)-S(1A)	124.9(3)
C(23)-C(22)-S(1A)	115.23(19)
S(1B)-C(22)-S(1A)	17.36(11)
S(1)-C(22)-S(1A)	5.06(8)
C(24)-C(23)-C(22)	119.9(2)
C(23)-C(24)-C(25)	120.3(3)
C(26)-C(25)-C(24)	118.7(3)
C(26)-C(25)-C(28)	122.8(3)
C(24)-C(25)-C(28)	118.5(4)
C(27)-C(26)-C(25)	121.4(3)
C(26)-C(27)-C(22)	120.0(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for rovis21. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	16(1)	29(1)	0(1)	3(1)	1(1)
N(1)	22(1)	40(1)	42(1)	-22(1)	21(1)	-13(1)
N(2)	27(1)	49(1)	55(1)	-32(1)	29(1)	-18(1)
C(1)	21(1)	19(1)	23(1)	-2(1)	9(1)	-1(1)
C(2)	19(1)	20(1)	24(1)	-4(1)	8(1)	1(1)
C(3)	24(1)	21(1)	24(1)	-1(1)	6(1)	5(1)
C(4)	34(1)	23(1)	29(1)	-1(1)	0(1)	6(1)
C(5)	20(1)	16(1)	22(1)	0(1)	7(1)	-3(1)
C(6)	26(1)	25(1)	24(1)	-2(1)	6(1)	-3(1)
C(7)	34(1)	36(1)	23(1)	5(1)	8(1)	-1(1)
C(8)	29(1)	22(1)	31(1)	7(1)	10(1)	-3(1)
C(9)	15(1)	20(1)	21(1)	2(1)	5(1)	1(1)
C(10)	19(1)	21(1)	34(1)	-3(1)	8(1)	0(1)
C(11)	28(1)	34(1)	34(1)	-10(1)	7(1)	7(1)
C(12)	30(1)	48(2)	25(1)	0(1)	13(1)	9(1)
C(13)	26(1)	34(1)	29(1)	8(1)	12(1)	1(1)

C(14)	22(1)	22(1)	24(1)	1(1)	7(1)	-2(1)
C(15)	30(1)	26(1)	24(1)	-1(1)	6(1)	2(1)
C(16)	47(1)	28(1)	27(1)	-2(1)	-2(1)	11(1)
C(17)	54(1)	31(1)	27(1)	-3(1)	-2(1)	-1(1)
C(18)	34(1)	43(2)	29(1)	3(1)	2(1)	-8(1)
C(19)	26(1)	42(2)	41(1)	1(1)	3(1)	3(1)
C(20)	30(1)	30(1)	37(1)	-6(1)	6(1)	5(1)
C(21)	18(1)	37(1)	28(1)	-13(1)	7(1)	-1(1)
C(22)	55(2)	30(1)	68(2)	14(1)	53(1)	8(1)
C(23)	36(1)	44(2)	49(1)	4(1)	23(1)	10(1)
C(24)	36(1)	81(2)	39(1)	12(1)	16(1)	16(1)
C(25)	45(2)	134(3)	43(2)	47(2)	31(1)	36(2)
C(26)	83(2)	130(4)	89(3)	74(3)	64(2)	74(3)
C(27)	93(2)	53(2)	108(3)	40(2)	79(2)	43(2)
C(28)	44(2)	275(6)	39(2)	45(3)	16(1)	48(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for rovis21.

	x	y	z	U(eq)
HA	599(13)	10430(40)	4491(11)	37(7)
H(1B)	2656	13228	4658	24
H(2C)	2578	10055	3813	24
H(3B)	2757	12484	3110	28
H(4A)	2546	16204	3202	36
H(4B)	1930	15763	3572	36
H(6A)	4644	13259	5159	30
H(6B)	3928	14806	5129	30
H(7A)	3387	12207	5665	37
H(7B)	4201	11123	5862	37
H(8A)	3119	9375	4941	32
H(8B)	3987	8849	5005	32
H(10A)	3756	8301	3894	29
H(11A)	4282	7782	3075	38

