Selective alkylidene carbene insertion reactions

- Studies towards the synthesis of ingenol

by

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Abstract

Alkylidene carbenes are reactive intermediates in organic chemistry. Intramolecular 1,5 C-H insertion reactions lead to cyclopentenes with retention of configuration. Insertions into O-Si or O-H bonds form dihydrofurans. Chapter 1 reviews of the chemistry of alkylidene carbenes, focusing on their reactivity and the techniques that can be employed for their *in situ* generation. Factors governing the selectivity of these reactive intermediates are discussed. Previous investigations in the Grainger group on the use of alkylidene carbenes in model studies towards the synthesis of the cyclopentene A-ring of ingenol, a biologically active diterpene, are described.

Chapter 2 describes an investigation into hydroxycyclopentene annulation using the 1,5 C-H insertion reaction of α-hydroxyalkylidene carbenes on a 2,4-dimethyl-substituted 8-oxabicyclic ring system. Syntheses of α,β-epoxy-*N*-aziridinylimines, known precursors to α-hydroxyalkylidene carbenes, are achieved in 5-6 steps through initial stereoselective addition of a vinyllithium species to 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one. The diastereoselectivity of the alkylidene carbene insertion reaction is reversed upon protection of a tertiary alcohol at C-3 of the oxabicylic ring system as a trimethylsilyl ether.

Application of the hydroxycyclopentene annulation on an 8-oxabicyclic ring system bearing a benzyloxy substituent on the 2-position is described in chapter 3. Selective insertion adjacent to the benzyloxy group is observed irrespective of the tertiary alcohol substituent at C-3. Competing O-H and O-Si insertion, fragmentation and 1,2-rerrangement occur to a much greater extent than for the 2,4-dimethyl system.

Chapter 4 compares the selectivity of alkylidene carbenes generated in the dimethyl and benzyloxy-substituted oxabicyclic ring systems. Alkylidene carbenes lacking the α-hydroxy group, generated from vinyl chlorides or ketones, show similar reactivity differences in the 3-trimethylsilyloxyoxabicyclic systems as those bearing the α-hydroxyl group. The ratio of C-H insertion to O-Si insertion depends on the method of generation employed.

Abbreviations

°C	degrees Celsius
Å	angstrom (10^{-10} m)
Ac	acetyl
acac	acetoacetate
app.	apparent
aq	aqueous
Ar	aryl
Boc	*t*-butyloxycarbonyl
br	broad
BTMSA	bis(trimethylsilyl)acetylene
Bu	butyl
cal	calories
cat.	catalytic
cm^{-1}	wavenumbers
Cp	cyclopentadienyl
CuAAC	copper-catalysed azide-alkyne cycloaddition
Cy	cyclohexyl
d	doublet
d.r.	diastereomeric ratio
DAMP	diazomethyl phosphonate
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dec	decyl
dec.	decomposes
DHP	3,4-dihydropyran

DIBAL-H	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
E	entgegen (opposite, *trans*)
EBX	ethynyl-1,2-benziodoxol-3(1*H*)-one
EI	electron impact ionisation
eq	equivalent
ES	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
g	gram(s)
gem	geminal
h	hour(s)
Hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
Hz	hertz

IBX	2-iodoxybenzoic acid
Im	imidazole
^{i}Pr	isopropyl
J	coupling constant (Hz)
L	litres
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar (mol L^{-1})
m.p.	melting point
m/*z*	mass/charge
MAO	methylaluminoxane
*m*CPBA	*meta*-chloroperbenzoic acid
MEM	β-methoxyethoxymethyl
mol	moles
Ms	mesyl (methanesulfonyl)
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
Pent	pentyl
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	part(s) per million

PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
qd	quartet of doublets
R_f	retention factor
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TCA	1,1,3-trichloroacetone
tert. or *t*	tertiary
TES	triethylsilyl
Tf	triflyl (trifluoromethylsulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	1,1,1-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Ts	tosyl (*para*-toluenesulfonyl)
XRD	X-Ray diffraction
Z	zusammen (together, *cis*)

Contents

Chapter one - Introduction

1.1 Alkylidene carbenes

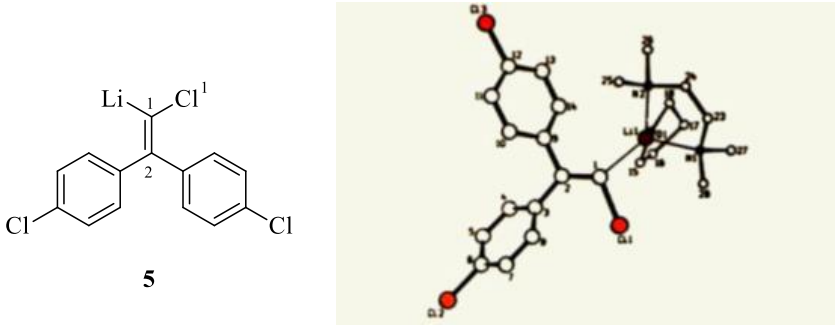
Alkylidene carbenes, also known as alkenylidenes, have seen increased use in organic synthesis in recent years.[1] As carbenes can undergo insertion into unactivated C-H bonds, only one of the carbon atoms needs to be functionalised as a carbene precursor. This is in contrast to many alternative C-C bond forming reactions, which require the prior functionalisation of both carbon atoms. As such, the use of carbenes may allow for the development of more efficient synthetic routes.[2] Unlike simple alkylcarbenes, which tend to react indiscriminately with neighbouring C-H bonds,[3] alkylidene carbenes display increased regioselectivity, especially in C-H insertion reactions.[1]

Carbenes are neutral species containing a carbon atom with only 6 valence electrons, and as a result are highly electrophilic. In alkylidene carbenes, the carbenic centre is located on the terminus of a carbon-carbon double bond. The carbenic carbon is effectively sp hybridised and can exist in either a singlet or triplet state (**Figure 1**). In the singlet state **1**, both electrons are located in the sp non-bonding orbital (HOMO), with the p orbital (LUMO) empty. In the triplet state **2**, the sp orbital and p orbital each contain one electron, and can be considered as a diradical, reacting in stepwise radical reactions. Calculations have shown that the singlet state is lower in energy by 48 kcal mol^{-1},[4] and so most alkylidene carbenes exist in this form. The high reactivity of alkylidene carbenes means they have to be generated *in situ*, and depending on the generation method employed, react as either the free carbene **3** or metal carbenoid **4**. Both forms generally demonstrate similar reactivity.

1 **2** **3** **4**

Figure 1

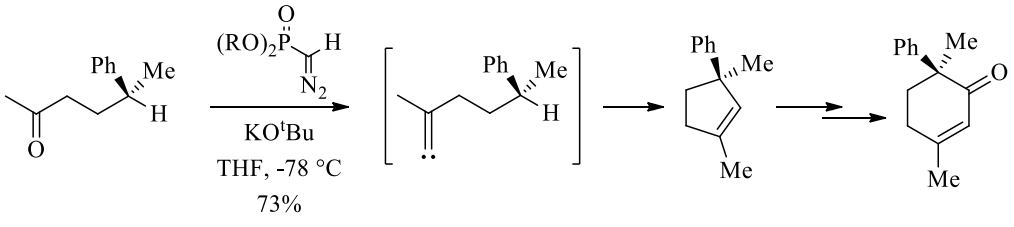
Structurally similar Li-Cl carbenoids **5** have previously been isolated and characterised by XRD at low temperatures (**Figure 2**).[5] Of particular interest are the bond angles at C1 and C2 within the carbenoid structure. The Cl^1-C^1-C^2 angle was measured to be 112.5°, smaller than the expected trigonal angle of 120°, while the Li-C^1-C^2 angle of 137.1° is much larger than expected.



5

Figure 2

As carbenes have only six valence electrons, they are strongly electrophilic in character. Most alkylidene carbenes react in the singlet state, participating in cheletropic reactions as either nucleophiles or electrophiles. The preference for reacting through the singlet state can be seen through the reaction of alkylidene carbenes at stereogenic centres, in which the stereochemistry of the starting material is retained in the product. Conversion of ketone **6** into cyclopentene **8** via alkylidene carbene **7** was determined to proceed with a stereospecificity of at least 99%, calculated after conversion to enone **9** (**Scheme 1**). [6]

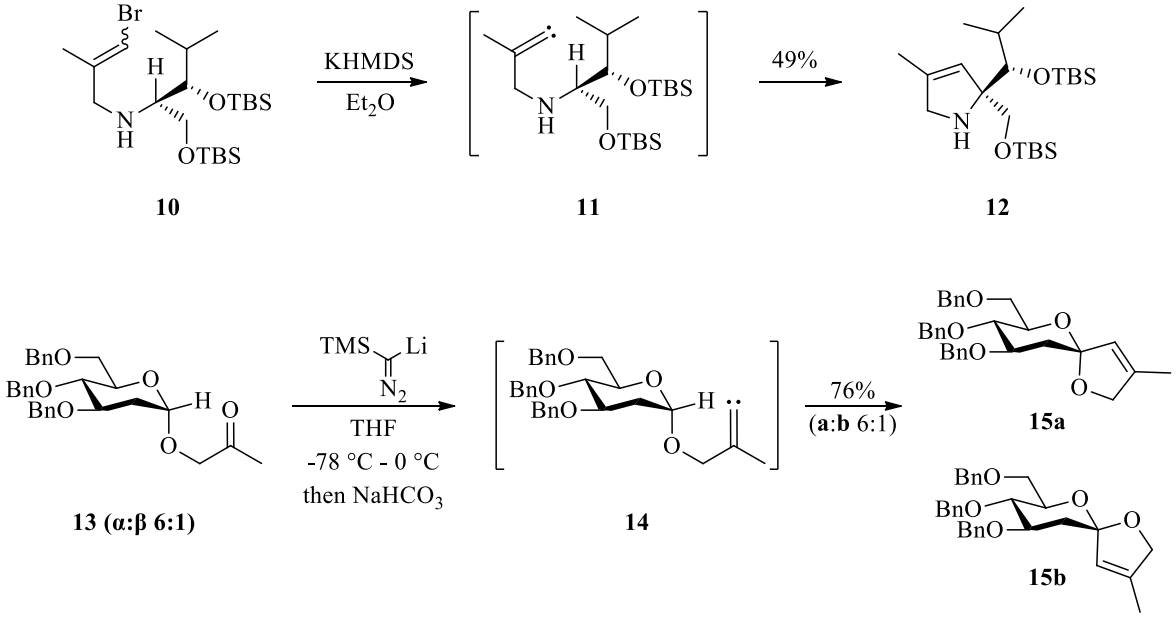


6 **7** **8** **9**

Scheme 1

1.2 General reactivity of alkylidene carbenes

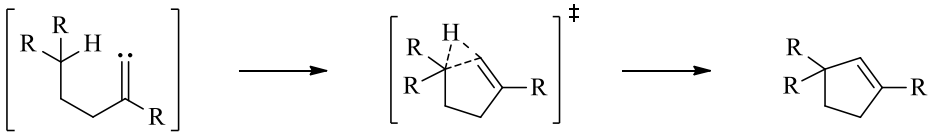
Alkylidene carbenes have been proposed as intermediates in a number of reactions, most notably the formation of cyclopentenes and alkynes, from ketones and aldehydes respectively.[1d, e] The intramolecular C-H insertion reaction of alkylidene carbenes proceeds with remarkable selectivity, with 5-membered rings produced, irrespective of the substitution pattern, generating secondary, tertiary and quaternary centres. Additionally, the high stereospecificity of the reaction results in retention of stereochemistry when reacting at stereogenic centres.[7] If a heteroatom is present in the carbon chain, a heterocycle is formed,[8] demonstrated by the formation of dihydropyrrole **12** from vinyl bromide **10**,[8a] and dihydrofurans **15a** and **15b** from the α and β isomers of ketone **13**.[8b] These reactions proceed though alkylidene carbene intermediates **11** and **14** respectively.



Scheme 2

While the exact mechanism of 1,5 C-H insertion remains elusive, the stereochemical data obtained suggests a reaction pathway without any long-lived intermediates such as diradicals or zwitterions, which could result in the loss of stereochemical information. It is believed that an interaction between the empty p orbital of the carbenic carbon and the σ

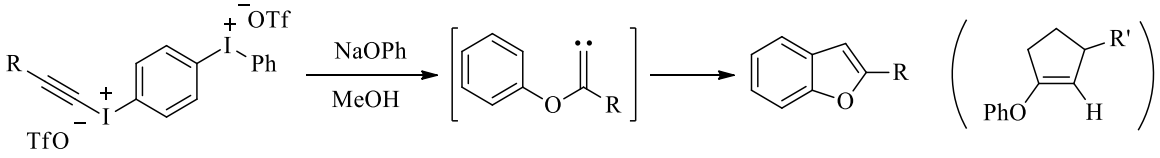
electrons in the C-H bond leads to a transition state such as **16**, before the insertion is complete (**Scheme 3**).[6]



16

Scheme 3

Furthermore, this cyclisation is not limited to reactions with sp^3 C-H centres as it has been demonstrated that alkylidene carbenes will undergo 1,5 C-H insertion into relatively strong sp^2 C-H bonds.[9] Kitamura reported the formation of benzofuran systems **19a-d** upon treating alkynyliodonium salts **17a-d** with sodium phenoxide, with the reaction proceeding through alkylidene carbene **18** (**Scheme 4**).[9d]



17a R=^{n}Bu
17b R=^{t}Bu
17c R=^{n}Hex
17d R=^{n}Dec

18

19a 62%
19b 59%
19c 62%
19d 49%

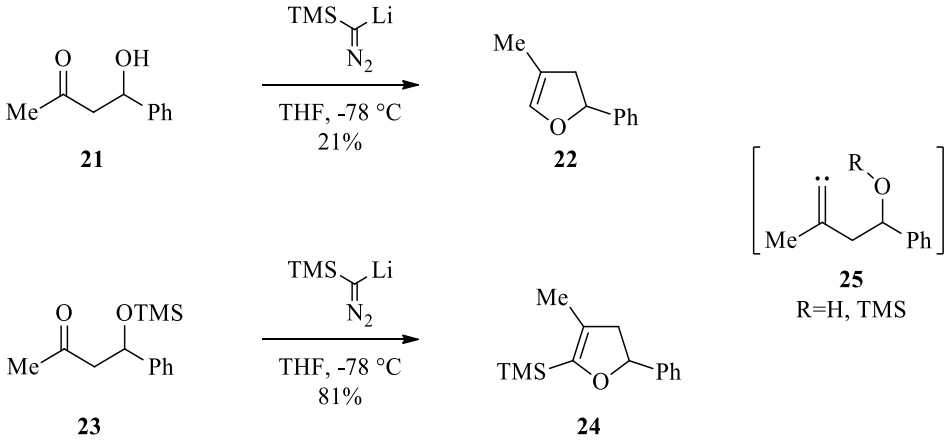
20a R'=Me
20c R'=^{n}Pr
20d R'=^{n}Hex
not seen

Scheme 4

It is interesting to note that the formation of benzofurans is preferred over insertion into the side chain, with no formation of cyclic enol ether **20** seen. This selectivity is believed to be due to an interaction between the empty p orbital of the alkylidene carbene and the π-system of the aromatic ring, resulting in aromatic 1,5 C-H insertion becoming more favourable than aliphatic 1,5 C-H insertion.[9d]

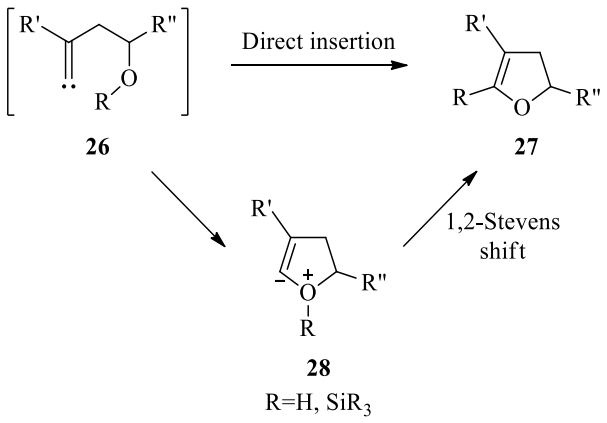
The insertion of alkylidene carbenes into σ-bonds is not limited to C-H functionalities. It has been demonstrated that alkylidene carbenes will undergo formal O-H insertions, as well

as formal O-Si insertions. These reactions proceed readily, due to the high electrophilicity of alkylidene carbenes. Shiori demonstrated the formation of dihydrofuran **22** from β-hydroxy ketone **21**, while the more efficient synthesis of the silylated derivative **24** was achieved from β-trimethylsilyloxy ketone **23**, with both reactions proceeding via an alkylidene carbene intermediate **25** (**Scheme 5**).[10]



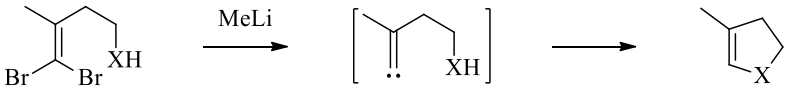
Scheme 5

It is believed that these products can form through one of two possible mechanisms (**Scheme 6**).[11] The alkylidene carbene **26** can undergo a direct insertion into the O-Si bond, forming dihydrofuran **27** directly via a transition state similar to that for C-H insertion. Alternatively, the reaction could proceed through the formation of an oxonium ylide **28**, followed by a 1,2-Stevens shift of the oxygen substituent.



Scheme 6

Insertions into other heteroatom-hydrogen σ-bonds have also been described,[12] with Baird reporting dihydropyrrole **30** and dihydrothiophene **32** ring systems being formed from dibromoalkenes **29** and **31** via N-H and S-H insertion respectively (**Scheme 7**).[12a]

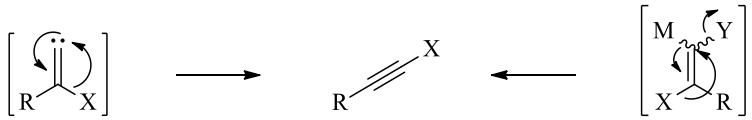


29 X=N^{i}Pr
31 X=S

30 49%
32 71%

Scheme 7

In addition to undergoing insertion reactions, alkylidene carbenes have also been shown to perform 1,2-migration reactions to form alkynes (**Scheme 8**). This rearrangement is known as the Fritsch-Buttenberg-Wiechell (FBW) rearrangement.

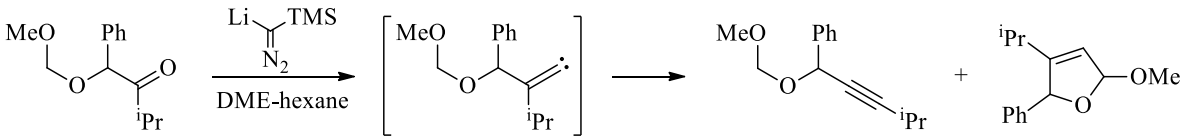


Scheme 8

In theory, migration and insertion reactions of alkylidene carbenes are in competition with each other. However, where X is a hydrogen atom,[13] an aryl substituent[14], or a halogen[15] then 1,2-migration generally will occur faster than any 1,5 C-H insertion reaction available. It has been demonstrated in diaryl systems of alkylidene carbenoids (**Scheme 8**, R=Ar, X=Ar) that the group *trans* to the leaving group Y preferentially migrates.[16] However, later studies have shown this may not be absolute.[17]

Generally, alkyl groups show poor migratory aptitude towards alkylidene carbenes; however alkynes formed via alkyl migration have been reported in reactions performed at high temperatures.[18] Furthermore, Wills described the preferential migration of an isopropyl group, giving alkyne **34** from ketone **33** (**Scheme 9**).[19] The corresponding dihydrofuran **35** was recovered in only low yield. This result was attributed to the increased electron-donating

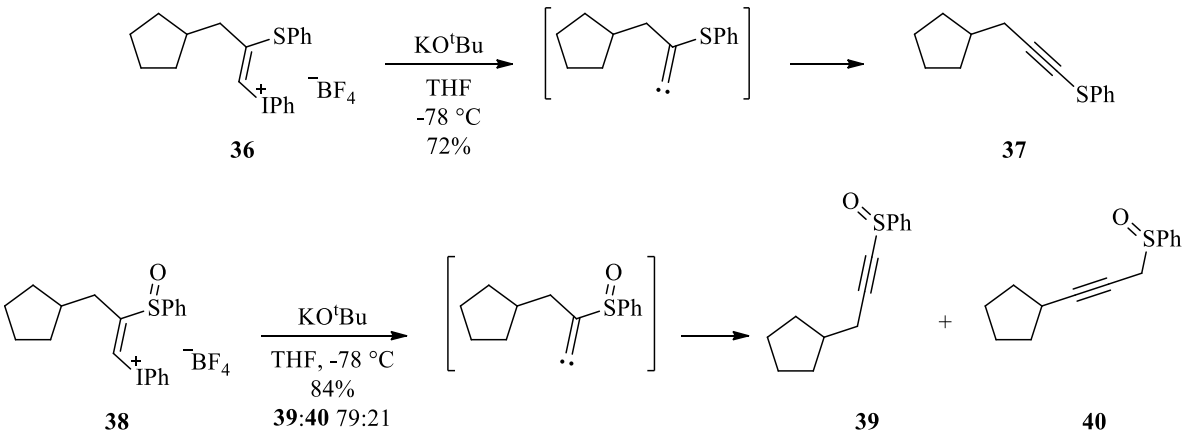
properties of the isopropyl group better stabilising any developing positive charge. In addition, alkynes have also been reported as the major product from less reactive alkylidene carbenoids bearing alkyl substituents.[17, 20]



33 **34** 63% **35** 4%

Scheme 9

Some sulfenyl and sulfinyl groups have shown a tendency to migrate, with alkynyl sulfides **37** and sulfoxides **39** being synthesised through this route, from vinyl iodonium salts **36** and **38** respectively (**Scheme 10**).[21] Sufonyl groups will migrate under certain condtions,[22] but alkylidene carbenes with β-sulfonyl substituent tend to undergo insertion reactions.[22-23]



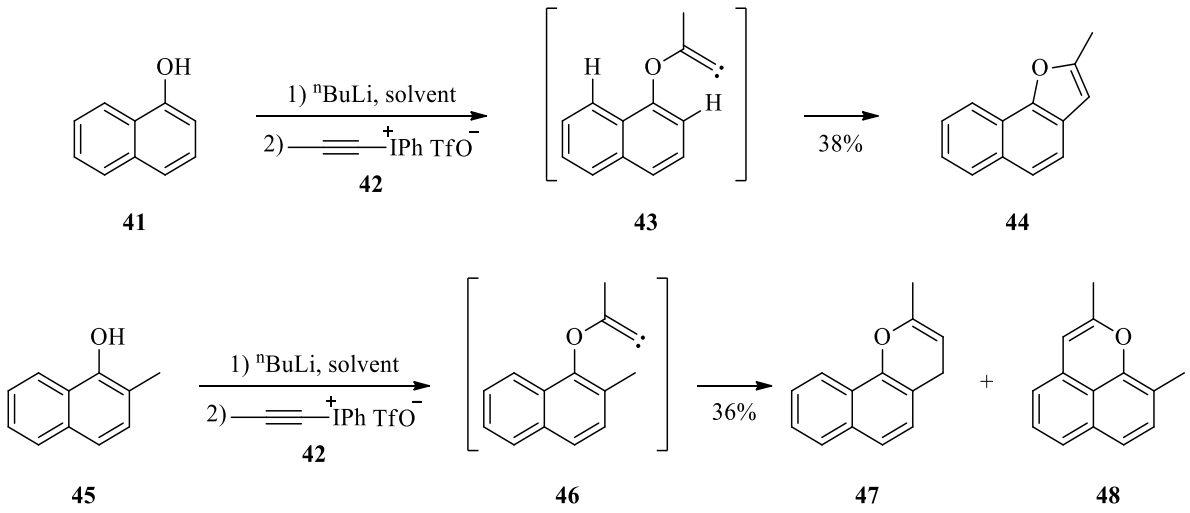
36 **37** **38** **39**:**40** 79:21 **39** **40**

Scheme 10

While 1,5 insertion reactions and 1,2-migrations represent the key, widely utilised reactions which alkylidene carbene intermediates can undergo, in recent years the observed reactivity of this versatile intermediate has expanded significantly.

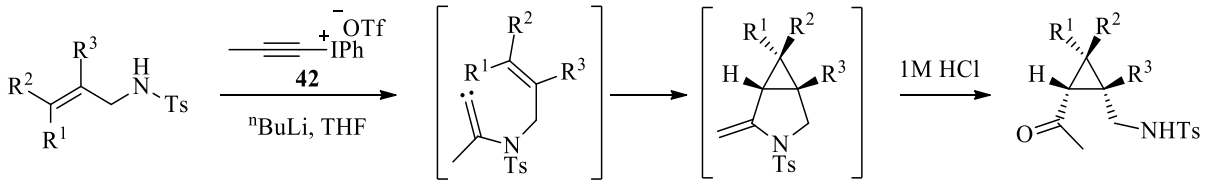
It has been demonstrated that 1,6 C-H insertion reactions can occur in substrates where 1,5 C-H insertion is not possible.[24] Feldman reported that treatment of the anion of 1-

naphthol **41** with alkynyliodonium **42** gave rise to the furan product **44**, via alkylidene carbene **43**, while 2-methyl-1-naphthol **45** gave a mixture of pyrans **47** and **48**, under the same reaction conditions (**Scheme 11**).[24b] The ratio of **47** and **48** varied slightly with different solvents (2:1 in THF, 1.5:1 in CH_3CN, 1:1 in DME) but no significant preference for either isomer was achieved.



Scheme 11

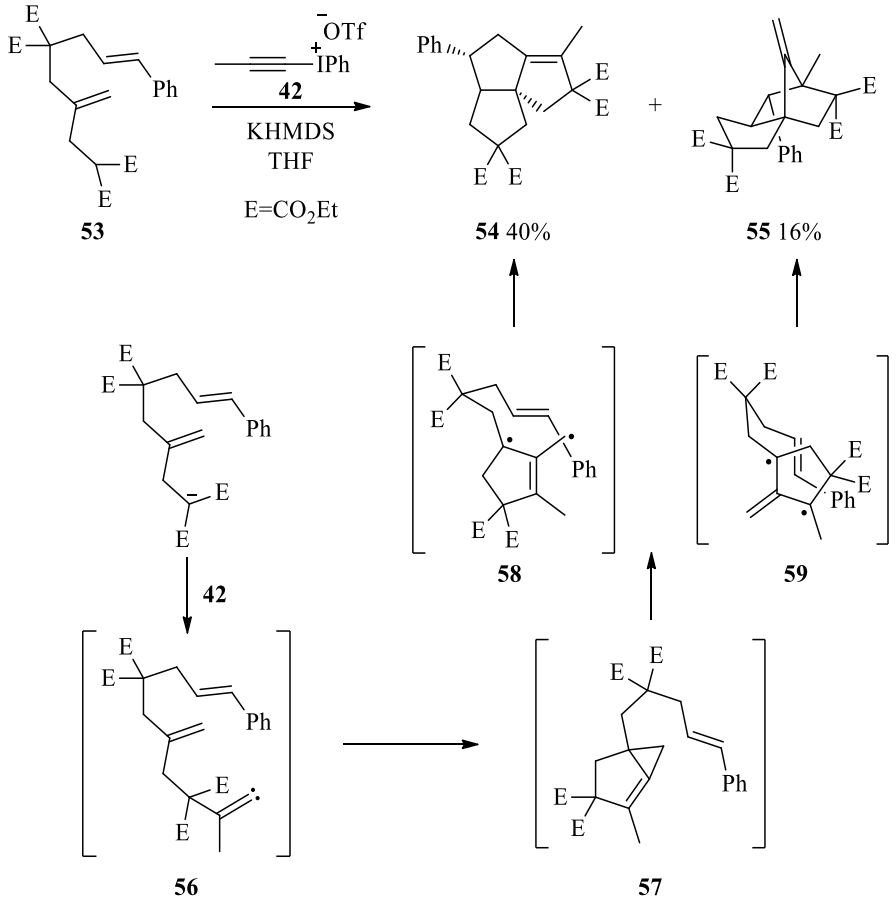
Alkylidene carbenes have also been shown to undergo [2+1] cycloaddition reaction with alkenes, giving rise to cyclopropane products. Due the instability of these products, this reaction is not commonly employed; however, subsequent fragmentation can lead to interesting new structures. Lee reported the stereoselective synthesis of 1-acetyl-2-aminomethylcyclopropanes **52** from the reaction between allylic sulfonamides **49** and alkynyliodonium **42**.[25] The reaction is proposed to proceed through the cyclisation between alkylidene carbene **50** and the tethered alkene. The resulting azabicyclo[3.1.0]hexanes **51** decomposed upon treatment with acid to give **52** (**Scheme 12**).



R^1=H, R^2=H, R^3=H 76% R^1=Et, R^2=H, R^3=H 61%
R^1=H, R^2=Me, R^3=H 54% R^1=H, R^2=H, R^3=Me 70%
R^1=H, R^2=Et, R^3=H 51% R^1=Me, R^2=Me, R^3=H 52%

Scheme 12

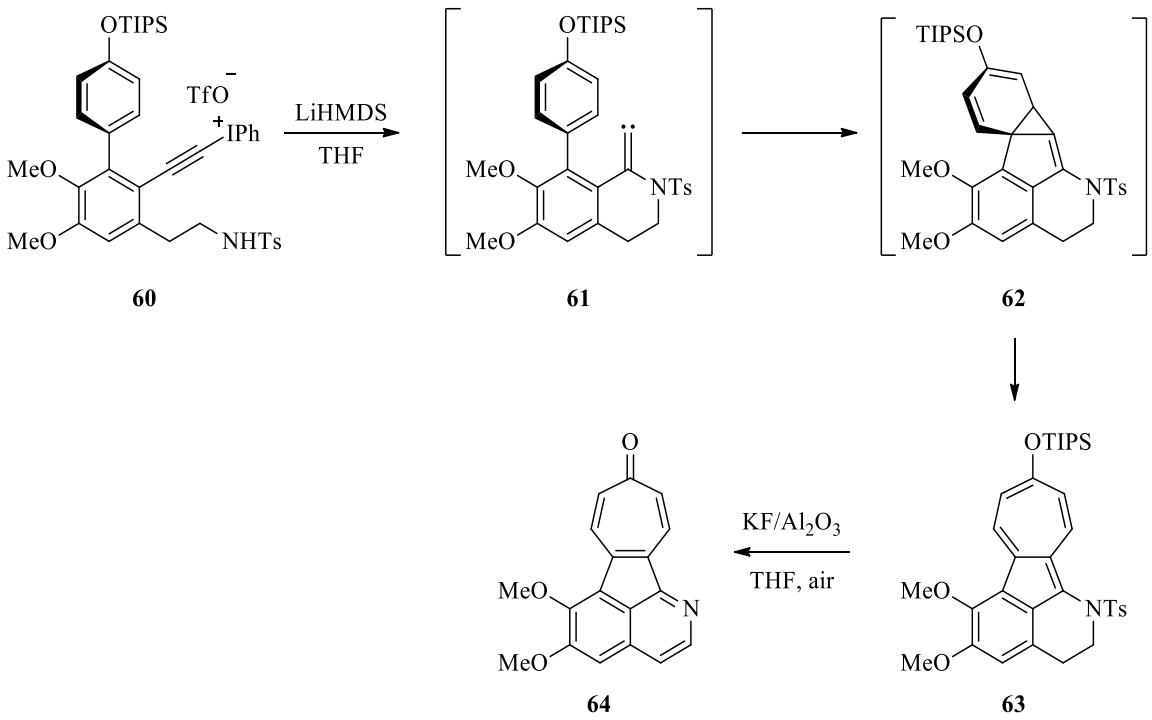
The fragmentation of strained bicycloalkene products to form trimethylenemethane diyls has also been utilised as an effective way of synthesising complex rings systems.[26] Lee reported the synthesis of angularly fused triquinane **54** from the diene **53**, by treating **53** with KHMDS and alkynyliodonium triflate **42** (**Scheme 13**).[26e]



Scheme 13

The reaction is believed to proceed through initial addition to the alkynyliodonium species **42** to give alkylidene carbene **56**, which undergoes a [2+1] cycloaddition with the 1,1-disubstituted alkene to give bicycloalkene **57**. This can fragment to give two isomeric trimethylenemethane derivatives **58** and **59**, which undergo a [3+2] cyclisation to give the products **54** and **55** respectively. Lee has expanded on this work, reporting the synthesis of triquinanes by generating the initial alkylidene carbene from α,β-epoxy-*N*-aziridinylimines[26b] and ketones.[26c]

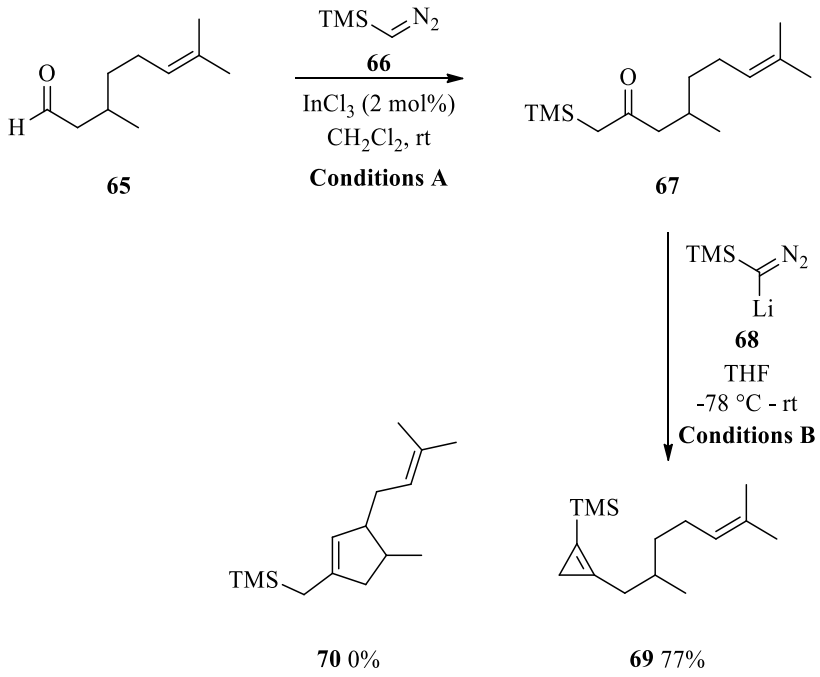
This reactivity is not only limited to alkene π-systems, as alkylidene carbenes have also been shown to insert into the π-system of aromatic rings.[27] Feldman demonstrated the insertion of alkylidene carbene **61**, derived from the intramolecular nucleophilic attack onto alkynyliodonium species **60**, generating the polycycle **62** which subsequently underwent a ring expansion to cycloheptatriene **63**. Treatment of **63** with KF/Al_2O_3 in air gave the tropoloisoquinoline alkaloid pareitropone **64** (**Scheme 14**).[27a, b]



60 **61** **62** **64** **63**

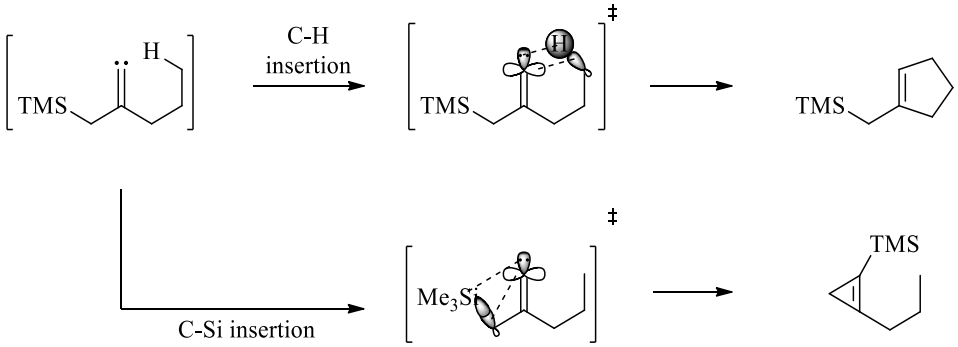
Scheme 14

Recently, Lee reported the synthesis of cyclopropenes through the generation of alkylidene carbenes from α-silyl ketones.[28] Treatment of citronellal **65** with trimethylsilyldiazomethane **66** in the presence of catalytic $InCl_3$ allowed access to α-silyl ketone **67**, which was subsequently treated, without purification, with lithiated trimethylsilyldiazomethane **68**, giving rise to cyclopropene **69** in 77% yield (**Scheme 15**). The corresponding cyclopentene **70** was not observed.



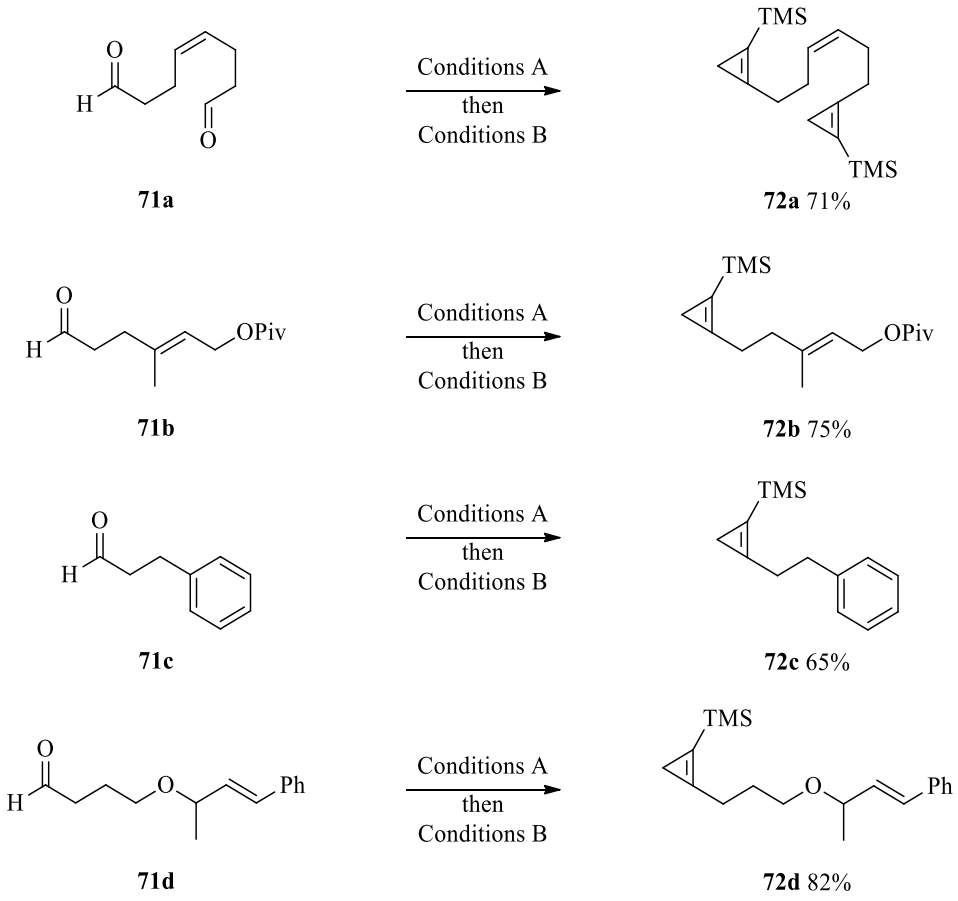
Scheme 15

It was proposed that the cyclopropene arose from the insertion of the alkylidene carbene into the nearby C-Si bond. Lee suggested that the interaction between the empty p-orbital of the carbene and the C-Si σ-bond was more favourable than the interaction with the relatively remote C-H σ-bond (**Scheme 16**).



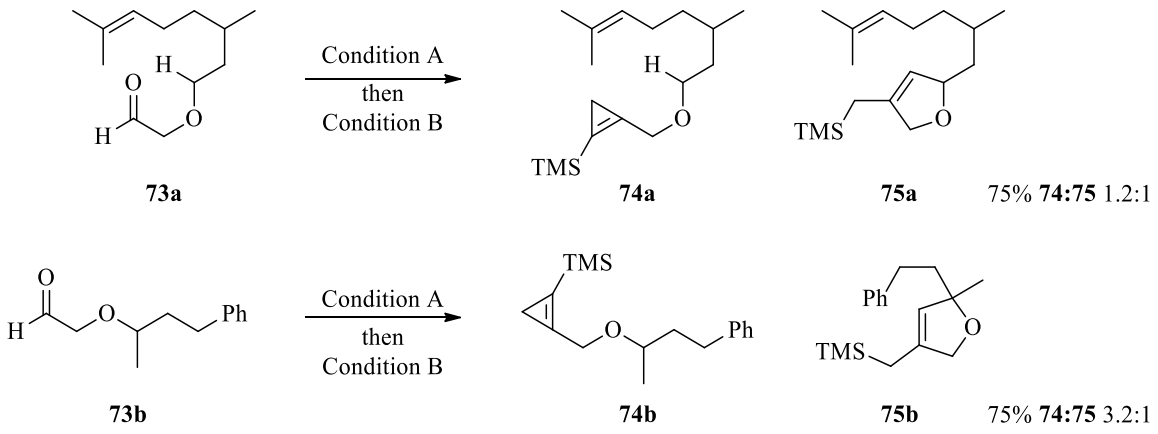
Scheme 16

The reaction was carried out on a range of substrates, including those containing straight and branched chain alkyl groups, varying degrees of unsaturation (both *cis* and *trans*) and aromatic substituents (**Scheme 17**). It is interesting to note that cyclopropenation occurred even in cases where C-H insertion was possible, including **71d** which has an oxygen atom adjacent to the potential insertion site.



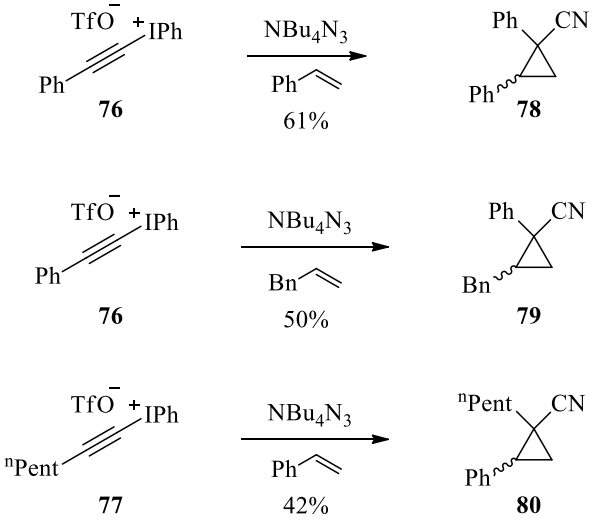
Scheme 17

Indeed, it required substrates where the oxygen atom was part of the new ring formed, which are more activated towards C-H insertion (*vide infra*) in order to allow this reaction to compete (**Scheme 18**). Even so, cyclopropenes remained the major products isolated from the reaction, suggesting that this reaction pathway is much more favourable.



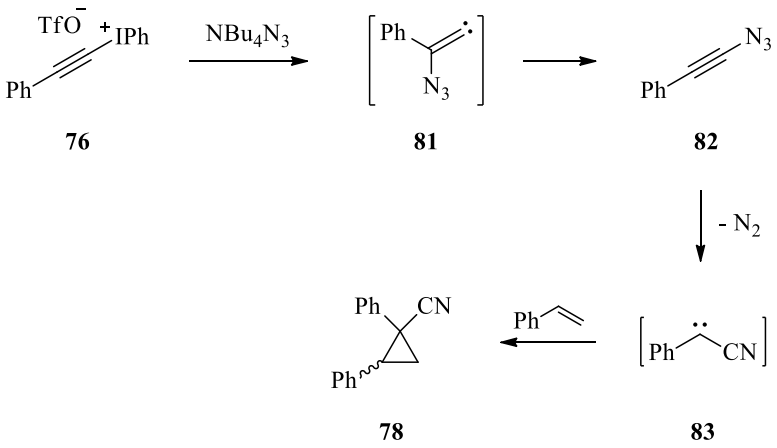
Scheme 18

In 2012, Croatt described the generation of cyanocarbenes via an intermediate alkylidene carbene.[29] Treating alkynyliodonium salts **76** and **77** with tetrabutylammonium azide gave rise to cyanocyclopropanes **78**-**80** after reaction with the alkene solvent (**Scheme 19**).



Scheme 19

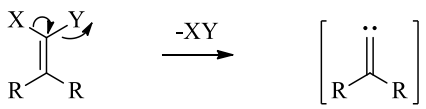
The reaction is thought to proceed through initial formation of the alkylidene carbene **81** via nucleophilic attack on the β-position of the alkynyliodonium species **76**. Subsequent 1,2-migration results in the formation of alkynyl azide **82** which extrudes N_2 to form the cyanocarbene **83**. This is then trapped by the alkene to give the cyclopropane **78** (**Scheme 20**).



Scheme 20

1.3 Generation of alkylidene carbenes

As previously mentioned (**Section 1.3**), the high reactivity of alkylidene carbenes necessitates their *in situ* generation. The techniques commonly utilised employ variations on α-elimination, with the most widely used being reductive elimination of metal carbenoids, use of diazo olefination reagents and the use of alkynyl iodonium salts. All these techniques involve an elimination reaction from a carbon-carbon double bond terminus, leaving the required full sp orbital and empty p orbital on the terminal carbon (**Scheme 21**).

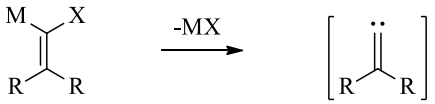


Scheme 21

1.3.1 Generation through α-elimination of metal carbenoids

Alkylidene carbenes can be generated through the reductive elimination of metal carbenoids **84**, also known as metal vinylidenes (**Scheme 22**).[30] While it is unknown whether

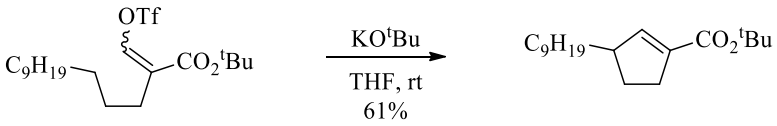
the metal fully dissociates from the carbenic centre, both the metal carbenoid and 'free' carbene display the same reactivity.



84

Scheme 22

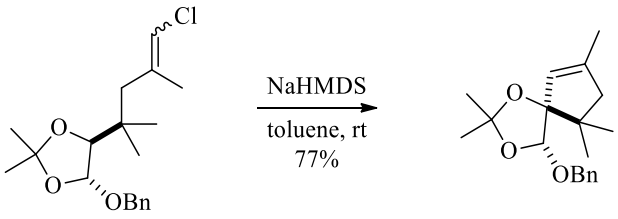
Carbenoids such as **84** are readily available through a variety of methods. One of the most widely used is through the base-induced elimination of vinyl halides[18a, 31] or vinyl triflates.[13b, 32] Ohira reported the synthesis of cyclopentene **86** from vinyl triflate **85** using KO^{t}Bu as a base (**Scheme 23**).[32]



85 **86**

Scheme 23

In recent times, the most commonly employed tactic is the deprotonation of vinyl chlorides with either NaHMDS or KHMDS. Taber reported the use of NaHMDS to synthesise cyclopentene **88** in good yield from vinyl chloride **87** (**Scheme 24**).[31c]

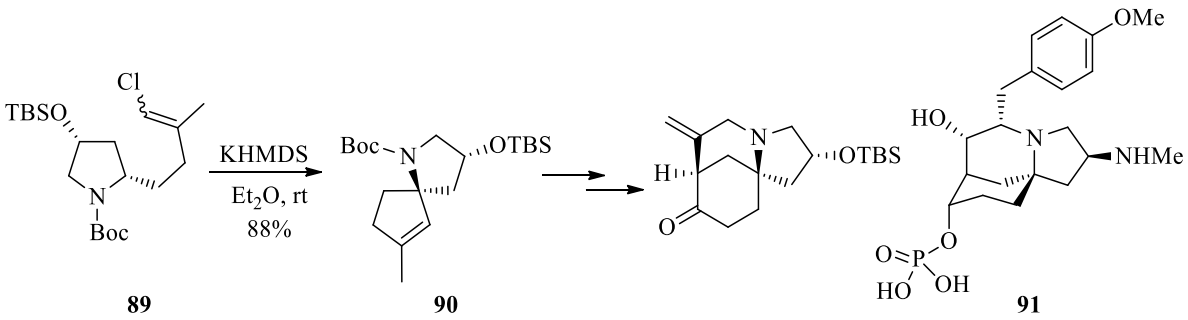


87 **88**

Scheme 24

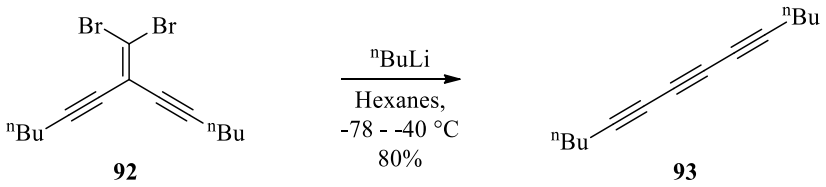
Similarly, Hayes reported the synthesis enantiopure pyrrolidine **90** from vinyl chloride **89**, employing KHMDS as a base (**Scheme 25**), using this strategy to synthesise the tricyclic

core of (-)-FR901483 **91**.[33] Hayes has employed similar methodology to synthesise a number of nitrogen-containing complex molecules.[34]



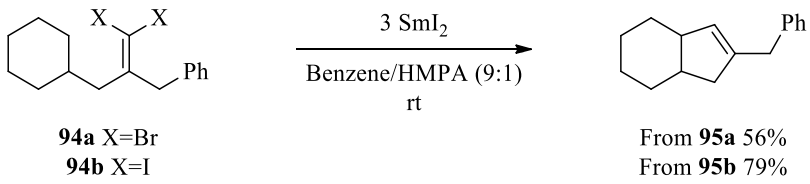
Scheme 25

Alternatively, metal carbenoids can be accessed via metal-halogen exchange of a dihaloalkene. Tykwinski employed this strategy in the synthesis of polyynes via a 1,2-migration, including triyne **93** in good yield from dibromoalkene **92** (**Scheme 26**).[35] This reaction also displays the migratory aptitude of the alkynyl functionality. This method has been widely used in the synthesis of polyynes.[36]



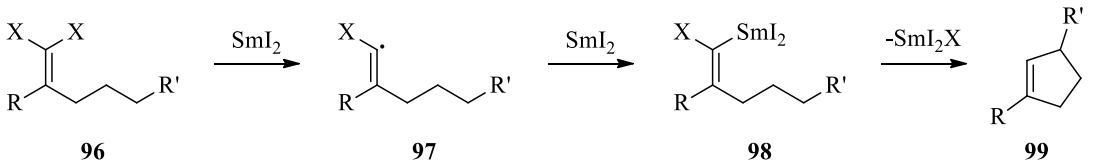
Scheme 26

Tani reported the formation of cyclopentene **95** by treating dihaloalkene **94** with SmI_2 and HMPA (**Scheme 27**).[37]



Scheme 27

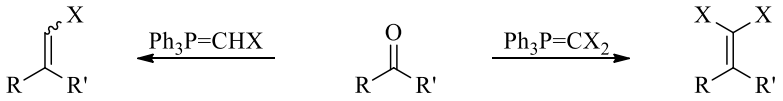
While the reaction shown in **Scheme 26** is believed to proceed through lithium-halogen exchange, the transformation in **Scheme 27** is more likely to proceed via halogen abstraction from dihaloalkene **96** to give vinyl radical **97**, which is further reduced by a second equivalent of SmI_2 to give carbenoid **98**. This reacts to form cyclopentene **99** via 1,5 C-H insertion.[37]



96 **97** **98** **99**

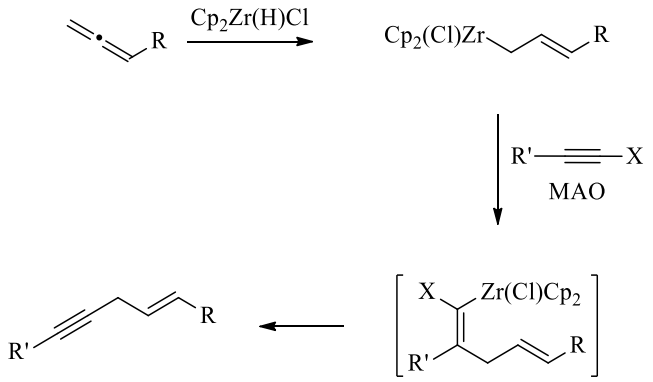
Scheme 28

The use of vinyl halides and dihaloalkenes as precursors to alkylidene carbenes is attractive as these functionalities are readily available from the corresponding carbonyl compound (**Scheme 29**).[31c, 35]



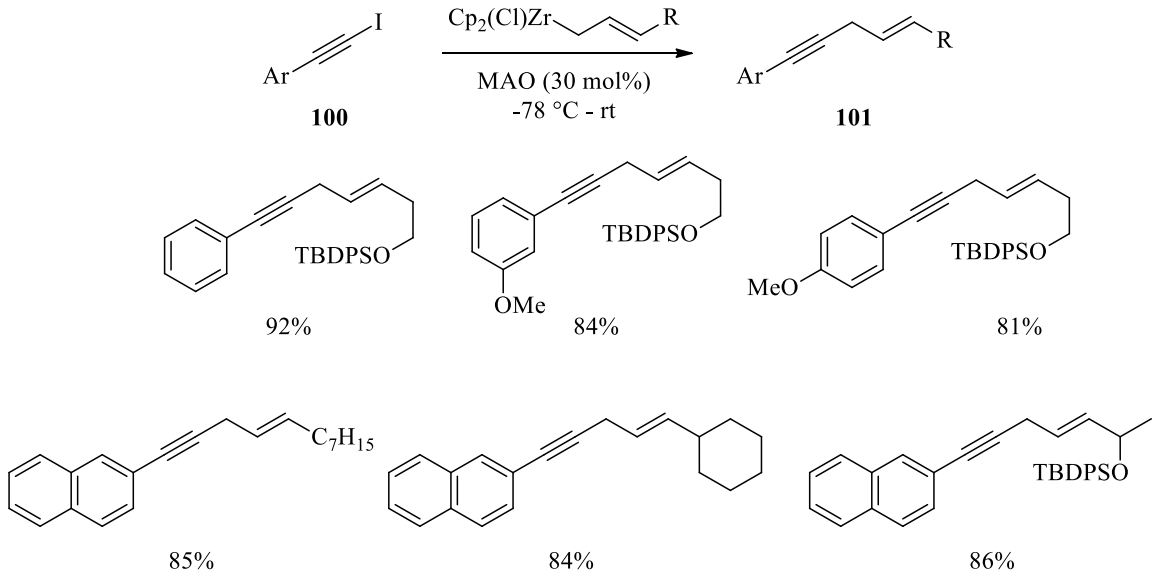
Scheme 29

Various other methods of accessing alkylidene carbenoids, without requiring prior installation of a carbonyl functional group, have also been reported. Suzuki described the generation of zirconium alkylidene carbenoids via allylzirconation of haloalkynes in the presence of methylaluminoxane (MAO).[20b] The allylzirconium reagents themselves could be accessed via hydrozirconation of allenes (**Scheme 30**).



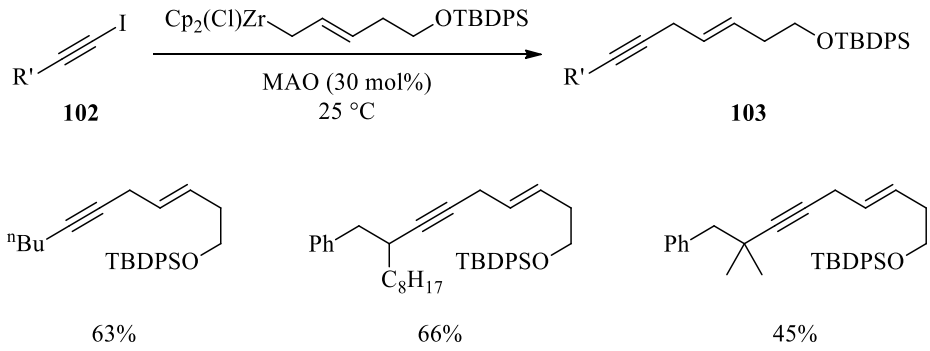
Scheme 30

This methodology was applied to the synthesis of a range of aryl enynes **101** from aryl iodoalkynes **100** (**Scheme 31**).



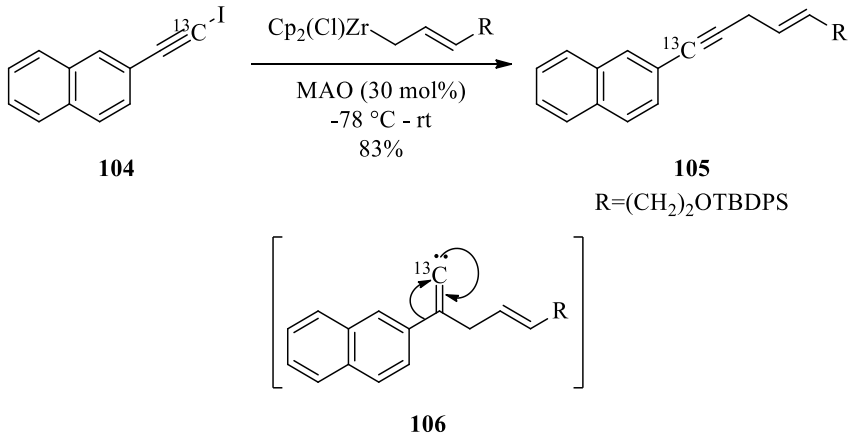
Scheme 31

Interestingly, when the same methodology was applied to alkyl iodoalkynes **102**, the products observed were again the product of 1,2-migration **103**, albeit requiring higher temperatures and in lower yields, even in cases where 1,5 C-H insertion was possible (**Scheme 32**).



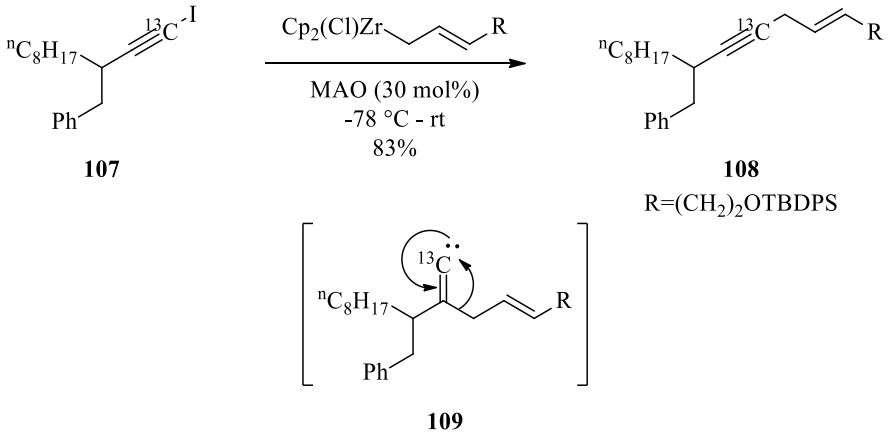
Scheme 32

NMR labelling studies of the reaction showed a clear difference in how the two classes of substrates proceeded through the reaction. When the ^{13}C-labelled iodoalkyne **104** was subjected to the reaction conditions, the product **105** had the ^{13}C label directly attached to the naphthyl group, consistent with a 1,2-shift of the aryl group **106** (**Scheme 33**).



Scheme 33

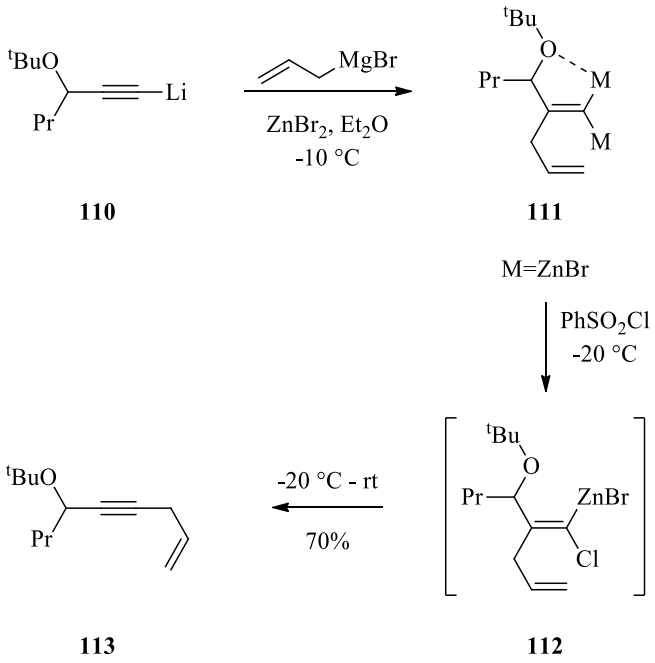
However, in the reaction with the labelled alkyl iodoalkyne **107**, the product **108** showed no change in the position of the ^{13}C label, suggesting that, in this case, the migrating group was the allyl substituent in **109** (**Scheme 34**).



Scheme 34

This results suggests that, in the absence of more suitable migratory groups, the allyl functionality is able to undergo a 1,2-migration reaction, giving rise to alkynes. The lack of evidence of any 1,5 C-H insertion products suggests that this process is faster than any competing insertion pathways.

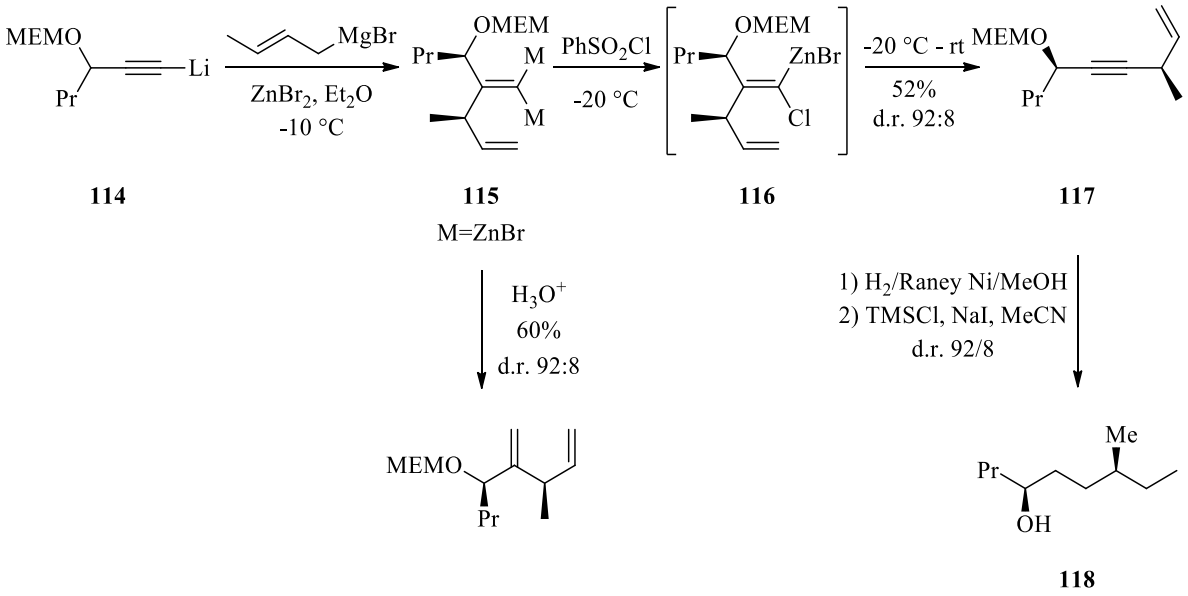
Normant described the synthesis of alkynes from zinc carbenoids, generated from bismetalloalkenes.[17, 20a] Treatment of alkynyllithium **110** with allyl Grignard gave rise to bismetalloalkene **111**, which reacts with phenylsulfonyl chloride to give alkylidene carbenoid **112**. Previous studies had demonstrated that this chlorination occurred stereoselectively, with the non-chelated Zn reacting preferentially.[38] At low temperatures, these can be quenched with a second halogenating reagent. However, if the reaction is warmed to room temperature, they cleanly rearrange to give the alkyne **113** (**Scheme 35**).



Scheme 35

The use of a zinc carbenoid was thought to be necessary for a clean reaction, as when the lithium carbenoid was generated, a complex mixture of products was observed, with the alkyne present in only small amounts (<10%).

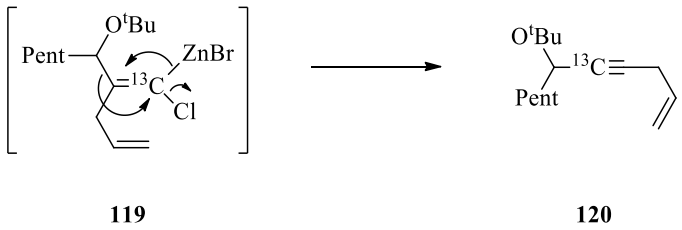
Normant was also able to demonstrate the stereospecificity of the migration. By quenching the bismetalloalkene **115** with acid, it could be seen that the initial addition of the allyl Grignard to the alkynyllithium **114** occurred with a diastereomeric ratio of 92:8. Since **117** is also formed as a 92:8 mixture of diastereoisomers, the generation of alkylidene carbene **116** and its subsequent rearrangement to alkyne **117** occurs in a stereospecific fashion (**Scheme 36**).



Scheme 36

To determine whether the migration had occurred with retention or inversion, **117** was fully reduced, and the MEM group removed to give **118**. This was then compared to a sample of (*S*,*S*)-**118**, which was shown to be the major product from the zinc carbenoid reaction. It was concluded that the migration occurred with complete retention of stereochemistry.

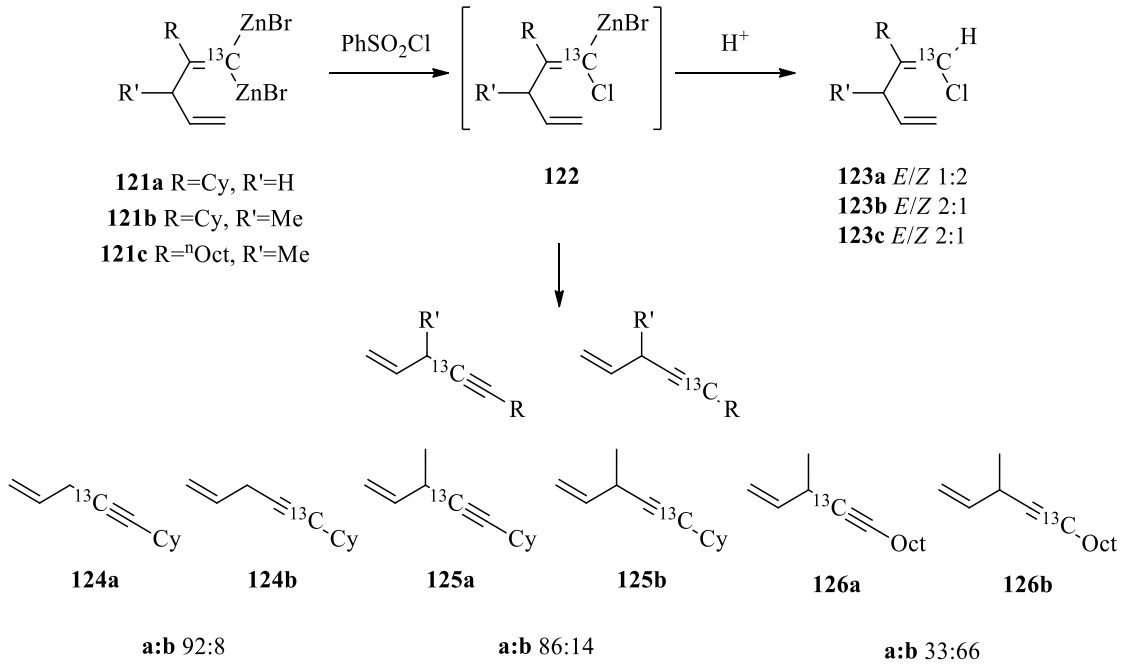
NMR studies were employed to determine which group underwent migration.[17] Generation of ^{13}C-labelled carbenoid **119** gave rise to enyne **120**, indicating that the ether substituent *trans* to the chlorine was migrating in this case (**Scheme 37**).



Scheme 37

The absence of the chelating substituent drastically reduced the stereoselectivity of the carbenoid formation, as was seen by the low ratios of vinyl chlorides **123a-c** when the carbenoid **122** was quenched with acid (**Scheme 38**). However, this appears to have had little

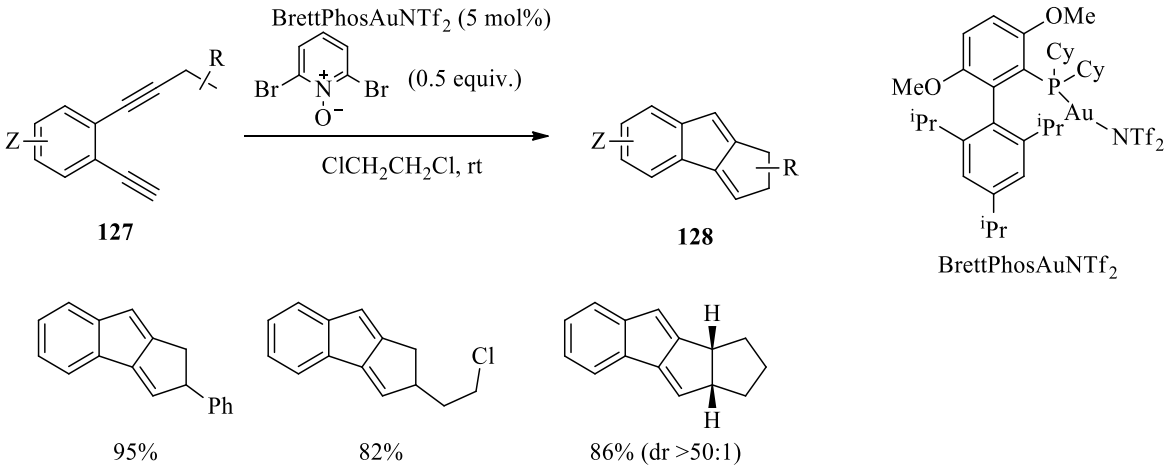
or no bearing on the outcome of the reaction, as the formation of enynes occurred with higher selectivity. The reaction of **121a** gave **124a** and **124b** in a ratio of 92:8 indicating that the preferred migrating group was the allyl substituent, regardless of whether it was *cis* or *trans* to the chloride leaving group. Similarly, the observation of **125a** as the major product in the reaction of **121b** indicates the preferred migration of the substituted allyl group over the cyclohexyl, albeit less so than the allyl group itself. Additionally, the predominance of **126b** shows that the octyl group migrates in preference to the substituted allyl, even if it is primarily *cis* to the chlorine.



Scheme 38

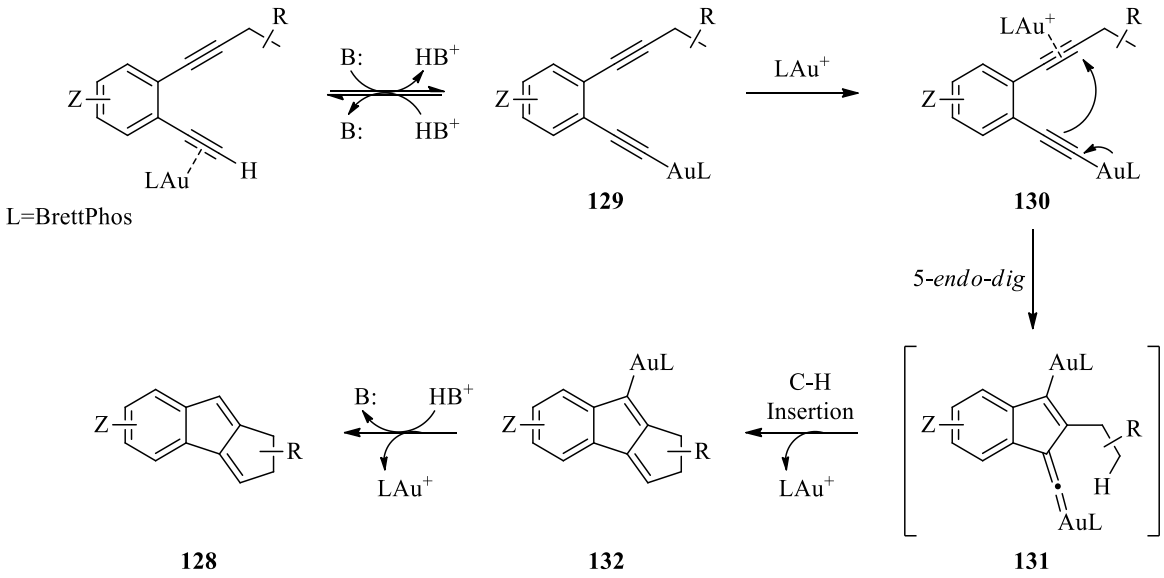
The extensive work on zirconium and zinc carbenoids by Suzuki and Normant respectively, has demonstrated that under the right conditions, alkyl substituted alkylidene carbenoids are capable of undergoing 1,2-migration reaction to form alkynes. It is also important to note that no evidence of 1,5 C-H insertion was reported, even in examples where it was possible, despite this generally being the preferred pathway for alkylidene carbenes bearing alkyl groups.

A number of methods have been reported in which metal carbenoids are generated through catalytic methods, with metal vinylidene complexes being proposed as intermediates in several carbon-heteroatom and carbon-carbon forming processes.[39] Independently of each other, Zhang and Hashmi reported the generation of gold vinylidene complexes from terminal alkynes using a gold catalyst.[40] Zhang reported the synthesis of a range of fused polycycles **128** from diynes **127** employing a strategy which utilised the activation of both alkynes (**Scheme 39**).[40e]



Scheme 39

Zhang proposed that the reaction proceeds through the formation of alkynylgold complex **129**, with the *N*-oxide acting as a base to remove the proton from the terminal alkyne. The internal alkyne is then activated by another molecule of the catalyst, giving **130**, which undergoes a 5-*endo-dig* cyclisation, resulting in the formation of gold vinylidene **131**. This can then perform a 1,5 C-H insertion reaction, leading to **132**, which gives the product **128** after protodeauration (**Scheme 40**).



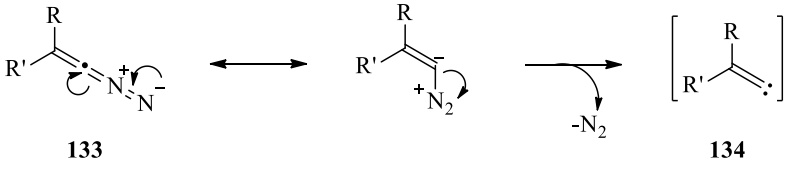
Scheme 40

Hashmi reported the synthesis of similar polycyclic systems from aromatic diynes, again employing a double activation strategy with gold catalysis.[40a-d]

The increasing research into metal vinylidene complexes may offer the best access to the development of asymmetric alkylidene carbene chemistry.

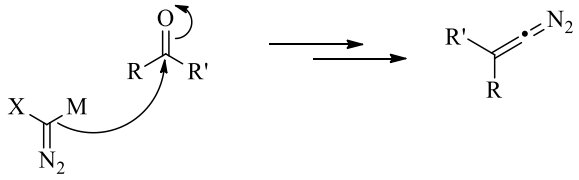
1.3.2 Generation from diazoalkenes

The α-diazo carbonyl functionality is a common precursor to carbenes. However, it often requires the use of a metal catalyst to facilitate the extrusion of nitrogen to give the required carbene complex at a reasonable temperature.[41] However, 1-diazoalkenes **133** readily undergo loss of nitrogen to afford the related alkylidene carbene **134** (**Scheme 41**). There are a number of ways which allow *in situ* generation of this alkylidene precursor.



Scheme 41

The most widely employed technique for accessing diazoalkenes is the reaction of aldehydes or ketones in a modified Horner-Wadsworth-Emmons reaction,[42] or in a modified Peterson olefination.[43] These reactions employ the use of deprotonated diazomethylphosphonate (DAMP) esters **135a** and lithiated diazomethylsilane **135b**, respectively.

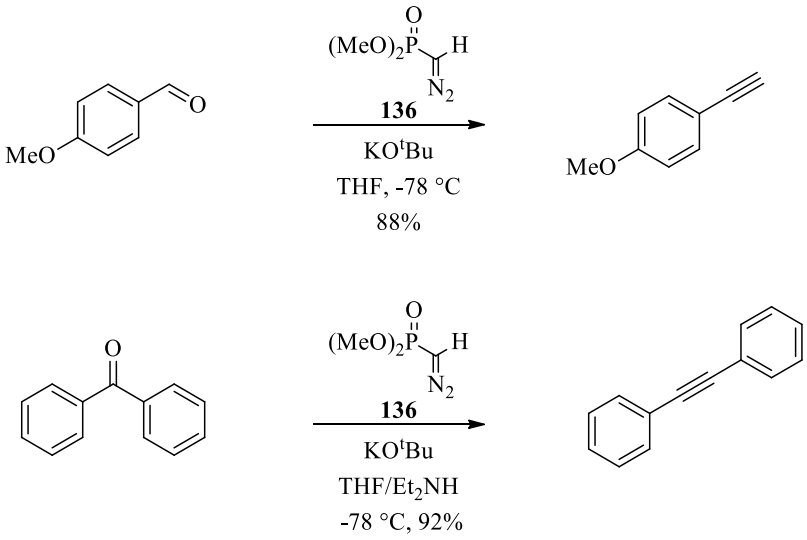


135a X=PO(OR")$_2$
135b X=SiMe$_3$

Scheme 42

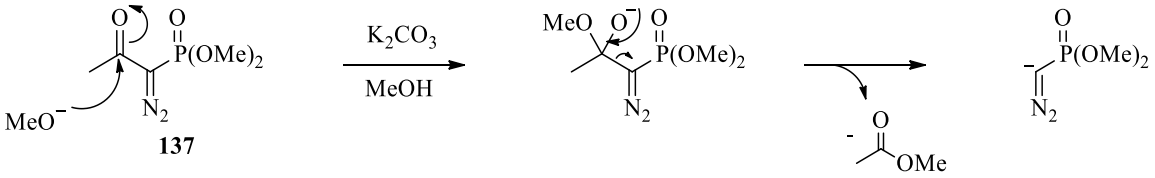
The reaction proceeds through the established mechanism for both the HWE and Peterson reactions, with initial nucleophilic attack on the carbonyl functionality by the deprotonated olefination reagent, with subsequent elimination to give the 1-diazoalkene (**Scheme 42**).

The base-promoted reaction of dimethyl (diazomethyl)phosphonate **136** (Seyferth-Gilbert reagent) with aldehydes and aryl ketones to form alkynes, is known as the Seyferth-Gilbert homologation.[44] The base employed is usually KO^{t}Bu. Gilbert used this method to synthesise a number of terminal and diaryl alkynes (**Scheme 43**).[44a]



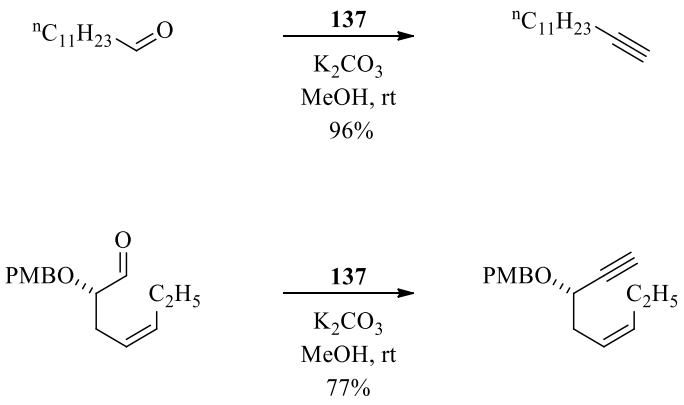
Scheme 43

Ohira expanded on this work by generating the anion of **136** *in situ* under much milder conditions, through acyl cleavage of dimethyl 1-diazo-2-oxopropylphosphonate **137** with K_2CO_3 in MeOH (**Scheme 44**).[45]



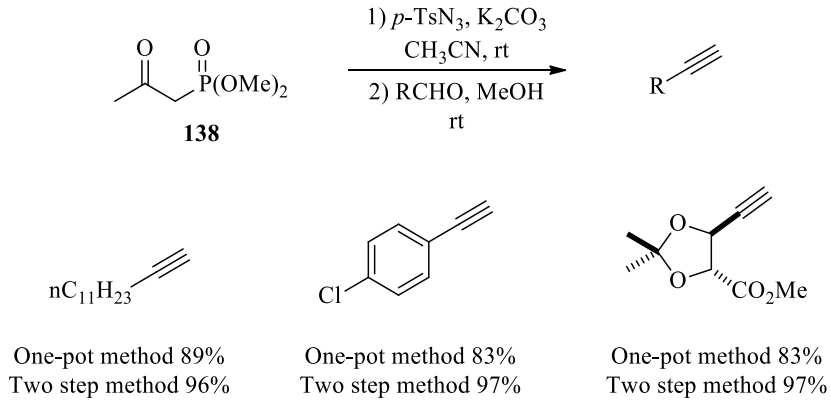
Scheme 44

Bestmann expanded the scope of alkyne formation by using this methodology to synthesise *n*-alkyl-substituted alkynes from the corresponding aldehydes.[46] This allowed for the generation of alkynes in good yields from enolisable aldehydes, which may be expected to undergo aldol transformations under the original Seyferth-Gilbert conditions. Bestmann also demonstrated that aldehydes with α-stereocentres react in good yields, with no erosion of stereochemistry (**Scheme 45**). Phosphonate **137** has become known as the Bestmann-Ohira reagent and has largely replaced the Seyferth-Gilbert reagent in these types of reactions.



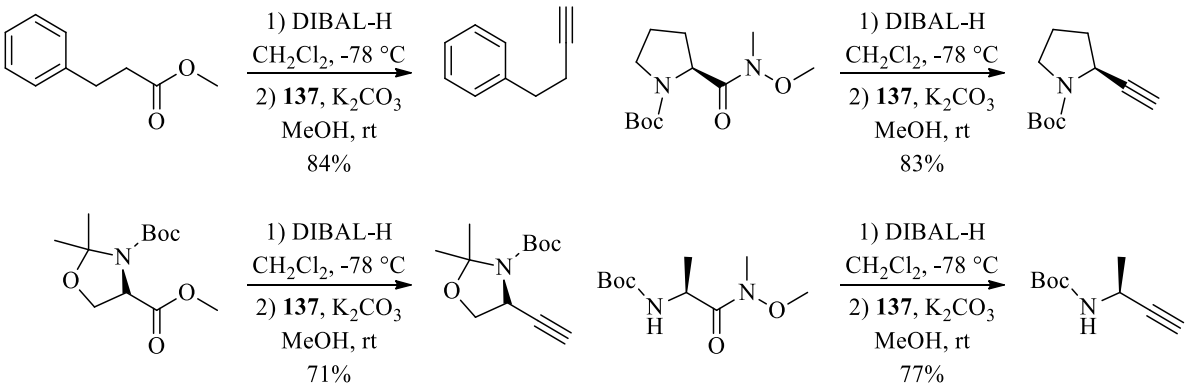
Scheme 45

Both **136** and **137** are readily synthesised using diazo transfer reagents.[47] However, Bestmann reported a one-pot diazo transfer-alkyne synthesis, allowing access to alkynes directly from dimethyl 2-oxopropylphosphonate **138** (**Scheme 46**).[48]



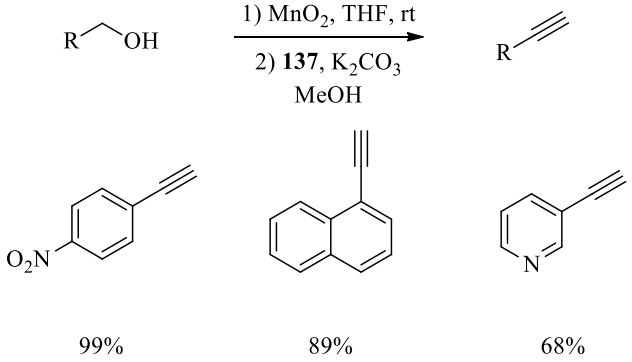
Scheme 46

Additionally, the recent development of a number of sequential one-pot procedures has led to direct access to alkynes from esters, Weinreb amides and alcohols.[49] Hinkle reported the synthesis of terminal alkynes in good yields through a partial reduction of esters or Weinreb amides, followed by reaction with the Bestmann-Ohira reagent (**Scheme 47**).[49a]



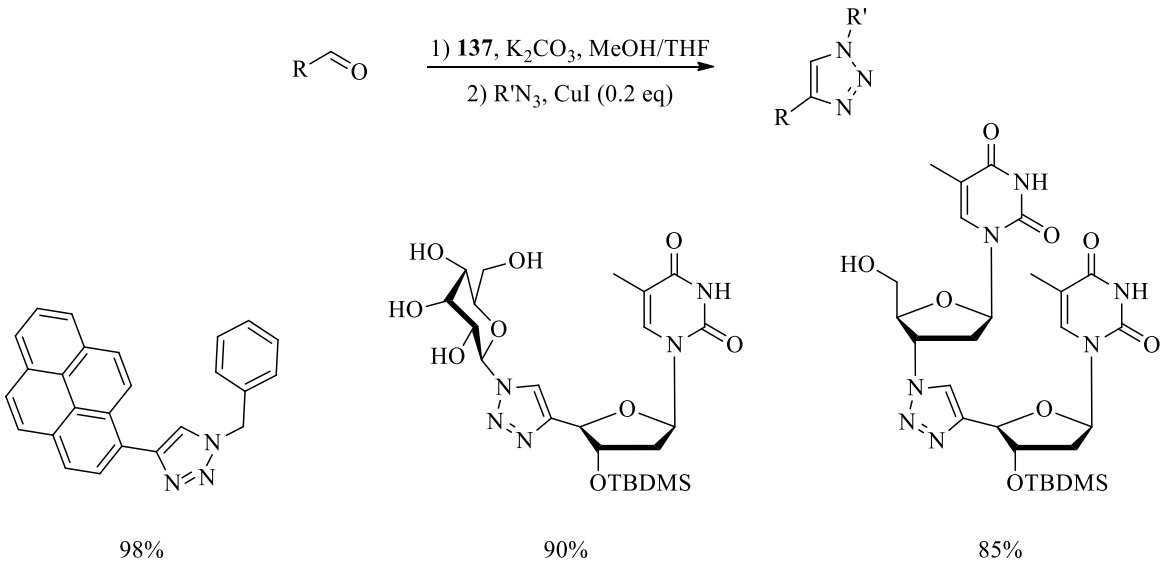
Scheme 47

Taylor reported the generation of terminal alkynes from activated alcohols via oxidation with MnO_2 and subsequent reaction with the Bestmann-Ohira reagent (**Scheme 48**).[49b]



Scheme 48

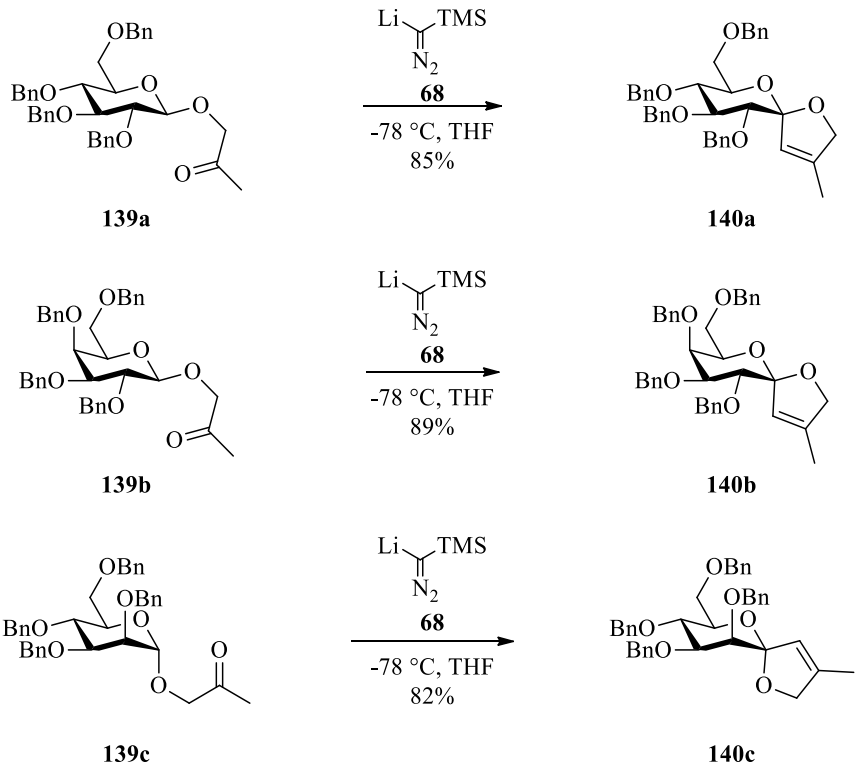
Furthermore, Smietana and Vasseur reported the synthesis of triazoles from aldehydes through a sequential Seyferth-Gilbert homologation followed by a copper-catalysed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) (**Scheme 49**).[50] They applied this procedure to the synthesis of a wide array of complex triazoles.



98% 90% 85%

Scheme 49

Similarly, the modified Peterson has seen significant use in organic synthesis. Wardrop reported the formation of a range of [4.5]spiroketal glycosides **140a-c** in excellent yields from the precursor ketones **139a-c**, using this procedure (**Scheme 50**).[51]



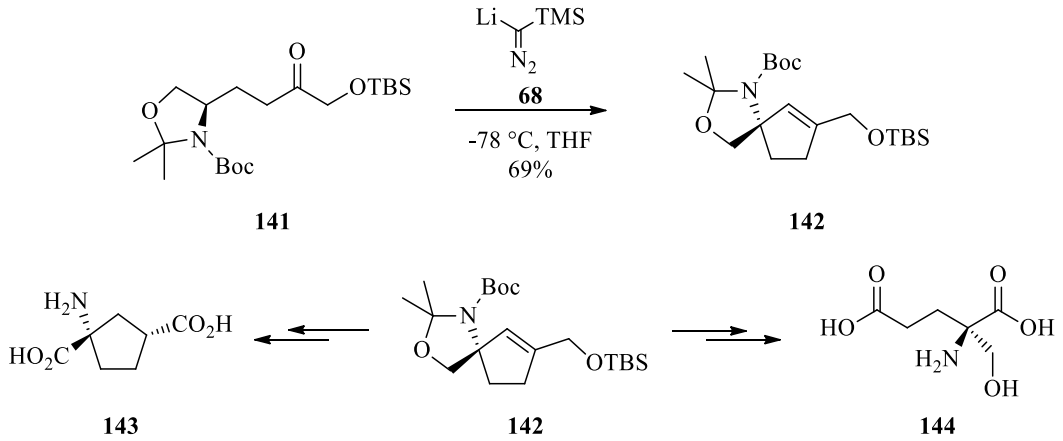
139a **140a**

139b **140b**

139c **140c**

Scheme 50

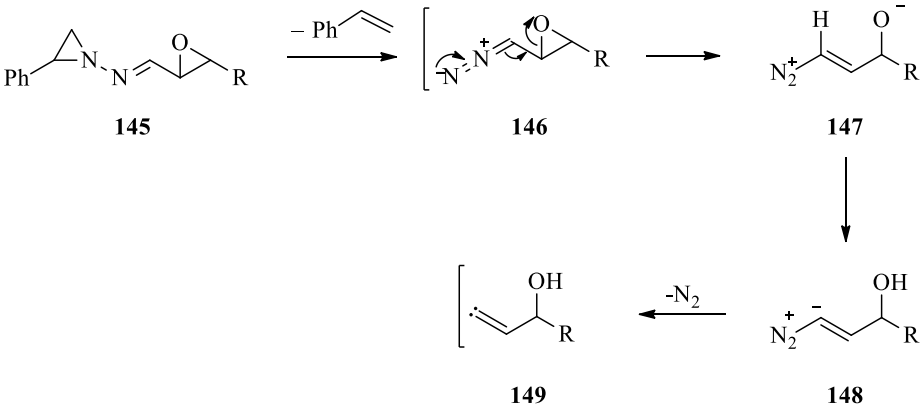
Hayes also employed this technique in synthesising the spirocycle **142** in an enantiomerically pure form from ketone **141** (**Scheme 51**).[7b, 52] **142** was a key intermediate in Hayes syntheses of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid **143** and (2*R*)-hydroxymethyl glutamic acid **144**.[52]



Scheme 51

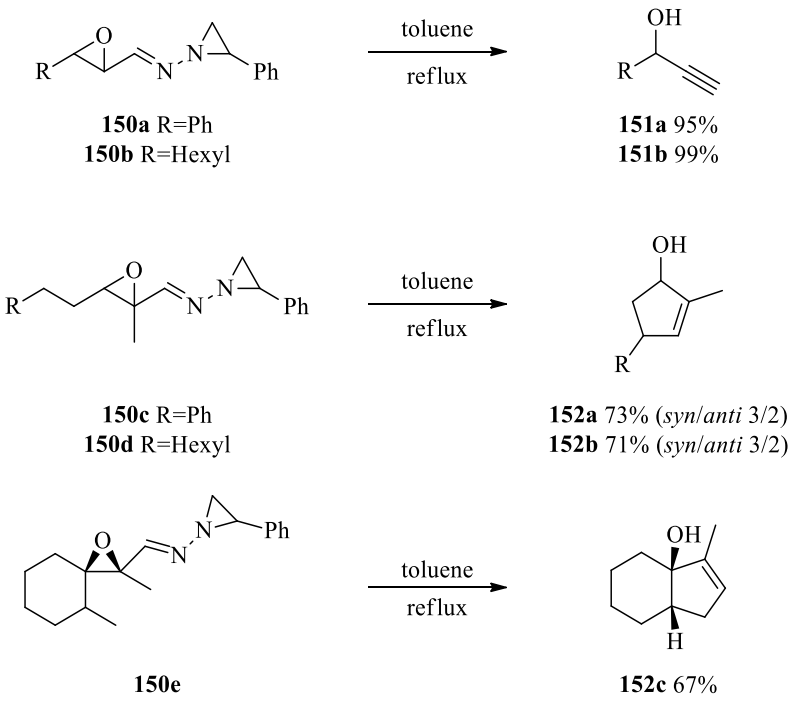
While the use of a modified olefination reaction has proven useful in the generation of alkylidene carbenes, a potential drawback is the basic conditions required.

The thermal decomposition of α,β-epoxy-*N*-aziridinylimines allows for the generation of alkylidene carbenes under neutral conditions.[53] This approach also offers an additional benefit as it allows for the generation of an alkylidene carbene with a β-hydroxyl group. The decomposition is thought to proceed in a similar fashion to the Eschenmoser fragmentation.[54] Heating **145** in toluene generates diazo compound **146**, with concurrent loss of styrene. Opening of the epoxide generates the double bond, and proton transfer from the vinyl carbon to the oxygen in betaine **147** gives the hydroxyl group and leads to diazonium ylide **148**. This extrudes nitrogen, resulting in β-hydroxy alkylidene carbene **149** (**Scheme 52**). The *N*-azirindinylimines are readily available by treating the corresponding carbonyl compound with *N*-azirdinylamines.



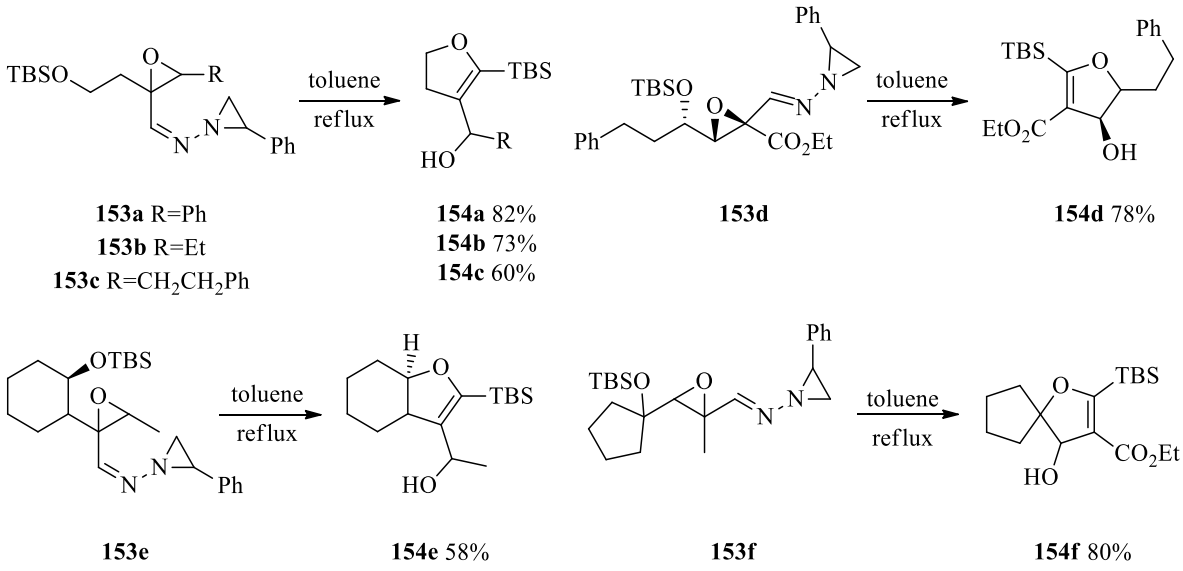
Scheme 52

Kim reported the successful synthesis both of propargyl alcohols **151a-b** and cyclopentenols **152a-c** by refluxing the *N*-azidinylimines **150a-e** in toluene (**Scheme 53**).[55]



Scheme 53

Kim later expanded the scope of this methodology to include the formation of silylated dihydrofurans **154a-f** through a 1,5 O-Si insertion pathway from *N*-azirdinylimies **153a-f** (**Scheme 54**).[11b]



153a R=Ph
153b R=Et
153c R=CH_2CH_2Ph

154a 82%
154b 73%
154c 60%

153d

154d 78%

153e

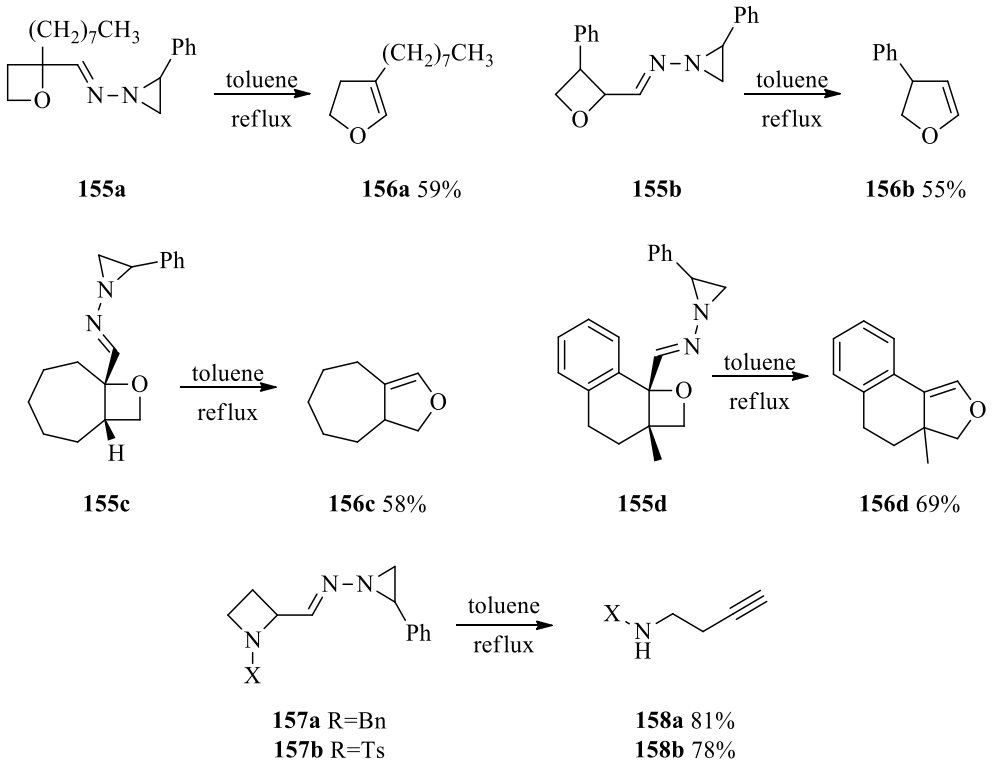
154e 58%

153f

154f 80%

Scheme 54

Kim also demonstrated that 4-membered heterocycles could open under similar conditons.[56] Thus, α-oxetanyl-*N*-aziridinylimines **155a-d** gave dihydrofurans **156a-d** via 1,5 O-H insertion, while α-azetidinyl-*N*-azirdinylimines **157a-b** gave homopropargyl amines **158a-b** via 1,2-migration (**Scheme 55**). Kim also reported that when heterocyclic systems larger than 4-membered rings were used, then the reaction pathway did not proceed through the alkylidene carbene, suggesting that the relief of ring strain plays a key role in the generation of the alkylidene carbene.

