Construction of Carbocycles *via* Oxonium Ylides Generation and Rearrangement: Towards the Synthesis of Taxol

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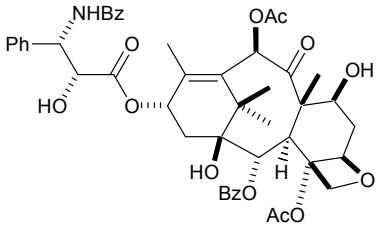
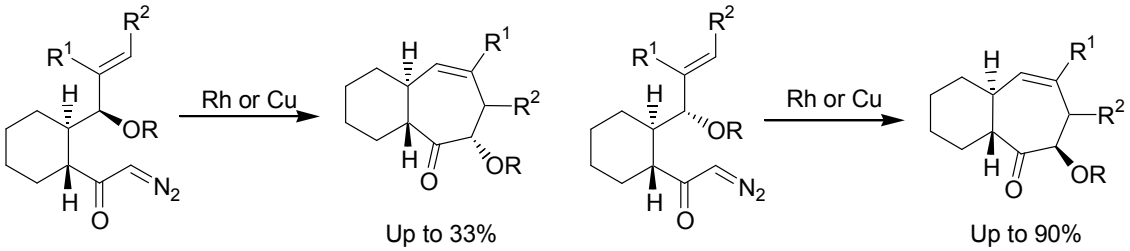
Abstract

The diterpenoid natural product Taxol, first discovered in the late 1960's, is one of the most important current drugs for the treatment of several cancers including breast and ovarian cancers. Although tremendous efforts towards its synthesis have been made in the last two decades, resulting in six elegant total syntheses, Taxol still constitutes a remarkable challenge for organic chemists due to its unique structural framework.

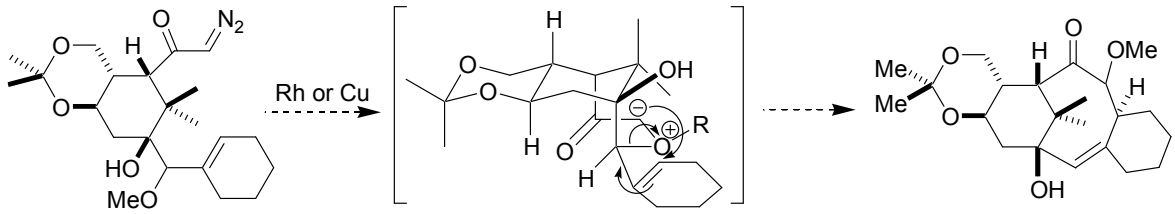


Taxol

The high level of interest has spilled over to our laboratory, the purpose of this thesis was to develop an approach for the construction of medium-ring fused polycarbocyclic systems, which would then be applied to the synthesis of the sterically hindered eight-membered ring of the tricyclic core system of Taxol. Described herein is the continuation of efforts focused towards the access of fused medium-ring carbocycles by tandem catalytic oxonium ylide generation and rearrangement. The novel method in which intramolecular reaction of metal carbenoids with α-vinyl ethers and subsequent [2,3]-rearrangement of the cyclic oxonium ylide intermediates has been used as a powerful strategy to produce linearly fused bicyclic and tricyclic systems.



Following the success of our methodology, a key diazoketone intermediate was chosen to establish the viability of our strategy, before embarking on the total synthesis of Taxol. The efficient synthesis of the required diazoketone is discussed in detail, after the exploration of many different approaches. Finally, studies concerning the catalytic decomposition of the diazoketone towards the tricyclic core system of Taxol are presented.



Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently submitted, in candidature for any other degree. Portions of the work described herein have been published elsewhere as listed below.

I also declare that the work presented in this thesis is the result of my own investigations and where the work of other investigators has been used, this has been fully acknowledged in the text.

Rapid synthesis of medium-ring fused polycarbocyclic systems by rearrangement of carbenoid-derived oxonium ylides – J. Stephen Clark, Carine Guérot, Claire Wilson, Alexander J. Blake *Chem. Comm.* **2007**, 4134.

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Many Thanks to all, you made these three years unforgettable and enjoyable, both in the storm and the sunshine of this fulfilling journey.

Abbreviations

p-ASBA	*p*-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
acam	acetamidate
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aromatic
BHT	2,6-di-*tert*-butyl-*p*-tolyl
Bn	benzyl
BOM	benzyloxymethyl
BRSM	based on recovered starting material
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CM	cross-metathesis
COD	1,5-cyclooctadienyl
Cp	cyclopentadienyl
m-CPBA	*m*-chloroperbenzoic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBB	4,4'-di(tert-butyl)-1,1'-biphenyl
DBU	1,8-diazobicyclo-[5,4,0]-undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCHMS	dicyclohexylmethylsilyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHQ-PHN	dihydroquinine-9-*O*-(9'-phenanthryl) ether
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride

DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane (ethylene glycol dimethyl ether)
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DOSP	(*N*-dodecylbenzenesulfonyl)prolinate
d.r.	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Et	ethyl
EWG	electron-withdrawing group
hfacac	hexafluoroacetylacetonate
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
LTMP	lithium tetramethylpiperidide
MABR	methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide)
MAD	methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
Me	methyl
MEM	methoxyethoxymethyl
MEOX	oxazolidine-4-carboxylic acid methyl ester
MEPY	pyrrolidine-4-carboxylic acid methyl ester
ML_n	transition metal with ligands
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
pfb	perfluorobutyrate
Ph	phenyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium-*p*-toleuenesulfonate
Pr	propyl
PTSA	*p*-toluenesulfonic acid
pttl	*N*-phtaloyl-*tert*-leucinate
py	pyridine
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
ROM	ring-opening metathesis
r.t.	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n* butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluromethanesulfonyl (triflyl)
tfa	trifluoroacetate
tfacac	trifluoroacetylacetonate
tfacam	trifluoroacetamide
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
Tol	*p*-methylphenyl
Tos, Ts	*p*-toluenesulfonyl (tosyl)
tpa	triphenylacetate
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl
Tris	2,4,6-triisopropylbenzenesulfonyl (trisyl)
Troc	trichloroethoxycarbonyl

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Introduction

1. The chemistry of α-diazocarbonyl compounds

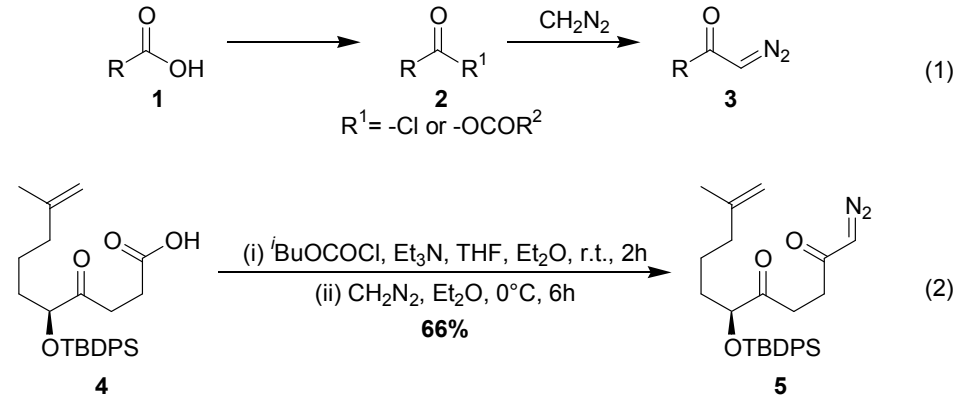
The chemistry of diazo compounds has a long history. Their ease of preparation, relative stability and facile decomposition, under thermal, photochemical and acid or transition-metal catalysed conditions to give useful reactive intermediates make them attractive compounds for organic synthesis. In particular, diazocarbonyl compounds have found wide application in the generation of metal carbenoids.

1.1. Synthesis of α-diazocarbonyl compounds[1]

Since the first preparation of an α-diazocarbonyl compound, from a natural amino acid through the diazotization, first reported by Curtius in 1883,[2] various methodologies have been developed and to date, there are several well established methods for the preparation of different types of diazocarbonyl compounds. Acylation of diazomethane with an acyl halide or anhydride and diazo transfer from an azide reagent to the carbon adjacent to a carbonyl group are the two basic methods most frequently employed to prepare diazocarbonyl compounds. Despite the hazardous nature of diazomethane, the first method remains the most important for the synthesis of acyclic terminal α-diazoketones.

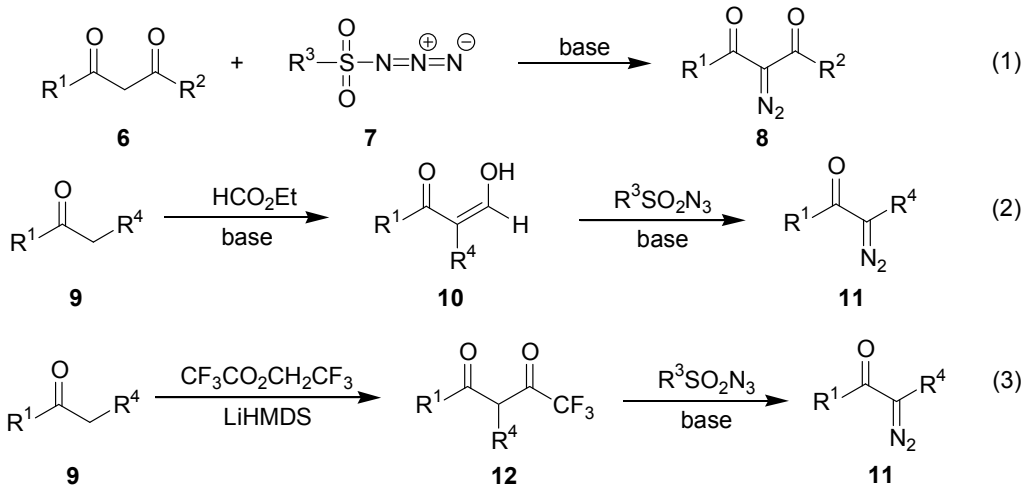
In the late 1920's, Arndt and Eistert successfully synthesised diazoketones **3** by acylation of diazomethane (**Scheme 1**, equation 1).[3] This reaction involves the addition of an acid chloride **2** (R^1 = Cl) to an etheral solution of diazomethane. A large excess of diazomethane is usually required to consume the hydrogen chloride that is produced as a byproduct in the reaction sequence, thereby avoiding the formation of chloromethyl ketone. Mixed anhydrides **2** (R^1 = $OCOR^2$) are also used as precursors of diazoketones in the case of acid-sensitive substrates. Convenient *in situ* generation of diazoketones *via* the mixed anhydride method is now possible by reaction of carboxylic acids with chloroformates (e.g. methyl, ethyl or isobutyl chloroformate), followed by treatment of the

intermediate mixed anhydride with diazomethane. For example, diazoketone **5**, the key intermediate for the asymmetric total synthesis of (–)-indicol, has been prepared after activation of the acid **4** by mixed anhydride formation using isobutyl chloroformate (**Scheme 1**, equation 2).[4]



Scheme 1. (1) General scheme for the preparation of diazoketone *via* acylation. (2) Synthesis of diazoketone **5**, key intermediate in the asymmetric total synthesis of (–)-indicol.

The method of choice for the preparation of cyclic α-diazocarbonyl compounds is diazo transfer. This strategy has also been applied to many acyclic systems not accessible by the acyl-transfer processes. This concept was first described by Dimroth in 1910,[5] and was extensively studied by Regitz in 1967.[6] Diazo transfer reactions of active methylene compounds **6** generally use *p*-sulfonyl azide **7** as a diazo transfer reagent in the presence of a sufficiently strong base to deprotonate the substrate (**Scheme 2**, equation 1). Thus, malonic esters, β-ketoesters, β-ketoamides and β-diketones are readily converted into 2-diazo-1,3-dicarbonyl products **8** after exposure to tosyl azide using triethylamine as the base. However, simple ketones **9**, such as α-methyl ketones, usually do not react directly with sulfonyl azides, so they need to be activated by formylation (Claisen condensation of the ketone with ethyl formate) (**Scheme 2**, equation 2). The resulting α-formyl ketones **10** undergo the actual diazo transfer to give the corresponding α-diazoketones **11**, in a process referred to as the deformylating diazo transfer. When the substrate is a base-sensitive one such as an α,β-enone, the deformylating diazo transfer usually gives a low yield, but Doyle and Danheiser found that activation of the carbonyl compound **9** by the introduction of a trifluoroacetyl group **12** leads to better yields (**Scheme 2**, equation 3).[7]



6 7 8 9 10 11 9 12 11

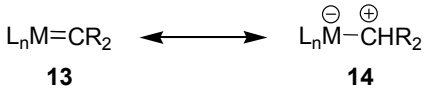
(1) (2) (3)

R^1, R^2= aryl, alkyl, *O*-alkyl, *O*-aryl, NH_2, NR_2; R^3= Me, *p*-tolyl, *p*-CO_2H-phenyl; R^4= aryl, alkyl

Scheme 2. (1) Regitz diazo transfer. (2) Deformylating diazo transfer. (3) Detrifluoroacetylating diazo transfer.

1.2. Generation of metal carbenoids from diazo compounds

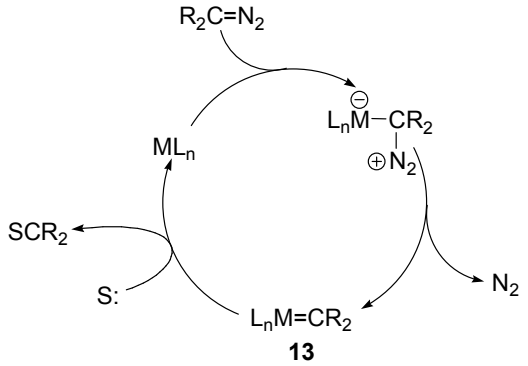
Catalytic methods allow a vast array of transformations *via* metal carbene intermediates to be explored, and are the most versatile available to the synthetic chemist. The synthetic utility of free carbenes is limited partly because of their methods of generation (usually thermal or photochemical), and also because of their high reactivity and consequent low selectivity. It is often better to use metal-complexed carbenes generated by the decomposition of diazo compounds with transition metals.[8] Indeed, carbenoid-mediated transformations usually proceed with higher selectivity and greater yield than the corresponding reactions of free carbenes, due to the influence of metals and ligands on the reactivity of the carbenoids. The reactivity and stability of metal-carbene complexes are largely determined by the degree of π-back donation from the metal to the carbene. Electrophilic transition metal carbene intermediates are widely referred to as carbenoids and their electrophilicity is illustrated by two resonance forms: the formal metal carbene **13** and the metal stabilised carbocation **14** (**Figure 1**).



13 **14**

Figure 1.

The generally accepted mechanism for the catalytic decomposition of diazo compounds starts with a nucleophilic addition of the diazo compound to the metal complex followed by loss of dinitrogen to produce a metal stabilised carbene or metal carbenoid **13**. An electron rich substrate (S:) can then reacts with the electrophilic metal carbenoid, resulting in the regeneration of the transition metal complex (**Scheme 3**).



Scheme 3. Mechanism for catalytic decomposition of diazo compounds.

The type of metal complex and the ligands used can have profound effects on the regio-, chemo- and stereoselectivity. The first example of a metal-mediated reaction of an α-diazocarbonyl compound was reported by Silberrad and Roy in 1906.[9] They used copper dust to accelerate the decomposition of ethyl diazoacetate. Until late 1970's, catalytic decomposition reactions of diazo compounds were usually carried out in presence of copper. Since then, dirhodium tetracarboxylates have been introduced and have become the catalysts of choice, and a much wider range of carbenoid precursors has been developed. Lewis acid transition metal complexes are effective catalysts for this type of diazodecomposition. Their catalytic activity depends on coordinative unsaturation at their metal centre(s), which allows them to react as electrophiles with diazocompounds. The most important metals being used for carbene generation are copper and rhodium, but cobalt, palladium, ruthenium, iron, and etc. have also been used successfully.[10] Specific metal-ligand combinations can allow the metallocarbene to discriminate between potentially competing carbene reactions (such as cyclopropanation and C-H insertion) and/or paths to different stereoisomers, by controlling the stereoselectivity of a reaction.

The development of catalysts for the decomposition of diazo compounds began in early 1960's with the introduction of copper compounds possessing well-defined ligands. Phosphite ligated copper(I) chloride **14**,[11] copper(II) acetylacetonate **15**,[12] its hexafluoro and trifluoro analogues **16** and **17** respectively,[13] were developed as organic solvent soluble alternatives to the commonly used copper bronze and copper(II) sulfate (**Figure 2**).

Subsequently, copper(I) triflate[14] was introduced as a highly active catalyst and at this time attention was drawn to Cu(I) as the active form, rather than Cu(II), for diazo decomposition. Chiral copper(II) complexes, such as bisoxazoline complexes **18**, were also developed for asymmetric diazo decomposition.[15]

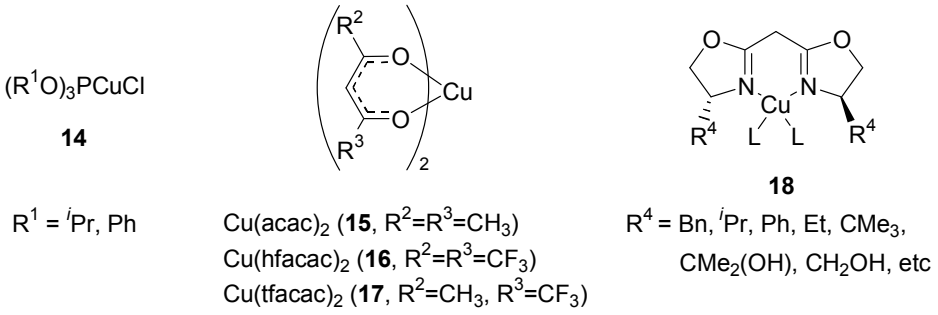


Figure 2. Representative copper catalysts.

The enormous utility of rhodium as a transition metal capable of initiating catalytic decomposition of diazo compounds has become well recognized. Rhodium-mediated carbenoid reactions generally proceed under much milder conditions compared to those involving copper complexes. Teyssié and co-workers were the first to discover that dirhodium(II) tetraacetate **19** is highly active for diazo decomposition.[16] Initially, $Rh_2(OAc)_4$ was used for O-H insertion reactions but subsequently it found application in cyclopropanation and cyclopropenation reactions and for ylide generation (**Figure 3**). It was established that the selectivity in rhodium carbenoid transformations is greatly influenced by the electronic properties of the bridging dirhodium(II) ligands.

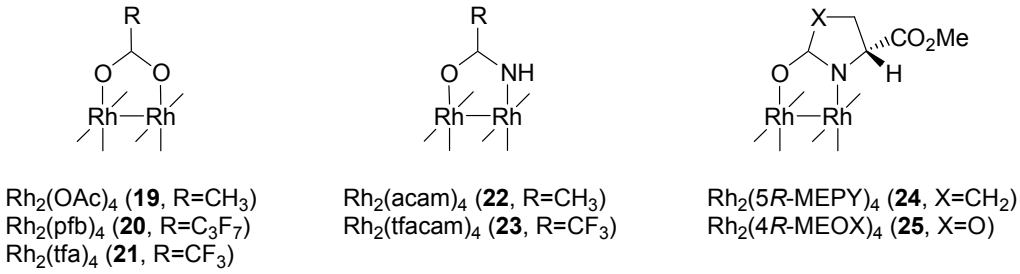


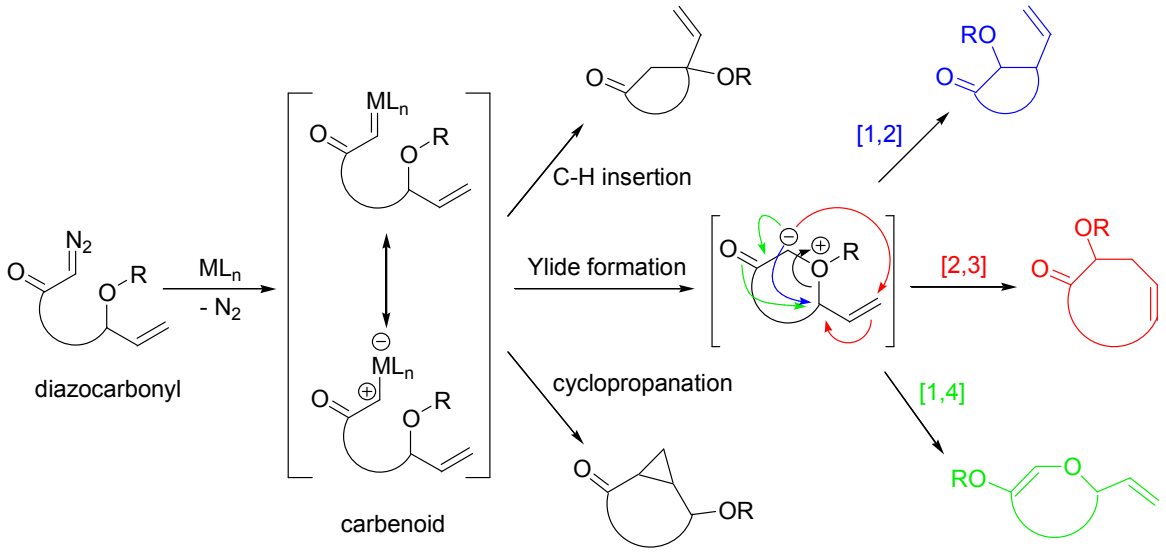
Figure 3. Representative rhodium catalysts.

Dirhodium(II) perfluorobutyrate **20**, whose ligands are strongly electron-withdrawing, shows high reactivity for diazo decomposition, but gives low stereo- and regiocontrol in metal carbene transformations.[17] In contrast, dirhodium(II) carboxamides, including dirhodium acetamide **22**, exhibit lower reactivity and higher selectivity.[17a,18] Steric influences on selectivity have received limited attention. Dirhodium(II) complexes

containing chiral ligands have also been widely developed and used in asymmetric carbenoid transformations.[19]

1.3. *Reactions of metal carbenoids*

The use of metal catalysed reactions of α-diazocarbonyl compounds is not only limited to cyclopropanation, even though many studies have been centered on this transformation. Metallocarbenoid reactions involving X-H insertions (X = C, O, S, N, Si, etc) or ylide generation followed by rearrangement have also been used to prepare complex synthetic targets (**Scheme 4**).[1b,10b,20] Cyclopropanation and C-H insertion reactions will be briefly discussed in this thesis, whereas the oxonium ylide formation and rearrangement reactions will be our primary focus of discussion.

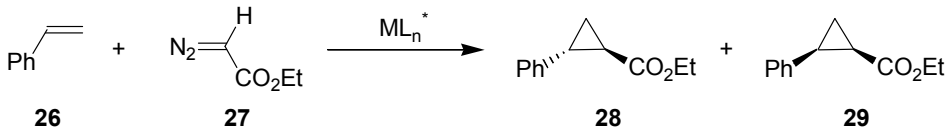


Scheme 4. Representative reactions of metal carbenoids.

1.3.1. *Cyclopropanation of alkenes*

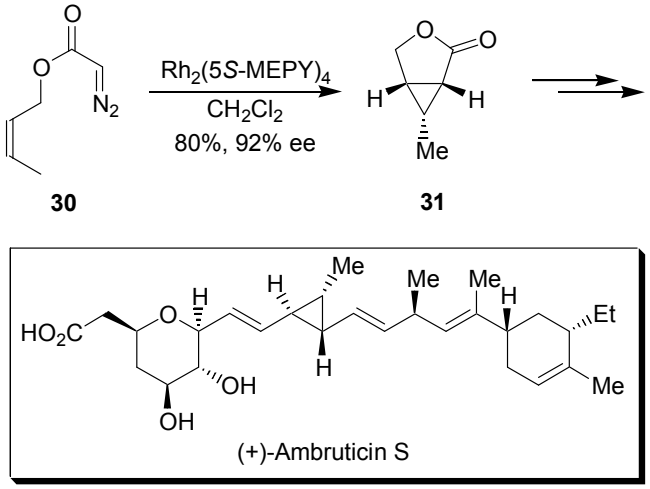
Three-membered rings are very important building blocks in organic synthesis because they are structural subunits in many biologically active natural/unatural products and synthetic intermediates. Consequently, great efforts have been made to develop efficient stereoselective methods for the synthesis of cyclopropanes. In particular, the cyclopropanation of olefins using diazocompounds has received considerable attention during the last few decades. Highly effective and stereocontrolled syntheses of

functionalised cyclopropanes have been achieved using catalysts based on copper, rhodium and, more recently ruthenium.[20,21] In this process, up to three stereogenic centres are created in one step. Both stereoselective (diastereo- and enantioselective) inter- and intramolecular cyclopropanation reactions have been extensively studied. Since the first report in 1966 that a homogeneous chiral catalyst could provide enantiocontrol during cyclopropanation,[12,22] albeit with low ee, the reaction between styrene **26** and ethyl diazoacetate **27** has served as the bench-mark reaction for the discovery of almost every new catalyst in this area of study (**Scheme 5**).



Scheme 5. Reaction between styrene and ethyl diazoacetate for chiral catalyst viability test.

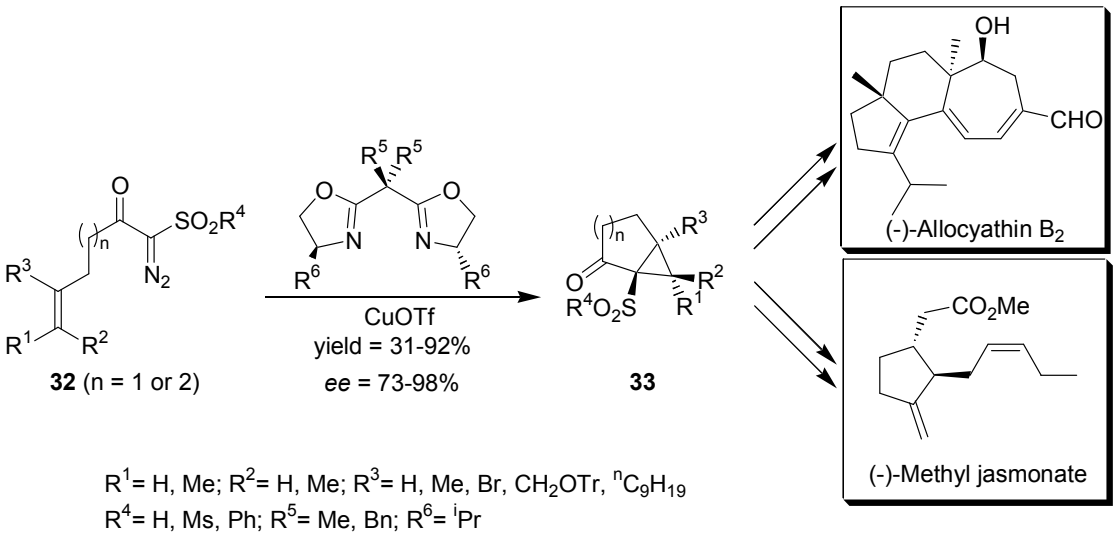
Indeed, the most elegant strategy for the preparation of enantiomerically enriched cyclopropanes is based on the use of chiral catalysts. For example, the enantioselective intramolecular cyclopropanation of allylic diazoacetate **30** has been developed to synthesise the bicyclic lactone **31** with very high enantioselectivity using the chiral rhodium complex [Rh_2(5*S*-MEPY)$_4$] (**Scheme 6**).[23] This reaction has recently been used in a synthesis of the optically active cyclopropane unit of the antifungal antibiotic (+)-ambruticin S.[24]



Scheme 6. Synthesis of (+)-ambruticin S *via* enantioselective intramolecular cyclopropanation of **30**.

Recently, Nakada reported a number of highly enantioselective Cu-catalysed intramolecular cyclopropanation reactions of α-diazo-β-keto sulfones **32** (**Scheme 7**).[25] Nakada's methodology has been successfully applied to the total synthesis of several

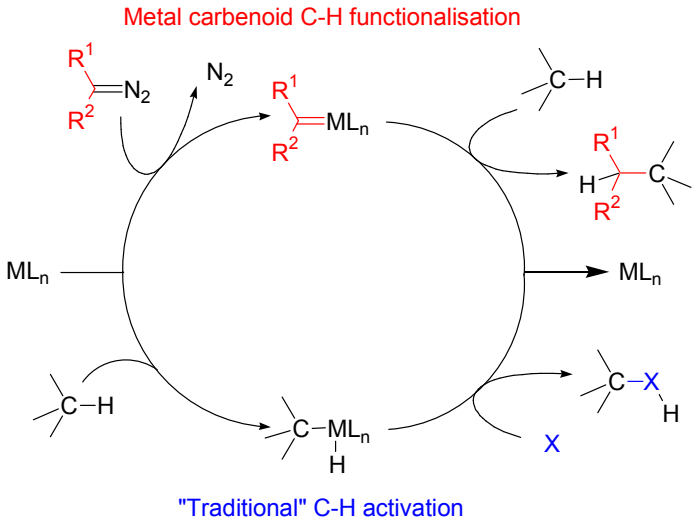
biologically active natural products, such as (–)-allocyathin B_2, (–)-malyngolide and (–)-methyl jasmonate.[26]



Scheme 7. Synthesis of (–)-allocyathin B_2 and (–)-methyl jasmonate *via* enantioselective intramolecular cyclopropanation of **32**.

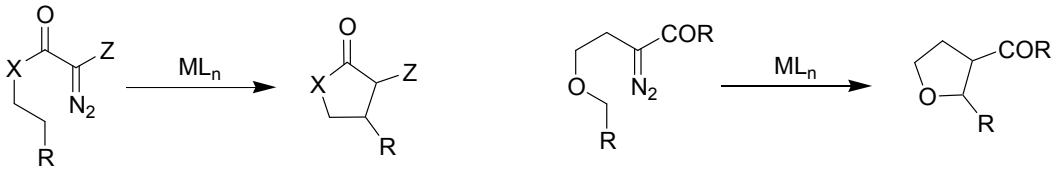
1.3.2. C-H Insertion reactions

Together with cyclopropanation, X-H bond insertion reactions are characteristic reactions of metal carbenes. In particular, unfunctionalised C-H bond insertion by carbenoids provides a very important approach for C-H bond activation.[27] Although, organometallic chemists have focused much attention on developing "C-H activation" strategies, in this process, either a highly reactive metal complex inserts into a C-H bond, activating the system for subsequent transformation, or less reactive metal complexes are directed to the site of transformation by a neighbouring functionality (**Scheme 8**).[28] Thus, the mechanism of the carbene complex reaction is different to those of other C-H activation reactions that involve metal/C-H interactions. Indeed, in metal carbenoid-induced C-H activation, the metal is not thought to interact directly with the alkane C-H bond. This is different to most other C-H activation reactions, which involve oxidative addition of the metal across the alkane C-H bond.



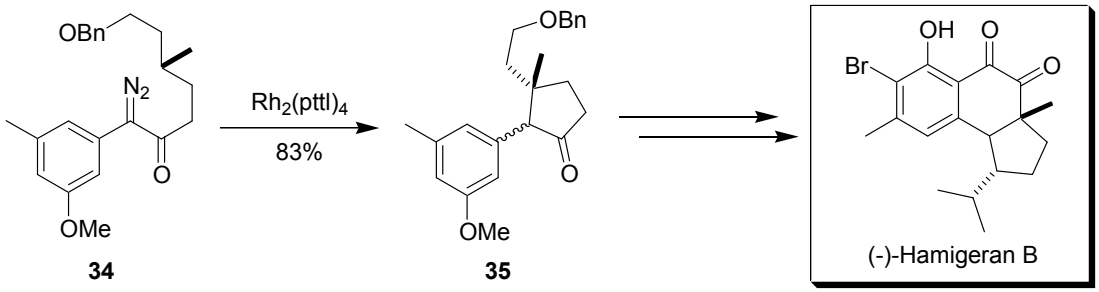
Scheme 8. Metal carbenoid C-H functionalisation *versus* the "traditional" C-H activation.

Intramolecular C-H activation reactions permit remote functionalisation through C-C bond formation. This type of reaction offers a general approach for the synthesis of a variety of carbocycles and heterocycles in a regio- and stereocontrolled manner. It has been well documented that the reactivity of the C-H bond is influenced by electronic and steric factors. In most cases, the formation of a five-membered ring is predominant.[1b,20d] This strategy has been used for the synthesis of cyclopentanones, dihydrofuranones, γ-lactones, γ-lactams, tetrahydrofurans, etc. (**Scheme 9**).[29] The reactivity of the substrates increases dramatically with increasing number of alkyl substituents: 1°CH << 2°CH < 3°CH and adjacent heteroatoms (such as O and N) substitution. However, conformational stability based on steric influences can determine the product formation.[17a,20d,30]



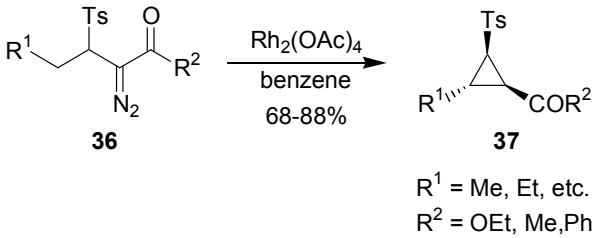
Scheme 9. C-H insertion for the synthesis of cyclopentanones (X = CH_2, Z = H, COR, $PO(OR)_2$), γ-lactones (X = O, Z = H, COR), γ-lactames (X = N, Z = H, COR), tetrahydrofurans.

