# Methodology Studies on One and Two Carbon Ring Expansion on Polyether Polycyclic Natural Products

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## Abstract

Medium sized cyclic ethers are found in many natural products, with the most notable example being the polyether polycyclic family of marine toxins. Due to their increased size loss of entropy, torsional strain and unfavourable transannular interactions, as well as other effects require different synthetic approaches than the smaller homologues. In this work, different pathways were explored for the efficient synthesis of the seven-, eight- and nine- membered rings of marine polyether polycyclic natural products, through the expansion of a common six-membered ether substrate. The effect of the Lewis acid promoted TMS-diazomethane ring expansion of cyclic ketones was investigated and was successfully applied for the efficient synthesis of the oxepane and oxocane ring systems. Furthemore, a [2+2] cycloaddition between a seven-membered cyclic silyl enol ether and ethyl propiolate was examined for the concise formation of nine-membered cyclic ethers from an easily accessible substrate.

## Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I further declare that the work presented in this manuscript is the result of my own investigation. Where the work of others has been utilized, this has been acknowledged in the appropriate manner.

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Prof. J. Stephen Clark

## Acknowledgements

First of all, I would like to thank my supervisor Prof. Stephen J. Clark for giving me the opportunity to join his group and work on this exciting project. During my time in the University of Glasgow his guidance, support and encouragement have been of great value. It has been an honor to have been one of his students.

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Finally, I would like to thank all the technicians and everyone behind the scenes who made everything work so smoothly. While I do not know many of you by name, I know that your work has been very helpful to mine. Thank you for that.

This list would not be complete without thanking my family and friends for their support, especially when things were not as great as imagined. Most importantly I would like to thank my partner, Anastasia. Thank you for being there for this journey and still keeping me going.

## Abbreviations

| | |
|---|---|
| 2,6 lutidine | 2,6-dimethylpyridine |
| AIBN | azobisisobutyronitrile |
| Cat. | catalyst |
| CSA | camphorsulfonic acid |
| DAD | dimethylaluminum 2, 6-di-t-butyl-4-methylphenoxide |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMP | Dess Martin Periodinane |
| DMSO | dimethyl sulfoxide |
| dr | diastereomeric ratio |
| ee | enantiomeric excess |
| fod | 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato |
| hfac | hexafluoroacetylacetone |
| HFIP | hexafluoroisopropanol |
| *hv* | light |
| KHDMS | potassium bis(trimethylsilyl)amide |
| LAH | lithium aluminium hydride |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| MAD | methylaluminum bis (2, 6-di-t-butyl-4-methylphenoxide) |
| Mc | monochlate |
| mCPBA | meta-chloroperoxybenzoic acid |
| MeCN | acetonitrile |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| Np | *2*-naphthyl |
| PPTS | pyridinium *p*-toluenesulfonate |
| TBAF | tetra-*n*-butylammonium fluoride |

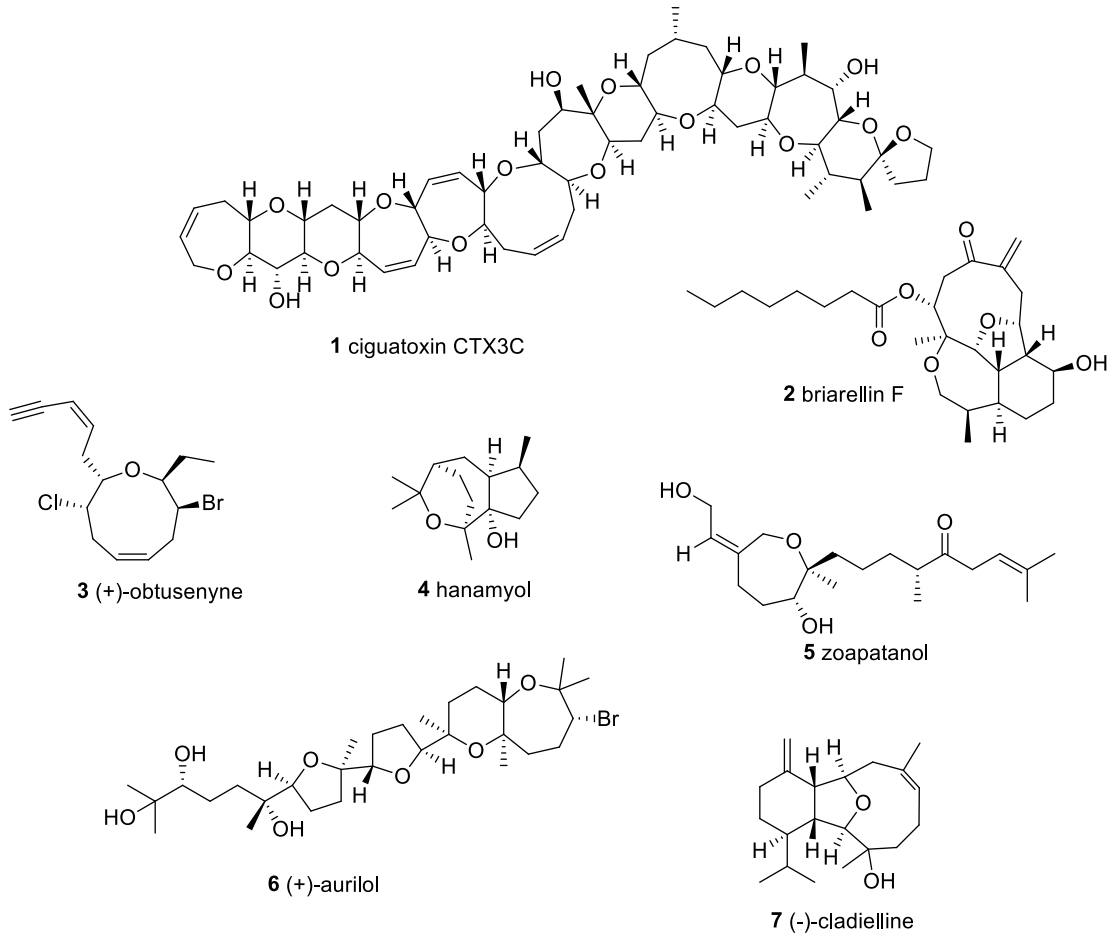
| | |
|---|---|
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TMG | tetramethyl-guanidine |
| TMS | trimethylsilyl |
| TMSD | trimethylsilyl diazomethane |
| TMSOTf | trimethylsilyl triflate |
| tol | toluene |

# Contents

# 1. Introduction

## Medium sized cyclic ethers in natural products

Medium sized cyclic ethers are present in a vast array of natural products deriving from many different species of organisms. Their significant biological properties include anticancer, antibacterial and antifungal activity, while those with harmful effects on humans (e.g. their neurotoxicity) are being utilized as tools to better understand the activity of the biological systems involved.[1] Those properties paired with their complex and impressive structures have made medium-sized oxacycles attractive targets for total synthesis.




**Scheme 1.** *Natural products containing medium sized cyclic ethers*

While the literature contains abundant strategies and methods for the synthesis of six-membered or smaller cyclic ethers, the formation of medium-sized oxacycles still poses a challenge to the synthetic chemists. The formation of cyclic systems with ring sizes greater than six becomes incrementally less favorable with increasing ring size as factors such as loss of entropy, torsional strain and unfavorable transannular interactions, as well as other effects, have an impact on the outcome of the reaction. Consequently, methodology designed for the synthesis of five- and six-membered oxacycles is not always applicable to the construction of larger rings.

## Synthetic strategies for the formation of medium sized cyclic ethers

Synthesis of medium-sized cyclic ethers constitutes a very fascinating topic in the field of synthetic chemistry. This structural motif, which is found in many natural products and also in medicinal compounds, has gained considerable attention in recent years. As common cyclization strategies employed for the synthesis of five- and six-membered rings are not always applicable for entropic and enthalpic reasons, specialized methodologies have been developed and applied. In this report the methodologies are classified in five categories: (1) ring expansion and rearrangement reactions, (2) epoxide opening and rearrangement, (3) C-C bond formation, (4) C-O bond formation and (5) ring-closing metathesis.

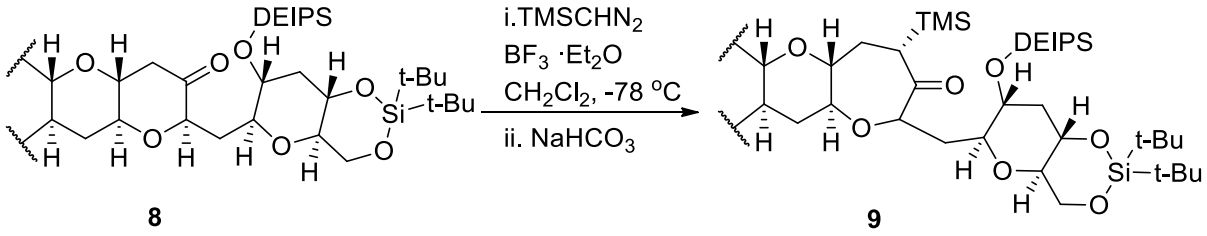
### 1.1 Formation via Ring Expansion

Medium-sized cyclic ethers can be conveniently accessed through ring expansion reactions and related rearrangement processes. This approach to the synthesis of larger oxacycles is considered advantageous because it avoids the entropic penalty associated with the cyclization of completely acyclic precursors to rings that possess significant transannular strain.

## 1.1.1 Side chain incorporation

One of the most versatile and commonly used ring expansion reactions in the field of polyether polycyclic marine natural products is Lewis acid promoted ketone homologation with diazoalkanes. Several total syntheses of those products have utilized this reaction for the formation of oxepanes because it provides a single step ring expansion with high regioselectivity.[2]

For example, in Mori's synthesis of gymnocin B (Scheme 2), ring expansion with TMS-diazomethane is employed at a late stage in the synthesis, showcasing the selectivity of the reagent in this family of substrates.[3] Treatment of ketone **8** with TMS-diazomethane in the presence of boron trifluoride diethyl etherate results in the formation of the α-trimethylsilyl ring-expanded ketone **9**. In this report, the target enone is obtained by 1,3-Brook rearrangement followed by Saegusa-Ito oxidation of the silyl ketone **9** with 53% yield over 3 steps. While this procedure provides easy access to the enone, treatment with acidic instead of basic conditions would provide the unsubstituted homologated ketone.

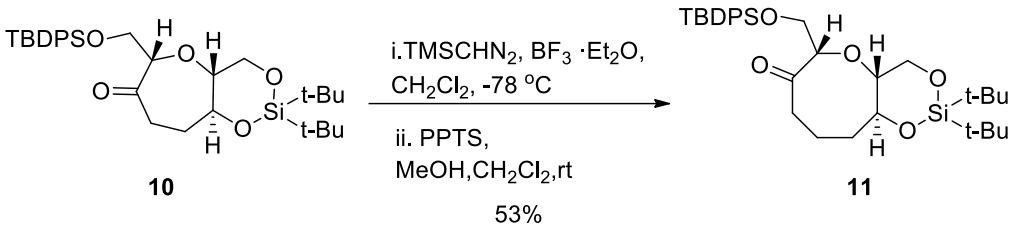



**8** **9**

**Scheme 2.** *Expansion of six membered cyclic ketone with TMSD*

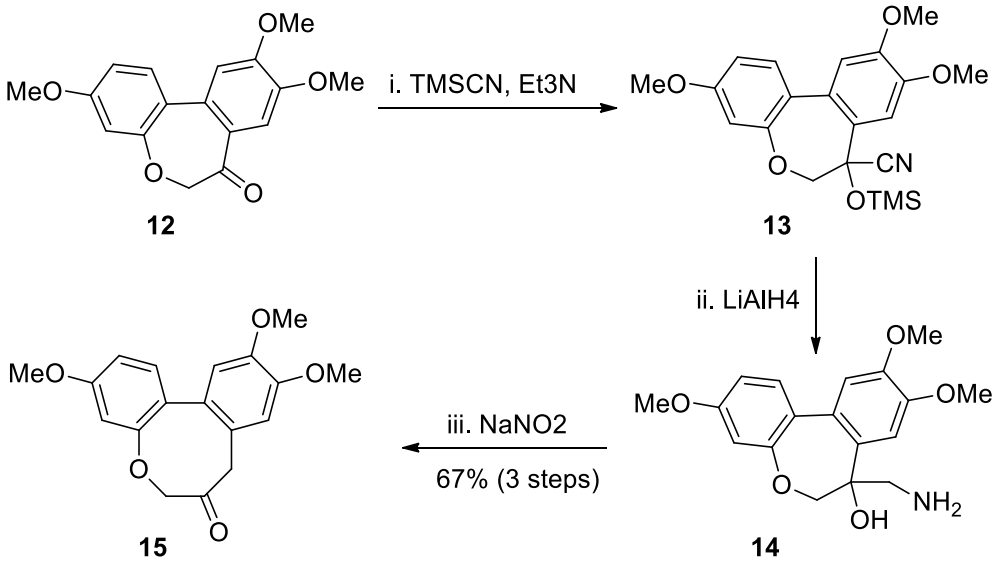
Although the formation of eight-membered rings in marine polyether toxins is commonly approached by the use of other synthetic strategies, the method has been employed for the formation of oxocane systems from tetrahydropyrans in an iterative fashion (Scheme 3).[4] When compound **10** is treated with TMS-diazomethane, the product **11** is isolated in a moderate yield as a result of the reduced reactivity of the oxepane and the general distortion of the ring. The lowered reactivity was also observed by Hirama when he attempted to use the reaction to form the eight-membered E-ring of ciguatoxin.[5] In this case, an $AlMe_3$-mediated ring expansion reaction with TMS-diazomethane afforded a 53%

yield of the desired ketone **11** and an epoxide by-product in 1.5:1 ratio, attesting to the low reactivity of the substrate.



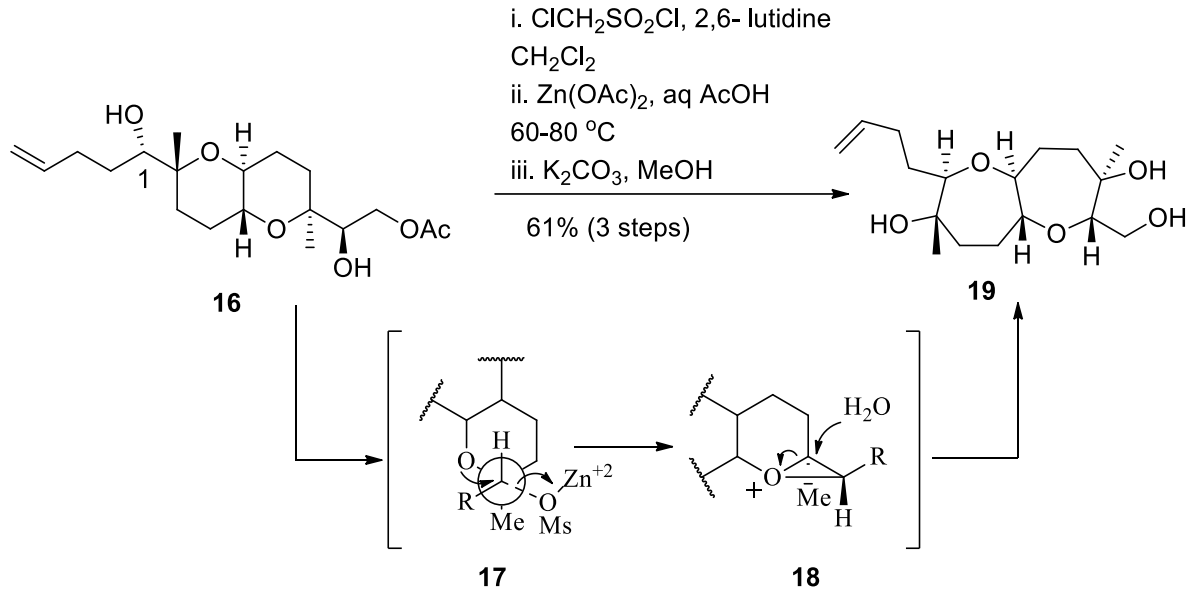

**Scheme 3.** *Expansion of seven membered cyclic ketone with TMSD*

Another approach to the homologation of cyclic ketones is the Tiffeneau-Demjanov rearrangement reaction, which can be applied for the expansion of four- to eight-membered rings (Scheme 4).[6] The reaction proceeds with the diazotization of the ß-amino alchohol **14** followed by substitution of the diazonium cation through a pinacol-type rearrangement.[7] This methodology has been used at a late stage in the synthesis of protosapanin A with excellent efficiency.[8] Nucleophilic addition with trimethylsilyl cyanide to compound **12** and subsequent reduction with $LiAlH_4$ affords the *β*-amino alcohol **14**, which upon treatment with $NaNO_2$ furnishes the eight-membered oxacycle in 60% yield over three steps.




**Scheme 4.** *Tiffeneau-Demjanov ring expansion*

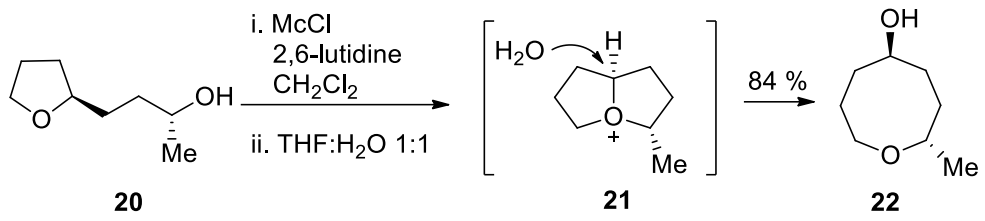
Nakata has developed an efficient and stereoselective method for the ring expansion of cyclic ethers bearing a mesylate or monochlate group at the C1 position in the side chain (Scheme 5).[9] Initial protection of the diol **16** with mesylate or monochlate chloride followed by treatment of the bis-mesylate with $Zn(OAc)_2$ in acidic aqueous medium afforded the bis-expanded product **19** in one step and with excellent yield. Various metal salts were examined as promoters for the reaction, while the use of monochlate over mesylate showed better results when the reaction was applied to the synthesis of hemibrevetoxin B (Scheme 5).[10] Further studies on the reaction with various side chains showed that it is compatible with ester and alcohol groups without any impact on stereoselectivity or yield.[11] Detailed investigation of the reaction suggests that the antiperiplanar alignment of the C-O bond of the ether and the mesyloxy group to generate an oxonium ion is the crucial step in the reaction and also explains the observed stereoselectivity.




**Scheme 5.** *Ring expansion with monochlate bearing side chain incorporation*

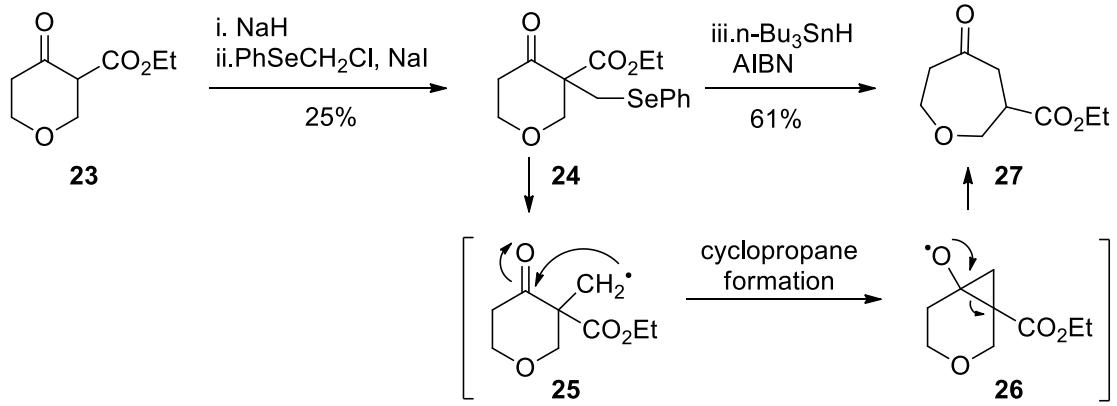
The versatility of the reaction was further expanded, this time in the formation of oxocanes from substituted tetrahydrofurans (Scheme 6).[12] The terminal alcohol in the linear side chain of the furan **20** is transformed to the corresponding monochlate and in a solution of aqueous THF the meso-

bicyclo[3.3.0]oxonium ion **21** is formed as an intermediate before being attacked by water to afford the oxocane **22** in excellent yield.




**Scheme 6.** *Ring expansion of THF ring with monochlate mediated side chain incorporation*

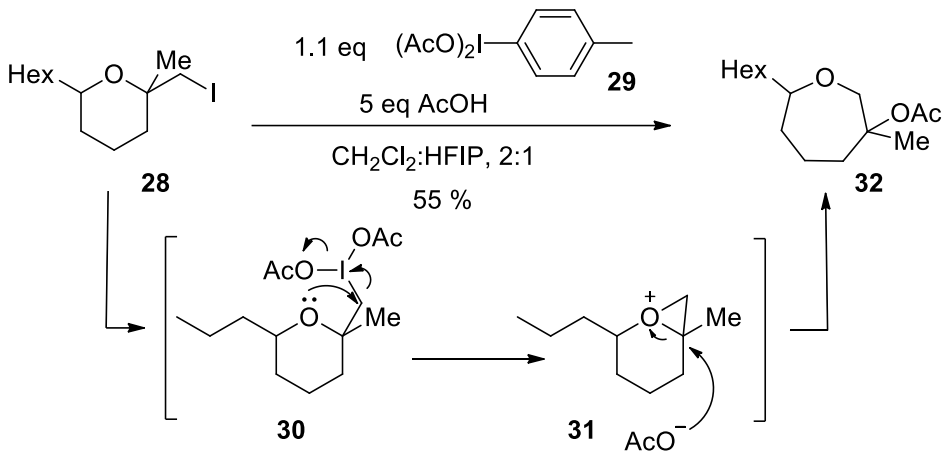
Ring expansion of small sized rings with a ß- keto ester functionality can be achieved through a radical reaction when using the Dowd-Beckwith ring enlargement (Scheme 7).[13] This method is of particular interest because it can used to accomplish ring expansion of up to four carbons in only two steps, depending on the selenide used.[14] Groups such as iodine and bromine can be used instead of the phenyl selenide along with a variety of radical initiators.[15,16] The first step of the reaction is introduction of the methylene phenyl selenide in the α-position while slow addition of tributyltin hydride and AIBN results in the expanded product.




**Scheme 7.** *Dowd-Beckwith ring expansion*

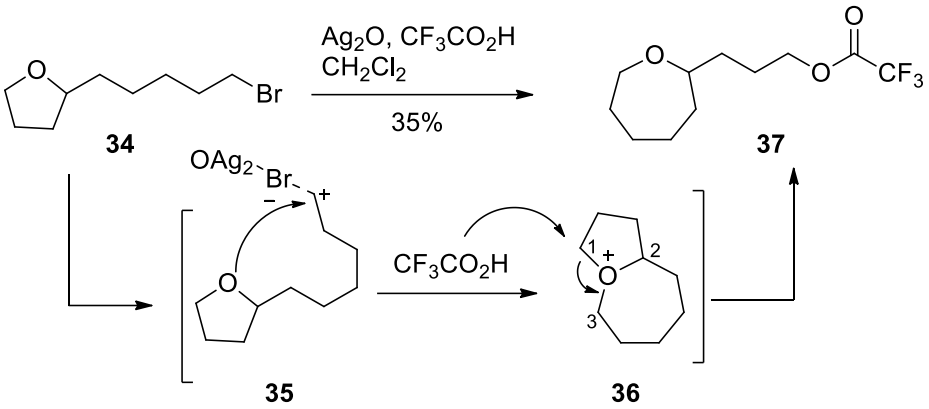
An additional method for the stereoselective expansion of cyclic ethers has been introduced by the Hara group in which hypervalent iodine is used as the leaving group (Scheme 8).[17,18] The reaction is postulated to proceed by a mechanism that is similar to that of the mesylate expansion reaction (Scheme 5). Initial

formation of the bis-acetoxy iodine followed by nucleophilic attack of the ethereal oxygen and expulsion of the iodine group leads to the formation of the oxonium intermediate **31** that, upon nucleophilic attack by acetate, yields the substituted oxepane **32**.



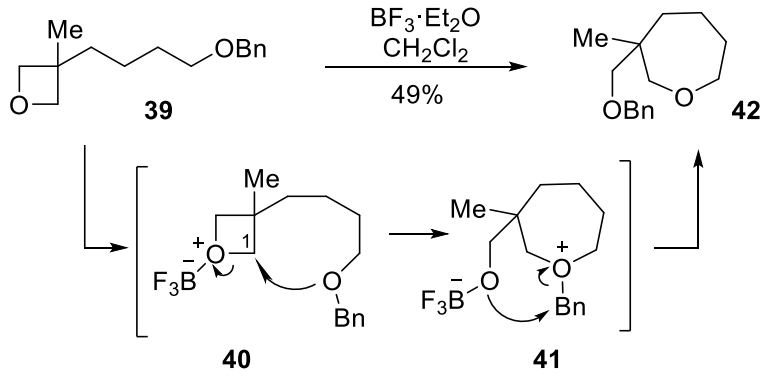

**Scheme 8.** *Ring expansion with hypervalent iodine*

Another strategy for the formation of oxepanes and medium-sized cyclic ethers starting from smaller rings was reported by Oku.[19] The methodology has been applied to the incorporation of a linear five-membered side chain into a tetrahydrofuran to form an intermediate that then delivers an oxepane product (Scheme 9). The reaction is similar to previous examples and involves formation of an oxonium intermediate followed by the attack of TFA. Of the three carbons bonded to oxygen in the oxonium ion **36**, C1 is the preferred site of attack possibly due to the release of the steric strain. This conclusion is further supported by the observation that elongation or shortening of the side chain leads to none the expected product.




**Scheme 9.** *Silver (I) oxide mediated side chain incorporation – ring expansion*

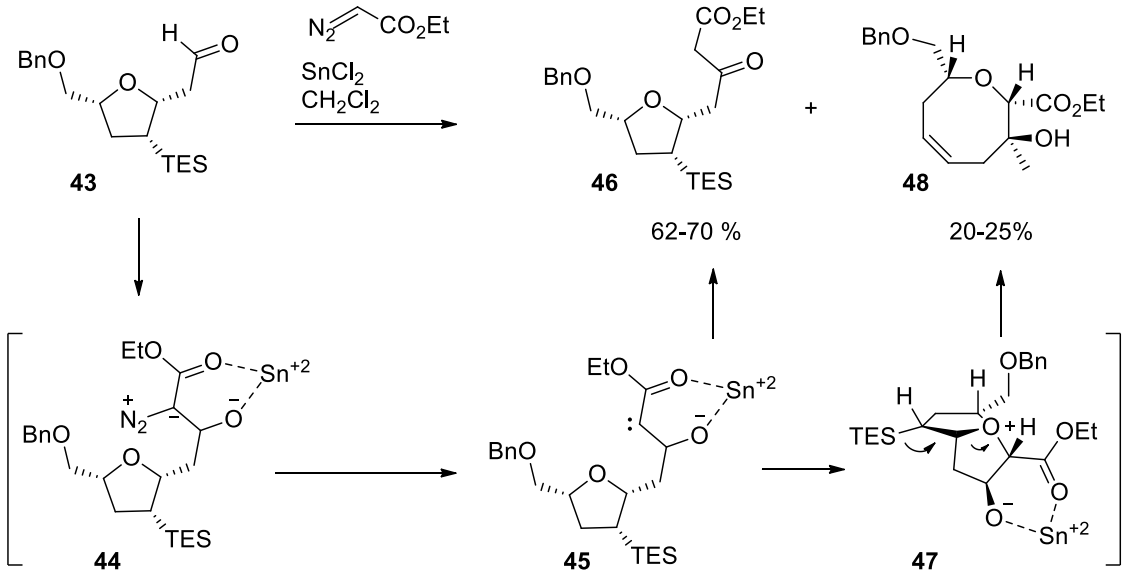
The Masaki group has taken advantage of the great strain involved in epoxides and oxetanes in order to develop a novel method that involves their rearrangement to give expanded cyclic ethers accompanied by transfer of the ethereal groups (Scheme 10).[20] Treatment of oxetane **39** with boron trifluoride diethyl etherate facilitates nucleophilic attack of the protected alcohol. Oxonium **40** is then further rearranged by the migration of the benzyl group to form oxepane **42**. Although this method requires very mild conditions, the moderate yield and the lack of stereoselectivity have not encouraged its widespread exploitation for the formation of medium-sized ethers.




**Scheme 10.** *Lewis acid catalyzed oxetane expansion*

In a study performed by the Li group concerning the synthesis of the $\Delta^4$-oxocene core of the laurencin family natural products, an enantioselective approach for the ring expansion was investigated.[21] The tetrahydrofuran precursor **43** was expanded to give an eight-membered ring following an oxo-carbenoid insertion and a ß-silyl fragmentation sequence (Scheme 11). Treatment of aldehyde **43**

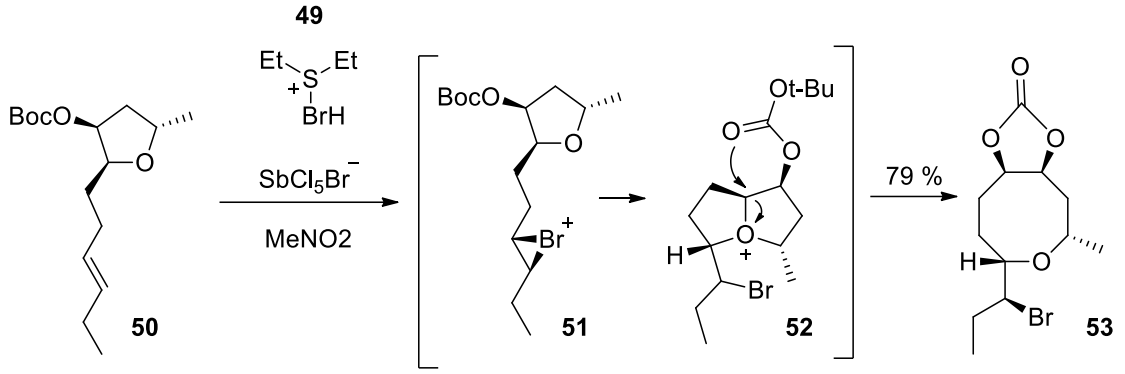
with a slight excess of ethyl diazoacetate in the presence of catalytic amount of anhydrous $SnCl_2$ in $CH_2Cl_2$ at room temperature afforded the ß-keto ester **46** as the major product together with $\Delta^4$-oxocene as a single diastereomer. The reaction is postulated to proceed through a mechanism in which aldol condensation between ethyl diazoacetate and **43** results in successive elimination of nitrogen and generation of the carbene **45**. This intermediate can be converted to ß-keto ester **46** through a hydride shift or can form the tricyclic oxonium ylide **47** by nucleophilic attack of the tetrahydrofuran oxygen onto the carbene. Finally, ß-syn-elimination and fragmentation of the TES group leads to the oxocene **48**.




**Scheme 11.** *Synthesis of the $\Delta^4$-oxocene core through an oxonium formation – ß-silyl fragmentation sequence*

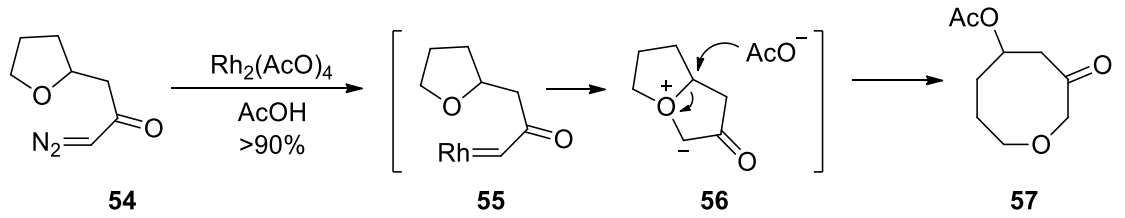
A related approach has been disclosed by Snyder in which bromonium ion induced ring expansion has been used to produce eight- and nine-membered oxacycles from tetrahydrofuran and tetrahydropyran respectively (Scheme 12).[22] The results demonstrate the usefulness of this reaction because it is fast, efficient and regioselective and stereoselective. This methodology has been applied to the synthesis of the *Laurencia-type* bromoethers.[23] The reaction initiates by reaction of the alkene with bromodiethylsulfonium bromopentachloroantimonate **49** to generate the bromonium ion **51**. Attack of the tetrahydrofuran oxygen on the bromonium ion, in a 5-exo fashion, forms the

oxonium bicycle **52**. Nucleophilic addition by the neighboring carbonate opens the bicyclic oxonium ion stereoselectively to produce the oxocane **53**.




**Scheme 12**. *Ring expansion of THF ring through a bromonium ring opening – oxonium formation – opening cascade*

Eight- to eleven-membered cyclic keto ethers can be readily accessed from diazoacetonyl substituted cyclic ethers in a single step, by use of rhodium(II) acetate in catalytic amounts (Scheme 13).[24] Initial complexation of the rhodium catalyst with the diazoacetonyl **54** forms the carbenoid **55** that reacts with the ring oxygen to give the bicyclic oxonium ylide **56**. Nucleophilic attack by acetate ion at the quaternary carbon furnishes the oxocane **57** in an excellent yield.

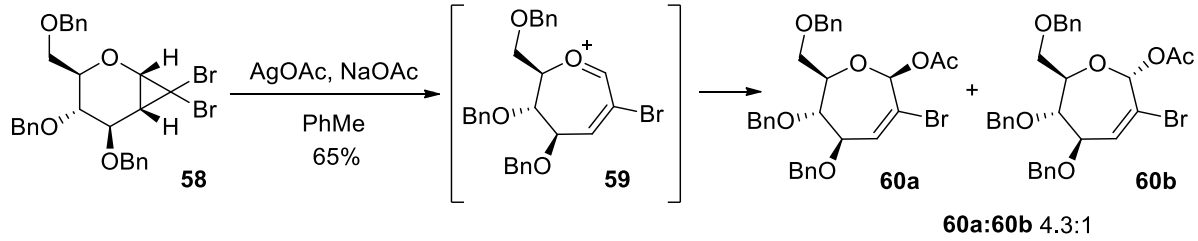



**Scheme 13.** *Rhodium catalyzed diazo-side chain incorporation- ring expansion of THF ring*

## 1.1.2 Ring Expansion of Bicyclic Substrates

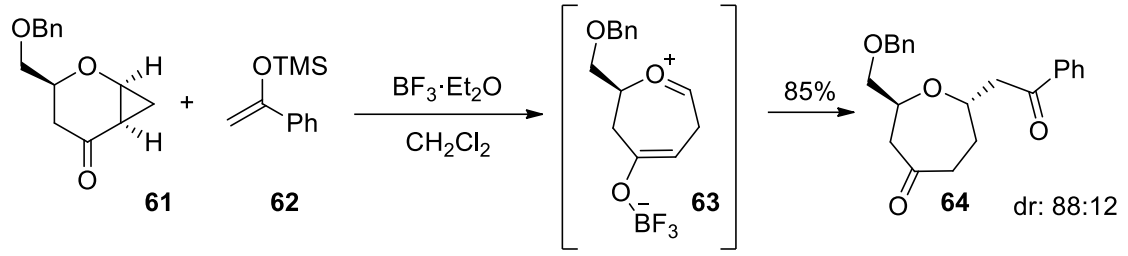
Cyclopropane fused oxacycles can be converted into the corresponding single carbon expanded oxacycles by opening of the cyclopropane.

Work by Harvey et al. has resulted in the development of a new method for the synthesis of brominated septanosides from glucal derivatives (Scheme 14).[25] Treatment of **58** with silver acetate in refluxing toluene results in elimination of one of bromine atoms as a bromide ion and this is followed by electrocyclic opening of the cyclopropane. The resulting oxonium ion **59** is then attacked by the acetate ion that acts as the nucleophile to afford the epimeric oxepanes.



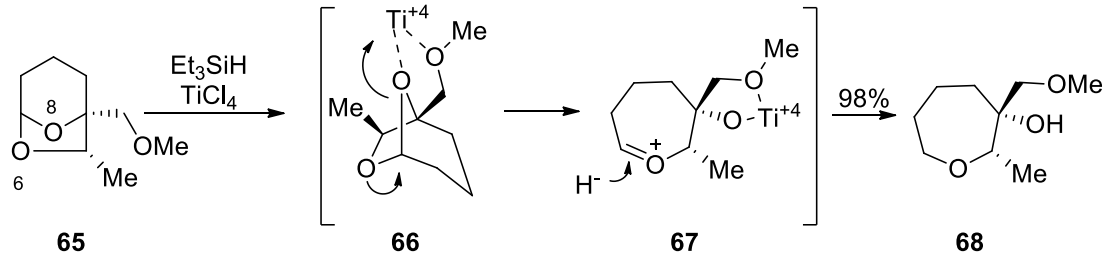

**Scheme 14.** *Septanoside formation from fused cyclopropane ring opening*

Comparable results were observed when the ring expansion reaction of a cyclopropapyran-5-one was performed in the presence of a which silyl enol ether (Scheme 15).[26] In this case, oxepanone **64** is formed by the nucleophilic attack of the silyl enol ether **62** on the oxonium ion **63**, which is formed by the cyclopropane ring opening. For reasons that are similar to those in the case of septanoside formation (*vide supra*), the stereoselectivity can be attributed to steric effects from proximal benzyl group. This method provides an efficient route to the formation of α-substituted seven-membered ethers.



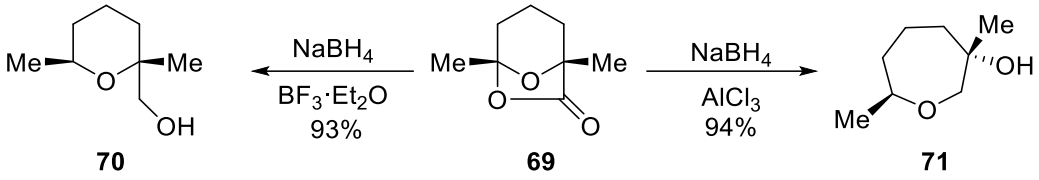

**Scheme 15.** *Fused cyclopropane ring opening and subsequent silyl enolate addition*

Oxepane formation can also be achieved through the controlled cleavage of 6,9-dioxabicyclo[3.2.1]octane systems in the presence of Lewis acids (Scheme 16). Work performed by the Utaka group showcased the formation of expanded oxacycles and demonstrated the importance of the Lewis acid used.[27] While treatment of the acetals with strong Lewis acids like $TiCl_4$ afforded the oxepane **68** in 98% yield, the use of milder metal salts like $SnCl_4$ did not result in product formation. It is postulated that the different pathways result from the oxophilicity of the Lewis acid and the preference for coordination to *O-8* instead of *O-6*.



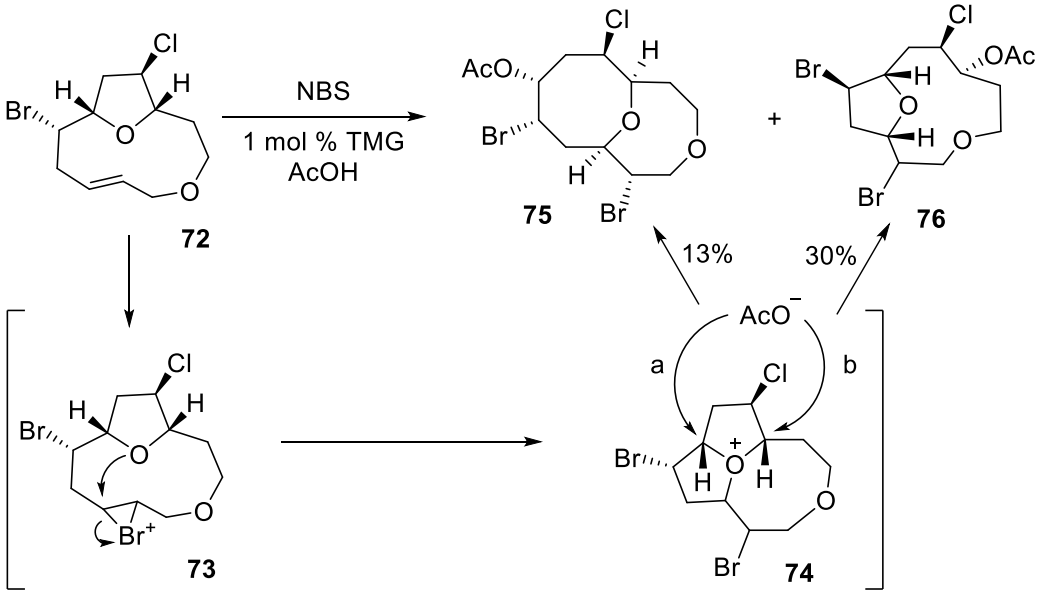

**Scheme 16.** *Lewis acid mediated cleavage of 6,9-dioxabicyclo[3.2.1]octane*

Ring expansion originating from the cleavage of bicyclic acetals was further studied by Lee et al. (Scheme 17).[28] In this study, ketal-lactones were treated with various Lewis acids in the presence of a hydride source. Interestingly, reactions with $BF_3{\cdot}Et_2O$ and $AlCl_3$ afforded products **70** and **71** in 93% and 94% yield respectively and showed the selectivity that arises from the choice of Lewis acid. It was suggested that the vacant d orbitals in $AlCl_3$ that are absent its counterpart could lead to discrimination between and preferential bonding to the acetal oxygens.