H(12A)	4935	10645	2744	39
H(13A)	5090	14005	3259	34
H(14A)	4524	14579	4055	27
H(16A)	2035	9312	2554	43
H(17A)	1053	8376	1762	47
H(18A)	59	10798	1464	43
H(19A)	43	14121	1969	44
H(20A)	1018	15056	2769	39
H(21A)	1275	12416	3964	33
H(23A)	1045	10949	5713	49
H(24A)	1981	12076	6514	61
H(26A)	3162	6629	6317	112
H(27A)	2244	5524	5515	91
H(28A)	3701	9277	7084	177
H(28B)	3093	10349	7379	177
H(28C)	3442	11738	6929	177

Chapter 6 Experimental

[1, 3] Rearrangement of 1,3-Dioxepins: A Rapid Total Synthesis of (+/-)-Sylvone and an Approach to Lophirone H

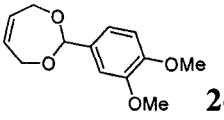
General Methods: All reactions were performed under an inert atmosphere of argon in flame-dried glassware with magnetic stirring. Acetonitrile (ACS grade) and propionitrile were purchased from Fisher Scientific and distilled from CaH_2 before use. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate followed by heating.

TMSOTf was purchased from Fluka and was used as a 0.2M stock solution in acetonitrile or propionitrile and used within five days. All other chemicals were purchased from Aldrich Chemical Co. and used without further purification.

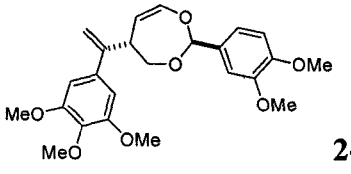
^1H NMR spectra are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.23 ppm. Mass spectra were obtained on Fisons VG Autospec.

Procedure for the stereoselective ring contraction of (11). The ring contraction was performed on a 0.66 mmol scale. A flame-dried round-bottom flask was purged with argon then charged with propionitrile (0.1 M with respect to 1,3-dioxepin) and 0.1 eq. of TMSOTf. The solution was cooled to -78 °C. A separate flame-dried round-bottomed flask was purged with argon and charged with propionitirile (0.1 M with respect to 1,3-

dioxepin) and 1 eq. of **11**. The solution was then cooled to -78 °C. The solution containing **11** was transferred via cannula to the solution containing Lewis acid at an approximate rate of 1 ml/min. The solution was allowed to mix for 1h at -78 °C. When the reaction was complete the Lewis acid was quenched with 1 eq. of NEt_3 and subsequently poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted 3 x Et_2O, then the organic layer was dried with $MgSO_4$. After filtration the solvent removed in *vacuo* and the crude product was carried through the remainder of the synthetic steps to afford **1** (+/-)-sylvone.

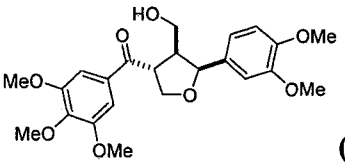


2-(3,4-Dimethoxy-phenyl)-4,7-dihydro-[1,3]dioxepine (9). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.08-7.02 (2H m), 6.84 (1H, d, J = 8.1 Hz), 5.79 (1H, s), 5.75 (2H, s), 4.41-4.19 (4H, m), 3.88 (3H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 149.2, 148.9, 131.8, 130.2, 118.9, 110.8, 109.7, 102.3, 64.7. 56.1; IR (NaCl dep from $CHCl_3$) 2942, 2837, 1516, 1259, 1160, 777 cm^{-1}.

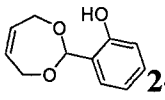


2-(3,4-Dimethoxy-phenyl)-5-[1-(3,4,5-trimethoxy-phenyl)-vinyl]-4,5-dihydro-[1,3]dioxepine (11). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.08-7.02 (2H, m), 6.84 (1H, d, J = 8.3 Hz), 6.62 (2H, s), 6.53 (1H, dd, J = 7.5, 3.0 Hz), 5.49 (1H, s), 5.38 (1H, s), 5.19 (1H, s), 5.01 (1H, d, J = 7.3 Hz), 4.23 (1H, d, J = 11.5, 4.5 Hz), 3.94-3.82 (16H, m), 3.38 (1H, dd, J = 11.1, 11.1 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 153.3, 149.6, 149.1, 148.4, 145.3, 138.2, 136.9, 131.6, 118.7, 114.2, 113.3, 110.9, 109.0, 106.4, 103.9,

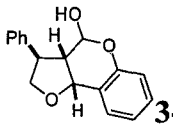
74.4, 61.1, 56.4, 56.2, 56.1, 46.9; IR (NaCl dep from $CHCl_3$) 2937, 2836, 1645, 1411, 1128, 732 cm^{-1}; HRMS (+TOF MS) calcd for $C_{24}H_{28}O_7$, 428.4700. Found 429.1893.