Recently, Taber and co-workers reported the C-H insertion reaction of α-aryl-α-diazoketones.[31] After screening many catalysts they found Hashimoto $Rh_2(pttl)_4$ catalyst[32] gave the highest yield. They used this strategy to prepare a variety of α-aryl cyclopentanones and in the following year, they also successfully applied this methodology to the synthesis of the natural product (–)-hamigeran B (**Scheme 10**).[33] It is noteworthy that they were able to generate a cyclopentanone quaternary centre, through this rhodium-mediated intramolecular C-H insertion reaction.



Scheme 10. Synthesis of (–)-hamigeran B *via* intramolecular 1,5 C-H insertion of **34**.

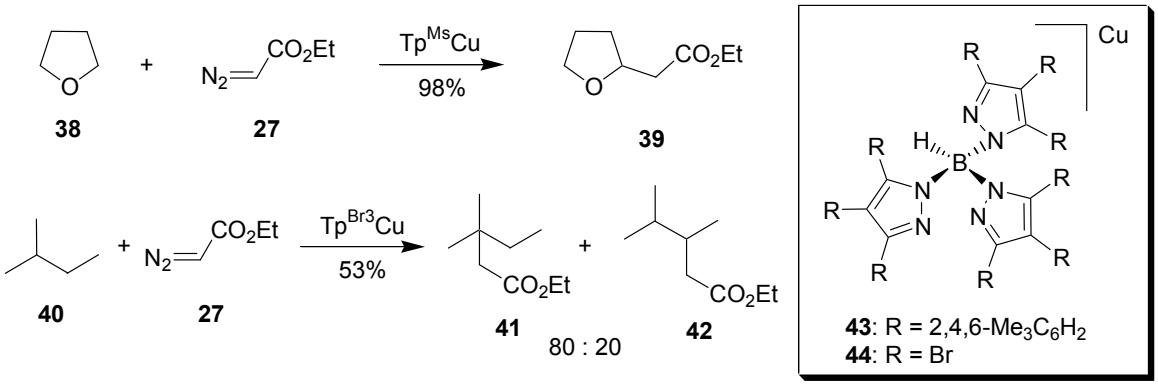
Although, intramolecular 1,5 C-H insertion is entropically favourable due to the formation of six-membered transition state, steric or electronic factors may override this entropic preference. Both 1,4 and 1,7 C-H insertions can occur when the C-H bond is activated by a neighbouring heteroatom, in most cases oxygen or nitrogen.[34] Some 1,6 C-H insertion reactions have also been reported for structurally rigid systems.[35] A 1,3 intramolecular C-H insertion reaction has been recently reported for the first time by Wang and co-workers (**Scheme 11**).[36] They showed that rhodium-mediated reaction of β-tosyl α-diazocarbonyl compounds **36** underwent an unprecedent formation of the three-membered ring **37** through 1,3 C-H bond insertion and that 1,2-hydride migration, usually a feasible process, did not occur.



Scheme 11. First example of 1,3 intramolecular C-H insertion in the Rh(II) carbene reactions.

For a long time, the intermolecular C-H insertion reaction was considered to be of little synthetic utility, because of the poor chemoselectivity. However, in the past few years, the situation has changed to some extent with the development of new catalytic systems and donor/acceptor-substituted carbenoids.[9b,27,37] Although dirhodium tetracarboxylates are widely used in intramolecular C-H insertion, they are usually less effective for the intermolecular C-H insertion of acceptor substituted carbenoids. The reaction displays very poor regioselectivity, and carbene dimerization dominates in this case. To avoid dimerization, one strategy is to increase the bulk of the ligand around the metal catalyst. Recently, higher yields in intermolecular C-H insertion reactions of

carbenoids prepared using bulky copper catalysts have been reported by Pérez and co-workers (**Scheme 12**). In the reaction between ethyl diazoacetate **27** and tetrahydrofuran **38**, the yield of the C-H insertion product could be improved to 98% using $Tp^{Ms}Cu$ catalyst **43**.[38] The C-H insertion reactions of alkanes catalysed by $Tp^{Br3}Cu$ catalyst **44** were also highly chemoselective.[39]



Scheme 12. Example of intermolecular C-H insertion reactions.

A major breakthrough in the field of the intermolecular C-H insertion was the discovery that the placement of a donor substituent (such as an aryl or vinyl group) on the carbene carbon generates stabilized intermediates capable of highly regioselective transformations.[27b] At this stage, it is important to emphasize the classification of the carbenoid intermediates into three major groups based on substituents on the carbenoid carbon: acceptor, acceptor/acceptor and acceptor/donor (**Figure 4**).

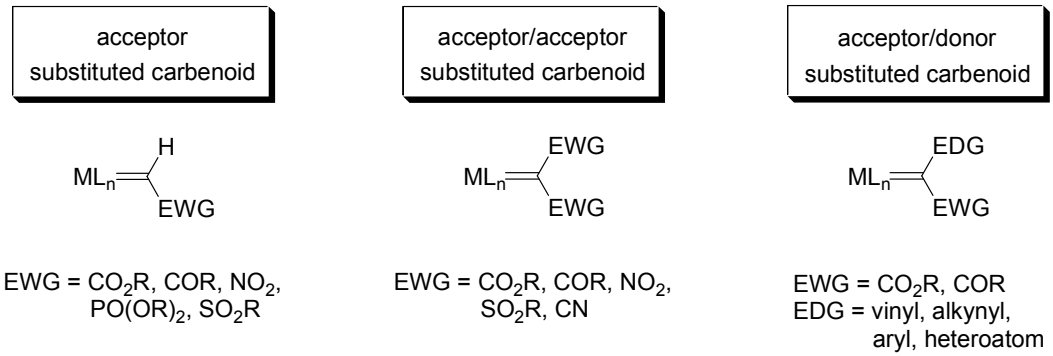
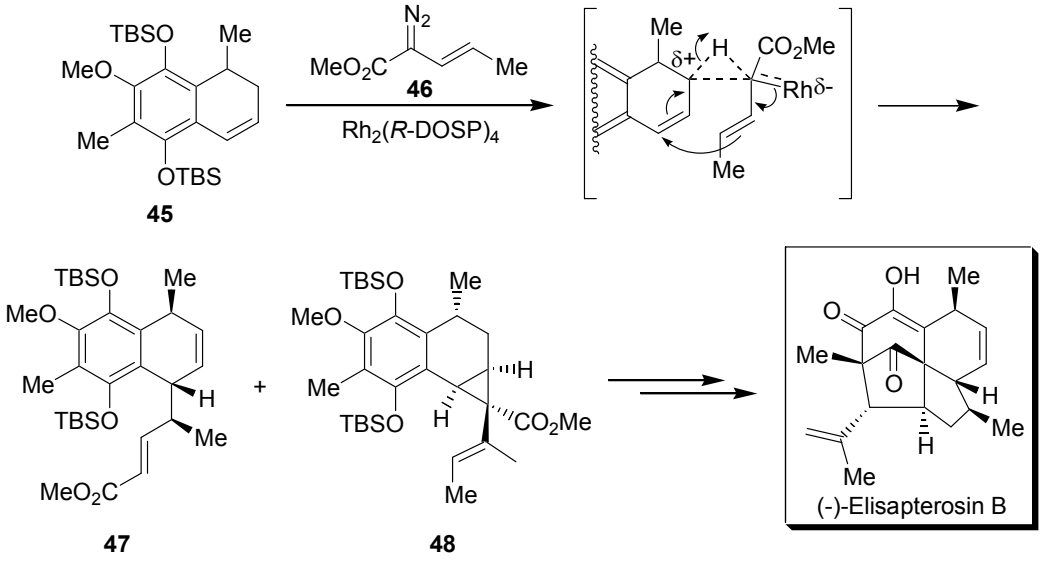


Figure 4. Classification of carbenoid intermediates.

The presence of both an electron-donating group (EDG) and an electron-withdrawing group (EWG) is necessary to reduce the carbene dimerization pathways and to increase the selectivity for intermolecular reactions. Metal carbenes derived from aryldiazoacetates and vinyldiazoacetates have been studied extensively. The Rh_2(*R*-DOSP)$_4$-mediated reactions of vinyl carbenoids with allylic substrates results in very

unusual chemistry, indeed the reaction undergoes a 'combined C-H activation/Cope rearrangement'.[40] This method has been applied to the total synthesis of a range of natural products including elisabethadione,[40a] elisapterosin B,[40b] colombiasin A[40b] and erogorgiaene.[40c] For example, the vinylcarbenoid generated from vinyldiazoacetate **46** activated the allylic C-H bond of the dihydronaphthalene **45**, which was followed by a Cope rearrangement to yield the core structure **47** (**Scheme 13**). The entire process is believed to occur *via* a concerted, ordered transition state that leads to higher stereoselectivity at all three stereocentres, than normally observed in a direct C-H insertion. In the presence of the chiral catalyst Rh_2(*R*-DOSP)$_4$, the other enantiomer of the dihydronaphthalene **45** reacts in an entirely different manner to form cyclopropanation product **48**. Thus, 1:1 mixture of the C-H functionalised product **47** and the cyclopropane **48** was obtained from the racemic dihydronaphtalene **45**. These two products were inseparable, so the mixture was hydrogenated and then reduced. At this stage the alcohol derived from C-H functionalisation was isolated in 34% yield over three steps as a single diastereoisomer in 95% ee. A further six steps were necessary to complete the total synthesis of (–)-elisapterosin B.



Scheme 13. Synthesis of (–)-elisapterosin B *via* a combined enantioselective intermolecular C-H insertion/Cope rearrangement of **45**.

1.3.3. Oxonium ylide generation and rearrangement

The interaction of the electron-deficient carbenoic carbon of the metal carbene intermediate with a pair of non-bonding electrons from a Lewis base (B:) generates a metal

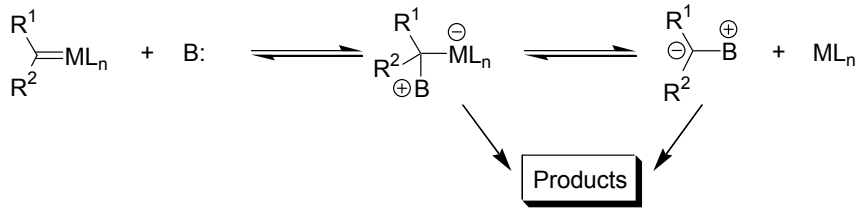
complex associated ylide or a free ylide (**Scheme 14**). The ylide intermediate thus generated is usually highly reactive and undergoes further reactions to give stable products. The common Lewis bases utilized to generate ylides include ethers, sulfides, amines, carbonyls and imines. Common reactions of the ylides include:

(1) [2,3]-sigmatropic rearrangement of allylic, propargylic and allenic ylides,

(2) [1,2]-shift (Stevens rearrangement),

(3) 1,3-dipolar cycloaddition of the ylides generated from carbonyl compounds or imines,

(4) nucleophilic addition/elimination.



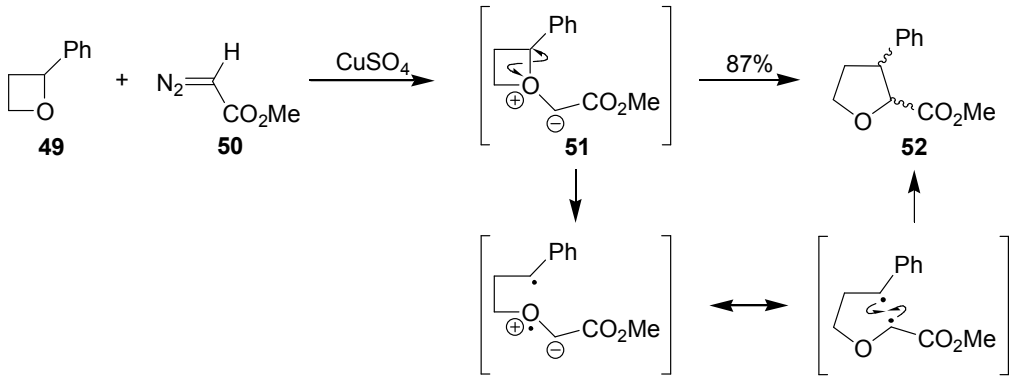
Scheme 14. Ylide formation.

Until recently, the chemistry of oxonium ylides had received little attention compared to ammoniun and sulfonium ylides.[1b,8,20d,41] Oxonium ylides are characterized by their instability and high reactivity; unlike the ammonium and sulfonium ylides, they have not been yet isolated and are difficult to characterize. Most of the evidence for their existence is circumstantial and is based on analysis of the products after the rearrangement of these putative intermediates. Over the past decade, oxonium ylides have found significant synthetic utility due to their easy generation by the reaction of metal carbenoids with ethers. The major reaction pathways for oxonium ylides are [2,3]-sigmatropic rearrangement, when an allyl group is present, and [1,2]-Stevens rearrangement. They may also undergo competing reactions such as β-eliminations and reactions with nucleophiles.

1.3.3.1. [1,2]-Stevens rearrangement of oxonium ylides

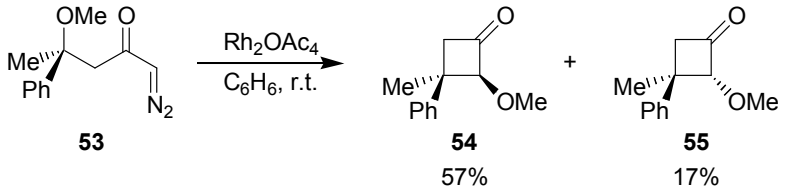
One of the earliest examples of the formation of an oxonium ylide was reported by Nozaki and co-workers (**Scheme 15**).[22b,42] The copper-catalysed reaction of ethyl diazoacetate **50** and phenyloxetane **49** delivered the tetrahydrofuran **52** in 87% yield. The isolation of the product **52** provided strong evidence for the formation of an oxonium ylide and its subsequent [1,2]-rearrangement. The oxonium ylide **51** is formed by the nucleophilic attack of a lone pair of the etheral oxygen of **49** on the metal carbenoid

generated from the diazocarbonyl compound **50**. The oxonium ylide **51** then undergoes a [1,2]-shift, even though concerted [1,2]-shifts are forbidden processes according to the Woodward-Hoffmann rules.[43] Indeed, the $[_{\pi}2_s + _{\omega}2_s]$ process for a reaction involving 4n electrons is symmetry-forbidden, moreover the reaction is symmetry-allowed for $[_{\pi}2_s + _{\omega}2_a]$ or $[_{\pi}2_a + _{\omega}2_s]$ processes but geometrically impossible. Evidence has been obtained that oxonium ylides rearrange by a homolysis-recombination mechanism.[44] Homolytic cleavage of the oxonium ylide intermediate produces a singlet radical pair, which then recombines quickly within a solvent-cage to deliver the [1,2]-shift product **52**.



Scheme 15. First example of [1,2]-shift of oxonium ylide and mechanism.

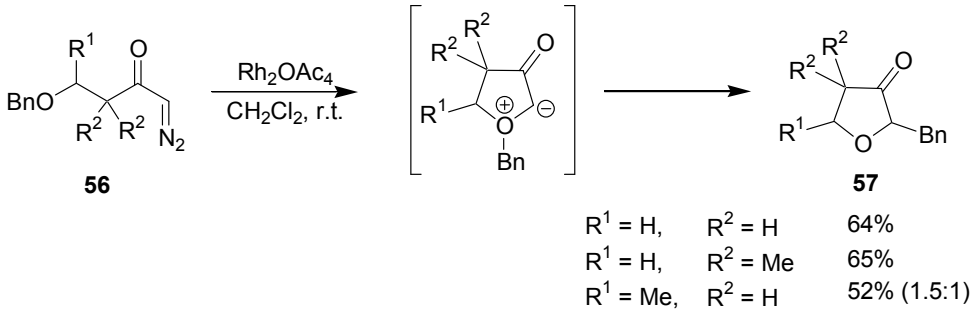
Since this early report, oxonium ylide generation followed by [1,2]-Stevens rearrangement has been found to be useful for the formation of new carbon-carbon bonds, and has been used extensively in organic synthesis. Johnson was the first to explore the intramolecular generation and rearrangement reaction of oxonium ylides and reported the synthesis of substituted carbocycles by a [1,2]-shift (**Scheme 16**).[45] He showed that the treatment of diazoketone **53** with rhodium(II) acetate delivered a mixture of cyclobutanones **54** and **55** by a ring-contracting [1,2]-shift of the intermediate oxonium ylide.



Scheme 16. Synthesis of carbocycles *via* [1,2]-shift of oxonium ylide.

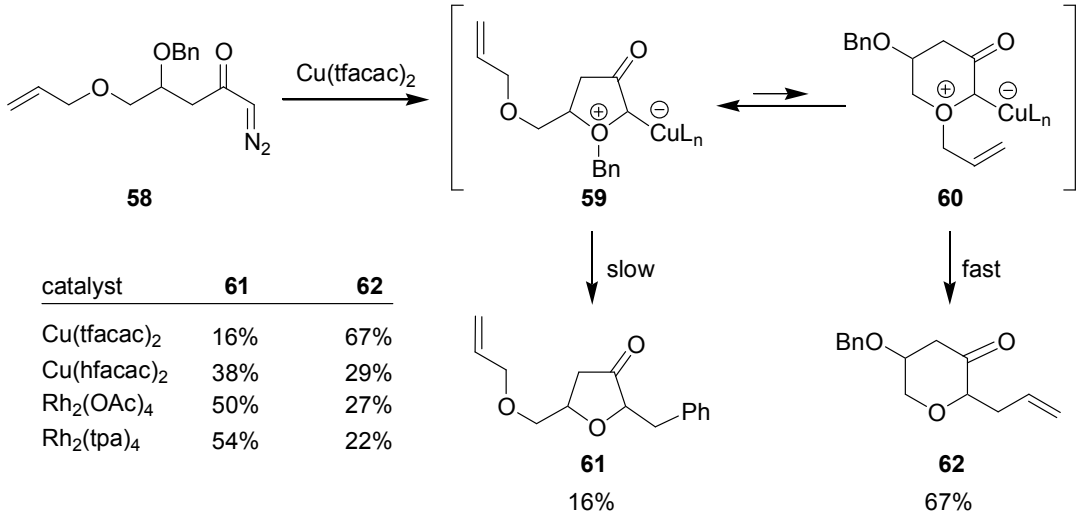
This approach was then used by West and co-workers to prepare a variety of substituted cyclic ethers (**Scheme 17**). They successfully utilized the tandem cyclic oxonium ylide generation/Stevens [1,2]-shift protocol to synthesise functionalised

tetrahydrofurans.[46] Catalytic decomposition of alkoxy-α-diazoketones **56** furnished the cyclic ethers **57** in good yield. They concluded that oxonium ylides generated from benzylic ethers generally undergo [1,2]-rearrangement with migration of the benzyl group rather than the ring contraction as described above.



Scheme 17. Synthesis of cyclic ethers *via* [1,2]-shift of oxonium ylide.

West and co-workers recently studied reactions of diazoketones in which competitive formation of two different oxonium ylides *via* the same metallocarbene precursor was possible (**Scheme 18**).[47] The metallocarbenoid could undergo intramolecular five or six-membered oxonium ylide formation. The study revealed that five-membered ylide formation is generally favoured. However, the properties of the migrating group in the subsequent rearrangement reaction may override the preferential formation of a five-membered ring. Indeed, when α-diazoketone **58** was treated with $Cu(tfacac)_2$, pyranone **62** was formed predominantly since allylic [2,3]-sigmatropic rearrangement is more feasible than a [1,2]-shift. This result strongly suggests that the two possible ylides **59** and **60** remain in equilibrium.



catalyst	61	62
$Cu(tfacac)_2$	16%	67%
$Cu(hfacac)_2$	38%	29%
$Rh_2(OAc)_4$	50%	27%
$Rh_2(tpa)_4$	54%	22%

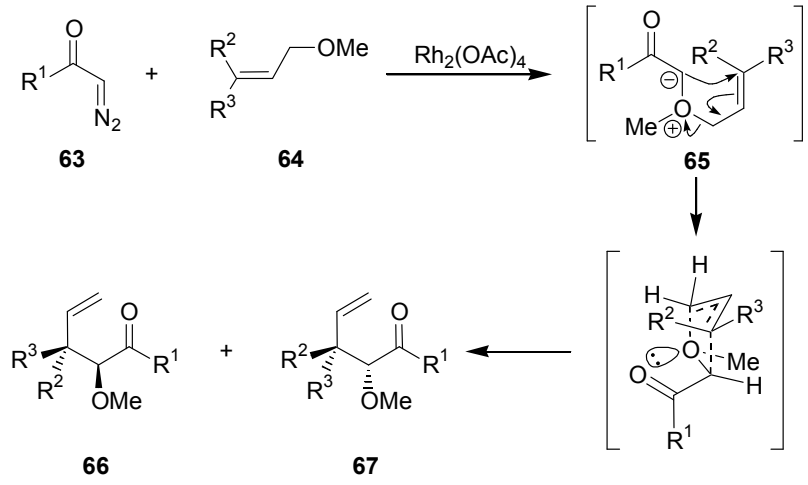
Scheme 18. Catalyst and ring size effects on preselectivity of oxonium ylide rearrangements .

They noticed that the catalyst can dramatically influence the reaction selectivity. When $Rh_2(OAc)_4$ and $Rh_2(tpa)_4$ were employed as catalysts, the reaction gave the five-membered ylide formation/[1,2]-benzyl shift product **61** predominantly. However, even a relatively minor change in the ligand of the copper catalyst (e.g. from $Cu[tfacac]_2$ to $Cu[hfacac]_2$) significantly altered the selectivity. The catalyst-dependent selectivity strongly suggests the involvement of a metal-associated ylide in the product-forming step. The catalyst may thus alter the properties of ylide and affect the equilibrium between different species such as **59** and **60**.

1.3.3.2. [2,3]-Sigmatropic rearrangement of allylic oxonium ylides

When an allylic ether is used for the ylide formation, the oxonium ylide that is generated may undergo [2,3]-sigmatropic rearrangement, which is one of the most versatile bond reorganisation processes in organic chemistry.

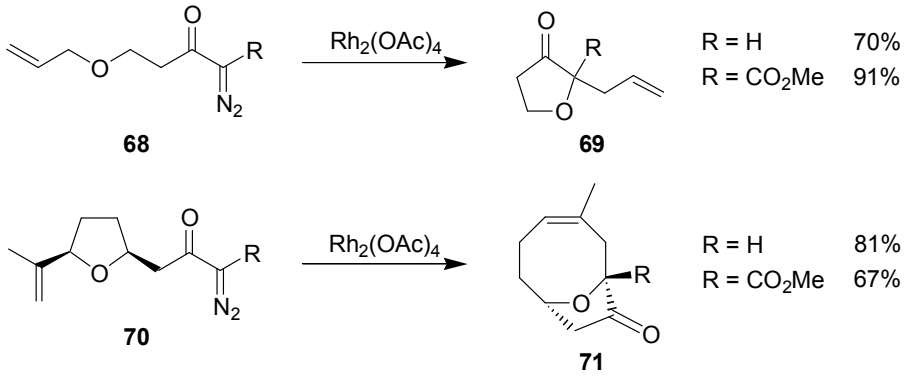
The intermolecular reaction has received considerable attention,[41] but competitive cyclopropanation is frequently a major problem. The degree to which cyclopropanation occurs is highly dependent on the steric environment around the ether oxygen, the alkene substituents and the catalyst. However, there are many reports demonstrating that predominant ylide formation and subsequent [2,3]-sigmatropic rearrangement can occur.



Scheme 19. Intermolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement.

For example, Doyle has explored the intermolecular generation of allylic oxonium ylides from simple allyl ethers (**Scheme 19**).[48] The generation of oxonium ylide **65** occurred almost exclusively, when diazoketone **63** and allylic methyl ether **64** were treated with rhodium(II) acetate. The alkene geometry was found to dictate the stereochemical course of the reaction, and the rearrangement of the putative oxonium ylide **65** is thought to proceed through an 'envelope' transition state in which steric interactions between the methyl substituent and the carbonyl group are minimised.

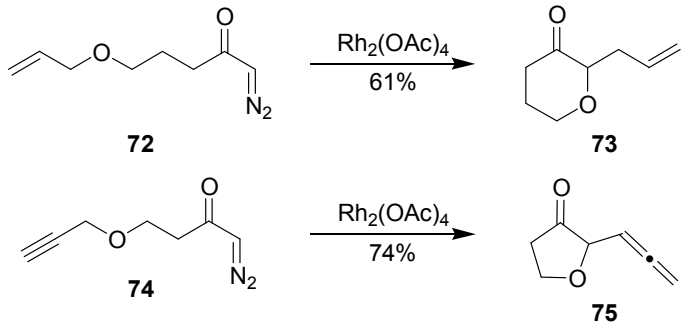
Intermolecular oxonium ylide formation and subsequent [2,3]-rearrangement reactions have found limited application in organic synthesis, compared to the more widely used intramolecular processes. Indeed, cyclic oxonium ylides are readily generated through intramolecular reaction of a metal carbene and a suitably positioned ethereal oxygen. This cyclic ylide formation/[2,3]-sigmatropic rearrangement reaction sequence has been employed by several groups for the synthesis of cyclic ethers and carbocycles. The first examples of intramolecular oxonium ylide and subsequent [2,3]-sigmatropic rearrangement were reported by Pirrung in 1986, where he described the construction of five-, six- and eight-membered oxygen heterocycles (**Scheme 20**).[49] Treatment of diazoketone **68** with rhodium(II) actetate produced furanone **69**, whereas diazoketone **70** afforded eight-membered ring oxygen heterocycle **71**. The ring expansion clearly illustrated the preference of the ylide to undergo symmetry allowed [2,3]-sigmatropic rearrangement over the symmetry forbidden [1,2]-process.



Scheme 20. Pirrung's synthesis of cyclic ethers *via* intramolecular oxonium ylide generation and [2,3]-sigmatropic rearrangement.

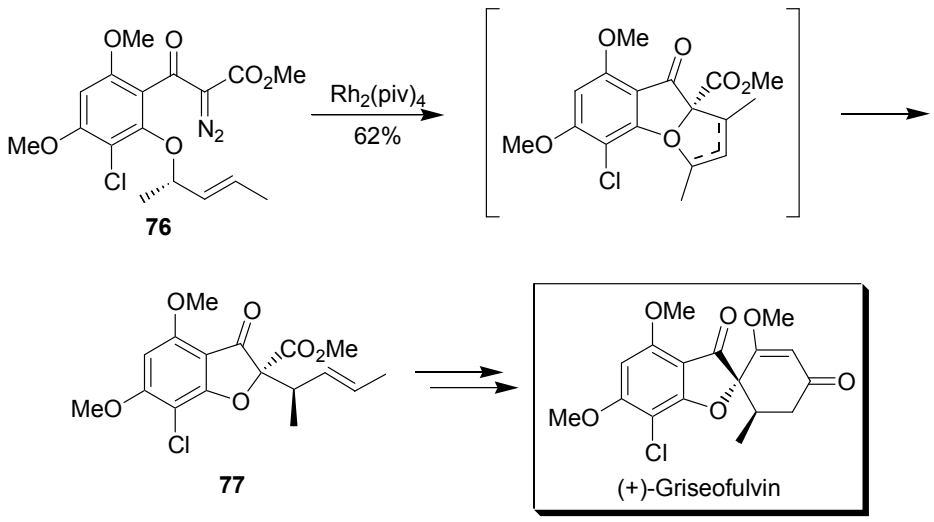
Simultaneously, Johnson and Roskamp also investigated this methodology and provided a set of additional examples (**Scheme 21**).[45] They found that diazoketone **72** was converted into the six-membered heterocycle **73**, and the propargylic ether **74** underwent

the [2,3]-rearrangement to provide the allene **75**. The latter example shows that the reaction is not only limited to allylic ethers.



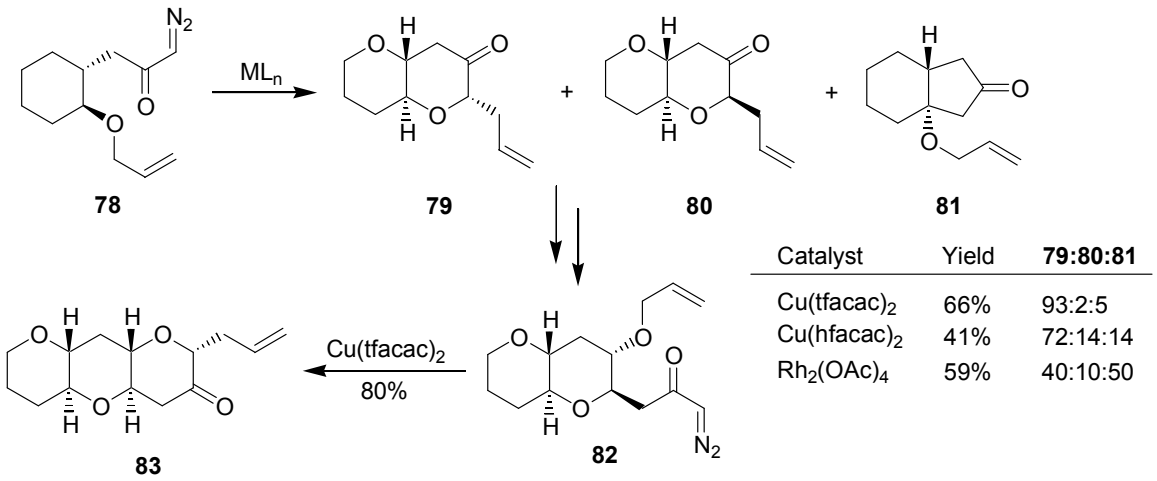
Scheme 21. Johnson and Roskamp's synthesis of cyclic ethers *via* [2,3]-sigmatropic rearrangement.

Catalytic oxonium ylide formation and [2,3]-sigmatropic rearrangement has been applied to the total synthesis of the anti-fungal agent (+)-griseofulvin.[50] Treatment of the enantiomerically pure diazoketone **76** with rhodium(II) pivalate in benzene under reflux afforded the rearrangement product **77** as a single diastereoisomer in good yield with high enantiomeric purity following 'transfer of chirality'. The stereochemistry of this process can be understood in terms of a transition state model that resembles an oxabicyclo[3.3.0]octane ring system with the key, stereochemistry-defining methyl group located on the convex face. A further six steps, including a Dieckmann cyclization to construct the spirocyclic core, were necessary to convert the benzofuranone intermediate **77** into the target natural product.



Scheme 22. Total synthesis of (+)-griseofulvin *via* [2,3]-rearrangement of oxonium ylide.

West and co-workers have developed an iterative approach to polycyclic ethers based on the [2,3]-sigmatropic rearrangement of cyclic oxonium ylides (**Scheme 23**).[51] The polycyclic etheral structure occurs in marine ladder polyether toxins, such as brevetoxin B. In the West's approach, the diazoketone **78** was treated with $Cu(tfacac)_2$ to give the [2,3]-rearrangement products **79** and **80** with high diastereoselectivity and good yields, along with a small amount of the C-H insertion product **81**. This study proved once again that copper catalysts favour ylide formation, while rhodium catalysts promote carbenoid C-H insertion. After epimerization, the mixture of diastereoisomers **79** and **80** was converted into diazoketone **82**, which was then subjected to the same $Cu(tfacac)_2$-catalysed ylide formation/[2,3]-sigmatropic rearrangement. Tris(tetrahydropyran) **83** was isolated in an excellent yield as the only detectable isomer.

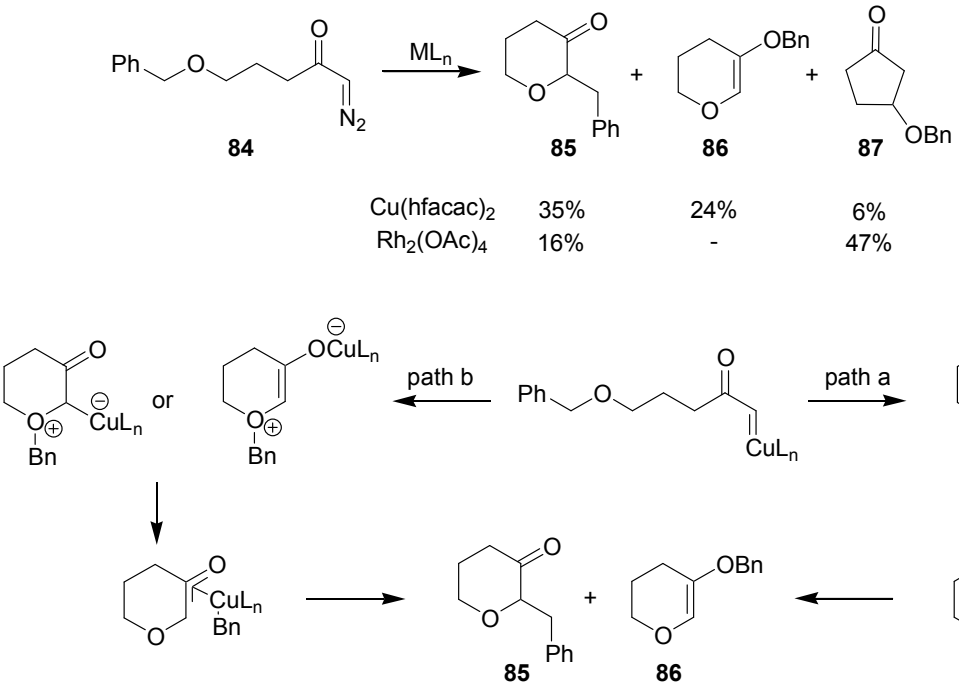


Scheme 23. Iterative approach to polycyclic ethers based on stereoselective oxonium ylide [2,3]-shifts.