**Scheme 17.** *Selective ring opening with different Lewis acids*

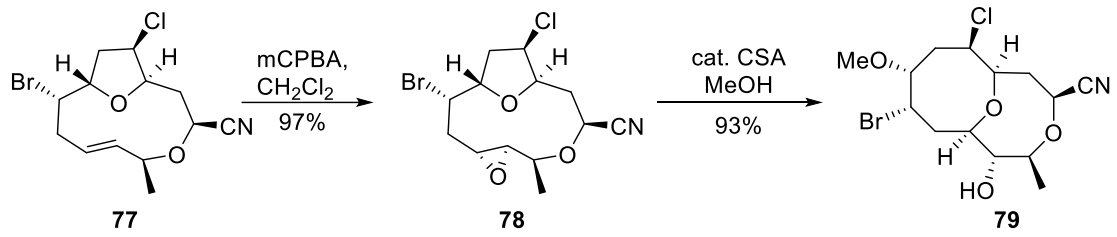
Braddock and co-workers have disclosed a new approach towards the synthesis of the obtusallene family of natural products thought exploiting a bromonium induced rearrangement (Scheme 18).[29] Treatment of the macrocycle **72** with *N*-bromosuccinimide and tetramethyl-guanidine (TMG) in catalytic amount results in the bromoniom cation **73**, that rearranges to the tricyclic oxonium intermediate **74**. This intermediate can react in two ways, depending on the carbon that the acetate will react with, with *pathway a* leading to the expanded oxacycle **75** and pathway *b* to the desired macrocycle **76**. While at this point the target was achieved, the structure and the competitive pathway for the synthesis of **75** made Braddock suggest that "*it may represent the core of an as yet undiscovered natural product from Laurencia species*".[29]




**Scheme 18.** *Bromonium induced rearrangements in the synthesis of the oxacyclic core of obtusallene family of natural products*

This novel structure was later found in metabolites of the Laurencia species, most notably in the Marilzabicycloallene family of products. Having experience

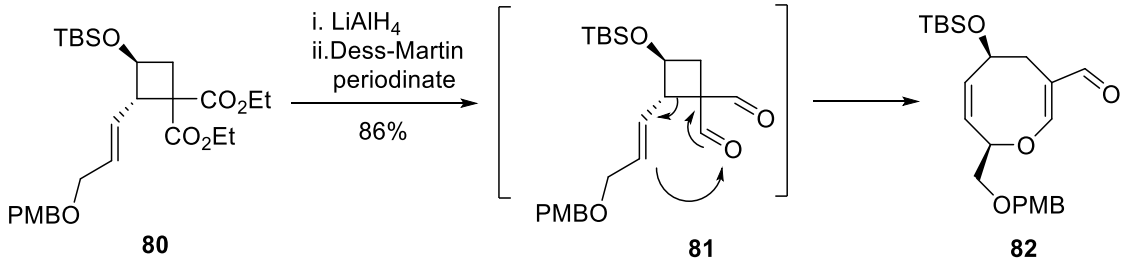
from previous studies, the Braddock group worked and optimized the previous protocol, using an epoxide instead of the bromonium cation for the transannular oxonium ion formation–fragmentation sequence (Scheme 19).[30] In comparison with the previous work, methanol exhibited a great preference for the desired pathway, furnishing the desired product **79** in 93% yield.




**Scheme 19.** *Synthesis of the fused bis-oxocane core of marilzabicycloallene family of natural products*

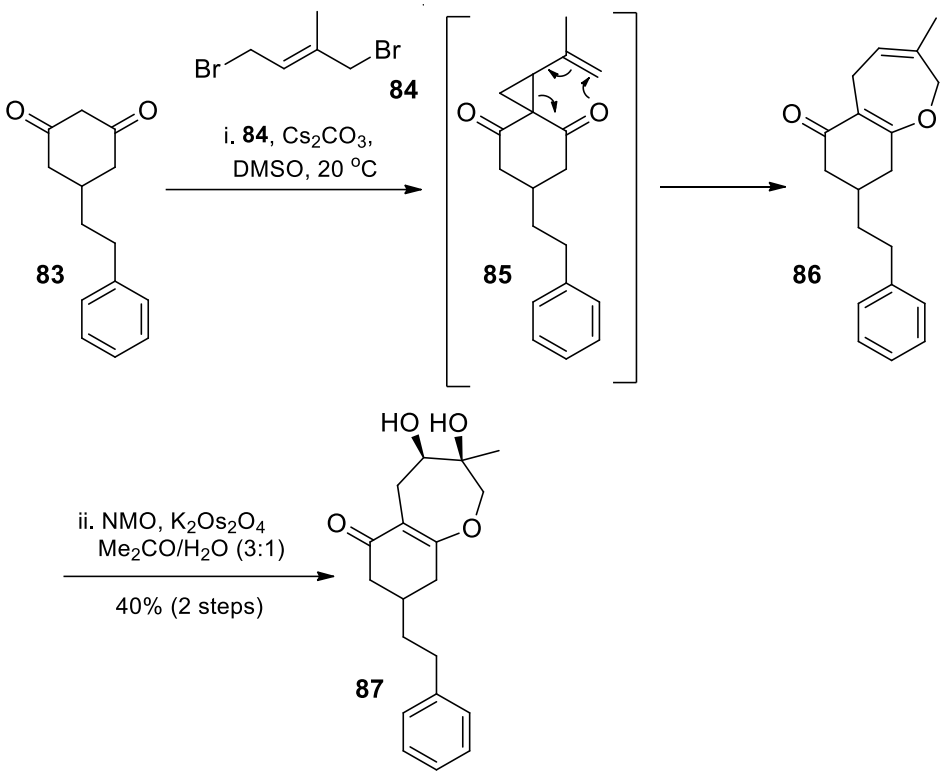
## 1.1.3 Pericyclic Cyclizations and Cycloaddition Reactions

In the total synthesis of (+)-laurenyne performed by Boeckman, a novel sigmatropic rearrangement for the formation of the oxocine ring system was examined (Scheme 20).[31] The highly functionalized cyclobutane was subjected to a reduction-oxidation sequence with LAH and the Dess-Martin periodinane, to afford the geminal aldehyde **81** as a key intermediate. Under mild heating at 45ºC, **81** was readily converted into the oxocine **82** in excellent yield. It was postulated that the reaction proceeds through a retro-Claisen rearrangement reaction and observations showed that at low temperatures the rearrangement to give the aldehyde **82** is irreversible.




**Scheme 20.** *Retro-Claisen rearrangement – Formation of oxocine ring*

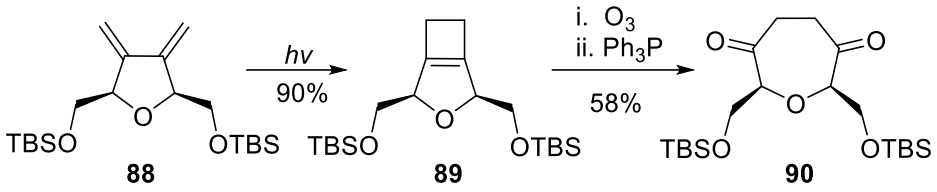
The use of a retro-Claisen rearrangement reaction for the formation of medium-sized ethers was further examined by Nay et al. and in particular the propensity for an oxacycle to form by reaction of a 2-vinylcyclopropanecarbonyl compound (Scheme 21).[32] In the concise synthesis of radulanin A, the 1,3-diketone **83** was treated with the dibromoisoprene to form the cyclopropane intermediate **85**. Spontaneous retro-Claisen rearrangement afforded the bicyclic ketone **86**, the core of the natural product, in one pot.




**Scheme 21.** *Retro-Claisen - cyclopropane opening cascade for the formation of oxepine ring*

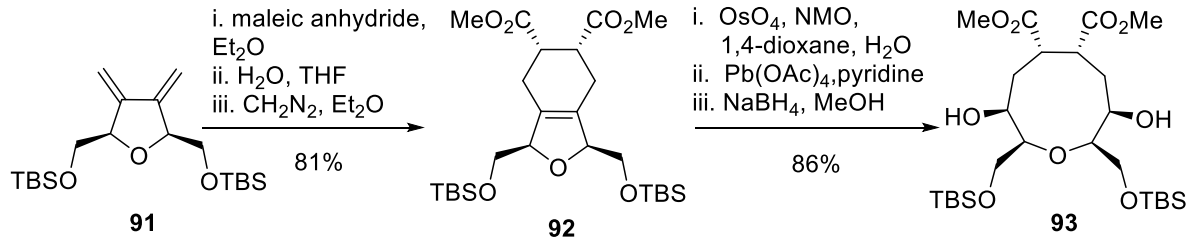
In studies concerning the total synthesis of ciguatoxin, Hirama et al. disclosed a new method for the formation of oxepanes that involves a light-mediated intramolecular annulation reaction (Scheme 22).[33] Irradiation of the diene **88** under a mercury lamp afforded the electrocyclisation product **89** in high yield. Ozonolysis of the resulting cyclobutene **89** furnished the desired symmetrical oxepane **90**. The diketone can be used as a scaffold for the synthesis of adjacent

rings or transformed into an eight-membered oxacycle in a further four steps through a cyclopropanation-ring expansion strategy.




**Scheme 22.** *Cyclobutene formation – ozonolysis sequence for the synthesis of the seven membered diketone*

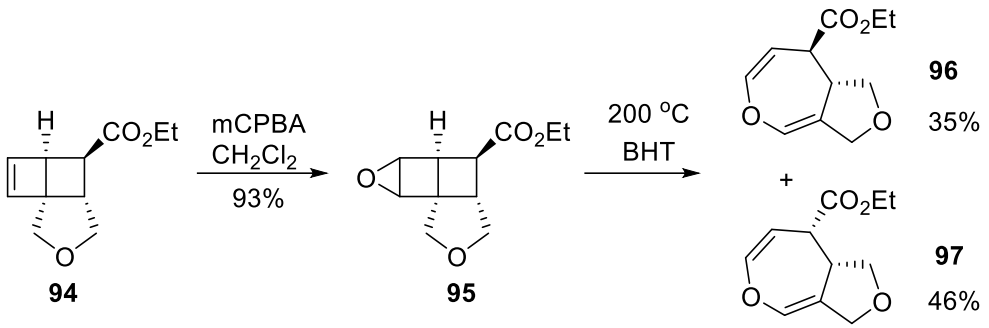
In the same publication, Hirama reported the formation of an oxonane system (Scheme 23).[33] Diene **91** was treated with maleic anhydride and the Diels-Alder product was converted to the 1,2 dicarboxylic acid. Esterification with diazomethane provides the bicyclic diester **92**. Sequential Upjohn dihydroxylation of the alkene to form a 1,2-diol, oxidative diol cleavage with lead(IV) acetate and reduction of the diketone with sodium borohydride furnished the desired nine-membered oxacycle **93** in excellent yield.




**Scheme 23.** *Diels Alder – dihydroxylation – ring opening sequence for the formation of oxonane functionalized cores.*

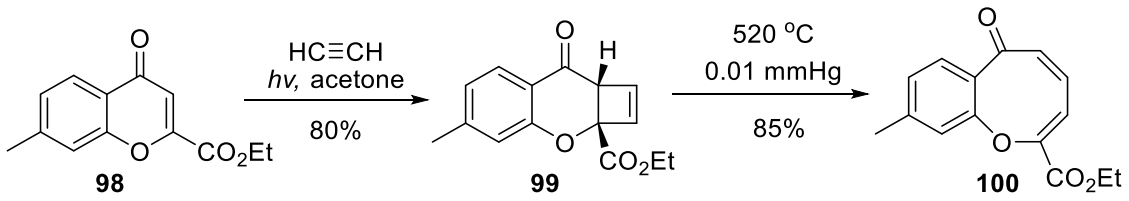
Snapper et al. reported the formation of oxepine derivatives by sequential epoxidation and thermal rearrangement of cyclobutene-containing systems (Scheme 24).[34] Treatment of the tricyclic alkene **94** with *m*CPBA resulted in the formation of the epoxide **95**. The significant strain of the system caused by the fusion of three rings was then exploited and the epoxide **95** underwent spontaneous ring expansion to form the oxepine epimers **96** and **97** when heated at elevated temperature. Addition of BHT is essential to prevent polymerization side reactions when the reaction was performed on a large scale. The author

suggested that the lack of reaction stereoselectivity was a consequence of biradical fragmentation during ring expansion.



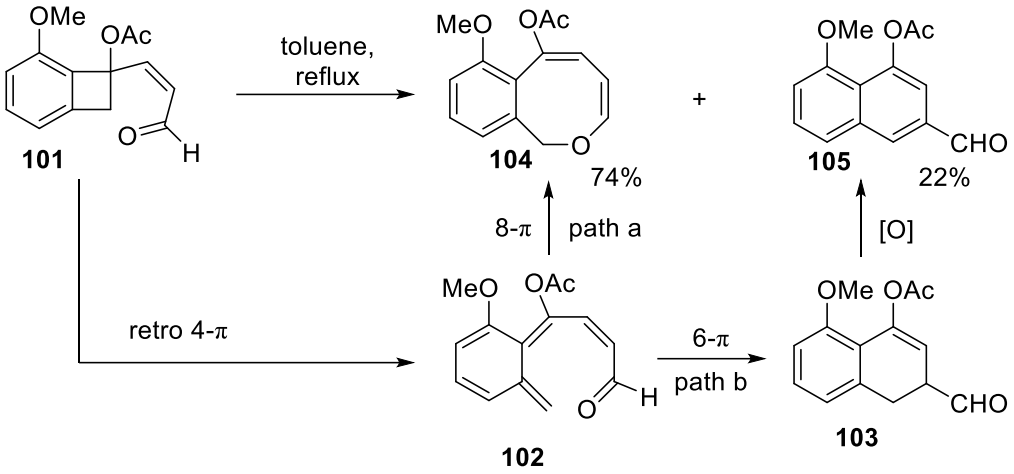

**Scheme 24.** *Opening of fused cyclobutene rings*

In the total synthesis of helianane published by Venkateswaran, expansion of a six-membered ether was achieved by a [2+2] cycloaddition reaction followed by the ring opening of the cyclobutene intermediate (Scheme 25).[35] Irradiation of the enol ether **98** in the presence of acetylene furnished the cyclobutene **99** in excellent yield. Synthesis of the eight-membered ring was accomplished by flash vacuum thermolysis to provide the desired diene **100** in high yield.




**Scheme 25.** *[2+2] cycloaddition and cyclobutene opening for the formation of the oxocine core of helianane*

Synthesis of 2-benzoxocin derivatives by an electrocyclic ring-opening / ring-closing cascade reaction has been reported by Suzuki and co-workers (Scheme 26).[36] 1-Acyloxybenzocyclobutene **101** underwent retro-4π-electrocyclization to form the conjugated aldehyde **102** when heated at reflux in toluene. This intermediate can rearrange through two competing pathways: oxo-8π-electrocyclization (path a) or 6π-electrocyclization (path b). Pathway a and b lead to the 2-benzoxocin **104** and the naphthalene **105** respectively.



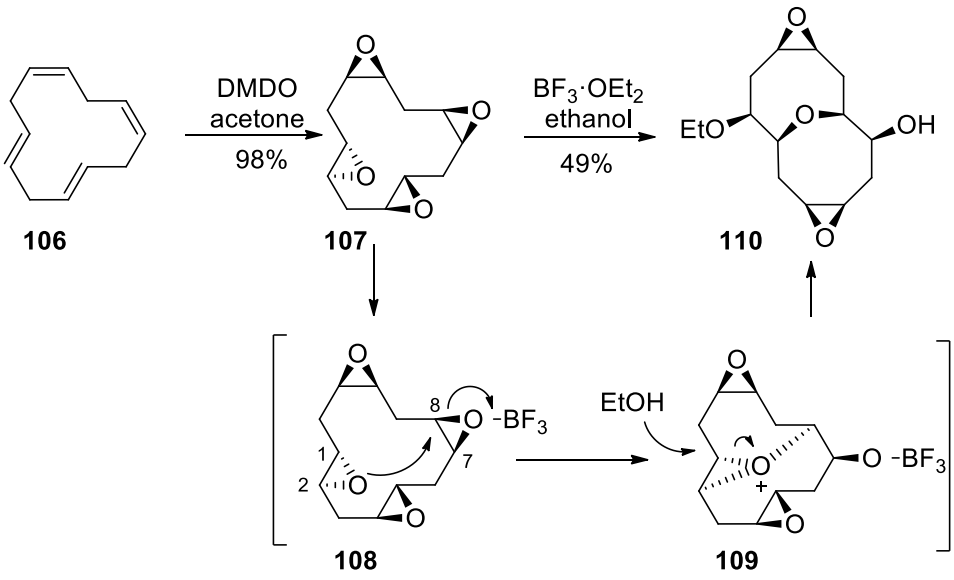

**Scheme 26.** *Electrocyclic ring opening – ring closing cascade*

## 1.2 Formation via Epoxide Rearrangement and Opening

Epoxides have been used extensively for the synthesis of medium-sized cyclic ethers because they are very accessible and reactive substrates. Furthermore, in the case of many marine natural products, formation of medium-sized cyclic ethers by opening an epoxide with an oxygen nucleophile mimics the biosynthetic route, which highlights the efficiency and efficacy of this strategy.

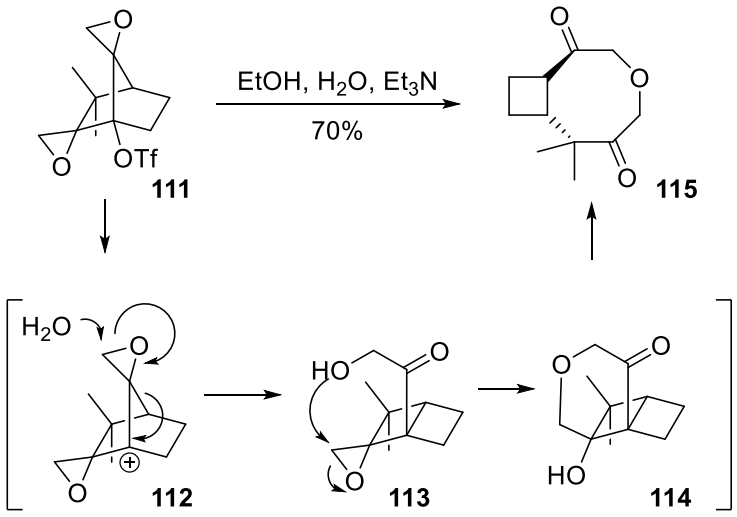
### 1.2.1 Epoxide Rearrangement

Parrain have reported a method for the preparation of fused oxocanes from macrocyclic polyepoxides by expansion of the work of Paquette and Vazeux on domino epoxide-opening reactions for the synthesis of topologically non-planar compounds (Scheme 27).[37,38] Epoxidation of every double bond of the macrocyclic polyene **106** leads to stereoselective formation of the polyepoxide **107**. It was proposed that the reaction proceeds by formation of a Lewis acid-base complex followed by nucleophilic attack of the C1-C2 epoxide onto the C7-C8 epoxide, which is located on the other side of the ring. Regioselective nucleophilic attack of ethanol furnishes the bridged bis-oxocane **110**. The domino epoxide opening sequence was reported to proceed regioselectively as byproducts arising from the reaction of another pair of epoxides were not observed.




**Scheme 27.** *Epoxide rearrangement fot the synthesis of fused bisoxocane moieties.*

A method for the synthesis of oxocane derivatives from camphor-derived bis-epoxides was devised by Martinez et al. in which sequential epoxide opening and rearrangement reactions were performed (Scheme 28).[39] The proposed mechanism of the reaction commences with loss of the triflate to generate the tertiary cation **112** which then initiates a pinacol-like rearrangement reaction to afford the α-hydroxy ketone **113**. Nucleophilic attack on the epoxide by the hydroxyl group leads to the 6-exo cyclisation product **114**. Finally, the oxocane **115** is delivered by a retro-aldol reaction of the tricyclic **114**.

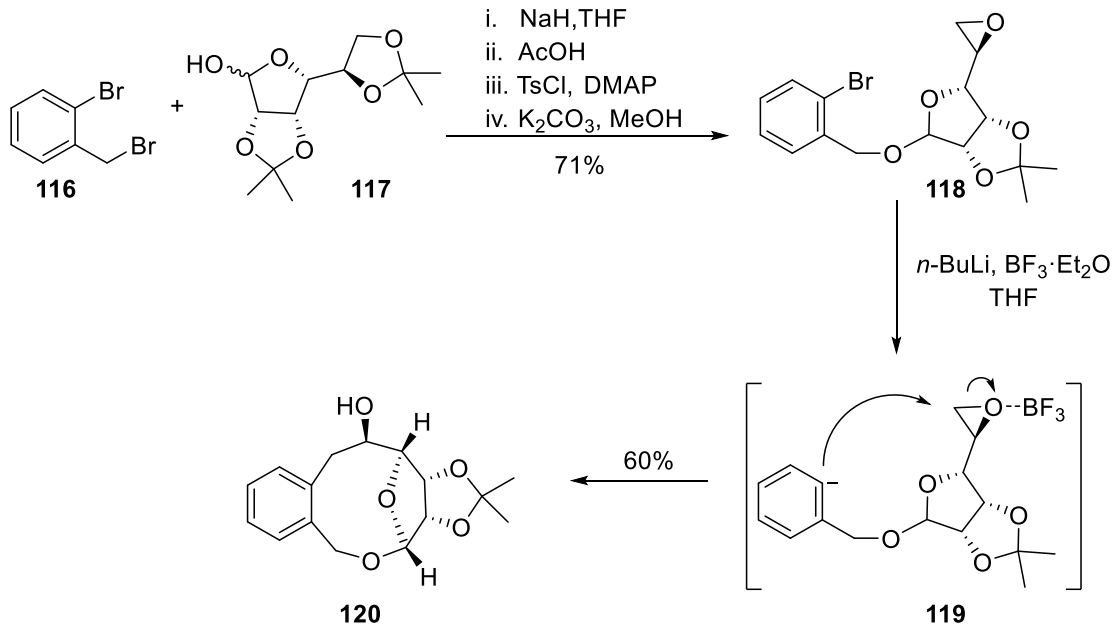



**Scheme 28.** *Rearrangment of di-spiro-epoxide camphor to oxocane*

## 1.2.2 Epoxide Opening with Carbon Nucleophiles

While many examples of epoxide opening with oxygen nucleophiles can be found in the literature, the use of carbon nucleophiles is more limited. A notable example of this approach has been reported by Chandrasekhar et al. during a synthesis of the marine product eleutherobin and its analogues (Scheme 29).[40]

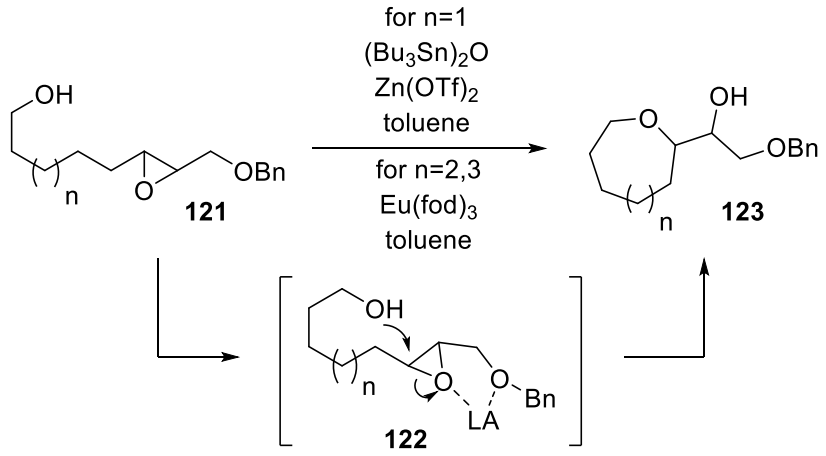
The synthesis commences with anomeric alkylation of the protected D-mannose with ortho-bromobenzyl bromide followed by selective deprotection of the ketal and formation of the epoxide. Treatment of the epoxide **118** with *n*-BuLi resulted in halogen-lithium exchange followed by opening of the epoxide with the aryl lithium to furnish the alcohol **120.**



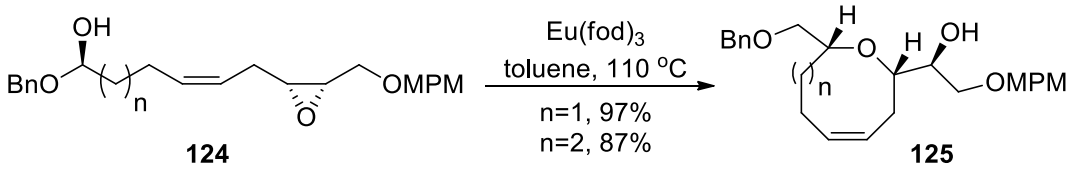

**Scheme 29.** *Synthesis of the eleutherobin core through an aryl lithium epoxide opening*

## 1.2.3 Epoxide Opening with Oxygen Nucleophiles

Suzuki has been a pioneer in the field of epoxide opening for the formation of medium-sized cyclic ethers. He examined how various Lewis acid promoters would facilitate the synthesis of medium-sized oxacycles. Initial investigations showed that $(Bu_3Sn)_2O$ and $Zn(OTf)_2$ are the promoters of choice for the formation of oxepanes (Scheme 30),[41] but are not suitable for the synthesis of larger cyclic homologues.[42] In order to circumvent the problem other Lewis acids were examined. $Eu(fod)_3$ was found to be effective and able to tolerate functionalized substrates (Scheme 31).[42] The reaction proceeds in the same fashion with both Lewis acids and *exo*- cyclization occurs presumably because of complexation of the Lewis acid to the epoxide oxygen and that of the adjacent ether.



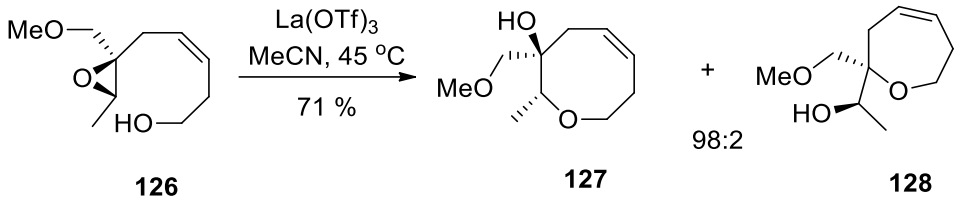

**Scheme 30.** *Initial investigation on Lewis acid catalysed epoxide opening- oxacycle formation*




**Scheme 31.** *Medium-sized oxacycle formation through alcohol induced epoxide opening*

In a similar fashion, cyclization of linear ω-hydroxy epoxides has been reported (Scheme 32).[43] In contrast to the previous example, $La(OTf)_3$ was employed as

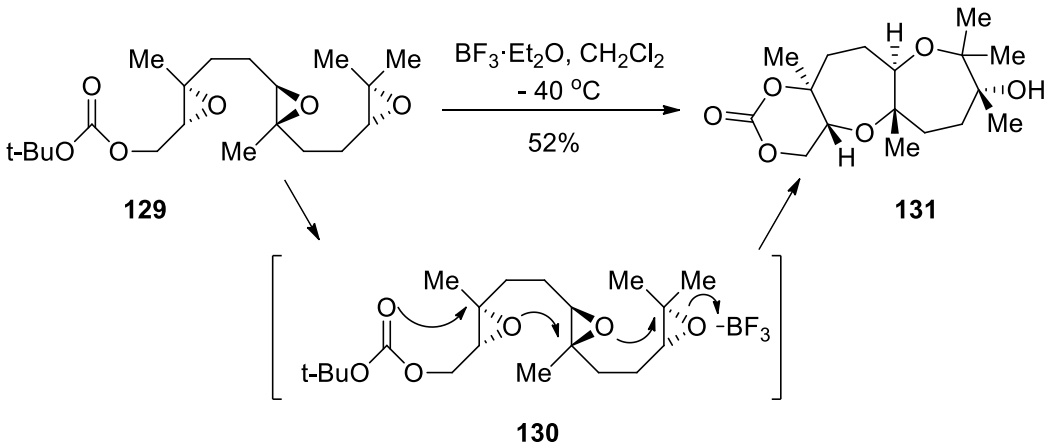
the Lewis acid to afford the *endo* product with high selectivity. The difference in the mode of ring closure in these examples can be explained by chelation effects.




**126** **127** **128**

**Scheme 32.** *Alcohol induced epoxide opening with lanthanium triflate*

McDonald et al. have reported the synthesis of fused bis-oxepanes as scaffolds for the synthesis of marine polyether polycyclic toxins.[44] The strategy for the synthesis of these compounds is based on the biosynthetic path and consists on a domino epoxide opening cascade in which a linear polyepoxide reacts to form a fused polycyclic (Scheme 33). Initial coordination of the boron trifluoride to the terminal epoxide facilitates a tandem epoxide opening, which concludes with the nucleophilic attack of the carbonyl group. The use of the bulky and less nucleophilic *t*-butyl carbonate is highly influential, as it provides the required *cis* ring-junction stereochemistry, whereas more nucleophilic groups (e.g. carbamate) result in *trans*- fused systems.[45] During the reaction, three rings and six stereocentres are formed in a single step. The final scaffold could be used for the total synthesis of fused polyether natural products.

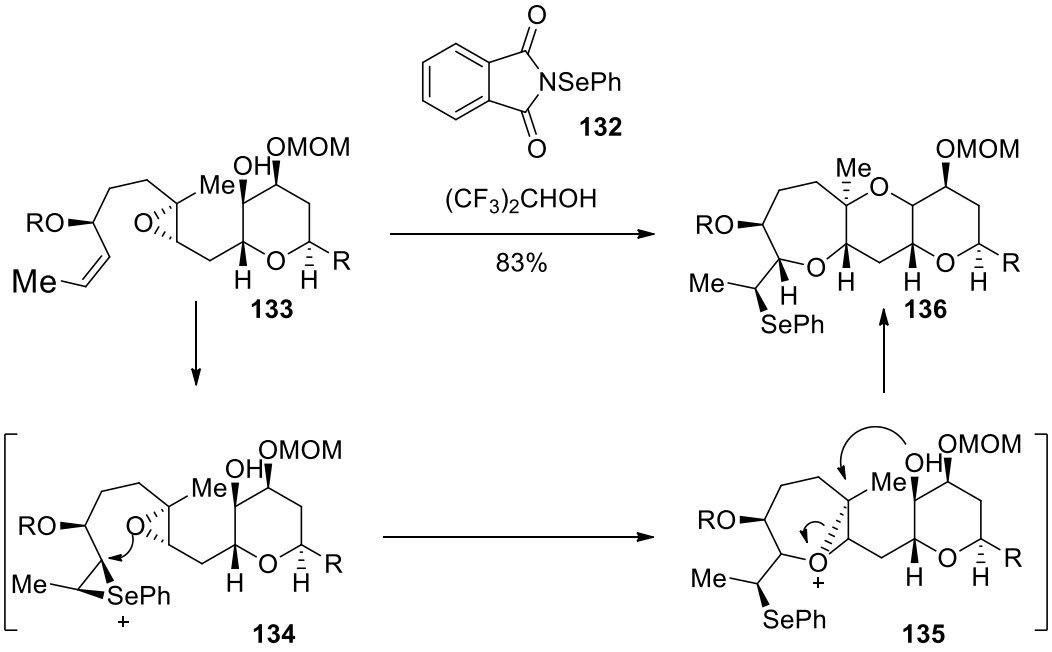



**129** **131**

**130**

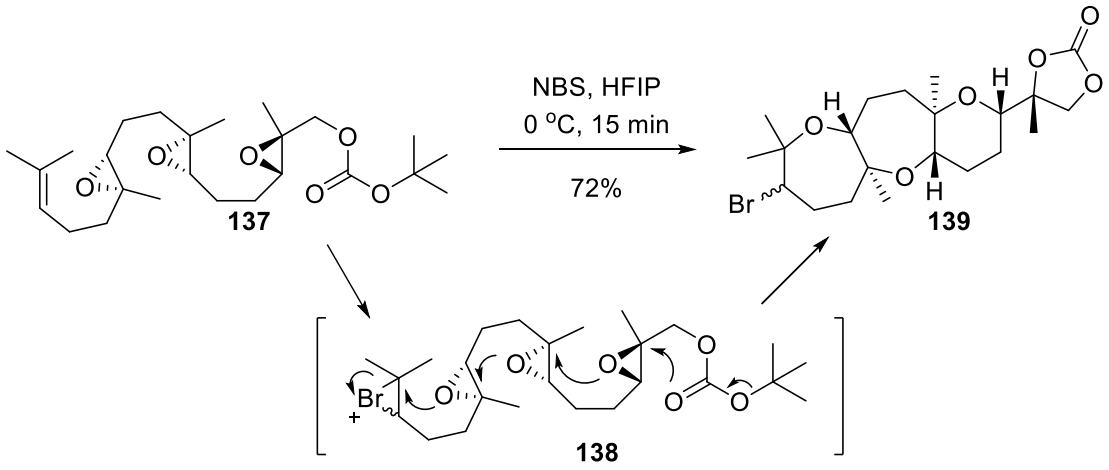
**Scheme 33.** *Epoxide opening cascade for the stereoselective formation of fused bis-oxepane rings*

A similar approach was employed by Holton for the total synthesis of hemibrevetoxin B.[46] The key step in the synthesis involved a cascade reaction between an epoxide and an epi-selenonium ion (Scheme 34). Reaction of the substrate **133** with *N*-(phenylseleno)phthalimide results in the formation of the epi-selenonium ion **134** and this intermediate is readily attacked by the epoxide to form oxonium ion **135**. Intramolecular attack by the hydroxyl group then furnishes the desired 6-*endo* product with the desired stereochemistry.




**Scheme 34.** *Episelenonium opening with an epoxide and subsequent rearrangements*

Another report concerning polyether synthesis by domino epoxide opening has been published by Jamison. In this case, a bromonium initiated chain reaction for the synthesis of the tricyclic core of *ent*-dioxepandehydrothyrsiferol was explored (Scheme 35). [47] Treatment of the polyepoxy alkene **137** with NBS in HFIP was found to generate the highly reactive bromonium cation **138** that then underwent sequential epoxide opening in an *endo* fashion. The reaction was complete in a very short amount of time and afforded the *trans*-fused oxacycle. The product was isolated as a mixture of two diastereoisomers originating from the formation of diastereomeric bromonium ions.




**Scheme 35.** *Bromonium initiated epoxide opening cascade*

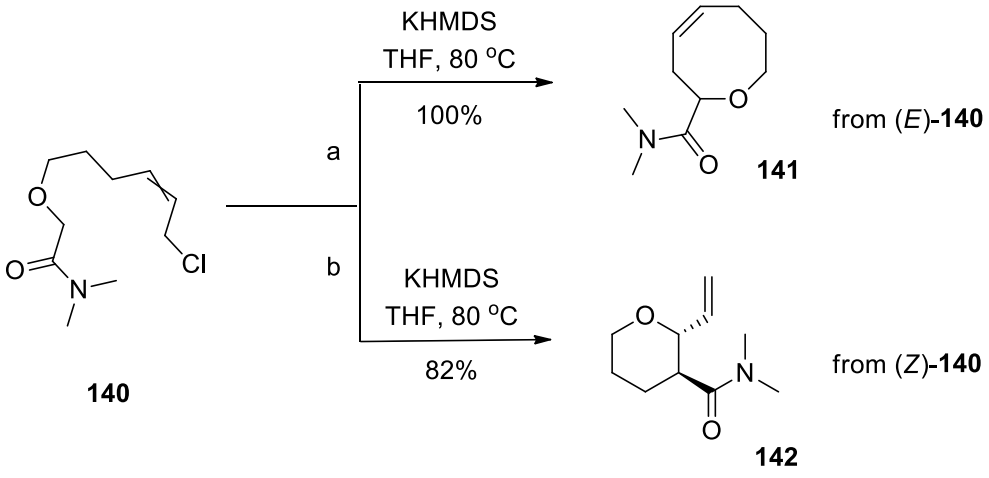
## 1.3 Cyclization via C-C Bond Formation

Formation of medium-sized cyclic ethers through carbon-carbon bond formation can be achieved by numerous reactions that have various degrees of success. Herein, illustrative examples of methodologies applied during total syntheses of natural products are presented.

### 1.3.1 Anion Alkylation

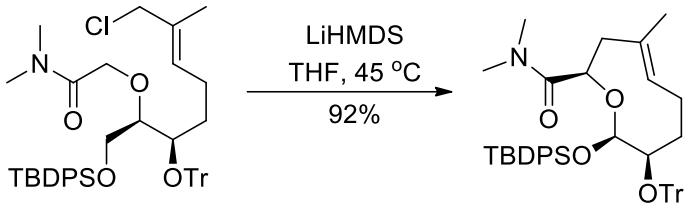
Although reactions of enolates are amongst the most popular in synthetic chemistry, few examples of intramolecular enolate alkylation methods for the synthesis of medium-sized cyclic ethers exist.

One of the most prominent examples of intramolecular enolate alkylation was initially disclosed by Kim et al. for the synthesis of the eight-membered oxacyclic core of (+)-3-(*Z*)-pinnatifidenyne.[48] In the course of studies concerning the cyclisation of the allylic chloride **140**, it was observed that the outcome of the reaction was dependent on the configuration of the alkene (Scheme 36). Thus, treatment of (*E*)-**140** with KHMDS afforded the oxocene **141**, whereas reaction of (*Z*)-**140** under the same conditions afforded the THP ring. Although pathway a proceeds by a standard $S_N2$ mechanism, reaction of *E*-**140** (pathway b) proceeds through an allylic displacement ($S_N2'$). This difference in the outcome of the reaction highlights the importance of the alkene geometry in governing the reaction pathway.




**Scheme 36.** *Intramolecular enolate alkylation for the synthesis of oxocene rings*

The same group used the strategy to accomplish the key step in first total synthesis of (*E*)-cladiellin and related natural products and thereby showcase its potential and its tolerance for highly functionalized substrates (Scheme 37).[49] Amide **143** was treated with LiHMDS to produce the nine-membered cyclic ether **144** in excellent yield. It was reported that LiHMDS should be used instead of KHMDS because use of the latter was found to result in decomposition, suggesting the presence of a lithium-chelated (*E*)-enolate intermediate.




**143** **144**

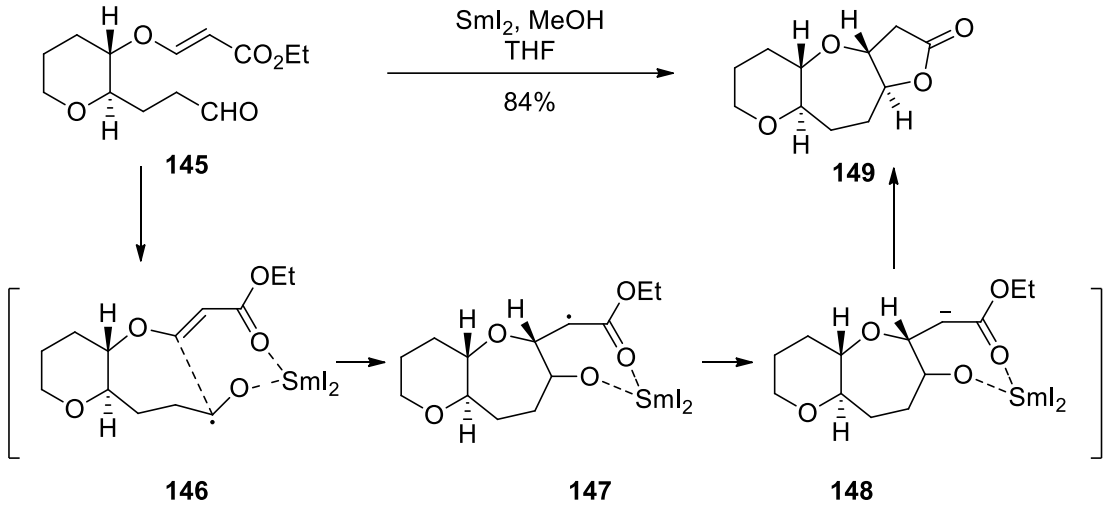
**Scheme 37.** *Synthesis of the oxonene core of (E)-cladiellin*

## 1.3.2 Radical Cyclization

One of the most prominent examples of radical cyclization in the field of marine polyether synthesis is the $SmI_2$ induced cyclization of ß-alkoxyacrylates. One of the benefits of the approach is formation of the desired stereoisomer of the product paired with a high yield. Furthermore, this methodology can be employed in an iterative manner for the formation of every ether ring.[2]

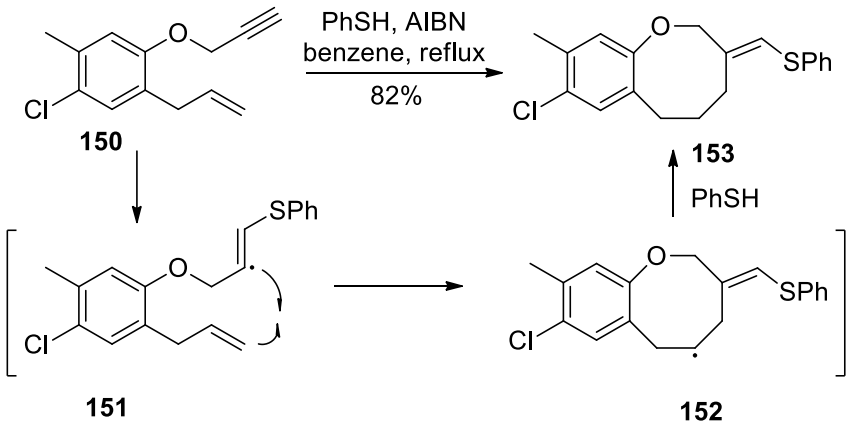
Nakata et al. were pioneers in the development of this methodology for iterative ring formation in marine polyether natural product synthesis.[50] A substrate bearing a *E*-ß-alkoxyacrylate side chain and a vicinal linear aldehyde or methyl ketone is reacted with two equivalents of $SmI_2$ to form the 2,3 di-substituted oxacycle (Scheme 38). The cyclization reaction is believed to proceed by single-electron reduction of the aldehyde with $SmI_2$ to produce a ketyl radical, followed by complexation with samarium. Formation of the C-C bond results in ring

closure and formation of the radical **148** that is reduced to the corresponding anion by the second equivalent of $SmI_2$. Protonation by methanol furnishes the oxepane product with the required stereochemistry and a γ- lactone.