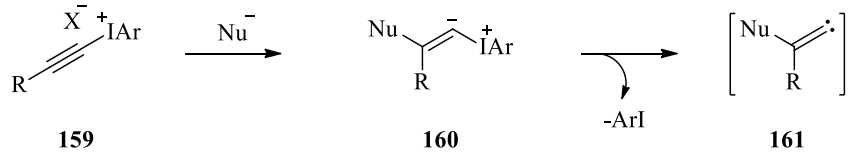


Scheme 55

The wide array of methods which can be employed to generate 1-diazoalkenes from readily accessible carbonyl compounds makes them an important intermediate from which to access alkylidene carbenes.

1.3.3 Generation using hypervalent iodine

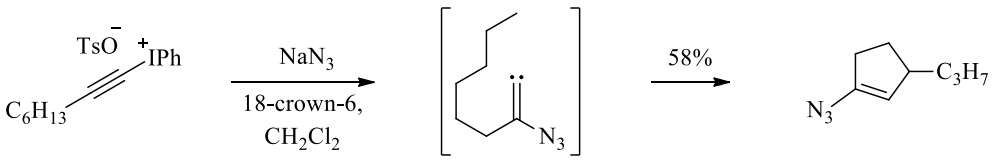
The addition of nucleophiles to alkynylaryliodonium salts, also referred to as 1-alkynyl(aryl)-λ^3-iodanes, has become a widely used method of generating alkylidene carbenes.[57] Aryliodine(III) groups have been shown to be strongly electron-withdrawing,[58] as well as demonstrating considerable leaving group ability,[59] making them ideal for this kind of transformation. The initial Michael addition to the iodonium species **159** results in iodonium ylide **160**, which eliminates the aryl iodide to give the corresponding carbene **161** (**Scheme 56**). An alternative approach to iodonium ylides such as **160** is the deprotonation of hypervalent vinyl iodonium salts, although this approach is far less common (**Scheme 10**).[21]



159 **160** **161**

Scheme 56

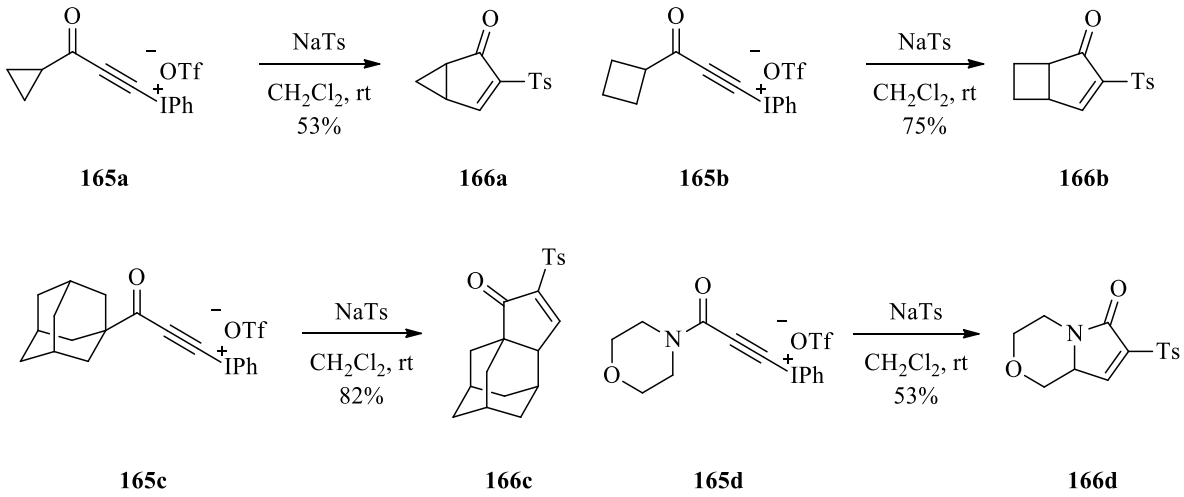
This is a versatile route, allowing for introduction of functionalities which may otherwise be difficult to incorporate. Stang reported the synthesis of cyclic vinyl azide **164**, by treating alkynyliodonium tosylate **162** with sodium azide. The intermediate alkylidene carbene **163** underwent 1,5 C-H insertion to form the carbocycle in moderate yield (**Scheme 57**).[60]



162 **163** **164**

Scheme 57

Stang also described the synthesis of a variety of fused cyclopentenones **166a-d** from the reaction between sodium *para*-toluenesulfinate and alkynyliodonium triflates **165a-d** (**Scheme 58**).[61]

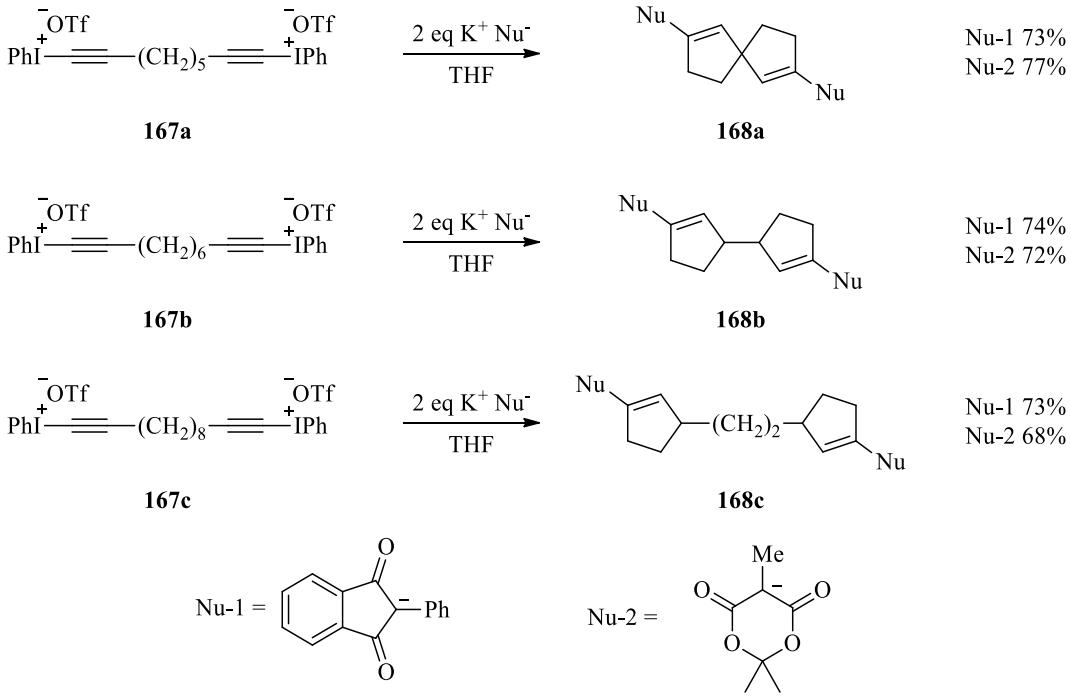


165a **166a** **165b** **166b**

165c **166c** **165d** **166d**

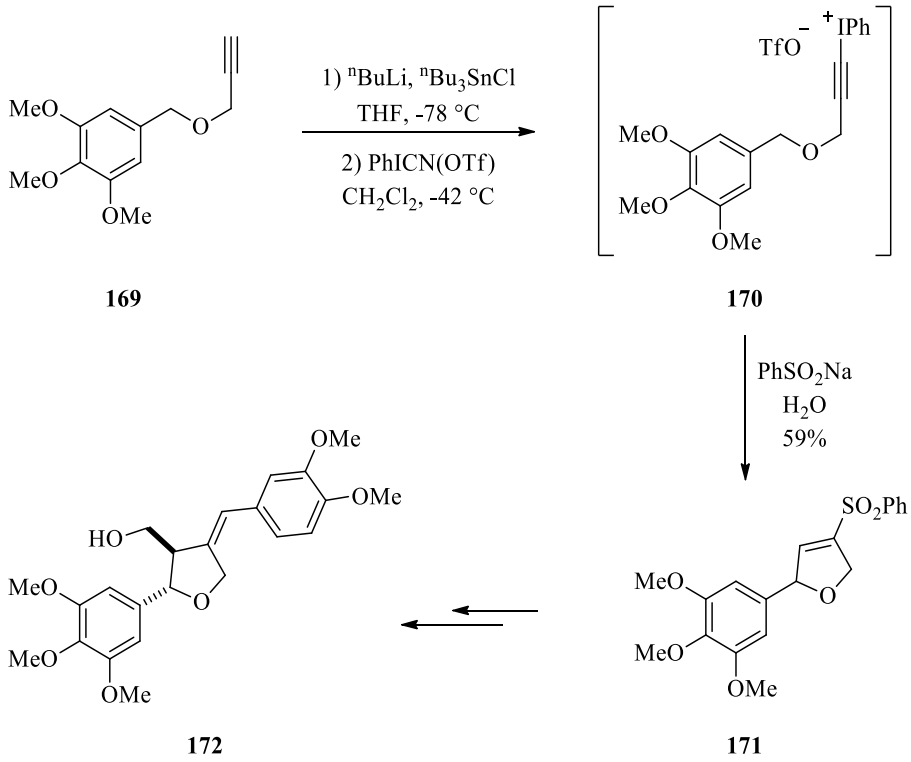
Scheme 58

Additionally, Stang reported the addition of the enolates of 1,3-dicarbonyls to bisiodonium triflates **167a-c** to give the bis-cyclopentene systems **168a-c** in good yield (**Scheme 59**).[62]



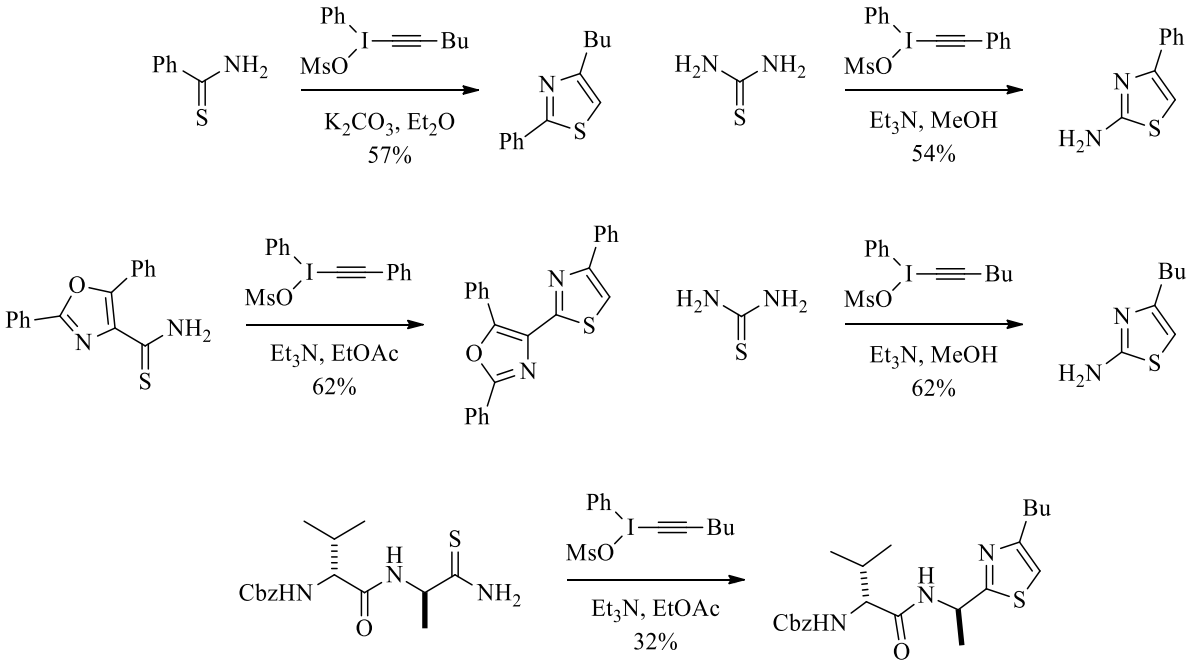
Scheme 59

A wide range of other nucleophiles have been used in intermolecular reactions to generate alkylidene carbenes from alkynyliodonium salts, including sulfonamides,[63] phenoxides,[9a] sulfinates,[64] 1,3-dicarbonyls,[65] tropolone,[9c] thiocyanates,[66] tellurides and selenides.[67] In particular, the addition of sodium sulfinate has been used extensively, and has been used in various natural product synthesis, including Wardrop's synthesis of (±)-magnofargesin **172**, with the synthesis of vinyl sulfone **171** from alkyne **169** via iodonium triflate **170** a key step (**Scheme 60**).[64b]



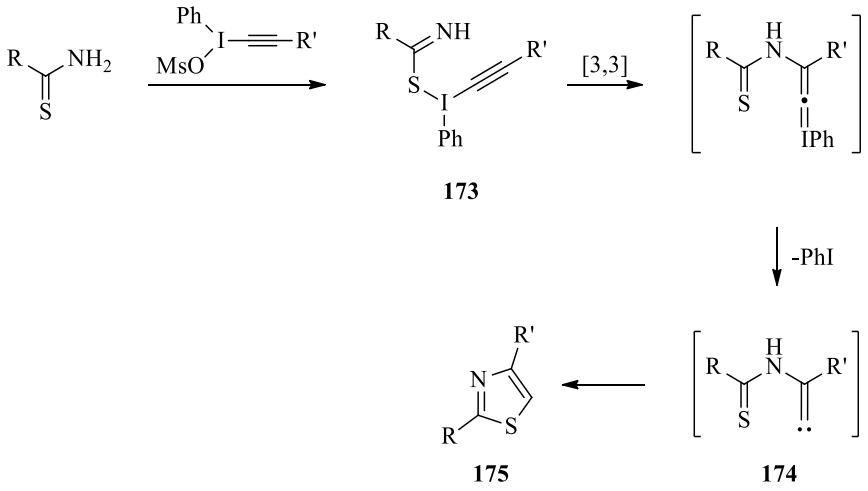
Scheme 60

Wipf reported the synthesis of thiazoles, a biologically important moiety, through the reaction between thioamides and alkynyliodonium mesylates (**Scheme 61**).[68]



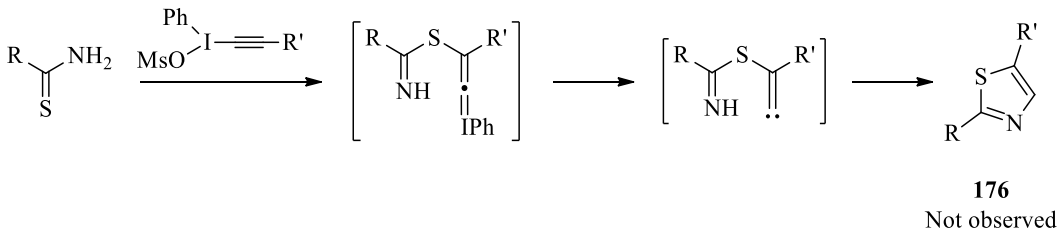
Scheme 61

Wipf postulated that the reaction proceeded through an initial ligand exchange at iodine to give **173**, followed by a Claisen-type [3,3]-sigmatropic rearrangement and loss of PhI to give the alkylidene carbene **174**. This undergoes a formal S-H insertion to give the heterocycle **175** after aromatisation (**Scheme 62**).



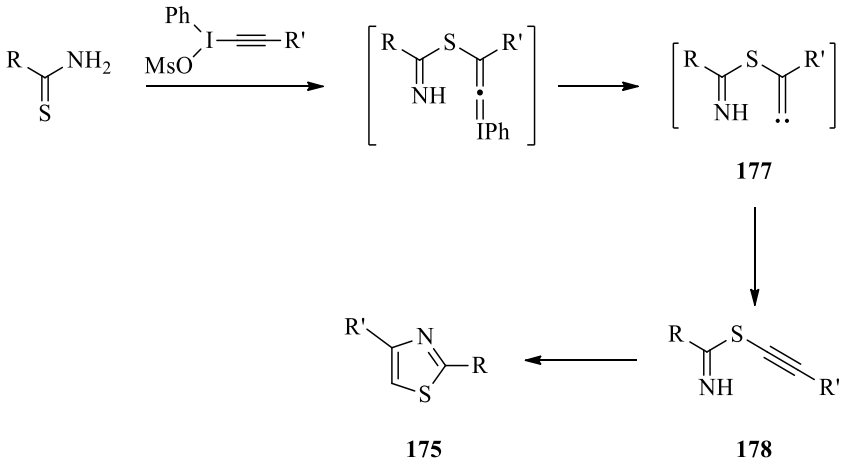
Scheme 62

An alternative mechanism involving Michael addition to the alkynyliodonium, with subsequent N-H insertion was discounted as this would form the opposite regioisomer of the thiazole, and there was no evidence of product **176** forming (**Scheme 63**).



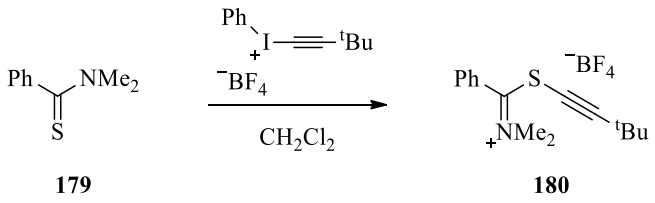
Scheme 63

Ochiai later proposed a third possible mechanism, that the reaction proceeded through initial Michael addition of the thioamide to the alkynyliodonium salt, afford the alkylidene carbene **177**, which underwent a subsequent 1,2-migration to form alkyne **178** as opposed to 1,5 C-H insertion. This alkyne would then undergo a 5-*endo-dig* cyclisation to form the thiazole **175** (**Scheme 64**).[69]



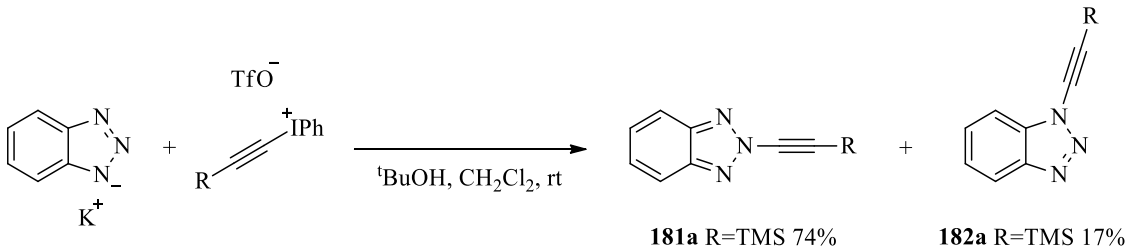
Scheme 64

Ochiai proposed that the known migratory aptitude of sulfenyl groups made this mechanism feasible,[21] and was able provide evidence of this mechanism by performing the reaction with *N*,*N*-dimethylthiobenzamide **179**. After the proposed alkyne formation, the thiobenzimidonium salt **180** generated would be unable to cyclise and its isolation provided strong evidence for **178** being an intermediate in the thiazole formation (**Scheme 65**).



Scheme 65

More recently, Kitamura reported the alkynylation of benzotriazole with alkynyliodonium triflates, where the initial conjugate addition is followed by 1,2-migration of the intermediate alkylidene carbene (**Scheme 66**).[70]



Scheme 66

It is interesting to note the preference for alkynylation at *N*-2 with the silylated alkynes, with reaction at *N*-1 preferred in the absence of silicon. This is believed to be due to unfavourable steric interaction between the benzotriazole and the silyl group, or iodonium substituents, in the event of nucleophilic attack from *N*-1 (**Figure 3**). These interactions are minimised in attack at *N*-2. Such interactions are absent in the desilylated reagent, and so attack from *N*-1 is preferred.

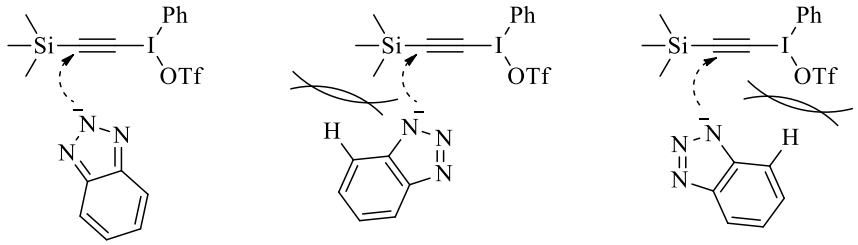
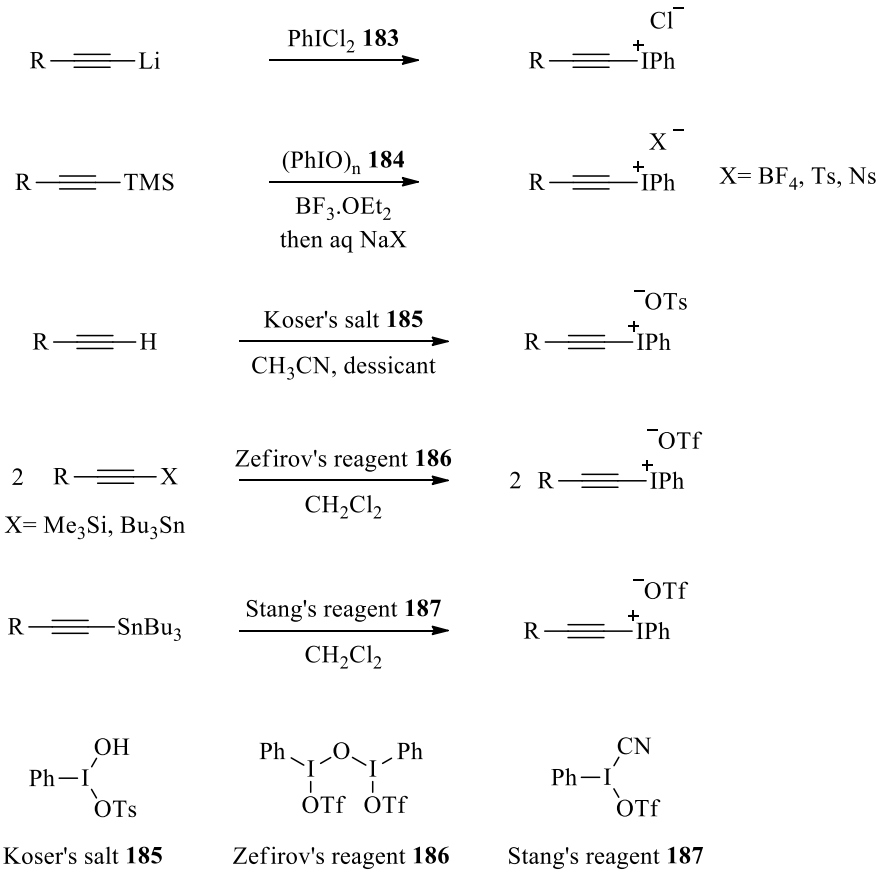


Figure 3

Intramolecular nucleophilic attack to form alkylidene carbenes from alkynyliodonium salts has also been reported.[63, 71]

A number of routes exist by which alkynyliodonium salts can be synthesised. Behringer first reported the synthesis of alkynyliodonium chlorides, in poor yield, through treatment of deprotonated phenylacetylene with dichloroiodobenzene **183** ($PhICl_2$).[72] Iodosylbenzene **184** (PhIO) has also been used successfully to access alkynyliodonium tetrafluoroborates and sulfonates from alkynylsilanes.[73] Alkynyliodonium tosylates have also been synthesised successfully through treatment of terminal alkynes with Koser's salt **185**

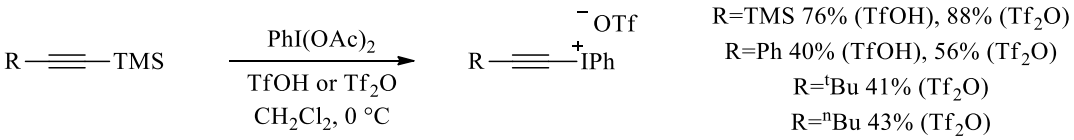
(PhI(OH)OTs).[74] The treatment of silyl or stannylacetylenes with Zefirov's reagent **186** (PhI(OTf)OI(OTf)Ph) affords access to alkynyliodonium triflates,[65c] as does reacting alkynylstannanes with Stang's reagent **187** (PhI(CN)OTf) (**Scheme 67**).[75] Koser's salt,[74c] Zefirov's reagent[65c] and Stang's reagent[75b] are readily available from bis(acetoxy)iodobenzene ($PhI(OAc)_2$). In recent times, the most commonly employed technique has been the treatment of alkynylstannanes with Stang's reagent. This method has allowed for the incorporation of a variety of functionalities, including alkyl, aryl, heteroaryl, halogens, carbonyls and sulfones, in yields ranging from 42% to 89%.[75b] Frequently, the iodonium salts generated by this method are used without purification.[22]



Scheme 67

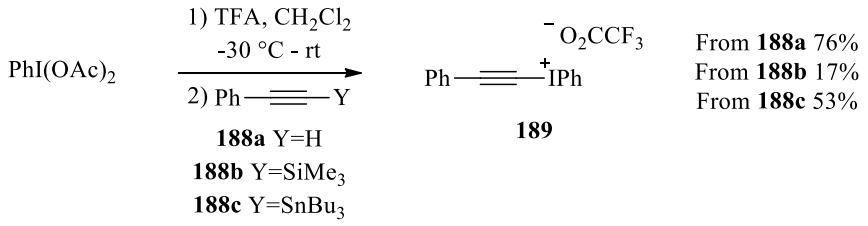
Kitamura reported the synthesis of alkynyliodonium triflates directly from $PhI(OAc)_2$, through reaction with silyl alkynes, in the presence of either TfOH or Tf_2O (Scheme 68).[76]

The use of Tf_2O gives a milder reaction system, as well as allowing for the use of only sub-stoichiometric amounts of the triflating reagent.



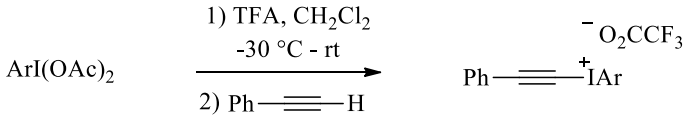
Scheme 68

Recently, Carroll reported the synthesis of alkynyliodonium trifluoroacetate salt **189** by treating $PhI(OAc)_2$ with TFA, with subsequent addition of alkynes **188a-c** (Scheme 69).[77] This method offers several advantages including avoiding the use of potentially toxic reagents (HCN generated from Stang's reagent **187**), air sensitive reagents (Zefirov's reagent **186**) and explosive reagents (PhIO **184**).

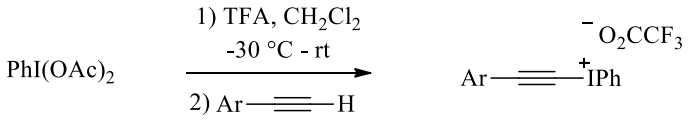


Scheme 69

This methodology also offered access to a range of alkynyliodonium trifluoroacetates, altering both the alkyne substituent and, more significantly, the non-participating aryl group on the iodine. Very little work has been reported previously where an aryl group other than phenyl had been utilised, and their synthetic utility was not investigated.[78] A range of alkynyliodonium trifluoroacetates were synthesised, bearing an array of aryl substituents on both the alkyne and iodine (**Scheme 70**).



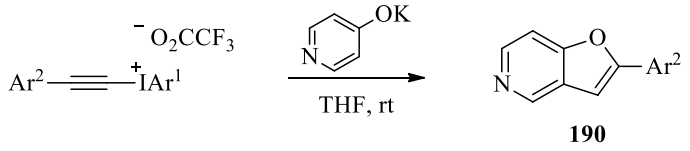
Ar=Ph 76%
Ar=4-Me-C_6H_4 85%
Ar=4-Cl-C_6H_4 76%
Ar=4-MeO-C_6H_4 71%
Ar=2-MeO-C_6H_4 56%
Ar=2-thiophene 30%
Ar=mesityl 64%



Ar=3-thiophene 76%
Ar=4-pentyl-C_6H_4 82%
Ar=4-Br-C_6H_4 66%
Ar=mesityl 45%
Ar=2,4,5-$(CH_3)_3C_6H_2$ 54%
Ar=4-MeO-C_6H_4 61%
Ar=2-MeO-C_6H_4 48%

Scheme 70

These reagents were employed in a reaction with potassium pyridine-4-olate to from 2-arylfuro[3,2-*c*]pyridines **190** via nucleophilic addition to the alkynyliodonium followed by 1,5 C-H insertion into the sp^2 C-H bond (**Scheme 71**).



190

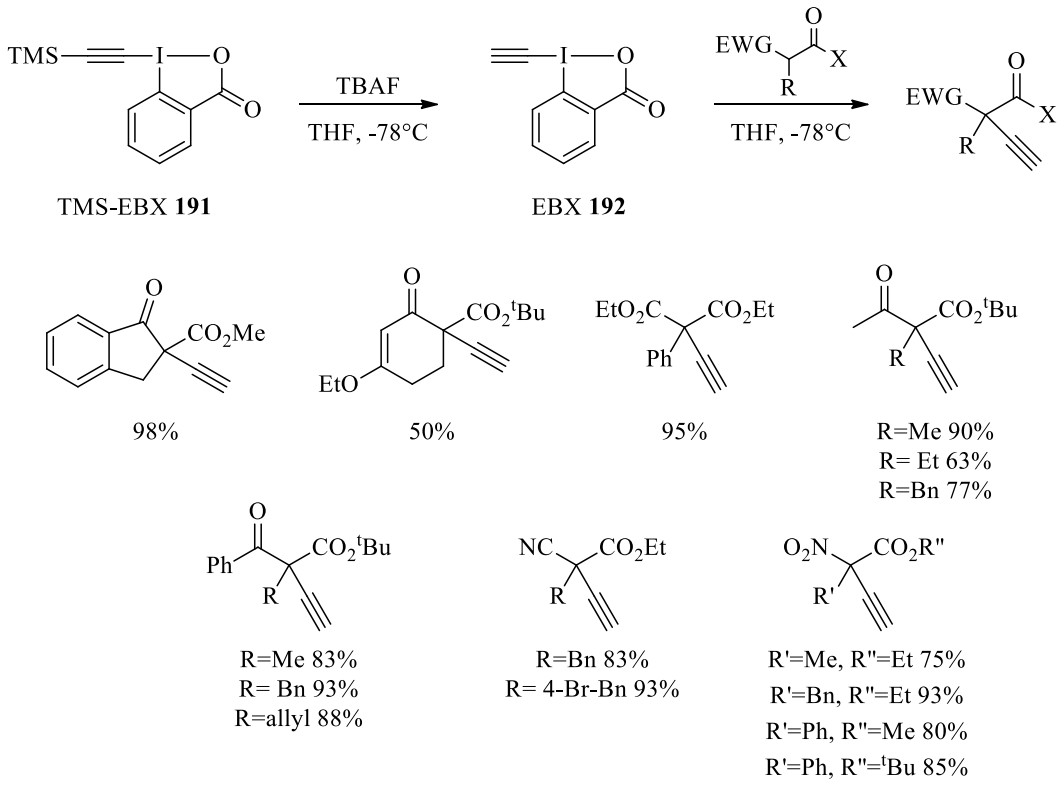
Ar^1=Ph, Ar^2=Ph 62%
Ar^1=4-MeO-C_6H_4, Ar^2=Ph 64%
Ar^1=4-Cl-C_6H_4, Ar^2=Ph 52%
Ar^1=mesityl, Ar^2=Ph 60%
Ar^1=Ph, Ar^2=3-thiophene 59%
Ar^1=Ph, Ar^2=4-pentyl-C_6H_4 50%
Ar^1=Ph,Ar^2=4-Br-C_6H_4 40%
Ar^1=Ph, Ar^2=mesityl 59%

Scheme 71

From these results, it was clear to see that altering the non-participating aryl group on the iodine, either electronically or sterically, had little or no effect on the outcome of the reaction.

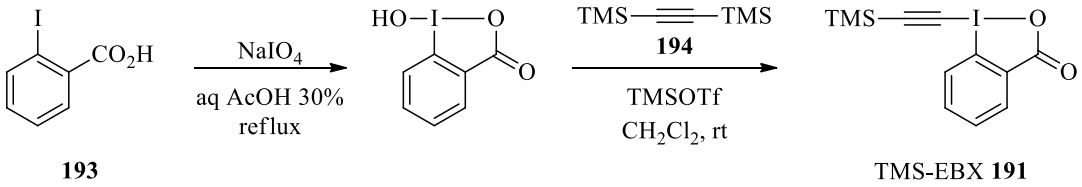
Waser reported the use of ethynyl-1,2-benziodoxol-3(1*H*)-one **192** (EBX) as a reagent for the alkynylation of electron-deficient esters.[79] Treatment of TMS-EBX **191** with TBAF

generated EBX *in situ*, which then reacted with the ester to give the product of α-alkynylation (**Scheme 72**). TBAF also acts as a base within the reaction.



Scheme 72

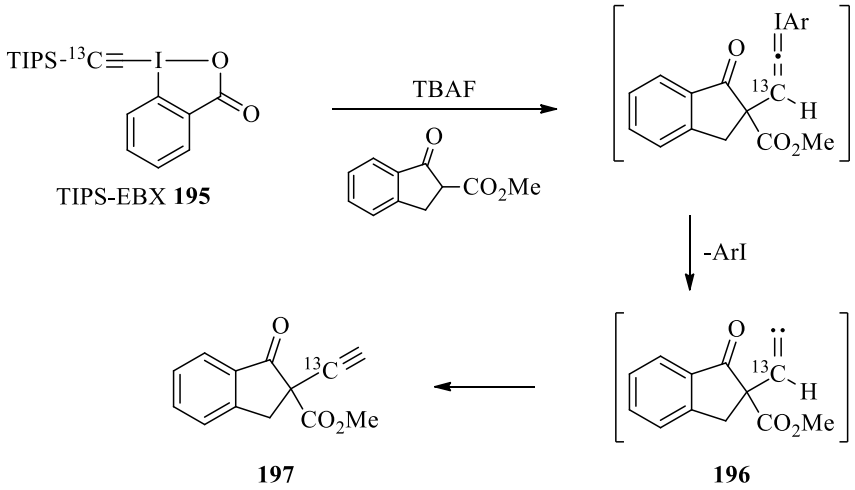
TMS-EBX **191** can be prepared simply by partial oxidation of 2-iodobenzoic acid **193**, followed be reaction with BTMSA **194** in the presence of a Lewis acid (**Scheme 73**).[80]



Scheme 73

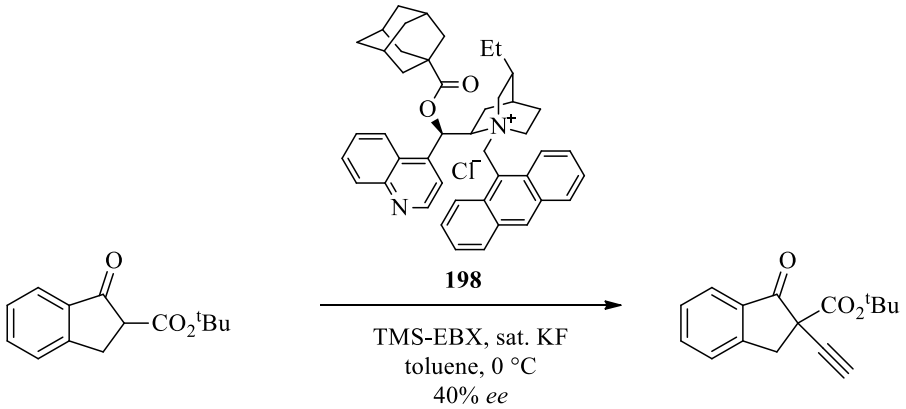
The reaction was shown to proceed through an alkylidene carbene by the use ^{13}C labelling (**Scheme 74**). By labelling the alkyne carbon bonded to the silicon in TIPS-EBX **195**, and determining its presence in the final product as being directly bonded to the α-position of the ketone, it suggests that initial nucleophilic attack occurs on the β-carbon of the

alkynyliodonium species, leading to alkylidene carbene **196**. This also suggests that the hydrogen is the migrating group, to form the final product **197**.



Scheme 74

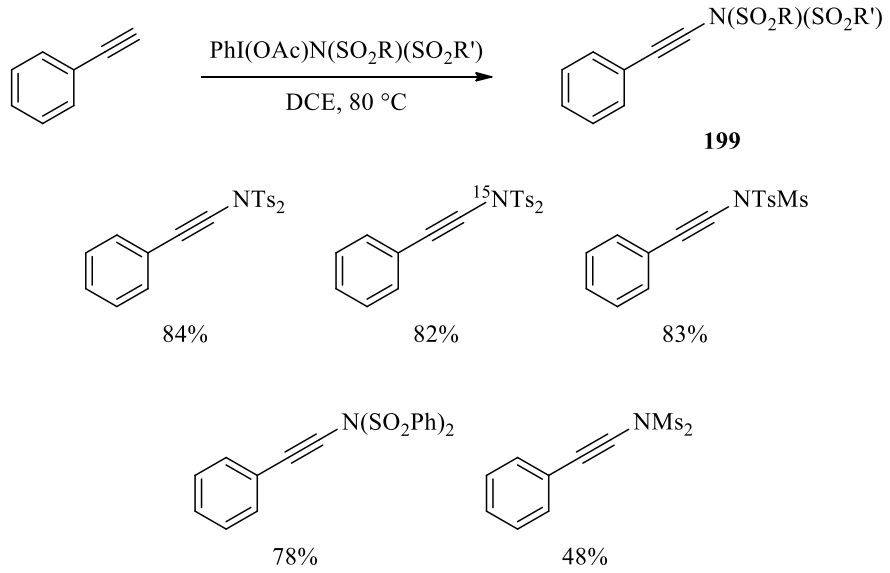
This chemistry was further expanded towards the asymmetric alkynylation of enolates. A modest enantioselectivity was obtained when the reaction was performed in the presence of a phase transfer catalyst **198** (**Scheme 75**).



Scheme 75

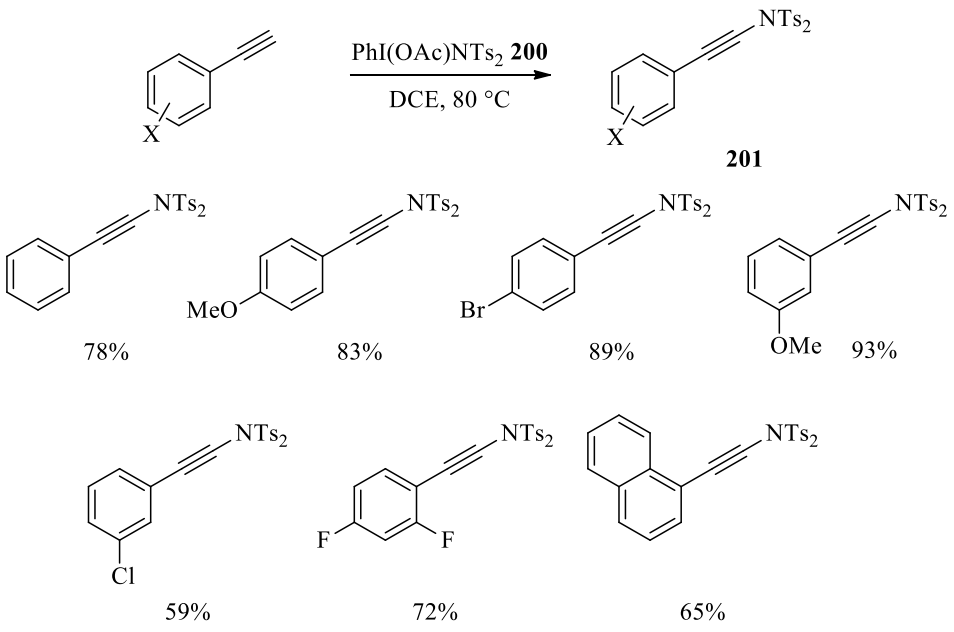
While the use of alkynyliodonium salts has allowed for the synthesis of cyclopentenes and alkynes with a wide range of functionalities, it usually requires the pre-functionalisation of an alkyne with the hypervalent iodine. Recently, Muniz has reported the synthesis of ynamides and cyclic enamides from terminal alkynes using a range of iodine(III) reagents,

which are readily available from $PhI(OAc)_2$.[81] Treatment of phenylacetylene with a variety of sulfonamide substituted iodine reagents gave ynamides **199** in good yields (**Scheme 76**).



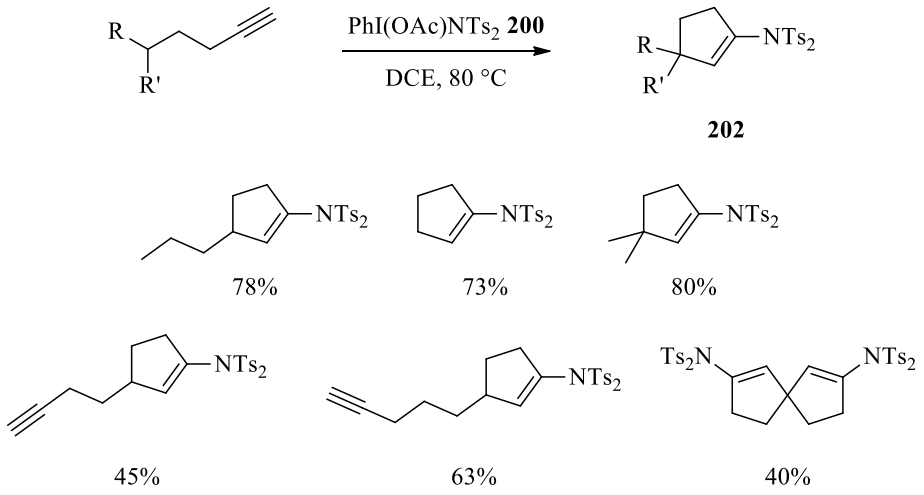
Scheme 76

The reaction was also shown to be successful in synthesising a range of bis-tosyl ynamides **201** from the corresponding acetylenes using hypervalent iodine reagent **200** substituted with only one *N*-ligand (**Scheme 77**).



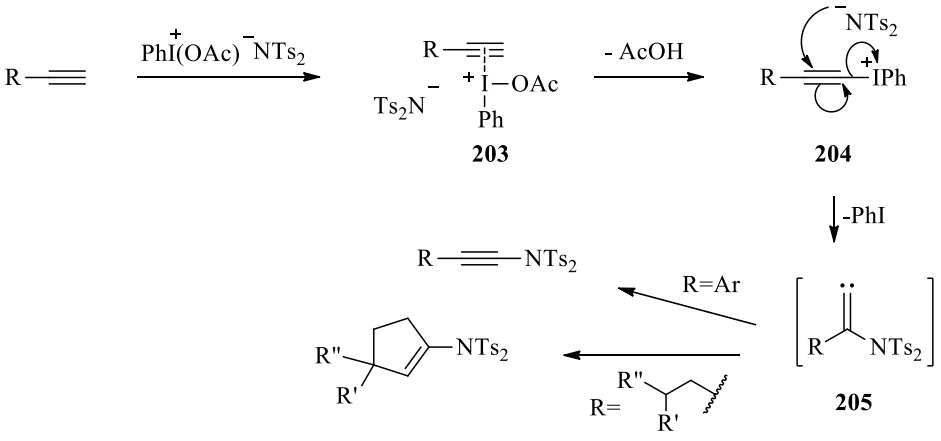
Scheme 77

The methodology has been applied to the synthesis of cyclic enamides **202**. Treating alkyl alkynes with **200** gave cyclisation products in good yields (**Scheme 78**).



Scheme 78

The proposed mechanism is as follows: the initial coordination of the electrophilic iodine (III) to the acetylene, forming complex **203**, increases the acidity of the alkyne C-H bond. Deprotonation of the alkyne leads to alkynyliodonium **204**. Nucleophilic attack on the β-carbon by the tosylamide anion, results in alkylidene carbene **205**, with concurrent loss of PhI. From here, 1,2-migration or 1,5 insertion occurs, depending on the substituent on the alkylidene carbene, leading to the observed products (**Scheme 79**).



Scheme 79

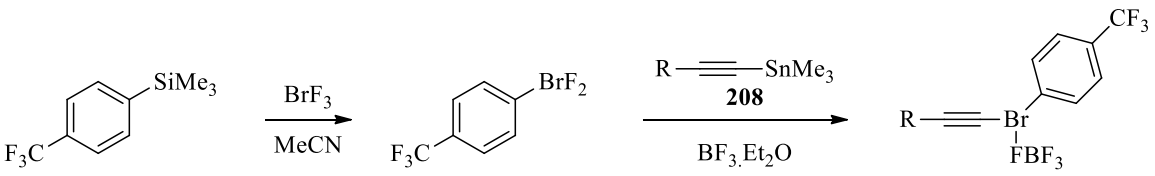
The recent developments by Muniz has allowed for the *in situ* generation and reaction of alkylidene carbenes directly from the terminal alkyne, eliminating the need to prepare alkynylstannanes or alkynyliodonium species. Recently, Olofsson has reported the synthesis of alkynyliodonium salts directly from terminal alkynes.[82] However, these intermediates have not yet been employed in the generation of alkylidene carbenes.

The relative ease of access to alkynyliodonium species, coupled with the wide range of functionalities that can be incorporated into the alkylidene carbenes generated from them, makes them important reagents in the use of alkylidene carbenes in organic synthesis.

1.3.4 Generation using hypervalent bromine

Recent expansion on the extensive work carried out on alkynyliodonium species as alkylidene carbene precursors has led to the investigation of the use of related alkynylbromonium, or 1-alkynyl(aryl)-λ^3-bromane, substrates in a similar fashion.[83] λ^3-bromanyl groups have been shown to have a greater Hammond substituent constant than the equivalent λ^3-iodanyl (σ_p=1.63 for $PhBrBF_4$ compared to σ_p=1.37 for $PhIBF_4$), suggesting that 1-alkynyl-λ^3-bromanes may be better Michael acceptors.[84]

Ochiai reported the synthesis of a number of alkynylbromonium tetrafluoroborates. Treatment of aryl silane **206** with BrF_3 gave rise to **207**, which subsequently reacted with alkynylstannanes **208a-g** to give the alkynylbromonium tetrafluoroborates **209a-g** (**Scheme 80**).[85]

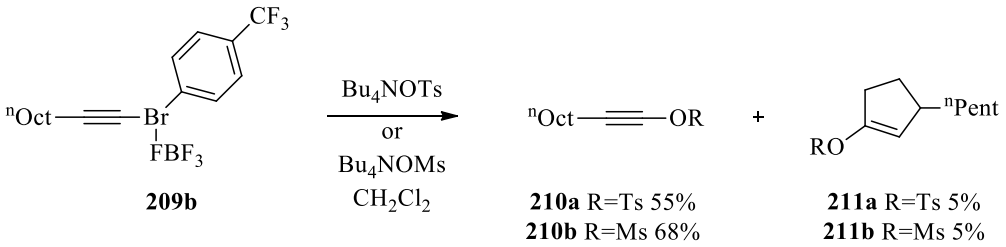


206 **207** **209**

209a R=^{n}Bu 76%
209b R=^{n}Oct 82%
209c R=^{i}Bu 83%
209d R=$(CH_2)_2CHMe_2$ 79%
209e R=Cy 83%
209f R=^{t}Bu 89%
209g R=$SiMe_3$ 78%

Scheme 80

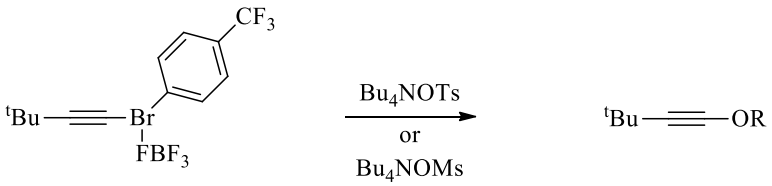
Ochiai demonstrated that these alkynylbromonium reagents underwent reaction with nucleophiles to give rise to alkynes **210** and cyclopentenes **211** (**Scheme 81**). In reacting with weak nucleophiles such as sulfonate anions, it can be seen that these reagents are, as was suspected, considerably more reactive than the corresponding iodonium reagents. Sulfonate anions will not react with alkynyliodonium salts.[60, 74c]



209b

210a R=Ts 55%
210b R=Ms 68%

211a R=Ts 5%
211b R=Ms 5%

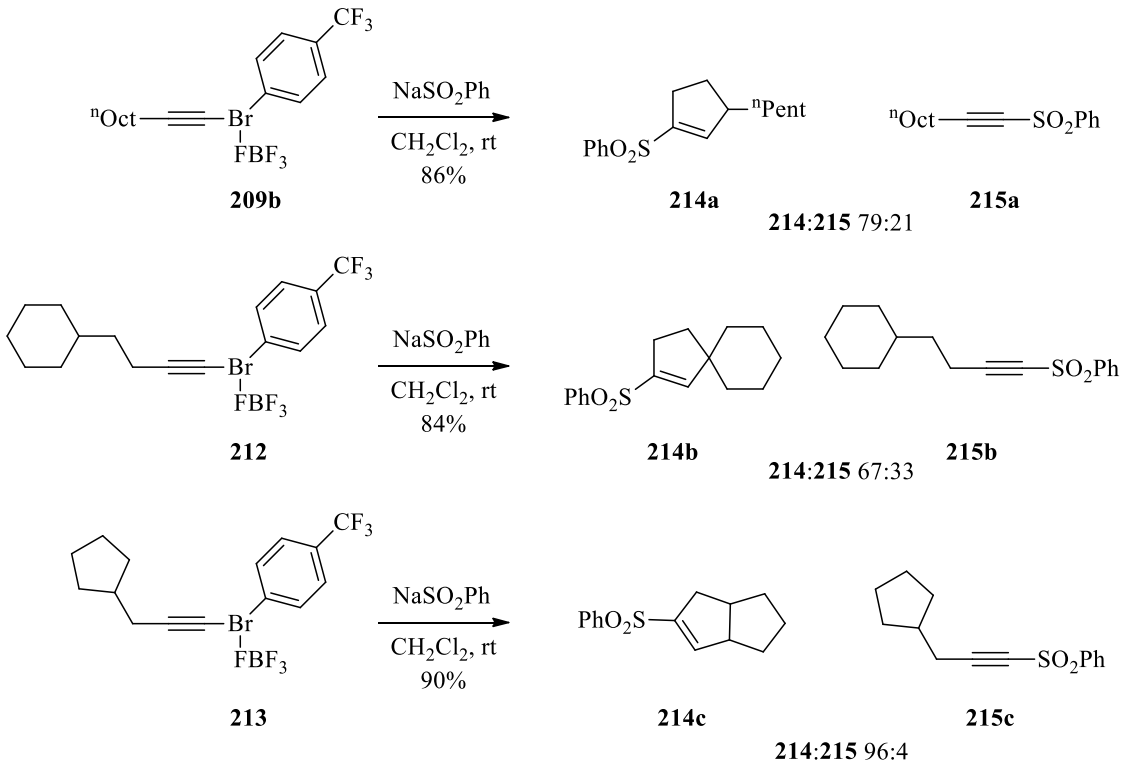


209f

210c R=Ts 76%
210d R=Ms 56%

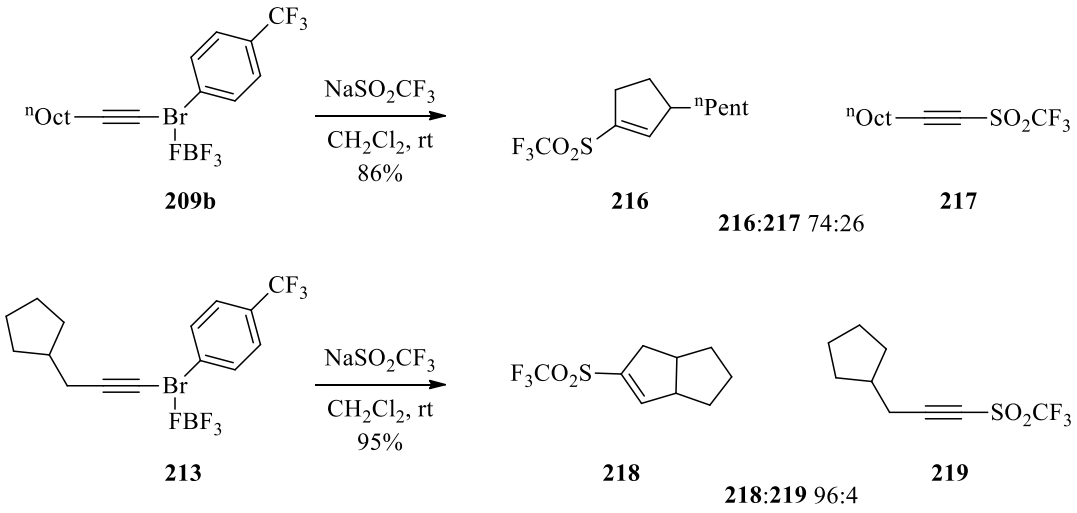
Scheme 81

Ochiai later expanded the use of alkynylbromonium reagents to include the formation of sulfone substituted cyclopentenes **214**, through their reaction with sodium phenylsulfinate (**Scheme 82**).[86] Alkynylsulfones **215** were also isolated from these reactions.



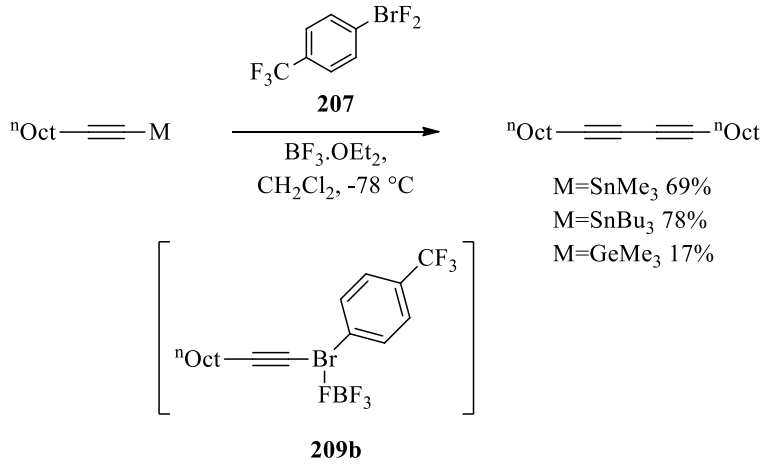
Scheme 82

Additionally, the use of sodium trifluoromethanesulfinate (triflinate) as a nucleophile was also reported, with the reaction with **209b** giving rise to a mixture of vinyl triflone **216** and alkynyl triflone **217** in good yield. A similar reaction between **213** and sodium triflinate gave the bicycle **218** in excellent selectivity (**Scheme 83**).



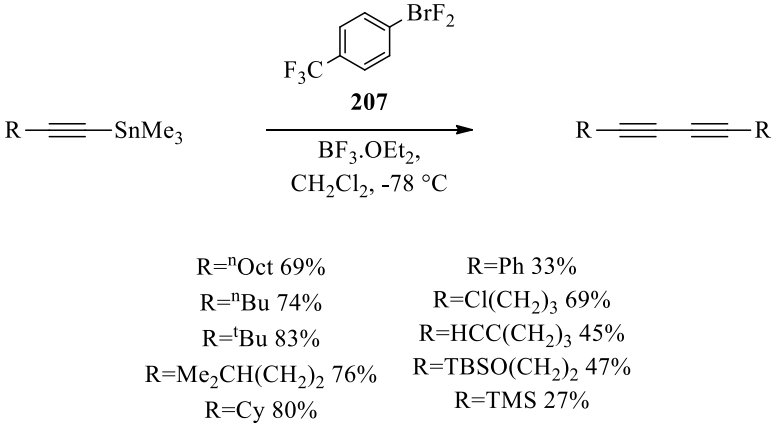
Scheme 83

The range of nucleophiles that underwent reaction with alkynylbromonium species was expanded to include metallated alkynes. Ochiai reported that treating alkynylstannanes and germanes with **207** resulted in an oxidative homocoupling of the alkynes (**Scheme 84**).[87] It was thought that the reaction proceeded through the initial formation of **209b**.



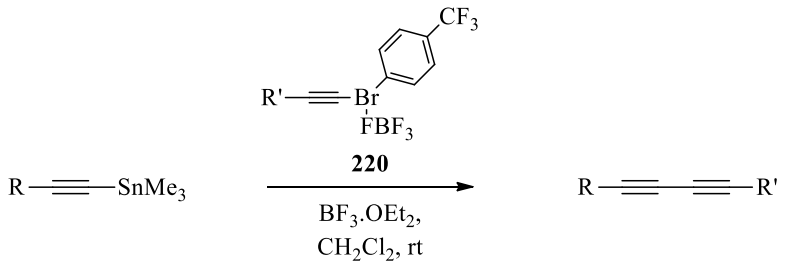
Scheme 84

The reaction was applied to the oxidative homocoupling of a range of alkynylstannanes, giving the diynes on good yield (**Scheme 85**).



Scheme 85

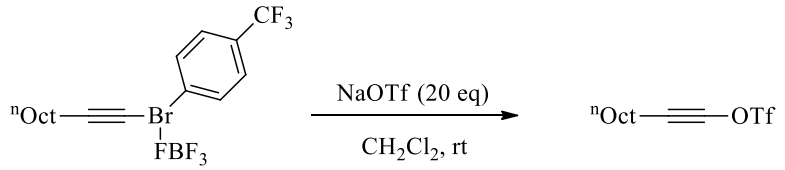
The methodology was also applied to various alkyne-alkyne oxidative cross-couplings between alkynylbromonium **220** and various alkynylstannanes to give unsymmetrical diynes (**Scheme 86**).



R=^{t}Bu, R'=^{n}Oct 76% R=^{n}Oct, R'=^{t}Bu 76%
R=Cy, R'=^{n}Oct 71% R=Cy, R'=^{t}Bu 74%
R=Ph, R'=^{n}Oct 66% R=^{n}Oct, R'=Cy 71%

Scheme 86

Ochiai also reported the synthesis of alkynyl triflate **221**, by reacting alkynylbromonium **209b** with a large excess of sodium triflate (**Scheme 87**). This example demonstrates the ability of alkynylbromonium as Michael acceptors, as triflate anions are generally held to be non-nucleophilic in nature.

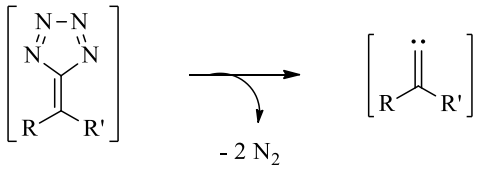


Scheme 87

The use of alkynylbromonium species holds great promise; however its application is severely limited by the required preparation of difluorobromonium reagents using BrF_3.

1.3.5 Generation from tetraazafulvenes

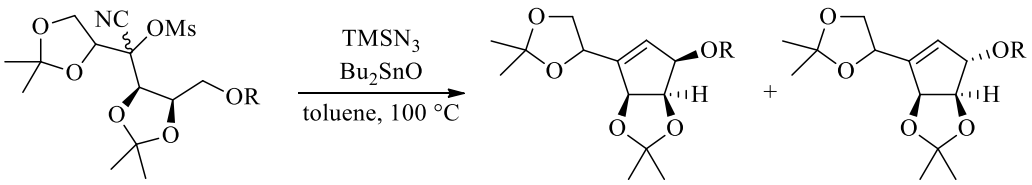
Related to the loss of nitrogen from 1-diazoalkenes is the fragmentation of tetraazafulvenes **222** to give alkylidene carbenes, with the loss of two molecules of nitrogen (**Scheme 88**). Like diazoalkenes, tetraazafulvenes are unstable and it is necessary to generate them *in situ* from more stable precursors.



222

Scheme 88

Postel reported the *in situ* generation of alkylidene carbenes when α-cyanomesylates **223** were treated with $TMSN_3$ in the presence of Bu_2SnO, giving rise to the cyclopentene diastereoisomers **224** and **225** (**Scheme 89**).[88]



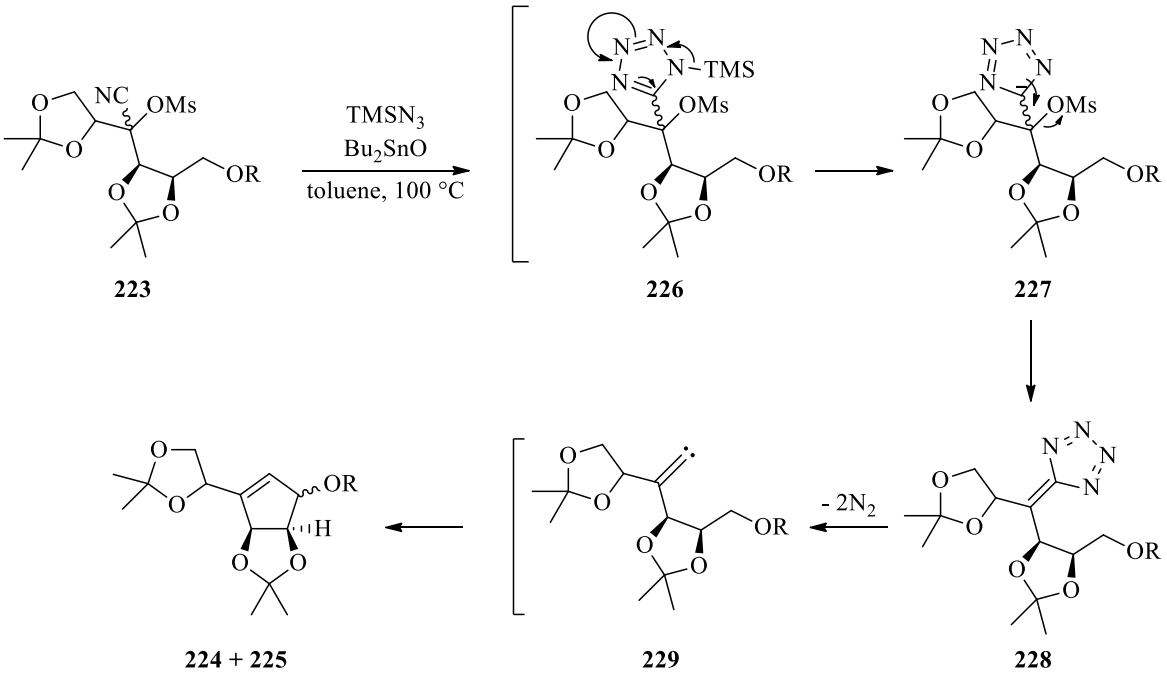
223

224a R=TBS 7%
224b R=Bz 5%

225a R=TBS 18%
225b R=Bz 36%

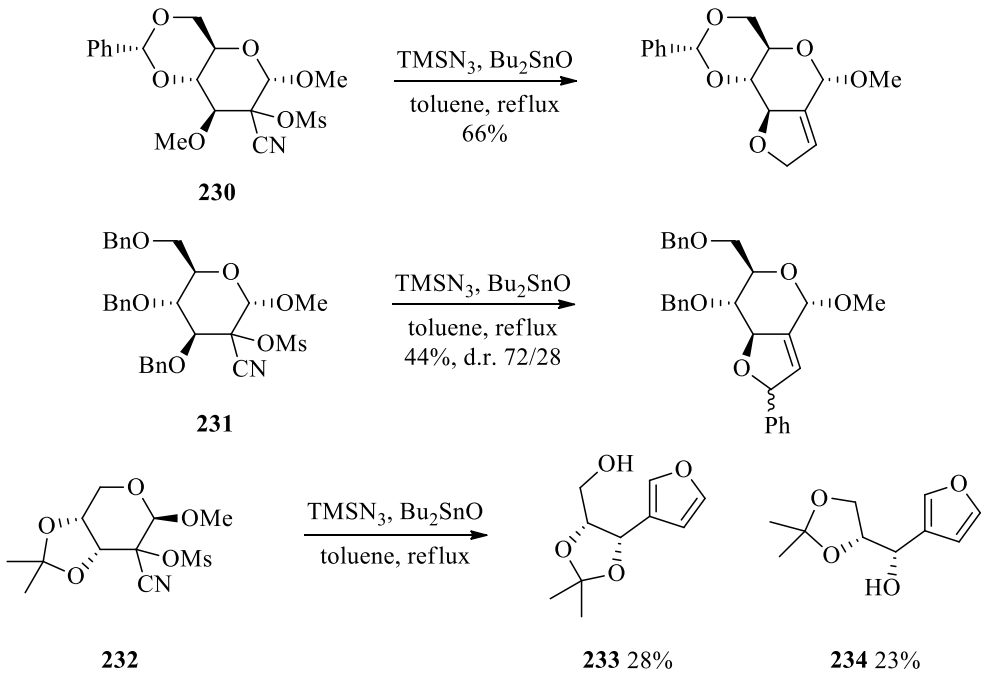
Scheme 89

The reaction is thought to proceed through initial cycloaddition between the nitrile group and the $TMSN_3$, leading to tetrazole **226**. Desilylation with subsequent rearrangement to 1*H*-tetrazole anion **227** is followed by elimination of the mesylate to give the tetraazafulvene **228**. The loss of two molecules of N_2 gives the alkylidene carbene **229** which undergoes 1,5 C-H insertion (**Scheme 90**). The Bu_2SnO is present to accelerate the initial cycloaddition.[89]



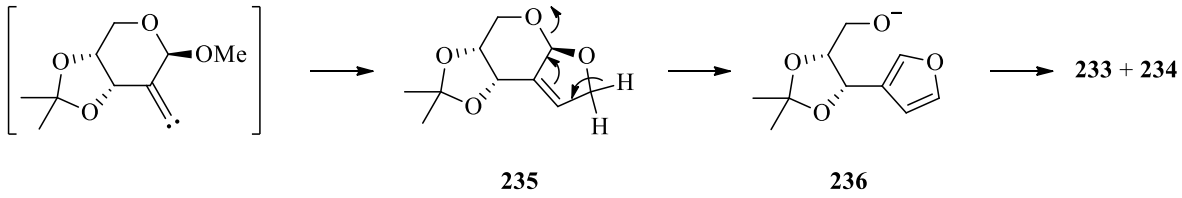
Scheme 90

Postel has recently reported the efficient synthesis of fused furopyran systems, and the isolation of β-substituted furans **233** and **234** by applying this methodology to sugar derivatives (**Scheme 91**).[90]



Scheme 91

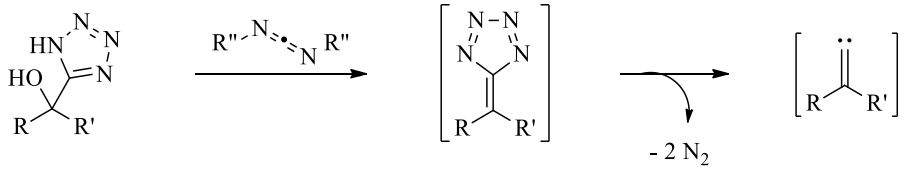
The furan formation is believed to proceed through 1,5 C-H insertion to give dihydrofuran **235**. This then fragments to form the furan **236** with concurrent opening of the pyran ring (**Scheme 92**).[90b] It is interesting to note that alkylidene carbenes derived from **230** and **231** preferentially insert into the C-4 substituent, whereas the alkylidene carbene from **232** inserts into the C-2 substituent.



235 **236**

Scheme 92

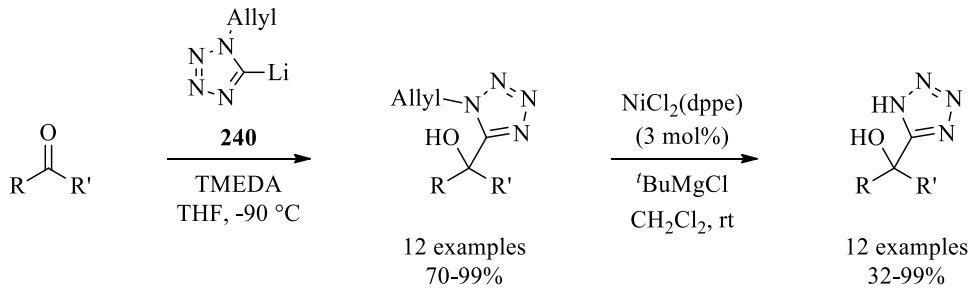
Recently, Wardrop reported the generation of alkylidene carbenes through the dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles **237** (**Scheme 93**).[91] The use of tetrazoles to generate alkylidene carbenes has been known for over 40 years,[92] but has received little attention since. The reaction is thought to proceed via dehydration of **237** to give the unstable tetraazafulvene **238**, which subsequently fragments to give the alkylidene carbene **239**.



237 **238** **239**

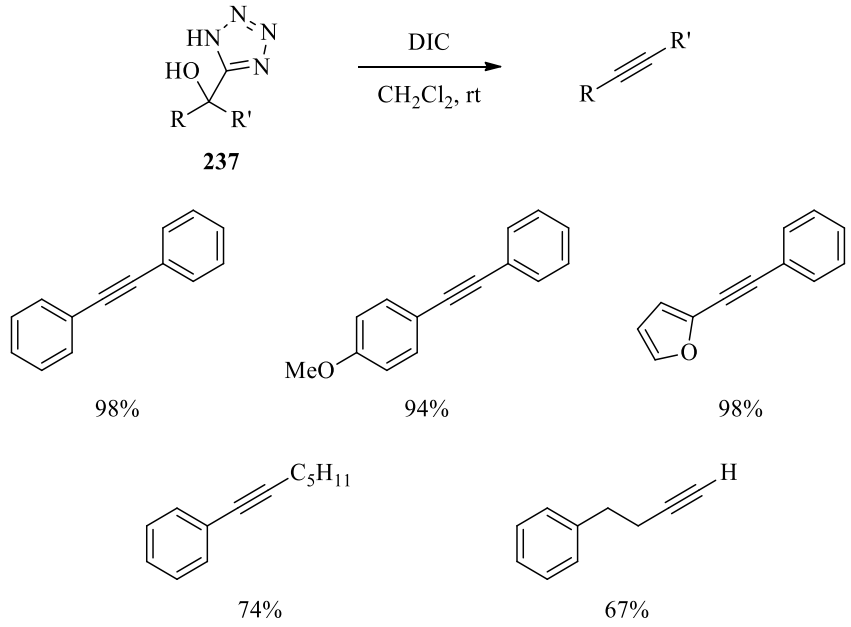
Scheme 93

The 5-hydroxyalkyl-1*H*-tetrazoles were readily prepared in two steps from the precursor carbonyl compounds via addition of 1-allyl-5-tetrazoyllithium **240** followed by Ni-catalysed de-*N*-allylation in the presence of ^{t}BuMgCl (**Scheme 94**). A range of substrates were prepared this way in mostly good yields.



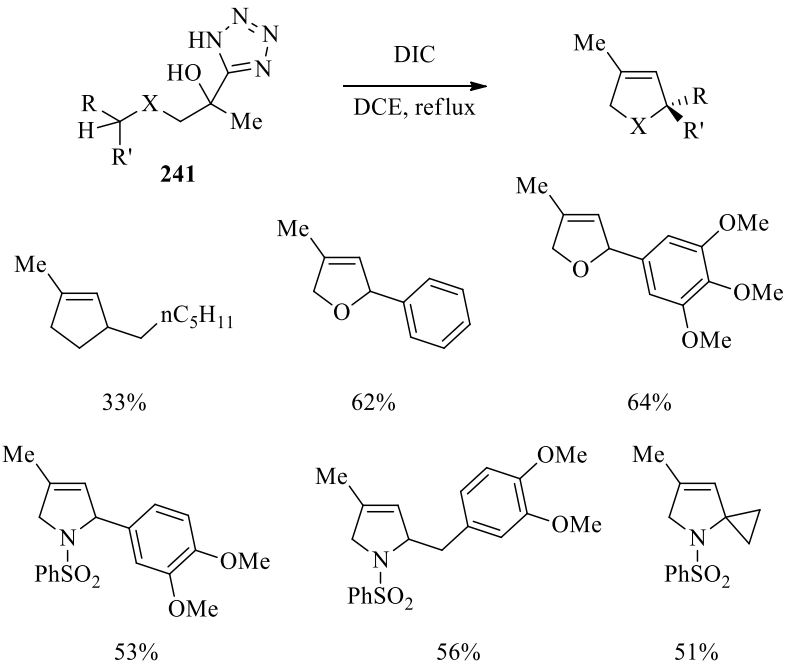
Scheme 94

Treatment of 5-hydroxyalkyl-1*H*-tetrazoles **237** with a range of carbodiimides afforded diarylalkynes in good yield, with diisopropylcarbodiimide (DIC) giving the best results (**Scheme 95**).



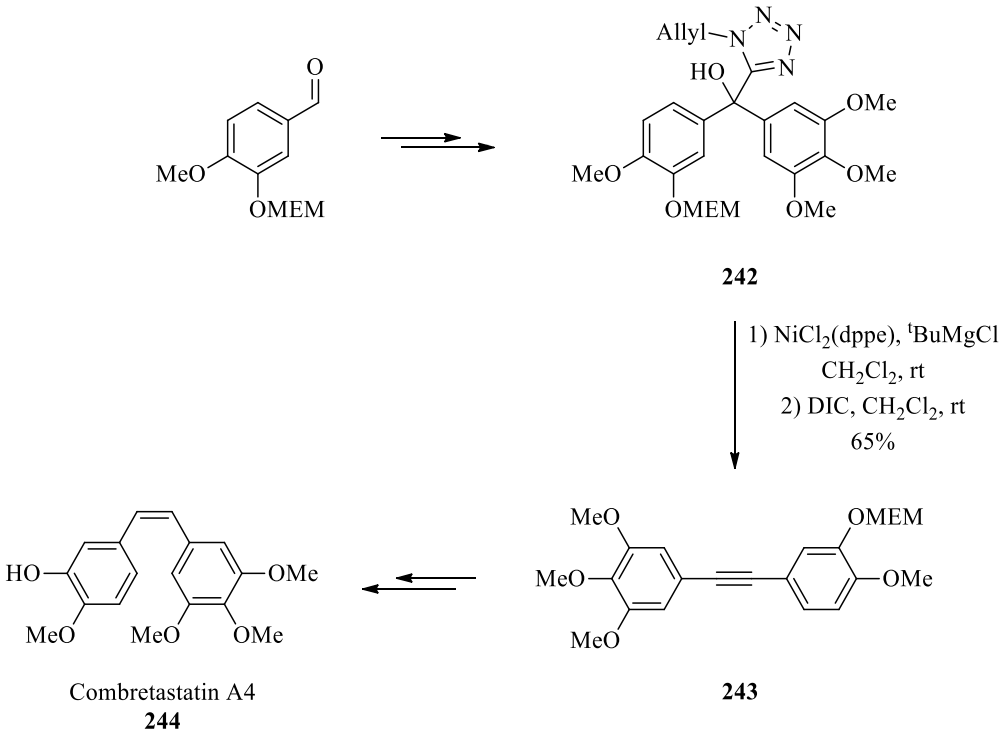
Scheme 95

The scope of the chemistry was further expanded to include the formation of ring systems through 1,5 C-H insertions reaction of the intermediate alkylidene carbene (**Scheme 96**). Treatment of tetrazoles **241** gave a variety of unsaturated ring systems in moderate yields. The conditions were more forcing than those required for the migration reaction, with refluxing DCE needed to ensure conversion.



Scheme 96

Wardrop also demonstrated the application of this chemistry to natural product synthesis, with the transformation of tetrazole **242** to alkyne **243** serving as a key step in the synthesis of combretastatin A4 **244** (**Scheme 97**).

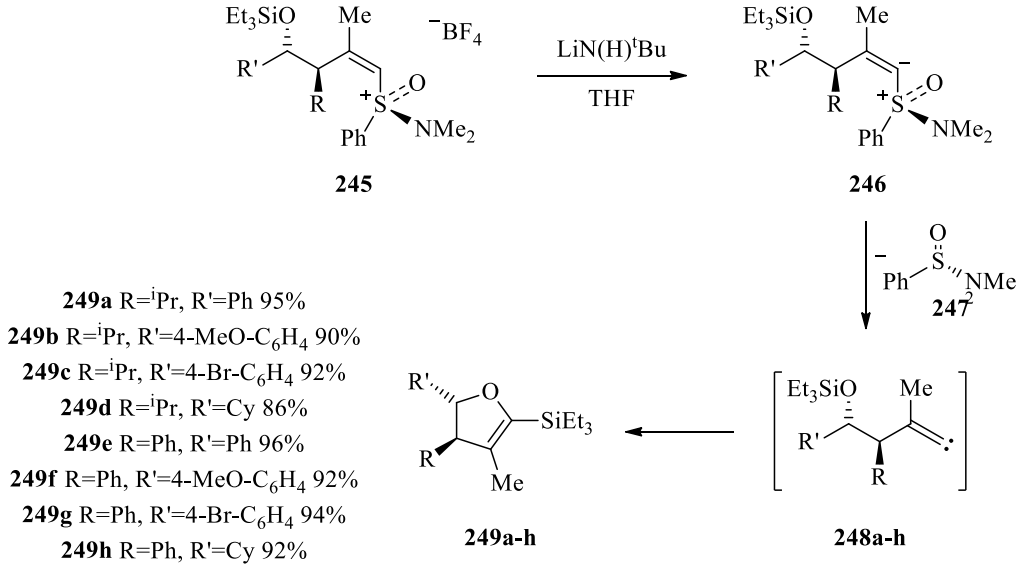


Scheme 97

While there are clear parallels between the extrusion of nitrogen from both diazoalkenes and tetraazafulvenes, it is possible generate tetraazafulvenes under neutral conditions, as opposed to the basic conditions frequently required to access diazoalkenes. However, there are far fewer examples of the use of tetraazafulvenes compared to diazoalkenes, perhaps due to the increased number of steps required.

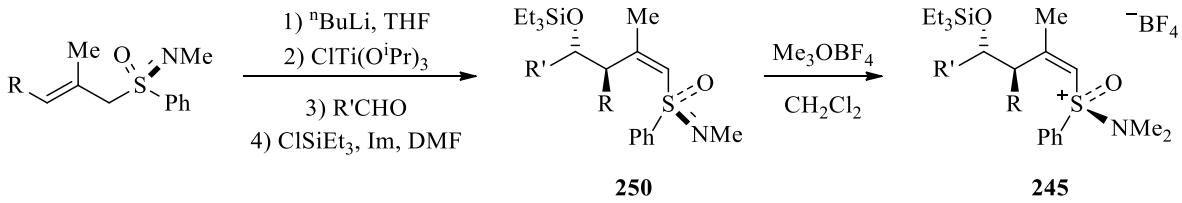
1.3.6 Generation from vinyl aminosulfoxonium salts

Gais reported the use of chiral vinyl aminosulfoxonium salts **245** which formed sulfur ylides **246** when treated with base. Subsequent loss of sulfinamide **247** gave alkylidene carbene **248** which underwent a formal 1,5 O-Si insertion reaction to give chiral dihydrofurans **249** in high yields (**Scheme 98**).[93]



Scheme 98

Accessing the alkylidene carbene directly from the aminosulfoxonium salts allowed for a more efficient synthesis of the chiral dihydrofurans. The sulfoximine had been used as a chiral auxiliary previously in the synthesis to install the stereochemistry of the substrate **250** with high diastereoselectivity (**Scheme 99**). Deriving the alkylidene carbene directly from the chiral auxiliary therefore eliminated the need for additional of steps to install another alkylidene carbene precursor.



Scheme 99

Additionally, the chiral sulfonamide **247** could be recovered in excellent yields (in excess of 85%) and recycled for use in subsequent reactions.

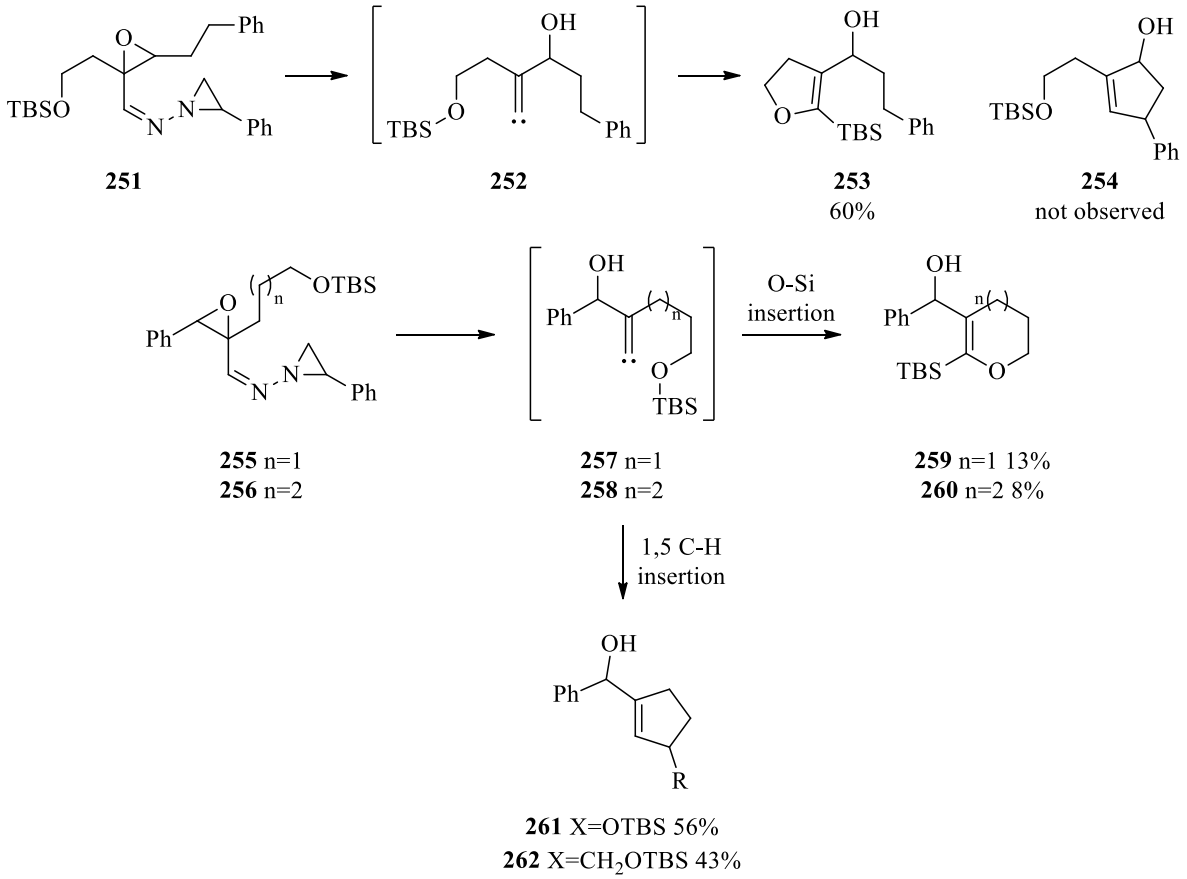
1.4 Selectivity of alkylidene carbenes

While alkylidene carbenes already offer increased selectivity over other simpler carbenes, in particular with relation to the regioselectivity of their insertion into unactivated C-H bonds, further selectivity can be achieved with these versatile intermediates.

1.4.1 Chemoselectivity and regioselectivity

Due to carbenes being strongly electron-deficient, they are highly electrophilic and so will react faster with functionalities which are relatively electron-rich. Such is the sensitivity of alkylidene carbenes to these electronic effects, they will preferentially undergo 1,5 C-H insertion reactions with tertiary C-H bonds in the presence of less substituted 1,5 C-H insertion sites.[94] The relative rates of reaction have been demonstrated to be 1:30:240 (primary/secondary/tertiary). In addition, it has also been shown that heteroatoms adjacent to C-H bonds will accelerate reaction at that site.[6, 95]

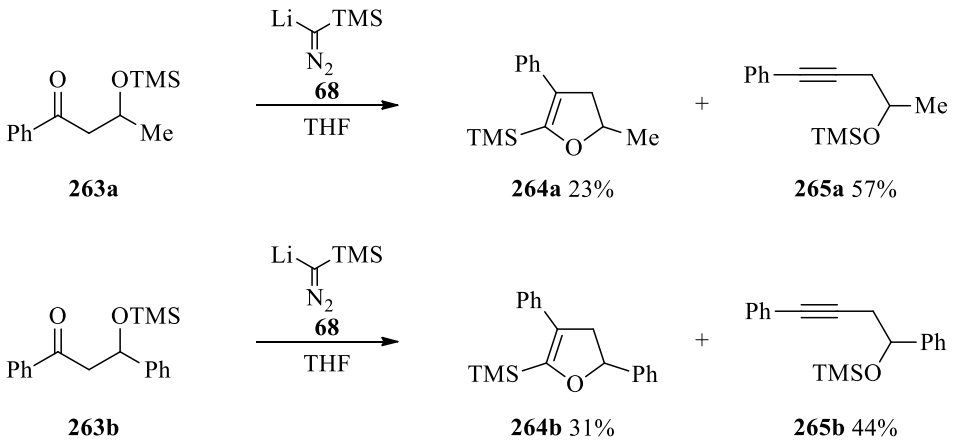
Insertions into O-Si bonds have been shown to occur faster than C-H insertion reactions, with Kim reporting the formation of **253** from azirindinylimine **251** with no evidence of **254** seen. However, this is only true for the formation of 5-membered rings as employing **255** and **256** in the same reaction gave mainly 1,5 C-H insertion products **261** and **262** respectively, with 1,6 O-Si insertion product **259** and 1,7 O-Si insertion product **260** formed in only low yields (**Scheme 100**).[11b]



Scheme 100

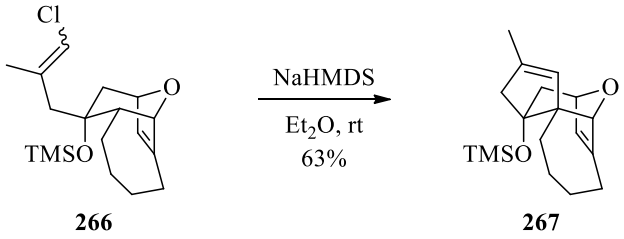
Insertions into heteroatom-hydrogen bonds has also been demonstrated to occur faster than 1,5 C-H insertion.[96]

While alkylidene carbenes with aryl substituents will usually undergo 1,2-migration reaction in preference to 1,5 C-H insertion reactions, Shioiri demonstrated that 1,5 O-Si insertion reaction can compete with the migration of phenyl groups with ketones **263** giving a mixture of alkynes **264** and dihydrofurans **265** (**Scheme 101**).[10] Additionally, Shioiri[10] and Kim[11b] both demonstrated that 1,2 hydrogen migration occurs faster than 1,5 O-Si insertion.



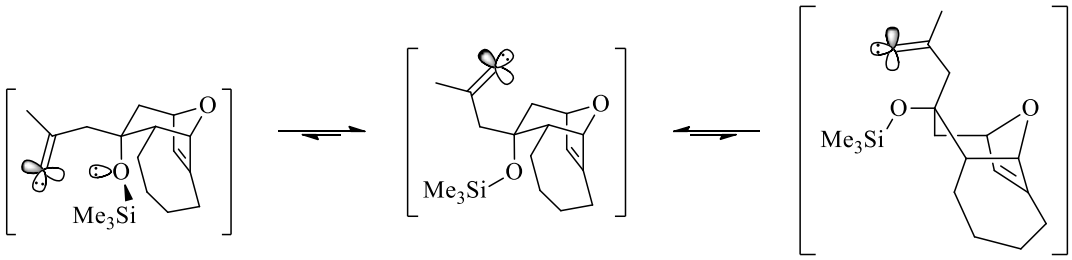
Scheme 101

However, it has also been demonstrated that structural features in the substrate can override such selectivities. Grainger demonstrated preferential C-H insertion over O-Si insertion in synthesising tetracycle **267** from vinyl chloride **266** (**Scheme 102**).[97]



Scheme 102

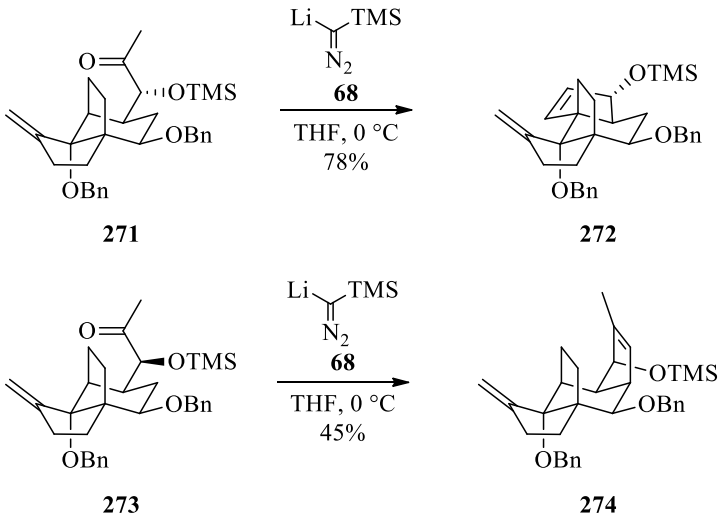
It was proposed that in order to undergo insertion into the O-Si bond, there must be an interaction between the O lone pair and the empty p-orbital on the alkylidene carbene. In this example, the bulky TMS group is expected to be orientated *exo* to the ring system in order to minimise any unfavourable steric interactions, resulting in **268** being the lowest energy conformation. This would result in both oxygen lone pairs siting in an *endo* orientation, unable to interact with the empty p-orbital. In order to achieve the necessary orbital overlap, the molecule must adopt a much higher energy conformation, either **269** or **270** (**Scheme 103**). As a result, the 1,5 C-H insertion pathway dominates.



269 **268** **270**

Scheme 103

Lee demonstrated that it was possible to override the preference for alkylidene carbenes to insert into tertiary C-H bonds over secondary C-H bonds (**Scheme 104**).[98] The alkylidene carbene generated from ketone **271** was shown to react exclusively with the tertiary C-H bond giving tetracycle **272** in good yield. However, the epimer **273** shows preferential insertion into the secondary C-H bond, giving **274**. It is believed that an unfavourable steric interaction between the OTMS group and the ring system in **273** disfavour the conformation for insertion into the tertiary C-H bond, allowing insertion to occur at the electronically less favoured methylene site.

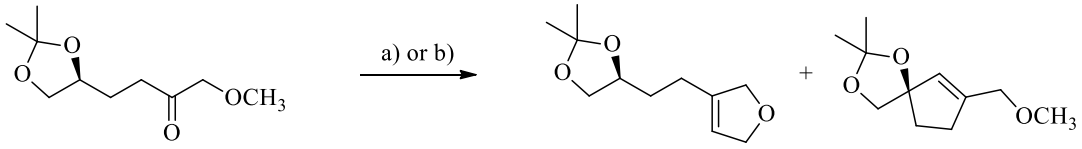


271 **272**

273 **274**

Scheme 104

Taber reported an increase in the regioselectivity of 1,5 C-H insertion reactions by altering the manner in which the alkylidene carbene was generated.[95b] Treating ketone **275** with $TMSCHN_2$ and MeLi, resulted in a mixture of dihydrofuran **276** and cyclopentene **277**, with a slight preference for insertion into the primary C-H over the tertiary C-H. When the same ketone was reacted under Wittig conditions, and the resulting vinyl halide treated with KHMDS, the ratio of **276** to **277** increased, again in favour of the dihydrofuran, in accordance with the increased activation effect seen from endo oxygen over *exo* oxygen (**Scheme 105**).



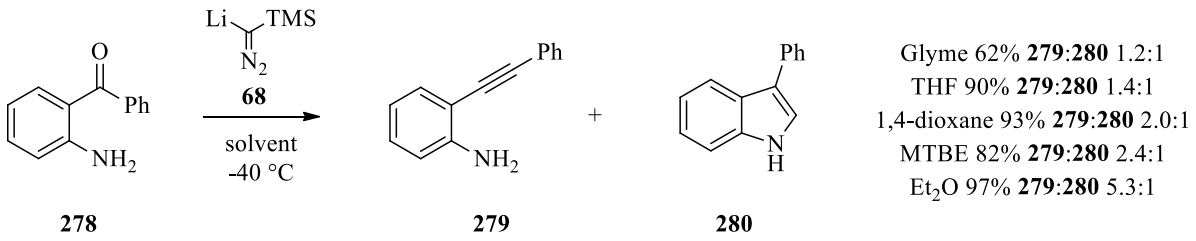
275 **276** **277**

a) $TMSCHN_2$/MeLi, 60%, **276**:**277** 55:45
b) Ph_3PCHCl then KHMDS, 93%, **276**:**277** 91:9

Scheme 105

Taber suggested that the increased selectivity seen is due to carbenes generated via α-elimination being more carbenoid in nature, and their reactivity is tempered by the coordination of metal salts. In this case, this results in an increased regioselectivity in the C-H insertion reaction.

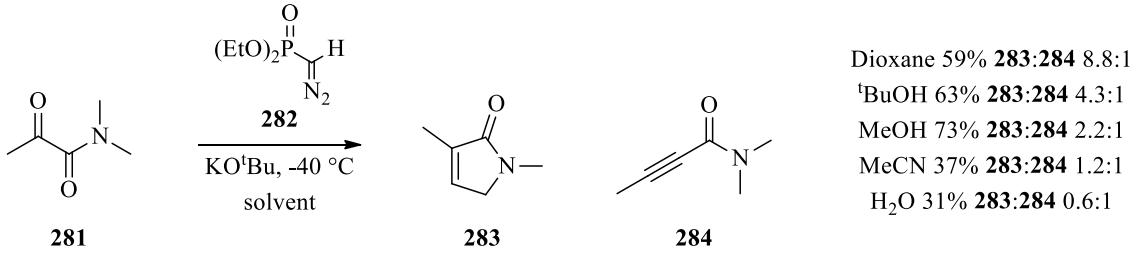
Taber also reported a change in chemoselectivity in a competition between N-H insertion and 1,2-aryl migration, the ratio of which could be altered by changing the reaction solvent.[99] Increasing the polarity of the solvent resulted in the increased formation of indole **280** in comparison to alkyne **279** when generating the alkylidene carbene from **278** (**Scheme 106**).



278 **279** **280**

Scheme 106

Gilbert had previously reported that increasing the polarity of the solvent used for the reaction of **281** with **282**, resulted in an increase in the formation of alkyne **284** via migration, compared to C-H insertion to form 3-pyrrol-2-one **283**, with an eventual reversal of selectivity occurring in water (**Scheme 107**).[100]



281 **283** **284**

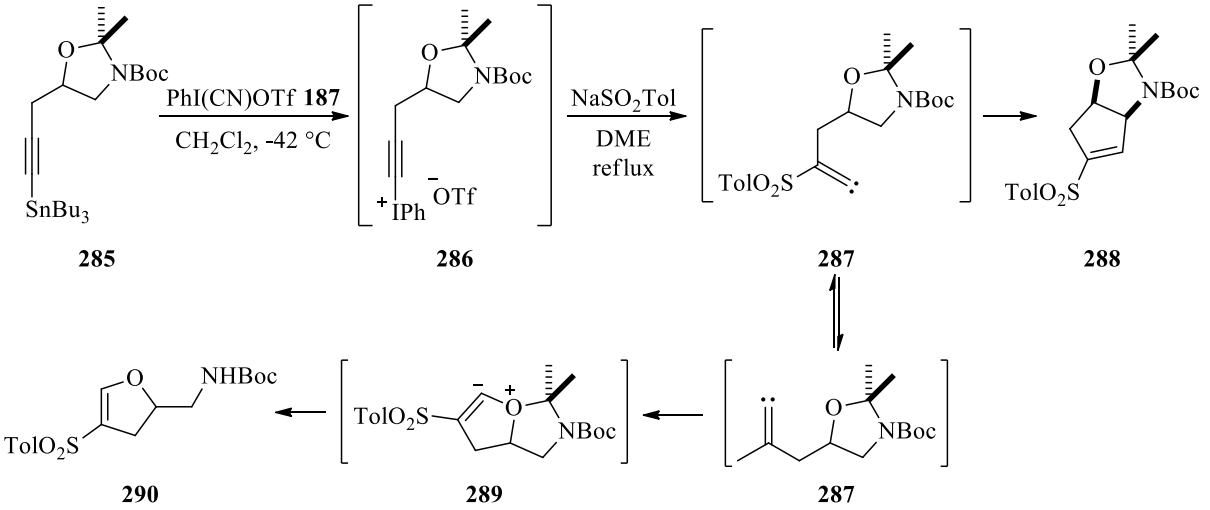
Scheme 107

Gilbert offered no rationale for these results; however Taber postulated that the use of more polar solvents caused a more pronounced change in the hybridisation of the alkylidene carbene. An earlier study by Garcia-Gabiray on alkyl carbenes suggested that less polar solvents could give rise to the triplet state, and thus differing reactivity.[101] However, Taber believed that both **279** and **280** arose from the singlet alkylidene carbene and so suggested that a solvent-induced change of the carbene hydridisation was more likely.

Despite the modest chemo- and regiocontrol achieved by altering the conditions under which the alkylidene carbene is generated, modification of the substrate is generally required in order to significantly affect the selectivity of alkylidene carbenes. In these cases, the observed selectivities are the result of the properties of the substrate undergoing reaction.