1.3.3.3. The [1,4]-shift reaction

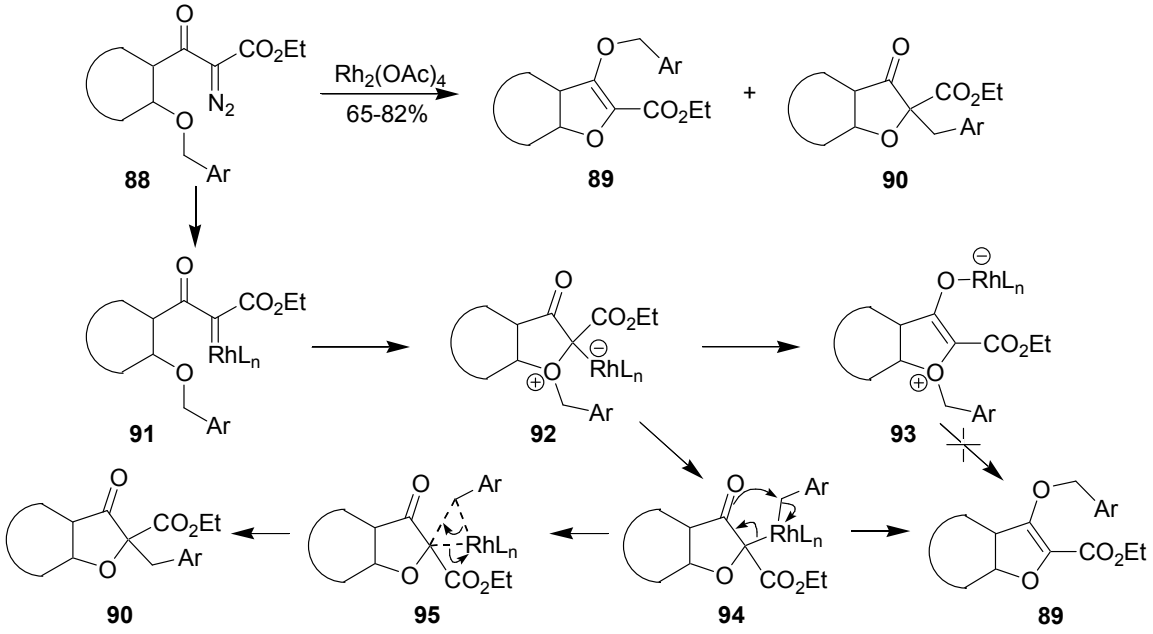
When oxonium ylide formation occurs, products derived from either [2,3]-sigmatropic rearrangement or [1,2]-migration are usually observed and products formed by [1,4]-migration are very unusual. Pirrung and co-workers were the first to notice an example of [1,4]-migration in a rhodium(II)-mediated reaction,[50] whereas West[52] and Clark[53] described the isolation of [1,4]-migration products in low yield when oxonium ylides were derived from copper(II) carbenoids. Indeed, diazoketone **84** underwent predominant C-H insertion when treated with $Rh_2(OAc)_4$, and only a small amount of [1,2]-shift product **85** was obtained (**Scheme 24**). However, the use of $Cu(hfacac)_2$ gave the [1,2]- and [1,4]-migration products **85** and **86** along with a small amount of the C-H insertion product **87**. West and co-workers proposed a mechanism for the formation of the

[1,2]- and [1,4]-migrated products. They firstly assumed that the [1,4]-migration product **86** is derived from the same ylide and radical pair intermediates that lead to the [1,2]-shift product **85**, but with recombination at oxygen instead of carbon (path a). However, because radical homodimers were not isolated, they suggested that an alternative, metal-assisted mechanism is operating in this case (path b).



Scheme 24. Copper-catalysed [1,4]-migration mechanism.

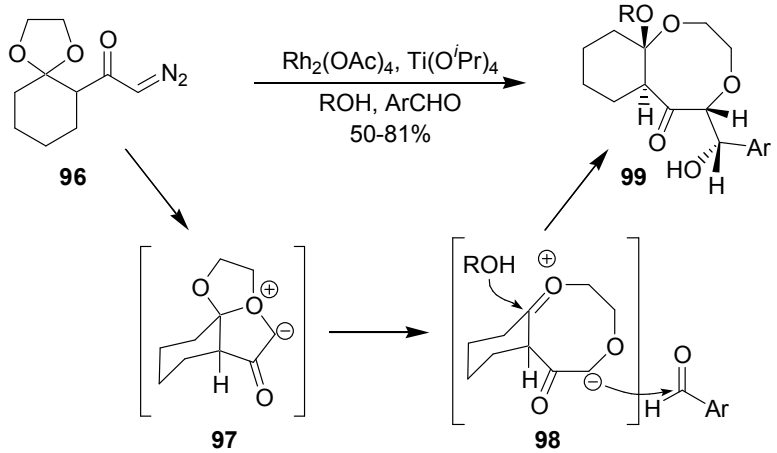
The formation of [1,4]-migration products has been observed to be the dominant pathway in the rhodium(II) catalysed decomposition of α-diazo β-keto esters in certain cases.[54] Since Rh(II)- and Cu(II)-catalysed reactions of diazo compounds give different product distributions, Dhavale and co-workers proposed an independent mechanism for the rhodium carbenoid-mediated [1,4]-rearrangement (**Scheme 25**).[54a] They suggested that the oxonium ylide **93** can not be a possible intermediate for the formation of [1,4]-migration because of the large distance between the migration origin and the terminus. To explain the outcome of the reaction, they proposed an intermediate **94** resulting from migration of the -CH_2Ar group from oxygen to Rh, and they considered **94** as the true intermediate in the formation of both [1,2]- and [1,4]-migration products **90** and **89** respectively. The selectivity of the [1,2] versus [1,4]-migration depends on the electronic nature of the migrating group. For electron-rich substituents only [1,4]-migration products were isolated, but in the case of electron-poor substituents, both products were obtained.



Scheme 25. Rhodium-catalysed [1,4]-migration mecahnism.

1.3.3.4. Miscellaneous reactions of oxonium ylides

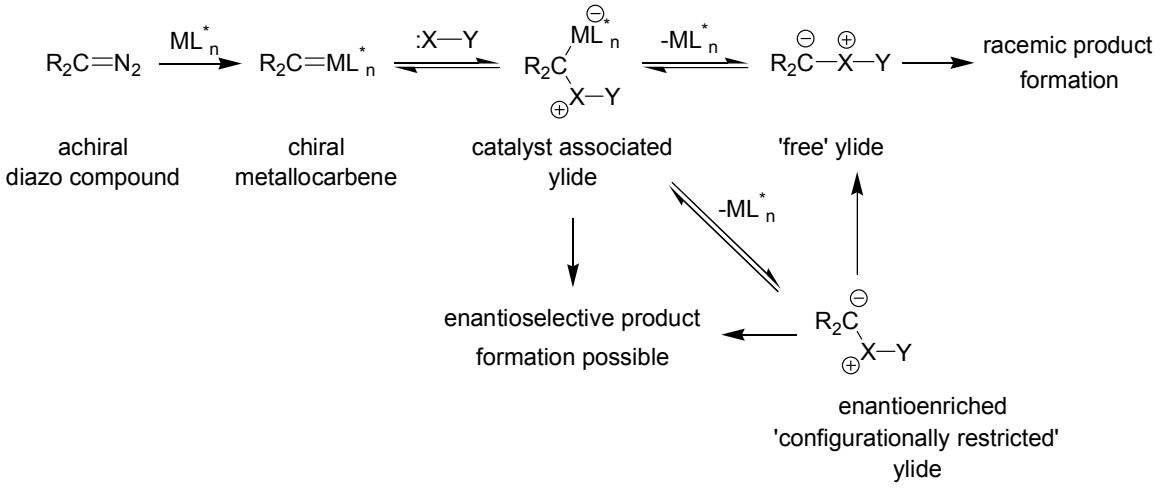
Besides undergoing [2,3]-sigmatropic rearrangement, [1,2]-shift and [1,4]-migration reactions, oxonium ylide intermediates can react with nucleophiles or react through other pathways. A recent example is a multicomponent reaction of the diazoketone **96** with an alcohol and an aldehyde (**Scheme 26**).[55] This reaction is presumed to involve a tricyclooxonium ylide intermediate **97** that undergoes ring opening to bicyclic zwitterion **98**. Subsequent selective nucleophilic attack of the alcohol and aldol condensation with the aldehyde gave the product **99**.



Scheme 26. Multicomponent reaction of oxonium ylide.

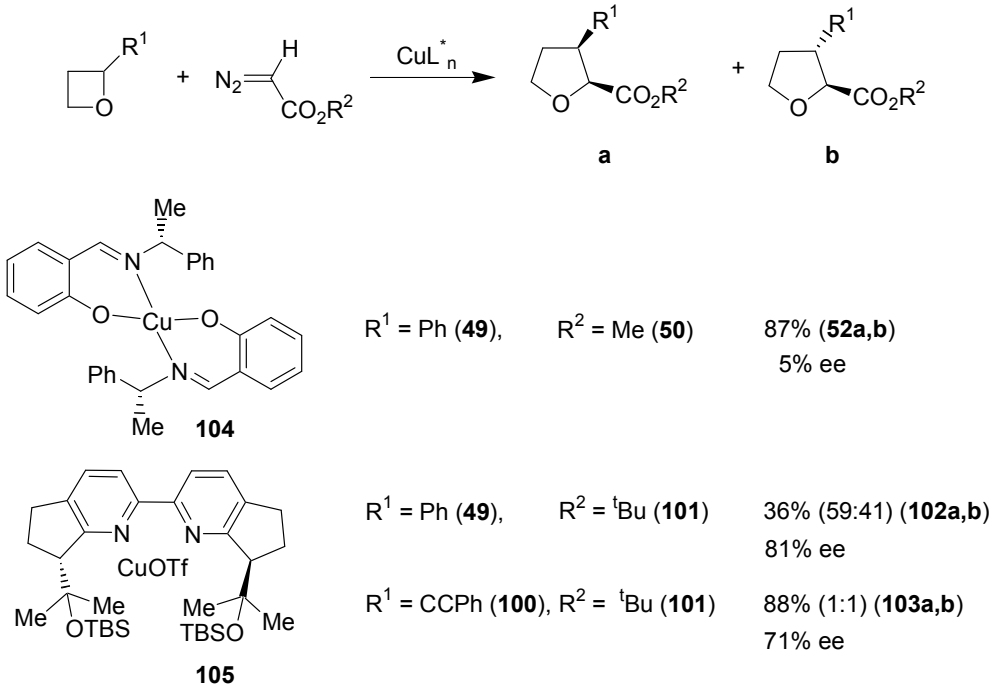
1.3.3.5. Enantioselective generation and rearrangement of oxonium ylides

The development of asymmetric versions of reactions involving oxonium ylides, in particular by using asymmetric catalysts, is very challenging.[20b,56] If the catalyst remains associated with the ylide during the subsequent rearrangement process, asymmetric induction might be observed (**Scheme 27**). However, if the catalyst dissociates and therefore is not involved in the ylide rearrangement step, it would lead to either a 'free' ylide, for which asymmetric induction would be very unlikely, or to an enantioenriched 'configurationally restricted' ylide, where subsequent enantioselective transformations might be possible (**Scheme 27**).



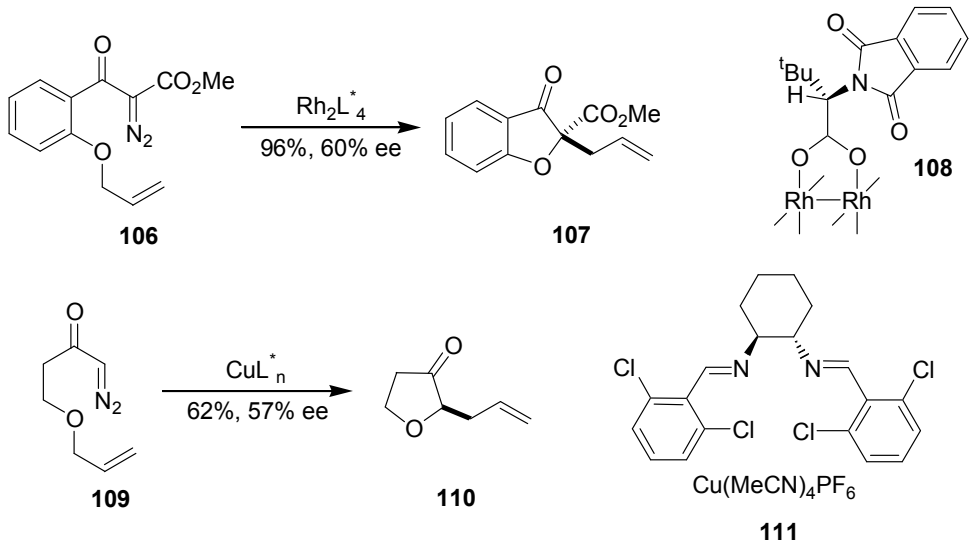
Scheme 27. Asymmetric ylide reactions.

Recent developments have shown that catalytic asymmetric synthesis is possible in several ylide transformations. Nozaki was the first to recognize the potential of the asymmetric reaction, and he showed that optically active tetrahydrofurans can be obtained from racemic oxetanes (**Scheme 28**).[42] The reaction of (±)-2-phenyl-oxetane **49** and methyl diazoacetate **50** with the chiral copper complex **104** furnished a mixture of diastereomeric tetrahydrofurans **52a** and **52b** resulting from a [1,2]-shift of the benzyl group. Although the products were obtained in good yield, the level of asymmetric induction was very low. These promising results prompted Katsuki to explore the reaction with another chiral copper complex (e.g. **105**). He obtained a mixture of *cis* and *trans* tetrahydrofurans **102a** and **102b**, but this time with high enantiomeric purity.[57]



Scheme 28. First examples of catalytic asymmetric [1,2]-shift of oxonium ylide.

The asymmetric version of the carbenoid-mediated ylide formation and [2,3]-sigmatropic rearrangement sequence has also been explored and was first reported by McKervey in 1992.[58] A chiral Rh(II) phosphate catalyst was employed, which resulted in enantioselectivities of up to 30% ee. Further improvement of enantiocontrol (up to 60% ee) was achieved when chiral carboxylate Rh(II) catalysts were used. Indeed, treatment of the diazoketone **106** with the chiral rhodium(II) complex **108** afforded the benzofuranone **107** in excellent yield and with reasonable enantiomeric purity (**Scheme 29**).



Scheme 29. First examples of catalytic asymmetric [2,3]-rearrangement of oxonium ylides.

Following this initial study, an intramolecular asymmetric tandem oxonium ylide formation and [2,3]-rearrangement sequence catalysed by a chiral Cu(I) diimine complex **111** was reported by Clark and co-workers.[59] The achiral diazoketone **109** was converted in the non-racemic cyclic ether **110** with up to 57% ee.

In summary, the formation of oxonium ylides and their subsequent rearrangement reactions are becoming increasingly popular reactions for organic synthesis. High levels of chemo-, regio- and stereoselectivity can be achieved by paying attention to the design of the substrate and the choice of the catalyst to favour the desired reaction pathway. Even though oxonium ylide chemistry has already been successfully applied in complex natural product synthesis, the potential of this chemistry is yet to be fully exploited.

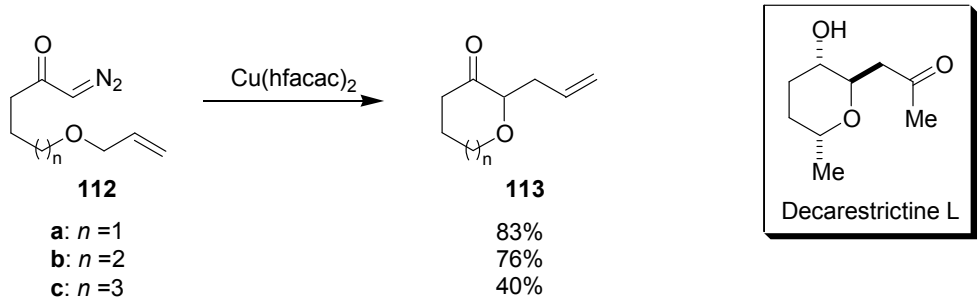
2. *Previous work performed by the Clark Group*

Over the last 15 years, the Clark Group has demonstrated the versatility of the metal carbenoids derived from diazocarbonyl compounds as intermediates for the synthesis of a variety of complex structures. The oxonium ylide generation and subsequent rearrangement has been studied extensively within the group, particularly with regard to the development of new methodologies for the synthesis of cyclic ethers and medium-ring carbocycles (the subject of the next chapter). This strategy was then applied to the synthesis of natural products.

2.1. Synthesis of cyclic ethers

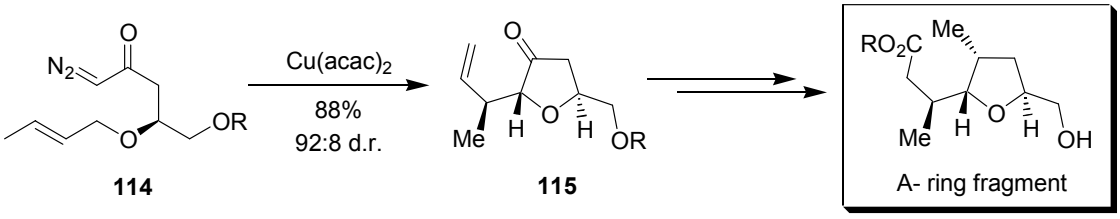
Initial work began with the synthesis of simple cyclic ethers such as tetrahydropyran-3-one **113a**, oxepan-3-one **113b** and oxocan-3-one **113c** from the diazoketones **112a**, **112b** and **112c** respectively.[60] Clark and co-workers discovered that copper-mediated reactions, especially those using $Cu(hfacac)_2$ as the catalyst, are particularly effective compared to rhodium-catalysed cyclisation reactions where unwanted C-H insertions were observed (**Scheme 30**). Having established this methodology, Clark and co-workers published a

short synthesis of (±)-decarestrictine L.[61] Few years later, a 10-step enantioselective synthesis was reported using the chiral pool starting material, ethyl (*R*)-3-hydroxybutyrate.[62]



Scheme 30. Copper-mediated synthesis of cyclic ethers, and its application to the total synthesis of decarestrictine L.

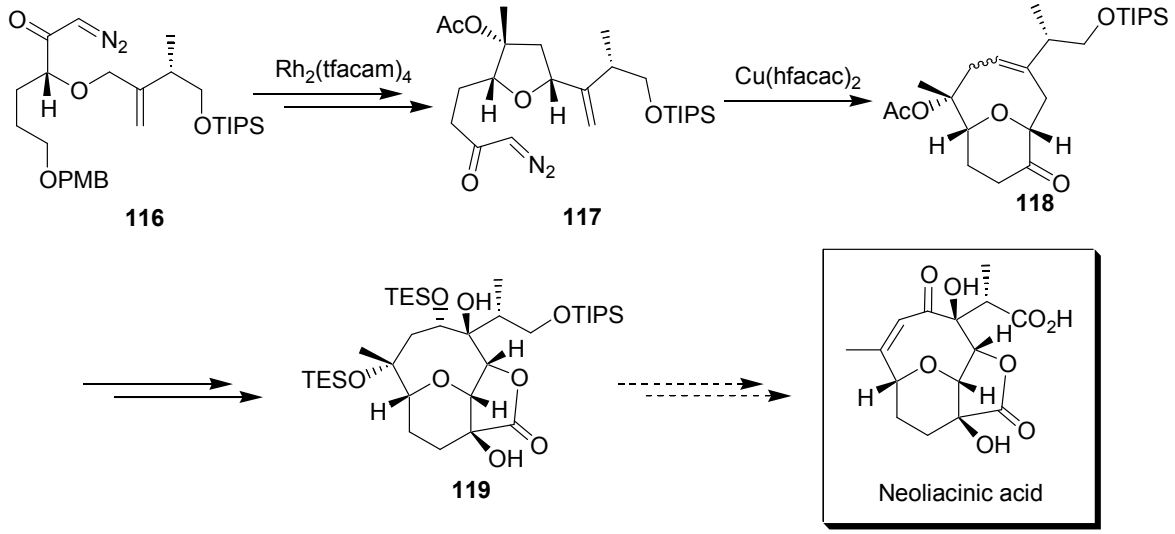
They also investigated the diastereoselective synthesis of 2,5-dialkyl tetrahydrofuran-3-ones.[63] It was found that the nature of the metal complex has a profound influence on the level of diastereocontrol achieved. When $Rh_2(OAc)_4$ was employed as the catalyst, a mixture of *cis*- and *trans* isomers was obtained in modest yield and low diastereoselectivity was observed. However, a dramatic improvement was achieved when employing copper catalysts, giving high levels of diastereoselectivity. This methodology has been used as the key step for the stereocontrolled synthesis of the A-ring fragment of the gambieric acid A. The copper-mediated cyclisation reaction furnished two of the four stereocentres in this case (**Scheme 31**).[64] The chiral diazoketone **114** was prepared starting from the commercially available (*S*)-dimethylmalate, and then was treated with $Cu(acac)_2$ to furnish the tetrahydrofuran ring **115**. The reaction delivered the required *trans*-3(*2H*)-furanone **115** in an excellent yield with absolute diastereoselectivity. The synthesis of the A-ring fragment was then completed; coupling of the A-ring fragment and further studies towards the total synthesis of gambieric acids are in progress.



Scheme 31. Stereoselective synthesis of the A-ring fragment of the gambieric acids.

2.2. *Synthesis of complex terpenoids: neoliacinic acid and the cladiellins*

The one-pot catalytic carbenoid formation, intramolecular oxonium ylide generation, and ylide rearrangement sequence has also been employed for the construction of bridged ether cores of sesquiterpene and diterpene natural products. Intense efforts have been rewarded by the synthesis of the core structure of neoliacinic acid,[65] and labiatin A.[66] Very recently, this work has been culminated by the total synthesis of the cladiellin/eunicellin natural product vigulariol.[67]

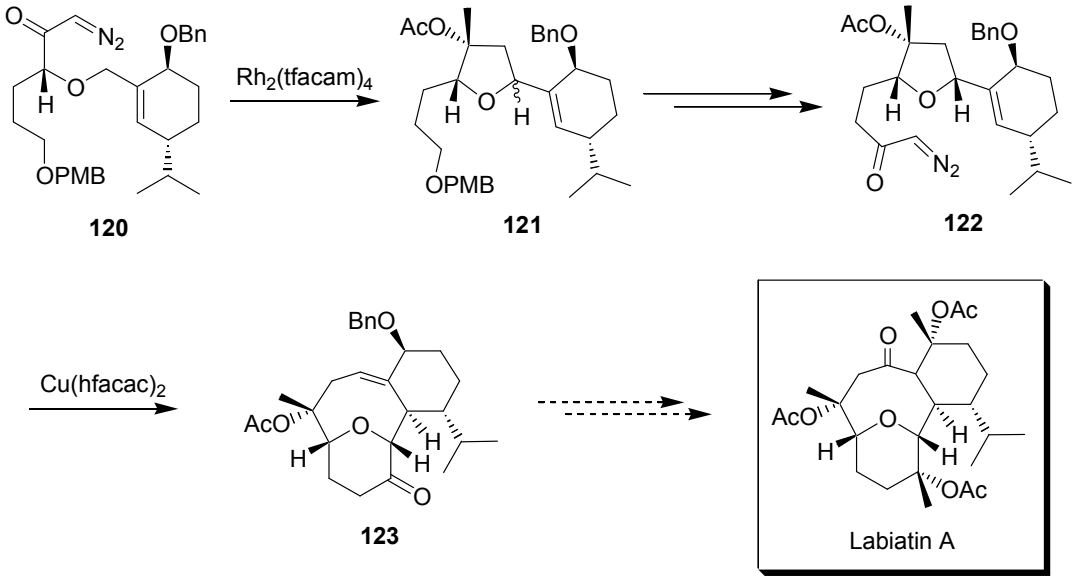


Scheme 32. Stereoselective construction of the tricyclic core of neoliacinic acid.

The fully functionalised tricyclic core of neoliacinic acid has been synthesised in a concise manner, using two metal carbenoid reactions: a C-H insertion reaction followed by an oxonium ylide formation and rearrangement reaction (**Scheme 32**).[65] The first key intermediate was obtained after exposure of the diazoketone **116** to rhodium(II) trifluoroacetamide giving intramolecular C-H insertion reaction. The intermediate carbenoid reacted to give good levels of diastereoselectivity, affording the required *cis* substituted cyclic ether, while producing minimal amounts of other C-H insertion products and those arising from competing cyclopropanation. This tetrahydrofuran was then converted into the key cyclisation precursor **117** in just a few steps. Treatment of the diazoketone **117** with copper(II) hexafluoroacetylacetonate afforded the bridged bicyclic ether **118** in 69% yield as a 3:2 mixture of *Z* and *E* isomers, by [2,3]-rearrangement of the intermediate oxonium ylide, along with a small amount of the [1,2]-shift compound. After

isomerisation of the mixture of alkenes **118**, the tricyclic core **119** was constructed by installation of the lactone.

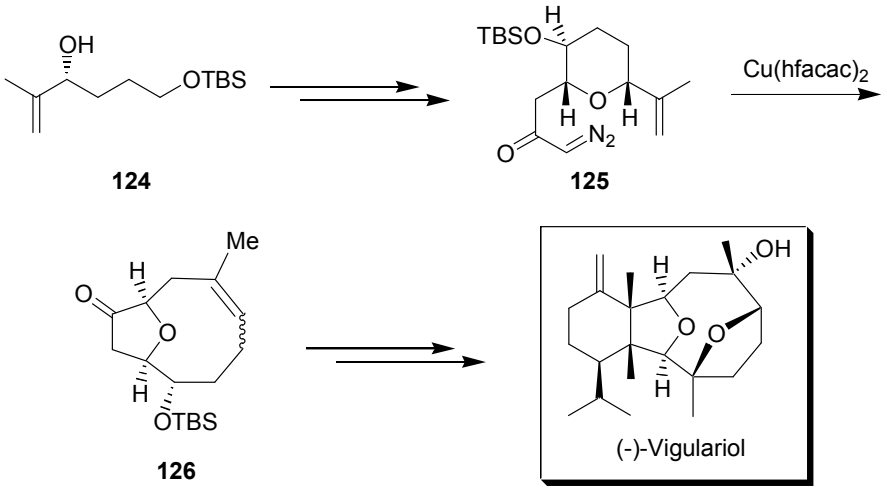
The tricyclic core of liabatin A has been synthesised by employing a similar strategy to that applied to the synthesis of neoliacinic acid (**Scheme 33**).[66] The rhodium-catalysed C-H insertion product **121** was prepared from diazoketone **120** in 66% yield (7:1, *cis*:*trans* ratio), and further synthetic manipulation produced the advanced diazoketone intermediate **122**. The copper-mediated cyclisation reaction afforded only the required [2,3]-rearrangement product **123** in an excellent 76% yield. It is worth noting that this transformation gave the desired tricyclic core with the correct relative stereochemistry. Studies towards the total synthesis of labiatin A are ongoing in the Clark group, using this strategy.



Scheme 33. Stereoselective construction of the tricyclic core of labiatin A.

The most recent success in the synthesis of members of the eunicellin family, is the asymmetric total synthesis of (–)-vigulariol, which has not yet been published (**Scheme 34**).[67a] Starting from the optically active allylic alcohol **124**, the synthesis of (–)-vigulariol was completed using the published synthetic route to (±) vigulariol.[67b] The key metal-mediated reaction once again proved to be extremely efficient. Indeed, treatment of the diazoketone **125**, prepared by a samarium diiodide-mediated reductive cyclisation reaction, with $Cu(hfacac)_2$ afforded the bicyclic core of cladiellins **126** in 96% yield as a mixture of *Z*- and *E*- isomers. The undesired *E*-isomer was smoothly converted to the *Z*-isomer upon treatment with AIBN and a sub-stoichiometric amount of ethanethiol. Intermolecular

Diels-Alder cycloaddition to install the cyclohexyl ring followed by further transformations completed the asymmetric total synthesis of (–)-vigulariol in 20 steps in an overall yield of 5.9%. The successful use of this strategy paves the way for the total syntheses of other cladiellin family members, such as orphirin B and (–)-cladiella-6,11-dien-3-ol.



Scheme 34. Asymmetric total synthesis of (-)-vigulariol.

3. *Synthesis of medium-ring carbocycles*

The widespread presence of fused carbocyclic systems containing medium-sized rings in the structural cores of numerous biologically relevant natural products offers significant synthetic challenges.[68] The well-known difficulties encountered when assembling seven- and eight-membered rings, due to unfavourable entropic and enthalpic factors,[69] makes the development of new, practical and efficient approaches to their construction an important objective.

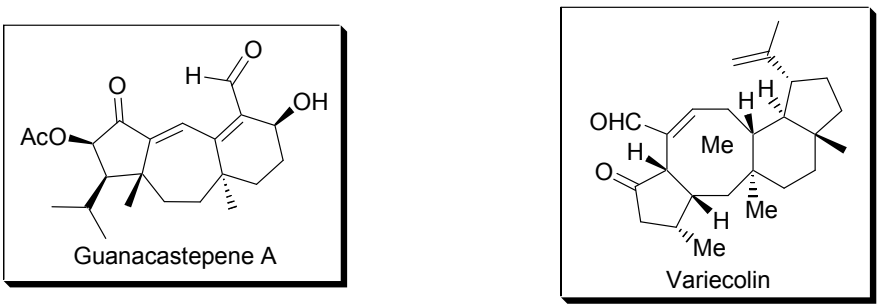
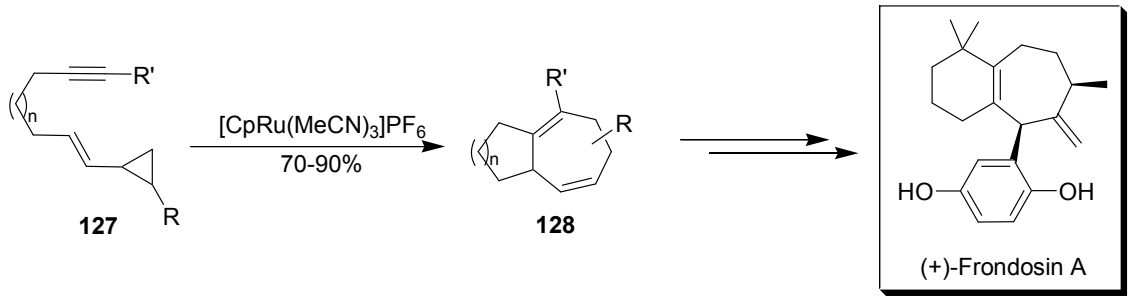


Figure 5. Representative fused medium-ring carbocyclic natural products: guanacastepene A and variecolin.

For example, the bioactive diterpenoid natural products guanacastepene A[70] and variecolin[71] contain a seven-membered ring and an eight-membered ring respectively as part of their polycyclic structures and nicely exemplify the synthetic challenges presented by linearly fused polycarbocyclic natural products (**Figure 5**).

3.1. General strategies for medium-ring synthesis

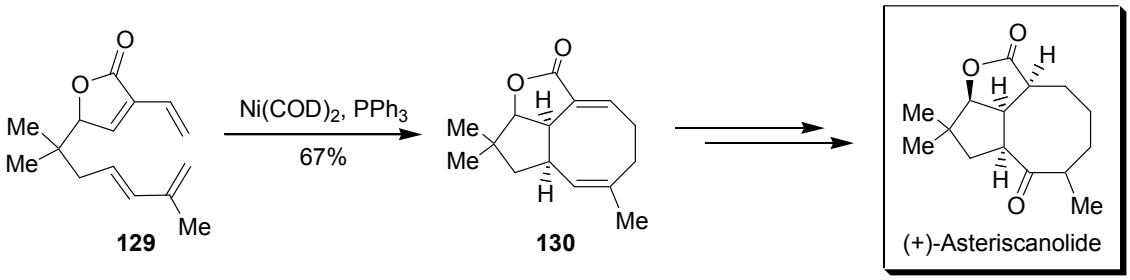
Several important methods have been developed for the construction of these structural motifs. The most popular approaches are cycloaddition reactions, ring expansion reactions and direct cyclisation reactions. Cycloadditions constitute one of the most powerful and versatile methods for the synthesis of carbocyclic systems. Cycloaddition processes are promoted by heat, light, Lewis acids and transition metals. Seven-membered rings are prepared generally by [5+2], [6+1] and [4+3] cycloadditions, and the eight-membered rings by [4+4], [4+2+2], [5+2+1] and [6+2] cycloadditions. One of the most interesting examples of the preparation of fused seven-membered carbocycles such as **128** is a ruthenium-catalysed intramolecular [5+2] cycloaddition of cyclopropylenynes **127** (**Scheme 35**).[72] This process provides a straightforward and atom-economical entry to a variety of cycloheptane-containing polycycles from readily available acyclic precursors. The reaction generally shows excellent chemo- and diastereoselectivity. This Ru-catalysed [5+2] cycloaddition has been applied in the synthesis of the natural product frondosin A, highlighting the efficiency of this methodology for the generation of complex fused ring-systems (**Scheme 35**).