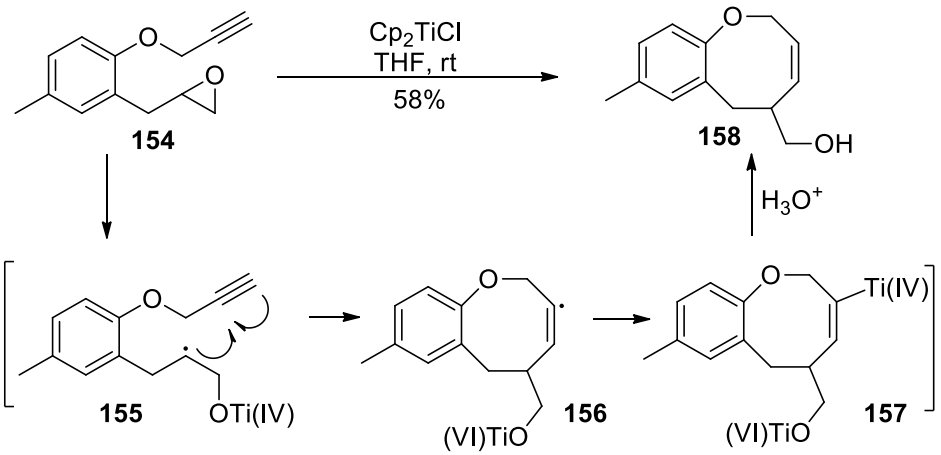

**Scheme 38.** *Samarium induced radical cyclization*

Another example of medium-sized cyclic ether synthesis by free radical cyclization is Majumdar's thiol-mediated synthesis of benzoxocine derivatives (Scheme 39).[51] Addition of thiophenol and AIBN to the enyne **150** leads to the regioselective addition of the thiol radical to form the intermediate **151**. Intramolecular 8-endo ring closure onto the alkene results to the benzoxocine **153**. Ring closure is facilitated by the planar and rigid structure of the substrate, which restricts the conformational freedom of the two side chains.




**Scheme 39.** *PhSH induced radical cyclization*

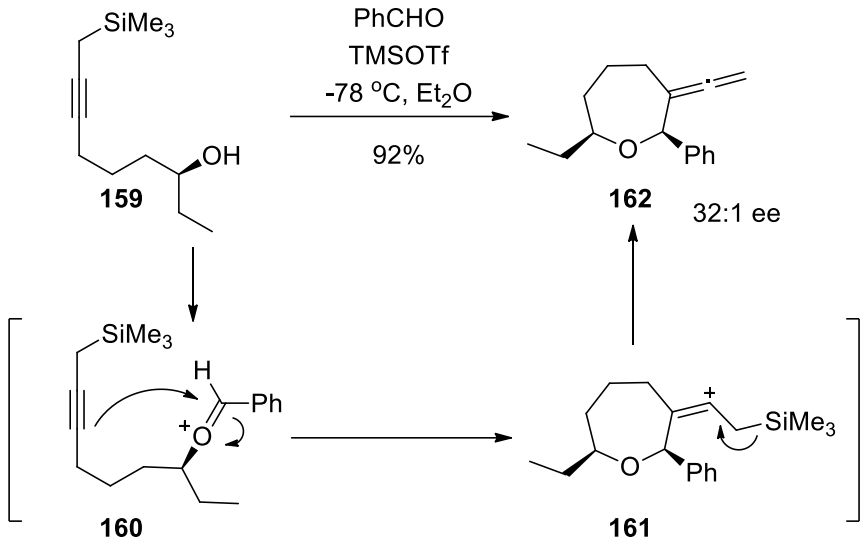
The synthesis of benzoxocine derivatives by a radical cyclization reaction has also been reported by Roy et al., who developed methodology in which a titanocene-mediated 8-endo radical reaction was used for ring formation (Scheme 40).[52] Reaction of epoxide **154** with titanocene generates the radical **155** and 8-endo cyclization produces the radical **156** that is immediately reduced by Ti(III) species. Protonation during aqueous workup furnishes the oxocine **158**.




**Scheme 40.** *Titanocene induced radical cyclization*

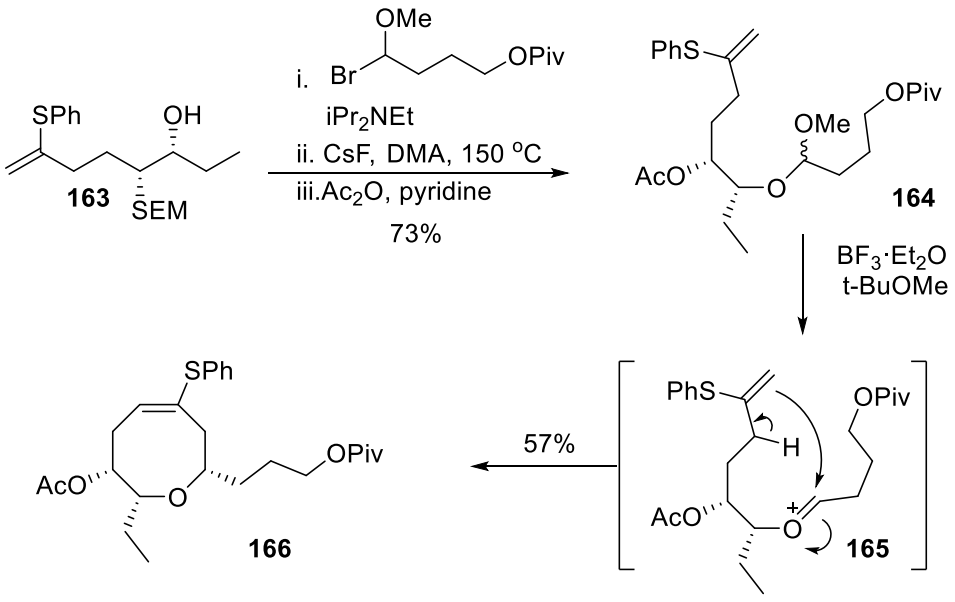
## 1.3.3 Cyclization via Prins-Type Reactions

An example of the use of Prins cyclization reaction to prepare medium-sized cyclic ethers comes from Furman et al., who employed propargylic silanes for the stereoselective synthesis of 2,7-disubstituted 3-vinylidene oxepanes (Scheme 41).[53] Treatment of the silane **159** with benzaldehyde and trimethylsilyl triflate afforded the oxepane product in an excellent yield with high diastereo-selectivity. A plausible reaction mechanism involves formation of the oxocarbenium ion **160** followed by the nucleophilic attack of the alkyne to form the oxepane **161**. Loss of the trimethylsilyl cation affords the desired allene product **162**. Although the reaction is efficient and selective, an aryl aldehyde is required as a reactant and this limits its applications because there is little variability with regard to the 2-substituent.




**Scheme 41.** *Prins-Type cyclization of propargyl silanes*

Novel methodology for the stereoselective synthesis of oxocene rings though a Prins rearrangement was reported by Overman et al. for the synthesis of (+)-laurencin (Scheme 42).[54] This method involves an intramolecular ene reaction and results in the cis orientation of the ether oxygen side chains. The alcohol **163** was reacted with the selected bromoether and manipulation of the protecting groups afforded the cyclization precursor **164**. Mechanistically, the cyclisation reaction is believed to proceed by formation of the oxocarbenium cation **165** followed by the ene reaction.

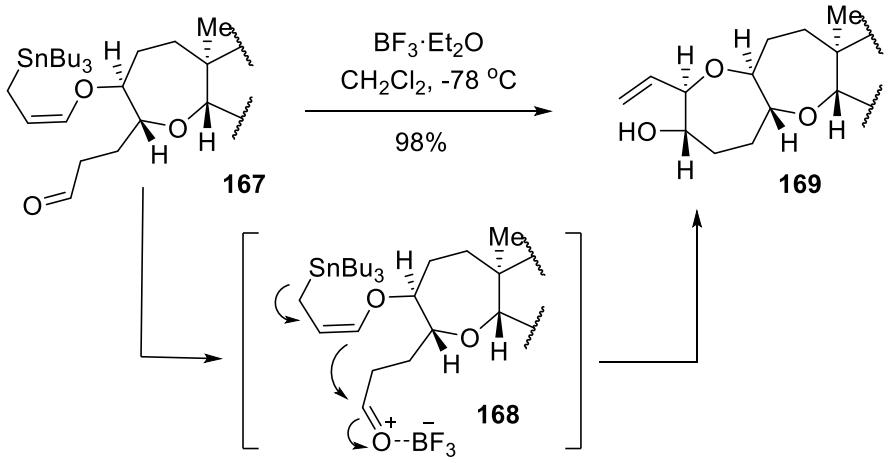



**Scheme 42.** *Prins cyclization of mixed acetal*

## 1.3.4 Organostannane mediated cyclization

Yamamoto et al. developed a novel method for the formation of cyclic ethers using organostannane chemistry.[55] This approach delivers excellent yields of the products with the required stereochemistry and has been employed during a total synthesis of hemibrevetoxin B.[56]

The reaction proceeds by intramolecular attack of the alkoxy allylstannane on the coordinated aldehyde to form the oxepane **169** as single diastereomer in almost quantitative yield (Scheme 43). Further modification of the product allow the allylstannane and aldehyde groups to be reinstated, enabling the iterative use of the reaction.



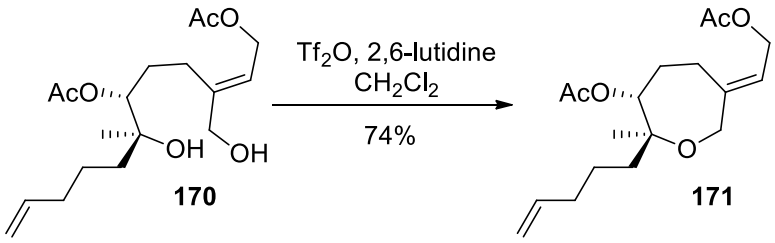

**Scheme 43.** *Synthesis of hemibrevetoxin B utilizing organostannane side chain cyclization*

## 1.4 Cyclization via C-O Bond Formation

One of the most appealing concepts for the synthesis of medium-sized cyclic ethers is the cyclization via carbon oxygen bond formation. Transformation of linear chains to oxacycles is a very interesting method and various approaches have been examined.

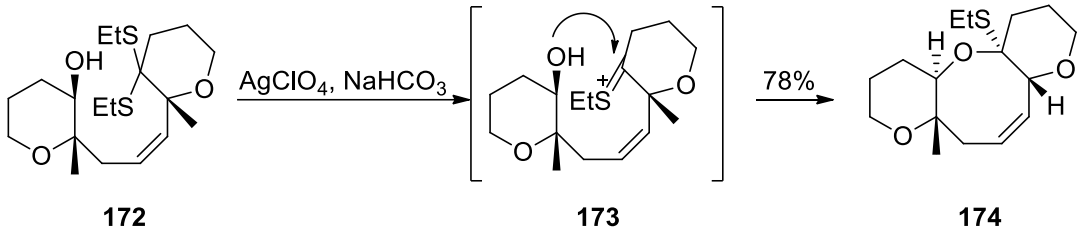
### 1.4.1 Intramolecular Alkylation

A key example of cyclisation with an oxygen nucleophile under acidic conditions was reported by Trost et al. as a key step in a total synthesis of (+)-zoapatanol (Scheme 44).[57] The 1,6-diol **170** was treated with triflic anhydride in the presence of 2,6-lutidine to form the oxepane core **171** in a stereoselective manner. Initial formation of the primary triflate leads to a spontaneous intramolecular $S_N2$ reaction that produces the cyclic ether.




**Scheme 44.** *Intramolecular alkylation – Ring Closure of diols*

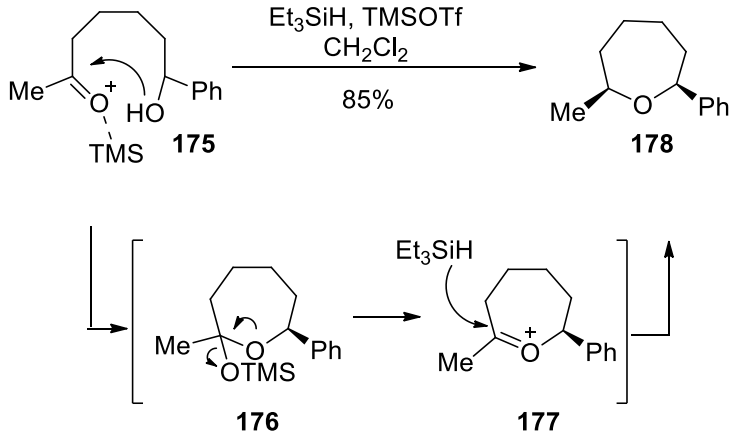
As oxocene ring is one the most strained of the cyclic ethers and examples of its formation via intramolecular $S_N2$ reactions are limited. In order to overcome this problem, Nicolaou et al. have developed methodology for the cyclization of hydroxy dithioketals to give medium-sized oxacycles (Scheme 45).[58] This method has been used in the total synthesis of brevetoxins A and B.[59,60] Treatment of the dithioketal **172** with $AgClO_4$ is postulated to form the highly reactive thionium ion **173** that readily undergoes ring closure to form the trans fused tricyclic system **174**. The conformation of the intermediate is of great importance and the absence of the double bond leads to failure of the reaction.




**Scheme 45.** *Cyclization of Hydroxy Dithioketal*

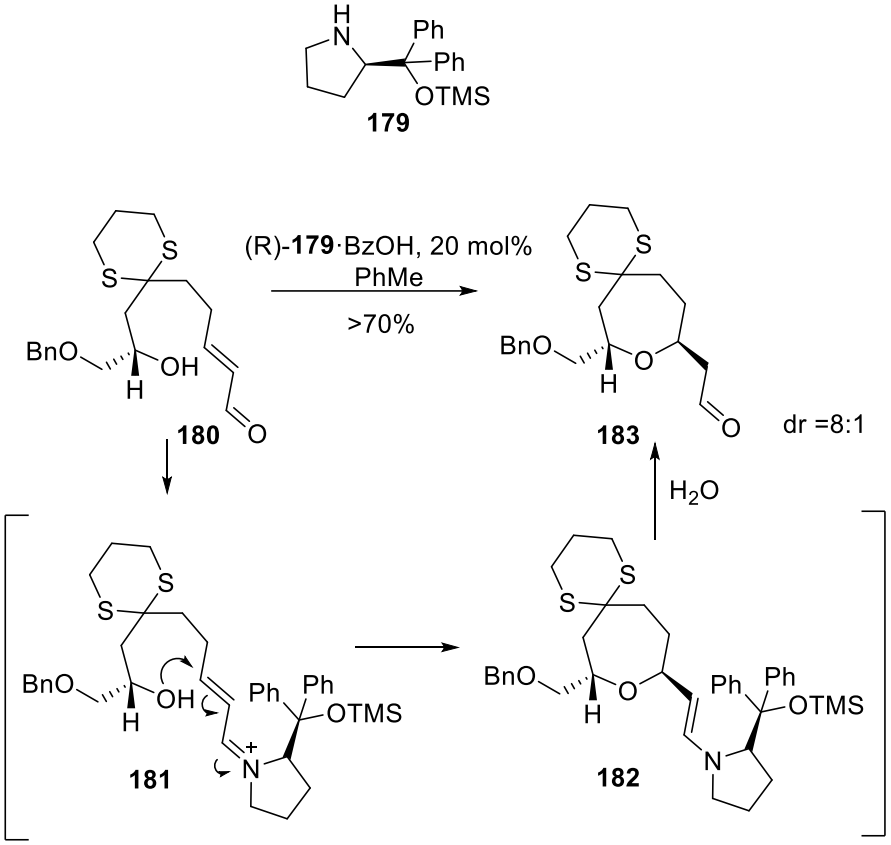
## 1.4.2 Reductive Etherification

In order to tackle the synthesis of the oxepane rings present in the marine ladder polyethers, the Nicolaou group adapted the work of Olah et al.[61] and developed a reductive etherification approach,[62] that was later used in the total synthesis of brevetoxin B.[63] Treatment of the hydroxy ketone **175** with excess of $Et_3SiH$ and TMSOTf furnished the oxepane ring **178** in high yield (Scheme 46). It is believed that sequential activation of the carbonyl oxygen with the trimethyl silyl group, nucleophilic attack of the hydroxyl group and expulsion of the TMSO group leads to formation on the oxocarbenium ion **177**, which is eventually reduced by the $Et_3SiH$. As for the stereoselectivity of the reaction, examples show that it is highly influenced by the α-substituents, with diastereoselectivity varying from 3:1 to 4:1 in favor of the isomer possessing the cis configuration.




**Scheme 46.** *Reductive etherification of hydroxy-ketones*

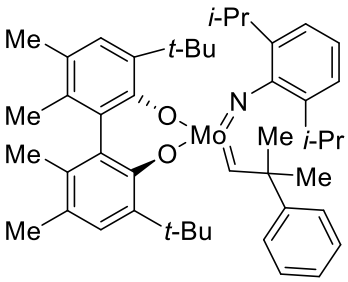
Hong et al. have disclosed a novel approach for the synthesis of trans α,α'-disubstituted oxepanes by an organocatalytic oxa-conjugate addition reaction (Scheme 47).[64] In this reaction, the conjugated aldehyde **180** is reacted with the pyrrolidine derivative to form the iminium ion **181**. Nucleophilic attack of the hydroxyl group leads to the intermediate cyclized enamine **182** and subsequent hydrolysis affords the desired aldehyde **183**.




**Scheme 47.** *Stereoselective oxa-conjugate addition of alcohol*

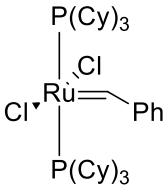
## 1.5 Cyclization via Ring-Closing Metathesis

The discovery of the olefin metathesis and the subsequent development of related methods has been a pivotal point in the field of natural product synthesis. More specifically, the cyclization of dienes to produce medium-sized ethers using ring-closing metathesis (RCM) has been studied and developed extensively. The reaction has been used for the efficient synthesis of many marine natural products such as the brevetoxins, ciguatoxins and laurencia red algae metabolites.[65]



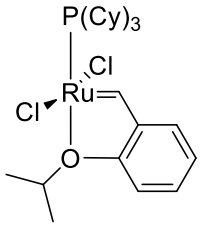

**184**

Schrock-Hoveyda Catalyst



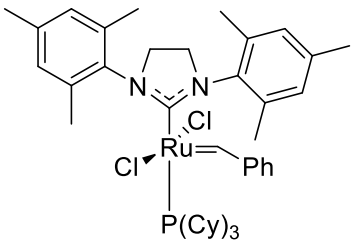

**185**

First Generation Grubbs catalyst



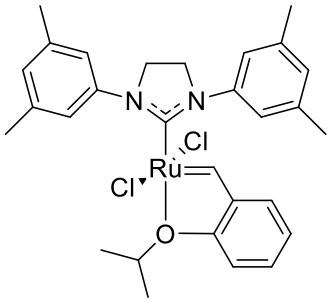

**186**

First Generation Hoveyda-Grubbs catalyst




**187**

Second Generation Grubbs catalyst



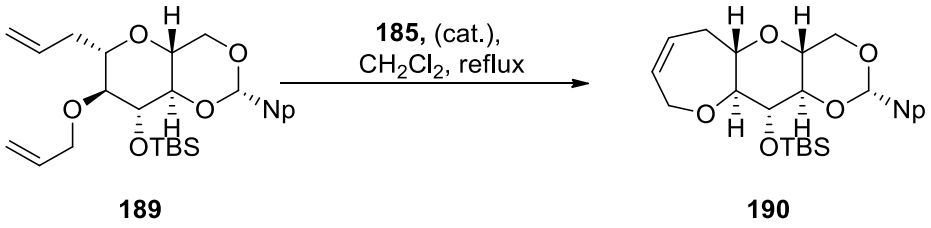

**188**

First Generation Hoveyda-Grubbs catalyst

**Scheme 48.** *Selection of the most known catalysts for olefin metathesis*

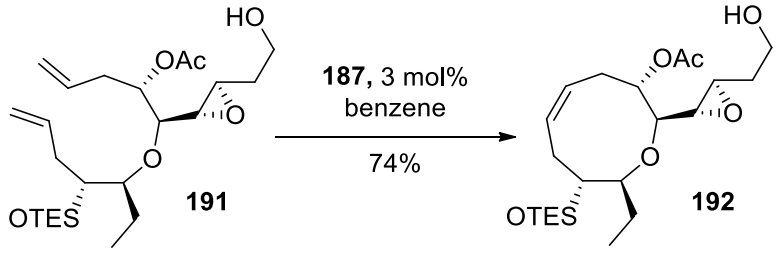
Ring-closing diene metathesis is most often accomplished by use of Schrock's molybdenum catalyst, Grubbs' ruthenium catalyst and the Hoveyda-Grubbs ruthenium catalyst, with the two latter being available in two generations (Scheme 48). What distinguishes these catalysts is their reactivity, tolerance to functional groups, thermal stability and, most importantly, tolerance to water residues and oxygen.

The general method involves treatment of the diene with a sub-stoichiometric amount of catalyst to form the (*Z*)-unsaturated oxacycle. Terminal dienes are transformed to the corresponding unsaturated oxacycles with high selectivity. The reaction has been performed effectively for the formation of seven- to nine-membered oxacycles.




**189** **190**

**Scheme 49.** *Synthesis of ABC fragment of CTX3C by Fujiwara*[66]

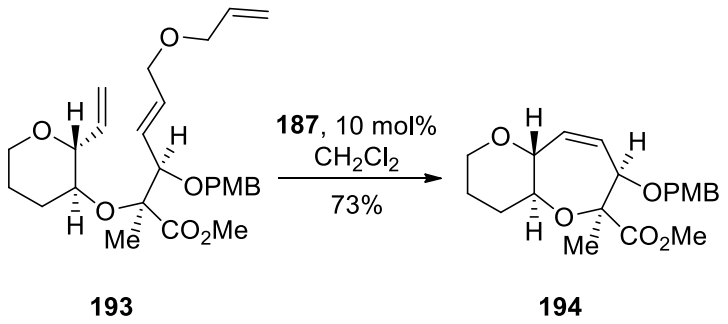



**Scheme 50**. *RCM of the oxacyclic core of (+)-obtusenyne by Crimmins*[67]

Although olefin metathesis is a reliable reaction for the ring closure, problems can arise when hindered olefins or if polyene substrates are used. Relay ring-closing metathesis has been developed by Hoye et al. as mean of controlling the reaction and facilitating the reaction of the ruthenium catalyst with hindered olefins.[68] This can be done by use of an "extension" group terminating in an

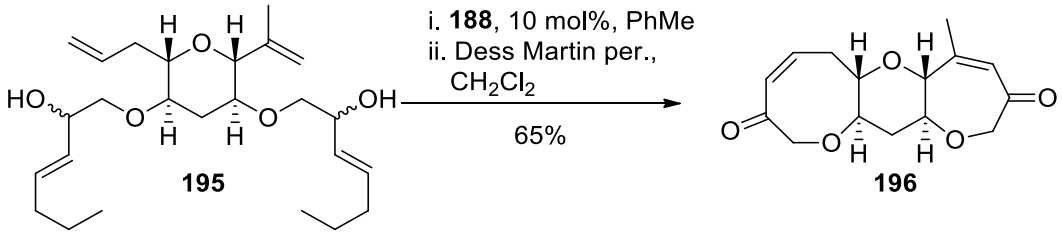
alkene (Scheme 51). The only function of the extension is to relay the catalyst from the terminal alkene to the one in the parent structure and it is not incorporated into the final product.

Fujiwara et al. have utilized this methodology to construct the BC- ring of armatol F.[69] Synthesis of the sterically hindered oxacyclic alkene **194** was performed by treatment of the substrate **193** with the Grubbs second generation catalyst and the allyl ether side chain participated in RRCM.




**Scheme 51.** *Relay RCM for the synthesis of trans-fused oxepane system*

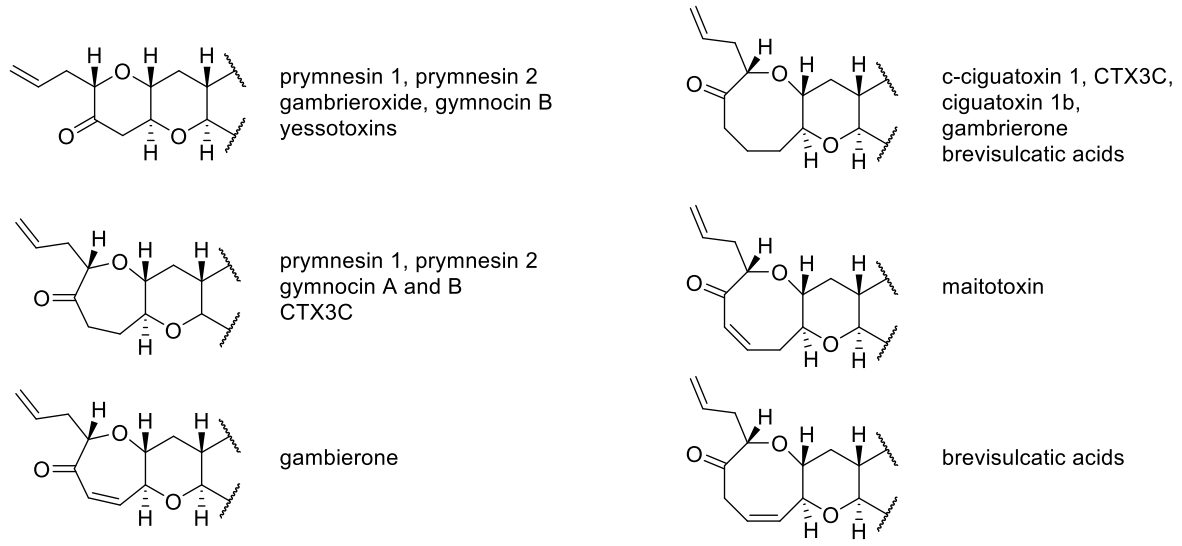
Exploiting the efficiency of the reaction, Clark et al. have developed a bidirectional ring-closing metathesis reaction for the synthesis of the IJK fragment of CTX3C (Scheme 52).[70] Oxidation of the bis-enone to the corresponding bis-allylic alcohol **195** was followed by treatment with the Hoveyda–Grubbs second generation complex and the resulting diol was then reacted with DMP to produce the tricyclic bis-enone **196**. The reduction-RCM-oxidation sequence was used to bypass the reduced reactivity of the bis-enone substrate.




**Scheme 52.** *Bi-directional RRCM for the IJK fragment of CTX3C*

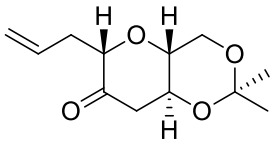
## 2. Results and discussion

Polyether polycyclic marine natural products possess in their structure medium-sized rings with ring sizes of seven, eight and nine and varying degrees of unsaturation (Scheme 53). While many different approaches to their formation exist,[2] the majority of approaches involve direct cyclization to the medium sized cyclic ether from a functionalized acyclic substrate. While this method has been used effectively for the total syntheses of some marine natural products, ring-expansion methodology still has potential advantages because it bypasses the entropic and enthalpic barriers associated with the formation of medium-sized oxacycles from open chain precursors.




**Scheme 53.** *Medium sized cyclic ethers in marine natural products*

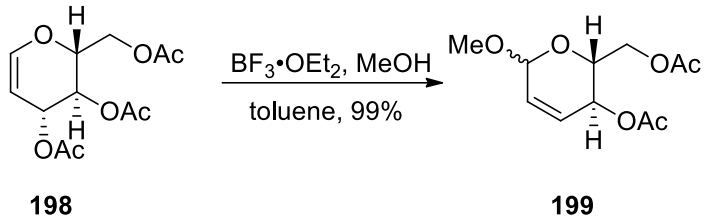
In this work, one- and two-carbon ring-expansion methods for the formation of the medium-sized rings of the polyether polycyclic natural products are examined. In order to study these methods, the model system **197** was chosen as the substrate as it bears many similarities to the sub-structures of polycyclic ether natural products. Based on the synthetic route previously developed by the Clark group, the synthesis of substrate **197** in sufficient quantities was the first task.




**197**

## 2.1 Synthesis of the six membered ketone

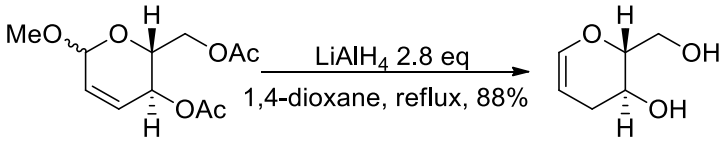
The synthesis commenced with the treatment of commercially available tri-O-acetyl-D-glucal **198** with methanol in the presence of boron trifluoride diethyl etherate. Ferrier rearrangement occurred under these conditions to give the acetal **199** in quantitative yield (Scheme 54).




**198** **199**

**Scheme 54.** *Ferrier rearrangement to the mixed acetal*

Based on previous experimental procedures developed in the Clark group,[71,72] the diol **200** was prepared by treating the acetal **199** with lithium aluminum hydride in 1,4 dioxane at reflux, which resulted in the reduction of the allylic methoxy group and deprotection of both hydroxyl groups simultaneously in one step (Scheme 55). Following the completion of the reaction, the mixture was quenched according to the Fieser work up procedure and left stirring overnight over $Na_2SO_4$. With longer times between quenching and filtration over celite, it was observed that the fine particulates coagulated to form a precipitate aggregate, making the handling easier.



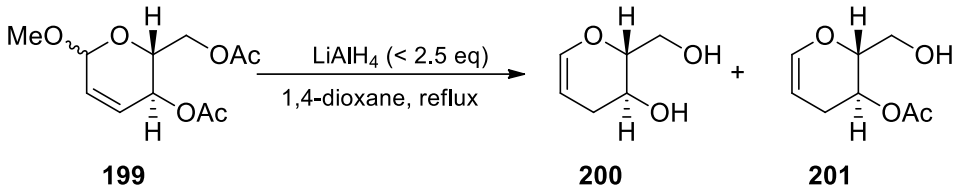

**199** **200**

**Scheme 55.** *Reduction of the mixed acetal to the enol ether diol*

There were concerns about rapid hydrogen gas evolution of the reaction at the first stage of heating, especially on large scale, and so the experimental procedure was modified. The reaction mixture was left to stir overnight at room temperature was then heated at reflux for 5 hours as per literature. Stirring the

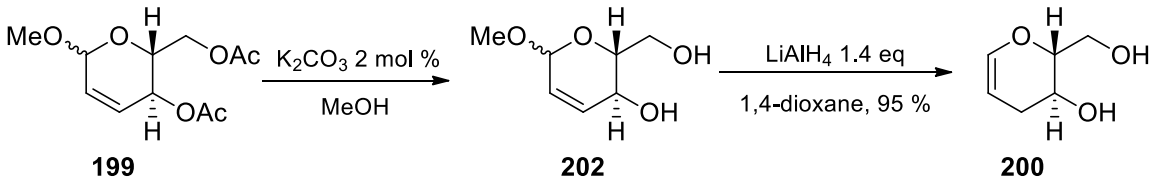
mixture at room temperature for an extended time seemed to solve the problem of the initial foaming. This can be explained by the reduced reaction rate as well as the selective reduction of the most labile group, the primary ester, instead of the simultaneous reduction of all three groups.

This modification proved to be adequate to eliminate foaming due to the production of hydrogen, with virtually no impact on the yield of the reaction. After this modification, attempts were made to reduce the quantity of LAH used in the reaction because quantities of 30 grams per batch were considered a potential hazard. Trials were performed using less than 2.5 eq of LAH but it was observed that the reaction did not proceed to completion.




**Scheme 56.** *Reduction of the mixed acetal with less than 2.5 eq of LAH*

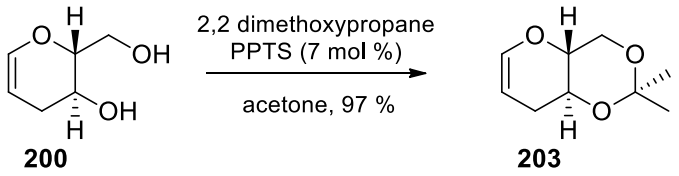
In order to minimize the amount of LAH required, a new strategy was explored. This involved the deprotection of the acetates in a solution of methanol using catalytic amounts of $K_2CO_3$ and treatment of the resulting diol **202** with LAH (Scheme 57). Surprisingly, the yield of the two-step reaction was found to be higher than that of the initial route, a result that can be explained by reduced material loss as a result of the smaller amount of slimy precipitate after the Fieser work-up of the reaction.




**Scheme 57.** *Alternative route to the diol*

Having eliminated the former concerns, the following step was the protection of the diol **200**. Treatment of the diol **200** with 2,2-dimethoxy-propane using PPTS

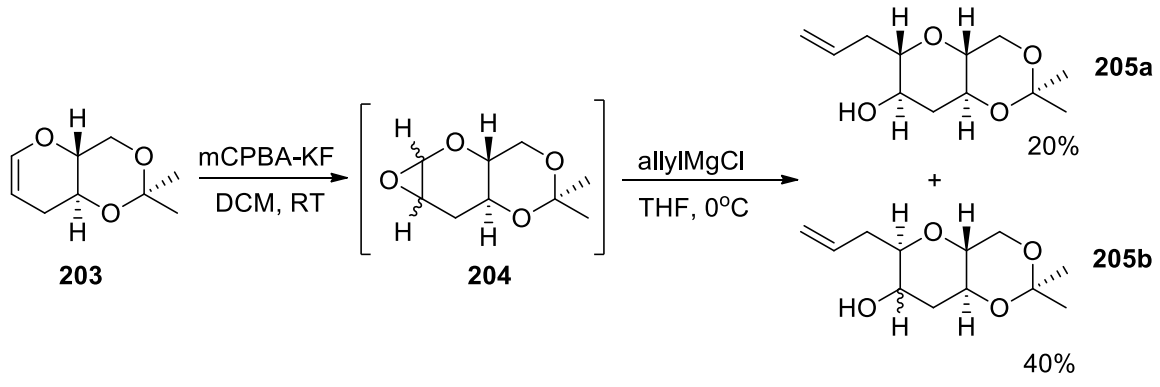
as catalyst, afforded the acetonide **203** in high yield without the need for chromatographic purification.




**Scheme 58.** *Acetonide protection*

Previous work in the group by Gibbard and Popadynec had shown that the acetonide protection of the diol is the most efficient choice for this route.[71,72] The TBS protected enol ether was found to afford the corresponding allylation product after epoxidation and ring opening, with a strong preference to the undesired stereochemistry, while the di-tert-butylsiloxane protected enol ether afforded a mixture of the diasteromers that was not separable by column chromatography. Even though there were concerns about the stability of the acetonide group under the conditions envisioned for the ring-expansion studies, late-stage deprotection and protection would circumvent those issues.

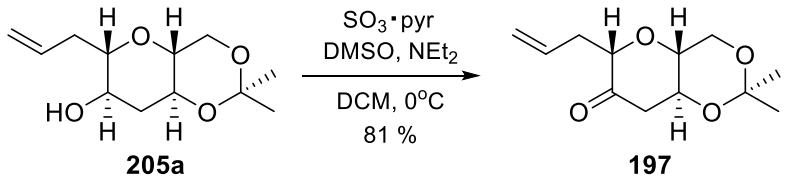
Having access to large amounts of the acetonide **203** the next step was the insertion of the allyl group. The procedure involved treatment of the enol ether **203** with Camp's heterogeneous mCPBA-KF complex in DCM to afford the unstable epoxide **204**. The epoxide was concentrated under reduced pressure and treated without any further purification with freshly prepared batches of allyl magnesium chloride. This procedure afforded the alcohols **205a** and **205b** in a 1:2 dr.




**Scheme 59.** *Epoxidation and allyl addition sequence*

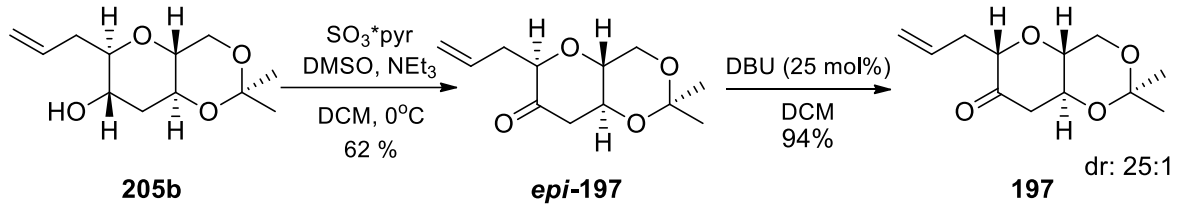
The apparent lack of stereoselectivily for epoxide formation, as is evident from the ratio of the alcohol products, can be explained by the lack of facial stereoselectivty, because there is no steric hindrance from adjacent groups, as there is in some similar substrates.[116]

Alcohol **205a** was then oxidized to the corresponding ketone using a Parikh-Doering oxidation reaction to afford the target intermediate ketone **197** in 84% yield.




**Scheme 60.** *Parikh Doering oxidation to ketone*

The undesired diasteromer product **205b** arising from the epoxide opening reaction was oxidized under the same conditions to afford the epimeric ketone ***epi*-197** that was epimerized by treatment with 25 mol% of DBU in the dark and resulted in 25:1 dr of product in favor of **197**.



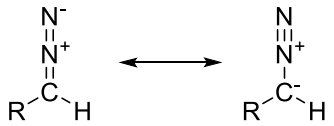

**Scheme 61.** *Oxidation- epimerization sequence of the undesired isomer*

In summary, ketone **197** was prepared in 37 % yield over 7 steps from tri-*O*-acetyl-D-glucal, purification of the product by flash column chromatography was required after just two of the steps. Further optimization of the LAH reduction resulted in a safer and higher yielding procedure. The unrequired diastereomer **205b** could be easily converted into the required isomer in high yield by epimerisation. The synthetic route now diverged from known intermediates previously made by the Clark group.

## 2.2 Cyclic ketone homologation – Ring Expansion

### 2.2.1 Reactivity of diazocompounds

The first report of diazo compounds was published by Curtius in 1883 and describes the synthesis of ethyl diazoacetate.[74] This was the beginning of the diazo chemistry. Diazo compounds are particularly attractive synthetic intermediates, participating in numerous reactions and providing the building blocks for the synthesis of many different systems, having been utilized in synthetic and medicinal chemistry for years. One of their key features is that they exhibit nucleophilic properties under basic or neutral conditions whereas their reactivity is reversed under acidic conditions where they behave as electrophiles.[75]

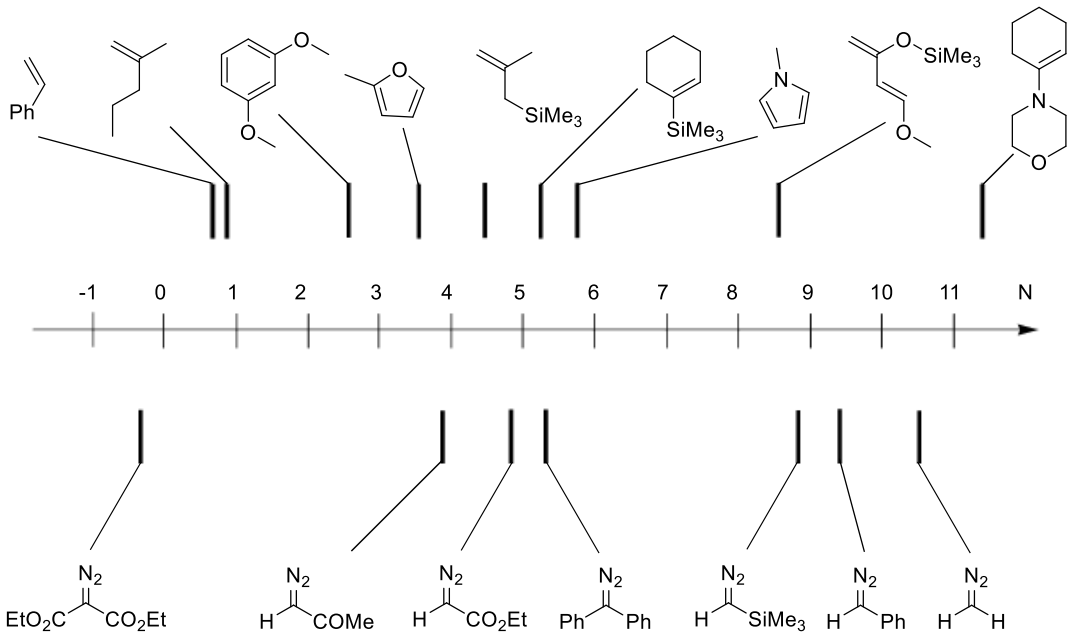


**Scheme 62.** *Resonance structures of diazoalkane*

The reactivity originates from the electron density of the carbon and is directly influenced by the adjacent substituent. Substituents with potential to delocalise the electron density through resonance effects reduce the reactivity, whereas groups without such abilities confer greater nucleophilicity. As a consequence of this property, diazo compounds can be classified into two major categories. The first group includes stabilized diazo compounds, in which that the adjacent substituent, such as a carbonyl, phosphoryl or sulfonyl group, can delocalise the electron density. The counterparts are referred to as non-stabilized diazo compounds; the substituent is commonly an alkyl- group or any group with similar electronic properties in these cases. The major difference between the two categories is their relative reactivity. Due to the delocalization of the electron density, stabilized diazo compounds are less reactive and are relatively stable, with many of them being commercially available.[76] In contrast, non-stabilized compounds are significantly more reactive. However, this creates drawbacks because many of them are unstable, have to be prepared immediately before the experiment and in the case of the simpler diazoalkanes

(e.g. diazomethane) they pose a health and safety hazard due to their significant toxicity and explosive nature.[77,78]

In recent literature, Mayr et al. performed extensive experiments to study the reactivity of various diazoalkanes (Scheme 63).[79] As seen in this work, the less stabilized diazomethane exhibits the highest nucleophilicity, which is comparable with that of enamines. Phenyl-diazomethane and TMS-diazomethane are not far behind, being located towards the upper end of the reactivity spectrum. On the other side, diazoalkanes with adjacent carbonyl groups are significantly less reactive, with the diethyl 2-diazomalonate being even less reactive than styrene. These results demonstrate in an excellent way the influence of substituents on the reactivity of diazomethane.