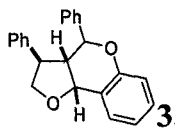
(+/-)-Sylvone (1). ^1H NMR (400 MHz $CDCl_3$) δ 7.41 (2H, s), 6.84 (3H, m), 5.03, (1H, d, J = 6.0 Hz), 4.43 (1H, dd, J = 7.9, 7.9 Hz), 4.24 (1H, dd, J = 8.1, 5.8 Hz), 3.96-3.77 (15H, m), 3.41 (1H, d, J = 6.4 Hz), 2.89 (1H, ddd, J = 6.2, 6.0, 2.8 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 198.7, 153.3, 149.1, 148.4, 142.9, 131.5, 130.6, 117.9, 111.2, 108.9, 106.4, 81.5, 69.1, 62.1, 61.1, 56.4, 56.0, 49.9, 48.9; IR (NaCl dep from $CHCl_3$) 3516, 2941, 1673, 1516, 1127, 731 cm^{-1}; MS (EI+ MS) calcd for $C_{23}H_{28}O_8$, 432.46. Found 433.3.



2-(4,7-Dihydro-[1,3]dioxepin-2-yl)-phenol (21). ^1H NMR (400 MHz $CDCl_3$) δ 8.15 (1H, s), 7.31-7.21 (2H, m), 6.92-6.86 (2H, m), 6.03 (1H, s), 5.79 (2H, s), 4.52-4.30 (4H, m).

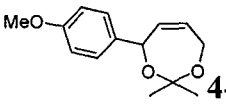


3-Phenyl-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-ol (22). ^1H NMR (400 MHz $CDCl_3$) δ 7.50-6.70 (9H, m), 5.27 (1H, d, J = 5.1 Hz), 4.25 (1H, dd, J = 8.8, 8.8 Hz), 3.90 (1H, dd, J = 8.4, 8.4 Hz), 3.46 (1H, ddd, J = 8.1, 8.1, 8.0 Hz), 3.10 (1H, d, J = 4.8 Hz), 2.74 (1H, ddd, J = 7.7, 7.7, 4.8 Hz), 1.58 (1H, s).

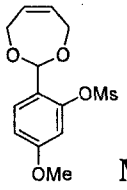


3,4-Diphenyl-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromene (24). ^1H NMR (400 MHz $CDCl_3$) δ 7.53-6.83 (14H, m), 6.19 (1H, d, J = 2.2 Hz), 5.55 (1H, d, J =

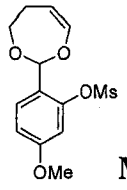
7.7 Hz), 4.18 (1H, dd, J = 8.4, 8.4 Hz), 3.97 (1H, dd, J = 8.4, 8.4 Hz), 3.43 (1H, ddd, J = 10.3, 10.3, 8.4 Hz), 3.16 (1H, ddd, J = 9.9, 7.7, 1.8 Hz).



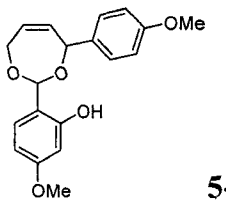
4-(4-Methoxy-phenyl)-2,2-dimethyl-4,7-dihydro-[1,3]dioxepine (28). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.32-7.23 (2H, m), 6.92-6.84 (2H, m), 5.75 (2H, s), 5.55 (1H, d, J = 3.7 Hz), 4.63 (1H, dd, J = 16.5, 4.0 Hz), 4.10 (1H, dd, J = 16.5, 2.2 Hz), 3.80 (3H, s), 1.54 (3H, s), 1.47 (3H, s).