Scheme 35. Application of Ru-catalysed intramolecular [5+2] cycloaddition to the total synthesis of (+)-frondosin A.

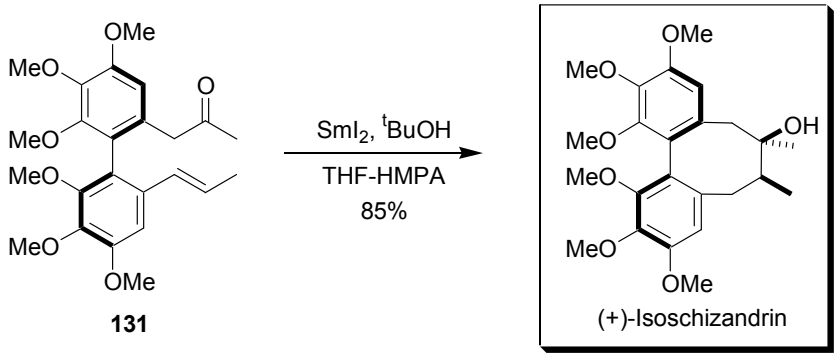
Wender and co-workers have greatly contributed to the development of fundamental strategies for 7- and 8-membered ring synthesis in which transition-metal catalysed cycloaddition reactions are employed. They reported the first examples of

intramolecular nickel-catalyzed [4+4] cycloaddition of bis-dienes,[73] which have been used to readily access the fused eight-membered ring core of taxol,[74] and in the total synthesis of (+)-asteriscanolide[75] and (±)-salsolene[76] (**Scheme 36**). Their interest in the synthesis of eight-membered rings has been rewarded by the discovery of rhodium-catalysed [6+2] cycloaddition of vinylcyclobutanones and alkenes,[77] [4+2+2] cycloaddition of 1,3-dienes, alkenes and alkynes,[78] [(5+2)+1] cycloaddition of vinylcyclopropanes, alkynes and carbon monoxide,[79] and [5+2] cycloaddition of vinylcyclopropanes and allenes.[80]



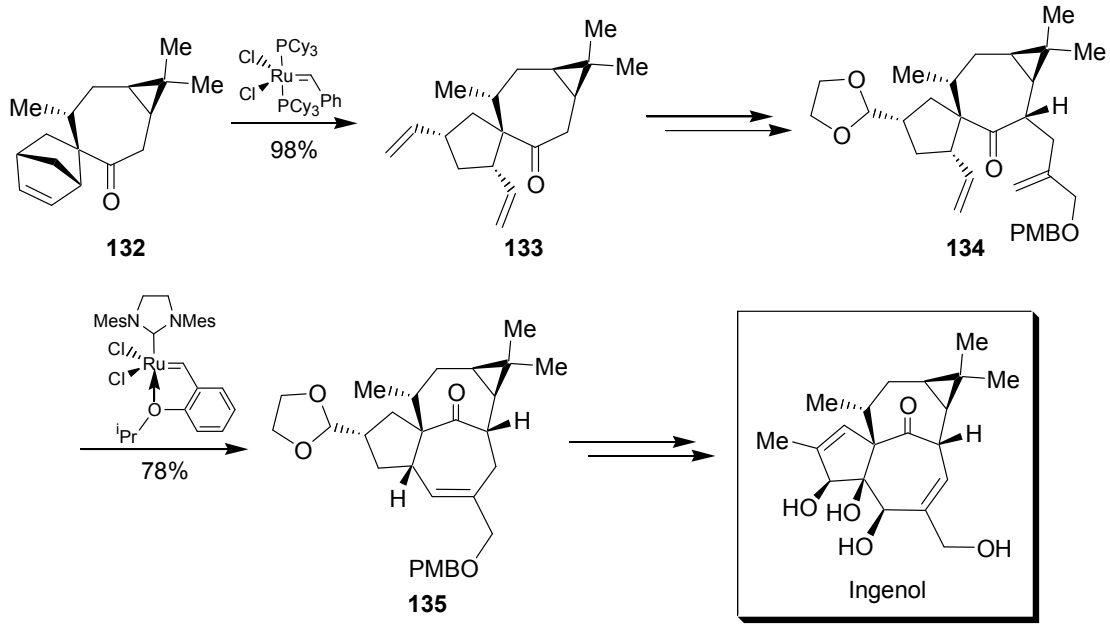
Scheme 36. Application of nickel-catalyzed [4+4] cycloaddition to the total synthesis of (+)-asteriscanolide.

One of the most attractive general approaches for the transformation of simple materials into monocyclic, bicyclic and polycyclic scaffolds is the direct cyclisation reaction. Samarium(II) diiodide mediated cyclisation reactions have found numerous applications in carbocycle construction.[81] Indeed, the SmI_2-mediated intra- and intermolecular Barbier reaction has been used for the preparation of the carbon framework of phorbol,[82] vinigrol[83] and variecolin.[84] The B-ring of the taxane skeleton has been prepared using SmI_2-mediated pinacol coupling[85] and Reformatsky reactions,[86] the later has also successfully been employed in a formal synthesis of (–)-octalactin A.[87] The carbonyl-olefin reductive coupling has also been applied to the synthesis of the tricyclic system of guanacastepene A,[88] and in two recent total syntheses of (–)-steganone[89] and (+)-isoschizandrin[90] (**Scheme 37**).



Scheme 37. Application of SmI_2-mediated cyclisation to the total synthesis of (+)-isoschizandrin.

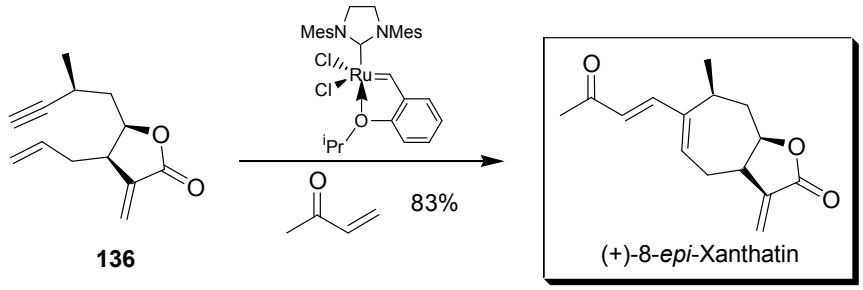
Another popular cyclisation method is ring-closing metathesis, which has emerged as a versatile and powerful reaction for the synthesis of a variety of 7- and 8-membered carbocyclic rings.[91] Although diene metathesis is the most widely utilized type of metathesis reaction, recent years have witnessed the discovery and development of both enyne and diyne metathesis. A number of carbocyclic natural products have been synthesised by these approaches. Wood and co-workers brilliantly used an olefin metathesis reaction in their total synthesis of ingenol (**Scheme 38**).[92] The readily available enantiomerically pure precursor **132** underwent smooth ring-opening metathesis (ROM) upon exposure to Grubbs 1st generation catalyst under an ethylene atmosphere to afford diene **133** in nearly quantitative yield. Following the uneventful advancement of diene **133** to give intermediate **134**, the stage was set for the pivotal ring-closing metathesis (RCM) reaction. The desired ring closure reaction was effected in good yield using Grubbs-Hoveyda catalyst;[93] further modifications of the cyclised product **135** provided the natural product ingenol.



Scheme 38. Application of metathesis reaction to the total synthesis of ingenol.

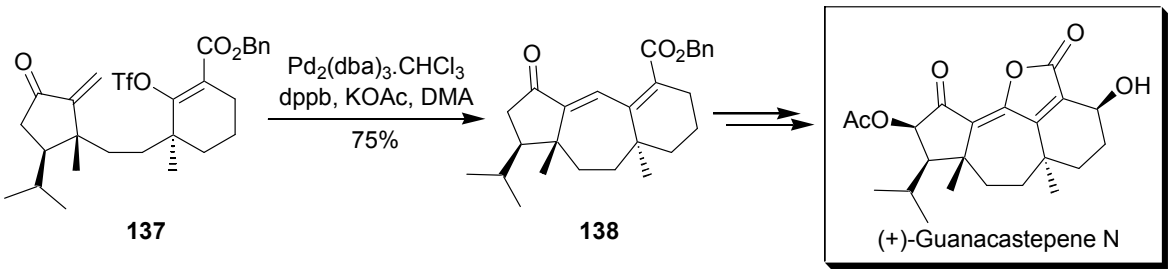
A catalytic asymmetric ring-opening/ring-closing metathesis cascade reaction has also been developed and then employed to furnish the sesquiterpenoid (+)-africanol using a chiral molybdenum-based catalyst.[94] The enyne-metathesis reaction is an extremely useful method for the construction of 1,3-diene systems, which are intermediates suitable to undergo further selective transformations. The use of enyne-metathesis reaction in cascade processes to generate complex polycyclic structures is one of the most exciting and powerful applications. The Hanna group made good use of this type of tandem RCM

process in their recent formal synthesis of guanacastepene A.[95] Another example is a domino intramolecular enyne metathesis/cross-metathesis (CM) which was used to construct the seven-membered carbocycle in the first total synthesis of (+)-8-*epi*-xanthatin (**Scheme 39**).[96]



Scheme 39. Application of metathesis reaction to the total synthesis of (+)-8-*epi*-xanthatin.

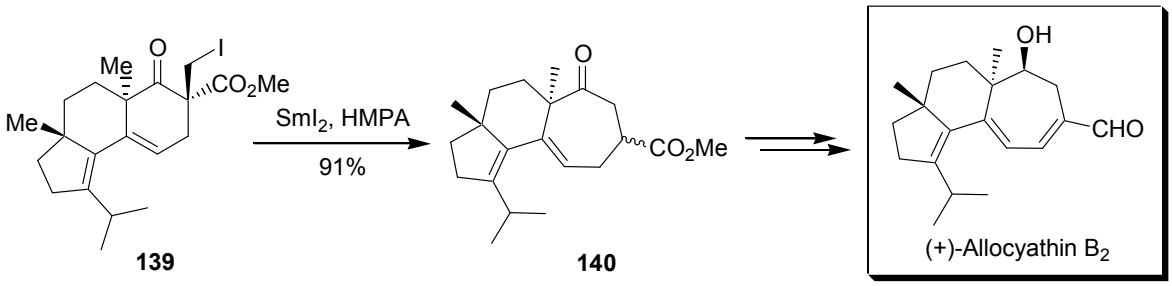
A variety of coupling reactions, including the well-known McMurry coupling, Heck/Stille reaction and Kishi reaction have found application in cycloheptanoid and cyclooctanoid synthesis. Recently, an uncommon 7-*endo* Heck cyclization has been used as the key step in the enantioselective total synthesis of guanacastepene N (**Scheme 40**).[97] Members of the guanacastepene family have attracted serious attention in the last decade because of their antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium,* and their unique tricyclotetradecane ring system composed of fused five-, six- and seven-membered rings. These diterpenes have stimulated much interest resulting in seven total syntheses to date.[95,97,98] Overman and co-workers prepared the central, highly-substituted cycloheptane ring **138** of guanacastepene N by an intramolecular Heck cyclisation of dienyl triflate **137**. The seven-membered ring was constructed by an unusual 7-*endo* pathway; normally the intramolecular Heck reaction proceeds to give 6-*exo* products.



Scheme 40. Application of Heck reaction to the total synthesis of (+)-guanacastepene N.

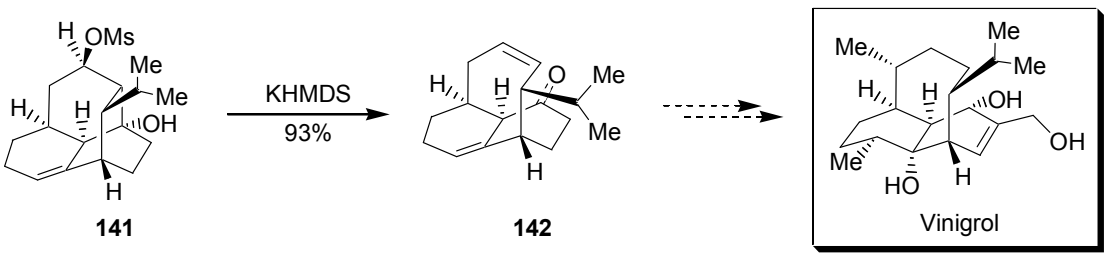
Seven- and eight-membered rings can also be generated indirectly, through fragmentation-recombination, ring expansion, ring contraction and rearrangement

reactions, etc. For example, Hasegawa developed a samarium(II)-diiodide promoted sequential cyclisation and ring expansion reaction.[99] This methodology proved to be very efficient and has since been used for the total synthesis of natural products, such as (±)-sarcodonin G,[100] (+)-allocyathin B_2[101] and (–)-erinacine B.[102] SmI_2 promotes the conversion of α-iodomethyl cyclic β-keto ester **139** to the corresponding one-carbon homologated γ-keto ester **140** by formation of methyl radical which undergoes cyclisation to give the cyclopropyl radical and further ring expansion (**Scheme 41**).



Scheme 41. Application of samarium-mediated ring expansion to the total synthesis of (+)-allocyathin B_2.

The Grob fragmentation is another reaction that offers a successful approach to the synthesis of medium-sized carbocycles. This reaction has been used by Holton in his total synthesis of Taxol,[103] and lately by Baran for the construction of the tricyclic core of vinigrol,[104] a particularly challenging target, no total synthesis of which had been reported. The tetracyclic 1,3-hydroxymesylate **141** was treated with KHMDS, triggering concerted fragmentation to afford the desired tricyclic carbon skeleton **142** in excellent yield (**Scheme 42**).



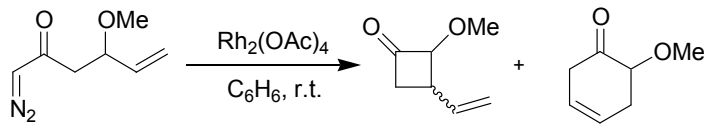
Scheme 42. Application of Grob fragmentation towards the total synthesis of vinigrol.

There are plenty of other methods for the construction of medium-sized carbocycles, including Brook rearrangement, aldol condensation, [3,3]-sigmatropic rearrangement (in particular Cope and Claisen rearrangements), pinacol rearrangement, radical cyclisation, manganese-, iron- and cobalt-mediated reactions. This list is not

exhaustive; this short overview has concentrated on total syntheses published in the last ten years and other methods will no doubt be developed to allow access to these structures.

3.2. Construction of medium-ring systems by oxonium ylide generation and rearrangement.

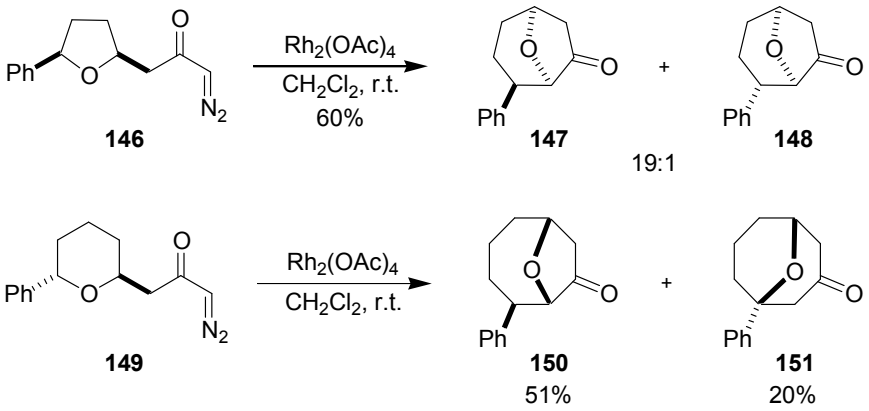
Catalytic generation and rearrangement of oxonium ylides offers a potentially versatile approach to the synthesis of carbocycles. The first example where carbocycles were constructed using this strategy comes from Johnson's original studies on the generation of oxonium ylides.[45] The rhodium-mediated reaction of the diazoketone **143** delivered mainly the cyclobutane **144** resulting from the [1,2]-rearrangement with ring contraction, but a small amount of the [2,3]-rearrangement product **145** was also isolated (**Scheme 43**). Although the carbocycles constructed were cyclobutanone and cyclohexenone, the reaction had potential for the synthesis of other ring sizes, provided that appropriate substrates were used.



143 **144** 45% (3:1) **145** 10%

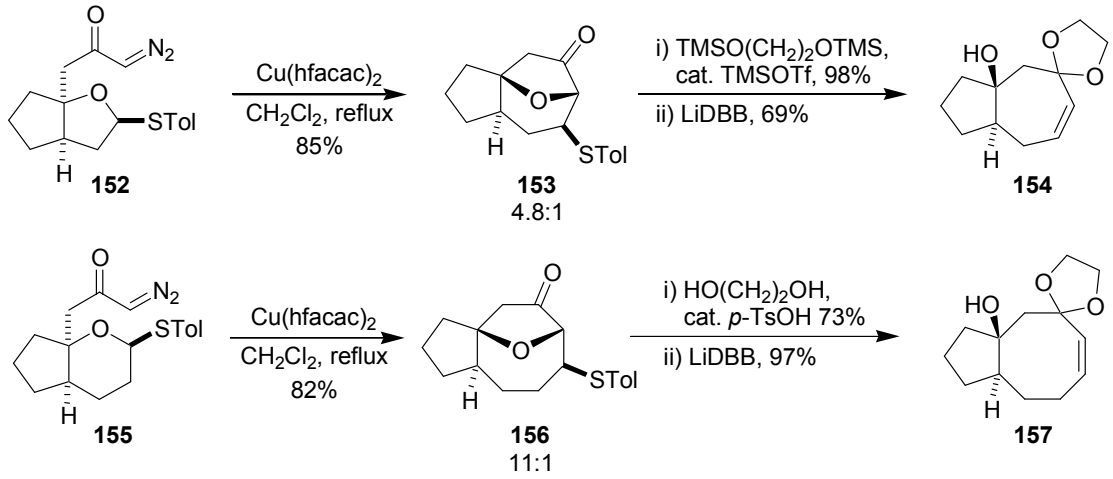
Scheme 43. First example of carbocycle construction by oxonium ylide generation and rearrangement.

Subsequently, West described the synthesis of *O*-bridged medium-sized rings *via* transient fused bicyclic oxonium ylides, generated by the reaction of $Rh_2(OAc)_4$ with cyclic ethers bearing a tethered diazoketone.[105] The tetrahydrofuran **146** underwent an efficient [1,2]-shift to give the ether-bridged cycloheptanones **147** and **148** with very good diastereoselectivity and predominant retention of configuration. This strategy was then extended to the formation of the cyclooctanones **150** and **151** using the tetrahydropyran **149** (**Scheme 44**).



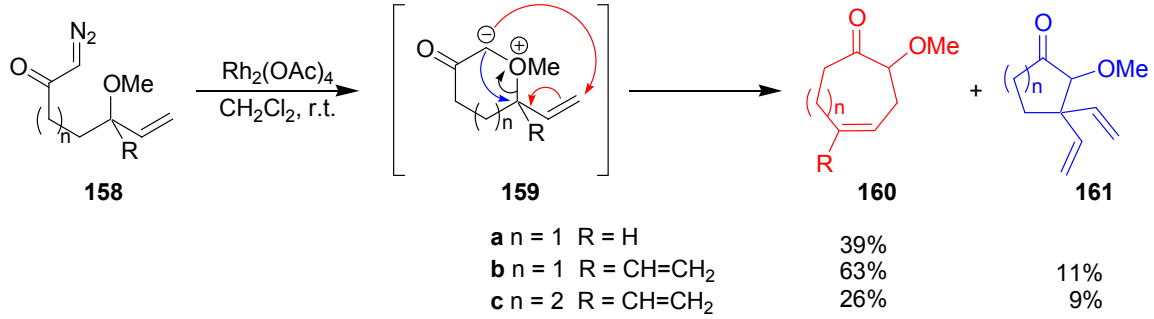
Scheme 44. Synthesis of *O*-bridged medium sized rings *via* [1,2]-shift.

West and co-workers also described the efficient synthesis of fused oxabicyclo[3.2.1]octanones and oxabicyclo[4.2.1]nonanones using sulfur-directed Stevens rearrangement of oxonium ylides (**Scheme 45**).[106] The mixed cyclic acetals with pendant diazoketone side chains underwent rearrangement to afford ether-bridged cycloheptane and cyclooctane ring systems. Thus, treatment of diazoketones **152** and **155** with $Cu(hfacac)_2$ provided the oxabicycles **153** and **156** respectively through a [1,2]-shift of the five-membered oxonium ylide intermediates. In some cases, minor amounts of products resulting from the [1,2]-shift of a sulfonium ylide were isolated. Importantly, the thioaryl group present in the product was used to direct the rearrangement as well as to trigger the cleavage of the bridging ether. After protection of the ketones, the electron transfer reductive desulfurisation produced the ring-opened products **154** and **157** in excellent yields.



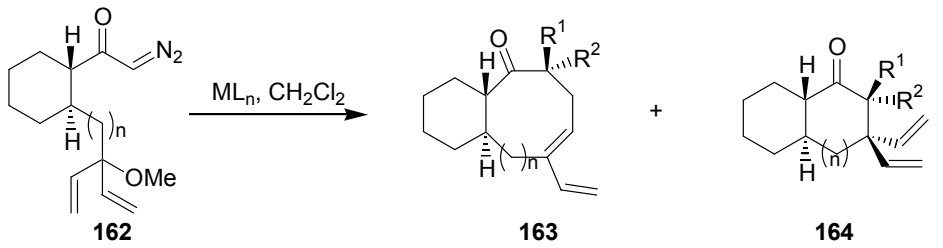
Scheme 45. Synthesis of fused medium rings *via* [1,2]-shift.

In the meantime, Clark and co-workers reported a novel method for the preparation of medium-ring cycloalkenones by tandem intramolecular generation and [2,3]-rearrangement of an oxonium ylide (**Scheme 46**).[107] Treatment of diazoketones **158** with rhodium(II) acetate resulted in the formation of a rhodium carbenoid species which was immediately trapped by the tethered allylic ether to generate a highly reactive ylide **159**. Subsequent ylide rearrangement delivered the cyclic ketones **160** and **161**. The major reaction pathway was ring-expanding [2,3]-rearrangement to give the medium ring ketone **160**, whereas the cyclic ketone **161** was formed as a minor product by a ring-contracting [1,2]-rearrangement.



Scheme 46. Synthesis of simple medium-ring ketones from acyclic precursors by [2,3]-rearrangement of catalytically generated oxonium ylides.

The synthesis of fused polycyclic compounds by employing conformationally constrained diazoketones as carbenoid precursors has been reported recently (**Scheme 47**).[108] The cyclisation reactions of substrates **162** gave some interesting and unpredicted results. In the case of diazoketone **162** (n = 0), treatment of the substrate with $Rh_2(OAc)_4$ resulted in the formation of the fused bicyclic diene **163** in 70% yield. The homologous diazoketone **162** (n = 1) also underwent catalytic ylide formation and rearrangement. However, in this case the best yield (71%) of diene **163** (mixture of diastereoisomers) was obtained when $Cu(tfacac)_2$ was employed as the catalyst; substantial amounts of [1,2]-rearrangement product **164** were obtained from the $Rh_2(OAc)_4$-catalysed reaction of this substrate.



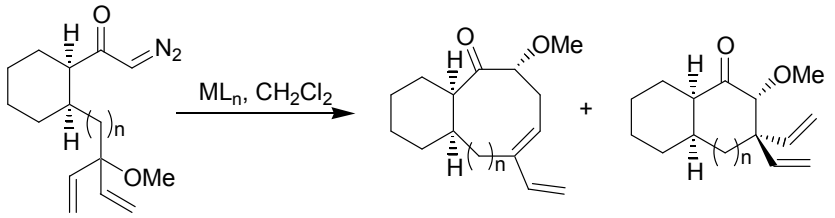
162 **163** **164**

n = 0	$Rh_2(OAc)_4$, 0°C	70% (**a**)	
n = 0	$Cu(tfacac)_2$, reflux	49% (**a**)	
n = 1	$Rh_2(OAc)_4$, r.t.		24% (**a**)
n = 1	$Cu(acac)_2$, reflux	17% (**a**) + 39%(**b**)	14% (**a**) + 8% (**b**)
n = 1	$Cu(tfacac)_2$, reflux	13% (**a**) + 58% (**b**)	8% (**a**) + 12% (**b**)

a: R^1 = OMe, R^2 = H; **b**: R^1 = H, R^2 = OMe

Scheme 47. Catalytic carbenoid generation, ylide formation and rearrangement using the *trans*-diazo ketone **162**.

The metal-catalysed reactions of substrates **165**, in which the diazoketone and ether-containing chains on the cyclohexane ring have a *cis* relationship, were also investigated (**Scheme 48**).[108] In these cases, the yields of diene **166** were lower than those of the *trans*-fused bicyclic products **163**, and substantial amounts of the corresponding [1,2]-rearrangement products **167** were isolated.



165 **166** **167**

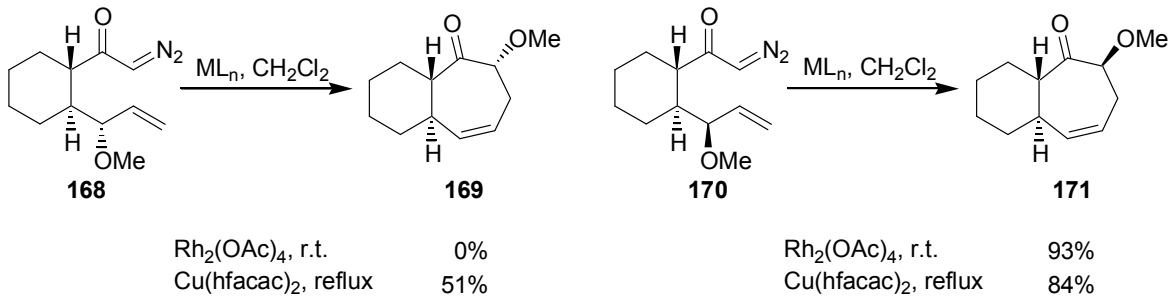
a n = 0	$Rh_2(OAc)_4$, r.t.	20%	47%
b n = 0	$Cu(hfacac)_2$, reflux	3%	14%
c n = 1	$Rh_2(OAc)_4$, r.t.	37%	41%
d n = 1	$Cu(acac)_2$, reflux	48%	15%

Scheme 48. Catalytic carbenoid generation, ylide formation and rearrangement using the *cis*-diazo ketone **165**.

The combined yields of ylide-derived products were high, but substantial amounts of [1,2]-rearrangement products were obtained in addition to the required [2,3]-rearrangement products. The divinyl substrates **162** and **165** were selected in order to avoid having an additional stereogenic centre at the ether-bearing carbon and to permit participation of the vinyl group in the rearrangement reaction, irrespective of the conformation of the intermediate cyclic oxonium ylide.

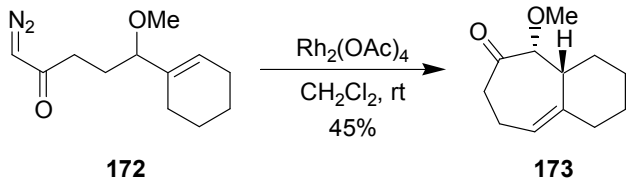
The reactions of the diastereomeric mono-vinyl systems **168** and **170** were then explored in order to discover whether substrates bearing a single vinyl group would

undergo the required rearrangement reaction (**Scheme 49**).[108] The *trans*-substituted cyclohexyl systems **168** and **170** differ only in the relative configuration at the vinyl-bearing stereogenic centre, but substrates of these types are potentially problematic because the stereochemistry of the additional stereogenic centre in the substrate must be defined and may have an unfavourable conformational influence. Interestingly, both substrates underwent the required ylide formation and rearrangement reaction, but the choice of the catalyst was crucial. In the case of the diazoketone **168**, copper(II) hexafluoroacetylacetonate was the catalyst of choice and the [2,3]-rearrangement product **169** was obtained in 51% yield. In contrast, the rhodium- and copper-catalysed reactions of the substrate **170** both afforded the ketone **171** in excellent yield.



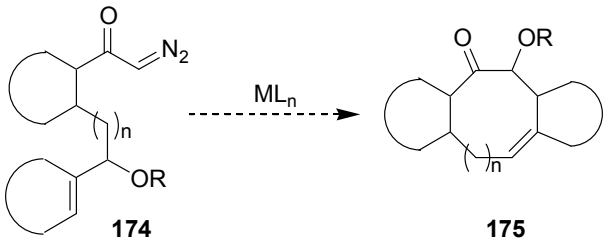
Scheme 49. Catalytic carbenoid generation, ylide formation and rearrangement using the mono-vinyl diazo ketones **168** and **170**.

Clearly, the presence of two vinyl groups is not essential for the success of the rearrangement reaction. However, the relative configurations of the stereogenic centres in the substrate have an important influence on the yield and stereochemical outcome of the reaction. In a final preliminary study, the cyclisation of the diazoketone **172** was investigated in order to discover whether it would be possible to access fused bicyclic systems from a substrate in which the alkene is embedded in a carbocyclic framework (**Scheme 50**). The rhodium-mediated reaction of the diazoketone **172** was successful and afforded the bicyclic ketone **173**, albeit in modest yield.[109]



Scheme 50. Catalytic carbenoid generation, ylide formation and rearrangement using the diazoketone **172**.

Oxonium ylide generation and [2,3]-rearrangement strategy was envisaged as novel way of accessing linearly fused polycarbocyclic systems. Two carbocycles, one attached to the diazocarbonyl functionality and the other containing an alkene, tethered by a hydrocarbon chain should react to give a middle ring and afford a linearly fused tricyclic system, once exposed to this reaction sequence (**Scheme 51**). This transformation would simply require the alkene to be contained in a ring as in the diazoketone **174**; the derived ylide intermediate would then undergo [2,3]-rearrangement to give the fused tricyclic system **175**. The catalytic oxonium ylide formation and rearrangement reaction would therefore be applicable to the synthesis of fused polycyclic compounds. A natural product that would possibly be amenable to synthesis using this methodology is the anti-cancer natural product Taxol.



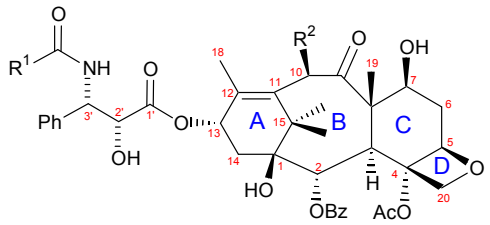
Scheme 51. Hypothetical strategy for the construction of fused medium-sized carbocycles by catalytic carbenoid generation, oxonium ylide formation and [2,3]-rearrangement.

4. The biology and chemistry of Taxol

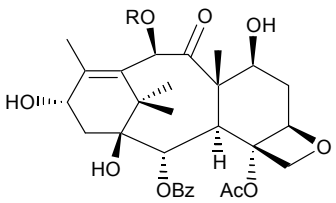
"With the possible exception of Viagra, probably no new drug in the last 40 years has generated as much public interest and excitement as has Taxol."[110]

Interest in Taxol has been fuelled primarily by its excellent clinical cytotoxicity against ovarian and breast cancer cells, but it was intensified by the severe supply problems during the period leading up to its general clinical use.[111] This problem was successfully solved by semi-synthesis and Taxol is now widely available. The diterpenoid natural product paclitaxel (Taxol) and its semi-synthetic analog docetaxel (Taxotere) are leading anti-cancer drugs in clinical use today (**Figure 6**). These two taxoid drugs were approved by the Food and Drug Administration (FDA) for the treatment of several carcinomas including breast, advanced ovarian, non-small-cell-lung (NSCLC), head and neck, and colon cancer,

as well as AIDS-related Kaposi's sarcoma.[112] These taxoids are the largest-selling anti-cancer drugs of all time, with estimated combined annual sales exceeding $3 billion worldwide.[113]



176: Taxol, R^1= Ph, R^2= OAc
177: Taxotere, R^1= ^{t}BuO, R^2= OH



178: 10-Deacetylbaccatin III R= H
179: Baccatin III, R^1= Ac

Figure 6. The taxane family of diterpenoids. Included are the clinically relevant Taxol (**176**) and Taxotere (**177**), their commercial precursors 10-deacetylbaccatin III (**178**) and baccatin III (**179**).