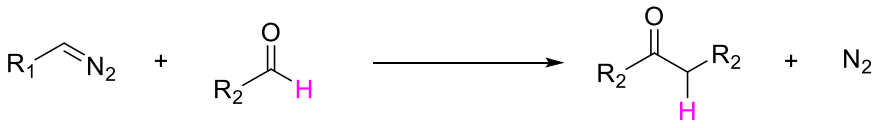



**Scheme 63.** *Index of relative reactivity of diazo-compounds and common nucleophiles*

## 2.2.2 Review on cyclic ketones homologation

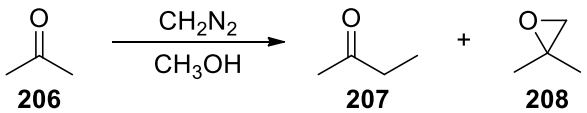
The reaction of carbonyl-containing compounds with diazoalkanes was firstly observed by Büchner and Curtius in 1885.[80] Even though the reaction of ketones and aldehydes with diazoalkanes has been examined by others,[81] Schotterberck was accredited with the discovery of the reaction of aldehydes with diazoalkanes in 1907.[82] Through methodical studies he confirmed that the reaction of various aliphatic aldehydes with diazomethane afforded the corresponding methyl ketones.

This reaction was later named in honor of the scientists as the Büchner-Curtius-Schlotterbeck reaction (Scheme 64). Although the reaction was reported at that time, application in linear and eventually cyclic ketones did not come until several decades later.



**Scheme 64.** *Büchner-Curtius-Schlotterbeck reaction*

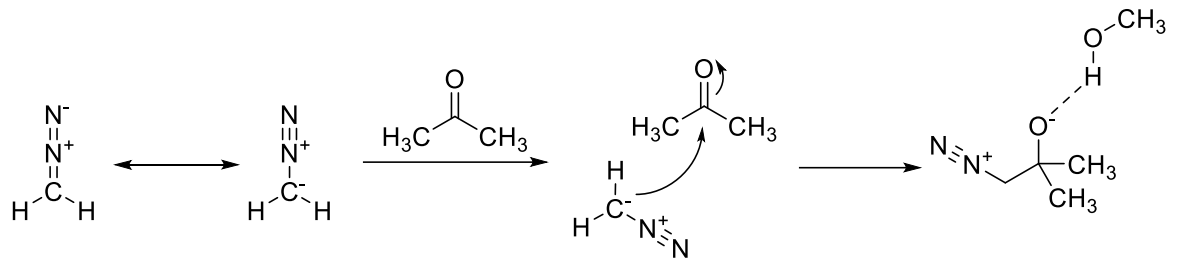
Meerwein in 1928 was the first to report a reaction between a ketone and diazomethane, in the presence of a protic solvent (Scheme 65).[83] According to his findings, treatment of acetone with diazomethane did not lead to product formation. However, in the presence of water or alcohols, acetone would react with diazomethane to afford dimethylethylene oxide and ethylmethylketone.




**Scheme 65.** *Reaction of acetone with diazomethane and methanol*

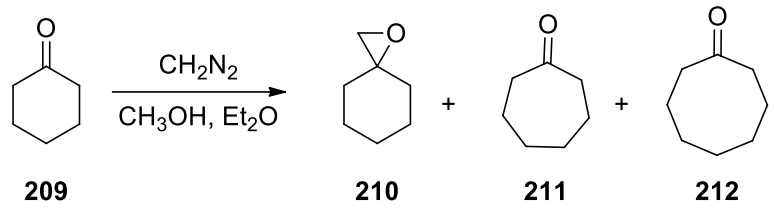
The novelty of this discovery can be explained by using a simple general model of acidic catalysis (Scheme 66). On the assumption that the initial step of the mechanism is nucleophilic attack of the carbonyl group by diazomethane, addition of a protic solvent facilitates the reaction by hydrogen bonding to the

newly formed alkoxide, stabilizing the intermediate and thus increasing the electrophilicity of the carbonyl group.



**Scheme 66.** *Mechanism of the reaction of diazo-compounds with ketones*

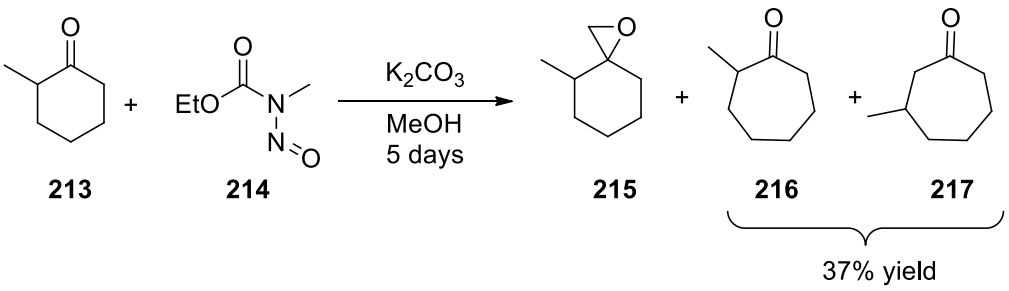
It was not long after this discovery that the first example of the homologation of cyclic ketones with diazomethane was published. In 1930, Mosettig reported the first ever ring expansion of a cyclic ketone by reaction with diazomethane.[84] According to his observations, cyclohexanone was totally unreactive when mixed with an excess of diazomethane in an ethereal solvent. However, when methanol was added to the reaction mixture, vigorous evolution of nitrogen gas was observed, and the reaction yielded a mixture of methylene-cyclohexane oxide, cycloheptanone and cyclooctanone (Scheme 67). The same procedure was repeated again, but this time cyclopentanone was used as the substrate. Analysis of the products of the reaction, showed the formation of methylene-cyclopentane oxide, cycloheptanone and cyclooctanone as major products. Cyclopentanone and cyclohexanone were not detected in the product mixture, which suggests that the full consumption of the starting material and consecutive ring expansion of the cyclohexanone had occurred. This can be rationalized by taking into account the increased torsional strain of the newly formed cyclohexane, by the introduction of an additional $sp^3$ hybridized center in the constrained ring system. The accepted relative reactivity of cyclic ketones is in the order of cyclohexanone >cyclopentanone >cycloheptanone >cyclooctanone.[85,86]




**Scheme 67.** *Reaction of cyclohexanone with diazomethane and methanol in diethyl ether*

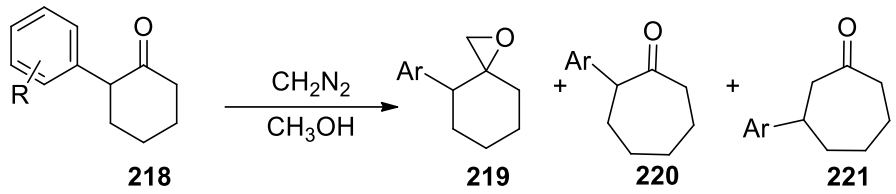
The aforementioned results show that the reaction of simple cyclic ketones with diazomethane cannot be controlled, especially when the product is more reactive than the starting material. The results also show that oxirane byproducts cannot be avoided with this approach, and that the use of protic solvents and extended reaction times dictate the use of excess diazomethane, because decomposition is significant.[87] Furthermore, the use of symmetric cycloketones does not give an insight on the regioselectivity of the methylene insertion.

The first reported example of ring expansion of asymmetric cyclic ketones was published by Adamson in 1939.[88] He explored the homologation of 2-methyl-cyclohexanone with in situ generated diazomethane and used methanol as the protic promoter (Scheme 68). The reaction produced both possible ring-expanded products in a combined yield of 37% along with the six membered epoxide. Even though both regioisomers were isolated and identified, the ratio between the two, thus the regioselectivity was not reported.




**Scheme 68.** *Reaction of 2-methyl-cyclohexanone with in situ generation of diazomethane*

Further research concerning the regioselectivity of the reaction of cyclic substrates was presented by Gutsche in 1949.[89,90] Five 2-aryl cyclohexanones were treated with diazomethane, in order to examine how the electronic (inductive) effects of various aryl substituents would influence the regioselectivity (Table 1).[91] The hypothesis was that a more electron-rich α-aryl group would promote the migration on that side of the molecule.



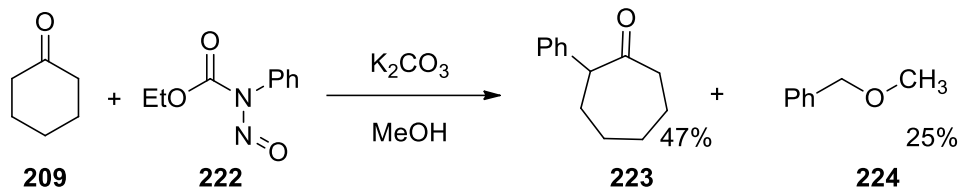

**218** **219** **220** **221**

| entry | R | *ρ* | 219(%) | 220(%) | 221(%) | rr (220:221) |
|---|---|---|---|---|---|---|
| 1 | H | 0 | 21 | 59 | 14 | 4.2:1 |
| 2 | p-$CH_3$ | −0.170 | 21 | 55 | 20 | 2.8:1 |
| 3 | p-$OCH_3$ | −0.268 | 14 | 57 | 21 | 2.7:1 |
| 4 | 2,3,4 -$OCH_3$ | - | 18 | 40 | 28 | 1.4:1 |
| 5 | p-Cl | +0.227 | 26 | 45 | 20 | 2.2:1 |

**Table 1**. *Investigation on the effect of the substituents based on their Hammett values and the regioselectivity of the reaction*

Based on the Hammett ρ values shown in Table 1, the substrate bearing a *p*-chlorophenyl substituent (entry 5) would be expected to exhibit the highest regioisomeric ratio and that bearing the 2,3,4-trimethoxyphenyl substituent (entry 4) the lowest. Unexpectedly the results were not in agreement with the hypothesis; the substrate with a phenyl substituent (entry 1) had the greatest regioselectivity. Although the lowest ratio was obtained for the substrate in entry 4, the isomer ratios are very similar and so no solid conclusions can be made. Gutsche came to the conclusion that the reaction is not affected significantly by substituents on the aromatic ring and that the observed differences in product ratios result from a combination of factors.

Gutsche's novel work in the field of diazomethane-mediated ring expansion continued and he was the first to report such reactions using phenyl diazomethane and other diazocompounds (Scheme 69).[92,93]

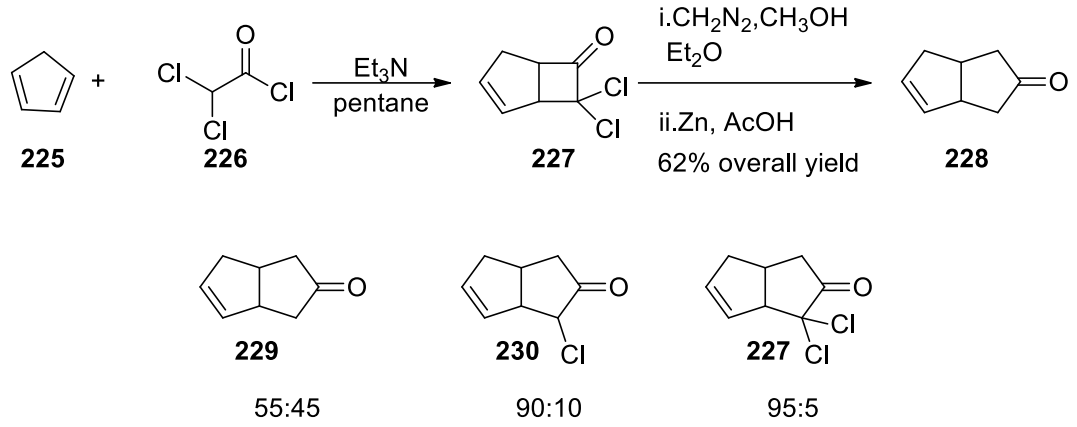



**209** **222** **223** **224**

**Scheme 69.** *Reaction of cyclohexanone with in situ generation of phenyl-diazomethane*

The conclusion from the data is that there is a strong preference for the migration of the less substituted and more accessible group, regardless of the aryl substituent.

Gutsche's hypothesis was reinvestigated later by Greene, who performed ring expansion studies on α-chloro substituted cyclobutanones (Scheme 70).[94] When des-, mono- and di-chloro cyclobutanones were used as substrates, a trend was observable: that the more electron-rich bond would migrate preferentially. A trend was also observed in the reaction rate which was accelerated by chloro-substitution. This can be rationalized by the electron donation from the carbonyl π orbital to the antibonding σ* orbital of the C-Cl bond and polarization of the C-O bond due to the adjacent chlorine(s). The des-chloro cyclobutane reacted to give a regioisomeric ratio of 55:45 in favor of **229** while the α,α-dichloro analogue reacted to give a product ratio of 95:5. In this work, epoxide formation is not observed, presumably due to the strain involved in the formation of a [2.3] spirocycle.

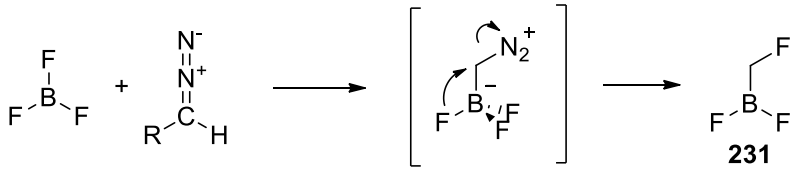



**Scheme 70.** *Green's investigation of the effects of substituents on the regioselectivity of the reaction*

## 2.2.3 Lewis Acid Promoted Homologation

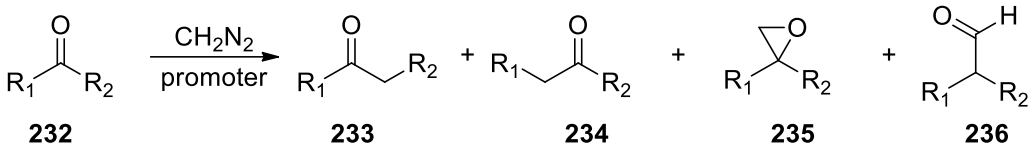
The use of protic solvents as promoters was a breakthrough in the field of diazoalkane mediated cycloketone enlargement and was utilized for many years. However, as seen in the previous chapter, the reactions suffered from extended reaction times, diazoalkane decomposition, uncontrolled over-homologation, poor regioselectivity and moderate yields in the case of bulky diazoalkanes. The rate-limiting step is the addition to the carbonyl group to form the intermediate betaine and so it was hypothesized that coordination of the carbonyl oxygen with a stronger acid than methanol would increase its electrophilicity and thereby accelerate the reaction. However, strong Brønsted acids were known to not be compatible with the diazocompounds and so a new family of promoters had to be found.

At the time there were literature examples that showed $BF_3$ is incompatible with diazomethane, the combination of which was known to result in the formation of polymethylene and fluoromethyl boron difluoride (Scheme 71).[95]




**Scheme 71.** *Decomposition of diazomethane in the presence of boron trifuoride*

In spite of perceived compatibility issues, House examined the usage of boron trifluoride etherate as a potential catalyst for the ketone homologation reaction in 1960.[96] The procedure involved complexation of the ketone with $BF_3 \cdot Et_2O$ (one equivalent) in an ethereal solution and the subsequent addition of diazomethane at 0 $^oC$. It is important to note that these reactions were not driven to full conversion in order to avoid any undesired over-homologation. By repeating the reaction using methanol as a promoter, direct comparisons between the two different catalysts could be made. The results reported in the original manuscript are presented in Table 2.




**232** **233** **234** **235** **236**

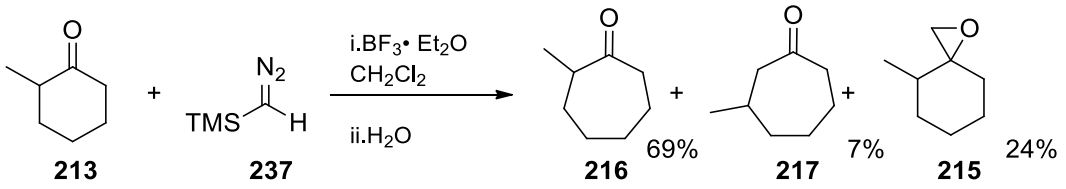
| entry | $R_1$ | $R_2$ | promoter | time | % conv. | 233:234:235:236 |
|---|---|---|---|---|---|---|
| 1 | Ph | $CH_3$ | $CH_3OH$ | 4 d | 55.8 | 4 : 69 : 27 : 0 |
| 2 | Ph | $CH_3$ | $BF_3{\cdot}Et_2O$ | 2 min | 36.3 | 22 : 78 : 0 : 0 |
| 3 | Bn | $CH_3$ | $CH_3OH$ | 3 d | 65.4 | 32.5 : 20.5 : 47 : 0 |
| 4 | Bn | $CH_3$ | $BF_3{\cdot}Et_2O$ | 2 min | 36.5 | 78.5 : 21.5 : 0 : 0 |
| 5 | Pr | $CH_3$ | $CH_3OH$ | 3 d | 25.0 | 33 : 34 : 33 : 0 |
| 6 | Pr | $CH_3$ | $BF_3{\cdot}Et_2O$ | 4 min | 19.0 | 50.5 : 49.5 : 0 : 0 |
| 7 | *i*-Pr | $CH_3$ | $CH_3OH$ | 1 d | 4.9 | 65.5 : 34.5 : 0 : 0 |
| 8 | *i*-Pr | $CH_3$ | $BF_3{\cdot}Et_2O$ | 2 min | 6.8 | 46 : 22.5 : 0 : 31.5 |
| 9 | *t*-Bu | $CH_3$ | $CH_3OH$ | - | 0 | nd |
| 10 | *t*-Bu | $CH_3$ | $BF_3{\cdot}Et_2O$ | 2 min | 0.8 | 44 : 15.5 : 0 : 40.5 |

**Table 2.** *Effect of promoter on the efficacy of the reaction*

From the experimental data the effect that $BF_3{\cdot}Et_2O$ has on the reaction is immediately noticeable. The reaction rate was improved significantly, and the desired products were obtained in a matter of minutes rather than days, even at a lower temperature. With the Lewis acid catalyst it was even possible to homologate pinacolone in reasonable yield (entry 10), a substrate that did not react when a protic solvent was used as the promoter. In addition to the improved overall efficiency of the reaction, there is striking absence of epoxide byproducts in most of cases. However, it should be noted that the aldehyde products obtained from most of the sterically hindered ketones (entries 8 and 10) are derived from epoxide rearrangement. This study of the regioselectivity shows that there is a preference for migration of the less hindered substituent as had been observed previously. Furthermore, the reversal of the regioselectivity in the case of phenyl- and benzyl- groups is in accordance with Gutsche's previous hypothesis.

With the use of Lewis acid catalysts, many of the problems observed previously, such as low reaction rate and degradation of diazomethane, were overcome and attention was given to controlling the reaction to avoid over-homologation and enhancing the regioselectivity.

The next breakthrough in the field was the introduction of TMS-diazomethane as an alternative to diazomethane, reported by Shiori.[97] As discussed, the use of diazomethane was hindered by the formation of products that could react with diazomethane and that were more reactive than the starting material in some cases. This novel reagent would avoid this problem by forming a bulky α-silyl ketone that would not react further due to increased steric hindrance. Furthermore, the protective group would be easily removed by an acidic work-up, without the need for further steps.[97] The only foreseeable disadvantage in this method would be the reduced nucleophilicity of the TMS-diazomethane, which would necessitate the use of a Lewis acid promoter. Based on House's studies,[96] it was found that $BF_3{\cdot}Et_2O$ was the best promoter for the reaction. Further optimization of the reaction revealed that a non-coordinating solvent as dichloromethane should be used instead of diethyl ether in most cases (Scheme 72).

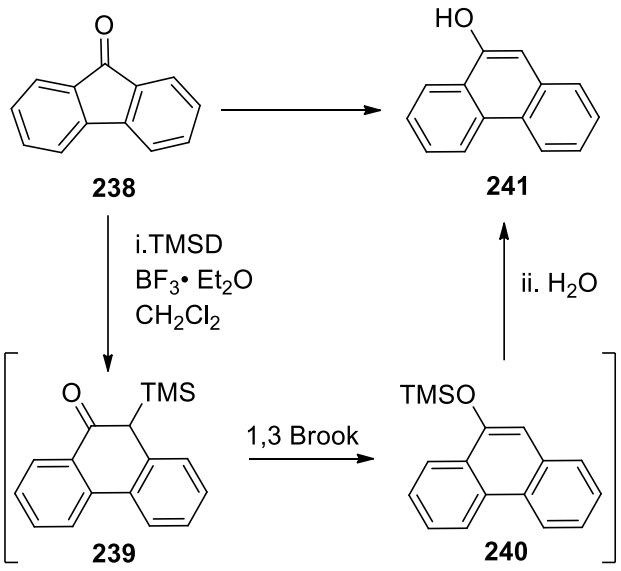



**Scheme 72.** *Reaction of 2-methyl-cyclohexanone with TMS- diazomethane*

Exposure of 2-methylcyclohexanone to 1.5 eq. of TMSD and 1.5 eq. of $BF_3{\cdot}Et_2O$ for 4 hours at –15 °C delivered the expanded products in 76% yield and with a regioisomeric ratio of 10:1 in favor of the product resulting from migration of the less substituted carbon. The enhanced product ratio can be attributed to the bulkiness of the TMS group which favours bond migration by the more accessible carbon. The new conditions demonstrated a two-fold increase in the efficiency of the reaction, in comparison to Adamson's procedure.

Trimethylsilyl-diazomethane constituted a great discovery because it performed almost equally well and at the same time it solved one of the main problems of diazomethane ring enlargement. Additionally, its greater thermal stability, lower volatility and later commercial availability has made it a surrogate for diazomethane and the reagent of choice for this family of reactions.

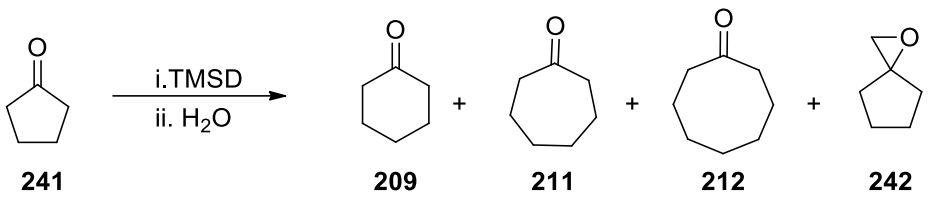
The convenience trimethylsilyl-diazomethane provides is supplemented by the possibility of further rearrangement of the α-trimethylsilyl ketone product. In the original publication by Shiori, ring expansion of fluorenone **238** affords the α-silyl ketone **239** and this intermediate was converted into the silyl enol ether through a 1,3 Brook rearrangement to give the phenol **241** (Scheme 73).[98] Despite the fact that trimethylsilyl enol ethers are generally unstable, they can be isolated and provide useful functionality for further synthesis.




**Scheme 73.** *Ring expansion and 1,3 Brook rearrangement of fluorenone*

Now that it had been established that a Lewis acid promoter was necessary for the reaction, Yamamoto studied the application of aluminium-based Lewis acids.[99] Initial studies focused on comparison of Shiori's conditions with trimethylaluminium-promoted ring expansion. Trimethylaluminium was thought to react with diazomethane in the same fashion as boron trifluoride to produce ethyl-dimethyl aluminum. In the case of cyclopentanone expansion, Shiori's protocol was inefficient and delivered an overall yield of 35% with an unsatisfactory distribution of products (Table 3). Replacement of the boron

promoter with trimethylaluminium increased the yield to 68% and the desired cyclohexanone was the major product.

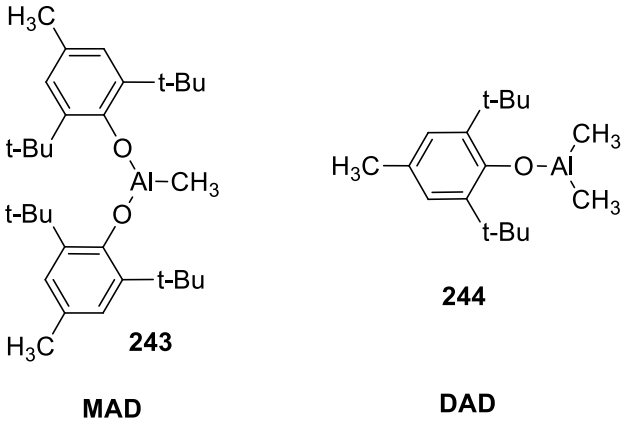



| Promoter | Conditions | Yield | 209:211:212:242 |
|---|---|---|---|
| $BF_3{\cdot}Et_2O$ | -20 °C to 0 °C | 35% | 64:23:10:3 |
| $AlMe_3$ | -20 °C | 68% | 96:2:0:2 |

**Table 3.** *Comparison studies of the effect of $AlMe_3$ and $BF_3{\cdot}Et_2O$ on the ring expansion of cyclopentanone*

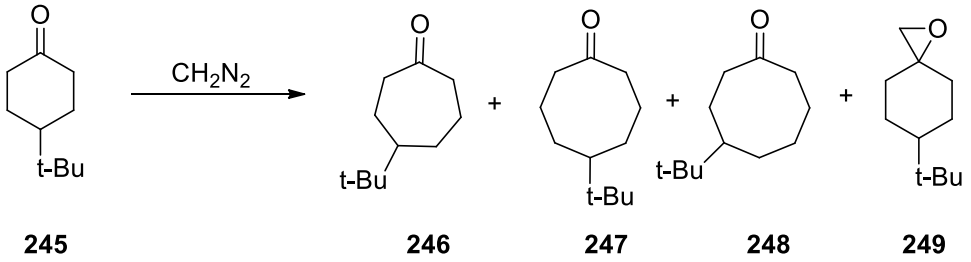
The over-expansion of the cyclopentanone with TMSD does not correspond to the control that the reagent gives during the reaction and can be explained by loss of the silyl group by a Lewis acid mediated cleavage or reaction with residual water in the reaction mixture.

Although trimethylaluminium produced great results with TMSD, reactions with diazomethane resulted in a less desirable product ratio. To enhance the ratio of products, bulkier aluminum promoters were examined, the most prominent of which were MAD and DAD.




**Scheme 74.** *MAD and DAD aluminum based Lewis Acids*

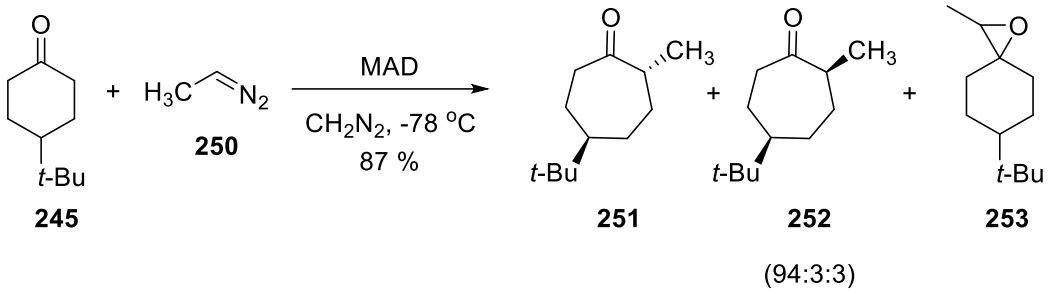
4-*tert*-Butylcyclohexanone was reacted with different promoters under various conditions (Table 4). Of the promoters used, MAD performed the best and it delivered the product in excellent yield along with trace amounts of various by-products.




| Entry | Promoter | Solvent | Temp (°C) | Yield (%) | 246:247:248:249 |
|---|---|---|---|---|---|
| 1 | $CH_3OH$ | $Et_2O$ | 0 | 63 | 50 : 25 : 25 : 0 |
| 2 | *i*-$Bu_3Al$ | $CH_2Cl_2$ | −78 | 68 | 54 : 22 : 22 : 2 |
| 3 | $(CH_3)_3Al$ | $CH_2Cl_2$ | −78 | 70 | 66: 15 : 15 : 4 |
| 4 | MAD | $CH_2Cl_2$ | −78 | 95 | 84 : 3 : 3 : 10 |

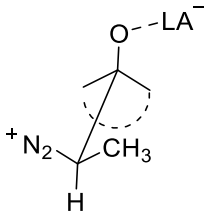
**Table 4.** *Comparison studies of the effect of Lewis acidic promoter on the ring expansion of 4-t-butyl-cyclohexanone*

Further studies were performed in order to examine the stereoselectivity of the reaction with various substituted diazocompounds (Scheme 79).




**Scheme 75.** *Examination of MAD as a Lewis acid promoter with substituted diazo-compounds*

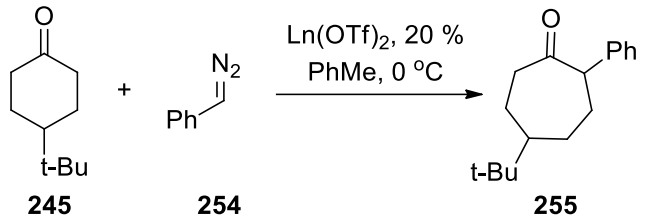
The reaction of diazomethane with 4-*tert*-butylcyclohexanone resulted in a mixture of the syn- and anti-products, showing great preference for the anti-configuration with 32:1 diasteromeric excess (Scheme 75). The observed stereoselectivity can be attributed to the axial attack of the diazoethane and the formation of an intermediate with a conformation in which the alkyl-group and the nitrogen antiperiplanar to the C-C bonds of the ring (Scheme 76). This conformation is favored because the steric hindrance is minimized. With the same reasoning disfavored equatorial attack would result in formation of the syn stereoisomer.




**Scheme 76.** *Plausible conformation of the reaction intermediate*

## 2.2.4 Rare Earth Metal Catalysis

House's and Yamamoto's work enabled the diazoalkane addition reaction to be optimised and provided a mechanistic insight into the reaction. However, the Lewis acids used did not display catalytic turnover, which necessitated their use in stoichiometric amounts. Based on previous results, Kingsbury investigated various alcohols as well as aluminium and boron derivatives as potential catalysts for the homologation reaction. Even though no single strong candidate was found amongst these promoters, it was found out that lanthanide triflates were able to catalyze the reaction with great efficacy even when only 5 mol % of catalyst was used (Table 5). [101]

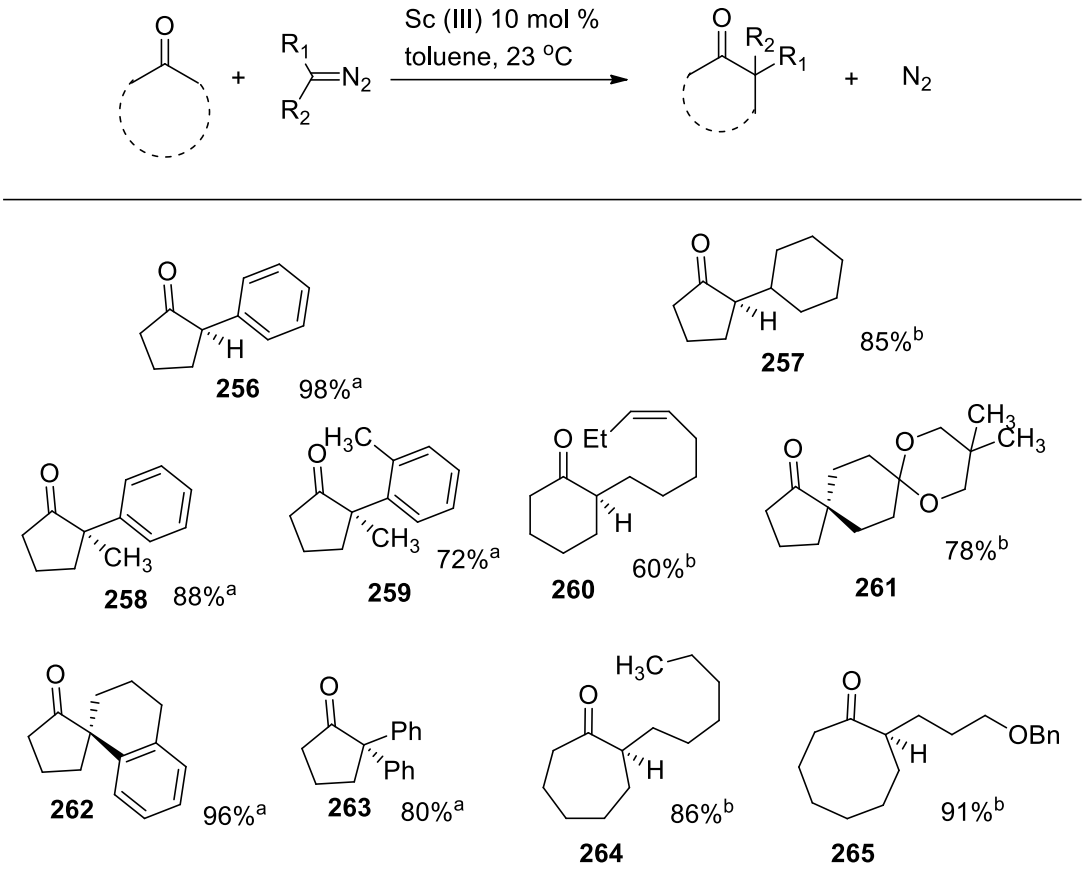



| Entry | Catalyst | Conversion (%) | Yield (%) |
|---|---|---|---|
| 1 | $Sc(OTf)_3$ | 100 | 92 |
| 2 | $Sc(OTf)_3$[a] | 100 | 85 |
| 3 | $Y(OTf)_3$ | 100 | nd |
| 4 | $La(OTf)_3$ | 100 | nd |
| 5 | $Sm(OTf)_3$ | 100 | nd |
| 6 | $Eu(OTf)_3$ | 100 | nd |

**Table 5.** *Comparison studies of the effect of rare earth triflates on the ring expansion of 4-t-butyl-cyclohexanone. a: 5 mol% catalytic loading*

Of the lanthanide catalysts examined, scandium(III) complexes performed the best. Their success over the other catalysts may be due to the fact that scandium(III) has the smallest ionic radius, which is only 75% of lanthanum's. [100] As expected, there is a negative correlation between the ionic radius and the Lewis acidity. The effectiveness of the two metals with the smallest radii, and

thus the highest Lewis acidicity, can be explained by the requirement for a strong Lewis acid. Kingsbury demonstrated the unmatched catalytic properties of the scandium(III) salts by using various diazoalkanes, many of which di-substituted, to explore the formation ring-expanded products bearing quaternary carbons (Scheme 77). [102]

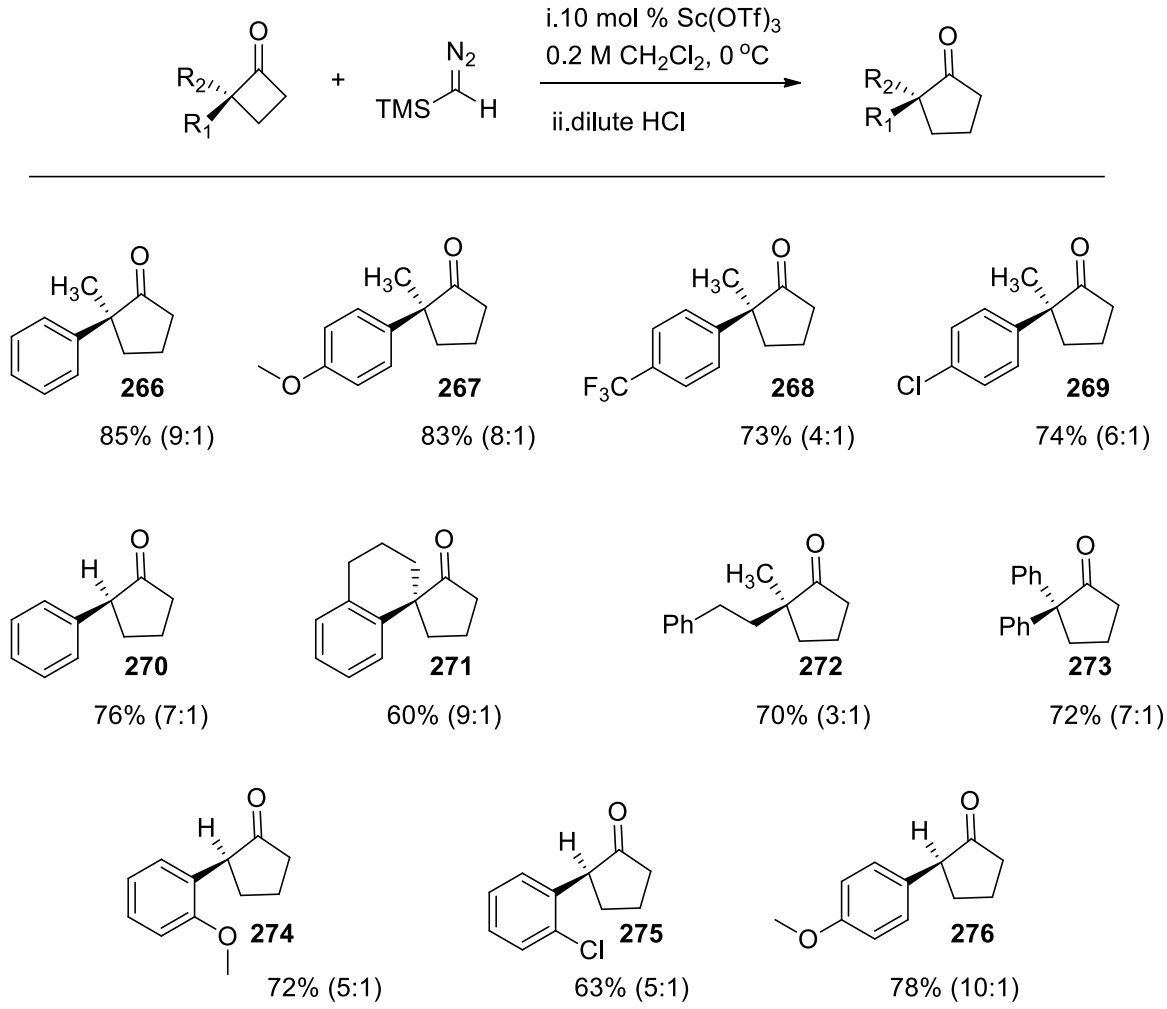



***Scheme 77**: Ring expansion products with various diazoalkanes. a: 10 mol % $Sc(OTf)_3$, b: 10 mol % $Sc(TMHD)_3$*

In the case of some diazoalkanes, $Sc(acac)_3$ and $Sc(tmhd)_3$ were preferred as catalysts over the triflate, in order to avoid Lewis acid promoted diazoalkane decomposition.

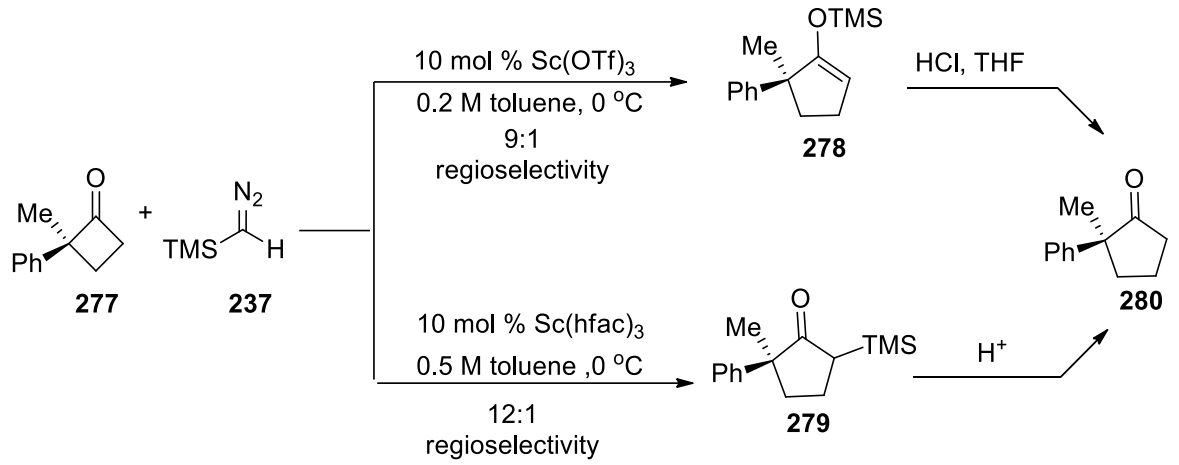
In further studies, a library of arylcyclobutanones was treated TMSD under the optimized conditions to demonstrate the regioselectivity of the ring expansion reaction with various substrates (Scheme 78).[104] While previous experiments by the group were performed in toluene, dichloromethane was employed as a solvent in this study and was found to give the same regioselectivity but increase

the reaction rate, possibly due the better solubility of $Sc(OTf)_3$. Coordinating solvents as $Et_2O$, THF and MeCN were evaluated but were found to be less effective.