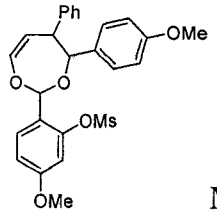
Methanesulfonic acid 2-(4,7-dihydro-[1,3]dioxepin-2-yl)-5-methoxy-phenyl ester (29). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.65 (1H, d, J = 8.8 Hz), 7.00 (1H, d, J = 2.6 Hz), 6.84 (1H, dd, J = 8.4, 2.6 Hz), 6.00 (1H, s), 5.77 (2H, s), 4.43-4.20 (4H, m), 3.82 (3H, s), 3.21 (3H, s).



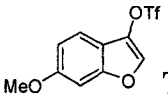
Methanesulfonic acid 2-(4,5-dihydro-[1,3]dioxepin-2-yl)-5-methoxy-phenyl ester (30). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.67 (1H, d, J =8.8 Hz), 6.90 (1H, d, J = 2.2 Hz), 6.87 (1H, dd, J = 8.4, 2.2 Hz), 6.45 (1H, dd, J = 7.0, 2.9 Hz), 5.62 (1H, s), 5.01 (1H, ddd, J = 7.3, 7.3, 2.6 Hz), 4.25-4.18 (1H, m), 3.82 (3H, s), 3.51 (1H, ddd, J = 11.7, 11.7, 2.2 Hz), 3.15 (3H, s), 2.62-2.55 (1H, m), 2.30-2.21 (1H, m).



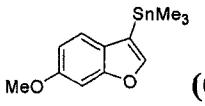
5-Methoxy-2-[4-(4-methoxy-phenyl)-4,7-dihydro-[1,3]dioxepin-2-yl]-phenol (32). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.21 (1H, s), 7.26-7.21 (2H, m), 7.13 (1H, d, J = 8.1 Hz), 6.91-6.86 (2H, m), 6.44-6.41 (2H, m), 5.96-5.81 (3H, m), 5.50-5.45 (1H, m), 4.62-4.49 (2H, m), 3.81 (3H, s), 3.78 (3H, s).



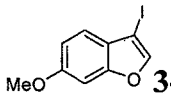
Methanesulfonic acid 5-methoxy-2-[4-(4-methoxy-phenyl)-5-phenyl-4,5-dihydro-[1,3]dioxepin-2-yl]-phenyl ester (33). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.80-6.60 (12H, m), 6.18 (1H, s), 5.75 (1H, d, J = 7.0 Hz), 5.06 (1H, dd, J = 6.6, 3.7 Hz), 4.36 (1H, dd, J = 7.0, 4.8 Hz), 3.95-3.88 (1H, m), 3.84 (3H, s), 3.81 (3H, s), 3.04 (3H, s).



Trifluoro-methanesulfonic acid 6-methoxy-benzofuran-3-yl ester (36). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.72 (1H, s), 7.46 (1H, d, J = 8.4 Hz), 6.98 (2H, m), 3.86 (3H, s).

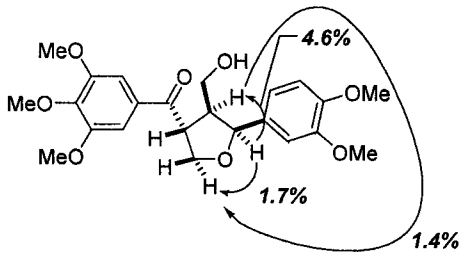


(6-Methoxy-benzofuran-3-yl)-trimethyl-stannane (37). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.54-7.26 (2H, m), 7.06 (1H, dd, J = 7.7, 2.2 Hz), 6.88 (1H, m), 3.85 (3H, s), 0.38 (9H, s).

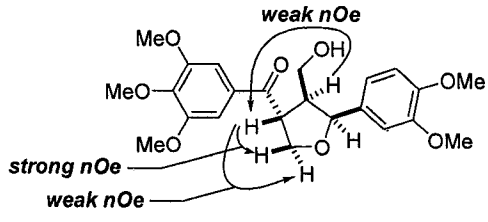


3-Iodo-6-methoxy-benzofuran (38). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.55 (1H, s), 7.26 (1H, d, J = 1.8 Hz), 6.96 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 8.8, 2.2 Hz), 3.87 (3H, s).