4.1. History of Taxol[114]

In 1960, the National Cancer Institute (NCI) commissioned US Department of Agriculture (USDA) botanists to collect plant samples. The study was part of a program initiated by NCI in 1958 to screen some 35000 plants for anti-cancer activity. In 1962, one of those botanists, Arthur S. Barclay, collected samples of twigs, leaves, fruit, stem and bark of the Pacific yew tree, *Taxus brevifolia* Nutt, in Washington state. These samples were then sent to and processed by the extraction laboratory under a contract from the NCI. The extract of one of the *Taxus* samples, the bark, was tested for bioactivity, and found to be cytotoxic to KB cells. Due to the activity of the bark sample, additional samples were collected and sent to the lab of Dr. Monroe E. Wall at Research Triangle Park, North Carolina, in 1964. The task was to isolate the active ingredient, but the isolation chemists only succeeded in 1967, and named the pure compound 'Taxol'. A few years later, Wall and his colleague Wani elucidated the chemical structure of Taxol based on X-ray analysis of the degradation products and ^{1}H NMR analysis of the pure compound.[115] This work revealed that Taxol **176** is a tetracyclic, highly oxygenated diterpene, comprising the "baccatin nucleus" and a "C-13 ester side chain" (**Figure 6**).

Initially, the future for Taxol was not bright because it had only modest activity *in vivo* against various leukaemias and the Walker 256 carcinosarcoma. In addition, it is also highly insoluble in water, and therefore would be a very difficult drug to formulate for administration by the normal route of injection. Moreover, due to its low natural abundance, adequate quantities of Taxol were not available for clinical use, it was isolated initially in only 0.01% yield from *Taxus brevifolia* bark. The bark is not abundant, because *Taxus brevifolia* usually grows as a rather small tree. So it was clear from the very beginning that obtaining an adequate supply of Taxol for clinical use would be an 'herculean' task. Despite these problems, additional testing was carried out in some new *in vivo* bioassays that were introduced by the NCI. By 1978, Taxol had shown excellent activity against two difficult and slow-growing tumours, B16 melanoma and the mammary xenograft. On the basis of this finding, the NCI took the courageous decision to invest in full scale, preclinical development of Taxol as an anticancer agent. The solubility problem had been sucessfully overcome with a formulation in ethanol and cremophor EL that turned out to have both negative and positive results. On the negative side, the high levels of cremophor required, led to hypersensitivity reactions and almost led to the withdrawal of Taxol from clinical trials. On the positive side, there was evidence that cremophor has a pharmaceutical effect over and above its surfactant properties and may act to reverse multidrug resistance.

4.2. The bioactivity of Taxol

Interest in Taxol as a potential drug candidate was increased significantly in 1979 when Susan Horwitz reported a completely new mechanism of action for Taxol.[116] It was shown that Taxol promotes the assembly of the proteins α- and β-tubulin into microtubules. A schematic representation of Taxol's effect on the tubulin polymerization process is shown in **Figure 7**.[110]

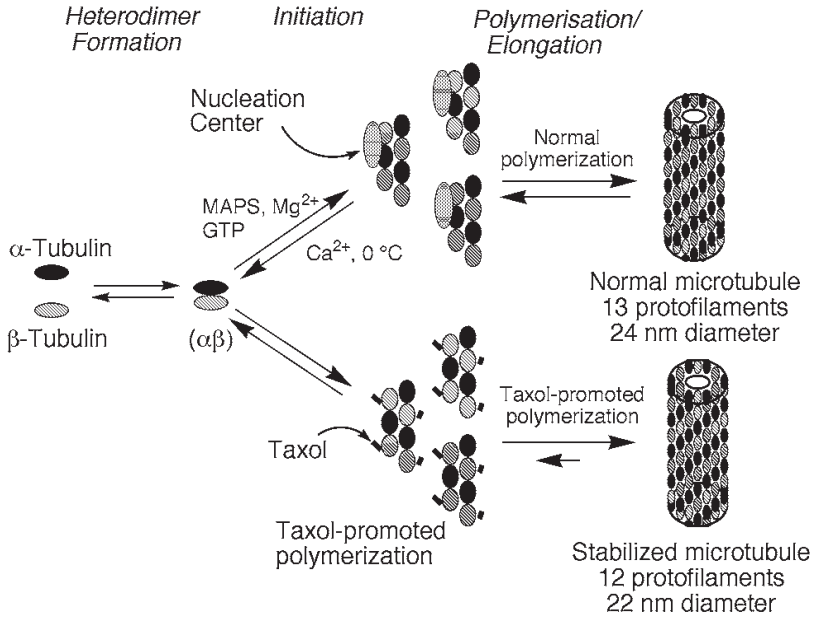


Figure 7. Taxol's mechanism of action.

Microtubules are extremely important for cell division by mitosis.[117] They assist in organelle formation, chromosomal separation and reorganisation of cellular material. Proper microtubule structure and function depends on maintaining a dynamic equilibrium between the microtubule and its building block, the αβ-tubulin heterodimer. Several compounds, including the clinically used drugs vinblastine (Velban™) and vincristine (Oncovin™), as well as colchicine were known to operate as spindle poisons by preventing the assembly of tubulin into microtubules, but Taxol was the first anti-cancer compound found to promote microtubule assembly. This discovery proved to be important in maintaining interest in the development of Taxol at a time when its initial clinical results were discouraging. In brief, Taxol binds to the β-tubulin of the assembled the αβ-tubulin heterodimer, which disrupts the delicate equilibrium by favouring the formation of a stabilized microtubule (**Figure 7**). The resulting microtubule/Taxol complex does not have the ability to disassemble. This binding occurs in the absence of cofactors, and the resulting disruption of the equilibrium between tubulin and microtubules also disrupts cell division and ultimately leads to cell death by apoptosis. For a long time, the binding of Taxol to tubulin polymers and the associated interruption of the cell cycle was thought to be its only significant mechanism of action. However, in recent years it has been increasingly clear that Taxol can induce programmed cell death (apoptosis) in cancer cells by binding to an apoptosis stopping protein called Bcl-2 (B-cell leukemia 2) and thus arrest its function. This second mechanism is independent of mitotic arrest. Indeed, Taxol is found to bind to the protein Bcl-2 triggering hyperphosphorylation of Bcl-2, thereby

inhibiting the anti-aptototic activity of Bcl-2 and promoting aptotosis.[118] One common characteristic of most cancer cells is their rapid rate of cell division. In order to accommodate this, the cytoskeleton of a cell undergoes extensive restructuring. Paclitaxel is an effective treatment for aggressive cancers because it adversely affects the process of cell division by preventing this restructuring. Cancer cells are also destroyed by the anti-Bcl-2 mechanism. Other cells are also affected adversely, but since cancer cells divide at a much faster rate than non-cancerous cells, they are far more susceptible to paclitaxel treatment.

Taxol went into Phase I clinical trials in 1984, and into Phase II trials in 1985. These trials were limited by the supply of the drug, but gave the first clear evidence of activity, with clinically relevant responses in ovarian cancer and in breast cancer reported in 1989[119] and 1991[120] respectively. It was demonstrated unambiguously that Taxol has significant activity against solid tumors and this finding generated enormous public interest in the drug. Further development of the drug for commercial use was assigned to Bristol-Myers Squibb, after a national competition to find the best development partner, and Taxol was approved for treatment of drug resistant ovarian cancer by the FDA in 1992 and breast cancer in 1994. Clinical use of Taxol has increased steadily since then, and today it is not only used for the treatment of ovarian and breast cancers but also for treatment of non-small-cell lung cancer, squamous cancers of the head and neck, and various other cancers.[121] Since the clinical success of Taxol and its semi-synthetic analog docetaxel (Taxotere), developed by Rhône-Poulenc (now Sanofi-Aventis), many chemical and biological investigations have been carried out with the main objectives of easing the supply problem, designing more potent and soluble analogs, and studying taxoid-microtubule interactions.

4.3. Supply crisis and solution

One of the initial concerns about Taxol as an anti-cancer drug was the obvious difficulty in ensuring an adequate supply, and these concerns reached a fever pitch in 1991 with the recognition of Taxol's activity against breast cancer.

From 1967 to 1993, almost all paclitaxel produced was derived from the bark of the Pacific yew. The processes used were the original isolation method of Wall and Wani but the harvesting kills the tree in the process. By 1987, the NCI had contracted Hauser Chemical Research of Boulder, Colorado to handle bark on the scale needed for Phase II

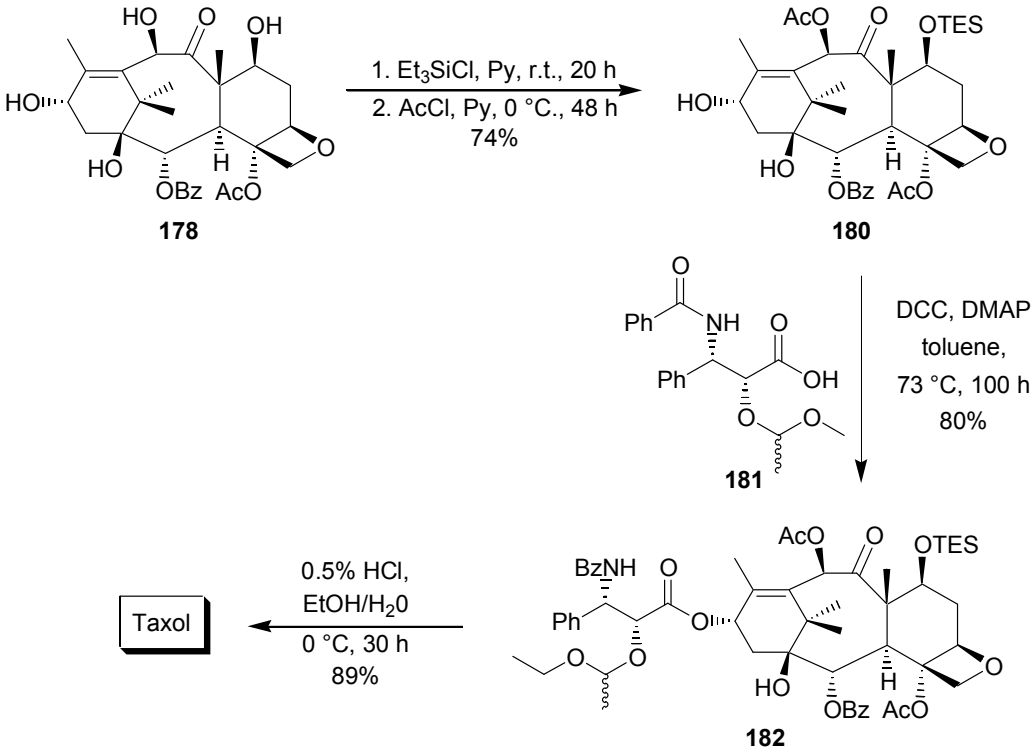
and III trials. While there was considerable uncertainty about how large the wild population of *Taxus brevifola* was and what the eventual demand for Taxol would be, it had been clear for many years that an alternative, sustainable source of supply would be needed.

The pacific yew is a coniferous tree which usually grows in the understory of old-growth stands of conifer or hardwood (**Figure 8** presents a typical setting). The tree grows slowly (a yew needs about 200 years to reach its adult size) and typical mature specimens rarely exceed 15 m in height and 60 cm in diameter. Because of their slow growth and a tendency to grow in dispersed microsites within the larger old-growth ecosystem, the density of the yew is quite low. Moreover, to obtain one kilogram of Taxol, 10 000 kilograms of bark are required, which, in turn, requires the sacrifice of about 3000 trees. Because of the relatively large amount of Taxol needed to treat a patient, this kilogram of Taxol is enough to treat only about 500 patients. The supply crisis created a conflict between environmentalists, who wished to preserve the old-growth forests of the Pacific Northwest of the USA, and cancer patients who were clamouring for the drug.

Figure 8. a) The Pacific yew, *Taxus brevifolia*. b) The European ornamental shrub *Taxus Baccata*

From the late 1970s, chemists in the US and France had been interested in Taxol. A number of US groups, including one led by Robert A. Holton, attempted a total synthesis of the molecule, starting from petrochemical-derived starting materials. This work was primarily motivated as a way of generating chemical knowledge, rather than with any expectation of developing a practical production technique. By contrast, the French group of Pierre Potier at the CNRS quickly recognized the problem related to yield. His laboratory was located on a campus populated by the related yew *Taxus baccata*, so that needles were available locally in large quantity (**Figure 8**).[122] By 1981, he had shown that it was feasible to isolate relatively large quantities of the compound 10-deacetylbaccatin III

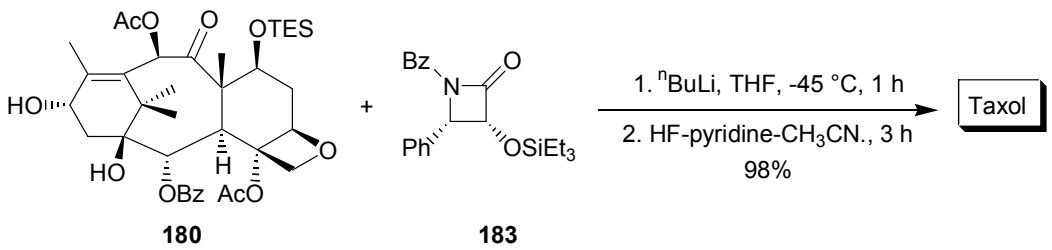
178, a plausible starting material for the semi-synthetic production route to Taxol. By 1988, he co-published with Greene a semi-synthetic route from needles of *Taxus baccata* (**Scheme 52**),[123] a renewable resource that can be harvested without hampering the tree growth. They found that the four hydroxy groups in 10-deacetylbaccatin III **178** exhibited different reactivities towards acylation. Thus, **178** was first converted into its C7- and C10-protected derivative **180**, which was then coupled with the side-chain equivalent **181** under the influence of DCC-DMAP. Specific conditions were essential for ester formation because of the steric hindrance around the C13 hydroxyl group. Acidic treatment of compound **182** provided Taxol in high yield. This semi-synthesis of Taxol from **178** has served as the standard protocol for modified procedures developed later. The view of the NCI, however, was that even this route was not practical and convenient.



Scheme 52. Potier and Greene's semi-synthesis of Taxol.

By 1988, and particularly following a publication by Potier and co-workers,[123] it was clear that a practical semi-synthetic production route would be important. By late 1989, Holton's group had developed a semi-synthetic route to paclitaxel with twice the yield of the Potier synthesis.[124] Florida State University, where Holton worked, signed a deal with Bristol-Myers Squibb (BMS) to license this route and for future patents. In 1992, Holton patented an improved process with an 80% yield (**Scheme 53**). BMS took the process in-house and started to manufacture paclitaxel in Ireland from 10-deacetylbaccatin

III isolated from the needles of the European yew.[125] In 1993, BMS finally brought Taxol to market and announced that they would cease reliance on Pacific yew bark by the end of 1995, effectively terminating the ecological controversy over its use.



180 **183**

Scheme 53. Holton's semi-synthesis of Taxol.

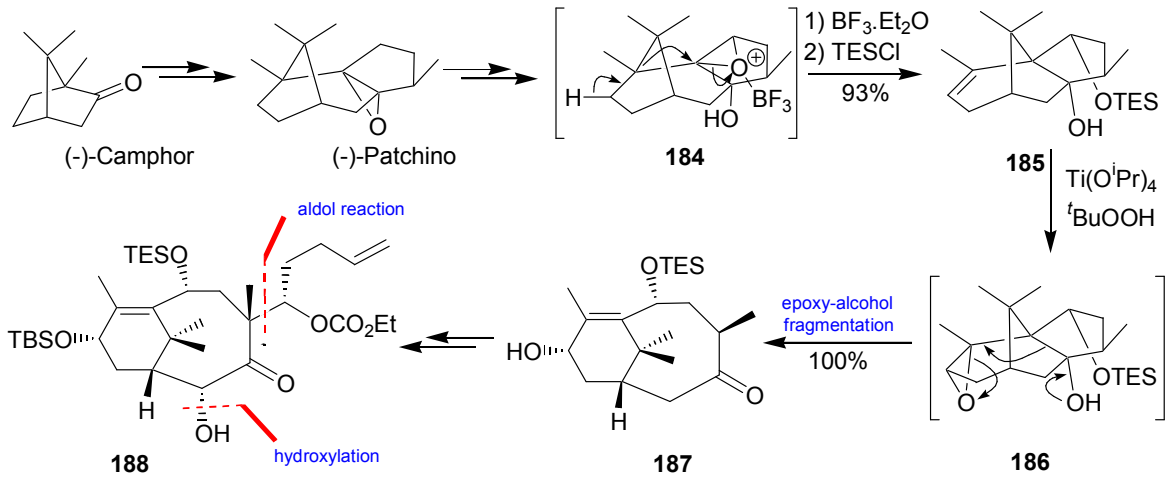
Currently, all paclitaxel production for BMS uses plant cell fermentation (PCF) technology developed by the biotechnology company Phyton Biotech, Inc and carried out at their plant in Germany.[126] This starts from a specific taxus cell line propagated in aqueous medium in large fermentation tanks. Paclitaxel is then extracted directly, purified by chromatography and isolated by crystallization. Compared to the semi-synthesis, PCF eliminates the need for many hazardous chemicals and saves a considerable amount of energy.

4.4. Total syntheses of Taxol

The molecular complexity of Taxol has attracted synthetic chemists since the report of its structure elucidation in 1971. Belonging to the diterpene class of natural products, Taxol is distinguished by a highly oxygenated tricyclic ring system with a distinctive ester side chain. The six-membered ring bearing a sensitive oxetane functional group contains five contiguous chiral centres, over the total of 11 chiral centres present in Taxol's molecular skeleton. With the combination of the central eight-membered carbocycle and intricate arrangement of oxygen-bearing stereocenters, Taxol presents itself as a considerable challenge to synthetic chemists and to the discipline of natural product synthesis. At present, six total syntheses of Taxol have been completed. Since baccatin III has been converted into Taxol by many different routes, a synthesis of baccatin III constitutes a formal synthesis of Taxol. The first two syntheses were published simultaneously in 1994 by Holton and Nicolaou .[127,128]

4.4.1. *Holton's Taxol total synthesis*

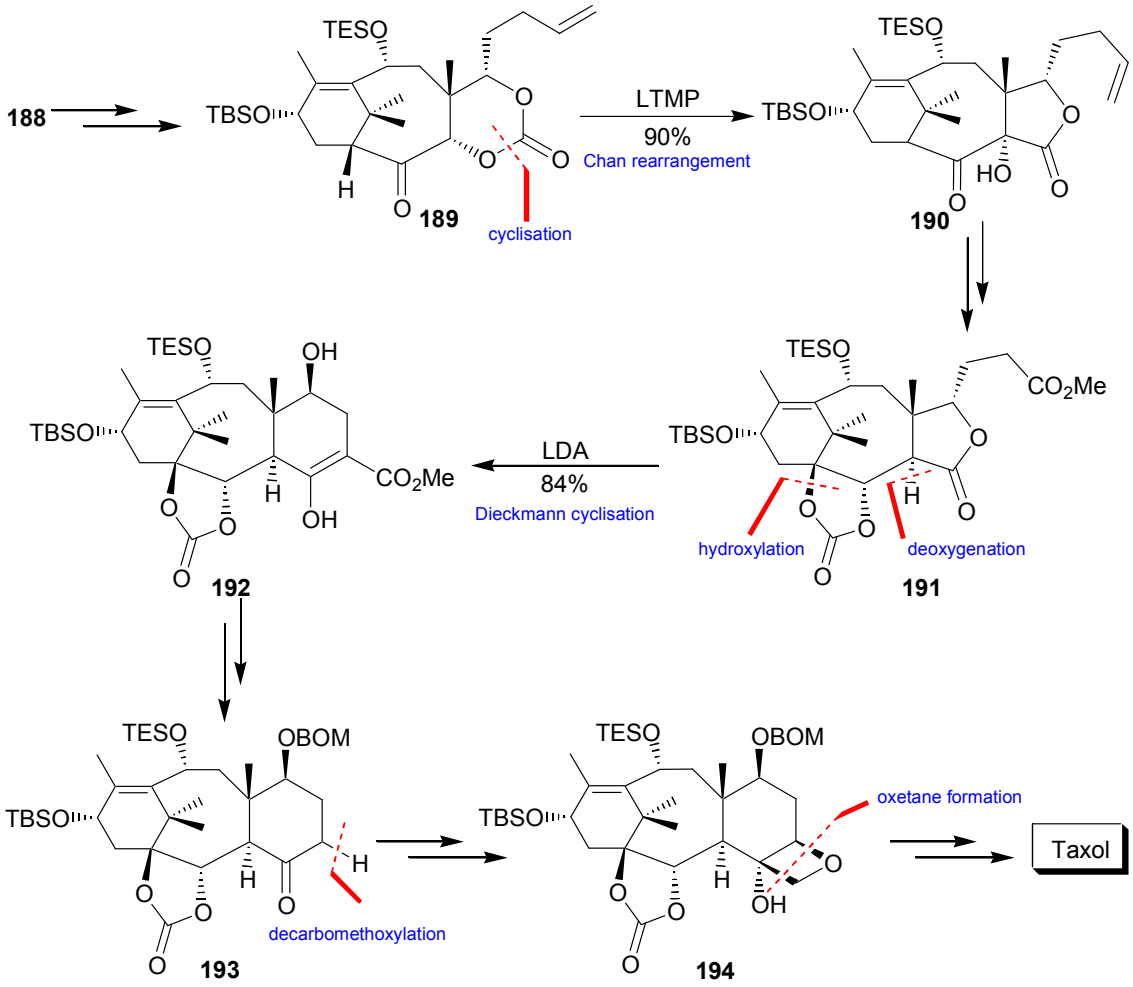
Holton reported a linear approach,[127] with a key step based on an epoxy-alcohol fragmentation to form the AB-ring carbon skeleton. The C- and D-rings were then added sequentially. The synthesis started from (–)-camphor which was converted to (–)-patchino as described by Büchi in 1964 (**Scheme 54**).[129] A sequence of rearrangement reactions (4 steps), an approach which Holton developed for the total synthesis of taxusin, was used to transform (–)-patchino into the required bicyclo-[3.3.0]-system **185**.[103, 130] The Lewis acid mediated opening of the epoxide **184** followed by a skeletal rearrangement and protection of the secondary alcohol delivered the allylic alcohol **185**. Hydroxyl-directed epoxidation of the alkene **185** gave an unstable intermediate which rearranged *in situ* and led to the keto alcohol **187**, containing the complete A-ring, together with all the necessary methyl groups and oxygen functionality in both the lower and upper regions suitably placed for further modification. A diastereoselective aldol reaction of **187** with 4-pentenal was followed by a α-hydroxylation with Davis oxaziridine[131] (chiral (+)-camphorsulfonyl oxaziridine) at C2 to give the hydroxy carbonate **188**.



Scheme 54. Synthesis of Holton's AB ring **188** by epoxy-alcohol fragmentation.

A series of redox reactions with carbonate rearrangement gave the new cyclic carbonate ester **189** (**Scheme 55**). The ketone **189** underwent an unusual stereoselective Chan rearrangement, when treated with lithium tetramethylpiperidide, furnishing the hydroxy lactone **190**. Deoxygenation of C13 with samarium(II) iodide, enantioselective hydroxylation of C2, cyclic carbonate generation and oxidative degradation of the vinyl

side chain furnished the methyl ester **191**. Dieckmann cyclisation of **191** to the enol ester **192** afforded the required ABC-ring skeleton. Decarbomethoxylation leading to **193**, was followed by the construction of the acetoxyoxetane fragment in several steps affording structure **194** possessing the complete taxane skeleton. Acetylation of the C4-hydroxyl proved to be difficult, due to the steric bulk present on the α-face of the molecule. This was followed by stepwise replacement of the protecting groups and coupling of the resulting alcohol with a β-lactam. Further desilylation gave Taxol in a 0.1% yield from commercially available materials.

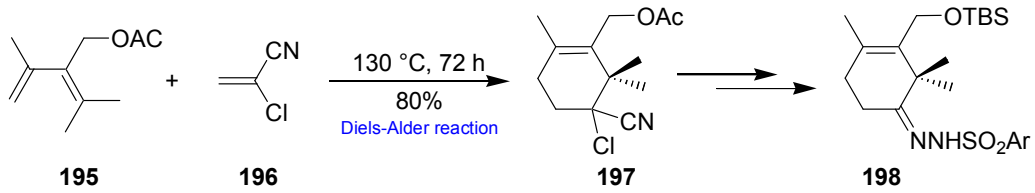


Scheme 55. Completion of Holton's Taxol synthesis by Chan rearrangement and Dieckmann cyclisation.

4.4.2. Nicolaou's Taxol total synthesis

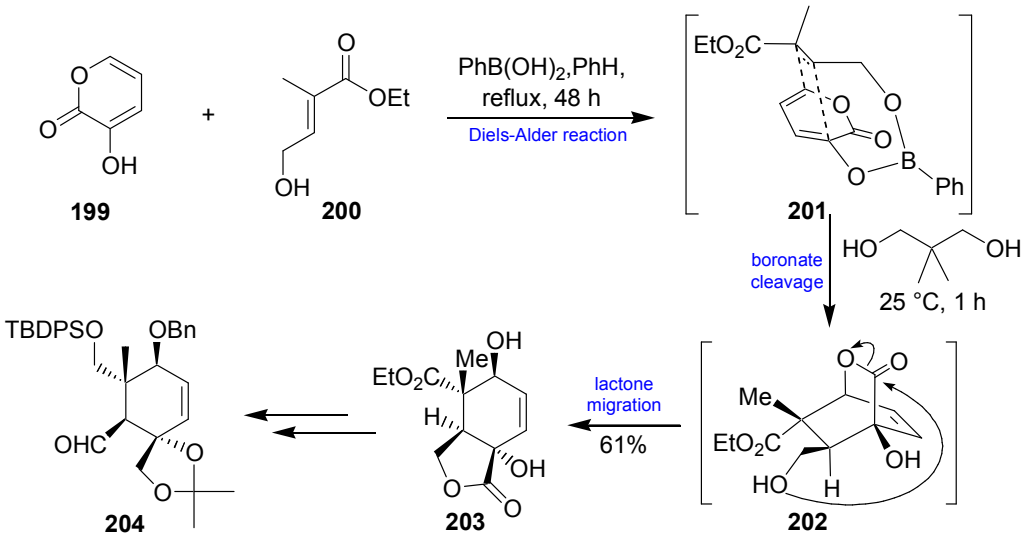
Nicolaou and co-workers completed the total synthesis of Taxol just a few weeks after Holton and used a convergent route to construct the ABC ring system.[128] The A-ring fragment was first synthesised by a high yielding Diels-Alder reaction of diene **195** and

1-chloroacrylonitrile **196**, which furnish cyclohexene **197** with complete regioselectivity (**Scheme 56**). This cycloadduct was then readily converted in three steps into the hydrazone **198**.



Scheme 56. Synthesis of Nicolaou's hydrazone **198** by Diels-Alder reaction.

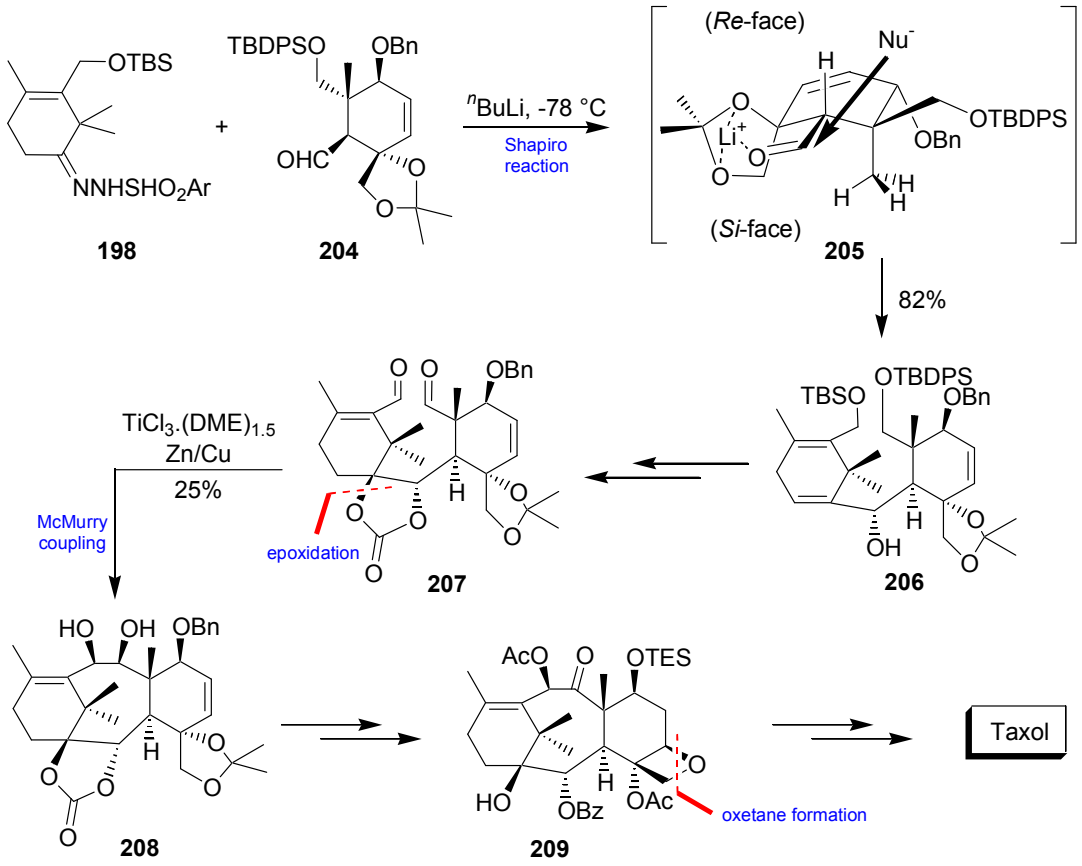
The C-ring was prepared similarly by a boron-mediated Diels-Alder reaction, a procedure developed by Narasaka and co-workers (**Scheme 57**).[132] Treatment of 3-hydroxy-2-pyrone **199** and dienophile **200** with phenyl boronic acid led to intermediate **201**, by the loss of two molecules of water, affording a template in which the diene and the dienophile are brought together for an *endo* Diels-Alder cycloaddition. The boron tether was cleaved upon work-up with ethylene glycol to liberate bicyclic system **202**. This Diels-Alder product **202** rearranged spontaneously through lactone migration to the [3.4.0]-bicyclic system **203**, presumably due to the strain. The required aldehyde **204** was then prepared from the cycloaddition product **203** in seven steps by additional functionalisations.



Scheme 57. Synthesis of Nicolaou's aldehyde **204** by Diels-Alder reaction.

Rings A and C were linked together by a Shapiro coupling reaction of hydrazone **198** and aldehyde **204**, affording the allylic alcohol **206** as a single diastereoisomer and in 82% yield (**Scheme 58**). The stereoselectivity probably resulted from the formation of the

chelated intermediate **205**. In this fixed conformation, the nucleophilic attack occurred at the *re*-face of the aldehyde, because the *si*-face was blocked by the axial C8 methyl group. The cyclic carbonate was introduced by a hydroxy-directed epoxidation, a $LiAlH_4$-mediated reductive ring-opening and finally a protection, which furnished the *trans*-carbonate **207**. After further functionalisations, ring closure of the dialdehyde **207** was performed by a McMurry-type cyclisation reaction giving the cyclised diol **208**, albeit in low yield. The ring D was then installed on the ring C after modification of the two hydroxyl groups.

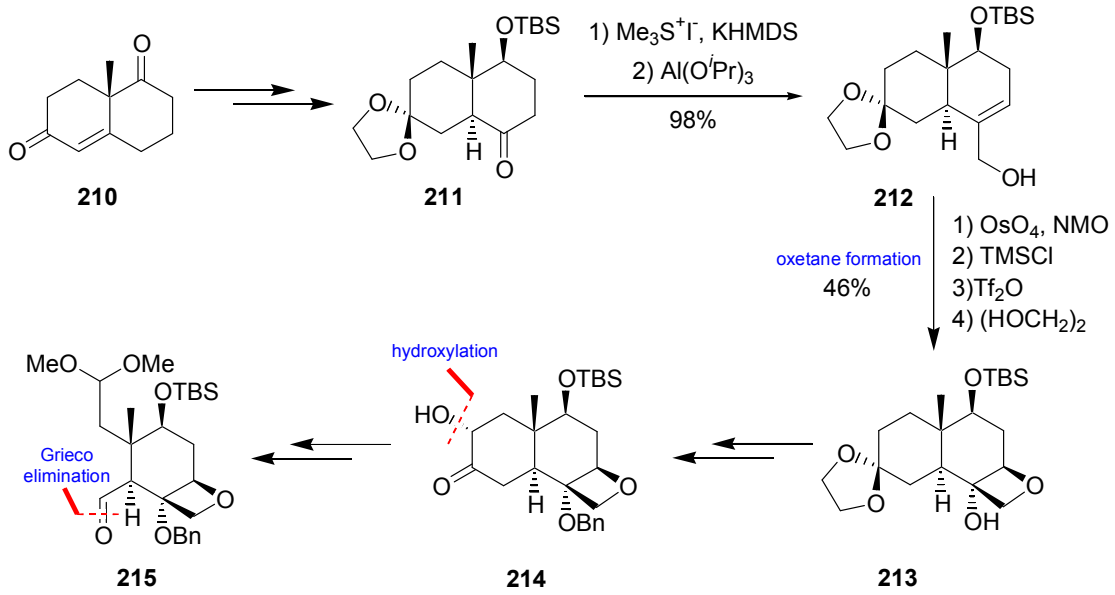


Scheme 58. Completion of Nicolaou's Taxol synthesis by Shapiro reaction and McMurry cyclisation.