***Scheme 78**. Regioselectivity studies on arylcyclobutane ring expansion. Yield reported for the isolated major product. Regiosomeric ratio reported in parenthesis.*

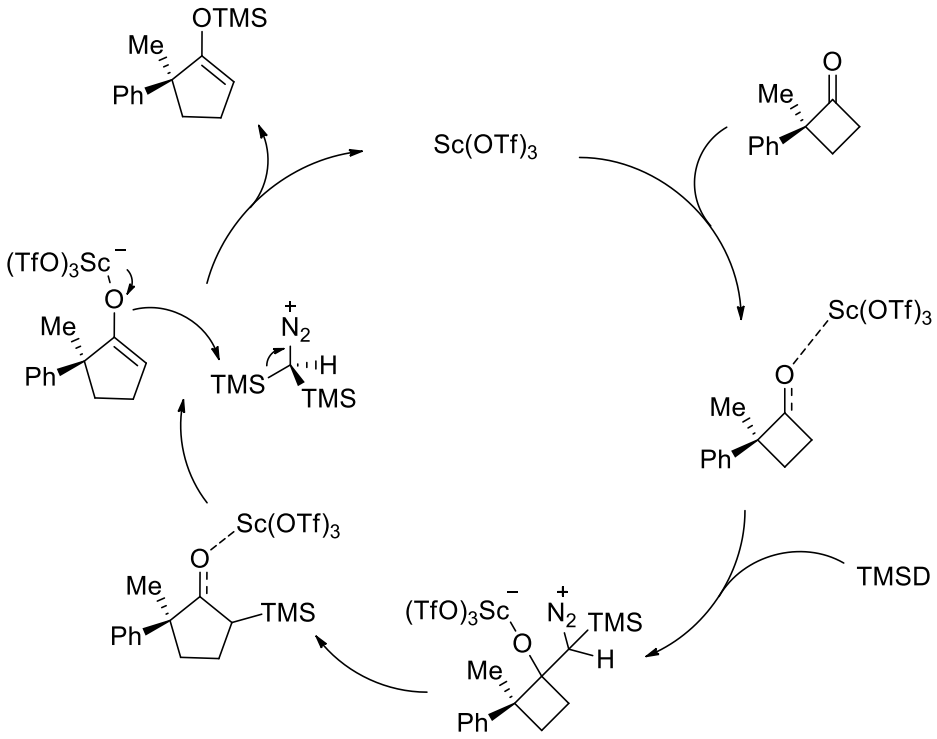
As can be seen from the results, arylcyclopentanones can be synthesised with increased regioselectivity under these conditions. While electronic effects derived from the substituent play a role in the reaction, the migration trend seems to somewhat less affected by this; the ratio is not greatly affected and steric hindrance seems to be more important. Further experimentation showed that the regioisomeric ratio depends on more than one factor, because catalyst choice can influence it by a significant amount (Scheme 79).




**Scheme 79.** *Expansion of substituted cyclopropanone with different scandium (III) Lewis acids*

The choice of scandium catalyst can influence the final product of the reaction. It was observed that the less bulky $Sc(OTf)_3$, would further participate as a catalyst to promote 1,3 Brook rearrangement of the intermediate α-silyl ketone and thereby produce the silyl enol ether. No other scandium(III) salt exhibited similar behavior under these reaction conditions,. In both pathways, the cyclopentanone can be accessed with an acidic wash in THF, making this transformation negligible if the enol ether is not the required product.

Kingsbury theorizes that after the initial formation of the α-silyl ketone, $Sc(OTf)_3$ coordinates again with the carbonyl oxygen and facilitates the formation of the enol ether, with the TMS cation being transferred to the TMSD, present in excess. *O*-silylation and subsequent dissociation of the catalyst completes the catalytic cycle and regenerates $Sc(OTf)_3$.

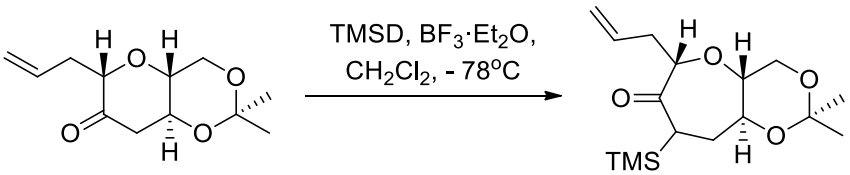



**Scheme 80.** *Catalytic cycle of Sc(OTf)₃*

## 2.3 Synthesis of the seven membered ring

While access to the seven-membered rings has been achieved through various routes as seen in Chapter 2.1, single carbon homologation was chosen as the method to be studied in this project. This method can be easily employed for the expansion of six-membered ketones because no functionalization is needed and there is a high tolerance for other groups. Furthermore it can be readily utilized in conjunction with iterative six-membered ring formation to diversify the ring systems.

Initial experiments were performed in which boron trifluoride etherate was used as the promoter, a procedure that had been reported by Mori in the synthesis of brevetoxin B, in order to assess the amount of TMSD needed.[105]




**197** **281**

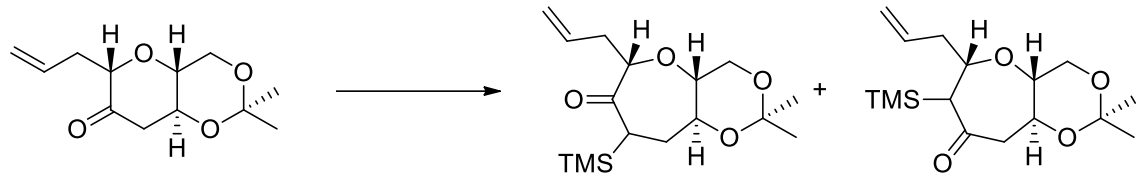
| # | Lewis Acid | Conditions | Yield |
|---|---|---|---|
| **1** | $BF_3{\cdot}Et_2O$ (1.1 eq) | TMSD 3.0 eq, -78 °C, 1.5h | 89 % |
| **2** | $BF_3{\cdot}Et_2O$ (1.1 eq) | TMSD 1.5 eq, -78 °C, 1.5h | 68 % |

**Table 6**. *Single carbon ring expansion with TMSD. a: Isolated yield*

A solution of the ketone **197** in dichloromethane at -78 °C was treated (dropwise addition) with 1.1eq $BF_3{\cdot}Et_2O$ followed by a slow addition of TMSD in hexanes. The resulting solution was quenched with a saturated solution of $NaHCO_3$ to ensure that the silyl group would not be cleaved. The use of stoichiometric amounts of TMS-diazomethane afforded in 68% yield; the yield could be improved significantly by the use of excess TMSD (3 eq). It is postulated that an excess of TMSD is required to compensate for the competitive decomposition of the diazoalkane by the Lewis acid.

Fortunately, in contrast with the literature, higher than the stoichiometric quantities did not result in by-product formation, which in turn lead to higher yields.

Although similar substrates have been examined in the past, in those cases the side chain contained a protected alcohol with bulky silyl groups.[103,105] Differences in side chain could influence the outcome of the reaction due to steric reasons as well as for electronic ones. As with previous work within the group, the method relies on future ring-closing metathesis reactions. Thus, ensuring that the reaction would work without modifications to the alkene, which would necessitate extra steps, was of great importance. Hence, various Lewis acid promoters and catalysts used in the literature were examined, to study the reactivity of the ketone **197** (Table 7).




**197** **281** **282**

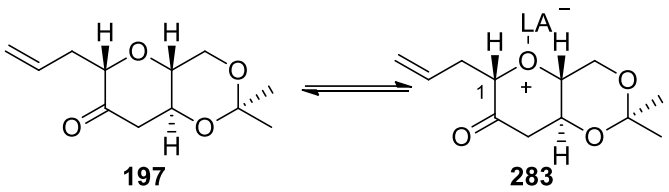
| # | Lewis Acid | Conditions | 281 % | (281:282)[a] |
|---|---|---|---|---|
| **1** | $BF_3{\cdot}Et_2O$ (1.1 eq) | TMSD 3 eq, -78 °C, 1.5h | 89% | nd |
| **2** | $BF_3{\cdot}Et_2O$ (1.1 eq) | TMSD 1.5 eq,-78 °C, 1.5h | 68 % | nd |
| **3** | $Me_3Al$ (1.1 eq) | TMSD, 3 eq, -40 °C to RT, 5h | 64% | 6:1 |
| **4** | MAD (1.1 eq) | TMSD, 3 eq, -78 to -20 °C, 5h | 39% | 2:1 |
| **6** | $Sc(OTf)_3$ (0.11 eq) | TMSD, 3 eq,-78 °C, 4h | nd | -- |
| **7** | $Sc(OTf)_3$ (0.11 eq) | TMSD, 3eq, RT, 16h | 44% | nd |
| **8** | $In(OTf)_3$ (0.10 eq) | TMSD, 3 eq,-78 °C, 4h | nd | -- |
| **9** | $In(OTf)_3$ (0.10 eq) | TMSD, 3eq, RT, 16h | 4% | -- |

**Table 7.** *Screening of Lewis acid catalysts for the ring expansion reaction,*

*a: ration of the two regioisomers, calculated after TMS- cleavage*

The Lewis acids were used as supplied, except $Sc(OTf)_3$ which was dried under high vacuum at 200 $^oC$ for 24 hours, and MAD which was synthesized from 3,5-di-*t*ert-4-butylhydroxytoluene and trimethylaluminium and used without further purification. When scandium(III) triflate was used in its commercially available anhydrous form it gave irreproducible results and produced a complex mixture of products. The reason of this behavior could be possibly attributed to residual moisture in the sample or decomposition and the production of triflic acid.

Analysis of the results suggests that the use of stronger Lewis acids has an impact on both the yield and regioselectivity. The strongest Lewis acid, $BF_3{\cdot}Et_2O$, performed the best, while MAD also performed well. Milder catalysts as scandium(III) triflate and trimethylaluminium required elevated temperatures and extended times but gave modest yields and product ratios. This trend could be attributed to the coordination of the stronger Lewis acid to the ethereal oxygen. As a result of the vicinal positive charge to C1, the reactivity of the former carbon to attack the newly inserted carbon originating from TMSD will be hindered, making the migration of the methylene group relatively more favorable (Scheme 81). Interestingly, the undesired regioisomer **282** was only observed with aluminum based Lewis acids. While the bulkier MAD was expected to enhance the selectivity of the reaction, for reasons not understood it yielded the highest ratio in regards to **282**.

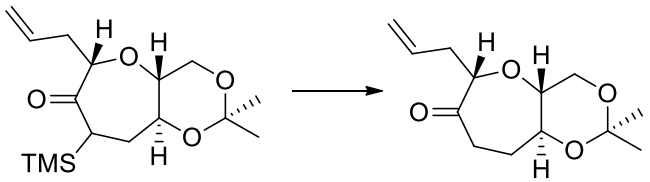



**Scheme 81.** *Coordination of the ethereal oxygen with the Lewis Acid promoter.*

As discussed previously, $Sc(OTf)_3$ facilitates 1,3-Brook rearrangement to give the corresponding silyl enol ether. Although the enol ether was a desired intermediate for further reactions, purification of it by column chromatography was not possible. Attempts to isolate the compound by column chromatography proved futile and partial decomposition to give ketone **284** was always observed, even when silica was doped with 1% triethylamine. The yield of the ketone **281**

was calculated after the quantitative TMS- cleavage with TBAF (*vide infra*). In a similar fashion the regioisomeric ratio of **281** and **282** in the case of aluminum based Lewis acids, was calculated after TMS- cleavage of the inseparable mixture of the two.

As the α-silyl ketone was an interesting intermediate and basic work-up conditions were employed in order to further utilize it. In order to access the desilylated seven membered ring, various reaction conditions were examined.




**281** **284**

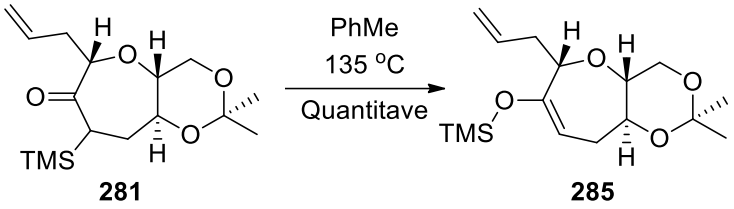
| # | Conditions | Yield |
|---|---|---|
| **1** | TBAF (3 eq) in THF | 92%` |
| **2** | HCl (0.5 M) in THF | acetonide deprotection |
| **3** | PPTS (5 mol %) in MeOH/DCM | acetonide deprotection |

**Table 8**. *Condition for the cleavage of the TMS- group*

Acidic cleavage of the silyl group was not possible, because the deprotection of the diol occured at a similar rate. In contrast, treatment of the intermediate with TBAF in THF afforded the desired product in an excellent yield and without the need for purification.

Now that formation of the saturated seven-membered ring had been accomplished, the next step was formation of the seven-membered enone.

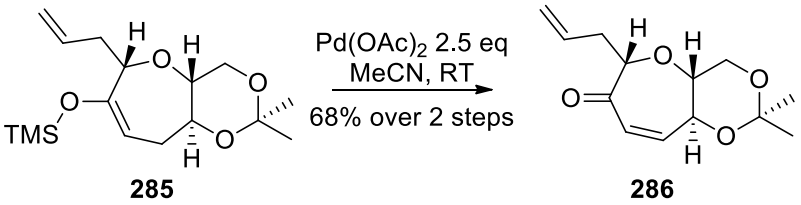
A solution of the α-silyl ketone **281** was heated in toluene, in a closed vial for 3 hours at 135 $^{o}$C, a to give the enol ether **285**, which resulted from 1,3-Brook rearrangement, in quantitative yield,.




**Scheme 82.** *1,3 Brook rearrangement*

The reaction proceeded smoothly and purification was not required. This is of great importance, because the silyl enol ether **285** is unstable on silica gel, as discussed previously.

The next target was the seven-membered enone, a substructure present in many polyether polycyclic natural products. Following the quantitative formation of the silyl enol ether by thermal rearrangement of the ring expansion intermediate **281**, Saegusa-Ito oxidation was deemed highly interesting because it would provide the enone in one step.

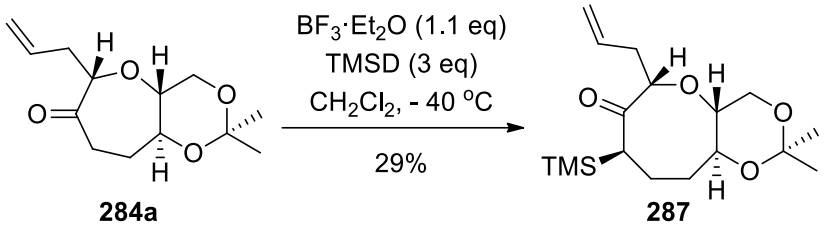



**Scheme 83.** *Saegusa Ito oxidation of the silyl enol ether*

Treatment of the unpurified silyl enol ether **285** with 2.5 equivalents of $Pd(OAc)_2$ in dry MeCN for 2.5 hours, resulted in formation of the required enone **286** in 68% yield over two steps.

After the successful application of this methodology for the synthesis of the seven-membered oxacycles **284** and **286**, interest was directed to the exploration of the use of the procedure to form eight-membered cyclic ethers. Oxepanone **284** was treated under the same conditions as the six-membered ketone **197**. Treatment with 3 equivalents of TMSD and 1.1 equivalents of $BF_3{\cdot}Et_2O$ at -78 °C for 2 hours resulted in the formation of only trace amounts of **287**. Elevation of the temperature to -40 °C and reaction for a further period of 3 hours afforded the desired oxocanone in 29% yield. Interestingly, formation of

the anticipated epoxide by-product was not observed, in contrast with observations with similar substrates.[5] The low reactivity of the substrate can be attributed to transannular strain and related effects that are present in medium-sized rings. The fact that the starting material was not fully consumed within the timeframe of the experiment supports this hypothesis and so a higher concentration or larger excess of the reagents should be considered in future.



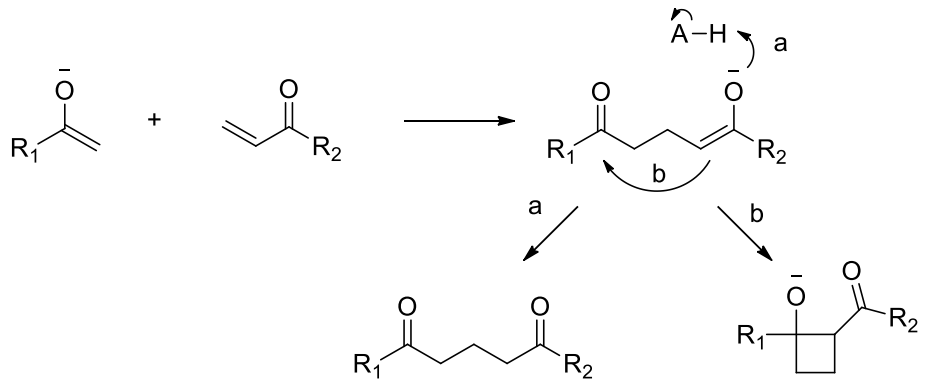

**284a** **287**

**Scheme 84.** *Single carbon ring expansion to the σ-silyl oxocanone*

Having completed one-carbon ring expansion reactions to prepare seven- and eight-membered oxacycles, focus was shifted to two-carbon ring expansion of the seven-membered ring to access the corresponding nine-membered cyclic ether. The approach envisioned was based on the use of the silyl enol ether intermediate **235** as a substrate for a [2+2] cycloaddition reaction that would lead to the formation of the nine- membered oxacycle.

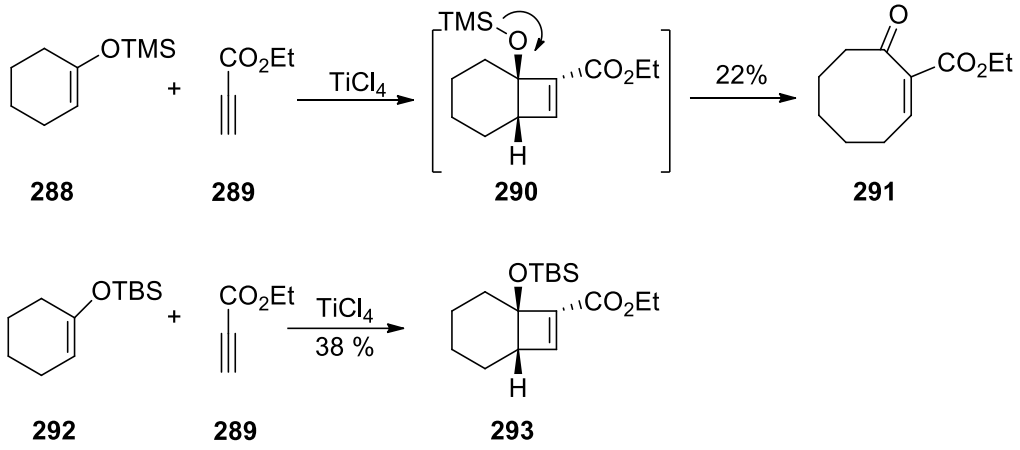
## 2.4 [2+2] cycloaddition of silyl enol ethers

[2+2] Cycloaddition reactions provide one of the most convenient approaches for the synthesis of cyclobutanes and their derivatives. These carbocyclic intermediates not only serve as in important biological compounds but can also undergo ring opening and ring expansion reactions as a result of their ring strain.[106] Since the concerted thermal [2+2] cyclization is disallowed by the Woodward Hoffmann rules, only a few reports exist for the efficient formation of four membered carbocycles, one of which is through Lewis acid catalysis. The reaction is thought to proceed in two steps. In the initial step, Mukaiyama-Michael addition to an enolate or enolate equivalent forms a linear keto-enolate.[107] At this point the reaction can be reported as a Mukaiyama-Michael addition if the intermediate is quenched by an external electrophile (e.g. proton, path a), or further intramolecular addition of the enolate can occur to form the cyclobutane ring (path b) (Scheme 85).



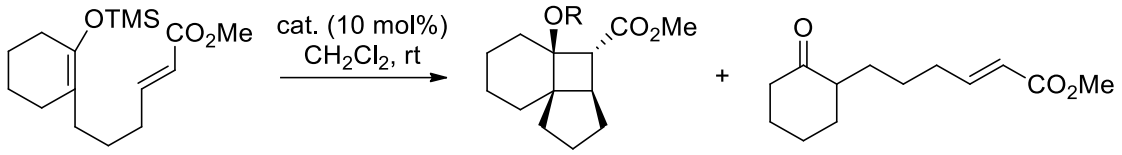

**Scheme 85.** *General pathway of [2+2] cycloadditions*

The original report on this reaction comes from Clark and Untch, who reported a novel two-carbon ring expansion process in which the cyclobutane intermediate formed by the [2+2] cycloaddition of silyl enol ether and ethyl propiolate undergoes ring opening (Scheme 86). [108] In this report, an extensive set of silyl enol ethers was tested and a stoichiometric amount of $TiCl_4$ was used as the Lewis acid catalyst. While the reaction performed as expected with TBS enol ethers, in the examples with TMS, loss of the TMS group and spontaneous ring opening was reported to give the ring-expanded product.




**Scheme 86.** *[2+2] cycloadditions of silyl enol ethers with ethyl propiolate*

The development of the Lewis acid catalyzed [2+2] cycloaddition reaction was further developed by Takasu et al., who reported the intramolecular cycloaddition of a silyl enol ether with an electron poor alkene **289**.[107] In this work, a variety of suitable Lewis acid catalysts was screend, as listed in Table 9. Evaluation of the results shows that aluminium-based Lewis acid catalysts as well as $TiCl_4$ facilitate the reaction. Furthermore, in the case of $EtAlCl_2$ and $TiCl_4$ deprotection of the alcohol was not observed. While the efficacy of other catalysts, such as $Sn(OTf)_2$, $SnCl_4$, and $InCl_3$, was only moderate, other lanthanide and transition metal Lewis acids were not suitable.

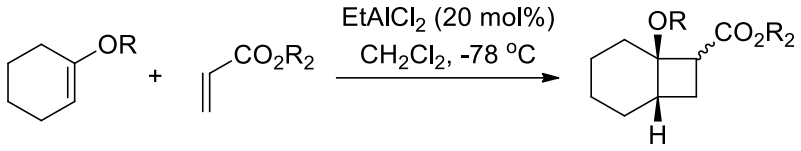



**294** **295** **296**

| Entry | Lewis Acid | Yield | | |
|---|---|---|---|---|
| | | **285,** R=TMS | **285,** R=H | **296** |
| 1 | $BF_3{\cdot}OEt_2$ | 17 | 0 | 32 |
| 2 | $Bu_2BOTf$ | 35 | 21 | 19 |
| 3 | $AlCl_3$ | 31 | 11 | 50 |
| 4 | $EtAlCl_2$ | 76 | 0 | 11 |
| 5 | $TiCl_4$ | 61 | 0 | 20 |
| 6 | $Sn(OTf)_2$ | 28 | 12 | 47 |

**Table 9.** *Screening of Lewis acid catalysts for the intermolecular [2+2] cycloadditions with silyl enol ethers*

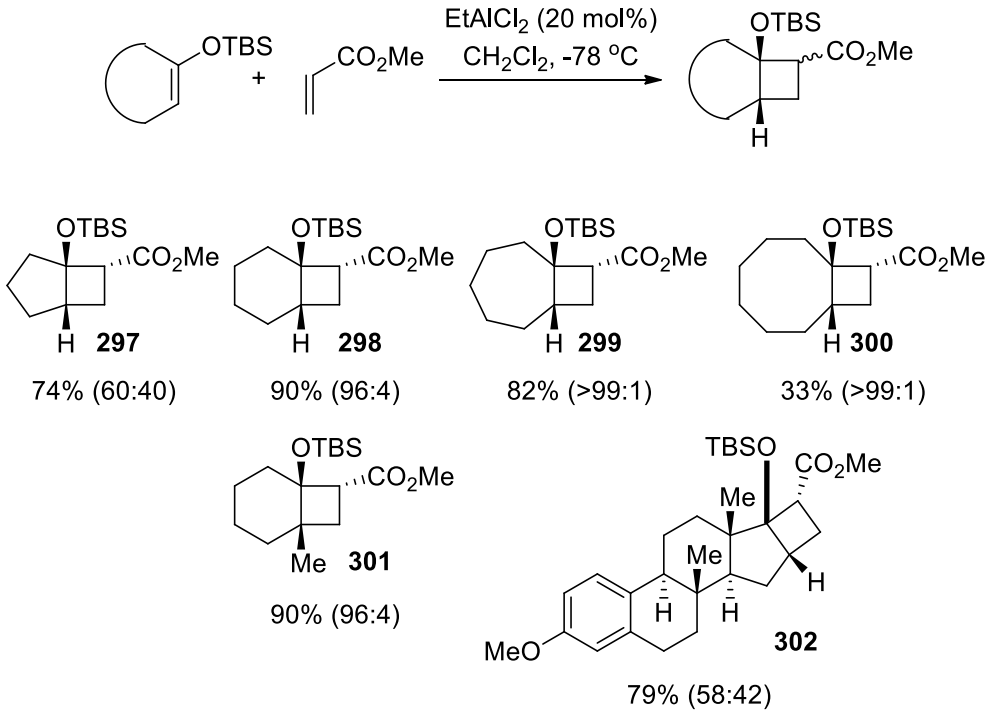
After a suitable catalyst had been identified, Takasu investigated the intermolecular version of this reaction in which a cyclic silyl enol ether was reacted with an α,β-unsaturated ester.[107] in the focus of this work was the identification of suitable silyl groups and an investigation of the effect of the ester. As seen in Table 9, TMS enol ether did not participate in the reaction, presumably due to hydration. In contrast, enol ethers possessing bulkier silyl groups, such as TBS and TIPS, delivered excellent results when paired with electron poor acrylates. While the trans- selectivity of the reaction is favoured in every case, selectivity is enhanced by the bulkiness of the silyl group, as seen in entries 5 and 6 (Table 10).




| # | $R_1$ | $R_2$ | Yield % | trans: cis |
|---|---|---|---|---|
| 1 | TMS | Me | nd | -- |
| 2 | TBS | Me | 79 | 76:24 |
| 3 | TBS | $CH_2CF_3$ | 58 | 80:20 |
| 4 | TBS | $C_6F_5$ | 89 | 94:6 |
| 5 | TBS | $CH(CF_3)_2$ | 93 | 93:7 |
| 6 | TIPS | $CH(CF_3)_2$ | 80 | >99:1 |

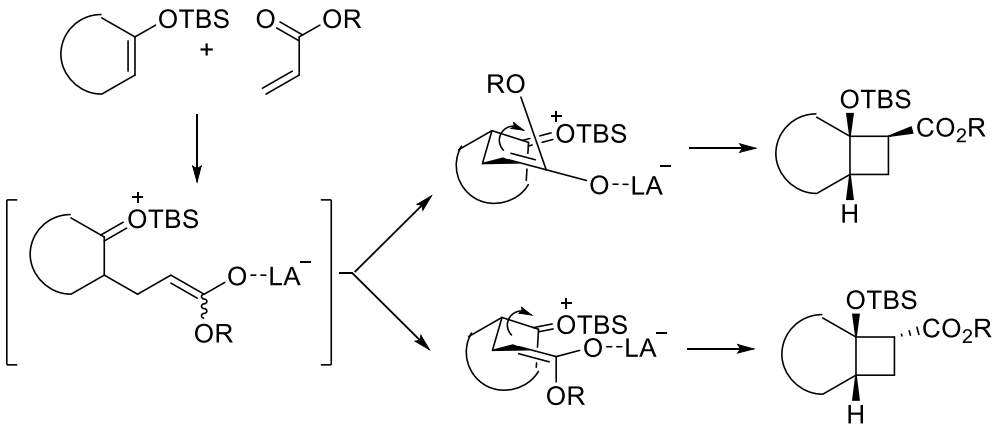
**Table 10.** *Investigation on the effect of substituents in the [2+2] cycloaddition*

Numerous carbocyclic enol ethers were reacted with methyl acrylate under optimised conditions to demonstrate the influence of ring size on stereoselectivity and efficiency of the reaction. Cyclic enol ethers with ring size greater than six formed the trans- isomer exclusively, while limited selectivity was observed in the case of five-membered rings. Furthermore, the efficiency of the reaction drops abruptly for larger rings (greater than seven-membered), presumably due to effects of the transannular strain. Substitution of the enol ether as seen in Table 10 did not affect the reaction.



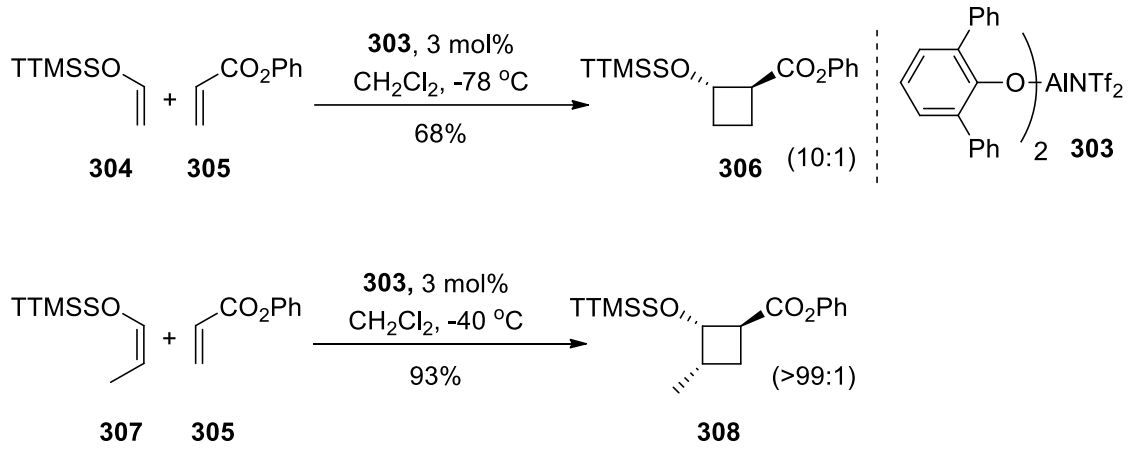

**Scheme 87.** *Examples of [2+2] cycloadditions of silyl enol ethers*

Mechanistic studies on the course of the reaction provided insight into the influence of the silyl group on the efficiency and stereoselectivity of the reaction. Initial formation of the Mukaiyama-Michael product can follow two distinct pathways, depending on the geometry of the enolate intermediate (Scheme 88). Chair-like conformations that are promoted via the use of a bulky silyl group lead to the trans configuration, while a boat-like conformation leads to the cis one. In this way, bulky silyl groups give better results due to better stabilization of the oxonium ion and enhanced stereoselectivity.




**Scheme 88.** *Suggested pathway for the formation of diasteromers*

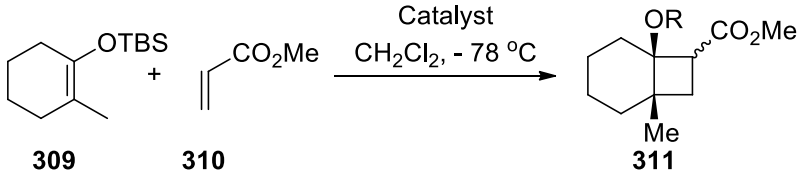
In a similar fashion to Takasu's work, Yamamoto examined [2+2] cycloaddition reactions between aldehyde-derived silyl enol ethers and acrylates.[109] Reactions of TBS and TIPS enol ethers were unsuccessful due to by-product formation and so substrates bearing extremely bulky silyl groups, such as tri(trimethylsilyl)silyl (TTMSS) and pentamethyldisilyl (PMDS), were examined with the expectation of better stabilization of the reaction intermediate. Further investigations concerning the choice of Lewis acid catalyst, revealed the efficiency of aluminium-triflimides as catalysts for the reaction, with bis(2,6-diphenylphenoxide) aluminium triflimide (BDAT) delivering the best results. This family of catalysts showed high efficiency, with only 3 mol% of the catalyst required to promote the reaction effectively. The optimized conditions were tested using a variety of methyl ketone derivatives and excellent results were obtained (Scheme 89).




**Scheme 89.** *[2+2] cycloadditions with "super silyl" enol ethers and a bulky Lewis acid*

In a further advance, Takasu et al. reported the use of trifluoromethanesulfonimide (triflamide) as a catalyst for the [2+2] cycloadditions of α,β-unsaturated esters and with silyl enol ethers.[110] Although $EtAlCl_2$ had already been shown to be a satisfactory catalyst, the high loading required meant that a new generation of catalysts could be even more effective. Indeed, triflimide performed the task even with a loading as low as 0.1 mol%, which demonstrates that is has an excellent catalytic turnover. One of the interesting implications of using triflimide is the fact that it is not the active form, but instead is a precursor of in situ generated $TBSNTf_2$. Triflimide reacts with the enol ether to produce the $TBSNTf_2$, explaining entry number 4 (Table

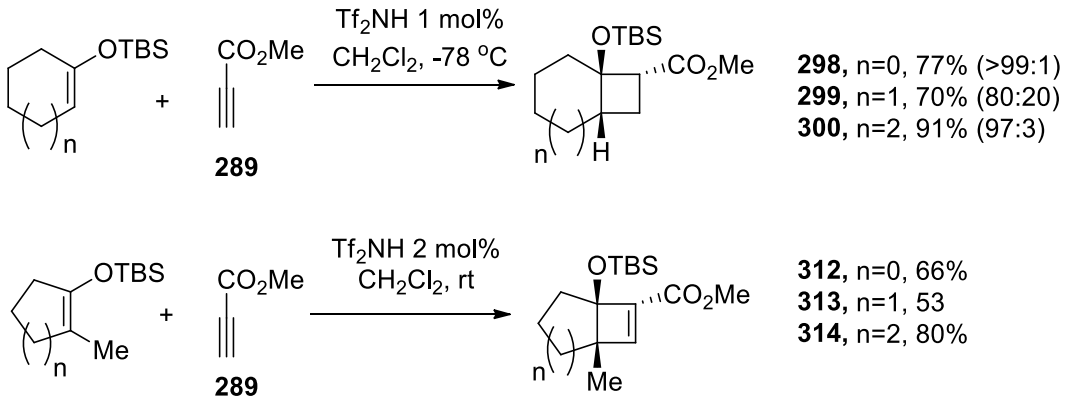
11). Furthermore, pre-formed $TBSNTf_2$ has been shown effectively promoted [2+2] cycloadditions of silyl enol ethers with acrylates.[111] This observation led the Takasu group to modify the procedure, forming the active form of the catalyst before addition of the substrate. Further examples show that triflimide catalysis can be used for the synthesis of cyclobutenes from methyl propiolate (Scheme 90).




| Entry | Catalyst | Yield % | trans: cis |
|---|---|---|---|
| 1 | $EtAlCl_2$ | 79 | 95:5 |
| 2 | $Tf_2NH$ [a] | 92 | >99:1 |
| 3 | $Tf_2NH$ [b] | 98 | >99:1 |
| 4 | $Tf_2NH$ [c] | Trace | -- |
| 5 | TfOH | nd | -- |

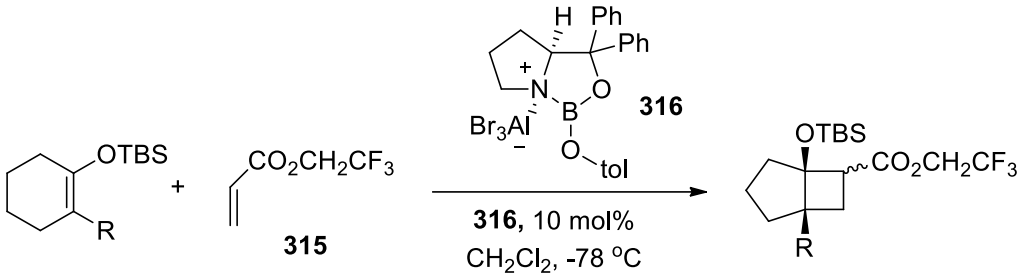
**Table 11.** *Examination of triflamide for [2+2] cycloadditions with silyl enol ethers*

*a: 0.1 mol%, b: 1 mol%, c: 100% mol%*




**Scheme 90.** *Examples of triflamide mediated [2+2] cycloadditions on carbocycles of various sizes*

Finally, Corey and Canales developed the first asymmetric catalytic [2+2] cycloaddition reaction in which a chiral aluminum-oxazaborolodine complex (**316**) was employed as the catalyst.[112] This reaction furnished the desired products in excellent yield and with high selectivity (Table 12). While endo-adducts are the preferred products, examples with methyl-substituted silyl enol ethers (entries 4 and 5) afforded the exo-adduct as the major product.



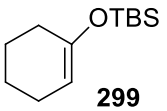
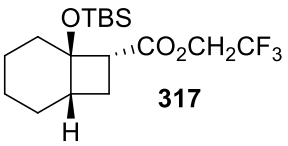
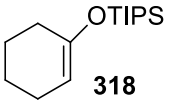
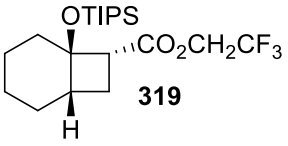
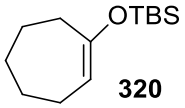
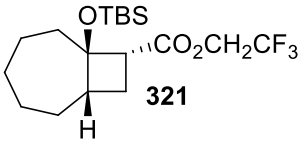
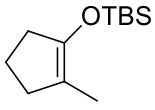
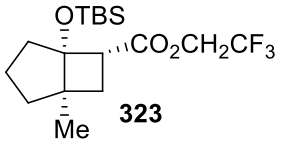
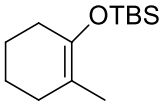
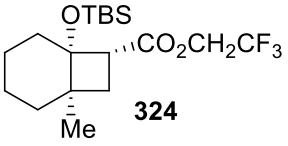
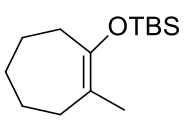
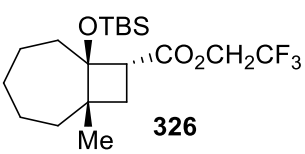
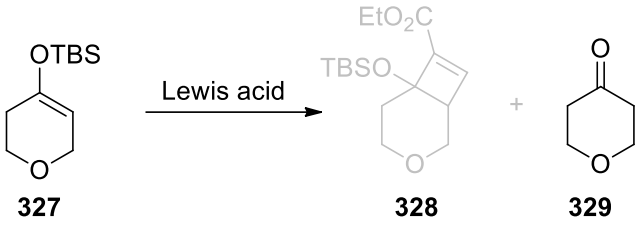

| Entry | Enol ether | Product | Yield % (endo:exo) | ee % |
|---|---|---|---|---|
| 1 |  **299** |  **317** | 97 (82:18) | 92 |
| 2 |  **318** |  **319** | 99 (97:3) | 92 |
| 3 |  **320** |  **321** | 99 (99:1) | 99 |
| 4 |  **322** |  **323** | 99 (1:99) | 98 |
| 5 |  **309** |  **324** | 99 (10:90) | 98 |
| 6 |  **325** |  **326** | 91 (96:4) | 98 |

**Table 12.** *[2+2] cycloadditions with a chiral aluminum-oxazaborolodine catalyst*

Although [2+2] cycloaddition is a very interesting approach for the introduction of a two-carbon unit into a synthetic scaffold by cyclobutane formation and ring expansion there are few literature examples of the use of this reaction for the synthesis of complex molecules. Furthermore, it appears that no such examples exist for oxacyclic substrates. Lewis acids have high affinity for oxygen atoms so it is necessary to screen suitable catalysts in order to assess the differences in reactivity of these systems when compared to that of the carbocyclic compounds used in the literature.

In parallel with this project, an investigation concerning the formation of cyclobutenes was perfomed by another member of the group. In this study, various catalysts for the [2+2] cyclization of silyl enol ethers and enamines with ethyl propiolate were explored.[113] A group of catalysts was examined for the reaction of a cyclohexanone-derived silyl enol ether and $TiCl_4$ was found to be the best promoter. Unfortunately, subsequent use of these conditions with tetrahydro-4H-pyran-4-one did not deliver the product, but resulted in deprotection or no reaction (Scheme 91).