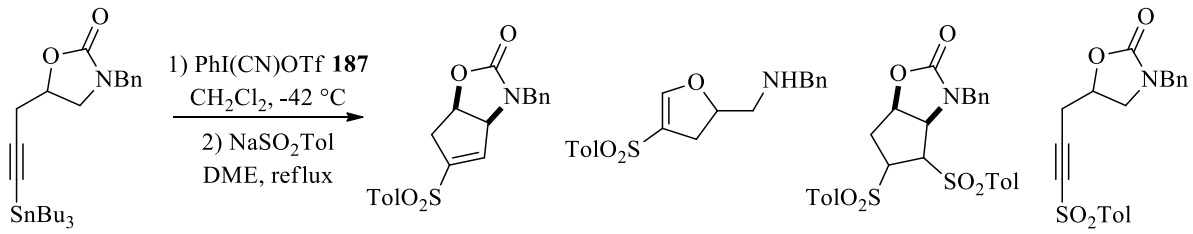
Feldman demonstrated this in his total syntheses of (-)-agelastatin A and (-)-agelastatin B.[22] In the course of these syntheses, it was shown how simple substrate modification can be used in order to achieve greater control in the reactivity of alkylidene carbenes.

Feldman's initial strategy was to synthesis vinyl sulfone **288** through the treatment of alkynylstannane **285** with Stang's reagent **187**, followed by reaction of the crude alkylnyliodonium salt **286** with $NaSO_2Tol$. However, the reaction gave a mixture of two products in very poor yield, with **288** constituting a very small portion of the recovered material. The main product was instead found to be **290**, which arose from capture of alkylidene carbene **287** with the oxygen lone-pair to give oxonium ylide **289** (**Scheme 108**).[22]



Scheme 108

Feldman postulated that replacing the *gem*-dimethyl protecting group with a more electron-withdrawing substituent would reduce the reactivity of the oxygen lone pairs towards the carbene and so the desired C-H insertion reaction would be able to occur. As such, alkynylstannane **291** was synthesised and subjected to the same reaction conditions giving a mixture of products (**Scheme 109**).

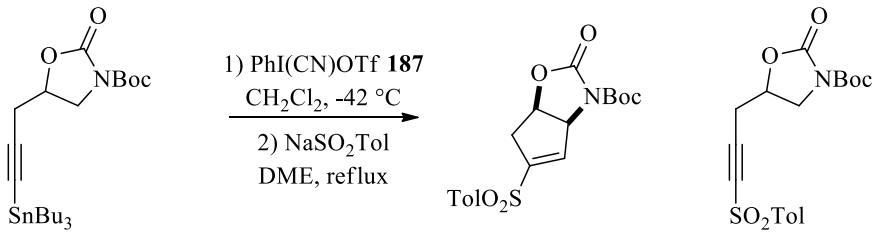


291 **292** 41% **293** 31% **294** 6% **295** <2%

Scheme 109

Feldman proposed that bis-sulfone **294** arose from vinyl sulfone **292** and so had reversed the ratio of C-H insertion/lone pair insertion from 1:3 to 1.5:1. Formation of alkynylsulfone **295** was likely the result of a 1,2-migration of the sulfone in the intermediate alkylidene carbene.

Issues with the later hydrolysis of the oxazalidinone prevented this from being a viable route to the natural products, and so the third route was attempted replacing the *N*-benzyl with *N*-Boc. Alkynylstannane **296** was subjected to the same reaction conditions and a mixture of vinyl sulfone **297** and alkynylsulfone **298** was isolated (**Scheme 110**). No evidence of reaction at the oxygen lone pair insertion was observed.



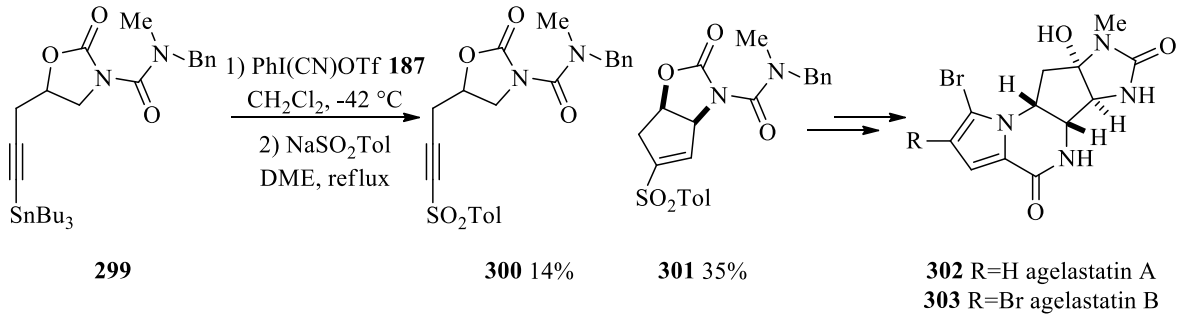
296 **297** 41% **298** 13%

Scheme 110

It was believed that replacing the benzyl protecting group with the Boc group results in the nitrogen lone pair being delocalised into the carbamate moiety, resulting in the oxygen lone pair being delocalised into the oxazolidinone carbonyl functionality. This would result in the oxygen lone pair being less available to interact with the alkylidene carbene, thereby diminishing, or in this case suppressing, the reaction at oxygen. However, the introduction of

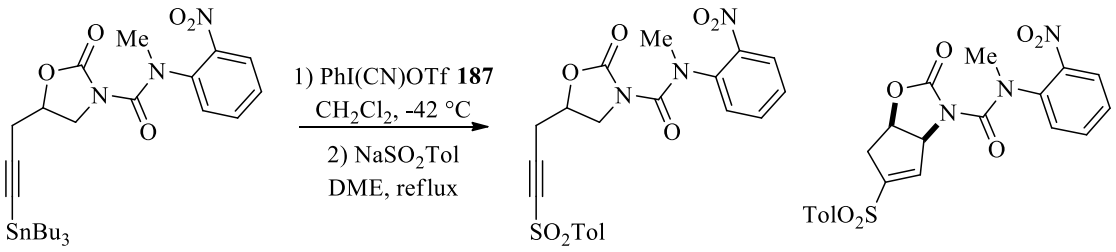
the Boc group most likely also results in the increased formation of alkynylsulfone **298**, as the C-H bond at which insertion is desired is now more electron-deficient (*N*-Boc vs *N*-benzyl) and so the C-H insertion reaction occurs more slowly, allowing the normally slower 1,2-sulfone shift to compete.[22]

Again, issues later in the synthesis forced Feldman to reconsider his approach to both natural products. The lability of the oxazolidinone carbonyl in this case meant a less electron-withdrawing group was required on nitrogen. The use of *N*-urea **299** fulfilled this need and when this substrate was exposed to the alkylidene carbene generation conditions, it could be seen that this change had little effect on the selectivity, with **300** and **301** isolated in similar ratio to that seen with the Boc group. This result suggested that the electronic influence of the urea was not significantly different to the Boc (**Scheme 111**).



Scheme 111

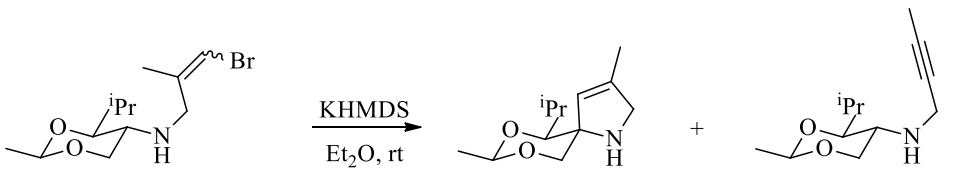
Feldman was able to access the racemates of **302** and **303** from **301**. However, in order to achieve more concise syntheses of the enantiomerically pure natural products, the benzyl substituent on the urea was switched for a *ortho*-nitrobenzyl group. Subjecting **304** to the same reaction conditions demonstrated the effect of introducing a more electron-withdrawing substituent on the C-H insertion reaction as alkynylsulfone **305** was now the major product from the reaction, due to the substantial reduction in the rate of the insertion reaction (**Scheme 112**). Despite this, **306** was converted into (-)-**302** and (-)-**303**.[22]



304 **305** 41% **306** 34%

Scheme 112

Wardrop described how the effect of the geometry of vinyl halides can influence the chemoselectivity of alkylidene carbene reactions.[102] When the mixture of (*E*/*Z*)-**307** was treated with KHMDS in ether, a mixture of dihydropyrrole **308** and alkyne **309** was recovered in a ~1.4:1 ratio. However, when a pure sample of (*E*)-**307** was reacted under the same conditions, the efficiency of the insertion reaction improved, giving the mixture of **308** and **309** in a ~2.7:1 ratio. Conversely, the pure sample of (*Z*)-**307** gave preferential formation of alkyne **309**, in a 3:1 mixture with **308** (**Scheme 113**).[102]



307 **308** **309**

From (*E*/*Z*)-**307** 50%
From (*E*)-**307** 67%
From (*Z*)-**307** 14%

From (*E*/*Z*)-**307** 36%
From (*E*)-**307** 25%
From (*Z*)-**307** 42%

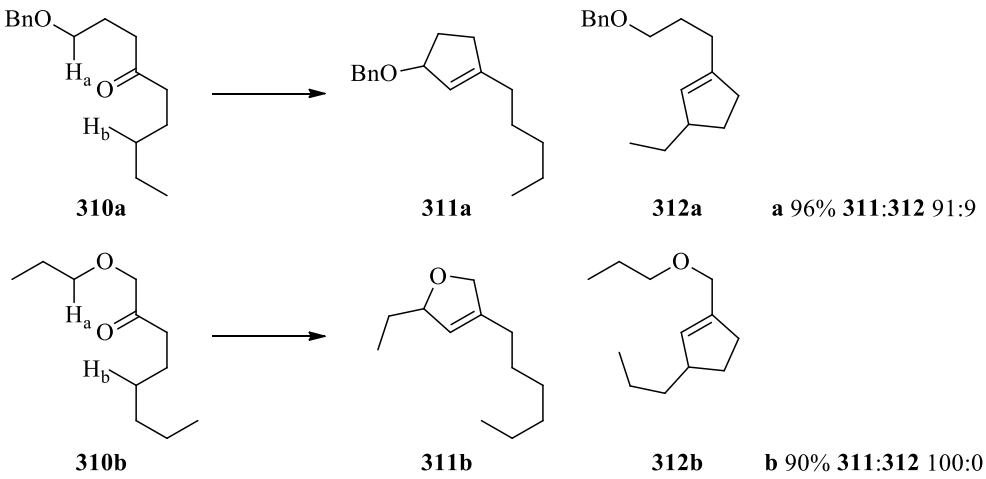
Scheme 113

This result is somewhat surprising as it has generally been shown that the alkene geometry has little effect on the efficiency of C-H insertion reactions.[7a] Wardrop offered no explanation for this unusual phenomenon, however, the subsequent work by Lee[103] suggests that the insertion into the desired C-H bond may be retarded due to the conformation rigidity of the dioxane system, coupled with the proximity of the bulky ^{i}Pr group, allowing the alkyne formation to compete (*vide infra*). However, why the efficiency of this reaction should depend on the geometry of the starting vinyl bromide remains unclear.

Recently, Lee has reported the various effects on the selectivity of C-H insertion reactions, in particular the role of adjacent oxygen atoms.[103] A series of reactions were designed in order to probe the how the selectivity of C-H insertions is affected by electronic, conformational, steric and stereoelectronic effects.

Electronic effect on C-H insertion selectivity

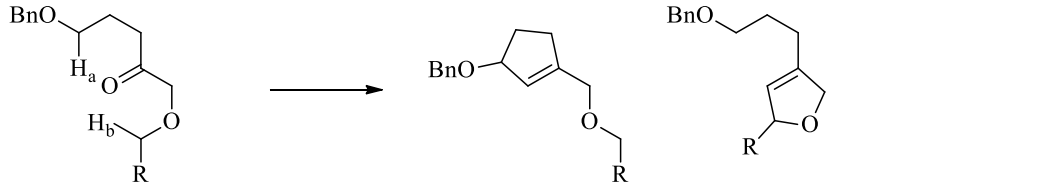
Substrates **310a-k** were designed to investigate how electronic effects controlled the selectivity of 1,5 C-H insertion reactions through a series of competition experiments. The ratio of the products **311** and **312** would offer clues as to the role of the oxygen atom in each case. In all cases, the alkylidene carbene was generated by reacting ketones with lithium (trimethylsilyl)diazomethane **68** in THF.



Scheme 114

It can be seen from the reactions with substrates **310a** and **310b** that there is a clear preference for insertion to occur next to the oxygen atom, with **311a** and **311b** formed in greater proportion (**Scheme 114**). It is also apparent that moving the oxygen so that it becomes *endo* in relation to the new ring increases this selectivity, as C-H insertion at H_b was completely suppressed. This increase in selectivity is believed to be due a Thorpe-Ingold effect, with a smaller C-O-C bond angle in **310b** relative to the C-C-C bond angle in **310a** resulting in a lower energy transition state for insertion into C-H_a.[103b]

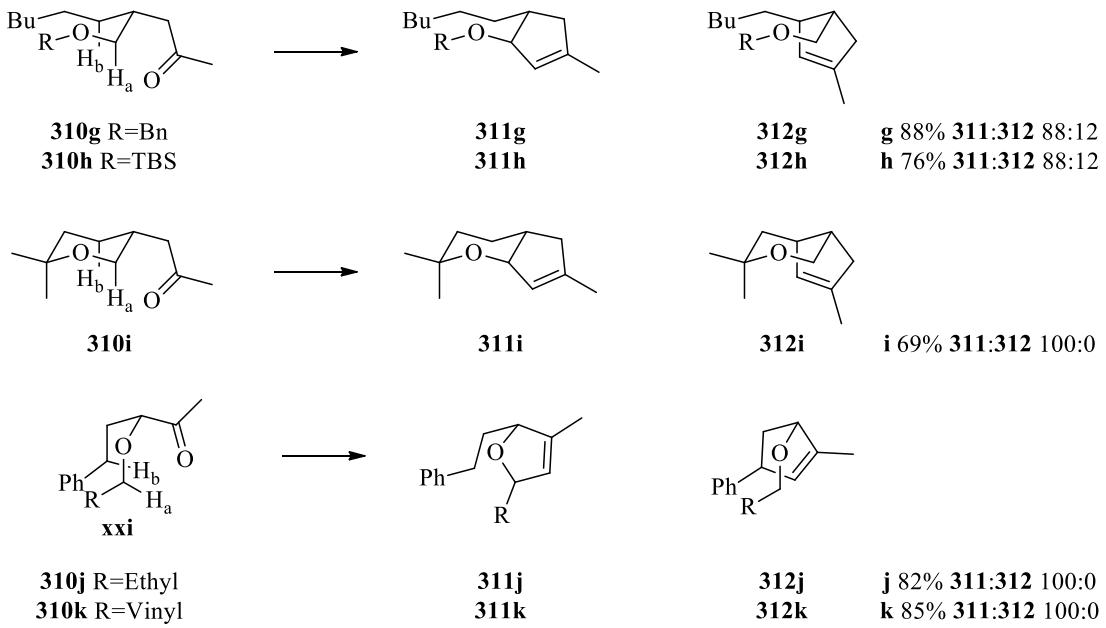
The relative activating effects of two different oxygens were analysed with substrates **310c-f** (**Scheme 115**). The previously seen trend is repeated where R is an alkyl group, with the *endo* oxygen having an increased effect. However, this effect is decreased by switching to the more inductively electron-withdrawing vinyl, ethynyl and OMe. Interestingly, only the inductive properties of the R-groups appeared to affect the selectivity, as the resonance effects, through lone-pair or π-electron donation would be expected to increase the likelihood of insertion at C-H_b.



310c R=Ethyl	**311c**	**312c**	**c** 96% **311**:**312** 33:67
310d R=Vinyl	**311d**	**312d**	**d** 89% **311**:**312** 40:60
310e R=Ethynyl	**311e**	**312e**	**e** 82% **311**:**312** 58:42
310f R=OMe	**311f**	**312f**	**f** 80% **311**:**312** 66:33

Scheme 115

Reaction with β-branched substrates **310g** and **310h** showed that altering the protecting group had no effect when only a single oxygen was present, with mixtures of **311g**/**312g** and **311h**/**312h** being generated in identical ratio. However, the more conformationally rigid **310i**, which has a similar electronic bias to **310g** and **310h**, showed much higher selectivity, giving **311i** exclusively. Similarly, substrates **310j** and **310k** gave only **311j** and **311k**, demonstrating the increased activating effect of an *endo* oxygen in α-branched substrates (**Scheme 116**).[103b]



310g R=Bn
310h R=TBS
311g
311h
312g
312h
g 88% **311**:**312** 88:12
h 76% **311**:**312** 88:12

310i
311i
312i
i 69% **311**:**312** 100:0

310j R=Ethyl
310k R=Vinyl
311j
311k
312j
312k
j 82% **311**:**312** 100:0
k 85% **311**:**312** 100:0

Scheme 116

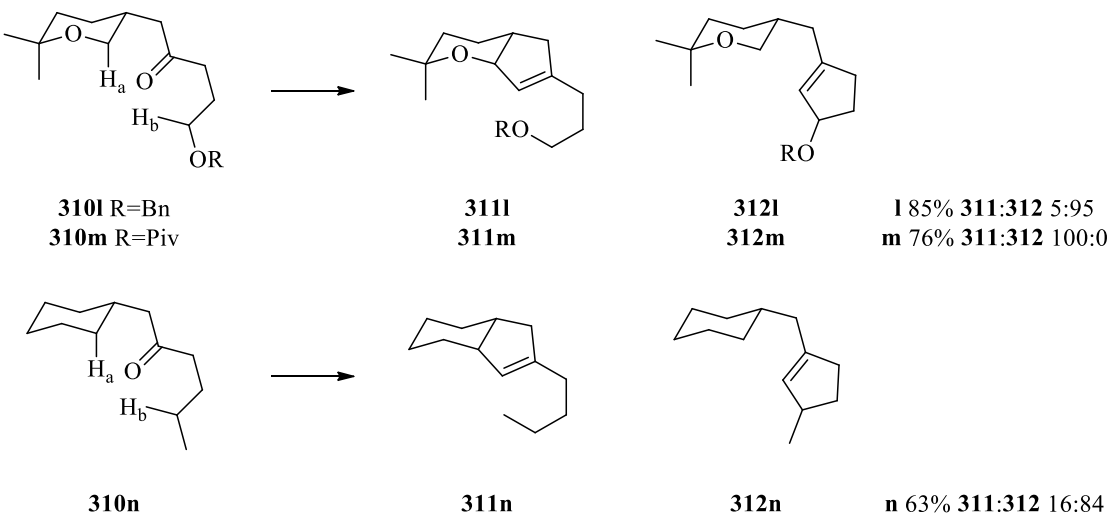
From these results, it can be seen how powerful the activating effect of the oxygen atom is with regards to the selectivity of C-H insertion reactions, especially if the oxygen will be located within the newly formed ring. However, the effect of the *endo* oxygen can be controlled, and the use of even mildly electron-withdrawing groups can result in an *exo* oxygen being a stronger activator.

Conformational Effect on C-H insertion selectivity

In order to ascertain the conformational effects on the selectivity of 1,5 C-H insertion reactions, a series of substrates **310l-s** were utilised which contained two potential reaction sites, one in a cyclic environment and one in an acyclic environment. It was believed that the selectivity of C-H insertion should be determined by the different conformational environments between the acyclic and cyclic reaction sites.

The reaction of pyran **310l** gave rise to a mixture of products, with insertion into C-H_b occurring preferentially. Conversely, replacing the benzyl substituent with the electron-withdrawing pivaloyl reversed this selectivity, with **311m**, the product of insertion into C-H_a, formed exclusively. In order to determine the conformational effects without the presence of

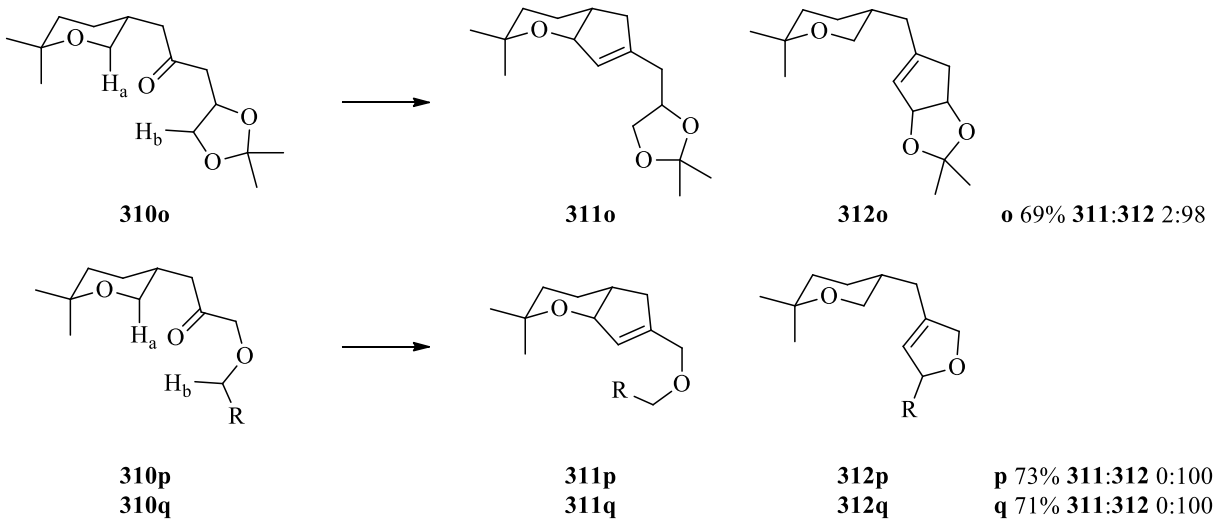
an activating oxygen, the reaction was performed on **310n**, which demonstrated preferential insertion into the acyclic portion of the molecule (**Scheme 117**).[103b]



Scheme 117

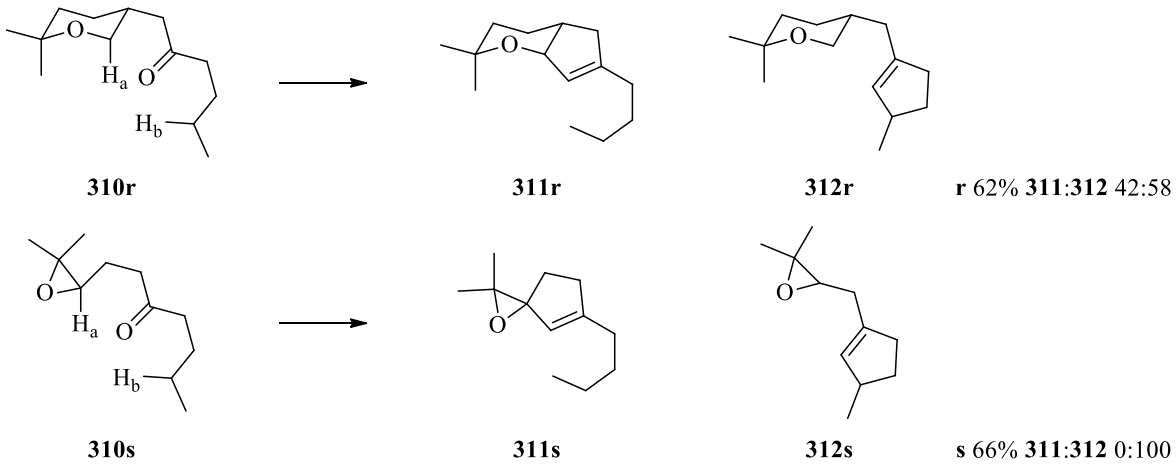
From these results Lee was able to draw two conclusions. Firstly, it is clear insertion into the more conformationally constrained C-H_a is a much slower process than insertion into the acyclic C-H_b in both the cyclohexyl and pyran systems. Additionally, Lee concluded that the activating effect of oxygen is more apparent in an acyclic environment than constrained systems. This is demonstrated by the higher selectivity for C-H_b insertion in **310l** than in **310n**. It can also be seen that this conformational effect is relatively subtle, as evidenced by the reversal of selectivity in **310m**.

In order to compare the relative conformational effects within 5 and 6 membered rings, the reaction was performed on **310o**. Lee reports that only a slight difference in reactivity was expected due to the subtle conformational differences between the two ring systems. However, **312o** was formed with near complete selectivity. Additionally, the enhanced effect of an *endo* oxygen was demonstrated with the exclusive formation of **312p** and **312q** from **310p** and **310q** respectively, compared to the result for **310l** (**Scheme 118**).



Scheme 118

Further evidence of the decreased activation from oxygen in conformationally constrained system was obtained from the reaction of substrate **310r**, where the slight preference for the formation of **312r** suggests that reaction at the unactivated acyclic C-H_b occurred faster than at C-H_a. It was also demonstrated that C-H_a in epoxide **310s** is entirely unreactive towards C-H insertion, with no evidence of **311s** seen. Lee postulated that this was due in part to the larger bond angle between C-H_a and the carbene, as well as the increased s-character of the C-H_a bond resulting in a stronger bond (**Scheme 119**).

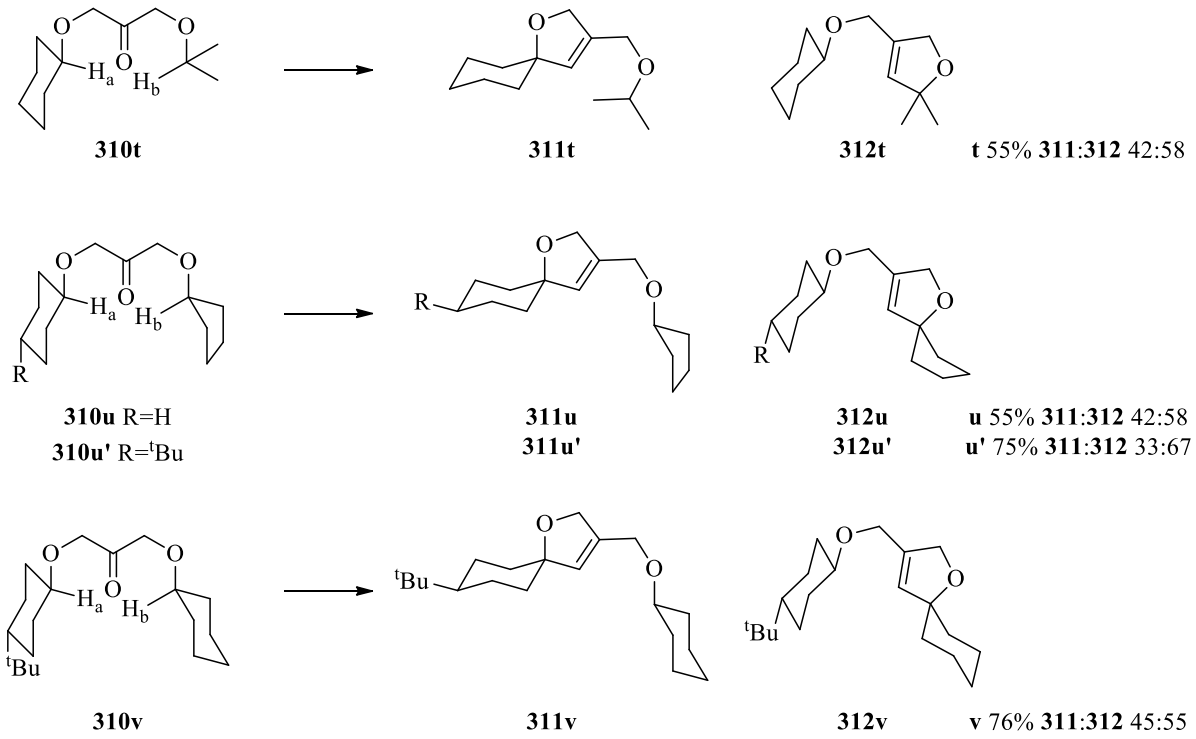


Scheme 119

Steric Effect on C-H insertion selectivity

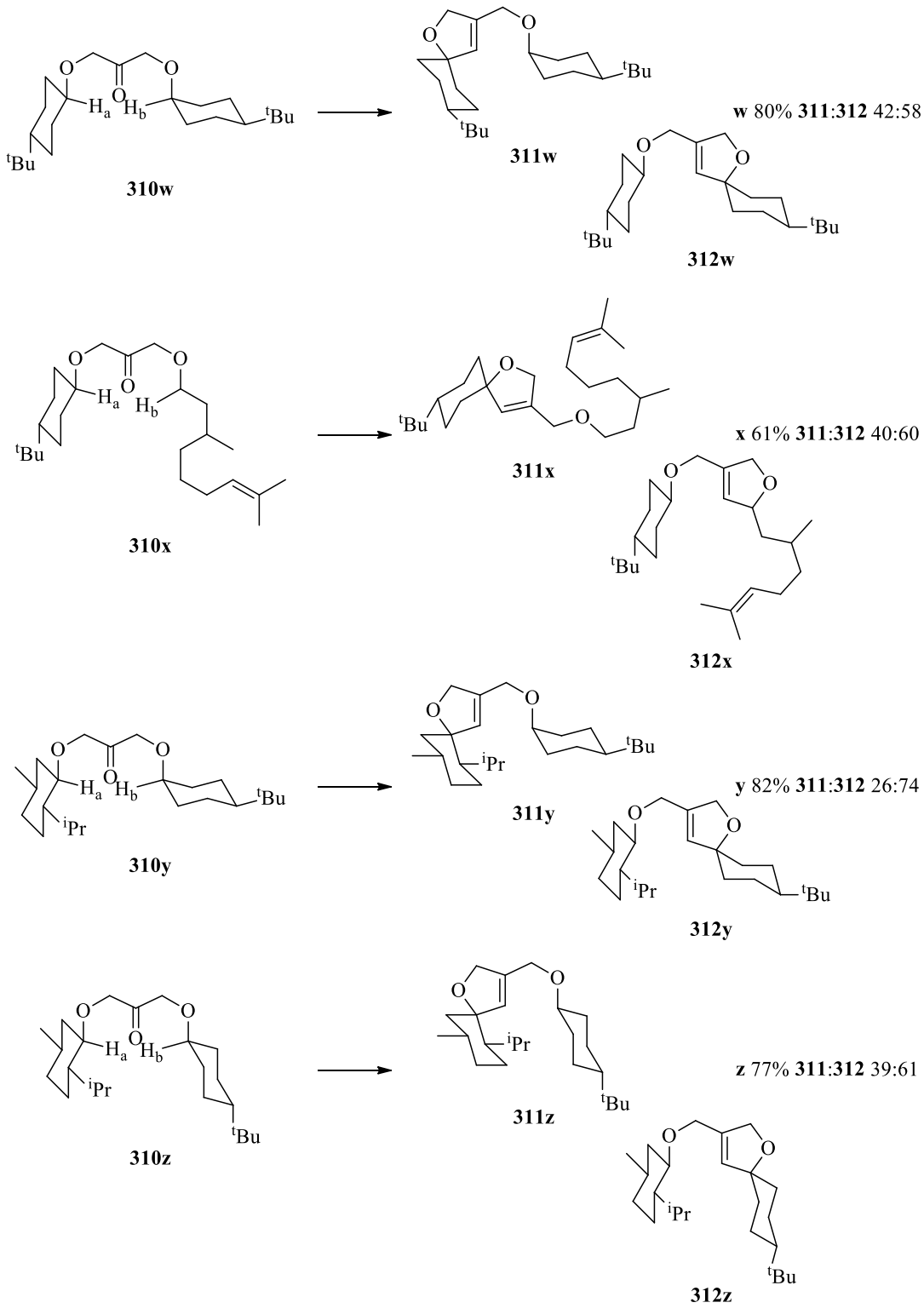
Lee continued to describe a series of experiments which would offer insight into the effects of sterics on C-H insertion reactions. It was argued that, due to the lack of steric encumbrance of an alkylidene carbene, that sterics would have a lesser role to play than electronics, however it may still play a role. As such, the reactions were performed on substrates **310t**-**z**.

The reaction of **310t** again demonstrated the diminished reactivity of C-H bonds in conformationally rigid systems, with **312t** forming in slight preference, through insertion into C-H_b. Additionally, the competition between tertiary C-H bonds in 5 and 6-membered rings in **310u** showed a preference for insertion into the 5-membered ring, forming **312u** as the major product. This selectivity was increased by adding a ^{t}Bu group to the cyclohexyl ring in **310u'**, increasing the constraint in the system, with the mixture of **311u'** and **312u'** containing **312u'** as the major product. The effect of the substituent on the cyclohexyl ring can further be seen in **310v**, where a slight preference is seen insertion into the ring without the addition substitution (**Scheme 120**).



Scheme 120

The reaction of **310w** demonstrated the first example where the selectivity could be influenced purely by sterics, and insertion into the less sterically hindered equatorial C-H_b was marginally more favourable, giving **312w** as the major isomer. The reaction of **310x** showed more favourable insertion into the secondary C-H_b over the tertiary C-H_a giving a mixture of **311x** and **312x** in a 40:60 ratio. This is surprising as C-H insertion into tertiary C-H bonds is usually favoured due to electronic factors.[94, 97] Substrate **310y** demonstrated that moving the steric encumbrance closer to the reactive site decreased the reactivity towards C-H insertion, as the mixture of **311y** and **312y** was found to be in a 26:74 ratio, the result of preferential insertion into the sterically less hindered C-H_b. A diminished selectivity was seen when both potential insertion sites were axial, as **310z** gave a 39:61 ratio of **311z** and **312z** (**Scheme 121**).[103b]



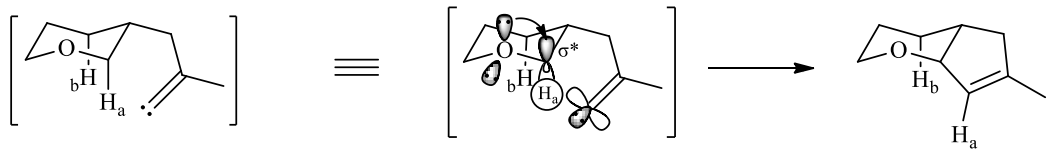
Scheme 121

From these results, Lee inferred that steric effects can play a role in determining the selectivity of C-H insertion reactions by reducing the rate at which insertion occur in more

sterically hindered environments. However, it can also be seen that this effect is minimal compared to electronic and conformational effects.[103b]

Stereoelectronic Effect on C-H insertion selectivity

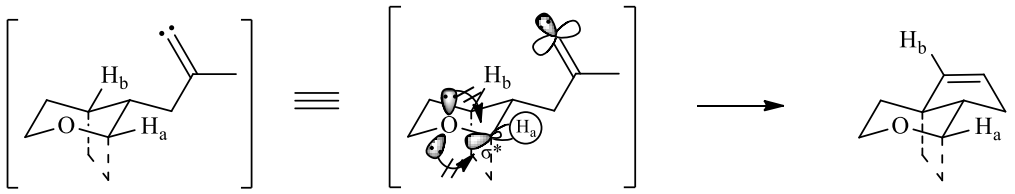
From the results that suggested a diminished activating effect of oxygen when it was contained within a cyclic system (e.g. **310l** and **310r**), Lee postulated that the directionality of the oxygen lone pair electrons in relation to the C-H bond involved in the insertion reaction must play an important role.[103] In alkylidene carbene **313**, Lee proposed that the most important orbital interaction would be the axial non-bonding orbital of the oxygen and the σ* orbital of the axial C-H_a bond. If this stereoelectronic effect was important, **313** should give **314** as the major product, via inserting selectively into the axial C-H_a bond as this would be more electron-rich in nature due to n(O)→σ*(C-H_a) electron delocalisation (**Scheme 122**).[103]



313 **314**

Scheme 122

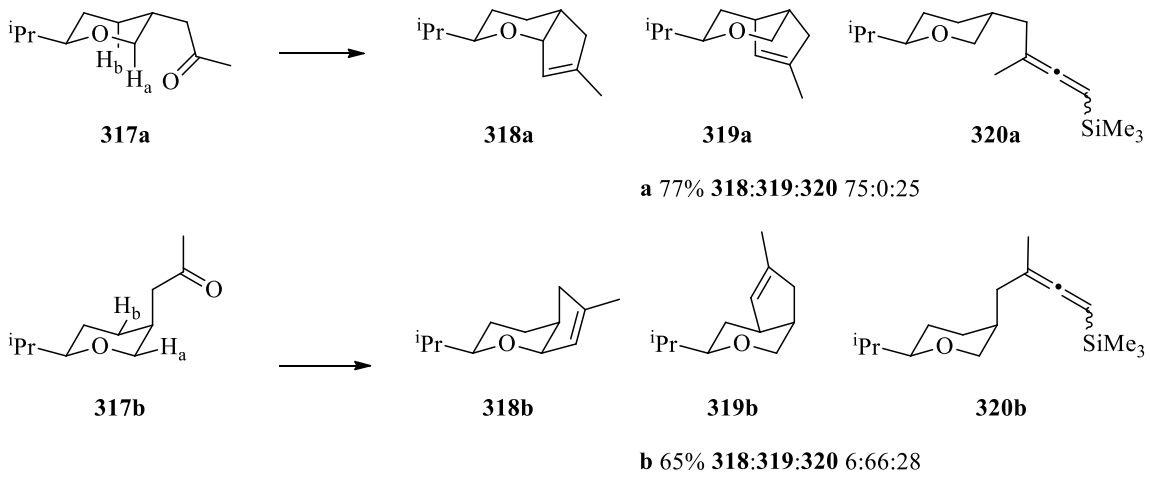
Conversely, Lee suggested that carbene **315** would be expected to react preferentially with C-H_b to give **316**. Due to poor orbital overlap, the electron-delocalisation n(O)→σ*(C-H_a) would be diminished, leading the oxygen to deactivate the C-H_a bond inductively (**Scheme 123**).[103]



315 **316**

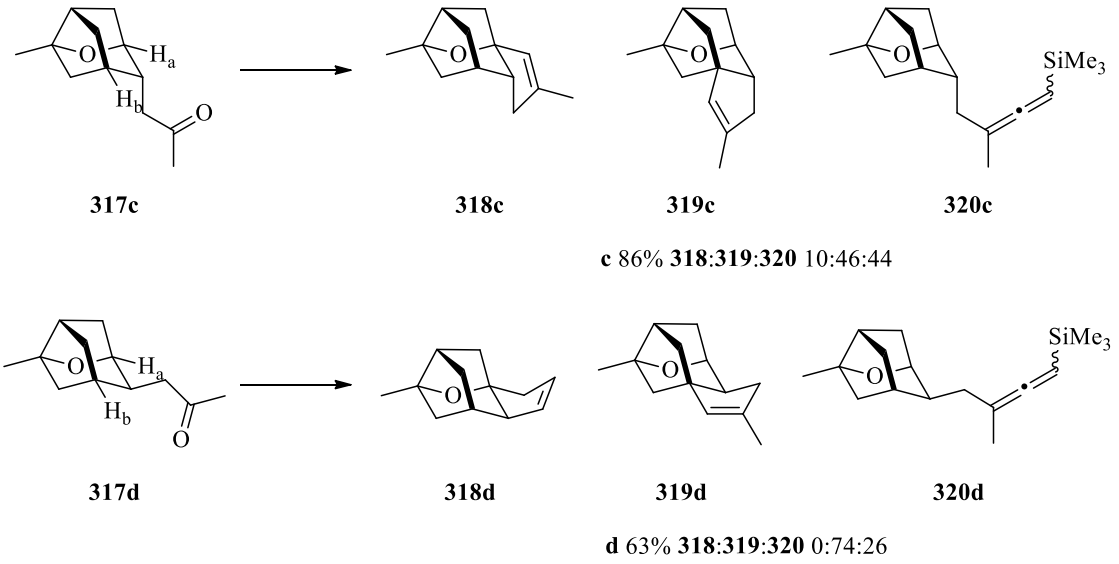
Scheme 123

In order to investigate this hypothesis, Lee designed two pairs of conformationally rigid diastereoisomers, **317a**/**317b** and **317c**/**317d**, which would display the insertion behaviour of **313** and **315**. As expected **317a** underwent selective insertion into C-H_a, giving **318a,** with no evidence of **319a** observed. It should also be noted that allenylsilane **320a** was observed as a significant product from the reaction. Conversely, **317b** gave a mixture of **318b** and **319b** in a 1:11 ratio, along with allenylsilane **320b**.



Scheme 124

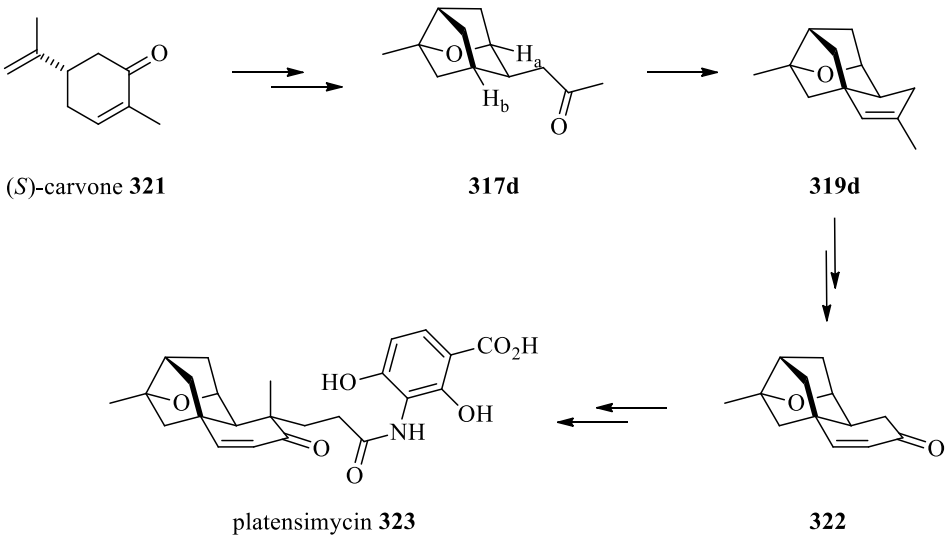
The reaction of substrate **317c** gave a mixture of **318c** and **319c** in 1:5 ratio, while **317d** gave **319d** exclusively. Both substrates were devoid of axial hydrogens. Allenylsilanes **320c** and **320d** were also observed in the respective reactions (**Scheme 125**).



Scheme 125

The preferred formation of **319c** and **319d** through insertion into the apparently less activated C-H_b bond was deemed to be due to the stereoelectronic effect that Lee had previously proposed.[103] The formation of allenylsilanes **320a-d** was thought to be due to an intermolecular process that occurs because of the lower reactivity of C-H bonds in conformationally constrained systems compared with those in more flexible systems.[103b] Lee was able to selectively synthesise these interesting functionalities by altering the reaction conditions.

Lee was able to exploit this selectivity in the synthesis of the core of the natural product platensimycin **323**, gaining rapid access to tetracycle **322** from (*S*)-carvone **321** (**Scheme 126**).

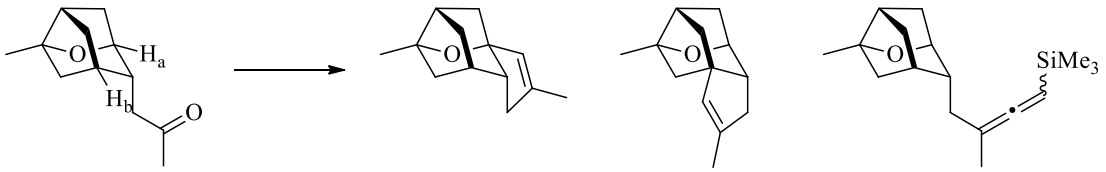


Scheme 126

The work by Lee *et al*. has offered significant insight into the role played by oxygen in affecting the selectivity of 1,5 C-H insertion reactions as well as addressing how various other subtle changes can drastically alter how this reaction proceeds.

As has already been described (**Scheme 124**, **Scheme 125**), Lee reported the formation of allenylsilanes in the reactions of substrates where the C-H required for insertion was relatively unreactive. These allenylsilanes **320a-d** were believed to arise via an intermolecular reaction of the intermediate alkylidene carbene. Feldman had also reported the prevalence of a seemingly less favourable reaction occurring in cases where the C-H required for insertion was relatively unreactive, with the synthesis of alkynylsulfones via 1,2-migration.[22]

By increasing the relative amount of $TMSCHN_2$ and $^{n}BuLi$ in the reaction, as well as increasing the reaction concentration, Lee was able to form **320c** preferentially (**Scheme 127**).

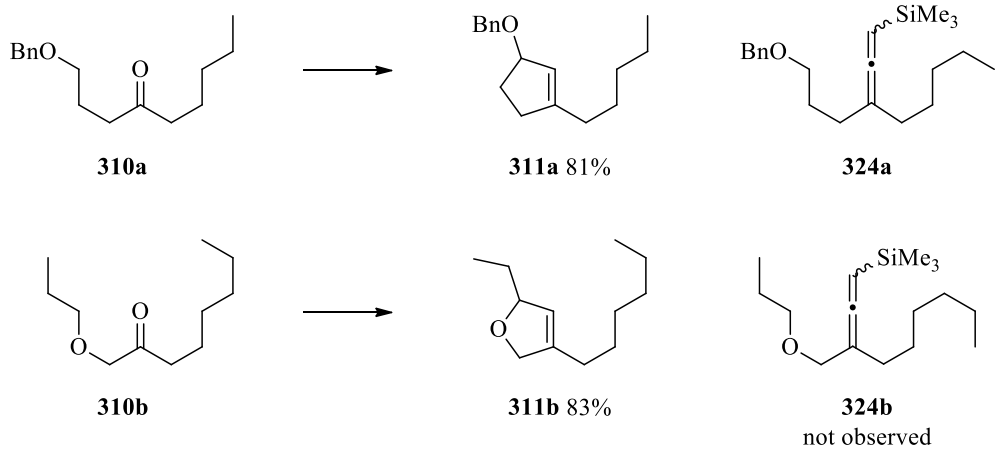


317c **318c** **319c** **320c**

$TMSCHN_2$ (1.6eq), ^nBuLi (1.7eq), 0.02M, -78 °C - rt 86% **318**:**319**:**320** 10:46:44
$TMSCHN_2$ (3eq), ^nBuLi (2eq), 0.06M -78 °C - rt 75% **318**:**319**:**320** 0:8:92

Scheme 127

Lee believed that a lower rate of C-H insertion was necessary for allenylsilane formation to occur as the reaction of substrates **310a** and **310b**, where the adjacent oxygen atoms promote C-H insertion, showed no evidence of **324a** and **324b** (**Scheme 128**).[103b]

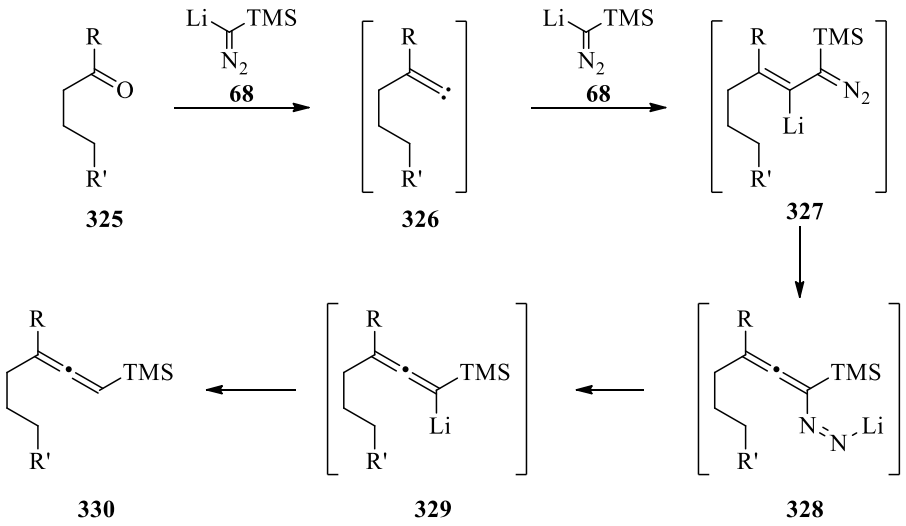


310a **311a** 81% **324a**

310b **311b** 83% **324b** not observed

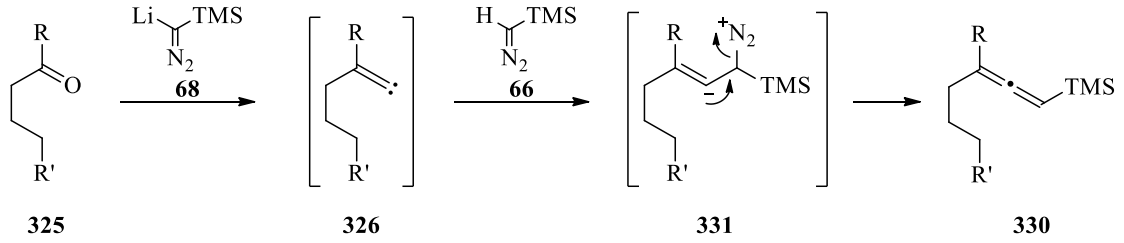
Scheme 128

Lee proposed that one of two intermolecular processes could explain the formation of the allenylsilanes. After the initial reaction between ketone **325** and **68** to give alkylidene carbene **326**, this can then react with a second molecule of **68** to generate adduct **327**. The loss of nitrogen via **328** would give the lithiated allenylsilane **329** which would lead to **330** upon protonation (**Scheme 129**).



Scheme 129

Alternatively, carbene **326** could react with free trimethylsilyldiazomethane **66** to form adduct **331**. Subsequent elimination of nitrogen would result in the formation of allenylsilane **330** (**Scheme 130**).

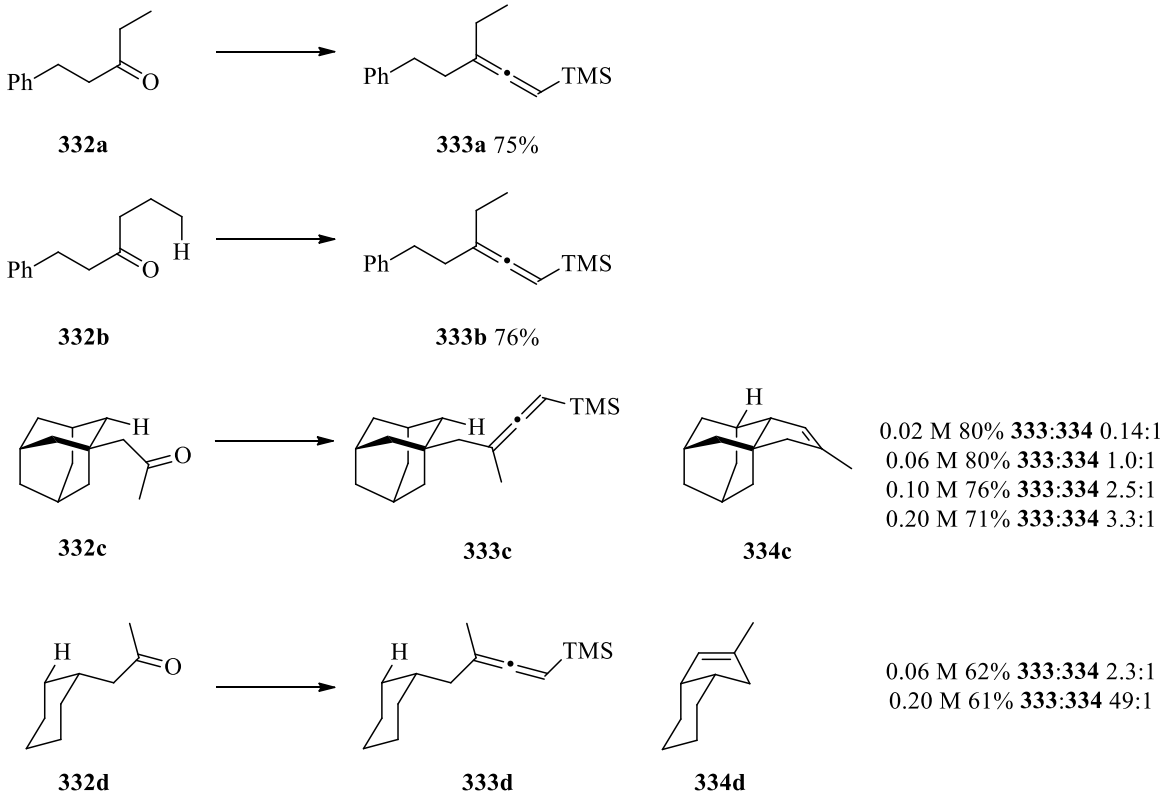


Scheme 130

Lee noted that increasing the amount of **66** in the reaction led to a proportional increase in the formation of allenylsilanes, while increasing the amount of the lithium derivative **68** led only to a minor yield improvement, suggesting that the mechanism in **Scheme 130** is the one by which the allenylsilane is formed.

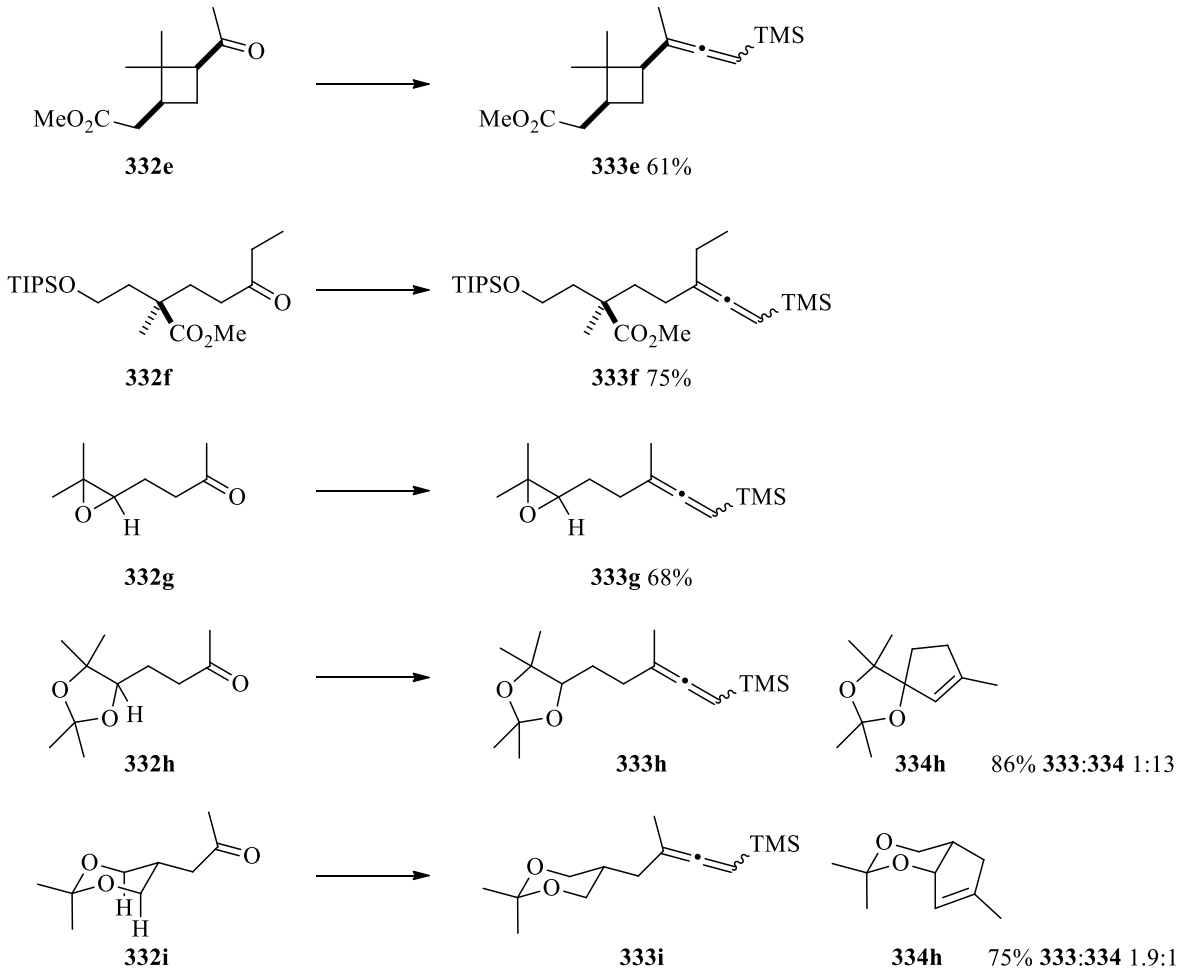
Lee then applied these conditions to a series of substrates (**Scheme 131**). It is interesting to note that **332b**, which has a potential 1,5 C-H insertion site, the allenylsilane **333b** was formed selectively. Substrates **332c** and **332d** gave a mixture of allenylsilane

formation and 1,5 C-H insertion, the ratio of which could be altered by varying the reaction concentration.



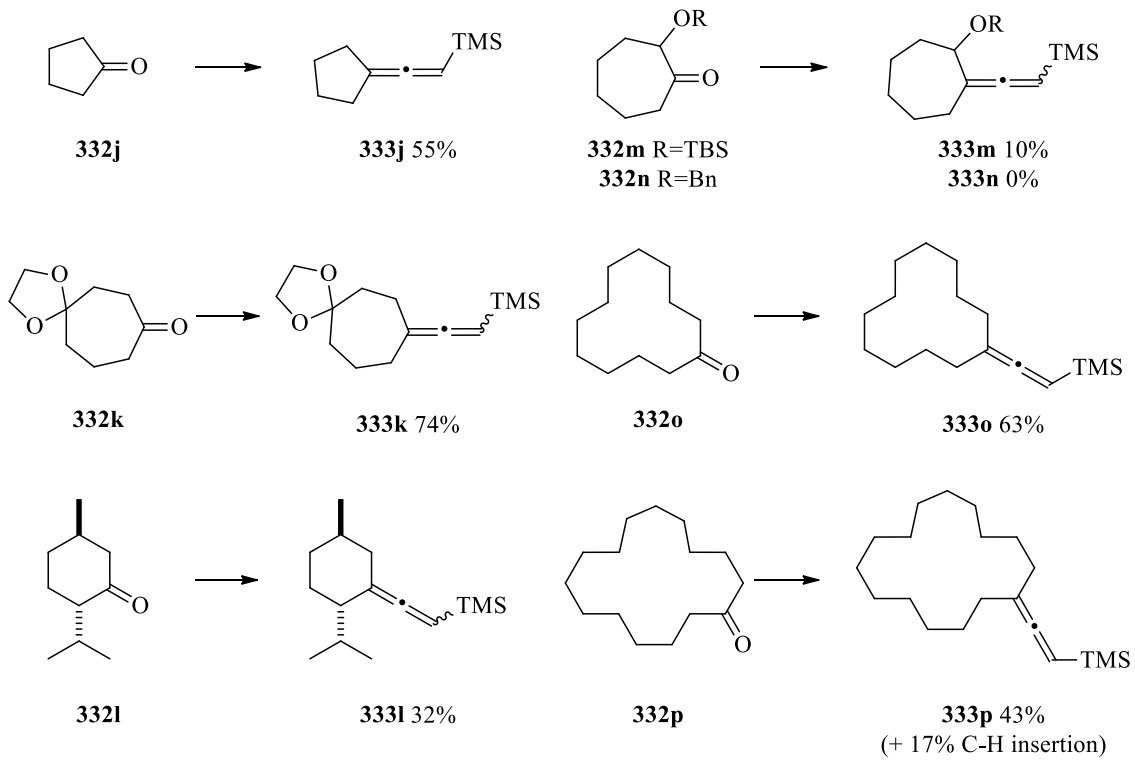
Scheme 131

The reaction was also able to encompass a range of functionalities, with substrates containing esters, silyl groups and strained ring systems giving the allenylsilanes in good yield (**Scheme 132**). Interestingly, similar effects that had governed the regioselectivity between competing C-H insertions also appeared to control the chemoselectivity in this instance, as epoxide **332g** showed no reactivity towards C-H insertion, while dioxolane **332h** showed a strong preference for C-H insertion reaction. Dioxane **332i** gave a mixture with a slight preference for allenylsilane formation. These results further demonstrate how subtle differences around a C-H bond can drastically affect its reactivity, allowing other pathways to compete and potentially dominate.



Scheme 132

Small- and medium-sized cyclic ketones proved to be good substrates due to the lack of competing C-H insertion reaction sites (**332j** and **332k**). However, substrates bearing α-substituents gave either poor yields or no reaction (**332l**, **332m**, and **332n**). Additionally, while 12-membered ring ketone **332o** gave allenylsilane **333o** exclusively in good yield, the 15-membered ring ketone **332p** gave a 2.5:1 mixture of allenylsilane **333p** and C-H insertion (**Scheme 133**).

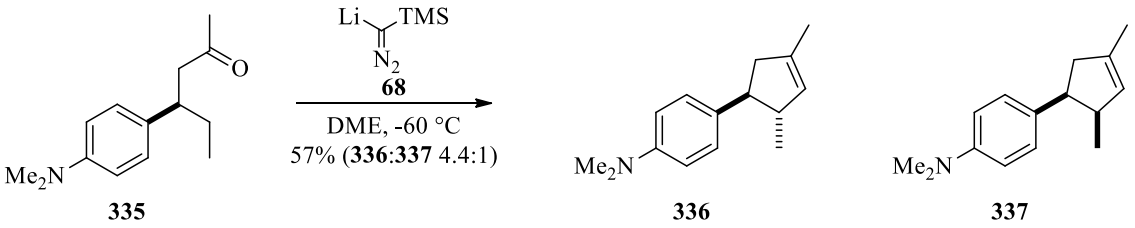


Scheme 133

The work carried out by Lee and Feldman demonstrate clearly how subtle differences to the environment in which a C-H bond is located in can result in drastic changes to the chemo- and regioselectivity of reactions of the alkylidene carbene. It is also clear that the conditions under which the alkylidene carbene is generated can also have a profound effect on selectivity.

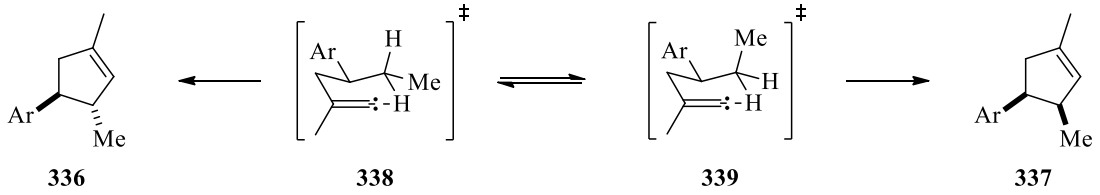
1.4.2 Diastereoselectivity

In 1994, Taber reported the first diastereoselective 1,5 C-H insertion reaction, synthesising cyclopentenes **336** and **337** as a 4.4:1 mixture of diastereoisomers, from ketone **335** (**Scheme 134**).[104]



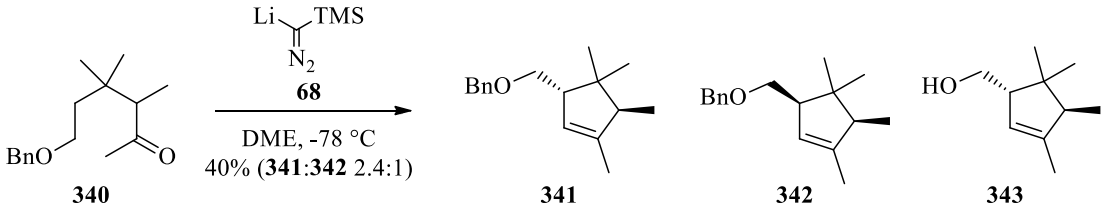
Scheme 134

Taber proposed that this selectivity arose from more favourable interactions within the transition state of the insertion reaction (**Scheme 135**). It was calculated that transition state **338**, with the methyl group in a pseudoequatorial position, was 1.5 kcal/mol lower in energy than **339**, resulting in the formation of the *anti* isomer **336** being more favourable than the *syn* isomer **337**.[105]



Scheme 135

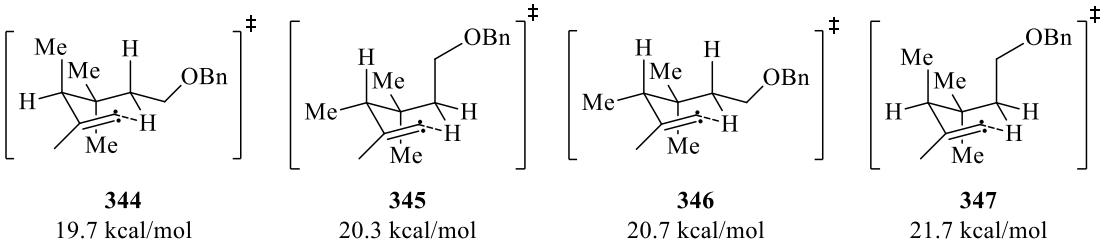
Taber also reported 1,3 diastereomeric induction in the reaction of ketone **340** to form cyclopentenes **341** and **342** in a 2.4:1 ratio (**Scheme 136**).[106] Taber utilised this diastereoselectivity in the total synthesis of α-necrodol **343**.[106]



Scheme 136

Taber proposed four possible transition states **344**-**347** for the 1,5 C-H insertion reaction (**Figure 4**). Calculations showed that **344** and **345**, which would lead to the *trans* product, were lower in energy than either **346** or **347**, which give the *cis* product. It is notable

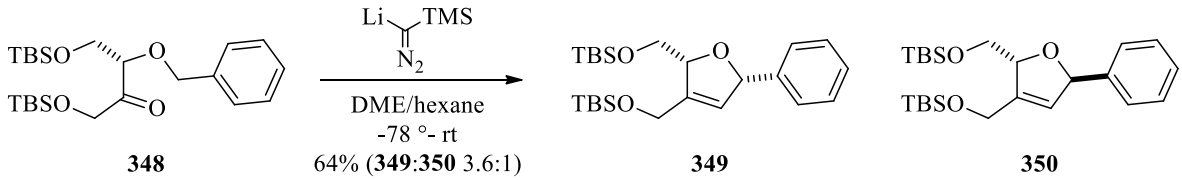
that **346**, with two pseudoequatorial substituents, is thought to be less stable that either **344** or **345**, which each contain one pseudoaxial substituent. This is believed to be due to the increased *gauche* interactions in **346** between the *gem*-dimethyl group and both pseudoequatorial substituents.[106]



344 19.7 kcal/mol | **345** 20.3 kcal/mol | **346** 20.7 kcal/mol | **347** 21.7 kcal/mol

Figure 4

Similarly, Wills reported 1,3 diastereomeric induction in the synthesis of dihydrofurans **349** and **350** from ketone **348** (**Scheme 137**).[107]



348 64% (**349**:**350** 3.6:1) **349** **350**

Scheme 137

Proposing similar transition states **351-354** to Taber,[105-106] Wills argued that the formation of **349** was more favourable due to the diminished steric interactions present in **351** by having both the CH_2OTBS and phenyl groups in pseudoequatorial positions (**Figure 5**).[107]

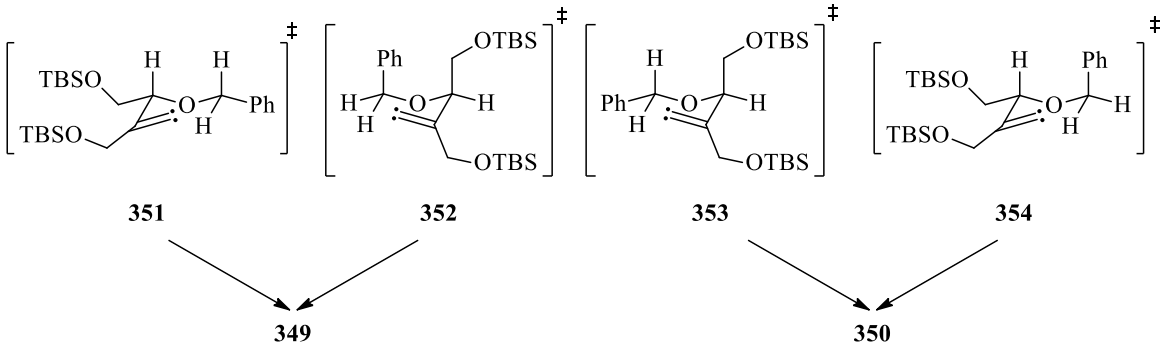
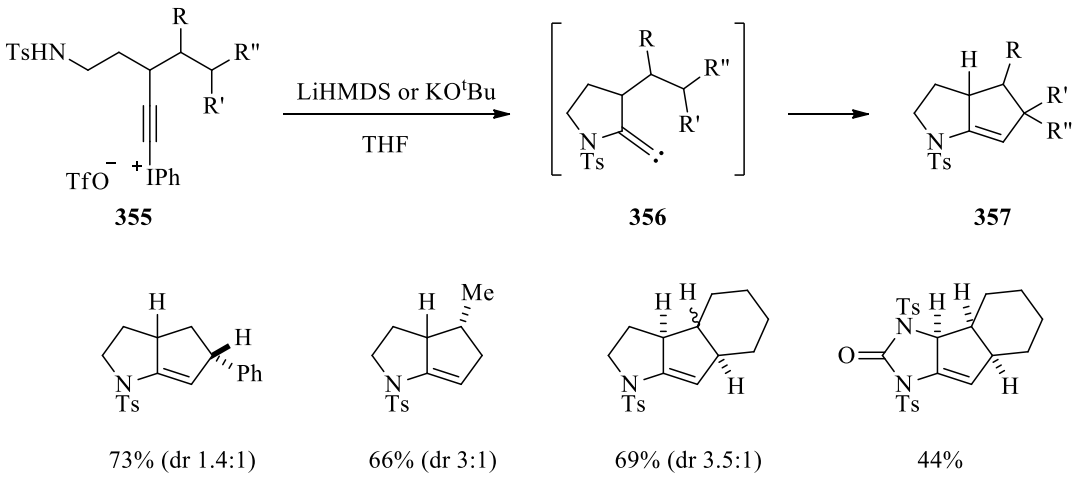


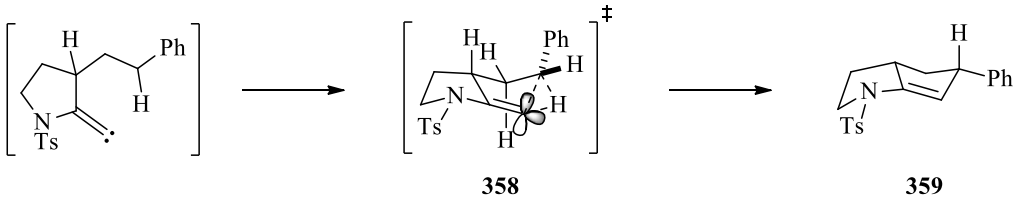
Figure 5

The manner in which subtle differences can affect the diastereoselectivity of the C-H insertion reaction can best be seen in the bicyclisation of alkynyliodonium salts with tethered nucleophiles. Treatment of sulfonamides **355** with base resulted in the alkaloid skeleton **357**, via nucleophilic attack with subsequent 1,5 C-H insertion of the resulting alkylidene carbene **356** (**Scheme 138**).[71a]



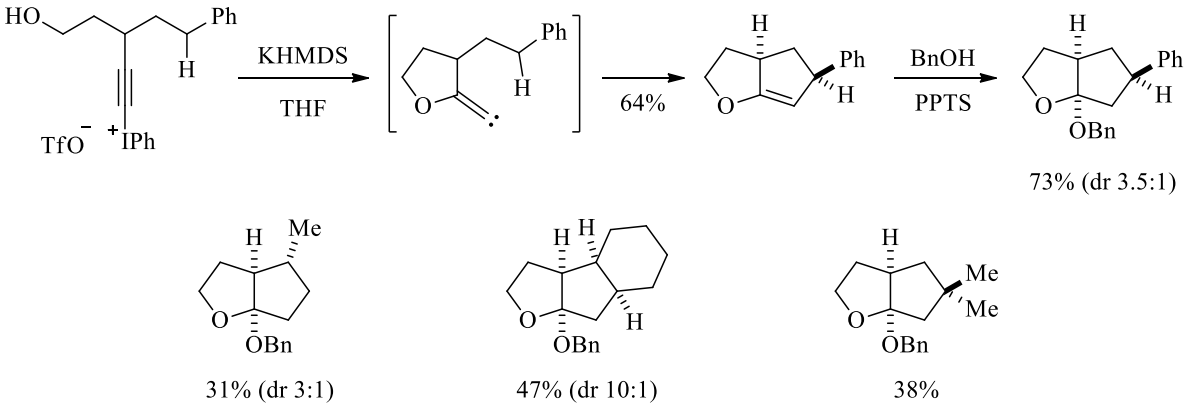
Scheme 138

The diastereoselectivity of the reaction was explained in terms of the transition state **358**,[6] where the steric interactions between the non-hydrogen group on C-5 and the rest of the molecule are minimised, leading to the major product **359** (**Scheme 139**).



Scheme 139

However, when the sulfonamides were replaced with alcohols, the resulting fused tetrahydrofurans were formed with higher diastereoselectivity (**Scheme 140**).[71b]



Scheme 140

Feldman argued that the alkylidene carbene generated in the oxygen system was less electrophilic than that in the nitrogen examples, and so was less reactive towards C-H insertion. This would result in a later, more product-like transition state where the steric interactions would be more apparent, resulting in higher diastereoselectivity.

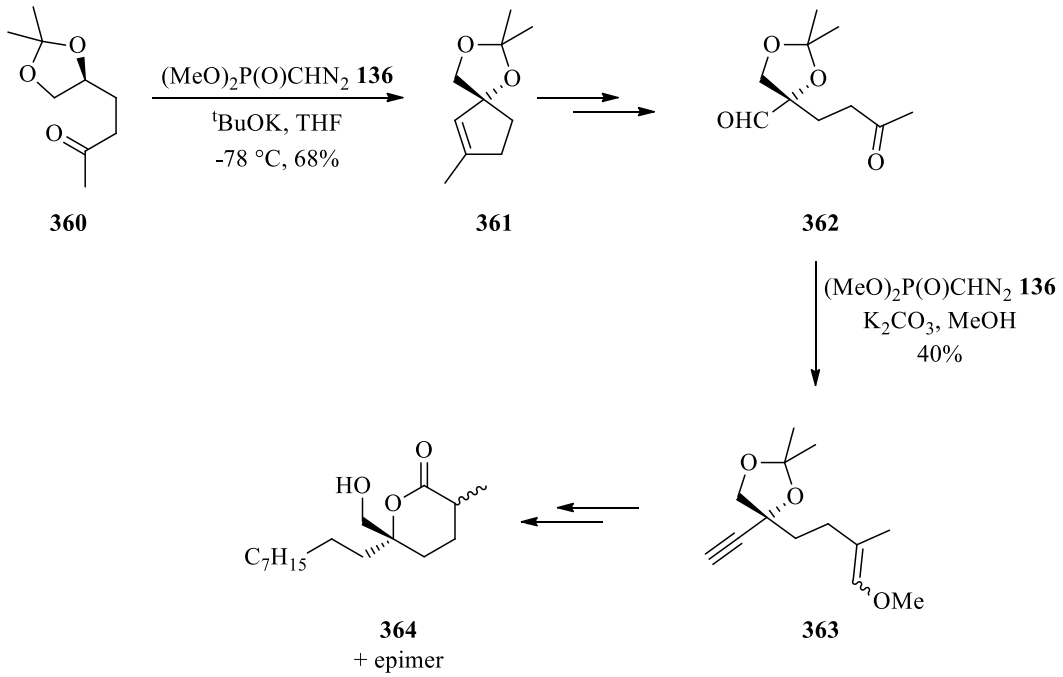
Again, this selectivity displays the sensitivity alkylidene carbenes have to the environment a C-H bond is located in. The energy differences between the transition states proposed by Taber[105-106] are by no means excessive, and yet reasonable diastereoselectivities are obtained.

1.5 Alkylidene carbenes in natural product synthesis

Due to their versatility and ease of generation, coupled with their high levels of selectivity, alkylidene carbenes have seen widespread use in the synthesis of a range of natural products. The natural products that alkylidene carbenes have been to synthesis or in studies towards their synthesis includes, but is not limited to: 14,15-dehydroforskolin,[108] (-)-discodermolide,[109] esperamicinone,[110] octalactin A and B,[111] tetronomycin,[112] (-)-neplanocin A,[113] oxo-*T*-cadinol,[114] (+)-cassiol,[105] (-)-haliclonadiamine,[115] (-)-morphine,[116] tetrodotoxin,[7e] and (+)-majusculone.[117]

However, Ohira's synthesis of (-)-malyngolide **364** best represents the versatility of alkylidene carbenes in natural product synthesis.[118] The cyclisation to from spirocycle **361**

from ketone **360**, via 1,5 C-H insertion, was later followed by the generation of **363** from δ-keto aldehyde **362** (**Scheme 141**). The aldehyde functionality is converted to the alkyne, while the methyl enol ether arises from the methanol solvent quenching the alkylidene carbene formed at the ketone position. This is possible due to the lack of a good migrating group and a feasible C-H insertion site. Additionally, the formation of spirocycle **361** again demonstrated the retention of stereochemistry associated with the C-H insertion reaction of alkylidene carbenes.



Scheme 141

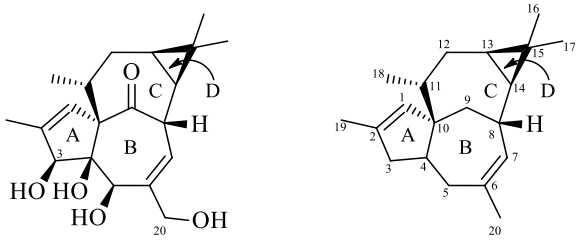
In conclusion, alkylidene carbenes are versatile reactive intermediates for organic chemists. A wide range of methods allow for their generation under a number of conditions, and their strict selectivity allows for the generation of useful functionalities which could otherwise require complex methods to install. In particular, the generation of alkynes from aldehydes and cyclopentene rings from ketones have become widely utilised reactions in organic synthesis. This concise route to cyclopentene rings also allows ease of access to cyclohexenones through an oxidative cleavage of the double bond followed by an

intramolecular aldol and dehydration sequence.[103a] Additionally, quaternary stereocentres can easily be produced from tertiary centres, with full retention of stereochemistry.

1.6 Previous and Proposed Work

1.6.1 Ingenol

Ingenol **366** (**Figure 6**) is a tetracyclic, highly oxygenated diterpene which was isolated from the *Euphorbia ingens* species of the *Euphorbiaceae* plant by the Hecker *et al*. in 1968.[119] Various esters, for example the 3,20-dibenzoate analogues (ingenane numbering **367** (**Figure 6**)),[120] of this natural product have been demonstrated to mimic diacylglycerol and behave as endogenous activators of protein kinase C (PKC).[121] Additionally, they have been found to exhibit a variety of biological activities including anti-tumour or tumour-promoting,[122] anti-leukaemia,[123] anti-HIV,[124] pro-inflammatory,[125] and molluscicidal properties.[126] This wide range of biological activity suggests that an efficient total synthesis of ingenol could be greatly beneficial to the development of new therapeutic agents.

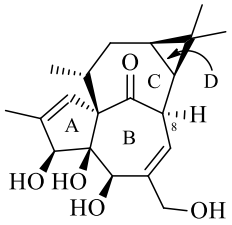


366 **367**

Figure 6

In addition to its biological importance, ingenol presents an formidable structural challenge, in particular the polyoxygenated upper face of the AB ring system, and the unusual *trans*-fused bicyclo[4.4.1]undecane BC ring junction.[127] Efficient synthesis of this inside-outside intrabridgehead stereochemistry, which places strain on the molecule,[128] is the most challenging obstacle to a successful synthesis of ingenol. Attempts to avoid this strained ring system have resulted in the synthesis of derivatives of isoingenol **368** (**Figure 7**), the epimer

at C-8. These artificial isomers, while more easily accessible, are completely devoid of biological activity,[129] demonstrating the importance of the inside-outside stereochemistry.



368

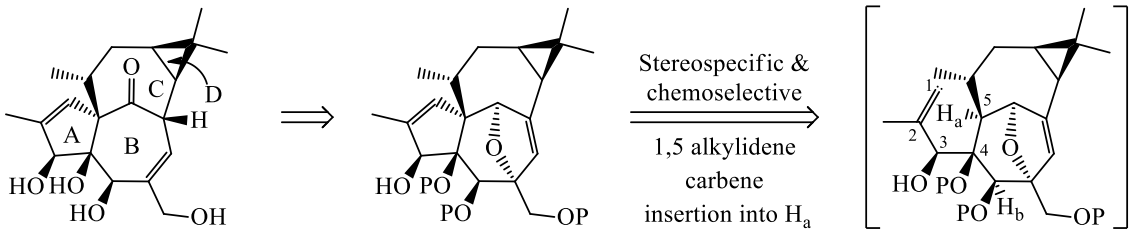
Figure 7

The daunting nature of this synthetic challenge is demonstrated by the scarcity of successful methods for generating this rare stereochemical motif. To date, only work reported by Winkler,[130] Funk,[131] Rigby,[132] Kigoshi,[133] Wood,[134] and Cha[135] has described the successful synthesis of the *trans* stereochemistry required for the total synthesis of ingenol, with Winkler,[136] Kuwajima[137] and Wood[138] describing total syntheses of ingenol, while Kigoshi[139] described an enantiomerically enriched formal synthesis. Wood's synthesis is the only reported total synthesis of enantiopure (+)-ingenol. Additionally, Kigoshi has described the synthesis of 13-oxyingenol and its derivatives.[140]

1.6.2 Grainger group approach to ingenol

While a variety of different and elegant routes have been employed in the synthesis of ingenol, all previous syntheses involved the initial construction of the carbocyclic system followed by lengthy incorporation of the appropriate functionality, leading to inefficient syntheses, with the shortest total synthesis of ingenol being 32 steps.[138]

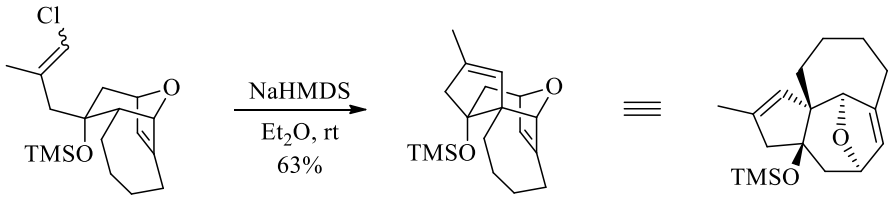
The Grainger group has sought to streamline this process by introducing the oxygen functionality concurrently with the construction of the tetracyclic core. Key to this strategy is a proposed stereospecific and chemoselective 1,5 C-H insertion of an alkylidene carbene **369** to form the AB ring junction with the correct stereochemistry (**Scheme 142**).



366 **369**

Scheme 142

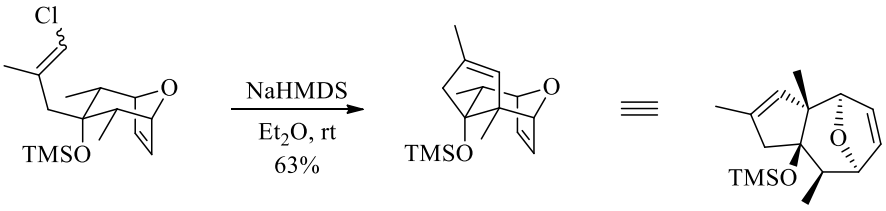
Grainger and Owoare previously described the selective synthesis of tetracycle **267** from vinyl chloride **266** via a selective C-H insertion into the tertiary C-H (**Scheme 143**).[97] This approach allowed access to the to the ABC ring system of ingenol, with the correct stereochemistry at the AB ring junction.



4 **5**

Scheme 143

Similarly, the base induced insertion of vinyl chloride **370** gave tricycle **371** in moderate yield (**Scheme 144**).[97]



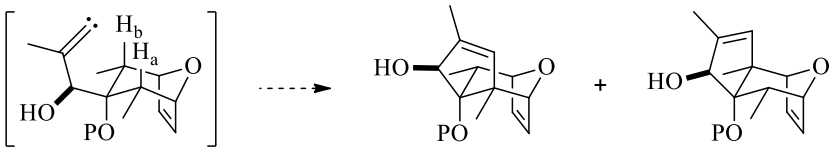
370 **371**

Scheme 144

While studies in the Grainger group had demonstrated the feasibility of employing a 1,5 alkylidene carbene C-H insertion reaction in the synthesis of the carbocyclic core of ingenol, they did not address the presence of a hydroxyl group on the A-ring. In order to

introduce the oxygen functionality in the A ring on a fully functionalised BCD ring system, an alkylidene carbene such as **369** is required (**Scheme 142**).

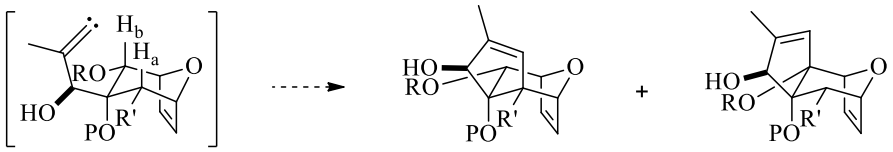
Initially, it was decided to employ a model system, using the 2,4-dimethyl substituted oxabicyclic system to investigate the feasibility of such a proposal (**Scheme 145**). The presence of the stereocentre within the alkylidene carbene **372** renders the two potential C-H insertion sites diastereotopic, leading to the possibility of two diastereoisomers **373** and **374** being formed. The ratio of these two diastereoisomers could offer insight into the directing effect of the oxygen substituent, allowing for these factors to be included in a potential synthesis of ingenol.



372 **373** **374**

Scheme 145

As the total synthesis of ingenol via this route would require an additional oxygen on the bicyclic system, a second model system was proposed (**Scheme 146**). The reaction of alkylidene carbene **375** could potentially lead to cyclopentenols **376** and **377**, with **376** being the preferred product for the total synthesis of ingenol.



375 **376** **377**

Scheme 146

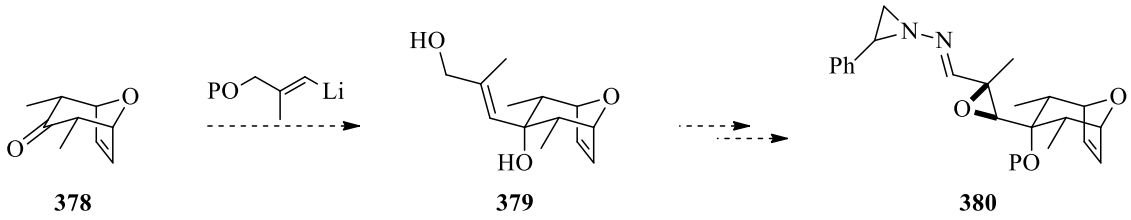
It was hoped that these model systems would offer insight into whether the use of hydroxyl substituted alkylidene carbenes could potentially be employed in a synthesis of

ingenol, through an investigation of the chemo-, regio- and diastereoselectivity of alkylidene carbene 1,5 C-H insertion reactions on 8-oxabicyclic ring systems.

Chapter two – Diastereoselective C-H insertion reactions

2.1 Proposed synthetic route

From the wide array of methods available for the generation of alkylidene carbenes, it was thought that the thermolysis of α,β-epoxy-*N*-aziridinylimines[55] would offer the most direct access to the desired alkylidene carbene. This method would lead directly to a cyclopentenol, removing the need for subsequent allylic oxidation of a cyclopentene after the 1,5 C-H insertion had occurred. As such, **380** was identified as the alkylidene carbene precursor required for the initial investigation. It was envisaged that **380** could be accessed *via* initial nucleophilic addition of a vinyllithium reagent to bicyclic ketone **378** to give diol **379**. Functional group interconversion should then allow access to **380** (**Scheme 147**).



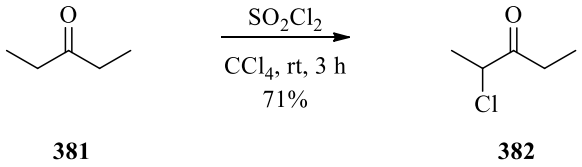
378 **379** **380**

Scheme 147

2.2 Synthesis of starting materials

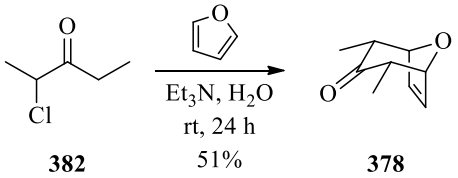
2.2.1 Synthesis of bicyclic ketone 378

Ketone **378** was synthesised *via* a known [4+3] cycloaddition reaction between α-chloroketone **382** and furan.[141] The α-chloroketone **382** was prepared by treating pentan-3-one with SO_2Cl_2 (**Scheme 148**).[141] Initially, the reaction was performed in DCE in order to avoid the use of CCl_4, the solvent used in the literature. However, this gave 2-chloropentan-3-one **382** in 54% yield, substantially lower than the 80% reported in the literature.[141] Additionally, significant quantities of the various α-dichloro isomers were present as a mixture with the final product, even after purification by distillation. As such the reaction was repeated in CCl_4, giving **382** in a more acceptable 71% yield, with no further purification needed.



Scheme 148

Ketone **382** was subsequently employed in a [4+3] cycloaddition reaction with furan, in the presence of Et_3N, to give bicyclic ketone **378** in 51% yield, comparable with the yield reported in the literature (**Scheme 149**).[141b] The pure product was isolated by crystallisation of the crude reaction mixture.



Scheme 149

Both these reactions could be performed on a large scale allowing access to large amounts of **378** in a fairly short period of time.

2.2.2 Synthesis of vinyl iodides

Vinyl iodides **383**, **384** and **385** (**Figure 8**) were all targeted as potential precursors to the desired vinyllithium reagent, as all three had been used in the presence of BuLi.[142] Additionally, all three protecting groups could subsequently be removed under relatively mild conditions giving access to diol **3**. As such, all three were investigated as possible nucleophile precursors.

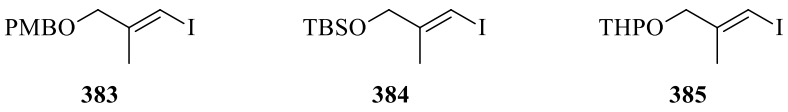
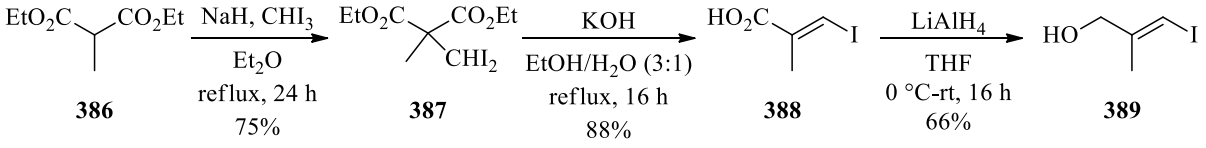


Figure 8

All three targets were readily accessible from allyl alcohol **389**, which in turn could be synthesised in 3 steps from commercially available diethyl methylmalonate **386** *via* a known literature procedure.[143] Alkylation of **386** with iodoform gave **387** in 75% yield. Treatment of **387** with KOH gave acid **388** in 88% yield, through a tandem hydrolysis-decarboxylation-elimination process. Subsequent reduction with $LiAlH_4$ gave the desired allyl alcohol **389** in 66% yield (**Scheme 150**).

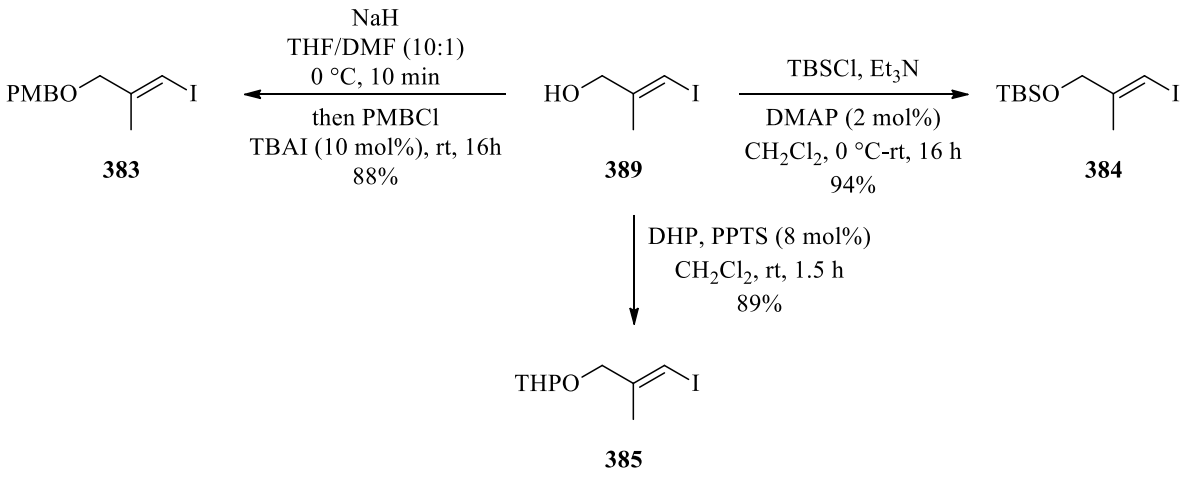


386 **387** **388** **389**

Scheme 150

^{1}H NMR indicated that the elimination reaction gave only one geometric isomer and nOe experiments on **389** confirmed the exclusive formation of the (*E*) isomer. While both **387** and **388** could be purified by vacuum distillation and column chromatography respectively, both crude products proved to be sufficiently clean to be used directly in the subsequent reactions.

Protection of the alcohol functionality in **389** allowed for the formation of **383**, **384** and **385** in excellent yields. Treating **389** with NaH followed by addition of PMBCl gave **383** in 88% yield,[144] while **384** was synthesised in 94% yield by reacting **389** with TBSCl, using DMAP as a catalyst.[145] **385** could readily be synthesised by treating **389** with DHP in the presence of catalytic PPTS (**Scheme 151**).[142e]



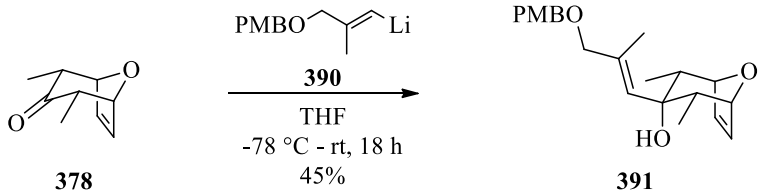
Scheme 151

2.3 Addition to ketone 378

Due to the conformational rigidity of the oxabicyclic framework, nucleophilic addition was expected to occur from the less hindered *exo* face of the ketone **378**, affording the axial alcohol.[146]

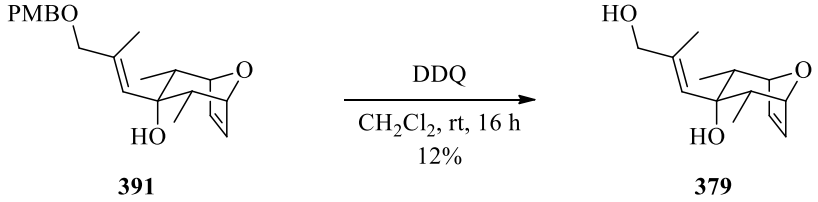
Initial studies focused on the use of the PMB protected vinyl iodide **383**. As selective access to both the free alcohol and its TMS ether of azirindinylimine **380** (**Scheme 147**) was desirable, the use of the PMB protecting group would allow for selective deprotection to the primary alcohol in the presence of the tertiary OTMS, should it be required.

Thus, bicyclic ketone **378** was treated with a slight excess of vinyllithium **390**, generated from pre-mixing equimolar amounts of **383** and ^{n}BuLi, to afford the mono-protected diol **391** (**Scheme 152**). Performing the reaction with 1.2 equivalents of the vinyllithium gave only 6% isolated yield of the desired product, however increasing this to 1.5 equivalents gave the desired product in 45% yield.



Scheme 152

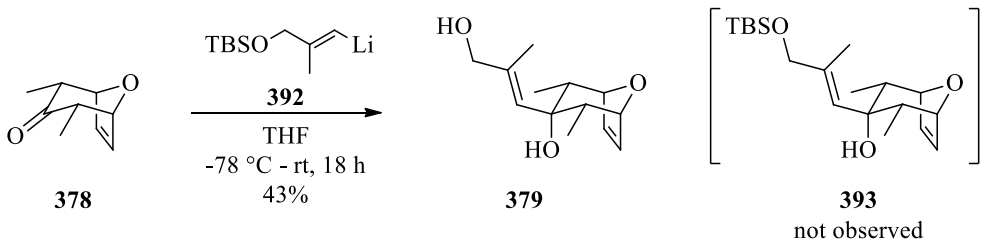
Subsequent removal of the PMB group was then attempted using DDQ (**Scheme 153**).[147] However, **379** was isolated in only 12% yield.



Scheme 153

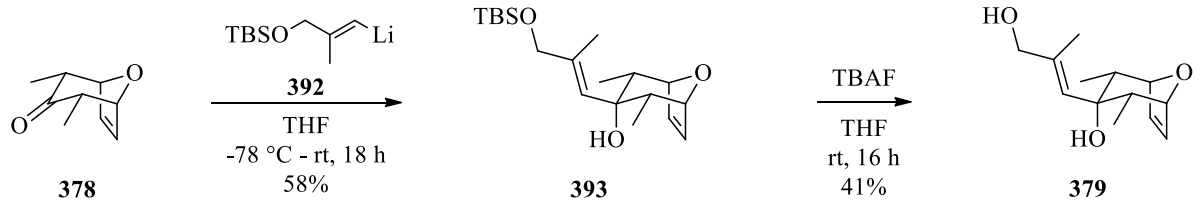
This poor result meant that the addition reaction with **383** was not optimised further and subsequent work focused on the use of other vinyl iodides.

Reacting ketone **378** with 1.5 equivalents of vinyllithium **392** initially gave no formation of **393**, with no conversion observed by TLC analysis. In this instance, the cooling bath was left in place for 3 h after the addition of ketone **378**, and so the reaction was repeated and the cooling bath removed immediately after the addition of the ketone **378**. Diol **379** was isolated from the reaction in 43% yield, with no evidence of the mono-silylated product **393** (**Scheme 154**). It should be noted that **378** was not fully consumed in the reaction.