A new hydroxyl group was first introduced in the allyl ether group in ring C by hydroboration and deprotection of the acetal group revealed the corresponding triol. Potier's mesylate protocol[133] was then applied to construct the oxetane ring. Removal of the protecting groups and introduction of appropriate substituents to C2 and C4 led to compound **209**. The C13-oxygenation was introduced by a chromium mediated allylic oxidation reaction followed by stereospecific reduction of the resulting enone. Coupling with a β-lactam side chain derivative followed by desilylation gave Taxol in a 0.01% yield from commercially available materials.

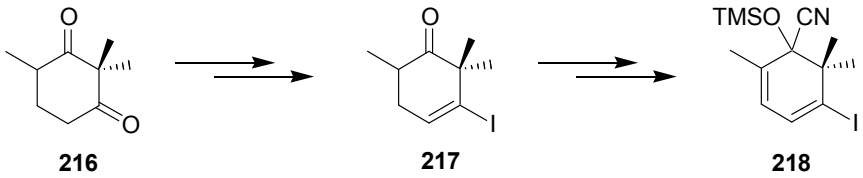
4.4.3. *Danishefsky's Taxol total synthesis*

The Danishefsky synthesis, published in 1996, is the only one to date to start with a preformed D-ring.[134] His synthesis is convergent, with a key step being the coupling of the A-ring fragment with a CD-ring fragment to give the central B-ring. Synthesis of the enantiomerically pure CD-ring fragment **215** starts with the Wieland-Miescher ketone **210**, which was first subjected to a redox reaction sequence to deliver the ketone **211** (**Scheme 59**). Conversion of the ketone **211** into the allylic alcohol **212** occurred by employing Corey's sulfonium ylide and a Lewis acid-induced epoxide opening reaction. Construction of the D ring was accomplished by dihydroxylation, selective silylation of the primary alcohol, triflation and alcohol-induced desilylation yielding oxetane **213**. Formation of the silyl enol ether, after deprotection of the acetal in **213**, followed by its hydroxylation *via* a modified Rubottom-type protocol led to the formation of the hydroxy ketone **214**. Ring fragmentation with $Pb(OAc)_4$ and further functionalisations were then necessary to obtain the required aldehyde coupling partner **215**.



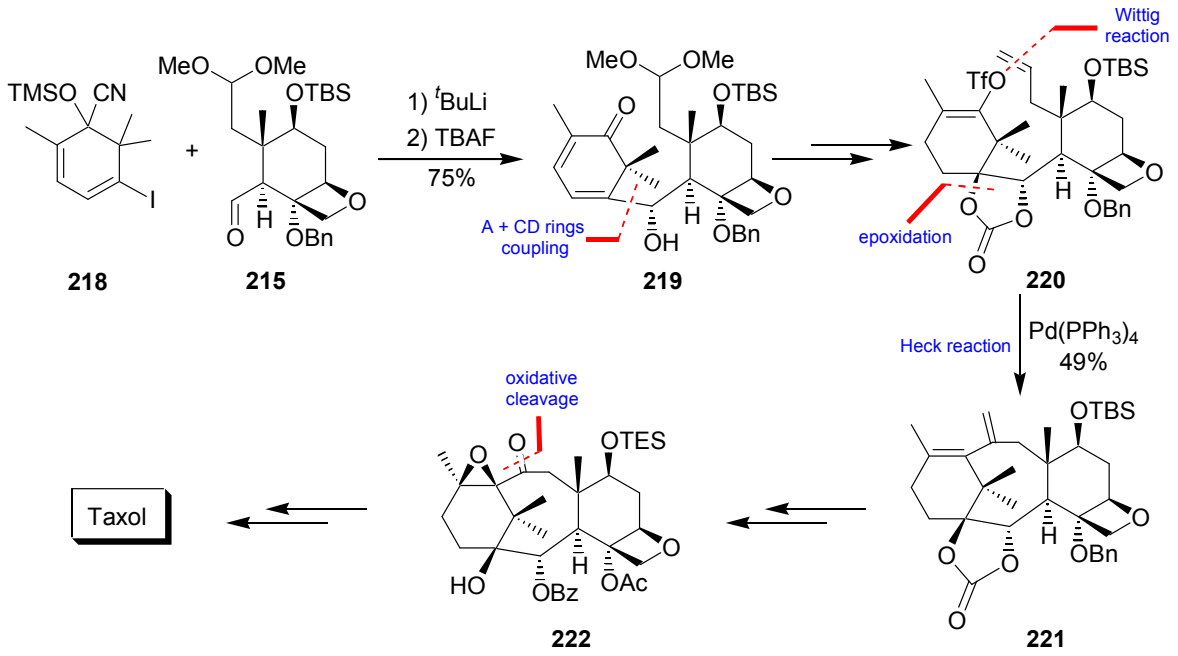
Scheme 59. Danishefsky's synthesis of the CD ring aldehyde **198**.

The A-ring precursor **218** was synthesised in 4 steps from the dione **216** (**Scheme 60**). Selective formation of the monohydrazone followed by treatment with iodine and DBU (Barton reaction) gave rise to an iododienone **217**, which was dehydrogenated and converted into the racemic cyanohydrin **218**.



Scheme 60. Danishefsky's synthesis of A-ring fragment **218**.

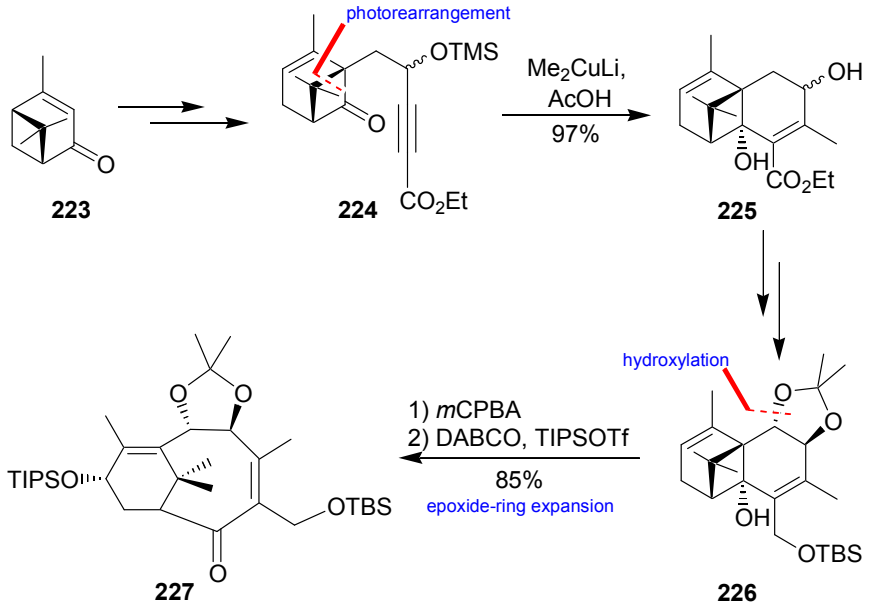
The A- and CD-fragments were linked together *via* nucleophilic addition of vinyl lithium derived from the iodide **218**, to the aldehyde **215** (**Scheme 61**). The next steps included epoxidation to introduce the C1 hydroxyl group, removal of the acetal protecting group from compound **219** and a Wittig reaction of the aldehyde thus formed to give the vinyl triflate **220**. Subsequent intramolecular Heck reaction with $Pd(PPh_3)_4$ gave diene **221** possessing the complete B-ring. The tricyclic intermediate **221** underwent regioselective epoxidation of the tetrasubstituted double bond, avoiding cleavage in later stages. The exocyclic alkene was then cleaved *via* sequential reaction with OsO_4 and $Pb(OAc)_4$ to form the ketone **222**. Additional functional group interconversions led to another successful synthesis of Taxol.



Scheme 61. Completion of Danishefsky's total synthesis of Taxol with a Heck reaction.

4.4.4. *Wender's Taxol total synthesis*

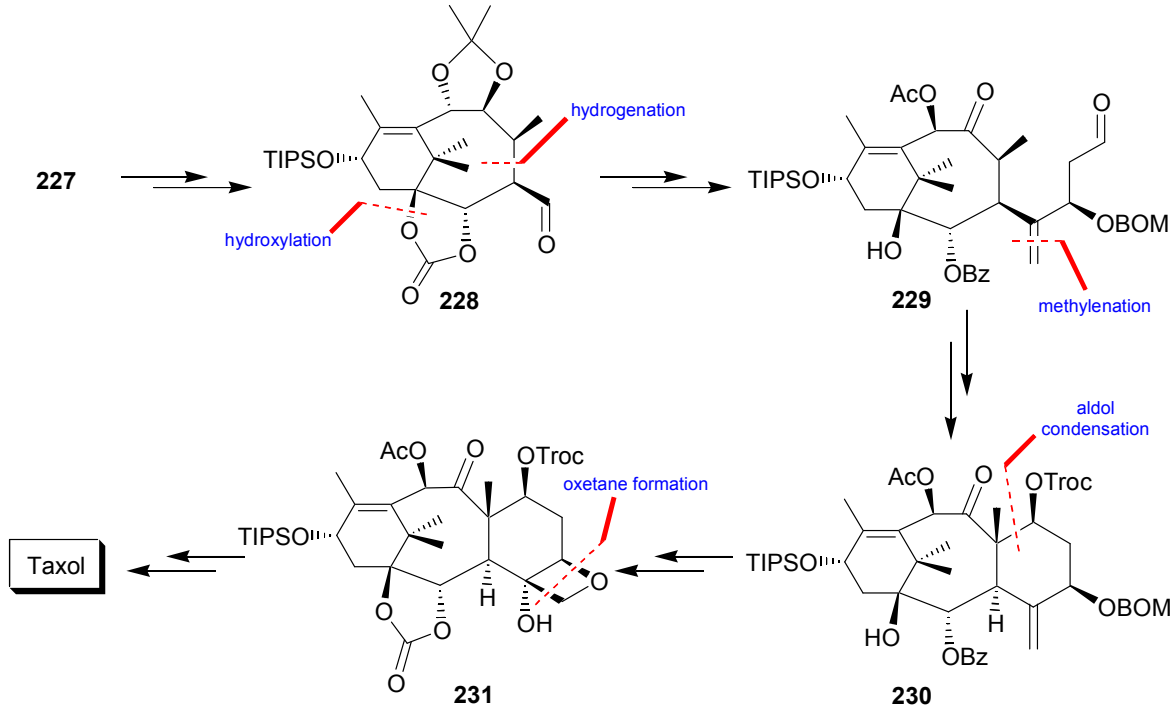
The Wender synthesis, like the Holton synthesis, is linear, starting from verbenone **223**, which provides 10 of the 20 carbon atoms of the baccatin III system.[135] Verbenone (an air oxidation product of pinene) was first converted into intermediate **224**, in four steps (**Scheme 62**). An α-alkylation/ozonolysis sequence introduced the acetaldehyde fragment, and a photochemical allylic rearrangement was followed by addition of the propiolate affording the ketone **224**. The C8 methyl group was then introduced by conjugate addition of methyl cuprate to the propionate **224**, which generated a C3 carbanion effecting intramolecular C2-C3 bond formation, thereby furnishing the B ring **225**. Further functionalisations, including a stereocontrolled Davis α-hydroxylation to introduce the C10 oxygen from the less hindered enolate face, provided the α-hydroxyketone **226**. The precursor of the AB-bicycle **226** was then subjected to a chemoselective epoxidation which was followed by a subsequent hydroxy-epoxy fragmentation induced by DABCO to afford the AB-ring system **227**.



Scheme 62. Wender's synthesis of AB-ring system **227** by an epoxide-ring expansion.

The aldehyde **228** was then prepared after introduction of the C1 hydroxyl in **227** and hydrogenation of the double bond from the α-face with Crabtree's catalyst (**Scheme 63**).[136] The required substituents were then introduced into ring B. Sequential homologation of the aldehyde **228** using a Wittig reaction, oxidation, methylenation using Eshenmoser's salt, addition of allylmagnesium bromide and transposition of the acetoxyketone with guanidinium base led to the ketoaldehyde **229**. Finally, intramolecular

aldol condensation between the ketone at C11 and the side chain aldehyde of **229**, in presence of DMAP, resulted in the construction of the ABC-ring system **230**. Ring D was then built up by oxidation of the corresponding double bond to give a diol after conversion of the C5-hydroxyl group into a bromide. Compound **231** possessing an oxetane fragment was obtained by an intramolecular S_N2 substitution reaction, and the synthesis was then completed by further functionalisations. To date, Wender's synthesis of Taxol is the shortest (37 steps) and most efficient (0.4% overall yield, starting from verbenone).

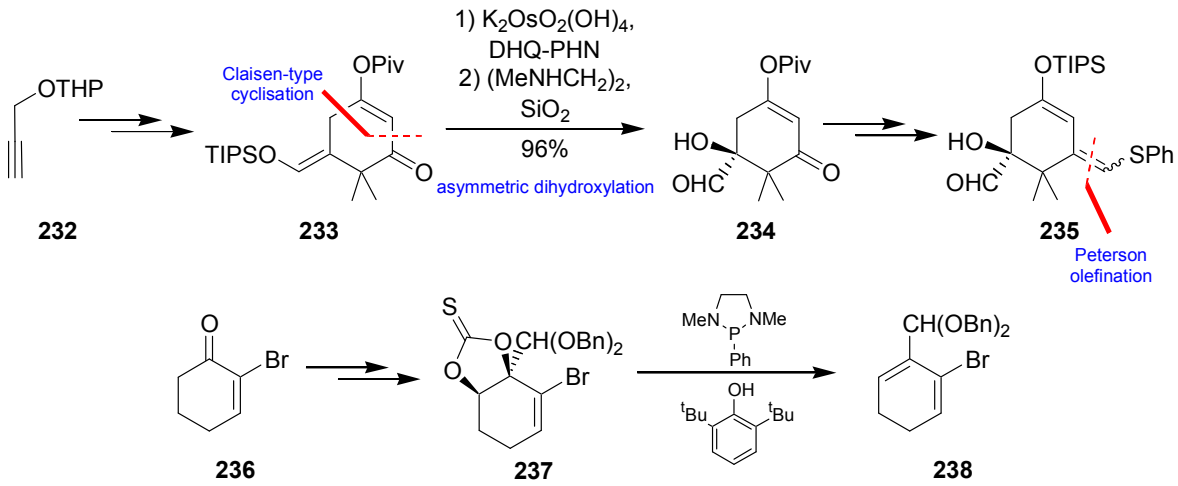


Scheme 63. Completion of Wender's Taxol total synthesis.

4.4.5. Kuwajima's Taxol total synthesis

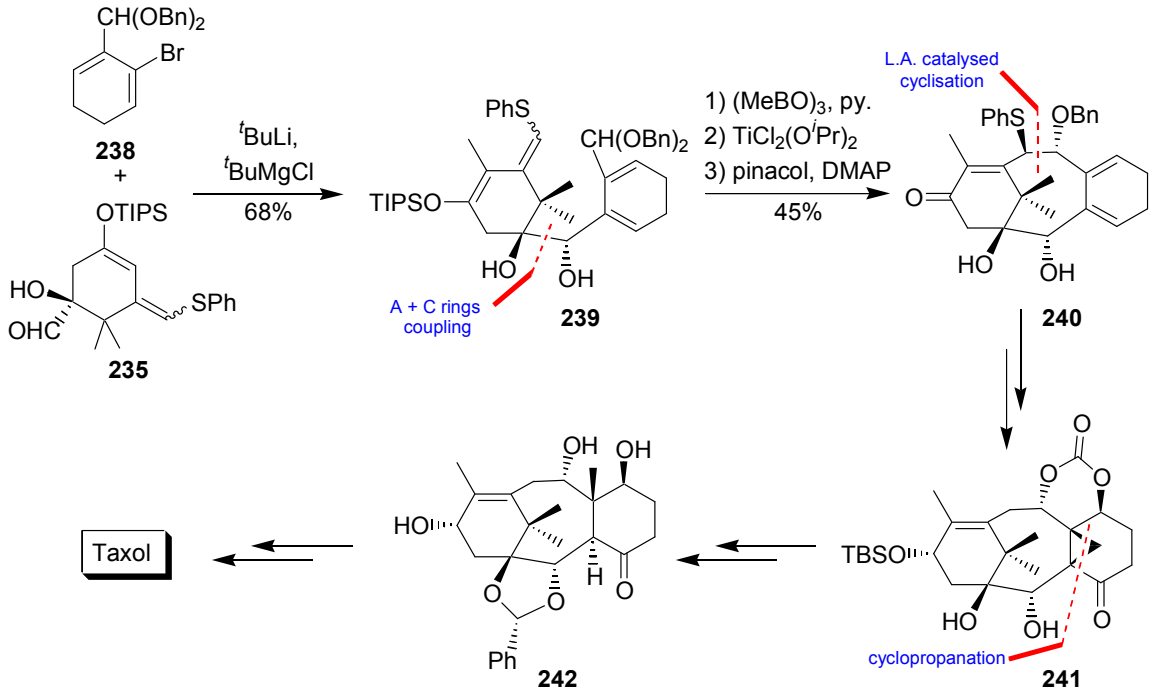
In 1998, Kuwajima reported the enantioselective total synthesis of Taxol, with full details published in 2000.[137] This synthesis is based upon a double coupling strategy for B-ring completion. The A-ring was prepared in eight steps from the protected propargylic alcohol **232** (**Scheme 64**). Addition of lithiated propargyl ether to propionaldehyde and a series of redox reactions followed by a Claisen-type condensation formed the enol silyl ether **233**. Sharpless's asymmetric dihydroxylation[138] in presence of DHQ-PHN as a chiral ligand produced pure α-hydroxyketone **234**, *via* conversion to an aminal. The A-ring synthon **235** was then revealed after interconversion of the protecting groups and a Peterson elimination of **234**. The C-ring precursor **238** was formed in six steps from 2-

bromocyclohexenone **236** (**Scheme 64**). 2-Bromocyclohexenone was first converted in thionocarbonate **237**, by introduction of a triethylsiloxy group and addition of PhSCH(Li)OMe to the carbonyl group. The required cyclohexadiene **238** was obtained following Corey's protocol,[139] using a diazaphospholidine and BHT.



Scheme 64. Kuwajima's synthesis of A-ring and C-ring fragments.

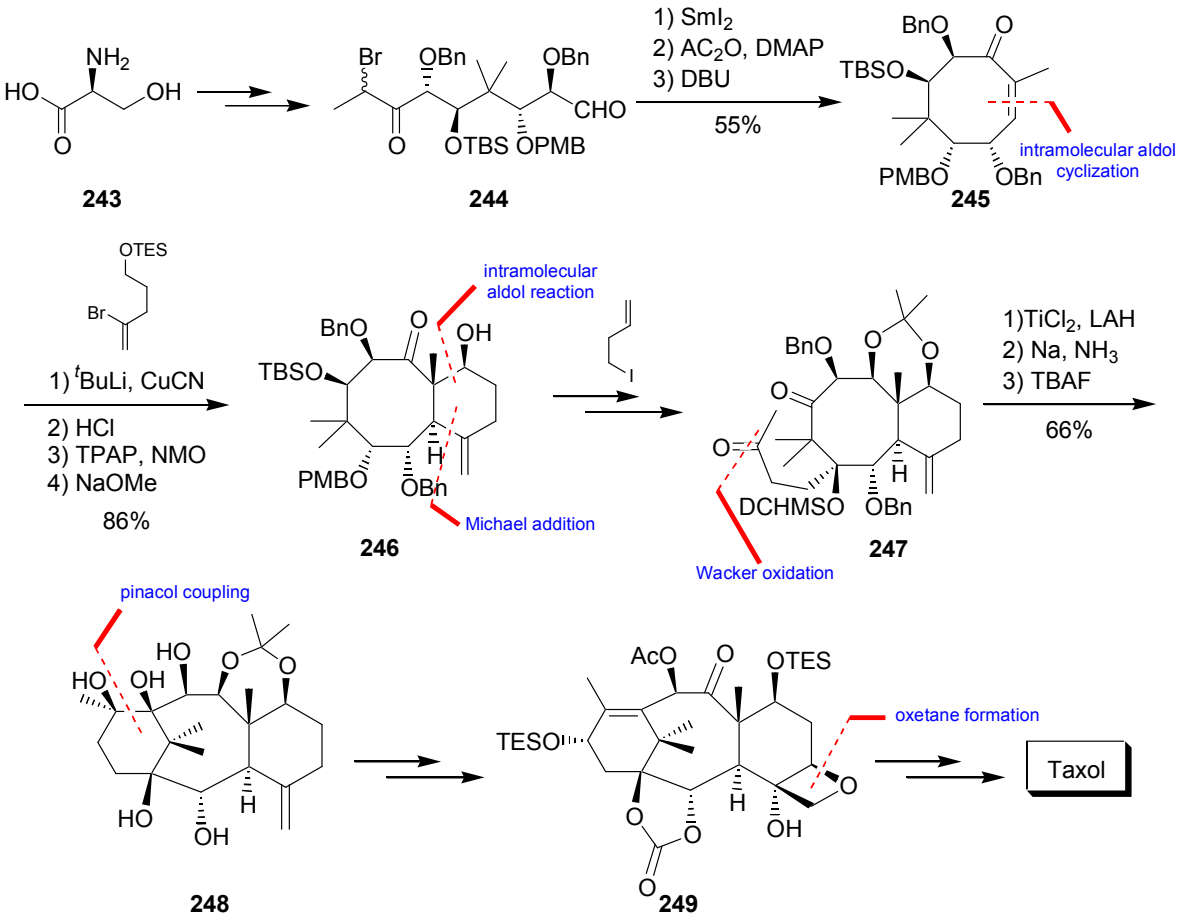
The optically pure A-ring **235** and the C-ring fragment **238** were then coupled together by a chelation-controlled addition mediated by Mg(II), delivering the intermediate **239** (**Scheme 65**). A novel Lewis acid-mediated eight-membered B-ring cyclisation was used to give the desired ABC *endo*-tricarbocycle **240**. Subsequent introduction of the oxygen group at C4 and C7 by singlet oxygen cycloaddition, cleavage of the phenylthio group by Bu_3SnH and a hydroxyl-directed cyclopropanation produced the substrate **241**. The C-19 methyl group was then introduced by reductive cleavage of the cyclopropane, which was followed by isomerisation of the resulting enol to the corresponding ketone affording the crucial synthetic intermediate ketone **242**. Further synthetic transformations, including incorporation of the oxetane ring and attachment of the C13 side chain, then provided Taxol.



Scheme 65. Completion of Kuwajima's Taxol total synthesis.

4.4.6. Mukaiyama's Taxol total synthesis

The final Taxol synthesis was reported by Mukaiyama in 1999 (**Scheme 66**).[86] The strategy used is unique since rings C and A were built up on a pre-existing B-ring, which was obtained by cyclisation of an acyclic precursor. Indeed, the first stage was the synthesis of the seven-membered carbon chain **244** from L-serine **243**, using a combination of asymmetric aldol reactions. The synthesis of the 8-membered ring compound **245** corresponding to the B-ring was then achieved by intramolecular aldol cyclisation using SmI_2. The C-ring was first attached to the B-ring by successive stereoselective Michael addition of a cuprate and an intramolecular aldol cyclisation, affording the BC-ring system **246**. Secondly, the A ring system **248** was constructed from the BC ring system *via* a stereoselective homoallylation, a Wacker oxidation and a pinacol coupling cyclisation of the two carbonyl groups in **247** with low valent titanium species. Finally, introduction of the C-13 hydroxyl group and oxetane formation led to the ABCD skeleton **249**. The total synthesis was then accomplished by a dehydration condensation reaction between the intermediate **249** and the side chain.

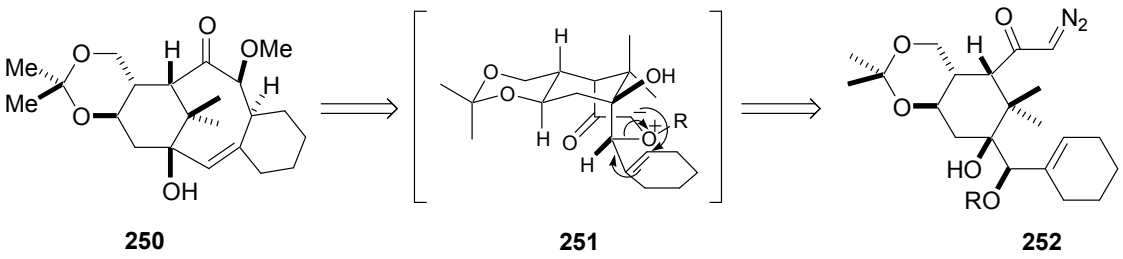


Scheme 66. Mukaiyama's synthesis of Taxol.

5. *A novel synthetic strategy directed towards the tricyclic core system of Taxol*

As mentioned earlier, the diterpenoid natural product Taxol, first discovered in the late 1960's, is one of the most important drugs for the treatment of several cancers including breast and ovarian cancers. Although tremendous efforts towards its synthesis have been made in the last two decades, resulting in six elegant total syntheses, Taxol still constitutes a remarkable challenge for organic chemists due to its unique structural framework. The high level of interest has spilled over to our laboratory, where we have spent several years developing a novel methodology for the construction of medium-ring carbocycles.[107,108] It was decided to take advantage of this strategy to develop a unique method for the construction of the B-ring core of Taxol.

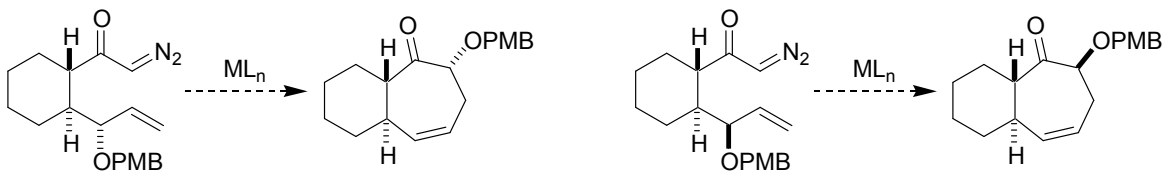
We decided to adopt a convergent approach where the A- and C- rings would be linked together to construct the central B ring, this strategy proved to be successful for three of the total syntheses (Nicolaou, Danishefsky and Kuwajima). Our efforts would focus on the access to the eight-membered ring using our methodology based on tandem catalytic oxonium ylide generation and rearrangement. Before embarking to the total synthesis of Taxol, the key diazoketone intermediate **252** was chosen to establish the viability of our strategy (**Scheme 67**). Thus, the A- and C-rings would be pre-installed prior to ring closure leading to the tricyclic core system of Taxol **250**. The use of carbenoids directed towards the synthesis of Taxol would make our approach very original, since there is no precedent for this in literature.



250 **251** **252**

Scheme 67. Synthetic strategy of the core structure of Taxol **250**.

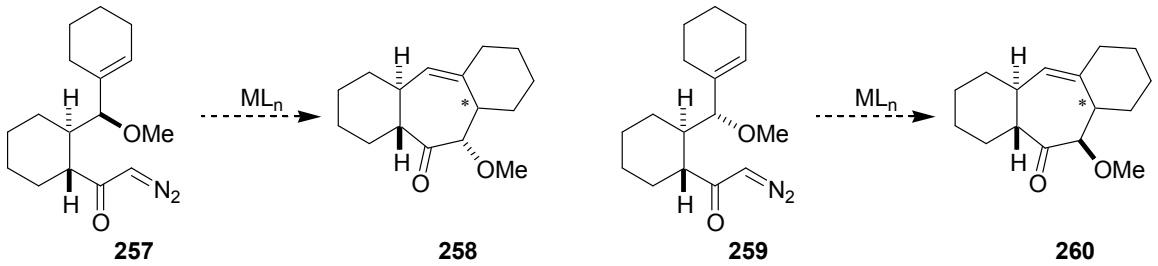
The research presented in this thesis was directed towards the synthesis of the tricyclic core system of Taxol by tandem oxonium ylide generation and subsequent [2,3]-sigmatropic rearrangement (**Scheme 67**). The substrate **252** is required to establish the viability of the key cyclisation reaction, which should proceed *via* the bridged oxonium ylide **251**. The *trans*-decalin-like conformation of the bicyclic acetonide will ensure that the side chain containing the diazoketone and the allylic ether are axially disposed. Consequently, the intermediate metal carbenoid generated from the diazoketone **252** will be suitably positioned to undergo favourable oxonium ylide formation. The relative configuration of the ether-bearing stereogenic centre and the nature of the ether substituent will both play a crucial role in ensuring that the cyclohexenyl group participates in the [2,3]-rearrangement reaction to give the core structure **250**.



253 **254** **255** **256**

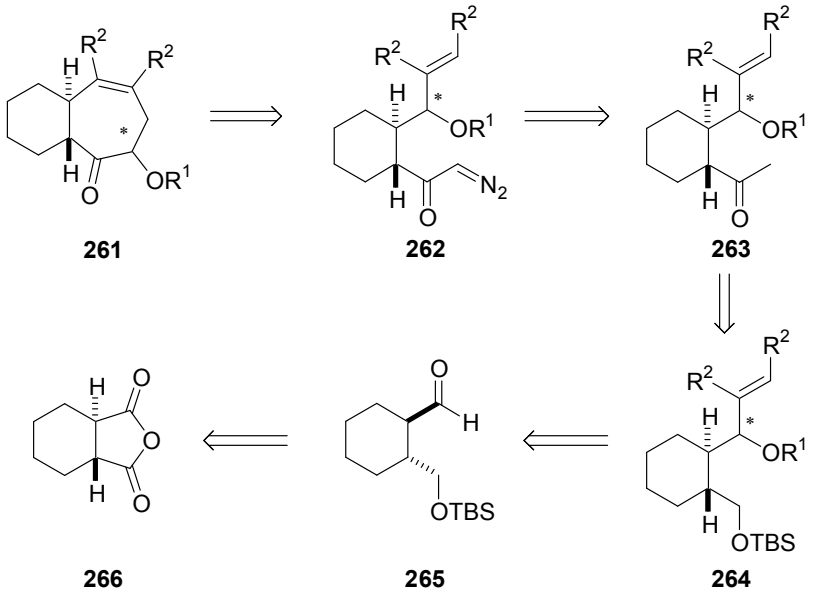
Scheme 68. Hypothetical rearrangement of diazoketones **253** and **255** bearing a *p*-methoxybenzyl group.

Before undertaking the synthesis of the tricyclic core system of Taxol, it was necessary to broaden the scope of the tandem oxonium ylide generation and rearrangement reaction. The first aim was to establish whether changing the ether substituent in the diazoketones **168** and **170** would affect the outcome of oxonium ylide generation and rearrangement reaction (see **Scheme 49**). Bicyclic models **253** and **254** have to be prepared to test the hypothesis and discover whether substrates bearing a different protecting group would undergo the required rearrangement reaction (**Scheme 68**). Consequently, to check if the nature of the substituent plays a crucial role, the methoxy group was to be replaced by the *p*-methoxybenzyl protecting group.



Scheme 69. Hypothetical rearrangement of diazoketones **257** and **259** bearing a cyclohexene.

Another aim of the project was to investigate whether this reaction could be used to prepare the tricyclic systems **258** and **260**, that are similar substrates to that needed for the synthesis of the ABC skeleton of Taxol. The compounds **257** and **259**, where the alkene is embedded in a ring, were proposed as model compounds in order to test the viability of the key reaction (**Scheme 69**).



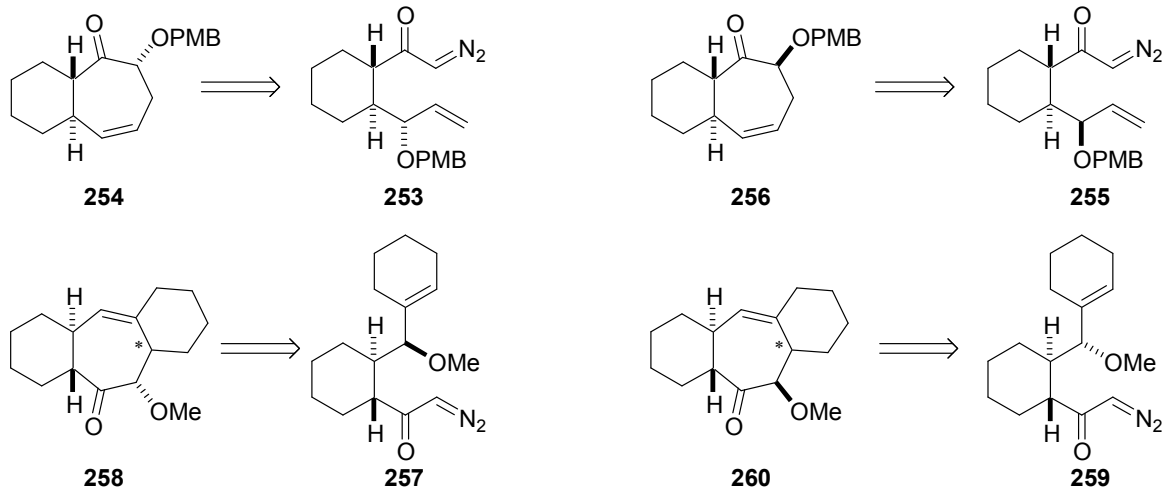
Scheme 70. General retrosynthetic analysis.