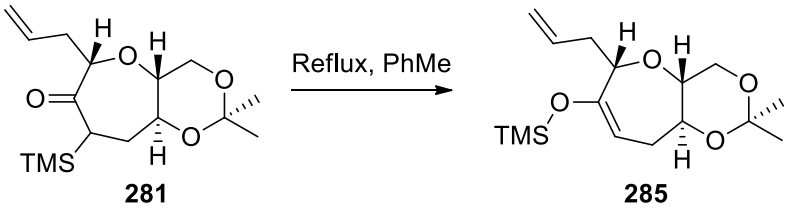



**327** **328** **329**

**Scheme 91.** *Exploration of [2+2] cycloadditions on oxacyclic silyl enol ethers*

## 2.5 Studies for the [2+2] cycloaddition of the seven membered oxacycle

Having completed the formation of the seven-membered ketone and enone, attention then shifted to the exploration of a novel strategy for the formation of a nine-membered oxacycle.

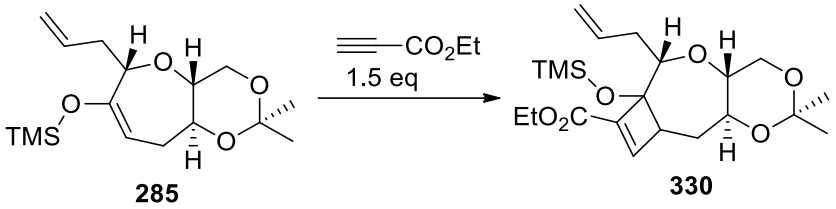



**281** **285**

**Scheme 92.** *Exploitation of the ring expansion intermediate for the [2+2] cycloaddition*

The α-silyl ketone product **281** resulting from the TMSD ring expansion reaction was deemed to be an interesting intermediate because 1,3-Brook rearrangement could be used to convert it into the TMS enol ether substrate required for the [2+2] cycloaddition reaction. Initial experimentation showed that thermal rearrangement of the α-silyl ketone product **281** by heating it at reflux in toluene for 3 hours furnished compound **285** in quantitative yield, without the need for further purification, enabling a one pot approach to be adopted.

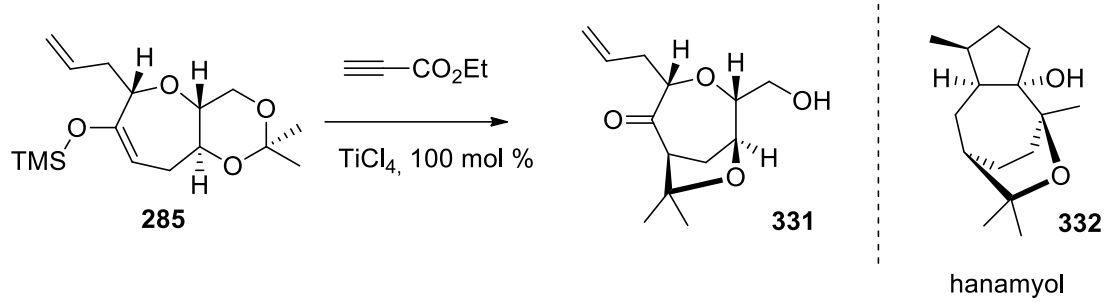
Various Lewis acid catalysts were examined for the reaction of **285** with ethyl propiolate, based on the previous reports of reactions with TMS enol ethers and oxacyclic substrates.[108, 113]




| # | Catalyst | Conditions | Yield |
|---|---|---|---|
| **1** | $TiCl_4$ | 100 mol %, DCM, -78 °C, 1h | 89% of **331** |
| **2** | $ZrCl_4$ | 10 mol %, DCM, -78 °C, 3h | SM |
| **3** | $ZrCl_4$ | 10 mol %, DCM, 25°C, 16h | 72% of **284** |
| **4** | $In(OTf)_3$ | 10 mol %, DCM, -78 °C, 3h | SM |
| **5** | $In(OTf)_3$ | 10 mol %, DCM, 25°C, 16h | 60 % of **284** |

**Table 13.** *Screening of Lewis acid catalysts and conditions for the [2+2] cycloaddition with ethyl propiolate*

Unfortunately, none of the reaction conditions delivered the required product. At low temperatures, there was no reaction, while warming reaction to room temperature resulted in an increase in the deprotection rate. A notable example is the reaction promoted by $TiCl_4$ (entry 1), the major product from which was identified as having a bridged bicyclic structure (Scheme 93). This product is believed to originate from the coordination of the Lewis acid to the less hindered oxygen atom of the acetonide protecting group, followed by intramolecular cyclization of the carbocation and the enol ether. This rearrangement seems particularly interesting for the synthesis of different natural products, e.g. hanamyol, which is however out of the scope of this project.



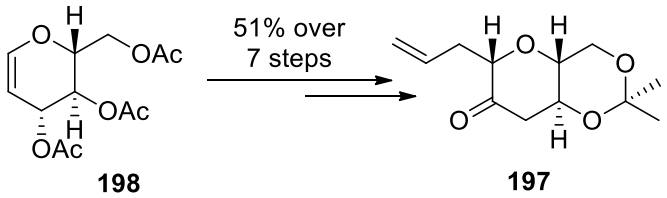

**Scheme 93**. *Intramolecular rearrangement of **285** in the presence of a strong Lewis acid*

The literature lacks examples of Lewis acid mediated [2+2] cycloadditions of comparable silyl enol ethers and so the reason for the failure of the reaction is unclear. While TMS- enol ethers are not the most suitable substrates as discussed before, Seyal's work with TBS-systems indicates that the major problem might not be due to nature of the silyl group but instead might be due to the presence of an ethereal oxygen in the ring.[113] No differences were observed between substrates with a ketal group and without. Lewis acids are good oxophiles and so it is possible that "consumption" through coordination with the ethereal oxygens might inhibit their catalytic action regarding the [2+2] cycloaddition reaction.

# 3. Conclusion

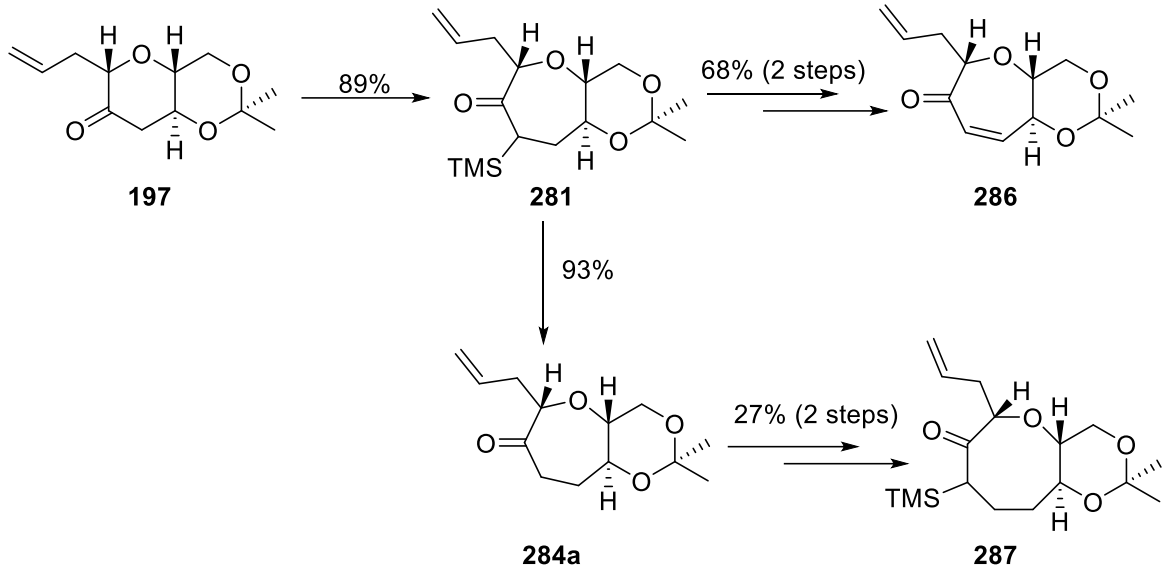
## 3.1 Summary of work

The target of this project was to explore various Lewis acid promoters for the TMS-diazomethane ring expansion on the six-membered cyclic ether **197**, optimize the conditions for the expansion step, and investigate a two-carbon ring expansion though a [2+2] cycloaddition between an intermediate silyl enol ether and ethyl propiolate. While the preparation of the ketone **197** was already reported, further optimization in the early steps afforded a safer, faster and more efficient approach for the synthesis of the diol in great scales. Ketone **197** was isolated in 37% yield over 7 steps.



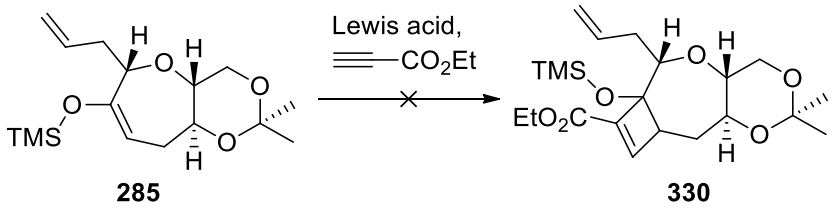

**Scheme 94.** *Synthesis of ketone **197***

Having established a convenient route to the necessary substrate, expansion to the seven-membered cyclic ether and further functionalization to the corresponding enone was achieved in an excellent yield. The oxocane derivative was then isolated in a moderate yield without byproducts formation, suggesting the versatility of the method as well as leaving room for further optimization.




**Scheme 95.** *Work on cyclic ketone homologation and access to derivatives*

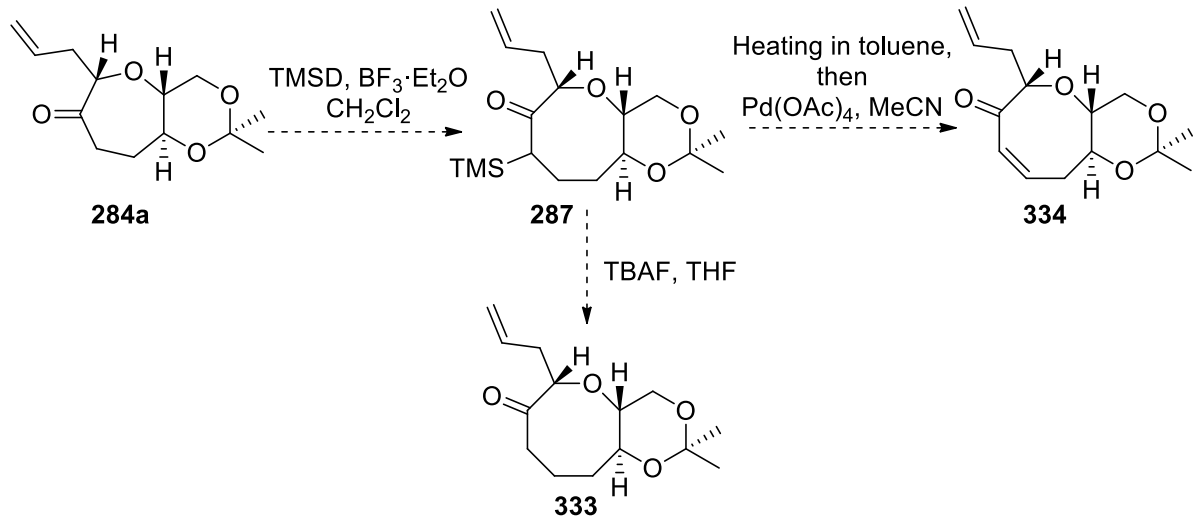
Finally, experimentation for the cyclobutene formation for the two-carbon ring expansion showed the limited reactivity of the substrate and the lability of the trimethylsilyl group under the tested conditions.




**Scheme 96.** *Exploration of the [2+2] cycloaddition of **285** with ethyl propiolate*

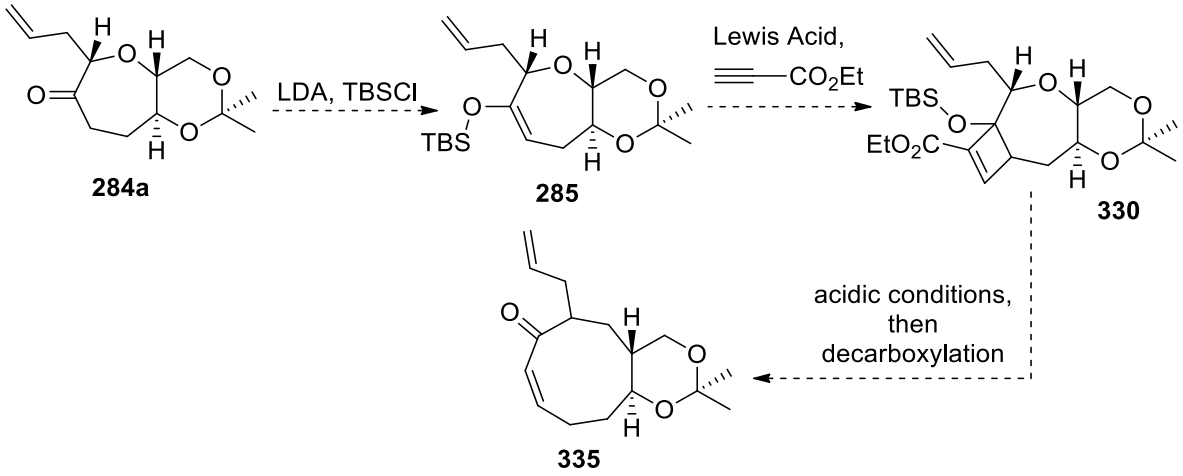
## 3.2 Future work

Access to the eight- membered cyclic ether **287** and derivatives is proposed to be achievable in a similar fashion to the seven- membered ones. While the ring expansion reaction to **287** was successful, higher concentration and elevated temperature is expected to lead in increased yield. Treatment of **287** with TBAF under the described conditions is expected to deliver ketone **333**, while 1,3 Brook rearrangement of the α-silyl ketone followed by Saegusa-Ito oxidation would deliver the eight- membered enone **334**.




**Scheme 97.** *Future work on the oxocane core*

The demonstrated [2+2] cycloaddition indicated the lability of the TMS- group used in this project. Following the general comments on the effect of the silyl substituent, bulkier groups like TBS- could be examined. Treatment of **284** with LDA and TBS chloride should deliver the silyl enol ether in excellent yield. Then, the effect of the Lewis acid catalyst can be evaluated again with a more comprehensive screening. Further treatment of the cyclobutene product under acidic conditions or elevated temperature is expected to deliver the nine-membered core **335**.




**Scheme 98.** *Future work on the [2+2] cycloaddition of silyl enol ether*

# 4. Experimental

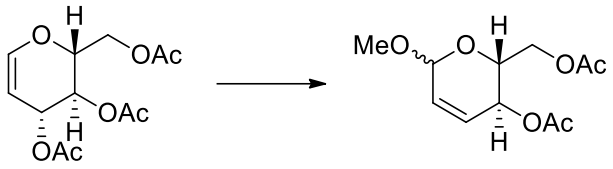
## General Experimental

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), dichloromethane ($CH_2Cl_2$) and diethyl ether ($Et_2O$) were purified using a Pure-Solv™ 500 Solvent Purification System. Other dry organic solvents and starting materials were obtained from commercial sources and used as received unless otherwise specified. Petroleum ether (PE) used for column chromatography was the 40–60 °C fraction. Triethylamine was distilled and stored under argon prior to use. 4 Å molecular sieves were oven dried prior to use. All reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminum backed plates F254. TLC plates were examined under UV light (254 nm wavelength) and stained using potassium permanganate solution, acidic ethanolic vanillin solution, acidic ethanolic anisaldehyde solution or cerium ammonium molybdate solution. Flash column chromatography was performed with silica gel (Geduran Si 60 35-70 µm) as solid support. IR spectra were recorded using a Shimadzu FT IR-8400S ATR instrument. The IR spectrum of each compound (solid or liquid) was acquired directly on a thin layer at ambient temperature. All $^1H$ NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at ambient temperature. Data are reported as follows; chemical shifts in ppm relative to $CHCl_3$ (7.26), $C_6D_5H$ (7.16) or $CDCl_2H$ (5.32) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) J (Hz), integration, and assignment. All $^{13}C$ NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at 101 MHz and 126 MHz at ambient temperature. Data are reported as follow; chemical shifts in ppm relative to $CDCl_3$(77.16), $C_6D_6$(128.06) or $CD_2Cl_2$(54.00) on the δ scale and assignment.

Optical rotations were recorded with an error of ≤±0.1 using an automatic polarimeter Autopol V. High resolution mass spectra (HRMS) were recorded by the University of Glasgow mass spectrometry service using positive chemical ionization (CI+) or positive ion electron impact (EI+) ionisation on a Jeol MStation JMS-700 instrument, or using positive or negative ion electrospray (ESI+/ESI-)

techniques on a Bruker micrOTOF-Q instrument. Compounds were named according to the IUPAC rules, whereas numbering of the carbons has been done independently to these rules to help at their identification.

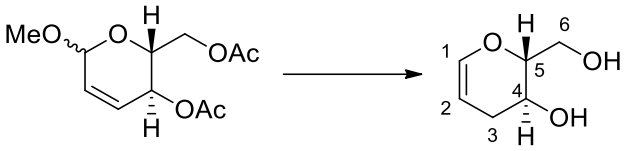
**(*2R*,*3S*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3-ol (199)**




**198** **199**

In a 2 L flask, tri-O-acetyl-D-glucal (250 g, 0.918 mol) was added and dissolved with 1.25 L of dry toluene. The solution was cooled to 0°C and dry methanol (62.5 mL, 1.595 mol) and of boron trifluoride diethyl etherate (62.5 mL, 506 mmol) were added dropwise. The resulting solution was stirred and kept at 0 °C for 1 hour. Saturated $NaHCO_3$ (200 mL) was added under vigorous stirring and solid $NaHCO_3$ (approximately 60 g) was added afterwards until the pH of the aqueous phase was basic and no gas evolution was observed. The aqueous phase was separated and the organic phase was extracted with brine (2 × 500 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give **199** as pale yellow oil (223 g, 99%) . The compound was not purified and used directly to the next step.

**(*2R*,*3S*)-2-(Hydroxymethyl)-3,4-dihydro-2H-pyran-3-ol (200)**




**199** **200**

To a vigorously stirred suspension of $LiAlH_4$ (3.60 g, 94.8 mmol) in 1,4-dioxane (100 mL,) at 0 ºC was added dropwise a solution of the acetal **199** (7.90 g, 32.3 mmol) in 1,4-dioxane (35 mL). The resultant suspension stirred overnight at RT and then stirred for 5 hours at reflux. After cooling, the reaction mixture was diluted with $Et_2O$ (150 mL) and the reaction was quenched cautiously by the sequential addition of water (4 mL), 6M NaOH (aq.) (4 mL) and water (4 mL). The whole mixture was then dried over $Na_2SO_4$ and stirred overnight. The resultant suspension was filtered through a pad of Celite and concentrated under reduced pressure to afford the diol **200** (3.72 g, 88 %) as a viscous pale yellow oil.

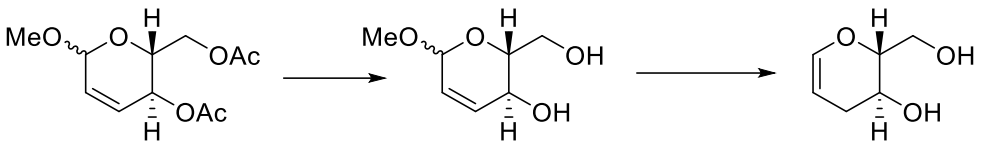
**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 6.32 (dt, *J* = 6.1, 2.0 Hz, 1H, CH-C1), 4.67 (ddd, *J* = 6.1, 5.1, 2.6 Hz, 1H, CH-C2), 4.05 – 3.91 (m, 1H, CH-C4), 3.93 – 3.81 (m, 2H, $CH_2$-C6), 3.68 (dt, *J* = 8.4, 4.2 Hz, 1H, CH-C5), 2.34 (dddd, *J* = 16.5, 6.2, 5.2, 1.6 Hz, 1H, $CH_2$-C3), 2.07 (ddt, *J* = 16.5, 8.7, 2.5 Hz, 1H, $CH_2$-C3).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 142.9 (CH-C1), 98.4 (CH-C2), 78.6 (CH-C5), 64.9 (CH-C4), 62.6 ($CH_2$-C6), 29.4 ($CH_2$-C3).

**HRMS** ESI $[C_6H_{10}O_3Na]^+$ found 153.0524, $[M+Na]^+$calculated 150.0522

Spectroscopic data match those in literature. [72]

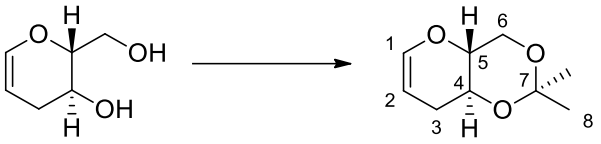
**Alternative route to diol 200**




**199** **202** **200**

To a solution of the acetal **199** (26.0 g, 106 mmol) in dry MeOH (145 mL) was added $K_2CO_3$ (283 mg, 2 mmol). The resulting solution was stirred overnight at room temperature. The mixture was filtered to remove the solids and concentrated under reduced pressure. The resulting diol **202** was dissolved in THF (100 mL) and was dropwise added to a suspension of LAH (6.0g, 150 mmol) in THF (200 mL) at 0 $^oC$. The resultant suspension stirred for 3 hours at RT and then stirred for 4 hours at reflux. The reaction mixture was diluted with $Et_2O$ (150 mL) and the reaction was quenched cautiously by the sequential addition of water (6 mL), 6M NaOH (aq.) (6 mL) and water (6 mL). The whole mixture was then dried over $Na_2SO_4$ and stirred overnight. The resultant suspension was filtered through a pad of Celite and concentrated under reduced pressure to afford the diol **200** (13.16 g, 95 %) as a viscous pale yellow oil.

**(*4aR*,*8aS*)-2,2-Dimethyl-2H,4H,4aH,8H,8aH-pyrano[3,2-d][1,3]dioxine (203)**




**200** **203**

To a solution of the diol **200** (11.8 g, 90.7 mmol) in a mixture of acetone (dried over 4 Å MS) and 2,2-dimethoxypropane (3:1, 450 mL) was added PPTS (1.80 g, 6.40 mmol, 7 mol%). The resultant solution was stirred overnight, diluted with water (100 mL) and stirred for a further 5 minutes. The mixture was further diluted with $NaHCO_3$ sat. (100 mL) and concentrated under vacuum to remove the volatiles. The mixture was extracted with DCM (3 × 300 mL) and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure to afford the acetonide **203** (14.96 g, 97%) as a volatile yellow oil.

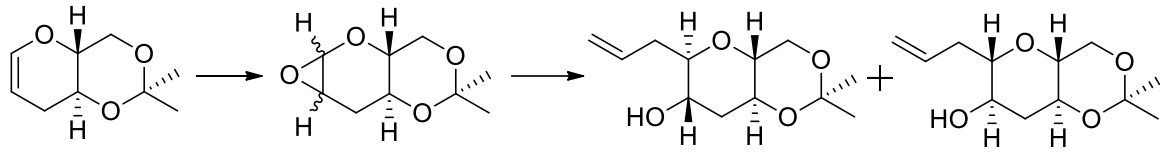
**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 6.29 (dtd, *J* = 6.1, 1.9, 0.9 Hz, 1H, CH-C1), 4.70 (td, *J* = 5.8, 2.2 Hz, 1H, CH-C2), 4.01 – 3.92 (m, 2H, CH-C4, $CH_2$-C6), 3.79 (t, *J* = 10.7 Hz, 1H, $CH_2$-C6), 3.61 (td, *J* = 10.0, 5.5 Hz, 1H, CH-C5), 2.19 (dtd, *J* = 16.1, 5.8, 1.6 Hz, 1H, $CH_2$-C3), 2.08 (ddt, *J* = 16.0, 9.7, 2.4 Hz, 1H, $CH_2$-C3), 1.54 (s, 3H, $CH_3$-C8), 1.43 (d, *J* = 0.7 Hz, 3H, $CH_3$-C8)

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 143.1 (CH-C1), 99.5 (C-C7), 98.8 (CH-C2), 71.0 (CH-C5), 67.4 (CH-C4), 62.3 ($CH_2$-C6), 29.2 ($CH_3$-C8), 26.8 ($CH_2$-C3), 19.1 ($CH_3$-C8).

**HRMS** EI+ $[C_9H_{14}O_3]^+$ found 170.0944, $[M]^+$ calculated 170.0943

Spectroscopic data match those in literature. [72]

**Epoxidation of 203 and epoxide opening with allylmagnesium chloride**

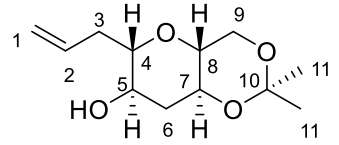


**203** **204** **205a** **205b**

A solution of mCPBA (72% by weight, 30.0 g, 125 mmol) in $CH_2Cl_2$ (750 mL) was dried over $MgSO_4$, filtered onto KF (14.5 g, 250 mmol) and stirred for 30 minutes to form a colorless suspension. A solution of enol ether **203** (8.51 g, 50.0 mmol) in $CH_2Cl_2$ (250 mL) was added dropwise and the mixture was stirred for 2.5 hours. The resulting mixture was filtered through a pad of $MgSO_4$ and concentrated under vacuum to afford the epoxide **204** as yellow oil.

The epoxide was dissolved in THF (250 mL) and added to a stirred solution of allyl magnesium chloride (250 mmol) in THF (750 mL) at 0 °C. The mixture was stirred for 3 hours and the reaction was quenched by cautious addition of water (500 mL). The resultant mixture was further diluted with brine (1.5 L) and extracted into $Et_2O$ (3 × 500 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20–100% $Et_2O$ in PE) to afford the desired alcohol isomer **205a** (2.25 g, 20 %) and undesired alcohol isomer **205b** (4.55 g, 40 %) as pale yellow oils.

**(*4aR,6S,7R,8aS*)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1,3]dioxin-7-ol (205a)**



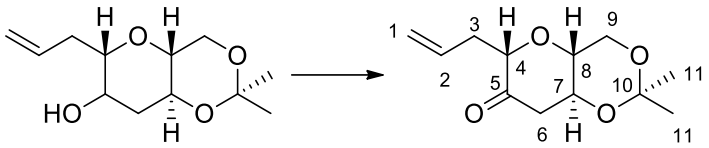
**$^{1}$H NMR (400 MHz, Chloroform-*d*) δ** 5.90 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, CH-C2), 5.19 – 5.03 (m, 2H, $CH_2$-C1), 3.89 (dd, *J* = 10.8, 5.3 Hz, 1H, $CH_2$-C9), 3.67 (t, *J* = 10.6 Hz, 1H, $CH_2$-C9), 3.59 – 3.40 (m, 2H, CH-C7, CH-C5), 3.28 – 3.09 (m, 2H, CH-C4, CH-C8), 2.56 (dddt, *J* = 14.6, 6.9, 4.0, 1.4 Hz, 1H, $CH_2$-C3), 2.37 – 2.19 (m, 2H, $CH_2$-C3, $CH_2$-C6), 1.73 (d, *J* = 4.5 Hz, 1H, HO-C5), 1.54 (q, *J* = 11.6, 11.4, 10.7 Hz, 1H, $CH_2$-C6), 1.50 – 1.45 (s, 3H, $CH_3$-C11), 1.40 (s, 3H, $CH_3$-C11).

**$^{13}$C NMR (101 MHz, Chloroform-*d*) δ** 135.1 (CH-C2), 117.7 ($CH_2$-C1), 99.6 (C-C10), 82.0 (CH-C4), 74.7(CH-C8), 70.0 (CH-C7), 69.4 (CH-C4), 63.2 ($CH_2$-C9), 39.1 ($CH_2$-C6), 37.00 ($CH_2$-C3), 29.7 ($CH_3$-C11), 19.6 ($CH_3$-C11).

**HRMS** ESI+ $[C_{12}H_{20}O_4Na]^+$ found 251.1244, $[M+Na]^+$ calculated 251.1254

Spectroscopic data match those in literature. [72]

**(4aR,6S,8aS)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1, 3]dioxin-7-one (197)**



**205a** **197**

To a suspension of $SO_3$·pyr (15.0 g, 94.2 mmol) in a mixture of DMSO and $CH_2Cl_2$ (200 mL, 1:1) at 0 °C was added $Et_3N$ (18.0 mL, 129.1 mmol) and followed by dropwise addition of a solution of the alcohol **205a** (4.50 g, 19.7 mmol) in $CH_2Cl_2$ (20 mL). The resultant solution was stirred for 3.5 hours and diluted with $Et_2O$ (200 mL). The mixture was washed with brine (3 × 100 mL) and the organic phase dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10–20% $Et_2O$ in PE) to afford the ketone **197** (3.62 g, 81 %) as a colorless oil

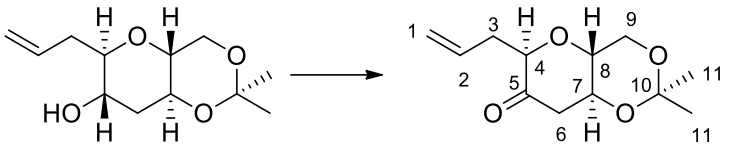
**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, CH-C2), 5.16 – 5.04 (m, 2H, CH-C1), 4.03 (dd, *J* = 11.0, 5.3 Hz, 1H, $CH_2$-C9), 3.96 – 3.91 (m, 1H, CH-C7), 3.89 (dd, *J* = 7.1, 4.2 Hz, 1H, CH-C4), 3.83 – 3.74 (m, 1H, $CH_2$-C9), 3.56 – 3.47 (m, 1H, CH-C8), 2.85 (dd, *J* = 15.6, 5.5 Hz, 1H, $CH_2$-C6), 2.69 – 2.60 (m, 1H, $CH_2$-C3), 2.54 – 2.43 (m, 1H, $CH_2$-C6), 2.37 (dt, *J* = 14.7, 7.1 Hz, 1H, $CH_2$-C3 ), 1.52 (s, 3H, $CH_3$-C11), 1.43 (s, 3H, $CH_3$-C11).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 204.5 (C-C5), 133.8 (CH-C2), 117.7 ($CH_2$-C1), 99.2 (C-C10), 83.4 (CH-C4), 73.1 (CH-C8), 69.3 (CH-C7), 62.6 ($CH_2$-C9), 45.4 ($CH_2$-C6), 33.8 ($CH_2$-C3), 29.1($CH_3$-C11), 19.1 ($CH_3$-C11).

**HRMS** ESI+ $[C_{12}H_{18}O_4Na]^+$ found 249.1089, $[M+Na]^+$ calculated 249.1097

Spectroscopic data match those in literature. [72]

**(*4aR*,*6R*,*8aS*)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1,3]dioxin-7-one (*epi*-197)**



**205b** ***epi*-197**

To a suspension of $SO_3$·pyr (3.60 g, 22.6 mmol) in a mixture of DMSO and $CH_2Cl_2$ (48 mL, 6:4) at 0 °C was added $NEt_3$ (4.0 mL, 28.7 mmol) and dropwise a solution of the alcohol **205b** (1.15 g, 5.04 mmol) in $CH_2Cl_2$ (10 mL). The resultant solution was stirred for 4 hours and diluted with $Et_2O$ (200 mL). The mixture was washed with brine (3 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% $Et_2O$ in PE) to afford the ketone ***epi*-197** (707 mg, 62 %) as a colorless oil.

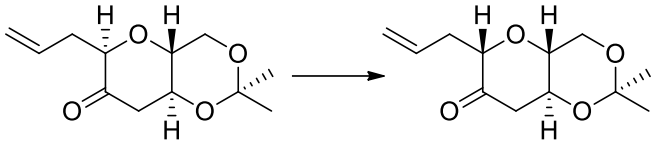
**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 5.77 (m, 1H, CH-C2), 5.16 (m, 1H, CH-C1), 5.13 (dd, *J* = 1.3 Hz, 1H, CH-C1), 4.13 (dd, *J* = 9.7, 5.3 Hz, 1H, CH-C4), 4.01 – 3.87 (m, 2H, CH-C7, $CH_2$-C9), 3.76 (t, *J* = 10.3 Hz, 1H, $CH_2$-C9), 3.67 (td, *J* = 9.6, 5.0 Hz, 1H, CH-C8), 2.82 (ddd, *J* = 16.2, 5.4, 1.1 Hz, 1H, $CH_2$-C6), 2.62 (dddt, *J* = 14.5, 9.7, 7.3, 1.2 Hz, 1H, $CH_2$-C3), 2.51 (dd, *J* = 16.2, 11.8 Hz, 1H, $CH_2$-C6), 2.39 (dddt, *J* = 14.6, 6.7, 5.3, 1.4 Hz, 1H, $CH_2$-C3), 1.52 (s, 3H, $CH_3$-C11), 1.43 (s, 3H, $CH_3$-C11).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 206.5 (C-C5), 132.5 (CH-C2), 118.5 ($CH_2$-C1), 99.3 (C-C10), 81.7 (CH-C4), 68.9 (CH-C7), 66.8 (CH-C8), 62.8 ($CH_2$-C9), 43.6 ($CH_2$-C6), 34.4 ($CH_2$-C3), 29.1 ($CH_3$-C11), 19.0 ($CH_3$-C11).

**HRMS** ESI+ $[C_{12}H_{18}O_4Na]^+$ found 249.1092, $[M+Na]^+$ calculated 249.1097

Spectroscopic data match those in literature. [72]

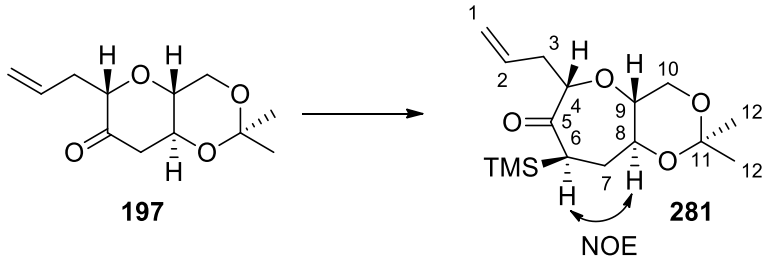
**Epimerisation of *epi*-197**



***epi*-197** **197**

To a solution of the ketone (650 mg, 2.87 mmol) in $CH_2Cl_2$ (30 mL) was added DBU (0.12 mL, 0.77 mmol). The resultant solution was stirred in the dark at room temperature for 24 hours. The mixture was washed with sat. $NH_4Cl$ (aq.) (2 × 30 mL) and brine (30 mL). The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20–80% $Et_2O$ in PE) to afford the ketone **197** (600 mg, 92 %) as a colorless oil.

**(*4aR,6S,8R,9aS*)-6-Allyl-2,2-dimethyl-8-(trimethylsilyl)tetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (281)**




To a solution of ketone **197** (50.0 mg, 0.22 mmol) in $CH_2Cl_2$ (2 mL) were added $BF_3{\cdot}Et_2O$ (0.03 mL, 0.25 mmol) and TMS-diazomethane in hexanes (0.132 mL, 2M, 0.66 mmol) at -78 °C. The resultant solution was stirred for 1.5 hours and quenched with sat. $NaHCO_3$ (aq.) (0.5 mL). The mixture was diluted with $Et_2O$ (2 mL), the phases were separated and the organic phase was washed with (2 x 3 mL) brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5 % $Et_2O$ in PE) to afford the TMS ketone **281** (62 mg, 89 %) as a colorless oil.

**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 5.73 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H, CH-C2), 5.13 – 4.99 (m, 2H, CH-C1), 3.87 – 3.83 (m, 1H, $CH_2$-C10), 3.83 – 3.78 (m, 1H, $CH_2$-C4), 3.71 – 3.65 (m, 1H, CH-C8), 3.67 – 3.61 (m, 1H, $CH_2$-C10), 3.20 (td, *J* = 9.7, 5.7 Hz, 1H, CH-C9), 2.42 (dd, *J* = 12.7, 3.2 Hz, 1H, CH-C6), 2.33 (tt, *J* = 7.0, 1.4 Hz, 2H, $CH_2$-C3), 1.95 (dt, *J* = 14.1, 3.4 Hz, 1H, $CH_2$-C7), 1.75 – 1.61 (m, 1H, $CH_2$-C7), 1.47 (s, 3H, $CH_3$-C12), 1.37 (s, 3H, $CH_3$-C12), 0.06 (s, 9H, $CH_3$-TMS).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 214.7 (C-C5), 135.1 (CH-C2), 120.1 (CH-C1) 100.8 (C-C11), 86.6 ($CH_2$-C4), 79.7 (CH-C9), 76.6 (CH-C8), 64.6 (CH-C10), 40.9 (CH-C6), 37.5 ($CH_2$-C3), 33.7 ($CH_2$-C7), 31.1 ($CH_3$-C12), 21.1 ($CH_3$-C12), -0.5 ($CH_3$-TMS).

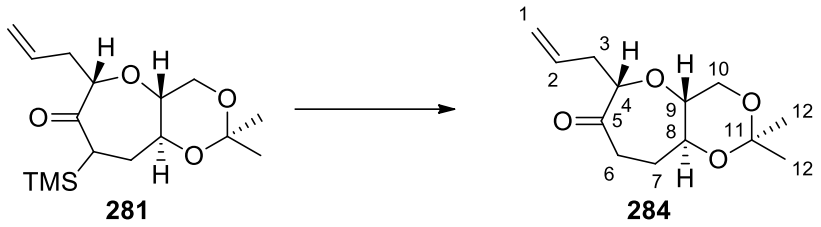
**HRMS** ESI+ $[C_{16}H_{28}NaO_4Si]^+$ found 335.1639, $[M+Na]^+$calculated 335.1649

**$[\alpha]_D$:** -112°, 19.8 °C, c=1.00 in $CHCl_3$

**$V_{max}$:** 2993, 2949, 2877, 1691, 1369, 1248, 1199, 1159, 1101, 1039, 839, 758, $cm^{-1}$

**$R_f$:** 0.55 (20% diethyl ether in petroleum ether)

**(*4aR,6S,9aS*)-6-Allyl-2,2-dimethyltetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (284)**




To a solution of α-silyl ketone **281** (420 mg, 1.34 mmol) in THF (20 mL) at room temperature, TBAF (1.40 g, 5.35 mmol) was added and the solution was stirred for 20 minutes. The solution was diluted with $Et_2O$ (10 mL) and $H_2O$ (10 mL) was added. The organic phase was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10 % $Et_2O$ in PE) to afford the ketone **284** (297 mg, 92 %) as a colorless oil.

**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 5.85 – 5.69 (m, 1H, CH-C2), 5.12 – 5.02 (m, 2H, $CH_2$-C1), 3.92 – 3.84 (m, 2H, CH-C4, $CH_2$-C10), 3.84 – 3.78 (m, 1H, CH-C8), 3.70 (dd, *J* = 11.3, 10.1 Hz, 1H, $CH_2$-C10), 3.11 (td, *J* = 9.8, 5.8 Hz, 1H, CH-C9), 2.82 (ddd, *J* = 14.0, 12.3, 2.6 Hz, 1H,$CH_2$-C6), 2.43 – 2.36 (m, 2H, $CH_2$-C3), 2.37 – 2.29 (m, 1H,$CH_2$-C6), 2.06 (dddd, *J* = 13.9, 7.0, 4.5, 2.6 Hz, 1H,$CH_2$-C7), 1.63 – 1.54 (m, 1H, $CH_2$-C7), 1.51 (d, *J* = 3.8 Hz, 3H, $CH_3$-C12), 1.38 (d, *J* = 0.8 Hz, 3H, $CH_3$-C12).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 214.8 (C-C5), 132.8 (CH-C2), 118.0 ($CH_2$-C1), 98.6 (C-C11), 86.9 (CH-C4), 77.4 (CH-C9), 73.3 (CH-C8), 62.6 ($CH_2$-C10), 37.2 ($CH_2$-C3), 36.9 ($CH_2$-C6), 29.8 ($CH_2$-C7), 29.0 ($CH_3$-C12), 19.0 ($CH_3$-C12).

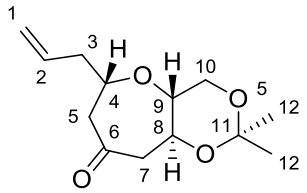
**HRMS:** ESI+ $[C_{13}H_{20}O_4Na]^+$ found 263.1260, $[M+Na]^+$calculated 263.1254

**$[\alpha]_D$:** -70.70°, 15.8 °C, c=1.00 in $CHCl_3$

**$V_{max}$:** 2993, 2939, 2876, 1718, 1371, 1271, 1196, 1155, 1099, 1042, 918, 864, $cm^{-1}$

**$R_f$:** 0.38 (20% diethyl ether in petroleum ether)

**(*4aR,6S,9aS*)-6-Allyl-2,2-dimethyltetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-8(4aH)-one**



**$^{1}$H NMR (400 MHz, Chloroform-*d*)** δ 5.77 (dddd, *J* = 19.3, 9.6, 7.4, 6.5 Hz, 1H, CH-C2), 5.14 – 5.05 (m, 2H, $CH_2$-C1), 3.90 (dd, *J* = 11.4, 5.5 Hz, 1H, $CH_2$-C10), 3.85 (ddd, *J* = 10.1, 5.0, 2.8 Hz, 1H, CH-C4), 3.80 (dq, *J* = 12.0, 3.3 Hz, 1H, CH-C8), 3.65 (dd, *J* = 11.4, 9.5 Hz, 1H, $CH_2$-C10), 3.45 (td, *J* = 9.2, 5.5 Hz, 1H, CH-C9), 2.88 (dd, *J* = 14.6, 11.5 Hz, 1H, $CH_2$-C7), 2.75 – 2.69 (m, 1H, $CH_2$-C7), 2.65 – 2.50 (m, 2H, $CH_2$-C5), 2.31 (dtt, *J* = 13.5, 6.7, 1.4 Hz, 1H, $CH_2$-C3), 2.19 (dddt, *J* = 14.3, 7.0, 5.6, 1.3 Hz, 1H, $CH_2$-C3), 1.45 (s, 3H, $CH_3$-C12), 1.38 (s, 3H, $CH_3$-C12).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 207.4 (C-C6), 133.5 (CH-C2), 118.0 ($CH_2$-C1), 98.9 (C-C11), 78.9 (CH-C9), 76.6 (CH-C4), 69.4 (CH-C8), 62.7 ($CH_2$-C10), 51.3 ($CH_2$-C5), 50.5 ($CH_2$-C7), 40.8 ($CH_2$-C3), 28.6 ($CH_3$-C12), 19.2 ($CH_3$-C12).