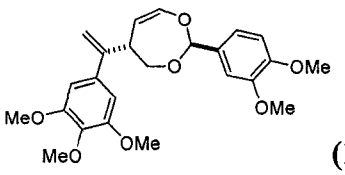
Stereochemical Assignment (nOe Experiments):



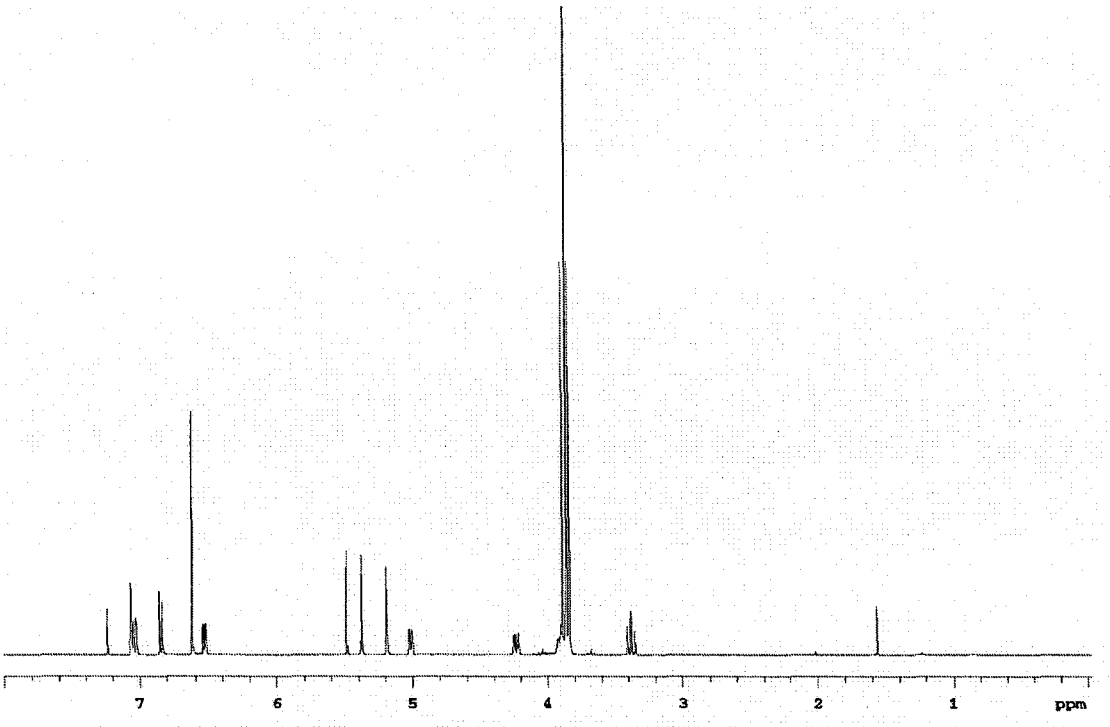
data from 1D nOe

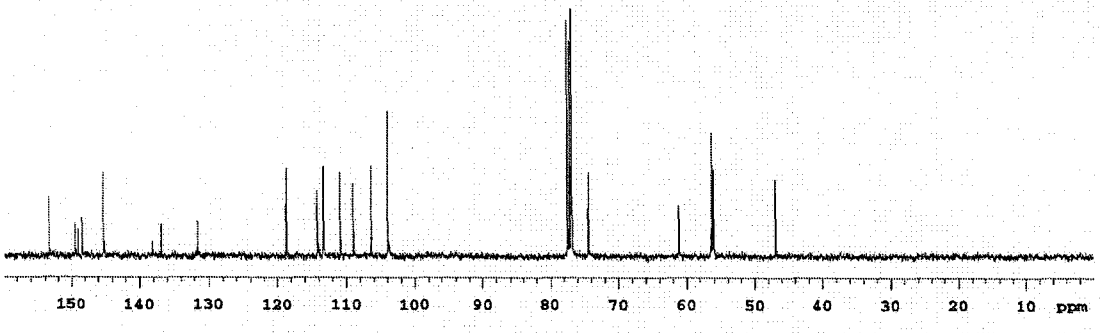


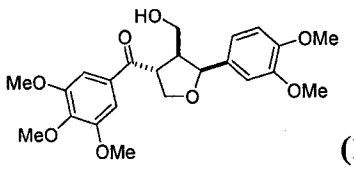
data from 2D nOe



(11).







(1).