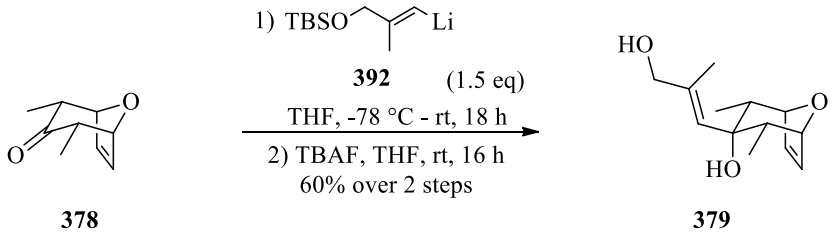
Scheme 154

Changing the reaction work-up from HCl to NH_4Cl resulted in the formation of **393** in 58% yield. Subsequent removal of the silyl protecting group with TBAF afforded **379** in 41% yield (**Scheme 155**).[148]



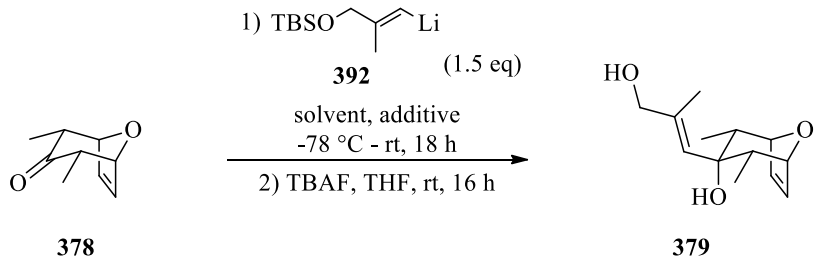
Scheme 155

The removal of the silyl protecting group was attempted on the crude product from the addition reaction. Under these conditions, **379** was isolated in 60% yield over two steps (**Scheme 156**).



Scheme 156

Attempts were made to optimise the addition to **378** by first altering the aggregation state of the organolithium reagent (**Scheme 157**, **Table 1**), as less aggregated organolithium reagents are known to be more reactive.[149] As such, the reaction was performed using Et_2O as the reaction solvent (**Entry 2**) as well as adding TMEDA to the reaction mixture to break up the lithium aggregates formed (**Entries 3 and 4**). However, these conditions offered no increase in yield, and unreacted ketone **378** was recovered in all cases.



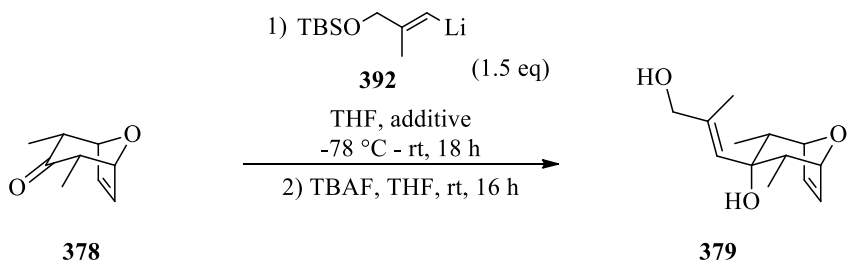
378 **379**

Scheme 157

Table 1 – Attempts to alter aggregation state of organolithium reagent

Entry	Solvent	Additive	Yield 379 (%)	Yield 378 (%)	Notes
1	THF	-	60	Trace	
2	Et_2O	-	46	17	
3	THF	TMEDA	29	35	TMEDA added after formation of **392**
4	THF	TMEDA	32	34	TMEDA added before formation of **392**

Conversion of the organolithium to an organocerium or Grignard reagent was then investigated (**Scheme 158**, **Table 2**). If deprotonation of the ketone was reducing the efficiency of the nucleophilic addition reaction, it was hoped the use of less basic Grignard and organocerium reagents would circumvent this issue.[150] In addition, organocerium reagents have been demonstrated to successfully undergo nucleophilic addition where other organometallic reagents have failed.[150b-d]



378 **379**

Scheme 158

Table 2 – Attempts to convert organolithium to other organometallics

Entry	Additive	Yield 379 (%)	Yield 378 (%)	Notes
1	$CeCl_3$	34	10	**392** added to $CeCl_3$ followed by **378**. 0.85 eq of $CeCl_3$ used.
2	$CeCl_3$	30	-	$CeCl_3$ added to **378** followed by **392**.
3	$CeCl_3$	39	48	**392** added to $CeCl_3$ followed by **378**.
4	$CeCl_3$	28	2	**392** added to $CeCl_3$ followed by **378**. 2 eq of organocerium used.
5	$MgBr_2$	0	90	**392** added to $MgBr_2$ followed by **378**.

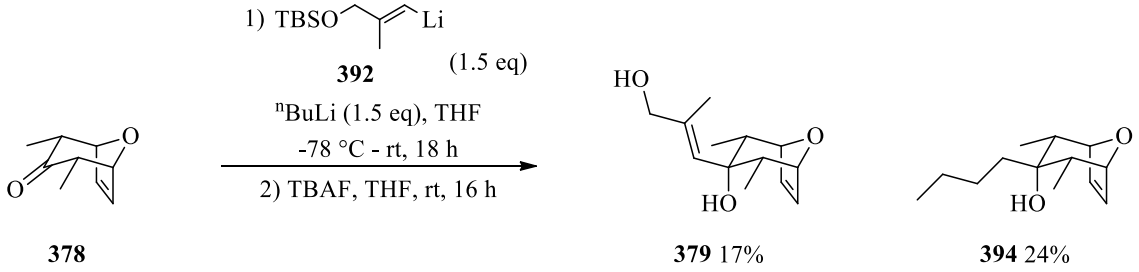
When the reaction was attempted in the presence of sub-stoichiometric $CeCl_3$, **379** was isolated in 34% yield while ketone **378** was recovered in 10% yield (**Table 2**, **Entry 1**). This suggests that a significant portion of the ketone was being consumed in side reactions, indicated by the numerous by-products visible by TLC. Unfortunately, none of these by-products could be isolated cleanly, so no information could be obtained about other reaction pathways occurring under these conditions. Similar results were seen when $CeCl_3$ was pre-mixed with **378** before the addition of vinyllithium **392** (**Entry 2**). A significant amount of ketone was visible by TLC and ^{1}H NMR of the crude reaction mixture; however this could not be recovered cleanly, again indicative of numerous side reactions occurring.

When vinyllithium **392** was mixed with equimolar amounts of $CeCl_3$ prior to the addition of **378**,[150b] the diol **379** was isolated in 39% yield, with **378** being recovered in 48% yield (**Table 2**, **Entry 3**). Despite the lower recovery of **379**, TLC indicated that only **378** and **379** were present in the reaction mixture, suggesting a much cleaner reaction. In the hope of

increasing the conversion to **379**, the reaction was repeated with two equivalents of organocerium present (**Entry 4**). Unfortunately, under these conditions the desired diol **379** was only obtained in 28% yield and the starting ketone **378** in only 2% yield. It remains unclear as to why increasing the amount of organocerium present would cause the significant decomposition seen.

The reaction was also attempted in the presence of stoichiometric $MgBr_2$, where the reactive species would be the vinyl Grignard.[151] However, no reaction occurred under these conditions, with the starting ketone **378** recovered in 90% yield (**Table 2**, **Entry 5**).

The lithium-halogen exchange between vinyl iodide **384** and ^{n}BuLi results in the formation of butyl iodide, which could also react as an electrophile with vinyllithium **392**. As such, the reaction was performed with an extra equivalent of ^{n}BuLi added to consume the butyl iodide formed (**Scheme 159**). However, while **378** was consumed completely, the desired product **379** was isolated only in low yield, with the major product **394** resulting from butyl addition to the ketone.



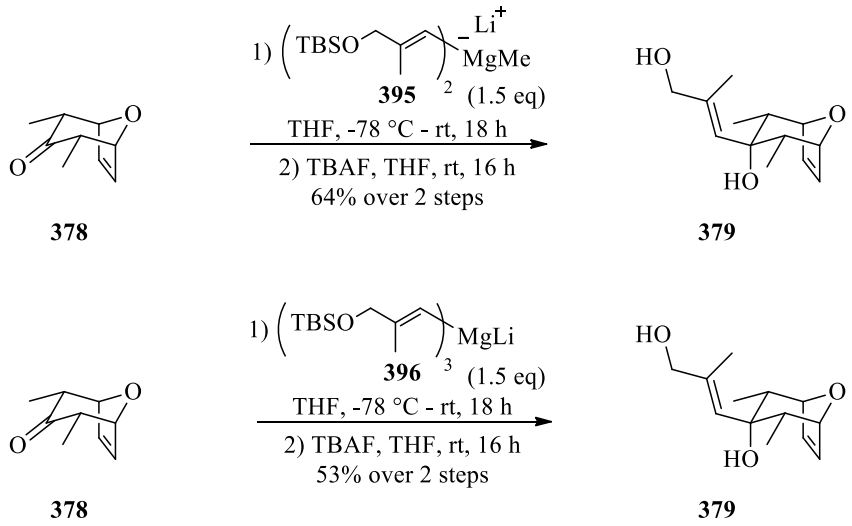
378 **379** 17% **394** 24%

Scheme 159

It was then decided to attempt the reaction employing the use of magnesium ate species. These formally negatively charged organomagnesium species have previously been employed in nucleophilic addition reactions to good effect.[152] Two classes of these reagents were of interest for the nucleophilic addition to ketone **378**, namely the types R_3MgLi and

$R_2MeMgLi$. These have been demonstrated to have increased nucleophilicity over the original RLi or RMgX, while the relative basicity was lower than the parent compound.[152b]

When the reaction was performed with magnesate **395**, full conversion of the ketone was seen, and the desired diol **379** was isolated in 64% yield. Only a trace amount of the product from addition of the methyl group was visible, but could not be recovered cleanly. Furthermore, performing the reaction with magnesate **396** gave **379** in 53% yield, again with full consumption of **378** (**Scheme 160**).

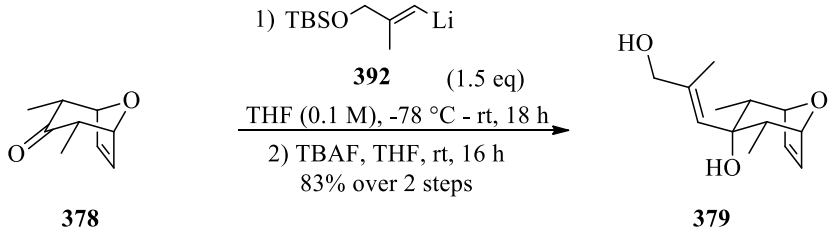


Scheme 160

While the use of **395** did offer a marginal increase in yield, it came at the expense of an extra equivalent of vinyl iodide **384**. As such, it was decided that the use of the vinyllithium **392** was the best way in which to access diol **379** efficiently.

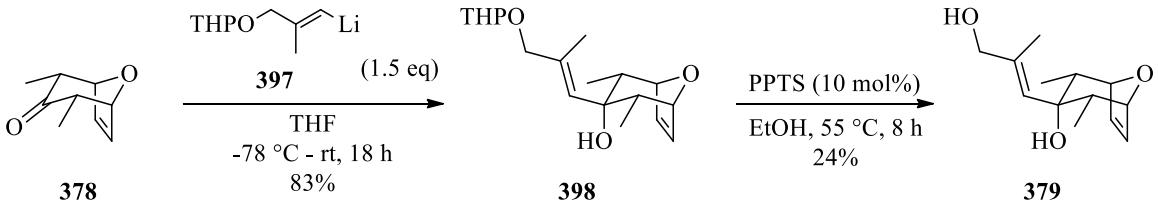
Employing 1.5 equivalents of **392** in THF offered good conversion to diol **379**. However, it was decided to increase the concentration of the reaction, as intermolecular reactions may be more efficient under more concentrated conditions. Pleasingly, increasing the concentration from 0.05 M to 0.1 M gave diol **379** in 83% yield over two steps (**Scheme 161**). Increasing the scale of the reaction from 1 mmol to ~6.6 mmol (1 g of **378**) regularly

gave yields of around 60-65%, allowing reasonably large quantities of **379** to be prepared using these conditions.



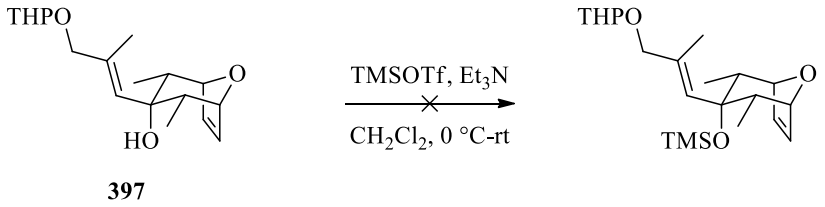
Scheme 161

Vinyllithium **397** could also be employed as a useful nucleophile for the addition to ketone **378**, using the optimised conditions used for the reaction with the TBS derivative, affording **398** in 83% yield (**Scheme 162**). It was subsequently demonstrated that the THP protecting group could be removed through the use of catalytic PPTS in hot EtOH to give **379**, albeit in a disappointing 24% yield.[153]



Scheme 162

While it was felt that very little optimisation would be needed to improve the yield for this deprotection, exposing **398** to TMSOTf in an attempt to protect the tertiary alcohol led to decomposition of the starting material (**Scheme 163**). Previous research in the Grainger group on related systems had shown TMSCl to be insufficiently reactive to protect such hindered tertiary alcohols.[97, 154] This suggested that if orthogonal protection of the alcohols was required, then the use of a THP protecting group may not be the most viable option. Fortunately, efficient access to **379** was possible using the TBS protected vinyllithium.



397

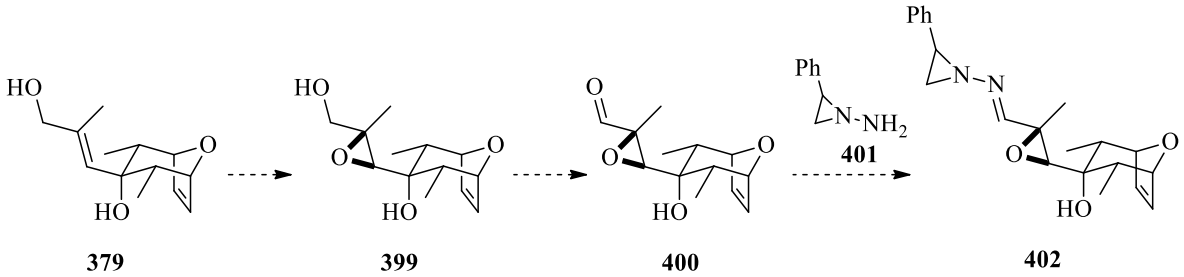
Scheme 163

With an efficient, scalable synthesis of **379** in hand, it was possible to progress towards the synthesis of the desired α,β-epoxy-*N*-aziridinylimine **380**.

It is interesting to note that there is an absence of $^{3}J_{H\text{-}H}$ coupling between the bridgehead protons and the adjacent protons on the ethylene bridge in **379**, **393** and all other examples based on the 2,4-dimethyl bicyclic system. Ketone **378** also displays this somewhat unusual lack of coupling.

2.4 Synthesis of α,β-epoxy-*N*-aziridinylimine 402

It was envisaged that **402** could be synthesised through a selective epoxidation of the allylic alcohol to give **399**, followed by oxidation of the primary alcohol to aldehyde **400**. Condensation with hydrazine **401** would then give rise to **402** (**Scheme 164**).

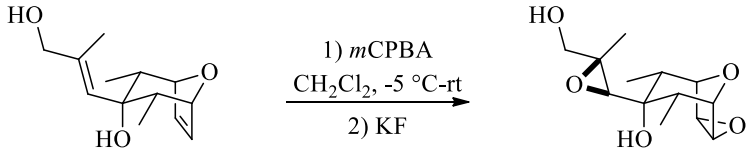


Scheme 164

2.4.1 Synthesis of epoxy alcohol 399

Initially, it was hoped that the presence of the allylic alcohols would direct epoxidation towards the desired alkene and that **399** could be synthesised through the reaction of **379** with *m*CPBA.[155] However, the addition of one equivalent of *m*CPBA gave incomplete

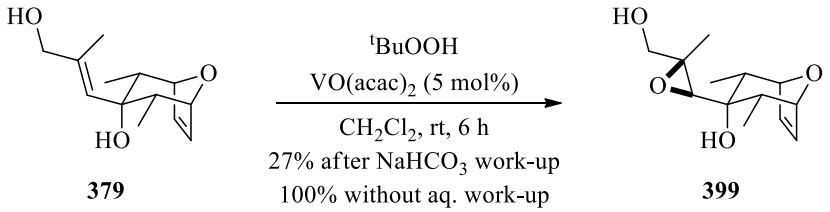
conversion of **379**, and the slow addition of a second equivalent did not give rise to **399**. The ^{1}H NMR spectra of the crude reaction mixture showed the absence of peaks between 5-6.5 ppm, suggesting that both alkenes had reacted. It is possible that **403** was formed within the reaction (**Scheme 165**), however the attempted isolation proved difficult and inconclusive.



379 **403**

Scheme 165

In contrast, reacting **379** with ^{t}BuOOH, in the presence of catalytic $VO(acac)_2$,[155b, 156] led to the isolation of monoepoxide **399** in 27% yield (**Scheme 166**).



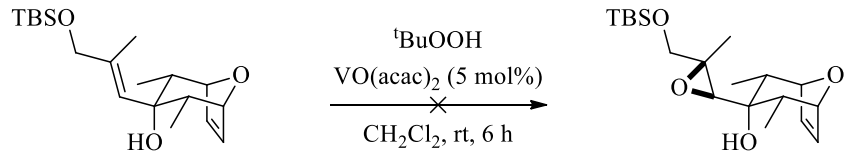
379 **399**

Scheme 166

Despite the successful reaction, the yield was disappointingly low. As no reducing agent was added to the reaction mixture to remove the excess ^{t}BuOOH, it was thought that concentrating the reaction in the presence of any remaining oxidant could lead to the decomposition of the product. In the hope of removing this obstruction, sodium metabisulfate was added to the reaction upon complete conversion. However, TLC analysis indicated that using either solid sodium metabisulfite or an aqueous solution resulted in significant degradation of the product. At this point, it was determined that the best course of action was to directly purify the reaction by column chromatography, thereby removing the catalyst and excess oxidant without any aqueous work-up. This approach worked well, affording **399** in

quantitative yield. As with the nucleophilic addition reaction, the epoxidation could be carried out on a gram scale, allowing large quantities of **399** to be produced.

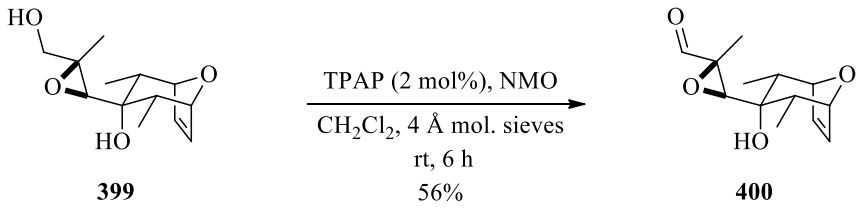
The epoxidation of **393** was also attempted, in order to ascertain if the TBS protecting group could be carried further into the synthesis if required (**Scheme 167**). However, no conversion of the starting material was seen, suggesting the presence of the primary alcohol is crucial to the successful epoxidation of the allylic alcohol.



Scheme 167

2.4.2 Synthesis of epoxy aldehyde 400

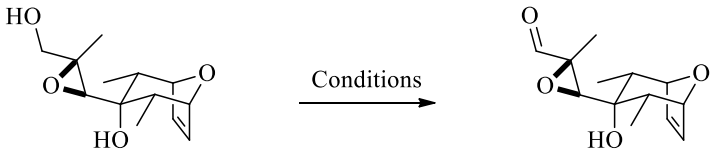
With a robust synthesis on **399** in place, an efficient synthesis of aldehyde **400** was sought. Initial studies focused on the use of TPAP with NMO as a co-oxidant,[26b] and these conditions gave **400** in 56% yield (**Scheme 168**).



Scheme 168

In an attempt to increase the efficiency of this reaction, the crude reaction mixture was filtered through silica, as an alternative to column chromatography. While this improved the yield to 75%, the product was found to still contain some TPAP impurities.

Due to the low yields and difficulties encountered with the use of TPAP as an oxidant, an investigation into the use of other oxidation conditions was carried out (**Scheme 169**, **Table 3**).



399 **400**

Scheme 169

Table 3 – Conditions for oxidation of 399 to epoxy aldehyde 400

Entry	Conditions	Yield (%)
1	TPAP (2 mol%), NMO, CH_2Cl_2, 4 Å mol. sieves, rt, 2 h	56
2	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C – rt, 30 min	11
3	IBX, DMSO/THF, rt, 18 h	52
4	DMP, $NaHCO_3$, CH_2Cl_2, rt, 2 h	90

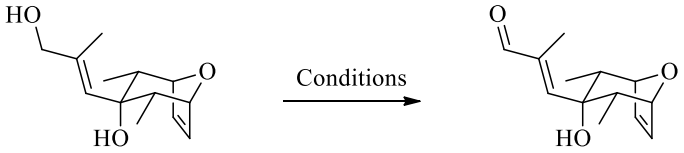
The use of Swern[157] conditions gave a very poor yield of **400** (**Table 3, Entry 2**), while employing IBX[158] gave **400** in a similar yield to that obtained with TPAP (**Entry 3**). Pleasingly, the use of DMP in the presence of $NaHCO_3$ gave **400** in excellent yield (**Entry 4**).[159] The $NaHCO_3$ was added in order to neutralise the AcOH generated in the reaction.

It is unclear why the yield is significantly higher when the oxidation is performed with DMP as opposed to the Swern or IBX conditions employed. One possibility is that neutralising the acid generated in the reaction prevents decomposition of the product or the starting alcohol, while the acid generated in the Swern and IBX reactions is not neutralised *in situ*. Additionally, the use of DMSO in these reactions may result in the loss of product to the aqueous phase during the work-up.

As with the previous reactions to give **379** and **399**, this transformation could be carried out on a gram scale, keeping with the scalable route to the desired alkylidene carbene precursor.

Alternative synthesis of 400

Due to the problems being encountered in both the formation of **399** and **400**, the possibility of reversing the order of epoxidation and oxidation was investigated. Thus, diol **379** was oxidised to α,β-unsaturated aldehyde **405** (**Scheme 170**, **Table 4**). Utilising the TPAP reaction conditions gave **405** in 53% yield (**Table 4**, **Entry 1**), however this could be increased to near quantitative isolation of **405** with the use of DMP (**Entry 2**).



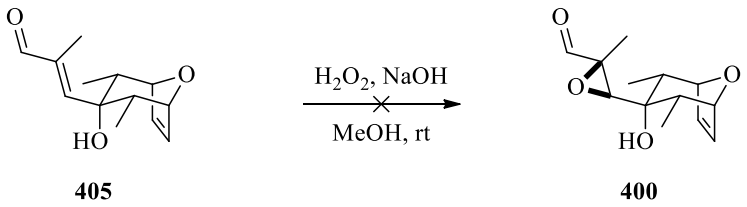
379 **405**

Scheme 170

Table 4 – Attempts to oxidise allylic alcohol 379 to enal 405

Entry	Conditions	Yield (%)
1	TPAP (2 mol%), NMO, CH_2Cl_2, 4 Å mol. sieves, rt, 2 h	53
2	DMP, $NaHCO_3$, CH_2Cl_2, rt, 2 h	99

Unfortunately, **405** did not undergo reaction with basic H_2O_2,[160] with only starting material being recovered (**Scheme 171**). The eventual success in the route described above led to focus being shifted away from this alternative route.

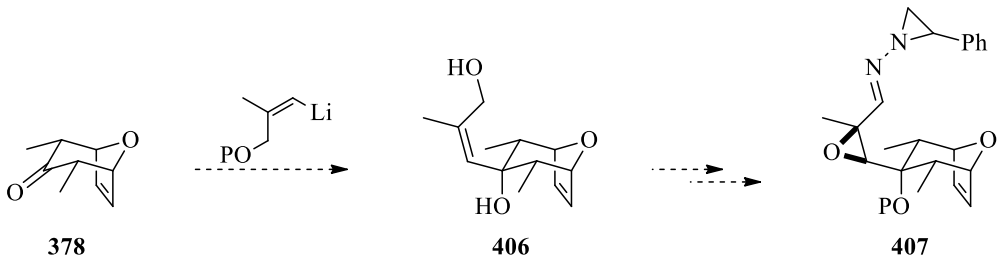


Scheme 171

2.4.4 Use of (*Z*)-vinyl iodide

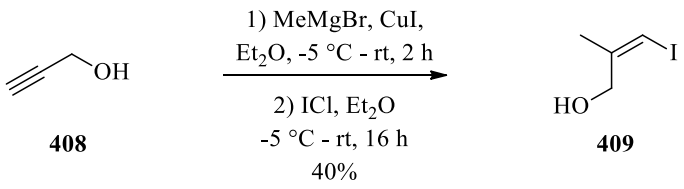
The potential of aziridinylimine **407** as an alkylidene carbene precursor was also investigated. Despite **407** being a stereoisomer of **380**, under the thermolysis conditions, it would generate the same alkylidene carbene, and so any influence on the selectivity would be unexpected. However, development of synthetic routes allowing access to both double bond isomers was thought beneficial for future studies on unsymmetrically substituted oxabicyclic ring systems (**Chapter 3**) where the epoxidation step becomes diastereoselective.

It was believed that **407** could be accessed *via* the same route as that used to synthesise **380** However, in order to access the required epoxide stereochemistry, the geometry of the initial vinyl iodide would have to be (*Z*) instead of the previously used (*E*) isomer (**Scheme 172**).



Scheme 172

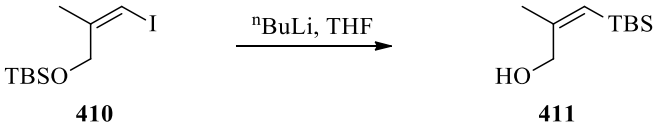
The starting (*Z*)-vinyl iodide **409** could be synthesised *via* treatment of propargyl alcohol **408** with MeMgBr in the presence of CuI, followed by the addition of ICl (**Scheme 173**).[161]



408 **409**

Scheme 173

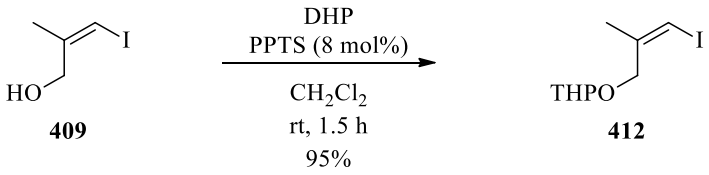
Despite the success achieved with the use of the TBS protecting group in the reactions with the (*E*)-vinyl iodide, literature precedent suggested that **410** would rearrange to the vinyl silane **411** when exposed to BuLi in THF, the optimal solvent for the addition reaction (**Scheme 174**).[162] As such it was decided to attempt the reaction with the THP protected derivative **412**.



410 **411**

Scheme 174

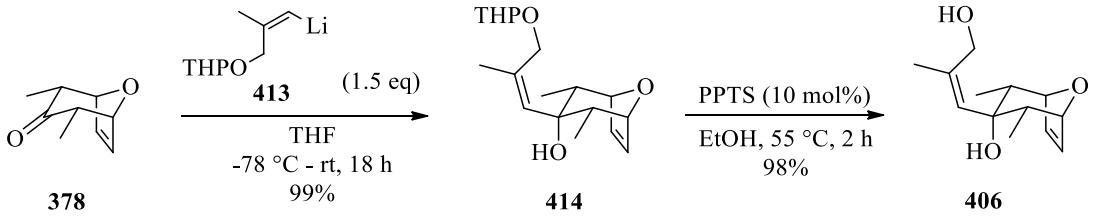
Treating **409** with DHP in the presence of catalytic PPTS afforded **412** in an excellent 95% yield (**Scheme 175**).[163]



409 **412**

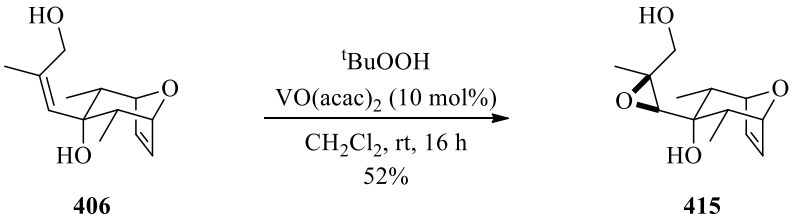
Scheme 175

Treating **412** with ^{n}BuLi gave vinyllithium **413** which underwent nucleophilic addition to ketone **378** to give **414** in 99% yield (**Scheme 176**). The removal of the THP protecting group also worked well, with diol **406** being formed in 98% yield when **414** was treated with catalytic PPTS.[153] The structure of **406** was confirmed using X-ray crystallography (see **Appendix AI**).



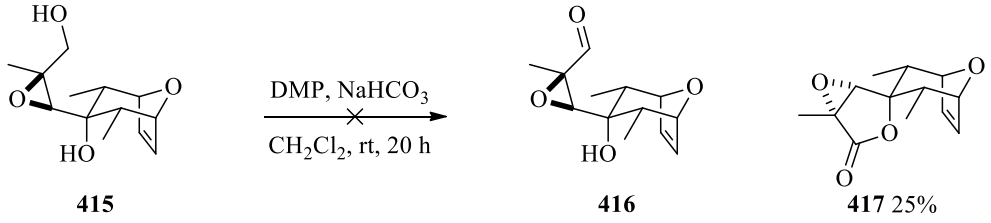
Scheme 176

The epoxidation of **406** proved to be more difficult than the same reaction on the (*E*) isomer. A higher catalyst loading and longer reaction time was required in order to achieve full consumption of **406**, and **415** was isolated in a much lower yield (**Scheme 177**).[155b, 156] Increasing the catalyst loading further resulted in increased degradation being observed by TLC. This decreased reactivity was attributed to the increased steric hindrance in the (*Z*)-isomer, due to the allylic alcohol being *cis* to the bicyclic ring system in this instance.



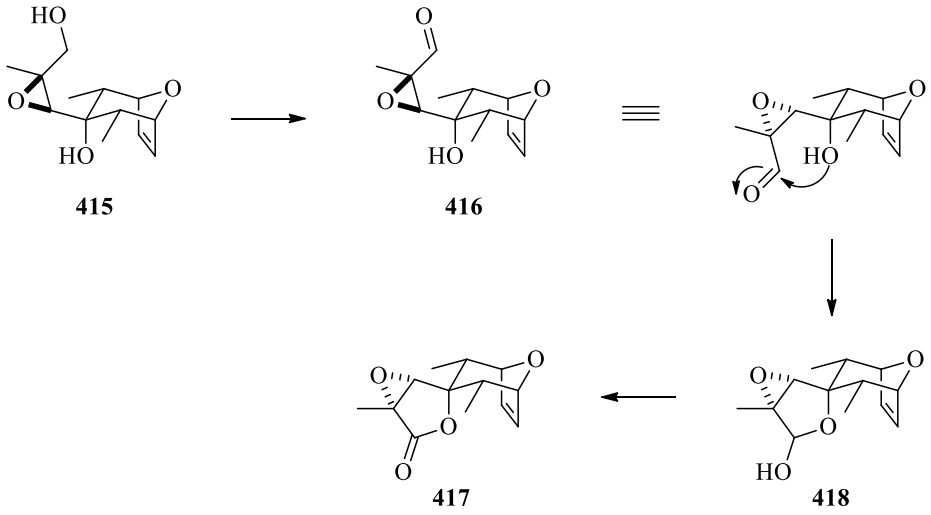
Scheme 177

Epoxy alcohol **415** was subsequently treated with DMP in the presence of $NaHCO_3$ in an attempt to synthesise the desired epoxy aldehyde **416**.[159] However, the reaction proved to be slow and messy, with only lactone **417** isolated from the reaction in low yield (**Scheme 178**).



Scheme 178

It was thought that after the initial oxidation, the tertiary alcohol cyclised onto the aldehyde to form lactol **418**, which is subsequently oxidised to the lactone **417** (**Scheme 179**).[164] However, attempting the reaction with only one equivalent of DMP led to a complex mixture of unidentified products.

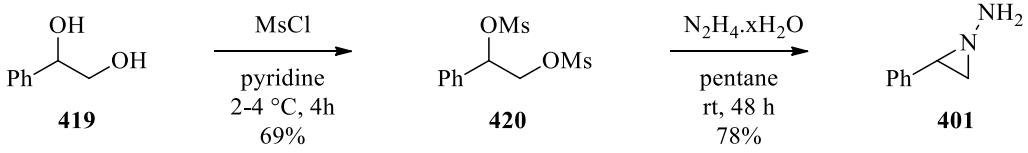


Scheme 179

As it seemed unlikely that the α,β-epoxy-*N*-aziridinylimine required to probe this issue could be synthesised, this investigation was not progressed further.

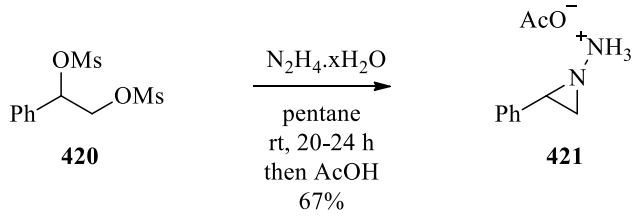
2.4.5 Synthesis of *N*-aminoaziridine 401

It was hoped that **402** could be synthesised *via* a condensation reaction between aldehyde **400** and *N*-aminoaziridine **401**, which could synthesised readily *via* a literature procedure.[165] Thus, styrene glycol **419** was reacted with excess mesyl chloride to give the dimesylate **420** in good yield, which was subsequently treated with hydrazine hydrate, to give **401** (**Scheme 180**).



Scheme 180

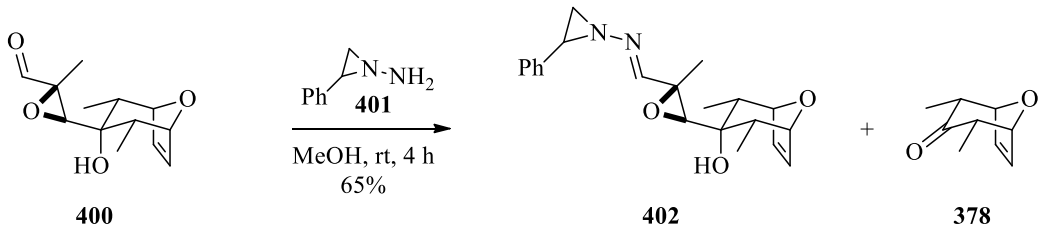
However, it proved difficult to isolate and store **401** cleanly, as its high instability resulted in a number of breakdown products, even when stored at -20 °C. As a result, it was decided to utilise the acetate salt of **401**, which had also been used in condensation reactions with aldehydes.[166] The salt **421** could be synthesised *via* a similar route, simply adding AcOH to the pentane solution of **401** obtained after work-up and collecting the precipitated salt by filtration (**Scheme 181**). It was also noted that significantly increasing the rate of stirring of the reaction between **420** and hydrazine hydrate reduced the reaction time, minimising any decomposition of **401** in solution, most likely due to the increased mixing of the pentane and hydrazine layers the increased stirring would cause.



Scheme 181

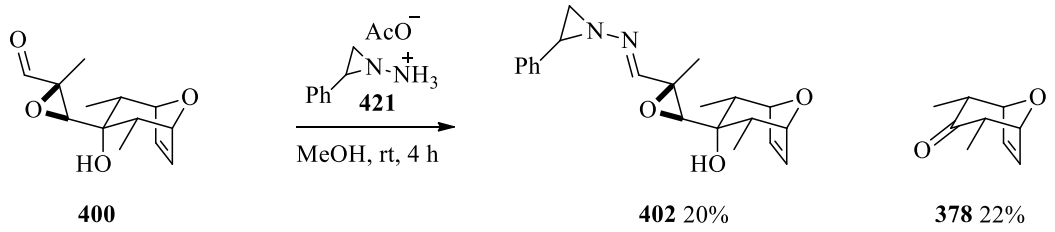
2.4.6 Synthesis of α,β-epoxy-*N*-aziridinylimine 402

With both **400** and **421** in hand, attempts were made to synthesise **402**. Despite its impurity, if used immediately **401** could be employed directly in the condensation reaction with **400** giving **402** (**Scheme 182**).[26b] However, **402** proved difficult to isolate cleanly, as both diastereoisomers of **402** co-eluted with an impurity later revealed to be ketone **378**.



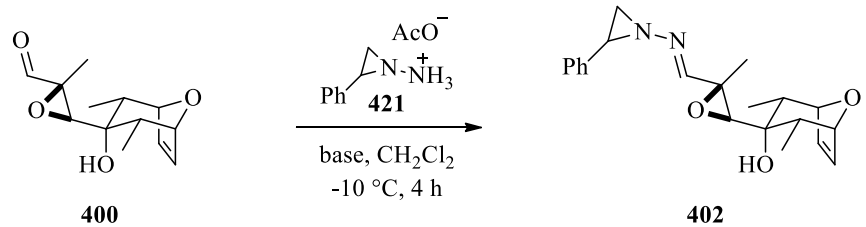
Scheme 182

Disappointingly, the reaction between **400** and **421** gave **402** in only low yield,[166a] with a large amount decomposition, from which only ketone **378** could be recovered (**Scheme 183**).



Scheme 183

As **421** was easier to isolate and store than its free hydrazine precursor, it was the preferred reagent for this reaction, so attempts were made to optimise the condensation reaction using **421**. Theorising that the AcOH generated from **421** may be causing the significant degradation seen, the reaction was performed with the addition of NaOAc to neutralise the acid (**Scheme 184**).[166b] Initially, this gave **402** in 81% yield, however on scaling the reaction up, the yields fell drastically (**Table 5**). Rationalising that the mixture of AcOH and NaOAc would most likely generate a buffer solution, which would still be mildly acidic, the reaction was subsequently attempted in the presence of excess $NaHCO_3$ in place of NaOAc to ensure the reaction mixture remained basic, similar to the strategy employed for the aldehyde formation with DMP. Unfortunately, decomposition was still observed and nothing could be isolated cleanly.



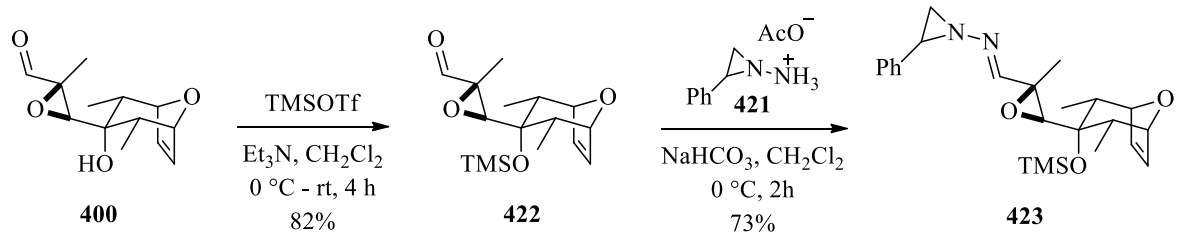
Scheme 184

Table 5 – Attempts to form α,β-epoxy-*N*-aziridinylimine 402

Entry	Base	Scale (mmol)	Yield (%)
1	NaOAc	0.21	81
2	NaOAc	0.86	51
3	NaOAc	1.15	32
4	$NaHCO_3$	0.29	Complex mixture

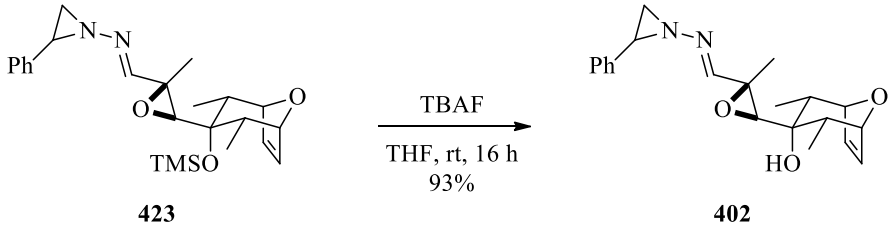
It was apparent that a new approach to **402** was required. As such, it was decided to protect the tertiary alcohol with a TMS group before attempting the condensation reaction. The TMS group was chosen because it had been employed on other tertiary alcohols of this type,[97] and the mild conditions for its removal would hopefully minimise any degradation of the aziridinylimine. Furthermore, it would allow access to a second substrate on which the diastereoselectivity of the C-H insertion reaction could be analysed, allowing a comparison between the reaction of the free alcohol and that of the silyl ether.

Aldehyde **400** was treated with TMSOTf in the hope that the silyl ether could be synthesised at the end of the already established sequence (**Scheme 185**).[97] Pleasingly, this gave **422** in 82% yield, eliminating the need for the route to be re-visited. Subsequent treatment of **422** with **421** in the presence of $NaHCO_3$ gave aziridinylimine **423** in a good, reproducible yield.



Scheme 185

Treating **423** with TBAF subsequently gave **402** in excellent yield (**Scheme 186**), with very little degradation observed. It should be noted that Et_3N was added to the column eluent in order to neutralise the silica and ensure no decomposition was occurring during purification.



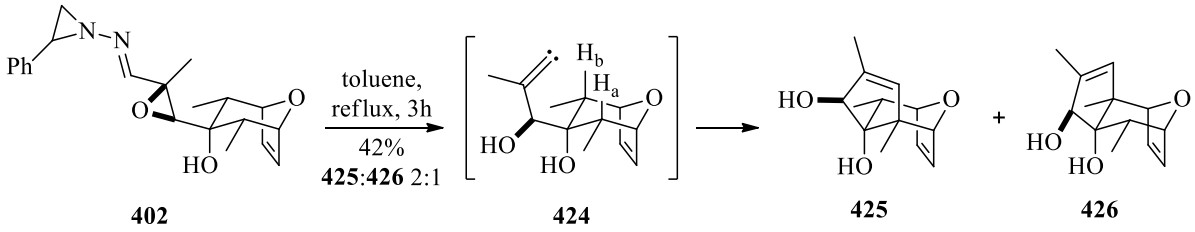
Scheme 186

Both **402** and **423** were isolated as a 1:1 mixture of inseparable diastereoisomers. However, this would have little bearing on the thermolysis reaction as the aziridine stereocentre would be lost through the alkylidene carbene generation.

2.5 Thermolysis of α,β-epoxy-*N*-azirdinylimines

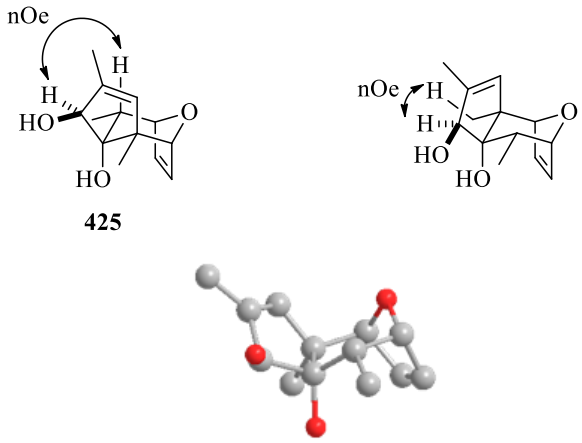
Refluxing a solution of **402** in toluene gave rise to a mixture of **425** and **426** in a combined 42% yield, consistent with the generation of an alkylidene carbene **424** (**Scheme 187**).[55] ^{1}H NMR analysis of the crude reaction mixture indicated that they were formed in a 2:1 ratio. nOe studies carried out on the major diastereoisomer showed a signal between the proton adjacent to the alcohol and the methine on the bicycle indicating that **425** was the major diastereoisomer (**Figure 9**). Similarly, when nOe studies were performed on the minor diastereoisomer, a signal between the proton adjacent to the alcohol and the methyl group was

visible, while no signal was seen to the methine group, confirming **426** as the minor diastereoisomer. Additionally, the structure of the minor diastereoisomer **426** was confirmed by X-ray crystallography (see **Appendix AII**)



402 **424** **425** **426**

Scheme 187

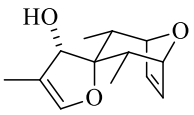


425

426

Figure 9

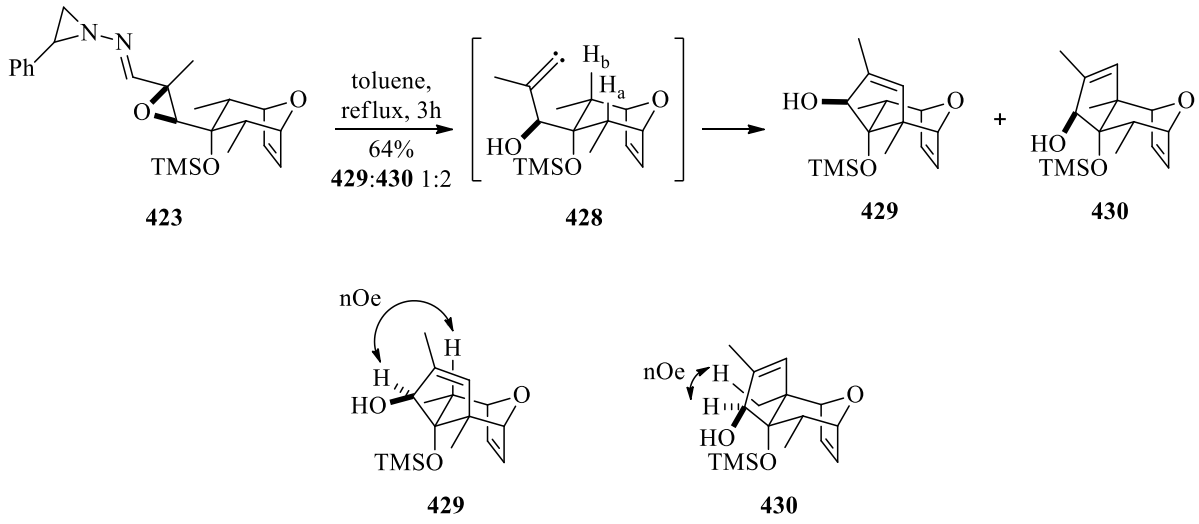
TLC analysis of the crude reaction mixture indicated the formation of a third, minor product. ^{1}H NMR of the crude reaction mixture suggested that this could be **427**, the product of formal insertion into the O-H bond (**Figure 10**). Unfortunately, it was not possible to isolate the pure product in any appreciable amount in order to confirm this. However, if this is the case, ^{1}H NMR of the crude mixture indicated that the ratio of C-H insertion to O-H insertion is approximately 6:1. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture also revealed the presence of ketone **378** in approximately 6:1 ratio compared to C-H insertion.



427

Figure 10

When **423** was subjected to the same reaction conditions as above, a mixture of **429** and **430** was isolated in a 64% combined yield, again indicative of the formation of an alkylidene carbene **428** (**Scheme 188**). Similarly, ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated a 2:1 ratio of the two products, and nOe studies were again used to confirm the identity of the major diastereoisomer. However, in this case, the major product was demonstrated to be **430**, indicating a reversal in the diastereoselectivity of the insertion reaction. There was no evidence of any insertion into the O-Si bond.



423 **428** **429** **430**

429 **430**

Scheme 188

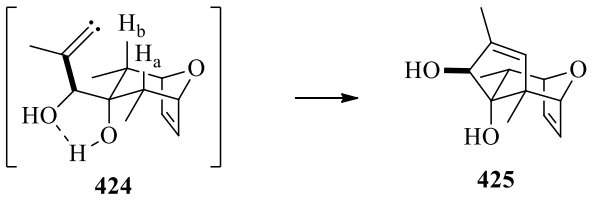
2.6 Explanation of selectivity

The results from the reactions above demonstrate two types of selectivity within the reaction of the alkylidene carbene – chemoselectivity and diastereoselectivity.

Despite the minor amount of suspected O-H insertion in the reaction of **402**, both systems displayed a clear preference for C-H insertion over the more preferable reactions at

oxygen.[11b] This preference for C-H insertion over O-Si insertion has been observed in similar oxabicyclic systems by the Grainger group, and has been attributed to an inability of the oxygen lone pairs to interact with the empty p-orbital on the alkylidene carbene due to increased steric interactions preventing the required rotation around the C-O bond from occurring (**Scheme 103**).[97] Although the higher temperature in the present case, and the smaller oxygen substituent, may allow for increased rotation about the C-O bond, this pathway remains surprisingly unfavourable.

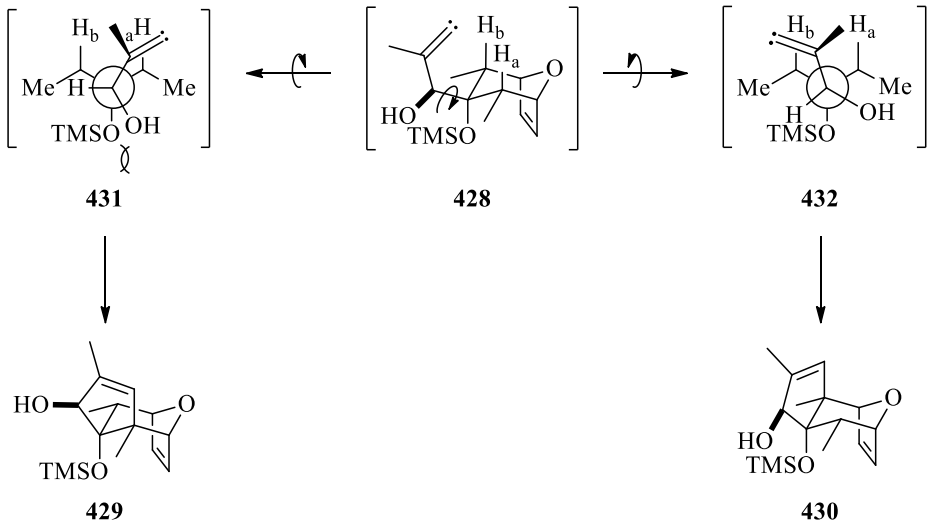
It was clear that the diastereoselectivity of the 1,5 C-H insertion reaction is dependent on the tertiary alcohol substituent, and while modest, is reversed in moving from an alcohol to the silyl ether. The diastereotopic group selectivity is controlled by the orientation about the HO-C-C-OR carbon-carbon bond within the carbene. In the reaction of tertiary alcohol **402**, the observed preference for insertion into C-H_a can be rationalised by a hydrogen bonding interaction within the newly generated vicinal diol **424**. This would the fix the conformation around the C-C bond, orientating the alkylidene carbene towards C-H_a, directing the reaction to this position (**Scheme 189**).



424 **425**

Scheme 189

In the reaction of TMS ether **423**, the insertion at C-H_a is disfavoured compared to the reaction at C-H_b, most likely due to the increased steric and/or electronic interactions between the silyl ether and the alcohol **431** (**Scheme 190**). Conversely, these interactions are minimised when reacting at C-H_b **432**, resulting in the reaction at C-H_b occurring preferentially.



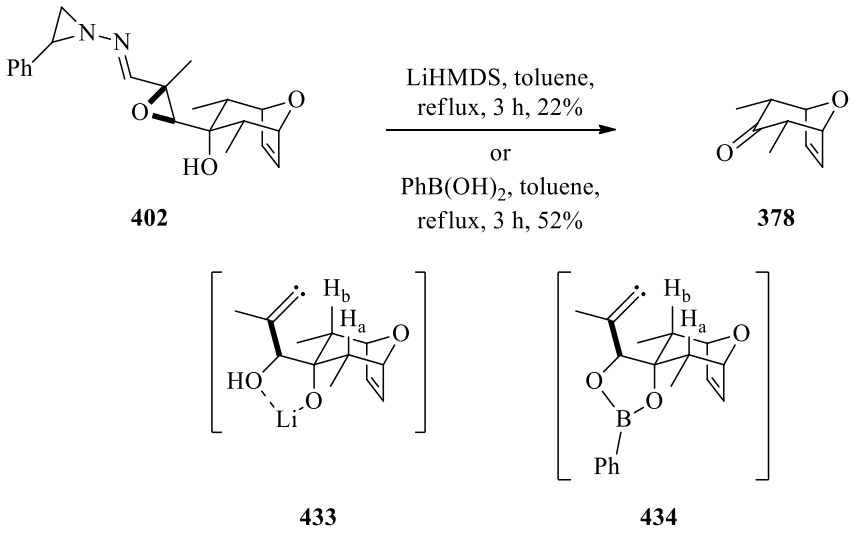
Scheme 190

2.7 Attempts to increase diastereoselectivity

2.7.1 Altering tertiary alcohol substituent

While it was clear that the diastereoselectivity of the C-H insertion reaction could be controlled, only modest selectivities were obtained. This suggests that the forces governing this selectivity were only modest. As such, attempts were made to further increase the selectivity towards one C-H over the other.

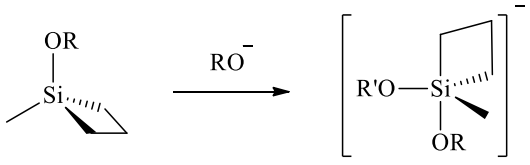
Initial efforts focused on directing the alkylidene carbene towards insertion at C-H_a. However, running the thermolysis of **402** in the presence of LiHMDS (to form a metal chelate **433** *in situ*) or $PhB(OH)_2$ (to form a cyclic boronate **434** *in situ*)[167] gave no 1,5 C-H insertion reaction. Instead, the only product recovered from either reaction was ketone **378**, *via* an unusual C-C bond fragmentation (**Scheme 191**).



402 **378** **433** **434**

Scheme 191

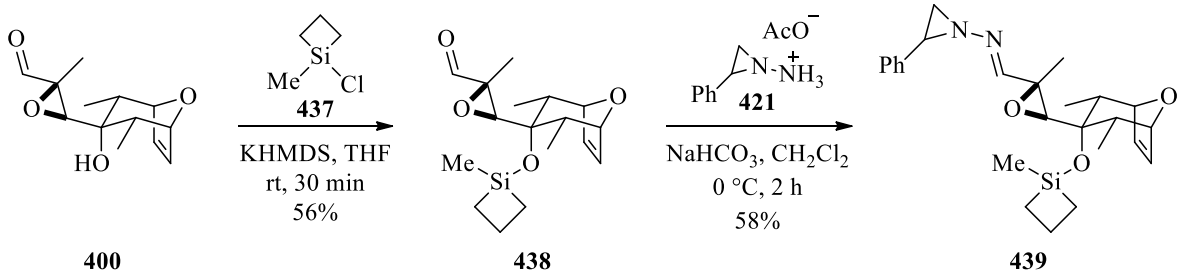
It was then decided to investigate the use of a siletane group on the tertiary alcohol. The presence of the 4-membered ring places strain on the tetrahedral silicon in **435**. The introduction of a Lewis base allows the silicon to adopt a trigonal bipyramidal structure **436**, which is better able to accommodate the 90° bond angle of the silacycle (**Scheme 192**). This release of ring strain results in the silicon being having an increased Lewis acidity compared to TMS.[168] It was hoped that this increased Lewis acidity would further direct the alkylidene carbene towards insertion at C-H_a.



435 **436**

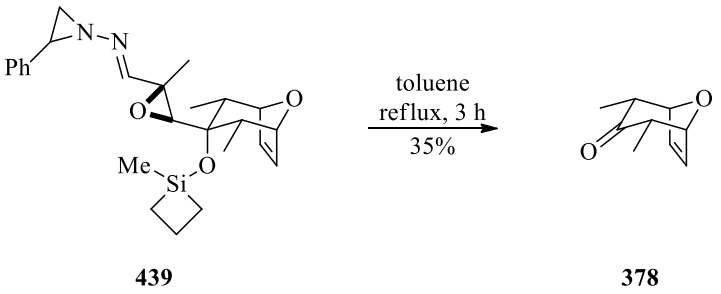
Scheme 192

The desired aziridinylimine **439** was synthesised in two steps from aldehyde **400**. Silyl ether formation with the commercially available silyl chloride **437** occurred in 56% yield to give **438**,[169] and the subsequent condensation with **421** giving **439** in 58% yield (**Scheme 193**).[166b]



Scheme 193

Unfortunately, refluxing a solution of **439** in toluene gave only ketone **378** in 35% yield (**Scheme 194**). While it was not possible to determine the mechanism of this fragmentation, it was possible to demonstrate that this unusual pathway was a function of aziridinylimine **439**, as refluxing aldehyde **438** in toluene gave no reaction, and **438** could be recovered in 95% yield.

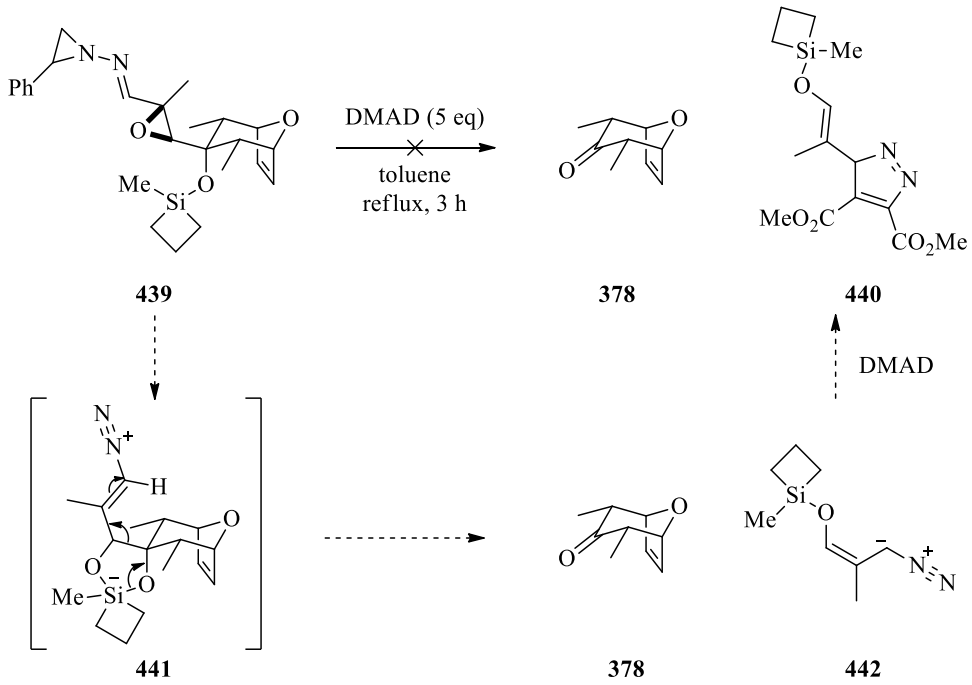


Scheme 194

A key step in the generation of alkylidene carbenes from α,β-epoxy-*N*-aziridinylimines is the proton transfer from the vinyl carbon to the oxygen of **147** to give **148** (**Scheme 52**).[55] One possibility is that the presence of a Lewis acid retards this proton transfer step.

The formation of ketone **378** was unexpected. Potentially, formation and fragmentation of a species such as **441** could result in the formation of ketone **378** and 1,3-dipole **442**. In order to test this theory, the thermolysis of **439** was performed in the presence of DMAD in order to trap the potential dipole as pyrazole **440** (**Scheme 195**). Unfortunately,

only degradation was seen by TLC analysis and ^{1}H NMR of the crude reaction mixture showed a complex mixture of products, none of which could be identified.



Scheme 195

The presence of small amounts of **378** in the thermolysis of **402** may be due to proton transfer from the tertiary alcohol to the secondary alkoxide competing with proton transfer from the vinyl carbon.

The use of hydrogen-bond acceptors to potentially direct the alkylidene carbene towards reaction at C-H_a was also investigated (**Figure 11**).

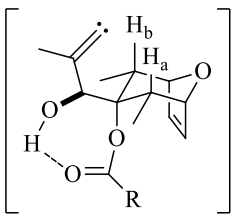
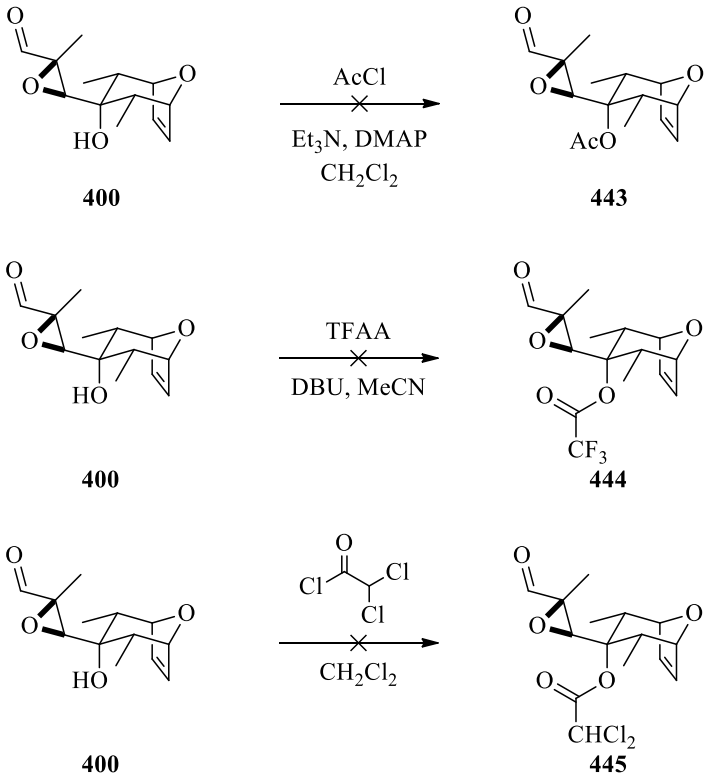


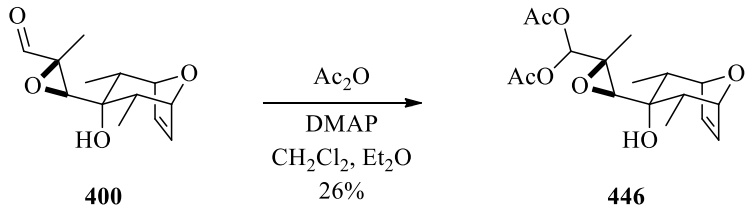
Figure 11

Unfortunately, tertiary alcohol **400** did not undergo acylation with AcCl,[170] TFAA[171] or dichloroacetyl chloride,[172] with only starting material recovered or degradation seen (**Scheme 196**).



Scheme 196

Reaction with Ac_2O gave only acetal **446**, with no reaction occurring at the tertiary alcohol (**Scheme 197**).[173]

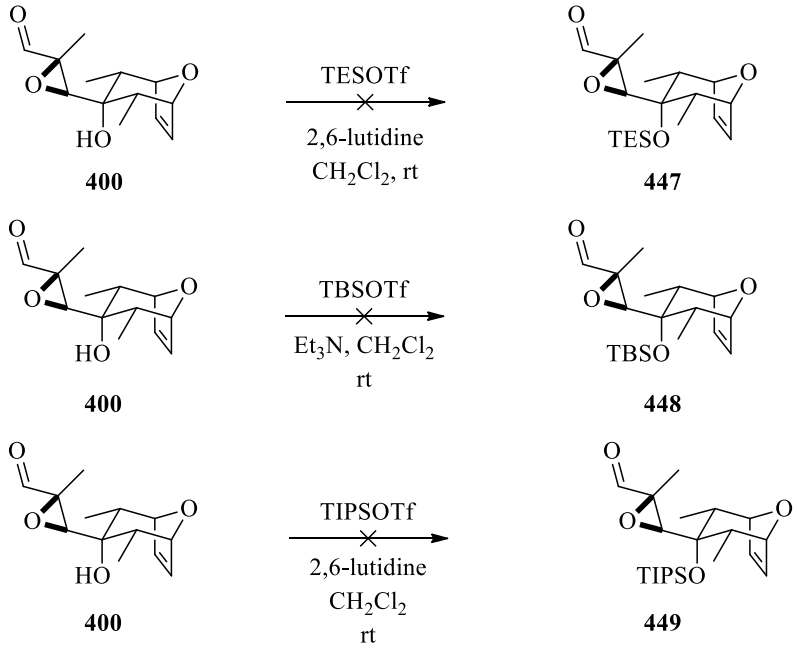


Scheme 197

The lack of reactivity of the tertiary alcohol did not allow investigation into the use of hydrogen bond acceptors in controlling the diastereoselectivity of the 1,5 C-H insertion reaction.

It was believed that the difficulties encountered in synthesising the required ester arose from the steric bulk around the alcohol. The successful incorporation of a TMS group was believed to be due to the relatively long O-Si bond placing the large silyl group further away from the oxabicycle. As such, it was decided to focus the investigation of the use of larger silyl groups.

However, the reaction of **400** with TESOTf[174] and TBSOTf[175] resulted in significant degradation seen in both cases (**Scheme 198**), and treating **400** with TIPSOTf gave rise to an unknown product, the structure of which could not be determined.[176]



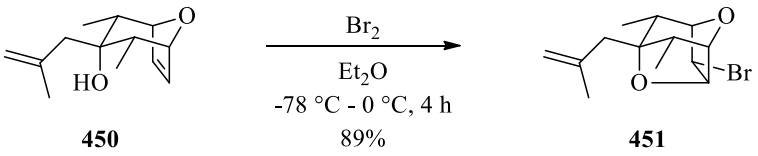
Scheme 198

At this point, it became clear that altering the substituent on the tertiary alcohol would not be a viable way in which to control the diastereoselectivity of a 1,5 C-H insertion reaction on the 8-oxabicyclic ring system. As such alternative approaches were investigated.

2.7.2 Bromoethers

Previous work in the Grainger group had shown that when bisalkene **450** was treated with Br_2, bromination occurred selectively at the endocyclic alkene (**Scheme 199**).[97] The

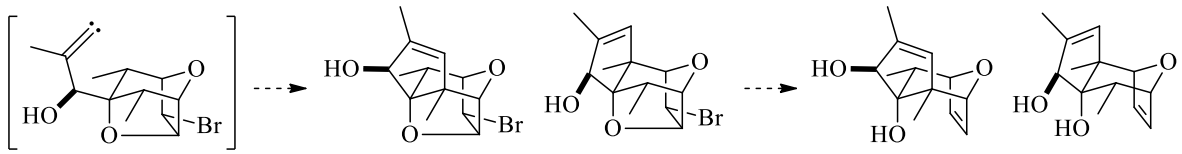
intermediate bromonium was then captured in an intramolecular fashion by the tertiary alcohol to give bromoether **451**.[177]



450 **451**

Scheme 199

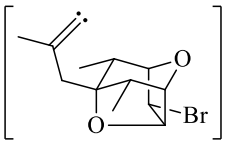
It was hoped that this selectivity could be exploited in order to achieve greater selectivity in the 1,5 C-H insertion reaction. It was believed that bromoether formation would cause the six-membered ring to twist slightly, moving one of the C-H bonds closer to the carbenic centre in alkylidene carbene **452**. While this would no longer be a diastereoselective process but instead a regioselective reaction, it was hoped that the dihydrofuran could be reformed *via* a reductive elimination of the bromoether,[178] rendering the overall transformation formally diastereoselective.



452 **425** **426**

Scheme 200

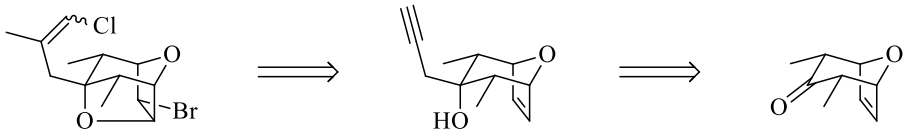
It was decided to initially focus on a route towards alkylidene carbene **453** in order to investigate whether such a tricyclic system would undergo a 1,5 C-H insertion reaction (**Figure 12**). If this approach proved successful, the use of bromoethers would then be expanded to include the α,β-epoxy-*N*-aziridinylimines, allowing the selectivity of alkylidene carbene **452** to be investigated.



453

Figure 12

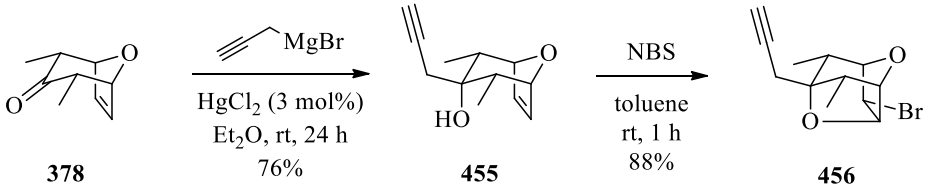
It was envisaged that **453** could be accessed from vinyl chloride **454** which in turn could be synthesis *via* an initial addition of a propargyl Grignard to ketone **378** (**Scheme 201**).



454 **455** **378**

Scheme 201

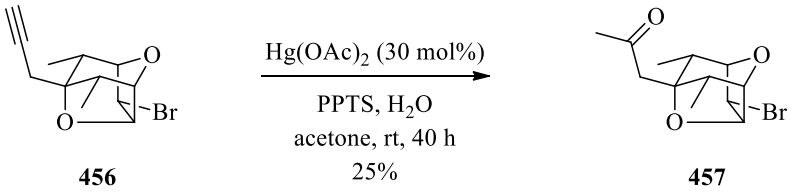
Pleasingly, treatment of **378** with propargyl Grignard in the presence of catalytic $HgCl_2$ gave **455** in 76% yield (**Scheme 202**).[179] Keen to avoid the use of Br_2, the cyclisation was instead attempted with NBS, and bromoether **456** was formed in 88% yield under these conditions.[177]



378 **455** **456**

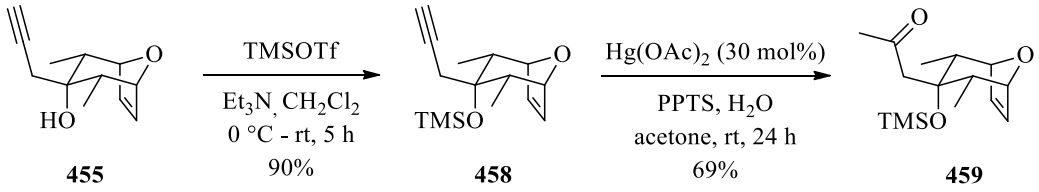
Scheme 202

However, subsequent hydration of alkyne **456** to give ketone **457** proved to be sluggish, with **457** being recovered in low yield (**Scheme 203**).[180]



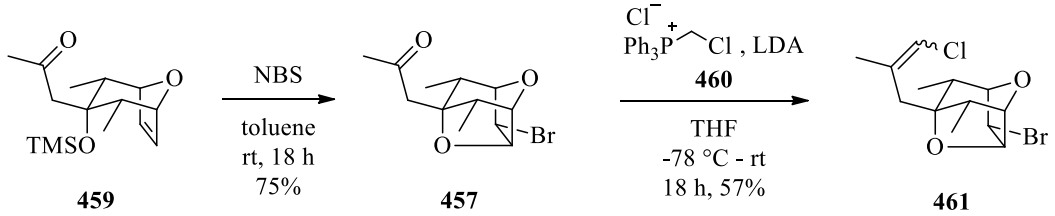
Scheme 203

It was therefore decided to perform the alkyne hydration prior to the formation of the bromoether. In order to avoid a competitive cyclisation of the tertiary alcohol onto the alkyne under hydration conditions,[154] it was necessary to protect the alcohol first. Thus, alcohol **455** was treated with TMSOTf to afford **458** in 90% yield (**Scheme 204**).[97] Subsequent hydration of the alkyne worked well, affording **459** in 69% yield.[180]



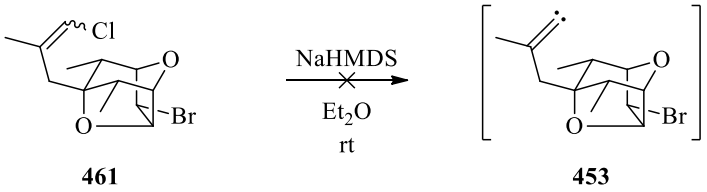
Scheme 204

It was hoped that exposing **459** to NBS would also allow for the formation of bromoether **457**, thereby removing the need for deprotecting the alcohol prior to cyclisation. This proved to be true and reacting **459** with NBS gave **457** in 75% yield (**Scheme 205**).[177] The target vinyl chloride was subsequently synthesised *via* a Wittig reaction with phosphonium salt **460** in the presence of LDA.[97] This afforded **461** as a 1:1 ratio of *E* and *Z* isomers, in 57% combined yield.



Scheme 205

Unfortunately, treatment of **461** with NaHMDS in Et_2O gave only degradation and nothing could be isolated from the reaction mixture (**Scheme 206**).



461 **453**

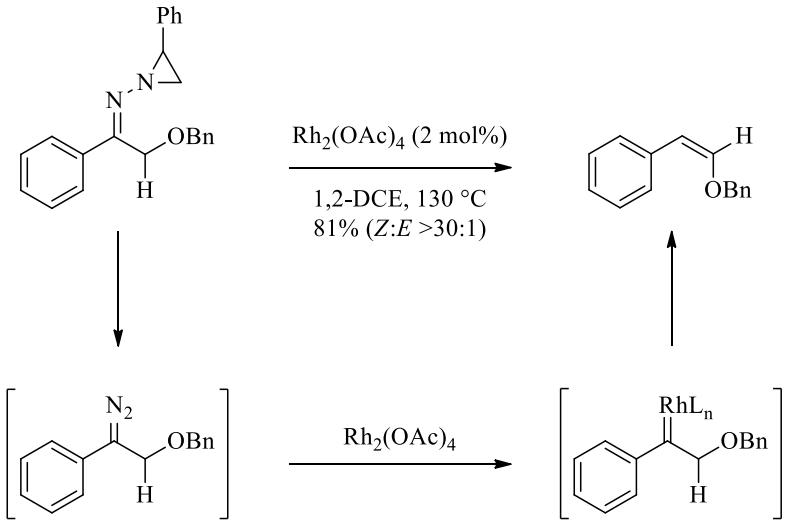
Scheme 206

Due to the lack of success in using bromoethers in an alkylidene carbene insertion reaction of **461**, this approach was not utilised in the thermolysis of α,β-epoxy-*N*-aziridinylimines.

2.7.3 Use of Rh-carbenoid

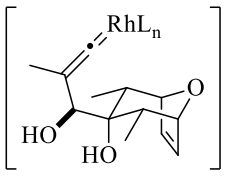
As it had previously been demonstrated that improved regioselectivity in C-H insertion reactions could be achieved by generating an alkylidene carbenoid as opposed to a 'naked' alkylidene carbene,[95b] it was desirable to investigate if this phenomenon could be exploited to increase the diastereoselectivity in the thermolysis of aziridinylimines.

Stoltz had demonstrated the generation of alkyl rhodium carbenoids *via* the *in situ* generation of diazoalkanes from Eschenmoser hydrazones (**Scheme 207**).[166a]



Scheme 207

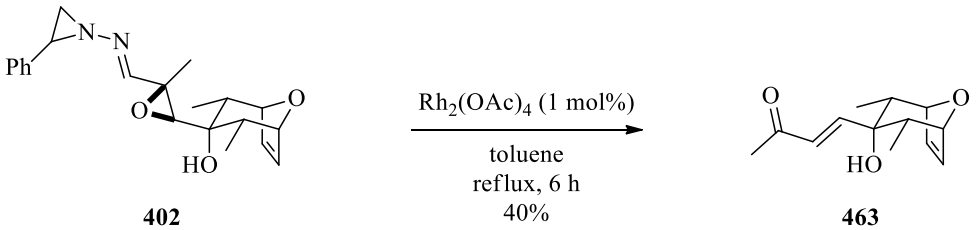
It was hoped that performing the thermolysis reaction in the presence of $Rh_2(OAc)_4$ would allow for the generation of carbenoid **462** (**Figure 13**), which it was hoped would exhibit greater selectivity in the C-H insertion reaction.



462

Figure 13

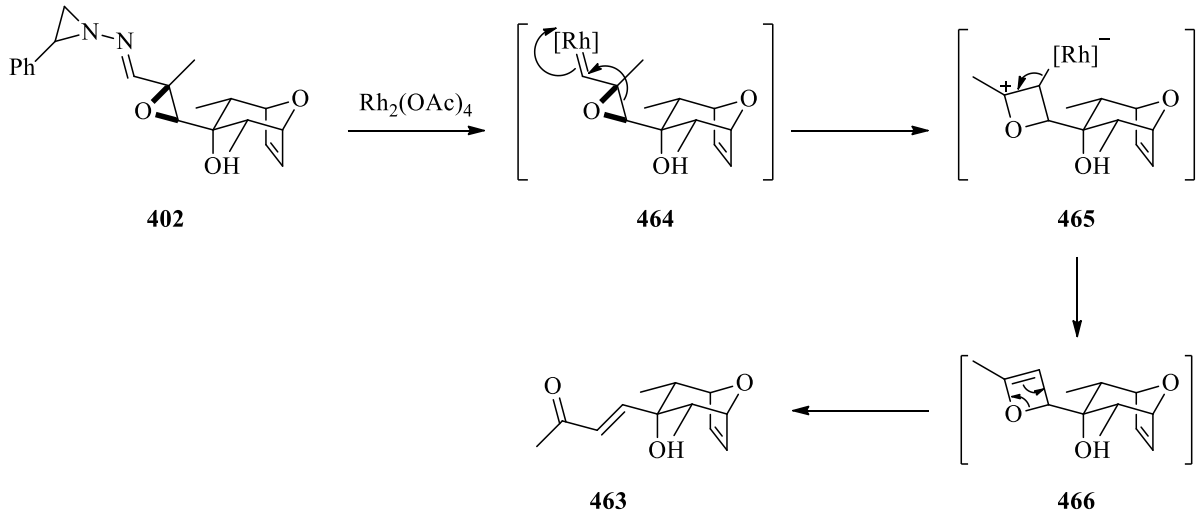
However, repeating the thermolysis of **402** in the presence of catalytic $Rh_2(OAc)_4$ gave enone **463** as the only recoverable product (**Scheme 208**).[166a]



402 **463**

Scheme 208

The formation of **463** is believed to be due to carbenoid **464** forming as opposed to the desired vinylidene **462**. Ring expansion of the epoxide gives cation **465**,[56b] which subsequently eliminates the rhodium to give oxetene **466**. An electrocyclic ring opening would result in the formation of the observed enone **463** (**Scheme 209**). Similar mechanisms have been proposed for the metal catalysed ring expansions of cyclopropanes to cyclobutenes.[181]

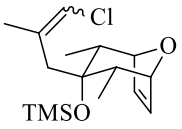


Scheme 209

2.8 Other approaches to diastereoselective C-H insertion reactions

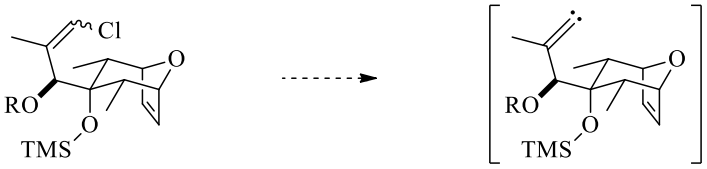
Due to the somewhat limited way in which the thermolysis of α,β-epoxy-*N*-aziridinylimines could be exploited as a precursor to an alkylidene carbene suitable for the synthesis of ingenol, it was decided to investigate other potential ways in which α-alkoxy alkylidene carbenes could be generated.

Previous work in the Grainger group had focused on generating the alkylidene carbene from vinyl chlorides such as **370** (**Figure 14**). Introducing an oxygen substituent on the α-position **467** should allow access to an alkylidene carbene **468** similar to that generated in the thermolysis of α,β-epoxy-*N*-aziridinylimines (**Scheme 210**).



370

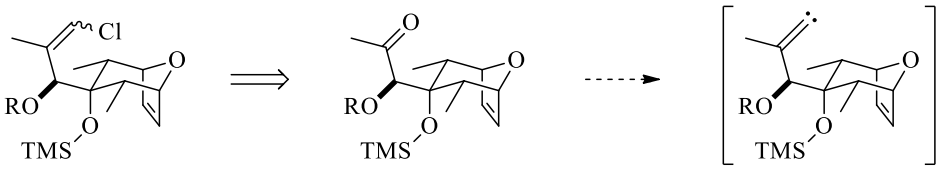
Figure 14



467 **468**

Scheme 210

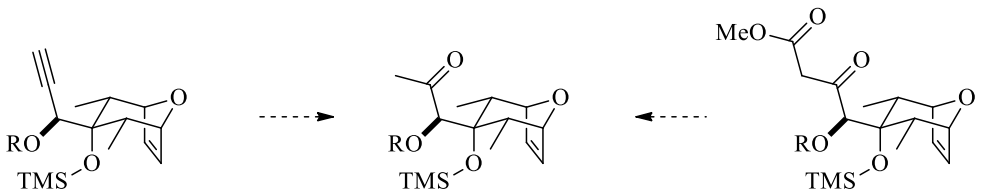
As vinyl chloride **370** was synthesised *via* a Wittig reaction on the corresponding ketone, it was envisaged that **467** could be synthesised in the same way (**Scheme 211**). Ketone **469** could also serve as a viable precursor to the desired alkylidene carbene **468**, allowing for a comparison to be made of how the method of generating the alkylidene carbene may affect the selectivity.[95b]



467 **469** **468**

Scheme 211

Based on previous work carried out in the Grainger group,[97, 154] there were two viable routes which allow access to ketone **469**. It was envisaged that hydration of an alkyne such as **470** would lead to the desired ketone **469**. Alternatively, a Krapcho decarboxylation of acetoacetate **471** would result in the formation of **469** (**Scheme 212**). Both **470** and **471** could be synthesised *via* addition of the appropriate nucleophile to bicyclic ketone **378**.



Scheme 212

2.8.1 Approach to α-alkoxy alkylidene carbenes using propargyl ethers

It was necessary to protect both the alcohol and acetylene functionalities of propargyl alcohol in order to employ the methylene group as a nucleophile. It was decided to focus initially on the use of **472** and **473** as potential nucleophile precursors (**Figure 15**). Both had previously been used in nucleophilic addition reactions to ketones.[182]

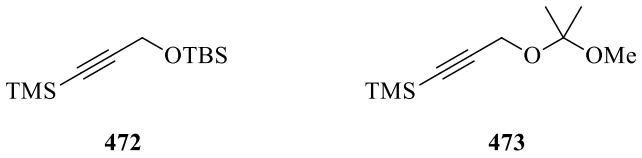
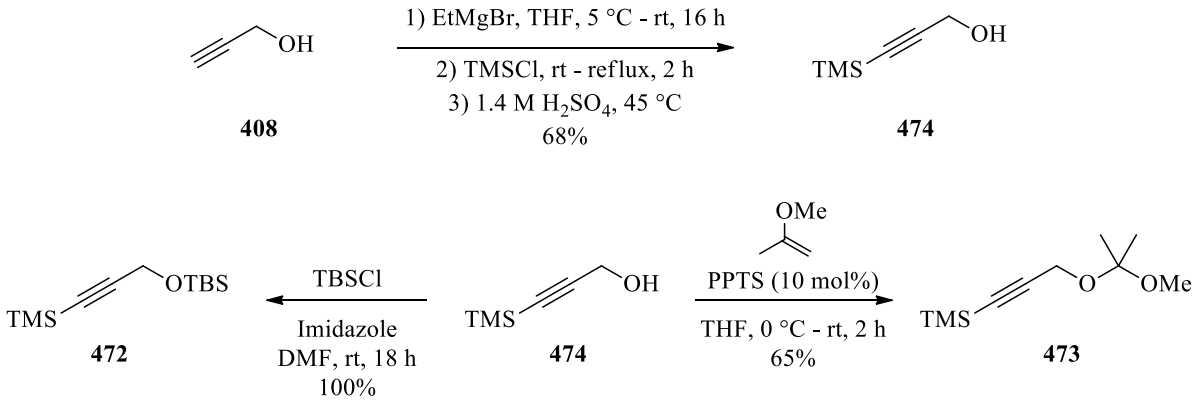


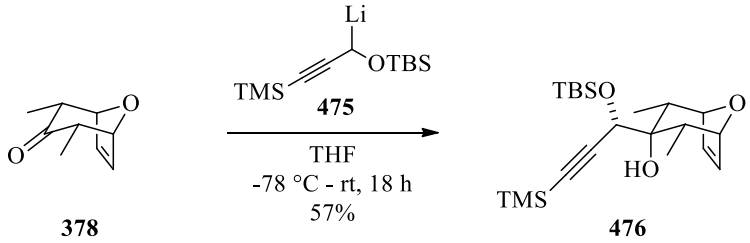
Figure 15

Treatment of propargyl alcohol **408** with EtMgBr and TMSCl, followed by H_2SO_4 gave alkynyl silane **474** in 68% yield (**Scheme 213**).[183] This approach was used as it would allow access to both **472** and **473** without having to deprotect the oxygen after the alkynylsilane had been installed. Propargyl ethers **472** and **473** could subsequently be synthesised through the reaction of **474** with TBSCl[184] and 2-methoxypropene[185] respectively.



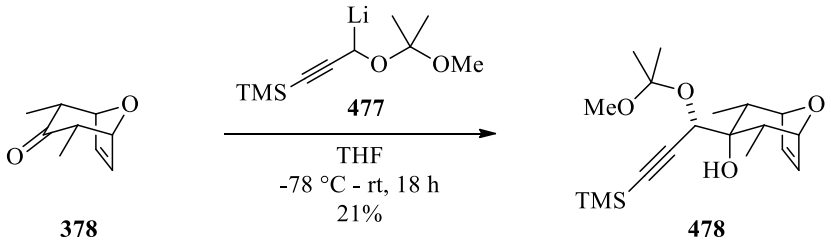
Scheme 213

Treating **472** with ^{n}BuLi gave propargyl lithium **475**, which underwent nucleophilic addition to ketone **378**, giving **476** in 57% yield (**Scheme 214**). Previous use of **475** employed ^{t}BuLi for its generation,[182a, b] however the yields of **476** were much more variable using these conditions.



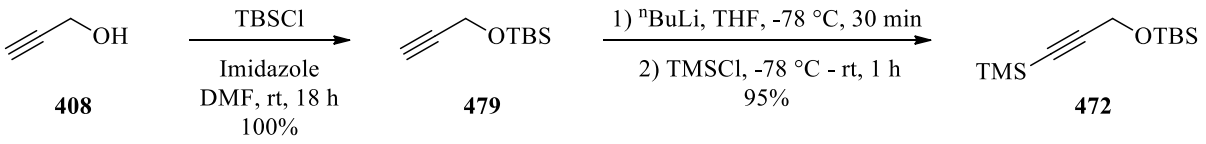
Scheme 214

The addition of propargyl ether **473**, *via* **477**, under the same reaction conditions gave **478** in a disappointing 21% yield (**Scheme 215**).



Scheme 215

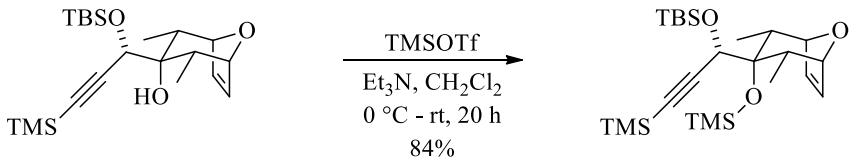
As it was felt that **472** was the best propargyl ether to employ in the addition reaction, its synthesis was altered, reversing the order of the protection reactions (**Scheme 216**). Protecting propargyl alcohol **408** with TBSCl gave **479** in quantitative yield,[186] and subsequent protection of the alkyne also occurred in excellent yield, giving **472** in 95% after treatment with ^{n}BuLi and TMSCl.[187]



408 **479** **472**

Scheme 216

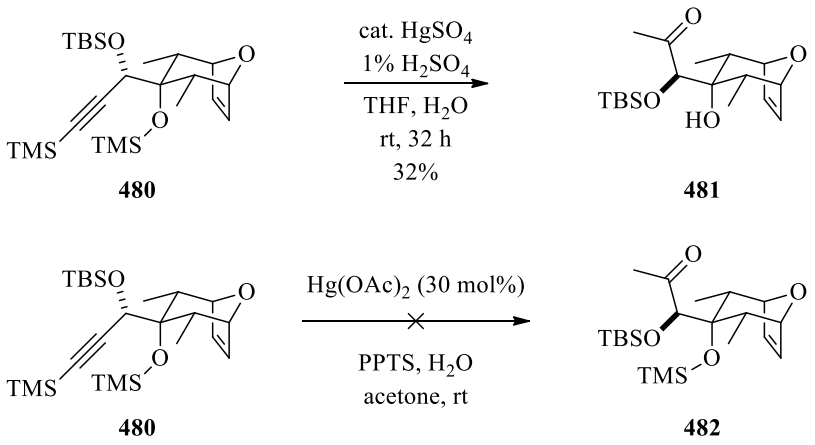
Literature precedent suggested that the alkynylsilane of **476** could be hydrated to the methyl ketone directly, without prior removal of the TMS group.[188] However, as mentioned previously (**Scheme 204**), it was believed that the presence of a tertiary alcohol would result in competing intramolecular attack on the activated alkyne under hydration conditions,[154] and so the alcohol was converted to the TMS ether **480** in excellent yield (**Scheme 217**).[97]



476 **480**

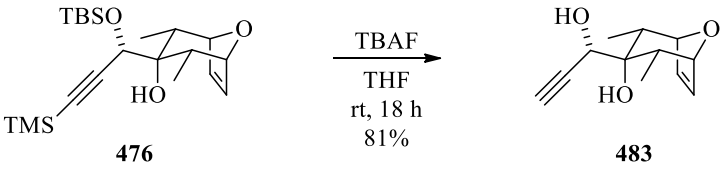
Scheme 217

Unfortunately, while treating **480** with $HgSO_4$ and H_2SO_4 led to hydration of the ketone, the TMS protecting group was also removed, with only **481** isolated in a low yield (**Scheme 218**).[188] Employing the milder conditions previously used in the hydration of alkyne **458**, without the propargyl substituent, gave no reaction, with only starting material recovered.[180]



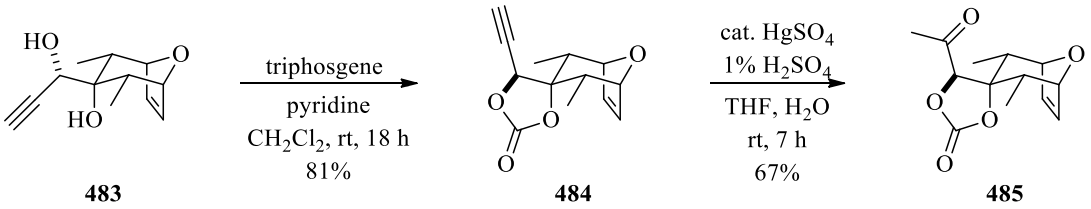
Scheme 218

It was thought that the steric encumbrance of the silyloxy substituent was preventing efficient activation of the alkyne by the Hg, so it was decided to tether the two oxygen atoms together in an effort to reduce the steric hindrance around the alkyne. Additionally, generating the alkylidene carbene in such a constrained system would presumably have a profound effect on the diastereoselectivity of the C-H insertion reaction. As such, **476** was treated with an excess of TBAF gave diol **483** in 81% yield (**Scheme 219**).[148]



Scheme 219

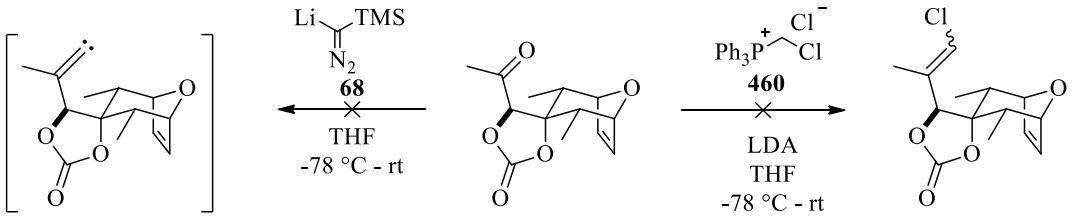
The subsequent reaction of **483** with triphosgene and pyridine gave carbonate **484**,[189] which was successfully converted to ketone **485** when exposed to $HgSO_4$ and H_2SO_4 (**Scheme 220**).[188]



483 **484** **485**

Scheme 220

Unfortunately, attempts to generate the alkylidene carbene **486** from ketone **485** proved unsuccessful. Reacting **485** with deprotonated (trimethylsilyl)diazomethane **68** showed no conversion of starting material,[103b] while a Wittig reaction with (chloromethyl)triphenylphosphonium chloride **460**, to give vinyl chloride **487**, gave the same result (**Scheme 221**).[97]

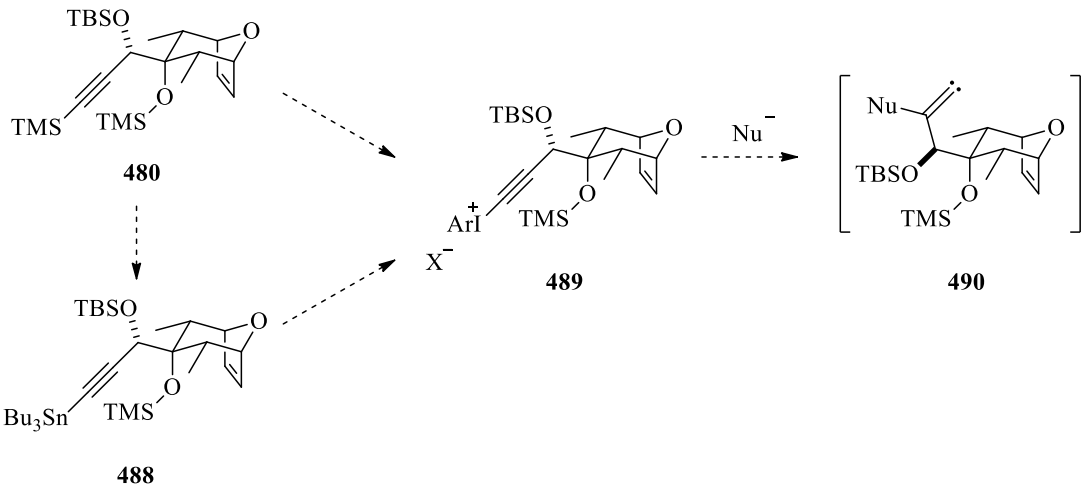


486 **485** **487**

Scheme 221

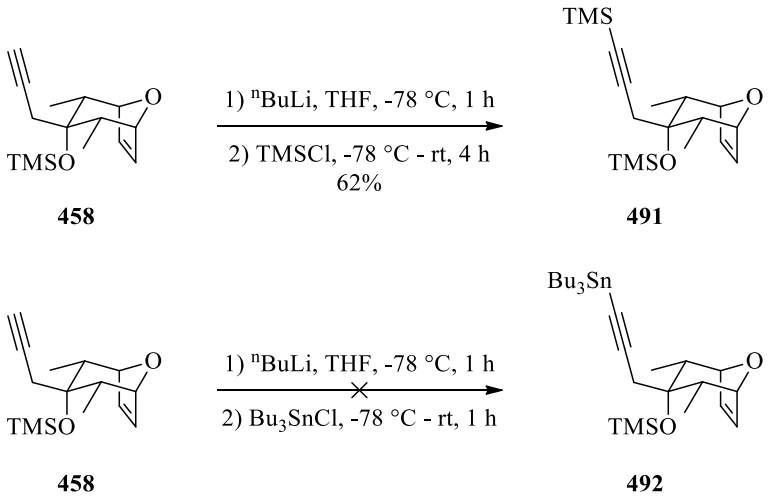
The poor reactivity of ketone **485** may be due to the presence of the α-oxygen substituent, which may cause an increased steric and electronic repulsion with an incoming nucleophile.

The lack of reactivity of **485** led to a change in strategy in using alkynylsilane **480** to generate alkylidene carbene **490**. As alkynylsilanes are commonly used to synthesise alkynyliodonium salts,[65c, 73a, 79] it was decided to use this approach to access the desired alkylidene carbene (**Scheme 222**). Additionally, the alkynylsilane could be converted to the alkynylstannane **488**, which would also serve as a viable precursor to alkynyliodonium salts.[75b, 77]



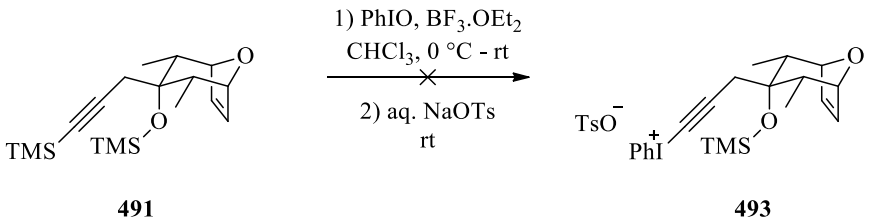
Scheme 222

It was decided to investigate the viability of this route using the simpler alkyne **458**, without the additional propargyl substitution. Alkyne **458** was readily converted into alkynylsilane **491** in moderate yield;[190] however conversion of **458** to the corresponding alkynylstannane **492** proved more problematic as **492** readily reverted back to the starting material (**Scheme 223**). Altering the work-up and basifying the column could not prevent this proto-demetallation from occurring, and following the reaction by TLC showed that this was occurring under the reaction conditions.



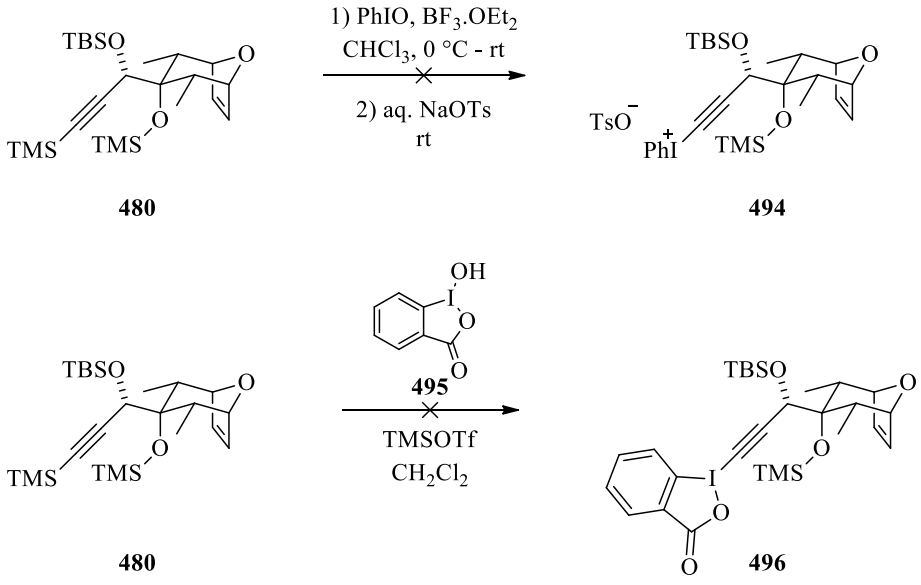
Scheme 223

Unfortunately, treating **491** with PhIO and $BF_3.OEt_2$ gave no recoverable products and TLC analysis of the reaction mixture indicated extensive decomposition (**Scheme 224**).[191]



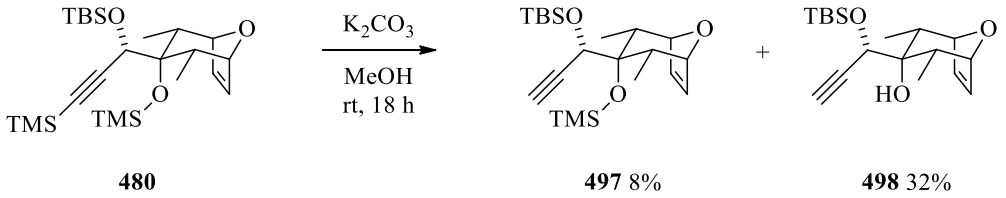
Scheme 224

Despite this lack of success, it was decided to attempt the reaction on the γ-silyloxy alkynylsilane. However, treating **480** with PhIO in the presence of $BF_3.OEt_2$ led to extensive decomposition of the starting material.[191] Similarly, nothing could be recovered from the reaction between **480** and 2-iodobenzoic acid derivative **495**, with TMSOTf as the Lewis acid (**Scheme 225**).[80]



Scheme 225

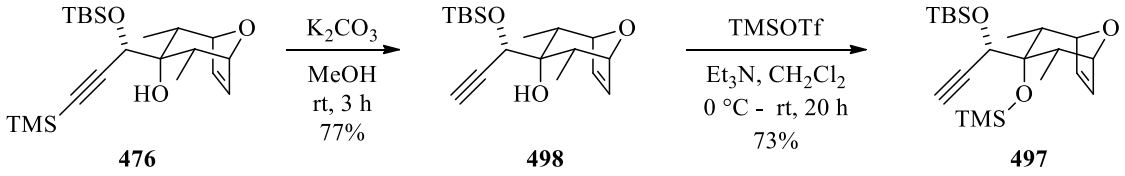
In order to progress towards the alkynylstannane **488**, it was necessary to remove the TMS group from the alkyne. Methanolysis of **480**,[192] successfully cleaved the desired TMS group, however the silyl group was also removed from the tertiary alcohol, giving both **497** and **498** in low yields (**Scheme 226**).