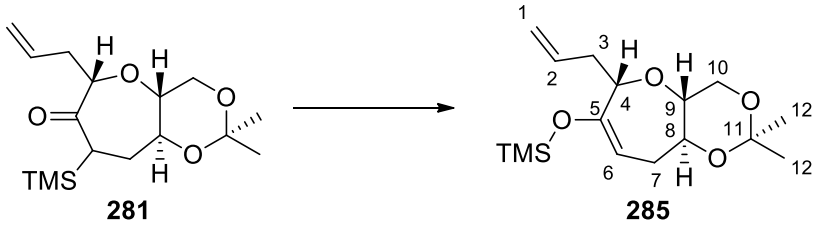
**HRMS:** ESI+ $[C_{13}H_{20}O_4Na]^+$ found 263.1252, $[M+Na]^+$calculated 263.1254

**$[\alpha]_D$:** + 64.3, 20.3 $^{o}$C, c=0.75 in $CHCl_3$

**$V_{max}$** 2993, 2880, 1703, 1641, 1371, 1278, 1198, 1151, 1090, 1040, 989, 916, 860 $cm^{-1}$

**$R_f$:** 0.20 (20% diethyl ether in petroleum ether)

**(((*4aR,6S,9aS*)-6-Allyl-2,2-dimethyl-4a,6,9,9a-tetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7-yl)oxy)trimethylsilane (285)**




A solution of TMS ketone **281** (100 mg, 0.32 mmol) in toluene (4.5 mL) was heated to reflux and stirred for 3 hours. The reaction mixture was cooled and then concentrated under reduced pressure to afford the TMS enol-ether **285**, as a colorless oil. Compound **285** was used crude in the following reactions.

**$^{1}$H NMR (400 MHz, Chloroform-*d*) δ** 5.84 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H, CH-C2), 5.11 – 5.00 (m, 2H, $CH_2$-C1), 4.97 (ddd, *J* = 9.1, 4.6, 1.5 Hz, 1H, CH-C6), 4.14 – 4.06 (m, 1H, CH-C4), 3.81 (dd, *J* = 11.1, 5.4 Hz, 1H, $CH_2$-C10), 3.67 – 3.61 (m, 1H, $CH_2$-C10), 3.58 (ddd, *J* = 10.0, 8.3, 2.7 Hz, 1H, CH-C8), 3.42 (ddd, *J* = 10.0, 9.1, 5.4 Hz, 1H, CH-C9), 2.46 – 2.13 (m, 4H, $CH_2$-C3, $CH_2$-C7), 1.46 (d, *J* = 0.7 Hz, 3H, $CH_3$-C12), 1.40 – 1.34 (m, 3H, $CH_3$-C12), 0.20 (s, 9H, TMS).

**$^{13}$C NMR (101 MHz, Chloroform-*d*) δ** 156.6 (C-C5), 135.5 (CH-C2), 116.4 ($CH_2$-C1), 102.9 (CH-C6), 98.7 (C-C11), 80.1 (CH-C4), 80.1 (CH-C9), 70.9 (CH-C8), 62.8 ($CH_2$-C10), 35.8 ($CH_2$-C3), 30.8 ($CH_2$-C7), 29.2 ($CH_3$-C12), 19.2 ($CH_3$-C12).

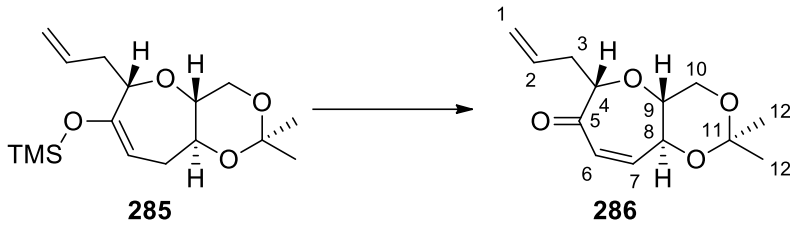
**HRMS:** ESI+ $[C_{13}H_{20}NaO_4]^+$ found 263.1260, $[M+Na]^+$calculated 263.1254

**$[\alpha]_D$:** -4.20 °, 15.0 °C, c=1.00 in $CHCl_3$

**$V_{max}$:** 2993, 2954, 2880, 2361, 1649, 1369, 1252, 1200, 155, 1098, 1034, 910, 878, 843, 760 $cm^{-1}$

**$R_f$:** 0.63 (20% diethyl ether in petroleum ether)

**(*4aR,6S,9aS*)-6-Allyl-2,2-dimethyl-6,9a-dihydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (286)**




To a solution of TMS enol ether **285** (130 mg, 0.42) in MeCN (20 ml) was added $Pd(OAc)_2$ (270 mg, 1.20 mmol, 2.5 eq.), and the reaction was stirred at 20 °C for 2.5 hours. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Flash chromatography on silica gel (10% $Et_2O$ in PE) afforded the enone **286** (67 mg, 68 % over two steps) as a colorless oil.

**$^1$H NMR (400 MHz, Chloroform-d) δ** 6.40 (dd, J = 12.7, 2.3 Hz, 1H, CH-C7), 6.01 (dd, J = 12.7, 2.7 Hz, 1H, CH-C6), 5.79 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H, CH-C2), 5.14 – 5.00 (m, 2H, $CH_2$-C1), 4.42 (dt, J = 9.0, 2.5 Hz, 1H, CH-C8), 4.24 (dd, J = 7.4, 4.2 Hz, 1H, CH-C4), 3.95 (dd, J = 11.2, 5.7 Hz, 1H, $CH_2$-C10), 3.76 (t, J = 10.7 Hz, 1H, CH2-C10), 3.53 (td, J = 9.6, 5.7 Hz, 1H, CH-C9), 2.65 – 2.52 (m, 1H, $CH_2$-C3), 2.43 (dt, J = 14.6, 7.3 Hz, 1H, $CH_2$-C3), 1.54 (s, 3H, $CH_3$-C12), 1.42 (s, 3H, $CH_3$-C12).

**$^{13}$C NMR (101 MHz, Chloroform-*d*) δ** 202.7 (C-C5), 144.6 (CH-C7), 133.2 (CH-C2), 128.6 (CH-C6), 117.8 ($CH_2$-C1), 99.2 (C-C11), 86.9 (CH-C4), 74.9 (CH-C9), 73.1 (CH-C8), 62.5 ($CH_2$-C10), 37.7 ($CH_2$-C3), 28.9 ($CH_3$-C12), 18.6 ($CH_3$-C12).

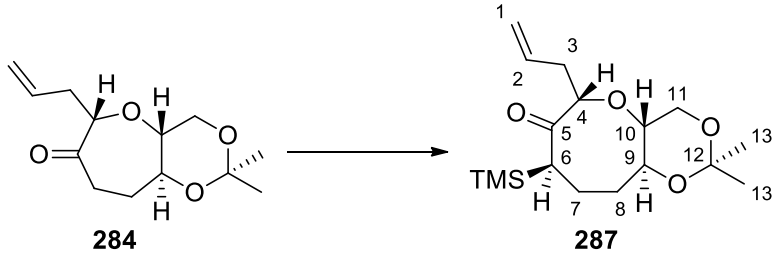
**HRMS:** ESI+ $[C_{13}H_{18}NaO_4]^+$ found 261.1091, $[M+Na]^+$calculated 261.1097

**$[\alpha]_D$:** 1.96°, 21.2°C, c=2.00 in $CHCl_3$

**$V_{max}$:** 2924, 2855, 1667, 1373, 1265, 1219, 1196, 1134, 1103, 1049, 941, 918 $cm^{-1}$

**$R_f$:** 0.25 (20% diethyl ether in petroleum ether)

**(*4aR,6S,8R,10aS*)-6-Allyl-2,2-dimethyl-8-(trimethylsilyl)hexahydro-[1,3]dioxino[5,4-b]oxocin-7(6H)-one (287)**




To a solution of ketone **284** (280 mg, 1.16 mmol) in $CH_2Cl_2$ (12 mL) were added $BF_3{\cdot}Et_2O$ (0.16 ml, 130 mmol) and TMS-diazomethane in hexanes (1.8 ml, 2M, 3.50 mmol) at -78 °C. The resultant solution was stirred for 1.5 hours. The reaction mixture was allowed to worm to -40 °C and the mixture was stirred for a further 3.5 hours before the reaction was quenched with sat. $NaHCO_3$ (aq.) (4 mL). The mixture was diluted with $Et_2O$ (10 mL), the phases were separated and the organic phase was washed with (2 × 20 ml) brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5 % $Et_2O$ in PE) to afford the TMS ketone **287** (110 mg, 29 %) as a colorless oil.

**$^1$H NMR (400 MHz, Chloroform-d) δ** 5.74 – 5.63 (m, 1H, CH-C2), 5.07 – 4.98 (m, 2H, $CH_2$-C1), 3.81 – 3.70 (m, 1H $CH_2$-C11), 3.70 – 3.63 (m, 1H, CH-C10), 3.59 (dd, J = 11.5, 9.8 Hz, 1H,$CH_2$-C11), 3.54 – 3.43 (m, 1H, CH-C4), 3.05 – 2.93 (m, 2H, CH-C6, CH-C9), 2.11 (tt, J = 6.8, 1.3 Hz, 2H, $CH_2$-C3), 1.93 – 1.79 (m, 1H, $CH_2$-C8), 1.78 – 1.68 (m, 2H, $CH_2$-C8, $CH_2$-C7), 1.65 – 1.55 (m, 1H, $CH_2$-C7), 1.39 (d, J = 11.8 Hz, 3H, $CH_3$-C13), 1.32 – 1.26 (m, 3H, $CH_3$-C13), 0.05 (s, 9H, TMS).

**$^{13}$C NMR (101 MHz, Chloroform-d) δ** 220.2 (C-5), 133.5 (CH-C2), 117.7 ($CH_2$-C1), 98.1 (C-C12), 88.4 (CH-C4), 80.2 (CH-C9), 73.5 ($CH_2$-C10), 62.8 ($CH_2$-C11), 36.3 ($CH_2$-C3), 35.5 ($CH_2$-C), 34.9 (CH-C6), 28.8 ($CH_3$-C13), 26.9 ($CH_2$-C8), 19.1 ($CH_3$-C13), -2.3 ($CH_3$-TMS).

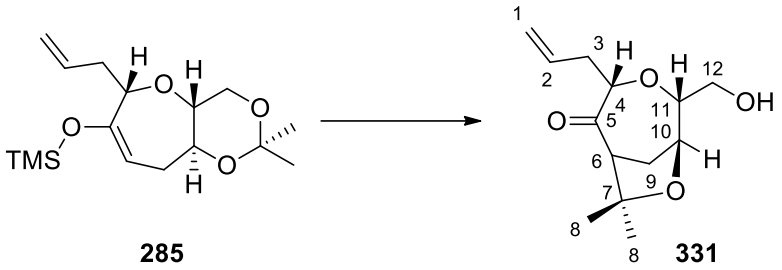
**HRMS:** ESI+ $[C_{17}H_{30}NaO_4Si]^+$ found 349.1793, $[M+Na]^+$calculated 349.1806

**$[\alpha]_D$:** -51.3°, 22.2°C, c=1.45 in $CHCl_3$

**$V_{max}$:** 2994, 2940, 1697, 1443, 1373, 1250, 1204, 1103, 1034, 918, 841 $cm^{-1}$

**$R_f$:** 0.45 (20% diethyl ether in petroleum ether)

**(*1S,2R,4S,6S*)-4-allyl-2-(hydroxymethyl)-8,8-dimethyl-3,9-dioxabicyclo[4.3.1]decan-5-one (331)**




**285** **331**

To a solution of silyl enol ether **285** (45 mg, 0.15 mmol) in $CH_2Cl_2$ (0.8 mL) was added $TiCl_4$ in DCM (0.15 mL, 1M, 0.15 mmol) and followed by ethyl propiolate (23 µL, 0.23 mmol) at -78°C. The resultant solution was stirred for 1 hour and quenched with sat. $NaHCO_3$ (aq.) (1 mL). The mixture was diluted with $Et_2O$ (1 mL) and the phases were separated. The organic phase was washed brine (2 × 3 mL and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10 % $Et_2O$ in PE) to afford the ketone **331** (28 mg, 89 %) as a colorless oil.

**$^1$H NMR (400 MHz, Chloroform-*d*)** δ 5.82 (dddd, *J* = 17.5, 10.2, 7.4, 6.3 Hz, 1H, CH-C2), 5.22 – 4.91 (m, 2H, $CH_2$-C1), 4.33 (dd, *J* = 7.4, 1.4 Hz, 1H, CH-C10), 4.07 (dd, *J* = 9.2, 4.0 Hz, 1H, CH-C4), 3.78 (dd, *J* = 8.5, 4.0 Hz, 1H, CH-C11), 3.64 – 3.53 (m, 1H, $CH_2$-C12), 3.46 (dd, *J* = 11.5, 8.5 Hz, 1H, $CH_2$-C12), 2.75 (dd, *J* = 5.5, 1.0 Hz, 1H, CH-C6), 2.66 (dddt, *J* = 15.0, 6.6, 4.0, 1.5 Hz, 1H, $CH_2$-C3), 2.45 – 2.35 (m, 2H, $CH_2$-C9), 2.36 – 2.21 (m, 1H, $CH_2$-C3), 1.95 (d, *J* = 8.9 Hz, 1H,HO-C12), 1.23 (s, 6H, $CH_3$-C8).

**$^{13}$C NMR (101 MHz, Chloroform-*d*)** δ 208.2 (C-C5), 134.5 (CH-C2), 117.5 (CH-C1), 84.3 (CH-C11), 83.2 (CH-C4), 81.9 (C-C7), 78.2 (CH-C10), 63.3($CH_2$-C12), 60.71 (CH-C6), 34.9 ($CH_2$-C3), 28.5 ($CH_3$-C8), 27.80 ($CH_2$-C7), 23.9 ($CH_3$-C8).

**HRMS** ESI+ $[C_{13}H_{20}NaO_4]^+$ found 263.1260, $[M+Na]^+$calculated 263.1254

**$[\alpha]_D$:** -17.7 °, 16.8 °C, c=1.00 in $CHCl_3$

**$V_{max}$:** 3445, 2978, 2924, 1701 1643, 1462, 1254, 1211, 1134, 1016, 918, 829 $cm^{-1}$

**$R_f$:** 0.32 (20% diethyl ether in petroleum ether)

# 5. References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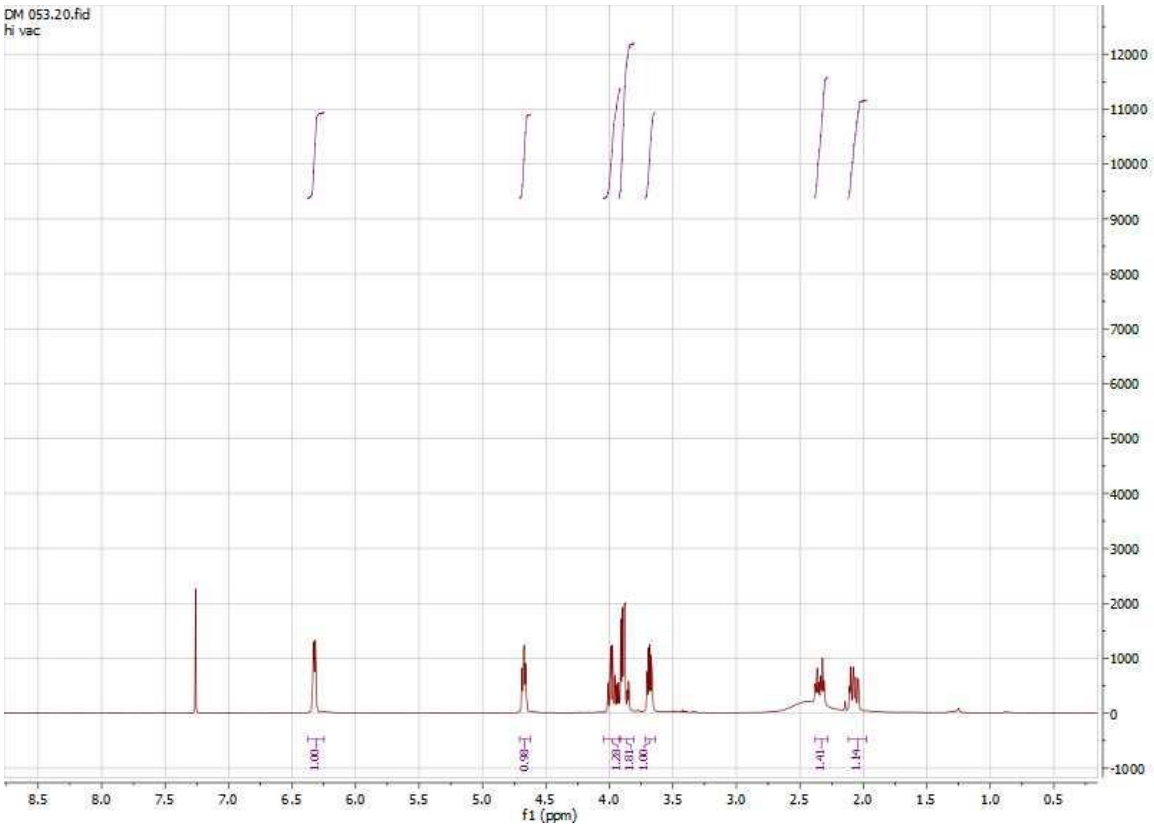
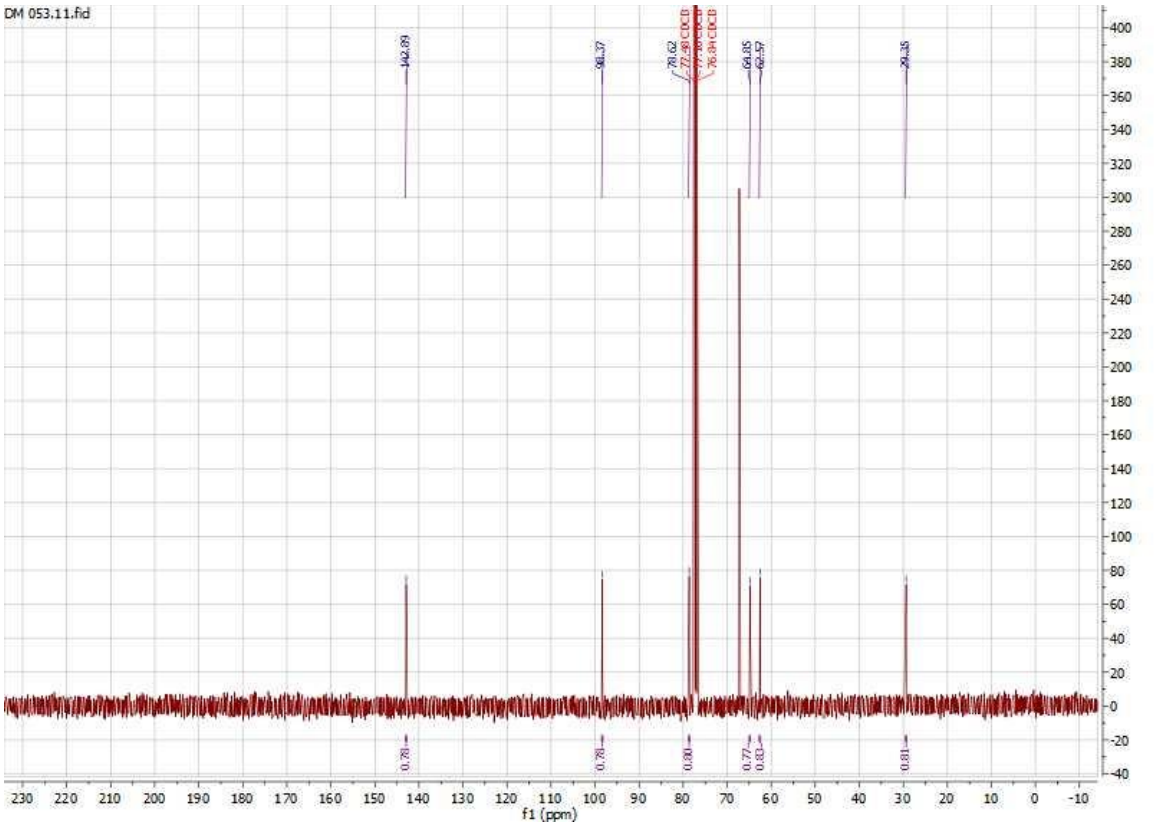
*113.* Hannan Seyal, MSc Thesis, *University of Glasgow*, **2020**

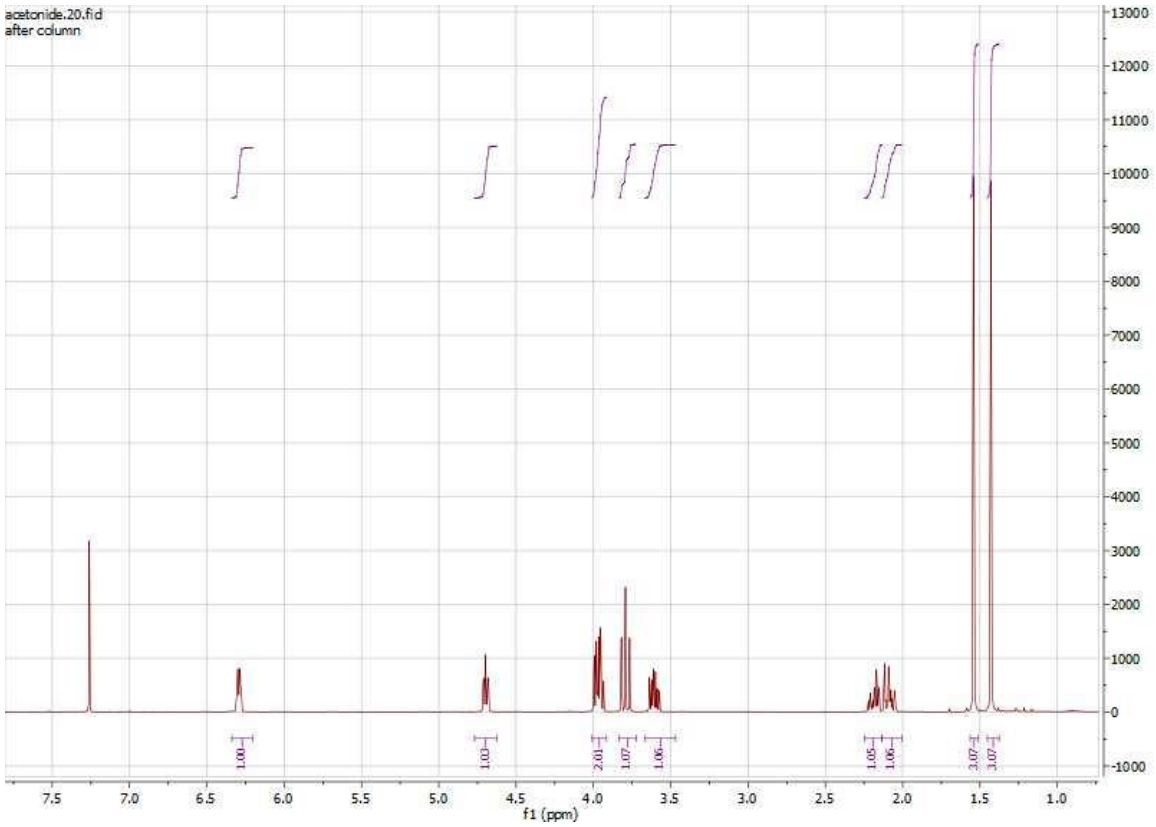
# 6. Appendix

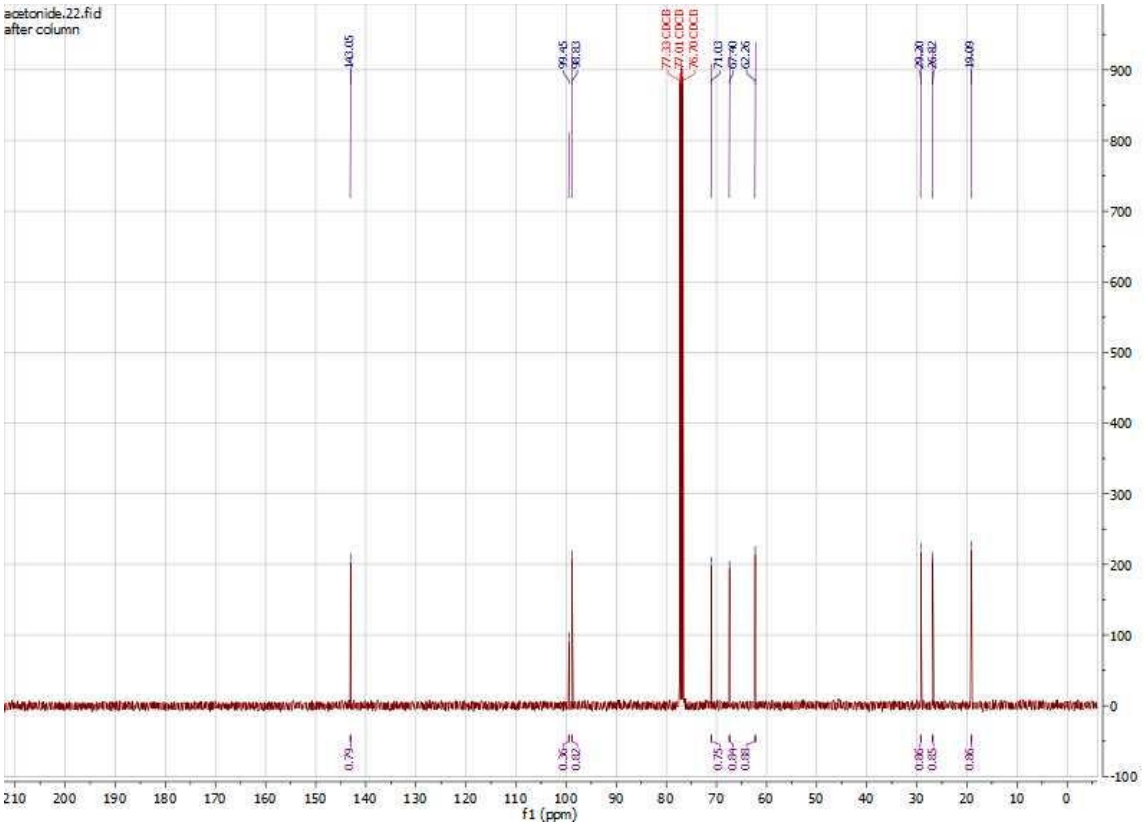
## (2R,3S)-2-(Hydroxymethyl)-3,4-dihydro-2H-pyran-3-ol (200)



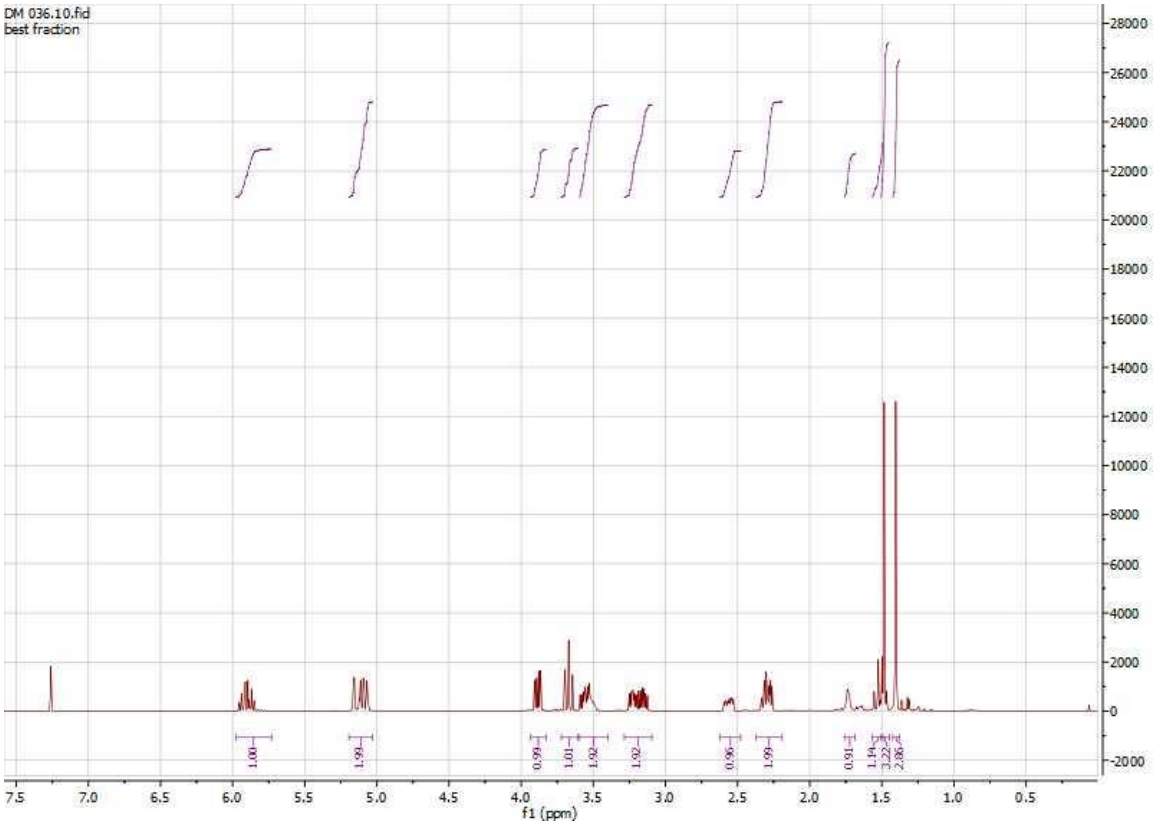



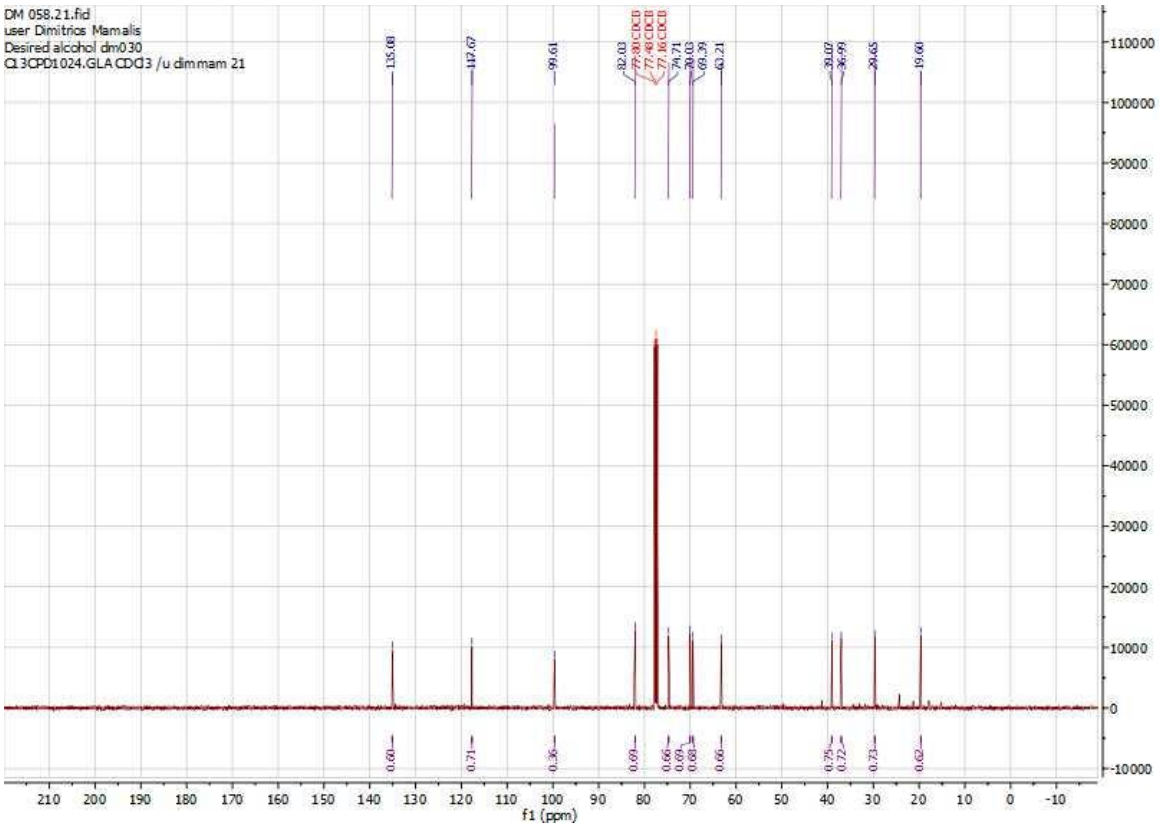
## (4aR,8aS)-2,2-Dimethyl-2H,4H,4aH,8H,8aH-pyrano[3,2-d][1,3]dioxine (203)



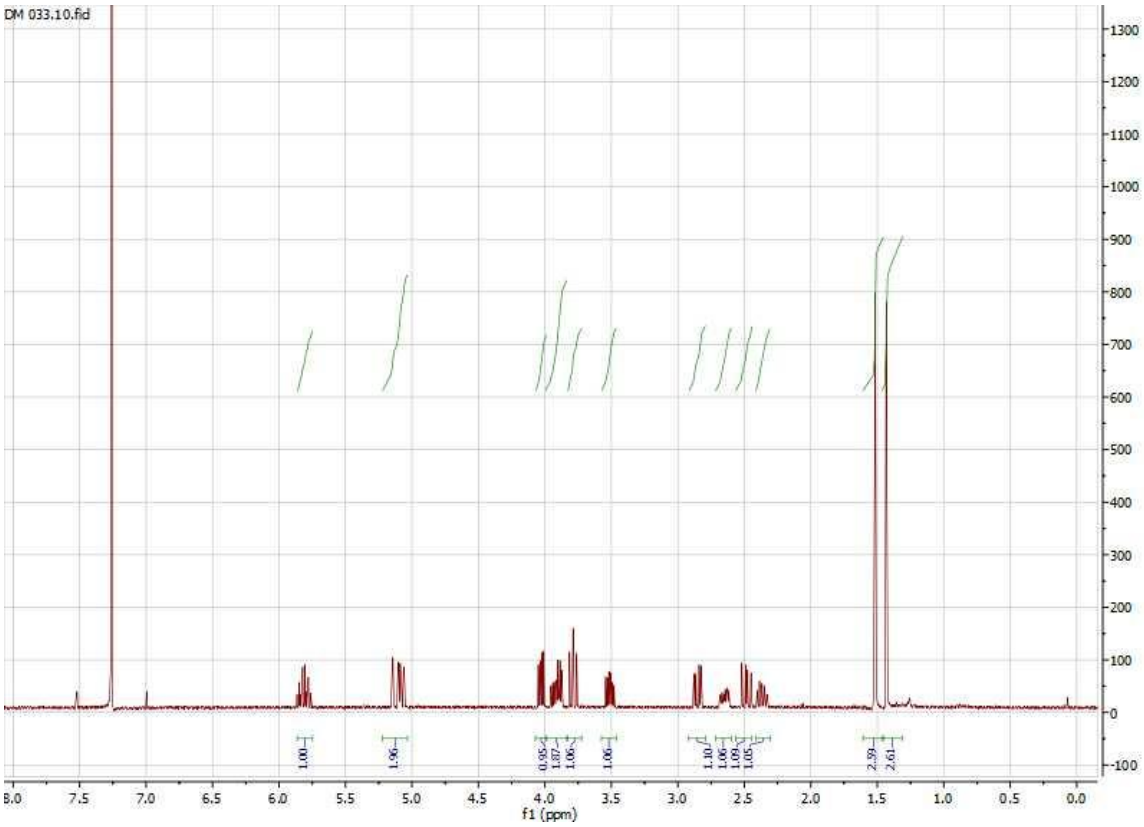



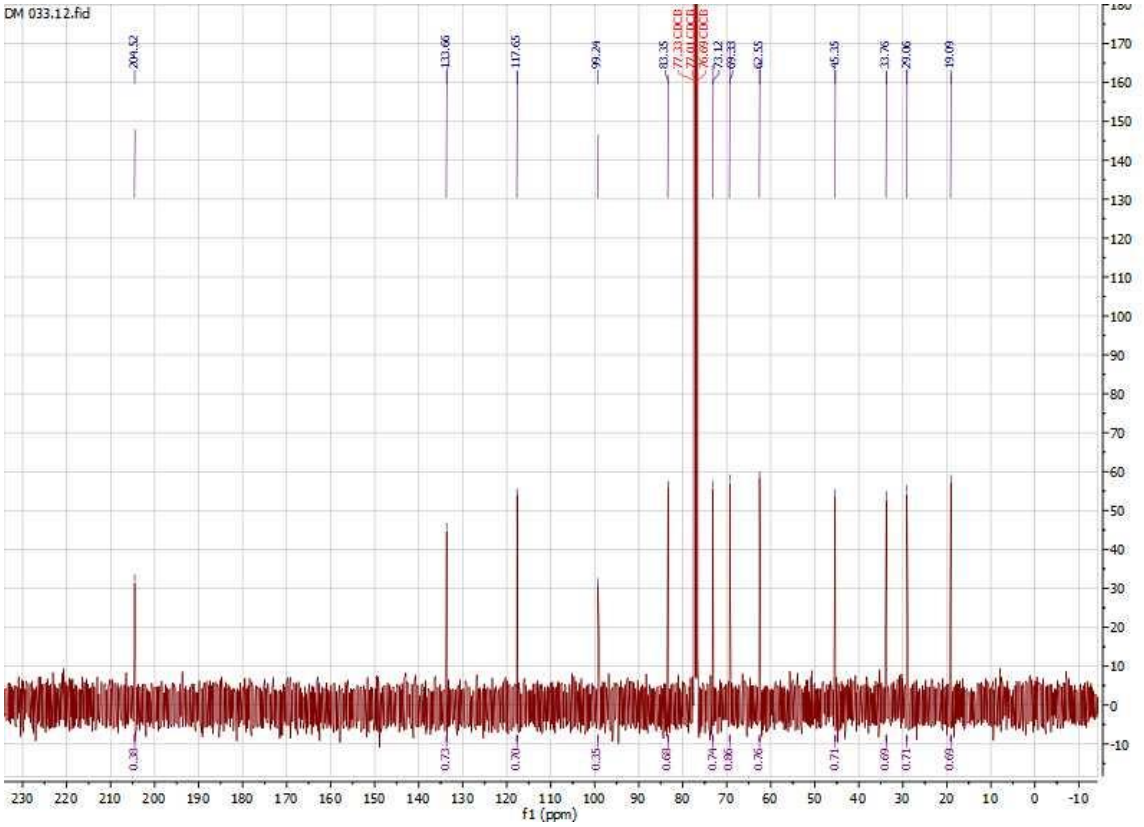
**(4aR,6S,7R,8aS)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1,3]dioxin-7-ol (205a)**