It was planned that the diazoketones **262** would be synthesised from commercially available *trans*-cyclohexane-1,2-dicarboxylic anhydride **266** (**Scheme 70**). It was expected that the methyl ketone **263** would undergo diazo transfer to yield diazoketone **262**. Functional group manipulations would reveal the allyl ether **264**. Both diastereoisomers of **264** would be obtained after protection of the alcohol derived from the coupling between aldehyde **265** and an appropriate Grignard reagent. The aldehyde **265** would be derived disconnected from the commercially available anhydride **266**.

Results and discussion

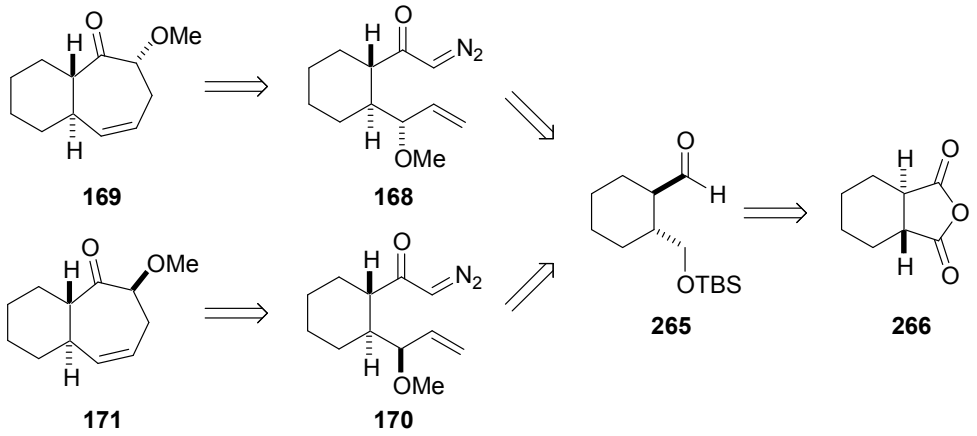
1. Synthesis of medium-ring fused carbocyclic systems

The first objective of the project was to investigate the possible construction of carbocycles *via* oxonium ylide generation and [2,3]-rearrangement. Our retrosynthetic analysis for the four targeted medium-ring fused carbocycles **254**, **256**, **258** and **260** ultimately led to the four diazoketones **253**, **255**, **257** and **259** respectively (**Scheme 71**).



Scheme 71. Four targeted medium-ring fused carbocycles.

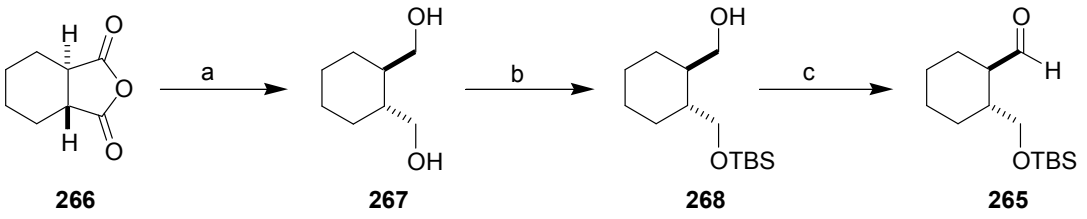
Previous work within the group has focused on the generation of the similar systems **169** and **171**, and so it was decided to pursue the same approach (**Scheme 72**). The starting material required for the synthesis was the commercially available compound *trans*-cyclohexane-1,2-dicarboxylic anhydride **266**, and the strategy involved the preparation of the aldehyde **265** as a common intermediate for the synthesis of both of the diastereomeric diazoketones **168** and **170**.



Scheme 72. Retrosynthetic analysis of carbocycles **169** and **171**.

1.1. Preparation of a common starting aldehyde 265

In order to investigate the key tandem oxonium ylide generation and rearrangement sequence, the common precursor aldehyde **265** required for all four diazoketones was synthesised (**Scheme 73**). Reduction of anhydride **266** with $LiAlH_4$ gave diol **267** in 94% yield.[140] Mono-protected alcohol **268** was obtained in a 60% yield employing *tert*-butyldimethylsilyl as the protecting group; 25% of diol **267** was recovered.[141] It is worth noting that double protection was not observed. Swern oxidation of the alcohol **268** gave the desired aldehyde **265**. The aldehyde **265** was found to decompose on silica gel but was successfully used without purification.



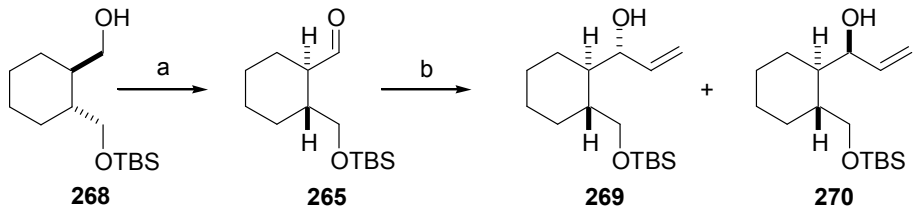
Scheme 73. **a** $LiAlH_4$, THF, r.t., 30 min, reflux, 2.5 h, 94%. **b** TBSCl, imidazole, THF, r.t., 18 h, 60%. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2 h. (ii) Et_3N, r.t..

1.2. Synthesis of bicyclic fused systems 254 and 256

In our study, we followed the reported procedure for the preparation of the diazoketones **168** and **170**, but in our case the methoxy group was replaced by a *p*-

methoxybenzyl (PMB) protecting group. The purpose of preparing these analogues was to establish whether competing reactions involving the carbenoid (e.g. cyclopropanation or C-H insertion) or the oxonium ylide (e.g. a [1,2]- or a [1,4]-shift) could be avoided and the desired pathway could be followed exclusively. We prepared substrates **253** and **255**, in which a PMB protecting group is employed to discover whether it is possible to perform [2,3]-rearrangement when oxygen is substituted with a group that is prone to undergo a [1,2]-shift.

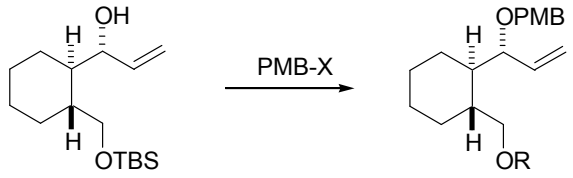
The synthesis of diastereoisomeric allylic alcohols **269** and **270** was then undertaken (**Scheme 74**). Swern oxidation of the alcohol **268** to give the aldehyde **265**, was followed by the addition of cerium(III) chloride and vinyl magnesium bromide at –78 °C to give a mixture of the diastereomeric alcohols **269** and **270** in a 76% combined yield over two steps. The relative configuration of the allylic alcohols **269** and **270** was assigned by comparison to the ^{1}H NMR spectra described in the thesis of S. Walls.[109] The major isomer **269** was isolated in 53% yield over two steps, and the minor isomer **270** in 13% yield.



Scheme 74. a (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2 h. (ii) Et_3N, r.t.. **b** (i) $CeCl_3$, THF, r.t., 2 h. (ii) CH_2=CHMgBr, THF, –78 °C to r.t., overnight. **269** 53% over 2 steps + **270** 13 % over 2 steps.

A variety of PMB-protected precursors and different reaction conditions were explored in order to determine the optimum conditions for the introduction of the *p*-methoxybenzyl group on the major isomer **269** (**Table 1**). First, the *p*-methoxybenzyl trichloroacetimidate was used in the presence of a catalytic amount of PPTS as a weak acid. The reaction gave the expected product **271** but in only 16% yield (entry 1). Using the same acetimidate with a catalytic amount of triflic acid, alcohol **269** remained unreacted (entry 2). In another attempt, the secondary alcohol **269** was converted into its PMB ether **271** after treatment with sodium hydride in DMF and reaction with PMBCl in only 18% yield (entry 3). Instead, *p*-methoxybenzyl bromide was prepared from *p*-methoxybenzyl alcohol and HBr in 73% yield and was used directly in the next step. The alcohol **269** was treated with sodium hydride in THF, followed by the addition of PMBBr and a catalytic amount of *tetra*-butylammonium iodide. The reaction mixture was quenched after two days of stirring, and afforded the primary alcohol **272**, after loss of the TBS group, in 61% yield

(entry 4). In a final attempt to improve the yield, the alcohol **269** was reacted with PMBBr and KHMDS in DMF for two days to generate the corresponding PMB ether **271** in 96% yield (entry 5).

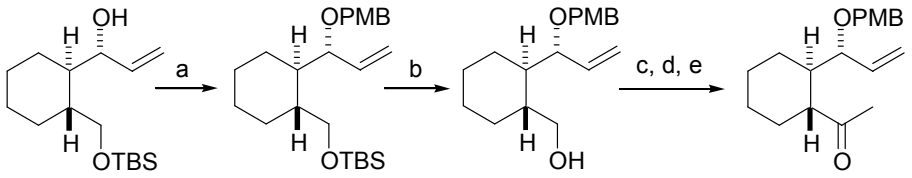


269 **271** and **272**

Entry	PMB-X	Conditions	Yield
1	$PMBOC(NH)CCl_3$	PPTS, CH_2Cl_2, r.t., 2 days	16% (**271**, R = TBS)
2	$PMBOC(NH)CCl_3$	TfOH, Et_2O, –10 °C to r.t., 2 days	-
3	PMBCl	NaH, DMF, 0 °C to r.t., 3 h	18% (**271**, R = TBS)
4	PMBBr	i) NaH, THF, 0 °C, 1h. ii) PMBBr, TBAI, r.t., 2 days	61% (**272**, R = H)
5	PMBBr	KHMDS, DMF, r.t., 2 days	96% (**271**, R = TBS)

Table 1. Different conditions to introduce the PMB group.

Removal of the TBS group afforded the primary alcohol **272** in 98% yield, which was then oxidised to give the corresponding aldehyde by Swern oxidation (**Scheme 75**). The aldehyde was converted into a secondary alcohol by reaction with methyl magnesium bromide. Oxidation of the crude alcohol by a Swern oxidation gave the methyl ketone **273** in a 71% yield from the alcohol **272**.

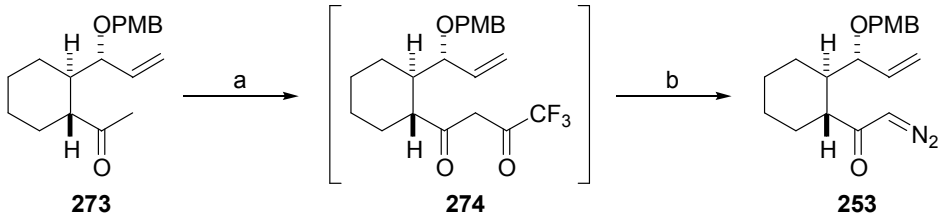


269 **271** **272** **273**

Scheme 75. **a** PMBBr, KHMDS, DMF, r.t., 2 days, 96%. **b** TBAF, THF, r.t. overnight, 93%. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t. **d** MeMgBr, THF, –78 °C to r.t., overnight. **e** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 71% over 3 steps.

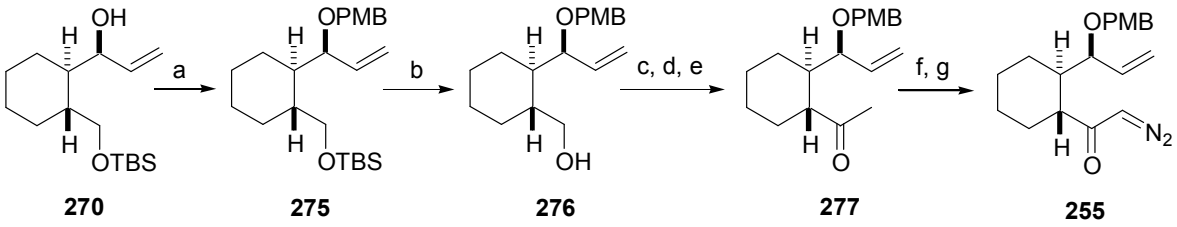
To synthesise the diazoketone **253** from the methyl ketone **273**, we decided to follow the Danheiser procedure (**Scheme 76**).[142] The methyl ketone **273** was first deprotonated with LHMDS then quenched with 2,2,2-trifluoroethyl trifluoroacetate to afford the

activated 1,3-dicarbonyl compound **274** which was used in the diazo transfer reaction without further purification. The α-trifluoroacetyl ketone **274** was then treated at room temperature with *p*-acetamidobenzenesulfonyl azide to afford the desired α-diazoketone **253** in 48% yield.



Scheme 76. a (i) LiHMDS, THF, –78 °C, 1 h. (ii) $CF_3CO_2CH_2CF_3$, –78 °C to r.t., 1.5 h. **b** *p*-ABSA, DBU, MeCN, r.t., 4 days. 48% from **273**.

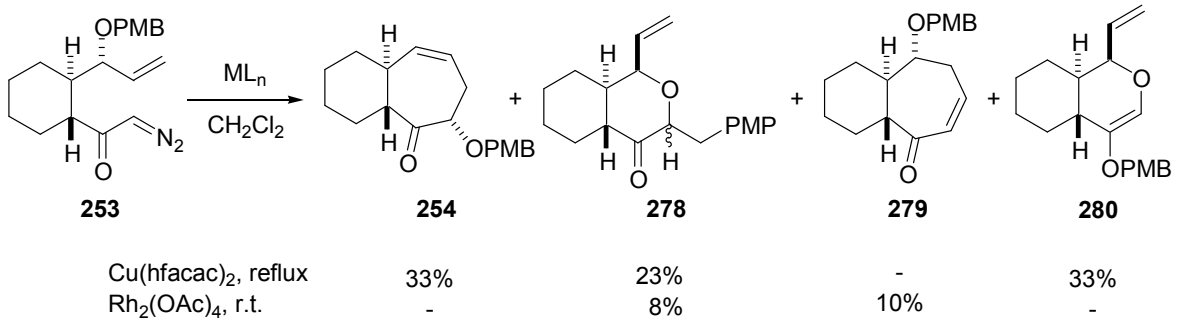
Following the successful synthesis of the *syn*-diazoketone **253**, the preparation of the analogous *anti*-diazoketone **255** was undertaken (**Scheme 77**). The alcohol **270** generated the corresponding PMB ether **275** in 87% yield using the previously described conditions. Removal of the TBS group afforded the primary alcohol **276** in 48% yield. The alcohol **276** was then oxidised into the corresponding methyl ketone **277** in 78% yield over three steps by sequential Swern oxidation, conversion of the alcohol into the methyl alcohol and finally Swern oxidation. The methyl ketone **277** was converted into the diazoketone **255** by a diazo transfer reaction in 65% yield.



Scheme 77. **a** PMBBr, KHMDS, DMF, r.t., 1 h, 87%. **b** TBAF, THF, r.t. overnight, 48%. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t. **d** MeMgBr, THF, –78 °C to r.t., overnight. **e** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 78% over 3 steps. **f** (i) LiHMDS, THF, –78 °C, 1 h. (ii) $CF_3CO_2CH_2CF_3$, –78 °C to r.t., 1 h. **g** *p*-ABSA, DBU, MeCN, r.t., 4 days. 65% from **277**.

With these two diazoketones **253** and **255** in hand, the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement sequence was explored in dichloromethane at room temperature using rhodium(II) acetate, and under reflux in the case of the copper(II) hexafluoroacetylacetonate mediated reaction. The copper-mediated reaction of the diazoketone **253** afforded a mixture of three products (**Scheme 78**): the expected [2,3]-

sigmatropic rearrangement product **254** in 33% yield, the product **280** derived from the [1,4]-migration of the PMB group in 33% yield and the ketone **278** resulting from a [1,2]-shift of the PMB group in 23% yield (2.4: 1 mixture of diastereoisomers). Whereas the rhodium-catalysed reaction failed to provide any of [2,3]-rearrangement product **254** but instead produced a small amount of the [1,2]-shift product **278** (8% yield) along with the unexpected cycloheptenone **279** (10% yield). The cycloheptenone is the formal product of the carbenoid insertion into an alkenyl C-H bond followed by a subsequent conjugation forming the enone.



Scheme 78. Catalytic decomposition of diazoketone **253**.

The low yield of the [2,3]-rearrangement product **254** suggests that the configuration at the vinyl-bearing stereogenic centre does not allow the system to adopt a conformation in which there is an efficient orbital overlap of the vinyl group and the ylide, leading to a relatively high energy transition state (**Figure 9**). It was attributed to unfavourable interactions between axial hydrogens of the cyclohexyl unit and the vinyl substituent in the conformation adopted by the oxonium ylide intermediate **281** during the [2,3]-rearrangement reaction.

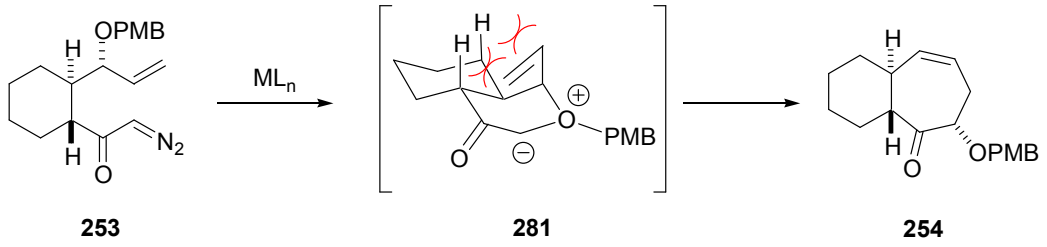


Figure 9. Unfavourable transition state for the rearrangement of oxonium ylide **281**.

The relative configuration of cycloheptenone **254** was determined by nOe experiments (**Figure 10**). Irradiation of the *p*-methoxybenzyloxy methine proton gave a clear nOe enhancement (0.7%) to the ring-junction methine proton in α of the α-carbonyl methine. This result indicates that these protons are on the same face of the molecule therefore the

p-methoxybenzyloxy methine proton and the α-carbonyl methine proton are assigned as up.

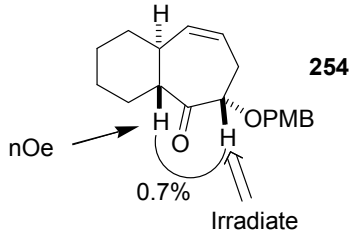
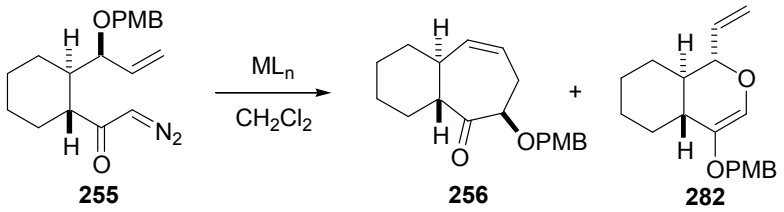


Figure 10.

The catalytic decomposition of the diastereomeric *anti*-diazoketone **255** was then undertaken (**Scheme 79**). The main product arising from treatment of the diastereomeric diazoketone **255** with copper(II) hexafluoroacetylacetonate as catalyst was the [1,4]-shift product **282** (38% yield) and only a relatively small amount of the [2,3]-rearrangement product **256** was produced (16% yield). The copper-mediated formation of formal [1,4]-shift products has already been described. Indeed, West and co-workers have reported the isolation of [1,4]-shift products derived from carbenoid-derived benzyl substituted oxonium ylides,[52] and Clark and co-workers have also reported the isolation of related products from allylic ether substrates.[53]



Scheme 79. Catalytic decomposition of diazoketone **255**.

It is relevant to note that the formation of [1,4]-migration products has also been described for rhodium-catalysed reaction. For example, Karche and co-workers have demonstrated that the dominant reaction pathway for oxonium ylides, derived from α-diazo-β-keto esters when treated with rhodium(II) acetate, led to [1,4]-migration products.[54] In our case, however, treatment of the diazoketone **255** with rhodium(II) actetate afforded none of the [1,4]-migration product and delivered the required [2,3]-rearrangement product **256** in a good 79% yield instead. Interestingly, products arising from competing C-H insertion or [1,2]-shift were not observed in this case.

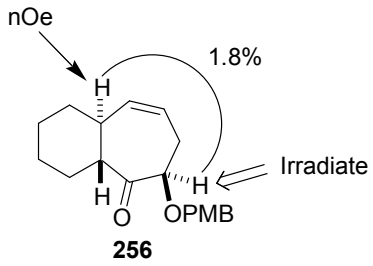


Figure 11.

The relative configuration of cycloheptenone **256** was determined by nOe experiments (**Figure 11**). Irradiation of the *p*-methoxybenzyloxy methine proton gave a clear nOe enhancement (1.8%) to the allylic ring-junction methine proton. This result indicates that these protons are on the same face of the molecule therefore the *p*-methoxybenzyloxy methine proton and the α-alkenyl methine proton are assigned as down. The [1,4]-shift product **282** proved to be a crystalline solid, which enabled its relative stereochemistry to be established by single crystal X-ray analysis (**Figure 12**).

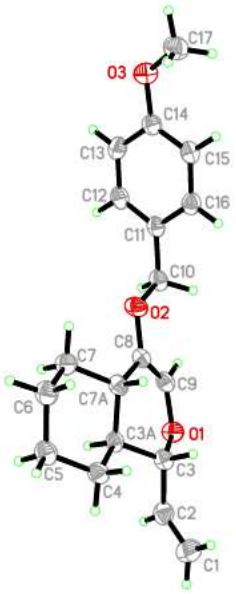


Figure 12. X-ray crystal structure of **282**.

As predicted from the previous studies, the success of the reaction is highly dependent of the relative configuration of the diazocarbonyl and vinyl functionality. Indeed, the higher yield of the cycloheptenone **256** from the *anti*-diazoketone **255** compared to the one **254** from the diastereomeric *syn*-diazoketone **253** is due to a more favourable orientation of the intramolecular oxonium ylide generated. The close proximity of the vinyl group to the oxonium ylide in **283** leads inevitably to the [2,3]-rearrangement product **256**, and competing reactions do not take place (**Figure 13**).

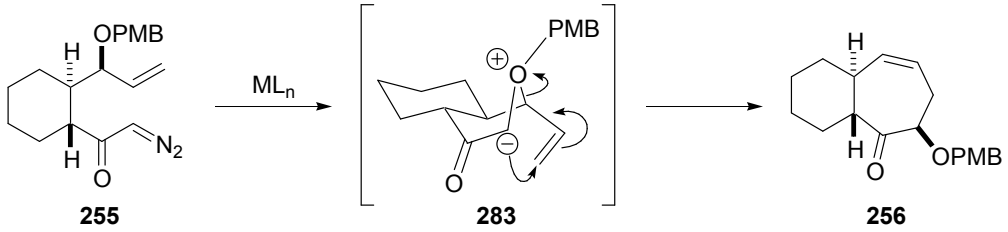
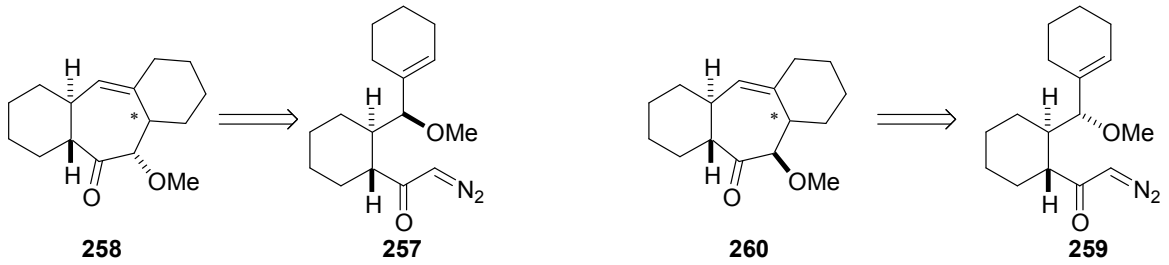


Figure 13. Transition state favoured for rearrangement of oxonium ylide **283**.

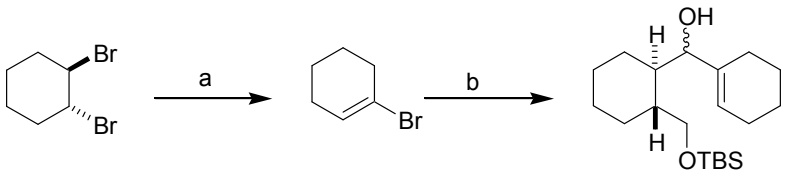
1.3. Synthesis of tricyclic fused systems 258 and 260

The successful formation of fused bicyclic carbocycles **254** and **256** suggested that it might be possible to use the tandem oxonium ylide generation and [2,3]-rearrangement reaction to construct linearly fused tricyclic compounds. The formation of such systems would require the creation of a third ring between two tethered single rings. To investigate this transformation, the synthesis of the diastereomeric cycloalkenes **257** and **259** was required (**Scheme 80**).



Scheme 80.

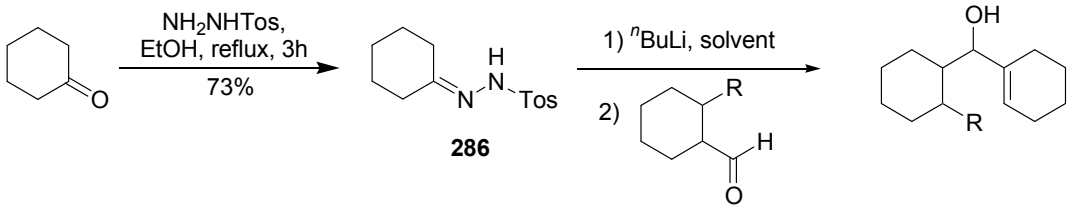
The decision was made to use a coupling reaction between the common precursor aldehyde **265** and a derivative of 1-bromocyclohexene to deliver the skeleton of both diazoketones **257** and **259**. The required vinylic halide, 1-bromocyclohexene, was prepared by *syn*-dehydrohalogenation of *trans*-1,2-dibromocyclohexane (**Scheme 81**).[143] Unfortunately isolation of the compound **284** was somewhat problematic because of its low boiling point. This vinylic bromide **284** was then used to prepare the Grignard reagent and this was then reacted with aldehyde **265** under chelated controlled conditions using $CeCl_3$.[144] The reaction afforded a mixture of two diastereoisomers **285** but the reaction was not reproducible. Instead, a lithium-halogen exchange of **284** with ^{t}BuLi and reaction with the aldehyde **265** gave two diastereoisomers of **285** in 7% yield.



284 **285**

Scheme 81. a ^{t}BuOH, $NaNH_2$, THF, –40 °C → r.t., 3.5 h, 42%. **b** (i) ^{t}BuLi, $CeCl_3$, THF, –78 °C to –30 °C, 30 min. (ii) aldehyde **265**, –30 °C to r.t., overnight, 7%.

Given the poor yield obtained for the coupling reaction between the aldehyde **265** and the vinylic bromide **284**, an alternative way of synthesising the alcohol **285** using a Shapiro reaction was investigated. The cyclohexanone tosylhydrazone **286** was prepared from cyclohexanone and tosylhydrazine in 73% yield.[145] The hydrazone **286** was converted into the lithiocyclohexene by the Shapiro reaction and this was reacted with the aldehyde **265** *in situ* to give a 6:1 mixture of diastereoisomers **285** in 13% yield and 11% of aldehyde was recovered (**Table 2**, entry 1). Optimisation of this coupling reaction using the Shapiro reaction was attempted but proved to be unsuccessful.



286

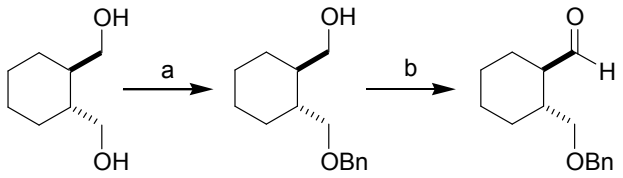
Entry	Aldehyde	Solvent	Yield
1	R = CH_2OTBS **265**	TMEDA	13% Pdt, 11% SM
2	R = CH_2OTBS **265**	THF	Only SM
3	R = H	TMEDA	100% conversion

Table 2. Different conditions for the Shapiro reaction.

Even though the reaction of the tosyl hydrazone **286** in TMEDA is known to increase the reactivity of the organolithium species, the reaction was attempted with THF as solvent. Unfortunately no reaction occurred at all in this case (entry 2). To explore the reactivity of the hydrazone, the simple aldehyde, cyclohexanecarboxyaldehyde, was subjected to the reaction conditions (entry 3). We observed 100% conversion with this simple aldehyde, suggesting that the procedure is efficient. It was thought that the aldehyde **265** failed to react due to steric hindrance.

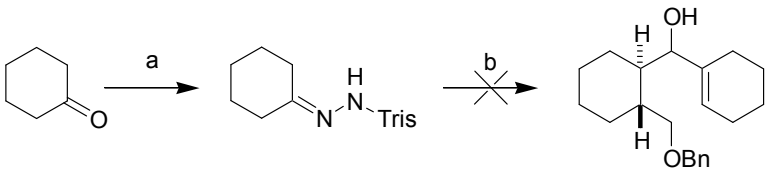
In an effort to increase the reaction yield (13%), we decided to prepare a less sterically hindered aldehyde and a more reactive hydrazone. The aldehyde **288** bearing a benzyl

group protecting the hydroxyl group was chosen and was prepared in two steps from the diol **267** (**Scheme 82**).[128b] At the same time, trisylhydrazone **289** was prepared starting from the cyclohexanone and ({2,4,6-triisopropylphenyl}sulfonyl)hydrazine in 69% yield (**Scheme 83**).[146] The trisylhydrazone **289** was treated with ^{n}BuLi in a 1:1 mixture of TMEDA and hexane and the aldehyde **288** was then added, but unfortunately the reaction did not proceed. In a second attempt using the same reagents, the reaction was performed in THF, but once again did not provide the expected compound.



267 **287** **288**

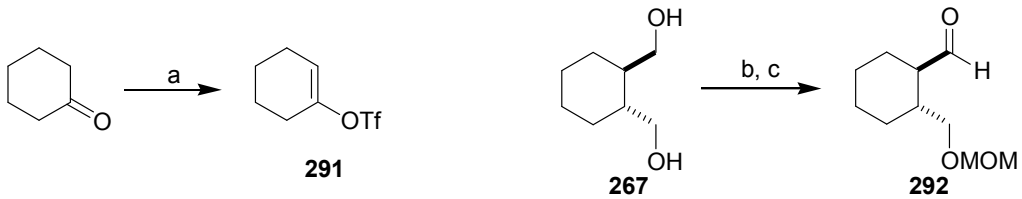
Scheme 82. a KH, $PhCH_2Br$, THF, 0 °C → r.t, 2.5 h, 59%. **b** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2 h. (ii) Et_3N, r.t., 98%



289 **290**

Scheme 83. a NH_2-NH-Tris, MeOH, HCl, –20 °C, overnight, 69%. **b** (i) ^{n}BuLi, TMEDA or THF, –78 °C to r.t., 40 min. (ii) aldehyde **288**, hexane/TMEDA, overnight.

Since satisfactory results were not obtained using the Shapiro reaction, an alternative coupling strategy, employing the Nozaki-Hiyama-Kishi reaction,[147] was investigated. Trifluoromethanesulfonic acid cyclohex-1-enyl ester **291** was prepared from cyclohexanone in 55% yield (**Scheme 84**).[148]

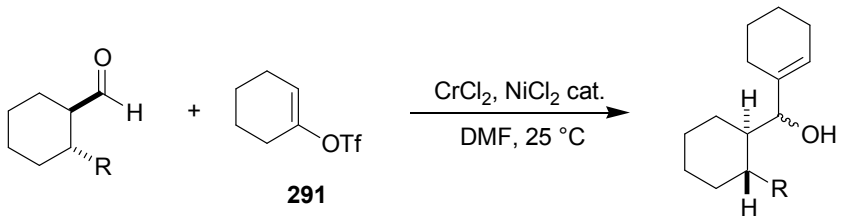


291 **267** **292**

Scheme 84. a (i) LDA, THF, -78 °C (ii) $PhN(SO_2CF_3)_2$, THF, -78 °C to 0 °C, 55 %. **b** i) NaH, THF, reflux, 2.5 h. (ii) MOMCl, 0 °C to r.t., overnight, 39%. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 74%.

Alkenyl triflate and various aldehydes were added to a mixture of anhydrous $CrCl_2$ and a catalytic amount of $NiCl_2$ in dry, degassed dimethylformamide (**Table 3**). The coupling reaction between the triflate **291** and the aldehyde **265** with 2% of nickel catalyst was first

tested but did not succeed (entry 1). So the catalyst loading was increased to 10% to promote the reaction but this attempt proved to be unsuccessful (entry 2). To test the reaction conditions a simple aldehyde, cyclohexanecarboxyaldehyde, was used and afforded 63% of the expected product (entry 3). It was thought that perhaps the protecting group on the other side of the molecule was too large to allow the reaction to occur. So the reaction was tested with two other substrates one bearing a benzyl group **288** and the other a MOM protecting group **292** (prepared as shown in **Scheme 84**). The coupling reaction was again unsuccessful (entries 4 and 5), suggesting there must be an alternative reason for the failure.