480 **497** 8% **498** 32%

Scheme 226

However, this problem could easily be solved by removing the silyl group from the alkyne prior to the protection of the tertiary alcohol (**Scheme 227**). Thus, treatment of **476** with methanolic K_2CO_3, gave **498** in 77% yield, which was subsequently reacted with TMSOTf to give **497** in 73% yield.



476 **498** **497**

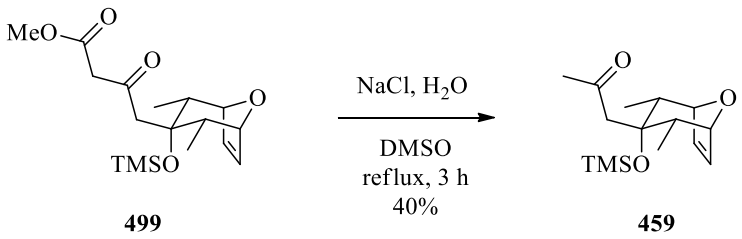
Scheme 227

However, the lack of success in synthesising the desired alkynyliodonium from alkynylsilanes, coupled with the difficulties experienced in synthesising the alkynylstannane without the additional oxygenation, led to this avenue of research being left unexplored.

2.8.2 Approach to α-alkoxy alkylidene carbenes using acetoacetates

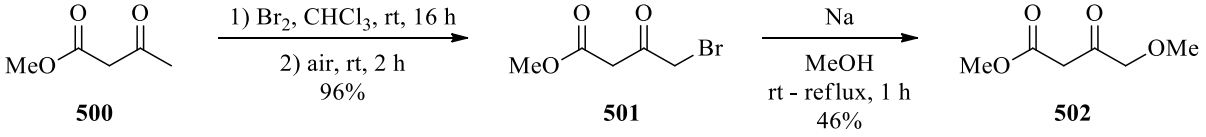
In conjunction with the research into the use of propargyl ethers as potential prcursors to ketone **469**, the possibility of synthesising **471** from γ-substituted acetoacetates was also investigated (**Scheme 212**).

Previous work in the Grainger group had demonstrated that a Krapcho decarboxylation of acetoacetate **499** offered a viable route to synthesise ketone (**Scheme 228**).[97] It was hoped that the introduction of an oxygen substituent prior to the decarboxylation would provide access to a ketone such as **469**.



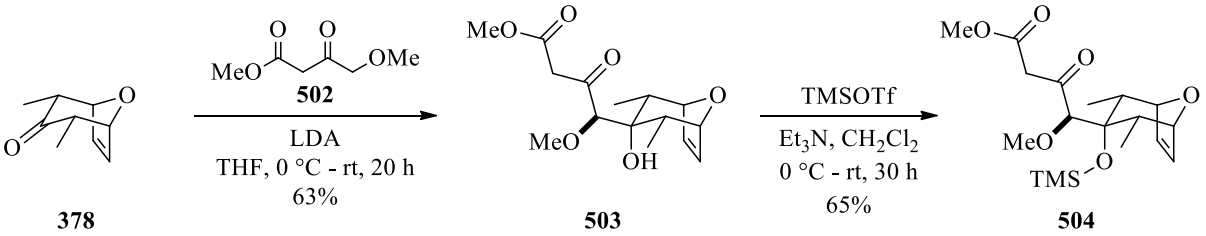
Scheme 228

Initial investigation focused on the use of the known acetoacetate **502**.[193] It was possible to synthesise **502** in two steps from methyl acetoacetate **500** *via* bromination to give **501**,[194] followed by subsequent displacement of the bromide with NaOMe (**Scheme 229**).[193]



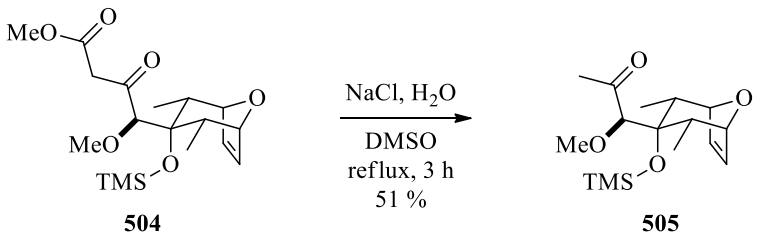
Scheme 229

Pleasingly, treatment of **502** with two equivalents of LDA, followed by addition to ketone **378** gave **503** in a reasonable yield.[97] Subsequent protection of the tertiary alcohol gave silyl ether **504** in 65% yield (**Scheme 230**).[97]



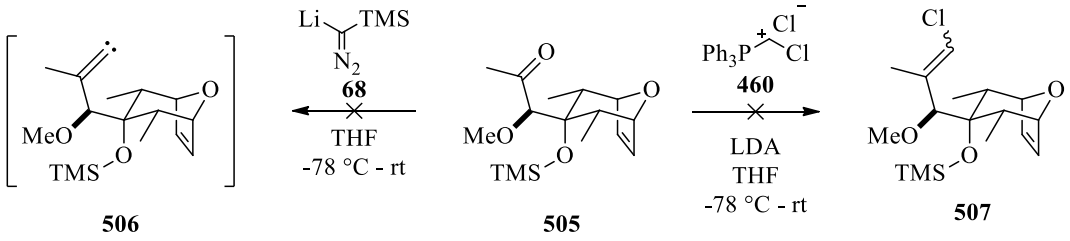
Scheme 230

Subjecting acetoacetate **504** to the Krapcho decarboxylation conditions subsequently gave the desired ketone **505** in 51% yield (**Scheme 231**).[97]



Scheme 231

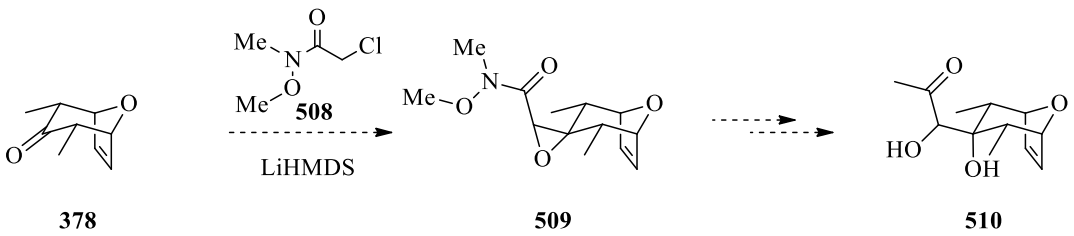
Disappointingly, as with ketone **485** (**Scheme 221**), ketone **505** proved unreactive to both the modified Peterson conditions[103b] and to the synthesis of the vinyl chloride **507** *via* a Wittig reaction,[97] demonstrating the poor reactivity of α-alkoxy ketones of this type (**Scheme 232**).



Scheme 232

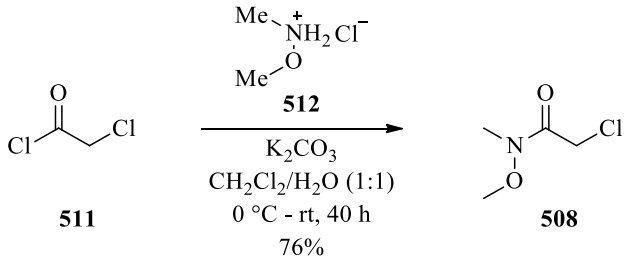
2.9 Alternative approaches to α-alkoxy ketones

In addition to the approaches described above, attempts were also made to synthesise α-alkoxy ketones using Weinreb amide **508** as a nucleophile (**Scheme 233**).[195] It was hoped that **508** would undergo a Darzens reactions with ketone **378** to give epoxide **509**, which could then be converted to the desired α-hydroxy ketone **510**.



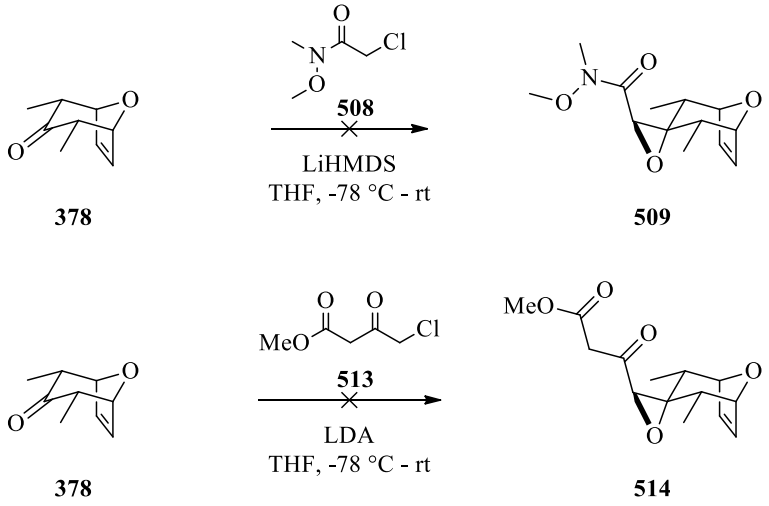
Scheme 233

Weinreb amide **508** was synthesised by treating chloroacetyl chloride **511** with amine salt **512** in the presence of K_2CO_3, affording **508** in 76% yield (**Scheme 234**).[196]



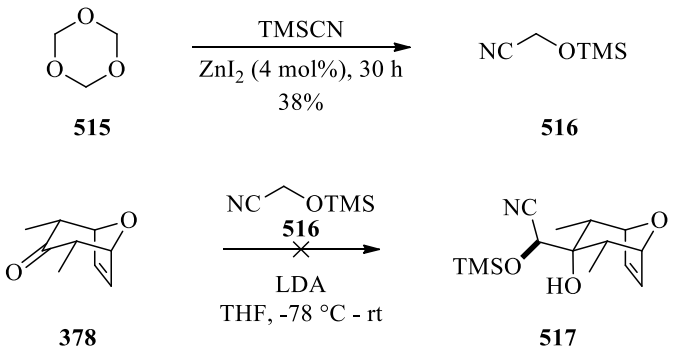
Scheme 234

Unfortunately, treating ketone **378** with amide **508** in the presence of LiHMDS gave no reaction (**Scheme 235**). Similarly, employing the γ-chloroacetoacetate **513** in the presence of excess LDA gave no conversion of starting material.



Scheme 235

The use of acetonitrile **516** as a nucleophile was also investigated. Cyanohydrin **516** was synthesised by treating 1,3,5-trioxane **515** with TMSCN in the presence of catalytic ZnI_2 (Scheme 236).[197] However, treating ketone **378** with **516** in the presence of LDA gave no reaction.[197]



Scheme 236

2.10 Conclusion

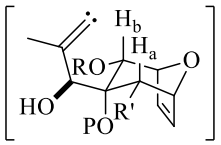
In conclusion, hydroxy cyclopentene annulation on oxabicyclic systems **402** and **423** using Kim's alkylidene carbene methodology has been achieved.[55] An efficient route to the alkylidene carbene precursors **402** and **423** has been developed, accessing the desired α,β-epoxy-*N*-aziridinylimines in 5-6 steps from the known bicyclic ketone **378**.[141] Attempts to employ other methods for α-alkoxy alkylidene carbene formation were thwarted by problems in the preparation of the carbene precursor.

Furthermore, the *in situ* formation of an alkoxy stereocentre β to the alkylidene carbene has been shown to result in diastereoselectivity in the 1,5 C-H insertion reaction. It has also been demonstrated that this diastereotopic group selectivity can be reversed by protecting the tertiary alcohol as its TMS ether.

Chapter three – Regioselective C-H insertion reactions

3.1 Introduction

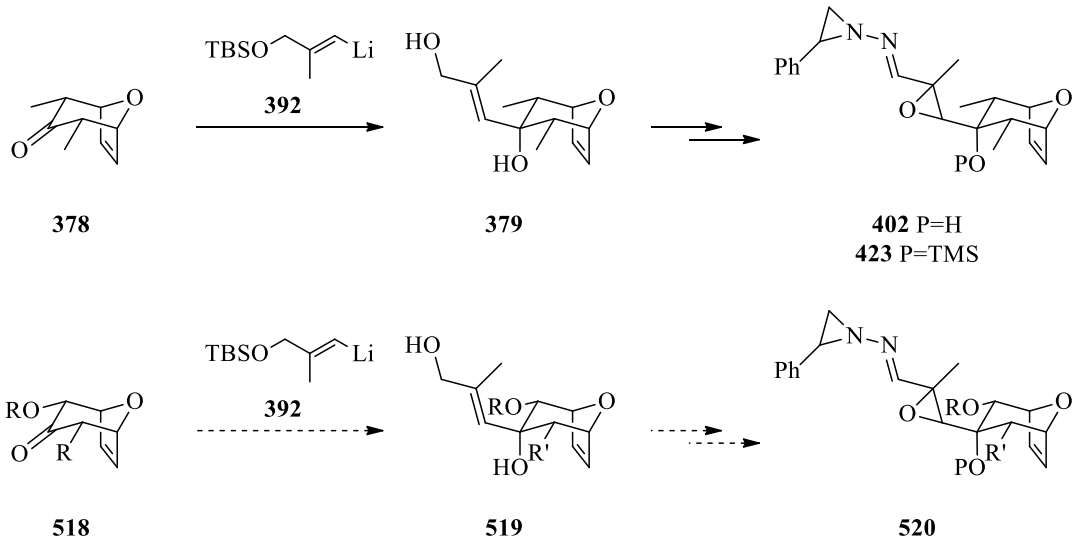
Due to the promising results obtained in the diastereoselective 1,5 C-H insertion reactions (**Chapter 2.5**), it was decided to employ the thermolysis of α,β-epoxy-*N*-aziridinylimines to investigate the selectivity of the insertion reaction of alkylidene carbene **375 (Figure 16)**.



375

Figure 16

In order to synthesise the desired aziridinylimine **520**, the methodology developed for the preparation of the aziridinylimines **402** and **423** from the dimethyl bicyclic ketone **378** was employed, beginning with the addition of vinyllithium **392** to ketone **518** to give diol **519** (**Scheme 237**).



378 **379** **402** P=H **423** P=TMS

518 **519** **520**

Scheme 237

The activating effect of an oxygen atom adjacent to a potential 1,5 C-H insertion site is well documented,[6, 95] so it was expected that alkylidene carbene **375** would preferentially insert into C-H_b to give **374** over **373** (**Scheme 146**).

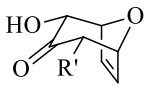
However, it has also been demonstrated that this activating effect can be decreased, and even completely suppressed, by altering the substituent on the oxygen atom (**Chapter 1**, **Page 66-69** and **78-80**).[22, 103] As the activating effect of the adjacent oxygen atom is believed to be the result of lone pair donation into the $\sigma^*_{C\text{-}H}$ orbital, this effect can potentially be reduced through the use of electron-withdrawing substituents,[22] as in **521**, or by fixing the orientation of the oxygen lone pairs such that overlap with the C-H anti-bonding orbital is less efficient,[103] as in **522** (**Figure 17**).

521
R=EWG

522

Figure 17

In order to investigate the electronic and stereoelectronic effects that would govern the regioselectivity of the C-H insertion reaction, ketone **523** was targeted as a potential versatile precursor to carbenes such as **521** and **522**, allowing for a range of functionalisation at the alcohol (**Figure 18**).



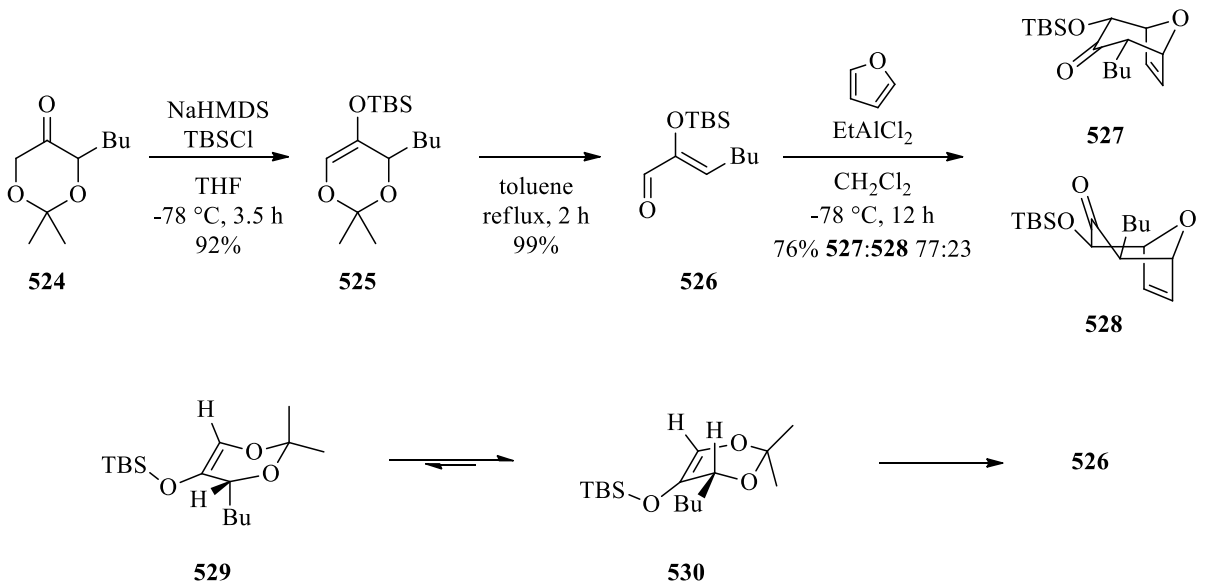
523

Figure 18

3.2 Synthetic approaches to α-alkoxy ketones

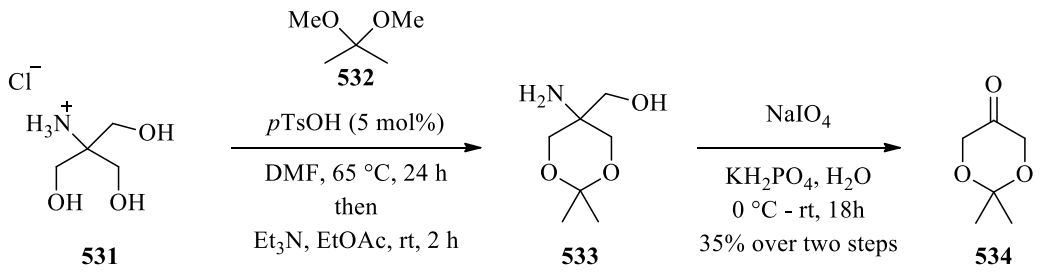
The α-silyloxy ketone **527** (**Scheme 238**) was thought to be an ideal bicyclic system on which to investigate the regioselectivity of the alkylidene carbene insertion reaction, as the silyl group could be readily altered. Additionally, the presence of the alkyl chain would serve as a mimic for the C-ring of ingenol, giving an indication as to how its presence would affect the selectivity of the insertion reaction.

Funk described the synthesis of bicyclic ketone **527** in three steps from dioxanone **524** (**Scheme 238**).[198] Formation of the kinetic silyl enol ether **525** was followed by a retrocycloaddition to selectively give the (*Z*)-isomer of the (silyloxy)enal **526**, with loss of acetone. Enol **526** was subsequently treated with furan in the presence of $EtAlCl_2$ to afford ketone **527** as the major isomer. The stereoselectivity observed in the formation of (silyloxy)enal **526** was thought to be due to a preference for the reaction to proceed *via* a boat-like conformer **530**, as opposed to **529** which suffers increased destabilisation due to the flagpole-flagpole interaction between the axial oxygen lone pair and the butyl group.



Scheme 238

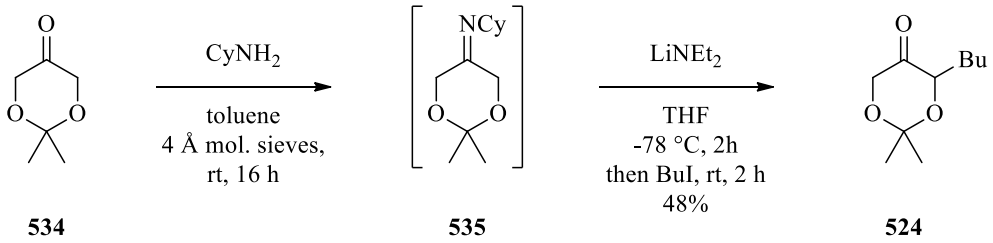
Dioxanone **534** was synthesised in two steps *via* a transketalisation between the commercially available Trizma hydrochloride **531** and 2,2-dimethoxypropane **532**, followed by oxidative cleavage of the resulting β-amino alcohol **533** (**Scheme 239**).[199]



Scheme 239

Previous use of dioxanone **534** in the Grainger group had shown it to be strongly hydrophilic, and multiple extractions (>25) were often required to ensure efficient recovery from the aqueous phase. This problem was circumvented through the use of a continuous extractor, which allowed for much more efficient extraction of the aqueous phase. Despite this, the yield was much lower than the 73% reported in the literature.[199]

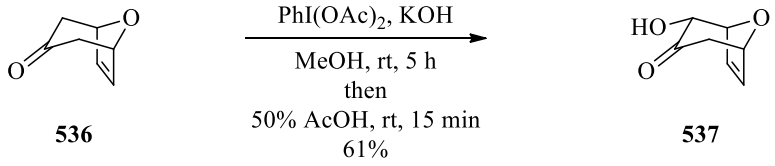
Subsequent alkylation of **534** was carried out by treatment with cyclohexylamine, to give the imine **535**, followed by $LiNEt_2$ and butyl iodide, affording **524** in 48% yield (**Scheme 240**).[198]



Scheme 240

Unfortunately, all attempts to repeat this methodology proved unsuccessful. The silyl enol ether proved difficult to isolate in pure form, and taking the impure product through the rest of the synthetic route did not give the desired ketone.

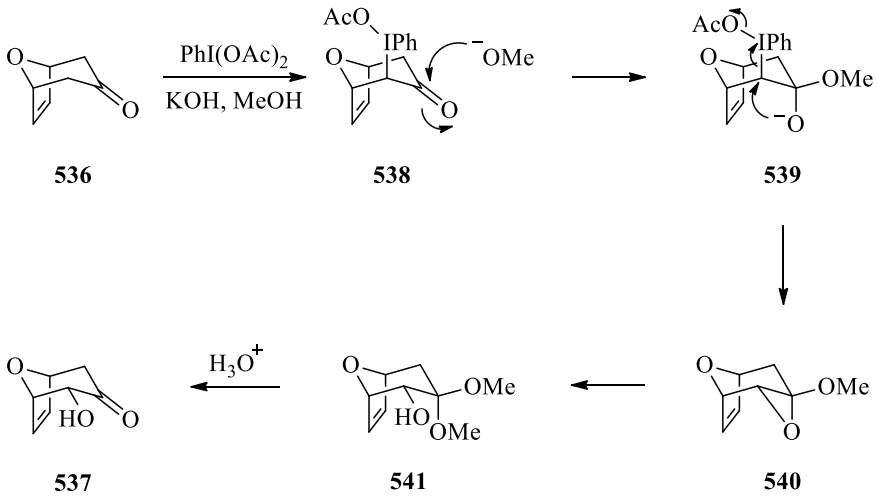
As a result of these difficulties, a new approach was devised. Cha had previously described the α-oxidation of **536** using Moriarty conditions to give **537**, with the hydroxyl group exclusively in the equatorial position (**Scheme 241**).[200]



536 **537**

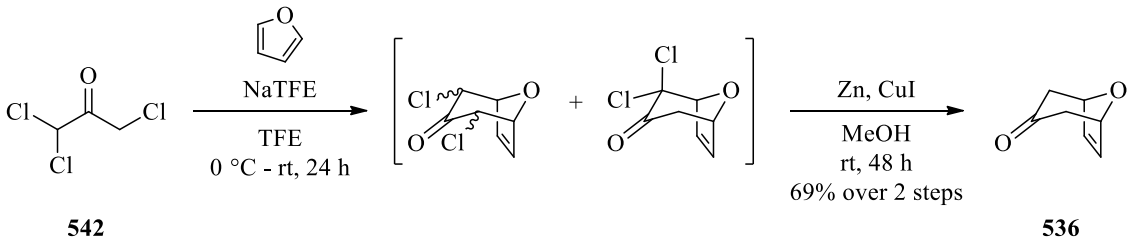
Scheme 241

The stereochemistry obtained is opposite to that observed when **536** is oxidised under Rubottom conditions or upon direct oxidation of the enolate, where the axial isomer dominates.[201] Initial attack of the enolate onto the $PhI(OAc)_2$ places the electrophile in the axial position, giving **538**. Subsequent attack on the ketone by methoxide generates an axial oxyanion **539**, which cyclises to give ketal **540**, liberating the phenyl iodide. The epoxide is then opened forming acetal **541**, with the hydroxyl group in the equatorial position. Hydrolysis of the acetal gives the desired ketone **537** (**Scheme 242**).



Scheme 242

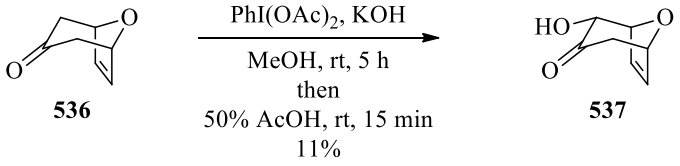
Bicyclic ketone **536** was synthesised *via* [4+3] cycloaddition between TCA **542** and furan in the presence of NaTFE, followed by dechlorination with a Zn/Cu couple, conditions developed by Föhlisch (**Scheme 243**).[202]



542 **536**

Scheme 243

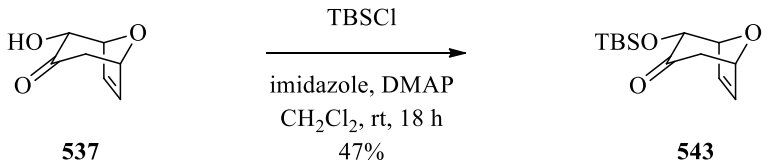
Unfortunately, when the Moriarty/Cha oxidation was attempted, it proved difficult to replicate the results achieved in the original publication, and **537** could only be isolated in very low yields, despite full conversion by TLC analysis (**Scheme 244**). It was believed that the product may be lost in the aqueous phase of the work-up. Removal of the MeOH prior to work-up failed to increase the recovery. Similarly, saturating the aqueous phase with NaCl or NH_4Cl did not improve the yield.



536 **537**

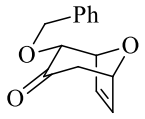
Scheme 244

Despite these difficulties, sufficient α-hydroxy ketone **537** was recovered to continue the synthesis. Thus, **537** was reacted with TBSCl to give the α-silyloxy ketone **543**, in moderate yield (**Scheme 245**).[201]



Scheme 245

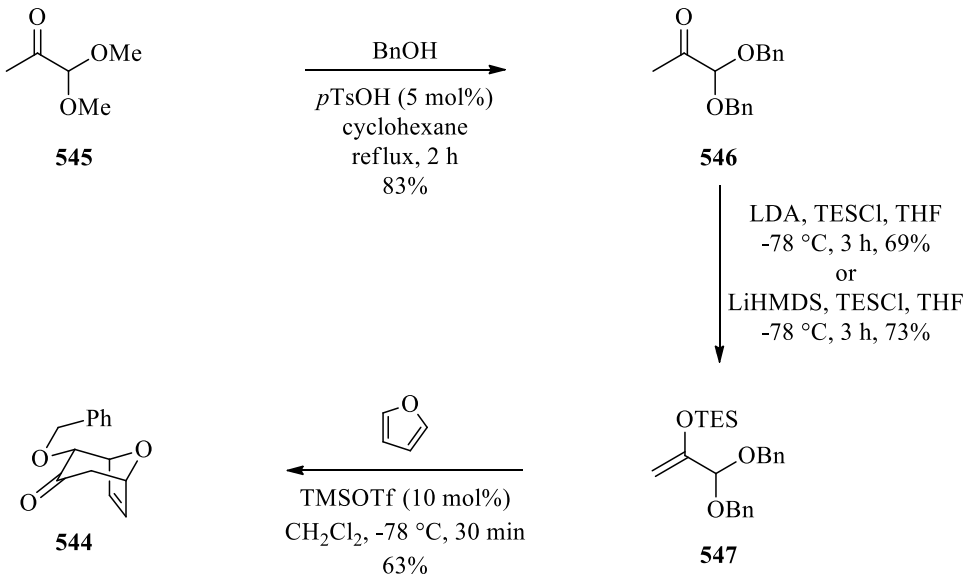
While it was felt that it would not be difficult to improve on the 47% yield obtained for the alcohol protection, the consistently poor yields obtained for the α-hydroxylation reaction did not make this a suitable route to a 2-oxygenated bicyclic ring system on which to investigate the regioselectivity of the alkylidene carbene insertion reaction. Instead, it was decided to use the known α-benzyloxy bicyclic ketone **544** to carry out the initial studies (**Figure 19**).[203] This would allow the regioselectivity of the insertion reaction to be investigated using a reasonably electronically neutral oxygen substituent, before attempting the reaction with alternative substituents. Potentially, the benzyl group could also be removed to give the free alcohol **537**.



544

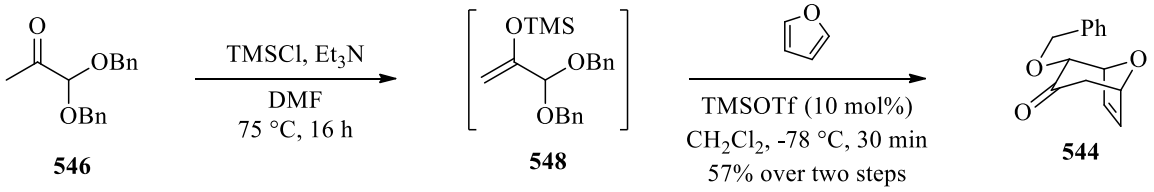
Figure 19

Ketone **544** was synthesised in three steps from the commercially available acetal **545** (**Scheme 246**).[203] Transacetalisation to the dibenzyl acetal **546** occurred in 83% yield, and subsequent formation of silyl enol ether **547**, using either LDA or LiHMDS as the base proceeded smoothly. The silyl enol ether **547** underwent [4+3] cycloaddition with furan in the presence of TMSOTf, to afford the desired ketone **544** in 63% yield. The yields obtained were comparable to those reported in the literature.[203]



Scheme 246

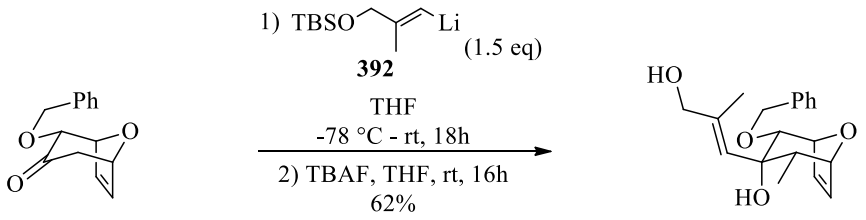
The reaction was amenable to scale up; on larger reaction scales (>30 mmol) silyl enol ether **548**, synthesised from **546** under thermodynamic conditions, was used in place of **547**. This gave **544** in 57% yield over two steps, similar to the literature yield (**Scheme 247**).[203]



Scheme 247

3.2 Synthesis of α,β-epoxy-*N*-aziridinylimines

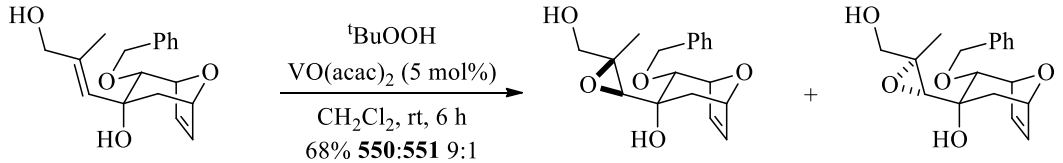
The desired aziridinylimines were synthesised using an analogous route as had previously been optimised on the dimethyl-substituted bicyclic system (**Chapter 2.4**). Initial nucleophilic addition of vinyllithium **392** to ketone **544**, followed by deprotection of the primary allylic alcohol, afforded the diol **549** in 62% yield (**Scheme 248**).



544 549

Scheme 248

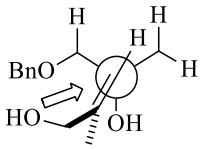
Epoxidation of **549** with catalytic $VO(acac)_2$ and ^tBuOOH gave a mixture of diastereoisomers **550** and **551** in 68% yield, in a 9:1 ratio (**Scheme 249**).[155b, 156] It was not possible to fully separate the isomers by column chromatography; however the majority of the major isomer could be isolated cleanly.



549 550 551

Scheme 249

It was demonstrated, through nOe studies carried out on **558** (*vide infra*), that **550** was the major isomer. This suggests that the epoxidation occurs through a structure such as **552**, where both the hydroxyl group and the benzyl ether can coordinate to the vanadium catalyst (**Figure 20**).[204]

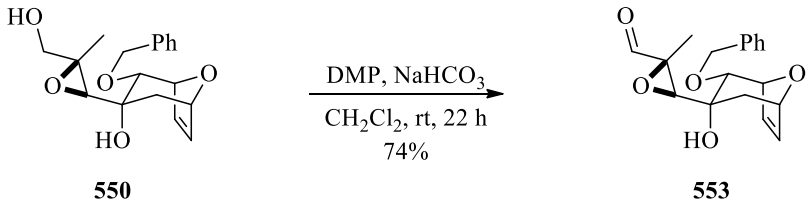


552

Figure 20

Oxidation of the major isomer to the corresponding aldehyde was carried out using DMP in the presence of $NaHCO_3$, affording **553** in 74% yield (**Scheme 250**).[159] The oxidation

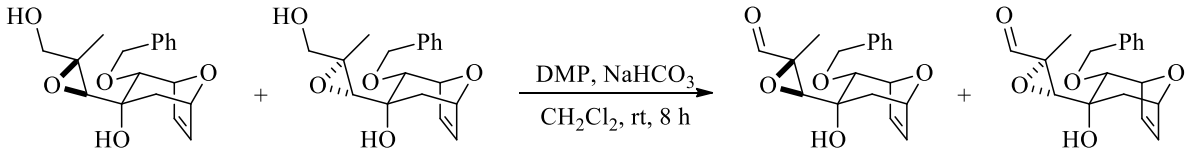
proved to be slower than the analogous reaction on the dimethyl-substituted bicyclic system **399** (**Scheme 169**), with additional DMP and longer reaction times required.



550 **553**

Scheme 250

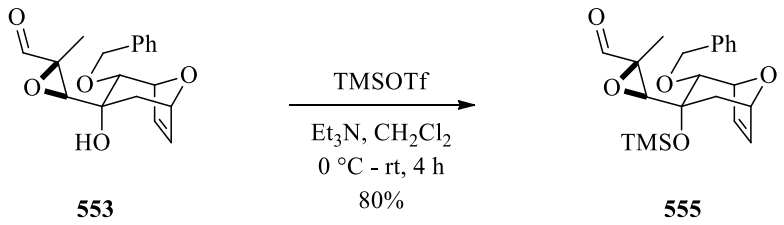
A 1:1 mixture of alcohols **550** and **551**, which could not be separated previously, was reacted under the same conditions (**Scheme 251**), and the corresponding aldehydes proved easier to separate, allowing the minor aldehyde **554** to be characterised. However, as it could only be recovered in low yields, it was not taken further in the synthetic sequence towards the aziridinylimine. It was not clear why the mixture of alcohols should give such poor yields compared to that for the pure alcohol.



550 1:1 **551** **553** 14% **554** 12%

Scheme 251

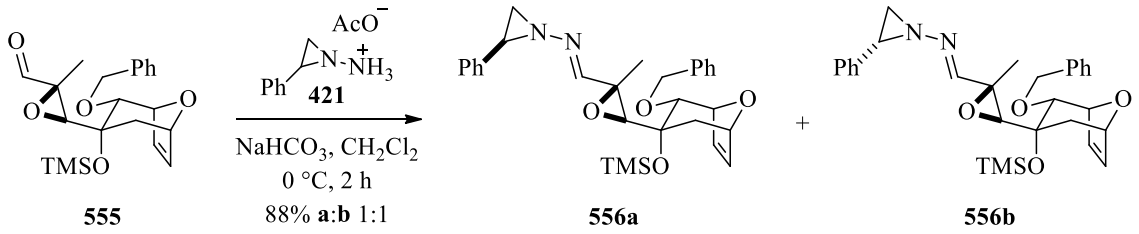
Optimisation work carried out on the dimethyl system had demonstrated that protection of the tertiary alcohol was necessary to ensure efficient synthesis of the aziridinylimine (**Chapter 2.4.6**). Therefore aldehyde **553** was treated with TMSOTf to afford silyl ether **555** in 80% yield (**Scheme 252**).[97]



553 **555**

Scheme 252

The subsequent condensation reaction between **555** and hydrazine salt **421** gave a 1:1 mixture of aziridinylimines **556a** and **556b** in excellent yield (**Scheme 253**). Both isomers could be separated and fully characterised. The mixture of diastereoisomers was used in the thermolysis reactions as the aziridine stereocentre would be lost.



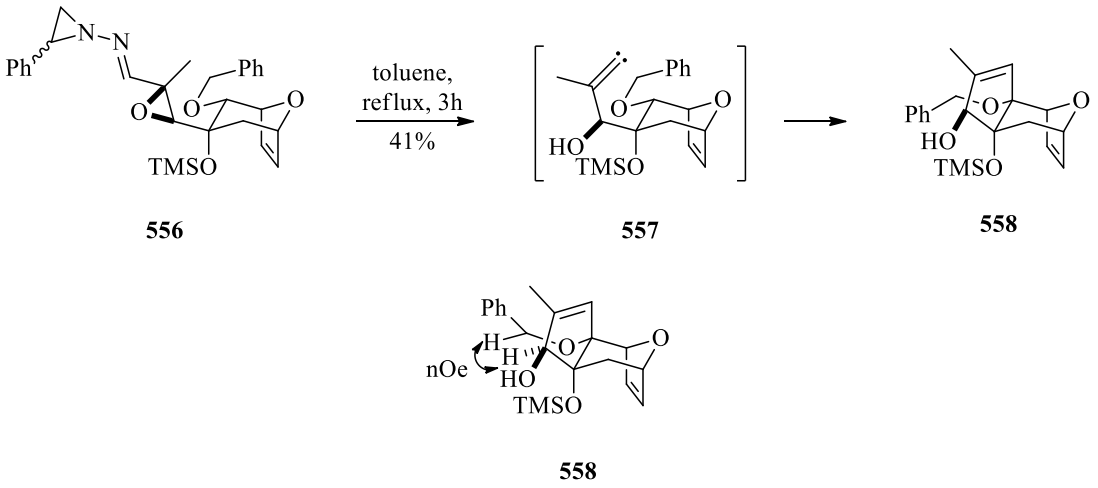
555 **556a** **556b**

Scheme 253

3.3 Thermolysis of α,β-epoxy-*N*-aziridinylimines

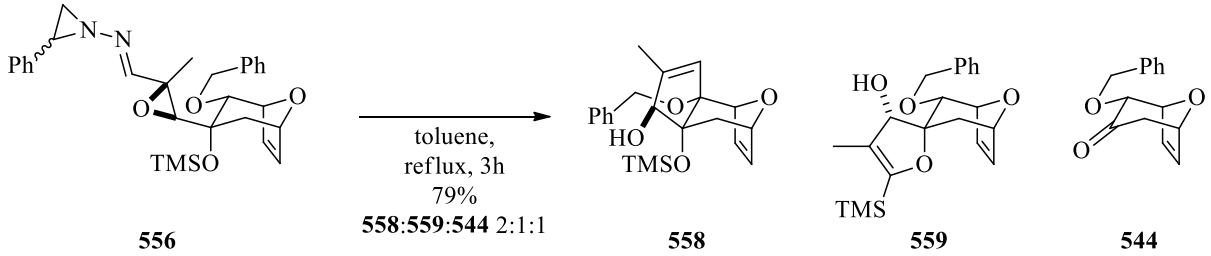
3.3.1 Thermolysis of α,β-epoxy-*N*-aziridinylimine 556

When the mixture of **556a** and **556b** was refluxed in toluene, three new products were visible by TLC analysis. However, only the cyclopentenol **558**, the results of selective 1,5 C-H insertion of alkylidene carbene **557**, could be isolated from the reaction mixture (**Scheme 254**).[55] The stereochemistry of **558** was confirmed by nOe analysis which showed a signal between the proton adjacent to the alcohol and one of the benzylic protons. This established that **550** was the major isomer in the epoxidation reaction (**Scheme 249**).



Scheme 254

Analysis of the ^{1}H NMR of the crude reaction mixture led to the remaining two products being identified as vinyl silane **559** and bicyclic ketone **544** (**Scheme 255**). Overall, the thermolysis of **556** afforded **558**, **559** and **544** in a 79% combined yield, in a 2:1:1 ratio.

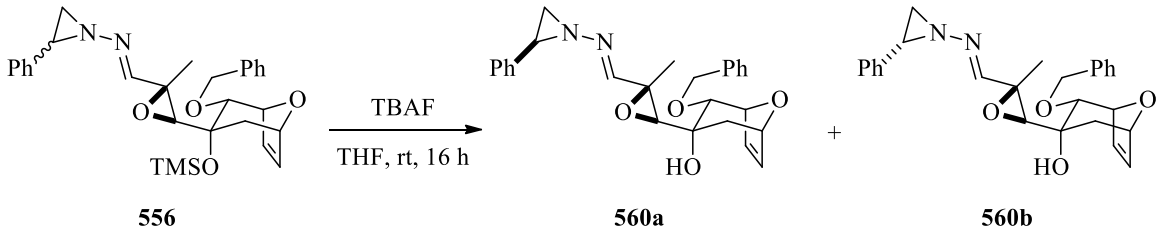


Scheme 255

In an effort to isolate **559**, the crude reaction mixture was treated with TBAF, in order to separate **558** from **559** and **544**. Unfortunately, **559** was found to decompose rapidly when purification of this reaction was attempted, and could not be isolated. Vinyl silane **559** was presumably formed by insertion of carbene **557** into the O-Si bond**.** Ketone **544** was likely formed *via* the C-C bond fragmentation that had been observed during the diastereoselectivity investigations (**Chapter 2.7**).

3.3.2 Thermolysis of α,β-epoxy-*N*-aziridinylimine 560

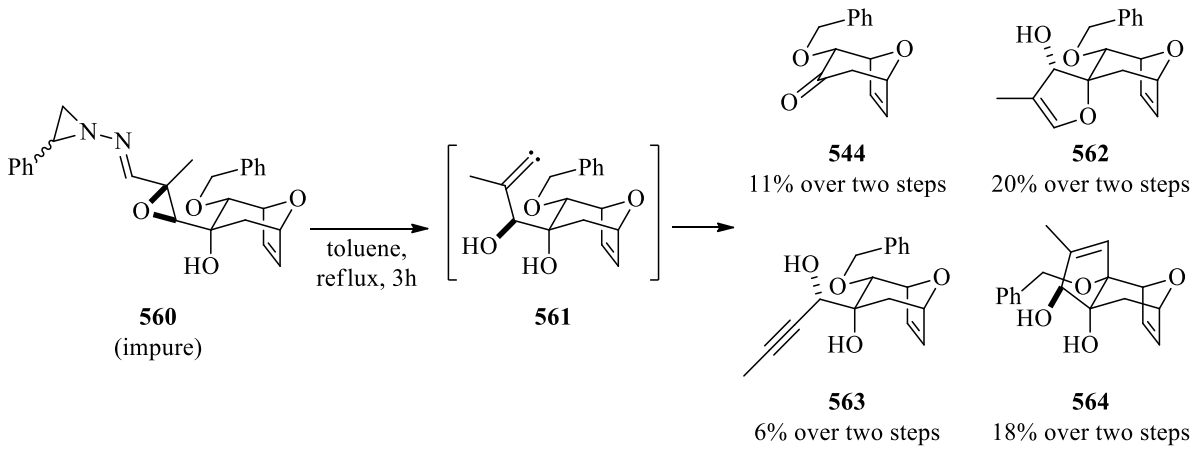
In order to investigate how the presence of the tertiary alcohol would affect the selectivity of the insertion reaction, the mixture of **556a** and **556b** was treated with TBAF (**Scheme 256**).[148]



556 **560a** **560b**

Scheme 256

Unfortunately, the two alcohols **560a** and **560b** could not be isolated cleanly, even when Et_3N was added to the eluent to prevent decomposition. As a result, the partially purified mixture was exposed to the conditions for the thermolysis reaction (**Scheme 257**).[55]



560 (impure) **561**

544 11% over two steps

562 20% over two steps

563 6% over two steps

564 18% over two steps

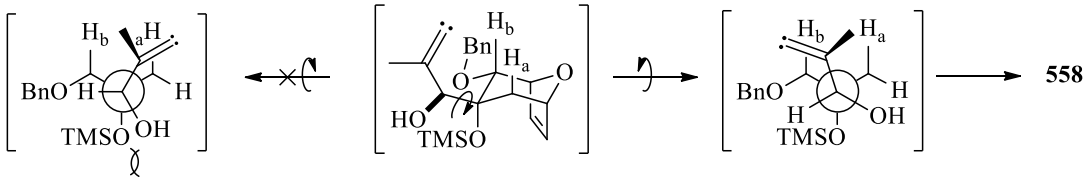
Scheme 257

TLC analysis of the reaction mixture indicated the formation of four new products. Fortunately, all four could be isolated and were identified as ketone **544**, dihydrofuran **562**, propargylic alcohol **563** and cyclopentenol **564**. The presence of **562**, **563** and **564** were indicative of the generation of alkylidene carbene **561**.

3.4 Explanation of selectivity

In the thermolyses of both the silyl ether **556** and alcohol **560**, there is no evidence of any insertion into the methylene group of the bicyclic system. The presence of an oxygen substituent adjacent to one of the potential C-H insertion sites is known to activate this site towards reaction,[6, 95] explaining why the only C-H insertion seen in both cases is at that position.

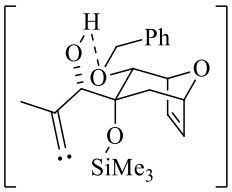
With the TMS protected substrate, the steric and electronic repulsion between the OTMS group and the newly formed alcohol would further direct the alkylidene carbene to react at this site, acting in concert with the stereoelectronic preference for reaction at this position (**Scheme 258**).



565 **557** **566**

Scheme 258

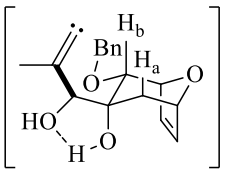
The formation of dihydrofuran **559** *via* insertion of the alkylidene carbene into the O-Si bond could potentially be encouraged through a hydrogen-bonding interaction between the newly formed alcohol and the neighbouring benzyl ether **567** (**Figure 21**). However, it is interesting to note that this reaction is less favourable than the C-H insertion reaction.[11b]



567

Figure 21

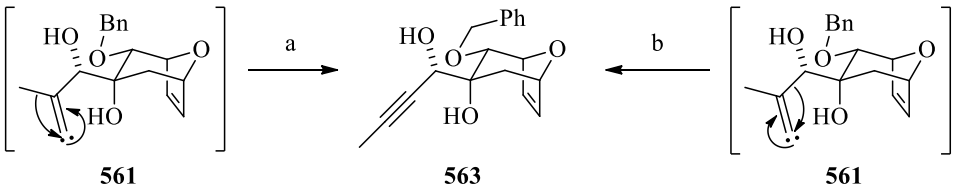
In the unprotected substrate **561**, there is a possibility of hydrogen bonding within the newly formed vicinal diol. However, such an interaction would direct the alkylidene carbene away from reaction at the tertiary C-H bond (**Figure 22**).



561

Figure 22

The lack of insertion at the CH_2 suggests that the stereoelectronic effect which accelerates reaction at the methine overrides any potential directing effect present in the new vicinal diol which may encourage reaction at the methylene. However, the formation of propargyl alcohol **563** suggests that this interaction may result in a decrease of the rates of C-H insertion and O-H insertion. From alkylidene carbene **561**, either the methyl substituent (route a) or the α-hydroxy alkyl group (route b) must undergo a 1,2-migration in order to form **563** (**Scheme 259**).



561 **563** **561**

Scheme 259

Wills has previously demonstrated both methyl and α-alkoxy alkyl to have poor migratory aptitude, and so alkylidene carbenes bearing these substituents preferably undergo insertion reactions (**Scheme 9**).[19b] However, Wardrop reported the competing alkyne formation through either migration of a methyl group or an α-amino alkyl group when attempting to carry out insertion into a conformationally rigid and sterically hindered C-H,[102] both of which would cause the rate of insertion to decrease (**Scheme 113**).[103b] The formation

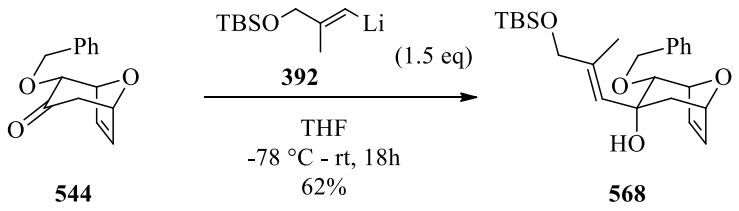
of **563**, even in low amounts such as in this case, suggests that the rate of C-H insertion and O-H insertion has been retarded to such a degree that other, generally less favourable pathways are able to occur.

The formation of dihydrofuran **562** may also be the result of the same hydrogen bonding interaction between the newly formed alcohol and the benzyl ether that has been proposed for the thermolysis of the TMS ether (**Figure 21**). The formation of ketone **544** is again thought to be due to the same C-C bond fragmentation seen previously.

3.5 Attempts to alter the oxygen substituent

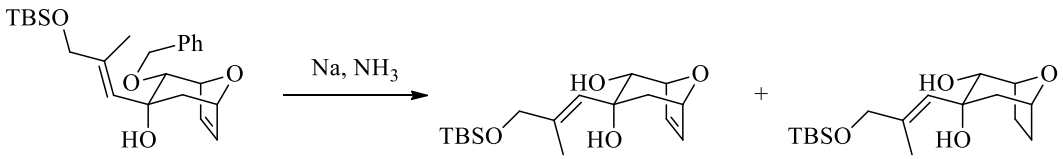
The results obtained with the 2-benzyloxy substituted system demonstrated that the directing effect in the new vicinal diol was not sufficient to override the stereoelectronic preference for the alkylidene carbene to insert into the C-H bond adjacent to the oxygen atom. As such, it was clear that the oxygen substituent would need to be altered in order to decrease the degree to which the oxygen lone pair could activate the C-H bond towards insertion.

Previous attempts to synthesise a bicyclic ketone which would allow for ease of access to a range of 2-alkoxy substituted bicyclic systems had been unsuccessful. Therefore, it was decided to attempt to remove the benzyl substituent, giving access to the free alcohol. It was felt that it was best to attempt this after the addition reaction had been carried out. As such, the mono-silylated diol **568** was synthesised using the optimised procedure described previously (**Scheme 260**).



Scheme 260

The presence of the two alkene groups meant that the benzyl group could not be removed *via* hydrogenolysis, and so it was decided to attempt the deprotection using dissolving metal, as this had been shown to cleave benzyl groups in the presence of alkenes.[205] However, while treating **568** with sodium in ammonia gave rise to the desired alcohol **569**, the over-reduced product **570** was recovered in almost equal amounts (**Scheme 261**).[206]



568 **569** 32% **570** 28%

Scheme 261

This result was somewhat surprising as sodium metal generally will not reduce alkenes.[205] It is unclear why it is possible to reduce the ethylene bridge in this instance.

This disappointing result suggested that this was not an appropriate method by which to investigate how altering the oxygen substituent would affect the regioselectivity of the C-H insertion reaction.

3.6 Conclusion

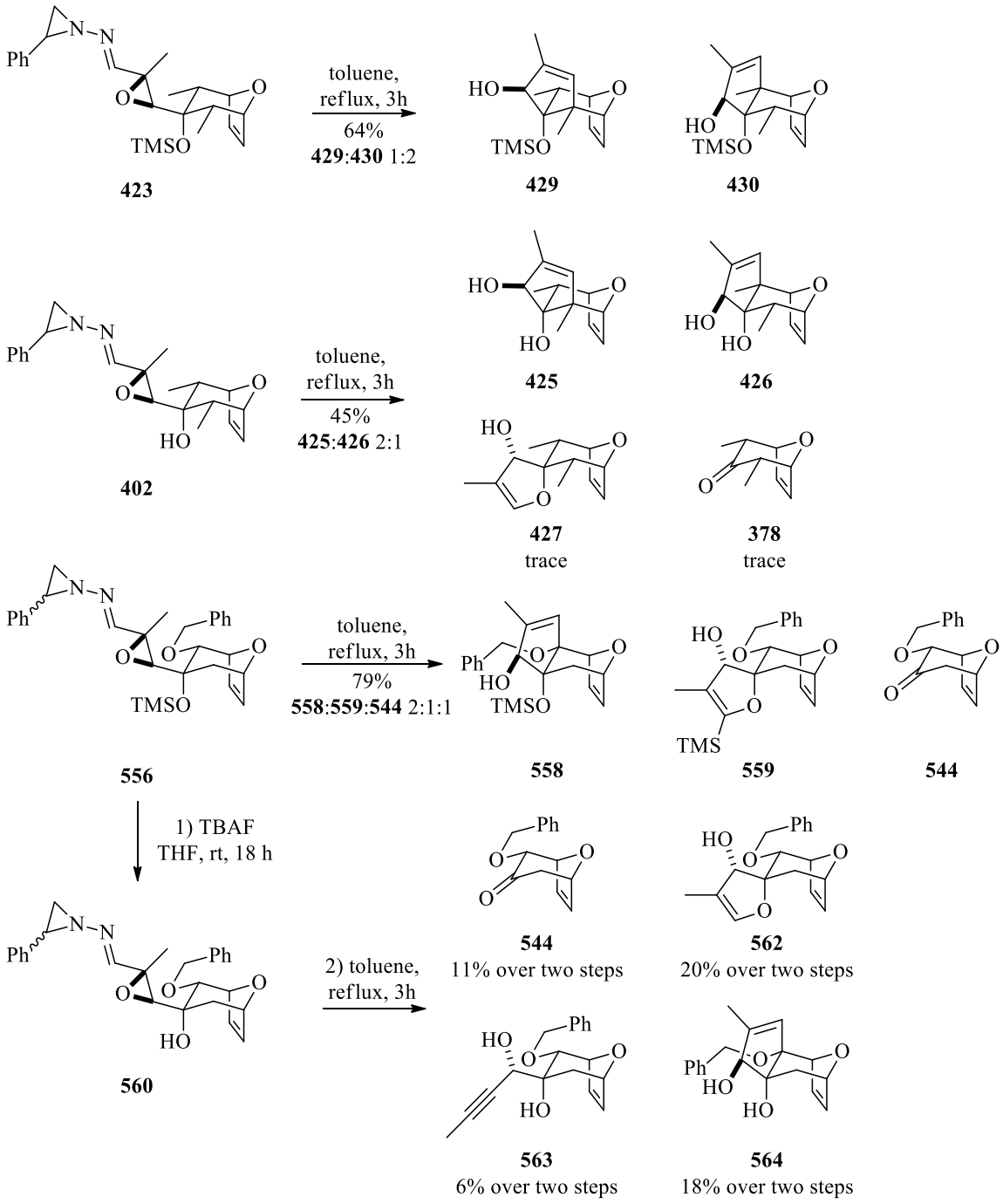
In summary, it has been possible to extend the hydroxy cyclopentene annulation using the Kim alkylidene carbene methodology to oxabicyclic systems carrying an additional benzyloxy substituent. The stereoelectronic preference for insertion next to the oxygen substituent overrides a potential intramolecular hydrogen bonding effect which would be expected to direct insertion towards a less electronically favoured site. A more generally unfavourable 1,2 migration process occurs for tertiary alcohol **560** (but not silyl ether **556**) suggesting the presence of such hydrogen bonding may affect the rate of the potential insertion reactions.

Difficulties encountered in synthesising alternative α-alkoxy oxabicyclic ketones meant it was not possible to investigate how altering oxygen substituent would affect the chemo- and regioselectivity obtained.

Chapter four – Comparison between dimethyl and benzyloxy-substituted bicyclic systems

4.1 Introduction

The results obtained in the thermolysis of α,β-epoxy-*N*-aziridinylimines **423**, **402**, **556** and **560** had raised a number of question about the reactivity of alkylidene carbenes in 8-oxabicyclic systems (**Scheme 262**).



Scheme 262

Apart from the trace of dihydrofuran **427** observed in the thermolysis of **402**, the alkylidene carbenes generated in the dimethyl oxabicyclic system (i.e. from **423** or **402**) showed little tendency towards insertion into the O-H or O-Si bond. This was surprising because these processes are generally faster than C-H insertion.[11b] In contrast, in the benzyloxy substituted system (**556** or **560**), O-Si and O-H insertions were a competing process, leading to dihydrofurans **559** and **562**.

Previous work in the Grainger group has also documented the lack of O-Si insertion when alkylidene carbenes were generated in a similar dimethyl-substituted 8-oxabicyclic system.[97] This lack of reactivity was attributed to the fact that the alkylidene carbene would need to pass through a high energy conformation in order to achieve the necessary interaction between the oxygen lone pair and the empty p-orbital of the alkylidene carbene for O-Si insertion to occur (**Scheme 103**).

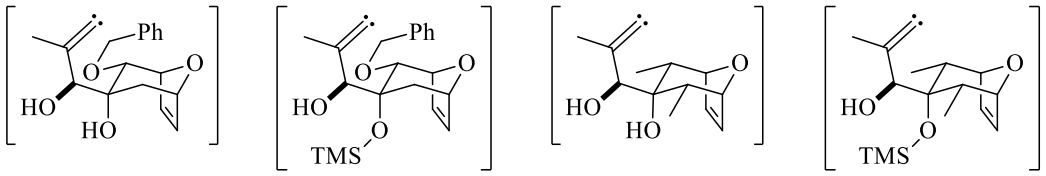
As the steric environment of the tertiary silyl ether of **402** and **556** was somewhat similar, the same interaction was expected to diminish the amount of insertion at oxygen in the benzyloxy-substituted bicycle system, especially as the oxygen substituent would be expected to accelerate the rate of insertion at the adjacent C-H bond. However, only a modest preference for C-H insertion is seen, with the ratio of C-H insertion **558** to O-Si insertion **559** found to be 2:1. Conversely, the thermolysis of **423** showed no evidence for O-Si insertion.

Thermolysis of alcohol **402** gave a small amount of insertion into the O-H bond (~6:1 in favour of C-H insertion). However, thermolysis of the corresponding benzyloxy derivative **560**, gave O-H insertion and C-H insertion in approximately equal proportions.

Removal of the TMS group would reduce the steric interactions during C-O bond rotation. Furthermore the O-H bond would have a different nature to the O-Si bond, which may allow formal O-H insertion to occur *via* a different mechanism. However, neither of

these considerations adequately explains why the dihydrofuran **562** is formed in much higher proportions in the benzyloxy substituted system.

Lee has previously reported that insertion into C-H bonds in a conformationally rigid environment is slower than reaction with C-H bonds in a more flexible environment.[103b] The conformational rigidity of both **561** and **557** (**Figure 23**) may result in their C-H insertion reactions being somewhat retarded, allowing reaction at the oxygen substituents to compete. However, **424** and **428** would be expected to have similar levels of rigidity, ruling this out as a major contributor to the increase in oxygen insertion observed in the benzyloxy substituted system.



561 **557** **424** **428**

Figure 23

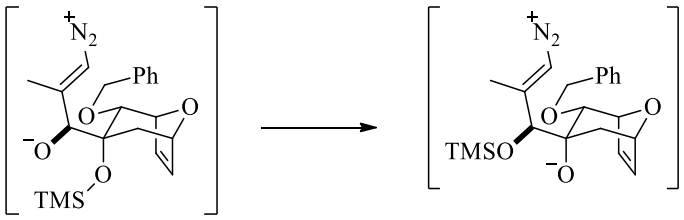
As has previously been proposed (**Chapter 3.4**), it is possible that hydrogen bonding between the secondary alcohol and the benzyl ether may be responsible for the increase in O-Si/O-H insertion observed in the thermolysis of **556** and **560** (**Figure 21**). Such an interaction would orientate the alkylidene carbene towards the oxygen substituent, thus favouring reaction at that site.

The isolation of propargyl alcohol **563** suggests that the insertion of alkylidene carbene **561** into either the C-H bond or the O-H bond is somewhat slower than insertion of alkylidene carbenes **424** and **428**, and is slower even compared to the alkylidene carbene **557** (**Figure 23**).

It is believed that hydrogen bonding within the newly formed vicinal diol, which would orientate the alkylidene carbene away from both the tertiary C-H and the O-H, is

responsible for these reactions being slower (**Figure 22**). While this could, in theory, promote reaction at the CH_2, analogous to tertiary C-H of the dimethyl substituted system **402**, alkylidene carbene 1,5 C-H insertion reactions at secondary C-H bonds are about six times slower than reaction at tertiary C-H bonds, so this is less likely to occur.[94] The reduced rate of the insertion reactions may allow for 1,2 migration to occur, especially considering the elevated temperature under which the reaction is conducted. Additionally, while trace amounts of the dimethyl bicyclic ketone were visible in the thermolysis of **402**, the TMS ether **423** gave no similar reaction. However, both benzyloxy derivatives **556** and **560** underwent this C-C bond fragmentation process as a competing process. It has previously been proposed that this fragmentation was the result of the alkoxide **147** from the opening of the epoxide being trapped before undergoing proton transfer from the vinylic carbon (**Scheme 52**).

For a similar process to occur during the thermolysis of **556**, the TMS group must be transferred from the tertiary alcohol of **571** to the secondary alcohol to give **572** (**Scheme 263**). This would suggest that the TMS group is more accessible in the OBn bicyclic system than in the dimethyl system. Such an increase in accessibility could also explain the increase in O-Si insertion observed in the benzyloxy system.

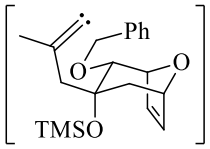


571 **572**

Scheme 263

In order to identify the reasons behind the differences in reactivity of the dimethyl and benzyloxy substituted bicyclic systems, it was necessary to demonstrate what role, if any, the additional hydroxyl group played in the observed reactivities. As such, it was decided to

investigate the reactivity of alkylidene carbene **573**, which does not possess a hydroxyl group α to the alkylidene carbene (**Figure 24**).



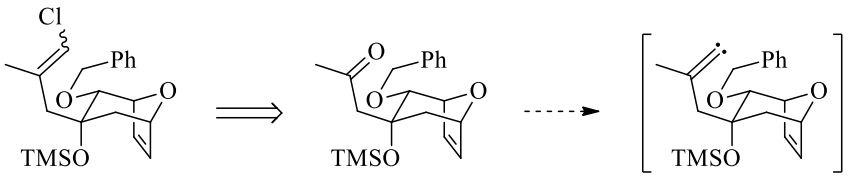
573

Figure 24

In addition, it was decided to investigate whether the method used to generate the alkylidene carbene would affect the chemoselectivity of the alkylidene carbene. Taber had previously reported an increased level of regioselectivity when generating metal carbenoids as opposed to carbenes (**Scheme 105**),[95b] however there are no reports on how a such a change affects chemoselectivity.

4.2 Proposed synthetic route

Deprotonation of vinyl chlorides has previously been successfully employed by the Grainger group for the *in situ* generation of alkylidene carbene in 8-oxabicyclic systems.[97] Therefore, **574** was deemed to be an appropriate target precursor (**Scheme 264**). Additionally, as **574** would be was synthesised from the corresponding ketone **575**, the 'naked' carbene could also be accessed readily.

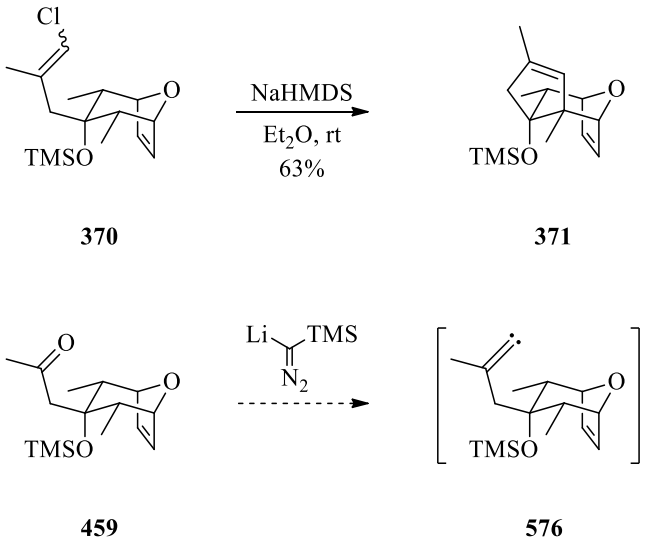


574 **575** **573**

Scheme 264

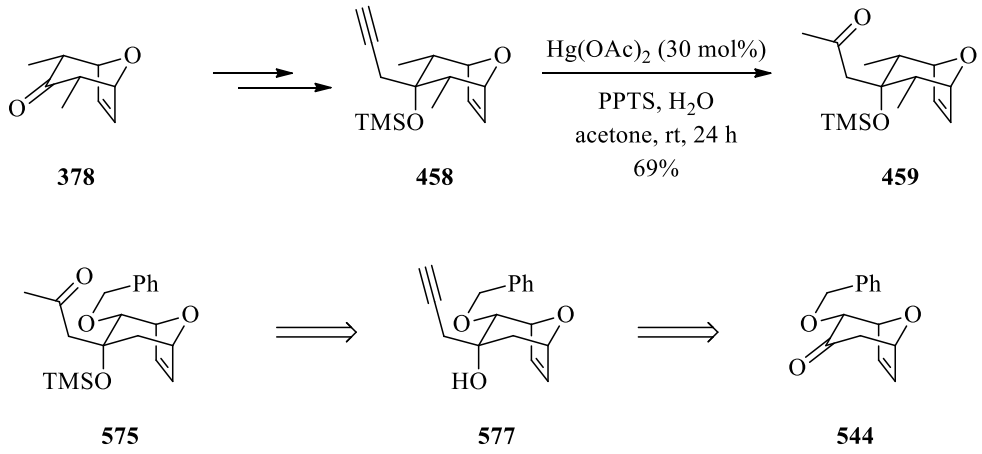
Whilst the alkylidene carbenoid generated from vinyl chloride **370** had been shown to undergo C-H insertion to give **371** exclusively,[97] the reactivity of the 'naked' carbene

generated from ketone **459** had not yet been determined (**Scheme 265**). Therefore, it was decided to attempt this reaction in order to ascertain whether the method of generation influences the chemoselectivity of the alkylidene carbene insertion **576**.



Scheme 265

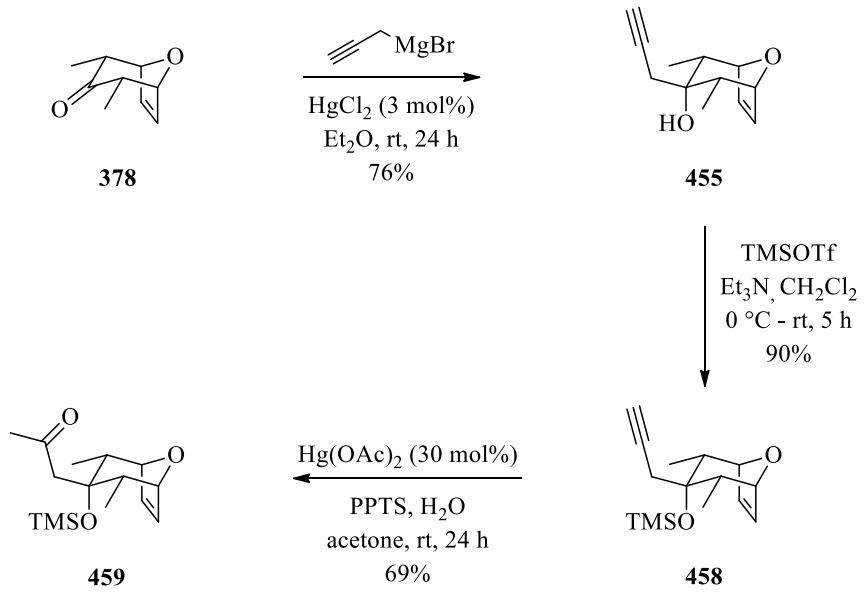
Ketone **459** had previously been synthesised *via* hydration of alkyne **458**, so the same methodology could be employed to synthesise ketone **575** (**Scheme 266**). The desired alkyne **576** could be synthesised *via* addition of propargyl Grignard to the bicyclic ketone **544**.



Scheme 266

4.3 Reactivity of the alkylidene carbene from ketone 459

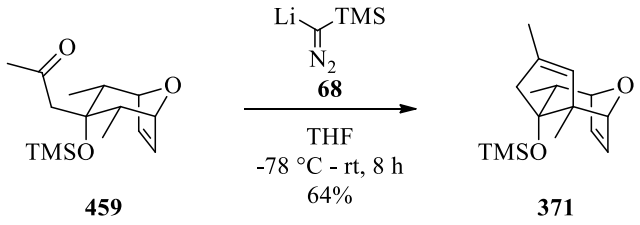
Ketone **459** was synthesised as previously described (**Scheme 267** and **Section 2.7.2**). Nucleophilic addition of propargyl Grignard to bicyclic ketone **378** gave **455** in 76% yield. Treatment of **455** with TMSOTf gave silyl ether **458** in 90% yield and subsequent mercury catalysed hydration gave the desired ketone **459** in 69% yield.



378 **455** **458** **459**

Scheme 267

Treatment of **459** with deprotonated trimethylsilyl(diazo)methane **68** gave exclusively tetracycle **371**, the product of C-H insertion, in 64% yield (**Scheme 268**).[103b] As with the reaction of the alkylidene carbene **574** generated from vinyl chloride **370** (**Scheme 265**), no evidence of insertion into the O-Si bond was observed.[97] This result confirmed that the alkylidene carbenes generated from the dimethyl-substituted bicycle **423** and **402** were unreactive towards O-Si insertion, irrespective of the generation method employed.

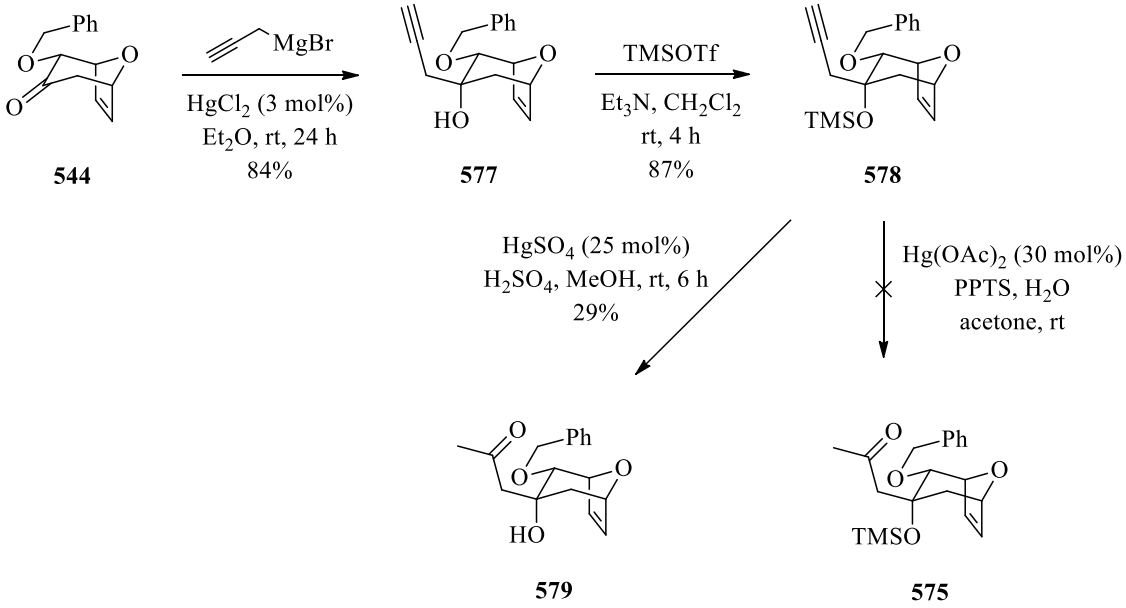


Scheme 268

4.4 Reactivity of alkylidene carbene 573

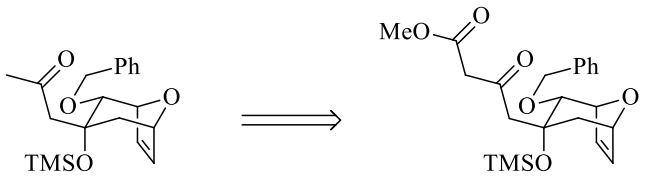
4.4.1 Synthesis of ketone 575 and vinyl chloride 574

It was envisaged that ketone **575** could be synthesised through the same route as that used for the dimethyl derivative **459**. As such, bicyclic ketone **544** was treated with propargyl Grignard in the presence of catalytic $HgCl_2$, to afford alcohol **576** in 84% yield (**Scheme 269**).[97] Subsequent treatment with TMSOTf gave silyl ether **577** in 87% yield.[97] Unfortunately, exposing **577** to the conditions for the alkyne hydration gave no conversion of the starting material.[180] Additionally, while employing harsher conditions led to the formation of the ketone, it also resulted in the removal of the TMS group, and only **578** was isolated in 29% yield.[207]



Scheme 269

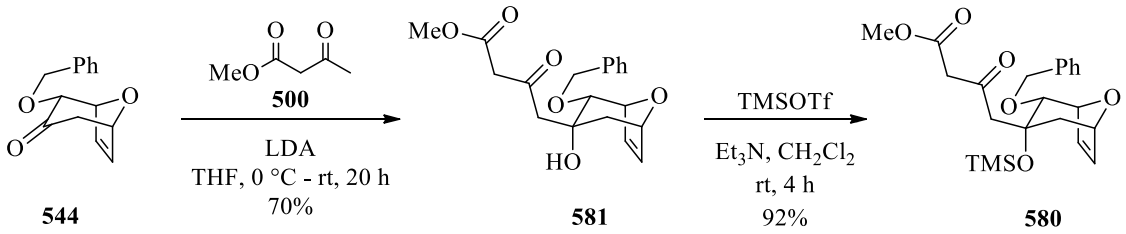
Due to this disappointing result, a new approach to ketone **575** was attempted. Based on previous work in the Grainger group,[97, 154] it was decided to synthesise the desired ketone *via* a Krapcho decarboxylation of acetoacetate **580** (**Scheme 270**).[97]



575 **580**

Scheme 270

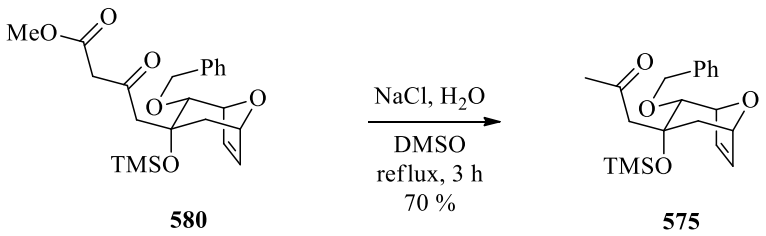
Treatment of methyl acetoacetate **500** with two equivalents of LDA, followed by addition of ketone **544** gave **581** in good yield. Subsequent protection of the tertiary alcohol gave silyl ether **580** in 92% yield (**Scheme 271**).[97]



544 **581** **580**

Scheme 271

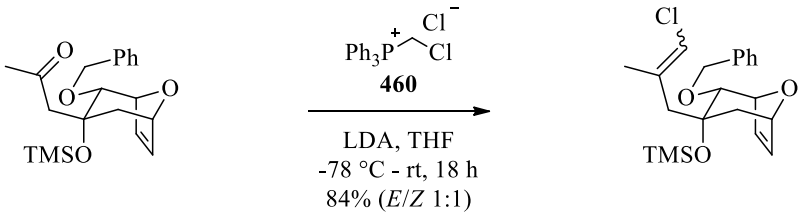
Pleasingly, treatment of **580** with NaCl in refluxing DMSO resulted in a successful decarboxylation (**Scheme 272**). Initially, the yields obtained were modest and inconsistent (29%-50%). The use of DMSO may have resulted in some the product being removed with the aqueous phase, despite multiple washes with CH_2Cl_2 in the workup. However, when the reaction mixture was purified immediately, without any aqueous work-up, **575** was obtained in higher yield and the results were more consistent.



580 **575**

Scheme 272

Ketone **575** was subsequently treated with (chloromethyl)triphenylphosphonium chloride **460** in the presence of LDA to afford vinyl chloride **574**, as a 1:1 mixture of isomers, in 84% yield (**Scheme 273**).



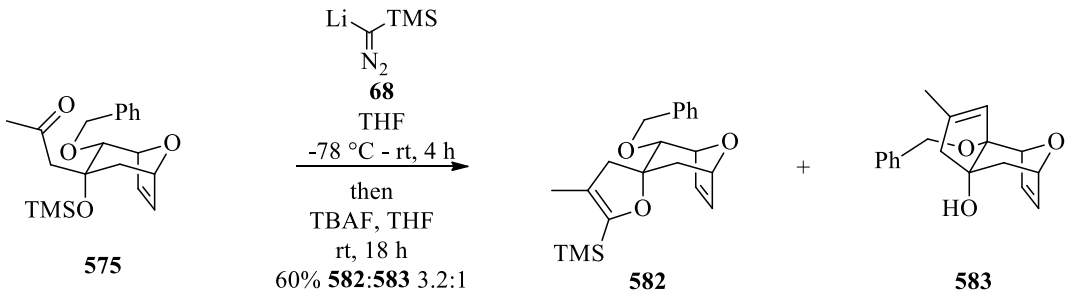
575 **574**

Scheme 273

4.4.2 Alkylidene carbene generation

Having successfully accessed both **574** and **575**, the chemoselectivity of the reaction of the alkylidene carbenes generated in the benzyloxy system was investigated. Treating ketone **575** with deprotonated trimethylsilyl(diazo)methane **68** gave rise to a mixture of two products.[103b] Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that the ratio of the products was 3.2:1.

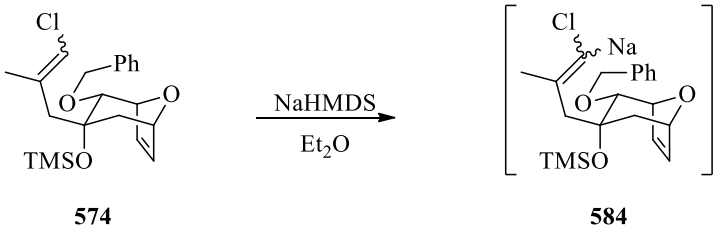
Unfortunately, it was not possible to separate the two products by column chromatography. Therefore, the crude mixture was treated with TBAF,[148] which facilitated easy separation of the two products. Analysis revealed the two products to be dihydrofuran **582** and cyclopentene **583**, with **582** being identified as the major product. Compounds **582** and **583** isolated in yields of 45% and 15% respectively (**Scheme 274**).



Scheme 274

The reaction of the vinyl chloride **574** proved to be troublesome. Treatment of **574** with NaHMDS in Et_2O[97] gave two new products which were visible by TLC; however only one of the two vinyl chlorides isomers was consumed. Analysis of the ^1H NMR spectrum of the crude reaction mixture revealed that the (*E*) isomer had not undergone any reaction. TLC analysis suggested that the products formed were the same as those seen in the reaction of ketone **575** with **68**.

When vinyl chloride **574** is treated with NaHMDS, the vinyl proton is removed to form carbenoid **584**, with the stereochemistry of the starting vinyl chloride retained (**Scheme 275**). Carbenoid **584** would then be expected to undergo C-H insertion or O-Si insertion.

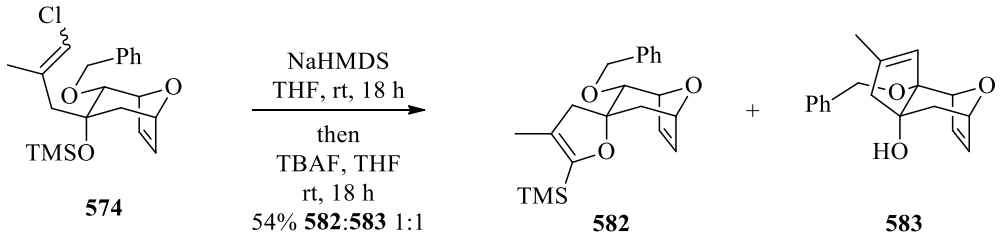


Scheme 275

There may be two possible reasons why only one of the vinyl chlorides underwent an insertion reaction. In the (*E*) isomer, the proton is more sterically encumbered due to the proximity of the bicyclic ring system. This may prevent efficient deprotonation by the bulky HMDS base. Alternatively, recovery of unreacted (*E*) vinyl chloride could indicate that the carbenoid is less reactive and is being re-protonated on work-up.

In order to ascertain which of these two explanations were true, the reaction was repeated and quenched with D_2O. No deuterium incorporation was observed, confirming that the (*E*) isomer was not being deprotonated to form the carbenoid.

When the reaction was carried out using KHMDS in Et_2O, a more reactive base, increased consumption of the starting material was observed. However, a significant amount of degradation was also seen, and nothing could be recovered cleanly from the reaction. Pleasingly, when the reaction solvent was changed to THF, full and clean consumption of the starting material was observed. Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated the two products formed were present in 1:1 ratio. As before, the crude reaction mixture was treated with TBAF prior to purification.[148] The products were subsequently identified as dihydrofuran **582** and cyclopentene **583**, the same as seen in the reaction of ketone **575**, and were isolated in 29% and 25% yields respectively (**Scheme 276**).



Scheme 276

4.4.3 Analysis of results

From the results obtained, it was immediately obvious that the presence of the additional oxygen was not a pre-requisite for efficient O-Si insertion. It had previously been proposed that a hydrogen bonding interaction between the secondary alcohol and the benzyl ether may encourage reaction with the silyl ether (**Figure 21**). However, it can be seen that this is not the case, as the reactions of both **574** and **575** both gave dihydrofuran **582**. Interestingly, the alkylidene carbene generated in the thermolysis of **556** appears to be less

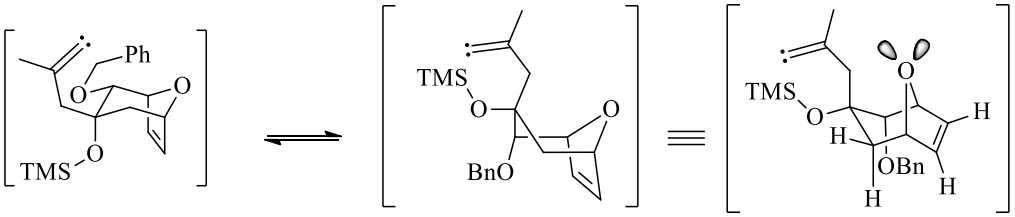
reactive towards O-Si insertion than that generated from ketone **575**, as the ratio fell upon introduction of the hydroxyl group.

There is a significant change in selectivity when the alkylidene carbeneoid is generated from vinyl chloride **574** as opposed to ketone **575**. Taber had previously reported an increase in the regiochemistry of C-H insertion reactions when generating the alkylidene carbenoid as opposed to the carbene (**Scheme 105**).[95b] This increase in selectivity was attributed to the different nature of the carbenoid, as the metal salt is still coordinated to the carbene, whereas the carbene from the diazoalkene has no such coordination. It is believed that a similar effect is at play here and the different nature of the carbene generated in the different experiments results in different chemoselectivity. However, there is no previous report into the manner in which the method of alkylidene carbene generation affects chemoselectivity or carbene reactivity, so it is unclear whether the generation of the carbenoid increases the rate of C-H insertion, or if the rate of O-Si insertion decreases.

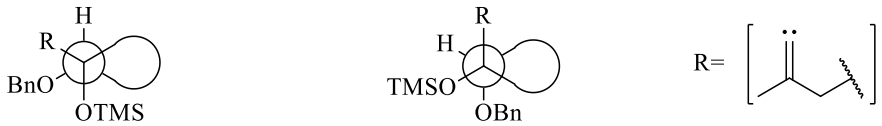
It is apparent that the benzyloxy substituted bicyclic system was more disposed to undergo O-Si insertion than the dimethyl system. Neither technique for the generation of the alkylidene carbene resulted in any O-Si insertion when employed on the dimethyl system. This suggested that there may be a difference in the conformation of the two bicycles which could reduce the rotation barrier around the C-O bond, allowing O-Si insertion to occur.

One possibility is that the benzyloxy bicyclic system may adopt a boat conformation **585**, instead of the presumed chair **573** (**Scheme 277**). Such a conformational change would reduce the steric clash between the R and OBn substituents on the bicycle. Additionally, as the flagstaff positions would be occupied by the oxygen lone pairs, the clash with the R substituent would be less pronounced than for a carbon. Furthermore, the 1,3-diaxial interactions between the alkene protons and the OBn and CH_2 would be reduced, as the planarity of the alkene would hold the protons away from these substituents in **586**. As can be

seen in **585**, the steric encumbrance around the C-OTMS bond in the boat conformation is smaller (equatorial rather than axial in **573**), and may allow for the interaction between the oxygen lone pairs and the empty orbital on the alkylidene carbene required for insertion to occur, as the rotation of the C-O bond would be less restricted.



573 **585** **586**



587 **588**

Scheme 277

Searching the Cambridge Structural Database revealed that 2-alkoxy substituted bicyclic systems, such as **589** and **590**, exist in the chair conformation (**Figure 25**).[208] The only reported examples where the boat conformation had been adopted were due to the presence of an additional ring, which forced the change in conformation, such as **591**.[209]

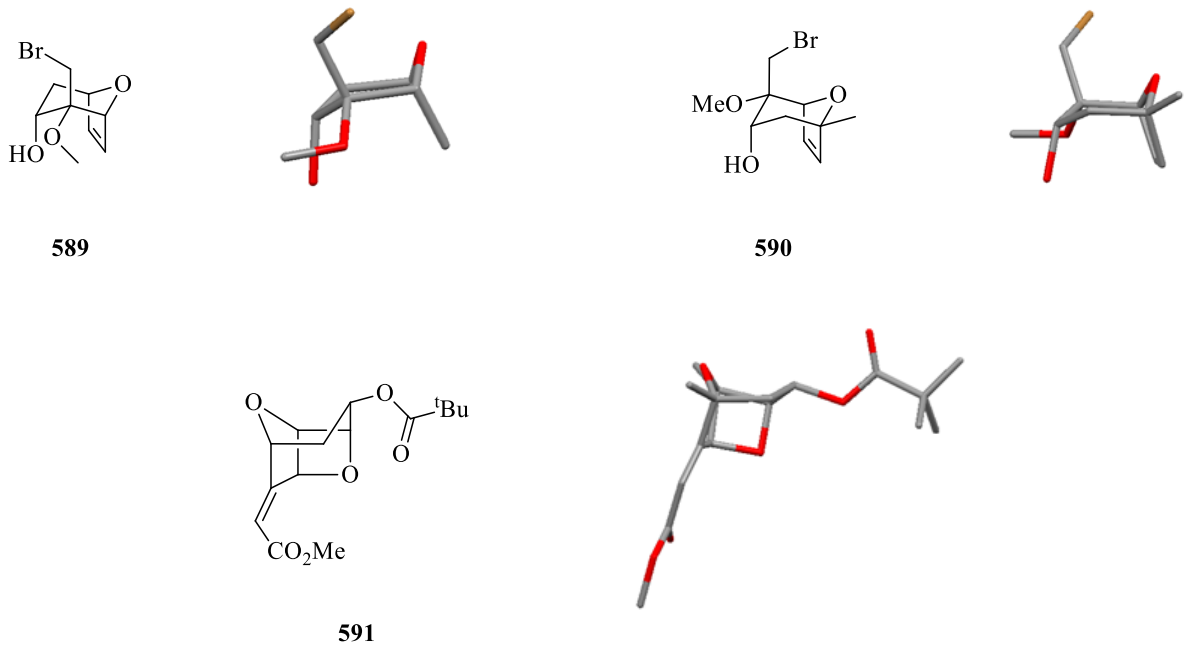


Figure 25

The through-space distance between the tertiary alcohol and the carbons of the ethylene bridge can be taken as a measure of the flattening of the tetrahydropyran ring from the idealised chair conformation. The through-space distance was measured to be 3.133 Å and 3.101 Å for **589** while the distances for **590** were calculated to be 3.065 Å and 3.067 Å. The same distances on the dimethyl compound **591** were found to be 2.973 Å and 2.980 Å (**Figure 26**), indicating that the tertiary alcohol is approximately the same degree of flattening is present in all three cases.

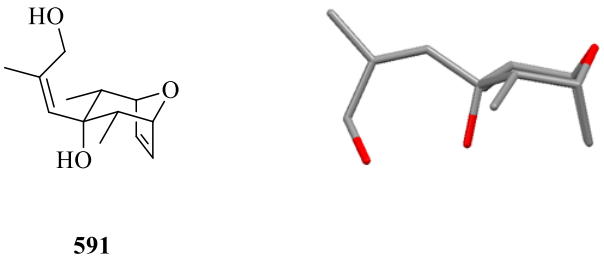


Figure 26

The results of this search suggested that the boat conformation is not more stable than the chair conformation in 2-alkoxy oxabicyclic systems and the minor structural differences

between the dimethyl and benzyloxy-substituted 8-oxabicyclic systems would not account for the differences in chemoselectivity seen. However, these reported structures only take into account the solid state structures of the bicyclic systems, and it remains possible that a boat-like reactive conformation of the benzyloxy-substituted system is more readily accessible than that of the dimethyl substituted oxabicyclic system.

4.5 Conclusion

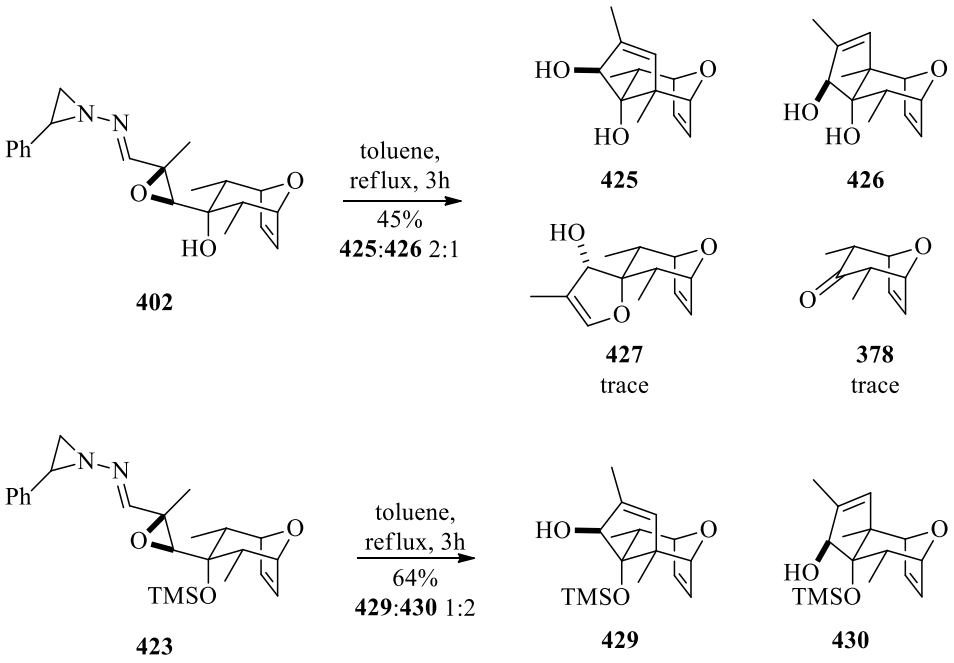
In conclusion, it has been demonstrated that benzyloxy-substituted oxabicyclic system undergo both C-H insertion and O-Si/O-H insertion reactions, irrespective of the method of alkylidene carbene generation employed. In contrast, alkylidene carbenes generated within the dimethyl-substituted bicyclic oxabicycle show a strong preference for C-H insertion. It has also been shown that altering the alkenylidene generation method within the benzyloxy-substituted system affects the ratio of O-Si to C-H insertion.

Chapter five – Conclusions and future work

5.1 Summary and Conclusions

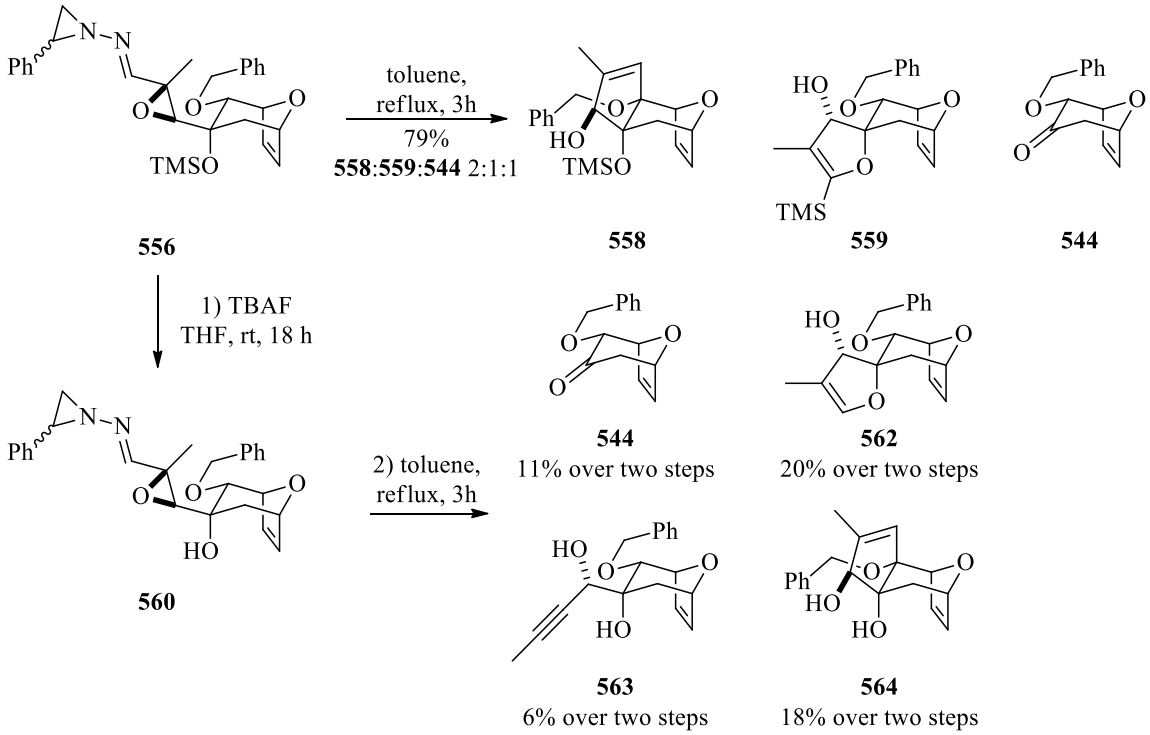
The use of the hydroxy cyclopentene annulation reaction as a potential route to the A-ring of ingenol **366** has been investigated on two model systems. Building on studies previously carried out in the Grainger group,[97, 154] the C-3 hydroxyl substituent of ingenol has been incorporated by employing Kim's alkylidene carbene methodology, which generates the carbene via the thermolysis of α,β-epoxy-*N*-aziridinylimines.[55] The desired aziridinylimines were synthesised from the known symmetrical 8-oxabicyclic ketone **378**.[141] The successful development of this route was crucial, as alternative methods of generating α-alkoxy alkylidene carbenes could not be employed due to difficulties in synthesising the appropriate precursors.

The introduction of the alcohol stereocentre α to the alkylidene carbene renders the two potential C-H insertion sites formally diastereotopic, and the insertion reactions have been shown to display a degree of diastereotopic group selectivity. This selectivity is reversed upon converting a tertiary alcohol to its TMS ether (**Scheme 278**).