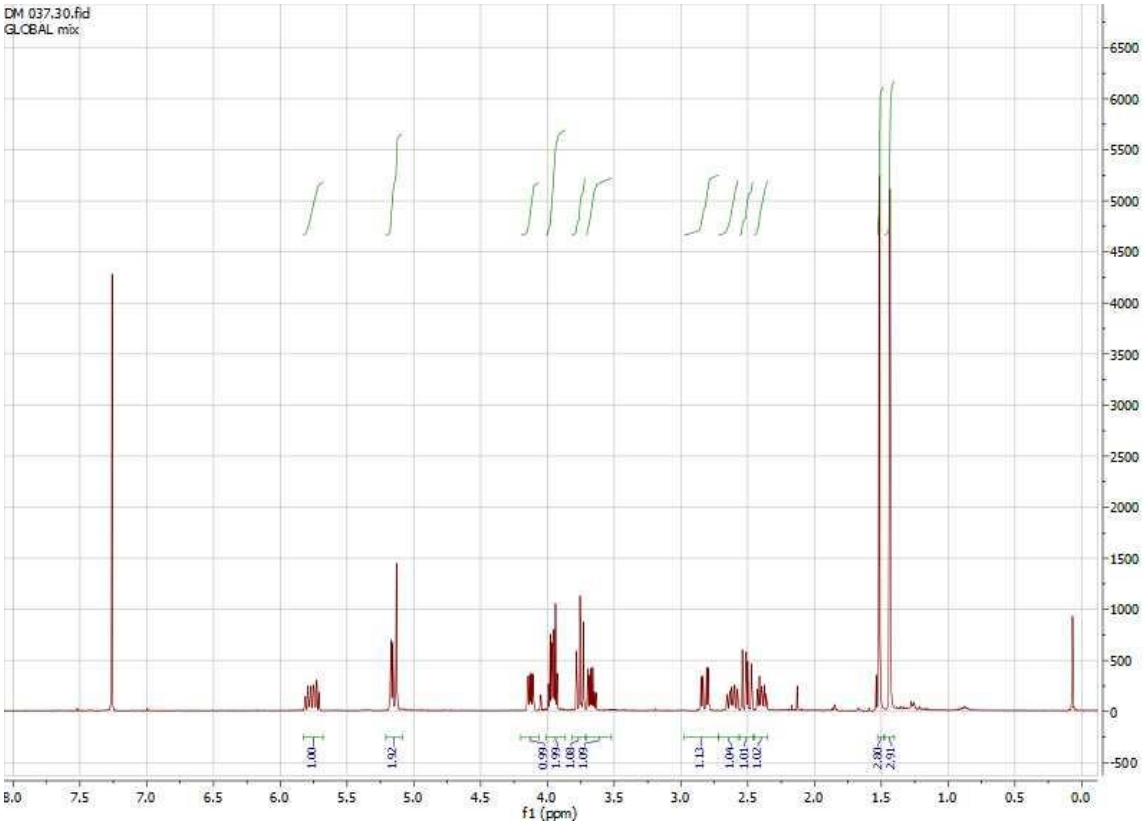



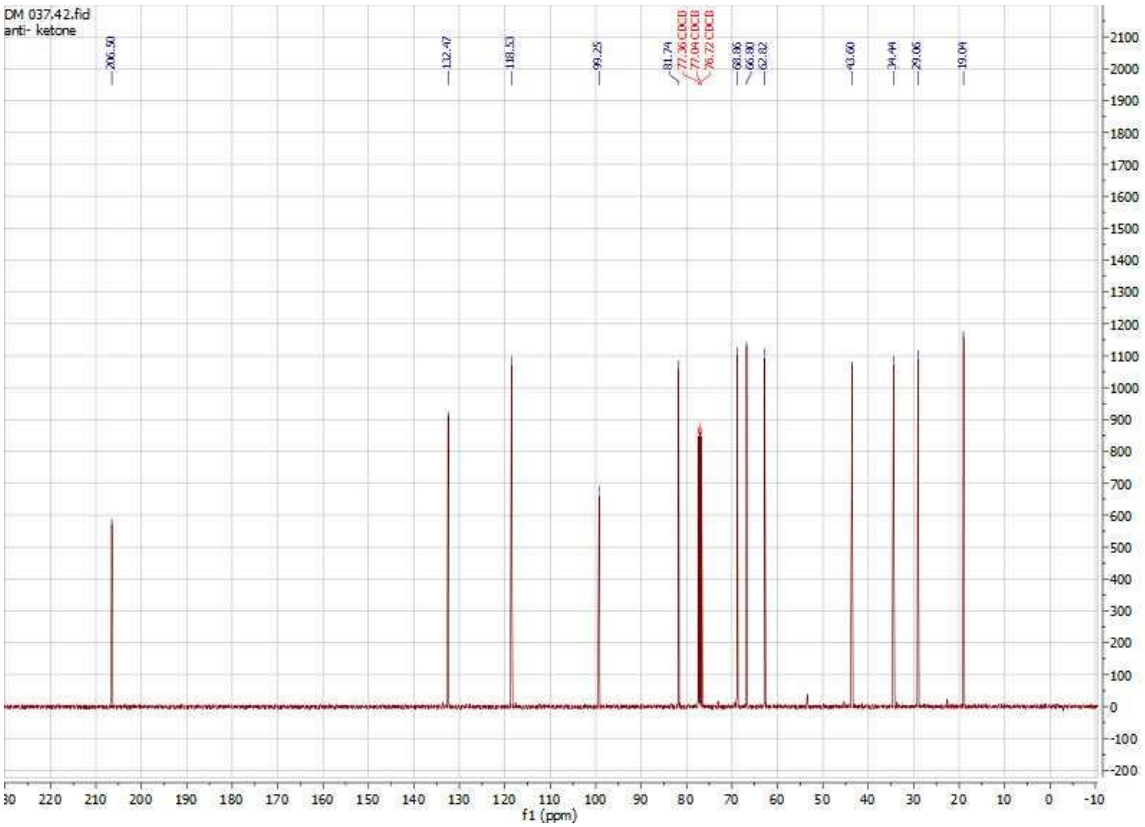
**(4aR,6S,8aS)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1,3]dioxin-7-one (197)**



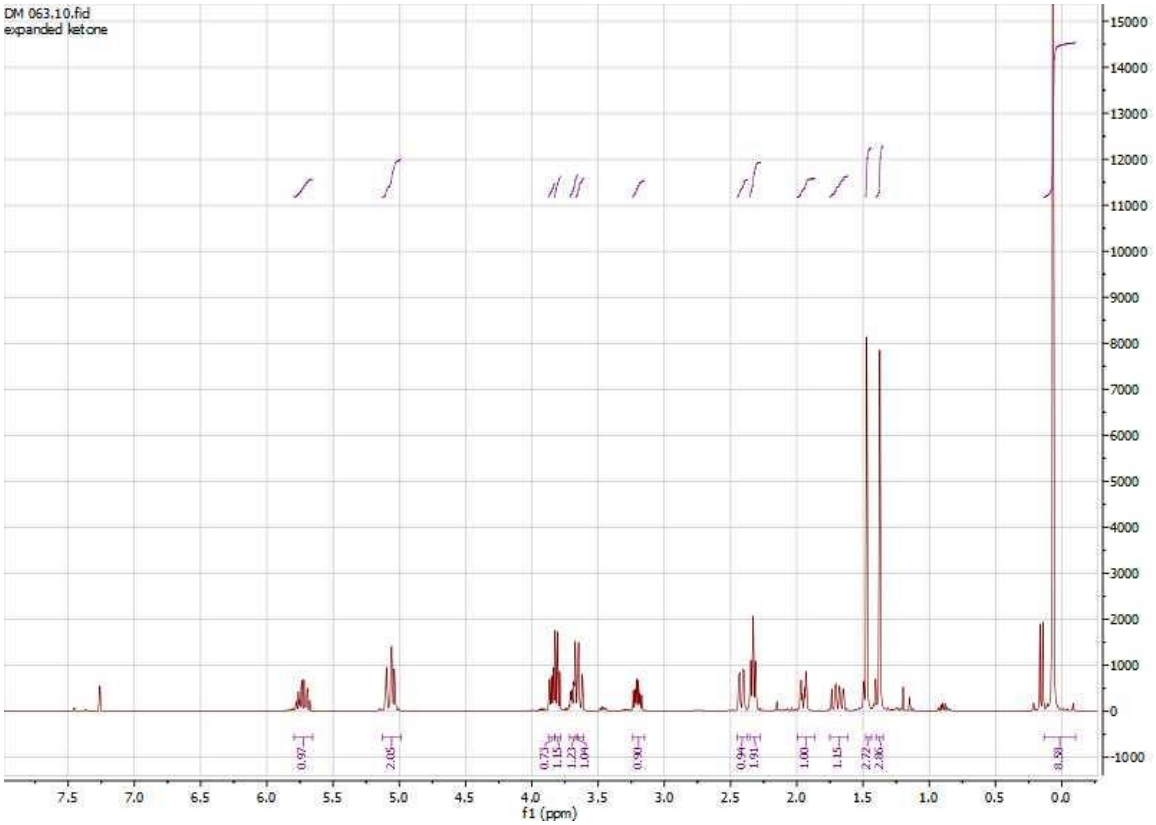



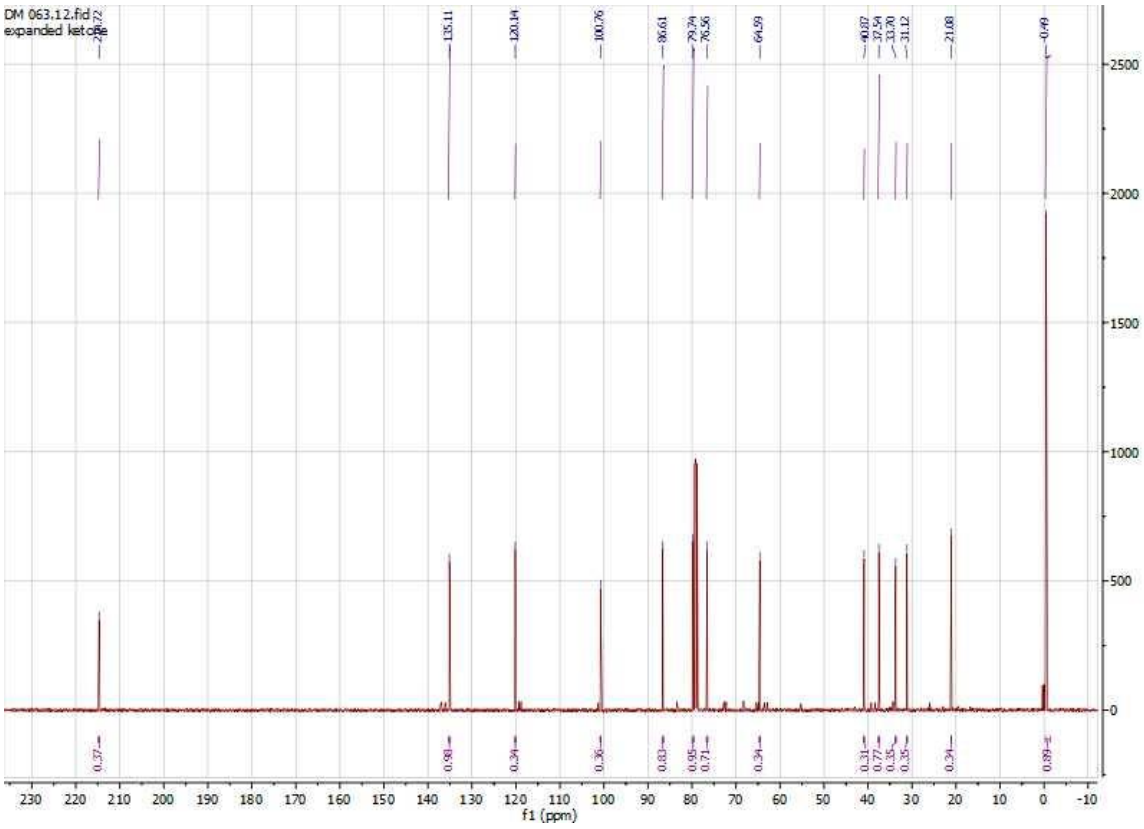
**(4aR,6R,8aS)-2,2-Dimethyl-6-(prop-2-en-1-yl)-hexahydro-2H-pyrano[3,2-d][1,3]dioxin-7-one (*epi*-197)**



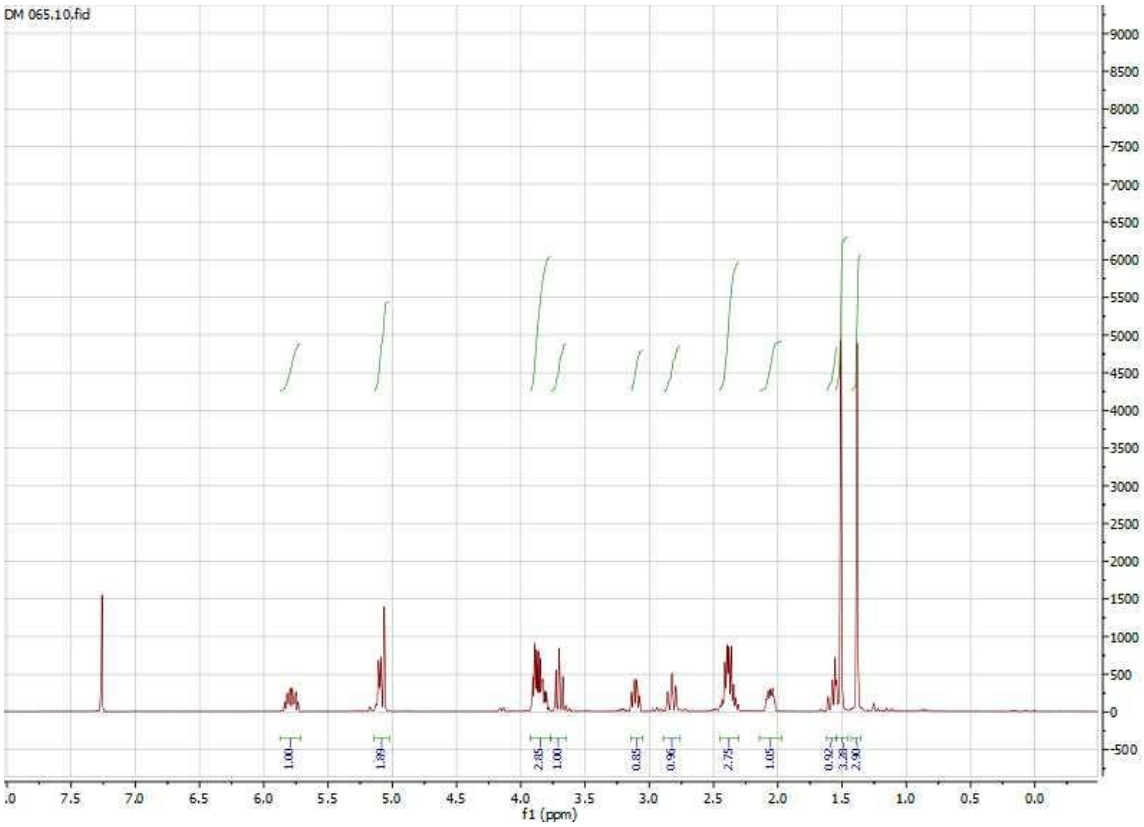



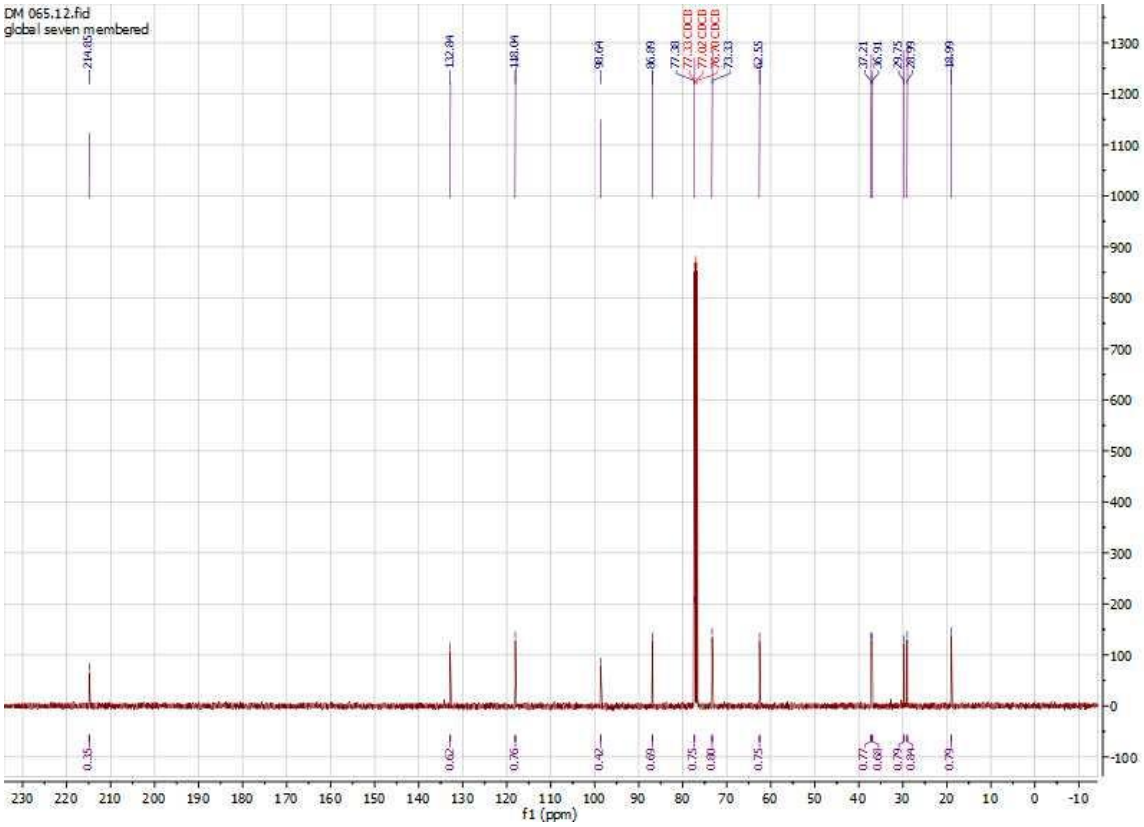
**(4aR,6S,8R,9aS)-6-Allyl-2,2-dimethyl-8-(trimethylsilyl)tetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (281)**



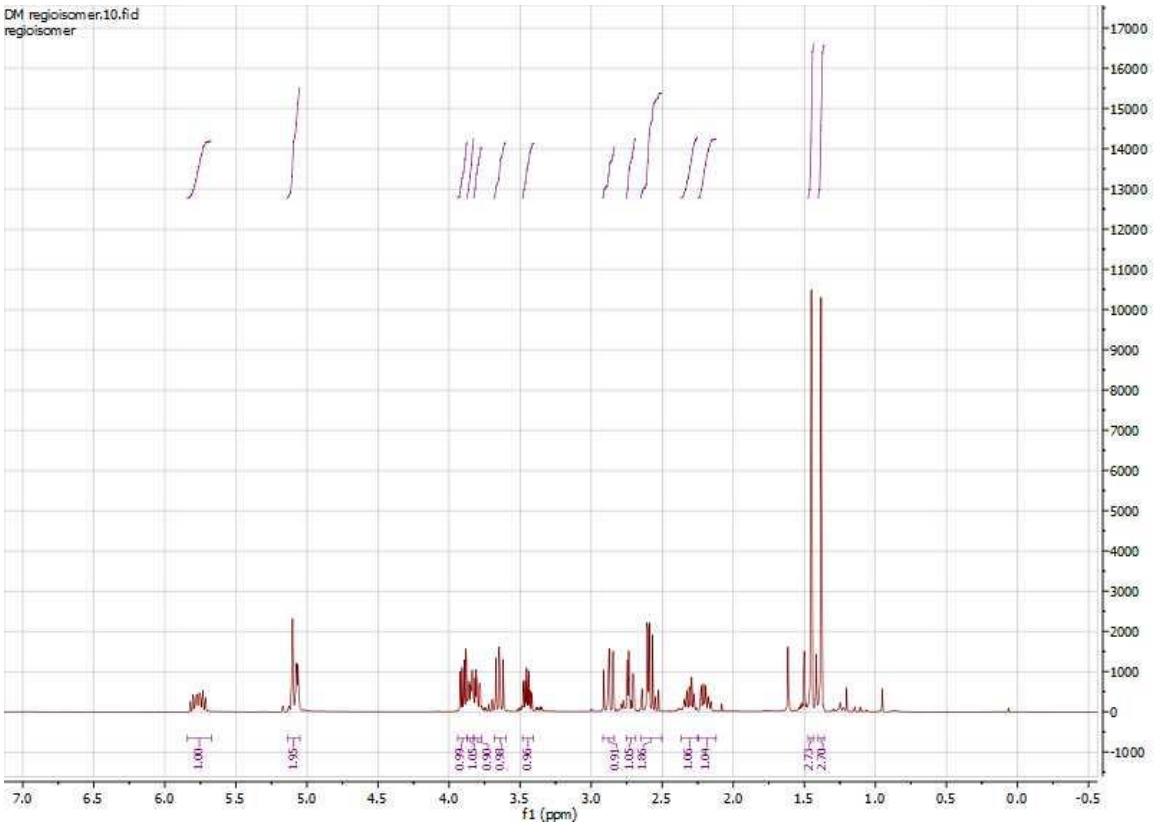



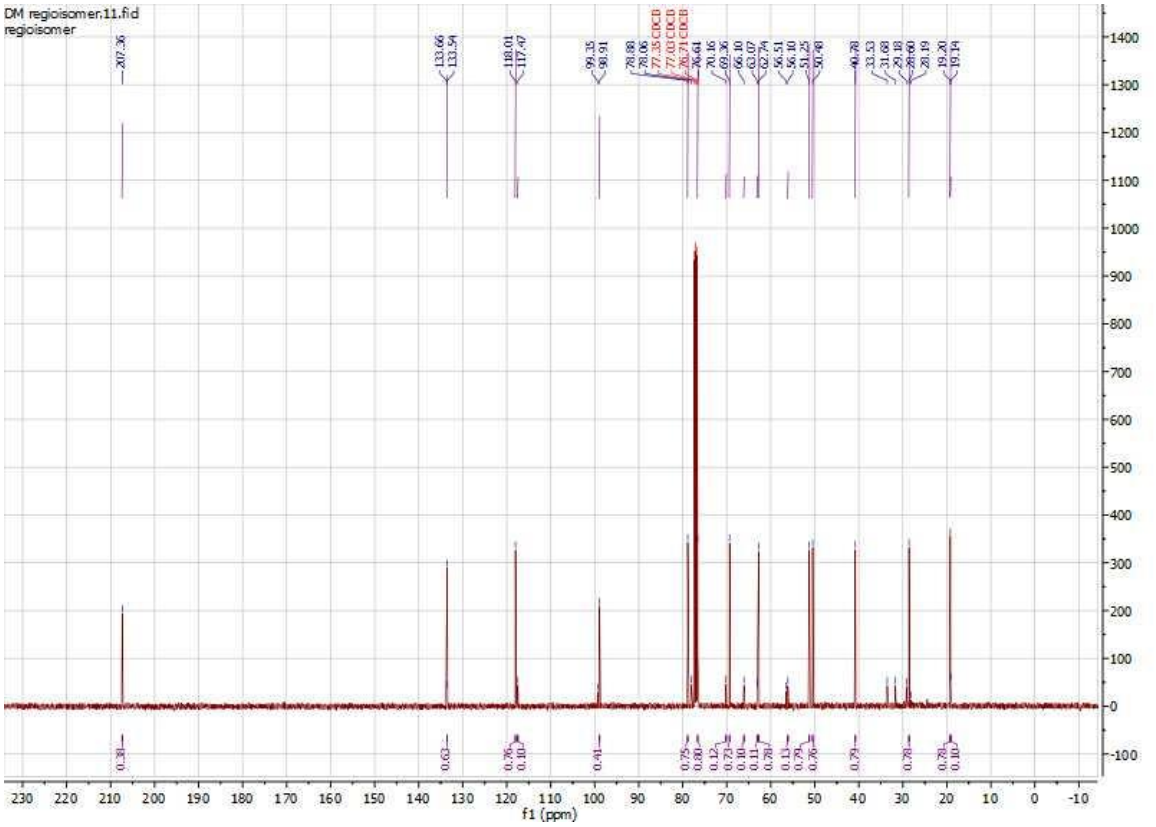
**(4aR,6S,9aS)-6-Allyl-2,2-dimethyltetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (284)**



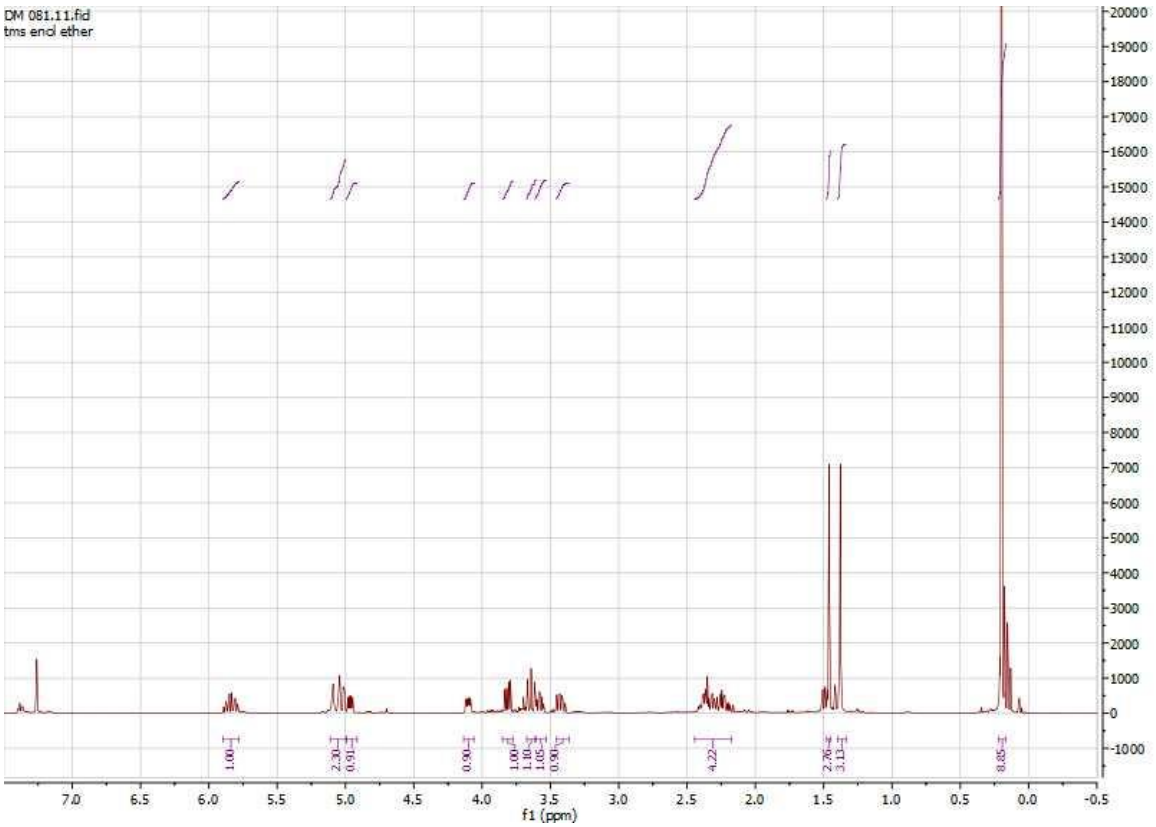



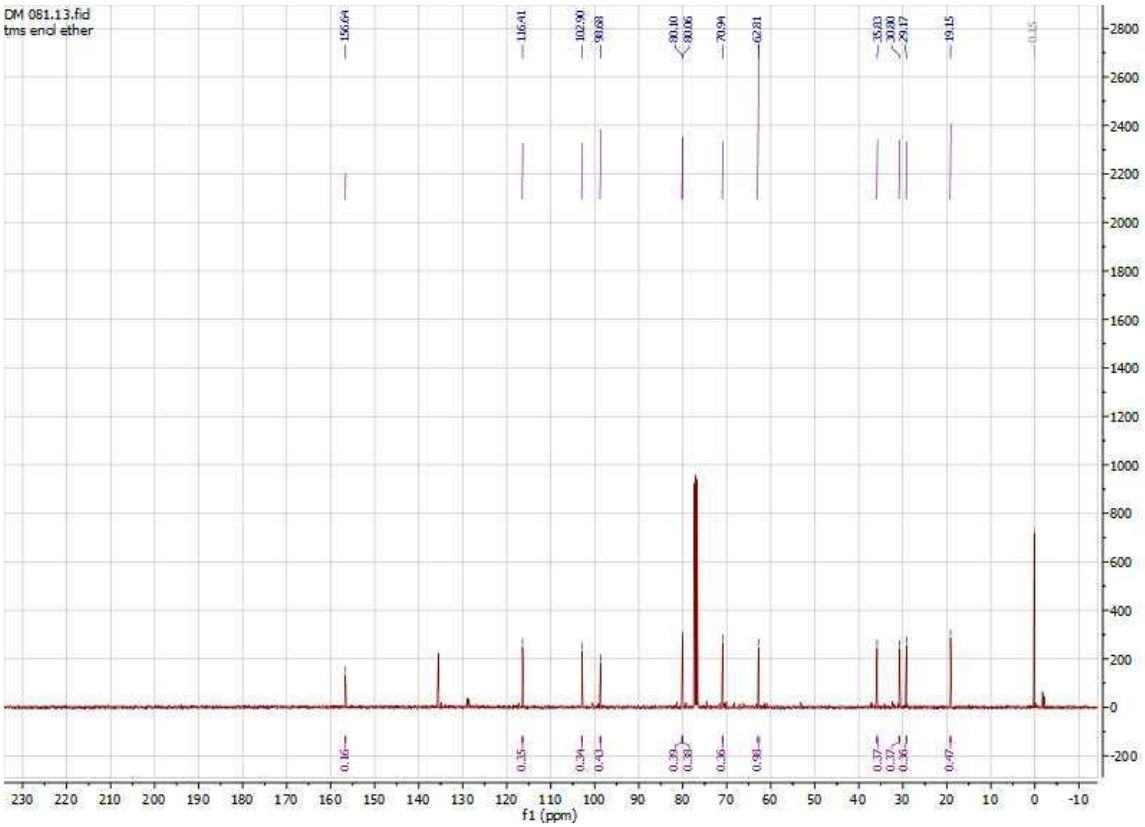
**(4aR,6S,9aS)-6-Allyl-2,2-dimethyltetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-8(4aH)-one**



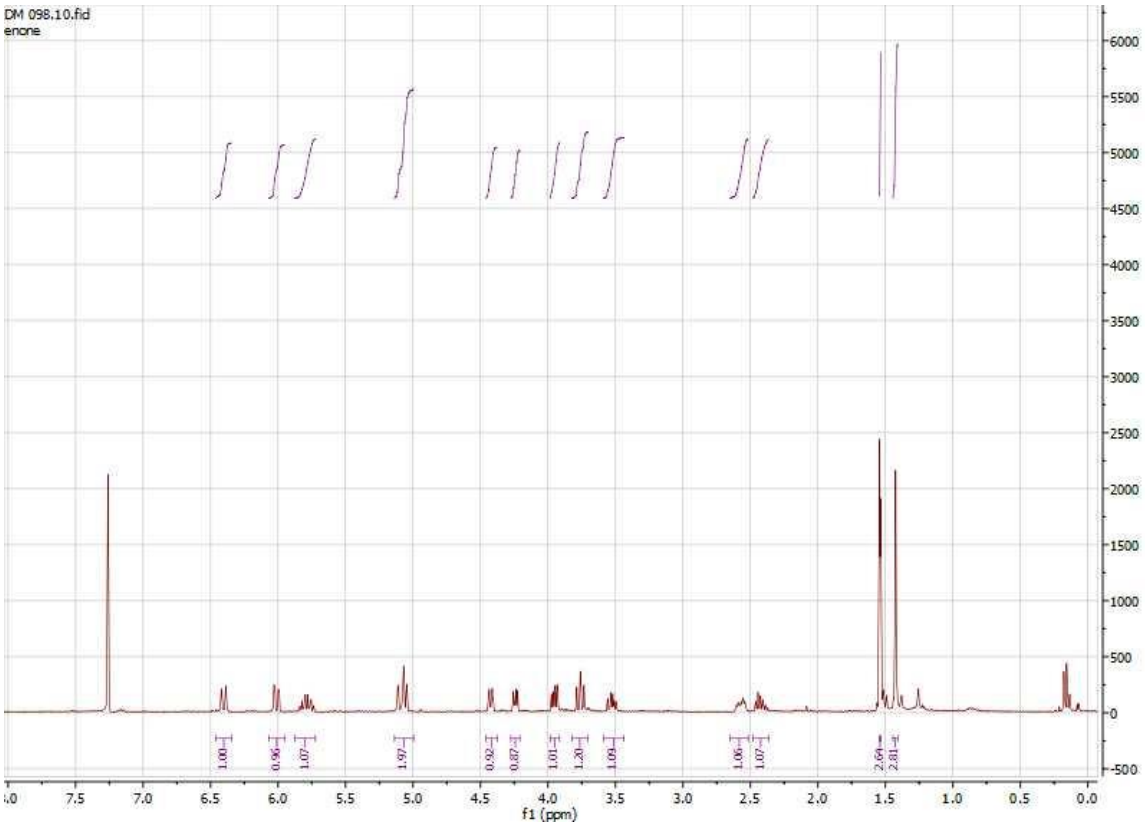



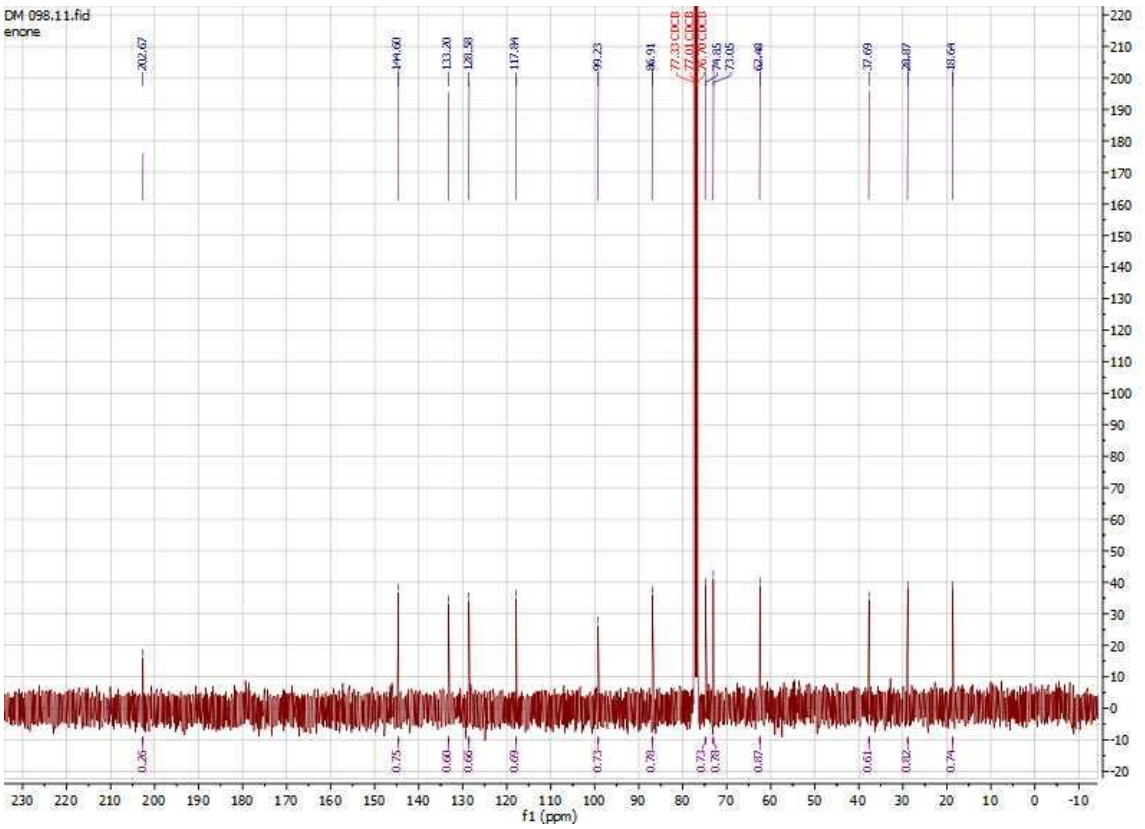
**(((4aR,6S,9aS)-6-Allyl-2,2-dimethyl-4a,6,9,9a-tetrahydro-4H-[1,3]dioxino[5,4-b]oxepin-7-yl)oxy)trimethylsilane (285)**



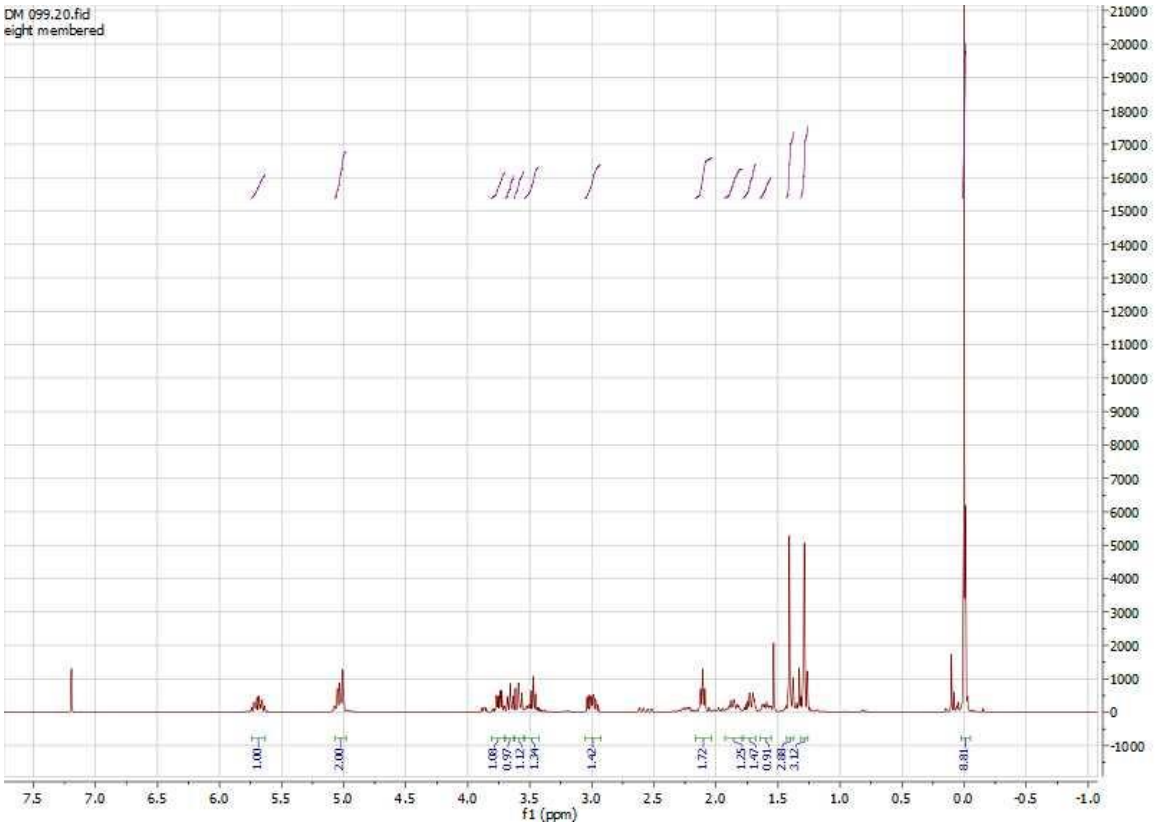



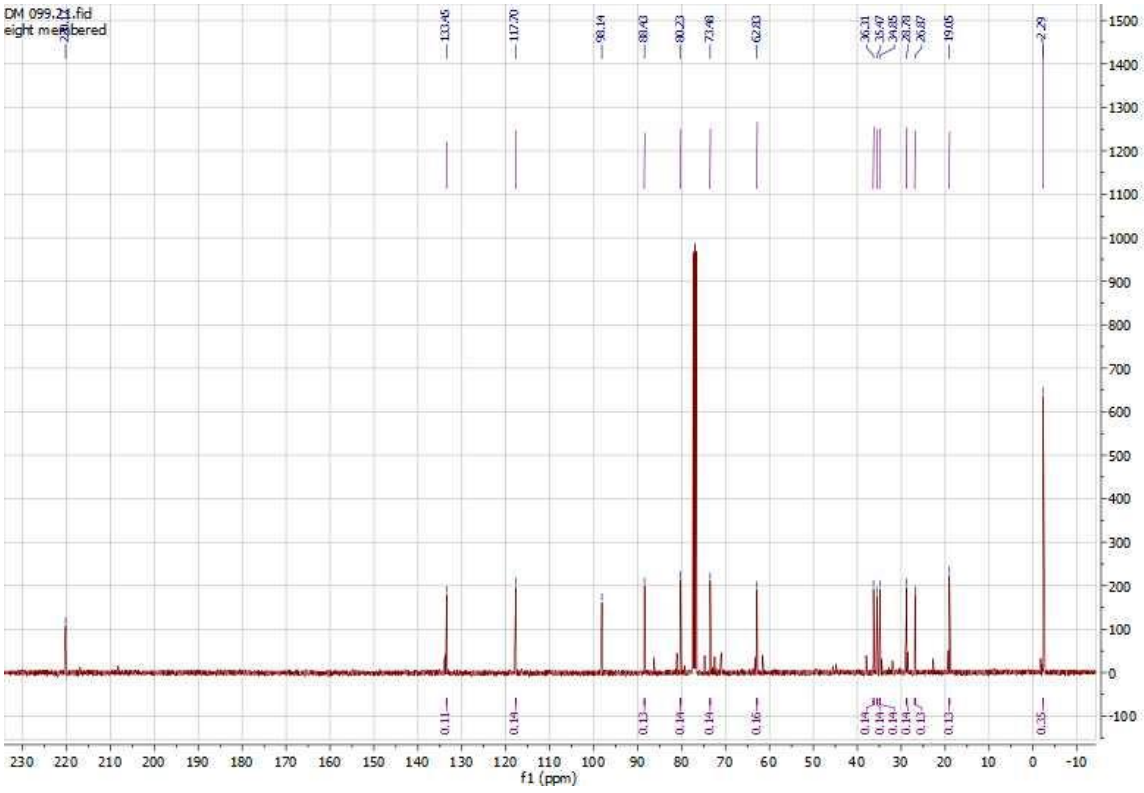
**(4aR,6S,9aS)-6-Allyl-2,2-dimethyl-6,9a-dihydro-4H-[1,3]dioxino[5,4-b]oxepin-7(4aH)-one (286)**



**(4aR,6S,8R,10aS)-6-Allyl-2,2-dimethyl-8-(trimethylsilyl)hexahydro-[1,3]dioxino[5,4-b]oxocin-7(6H)-one (287)**



**(1S,2R,4S,6S)-4-allyl-2-(hydroxymethyl)-8,8-dimethyl-3,9-dioxabicyclo[4.3.1]decan-5-one (331)**