Scheme 278

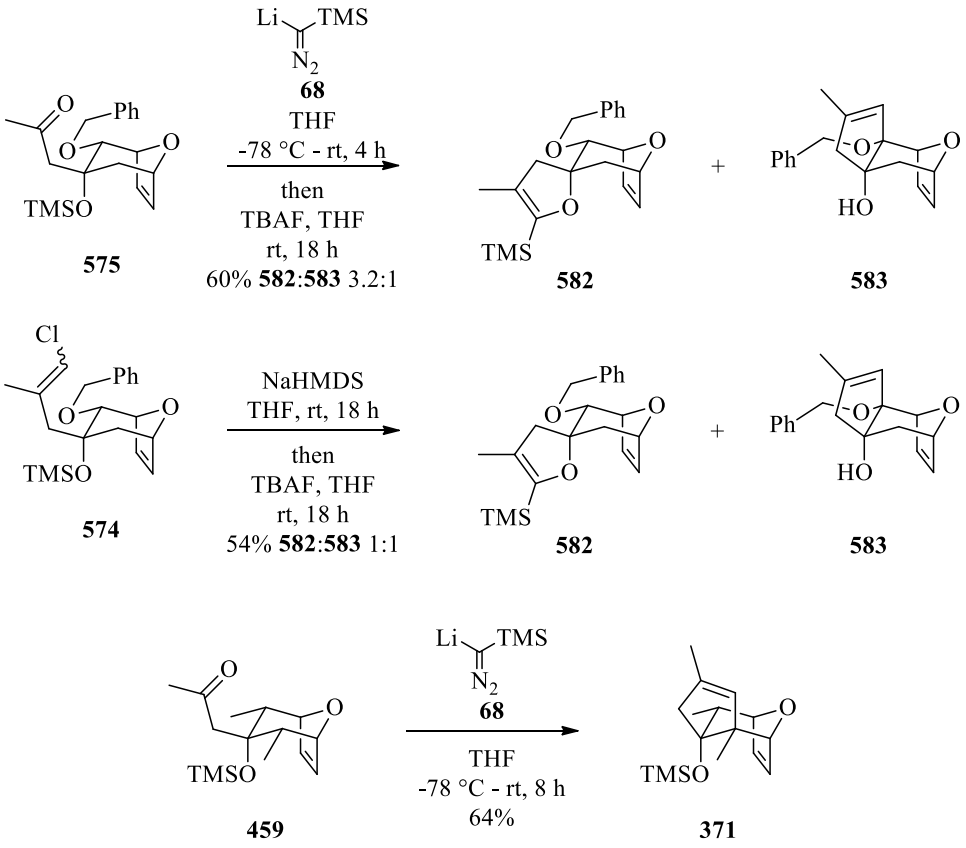
The methodology was subsequently expanded to an 8-oxabicyclic ring system bearing a 2-benzyloxy substituent.[203] Introducing this group exclusively controls the regioselectivity of the C-H insertion reaction, with insertion occurring adjacent to the oxygen atom, but results in the increased formation of products *via* alternative reaction pathways. Formal 1,5 O-H and 1,5 O-Si insertions, generally disfavoured in the 2,4-dimethyl analogue, compete with C-H insertion, as does fragmentation to form ketone **544**. In addition, the reaction of aziridinylimine **560**, bearing a tertiary alcohol, also gave rise to propargylic diol **563**, despite the alkylidene carbene substituents being unsuited to 1,2-migration (**Scheme 279**).[19b] Due to problems in synthesising other α-alkoxy substituted 8-oxabicyclic ketones, it was not possible to investigate the effects altering the nature of the oxygen substituent at C-2 would have on the observed chemo- and regioselectivities.



Scheme 279

The reactivity of alkylidene carbenes lacking the α-hydroxy substituent was also investigated further. It was demonstrated that the formation of spirocyclic dihydrofurans in 2-benzyloxy-substituted 8-oxabicycles occurs irrespective of whether the metal carbenoid of the

'naked' carbene is employed. However, the ratio of 1,5 C-H insertion to 1,5 O-Si insertion changes depending on the method used to generate the alkylidene carbene. It was also shown that 1,5 O-Si insertion does not occur in the 2,4-dimethyl 8-oxabicyclic system.



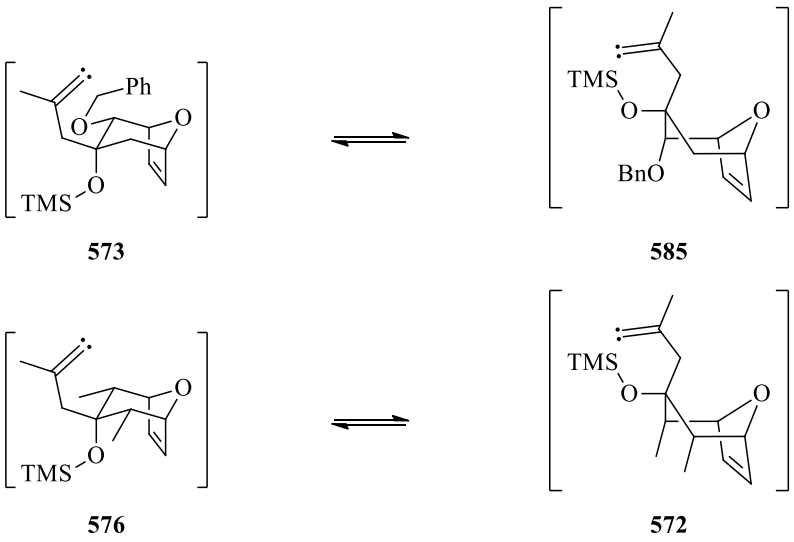
Scheme 280

In summary, the successful stereocontrolled annulation of cyclopentenes onto 8-oxabicyclic ring systems has increased the utility of these versatile and widely employed ring systems.[146b, c] More generally, the reactivity of synthetically important alkylidene carbenes has been further explored, demonstrating how minor structural changes can significantly alter selectivity.

5.2 Future Work

The successful application of this methodology to the total synthesis of ingenol **366** would require various selectivity issues to be overcome. In order to address the issue of chemoselectivity, it is necessary to determine why introducing the 2-benzyloxy substituent

alters the selectivity of the alkylidene carbene, with O-Si insertion a competing process, compared with exclusive C-H insertion in the dimethyl system. One possibility is that this change in selectivity may be due to a smaller energy difference between the chair **573** and boat **585** conformations of the benzyloxy substituted bicycle compared with the same conformational change in the dimethyl substituted system (**Scheme 281**). Computational calculations could be carried out on these four conformations in order to determine the feasibility of the argument.



Scheme 281

The regioselectivity of the C-H insertion reaction on the oxygen-substituted bicyclic system also has to be addressed in order to employ this methodology in a successful total synthesis of ingenol. In order to suppress insertion into the C-H bond next to the oxygen atom, the substituent on the oxygen would need to be converted to an electron-withdrawing group as in **521**, or a system which lessens the overlap between the oxygen lone pairs and the C-H anti-bonding orbital **522** (**Figure 27**). It is hoped that both these options can be investigated as potential solutions to control the regioselectivity of the C-H insertion reaction.

521
R=EWG

522

Figure 27

Additionally, incorporating an additional alkyl substituent on the bicyclic ring system (**Figure 27**, R'=alkyl) may also have an effect on the regioselectivity of the C-H insertion reaction as the reaction of alkylidene carbenes at tertiary C-H bonds is known to be faster than insertion at secondary C-H centres. Additionally, this alteration would also provide a closer mimic to the substrate that would be required were this methodology to be utilised in the natural product synthesis.

Chapter six – Experimental

6.1 General Experimental

All reagents were obtained commercially and were used as received, unless otherwise stated. The following cooling baths were used; 0 °C (ice/water), -5 °C → -20 °C (ice/water/salt) and -78 °C (dry ice/acetone). Purification was carried out according to standard laboratory methods.[210]

Dry THF was obtained by distilling from sodium and benzophenone or by passing through activated alumina columns. Et_2O, CH_2Cl_2, MeOH and toluene were dried by passing through activated alumina columns. TMEDA was distilled from CaH_2. TBAF was purchased as a 1 M solution in THF and used directly; ^{n}BuLi was purchased as either 2.5 M or 1.6 M solutions in hexanes, and the solutions were titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene ("BLUE"). EtMgBr was purchased as a 3 M solution in THF and used directly. NaHMDS was purchased as a 2 M solution in THF and used directly. KHMDS was purchased as a 0.5 M solution in toluene and used directly. LiHMDS was purchased as a 1 M solution in THF and was used directly. (Diazomethyl)trimethylsilane was purchased as a 2 M solution in hexanes and was used directly.

*m*CPBA was purified by washing with a pH 7 phosphate buffer unless otherwise stated. A buffer solution was prepared from 0.1 M NaOH (154 mL) and 0.2 M KH_2PO_4 (94 mL) and made up to 376 mL with distilled water. *m*CPBA (77% w/w, 10 g) was dissolved in Et_2O (100 mL) and washed four times with the buffer solution. The organic extract was dried over $MgSO_4$ and carefully evaporated under reduced pressure to yield pure *m*CPBA (7.3 g).

^{t}BuOOH was prepared as a 3.3 M solution in toluene using a known literature procedure.[211]

Analytical TLC was carried out on Merck 60 F245 aluminium backed silica plates. Short wave UV (245 nm) or vanillin solution were used to visualise components.

Flash chromatography was carried out using Merck silica gel 60.

Proton NMR spectra were obtained on a Bruker AVIII 300 Spectrometer or a Bruker AVIII 400 Spectrometer at 300 and 400 MHz, respectively. ^{13}C NMR spectra were obtained on a Bruker AVIII 400 Spectrometer or a Bruker AV 400 Spectrometer at 100 MHz and are ^{1}H decoupled. Chemical shifts (δ) are reported in ppm. Coupling constants (*J*) are reported in Hz and refer to $^{3}J_{H\text{-}H}$ unless otherwise stated. All NMR spectra were obtained as solutions in $CDCl_3$ and referenced to residual $CHCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.23) unless otherwise stated. Variable temperature experiments were performed on a Bruker AV 400 Spectrometer. nOe spectra were obtained on a Bruker AV 400 Spectrometer.

FTIR spectra were obtained from neat compounds using a Perkin Elmer Spectrum 100 FT-IR Spectrometer.

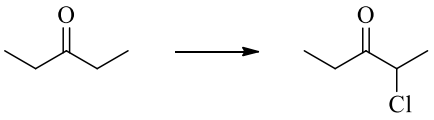
Mass spectra were recorded on a LCT spectrometer utilising electrospray ionisation (recorded in the positive mode) with a methanol mobile phase, or electron impact ionisation, and are reported as (*m*/*z* (%)). HRMS were recorded on a LCT spectrometer using lock mass incorporated into the mobile phase.

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected.

6.2 Experimental Procedure

Preparation of 2-chloropentan-3-one 382

Method A



A known compound prepared using a modified literature procedure.[141]

Reaction was performed under an argon atmosphere.

To a stirred solution of pentan-3-one **381** (6.94 g, 8.50 mL, 80.0 mmol) in 1,2-dichloroethane (20 mL) at 45 °C, sulfuryl chloride (7.10 mL, 88.0 mmol) was added drop-wise over 1 h. The reaction was stirred at 45 °C for 3 h before being allowed to cool to room temperature and the solvent was removed *in vacuo* without external heating. The residue was then distilled at 26 mmHg to afford **382** as the major component with a mixture of dichloro-products as a pale yellow liquid (5.21 g, 54%)

Method B

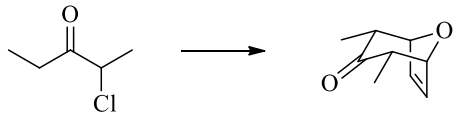
A known compound prepared using a literature procedure.[141]

Reaction was performed under an argon atmosphere.

To a stirred solution of pentan-3-one **381** (69.4 g, 85.0 mL, 800 mmol) in CCl_4 (200 mL) at 45 °C, sulfuryl chloride (71.0 mL, 880 mmol) was added drop-wise over 2 h. The reaction was stirred at 45 °C for 3 h before being allowed to cool to room temperature. The CCl_4 was removed *in vacuo*, to afford **382** as a clear liquid (68.3 g, 71%). δ_H (400 MHz, $CDCl_3$) 1.06 (t, 3H, *J* 7.3 Hz, C*H*$_3$CH$_2$), 1.56 (d, 3H, *J* 6.9 Hz, C*H*$_3$CHCl), 2.54-2.64 (m, 1H, C*H*$_2$), 2.69-2.79 (m, 1H, C*H*$_2$), 4.32 (q, 1H, *J* 6.9 Hz, C*H*Cl). δ_C (100 MHz, $CDCl_3$) 7.8 (CH_3, *C*H$_3$CH$_2$), 20.2 (CH_3, *C*H$_3$CHCl), 31.6 (CH_2, *C*H$_2$CH$_3$), 58.3 (CH, *C*HCl), 206.6 (C, *C*=O).

m/z (EI) 55 (8%), 57 (100), 63 (16), 65 (6), 120 ([M(^{35}Cl)]$^+$, 18), 122 ([M(^{37}Cl)]$^+$, 6). Literature values:[212] 1H NMR δ 4.35 (dd, 1H, *J* = 6.8 and 13.6 Hz, C(H)-Cl), 2.75 (dd, 1H, J = 7.2 and 14.0 Hz, C(O)CH_2), 2.65 (dd, 1H, J = 7.2 and 14.4 Hz, C(O)CH_2), 1.60 (d, 3H, J = 6.8 Hz, CH_3), 1.09 (t, 3H, J = 7.2 Hz, CH_3); 13C NMR δ 206.1, 58.3, 31.6, 20.2, 7.7.

Preparation of 2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one 378

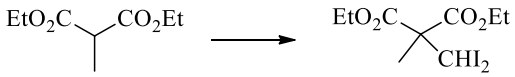


A known compound prepared using a literature procedure.[141]

To a solution of **382** (15.0 g, 125 mmol) and furan (36.0 mL, 500 mmol) in H_2O (125 mL) at room temperature, Et_3N (18.0 mL, 130 mmol) was added drop-wise over 30 min. The resulting solution was stirred at room temperature for 24 h before the reaction was quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were concentrated *in vacuo* and the resulting residue placed in the freezer overnight to crystallize. The resulting solid was filtered, washed with cold hexane. The filtrate was reduced *in vacuo*, placed in the freezer overnight and the resulting precipitate filtered. This process was repeated until no solid precipitated at -20 °C. The separate precipitates were combined and dried under vacuum at room temperature to afford **378** (9.24 g, 51%) as a pale yellow solid. δ_H (400 MHz, $CDCl_3$) 0.95 (d, 6H, *J* 7.1 Hz, C*H*$_3$), 2.79 (qd, 2H, *J* 7.0, 4.7 Hz, CH_3C*H*), 4.83 (d, 2H, *J* 4.5 Hz, C*H*O), 6.32 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.3 (2 x CH_3, *C*H_3), 50.6 (2 x CH, CH_3*C*H), 82.9 (2 x CH, =CH*C*HO), 133.7 (2 x CH, =*C*H), 206.1 (C, *C*=O). *m/z* (EI) 55 (5%), 67 (14), 68 (7), 81 (100), 95 (43), 96 (47), 109 (5), 137 ([M-O]$^+$, 27), 152 (M$^+$, 38), 153 ([M+H]$^+$, 5). Literature values:[213] δ_H (200 MHz, $CDCl_3$) 0.97 (d, 6H, *J* 7.0 Hz), 2.80 (qd, 2H, *J* 7.0, 4.4 Hz), 4.85 (d, 2H, *J* 4.4 Hz), 6.34 (s, 2H). δ_C (50 MHz, $CDCl_3$) 10.0, 50.3, 82.6, 133.5, 208.9. MS [GC-MS (CI), NH_3, 70 eV, 150 °C, *m/z*, (%)]: 187 (100, M+N_2H_5), 170 (82, M+NH_4), 153 (2, M+H), 152 (1, M$^+$). IR (KBr, υ,

cm^{-1}): 3080, 2974, 2950, 2885, 1715 (C=O, st), 1590 (C=C, st), 1460-1450 (C-C, δ), 1380 (C-H, δ), 1340, 1160, 1085, 920. EA Calculated for $C_9H_{12}O_2$: C (71.03%), H (7.95%). Found: C (71.42%), H (8.02%). GC (50 °C, 1 min, 10 °C/min, 250 °C, 1 min): t_R 11.80 min.

Preparation of diethyl 2-(diiodomethyl)-2-methylmalonate 387

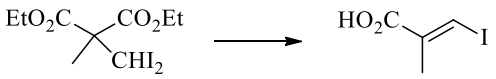


A known compound prepared using a modified literature procedure.[143]

Reaction was performed under an argon atmosphere.

To a stirred solution of NaH (60% in mineral oil, 4.85 g, 121 mmol) in Et_2O (200 mL), diethyl methylmalonate **386** (18.8 mL, 110 mmol) was added portion-wise over 10 min. The resulting suspension was heated at reflux for 2 h before iodoform (41.2 g, 110 mmol) was added in one portion. The reaction was then heated at reflux for 21 h before being quenched with HCl (150 mL of a 1 M aqueous solution) and extracted with Et_2O (3 x 50 mL). The combined organics were then washed with $Na_2S_2O_3$ (75 mL of a saturated aqueous solution) and the aqueous layer washed with Et_2O (2 x 30 mL). The solvent was evaporated *in vacuo* and the oil was washed with petrol and the resulting solid removed by filtration. The filtrate was washed with $Na_2S_2O_3$ (75 mL of a saturated aqueous solution), and the organics dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford **387** (36.5 g, 75%) as a dark orange liquid which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.28 (t, 6H, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.78 (s, 3H, C*H*$_3$CCO$_2$Et), 4.21 (q, 4H, *J* 7.1 Hz, C*H*$_2$CH$_3$), 5.75 (s, 1H, C*H*I$_2$). δ_C (100 MHz, $CDCl_3$) 14.2 (2 x CH_3, *C*H$_3$CH$_2$), 20.5 (CH_3, *C*H$_3$CCO$_2$Et), 62.9 (2 x CH_2, *C*H$_2$CH$_3$), 138.6 (CH, *C*HI$_2$), 138.6 (C, CH$_3$*C*CHI$_2$), 166.3 (2 x C, *C*=O). *m/z* (ES) 269 (11%), 309 (6), 369 (5), 463 ($[M+Na]^+$, 100). Literature values:[143a] δ_H (60 MHz, $CDCl_3$) 5.9 (1H, s, CHI_2), 4.3 (4H, q, *J* 6 Hz, OCH_2), 1.9 (3H, s, Me), 1.4 (6H, t, *J* 6 Hz, OCH_2*Me*).

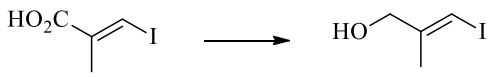
Preparation of (*E*)-3-iodo-2-methylacrylic acid 388



A known compound prepared using a modified literature procedure.[143]

To a stirred solution of **387** (24.9 g, 56.7 mmol) in EtOH/H_2O (3:1, 260 mL), potassium hydroxide (9.53 g, 170 mmol) was added. The resulting solution was heated at reflux for 16 h before being cooled to room temperature and concentrated *in vacuo*. The resulting suspension was treated with K_2CO_3 (150 mL of a 10% aqueous solution) and extracted with CH_2Cl_2 (2 x 50 mL). The basic layer was acidified with HCl (12 M aqueous solution) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **388** (10.6 g, 88%) as a pale yellow solid which was used without further purification. δ_H (400 MHz, $CDCl_3$) 2.06 (d, 3H, ^4J 1.2 Hz, =CC*H*$_3$), 8.03 (d, 1H, ^4J 1.2 Hz, =C*H*I), 11.36 (br. s, 1H, COO*H*). δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3, =C*C*H_3), 102.1 (CH, =*C*HI), 139.2 (C, =*C*CH_3), 169.3 (C, *C*OOH). *m/z* (EI) 85 (29%), 166 (13), 211 (M^+, 100). Literature values:[143a] 10.8 (1H, s, COOH), 7.9 (1H d, *J* 1 Hz, CHI), 2.0 (3H, d, *J* 1 Hz, Me). Found: C, 22.79; H, 2.46%, $C_4H_5IO_2$ requires C, 22.66, H, 2.38%.

Preparation of (*E*)-3-iodo-2-methylprop-2-en-1-ol 389



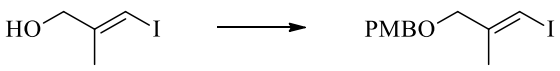
A known compound prepared using a literature procedure.[143]

Reaction was performed under an argon atmosphere.

To a stirred solution of **388** (10.6 g, 49.9 mmol), at 0 °C, $LiAlH_4$ (1.90 g, 49.9 mmol) was added portion-wise. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was then cooled to 0 °C and Na_2SO_4 (2.7 mL of a saturated

aqueous solution) was added. The resulting mixture was then diluted with Et_2O (70 mL) and added to H_2SO_4 (102 mL of a 2 M aqueous solution). The resulting layers were separated and the aqueous layer washed with CH_2Cl_2 (3 x 35 mL). The organics were combined and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (70 mL) and washed with K_2CO_3 (35 mL of a 10% aqueous solution). The basic layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **389** (6.59 g, 66%) as a yellow liquid. δ_H (400 MHz, $CDCl_3$) 1.75 (d, 3H, ^4J 0.8 Hz, =CC*H*$_3$), 3.25 (s, 1H, O*H*), 4.00 (d, 2H, ^4J 1.0 Hz, =CC*H*$_2$), 6.16-6.18 (m, 1H, =C*H*I). δ_C (100 MHz, $CDCl_3$) 21.4 (CH_3, =C*C*H$_3$), 66.9 (CH_2, =C*C*H$_2$), 77.4 (CH, =*C*HI), 147.1 (C, *C*=CHI). *m/z* (EI) 41 (10%), 43 (6), 53 (13), 71 (92), 72 (4), 126 (49), 127 (16), 140 (5), 166 (9), 182 (4), 182 (12), 195 (8), 198 (M^+, 100). Literature values:[143a] υ_{max} (film) 3350, 2940, 1620, 1450, 1380, 1280, 1080, 1020 cm^{-1}; δ_H 6.26 (1H, t, *J* 1.4 Hz, CHI), 4.09 (2H, s, CH_2), 2.71 (1H, br. s, OH), 1.83 (3H, d, *J* 1.4 Hz, Me); δ_C 147.2 (s, *C*=CHI), 77.2 (d, =CHI), 67.0 (t, CH_2), 21.3 (q, CH_3); *m*/*z* (EI) 198 (M^+, 11%), 91 (15), 71 (34), 57 (80), 43 (100). Found C, 24.32; H 3.67, C_4H_7IO requires C, 24.26; H, 3.56%.

Preparation of (*E*)-1-(((3-iodo-2-methylallyl)oxy)methyl)-4-methoxybenzene 383



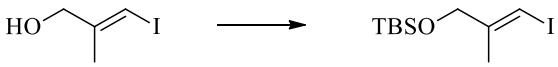
A known compound[142a, b] prepared using a modified literature procedure.[144]

Reaction was performed under an argon atmosphere.

To a solution of **389** (2.00 g, 10.1 mmol) in THF/DMF (10:1, 104 mL) at 0 °C, NaH (60% in mineral oil, 1.01 g, 25.1 mmol) was added in one portion. The reaction was stirred at 0 °C for 10 min before PMBCl (2.36 g, 2.05 mL, 15.1 mmol) and TBAI (372 mg, 1.00 mmol) were added in one portion. The reaction was stirred at room temperature for 16 h before being

quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **383** (2.70 g, 88%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 1.88 (d, 3H, ^4J 1.1 Hz, =CCH_3), 3.83 (s, 3H, OCH_3), 4.00 (d, 2H,^4J 1.1 Hz, =CCH_2), 4.44 (s, 2H, OCH_2C_{Ar}), 6.30 (q, 1H, ^4J 1.2 Hz, =C*H*I), 6.82-6.95 (m, 2H, CH_{Ar}COCH3), 7.21-7.32 (m, 2H, C$H_{Ar}CH_{Ar}$COCH$_3$). δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3, =C*C*H_3), 55.5 (CH_3, O*C*H_3), 71.8 (CH_2, O*C*H_2C_{Ar}), 73.9 (CH_2, =C*C*H_2), 78.7 (CH, =*C*HI), 114.0 (2 x CH, *C*H_{Ar}COCH$_3$), 129.5 (2 x CH, *C*$H_{Ar}CH_{Ar}$COCH$_3$), 130.1 (C, *C*CH_2O), 145.1 (C, =*C*CH_3), 159.5 (C, *C*OCH$_3$). *m/z* (ES) 308 (6%), 341 ([M+Na]$^+$, 10), 413 (100), 414 (11), 425 (24). Literature values:[142b] δ_H ($CDCl_3$, 400 MHz) 1.88 (s, 3H), 3.83 (s, 3H), 4.00 (s, 2H), 4.44 (s, 2H), 6.30 (s, 2H), 6.91 (d, *J* 8.3 Hz, 2H), 7.27 (d, *J* 8.3 Hz, 2H). δ_C ($CDCl_3$, 100.6 MHz) 21.6, 55.3, 71.7, 73.7, 78.6, 113.9, 129.4, 130.0, 145.0, 159.3.

Preparation of (*E*)-*tert*-butyl((3-iodo-2-methylallyl)oxy)dimethylsilane 384

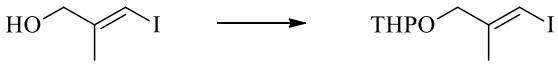


A known compound prepared using a literature procedure.[145]

To a solution of **389** (6.37 g, 32.2 mmol) in CH_2Cl_2 (69 mL) at 0 °C, TBSCl (5.40 g, 35.4 mmol), Et_3N (6.50 mL, 64.3 mmol) and DMAP (78 mg, 0.640 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. CH_2Cl_2 was evaporated *in vacuo*, and the resulting residue dissolved in Et_2O (50 mL). The resulting solution was washed with NH_4Cl (50 mL of a saturated aqueous solution) and $NaHCO_3$ (50 mL of a saturated aqueous solution) before being dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **384** (9.43 g, 94%) as a yellow liquid. The residue was used without further purification. δ_H (400 MHz, $CDCl_3$) 0.06 (s, 6H, Si(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 1.77 (s, 3H, =CCH_3), 4.09 (d, 2H, ^4J 1.0 Hz, =CCH_2), 6.19 (d, 1H, ^4J 1.1 Hz, =C*H*I). δ_C (100 MHz, $CDCl_3$) -5.2 (2

x CH_3, Si(CH_3)$_2$), 18.5 (C, SiC(CH_3)$_3$), 21.3 (CH_3, =CCH_3), 26.0 (3 x CH_3, SiC(CH_3)$_3$), 67.3 (CH_2, =CCH_2), 76.1 (CH, =CHI), 146.9 (C, C=CHI). *m/z* (ES) 269 (23%), 309 (15), 369 ([M+C_4H_9]$^+$, 100). Literature values:[145] IR (thin film) 2954, 2928, 1464, 1362, 1279, 1251, 1143, 1106 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, s), 4.10 (2H, s), 1.78 (3H, s), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (90 MHz, $CDCl_3$) 146.8, 75.9, 67.1, 31.6, 25.8, 25.7, 22.6, 21.2, 18.8, 14.1; HRFABMS calcd for M$^+$ ($C_{10}H_{21}$IOSi) 312.0408, found 312.0406.

Preparation of (*E*)-2-((3-iodo-2-methylallyl)oxy)tetrahydro-2*H*-pyran 385

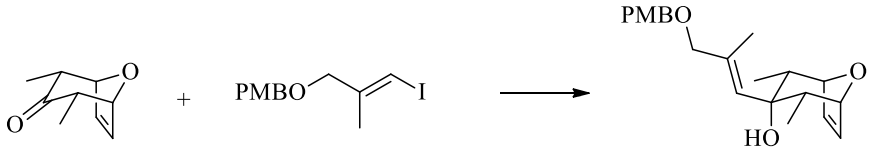


A known compound[142e] prepared using a modified literature route.[163]

To a solution of **389** (1.00 g, 5.00 mmol) in CH_2Cl_2 (20 mL) at room temperature, dihydropyran (546 mg, 0.590 mL, 6.50 mmol) was added, followed by PPTS (100 mg, 0.40 mmol). The reaction was stirred at room temperature for 1.5 h before being quenched with $NaHCO_3$ (50 mg), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Et_2O 70:30) to afford **385** (1.25 g, 89%) as a clear colourless liquid. δ_H (400 MHz, $CDCl_3$) 1.49-1.86 (m, 6H, CHCH_2, CHCH$_2$CH_2, OCH$_2$CH_2), 1.83 (d, 3H, ^4J 0.6 Hz, =CCH_3), 3.48-3.53 (m, 1H, CH$_2$CH_2O), 3.79-3.86 (m, 1H, CH$_2$CH_2O), 3.97 (dd, 1H, ^2J 12.8 Hz, ^4J 1.2 Hz, =CCH_2O), 4.17 (dd, 1H, ^2J 13.0 Hz, ^4J 0.8 Hz, =CCH_2O), 4.60 (t, 1H, J 3.5 Hz, OCHO), 6.25-6.27 (m, 1H, =CHI). δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2, CHCH$_2$$CH_2$), 21.9 ($CH_3$, =C$CH_3$), 25.6 ($CH_2$, OCH$_2$$CH_2$), 30.6 ($CH_2$, CHCH$_2$$CH_2$), 62.3 ($CH_2$, CH$_2$$CH_2$O), 70.6 ($CH_2$, =C$CH_2$O), 78.3 (CH, =$C$HI), 97.7 (CH, O$C$HO), 144.8 (C, C=CHI). *m/z* (EI) 85 ([THP]$^+$, 92%), 126 (I$^+$, 18), 180 ([M-OTHP]$^+$, 100), 197 ([M-THP]$^+$, 69). Literature values:[142e] ^{1}H NMR δ 1.4-2.0 (m, 6H), 1.85 (s, 3H), 3.4-3.6 (m, 1H), 3.75-3.90 (m, 1H), 3.9-4.05 (m, 1H), 4.1-4.25 (m, 1H), 4.60 (d, J 2.6 Hz, 1H), 6.25 (s, 1H); ^{13}C NMR δ

19.15, 21.63, 25.31, 30.36, 61.98, 70.47, 78.14, 97.44, 144.49; IR (neat) 3058, 2942, 1622, 1440, 1282, 1022 cm^{-1}.

Preparation of 3-*exo*-((*E*)-3-((4-methoxybenzyl)oxy)-2-methylprop-1-en-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 391



A novel compound prepared using a novel procedure.

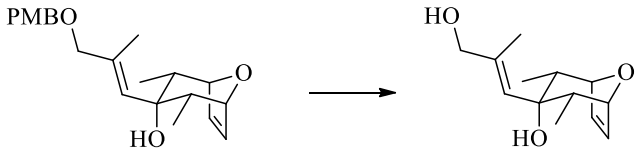
Reaction was performed under an argon atmosphere.

To a solution of **383** (523 mg, 1.72 mmol) in THF (20 mL) at -78 °C, ^{n}BuLi (1.95 M, 0.880 mL, 1.72 mmol) was added drop-wise. The resulting solution was stirred at -78 °C for 30 min before a solution of **378** (176 mg, 1.13 mmol) in THF (5 mL) was added in one portion. The reaction was stirred at room temperature for 2 h before being quenched with HCl (5 mL of a 1 M aqueous solution) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30) to afford **391** (174 mg, 45%) as a yellow solid. m.p. 34-36 °C. R_f 0.30 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3527, 2960, 2929, 2894, 2835, 1611, 1512, 1242, 1089, 1031, 930. δ_H (400 MHz, $CDCl_3$) 0.82 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 1.81 (d, 3H, ^{4}*J* 1.3 Hz, =CC*H*$_3$), 1.84 (s, 1H, O*H*), 2.14 (qd, 2H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 3.73 (s, 3H, OC*H*$_3$), 3.75 (d, 2H, ^{4}*J* 0.8 Hz, =CC*H*$_2$), 4.29 (s, 2H, OC*H*$_2$C$_{Ar}$), 4.46 (d, 2H, *J* 3.6 Hz, =CHC*H*O), 4.97-4.99 (m, 1H, C=C*H*), 6.49 (s, 2H, =C*H*CHO), 6.78-6.83 (d, 2H, C*H*COCH$_3$), 7.15-7.20 (m, 2H, C*H*CHCOCH$_3$). δ_C (100 MHz, $CDCl_3$) 10.9 (2 x CH$_3$, *C*H$_3$CH), 14.6 (CH$_3$, =C*C*H$_3$), 42.4 (2 x CH, CH$_3$*C*H), 55.1 (CH$_3$, O*C*H$_3$), 70.6 (CH$_2$, O*C*H$_2$C$_{Ar}$), 76.6 (C, *C*OH), 77.8 (CH$_2$, =*C*H$_2$), 82.4 (2 x CH, =CH*C*HO), 113.7 (2 x CH, *C*HCOCH$_3$), 129.2 (2 x CH, *C*HCHCOCH$_3$), 130.4 (C, *C*CH$_2$O), 133.0 (CH, C=*C*H), 133.4

(C, *C*=CH), 135.6 (2 x CH, =*C*HCHO), 159.0 (C, *C*OCH$_3$). *m/z* HRMS calcd for $C_{21}H_{28}NaO_4^+$ 367.188, found 367.1885, (ES) 367 ([M+Na]$^+$, 100%).

Preparation of 3-*exo*-((*E*)-3-hydroxy-2-methylprop-1-en-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 379

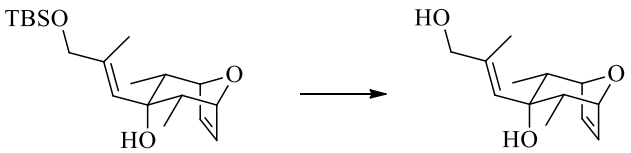
Method A



A novel compound prepared using a modified literature procedure.[147]

To a solution of **391** (48 mg, 0.140 mmol) in CH_2Cl_2 (8 mL) at room temperature DDQ (159 mg, 0.700 mmol) was added. The reaction was stirred at room temperature for 16 h before being washed with H_2O (5 mL) and $NaHCO_3$ (5 mL of a saturated aqueous solution). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 50:50) to afford **379** (3.9 mg, 12%) as a yellow solid.

Method B

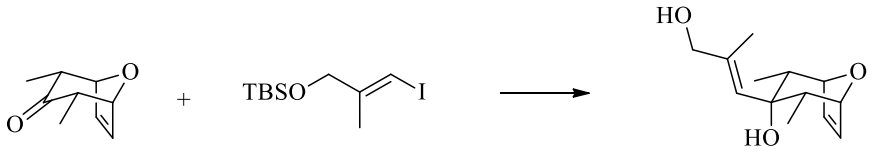


A novel compound prepared using a modified literature procedure.[148]

To a solution of **393** (231 mg, 0.680 mmol) in THF (10 mL) at room temperature TBAF (1 M, 0.820 mL, 0.820 mmol) was added in one portion. The reaction was stirred at

room temperature for 6 h before being washed with H_2O (10 mL). The aqueous layer was washed with Et_2O (2 x 10 mL), the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using column chromatography (hexane/EtOAc 50:50) to afford **379** (62.9 mg, 41%) as a white solid.

Method C

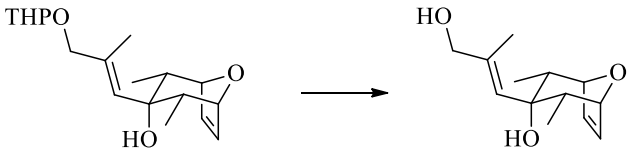


A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **384** (468 mg, 1.50 mmol) in THF (8 mL) at -78 °C, ^{n}BuLi (2.09 M, 0.720 mL, 1.50 mmol) was added drop-wise over 15 min. The reaction was stirred at -78 °C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (2 mL) was added. The reaction was allowed to warm to room temperature and was stirred at room temperature for 16 h before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in THF (20 mL) and TBAF (1 M, 1.20 mL, 1.20 mmol) was added. The reaction was stirred at room temperature for 16 h before being washed with H_2O (10 mL) and extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30→50:50) to afford **379** (186 mg, 83%) as a white solid.

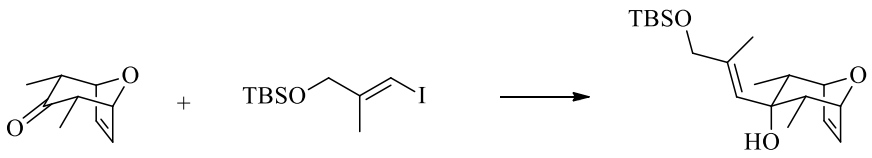
Method D



A novel compound prepared using a modified literature procedure.[153]

To a solution of **398** (110 mg, 0.390 mmol) in EtOH (2 mL) PPTS (10.0 mg, 0.040 mmol) was added. The resulting solution was stirred at 55 °C for 8 h before being allowed to cool to room temperature. The solvent was partially evaporated and the solution diluted with Et_2O (5 mL) and washed with brine (5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30→50:50) to afford **379** (21 mg, 24%) as a white solid. m.p. 124-126 °C. R_f 0.20 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3537, 3326, 2915, 1373, 1241, 1061, 1046, 930, 675. δ_H (400 MHz, $CDCl_3$) 0.86 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 1.85 (d, 3H, *J* 0.7 Hz, =CC*H*$_3$), 1.90 (s, 1H, O*H*), 2.18 (qd, 2H, *J* 7.3, 3.6 Hz, CH_3C*H*), 3.92 (s, 2H, =CC*H*$_2$), 4.51 (d, 2H, *J* 3.5 Hz, =CHC*H*O), 5.02 (s, 1H, C=C*H*), 6.55 (s, 2H, =C*H*CHO). δ_C (100 MHz, $CDCl_3$) 11.2 (2 x CH_3, *C*H_3CH), 14.7 (CH_3, =C*C*H_3), 42.7 (2 x CH, CH_3*C*H), 69.9 (CH_2, =C*C*H_2), 78.1 (C, *C*OH), 82.7 (2 x CH, =CH*C*HO), 130.8 (CH, C=*C*H), 135.9 (2 x CH, =*C*HCHO), 136.4 (C, *C*=CH). *m/z* HRMS calcd for $C_{13}H_{20}NaO_3^+$ 247.1310, found 247.1307; (ES) 233 (11%), 247 ([M+Na]$^+$, 100).

Preparation of 3-*exo*-((*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylprop-1-en-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 393

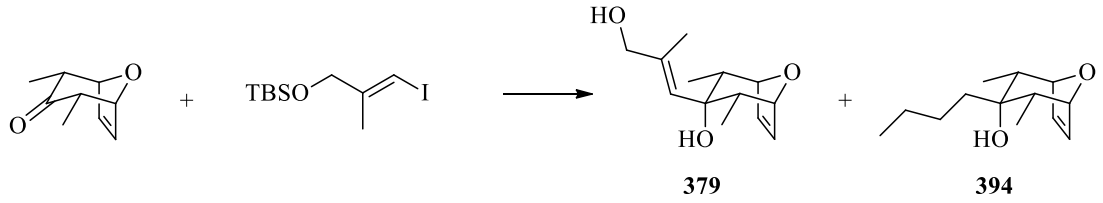


A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **384** (468 mg, 1.50 mmol) in THF (20 mL) at -78 °C, ^{n}BuLi (2.41 M, 0.620 mL, 1.50 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (5 mL) was added in one portion. The reaction was allowed to warm to room temperature and was stirred at room temperature for 16 h before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **393** (196 mg, 58%) as a white solid. m.p. 47-49 °C. R_f 0.47 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3548, 2956, 2929, 2893, 2857, 1459, 1373, 1251, 1067, 1043, 833, 775. δ_H (400 MHz, $CDCl_3$) 0.05 (s, 6H, Si(C*H*$_3$)$_2$), 0.87 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 0.90 (s, 9H, Si(C*H*$_3$)$_3$), 1.77 (d, 3H, ^{4}*J* 1.1 Hz, =CC*H*$_3$), 1.87 (s, 1H, O*H*), 2.17 (qd, 2H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 3.93 (d, 2H, ^{4}*J* 1.0 Hz, =CC*H*$_2$O), 4.52 (d, 2H, *J* 3.6 Hz, =CHC*H*O), 5.02-5.04 (m, 1H, C=C*H*), 6.55 (s, 2H, =C*H*CHO). δ_C (100 MHz, $CDCl_3$) -5.0 (3 x CH_3, Si(*C*H$_3$)$_2$), 11.2 (2 x CH_3, *C*H$_3$CH), 14.4 (CH_3, =C*C*H$_3$), 18.6 (C, Si*C*(CH$_3$)$_3$), 26.1 (3 x CH_3, SiC(*C*H$_3$)$_3$), 42.9 (2 x CH, CH$_3$*C*H), 68.9 (CH_2, =CC*H*$_2$O), 78.3 (C, *C*OH), 82.8 (2 x CH, =CH*C*HO), 129.1 (CH, C=*C*H), 135.9 (2 x CH, =*C*HCHO). *m/z* HRMS calcd for $C_{19}H_{34}NaO_3Si^+$ 361.2175, found 361.2169; (ES) 361 ([M+Na]$^+$, 100%); (ES) 361 (100%).

Preparation of 3-*exo*-((*E*)-3-hydroxy-2-methylprop-1-en-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 379 and 3-*exo*-butyl-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 394

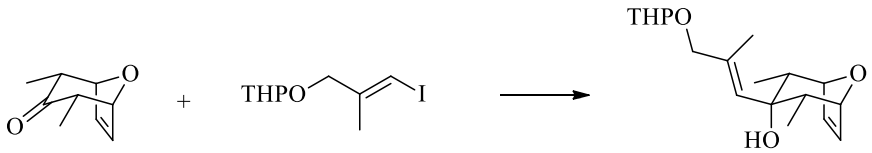


Novel compounds prepared using a novel procedure.

To a solution of **384** (468 mg, 1.50 mmol) in THF (20 mL) at -78 °C, ^{n}BuLi (1.47 M, 2.04 mL, 3.00 mmol) was added drop-wise over 15 min. The reaction was stirred at -78 °C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (5 mL) was added. The reaction was allowed to warm to room temperature and was stirred at room temperature for 5 h before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in THF (20 mL) and TBAF (1 M, 1.20 mL, 1.20 mmol) was added. The reaction was stirred at room temperature for 16 h before being washed with H_2O (10 mL) and extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10→50:50) to afford **394** (39 mg, 24%) as a white solid followed by **379** (50 mg, 17%) as a white solid. For analytical data of **379** see above. Analytical data for **394**. m.p. 42-44 °C. R_f 0.11 (hexane/EtOAc 90:10). υ_{max} neat/cm^{-1} 3435, 2979, 2954, 2925, 2867, 1467, 1453, 1045, 971, 912, 732. δ_H (400 MHz, $CDCl_3$) 0.85-0.91 (m, 9H, C*H*$_3$CH, CH$_2$C*H*$_3$), 1.17-1.38 (m, 6H, 3 x C*H*$_2$), 2.15 (qd, 2H, *J* 7.3, 3.8 Hz, CH$_3$C*H*), 4.48 (d, 2H, *J* 3.8 Hz, =CHC*H*O), 6.56 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.7 (2 x CH$_3$, *C*H$_3$CH), 14.2 (CH$_3$, CH$_2$*C*H$_3$), 23.6 (CH$_2$, *C*H$_2$), 27.0 (CH$_2$, *C*H$_2$), 37.6 (CH$_2$, *C*H$_2$), 38.7 (2 x CH, CH$_3$*C*H), 75.5 (C, *C*OH), 83.1 (2 x CH, =CH*C*HO), 136.0 (2 x CH, =*C*H). *m/z* HRMS calcd for

$C_{13}H_{22}NaO_2^+$ 210.1620 found 210.1625; (ES) 85 (72%), 97 (43), 135 (32), 153 ($[M-Bu]^+$, 93), 210 ($[M+Na]^+$, 100).

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((*E*)-2-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-en-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 398



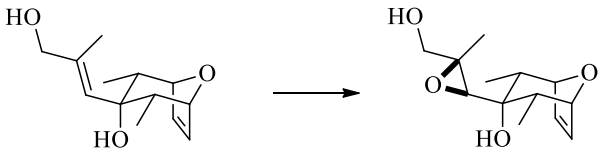
A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **385** (423 mg, 1.50 mmol) in THF (8 mL) at -78 °C, ^{n}BuLi (1.47 M, 1.02 mL, 1.50 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (2 mL) was added in one portion. The reaction was allowed to warm to room temperature and was stirred at room temperature for 16 h before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10→80:20) to afford **398** (255 mg, 83%) as a clear colourless oil. R_f 0.40 (hexane/EtOAc 70:30). υ_{max} neat/cm^{-1} 3584, 2930, 2871, 1453, 1373, 1200, 1113, 1019, 930, 905, 669.δ_H (400 MHz, $CDCl_3$) 0.88 (app. dd, 6H, *J* 7.3, 0.3 Hz, C*H*$_3$CH), 1.48-1.87 (m, 6H, OCH$_2$C*H*$_2$, CHCH$_2$C*H*$_2$, CHC*H*$_2$), 1.85 (d, 3H, ^{4}*J* 1.2 Hz, =CC*H*$_3$), 2.19 (app. pd, 2H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 3.45-3.51 (m, 1H, OC*H*$_2$CH$_2$), 3.81-3.89 (m, 2H, OC*H*$_2$CH$_2$, =CC*H*$_2$), 4.02 (d, 1H, ^{2}*J* 12.3 Hz, =CC*H*$_2$), 4.52 (d, 2H, *J* 3.6 Hz, =CHC*H*O), 4.55-4.58 (m, 1H, OC*H*O), 5.02-5.08 (m, 1H, C=C*H*), 6.56 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.2 (CH$_3$, *C*H$_3$CH), 11.3 (CH$_3$, *C*H$_3$CH), 15.0 (CH$_3$, =C*C*H$_3$), 19.8 (CH$_2$, CHCH$_2$*C*H$_2$), 25.7 (CH$_2$, OCH$_2$C*H*$_2$), 30.1 (CH$_2$, CH*C*H$_2$), 42.7 (2 x CH, CH$_3$*C*H), 62.6 (CH$_2$, O*C*H$_2$CH$_2$), 73.8 (CH$_2$, =C*C*H$_2$O), 78.2 (C,

*C*OH), 82.8 (2 x CH, =CH*C*HO), 97.4 (CH, O*C*HO), 132.6 (CH, C=*C*H), 133.6 (C, *C*=CH), 135.9 (2 x CH, =*C*H). *m/z* HRMS calcd for $C_{18}H_{28}NaO_4^+$ 331.1885, found 331.1871; (ES) 331 ($[M+Na]^+$, 100%).

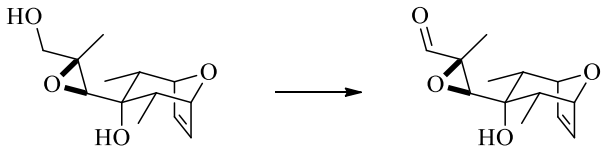
Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-(3-(hydroxymethyl)-3-methyloxiran-2-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 399



A novel compound prepared using a modified literature procedure.[155b]

To a solution of **379** (50 mg, 0.220 mmol) and $VO(acac)_2$ (1.20 mg, 4.4 µmol) in CH_2Cl_2 (3 mL) at room temperature, ^{t}BuOOH (3.3 M, 0.200 mL, 0.670 mmol) was added drop-wise over 10 min. The reaction was stirred for 6 h at room temperature. Upon complete conversion, the reaction was purified by column chromatography (hexane/EtOAc 50:50) to afford **399** (53mg, 100%) as a white solid. m.p. 94-96 °C. R_f 0.15 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3394, 2958, 2928, 2873, 1450, 1344, 1078, 1051, 933, 833, 670. δ_H (400 MHz, $CDCl_3$) 0.89 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.00 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.48 (s, 3H, C*H*$_3$CO), 1.76 (s, 1H, O*H*), 1.92 (br. s, 1H, O*H*), 2.15 (qd, 1H, *J* 7.3, 3.7 Hz, CH$_3$C*H*), 2.30 (qd, 1H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 2.76 (s, 1H, C*H*OC), 3.48-3.58 (m, 2H, OCC*H*$_2$), 4.46 (dd, 1H, *J* 3.6, 1.7 Hz, =CHC*H*O), 4.49 (dd, 1H, *J* 3.6, 1.7 Hz, =CHC*H*O), 6.43 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*), 6.47 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.4 (CH$_3$, *C*H$_3$CH), 11.5 (CH$_3$, *C*H$_3$CH), 15.3 (CH$_3$, *C*H$_3$CO), 38.2 (CH, CH$_3$*C*H), 42.7 (CH, CH$_3$*C*H), 60.1 (C, *C*OCH), 66.2 (CH$_2$, *C*H$_2$CO), 66.8 (CH, CO*C*H), 73.4 (C, *C*OH), 82.6 (CH, =CH*C*HO), 82.7 (CH, =CH*C*HO), 134.7 (CH, =*C*H), 134.9 (CH, =*C*H). *m/z* HRMS calcd for $C_{13}H_{20}NaO_4^+$ 263.1259, found 263.1268; (ES) 263 ($[M+Na]^+$, 100%).

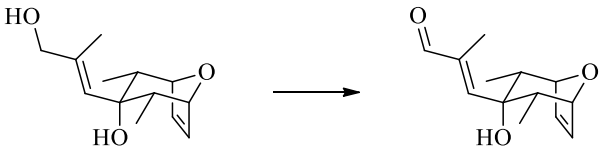
Preparation of (±)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 400



A novel compound prepared using a literature procedure.[159]

To a solution of **399** (833 mg, 3.47 mmol) in CH_2Cl_2 (43 mL) at room temperature, $NaHCO_3$ (2.92 g, 34.7 mmol) was added. The resulting solution was stirred for 30 min before being cooled to 0 °C. DMP (2.21 g, 5.21 mmol) was added to the reaction, and the mixture stirred at room temperature for 2.5 h. Upon completion, cold $NaHCO_3$ (20 mL of a saturated aqueous solution) was added, followed by $Na_2S_2O_3$ (20 mL of a saturated aqueous solution), and extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 75:25) to afford **400** (741 mg, 90%) as a white solid. m.p. 83-85 °C. R_f 0.58 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3571, 2967, 2826, 1725, 1086, 1048, 935, 837, 741. δ_H (400 MHz, $CDCl_3$) 0.88 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.05 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.63 (s, 3H, C*H*$_3$CO), 1.75 (s, 1H, O*H*), 2.13 (qd, 1H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 2.39 (qd, 1H, *J* 7.3, 3.7 Hz, CH$_3$C*H*), 2.75 (s, 1H, C*H*OC), 4.51 (dd, 2H, *J* 3.6, 1.5 Hz, =CHC*H*O), 6.49 (app. qd, 2H, *J* 6.1, 1.6 Hz, =C*H*), 8.81 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 10.9 (CH$_3$, *C*H$_3$CO), 11.4 (2 x CH$_3$, *C*H$_3$CH), 38.4 (CH, CH$_3$*C*H), 42.6 (CH, CH$_3$*C*H), 61.4 (C, CO*C*H), 66.1 (CH, *C*HOC), 73.9 (C, *C*OH), 82.4 (CH, =CH*C*HO), 82.5 (CH, =CH*C*HO), 134.9 (CH, =*C*H), 135.3 (CH, =*C*H), 200.1 (CH, *C*HO). *m/z* HRMS calcd for $C_{13}H_{18}NaO_4^+$ 261.1103, found 261.1109; (ES) 261 ($[M+Na]^+$, 6%), 293 ($[M+Na+MeOH]^+$, 100), 294 ([M+Na+MeOH+H], 18).

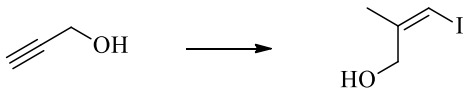
Preparation of (*E*)-3-(3-*exo*-hydroxy-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methylacrylaldehyde 405



A novel compound prepared using a literature procedure.[159]

To a solution of **379** (50 mg, 0.220 mmol) in CH_2Cl_2 (3 mL) at room temperature, $NaHCO_3$ (185 mg, 2.20 mmol) was added. The resulting solution was stirred for 30 min before being cooled to 0 °C. DMP (140 mg, 0.330 mmol) was added to the reaction, and the mixture stirred at room temperature for 2 h. Upon completion, cold $NaHCO_3$ (1.4 mL of a saturated aqueous solution) was added, followed by $Na_2S_2O_3$ (1.4 mL of a saturated aqueous solution), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 75:25) to afford **405** (49 mg, 100%) as a white solid. m.p. 101-103 °C. R_f 0.57 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3511, 2969, 1682, 1075, 1044. δ_H (400 MHz, $CDCl_3$) 0.87 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 1.93 (d, 3H, *J* 1.4 Hz, =CC*H*$_3$), 2.12 (s, 1H, O*H*), 2.29 (qd, 2H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 4.55 (d, 2H, *J* 3.6 Hz, =CHC*H*O), 5.92 (m, 1H, C=C*H*), 6.60 (s, 2H, =C*H*CHO), 9.33 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 10.1 (CH$_3$, =C*C*H$_3$), 11.3 (2 x CH$_3$, *C*H$_3$CH), 41.7 (2 x CH, CH$_3$*C*H), 79.1 (C, *C*OH), 82.3 (2 x CH, =CH*C*HO), 136.1 (2 x CH, =*C*HCHO), 140.0 (C, *C*=CH), 158.0 (CH, C=*C*H), 196.6 (CH, *C*HO). *m/z* HRMS calcd for $C_{13}H_{18}NaO_3^+$ 222.1256, found 222.1260; (EI) 81 (98%), 83 (49), 95 (100), 87 (91), 98 (89), 109 (43), 111 (44), 125 (36), 139 (26), 152 (34), 193 ([M-CHO]$^+$, 33), 222 ([M]$^+$, 10).

Preparation of (*Z*)-3-iodo-2-methylprop-2-en-1-ol 409

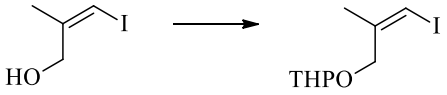


A known compound prepared using a modified literature procedure.[161a]

Reaction was performed under an argon atmosphere.

To a solution of propargyl alcohol **408** (2.00 g, 2.10 mL, 35.7 mmol) in anhydrous Et_2O (100 mL) at -5 °C, CuI (6.80 g, 35.7 mmol) was added. MeMgBr (3 M, 25.0 mL, 74.9 mmol) was then added slowly. The resulting suspension was allowed to warm to room temperature and stirred for 2 h. The reaction was cooled to -5 °C and a solution of ICl (5.80 g, 1.80 mL, 35.7 mmol) in Et_2O (35 mL) was added. The reaction was stirred at room temperature for 16 h, before being cooled to 0 °C and NH_4Cl (100 mL of a saturated aqueous solution) was added. The reaction was filtered through Celite® and the layers separated. The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organics washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **409** (2.85 g, 40%) as a clear, colourless liquid δ_H (400 MHz, $CDCl_3$) 1.95 (d, 3H, ^4J 1.5 Hz, C*H*$_3$), 2.38 (1H, s, O*H*), 4.21 (s, 2H, C*H*$_2$), 5.93-5.99 (m, 1H, C*H*I). δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3, *C*H_3), 68.2 (CH_2, *C*H_2), 75.0 (CH, *C*HI), 146.2 (C, *C*=CHI). *m/z* (EI) 71.0 ([M-I]$^+$, 44%), 126.9 (I^+, 52), 127.9 (I^+, 29), 198.0 (M^+, 100). Literature values:[161a] υ_{max} 3300 (OH), 3010 (C=CH), 2980 (aliphatic CH), 2960 (aliphatic CH), 1600 (C=C), 1050 (C-O); δ_H (200 MHz; $CDCl_3$) 1.71 (1H, s, O*H*, disappears upon addition of D_2O), 1.92 (3H, d, *J* 1.5 Hz, C*H*$_3$), 4.20 (2H, s, C*H*$_2$), 5.95 (1H, d, *J* 1.5 Hz, C=C*H*); δ_C (75.5 Hz; $CDCl_3$) 29.0, 68.3, 75.0, 102.3; *m/z* (FAB) 197.9742 (M^+, C_4H_7IO requires *m/z* = 197.9742, 11%), 181 (M^+-OH, 51), 167 (M^+-CH_2OH, 5).

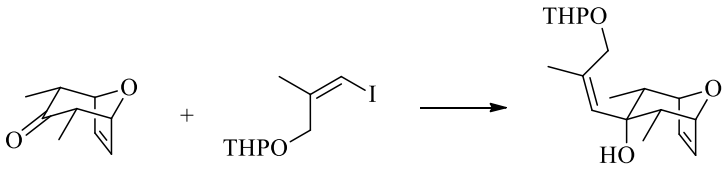
Preparation of (*Z*)-2-((3-iodo-2-methylallyl)oxy)tetrahydro-2*H*-pyran 412



A known compound prepared using a literature procedure.[163]

To a solution of **409** (2.20 g, 11.1 mmol) in CH_2Cl_2 (43 mL) at room temperature, dihydropyran (1.21 g, 1.31 mL, 14.4 mmol) was added followed by PPTS (223 mg, 0.90 mmol). The reaction was stirred at room temperature for 1.5 h before being quenched with $NaHCO_3$ (100 mg), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (Hex/Et_2O 70:30) to afford **412** (2.98 g, 95%) as a clear colourless liquid. δ_H (400 MHz, $CDCl_3$) 1.51-1.83 (m, 6H, CHC*H*$_2$, CHCH$_2$C*H*$_2$, OCH$_2$C*H*$_2$), 1.94 (d, 3H, ^4J 1.4 Hz, =CC*H*$_3$), 3.51-3.57 (m, 1H, CH$_2$C*H*$_2$O), 3.86-3.91 (m, 1H, CH$_2$C*H*$_2$O), 4.15 (d, 1H, ^2J 12.1 Hz, =CC*H*$_2$O), 4.26 (d, 1H, ^2J 12.2 Hz, =CC*H*$_2$O), 4.61 (t, 1H, *J* 3.5 Hz, OC*H*O), 6.01-6.03 (m, 1H, =C*H*I). δ_C (100 MHz, $CDCl_3$) 19.6 (CH$_2$, CHCH$_2$*C*H$_2$), 22.2 (CH$_3$, =C*C*H$_3$), 25.6 (CH$_2$, OCH$_2$*C*H$_2$), 30.7 (CH$_2$, CHCH$_2$*C*H$_2$), 62.4 (CH$_2$, CH$_2$*C*H$_2$O), 72.1 (CH$_2$, =C*C*H$_2$O), 75.8 (CH, =*C*HI), 98.3 (CH, O*C*HO), 144.6 (C, *C*=CHI). *m/z* (EI) 85 ([THP]$^+$, 100%), 126 (I$^+$, 16), 155 ([M-I]$^+$, 5), 180 ([M-OTHP]$^+$, 69), 197 ([M-THP]$^+$, 37). Literature values:[163] IR (neat) 2940, 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.62 (t, *J* 3.0 Hz, 1H), 4.26 (d, *J* 12.1 Hz, 1H), 4.16 (d, *J* 12.1 Hz, 1H), 3.85-3.95 (m, 1H), 3.5-3.6 (m, 1H), 1.95 (d, *J* 1.5 Hz, 3H), 1.5-1.9 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 98.4, 75.8, 72.1, 62.5, 30.7, 25.6, 22.2, 19.6; HRMS (CI) calcd. for $C_9H_{16}IO_2$ $(M+H)^+$ 283.0195, found 283.0198.

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((*Z*)-2-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-en-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 414



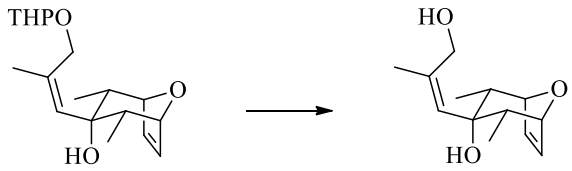
A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **412** (423 mg, 1.50 mmol) in THF (8 ml) at -78 °C, ^{n}BuLi (1.74 M, 0.860 ml, 1.50 mmol) was added drop-wise. The solution was stirred at -78°C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (2 mL) was added in one portion. The resulting solution was allowed to warm to room temperature over 16 h before being quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (2 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10→80:20) to afford **414** (303 mg, 99%) as a white solid. m.p. 48-50 °C. R_f 0.41 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3557, 2966, 2941, 2901, 2872, 1454, 1112, 1051, 1014, 980. δ_H (400 MHz, $CDCl_3$) 0.84 (app. t, 6H, *J* 7.4 Hz, C*H*$_3$CH), 1.49-1.82 (m, 6H, CHC*H*$_2$, CHCH$_2$C*H*$_2$, OCH$_2$C*H*$_2$), 1.78 (d, 3H, ^{4}*J* 1.4 Hz, =CC*H*$_3$), 2.05 (qd, 2H, *J* 7.4, 3.6 Hz, CH$_3$C*H*), 2.77 (s, 1H, O*H*), 3.48-3.53 (m, 1H, CH$_2$C*H*$_2$O), 3.81-3.86 (m, 1H, CH$_2$C*H*$_2$O), 4.24 (d, 1H, ^{2}*J* 11.5 Hz, =CC*H*$_2$O), 4.44 (d, 1H, ^{2}*J* 11.5 Hz, =CC*H*$_2$O), 4.49 (dd, 2H, *J* 3.6, 1.1 Hz, =CHC*H*O), 4.64 (t, 1H, *J* 3.4 Hz, OC*H*O), 4.97 (s, 1H, C=C*H*), 6.42-6.47 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.9 (2 x CH$_3$, *C*H$_3$CH), 19.4 (CH$_2$, CHCH$_2$*C*H$_2$), 24.2 (CH$_3$, =C*C*H$_3$), 25.6 (CH$_2$, OCH$_2$*C*H$_2$), 30.8 (CH$_2$, CH*C*H$_2$), 42.1 (CH, CH$_3$*C*H), 42.3 (CH, CH$_3$*C*H), 62.6 (CH$_2$, CH$_2$*C*H$_2$O), 66.1 (CH$_2$, =C*C*H$_2$O), 77.7 (C, *C*OH), 82.7 (2 x CH, =CH*C*HO), 97.5 (CH, O*C*HO), 133.6 (C, *C*=CH), 134.6 (CH,

C=*C*H), 135.4 (2 x CH, =*C*H). *m/z* HRMS calcd for $C_{18}H_{28}NaO_4^+$ 331.1885, found 331.1875; (ES) 331 ($[M+Na]^+$, 100%), 332 ($[M+Na+H]^+$, 8), 347 ($[M+K]^+$, 8).

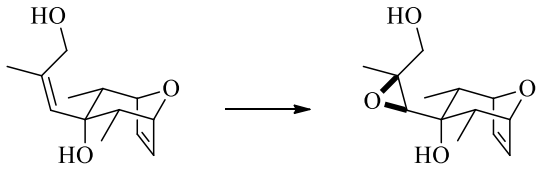
Preparation of 3-*exo*-((*Z*)-3-hydroxy-2-methylprop-1-en-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 406



A novel compound prepared using a modified literature procedure.[153]

To a solution of **414** (500 mg, 1.63 mmol) in EtOH (10 mL), PPTS (40.0 mg, 0.160 mmol) was added. The resulting solution was stirred at 55 °C for 2 h before being allowed to cool to room temperature. The solvent was evaporated and the residue purified by column chromatography (hexane/EtOAc 70:30→50:50) to afford **406** (338 mg, 98%) as clear crystals of XRD quality (See **Appendix AI**). m.p. 74-76 °C. R_f 0.33 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3675, 3218, 2987, 2970, 2901, 1452, 1393, 1065, 1046, 723. δ_H (400 MHz, $CDCl_3$) 0.88 (d, 6H, *J* 7.4 Hz, C*H*$_3$CH), 1.79 (d, 3H, ^4J 1.4 Hz, =CC*H*$_3$), 2.08 (qd, 2H, *J* 7.4, 3.6 Hz, CH$_3$C*H*), 2.52 (br. s, 1H, O*H*), 3.32 (br. s, 1H, O*H*), 3.99 (s, 2H, =CC*H*$_2$O), 4.53 (d, 2H, *J* 3.5 Hz, =CHC*H*O), 4.79 (d, 1H, *J* 1.1 Hz, C=C*H*), 6.58 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.0 (2 x CH$_3$, *C*H$_3$CH), 25.9 (CH$_3$, =C*C*H$_3$), 42.3 (2 x CH, CH$_3$*C*H), 63.0 (CH$_2$, =C*C*H$_2$O), 79.0 (C, *C*OH), 82.5 (2 x CH, =CH*C*HO), 132.2 (2 x CH, C=*C*H), 136.1 (CH, =*C*H), 137.9 (C, *C*=CH). *m/z* HRMS calcd for $C_{13}H_{20}NaO_3^+$ 247.1310, found 247.1312; (ES) 247 ($[M+Na]^+$, 100%), 248 ($[M+Na+H]^+$, 10).

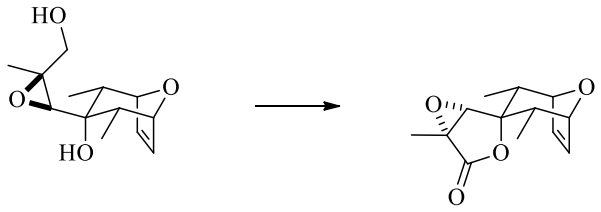
Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-((2*R*,3*S*)-3-(hydroxymethyl)-3-methyloxiran-2-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 415



A novel compound prepared using a modified literature procedure.[155b]

To a solution of **406** (171 mg, 0.760 mmol) and $VO(acac)_2$ (21 mg, 0.080 mmol) in CH_2Cl_2 (11 mL) at room temperature, ^tBuOOH (3.3 M, 0.280 mL, 0.910 mmol) was added drop-wise over 10 min. The reaction was stirred for 16 h at room temperature and ^tBuOOH (0.07 mL, 0.230 mmol) added. Upon complete conversion, the reaction was purified by column chromatography (hexane/EtOAc 50:50→20:80) to afford **415** (88 mg, 48%) as a clear colourless oil. R_f 0.20 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3407, 2968, 2933, 1456. δ_H (400 MHz, $CDCl_3$) 0.90 (d, 3H, *J* 7.4 Hz, C*H*$_3$CH), 1.03 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.35 (s, 3H, C*H*$_3$CO), 2.19 (qd, 1H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 2.28 (br. s, 2H, O*H*), 2.38 (qd, 1H, *J* 7.3, 3.7Hz, CH$_3$C*H*), 2.54 (s, 1H, C*H*OC), 3.71 (d, 1H, ^2J 12.1 Hz, OCC*H*$_2$), 4.00 (d, 1H, ^2J 12.1 Hz, OCC*H*$_2$), 4.49 (d, 1H, *J* 3.7 Hz, =CHC*H*O), 4.52 (d, 1H, *J* 3.6 Hz, =CHC*H*O), 6.51 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.4 (CH_3, *C*H$_3$CH), 11.6 (CH_3, *C*H$_3$CH), 21.9 (CH_3, *C*H$_3$CO), 39.6 (CH, CH$_3$*C*H), 41.8 (CH, CH$_3$*C*H), 61.6 (C, CHO*C*), 64.3 (CH_2, OC*C*H$_2$), 72.3 (CH, *C*HOC), 74.0 (C, *C*OH), 82.4 (CH, =CH*C*HO), 82.4 (CH, =CH*C*HO), 135.3 (CH, =*C*H), 135.6 (CH, =*C*H). *m/z* HRMS calcd for $C_{13}H_{20}NaO_4^+$ 263.1259, found 263.1261; (ES) 263 ($[M+Na]^+$, 100%).

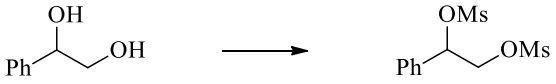
Preparation of (±)-(1*R*,1'*R*,2*S*,2'*S*,4'*R*,5*R*,5'*S*)-2',4',5-trimethyl-3,6,8'-trioxaspiro[bicyclo[3.1.0]hexane-2,3'-bicyclo[3.2.1]oct[6]en]-4-one 417



A novel compound prepared using a literature procedure.[159]

To a solution of **415** (88 mg, 0.370 mmol) in CH_2Cl_2 (5 mL) at 0 °C, $NaHCO_3$ (311 mg, 3.70 mmol) was added. The reaction was stirred for 30 min before DMP (233 mg, 0.550 mmol) was added. The reaction was stirred at room temperature for 2 h and DMP (233 mg, 0.550 mmol) was added. The reaction was stirred for 20 h at room temperature before being quenched with cold $NaHCO_3$ (4 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (4 mL of a saturated aqueous solution). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc 75:25) to afford **417** (22 mg, 25%) as a white solid. m.p. 162-165 °C. R_f 0.17 (hexane/EtOAc 75:25). υ_{max} neat/cm^{-1} 2941, 1769, 1456, 1048, 733. δ_H (400 MHz, $CDCl_3$) 0.79 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 0.96 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 1.58 (s, 3H, C*H*$_3$CC=O), 2.24 (qd, 1H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 2.54 (qd, 1H, *J* 7.2, 3.7 Hz, CH$_3$C*H*), 3.58 (s, 1H, C*H*OC), 4.44 (dd, 1H, *J* 3.6, 1.7 Hz, =CHC*H*O), 4.49 (dd, 1H, *J* 3.5, 1.6 Hz, =CHC*H*O), 6.32 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*), 6.36 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.9 (CH_3, *C*H$_3$CH), 11.0 (CH_3, *C*H$_3$CC=O), 12.2 (CH_3, *C*H$_3$CH), 38.5 (CH, CH$_3$*C*H), 39.7 (CH, CH$_3$*C*H), 55.8 (C, CHO*C*), 66.7 (CH, *C*HOC), 81.5 (CH, =CH*C*HO), 82.6 (CH, =CH*C*HO), 83.4 (C, *C*OC=O), 132.8 (CH, =*C*H), 134.1 (CH, =*C*H), 172.7 (C, *C*=O). *m/z* HRMS calcd for $C_{13}H_{16}O_4^+$ 236.1049, found 236.1043; (EI) 81 (48%), 95 (100), 96 (40), 236 ($[M]^+$, 14).

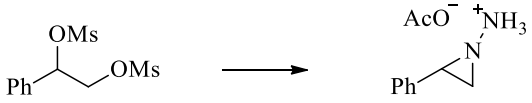
Preparation of (±)-1-phenylethane-1,2-diyl dimethanesulfonate 420



A known compound prepared using a literature procedure.[165]

To a solution of styrene glycol **419** (3.45 g, 25.0 mmol) in pyridine (9 mL) at -5 °C, mesylate chloride (6.47 g, 4.37 mL, 56.0 mmol) was added drop-wise. The reaction was stirred for 4 h, with the temperature maintained at 2-4 °C. After this time, the reaction was mixed with ice (60 g) and the resulting precipitate filtered under vacuum and washed with H_2O (20 mL). The remaining solid was dissolved in CH_2Cl_2 (25 mL), separated from the remaining H_2O and dried over $MgSO_4$. Pentane was added to the CH_2Cl_2 solution until precipitation began, at which point the mixture was placed in the freezer for 16 h. The resultant crystals were collected and washed with pentane (pre-cooled to 0 °C), before being dried under vacuum at room temperature to afford **420** (5.06 g, 69%) as a white solid. δ_H (400 MHz, $CDCl_3$) 2.86 (s, 3H, SCH_3), 3.07 (s, 3H, SCH_3), 4.39 (dd, 1H, ^2J 11.8 Hz, J 3.3 Hz, CH_2), 4.52 (dd, 1H, ^2J 11.8 Hz, J 8.7 Hz, CH_2), 5.80 (dd, 1H, J 8.7, 3.3 Hz, CH), 7.38-7.46 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 38.3 (CH_3, CH_3), 39.4 (CH_3, CH_3), 70.0 (CH_2, CH_2), 80.9 (CH, CH), 127.1 (2 x CH, CH_{Ar}), 129.5 (2 x CH, CH_{Ar}), 130.4 (CH, CH_{Ar}), 133.5 (C, CCH_{Ar}). *m/z* (ES) 166 (5%), 169 (8), 221 (4), 297 (18), 317 ($[M+Na]^+$, 100). Literature values:[165a] IR υ_{max} 3035, 1500, 1460, 1416, 1370, 1335, 1178, 1077, 1003, 976, 967, 920, 872 cm^{-1}. NMR: δ_H 2.86 (s, 3H), 3.06 (s, 3H), 4.35-4.56 (m, 2H), 5.68-5.92 (m, 1H), 7.40 (s, 5H). $C_{10}H_{14}O_6S_2$ (294.33) calcd. C 40.82 H 4.80 S 21.80% found C 41.01 H 4.80 S 21.71%.

Preparation of (±)-2-phenylaziridin-1-aminium acetate 421

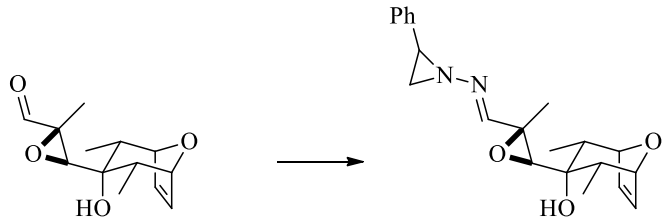


A known compound prepared using a literature procedure.[165]

To neat hydrazine hydrate (10.4 mL), **420** (4.14 g, 14.1 mmol) was added with gentle stirring. To the resulting mixture was added pentane (141 mL) and the resulting biphasic solution stirred vigorously. The stirring was adjusted so that both layers mixed, but none of the hydrazine was deposited on the upper walls of the flask. The reaction was stopped once two clear layers could be seen on cessation of stirring (20-24 h), and the layers were separated. The hydrazine layer was washed with pentane (2 x 25 mL) and the combined organics filtered through cotton wool. The solution was cooled to 0 °C and AcOH (0.810 mL, 14.1 mmol) added drop-wise over 10 min. The resulting suspension was stirred at 0 °C for 1 h before being filtered, washed with pentane (15 ml) and dried *in vacuo* to afford **421** (1.47 g, 61%) as a white solid. υ_{max} neat/cm^{-1} 2521, 2195, 1625, 1498, 1396, 1023, 730, 661. δ_H (400 MHz, $CDCl_3$) 2.08 (s, 3H, C*H*$_3$COO$^-$), 2.13 (dd, 1H, *J* 7.9 Hz, ^2J 0.8 Hz, C*H*$_2$), 2.16 (dd, 1H, *J* 4.9 Hz, ^2J 0.9 Hz, C*H*$_2$), 2.78 (dd, 1H, *J* 7.9, 4.9 Hz, C*H*), 6.52 (br. s, 3H, *H*$_3$N$^+$), 7.17-7.21 (m, 2H, *H*$_{Ar}$), 7.24-7.35 (m, 3H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3, *C*H$_3$COO$^-$), 41.1 (CH_2, *C*H$_2$), 45.8 (CH, C*H*), 126.5 (2 x CH, *C*H$_{Ar}$), 127.5 (CH, *C*H$_{Ar}$), 128.6 (2 x CH, *C*H$_{Ar}$), 138.2 (C, *C*CH$_{Ar}$), 176.0 (C, CH$_3$*C*OO$^-$). Literature values: IR: υ_{max} 3665, 1590 cm^{-1}. NMR: δ 1.90-2.22 (5H, AB part of ABX and C*H*$_2$ at δ 2.02), 2.67-2.95 (1H, X part of ABX), 6.50-6.70 (3H, NH_3), 7.0-7.14 (5H). $C_{10}H_{14}N_2O_2$ (194.23) calcd. C 61.83 H 7.27 N 14.32% found C 61.60 H 7.16 N 14.44%.

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((2*R*,3*R*)-3-methyl-3-((2-phenylaziridin-1-yl)imino)methyl)oxiran-2-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 402

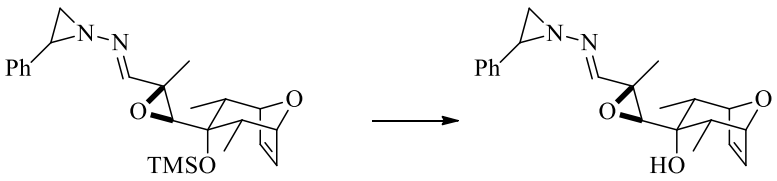
Method A



A novel compound prepared using a literature procedure.[166b]

To a solution of **400** (50 mg, 0.210 mmol) in CH_2Cl_2 (3 mL) at -10 °C, **421** (81 mg, 0.420 mmol) and NaOAc (36 mg, 0.440 mmol) were added. The resulting solution was stirred at -10 °C for 2 h before being filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10→80:20) to afford **402** (60 mg, 81% d.r. 1:1) as an impure yellow viscous oil.

Method B

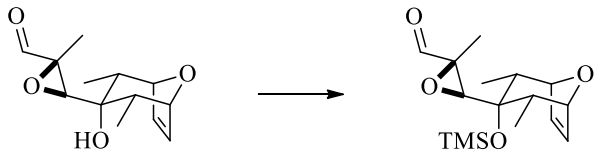


A novel compound prepared using a modified literature procedure.[148]

To a solution of **423** (50 mg, 0.120 mmol) in THF (2.4 mL) at room temperature, TBAF (1 M, 0.140 mL, 0.140 mmol) was added in one portion. The reaction was stirred at room temperature for 16 h before being washed with H_2O (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc 70:30, deactivated with 0.1% Et_3N) to afford **402** (40 mg, 93%, d.r. 1:1) as a bright yellow oil. R_f 0.40

(hexane/EtOAc 70:30). υ_{max} neat/cm^{-1} 3570, 2934, 1456, 1079, 1051, 932, 725, 697, 664. δ_H (400 MHz, $CDCl_3$) 0.90 (2 x d, 3H, *J* 7.3 Hz, C*H*$_3$CH, Isomer A+B), 1.02 (2 x d, 3H, *J* 7.3 Hz, C*H*$_3$CH, Isomer A+B), 1.67 (2 x s, 3H, C*H*$_3$CO, Isomer A+B), 1.74 (s, 1H, O*H*, Isomer A+B), 2.15 (qd, 1H, *J* 7.3, 3.7 Hz, CH$_3$C*H*, Isomer A+B), 2.31 (qd, 1H, *J* 7.0, 3.2 Hz, CH$_3$C*H*, Isomer A+B), 2.36 (dt, 1H, *J* 4.5 Hz, ^{2}*J* 0.5 Hz, C*H*$_2$N, Isomer A+B), 2.42 (dd, 0.5H, *J* 7.7 Hz, ^{2}*J* 0.5 Hz, C*H*$_2$N, Isomer B), 2.48 (dd, 0.5H, *J* 7.6 Hz, ^{2}*J* 0.5 Hz, C*H*$_2$N, Isomer A), 2.63 (2 x s, 1H, C*H*OC, Isomer A+B), 3.01 (dd, 0.5H, *J* 7.8, 4.8 Hz, C*H*N, Isomer A), 3.07 (dd, 0.5H, *J* 7.8, 4.9 Hz, C*H*N, Isomer B), 4.48 (dd, 1H, *J* 3.3, 1.2 Hz, =CHC*H*O, Isomer A+B), 4.49-4.51 (m, 1H, =CHC*H*O, Isomer A+B), 6.45 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*, Isomer A+B), 6.48 (dd, 1H, *J* 6.1, 1.5 Hz, =C*H*, Isomer A+B), 7.21-7.34 (m, 5H, *H*$_{Ar}$), 7.38 (2 x s, 1H, C*H*=N, Isomer A+B). δ_C (100 MHz, $CDCl_3$) 11.4 (CH$_3$, *C*H$_3$CH, Isomer A+B), 14.4 (CH$_3$, *C*H$_3$CO, Isomer A+B), 38.3 (CH, CH$_3$*C*H, Isomer A+B), 40.5 (0.5 x CH$_2$, *C*H$_2$N, Isomer A), 41.0 (0.5 x CH$_2$, *C*H$_2$N, Isomer B), 42.6 (CH, CH$_3$*C*H, Isomer A+B), 43.9 (0.5 x CH, *C*HN, Isomer B), 44.5 (0.5 x CH, *C*HN, Isomer A), 58.2 (C, CHO*C*, Isomer A+B), 69.5 (CH, *C*HOC, Isomer A+B), 73.7 (C, *C*OH, Isomer A+B), 82.5 (2 x CH, =CH*C*HO, Isomer A+B), 126.5 (2 x CH, *C*H$_{Ar}$, Isomer A+B), 127.5 (CH, *C*H$_{Ar}$, Isomer A+B), 128.6 (2 x CH, *C*H$_{Ar}$, Isomer A+B), 134.8 (CH, =*C*H, Isomer A+B), 135.0 (CH, =*C*H, Isomer A+B), 138.3 (0.5 x C, *C*CH$_{Ar}$, Isomer A), 138.4 (0.5 x C, *C*CH$_{Ar}$, Isomer B), 163.5 (CH, *C*H=N, Isomer A+B). *m/z* HRMS calcd for $C_{21}H_{26}N_2NaO_3^+$ 377.1847, found 377.1844; (ES) 377 ($[M+Na]^+$, 100%), 378 ($[M+Na+H]^+$, 17).

Preparation of (±)-(2*S*,3*S*)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 422

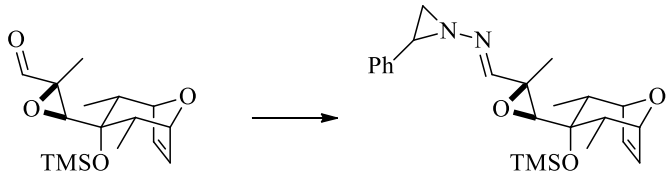


A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **400** (30 mg, 0.130 mmol) and Et_3N (49 mg, 0.070 mL, 0.480 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C, TMSOTf (73 mg, 0.060 mL, 0.320 mmol) was added drop-wise. The reaction was stirred at room temperature for 4 h before being quenched with $NaHCO_3$ (1 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **422** (33 mg, 82%) as a white solid. m.p. 58-60 °C. R_f 0.41 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2963, 2935, 1731, 1250, 1088, 718. δ_H (400 MHz, $CDCl_3$) 0.17 (s, 9H, Si(C*H*$_3$)$_3$), 0.85 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 0.89 (d, 3H, *J* 7.0 Hz, C*H*$_3$CH), 1.64 (s, 3H, C*H*$_3$CO), 1.94-2.06 (m, 2H, CH$_3$C*H*), 3.09 (s, 1H, COC*H*), 4.37 (dd, 1H, *J* 3.7, 1.4 Hz, =CHC*H*O), 4.43 (dd, 1H, *J* 3.9, 1.3 Hz, =CHC*H*O), 6.18-6.23 (m, 2H, =C*H*), 8.74 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 2.6 (3 x CH_3, Si(*C*H$_3$)$_3$), 10.0 (CH_3, *C*H$_3$CO), 12.8 (CH_3, *C*H$_3$CH), 13.3 (CH_3, *C*H$_3$CH), 37.8 (CH, CH$_3$*C*H), 40.7 (CH, CH$_3$*C*H), 62.0 (C, *C*OCH), 66.2 (CH, *C*HCO), 78.7 (C, *C*OSi), 82.5 (CH, =CH*C*HO), 82.6 (CH, =CH*C*HO), 132.6 (CH, =*C*H), 133.6 (CH, =*C*H), 199.7 (CH, *C*HO). *m/z* HRMS calcd for $C_{16}H_{26}NaO_4Si^+$ 333.1498, found 333.1507; (ES) 333 ($[M+Na]^+$, 12%), 365 ($[M+Na+MeOH]^+$, 100), 366 ($[M+Na+MeOH+H]^+$, 19).

Preparation of (±)-(*E*)-*N*-(((2*R*,3*S*)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxiran-2-yl)methylene)-2-phenylaziridin-1-amine 423

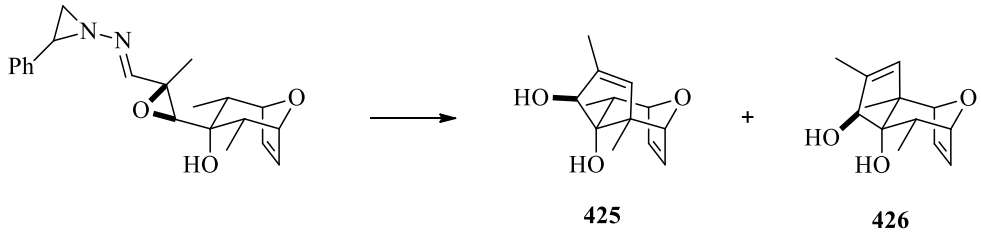


A novel compound prepared using a modified literature procedure.[166b]

To a solution of **422** (547 mg, 1.78 mmol) in CH_2Cl_2 (25 mL) at 0 °C, $NaHCO_3$ (1.5 g, 17.8 mmol) and **421** (690 mg, 3.56 mmol) were added. The reaction was stirred at 0 °C for 2 h, then washed with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography (hexane/EtOAc 90:10) to afford **423** (548 mg, 73%, d.r. 1:1) as a bright yellow oil. R_f 0.41 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2955, 1456, 1250, 1086, 834. δ_H (400 MHz, $CDCl_3$) 0.14 (2 x s, 9H, $(CH_3)_3Si$), 0.84-0.90 (m, 6H, CH_3CH, Isomer A+B), 1.67 (s, 3H, CH_3CO, Isomer A+B), 1.99-2.13 (m, 2H, CH_3CH, Isomer A+B), 2.38 (dd, 1H, *J* 4.9 Hz, ^2J 0.9 Hz, CH_2N, Isomer A+B), 2.41 (dd, 0.5H, *J* 7.8 Hz, ^2J 0.9 Hz, CH_2N, Isomer A), 2.51 (dd, 0.5H, *J* 7.8 Hz, ^2J 0.9 Hz, CH_2N, Isomer B), 2.97 (2 x s, 1H, CHOC, Isomer A+B), 3.01 (dd, 0.5H, *J* 7.7, 4.8 Hz, CHN, Isomer A), 3.04 (dd, 0.5H, *J* 7.8, 4.9 Hz, CHN, Isomer B), 4.36-4.38 (m, 1H, =CHCHO, Isomer A+B), 4.42 (dd, 1H, *J* 3.8, 0.9 Hz, =CHCHO, Isomer A+B), 6.17-6.22 (m, 2H, =CH, Isomer A+B), 7.22-7.36 (m, 6H, CH=N, H_{Ar}, Isomer A+B). δ_C (100 MHz, $CDCl_3$) 2.5 (3 x CH_3, $Si(CH_3)_3$), 12.9 (CH_3, CH_3CH, Isomer A+B), 13.2 (CH_3, CH_3CH, Isomer A+B), 13.5 (CH_3, CH_3CO, Isomer A+B), 38.0 (CH, CH_3CH, Isomer A+B), 40.6 (0.5 x CH_2, CH_2N, Isomer B), 40.7 (CH, CH_3CH, Isomer A+B), 41.1 (0.5 x CH_2, CH_2N, Isomer A), 44.0 (0.5 x CH, CHN, Isomer B), 44.8 (0.5 x CH, CHN, Isomer A), 58.7 (C, CHOC, Isomer A+B), 69.7 (0.5 x CH, CHOC, Isomer A),

69.8 (0.5 x CH, *C*HOC, Isomer B), 78.7 (C, *C*OSi, Isomer A+B), 82.7 (2 x CH, =CH*C*HO, Isomer A+B), 126.6 (2 x CH, *C*H_{Ar}, Isomer A+B), 127.6 (CH, *C*H_{Ar}, Isomer A+B), 128.7 (2 x CH, *C*H_{Ar}, Isomer A+B), 132.6 (CH, =*C*H, Isomer A+B), 133.6 (CH, =*C*H, Isomer A+B), 138.3 (0.5 x C, *C*CH_{Ar}, Isomer A), 138.4 (0.5 x C, *C*CH_{Ar}, Isomer B), 163.9 (0.5 x CH, *C*H=N, Isomer A), 164.2 (0.5 x CH, *C*H=N, Isomer B). *m/z* HRMS calcd for $C_{24}H_{34}N_2NaO_3Si^+$ 449.2236, found 449.2244; (ES) 449 ($[M+Na]^+$, 100%), 450 ($[M+Na+H]^+$, 19).

Preparation of (1*S*,3a*R*,4*R*,7*S*,8*R*,8a*R*)-2,3a,8-trimethyl-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulene-1,8a-diol 425 and (1*S*,3a*S*,4*S*,7*R*,8*S*,8a*S*)-2,3a,8-trimethyl-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulene-1,8a-diol 426



425 **426**

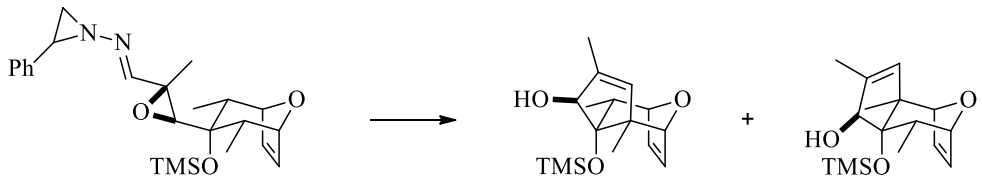
Novel compounds prepared using a modified literature procedure.[55]

Reaction was performed under an argon atmosphere.

A solution of **402** (154 mg, 0.440 mmol) in toluene (88 mL) was heated at reflux for 6 h. After this time the toluene was evaporated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30→50:50) to afford **425** (28 mg, 30%) as a pale yellow solid followed by **426** (11 mg, 12%) as a pale yellow crystal of XRD quality (See **Appendix AII**). Data for **425**. m.p. 109-112 °C. R_f 0.28 (hexane/EtOAc 1:1). υ_{max} neat/cm^{-1} 3334, 2963, 2932, 2890, 1722, 1446, 1352, 1192, 1052, 952, 907, 654. δ_H (400 MHz, $CDCl_3$) 0.90 (d, 3H, *J* 7.4 Hz, CH_3CH), 0.96 (s, 3H, CH_3C), 1.82-1.88 (m, 4H, CH_3C*H*, =CCH_3), 2.58 (s, 1H, O*H*), 3.66 (s, 1H, C*H*OH), 4.42-4.47 (m, 2H, =CHC*H*O), 5.65 (q, 1H, ^4J 1.5 Hz, C=C*H*), 6.43 (app. qd, 2H, *J* 6.2, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.2 (CH_3, *C*H_3CH), 15.7 (CH_3, =C*C*H_3),

22.4 (CH_3, *C*H_3C), 38.5 (CH, CH_3*C*H), 51.5 (C, *C*CHO), 78.1 (C, *C*OH), 82.5 (CH, =CH*C*HC), 83.6 (CH, =CH*C*HCH), 84.0 (CH, *C*HOH), 132.9 (CH, =*C*HCHCH), 134.5 (CH, =*C*HCHC), 137.5 (C, *C*=CH), 138.6 (CH, C=*C*H). *m/z* HRMS calcd for $C_{13}H_{18}NaO_3^+$ 245.1154, found 245.1149; (ES) 245 ($[M+Na]^+$, 100%), 246 ($[M+Na+H]^+$, 6). Data for **426**. m.p. 187-190 °C. R_f 0.15 (hexane/EtOAc 1:1). υ_{max} neat/cm^{-1} 3516, 3401, 2927, 2871, 1721, 1447, 1285, 1041, 1029, 954, 734, 560. δ_H (400 MHz, $CDCl_3$) 0.86 (s, 3H, C*H*$_3$C), 0.99 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.73 (t, 3H, ^4J 1.5 Hz, =CC*H*$_3$), 2.39 (qd, 1H, *J* 7.2, 3.6 Hz, CH_3C*H*), 4.37 (d, 1H, *J* 1.2 Hz, =CHC*H*C), 4.43 (dd, 1H, *J* 4.0, 1.2 Hz, =CHC*H*CH), 4.57 (br. s, 1H, C*H*OH), 5.45-5.48 (m, 1H, C=C*H*), 6.44-6.48 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 12.9 (CH_3, *C*H_3CH), 13.8 (CH_3, =C*C*H_3), 19.3 (CH_3, *C*H_3C), 33.9 (CH, CH_3*C*H), 48.7 (C, *C*CHO), 82.3 (CH, =CH*C*HCH), 83.7 (CH, =CH*C*HC), 84.8 (C, *C*OH), 86.3 (CH, *C*HOH), 132.6 (CH, C=*C*H), 134.0 (CH, =*C*HCHCH), 134.8 (CH, =*C*HCHC), 138.4 (C, *C*=CH). *m/z* HRMS calcd for $C_{13}H_{18}NaO_3^+$ 245.1154, found 245.1159; (ES) 245 ($[M+Na]^+$, 100%).

Preparation of (1*S*,3a*R*,4*R*,7*S*,8*R*,8a*R*)-2,3a,8-trimethyl-8a-((trimethylsilyl)oxy)-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulen-1-ol 429 and (1*S*,3a*S*,4*S*,7*R*,8*S*,8a*S*)-2,3a,8-trimethyl-8a-((trimethylsilyl)oxy)-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulen-1-ol 430



429 **430**

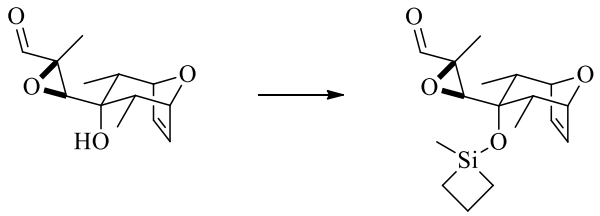
Novel compounds prepared using a modified literature procedure.[55]

Reaction was performed under an argon atmosphere.

A solution of **423** (190 mg, 0.450 mmol) in toluene (90 mL) was heated at reflux for 3 h. After this time the toluene was evaporated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **429** (27 mg, 21%) as a pale yellow solid

followed by **430** (57 mg, 43%) as a pale yellow solid. Data for **429**. m.p. 140-142 °C. R_f 0.40 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3404, 2962, 2961, 2907, 2887, 1445, 1245, 909, 834, 730. δ_H (400 MHz, $CDCl_3$) 0.11 (s, 9H, Si(C*H*$_3$)$_3$), 0.85 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 0.91 (s, 3H, C*H*$_3$C), 1.25 (br. s, 1H, O*H*), 1.74 (qd, 1H, *J* 7.3, 3.6 Hz, CH$_3$C*H*), 1.80 (d, 3H, ^{4}*J* 1.5 Hz, =CC*H*$_3$), 3.60 (br. s, 1H, C*H*OH), 4.33-4.42 (m, 2H, =CHC*H*O), 5.59 (m, 1H, C=C*H*), 6.20 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHCH), 6.25 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHC). δ_C (100 MHz, $CDCl_3$) 3.1 (3 x CH_3, Si(*C*H$_3$)$_3$), 12.5 (CH_3, *C*H$_3$CH), 15.6 (CH_3, =C*C*H$_3$), 23.9 (CH_3 *C*H$_3$C), 38.3 (CH, CH$_3$*C*H), 51.4 (C, *C*CHO), 82.8 (CH, =CH*C*HC), 83.8 (CH, CH*C*HCH), 83.9 (C, *C*OSi), 84.0 (CH, *C*HOH), 132.3 (CH, =*C*HCHCH), 133.2 (CH, =*C*HCHC), 138.0 (CH, C=*C*H), 138.7 (C, *C*=CH). *m/z* HRMS calcd for $C_{16}H_{26}NaO_3Si$ 317.1549, found 317.1545; (ES) 317 ($[M+Na]^+$, 100%), 318 ($[M+Na+H]^+$, 8). Data for **430**. m.p. 117-119 °C. R_f 0.53 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3403, 2963, 2931, 2908, 2888, 1246, 1050, 891, 834. δ_H (400 MHz, $CDCl_3$) 0.14 (s, 9H, Si(C*H*$_3$)$_3$), 0.78 (s, 3H, C*H*$_3$C), 0.90 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 1.25 (br. s, 1H, O*H*), 1.70 (t, 3H, ^{4}*J* 1.3 Hz, =CC*H*$_3$), 2.19 (qd, 1H, *J* 7.1, 4.1 Hz, CH$_3$C*H*), 4.27 (d, 1H, *J* 1.0 Hz, =CHC*H*C), 4.35 (dd, 1H, *J* 4.0, 1.1 Hz, =CHC*H*CH), 4.54 (br. s, 1H, C*H*OH), 5.47 (m, 1H, C=C*H*), 6.17-6.21 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 2.4 (3 x CH_3, Si(*C*H$_3$)$_3$), 13.8 (CH_3, =C*C*H$_3$), 13.9 (CH, *C*H$_3$CH), 20.6 (CH_3, *C*H$_3$C), 34.1 (CH, CH$_3$*C*H), 49.0 (C, *C*CHO), 82.4 (CH, =CH*C*HCH), 83.9 (CH, =CH*C*HC), 86.6 (CH, *C*HOH), 87.7 (C, *C*OSi), 132.2 (CH, =*C*H), 132.6 (CH, =*C*H), 134.1 (CH, C=*C*H), 137.6 (C, *C*=CH). *m/z* HRMS calcd for $C_{16}H_{26}NaO_3Si^+$ 317.1549, found 317.1552; (ES) 317 ($[M+Na]^+$, 100%), 318 ($[M+Na+H]^+$, 9).

Preparation of (±)-(2*S*,3*S*)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((1-methylsiletan-1-yl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 438



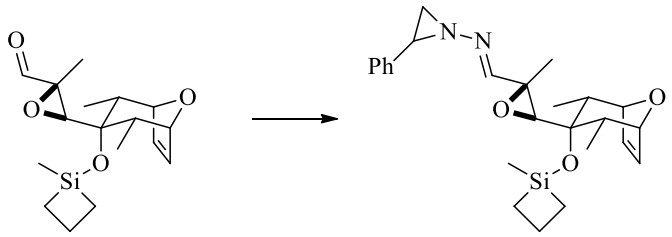
A novel compound prepared using a literature procedure.[169]

Reaction was performed under an argon atmosphere.

To a solution of **400** (50 mg, 0.210 mmol) in THF (1.2 mL) at 0 °C, KHMDS (0.5 M, 1.26 mL, 0.630 mmol) was added drop-wise. 1-Chloro-1-methylsilacyclobutane **437** (76 mg, 0.080 mL, 0.630 mmol) was added immediately and the reaction stirred at room temperature for 30 min. The reaction was quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution) and extracted with EtOAc (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc 90:10) to afford **438** (38 mg, 56%) as a clear colourless oil. R_f 0.26 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2968, 2933, 1731, 1251, 1076. δ_H (400 MHz, $CDCl_3$) 0.30 (s, 3H, SiCH_3), 0.89 (2 x d, 6H, *J* 7.0 Hz, CH_3CH), 1.21-1.27 (m, 3H, SiCH_2), 1.33-1.51 (m, 2H, SiCH_2, $SiCH_2CH_2$), 1.64 (s, 3H, CH_3CCO), 1.91-2.08 (m, 3H, CH_3CH, $SiCH_2CH_2$), 3.18 (s, 1H, C*H*OC), 4.40 (dd, 1H, *J* 3.5, 1.1 Hz, C*H*OCH), 4.45 (dd, 1H, *J* 3.7, 1.0 Hz, C*H*OCH), 6.23 (app. qd, 2H, *J* 6.3, 1.1 Hz, =C*H*), 8.74 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 0.09 (CH_3, SiCH_3), 10.0 (CH_3, CH_3CCHO), 12.5 (CH_3, CH_3CH), 12.9 (CH_2, $SiCH_2CH_2$), 13.0 (CH_3, CH_3CH), 21.4 (CH_2, SiCH_2), 22.2 (CH_2, SiCH_2), 37.5 (CH, CH_3CH), 40.7 (CH, CH_3CH), 61.9 (C, CHCO), 66.2 (CH, CHOC), 79.4 (C, COSi), 82.4 (2 x CH, CHOCH), 132.7 (CH, =CH), 133.6 (CH, =CH), 199.7 (CH, CHO). *m/z* HRMS calcd for $C_{17}H_{26}NaO_4Si^+$

345.1498, found 345.1500; (ES) 345 ($[M+Na]^+$, 8%), 377 ($[M+Na+MeOH]^+$, 100), 378 ($[M+Na+MeOH+H]^+$, 10).

Preparation of (±)-(*E*)-N-(((2*R*,3*S*)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((1-methylsiletan-1-yl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxiran-2-yl)methylene)-2-phenylaziridin-1-amine 439

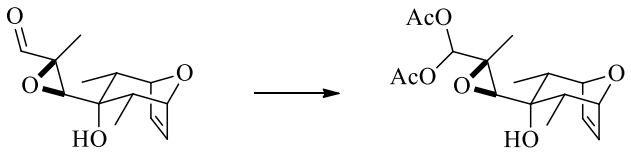


A novel compound prepared using a modified literature procedure.[166b]

To a solution of **438** (38 mg, 0.120 mmol) in CH_2Cl_2 (2 mL) at 0 °C, $NaHCO_3$ (101 mg, 1.20 mmol) and **421** (47 mg, 0.240 mmol) were added. The reaction was stirred at 0 °C for 2 h, then washed with H_2O (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **439** (27 mg, 50%, d.r. 1:1) as yellow oil. R_f 0.41 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2964, 2932, 1457, 1122, 1083, 916, 720, 696. δ_H (400 MHz, $CDCl_3$) 0.27 (2 x s, 3H, SiC*H*$_3$, Isomer A+B), 0.87 (2 x d, 3H, *J* 6.9 Hz, C*H*$_3$CH, Isomer A+B), 0.91 (2 x d, 3H, *J* 7.1 Hz, C*H*$_3$CH, Isomer A+B), 1.13-1.37 (m, 5H, SiC*H*$_2$, SiCH$_2$C*H*$_2$, Isomer A+B), 1.68 (s, 3H, C*H*$_3$CO), 1.89-1.99 (m, 1H, SiCH$_2$C*H*$_2$, Isomer A+B), 2.07-2.14 (m, 2H, CH$_3$C*H*), 2.39 (dd, 1H, *J* 4.9 Hz, ^2J 0.7 Hz, C*H*$_2$N, Isomer A+B), 2.42 (dd, 0.5H, *J* 7.8 Hz, ^2J 0.7 Hz, C*H*$_2$N, Isomer A), 2.50 (dd, 0.5H, *J* 7.8 Hz, ^2J 0.6 Hz, C*H*$_2$N, Isomer B), 3.02 (dd, 0.5H, *J* 7.8, 4.9 Hz, C*H*N, Isomer B), 3.08-3.13 (m, 1.5H, C*H*OC, Isomer A+B, C*H*N, Isomer A), 4.38-4.42 (m, 1H, =CHC*H*O, Isomer A+B), 4.45 (dd, 1H, *J* 3.8, 1.1 Hz, =CHC*H*O, Isomer A+B), 6.19-6.25 (m, 2H, =C*H*, Isomer A+B), 7.23-7.35 (m, 5H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 0.1 (CH_3, Si*C*H$_3$, Isomer A+B), 12.6 (CH_3,

CH_3CH, Isomer A+B), 12.9 (CH_2, SiCH_2*C*H_2, Isomer A+B), 13.0 (CH_3, *C*H_3CH, Isomer A+B), 13.5 (CH_3, *C*H_3CO, Isomer A+B), 21.4 (CH_2, SiCH_2, Isomer A+B), 22.0 (CH_2, Si*C*H_2, Isomer A+B), 37.6 (CH, CH_3*C*H, Isomer A+B), 40.6 (CH, CH_3*C*H, Isomer A+B), 41.2 (0.5 x CH_2, *C*H_2N, Isomer B), 42.0 (0.5 x CH_2, *C*H_2N, Isomer A), 44.0 (0.5 x CH, *C*HN, Isomer A), 44.7 (0.5 x CH, *C*HN, Isomer B), 58.7 (C, CHO*C*, Isomer A+B), 69.6 (0.5 x CH, *C*HOC, Isomer A), 69.7 (0.5 x CH, *C*HOC, Isomer B), 79.4 (C, *C*OSi, Isomer A+B), 82.5 (2 x CH, =CH*C*HO, Isomer A+B), 126.5 (2 x CH, *C*H_{Ar}, Isomer A+B), 127.6 (CH, *C*H_{Ar}, Isomer A+B), 128.6 (2 x CH, *C*H_{Ar}, Isomer A+B), 132.7 (CH, =*C*H, Isomer A+B), 133.5 (CH, =*C*H, Isomer A+B), 138.3 (0.5 x C, *C*CH_{Ar}, Isomer A), 138.4 (0.5 x C, *C*CH_{Ar}, Isomer B), 163.8 (0.5 x CH, *C*H=N, Isomer A), 164.1 (0.5 x CH, *C*H=N, Isomer B). *m/z* HRMS calcd for $C_{25}H_{34}N_2NaO_3Si^+$ 461.2236, found 461.2239; (ES) 461 ($[M+Na]^+$, 100%), 462 ($[M+Na+H]^+$, 19).

Preparation of (±)-((2*S*,3*R*)-3-((1*R*,2*S*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxiran-2-yl)methylene diacetate 446

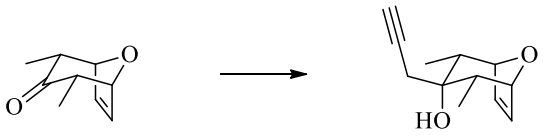


A novel compound prepared using a literature procedure.[173]

To a solution of **400** (50 mg, 0.210 mmol) in CH_2Cl_2 (0.42 mL) at 0 °C, DMAP (28 mg, 0.230 mmol) was added. A solution of Ac_2O (0.27 mL) in Et_2O (1.05 mL) was then added to the reaction. The reaction was stirred at room temperature and was followed by TLC. Upon completion, the mixture was washed with HCl (0.6 mL of a 1 M aqueous solution) and brine (5 mL) and the aqueous extracted with Et_2O (3 x 5 mL) and CH_2Cl_2 (1 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc 75:25) to afford **446** (18 mg, 26%) as

a clear, colourless oil. R_f 0.16 (petrol/EtOAc 75:25). υ_{max} neat/cm^{-1} 2956, 2918, 2850, 1762, 1462, 1375, 1199, 1008, 933, 670. δ_H (400 MHz, $CDCl_3$) 0.88 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 0.99 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.60 (s, 3H, C*H*$_3$CO), 2.08 (s, 3H, C*H*$_3$C=O), 2.11-2.19 (m, 4H, C*H*$_3$C=O, CH$_3$C*H*), 2.31 (qd, 1H, *J* 7.3, 3.7 Hz, CH$_3$C*H*), 2.77 (s, 1H, C*H*OC), 4.47 (dd, 1H, *J* 3.6, 1.6 Hz, =CHC*H*O), 4.49 (dd, 1H, *J* 3.6, 1.6 Hz, =CHC*H*O), 6.29 (s, 1H, C*H*(OAc)$_2$), 6.45 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*), 6.48 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.1 (CH$_3$, *C*H$_3$CH), 11.3 (CH$_3$, *C*H$_3$CH), 12.1 (CH$_3$, *C*H$_3$CO), 20.8 (CH$_3$, *C*H$_3$C=O), 20.9 (CH$_3$, *C*H$_3$C=O), 38.2 (CH, CH$_3$*C*H), 42.3 (CH, CH$_3$*C*H), 58.2 (C, CHO*C*), 67.8 (CH, *C*HOC), 73.4 (C, *C*OH), 82.5 (CH, =CH*C*HO), 82.6 (CH, =CH*C*HO), 91.9 (CH, *C*H(OAc)$_2$), 134.9 (CH, =*C*H), 135.1 (CH, =*C*H), 168.4 (C, *C*=O), 168.9 (C, *C*=O). *m*/*z* HRMS calcd for $C_{17}H_{24}NaO_7$ 363.1420, found 363.1423; (ES) 307 ($[M+Na]^+$, 100%), 308 ($[M+Na+H]^+$, 20).

Preparation of 3-*exo*-(prop-2-yn-1-yl)-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 455



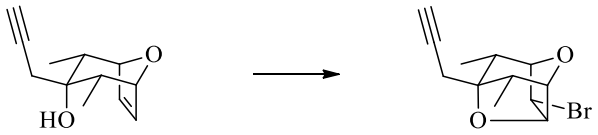
A known compound prepared using a literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a suspension of Mg (314 mg, 13.1 mmol) and $HgCl_2$ (54 mg, 0.200 mmol) in Et_2O (10 mL) at room temperature, propargyl bromide (80% in toluene, 1.50 mL, 13.1 mmol) was added at a rate to maintain a gentle reflux. The resulting solution was cooled to 0 °C and a solution of **378** (1.00 g, 6.57 mmol) in Et_2O (6 mL). The reaction was allowed to warm to room temperature over 2 h before being stirred at room temperature for 24 h. The reaction was quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with Et_2O (3

x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc 75:25) to afford **455** (958 mg, 76%) as a white solid. δ_H (400 MHz, $CDCl_3$) 0.91 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 1.87 (s, 1H, O*H*), 2.05 (t, 1H, *J* 2.7 Hz, ≡C*H*), 2.30 (d, 2H, *J* 2.7 Hz, ≡CC*H*$_2$), 2.52 (qd, 2H, *J* 7.3, 3.7 Hz, CH$_3$C*H*), 4.52 (d, 2H, *J* 3.7 Hz, =CHC*H*O), 6.57 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.5 (2 x CH_3, *C*H$_3$CH), 28.0 (CH_2, ≡C*C*H$_2$), 38.8 (2 x CH, CH$_3$*C*H), 71.5 (CH, ≡*C*H), 75.1 (C, *C*OH), 81.1 (C, *C*≡CH), 82.9 (2 x CH, =CH*C*HO), 136.0 (2 x CH, =*C*H). *m/z* (EI) 81 (100%), 85 (61), 152 ([M-propargyl-H]$^+$, 33), 153 ([M-propargyl]$^+$, 27), 177 ([M-OH]$^+$, 5), 192 ([M]$^+$, 1). Literature values:[97] υ_{max} 3557 (*br*), 3246, 2926, 1456, 1215 cm^{-1}, δ_H (360 MHz; $CDCl_3$) 0.92 (d, *J* 7.3 Hz, 6H), 1.88 (s, 1H), 2.07 (t, *J* 2.8 Hz, 1H), 2.31 (d, *J* 2.7 Hz, 2H), 2.48-2.54 (m, 2H), 4.54 (d, *J* 3.6 Hz, 2H), 6.58 (s, 2H); δ_C (90 MHz, $CDCl_3$) 10.7 (CH_3), 28.2 (CH_2), 39.0 (CH), 71.7 (C), 81.3 (C), 83.01 (CH), 136.1 (CH); *m/z* (EI) 192 (M^+; 1.5%), 177 (11), 85 (100); HRMS calcd for $C_{12}H_{16}O_2Na^+$ 215.1043, found 215.1045.

Preparation of (±)-(2*S*,3*S*,3a*S*,5*R*,7*R*)-6-bromo-3,7-dimethyl-2-(prop-2-yn-1-yl)hexahydro-2,5-methanofuro[3,2-b]furan 456



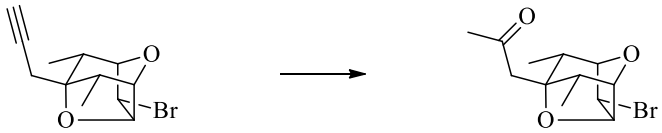
A novel compound prepared using a modified literature procedure.[177]

To a solution of **455** (200 mg, 1.04 mmol) in toluene (10 mL) at room temperature, NBS (185 mg, 1.04 mmol) was added. The reaction was stirred at room temperature for 20 h before more NBS (185 mg, 1.04 mmol) was added. The reaction was stirred at room temperature for a further 7 h before being quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and extracted with EtOAc (3 x 10 mL). The combined organics were dried

over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **456** (248 mg, 88%) as a white solid. m.p. 68-70 °C. R_f 0.16 (petrol/EtOAc 75:25). υ_{max} neat/cm^{-1} 3271, 2969, 2932, 2908, 2116, 1452, 1435, 992, 967, 904, 858, 677, 656. δ_H (400 MHz, $CDCl_3$) 0.88 (d, 3H, *J* 7.1 Hz, OCHCHCHC*H*$_3$), 1.02 (d, 3H, *J* 7.1 Hz, BrCHCHCHC*H*$_3$), 1.93 (t, 1H, ^4J 2.7 Hz, C≡C*H*), 2.25 (dd, 1H, ^2J 16.9 Hz, ^4J 2.8 Hz, ≡CC*H*$_2$), 2.37-2.46 (m, 2H, ≡CC*H*$_2$, BrCHCHC*H*), 2.51 (q, 1H, *J* 7.1 Hz, OCHCHC*H*), 4.23 (dd, 1H, *J* 4.0, 1.6 Hz, BrCHC*H*), 4.48 (s, 1H, BrC*H*CHCH), 4.51 (d, 1H, *J* 3.6 Hz, OCHC*H*), 4.68 (br. s, 1H, OC*H*CHCH). δ_C (100 MHz, $CDCl_3$) 10.8 (CH_3, OCHCHCH*C*H$_3$), 11.4 (CH_3, BrCHCHCH*C*H$_3$), 20.0 (CH_2, ≡C*C*H$_2$), 41.1 (CH, BrCHCH*C*H), 46.3 (CH, OCHCH*C*H), 52.1 (CH, BrC*H*CHO), 70.1 (CH, C≡*C*H), 78.8 (C, *C*≡CH), 84.5 (CH, OCH*C*H), 84.8 (CH, BrCH*C*H), 85.2 (CH, O*C*HCHCH), 85.8 (C, *C*O). *m*/*z* HRMS calcd for $C_{12}H_{15}{}^{79}BrO_2{}^+$ 270.0255, found 270.0261; (EI) 133 (100%), 161 (60), 162 (64), 191([M-Br]$^+$, 46), 241 ([M(^{79}Br)-C≡CH]$^+$, 64), 243 ([M(^{81}Br)-C≡CH]$^+$, 61), 270 ([M(^{79}Br)]$^+$, 16), 272 ([M(^{81}Br)]$^+$, 15).

Preparation of (±)-1-((2*S*,3*S*,3a*S*,5*R*,7*R*)-6-bromo-3,7-dimethylhexahydro-2,5-methanofuro[3,2-b]furan-2-yl)propan-2-one 457

Method A

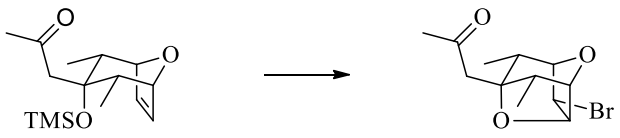


A novel compound prepared using a literature procedure.[97]

To a solution of **456** (50 mg, 0.180 mmol) and HgO (39 mg, 0.18 mmol) in acetone (0.8 mL), H_2SO_4 (10 µl of a 0.74 M aqueous solution) was added drop-wise. The reaction was stirred at room temperature for 18 h before being diluted with H_2O (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in*

vacuo. The residue was purified by column chromatography (hexane/EtOAc 85:15) to afford **457** (13 mg, 26%) as a clear colourless oil.

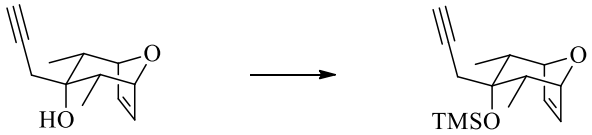
Method B



A novel compound prepared using a modified literature procedure.[177]

To a solution of **459** (29 mg, 0.100 mmol) in toluene (1 mL) at room temperature, NBS (18 mg, 0.100 mmol) was added. The reaction was stirred at room temperature for 18 h before being quenched with $NaHCO_3$ (1 mL of a saturated aqueous solution) and extracted with EtOAc (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **457** (22 mg, 75%) as a clear colourless oil. R_f 0.36 (petrol/EtOAc 80:20). υ_{max} neat/cm^{-1} 2975, 2918, 2880, 2850, 1714, 1462, 1417, 1367, 1003, 995, 958, 899, 756, 699. δ_H (400 MHz, $CDCl_3$) 0.74 (d, 3H, *J* 7.1 Hz, OCHCHCHC*H*$_3$), 0.88 (d, 3H, *J* 7.2 Hz, BrCHCHCHC*H*$_3$), 2.15 (s, 3H, C*H*$_3$C=O), 2.46-2.58 (m, 2H, C*H*$_2$C=O, BrCHCHC*H*), 2.71 (q, 1H, *J* 7.1 Hz, OCHCHC*H*), 2.82 (d, 1H, ^2J 18.5 Hz, C*H*$_2$C=O), 4.18 (dd, 1H, *J* 3.9, 1.6 Hz, BrCHC*H*), 4.46 (s, 1H, BrC*H*), 4.52 (d, 1H, *J* 3.6 Hz, OCHC*H*), 4.61 (br. s, 1H, OC*H*). δ_C (100 MHz, $CDCl_3$) 11.3 (CH_3, OCHCHCH*C*H$_3$), 11.9 (CH_3, BrCHCHCH*C*H$_3$), 30.9 (CH_3, *C*H$_3$C=O), 41.0 (CH, BrCHCH*C*H), 43.3 (CH_2, *C*H$_2$C=O), 45.9 (CH, OCHCH*C*H), 52.1 (CH, Br*C*H), 83.6 (CH, O*C*H), 84.6 (CH, BrCH*C*H), 84.8 (C, *C*O), 85.0 (CH, OCH*C*H), 204.6 (C, *C*=O). *m*/*z* HRMS calcd for $C_{12}H_{17}{}^{79}BrO_3{}^+$ 288.0361, found 288.0367; (EI) 95 (56%), 137 (69), 151 (100), 209 ([M-Br], 69), 288 ([M(^{79}Br), 13), 290 ([M(^{81}Br), 13).

Preparation of ((2,4-*endo*,*endo*-dimethyl-3-*exo*-(prop-2-yn-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)oxy)trimethylsilane 458

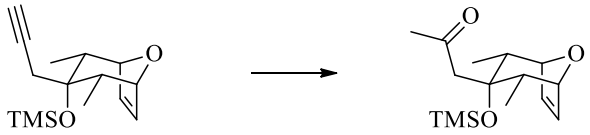


A known compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **455** (732 mg, 3.80 mmol) and Et_3N (1.56 g, 2.10 mL, 15.2 mmol) in CH_2Cl_2 (38 mL) at 0 °C, TMSOTf (2.20 g, 1.79 mL, 9.90 mmol) was added drop-wise. The reaction was stirred at room temperature for 5 h. The reaction was quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc 95:5) to afford **458** (907 mg, 90%) as a white solid. δ_H (400 MHz, $CDCl_3$) 0.07 (s, 9H, Si(C*H*$_3$)$_3$), 0.82 (d, 6H, *J* 7.2 Hz, C*H*$_3$CH), 2.06 (t, 1H, *J* 2.7 Hz, C*H*), 2.37 (d, 2H, *J* 2.7 Hz, ≡CC*H*$_2$), 2.45 (qd , 2H, *J* 7.2, 3.6 Hz, CH$_3$C*H*), 4.42 (d, 2H, *J* 3.5 Hz, =CHC*H*O), 6.21 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 3.0 (3 x CH_3, Si(*C*H$_3$)$_3$), 11.8 (2 x CH_3, *C*H$_3$CH), 28.9 (CH_2, ≡C*C*H$_2$), 38.8 (2 x CH, CH$_3$*C*H), 71.6 (CH, ≡*C*H), 79.2 (C, *C*OSi), 81.3 (C, *C*≡CH), 82.9 (2 x CH, =CH*C*HO), 133.1 (2 x CH, =*C*H). *m/z* (EI) 153 ([M-propargyl-TMS]$^+$, 64%), 225 ([M-propargyl]$^+$, 100), 235 ([M-(2 x Me)]$^+$, 61), 249 ([M-Me]$^+$, 11), 264 ([M]$^+$, 2). Literature values:[97] υ_{max} (neat) 3313, 2926, 1456, 1217 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.00 (s, 9H), 0.74 (d, *J* 7.2 Hz, 6H), 1.99 (t, *J* 2.7 Hz, 1H), 2.30 (d, *J* 2.7 Hz, 2H), 2.38-2.42 (m, 2H), 4.35 (d, *J* 3.5 Hz, 2H), 6.13 (s, 2H); δ_C (90 MHz; $CDCl_3$) 3.2 (CH_3), 12.0 (CH_3), 29.1 (CH_2), 39.0 (CH), 71.8 (CH), 79.4 (C), 81.5 (CH), 83.0 (CH), 133.3 (CH); *m/z* (EI) 264 (M$^+$; 4%), 225 (97), 73 (63); HRMS calcd for $C_{15}H_{24}O_2SiNa^+$ 287.1438, found 287.1431.

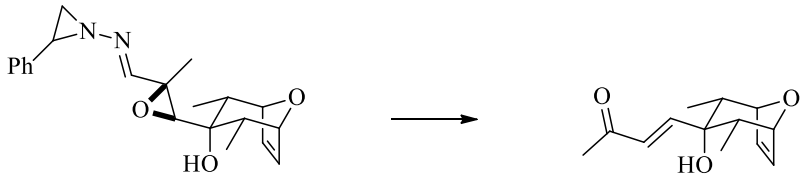
Preparation of 1-(2,4-*endo*,*endo*-dimethyl-3-*exo*-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)propan-2-one 459



A known compound[97] prepared using a literature procedure.[180]

To a solution of **458** (200 mg, 0.750 mmol) and H_2O (30 µl, 1.50 mmol) in acetone (6 mL) at room temperature, PPTS (283 mg, 1.13 mmol) and $Hg(OAc)_2$ (72 mg, 0.230 mmol) were added. The reaction was stirred at room temperature for 24 h. The reaction was diluted with Et_2O, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc 90:10) to afford **459** (145 mg, 69%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 0.85 (d, 6H, *J* 7.2 Hz, C*H*$_3$CH), 2.16 (s, 3H, C*H*$_3$C=O), 2.29 (qd, 2H, *J* 7.2, 3.6 Hz, CH$_3$C*H*), 2.62 (s, 2H, C*H*$_2$C=O), 4.39 (d, 2H, *J* 3.5 Hz, =CHC*H*O), 6.19 (s, 2H, =CH). δ_C (100 MHz, $CDCl_3$) 3.1 (3 x CH_3, Si(*C*H$_3$)$_3$), 12.0 (2 x CH_3, *C*H$_3$CH), 33.1 (CH_3, *C*H$_3$C=O), 39.5 (2 x CH, CH$_3$C*H*), 50.7 (CH_2, *C*H$_2$C=O), 79.0 (C, *C*OSi), 82.8 (2 x CH, =CH*C*HO), 133.4 (2 x CH, =*C*H), 206.3 (C, *C*=O). *m/z* (EI) 209 ([M-TMS]$^+$, 20%), 225 ([M-CH_2COCH_3]$^+$, 18), 267 ([M-Me]$^+$, 22), 282 ([M]$^+$, 1). Literature values:[97] υ_{max} (neat) 2953, 1705, 1415, 1105 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.00 (s, 9H), 0.76 (d, *J* 7.2 Hz, 6H), 2.08 (s, 3H), 2.15-2.22 (m, 2H), 2.53 (s, 2H), 4.30 (d, *J* 3.5 Hz, 2H), 6.10 (s, 2H); δ_C (90 MHz, $CDCl_3$) 3.2 (CH_3), 12.1 (CH_3), 33.3 (CH), 39.6 (CH_3), 50.9 (CH_2), 79.2 (C), 83.0 (CH), 133.5 (CH), 206.6 (C); *m/z* (EI) 282 (M$^+$, 20%), 130 (100), 73 (70); HRMS calcd for $C_{15}H_{26}O_3SiNa^+$ 305.1547, found 305.1543.

Preparation of (*E*)-4-(3-*exo*-hydroxy-2,4-*endo*,*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)but-3-en-2-one 463

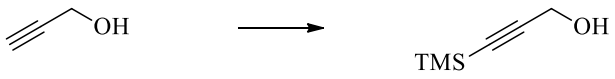


A novel compound prepared using a modified literature procedure.[166a]

Reaction was performed under an argon atmosphere.

To a solution of **402** (131 mg, 0.370 mmol) in toluene (74 mL), $Rh_2(OAc)_4$ (1.6 mg, 3.70 μmol) was added. The resulting solution was stirred at reflux for 6 h. Upon completion, the toluene was evaporated and the residue purified by column chromatography (hexane/EtOAc 70:30→50:50) to afford **463** (31 mg, 40%) as a pale yellow solid. m.p. 102-104 °C. R_f 0.18 (hexane/EtOAc 70:30). υ_{max} neat/cm^{-1} 3519, 2979, 2965, 2928, 1685, 1622, 1312, 1000, 734. δ_H (400 MHz, $CDCl_3$) 0.80 (d, 6H, *J* 7.3 Hz, C*H*$_3$CH), 2.05 (d, 1H, O*H*), 2.18 (qd, 2H, *J* 7.2, 3.6 Hz, CH$_3$C*H*), 2.25 (s, 3H, C*H*$_3$C=O), 4.56 (d, 2H, *J* 3.6 Hz, =CHC*H*O), 6.24 (d, 1H, *J* 15.6 Hz, CH=C*H*C=O), 6.34 (dd, 1H, *J* 15.6 Hz, ^4J 1.7 Hz, C*H*=CHC=O), 6.59 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.3 (2 x CH_3, *C*H$_3$CH), 28.1 (CH_3, *C*H$_3$C=O), 40.4 (2 x CH, CH$_3$*C*H), 75.8 (C, *C*OH), 82.1 (2 x CH, =CH*C*HO), 129.3 (CH, CH=*C*HC=O), 135.9 (2 x CH, =*C*H), 150.2 (CH, *C*H=CHC=O), 198.3 (C, *C*=O). *m*/*z* HRMS calcd for $C_{13}H_{18}NaO_3^+$ 245.1154, found 245.1142; (ES) 225 (34%), 245 ([M+Na]$^+$, 100), 267 (8), 277 ([M+Na+MeOH]$^+$, 12).

Preparation of 3-(trimethylsilyl)prop-2-yn-1-ol 474

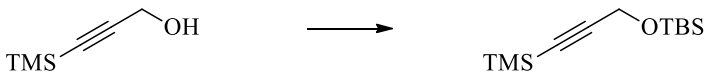


A known compound prepared using a literature procedure.[183]

Reaction was performed under an argon atmosphere.

To a solution of EtMgBr (3 M, 16.6 mL, 49.8 mmol) in THF (8.3 mL) at 5 °C, propargyl alcohol **408** (1.00 g, 1.04 mL, 17.8 mmol) in THF (1.7 mL) was added drop-wise, while maintaining the temperature below 10 °C. The reaction was stirred at room temperature for 16 h. TMSCl (5.40 g, 6.30 mL, 49.8 mmol) was added drop-wise while maintaining the temperature below 25 °C. Upon completion of addition, the mixture was heated to reflux for 2 h. The reaction was cooled to 20 °C and H_2SO_4 (20 mL of a 1.4 M aqueous solution) was added while maintaining the temperature below 45 °C. The mixture was stirred for 5 min and Et_2O (15 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organics were washed with H_2O (2 x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by Kügelrohr distillation (80 °C, 1.0 Torr) to afford **474** (1.56 g, 68%) as a clear liquid. δ_H (400 MHz, $CDCl_3$) 0.17 (s, 9H, Si(*C*H_3)$_3$), 1.75 (br. s, 1H, O*H*), 4.26 (d, 2H, *J* 3.5 Hz, C*H*$_2$). δ_C (100 MHz, $CDCl_3$) 0.0 (3 x CH_3, Si(*C*H_3)$_3$), 51.9 (CH_2, *C*H_2), 90.9 (C, *C*≡CSi(CH$_3$)$_3$), 104.0 (C, *C*≡CH_2). *m*/*z* (EI) 45 ([CCH_2OH]$^+$, 27%), 75 ([TMS]$^+$, 26), 85 ([M-(CCH_2OH)]$^+$, 100), 113 ([M-(OH)]$^+$, 100), 128 ([M]$^+$, 11). Literature values:[214] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (2H, s), 1.62 (1H, bs), 0.19 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.2, 90.5, 51.5, -0.1. IR (thin film NaCl) 3430, 2200, 1036 cm^{-1}. HRMS ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_6H_{12}OSiNa$, 151.0555; found, 151.0553.

Preparation of *tert*-butyldimethyl((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)silane 472

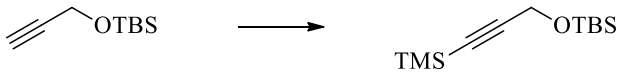


Method A

A known compound prepared using a literature procedure.[184]

To a solution of **474** (1.56 g, 12.2 mmol) in DMF (4.2 mL) at room temperature, imidazole (1.66 g, 24.4 mmol) and TBSCl (2.22 g, 14.6 mmol) were added. The reaction was stirred at room temperature for 18 h before being diluted with H_2O (5 mL) and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **472** (2.90 g, 98%) as a pale yellow liquid that was used without further purification.

Method B

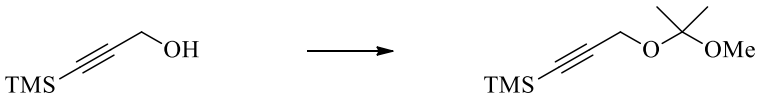


A known compound prepared using a modified literature procedure.[187]

Reaction was performed under an argon atmosphere.

To a solution of **479** (1.00 g, 5.88 mmol) in THF (5.5 mL) at –78 °C, ^{n}BuLi (1.36 M, 4.50 mL, 6.18 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before TMSCl (741 mg, 0.860 mL, 6.82 mmol) was added drop-wise. The mixture was stirred at -78 °C for 30 min before being warmed to room temperature and stirred at room temperature for 1 h. The reaction was quenched with $NaHCO_3$ (6 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 10 mL). The combined organics were washed H_2O (10 mL) and brine (10 mL) before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by Kügelrohr distillation (130 °C, 1.0 Torr) to afford **472** (1.35 g, 95%) as a clear liquid. υ_{max} neat/cm^{-1} 2957, 2930, 2858, 2178, 1251, 1091, 831, 775. δ_H (400 MHz, $CDCl_3$) 0.13 (s, 6H, Si(CH_3)$_2$), 0.16 (s, 9H, Si(CH_3)$_3$), 0.91 (s, 9H, SiC(CH_3)$_3$), 4.31 (s, 2H, CH_2). δ_C (100 MHz, $CDCl_3$) -4.8 (2 x CH_3, Si(*C*H_3)$_2$), 0.0 (3 x CH_3, Si(*C*H_3)$_3$), 18.5 (C, Si*C*(CH$_3$)$_3$), 26.1 (3 x CH_3, SiC(*C*H_3)$_3$), 52.5 (CH_2, *C*H_2), 89.9 (C, *C*Si(CH$_3$)$_3$), 104.8 (*C*CH$_2$). *m*/*z* HRMS calcd for $C_{12}H_{26}NaOSi_2^+$ 265.1420, found 265.1433; (ES) 265 ([M+Na]$^+$, 100%), 266 ([M+Na+H]$^+$, 8).

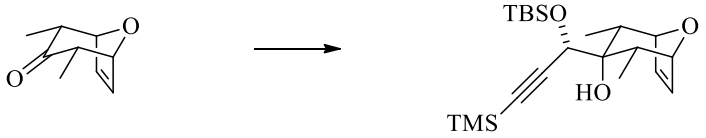
Preparation of (3-((2-methoxypropan-2-yl)oxy)prop-1-yn-1-yl)trimethylsilane 473



A known compound prepared using a modified literature procedure.[187]

To a solution of **474** (2.00 g, 15.6 mmol) and 2-methoxypropene (11.3 g, 15.0 mL, 156 mmol) in THF (52 mL) at 0 °C, PPTS (392 mg, 1.56 mmol) was added. The reaction was stirred at room temperature for 2 h. The reaction was quenched with K_2CO_3 (10 mL of a saturated aqueous solution) and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organics were washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **473** (2.02 g, 65%) as a clear, colourless liquid that was used without further purification. δ_H (400 MHz, $CDCl_3$) 0.17 (s, 9H, Si(CH_3)$_3$), 1.37 (s, 6H, 2 x CH_3), 3.22 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2). δ_C (100 MHz, $CDCl_3$) 0.0 (3 x CH_3, Si(CH_3)$_3$), 24.6 (2 x CH_3, CH_3), 49.0 (CH_3, OCH_3), 50.0 (CH_2, CH_2), 90.0 (C, CSi(CH_3)$_3$), 101.0 (C, COCH_3), 103.0 (C, $C$$CH_2$). *m*/*z* (ES) 212 ([M+Na-Me]$^+$, 100%), 213 ([M+Na+H-Me]$^+$, 14). Literature values:[187] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.33 (s, 6H), 3.18 (s, 3H), 4.07 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 0.29, 24.25, 48.69, 49.62, 93.35, 100.70, 102.62. IR (film): υ 2990, 2960, 2172, 1380, 1213, 1149, 1049, 844, 760.

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-((*S*)-1-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 476

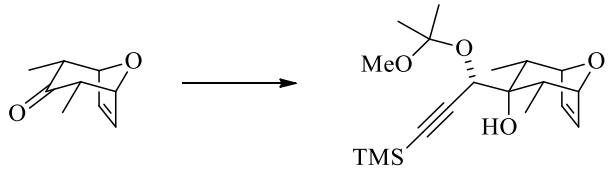


A novel compound prepared using a modified literature procedure.[182a]

Reaction was performed under an argon atmosphere.

To a solution of **472** (620 mg, 2.56 mmol) in THF (15 mL) at -78 °C, ^{n}BuLi (1.35 M, 1.90 mL, 2.56 mmol) was added drop-wise. The solution was stirred for 10 min before a solution of **378** (300 mg, 1.97 mmol) in THF (5 mL) was added in one portion. The reaction was stirred at room temperature for 18 h before being quenched with NH_4Cl (20 mL of a saturated aqueous solution) and the aqueous extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **476** (444 mg, 57%) as a yellow solid. m.p 80-82 °C. R_f 0.23 (hexane/EtOAc 95:5). υ_{max} neat/cm^{-1} 3299, 2960, 2932, 2854, 2173, 1471, 1248, 1078, 832. δ_H (400 MHz, $CDCl_3$) 0.09 (s, 3H, Si(C*H*$_3$)$_2$), 0.14 (s, 3H, Si(C*H*$_3$)$_2$), 0.19 (s, 9H, Si(C*H*$_3$)$_3$), 0.88-0.91 (m, 12H, SiC(C*H*$_3$)$_3$, C*H*$_3$CH) 0.94 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 1.95 (d, 1H, ^{4}*J* 5.2 Hz, O*H*), 2.39 (qd, 1H, *J* 7.3, 3.8 Hz, CH$_3$C*H*), 2.65 (qd, 1H, *J* 7.2, 3.9 Hz, CH$_3$C*H*), 4.31 (d, 1H, ^{4}*J* 6.0 Hz, C*H*OSi), 4.37 (app. t, 2H, *J* 3.7 Hz, =CHC*H*O), 6.30 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) -1.7 (2 x CH_3, Si(*C*H$_3$)$_2$), 0.0 (3 x CH_3, Si(*C*H$_3$)$_3$), 12.4 (CH_3, *C*H$_3$CH), 14.5 (CH_3, *C*H$_3$CH), 20.3 (C, Si*C*(CH$_3$)$_3$), 27.0 (3 x CH_3, SiC(*C*H$_3$)$_3$), 37.0 (CH, CH$_3$*C*H), 38.1 (CH, CH$_3$*C*H), 69.9 (CH, *C*HOSi), 81.3 (C, *C*OH), 82.5 (CH, =CH*C*HO), 83.3 (CH, =CH*C*HO), 93.5 (C, C≡*C*Si), 105.7 (C, *C*≡CSi), 133.3 (CH, =*C*H), 134.0 (CH, =*C*H). *m/z* HRMS calcd for $C_{21}H_{38}NaO_3Si_2^+$ 417.2257, found 417.2247; (ES) 417 ([M+Na]$^+$, 100%), 418 ([M+Na+H]$^+$, 21).

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-((*S*)-1-((2-methoxypropan-2-yl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 478

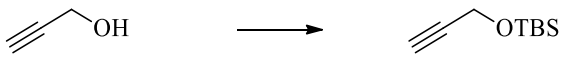


A novel compound prepared using a modified literature procedure.[182a]

Reaction was performed under an argon atmosphere.

To a solution of **473** (260 mg, 1.30 mmol) in THF (7.5 mL) at -78 °C, ^{n}BuLi (1.46 M, 0.890 mL, 1.30 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before a solution of **378** (152 mg, 1.00 mmol) in THF (2.5 mL) was added. The reaction was allowed to warm to room temperature and was stirred at room temperature for 18 h before being quenched with NH_4Cl (10 mL or a saturated aqueous solution) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **478** (75 mg, 21%) as a clear colourless oil. R_f 0.16 (hexane/EtOAc 90:10). υ_{max} neat/cm^{-1} 3400, 2961, 2936, 2174, 1374, 1249, 1046, 839, 759. δ_H (400 MHz, $CDCl_3$) 0.16 (s, 9H, Si(C*H*$_3$)$_3$), 0.92 (2 x d, 6H, *J* 7.2 Hz, C*H*$_3$CH), 1.34 (s, 3H, OCC*H*$_3$), 1.43 (s, 3H, OCC*H*$_3$), 2.31-2.40 (m, 2H, CH$_3$C*H*, O*H*), 2.66 (qd, 1H, *J* 7.2, 3.9 Hz, CH$_3$C*H*), 3.26 (s, 3H, OC*H*$_3$), 4.19 (s, 1H, C*H*OC), 4.37-4.47 (m, 2H, =CHC*H*), 6.37 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*), 6.39 (dd, 1H, *J* 6.1, 1.5 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 0.0 (3 x CH_3, Si(*C*H$_3$)$_3$), 11.4 (CH_3, *C*H$_3$CH), 11.8 (CH_3, *C*H$_3$CH), 24.9 (CH_3, OC*C*H$_3$), 25.5 (CH_3, OC*C*H$_3$), 36.8 (CH, CH$_3$*C*H), 36.9 (CH, CH$_3$*C*H), 50.2 (CH_3, O*C*H$_3$), 68.4 (CH, *C*HOC), 75.3 (C, *C*OH), 82.5 (CH, =CH*C*H), 83.2 (CH, =CH*C*H), 92.8 (C, C≡*C*Si), 102.3 (C, *C*OCH$_3$), 105.1 (C, *C*≡CSi), 133.6 (CH, =*C*H), 134.1 (CH, =*C*H). *m*/*z* HRMS calcd for $C_{19}H_{32}O_4NaSi^+$ 375.1968, found 375.1954; (ES) 375 ([M+Na]$^+$, 100%), 376 ([M+Na+H]$^+$, 58).

Preparation of tert-butyldimethyl(prop-2-yn-1-yloxy)silane 479

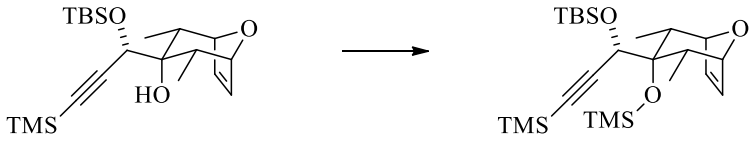


A known compound prepared using a modified literature procedure.[186]

To a solution of propargyl alcohol **408** (2.00 g, 2.08 mL, 35.7 mmol) in DMF (12 mL) at 0 °C, imidazole (4.90 g, 71.4 mmol) and TBSCl (6.50 g, 42.9 mmol) were added. The

reaction was stirred at room temperature for 18 h before being diluted with H_2O (10 mL), and the aqueous layer extracted with Et_2O (3 x 15 mL). The combined organics were washed with brine (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **479** (6.75 g, 100%) as a clear colourless liquid that was used without further purification. υ_{max} neat/cm^{-1} 3312, 2930, 2858, 1253, 1088. δ_H (400 MHz, $CDCl_3$) 0.12 (s, 6H, Si(CH_3)$_2$), 0.91 (s, 9H, SiC(CH_3)$_3$), 2.38 (t, 1H, ^4J 2.4 Hz, C≡C*H*), 4.31 (d, 2H, ^4J 2.4 Hz, CH_2). δ_C (100 MHz, $CDCl_3$) 5.0 (2 x CH_3, Si(CH_3)$_2$), 18.5 (C, SiC(CH_3)$_3$), 26.0 (3 x CH_3, SiC(CH_3)$_3$), 51.7 (CH_2, CH_2), 72.8 (CH, C≡CH), 82.6 (C, C≡CH). Literature values:[186] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (2H, d, *J* 2 Hz), 2.39 (1H, t, *J* 2 Hz), 0.91 (9H, s), 0.131 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.5, 73.1, 51.6, 25.9, 18.4, -5.0.

Preparation of (±)-*tert*-butyl(((*S*)-1-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)oxy)dimethylsilane 480



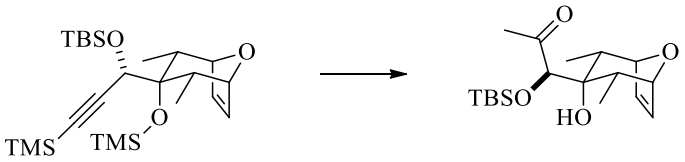
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **476** (142 mg, 0.360 mmol) and Et_3N (146 mg, 0.200 mL, 1.44 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C, TMSOTf (208 mg, 0.170 mL, 0.940 mmol) was added drop-wise. The reaction was allowed to warm to room temperature and was stirred for 20 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford **480** (142 mg, 84%) as a white solid. m.p. 44-46 °C. R_f 0.23 (hexane/EtOAc 95:5). υ_{max} neat/cm^{-1} 2960,

2928, 2881, 2851, 2174, 1249, 1086, 831. δ_H (400 MHz, $CDCl_3$) 0.10 (s, 3H, Si(CH_3)$_2$), 0.15 (2 x s, 18H, OSi(CH_3)$_3$, CSi(CH_3)$_3$), 0.17 (s, 3H, Si(CH_3)$_2$), 0.78 (d, 3H, *J* 7.3 Hz, CH_3CH), 0.93 (s, 9H, SiC(CH_3)$_3$), 1.04 (d, 3H, *J* 7.1 Hz, CH_3CH), 2.34 (qd, 1H, *J* 7.3, 3.8 Hz, CH_3C*H*), 2.51 (qd, 1H, *J* 7.1, 4.0 Hz, CH_3C*H*), 4.08 (s, 1H, C*H*OSi), 4.34-4.38 (m, 2H, =CHC*H*O), 6.19 (dd, 1H, *J* 6.1, 1.5 Hz, =C*H*), 6.25 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) -4.8 (CH_3, Si(*C*H_3)$_2$), -4.0 (CH_3, Si(*C*H_3)$_2$), -0.3 (3 x CH_3, Si(*C*H_3)$_3$), 3.2 (3 x CH_3, Si(*C*H_3)$_3$), 11.9 (CH_3, *C*H_3CH), 13.5 (CH_3, *C*H_3CH), 18.4 (C, Si*C*(CH$_3$)$_3$), 26.1 (3 x CH_3, SiC(*C*H_3)$_3$), 35.9 (CH, CH_3*C*H), 36.7 (CH, CH_3*C*H), 66.9 (CH, *C*HOSi), 82.2 (C, *C*OSi), 82.7 (CH, =CH*C*HO), 83.4 (CH, =CH*C*HO), 93.2 (C, C≡*C*Si(CH$_3$)$_3$), 108.0 (C, *C*≡CSi(CH$_3$)$_3$), 133.0 (CH, =*C*H), 133.7 (CH, =*C*H). *m*/*z* HRMS calcd for $C_{24}H_{46}NaO_3Si_3^+$ 489.2653, found 489.2643; (ES) 489 ([M+Na]$^+$, 100%), 490 ([M+Na+H]$^+$, 74).

Preparation of (±)-(*R*)-1-((tert-butyldimethylsilyl)oxy)-1-((1*R*,2*S*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)propan-2-one 481

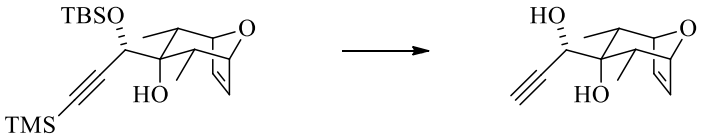


A novel compound prepared using a literature procedure.[188]

To a solution of **480** (50 mg, 0.110 mmol) in THF (2.2 mL) and H_2O (1.1 mL) at room temperature, a saturated solution of $HgSO_4$ in H_2SO_4 (0.230 mL of a 1% aqueous solution) was added drop-wise. The reaction was stirred for 20 h at room temperature before more $HgSO_4$/H_2SO_4 (0.230 mL) was added. The reaction was stirred a further 7 h and more $HgSO_4$/H_2SO_4 (0.230 mL) was added. The reaction was stirred for a further 5 h before being quenched with brine (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with H_2O (5 mL) and brine (5 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc

90:10) to afford **481** (12 mg, 32%) as a white solid. m.p 65-68 °C. R_f 0.14 (hexane/EtOAc 90:10). υ_{max} neat/cm^{-1} 2929, 2856, 1706, 1251, 1082, 835. δ_H (400 MHz, $CDCl_3$) 0.12 (s, 3H, Si(CH_3)$_2$), 0.18 (s, 3H, Si(CH_3)$_2$), 0.88 (d, 3H, *J* 7.1 Hz, CH_3CH), 0.92 (s, 9H, SiC(CH_3)$_3$), 1.03 (d, 3H, *J* 7.2 Hz, CH_3CH), 1.76 (qd, 1H, *J* 7.1, 3.9 Hz, CH$_3$C*H*), 2.33 (qd, 1H, *J* 7.2, 3.7 Hz, CH$_3$C*H*), 2.43 (s, 3H, CH_3C=O), 3.48 (d, 1H, *J* 6.3 Hz, CHO*H*), 4.09 (d, 1H, *J* 6.3 Hz, C*H*OH), 4.29 (dd, 1H, *J* 3.8, 1.8 Hz, =CHC*H*O), 4.43 (dd, 1H, *J* 3.8, 1.8 Hz, =CHC*H*O), 6.27 (dd, 1H, *J* 6.1, 1.8 Hz, =C*H*), 6.34 (dd, 1H, *J* 6.1, 1.8 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) -1.9 (CH_3, Si(*C*H$_3$)$_2$), -1.1 (CH_3, Si(*C*H$_3$)$_2$), 12.0 (CH_3, *C*H$_3$CH), 14.1 (CH_3, *C*H$_3$CH), 20.6 (C, Si*C*(CH$_3$)$_3$), 27.1 (CH_3, SiC(*C*H$_3$)$_3$), 30.1 (CH_3, *C*H$_3$C=O), 39.4 (CH, CH$_3$C*H*), 39.9 (CH, CH$_3$*C*H), 80.3 (C, *C*OH), 82.4 (CH, =CH*C*HO), 83.2 (CH, *C*HOSi), 83.3 (CH, =CH*C*HO), 133.5 (CH, =*C*H), 134.0 (CH, =*C*H), 209.3 (C, *C*=O). *m*/*z* HRMS calcd for $C_{18}H_{32}NaO_4Si^+$ 363.1968, found 363.1969; (ES) 363 ([M+Na]$^+$, 100%), 364 ([M+Na+H]$^+$, 8).

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-((*S*)-1-hydroxyprop-2-yn-1-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 483

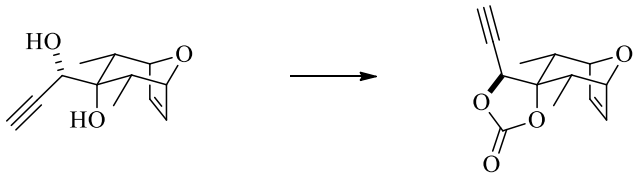


A novel compound prepared using a modified literature procedure.[148]

To a solution of **476** (225 mg, 0.570 mmol) in THF (6 mL) at room temperature, TBAF (1 M, 1.42 mL, 1.42 mmol) was added in one portion. The reaction was stirred at room temperature for 18 h before being washed with H_2O (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 60:40) to afford **483** (96 mg, 81%) as a white solid. m.p 127-129 °C. R_f 0.34 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3576, 3334, 3260, 2961, 1309, 1231, 1042, 933, 683. δ_H (400 MHz, $CDCl_3$)

0.90 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.01 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 2.23 (s, 1H, O*H*), 2.31 (qd, 1H, *J* 7.2, 3.9 Hz, CH$_3$C*H*), 2.58 (d, 1H, ^{4}*J* 2.3 Hz, C≡C*H*), 2.70-2.81 (m, 2H, CH$_3$C*H*, O*H*), 4.31 (t, 1H, *J* 2.6 Hz, C*H*OH), 4.46 (d, 2H, *J* 3.8 Hz, =CHC*H*O), 6.49 (app. qd, 2H, *J* 6.1, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 11.4 (CH$_3$, *C*H$_3$CH), 12.5 (CH$_3$, *C*H$_3$CH), 37.1 (CH, CH$_3$*C*H), 37.2 (CH, CH$_3$*C*H), 68.9 (CH, *C*HOH), 76.2 (C, *C*OH), 76.4 (CH, C≡*C*H), 82.1 (C, *C*≡CH), 82.4 (CH, =CH*C*HO), 83.2 (CH, =CH*C*HO), 135.0 (2 x CH, =*C*H). *m*/*z* HRMS calcd for $C_{12}H_{16}NaO_3^+$ 231.0997, found 231.0993; (ES) 231 ([M+Na]$^+$, 100%).

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*,5'*S*)-5'-ethynyl-2,4-dimethyl-8-oxaspiro[bicyclo[3.2.1]oct[6]ene-3,4'-[1,3]dioxolan]-2'-one 484



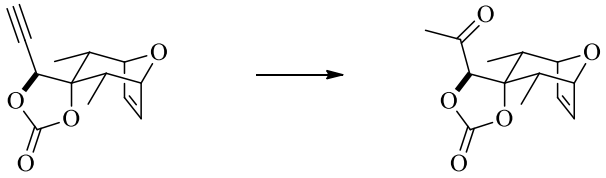
A novel compound prepared using a literature procedure.[189]

Reaction was performed under an argon atmosphere.

To a solution of **483** (78 mg, 0.380 mmol) and pyridine (180 mg, 0.180 mL, 2.28 mmol) in CH_2Cl_2 (15 mL) at room temperature, triphosgene (564 mg, 1.90 mmol) was added over 5 min. The reaction was stirred at room temperature for 1 h before being diluted with Et_2O (15 mL) and washed with $NaHCO_3$ (10 mL of a saturated aqueous solution), H_2O (10 mL) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **484** (71 mg, 80%) as a white solid. m.p. >165 °C (dec.). R_f 0.18 (hexane/EtOAc 80:20). υ_{max} neat/cm^{-1} 3224, 2970, 2123, 1798, 1210, 1176, 1047, 1016, 938, 767, 722. δ_H (400 MHz, $CDCl_3$) 0.93 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 1.02 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 2.10 (dq, 1H, *J* 7.2, 3.7 Hz, CH$_3$C*H*), 2.79 (dq, 1H, *J* 7.1, 3.7 Hz, CH$_3$C*H*), 2.85 (d, 1H, ^{4}*J* 2.4 Hz, C≡C*H*), 4.52-

4.57 (m, 2H, =CHC*H*O), 4.95 (d, 1H, ^4J 2.4 Hz, C*H*OC=O), 6.35-6.40 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.1 (CH_3, *C*H_3CH), 10.7 (CH_3, *C*H_3CH), 39.7 (CH, CH_3*C*H), 40.5 (CH, CH_3*C*H), 74.2 (CH, *C*HOC=O), 74.6 (C, *C*OC=O), 81.0 (CH, C≡*C*H), 81.4 (CH, =CH*C*HO), 81.9 (CH, =CH*C*HO), 86.6 (C, *C*≡CH), 132.9 (CH, =*C*H), 133.7 (CH, =*C*H), 153.7 (C, *C*=O). *m/z* HRMS calcd for $C_{13}H_{14}NaO_4^+$ 257.0790, found 257.0783; (ES) 257 ($[M+Na]^+$, 100%), 258 ($[M+Na]^+$, 6), 289 ($[M+Na+MeOH]^+$, 13).

Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*,5'*R*)-5'-acetyl-2,4-dimethyl-8-oxaspiro[bicyclo[3.2.1]oct[6]ene-3,4'-[1,3]dioxolan]-2'-one 485

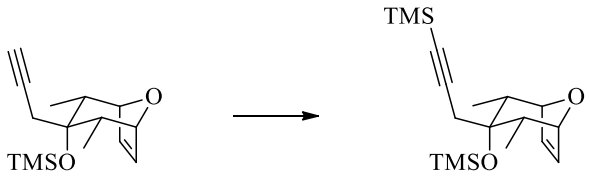


A novel compound prepared using a literature procedure.[188]

To a solution of **484** (62 mg, 0.260 mmol) in THF (5.2 mL) and H_2O (2.6 mL) at room temperature, a saturated solution of $HgSO_4$ in H_2SO_4 (0.550 mL of a 1% aqueous solution) was added drop-wise. The reaction was stirred at room temperature for 7 h before being quenched with brine (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30) to afford **485** (44 mg, 67%) as a white solid. m.p 128-131 °C. R_f 0.13 (hexane/EtOAc 70:30). υ_{max} neat/cm^{-1} 2987, 2922, 1796, 1727, 1362, 1212, 1049, 938, 767, 723. δ_H (400 MHz, $CDCl_3$) 0.84 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 0.96 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 2.34-2.41 (m, 5H, CH_3C*H*, C*H*$_3$C=O), 4.48 (dd, 1H, *J* 3.7, 1.5 Hz, =CHC*H*O), 4.51 (s, 1H, C*H*OC=O), 4.55 (dd, 1H, *J* 3.6, 1.5 Hz, =CHC*H*O), 6.37 (app. qd, 2H, *J* 6.2, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) 10.0 (CH_3, *C*H_3CH), 11.1 (CH_3, *C*H_3CH), 28.6 (CH_3, *C*H_3C=O), 37.9 (CH, CH_3*C*H), 41.7 (CH, CH_3*C*H), 81.3 (CH, =CH*C*HO), 81.7 (CH, =CH*C*HO), 85.6 (CH, *C*HOC=O), 88.3 (C,

*C*OC=O), 133.3 (CH, =*C*H), 133.5 (CH, =*C*H), 153.5 (C, O*C*=O), 203.4 (C, *C*=O). *m*/*z* HRMS calcd for $C_{13}H_{16}NaO_5^+$ 275.0895, found 275.0894; (ES) 275 ($[M+Na]^+$, 100%).

Preparation of (3-(2,4-*endo*,*endo*-dimethyl-3 -((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)prop-1-yn-1-yl)trimethylsilane 491

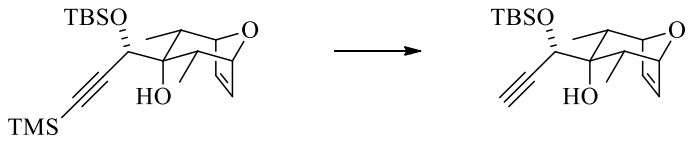


A novel compound prepared using a modified literature procedure.[190]

Reaction was performed under an argon atmosphere.

To a solution of **458** (200 mg, 0.750 mmol) in THF (20 mL) at -78 °C, ^{n}BuLi (1.48 M, 0.610 mL, 0.910 mmol) was added drop-wise. The reaction was stirred at -78 °C for 1 h before TMSCl (99.0 mg, 0.120 mL, 0.910 mmol) was added drop-wise. The reaction was allowed to warm to room temperature and was stirred at room temperature for 4 h. The reaction was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford **491** (158 mg, 62%) as a clear colourless oil. R_f 0.11 (hexane/EtOAc 99:1). υ_{max} neat/cm^{-1} 2959, 2934, 2176, 1248, 833. δ_H (400 MHz, $CDCl_3$) 0.07 (s, 9H, OSi(C*H*$_3$)$_3$), 0.16 (s, 9H, CSi(C*H*$_3$)$_3$), 0.82 (d, 6H, *J* 7.2 Hz, C*H*$_3$CH), 2.34-2.41 (m, 4H, C*H*CH$_3$, C*H*$_2$C≡C), 4.40 (d, 2H, *J* 3.5 Hz, C*H*OCH), 6.19 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 0.3 (3 x CH$_3$, Si(*C*H$_3$)$_3$), 3.0 (3 x CH$_3$, OSi(*C*H$_3$)$_3$), 11.9 (2 x CH$_3$, *C*H$_3$CH), 30.7 (CH$_2$, *C*H$_2$C≡C), 39.1 (2 x CH, *C*HCH$_3$), 79.3 (C, *C*OSi), 82.9 (2 x CH, =CH*C*HO), 88.1 (C, C≡*C*Si), 104.0 (C, *C*≡CSi), 133.1 (2 x CH, =*C*H). *m*/*z* HRMS calcd for $C_{18}H_{32}NaO_2Si_2^+$ 359.1839, found 359.1848; (ES) 359 ($[M+Na]^+$, 100%), 360 ($[M+Na+H]^+$, 23).

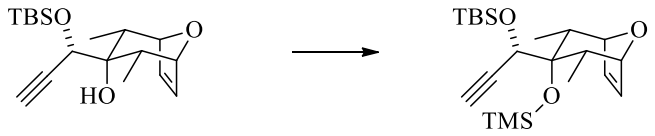
Preparation of (±)-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-((*S*)-1-((tert-butyldimethylsilyl)oxy)prop-2-yn-1-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol 498



A novel compound prepared using a literature procedure.[192]

To a solution of **476** (50 mg, 0.130 mmol) in MeOH (1.4 mL) and H_2O (0.4 mL) at 0 °C, K_2CO_3 (35 mg, 0.250 mmol) was added. The reaction was stirred at 0 °C for 3 h before being partitioned between EtOAc (5 mL) and H_2O (5 mL). The aqueous layer was extracted with EtOAc and the combined organics concentrated *in vacuo*. The residue was dissolved in EtOAc (5 mL) and washed with H_2O (3 x 2 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **498** (33 mg, 77%) as a white solid. m.p 84-86 °C. R_f 0.23 (hexane/EtOAc 95:5). υ_{max} neat/cm^{-1} 3545, 3227, 2930, 2858, 2111, 1051, 835. δ_H (400 MHz, $CDCl_3$) 0.12 (s, 3H, Si(C*H*$_3$)$_2$), 0.17 (s, 3H, Si(C*H*$_3$)$_2$), 0.91 (m, 12H, SiC(C*H*$_3$)$_3$, C*H*$_3$CH), 0.95 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 2.28 (qd, 1H, *J* 7.2, 4.0 Hz, CH$_3$C*H*), 2.41 (s, 1H, O*H*), 2.54 (d, 1H, ^{4}*J* 2.2 Hz, C≡C*H*), 2.69 (qd, 1H, *J* 7.2, 4.0 Hz, CH$_3$C*H*), 4.17 (d, 1H, ^{4}*J* 2.2 Hz, C*H*OSi), 4.42-4.46 (m, 2H, =CHC*H*O), 6.38 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*), 6.41 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) -5.3 (CH$_3$, Si(*C*H$_3$)$_2$), -4.4 (CH$_3$, Si(*C*H$_3$)$_2$), 11.5 (CH$_3$, *C*H$_3$CH), 11.9 (CH$_3$, *C*H$_3$CH), 18.3 (C, Si*C*(CH$_3$)$_3$), 25.9 (3 x CH$_3$, SiC(*C*H$_3$)$_3$), 36.6 (CH, CH$_3$*C*H), 36.8 (CH, CH$_3$*C*H), 69.6 (CH, *C*HOSi), 75.5 (C, *C*≡CH), 76.4 (CH, C≡*C*H), 82.4 (CH, =CH*C*HO), 83.1 (C, *C*OH), 83.3 (CH, =CH*C*HO), 133.6 (CH, =*C*H), 134.0 (CH, =*C*H). *m*/*z* HRMS calcd for $C_{18}H_{30}NaO_3Si^+$ 345.1862, found 345.1861; (ES) 345 ([M+Na]$^+$, 100%), 346 ([M+Na+H]$^+$, 24).

Preparation of (±)-*tert*-butyl(((*S*)-1-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)prop-2-yn-1-yl)oxy)dimethylsilane 497



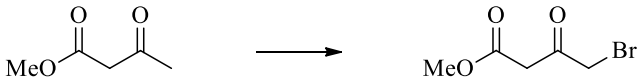
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **498** (40 mg, 0.130 mmol) and Et_3N (51 mg, 0.070 mL, 0.500 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C, TMSOTf (73 mg, 0.060 mL, 0.330 mmol) was added drop-wise. The reaction was allowed to warm to room temperature and was stirred for 20 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford **497** (37 mg, 73%) as a white solid. m.p 75-78 °C. R_f 0.28 (hexane/EtOAc 98:2). υ_{max} neat/cm^{-1} 3231, 2938, 2928, 2856, 2110, 1248, 1112, 831. δ_H (400 MHz, $CDCl_3$) 0.11 (s, 3H, Si(C*H*$_3$)$_2$), 0.15 (s, 9H, Si(C*H*$_3$)$_3$), 0.18 (s, 3H, Si(*C*H$_3$)$_2$), 0.80 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 0.93 (s, 9H, SiC(C*H*$_3$)$_3$), 1.03 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 2.35 (qd, 1H, *J* 7.2, 3.8 Hz, CH$_3$C*H*), 2.42 (d, 1H, ^{4}*J* 2.3 Hz, C≡C*H*), 2.54 (qd, 1H, *J* 7.1, 4.0 Hz, CH$_3$C*H*), 4.11 (d, 1H, ^{4}*J* 2.4 Hz, C*H*OSi), 4.35-4.39 (m, 2H, =CHC*H*O), 6.21 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*), 6.26 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*). δ_C (100 MHz, $CDCl_3$) -4.8 (CH$_3$, Si(*C*H$_3$)$_2$), -4.0 (CH$_3$, Si(*C*H$_3$)$_2$), 3.2 (3 x CH$_3$, Si(*C*H$_3$)$_3$), 12.1 (CH$_3$, *C*H$_3$CH), 13.5 (CH$_3$, *C*H$_3$CH), 18.4 (C, Si*C*(CH$_3$)$_3$), 26.1 (3 x CH$_3$, SiC(*C*H$_3$)$_3$), 36.0 (CH, CH$_3$*C*H), 36.7 (CH, CH$_3$*C*H), 66.6 (CH, *C*HOSi), 76.8 (CH, C≡*C*H), 82.0 (C, *C*≡CH), 82.8 (CH, =CH*C*HO), 83.4 (CH, =CH*C*HO), 85.7 (C, *C*OSi), 133.0 (CH, =*C*H), 133.6 (CH, =*C*H).

m/*z* HRMS calcd for $C_{21}H_{38}NaO_3Si_2^+$ 417.2257, found 417.2241; (ES) 417 ($[M+Na]^+$, 100%), 418 ($[M+Na+H]^+$, 57).

Preparation of Methyl 4-bromo-3-oxobutanoate 501

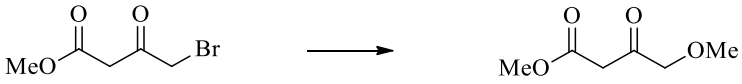


A known compound prepared using a literature procedure.[194]

Reaction was performed under an argon atmosphere.

To a solution of methyl acetoacetate **500** (1.00 g, 0.930 mL, 8.60 mmol) in $CHCl_3$ (3 mL) at 0 °C, a solution of Br_2 (1.37 g, 0.440 mL, 8.60 mmol) in $CHCl_3$ (2 mL) was added drop-wise. The reaction was stirred at room temperature for 16 h before air was blown through the reaction for 2 h. The reaction was washed with cold H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **501** (1.62 g, 96%) as an orange liquid. υ_{max} neat/cm^{-1} 2956, 2902, 1719, 1658, 1631, 1437, 1325, 1241, 1196, 1009, 810, 706. ^{1}H NMR indicates that **501** exists in ~8:1 keto:enol ratio. The data reported is of the major keto tautomer. δ_H (400 MHz, $CDCl_3$) 3.72 (s, 2H, C*H*$_2$CO$_2$Me), 3.76 (s, 3H, OC*H*$_3$), 4.04 (s, 2H, C*H*$_2$Br). δ_C (100 MHz, $CDCl_3$) 34.0 (CH_2, *C*H_2Br), 46.0 (CH_2, *C*H_2CO$_2$Me), 52.8 (CH_3, O*C*H_3), 167.2 (C, *C*O$_2$Me), 194.6 (C, *C*=O). Literature values:[215] IR (CCl_4): 3030, 3000, 2955, 2845, 1745, 1720, 1657, 1630, 1447, 1437, 1401, 1365, 1325, 1240, 1170, 1155, 1075, 1009, 948, 913, 860. ^{1}H NMR (90 MHz, CCl_4): *Keto form*: 3.62 (s, 2H); 3.73 (s, 3H), 3.99 (s, 2H). *Enol form*: 3.74 (s, 3H); 3.82 (s, 2H); 5.25 (s, 1H); 11.88 (s, 1H). MS: 196 (M^+, 2%), 194 (M^+, 2), 165 (10), 164 (6), 163 (10), 162 (6), 138 (6), 123 (16), 115 (27), 101 (100), 85 (10), 93 (10), 74 (2), 69 (26), 59 (32), 57 (11), 55 (4), 43 (82), 42 (30).

Preparation of Methyl 4-methoxy-3-oxobutanoate 502

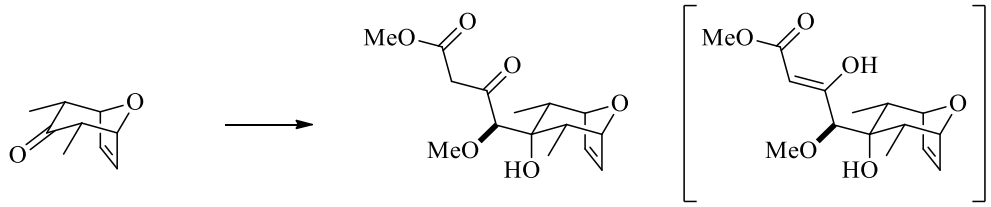


A known compound prepared using a literature procedure.[193]

Reaction was performed under an argon atmosphere.

To a flask containing MeOH (40 mL) at room temperature, Na (1.76 g, 76.5 mmol) was added portion-wise. Upon complete dissolution of Na, the resulting solution of NaOMe was heated to reflux. A solution of **501** (5.00 g, 25.5 mmol) in MeOH (7 mL) was added drop-wise over 40 min. The reaction was heated at reflux for 30 min before being cooled to room temperature and neutralised with HCl (10 mL of a 6 M aqueous solution). The resulting suspension was filtered and concentrated *in vacuo*. The residue was poured into H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by Kügelrohr distillation (150 °C. 1.0 Torr) to afford **502** (1.70 g, 46%) as a clear, colourless liquid. υ_{max} neat/cm^{-1} 1751, 1721, 1654, 1636. ^1H NMR indicates that **502** exists in ~15:1 keto:enol ratio. The data reported is of the major keto tautomer. δ_H (400 MHz, $CDCl_3$) 3.42 (s, 3H, CH_2OCH_3), 3.52 (s, 2H, CH_2CO_2Me), 3.73 (s, 3H, CO_2CH_3), 4.07 (s, 2H, CH_2OMe). δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2, CH_2CO_2Me), 52.6 (CH_3, CO_2CH_3), 59.6 (CH_3, CH_2OCH_3), 77.6 (CH_2, CH_2OCH_3), 167.6 (C, CO_2Me), 201.7 (C, C=O). Literature values:[193] IR υ_{max} (film) 1750, 1720, 1655, 1635 cm^{-1}; NMR ($CDCl_3$) δ (keto form) 3.43 (s, OCH_3), 3.53 (s, CH_2CO_2Me), 3.75 (s, CO_2CH_3), 4.08 (s, CH_2OMe) and (enol form) 4.00 (s, CH_2OMe), 5.29 (s, =CH), 11.88 (s, OH).

Preparation of (±)-Methyl 4-((1*R*,2*S*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-4-methoxy-3-oxobutanoate 503



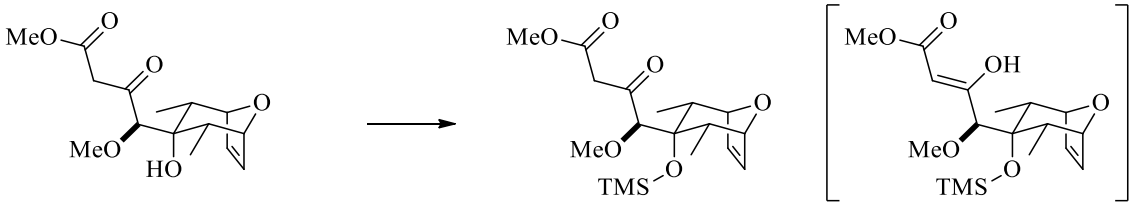
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of diisopropylamine (810 mg, 1.12 mL, 8.00 mmol) in THF (8 mL) at 0 °C, ^{n}BuLi (1.6 M, 5.00 mL, 8.00 mmol) was added drop-wise. The reaction was stirred for 30 min at 0 °C before **502** (584 mg, 4.00 mmol) was added drop-wise and the reaction stirred at 0 °C for 1 h before a solution of **378** (152 mg, 1.00 mmol) in THF (2 mL) was added in one portion. The reaction was allowed to warm to room temperature and stirred at room temperature for 20 h. The reaction was quenched with HCl (10 mL of a 1 M aqueous solution) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30) to afford **503** (187 mg, 63%) as a bright yellow oil. R_f 0.23 (hexane/EtOAc 70:30). υ_{max} neat/cm^{-1} 3575, 2936, 1743, 1715, 1314, 1103, 934, 731, 666. ^{1}H NMR indicates that **503** exists in ~3:1 keto:enol ratio. The data reported is of the major keto tautomer with identifiable enol peaks following. δ_H (400 MHz, $CDCl_3$) 0.75 (d, 3H, *J* 7.2 Hz, C*H*$_3$CH), 0.95 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 2.28-2.36 (m, 2H, CH$_3$C*H*, O*H*), 2.52 (qd, 1H, *J* 7.2, 4.1 Hz, CH$_3$C*H*), 3.38 (s, 3H, CHOC*H*$_3$), 3.61 (s, 1H, C*H*OCH$_3$), 3.63 (d, 1H, ^{2}*J* 16.3 Hz, C*H*$_2$CO$_2$Me), 3.72 (s, 3H, CO$_2$C*H*$_3$), 3.73 (d, 1H, ^{2}*J* 16.3 Hz, C*H*$_2$CO$_2$Me), 4.42-4.44 (m, 1H, =CHC*H*O), 4.47-4.49 (m, 1H, =CHC*H*O), 6.47 (br. s, 2H, =C*H*). Enol peaks 0.89 (2 x d, 6H, *J* 7.2 Hz, C*H*$_3$CH), 3.36 (s, 3H, CHOC*H*$_3$), 5.36 (s, 1H, C*H*=COH), 6.36 (dd, 1H, *J* 6.2, 1.6

Hz, =C*H*), 6.39 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*), 12.23 (s, 1H, CH=CO*H*). δ_C (100 MHz, $CDCl_3$) 11.2 (CH_3, *C*H_3CH), 11.7 (CH_3, *C*H_3CH), 36.3 (CH, CH_3*C*H), 38.2 (CH, CH_3*C*H), 48.5 (*C*H_2CO_2Me), 52.4 (CH_3, CO_2*C*H_3), 59.8 (CH_3, CHO*C*H_3), 78.2 (C, *C*OH), 82.4 (CH, =CH*C*H), 82.8 (CH, =CH*C*H), 88.6 (CH, *C*HOMe), 134.9 (CH, =*C*H), 135.6 (CH, =*C*H), 168.1 (C, *C*O_2Me), 205.7 (C, *C*=O). Enol peaks 11.5 (CH_3, *C*H_3CH), 11.7 (CH_3, *C*H_3CH), 36.6 (CH, CH_3*C*H), 37.3 (CH, CH_3*C*H), 51.7 (CH_3, CO_2*C*H_3), 82.5 (CH, =CH*C*H), 83.0 (CH, =CH*C*H), 90.9 (CH, *C*H=COH), 133.9 (2 x CH, =*C*H), 173.1 (C, *C*O_2CH_3), 174.8 (C, CH=*C*OH). *m*/*z* HRMS calcd for $C_{15}H_{22}NaO_6^+$ 321.1314, found 321.1310; (ES) 321 ($[M+Na]^+$, 100%).

Preparation of (±)-Methyl 4-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-4-methoxy-3-oxobutanoate 504



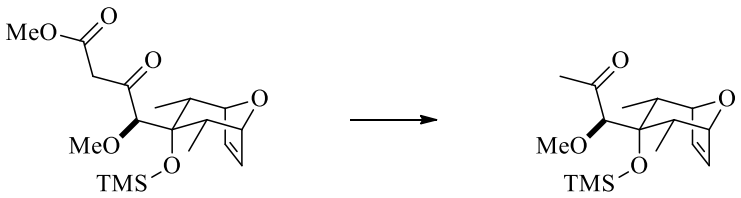
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **503** (179 mg, 0.600 mmol) and Et_3N (244 mg, 0.340 mL, 2.41 mmol) in CH_2Cl_2 (6 mL) at 0 °C, TMSOTf (347 mg, 0.280 mL, 1.56 mmol) was added drop-wise. The reaction was allowed to warm to room temperature and was stirred at room temperature for 24 h. Additional Et_3N (244 mg, 0.340 mL, 2.41 mmol) and TMSOTf (347 mg, 0.280 mL, 1.56 mmol) were added and the reaction stirred for a further 6 h before being quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **504** (144 mg,

65%) as a bright yellow oil. R_f 0.14 (hexane/EtOAc 95:5). υ_{max} neat/cm^{-1} 2952, 2932, 1751, 1716, 1656, 1624, 1223, 1117, 1097, 874, 834, 707. ^{1}H NMR indicates that **504** exists in ~3:2 enol:keto ratio. The data reported is of the major enol tautomer with keto peaks following. δ_H (400 MHz, $CDCl_3$) Enol Peaks: 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 0.86 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 0.91 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 2.14-25 (m, 1H, CH_3C*H*), 2.39 (qd, 1H, *J* 7.1, 3.8 Hz, CH_3C*H*), 3.24 (s, 3H, OC*H*$_3$), 3.59 (s, 1H, C*H*OCH_3), 3.77 (s, 3H, CO_2C*H*$_3$), 4.31 (d, 1H, *J* 3.7 Hz, =CHC*H*), 4.34 (d, 1H, *J* 3.8 Hz, =CHC*H*), 5.24 (s, 1H, C*H*=COH), 6.18-6.19 (m, 2H, =C*H*), 12.15 (s, 1H, CH=CO*H*). Keto peaks 0.11 (s, 9H, Si(C*H*$_3$)$_3$), 0.80 (d, 3H, *J* 7.0 Hz, C*H*$_3$CH), 0.96 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 2.08 (qd, 1H, *J* 7.1, 3.8 Hz, CH_3C*H*), 2.14-2.25 (m, 1H, CH_3C*H*), 3.35 (s, 3H, OC*H*$_3$), 3.47 (s, 1H, C*H*OCH_3), 3.58 (d, 1H, ^{2}*J* 16.2 Hz, C*H*$_2$$CO_2CH_3$), 3.71-3.75 (m, 4H, C*H*$_2$$CO_2CH_3$, CO_2C*H*$_3$), 4.34 (d, 1H, *J* 3.8 Hz, =CHC*H*), 4.36 (d, 1H, *J* 3.8 Hz, =CHC*H*), 6.19-6.20 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) Enol peaks: 2.9 (3 x CH_3, Si(*C*H$_3$)$_3$), 12.4 (CH_3, *C*H$_3$CH), 13.7 (CH_3, *C*H$_3$CH), 37.5 (CH, CH_3*C*H), 37.6 (CH, CH_3*C*H), 51.6 (CH_3, CO_2*C*H$_3$), 57.2 (CH_3, O*C*H$_3$), 80.8 (C, *C*OSi), 82.4 (CH, =CH*C*H), 83.4 (CH, =CH*C*H), 87.4 (CH, *C*HOCH_3), 92.2 (CH, *C*H=COH), 133.4 (2 x CH, =*C*H), 172.9 (C, *C*O_2CH_3), 174.4 (C, CH=*C*OH). Keto peaks: 2.6 (3 x CH_3, Si(*C*H$_3$)$_3$), 12.7 (CH_3, *C*H$_3$CH), 13.3 (CH_3, *C*H$_3$CH), 36.9 (CH, CH_3*C*H), 39.1 (CH, CH_3*C*H), 46.3 (CH_2, *C*H$_2$$CO_2CH_3$), 52.6 ($CH_3$, CO_2*C*H$_3$), 59.1 (CH_3, O*C*H$_3$), 81.0 (C, *C*OSi), 82.3 (CH, =CH*C*H), 82.9 (CH, =CH*C*H), 91.9 (CH, *C*HOCH_3), 133.0 (CH, =*C*H), 133.3 (CH, =*C*H), 167.7 (C, *C*O_2CH_3), 205.3 (C, *C*=O). *m/z* HRMS calcd for $C_{18}H_{30}NaO_6Si^+$ 393.1709, found 393.1706; (ES) 393 ([M+Na]$^+$, 100%).

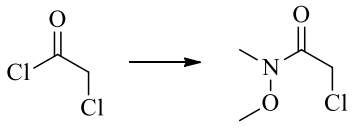
Preparation of (±)-1-((1*R*,2*S*,3*S*,4*R*,5*S*)-2,4-dimethyl-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-1-methoxypropan-2-one 505



A novel compound prepared using a modified literature procedure.[97]

To a solution of **504** (135 mg, 0.370 mmol) and H_2O (0.030 mL, 1.48 mmol) in DMSO (1 mL), NaCl (43 mg, 0.730 mmol) was added. The mixture was heated to reflux for 3 h before being allowed to cool to room temperature. The reaction was purified by column chromatography (hexane/EtOAc 95:5) to afford **505** (59 mg, 51%) as a white solid. m.p. 84-86 °C. R_f 0.15 (hexane/EtOAc 95:5). υ_{max} neat/cm^{-1} 2967, 2932, 1700, 1111, 1095, 878, 834, 695. δ_H (400 MHz, $CDCl_3$) 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 0.82 (d, 3H, *J* 7.0 Hz, C*H*$_3$CH), 0.98 (d, 3H, *J* 7.1 Hz, C*H*$_3$CH), 1.99 (qd, 1H, *J* 7.1, 3.8 Hz, CH$_3$C*H*), 2.17 (qd, 1H, *J* 7.0, 3.9 Hz, CH$_3$C*H*), 2.24 (s, 3H, C*H*$_3$C=O), 3.28 (s, 3H, OC*H*$_3$), 3.41 (s, 1H, C*H*OCH$_3$), 4.30 (d, 1H, *J* 3.7 Hz, =CHC*H*), 4.35 (d, 1H, *J* 3.8 Hz, =CHC*H*), 6.19 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 2.7 (3 x CH$_3$, Si(*C*H$_3$)$_3$), 12.6 (CH$_3$, *C*H$_3$CH), 13.5 (CH$_3$, *C*H$_3$CH), 27.3 (CH$_3$, *C*H$_3$C=O), 36.9 (CH, CH$_3$*C*H), 39.7 (CH, CH$_3$*C*H), 58.5 (CH$_3$, O*C*H$_3$), 80.2 (C, *C*OSi), 82.3 (CH, =CH*C*H), 83.1 (CH, =CH*C*H), 93.0 (CH, *C*HOCH$_3$), 133.4 (2 x CH, =*C*H), 211.4 (C, *C*=O). *m*/*z* HRMS calcd for $C_{16}H_{28}NaO_4Si^+$ 335.1655, found 335.1639; (ES) 335 ($[M+Na]^+$, 100%).

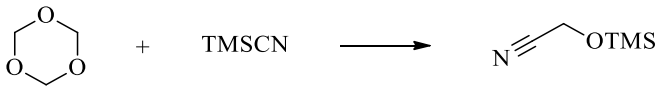
Preparation of 2-chloro-*N*-methoxy-*N*-methylacetamide 508



A known compound prepared using a literature procedure.[196]

To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride **512** (2.93 g, 30.0 mmol) in H_2O (20 mL), a solution of chloroacetyl chloride **511** (4.06 g, 2.86 mL, 36.0 mmol) in CH_2Cl_2 (20 mL) was added. The resultant biphasic mixture was cooled to 0 °C and K_2CO_3 (7.45 g, 54.0 mmol) added slowly. The reaction was allowed to warm to room temperature and stirred for 40 h. The layers were separated and the organic layer washed with $NaHCO_3$ (10 mL of a saturated aqueous solution). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **508** (3.15 g, 76%) as a white crystalline solid. δ_H (400 MHz, $CDCl_3$) 3.17 (s, 3H, NC*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 4.19 (s, 2H, C*H*$_2$Cl). δ_C (100 MHz, $CDCl_3$) 32.6 (CH_3, N*C*H$_3$), 40.9 (CH_2, *C*H$_2$Cl), 61.7 (CH_3, O*C*H$_3$), 167.4 (C, *C*=O). *m/z* (ES) 58 (14%), 61 (100), 77 (74), 79 (26), 107 (71), 109 (23), 137 ([M(^{35}Cl)$^+$, 57), 139 ([M(^{37}Cl)$^+$, 20). Literature values:[216] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 3.64 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 61.4, 40.6, 32.3. IR (neat) υ_{max} 2946, 1665, 1468, 1417, 1390, 1277, 1182, 1104, 994, 769 cm^{-1}. MS (EI) *m*/*z* (%): 137 (0.4, [M$^+$]), 107 (8), 79 (8), 77 (25), 61 (100), 58 (18), 49 (10). HRMS (ESI) for $C_4H_8ClNO_2Na$: cald 160.0141; found 160.0138.

Preparation of 2-((trimethylsilyl)oxy)acetonitrile 516



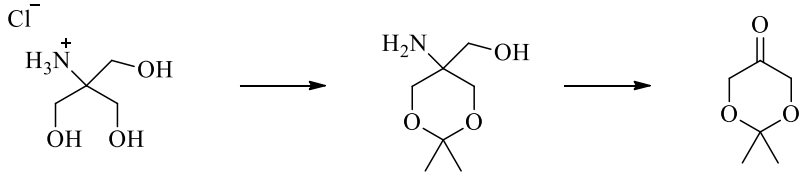
A known compound prepared using a literature procedure.[197]

Reaction was performed under an argon atmosphere.

To a mixture of 1,3,5-trioxane **515** (303 mg, 3.36 mmol) and TMSCN (1.00 g, 1.26 mL, 10.1 mmol) at room temperature, ZnI_2 (22 mg, 0.070 mmol) was added. The reaction was stirred at room temperature for 24 h before additional ZnI_2 (22 mg, 0.070 mmol) was added. The reaction was stirred at room temperature for 6 h. The mixture was purified by Kügelrohr distillation (80 °C, 1.0 Torr) to afford **516** (498 mg, 38%) as a clear colourless liquid. υ_{max}

neat/cm^{-1} 2961, 1452, 1254, 1107, 838. δ_H (300 MHz, $CDCl_3$) 0.21 (s, 9H, Si(CH_3)$_3$), 4.35 (s, 2H, CH_2CN). δ_C (100 MHz, $CDCl_3$) -0.5 (3 x CH_3, Si(CH_3)$_3$), 49.2 (CH_2, CH_2CN), 117.9 (C, C≡N).

Preparation of 2,2-dimethyl-1,3-dioxan-5-one 534



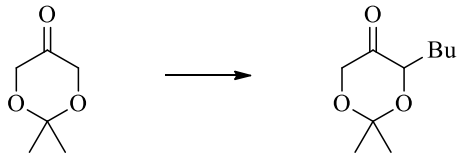
A known compound prepared using a modified literature procedure.[199]

To a solution of Trizma® hydrochloride **531** (20.0 g, 127 mmol) and 2,2-dimethoxypropane **532** (15.0 g, 17.7 mL, 144 mmol) in DMF (104 mL), *p*TsOH (1.20 g, 6.80 mmol) was added and the resulting solution heated to 65 °C for 24 h. The reaction was cooled to room temperature and Et_3N (675 mg, 0.930 mL, 6.67 mmol) added, before the solvent was evaporated. The resulting residue was dissolved in EtOAc (310 mL) and Et_3N (10.9 g, 15.0 mL 107 mmol) added. The mixture was stirred at room temperature for 2 h and the resultant precipitate filtered. The filtrate was evaporated *in vacuo* to afford the crude β-amino alcohol **533** (15.6 g).

To a solution of **533** (15.6 g, 96.0 mmol) in H_2O (408 mL), KH_2PO_4 (13.1 g, 96.0 mmol) was added. The resulting solution was cooled to 0 °C and $NaIO_4$ (192 mL of a 0.5 M aqueous solution, 96.0 mmol) was added drop-wise over 2 h, maintaining the temperature between 0 °C and 10 °C. The reaction was stirred for 18 h at room temperature, before being extracted with CH_2Cl_2 on a continuous extractor for 18 h. The combined organics were collected and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Et_2O 50:50) to afford **534** (5.70 g, 35% over two steps) as a clear liquid. δ_H (400 MHz, $CDCl_3$) 1.42 (s, 6H, CH_3), 4.11 (s, 4H, CH_2). δ_C (100 MHz, $CDCl_3$) 23.6 (2 x CH_3, *C*H-

$_3$), 66.9 (2 x CH_2, *C*H_2), 100.2 (C, *C*(CH_3)), 208.1 (C=O). *m/z* (ES) 43 (33%), 72 (60), 100 (68), 115 ([M-Me]$^+$, 100), 130 (M^+, 87). Literature values:[199, 217] IR ($CHCl_3$) υ 1755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 6H), 4.15 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 66.7, 100.0, 207.9 ppm.

Preparation of 4-butyl-2,2-dimethyl-1,3-dioxan-5-one 524



A known compound prepared using a literature procedure.[198]

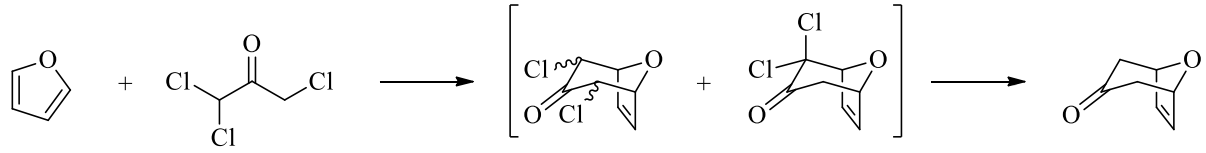
To a solution of **534** (2.39 g, 18.4 mmol) in toluene (61 mL), 4 Å molecular sieves (2.50 g) and cyclohexylamine (3.64 g, 4.20 mL, 36.8 mmol) were added. The resulting solution was stirred at room temperature for 16 h before being filtered and concentrated *in vacuo* to afford the imine **535**.

Reaction was performed under an argon atmosphere.

To a solution of diethylamine (1.40 g, 1.98 mL, 20.2 mmol) in THF (18 mL) at -35 °C, ^{n}BuLi (1.39 M, 14.6 mL, 20.2 mmol) was added drop-wise. The resulting $LiNEt_2$ solution was cooled to -78 °C and a solution of the imine **535** in THF (18 mL) was added drop-wise. The reaction was allowed to warm to -35 °C over 2 h, before again being cooled to -78 °C. Iodobutane (6.80 g, 4.20 mL, 36.8 mmol) was added and the reaction allowed to warm to room temperature over 2 h. The reaction was quenched with NH_4Cl (30 mL of a saturated aqueous solution), before being stirred at room temperature for 30 min and extracted with Et_2O (2 x 25 mL). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **524** (1.66 g, 48%) as a clear, colourless liquid. δ_H (400 MHz, $CDCl_3$) 0.90 (t, 3H, *J* 7.1 Hz,

CH_3CH_2), 1.19-1.62 (m, 5H, 3 x CH_2), 1.42 (s, 3H, CCH_3), 1.44 (s, 3H, CCH_3), 1.76-1.91 (m, 1H, C*H*), 3.97 (d, 1H, *J* 16.9 Hz, CH_2O), 4.18-4.21 (m, 1H, C*H*), 4.24 (dd, 1H, *J* 1.4, 16.9 Hz, CH_2O). δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, *C*H_3), 22.3 (CH_2, *C*H_2), 23.8 (CH_3, C*C*H_3), 24.2 (CH_3, C*C*H_3), 27.4 (CH_2, *C*H_2), 28.4 (CH_2, *C*H_2), 66.8 (CH_2, *C*H_2O), 74.9 (CH, *C*HO), 100.9 (C, O*C*O), 210.0 (C, *C*=O). *m/z* (ES) 72 (100%), 100 (49), 128 ([M-Bu]$^+$, 45), 171 ([M-Me]$^+$, 21), 186 (M+H$^+$, 3). Literature values:[198] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (t, *J* 7.0 Hz, 3H), 1.15-1.50 (m, 5H), 1.34 (s, 3H), 1.37 (s, 3H), 1.76 (dtd, *J* 5.2, 8.8, 10.2 Hz, 1H), 3.88 (d, *J* 17.0 Hz, 1H), 4.08-4.15 (m, 1H), 4.16 (dd, *J* 1.4, 17.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.3, 23.7, 23.8, 27.1, 28.0, 65.4, 74.5, 100.5, 209.6; IR (neat) 2957, 1748 cm^{-1}; HRMS (M-H$^+$) calcd for $C_{10}H_{17}O_3$ 185.1178, found 185.1174.

Preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-one 536



A known compound prepared using a modified literature procedure.[202a]

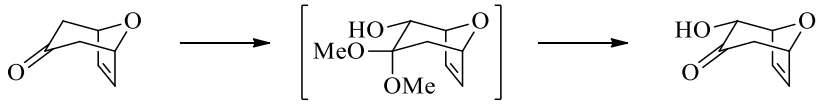
Reaction was performed under an argon atmosphere.

To a flask containing TFE (69 mL) at room temperature, sodium (2.40 g, 103 mmol) was added portion-wise with stirring, ensuring the temperature stayed below 25 °C. The reaction stirred at room temperature until the sodium had completely dissolved. The resulting solution of NaTFE (1.5 M) was added drop-wise to a solution of furan (2.00 g, 2.08 mL, 29.4 mmol) in TFE (49 mL) at 0 °C. Simultaneously, a solution of TCA **542** (14.2 g, 9.40 mL, 88.2 mmol) in TFE (49 mL) was added to the furan solution drop-wise. The reaction was allowed to warm to room temperature and was stirred at room temperature for 24 h before being quenched with H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were concentrated *in vacuo* to afford a mixture of α-chloro ketone isomers.

Reaction performed under an argon atmosphere.

To a mixture of Zn dust (19.2 g, 294 mmol) and CuI (16.8 g, 88.2 mmol) at room temperature, MeOH (20 mL) was added drop-wise with good stirring, ensuring to wash the sides of the flask. The reaction was stirred until the solid was black and grainy before being diluted with MeOH (40 mL). A solution of the α-chloro ketone isomers in MeOH (230 mL) was added over 20 min. The reaction was stirred at room temperature for 48 h before being filtered through Celite®. The filtrate was concentrated *in vacuo*, washed with HCl (100 mL of a 1 M aqueous solution) and extracted with EtOAc (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **536** (2.53 g, 69%) as a brown solid. υ_{max} neat/cm^{-1} 2968, 2909, 2894, 1706, 1340, 1180, 1035, 1029, 945, 844, 738, 710. δ_H (400 MHz, $CDCl_3$) 2.35 (d, 2H, ^2J 16.1 Hz, CH_{2eq}C=O), 2.77 (dd, 2H, ^2J 17.0 Hz, J 5.1 Hz, CH_{2ax}C=O), 5.06 (d, 2H, J 5.1 Hz, =CHC*H*O), 6.27 (s, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 46.9 (2 x CH_2, *C*H_2C=O), 77.4 (2 x CH, =CH*C*HO), 133.5 (2 x CH, =*C*H), 206.0 (C, *C*=O). Literature values:[218] FTIR (neat, cm^{-1}) 2962, 2916, 1714, 1246, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, 2H), 5.06 (d, J 5.1 Hz, 2H), 2.76 (dd, J 17.0, 5.2 Hz, 2H), 2.34 (dd, J 16.3 Hz, 0.6 Hz, 2H); ^{13}C NMR (125.7 Hz, $CDCl_3$) δ 205.3, 133.3, 77.2, 46.7; EI-HRMS *m*/*z* calcd for $C_7H_8O_2$: 124.05243 [M^+], found: 124.05256.

Preparation of (±)-(1*S*,2*R*,5*S*)-2-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one 537

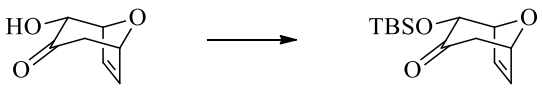


A known compound prepared by a literature procedure.[200]

To a solution of KOH (116 mg, 2.42 mmol) in MeOH (2.5 mL) at 5 °C, a solution of **536** (100 mg, 0.810 mmol) in MeOH (3.5 mL) was added drop-wise over 15 min. The

mixture was allowed to stir for 10 min. $PhI(OAc)_2$ (287 mg, 0.890 mmol) was added in 4 portions over 10 min. The reaction was stirred at room temperature for 18 h before being quenched with H_2O (6 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in AcOH (1.4 mL of a 50% aqueous solution) and stirred at room temperature for 15 h before being diluted with EtOAc (10 mL) and washed with H_2O (5 mL), $NaHCO_3$ (5 mL of a saturated aqueous solution) and brine (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 50:50) to afford **537** (12 mg, 11%) as a clear colourless oil. R_f 0.41 (hexane/EtOAc 50:50). υ_{max} neat/cm^{-1} 3368, 2984, 2860, 1708, 1172, 1110, 1088, 1036, 882, 841, 729. δ_H (400 MHz, $CDCl_3$) 2.48 (d, 1H, ^2J 14.9 Hz, CH_{2eq}), 2.86-2.92 (m, 1H, CH_{2ax}), 3.51 (d, 1H, *J* 2.8 Hz, O*H*), 4.37 (dd, 1H, *J* 5.2, 2.5 Hz, C*H*OH), 5.03-5.10 (m, 2H, =CHC*H*), 6.25-6.34 (m, 2H, =C*H*). δ_C (100 MHz, $CDCl_3$) 45.2 (CH_2, *C*H_2), 78.7 (CH, *C*HOH), 79.1 (CH, =CH*C*H), 80.9 (CH, =CH*C*H), 132.0 (CH, =*C*H), 134.8 (CH, =*C*H), 206.6 (C, *C*=O). *m/z* HRMS calcd for $C_7H_8NaO_3^+$ 163.0371, found 163.0355; (ES) 163 ($[M+Na]^+$, 100). Literature values:[200] IR (film) 3427, 3091, 1720, 1336 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.31-6.27 (m, 2H), 5.07-5.05 (m, 2H), 4.36 (dd, *J* 2.4, 5.0 Hz, 1H), 3.53 (d, *J* 2.4 Hz, 1H), 2.88 (dd, *J* 5.0, 15.0 Hz, 1H), 2.47 (d, *J* 15.0 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.4, 134.6, 131.8, 80.7, 78.9, 78.5, 45.0.

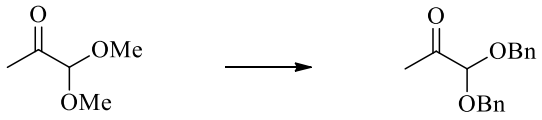
Preparation of (±)-(1*S*,2*R*,5*S*)-2-((*tert*-butyldimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one 543



A novel compound prepared using a modified literature procedure.[201]

To a solution of **537** (94 mg, 0.670 mmol), imidazole (183 mg, 2.69 mmol) and DMAP (9 mg, 0.070 mmol) in CH_2Cl_2 (4 mL) at room temperature, TBSCl (205 mg, 1.35 mmol) was added. The reaction was stirred at room temperature for 18 h before being poured into a mixture of $NaHCO_3$ (5 mL of a saturated aqueous solution) and petrol (5 mL). The layers were separated and the aqueous layer extracted with petrol (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc 95:5) to afford **543** (81 mg, 47%) as a clear, colourless oil. R_f 0.42 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2954, 2929, 2856, 1728, 1328, 1153, 1115, 969, 883, 833, 778. δ_H (400 MHz, $CDCl_3$) 0.07 (s, 3H, Si(CH_3)$_2$), 0.14 (s, 3H, Si(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 2.36 (d, 1H, ^2J 15.5 Hz, CH_{2eq}), 2.74 (dd, 1H, ^2J 15.5 Hz, *J* 4.9 Hz, CH_{2ax}), 4.31 (d, 1H, *J* 5.2 Hz, C*H*OSi), 4.86 (dd, 1H, *J* 5.2, 1.6 Hz, =CHC*H*CHO), 4.98-5.01 (m, 1H, =CHC*H*CH_2), 6.27 (dd, 1H, *J* 6.1, 1.5 Hz, =C*H*CHCHO), 6.31 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHCH_2). δ_C (100 MHz, $CDCl_3$), -5.3 (CH_3, Si(*C*H_3)$_2$), -4.4 (CH_3, Si(*C*H_3)$_2$), 18.6 (C, Si*C*(CH_3)$_3$), 26.0 (3 x CH_3, SiC(*C*H_3)$_3$), 45.8 (CH_2, *C*H_2), 78.6 (CH, =CH*C*HCH_2), 79.8 (CH, *C*HOSi), 81.6 (CH, =CH*C*HCHO), 132.3 (CH, =*C*HCHCH_2), 134.7 (CH, =*C*HCHCHO), 204.8 (C, *C*=O). *m*/*z* HRMS calcd for $C_{13}H_{22}NaO_3Si^+$ 277.1236, found 277.1227; (ES) 277 ($[M+Na]^+$, 100).

Preparation of 1,1-bis(benzyloxy)propan-2-one 546



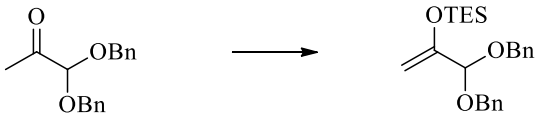
A known compound prepared using a literature procedure.[203]

A solution of methylglyoxal 1,1-dimethyl acetal **545** (3.55 mL, 30.0 mmol), benzyl alcohol (6.84 mL, 66.0 mmol) and *p*TsOH (290 mg, 1.50 mmol) in cyclohexane (15 mL) was fitted with a Dean-Stark trap, and heated to reflux for 2 h. Upon completion, ~2.5 mL of MeOH was removed. The reaction was then cooled to room temperature, and washed with

K_2CO_3 (8 mL of a saturated aqueous solution) and H_2O (6 mL). The aqueous layer was extracted with cyclohexane (2 x 15 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol:Et_2O 95:5) to afford **546** (6.73 g, 83%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 2.26 (s, 3H, C*H*$_3$), 4.60 (d, 2H, ^2J 11.8 Hz, C*H*$_2$), 4.69 (d, 2H, ^2J 11.8 Hz, C*H*$_2$), 4.74 (s, 1H, C*H*), 7.30-7.34 (m, 10H, C*H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 25.2 (CH_3, *C*H_3), 69.5 (2 x CH_2, *C*H_2), 101.2 (CH, *C*H), 128.3 (6 x CH, *C*H_{Ar}), 128.7 (4 x CH, *C*H_{Ar}), 137.1 (2 x C, *C*CH_{Ar}), 204.0 (C, *C*=O). *m/z* (ES) 293 ([M+Na]$^+$, 100%), 294 ([M+Na+H]$^+$, 10), 309 ([M+K]$^+$, 9). Literature values:[203] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 4.68 (d, *J* 12 Hz, 2H), 4.78 (d, *J* 12 Hz, 2H), 4.84 (s, 1H), 7.41-7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.0, 69.2, 101.0, 127.4, 128.0, 128.5, 137.0, 203.7. EI-MS (*m*/*z*): 271 (5), 259 (15), 228 (10), 182 (18), 181 (100), 165 (14); HRMS (FAB) (*m*/*z*): calcd for $C_{17}H_{19}O_2$ (M^++1) 271.1334, observed 271.1308.

Preparation of ((3,3-bis(benzyloxy)prop-1-en-2-yl)oxy)triethylsilane 547

Method A



A known compound prepared using a literature procedure.[203]

Reaction was performed under an argon atmosphere.

To a solution of diisopropylamine (2.55 g, 3.60 mL, 25.2 mmol) in THF (21 mL) at -78 °C, ^{n}BuLi (1.39 M, 18.1 mL, 25.2 mmol) was added drop-wise. The resultant LDA solution was added, over 10 min via syringe, to a solution of **546** (5.70 g, 21.0 mmol) and TESCl (4.75 g, 5.29 mL, 31.5 mmol) in THF (26 mL) at -78 °C. Et_3N (9.50 g, 13.1 mL, 94.5 mmol) was added immediately over 10 min. The resulting solution was stirred at -78 °C for 3

h before H_2O (18 mL) was added and the cooling was removed. The mixture was stirred vigorously until it had warmed to room temperature. The resulting layers were separated and the aqueous layer extracted with cyclohexane (2 x 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol:Et_2O 99:1, deactivated with 0.1% Et_3N) to afford **547** (5.56 g, 69%) as a clear, colourless oil.

Method B

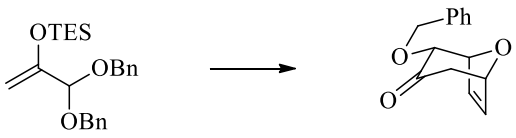
A known compound prepared using a modified literature procedure.[203]

Reaction was performed under an argon atmosphere.

To a solution of LiHMDS (1 M, 28.8 mL, 28.8 mmol) in THF (59 mL) at -78 °C, TESCl (5.43 g, 6.04 mL, 36.0 mmol) was added drop-wise, followed by **546** (6.47 g, 24.0 mmol) drop-wise. The resulting solution was stirred at -78 °C for 3 h before H_2O (21 mL) was added and the cooling was removed. The mixture was stirred vigorously until it warmed to room temperature. The resulting layers were separated and the aqueous layer extracted with cyclohexane (2 x 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol:Et_2O 99:1, deactivated with 0.1% Et_3N) to afford **547** (6.72 g, 73%) as a clear, colourless oil. δ_H (400 MHz, $CDCl_3$) 0.73 (q, 6H, *J* 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$), 1.00 (t, 9H, *J* 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$), 4.42 (s, 1H, C=C*H*$_2$), 4.60 (d, 2H, ^{2}*J* 11.9 Hz, OC*H*$_2$), 4.68 (d, 2H, ^{2}*J* 11.9 Hz, OC*H*$_2$), 4.74 (s, 1H, C=C*H*$_2$), 4.94 (s, 1H, C*H*), 7.28-7.36 (m, 10H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 5.1 (3 x CH_2, Si(*C*H$_2$CH$_3$)$_3$), 6.9 (3 x CH_3, Si(CH$_2$*C*H$_3$)$_3$), 67.5 (2 x CH_2, O*C*H$_2$), 92.5 (CH_2, C=*C*H$_2$), 99.4 (CH, O*C*H), 127.7 (2 x CH, *C*H$_{Ar}$), 127.9 (4 x CH, *C*H$_{Ar}$), 128.5 (4 x CH, *C*H$_{Ar}$), 138.4 (C, *C*CH$_{Ar}$), 154.0 (C, *C*=CH$_2$). *m/z* (ES) 407 ([M+Na]$^+$, 100%). Literature values:[203] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.69 (q, *J* 7.8 Hz, 6H), 0.95 (t, *J* 8.1 Hz, 9H), 4.37 (d, *J* 1.2 Hz, 1H), 4.57 (d, *J* 12 Hz, 2H), 4.63 (d, *J* 11.7 Hz, 2H), 4.70 (s, 1H), 4.89 (s, 1H), 7.31-7.26 (m, 10H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.9, 6.7, 67.6, 92.3, 99.2, 127.5, 127.8, 128.4, 138.2, 153.8. EI-MS (*m*/*z*): no M^+, 279 (9), 249 (4), 248 (3), 193 (4), 187 (6), 181 (7), 159 (14), 157 (13), 115 (17), 91 (100).

Preparation of 2α-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one 544



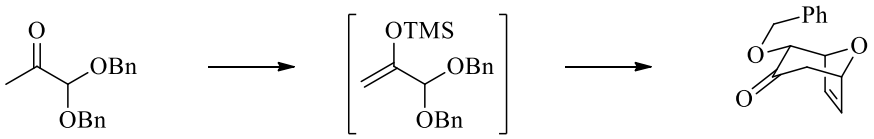
Method A

A known compound prepared using a literature procedure.[203]

Reaction was performed under an argon atmosphere.

To a solution of **547** (854 mg, 2.20 mmol) in CH_2Cl_2 (2.3 mL) at -78 °C, furan (150 mg, 0.160 mL, 2.20 mmol) was added via syringe. The reaction was stirred for 15 min before TMSOTf (49 mg, 0.040 mL, 0.220 mmol) was added. The resulting mixture was stirred at -78 °C for 30 min, after which $NaHCO_3$ (2.3 mL of a saturated aqueous solution) was added. The cooling was removed and the mixture stirred vigorously until it had reached room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol:Et_2O 75:25) to afford **544** (318 mg, 63%) as a white solid.

Method B



A known compound prepared using a literature procedure.[203]

Reaction was performed under an argon atmosphere.

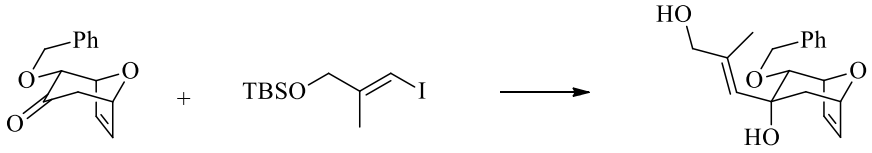
To a solution of **546** (15.6 g, 59.1 mmol) in DMF (20 mL) at room temperature, TMSCl (14.4 g, 16.8 mL, 133 mmol) was added. The mixture was heated to 75 °C and Et_3N (16.7 g, 23.1 mL, 165.5 mmol) added via syringe pump (60 mL h^{-1}). The reaction was stirred at 75 °C for 16 h before being cooled to 0 °C and washed with cold NH_4Cl (30 mL of a saturated aqueous solution) and H_2O (10 mL). The aqueous layer was extracted with cyclohexane (4 x 30 mL) and the combined organics dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the silyl enol ether **548** (18.3 g).

Reaction was performed under an argon atmosphere.

To a solution of crude **548** in CH_2Cl_2 (56 mL) at -78 °C, furan (3.63 g, 3.80 mL, 53.3 mmol) was added. The mixture was stirred for 15 min before TMSOTf (1.18 g, 0.96 mL, 5.33 mmol) was added drop-wise. The reaction was stirred for 30 min at -78 °C before $NaHCO_3$ (18.3 mL of a saturated aqueous solution) was added. The cooling was removed and the reaction stirred vigorously until it reached room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/Et_2O 75:25) to afford **544** (7.7 g, 57% over two steps) as a white solid. δ_H (400 MHz, $CDCl_3$) 2.38 (d, 1H, ^2J 15.4 Hz, =CHCHCH_{2eq}), 2.76 (dd, 1H, ^2J 15.4 Hz, J 4.9 Hz, =CHCHCH_{2ax}), 4.13 (d, 1H, J 5.0 Hz, CHOCH_2), 4.64 (d, 1H, ^2J 12.1 Hz, CH_2O), 4.91 (dd, 1H, J 5.0, 1.6 Hz, =CHCHCH), 4.96-5.01 (m, 2H, =CHC$H$$CH_2$, C$H_2$O), 6.30 (dd, 1H, J 6.0, 1.6 Hz, =CHCHCH_2), 6.34 (dd, 1H, J 6.0, 1.7 Hz, =CHCHCH), 7.28-7.39 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 46.2 (CH_2, =CHCH$C$$H_2$), 73.7 ($CH_2$, $C$$H_2$O), 78.6 (CH, =CH$CHCH_2$), 80.0 (CH, =CH$C$HCH), 84.4 (CH, CHOCH_2), 128.1 (2 x CH, $C$$H_{Ar}$), 128.2 (CH, $C$$H_{Ar}$), 128.7 (2 x CH, $C$$H_{Ar}$), 132.0 (CH, =$CHCHCH_2$), 134.8 (CH, =$C$HCHCH), 137.8 (C, $C$$CH_{Ar}$), 205.1 (C, C=O). *m/z* (EI) 91 ($[Bn]^+$, 100%), 139 ($[M\text{-}Bn]^+$, 10), 158 (11), 201

(11), 230 ([M]$^+$, 9). Literature values:[203] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (d, *J* 15.5 Hz, 1H), 2.75 (dd, *J* 15, 5 Hz, 1H), 4.13 (d, *J* 5 Hz, 1H), 4.64 (d, *J* 12 Hz, 1H), 4.91 (dd, *J* 5, 1.5 Hz, 1H), 4.99 (m, 2H), 6.30 (dd, *J* 6.5, 1.5 Hz, 1H), 6.34 (dd, *J* 6, 2 Hz, 1H), 7.39-7.31 (m, 5H); ^{13} C NMR (125 <Hz, $CDCl_3$) δ: 46.1, 73.7, 78.6, 80.0, 84.3, 128.1, 128.7, 132.0, 134.8, 137.8, 205.2. IR ($CHCl_3$) cm^{-1}: 1724, 1112, 731, 697; EI-MS (rt): 230 (6, M$^+$), 201, (4), 158 (38), 139 (31, M$^+$-Bn), 121 (10), 108 (25), 91 (100), 81 (30), 77 (14), 69 (23). Anal. Calcd for $C_{14}H_{14}O_3$: C, 72.89; H, 6.05. Found: C, 73.03; H, 6.13.

Preparation of (±)-(1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-((*E*)-3-hydroxy-2-methylprop-1-en-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 549



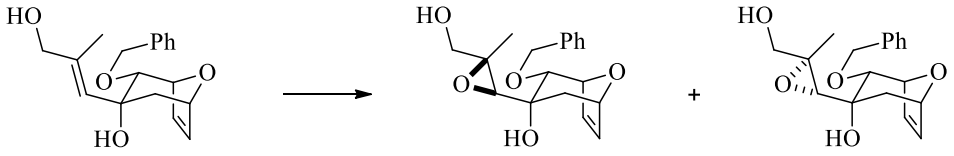
A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **384** (2.04 g, 6.53 mmol) in THF (43 mL) at -78 °C, ^{n}BuLi (1.41 M, 4.63 mL, 6.53 mmol) was added drop-wise. The resulting mixture was stirred at -78 °C for 30 min before a solution of **544** (1.00 g, 4.35 mmol) in THF (9 mL) was added. The reaction was allowed to warm to room temperature for and was stirred at room temperature for 24 h before being quenched with NH_4Cl (30 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in THF (43 mL) and TBAF (1 M, 5.20 mL, 5.20 mmol) was added. The reaction was stirred at room temperature for 18 h before being washed with H_2O (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 40:60) to afford **549** (858 mg, 62%)

as a yellow solid. m.p. 52-54 °C. R_f 0.14 (hexane/EtOAc 40:60). υ_{max} neat/cm^{-1} 3443, 2940, 2873, 1454, 1314, 1053, 884, 731, 696. δ_H (400 MHz, $CDCl_3$) 1.79 (d, 3H, *J* 1.2 Hz, =CC*H*$_3$), 1.90 (dd, 1H, ^2J 14.6 Hz, *J* 0.9 Hz, =CHCHC*H*$_{2eq}$), 2.03 (dd, 1H, ^2J 14.7 Hz, *J* 4.5 Hz, =CHCHC*H*$_{2ax}$), 3.00 (s, 1H, O*H*), 3.76 (d, 1H, *J* 4.4 Hz, =CHCHC*H*O), 3.87 (d, 2H, ^4J 0.8 Hz, =CC*H*$_2$), 4.62 (d, 1H, ^2J 12.0 Hz, C*H*$_2$O), 4.64-4.68 (m, 2H, =CHC*H*CH, C*H*$_2$O), 4.74 (br. d, 1H, *J* 4.5 Hz, =CHC*H*CH$_2$), 5.35 (m, 1H, C=C*H*), 6.26 (dd, 1H, *J* 6.2, 1.7 Hz, =C*H*CHCH), 6.32 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH$_2$), 7.25-7.40 (m, 5H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3, =C*C*H$_3$), 38.3 (CH_2, =CHCH*C*H$_2$), 69.2 (CH_2, =C*C*H$_2$), 72.8 (CH_2, *C*H$_2$O), 73.4 (C, *C*OH), 78.2 (CH, =CH*C*HCH), 78.8 (CH, =CH*C*HCH$_2$), 78.8 (CH, =CHCH*C*HO), 128.3 (3 x CH, *C*H$_{Ar}$), 128.6 (2 x CH, *C*H$_{Ar}$), 130.9 (CH, =*C*HCHCH), 134.3 (CH, C=*C*H), 135.8 (CH, =*C*HCHCH$_2$), 136.2 (C, *C*=CH), 137.8 (C, *C*CH$_{Ar}$). *m*/*z* HRMS calcd for $C_{18}H_{22}NaO_4^+$ 325.1416, found 325.1411; (ES) 325 ($[M+Na]^+$, 100%).

Preparation of (±)-(1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-((2*R*,3*R*)-3-(hydroxymethyl)-3-methyloxiran-2-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 550 and (±)-(1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-((2*S*,3*S*)-3-(hydroxymethyl)-3-methyloxiran-2-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 551



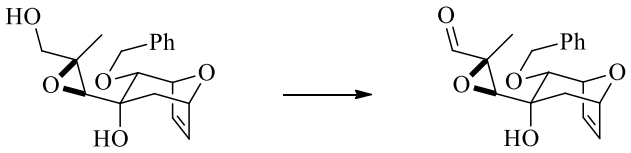
550 **551**

Novel compounds prepared using a literature procedure.[155b]

To a solution of **549** (621 mg, 2.06 mmol) and $VO(acac)_2$ (26.4 mg, 0.10 mmol) in CH_2Cl_2 (30 mL) at room temperature, ^{t}BuOOH (3.3 M, 1.87 mL, 6.18 mmol) was added drop-wise over 10 min. The reaction was stirred for 6 h at room temperature. Upon complete conversion the reaction was partially concentrated and purified by column chromatography

(petrol/EtOAc 40:60) to afford **550** and **551** (446 mg, 68%, 9:1 d.r.) as a clear, pale yellow oil. Analytical data for **550**. m.p. 109-112 °C. R_f 0.26 (petrol/EtOAc 40:60). υ_{max} neat/cm^{-1} 3476, 3405, 2945, 2929, 1457, 1052, 982, 882, 741, 720, 682. δ_H (400 MHz, $CDCl_3$) 1.49 (s, 3H, C*H*$_3$CO), 1.69 (d, 1H, ^2J 14.4 Hz, =CHCHC*H*$_{2eq}$), 1.97 (dd, 1H, ^2J 14.4 Hz, J 4.5 Hz, =CHCHC*H*$_{2ax}$), 2.81 (s, 1H, C*H*OC), 2.92 (br. s, 1H, O*H*), 3.58 (ABq, 2H, ^2J 12.3 Hz, C*H*$_2$CO), 3.75 (d, 1H, J 4.4 Hz, =CHCHC*H*), 4.63 (dd, 1H, J 4.4, 1.7 Hz, =CHC*H*CH), 4.69 (d, 1H, ^2J 11.8 Hz, C*H*$_2$O), 4.74 (br. d, 1H, J 4.5 Hz, =CHC*H*CH$_2$), 4.81 (d, 1H, ^2J 11.7 Hz, C*H*$_2$O), 6.25 (dd, 1H, J 6.1, 1.6 Hz, =C*H*CHCH), 6.30 (dd, 1H, J 6.1, 1.6 Hz, =C*H*CHCH$_2$), 7.28-7.50 (m, 5H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, *C*H$_3$CO), 33.8 (CH_2, =CHCH*C*H$_2$), 60.7 (C, CHO*C*), 65.7 (CH_2, *C*H$_2$CO), 66.0 (CH, *C*HOC), 70.0 (C, *C*OH), 73.0 (CH_2, C*H*$_2$O), 78.2 (2 x CH, =CH*C*HCH$_2$, =CH*C*HCH), 79.3 (CH, =CHCH*C*H), 128.3 (3 x CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 131.1 (CH, =*C*HCHCH), 135.2 (CH, =*C*HCHCH$_2$), 137.9 (C, *C*CH$_{Ar}$). *m*/*z* HRMS calcd for $C_{18}H_{22}NaO_5^+$ 341.1365, found 341.1370; (ES) 341 ([M+Na]$^+$, 100%), 342 ([M+Na+H]$^+$, 17).

Preparation of (±)-(2*S*,3*R*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 553

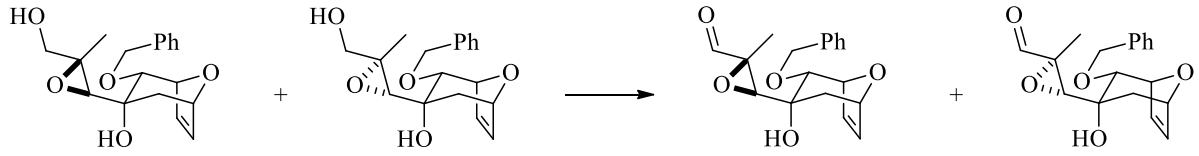


A novel compound prepared using a literature procedure.[159]

To a solution of **550** (389 mg, 1.22 mmol) in CH_2Cl_2 (12 mL) at room temperature, $NaHCO_3$ (823 mg, 9.80 mmol) was added. The resulting suspension was stirred at room temperature for 30 min before being cooled to 0 °C. DMP (623 mg, 1.47 mmol) was added and the reaction stirred at room temperature for 7 h before additional DMP (311 mg, 0.740 mmol) was added and the reaction stirred for a further 3 h. Additional DMP

(311 mg, 0.740 mmol) was added and the reaction stirred for 12 h. Upon completion, the reaction was quenched with cold $NaHCO_3$ (6.1 mL of a saturated aqueous solution), followed by NaS_2O_3 (6.1 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30) to afford **553** (284 mg, 74%) as a white solid. m.p. 95-97 °C. R_f 0.33 (petrol/EtOAc 70:30). υ_{max} neat/cm^{-1} 3537, 2967, 2939, 1723, 1100, 1049, 887, 732, 695. δ_H (400 MHz, $CDCl_3$) 1.62 (s, 3H, CH_3CO), 1.67 (d, 1H, ^2J 14.4 Hz, =CHCHCH_{2eq}), 1.90 (ddd, 1H, ^2J 14.4 Hz, J 4.5 Hz, ^4J 1.6 Hz, =CHCHCH_{2ax}), 2.81 (s, 1H, C*H*OC), 3.02 (d, 1H, ^4J 1.6 Hz, O*H*), 3.82 (d, 1H, J 4.4 Hz, =CHCHC*H*), 4.66 (dd, 1H, J 4.4, 1.7 Hz, =CHC*H*CH), 4.71-4.76 (m, 2H, =CHC*H*CH_2, CH_2O), 4.84 (d, 1H, ^2J 11.7 Hz, CH_2O), 6.24 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH), 6.29 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH_2), 7.29-7.47 (m, 5H, H_{Ar}), 8.82 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 9.7 (CH_3, *C*H_3CO), 33.4 (CH_2, =CHCH*C*H_2), 61.8 (C, CHO*C*), 65.7 (CH, *C*HOC), 70.2 (C, *C*OH), 73.0 (CH_2, *C*H_2O), 78.0 (2 x CH, =CHC*H*CH, =CHC*H*CH_2), 78.6 (CH, =CHCH*C*H), 128.3 (2 x CH, *C*H_{Ar}), 128.5 (CH, *C*H_{Ar}), 128.8 (2 x CH, *C*H_{Ar}), 130.8 (CH, =*C*HCHCH), 135.3 (CH, =*C*HCHCH_2), 137.5 (C, *C*CH_{Ar}), 199.5 (CH, *C*HO). *m*/*z* HRMS calcd for $C_{18}H_{20}NaO_5^+$ 339.1208, found 339.1220; (ES) 339 ($[M+Na]^+$, 60%), 340 ($[M+Na+H]^+$, 6), 371 ($[M+Na+MeOH]^+$, 100), 372 ($[M+Na+MeOH+H]^+$, 27).

Preparation of (±)-(2*S*,3*R*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 553 and (2*R*,3*S*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 554



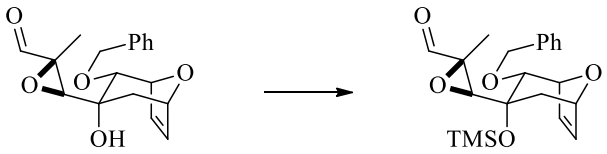
553 **554**

Novel compounds prepared using a literature procedure.[159]

To a solution of **550** and **551** (214 mg, 0.640 mmol, 1:1 d.r.) in CH_2Cl_2 (8 mL) at room temperature, $NaHCO_3$ (538 mg, 6.40 mmol) was added. The resulting suspension was stirred at room temperature for 30 min before being cooled to 0 °C. DMP (407 mg, 0.960 mmol) was added and the reaction stirred at room temperature for 2 h before additional DMP (204 mg, 0.480 mmol) was added and the reaction stirred for a further 2 h. The reaction was quenched with cold $NaHCO_3$ (4.1 mL of a saturated aqueous solution), followed by $Na_2S_2O_3$ (4.1 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30) to afford **553** (36 mg, 14%) as a white solid followed by **554** (31 mg, 12%) as a clear colourless oil. For analytical data of **553** see above. Analytical data for **554**. R_f 0.21 (petrol/EtOAc 70:30). υ_{max} neat/cm^{-1} 3526, 2945, 1725, 1087, 1052, 886, 732, 697. δ_H (400 MHz, $CDCl_3$) 1.59 (s, 3H, CH_3CO), 1.86 (dd, 1H, ^2J 14.3 Hz, ^4J 0.6 Hz, =CHCHCH_{2eq}), 2.13 (dd, 1H, ^2J 14.4 Hz, J 4.6 Hz, =CHCHCH_{2ax}), 2.84 (s, 1H, C*H*OC), 3.72 (d, 1H, J 4.4 Hz, =CHCHC*H*), 4.66 (d, 1H, ^2J 11.6 Hz, CH_2O), 4.69-4.73 (m, 2H, =CHC*H*CH, CH_2O), 4.80 (d, 1H, J 4.6 Hz, =CHC*H*CH_2), 6.27 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH), 6.33 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH_2), 7.28-7.41 (m, 5H, H_{Ar}), 8.73 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 10.5 (CH_3, CH_3CO), 35.9 (CH_2, =CHCH*C*H_2), 62.8

(C, CHO*C*), 65.7 (CH, *C*HOC), 72.2 (C, *C*OH) 72.7 (CH_2, *C*H_2O), 74.9 (CH, =CHCH*C*H), 77.2 (CH, =CHC*H*CH), 78.3 (CH, =CHC*H*CH_2), 128.5 (2 x CH, *C*H_{Ar}), 128.7 (CH, *C*H_{Ar}), 129.0 (2 x CH, *C*H_{Ar}), 130.7 (CH, =*C*HCHCH), 136.1 (CH, =*C*HCHCH_2), 137.0 (C, *C*CH_{Ar}), 199.6 (CH, *C*HO). *m*/*z* HRMS calcd for $C_{18}H_{20}NaO_5^+$ 339.1208, found 339.1217; (ES) 339 ($[M+Na]^+$, 26%), 371 ($[M+Na+MeOH]^+$, 100), 372 ($[M+Na+MeOH+H]^+$, 12).

Preparation of (2*S*,3*S*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxirane-2-carbaldehyde 555



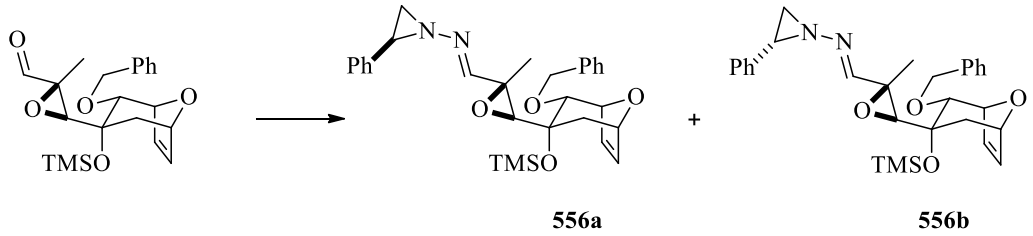
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **553** (204 mg, 0.650 mmol) and Et_3N (263 mg, 0.360 mL, 2.60 mmol) in CH_2Cl_2 (6.5 mL) at 0 °C, TMSOTf (376 mg, 0.310 mL, 1.69 mmol) was added drop-wise. The reaction was stirred at room temperature for 4 h before being quenched with $NaHCO_3$ (1 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and dried *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **555** (201 mg, 80%) as a white solid. m.p. 107-109 °C. R_f 0.21 (petrol/EtOAc 70:30). υ_{max} neat/cm^{-1} 2956, 2910, 2868, 2848, 1725, 1238, 1104, 907, 836, 690. δ_H (400 MHz, $CDCl_3$) 0.13 (s, 9H, Si(C*H*$_3$)$_3$), 1.49 (s, 3H, C*H*$_3$CO), 1.63 (dd, 1H, ^2J 14.5 Hz, *J* 1.0 Hz, =CHCHC*H*$_{2eq}$), 1.91 (dd, 1H, ^2J 14.6 Hz, *J* 4.4 Hz, =CHCHC*H*$_{2ax}$), 2.88 (s, 1H, C*H*OC), 3.61 (d, 1H, *J* 4.0 Hz, =CHCHC*H*), 4.62-4.72 (m, 4H, =CHC*H*CH, =CHC*H*CH_2, C*H*$_2$O), 6.19 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH), 6.26 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH_2), 7.28-7.41 (m, 5H, *H*$_{Ar}$), 8.65 (s, 1H, C*H*O). δ_C (100 MHz, $CDCl_3$) 3.4 (3 x CH_3, Si(*C*H$_3$)$_3$), 10.0 (CH_3, *C*H$_3$CO), 36.9 (CH_2, =CHCHC*H*$_2$), 61.3 (C,

CHO*C*), 66.5 (CH, *C*HOC), 71.9 (CH_2, *C*H_2O), 75.1 (C, *C*OH), 77.5 (CH, =CHC*H*CH), 78.1 (CH, =CHC*H*CH_2), 79.1 (CH, =CHCHC*H*), 128.5 (CH, *C*H_{Ar}), 128.6 (2 x CH, *C*H_{Ar}), 128.8 (2 x CH, *C*H_{Ar}), 131.9 (CH, =*C*HCHCH_2), 134.5 (CH, =*C*HCHCH), 137.7 (C, *C*CH_{Ar}), 199.4 (CH, *C*HO). *m*/*z* HRMS calcd for $C_{22}H_{32}NaO_6Si^+$ 443.1866, found 443.1871; (ES) 411 ($[M+Na]^+$, 25%), 443 ($[M+Na+MeOH]^+$, 100), 444 ($[M+Na+MeOH+H]^+$, 13).

Preparation of (±)-*N*-(((2*R*,3*S*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxiran-2-yl)methylene)-2-phenylaziridin-1-amine 556a and (±)-*N*-(((2*R*,3*S*)-3-((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-methyloxiran-2-yl)methylene)-2-phenylaziridin-1-amine 556b



556a **556b**

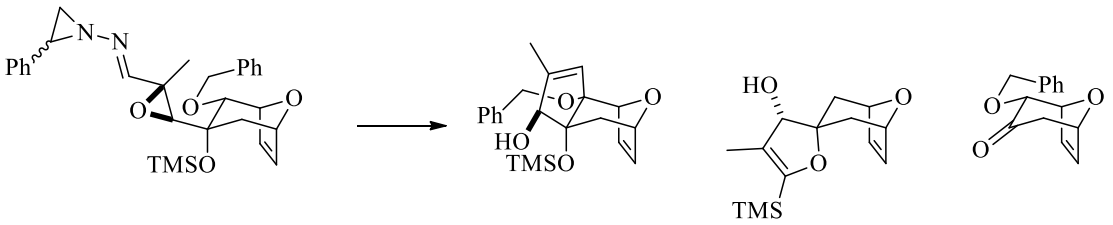
Novel compounds prepared using a modified literature procedure.[166b]

To a solution of **555** (250 mg, 0.640 mmol) in CH_2Cl_2 (9 mL) at 0 °C, $NaHCO_3$ (521 mg, 6.20 mmol) was added followed by **421** (239 mg, 1.23 mmol). The reaction was stirred at 0 °C for 2 h before being washed with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **556a** and **556b** (285 mg, 88%, 1:1 d.r.) as a yellow oil. Analytical data for **556a** (Absolute stereochemistry at C-11 arbitrarily assigned). R_f 0.14 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 3060, 3031, 2960, 2917, 2870, 1637, 1494, 1243, 1144, 1101, 899, 835, 694. δ_H (400 MHz, $CDCl_3$) 0.11 (s, 9H, $Si(CH_3)_3$), 1.55 (s, 3H, C*H*$_3$CO), 1.65 (d, 1H, ^2J 14.6 Hz, =CHCHCH_{2eq}), 1.99 (dd, 1H, ^2J 14.5 Hz, *J* 4.5 Hz, =CHCHCH_{2ax}), 2.36 (d, 1H, *J* 4.9 Hz, CH_2N), 2.41 (d, 1H,

J 7.2 Hz, C*H*$_2$N), 2.80 (s, 1H, C*H*OC), 3.05 (dd, 1H, *J* 7.8, 4.9 Hz, C*H*N), 3.62 (d, 1H, *J* 4.0 Hz, =CHCHC*H*), 4.62 (dd, 1H, *J* 4.0, 1.7 Hz, =CHC*H*CH), 4.66 (s, 2H, C*H*$_2$O), 4.68 (br. d, 1H, *J* 4.5 Hz, =CHC*H*CH$_2$), 6.18 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHCH$_2$), 6.24 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH), 7.23-7.37 (m, 11H, *H*$_{Ar}$, C*H*=N). δ_C (100 MHz, $CDCl_3$) 3.4 (3 x CH_3, Si(*C*H$_3$)$_3$), 13.4 (CH_3, *C*H$_3$CO), 37.1 (CH_2, =CHCHC*H*$_2$), 40.9 (CH_2, *C*H$_2$N), 44.0 (CH, *C*HN), 58.2 (C, CHO*C*), 69.8 (CH, *C*HOC), 72.1 (CH_2, *C*H$_2$O), 75.2 (C, *C*OSi), 77.8 (CH, =CH*C*HCH), 78.2 (CH, =CH*C*HCH$_2$), 79.5 (CH, =CHCH*C*H), 126.6 (2 x CH, *C*H$_{Ar}$), 127.6 (CH, *C*H$_{Ar}$), 128.3 (CH, *C*H$_{Ar}$), 128.5 (2 x CH, *C*H$_{Ar}$), 128.6 (2 x CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 131.9 (CH, =*C*HCHCH), 134.5 (CH, =*C*HCHCH$_2$), 137.9 (C, CH$_2$*C*CH$_{Ar}$), 138.5 (C, CH*C*CH$_{Ar}$), 163.5 (CH, *C*H=N). *m*/*z* HRMS calcd for $C_{29}H_{36}N_2NaO_4Si^+$ 527.2342, found 527.2355; (ES) 527 ([M+Na]$^+$, 100%), 528 ([M+Na+H]$^+$, 21). Analytical data for **556b** (Absolute stereochemistry at C-11 arbitrarily assigned). R_f 0.08 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 3032, 2952, 1636, 1455, 1244, 1146, 1100, 900, 835, 750, 694. δ_H (400 MHz, $CDCl_3$) 0.11 (s, 9H, Si(CH$_3$)$_3$), 1.55 (s, 3H, C*H*$_3$CO), 1.65 (d, 1H, ^2J 14.5 Hz, =CHCHC*H*$_{2eq}$), 1.99 (dt, 1H, ^2J 14.5 Hz, *J* 2.3 Hz, =CHCHC*H*$_{2ax}$), 2.37 (d, 1H, *J* 5.0 Hz, C*H*$_2$N), 2.46 (d, 1H, *J* 7.7 Hz, C*H*$_2$N), 2.81 (s, 1H, C*H*OC), 3.01 (dd, 1H, *J* 7.7, 4.9 Hz, C*H*N), 3.62 (d, 1H, *J* 4.0 Hz, =CHCHC*H*), 4.62 (dd, 1H, *J* 3.9, 1.3 Hz, =CHC*H*CH), 4.66 (d, 2H, ^2J 2.9 Hz, C*H*$_2$O), 4.68 (br. d, 1H, *J* 4.4 Hz, =CHC*H*CH$_2$), 6.18 (dd, 1H, *J* 6.1, 1.4 Hz, =CHCHCH$_2$), 6.24 (dd, 1H, *J* 6.1, 1.5 Hz, =CHCHCH), 7.22-7.38 (m, 11H, *H*$_{Ar}$, C*H*=N). δ_C (100 MHz, $CDCl_3$) 3.4 (3 x CH_3, Si(*C*H$_3$)$_3$), 13.4 (CH_3, *C*H$_3$CO), 37.1 (CH_2, =CHCH*C*H$_2$), 40.5 (CH_2, *C*H$_2$N), 44.6 (CH, *C*HN), 58.2 (C, CHO*C*), 69.8 (CH, *C*HOC), 72.1 (CH_2, *C*H$_2$O), 75.2 (C, *C*OSi), 77.8 (CH, =CH*C*HCH), 78.2 (CH, =CH*C*HCH$_2$), 79.5 (CH, =CHCH*C*H), 126.6 (2 x CH, *C*H$_{Ar}$), 127.6 (CH, *C*H$_{Ar}$), 128.3 (CH, *C*H$_{Ar}$), 128.5 (2 x CH, *C*H$_{Ar}$), 128.6 (2 x CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 131.9 (CH, =*C*HCHCH), 134.5 (CH, =*C*HCHCH$_2$), 138.0 (C, CH$_2$*C*CH$_{Ar}$), 138.4 (C, CH*C*CH$_{Ar}$), 163.6 (CH, *C*H=N). *m*/*z* HRMS calcd for $C_{29}H_{36}N_2NaO_4Si^+$ 527.2342, found

527.2349; (ES) 395 ([M+Na-(N_2CH_2CHPh)]$^+$, 3%), 527 ([M+Na]$^+$, 100), 528 ([M+Na+H]$^+$, 16).

Thermolysis of 556



558 **559** **544**

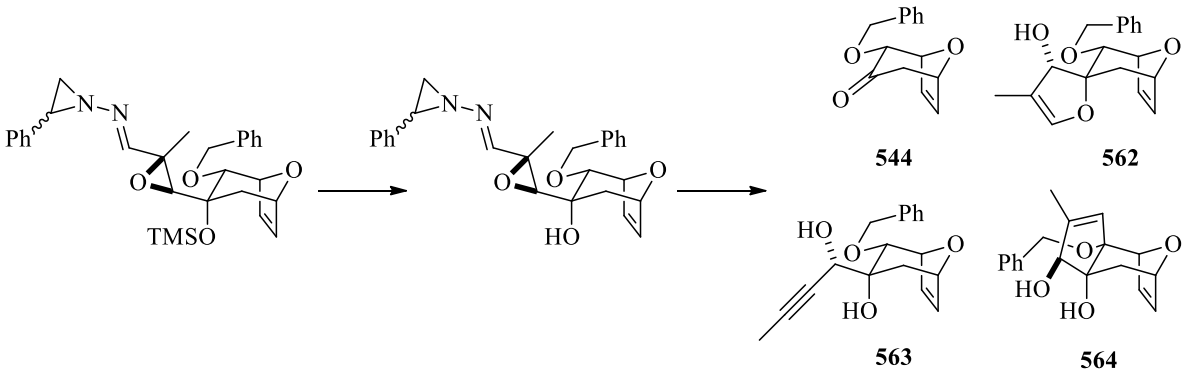
Novel compounds prepared using a modified literature procedure.[55]

Reaction was performed under an argon atmosphere.

A solution of **556** (55 mg, 0.110 mmol) in toluene (22 mL) was heated to reflux for 3 h. After this time the toluene was evaporated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 85:15) to afford **558**, **559** and **544** as a 2:1:1 mixture (79% combined). Analytical data for **558**. m.p. 94-97 °C. R_f 0.32 (petrol/EtOAc 75:25). υ_{max} neat/cm^{-1} 3487, 3423, 3028, 2940, 1246, 1131, 1111, 1091, 1066, 907, 834, 743. δ_H (400 MHz, $CDCl_3$) 0.09 (s, 9H, Si(CH_3)$_3$), 1.56 (dd, 1H, ^2J 14.1 Hz, J 1.3 Hz, =CHCHCH_{2eq}), 1.87 (s, 3H, =CCH_3), 2.05 (d, 1H, J 8.0 Hz, OH), 2.21 (dd, 1H, ^2J 14.1 Hz, J 5.3 Hz, =CHCHCH_{2ax}), 4.42 (d, 1H, ^2J 11.6 Hz, CH_2O), 4.47 (d, 1H, J 6.9 Hz, =CCHOH), 4.50-4.55 (m, 2H, =CHCHC, CH_2O), 4.73 (br. d, 1H, J 5.2 Hz, =CHCHCH_2), 5.51-5.61 (m, 1H, C=CH), 6.21 (dd, 1H, J 6.0, 1.5 Hz, =CHCHCH_2), 6.31 (dd, 1H, J 6.0 , 1.7 Hz, =CHCHC), 7.19-7.42 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 2.7 (3 x CH_3, Si(CH_3)$_3$), 14.3 (CH_3, =CCH_3), 33.5 (CH_2, =CHCHCH_2), 66.5 (CH_2, CH_2O), 77.8 (CH, =CHCHCH$_2$), 81.1 (CH, =CHCHC), 83.7 (C, =CHCHC), 84.2 (C, COH), 86.2 (CH, CHOH), 127.3 (2 x CH, CH_{Ar}), 128.1 (CH, CH_{Ar}), 128.4 (2 x CH, C=CH), 131.7 (CH, =CHCHC), 133.7 (CH, =CHCHCH$_2$), 140.1 (C,

CCH_{Ar}), 146.9 (C, *C*=CH). *m*/*z* HRMS calcd for $C_{21}H_{28}NaO_4Si^+$ 395.1655, found 395.1654; (ES) 395 ($[M+Na]^+$, 100%), 396 ($[M+Na+H]^+$, 22).

Preparation of (±)-(1*S*,2*R*,2'*R*,3'*S*,5*S*)-2-(benzyloxy)-4'-methyl-3'*H*-8-oxaspiro[bicyclo[3.2.1]oct[6]ene-3,2'-furan]-3'-ol 562 and (±)-(1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-((*S*)-1-hydroxybut-2-yn-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 563 and (±)-(1*S*,3a*R*,4*S*,7*S*,8a*R*)-3a-(benzyloxy)-2-methyl-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulene-1,8a-diol 564



Novel compounds prepared using a modified literature procedure.[55]

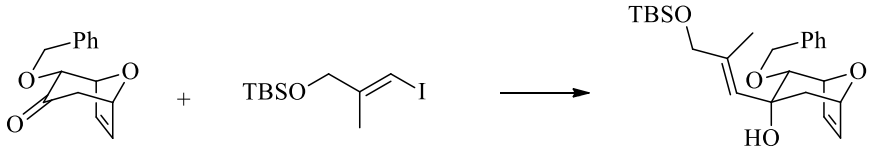
Reaction was performed under an argon atmosphere.

To a solution of **556** (241 mg, 0.480 mmol) in THF (10 mL) at room temperature, TBAF (1 M, 0.580 mL, 0.580 mmol) was added. The reaction was stirred at room temperature for 3 h before being quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20, deactivated with 0.1% Et_3N) to afford **560** as an impure mixture of diastereoisomers. A solution of the crude **560** in toluene (74 mL) was heated to reflux for 3 h. After this time the toluene was evaporated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 75:25→50:50) to afford **544** (13 mg, 11%) as a clear oil followed by **562** (28 mg, 20%) as an off-white solid followed by **563** (8.5 mg, 6%) as a clear oil followed by **564** (27 mg, 18%) as an off-white solid.

Analytical data for **562**. m.p. 109-111 °C. R_f 0.31 (petrol/EtOAc 75:25). υ_{max} neat/cm^{-1} 3442, 2937, 1675, 1675, 1454, 1048, 982, 732, 696. δ_H (400 MHz, $CDCl_3$) 1.66 (d, 1H, *J* 11.9 Hz, O*H*), 1.66 (br. s, 3H, =CCH_3), 1.74 (dd, 1H, ^2J 14.2 Hz, *J* 1.1 Hz, =CHCHCH_{2eq}), 1.95 (dd, 1H, ^2J 14.3 Hz, *J* 4.0 Hz, =CHCHCH_{2ax}), 4.08 (d, 1H, *J* 11.9 Hz, C*H*OH), 4.27 (d, 1H, *J* 3.9 Hz, =CHCHC*H*), 4.63 (d, 1H, ^2J 11.8 Hz, CH_2O), 4.72-4.77 (m, 3H, =CHC*H*CH, =CHC*H*CH_2, CH_2O), 6.13 (s, 1H, C=C*H*), 6.24 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH), 6.36 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH_2), 7.30-7.36 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 8.8 (CH_3, =C*C*H_3), 39.8 (CH_2, =CHCH*C*H_2), 72.0 (CH_2, CH_2O), 75.8 (CH, =CHCH*C*H), 77.1 (CH, =CH*C*HCH_2), 78.6 (CH, =CH*C*HCH), 86.9 (CH, *C*HOH), 87.2 (C, *C*O), 111.9 (C, *C*=CH), 128.1 (2 x CH, *C*H_{Ar}), 128.3 (CH, *C*H_{Ar}), 128.8 (2 x CH, *C*H_{Ar}), 131.7 (CH, =*C*HCHCH_2), 134.7 (CH, =*C*HCHCH), 138.1 (C, *C*CH_{Ar}), 142.9 (CH, C=*C*H). *m*/*z* HRMS calcd for $C_{18}H_{20}NaO_4^+$ 323.1259, found 323.1267; (ES) 323 ($[M+Na]^+$, 100%), 324 ($[M+Na+H]^+$, 12). Analytical data for **563**. R_f 0.22 (petrol/EtOAc 50:50). υ_{max} neat/cm^{-1} 3416, 2922, 2868, 1719, 1050, 1454, 1050, 727, 697. δ_H (400 MHz, $CDCl_3$) 1.70 (d, 1H, ^2J 14.6 Hz, =CHCHCH_{2eq}), 1.86 (d, 3H, ^4J 2.2 Hz, ≡CCH_3), 2.26 (dd, 1H, ^2J 14.5 Hz, *J* 4.6 Hz, =CHCHCH_{2ax}), 3.92 (d, 1H, *J* 4.5 Hz, =CHCHC*H*), 4.14 (q, 1H, ^4J 2.0 Hz, C*H*OH), 4.62-4.73 (m, 3H, =CHC*H*CH, CH_2O), 4.82 (d, 1H, *J* 4.6 Hz, =CHC*H*CH_2), 6.25 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHCH), 6.31 (dd, 1H, *J* 6.1, 1.6 Hz, =C*H*CHCH_2), 7.34-7.38 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 4.0 (CH_3, ≡C*C*H_3), 31.4 (CH_2, =CHCHC*H*$_2$), 70.0 (CH, *C*HOH), 73.0 (CH_2, *C*H_2O), 74.6 (CH, =CHCH*C*H), 75.2 (C, *C*OH), 76.6 (C, ≡*C*CH_3), 77.0 (CH, =CH*C*HCH), 78.7 (CH, =CH*C*HCH_2), 84.0 (C, *C*≡CCH_3), 128.3 (2 x CH, *C*H_{Ar}), 128.5 (CH, *C*H_{Ar}), 128.8 (2 x CH, *C*H_{Ar}), 130.6 (CH, =*C*HCHCH), 136.1 (CH, =*C*HCHCH_2), 137.5 (C, *C*CH_{Ar}). *m*/*z* HRMS calcd for $C_{18}H_{20}NaO_4^+$ 323.1259, found 323.1258; (ES) 323 ($[M+Na]^+$, 100%), 324 ($[M+Na+H]^+$, 19). Analytical data for **564**. m.p. 93-95 °C. R_f 0.16 (petrol/EtOAc 50:50). υ_{max} neat/cm^{-1} 3508, 3370, 3035, 2937, 2875, 2851, 1316, 1051, 882, 737, 696. δ_H (400 MHz, $CDCl_3$) 1.55 (dd, 1H, ^2J 14.7 Hz, *J* 1.2 Hz, =CHCHCH_{2eq}), 1.86 (t, 3H, ^4J 1.3 Hz, =CCH_3),

2.10 (dd, 1H, ^{2}J 14.7 Hz, J 4.5 Hz, =CHCHCH_{2ax}), 4.43 (d, 1H, ^{2}J 11.2 Hz, CH_2O), 4.49 (d, 1H, ^{2}J 11.2 Hz, CH_2O), 4.54 (br. s, 1H, C*H*OH), 4.69 (d, 1H, J 1.7 Hz, =CHC*H*C), 4.76 (d, 1H, J 4.4 Hz, =CHC*H*CH$_2$), 5.64-5.69 (m, 1H, C=C*H*), 6.25 (dd, 1H, J 6.1, 1.6 Hz, =C*H*CHCH$_2$), 6.31 (dd, 1H, J 6.1, 1.6 Hz, =C*H*CHC), 7.24-7.38 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3, =C*C*H$_3$), 31.3 (CH_2, =CHCH*C*H$_2$), 66.4 (CH_2, *C*H$_2$O), 78.1 (CH, =CH*C*HCH$_2$), 79.5 (CH, =CH*C*HC), 81.7 (C, *C*OH), 81.9 (C, =CHCH*C*), 86.4 (CH, *C*HOH), 125.3 (CH, C=*C*H), 127.6 (2 x CH, *C*H$_{Ar}$), 127.9 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 130.7 (CH, =*C*HCHCH$_2$), 135.1 (CH, =*C*HCHC), 138.7 (C, *C*CH$_{Ar}$), 149.7 (C, *C*=CH). *m*/*z* HRMS calcd for $C_{18}H_{20}NaO_4^+$ 323.1259, found 323.1244; (ES) 323 ([M+Na]$^+$, 100%), 324 ([M+Na+H]$^+$, 17).

Preparation of (±)-(1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-((*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylprop-1-en-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 568



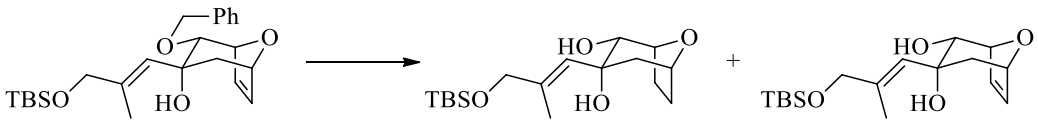
A novel compound prepared using a novel procedure.

Reaction was performed under an argon atmosphere.

To a solution of **384** (2.04 g, 6.53 mmol) in THF (43 mL) at -78 °C, ^{n}BuLi (1.57 M, 4.16 mL, 6.53 mmol) was added drop-wise. The resulting mixture was stirred at -78 °C for 30 min. A solution of **378** (1.00 g, 4.35 mmol) in THF (9 mL) was added in one portion before the reaction was stirred at room temperature for 24 h. The reaction was quenched with NH_4Cl (30 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford **568** (1.12 g, 62%) as a clear yellow oil. R_f 0.19 (hexane/EtOAc 90:10). υ_{max} neat/cm^{-1} 3552, 2953,

2929, 2856, 1251, 1055, 834, 696. δ_H (400 MHz, $CDCl_3$) 0.07 (s, 6H, Si(CH_3)$_2$), 0.92 (s, 9H, SiC(CH_3)$_3$), 1.76 (d, 3H, ^4J 0.9 Hz, =CCH_3), 1.92 (d, 1H, ^2J 14.6 Hz, =CHCHCH_{2eq}), 2.06 (ddd, 1H, ^2J 14.6 Hz, J 4.4 Hz, ^4J 1.4 Hz, =CHCHCH_{2ax}), 2.96 (d, 1H, ^4J 1.2 Hz, O*H*), 3.79 (d, 1H, J 4.4 Hz, =CHCHC*H*), 3.93 (d, 2H, ^4J 0.9 Hz, =CCH_2), 4.59 (d, 1H, ^2J 11.8 Hz, OCH_2), 4.63 (dd, 1H, J 4.4, 1.7 Hz, =CHC*H*CH), 4.70 (d, 1H, ^2J 11.8 Hz, OCH_2), 4.74 (m, 1H, =CHC*H*CH$_2$), 5.47 (app. dd, 1H, ^4J 2.7, 1.4 Hz, C=C*H*), 6.26 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH), 6.32 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH$_2$), 7.27-7.38 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) -5.0 (2 x CH_3, Si(CH_3)$_2$), 14.5 (CH_3, =CCH_3), 18.6 (C, SiC(CH_3)$_3$), 26.2 (3 x CH_3, SiC(CH_3)$_3$), 38.4 (CH_2, =CHCHCH_2), 68.9 (CH_2, =CCH_2), 73.1 (CH_2, OCH_2), 73.6 (C, *C*OH), 78.5 (CH, =CHCH*C*H), 79.0 (CH, =CH*C*HCH$_2$), 79.4 (CH, =CHCHC*H*), 128.1, (2 x CH, *C*H$_{Ar}$), 128.2 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 130.9 (CH, =*C*HCHCH), 133.2 (CH, C=*C*H), 135.8 (C, *C*=CH), 135.9 (CH, =*C*HCHCH$_2$), 138.0 (C, *C*CH$_{Ar}$). *m*/*z* HRMS calcd for $C_{24}H_{36}NaO_4Si^+$ 439.2281, found 439.2271; (ES) 439 ([M+Na]$^+$, 100%), 440 ([M+Na+H]$^+$, 36).

Preparation of (±)-(1*S*,2*R*,3*R*,5*R*)-3-((*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylprop-1-en-1-yl)-8-oxabicyclo[3.2.1]octane-2,3-diol 570 and (±)-(1*S*,2*R*,3*R*,5*S*)-3-((*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylprop-1-en-1-yl)-8-oxabicyclo[3.2.1]oct-6-ene-2,3-diol 569



570 **569**

Novel compounds prepared using a modified literature procedure.[206]

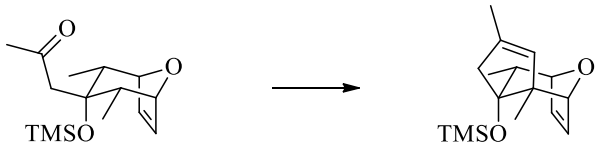
Reaction was performed under an argon atmosphere.

NH_3 (6 mL) was condensed into a flask containing **568** (70 mg, 0.170 mmol). Sodium was added portion-wise until the blue colour remained for 30 min. The reaction was quenched

with NH_4Cl (200 mg) before the NH_3 was allowed to evaporate. H_2O (25 mL) was added and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 80:20) to afford **570** (16 mg, 28%) as a clear colourless oil followed by **569** (18 mg, 32%) as a clear, colourless oil. Analytical data for **570**. R_f 0.17 (hexane 80:20). υ_{max} neat/cm^{-1} 3445, 3366, 3292, 2949, 2928, 2885, 2857, 1462, 1253, 1109, 1055, 1040, 834, 775. δ_H (400 MHz, $CDCl_3$) 0.06 (s, 6H, Si(C*H*$_3$)$_2$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 1.70-1.78 (m, 1H, C*H*$_2$CHCH), 1.81 (d, 3H, ^4J 1.1 Hz, =CC*H*$_3$), 1.82-1.92 (m, 1H, C*H*$_2$CHCH$_2$), 1.95-2.02 (m, 2H, CH$_2$CHC*H*$_2$), 2.12-2.26 (m, 1H, C*H*$_2$CHCH$_2$), 2.26-2.38 (m, 2H, C*H*$_2$CHCH$_2$, CHO*H*), 2.51 (s, 1H, CO*H*), 3.80 (app. t, 1H, *J* 5.1 Hz, C*H*OH), 3.93 (br. s, 2H, =CC*H*$_2$), 4.23 (dd, 1H, *J* 7.5, 4.4 Hz, CH$_2$C*H*CH), 4.33-4.37 (m, 1H, CH$_2$C*H*CH$_2$), 5.43 (dd, 1H, ^4J 2.8, 1.3 Hz, C=C*H*). δ_C (100 MHz, $CDCl_3$) -5.0 (2 x CH_3, Si(*C*H$_3$)$_2$), 14.4 (CH_3, =C*C*H$_3$), 18.6 (C, Si*C*(CH$_3$)$_3$), 24.1 (CH_2, *C*H$_2$CHCH), 26.1 (3 x CH_3, SiC(*C*H$_3$)$_3$), 28.3 (CH_2, *C*H$_2$CHCH$_2$), 42.3 (CH_2, CH$_2$CH*C*H$_2$), 68.8 (CH, =C*C*H$_2$), 73.8 (CH, *C*HOH), 73.9 (C, *C*OH), 74.7 (CH, CH$_2$*C*HCH$_2$), 77.0 (CH, CH$_2$*C*HCH), 130.6 (CH, C=*C*H), 137.9 (C, *C*=CH). *m*/*z* HRMS calcd for $C_{17}H_{32}NaO_4Si^+$ 351.1968, found 351.1953; (ES) 351 ([M+Na]$^+$, 100%).. Analytical data for **569**. R_f 0.09 (hexane 80:20). υ_{max} neat/cm^{-1} 3539, 3390, 3256, 2951, 2927, 2857, 1460, 1255, 1105, 1053, 834, 775, 683. δ_H (400 MHz, $CDCl_3$) 0.05 (s, 6H, Si(C*H*$_3$)$_2$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 1.79 (d, 3H, ^4J 1.0 Hz, =CC*H*$_3$), 2.04 (dd, 1H, ^2J 15.0 Hz, *J* 0.8 Hz, =CHCHC*H*$_{2eq}$), 2.23 (dd, 1H, ^2J 15.0 Hz, *J* 4.4 Hz, =CHCHC*H*$_{2ax}$), 2.48 (s, 1H, CO*H*), 2.82 (d, 1H, *J* 7.9 Hz, CHO*H*), 3.89 (dd, 1H, *J* 7.8, 4.4 Hz, C*H*OH), 3.95 (d, 2H, ^4J 0.9 Hz, =CC*H*$_2$), 4.67 (dd, 1H, *J* 4.4, 1.8 Hz, =CHC*H*CH), 4.75-4.81 (m, 1H, =CHC*H*CH$_2$), 5.39 (br. s, 1H, C=C*H*), 6.48 (dd, 1H, *J* 6.1, 1.8 Hz, =C*H*CHCH$_2$), 6.52 (dd, 1H, *J* 6.1 1.8 Hz, =C*H*CHCH). δ_C (100 MHz, $CDCl_3$) -5.0 (2 x CH_3, Si(*C*H$_3$)$_2$), 14.6 (CH_3, =C*C*H$_3$), 18.6 (C, Si*C*(CH$_3$)$_3$), 26.1 (3 x CH_3, SiC(*C*H$_3$)$_3$), 39.7 (CH_2, =CHCH*C*H$_2$), 68.8 (CH_2, =C*C*H$_2$), 73.2 (CH, *C*HOH), 74.9 (C, *C*OH), 78.5 (CH, =CH*C*HCH$_2$), 80.6 (CH, =CH*C*HCH), 130.0 (CH,

C=*C*H), 133.9 (CH, =*C*HCHCH), 136.9 (CH, =*C*HCHCH$_2$), 137.8 (C, *C*=CH). *m*/*z* HRMS calcd for $C_{17}H_{30}NaO_4Si^+$ 349.1816, found 349.1811; (ES) 349 ([M+Na]$^+$, 100%).

Preparation of (±)-trimethyl(((3a*R*,4*R*,7*S*,8*R*,8a*R*)-2,3a,8-trimethyl-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulen-8a-yl)oxy)silane 371



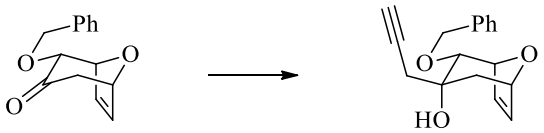
A known compound[97] prepared using a literature procedure.[103b]

Reaction was performed under an argon atmosphere.

To a solution of (diazomethyl)trimethylsilane (2 M, 0.140 mL, 0.270 mmol) in THF (6.9 mL) at -78 °C, ^{n}BuLi (2.14 M, 0.130 mL, 0.290 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before a solution of **459** (50 mg, 0.180 mmol) in THF (2.1 mL) was added drop-wise. The resulting mixture was stirred at -78 °C for 1 h, then stirred at room temperature for 3 h, before being quenched with H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Ethyl Acetate 98:2) to afford **371** (32 mg, 64%) as a clear, colourless oil. υ_{max} neat/cm^{-1} 2960, 2922, 1248, 1093, 901. δ_H (400 MHz, $CDCl_3$) 0.08 (s, 9H, Si(C*H*$_3$)$_3$), 0.78 (s, 3H, C*H*$_3$C), 0.81 (d, 3H, *J* 7.3 Hz, C*H*$_3$CH), 1.67 (s, 3H, =CC*H*$_3$), 1.90 (qd, 1H, *J* 7.3, 3.5 Hz, CH$_3$C*H*), 1.98 (d, 1H, ^{2}*J* 14.8 Hz, =CC*H*$_2$), 2.40 (d, 1H, ^{2}*J* 14.8 Hz, =CC*H*$_2$), 4.33 (dd, 1H, *J* 3.4, 1.6 Hz, =CHC*H*CH), 4.36 (d, 1H, *J* 1.3 Hz, =CHC*H*C), 5.37 (s, 1H, C=C*H*), 6.15 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*CHC), 6.20 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*CHCH). δ_C (100 MHz, $CDCl_3$) 2.5 (3 x CH$_3$, Si,(*C*H$_3$)$_3$), 12.3 (CH$_3$, *C*H$_3$CH), 17.7 (CH$_3$, =C*C*H$_3$), 19.9 (CH$_3$, *C*H$_3$C), 40.0 (CH, CH$_3$*C*H), 49.1 (CH$_2$, =C*C*H$_2$), 52.0 (C, *C*CHO), 82.6 (CH, =CH*C*HCH), 83.7 (CH, =CH*C*HC), 84.5 (C, *C*OSi), 132.1 (CH, =*C*HCHC), 132.7 (CH, =*C*HCHCH), 133.4

(CH, C=*C*H), 136.0 (C, *C*=CH). Literature values:[97] υ_{max} (neat) 2916, 1247, 1041 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.09 (s, 9H), 0.80 (s, 3H), 0.85 (d, *J* 7.3 Hz, 3H), 1.58 (s, 3H), 1.87-1.95 (m, 1H), 2.0 (d, *J* 14.8 Hz, 1H), 2.42 (d, *J* 14.8 Hz, 1H), 4.35 (q, *J* 3.4, 1.6 Hz, 2H), 4.37 (d, *J* 1.0 Hz, 1H), 5.39 (s, 1H), 6.15-6.21 (m, 2H); δ_C (90 MHz, $CDCl_3$) 2.7 (CH_3), 12.5 (CH_3), 17.9 (CH_3), 40.2 (CH), 49.3 (CH_2), 52.2 (C), 82.0 (CH), 83.9 (CH), 84.7 (C), 132.3 (CH), 132.9 (CH), 133.7 (CH), 136.2 (C); *m*/*z* (EI) 278 (M^+; 14%), 183 (100), 73 (98); HRMS calcd for $C_{16}H_{26}O_2SiNa^+$ 301.1594, found 301.1582.

Preparation of (±)-(1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-(prop-2-yn-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol 577



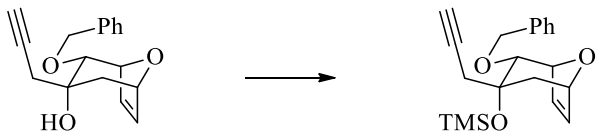
A novel compound prepared using a literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution suspension of Mg (209 mg, 8.70 mmol) and $HgCl_2$ (35 mg, 0.130 mmol) in Et_2O (7 mL) at room temperature, propargyl bromide (1.31 g, 1.00 mL, 8.70 mmol) was added drop-wise, at a rate to maintain a gentle reflux. Upon complete dissolution, the reaction was cooled to 0 °C and a solution of **544** (1.00 g, 4.35 mmol) in Et_2O (8 mL) was added. A thick emulsion was formed so additional Et_2O (5 mL) was added to enable stirring. The reaction was allowed to warm to room temperature over 2 h and was allowed to stir at room temperature for 24 h. The reaction was quenched with NH_4Cl (25 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 75:25) to afford **557** (981 mg, 84%) as a white solid. m.p. 60-62 °C. R_f 0.25 (hexane/EtOAc 75:25). υ_{max} neat/cm^{-1} 3539, 3290, 3031, 2946, 1725, 1454,

1349, 1087, 1052, 878, 723, 697. δ_H (400 MHz, $CDCl_3$) 1.74 (d, 1H, ^2J 14.3 Hz, =CHCHCH_{2eq}), 2.03 (t, 1H, ^4J 2.7 Hz, ≡C*H*), 2.18-2.29 (dd, 2H, CHCHCH_{2ax}, ≡CCH_2), 2.23 (dd, 1H, ^2J 16.7 Hz, ^4J 2.7 Hz, ≡CCH_2), 2.90 (d, 1H, ^4J 1.6 Hz, O*H*), 3.91 (d, 1H, *J* 4.3 Hz, =CHCHC*H*), 4.67 (dd, 1H, *J* 4.3, 1.7 Hz, =CHC*H*CH), 4.69-4.78 (m, 3H, CH_2O, =CHC*H*CH_2), 6.25 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH), 6.32 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH_2), 7.33-7.39 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 33.6 (CH_2, ≡C*C*H_2), 35.8 (CH_2, =CHCH*C*H_2), 71.2 (CH, C≡*C*H), 72.2 (C, *C*OH), 73.2 (CH_2, *C*H_2O), 76.3 (CH, =CHCH*C*H), 77.4 (CH, =CH*C*HCH), 78.7 (CH, =CH*C*HCH), 80.9 (C, *C*≡CH), 128.2 (2 x CH, *C*H_{Ar}), 128.5 (CH, *C*H_{Ar}), 128.8 (2 x CH, *C*H_{Ar}), 130.7 (CH, =*C*HCHCH), 136.0 (CH, =*C*HCHCH_2), 137.8 (C, *C*CH_{Ar}). *m*/*z* HRMS calcd for $C_{17}H_{18}NaO_3^+$ 293.1154, found 293.1142; (ES) 293 ($[M+Na]^+$, 100).

Preparation of (±)-(((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-(prop-2-yn-1-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)oxy)trimethylsilane 578



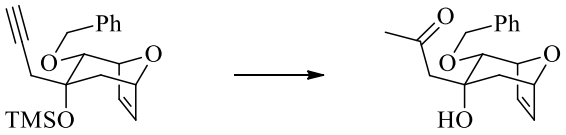
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **577** (35 mg, 0.130 mmol) and Et_3N (53 mg, 0.070 mL, 0.520 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C, TMSOTf (76 mg, 0.060 mL, 0.340 mmol) was added drop-wise. The reaction was allowed to warm to room temperature and was stirred at room temperature for 4 h before being quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford **578** (39 mg, 87%) as a pale yellow oil. R_f 0.25 (hexane/EtOAc

75:25). υ_{max} neat/cm^{-1} 3307, 3032, 2951, 1243, 1135, 1105, 1078, 834, 750, 724, 697. δ_H (400 MHz, $CDCl_3$) 0.05 (s, 9H, Si(CH_3)$_3$), 1.74 (dd, 1H, ^2J 14.0 Hz, J 1.1 Hz, =CHCHCH_{2eq}), 2.03 (t, 1H, ^4J 2.7 Hz, C≡CH), 2.21 (dd, 1H, ^2J 14.0 Hz, J 4.2 Hz, =CHCHCH_{2ax}), 2.35 (dd, 1H, ^2J 16.4 Hz, ^4J 2.7 Hz, ≡CCH_2), 2.41 (dd, 1H, ^2J 16.4 Hz, ^4J 2.6 Hz, ≡CCH_2), 3.77 (d, 1H, J 3.8 Hz, =CHCHCH), 4.60-4.77 (m, 4H, =CHCHCH, =CHCHCH$_2$, CH_2O), 6.15-6.24 (m, 2H, =CH), 7.22-7.49 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 2.9 (3 x CH_3, Si(CH_3)$_3$), 31.5 (CH_2, ≡CCH_2), 39.2 (CH_2, =CHCHCH_2), 71.5 (CH, C≡CH), 72.9 (CH_2, CH_2O), 76.2 (C, COSi), 77.5 (CH, =CHCHCH), 78.3 (CH, =CHCHCH), 78.9 (CH, =CHCHCH$_2$), 81.2 (C, C≡CH), 128.2 (CH, CH_{Ar}), 128.6 (2 x CH, CH_{Ar}), 128.7 (2 x CH, CH_{Ar}), 131.5 (CH, =CHCHCH), 134.6 (CH, =CHCHCH$_2$), 138.2 (C, CCH$_{Ar}$). *m/z* HRMS calcd for $C_{20}H_{26}NaO_3Si^+$ 365.1549, found 365.1552; (ES) 365 ([M+Na]$^+$, 100).

Preparation of (±)-1-((1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)propan-2-one 579

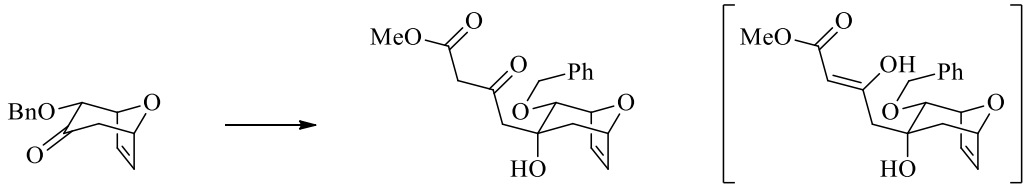


A novel compound prepared using a literature compound.[207]

To a solution of **578** (50 mg, 0.150 mmol) and $HgSO_4$ (11.1 mg, 0.040 mmol) in MeOH (0.6 mL) at 0 °C, H_2SO_4 (0.15 mL of a 10% v/v aqueous solution) was added drop-wise. The reaction was allowed to warm to room temperature and stirred at room temperature for 6 h. The reaction was adjusted to pH 7 with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 75:25→70:30) to afford **579** (13 mg, 29%) as a clear, colourless oil. R_f 0.11 (hexane/EtOAc 75:25). υ_{max} neat/cm^{-1} 3544, 2956, 1699, 1352, 1067, 1052, 882, 725, 698. δ_H

(400 MHz, $CDCl_3$) 1.80 (dd, 1H, ^2J 14.5 Hz, J 0.6 Hz, =CHCHCH_{2eq}), 2.04 (ddd, 1H, ^2J 14.4 Hz, J 4.4 Hz, ^4J 1.3 Hz, =CHCHCH_{2ax}), 2.11 (s, 3H, CH_3C=O), 2.32 (d, 1H, ^2J 13.5 Hz, CH_2C=O), 2.60 (d, 1H, ^2J 13.5 Hz, CH_2C=O), 3.03 (d, 1H, ^4J 1.2 Hz, OH), 3.68 (d, 1H, J 4.2 Hz, =CHCHCH), 4.60 (d, 1H, ^2J 11.5 Hz, CH_2O), 4.67-4.72 (m, 2H, CH_2O, =CHCHCH), 4.74 (br. d, 1H, J 4.4 Hz, =CHCHCH_2), 6.26 (dd, 1H, J 6.1, 1.7 Hz, =CHCHCH), 6.32 (dd, 1H, J 6.1, 1.7 Hz, =CHCHCH_2), 7.31-7.40 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 32.6 (CH_3, CH$_3$C=O), 37.7 (CH_2, =CHCHCH$_2$), 56.7 (CH_2, CH$_2$C=O), 72.6 (C, COSi), 72.7 (CH_2, CH$_2$O), 77.3 (CH, =CHCHCH), 77.9 (CH, =CHCHCH), 78.6 (CH, =CHCHCH$_2$), 128.5 (2 x CH, CH$_{Ar}$), 128.5 (CH, CH$_{Ar}$), 128.8 (2 x CH, CH$_{Ar}$), 131.0 (CH, =CHCHCH), 136.1 (CH, =CHCHCH$_2$), 137.7 (C, CCH$_{Ar}$), 207.9 (C, C=O). m/z HRMS calcd for $C_{17}H_{20}NaO_4^+$ 311.1259, found 311.1251; (ES) 253 ([M+Na-(CH$_3$C(O=)CH$_2$)]$^+$, 81%), 311 ([M+Na]$^+$, 100).

Preparation of (±)-Methyl 4-((1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-3-oxobutanoate 581



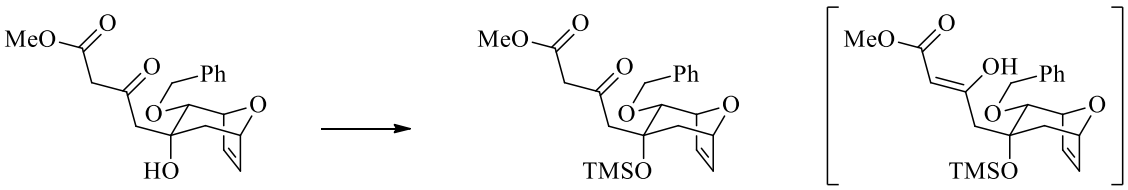
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of diisopropylamine (1.76 g, 2.44 mL, 17.4 mmol) in THF (18 mL) at 0 °C, ^{n}BuLi (1.6 M, 10.9 mL, 17.4 mmol) was added drop-wise. The resulting solution was stirred at 0 °C for 30 min before methyl acetoacetate **500** (1.01 g, 0.940 mL, 8.70 mmol) was added drop-wise. The reaction was stirred for 1 h at 0 °C before a solution of **544** (500 mg, 2.17 mmol) in THF (4 mL) was added in one portion. The reaction was stirred at room temperature for 20 h before being quenched with HCl (20 mL of a 1 M aqueous solution) and

extracted with Et_2O (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 70:30→60:40) to afford **581** (547 mg, 70%) as a bright yellow oil. R_f 0.09 (hexane/EtOAc 75:25). υ_{max} neat/cm^{-1} 3535, 2951, 1742, 1704, 1322, 1052, 726, 699. ^1H NMR indicates that **581** exists in ~6:1 keto:enol ratio. The data reported is of the major keto tautomer with identifiable enol peaks following. δ_H (400 MHz, $CDCl_3$) 1.80 (d, 1H, ^2J 14.4 Hz, =CHCHCH_{2eq}), 2.04 (ddd, 1H, ^2J 14.4 Hz, J 4.4 Hz, ^4J 1.2 Hz, =CHCHCH_{2ax}), 2.41 (d, 1H, ^2J 13.3 Hz, CH_2C=O), 2.73 (d, 1H, ^2J 13.3 Hz, CH_2C=O), 3.46 (d, 1H, ^2J 15.9 Hz, CH_2CO_2Me), 3.54 (d, 1H, ^2J 15.9 Hz, CH_2CO_2Me), 3.66 (d, 1H, J 4.2 Hz, =CHCHC*H*), 3.68 (s, 3H, OCH_3), 4.61 (d, 1H, ^2J 11.6 Hz, CH_2O), 4.66-4.70 (m, 2H, =CHC*H*CH, CH_2O), 4.74 (d, 1H, J 4.4 Hz, =CHC*H*CH_2), 6.26 (dd, 1H, J 6.1, 1.7 Hz, =C*H*CHCH), 6.33 (dd, 1H, J 6.1, 1.7 Hz, =C*H*$CHCH_2$), 7.36 (m, 5H, H_{Ar}). Enol Peaks: 4.98 (s, 1H, C*H*=COH), 12.07 (s, 1H, CH=CO*H*). δ_C (100 MHz, $CDCl_3$) 37.8 (CH_2, =CHCH*C*H_2), 51.0 (CH_2, *C*H_2CO_2Me), 52.4 (CH_3, O*C*H_3), 56.1 (CH_2, *C*H_2C=O), 72.8 (CH_2, C*H*$_2$O), 77.3 (CH, =CH*C*HCH), 77.5 (C, *C*OH), 77.9 (CH, =CHCH*C*H), 78.6 (CH, =CH*C*HCH_2), 128.3 (2 x CH, *C*H_{Ar}), 128.6 (CH, *C*H_{Ar}), 128.9 (2 x CH, *C*H_{Ar}), 131.0 (CH, =*C*H), 136.3 (CH, =*C*H), 137.6 (C, *C*CH_{Ar}), 168.0 (C, *C*O_2Me), 201.7 (C, *C*=O). Enol Peaks: 92.3 (CH, *C*H=COH). *m*/*z* HRMS calcd for $C_{19}H_{22}NaO_6^+$ 369.1314, found 369.1330; (ES) 253 ([M-Bn], 47%), 369 ($[M+Na]^+$, 100%), 370 ($[M+Na+H]^+$, 33).

Preparation of (±)-Methyl 4-((1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-3-oxobutanoate 580



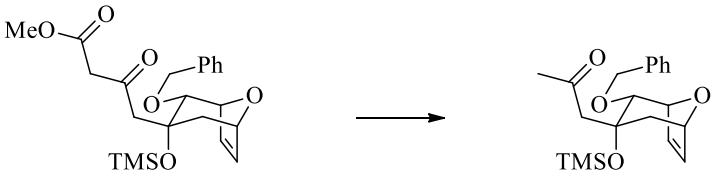
A novel compound prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a solution of **581** (393 mg, 1.10 mmol) and Et_3N (445 mg, 0.610 mL, 4.40 mmol) in CH_2Cl_2 (11 mL) at 0 °C, TMSOTf (636 mg, 0.520 mL, 2.86 mmol) was added drop-wise. The reaction was stirred at room temperature for 5 h before being quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and dried *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 85:15) to afford **580** (421 mg, 92%) as a bright yellow oil. R_f 0.11 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2952, 1747, 1718, 1650, 1626, 1242, 1077, 834, 750, 726, 698. ^{1}H NMR indicates that **580** exists in ~3:1 keto:enol ratio. The data reported is of the major keto tautomer with identifiable enol peaks following. δ_H (400 MHz, $CDCl_3$) 0.04 (s, 9H, Si(C*H*)$_3$), 1.80 (dd, 1H, ^2J 14.0 Hz, J 1.1 Hz, =CHCHCH_{2eq}), 2.09 (dd, 1H, ^2J 14.0 Hz, J 4.2 Hz, =CHCHCH_{2ax}), 2.56 (d, 1H, ^2J 15.9 Hz, CH_2C=O), 2.77 (d, 1H, ^2J 15.9 Hz, CH_2C=O), 3.31 (d, 1H, ^2J 15.7 Hz, CH_2CO$_2$Me), 3.36 (d, 1H, ^2J 15.7 Hz, CH_2CO$_2$Me), 3.68 (d, 1H, J 3.8 Hz, =CHCHC*H*), 3.71 (s, 3H, OCH_3), 4.57 (d, 1H, ^2J 11.7 Hz, CH_2O), 4.62 (dd, 1H, J 3.8, 1.4 Hz, =CHC*H*CH), 4.66-4.70 (m, 2H, =CHC*H*CH$_2$, CH_2O), 6.17 (app. qd, 2H, J 6.2, 1.5 Hz, =C*H*CHCH$_2$, =C*H*CHCH), 7.31-7.38 (m, 5H, H_{Ar}). Enol peaks: 1.65 (dd, 1H, ^2J 14.1 Hz, J 1.1 Hz, =CHCHCH_{2eq}), 2.18 (dd, 1H, ^2J 14.1 Hz, J 4.2 Hz, =CHCHCH_{2ax}), 2.31 (d, 1H, ^2J 13.2 Hz, CH_2C=O), 2.46 (d, 1H, ^2J 13.2 Hz, CH_2C=O), 4.93 (s, 1H, C*H*=COH), 12.08 (s, 1H, CH=O*H*). δ_C (100 MHz, $CDCl_3$) 3.1 (3 x CH_3, Si(*C*H$_3$)$_3$), 39.6 (CH_2, =CHCH*C*H$_2$), 50.8 (CH_2, *C*H$_2$CO$_2$Me), 52.4 (CH_3, OCH_3), 54.0 (CH_2, *C*H$_2$C=O), 72.4 (CH_2, *C*H$_2$O), 75.6 (C, *C*OSi), 77.4 (CH, =CH*C*HCH), 78.6 (CH, =CH*C*HCH$_2$), 78.7 (CH, =CHCH*C*H), 128.3 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 128.9 (2 x CH, *C*H$_{Ar}$), 131.6 (CH, =*C*HCHCH$_2$), 134.7 (CH, =*C*HCHCH), 138.0 (C, *C*CH$_{Ar}$), 167.6 (C, *C*O$_2$CH$_3$), 200.3 (C, *C*=O). Enol Peaks: 39.2 (CH_2, =CHCH*C*H$_2$), 47.6 (CH_2, *C*H$_2$C=O), 51.3 (CH_3, OCH_3), 92.6 (CH, *C*H=COH), 172.9 (C, *C*O$_2$Me), 174.8 (CH=*C*OH). *m*/*z* HRMS calcd for

$C_{22}H_{30}NaO_6Si^+$ 441.1709, found 441.1723; (ES) 441 ($[M+Na]^+$, 100%), 442 ($[M+Na+H]^+$, 15).

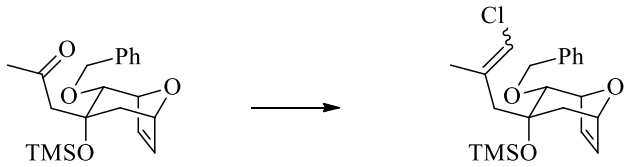
Preparation of (±)-1-((1*S*,2*R*,3*R*,5*S*)-2-(benzyloxy)-3-((trimethylsilyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)propan-2-one 575



A novel compound prepared using a modified literature procedure.[97]

To a solution of **580** (53 mg, 0.130 mmol) and H_2O (0.05 mL, 0.520 mmol) in DMSO (0.34 mL), NaCl (15 mg, 0.250 mmol) was added. The mixture was heated to reflux for 3 h before being allowed to cool to room temperature. The reaction was purified by column chromatography (hexane/EtOAc 90:10) to afford **575** (33 mg, 70%) as a clear colourless oil. R_f 0.31 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 2951, 1703, 1354, 1243, 1102, 834, 750, 725, 698. δ_H (400 MHz, $CDCl_3$) 0.04 (s, 9H, Si(C*H*$_3$)$_3$), 1.79 (dd, 1H, ^2J 14.0 Hz, *J* 1.2 Hz, =CHCHC*H*$_{2eq}$), 2.04 (s, 3H, C*H*$_3$C=O), 2.09 (dd, 1H, ^2J 14.0 Hz, *J* 4.2 Hz, =CHCHC*H*$_{2ax}$), 2.45 (d, 1H, ^2J 15.3 Hz, C*H*$_2$C=O), 2.69 (d, 1H, ^2J 15.3 Hz, C*H*$_2$C=O), 3.68 (d, 1H, *J* 3.9 Hz, =CHCHC*H*), 4.58 (d, 1H, ^2J 11.7 Hz, C*H*$_2$O), 4.62 (dd, 1H, *J* 3.8, 1.6 Hz, =CHC*H*CH), 4.65-4.71 (m, 2H, =CHC*H*CH$_2$, C*H*$_2$O), 6.16 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*CHCH$_2$), 6.19 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*CHCH), 7.28-7.39 (m, 5H, *H*$_{Ar}$). δ_C (100 MHz, $CDCl_3$) 3.1 (3 x CH_3, Si(*C*H$_3$)$_3$), 32.4 (CH_3, *C*H$_3$C=O), 39.7 (CH_2, =CHCHC*H*$_2$), 54.7 (CH_2, C*H*$_2$C=O), 72.5 (CH_2, C*H*$_2$O), 75.6 (C, *C*OSi), 77.5 (CH, =CH*C*HCH), 78.7 (CH, =CH*C*HCH$_2$), 78.8 (CH, =CHCH*C*H), 128.3 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 128.9 (2 x CH, *C*H$_{Ar}$), 131.7 (CH, =*C*HCHCH), 134.7 (CH, =*C*HCHCH$_2$), 138.1 (C, *C*CH$_{Ar}$), 206.5 (C, *C*=O). *m*/*z* HRMS calcd for $C_{20}H_{28}NaO_4Si^+$ 383.1655, found 383.1660; (ES) 383 ($[M+Na]^+$, 100%).

Preparation of (*Z*)-(±)-(((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-(3-chloro-2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)oxy)trimethylsilane (*Z*)-574 and (*E*)-(±)-(((1*S*,2*R*,3*S*,5*S*)-2-(benzyloxy)-3-(3-chloro-2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)oxy)trimethylsilane (*E*)-574



Novel compounds prepared using a modified literature procedure.[97]

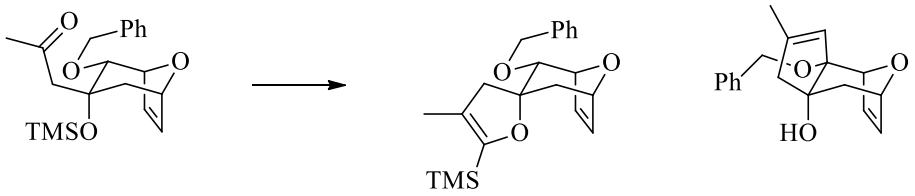
Reaction was performed under an argon atmosphere.

To a solution of diisopropylamine (87 mg, 0.120 mL, 0.860 mmol) in THF (2.5 mL) at 0 °C, ^{n}BuLi (1.42 M, 0.610 mL, 0.860 mmol) was added drop-wise. The reaction was stirred for 45 min before being cooled to -78 °C. (Chloromethyl)triphenylphosphonium chloride (297 mg, 0.860 mmol) was added portion-wise and the suspension stirred at -78 °C for 30 min. A solution of **575** (142 mg, 0.390 mmol) in THF (2.5 mL) was added over 5 min and the reaction was allowed to warm to room temperature of 16 h. The reaction was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford **(*Z*)-574** followed by **(*E*)-574** (122 mg, 80% *E*:*Z* 1:1) as clear, colourless oils. Analytical data for **(*Z*)-574**. R_f 0.16 (petrol/EtOAc 99:1). υ_{max} neat/cm^{-1} 2952, 1243, 1097, 833, 750, 724, 697. δ_H (400 MHz, $CDCl_3$) 0.05 (s, 9H, $Si(CH_3)_3$), 1.60 (dd, 1H, ^2J 14.2 Hz, J 1.1 Hz, =CHCHCH_{2eq}), 1.79 (d, 3H, ^4J 1.4 Hz, =CCH_3), 2.00 (dd, 1H, ^2J 14.2 Hz, J 4.3 Hz, =CHCHCH_{2ax}), 2.47 (d, 1H, ^2J 13.7 Hz, =CCH_2), 2.60 (d, 1H, ^2J 13.6 Hz, =CCH_2), 3.63 (d, 1H, J 3.9 Hz, =CHCHC*H*), 4.63 (dd, 1H, J 3.8, 1.6 Hz, =CHC*H*CH_2), 4.65-4.69 (m, 2H, =CHC*H*CH, CH_2O), 4.71 (d, 1H, ^2J 11.6 Hz, CH_2O), 5.92 (br. s, 1H,

=C*H*Cl), 6.16 (dd, 1H, *J* 6.2, 1.5 Hz, =C*H*CHCH), 6.19 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*CHCH$_2$), 7.28-7.43 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 3.5 (3 x CH_3, $Si(CH_3)_3$), 23.2 (CH_3, =C*C*H$_3$), 38.6 (CH_2, =CHCH*C*H$_2$), 44.5 (CH_2, =C*C*H$_2$), 72.5 (CH_2, *C*H$_2$O), 77.2 (C, *C*OSi), 77.4 (CH, =CH*C*HCH$_2$), 78.8 (CH, =CH*C*HCH), 80.9 (CH, =CHCH*C*H), 115.1 (CH, =*C*HCl), 128.2 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 128.8 (2 x CH, *C*H$_{Ar}$), 131.6 (CH, =*C*HCHCH$_2$), 134.6 (CH, =*C*HCHCH), 135.9 (C, *C*=CHCl), 138.2 (C, *C*CH$_{Ar}$). *m*/*z* HRMS calcd for $C_{21}H_{29}{}^{35}ClNaO_3Si^+$ 415.1472, found 415.1479; (ES) 415 ([M(^{35}Cl)+Na]$^+$, 100%), 417 ([M(^{37}Cl)+Na]$^+$, 38%). Analytical data for **(*E*)-574**. R_f 0.20 (petrol/EtOAc 99:1). υ_{max} neat/cm^{-1} 2951, 1244, 1100, 1077, 834, 750, 725, 698. δ_H (400 MHz, $CDCl_3$) 0.04 (s, 9H, Si(C*H*$_3$)$_3$), 1.59 (dd, 1H, ^2J 14.1 Hz, *J* 1.2 Hz, =CHCHC*H*$_{2eq}$), 1.79 (d, 3H, ^4J 1.2 Hz, =CC*H*$_3$), 1.93 (dd, 1H, ^2J 14.1 Hz, *J* 4.2 Hz, =CHCHC*H*$_{2ax}$), 2.17 (d, 1H, ^2J 14.2 Hz, =CC*H*$_2$), 2.37 (d, 1H, ^2J 14.2 Hz, =CC*H*$_2$), 3.52 (d, 1H, 3.9 Hz, =CHCHC*H*), 4.61 (d, 1H, ^2J 11.7 Hz, C*H*$_2$O), 4.64-4.71 (m, 3H, =CHC*H*CH, =CHC*H*CH$_2$, C*H*$_2$O), 5.70 (d, 1H, ^4J 1.1 Hz, =C*H*Cl), 6.16 (dd, 1H, *J* 6.2, 1.6 Hz, =C*H*CHCH), 6.19 (dd, 1H, *J* 6.1, 1.7 Hz, =C*H*CHCH$_2$), 7.30-7.37 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 3.4 (3 x CH_3, Si(*C*H$_3$)$_3$), 19.0 (CH_3, =C*C*H$_3$), 39.3 (CH_2, =CHCHC*H*$_2$), 49.8 (CH_2, =C*C*H$_2$), 72.7 (CH_2, *C*H$_2$O), 77.1 (C, *C*OSi), 77.4 (CH, =CH*C*HCH), 78.8 (CH, =CH*C*HCH$_2$), 79.3 (CH, =CHCH*C*H), 116.2 (CH, =*C*HCl), 128.4 (CH, *C*H$_{Ar}$), 128.7 (2 x CH, *C*H$_{Ar}$), 128.9 (2 x CH, *C*H$_{Ar}$), 131.6 (CH, =*C*HCHCH$_2$), 134.5 (CH, =*C*HCHCH), 135.1 (C, *C*=CHCl), 138.0 (C, *C*CH$_{Ar}$). *m*/*z* HRMS calcd for $C_{21}H_{29}{}^{35}ClNaO_3Si^+$ 415.1472, found 415.1485; (ES) 415 ([M(^{35}Cl)+Na]$^+$, 100%), 417 ([M(^{37}Cl)+Na]$^+$, 20%).

Preparation of (±)-((1*S*,2*R*,2'*S*,5*S*)-2-(benzyloxy)-4'-methyl-3'*H*-8-oxaspiro[bicyclo[3.2.1]oct[6]ene-3,2'-furan]-5'-yl)trimethylsilane 582 and (±)-(3a*R*,4*S*,7*S*,8a*S*)-3a-(benzyloxy)-2-methyl-1,3a,4,7,8,8a-hexahydro-4,7-epoxyazulen-8a-ol 583

Method A



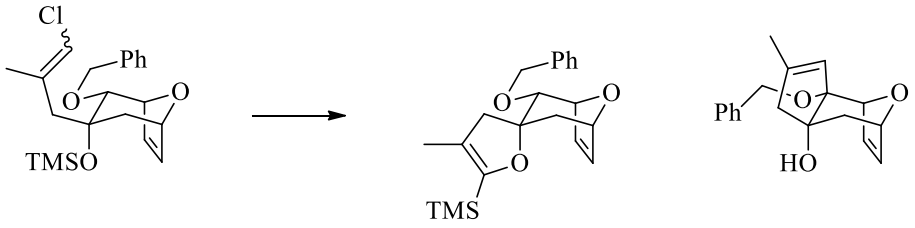
582 **583**

Novel compounds prepared using a literature procedure.[103b]

Reaction was performed under an argon atmosphere.

To a solution of (diazomethyl)trimethylsilane (2 M, 0.110 mL, 0.210 mmol) in THF (5.4 mL) at -78 °C, ^{n}BuLi (1.6 M, 0.140 mL, 0.220 mmol) was added drop-wise. The reaction was stirred at -78 °C for 30 min before a solution of **575** (50 mg, 0.140 mmol) in THF (1.6 mL) was added drop-wise. The resulting mixture was stirred at -78 °C for 1 h, then stirred at room temperature for 3 h, before being quenched with H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was dissolved in THF (1.4 mL) and TBAF (1 M, 0.170 mL, 0.170 mmol) added. The reaction was stirred for 18 h at room temperature before being washed with H_2O (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2→90:10) to afford **582** (22 mg, 45%) as a clear, colourless oil followed by **583** (6 mg, 15%) as a clear, colourless oil.

Method B



582 **583**

Novel compounds prepared using a modified literature procedure.[97]

Reaction was performed under an argon atmosphere.

To a mixture of **(*Z*)-** and **(*E*)-574** (36mg, 0.090 mmol) in THF (0.7 mL) at room temperature, NaHMDS (2 M, 0.180 mL, 0.360 mmol) was added drop-wise. The reaction was stirred at room temperature for 18 h. The reaction was quenched with NH_4Cl (2 mL of a saturated aqueous solution) before H_2O (2 mL) and EtOAc (5 mL) were added and the layers separated. The aqueous layer was washed with EtOAc (2 x 5 mL) and CH_2Cl_2 (1 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was dissolved in THF (1.8 mL) and TBAF (1 M, 0.110 mL, 0.110 mmol) added. The reaction was stirred for 18 h at room temperature before being washed with H_2O (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2→90:10) to afford **582** (8 mg, 25%) as a clear, colourless oil followed by **583** (7 mg, 29%) as a clear, colourless oil. Analytical data for **582**. R_f 0.13 (petrol/EtOAc 98:2). υ_{max} neat/cm^{-1} 2951, 2911, 1309, 1246, 1050, 837, 696. δ_H (400 MHz, $CDCl_3$) 0.08 (s, 9H, $Si(CH_3)_3$), 1.60 (s, 3H, $=CCH_3$), 1.79 (dd, 1H, ^2J 14.1 Hz, J 1.5 Hz, $=CHCHCH_{2eq}$), 1.85 (dd, 1H, ^2J 14.2 Hz, J 3.6 Hz, $=CHCHCH_{2ax}$), 2.23 (dd, 1H, ^2J 15.9 Hz, ^4J 0.9 Hz, $=CCH_2$), 2.44 (dd, 1H, ^2J 15.9 Hz, ^4J 1.0 Hz, $=CCH_2$), 3.55 (d, 1H, J 3.7 Hz, $=CHCHCH$), 4.52 (d, 1H, ^2J 12.2 Hz, CH_2O), 4.64-4.70 (m, 3H, $=CHCHCH$, $=CHCHCH_2$, CH_2O), 6.13 (dd, 1H, J 6.1, 1.4 Hz, $=CHCHCH_2$), 6.20 (dd, 1H, J 6.1, 1.4 Hz, $=CHCHCH$), 7.19-7.33 (m, 5H, H_{Ar}). δ_C

(100 MHz, $CDCl_3$) -1.3 (3 x CH_3, Si(CH_3)$_3$), 12.2 (CH_3, =CCH_3), 41.6 (CH_2, =CHCHCH_2), 51.7 (CH_2, =CCH_2), 72.5 (CH_2, CH_2O), 78.6 (CH, =CHCHCH), 79.1 (CH, =CHCHCH$_2$), 83.3 (CH, =CHCHCH), 84.5 (C, COCSi), 117.6 (C, C=CSi), 127.4 (2 x CH, CH_{Ar}), 127.6 (CH, CH_{Ar}), 128.4 (2 x CH, CH_{Ar}), 131.3 (CH, =CHCHCH), 133.7 (CH, =CHCHCH$_2$), 139.3 (C, CCH$_{Ar}$), 153.8 (C, C=CSi). *m/z* HRMS calcd for $C_{21}H_{28}NaO_3Si^+$ 379.1705, found 379.1717; (ES) 379 ([M+Na]$^+$, 100%), 380 ([M+Na+H]$^+$, 46). Analytical data for **583**. R_f 0.10 (petrol/EtOAc 90:10). υ_{max} neat/cm^{-1} 3537, 2918, 1441, 1086, 1051, 886, 727, 697. δ_H (400 MHz, $CDCl_3$) 1.76 (dd, 1H, ^2J 14.2 Hz, J 4.1 Hz, =CHCHCH_{2ax}), 1.85 (br. s, 3H, =CCH_3), 1.95 (dd, 1H, ^2J 14.2 Hz, J 1.2 Hz, =CHCHCH_{2eq}), 2.19 (d, 1H, ^2J 16.2 Hz, =CCH_2), 2.54 (d, 1H, ^2J 16.2 Hz, =CCH_2), 3.08 (s, 1H, OH), 4.49 (ABq, 2H, ^2J 11.4 Hz, CH_2O), 4.67 (dt, 1H, J 4.2, 1.0 Hz, =CHCHCH$_2$), 4.73 (s, 1H, =CHCHC), 5.56 (m, 1H, =CH), 6.29-6.33 (m, 2H, =CHCHCH$_2$, =CHCHCH), 7.27-7.36 (m, 5H, H_{Ar}). δ_C (100 MHz, $CDCl_3$) 18.0 (CH_3, =CCH_3), 39.6 (CH_2, =CHCHCH_2), 54.7 (CH_2, =CCH_2), 65.9 (CH_2, CH_2O), 78.1 (CH, =CHCHCH$_2$), 78.1 (C, =CHCHC), 79.9 (CH, =CHCHC), 85.2 (C, COH), 125.7 (CH, C=CH), 127.5 (2 x CH, CH_{Ar}), 127.7 (CH, CH_{Ar}), 128.6 (2 x CH, CH_{Ar}), 131.9 (CH, =CHCHCH$_2$), 134.5 (CH, =CHCHC), 139.3 (C, CCH$_{Ar}$), 147.8 (C, C=CH). *m/z* HRMS calcd for $C_{18}H_{20}NaO_3^+$ 307.1310, found 307.1295; (ES) 307 ([M+Na]$^+$, 100%), 308 ([M+Na+H]$^+$, 20).

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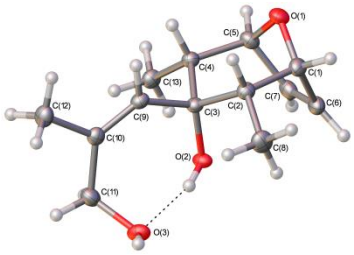
Appendices

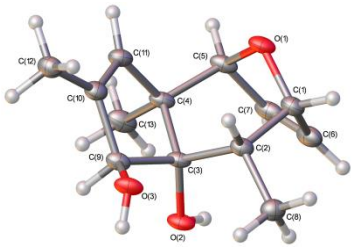
AI - X-ray data for 406



Crystal structure of **406** with ellipsoids drawn at the 50 % probability level. Hydrogen bonds are shown with black dotted lines. Crystal obtained *via* slow evaporation of CH_2Cl_2.

Identification code	**406**	
Empirical formula	$C_{13}H_{20}O_3$	
Formula weight	224.29	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 7.8744(4) Å	α= 90°.
	b = 18.9470(8) Å	β= 105.808(2)°.
	c = 8.5585(4) Å	γ= 90°.
Volume	1228.60(10) $Å^3$	
Z	4	
Density (calculated)	1.213 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	488	
Crystal size	0.28 x 0.12 x 0.07 mm^3	
Theta range for data collection	3.28 to 27.48°.	
Index ranges	-10<=h<=9, -24<=k<=24, -11<=l<=11	
Reflections collected	10487	
Independent reflections	2796 [R(int) = 0.0327]	
Completeness to theta = 27.48°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9941 and 0.9767	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2796 / 0 / 150	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.0979	
R indices (all data)	R1 = 0.0554, wR2 = 0.1047	
Largest diff. peak and hole	0.324 and -0.227 $e.Å^{-3}$	

AII - X-ray data for 426



Crystal structure of **426** with ellipsoids drawn at the 50 % probability level. Crystal obtained *via* slow evaporation of CH_2Cl_2.

Identification code	**426**	
Empirical formula	$C_{13}H_{18}O_3$	
Formula weight	222.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P bca	
Unit cell dimensions	a = 13.4833(5) Å	α= 90°.
	b = 11.3687(5) Å	β= 90°.
	c = 14.6074(8) Å	γ = 90°.
Volume	2239.13(18) $Å^3$	
Z	8	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	960	
Crystal size	0.28 x 0.28 x 0.04 mm^3	
Theta range for data collection	3.17 to 27.47°.	
Index ranges	-17<=h<=17, -14<=k<=14, -18<=l<=18	
Reflections collected	24957	
Independent reflections	2558 [R(int) = 0.0685]	
Completeness to theta = 27.47°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9963 and 0.9746	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2558 / 0 / 150	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0494, wR2 = 0.1116	
R indices (all data)	R1 = 0.0666, wR2 = 0.1200	
Largest diff. peak and hole	0.300 and -0.213 $e.Å^{-3}$	