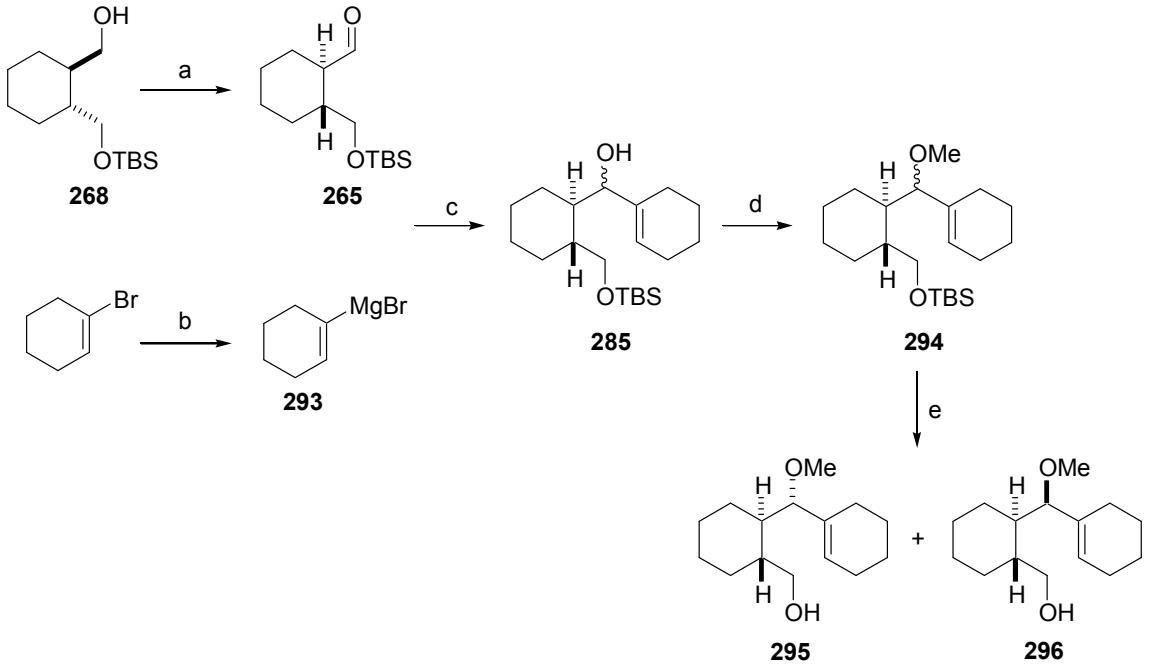


Entry	$NiCl_2$	Aldehyde	Time	Yield
1	2% mol	R = CH_2OTBS **265**	1 week	Only SM
2	10% mol	R = CH_2OTBS **265**	1 week	Only SM
3	2% mol	R = H	3 h	63%
4	2% mol	R = CH_2OBn **288**	1 month	Only SM
5	2% mol	R = CH_2OMOM **292**	1 month	Only SM

Table 3. Different conditions for the Nozashi-Hiyama-Kishi coupling reaction.

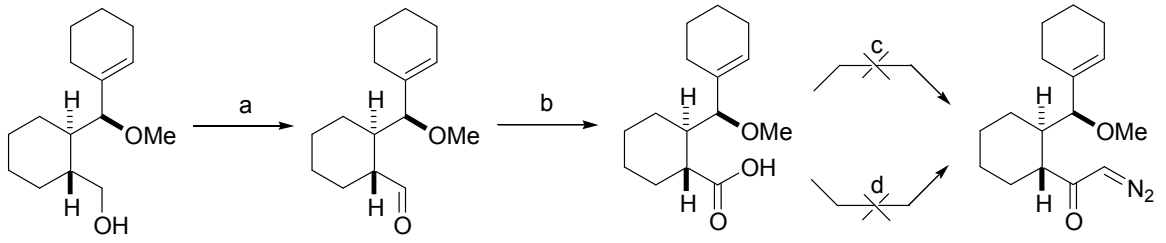
It was thought at this stage, that the preparation of the Grignard reagent **293** using another approach might lead to a better result (**Scheme 85**). 1-Bromocyclohexene first underwent lithiation with *t*butyllithium, and then transmetallation with magnesium bromide to give the corresponding Grignard reagent **293**. Gratifyingly, the coupling reaction between the aldehyde **265** with the Grignard reagent **293** proceeded smoothly to furnish the desired alcohols **285**. The ^1H NMR spectrum of the crude reaction mixture revealed that the reaction reached completion (100% conversion), and that a good 9:1 ratio of diastereoisomeric alcohols **285** was obtained. Methylation of the secondary alcohols **285**, followed by removal of the silyl group with TBAF afforded the mixture of the two diastereoisomeric alcohols **295** and **296** in an excellent 81% yield over four steps. After purification, the major isomer **295** was isolated in 65% yield, but the stereochemistry of the

stereogenic centre was not confirmed yet at that time. Attempts to crystallise the alcohols by formation of *p*-nitrobenzoyl and 3,5-dinitrobenzoyl esters were unsuccessful.



Scheme 85. a (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2.5 h. (ii) Et_3N, r.t. **b** (i) ^{t}BuLi, Et_2O, –78 °C, 1 h, r.t., 40 min. (ii) $MgBr_2$, –78 °C, 30 min. **c** Et_2O, –78 °C, 1.5 h. **d** (i) NaH, THF, 25 °C → reflux, 1.5 h (ii) MeI, 25 °C → reflux, 1.5 h. **e** TBAF, THF, r.t., overnight, 81 % over 4 steps: 65% of major diastereoisomer **295** + 15% of mixture.

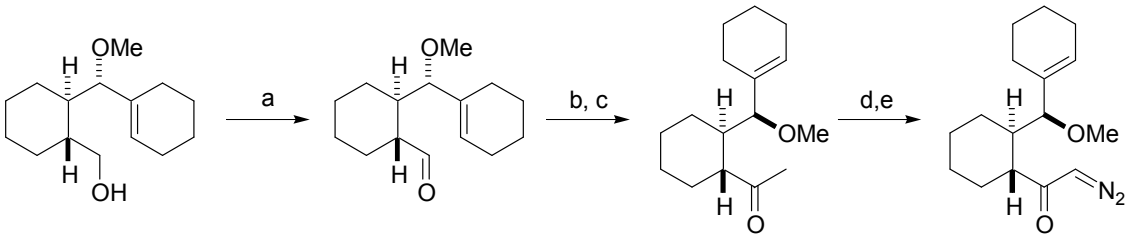
With the development of a straightforward approach to the preparation of the alcohol **295**, we then focused on the synthesis of the required diazoketone **257**. The major diastereomer **295** underwent Swern oxidation to produce the corresponding aldehyde **297**, which was then oxidised to give the carboxylic acid **298** under the classic Pinnick oxidation conditions, in 85% yield over two steps (**Scheme 86**). Attempts to convert the carboxylic acid **298** into the diazoketone **257** by activation of the carboxylic acid followed by treatment with diazomethane were then undertaken. The carboxylic acid **298** was first converted into mixed anhydride by reaction with ^{i}butyl chloroformate, which was then added to an etheral solution of diazomethane. Unfortunately, the mixed anhydride remained unreacted after stirring overnight and no diazoketone was isolated. Secondly, the carboxylic acid **298** was treated with sodium methoxide followed by oxalyl chloride in benzene to generate the acid chloride intermediate and this was added to an etheral solution of diazomethane. Regrettably, the acid chloride decomposed prior to the reaction with diazomethane, and the required diazoketone **257** was not isolated.



295 **297** **298** **257**

Scheme 86. a $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 90%. **b** $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4.2H_2O$, ^{t}BuOH : H_2O (1:2), r.t., 40 min, 94%. **c** (i) ^{t}BuCO$_2$Cl, Et_3N, Et_2O, 25 °C, 3.5 h (ii) CH_2N_2, Et_2O, 0 °C → r.t., overnight **d** (i) NaOMe, MeOH, r.t., 15 min. (ii) $(COCl)_2$, benzene, r.t., 3 h. (iii) CH_2N_2, Et_2O, CH_2Cl_2, 0 °C → r.t., 20 h.

Work by Danheiser[142] and co-workers provided an alternative route to the target diazoketone **257** since classical reactions between an activated carboxylic acid and diazomethane did not provide the expected diazoketone **257**. The Danheiser diazo transfer route required the synthesis of the methyl ketone **299**, as mentioned earlier. The major diastereomer **295** underwent a Swern oxidation to produce the corresponding aldehyde **297** (**Scheme 87**). Treatment of the aldehyde with methylmagnesium bromide provided the corresponding secondary alcohol as a mixture of diastereoisomers, which were used without further purification in the next step. Oxidation of the alcohol by Swern oxidation gave the methyl ketone **299** in a 66% yield from the alcohol **295**. This methyl ketone was then converted into the corresponding diazoketone **257** in 63% yield.

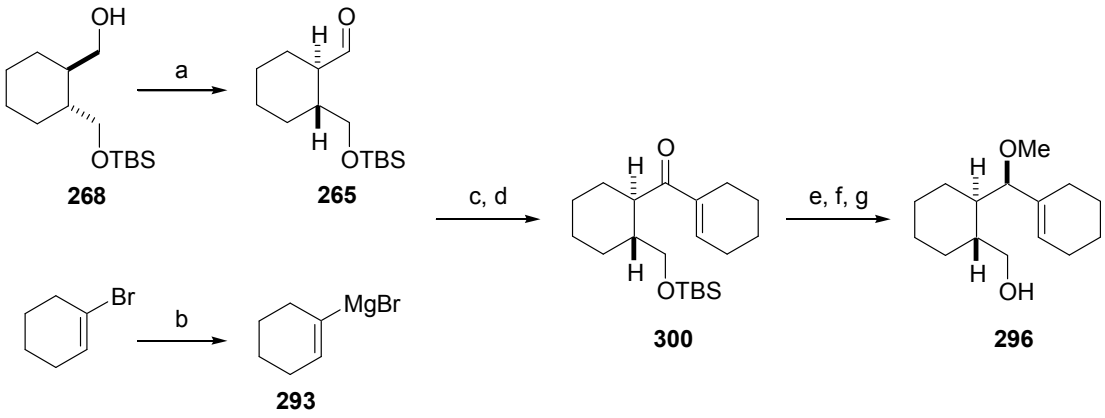


295 **297** **299** **257**

Scheme 87. a (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t. **b** MeMgBr, THF, –78 °C → r.t., overnight. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h. (ii) Et_3N, r.t., 66% over 3 steps. **d** (i) LiHMDS, THF, –78 °C, 2 h. (ii) $CF_3CO_2CH_2CF_3$, –78 °C → r.t., 1 h. **e** *p*-ABSA, DBU, MeCN, r.t., 4 days. 63% from **299**.

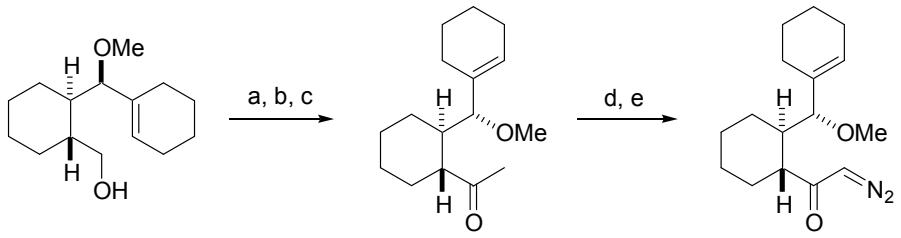
It was then necessary to prepare the other diastereoisomeric diazoketone **259**, with the vinyl group on the bottom face of the diazoketone, in order to compare the reactivities of both substrates towards the metal catalysed reaction. The decision was made to oxidise the mixture of alcohols **295** and **296** and then perform stereoselective ketone reduction to get the desired alcohol **296** predominantly. Oxidation of the mixture of diastereoisomers **295** and **296** with manganese dioxide was first attempted but failed to deliver any of the desired

ketone **300**. In a second attempt, the Swern oxidation delivered the ketone **300** but in only 17% yield over three steps. Whereas, the oxidation of the mixture of diastereoisomers **295** and **296** using Dess-Martin periodinane afforded nicely the ketone **300** in 79% yield over three steps, starting from the alcohol **268** (**Scheme 88**). Subsequent Luche reduction of the enone gave the desired alcohol. This reaction sequence permitted to the ratio of diastereoisomers to be changed from 9:1 (**295**: **296**) to 1:19. Methylation of the secondary alcohol, followed by removal of the silyl group with TBAF produced the diastereoisomer **296** in 40% yield over three steps.



Scheme 88. a (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1. 5h. (ii) Et_3N, r.t. **b** (i) ^tBuLi, Et_2O, –78 °C → 25 °C, 1.5 h. (ii) $MgBr_2$, –78 °C, 30 min. **c** Et_2O, –78 °C, 1.5 h. **d** DMP, CH_2Cl_2, r.t., 2h, 79% over 3 steps **e** $NaBH_4$, $CeCl_3.7H_2O$, MeOH, –78 °C→ 25 °C, overnight. **f** (i) NaH, THF, 25 °C → reflux, 1.5 h (ii) MeI, 25 °C → reflux, 1.5 h. **g** TBAF, THF, r.t., overnight, 40% over 3 steps.

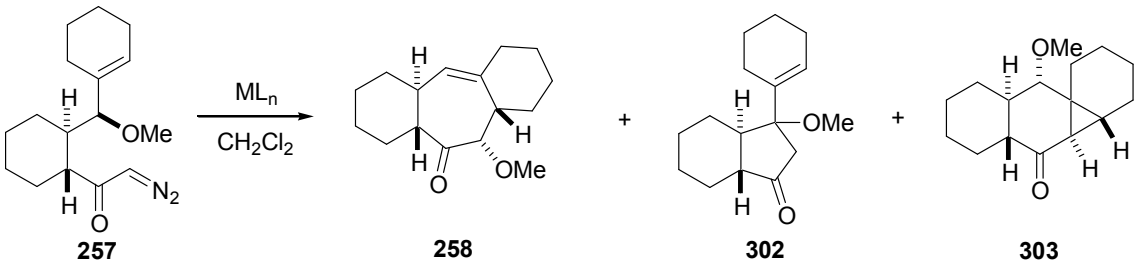
The strategy previously described for the preparation of the *syn*-diazoketone **257** was employed to synthesise the desired *anti*-diazoketone **259** (**Scheme 89**). The alcohol **296** first underwent Swern oxidation to produce the corresponding aldehyde, and treatment with methylmagnesium bromide then provided the corresponding secondary alcohol as a mixture of diastereoisomers. Subsequent Swern oxidation of the alcohol delivered the methyl ketone **301** in a 56% yield from the alcohol **296**. The methyl ketone **301** was deprotonated with LiHMDS and quenched with 2,2,2-trifluoroethyl trifluoroacetate to afford the activated 1,3-dicarbonyl compound, which was then treated at room temperature with *p*-acetamidobenzenesulfonyl azide to give the desired α-diazoketone **259** in 63% yield.



296 **301** **259**

Scheme 89. a (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t. **b** MeMgBr, THF, –78 °C → r.t., overnight. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 56% over 3 steps. **d** (i) LiHMDS, THF, –78 °C, 1.5 h. (ii) $CF_3CO_2CH_2CF_3$, –78 °C → r.t., 1 h. **e** *p*-ABSA, DBU, MeCN, r.t., 4 days. 63% from **301**.

With these two diazoketones **257** and **259** in hand, the tandem oxonium ylide formation and [2,3] sigmatropic rearrangement was explored using rhodium(II) acetate in dichloromethane at room temperature, and under reflux in the case of the copper(II) hexafluoroacetylacetonate mediated reaction (**Schemes 90 and 91**). In both cases, TLC indicated that the crude reaction mixture contained at least six products.



257 **258** **302** **303**

$Cu(hfacac)_2$, reflux	28%	-	-
$Rh_2(OAc)_4$, r.t.	3%	36%	27%

Scheme 90. Catalytic decomposition of *syn*-diazoketone **257**.

Treatment of the *syn*-diazoketone **257** with copper(II) hexafluoroacetylacetonate gave the [2,3]-rearrangement product **258** in only 28% yield (**Scheme 90**). In contrast, the rhodium(II) acetate catalysed reaction delivered the desired compound **258** in a very low yield (3%) and instead afforded the ketone **302**, arising from insertion of the carbenoid into allylic methine C-H bond, in 36% yield. Significant amounts of the alkene cyclopropanation product **303** (27% yield) were also obtained. The relative stereochemistry of the cyclopropane **303** was assigned on the basis of its X-ray crystal structure (**Figure 14**).

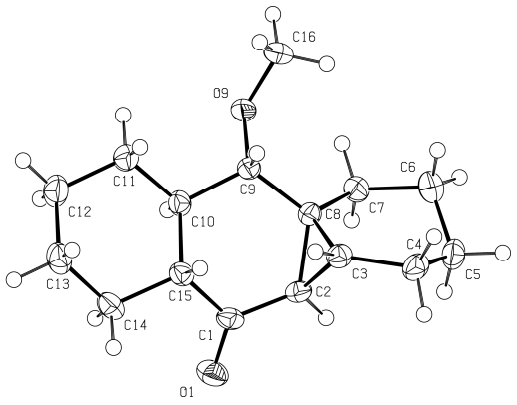


Figure 14. X-ray crystallography for the cyclopropane **303**.

The low yields of the [2,3]-rearrangement products **254** and **258** are not surprising given the results obtained in previous studies. For example, S. Walls obtained the [2,3]-rearrangement product **169** in 51% yield with $Cu(hfacac)_2$ and none when performing the reaction with rhodium(II) acetate (**Scheme 49**). Indeed, it had been established that [2,3]-rearrangement was unfavourable for systems with this relative (*syn*) configuration of side chains. The oxonium ylide derived from the diazoketone **257** is, as predicted, poorly configured for the ylide formation and [2,3]-rearrangement reaction (**Figure 15**).

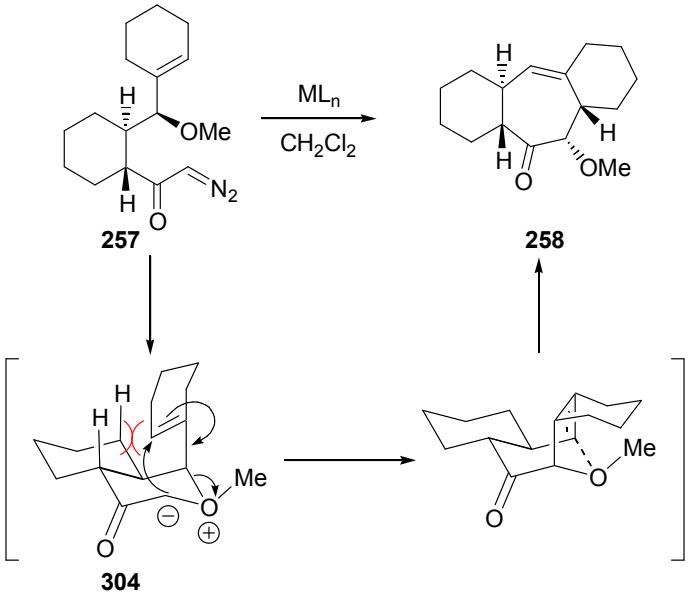


Figure 15. Unfavourable transition state for rearrangement of oxonium ylide **304**.

Inspection of the transition state leading to the cycloheptenone shows why the ylide formation and [2,3]-rearrangement reaction was disfavoured (**Figure 15**). Catalytic decomposition of the diazoketone **257** generated the oxonium ylide **304**, which then underwent the [2,3]-rearrangement reaction *via* the vinyl group on the top face to give

cycloheptenone **258**, but in poor yield. The rearrangement can proceed, but the strained axial position of the cyclohexene and its 1,3-diaxial interactions disfavour the process. Moreover, the results obtained for the copper- and rhodium-mediated reactions differ considerably, suggesting that the ylide intermediate is bound to the metal catalyst. In the case of the copper-catalysed reaction, only the [2,3]-rearrangement product was isolated. Whereas, when $Rh_2(OAc)_4$ was used as catalyst, the product derived from the oxonium ylide was obtained in a lower amount than the products derived from competitive carbenoid reactions, such as CH-insertion and cyclopropanation. This study revealed that the synthesis of the [2,3]-sigmatropic rearrangement products using *syn*-diazoketones (e.g.: **169**, **254** and **258**) could be performed only in moderate yield using a copper catalyst.

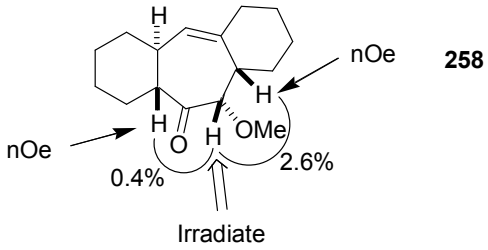
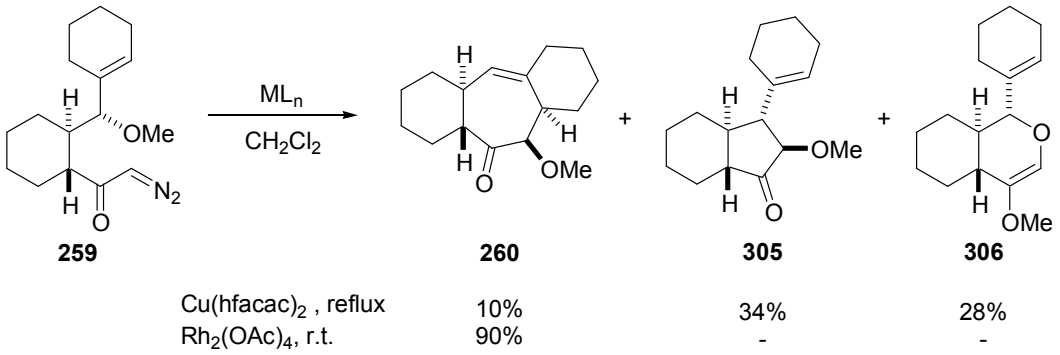


Figure 16.

The relative configuration of cycloheptenone **258** was determined by nOe experiments (**Figure 16**). Irradiation of the methoxy methine proton gave a clear nOe enhancement (2.6%) to the ring-junction methine proton adjacent to the methoxy group, and a nOe enhancement (0.4%) to the α-carbonyl methine. These results indicate that these three protons are on the same face of the molecule and so the methoxy methine proton and the α-methoxy methine proton are assigned as up.



Scheme 91. Catalytic decomposition of diazoketone **259**.

In the case of the *anti*-substrate **259** (**Scheme 91**), the copper-catalysed reaction afforded three ylide-derived products: the [2,3]-rearrangement product **260** in 10% yield,

the ring-contracted [1,2]-shift product **305** in 34% yield and the [1,4]-migration product **306** in 28% yield. In contrast, use of rhodium(II) acetate as the catalyst gave the tricyclic [2,3]-rearrangement product **260** in excellent yield. The ketone **260** was a crystalline solid and X-ray crystallography was used to establish the relative configuration (**Figure 17**).

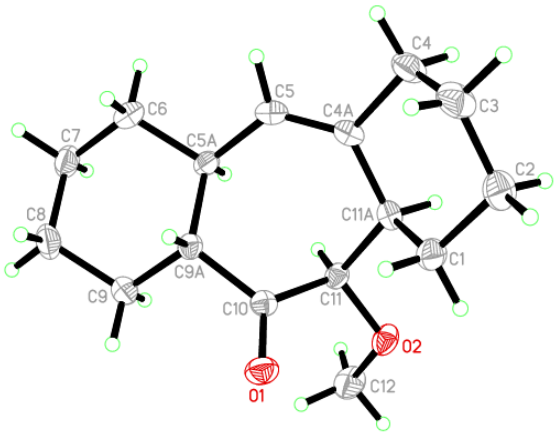


Figure 17. X-ray crystallography for the tricyclic [2,3]-rearrangement product **260**.

In this case, it appears that the relative (*anti*) configuration of the stereogenic centres in the ylide, generated by treatment of the diazoketone **259** with rhodium(II) acetate, facilitated the [2,3]-rearrangement *via* a low energy transition state (**Figure 18**). Whereas the copper-mediated reaction provided less of the intermediate ylide and there was significant competitive [1,4]-migration of the methyl group giving the unusual enol ether **306**. Once again, the results obtained provide circumstantial evidence for the involvement of the metal catalyst during both the generation and rearrangement of the ylide intermediate. From the results, it can be concluded that rhodium(II) acetate has to be employed if [2,3]-sigmatropic rearrangement products are to be prepared selectively using *anti*-diazoketones (e.g.: **171**, **256** and **260**). It is also worth noting that the [1,4]-migration products (**280**, **282** and **306**) have only been obtained when a copper catalyst has been employed.

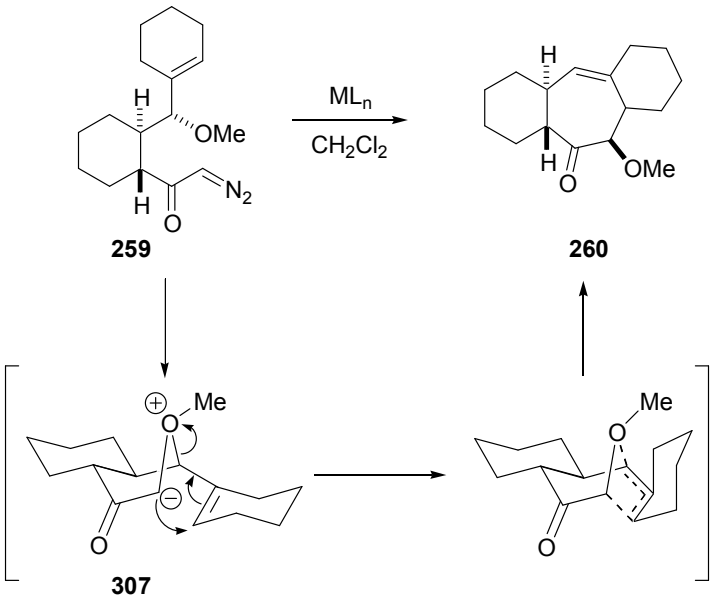
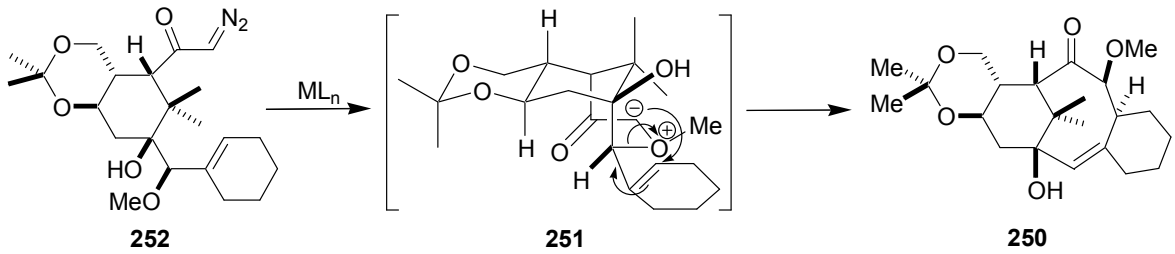


Figure 18. Favourable transition state for rearrangement of oxonium ylide **307**.

Several important findings emerge from the study described in this section. Firstly, we have shown that it is possible to construct fused bicyclic and tricyclic systems containing a seven-membered ring *via* carbenoid generation, ylide formation and [2,3]-sigmatropic rearrangement. However, the success of the [2,3]-rearrangement reaction is highly dependent on the relative (*syn*/anti) configuration of the stereocentres in the cyclic substrate and the choice of catalyst is crucial. Both [1,4]- and [1,2]-shift products can also be obtained if targeted specifically. The second significant finding is that *p*-methoxy benzyl ether substrates can be used instead of methyl ethers and under appropriate conditions competing [1,2]-Stevens rearrangement is not a major problem. Finally, it is significant that in all cases the copper- and rhodium- mediated reactions lead to widely differing outcomes with regard to the ratio of ylide-derived products. These discrepancies are difficult to rationalise if the reactions proceed through a free oxonium ylide intermediate in all cases. Consequently, it seems likely that in some or all cases, rearrangement products are being formed directly from metal-bound ylide intermediates, since the rhodium-mediated reactions gave consistently better results for the [2,3]-rearrangement than, those employing copper catalysts.

2. Towards the synthesis of the tricyclic core system of Taxol

The successful formation of fused tricyclic seven-membered carbocycles (**Schemes 90** and **91**) and bicyclic systems containing an eight-membered ring (results of S. Walls, **Scheme 47**) suggests that it might be possible to construct fused tricyclic systems containing an eight-membered ring using tandem oxonium ylide generation and [2,3]-rearrangement reaction. Many exciting synthetic applications of our findings to construct fused polycyclic compounds are conceivable. One of the most important polycarbocyclic natural product targets that should be amenable to synthesise by this methodology is the anticancer agent Taxol. Before tackling the total synthesis, a model of the tricyclic core system of Taxol **250** was chosen as a target in order to establish the viability of our strategy (**Scheme 92**). The key cyclisation was expected to proceed in good yield *via* the bridged oxonium ylide **251** since the vinyl group on the bottom face should be suitably positioned to undergo favourable oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement.



252 **251** **250**

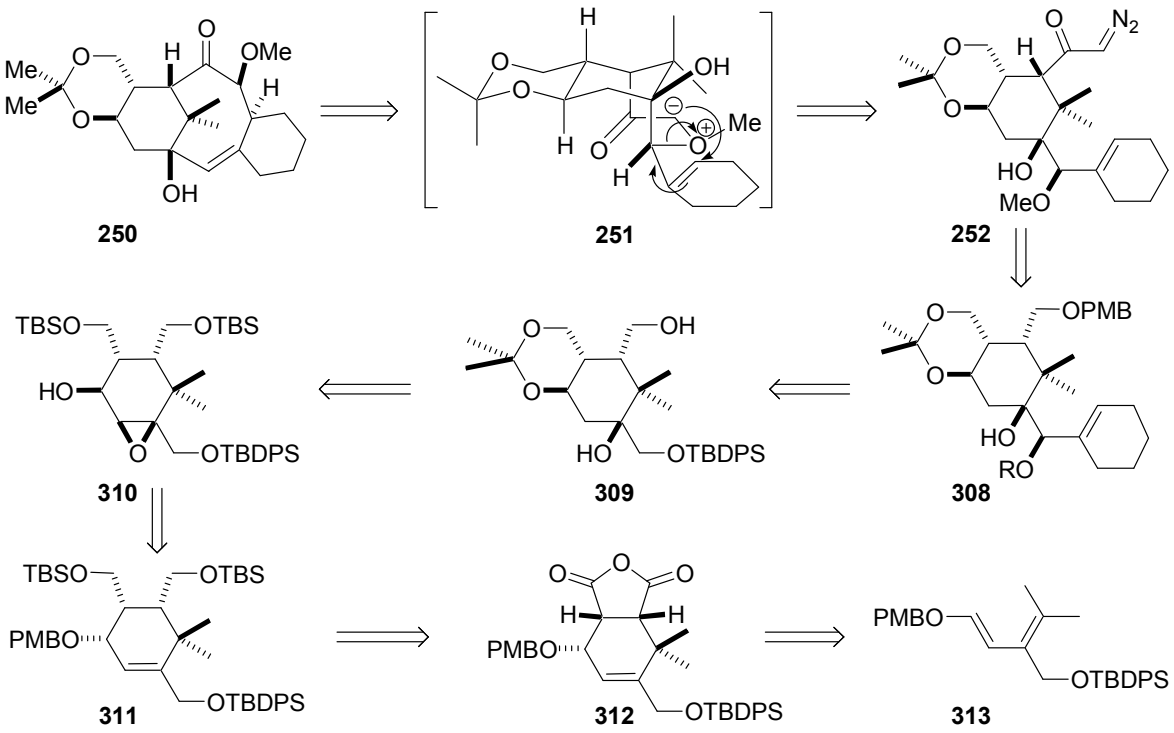
Scheme 92.

2.1. First route towards the tricyclic core of Taxol

2.1.1. Retrosynthetic analysis

It was envisaged that the substrate required to establish the viability of the key reaction would be prepared as shown in **Scheme 93**. Disconnection in the B ring reveals the conformationally locked diazoketone **252**, which should undergo the key cyclisation reaction via the bridged oxonium ylide **251**. The cyclisation precursor **252** would then be

obtained from the PMB-ether **308** using the standard protocol for diazoketone formation. A simplified C ring in **309** could be introduced, after functional group interconversions, addition of hexenyllithium to the resulting aldehyde and subsequent alkylation of the free hydroxyl group. In the event that this sequence does not deliver the required diastereoisomer, sequential oxidation and stereocontrolled reduction should be performed prior to alkylation. Reductive opening of the epoxide **310**, removal of the TBS protecting groups and acetonide formation would deliver the diol **309**. Deprotection of the PMB-ether **311** followed by vanadium-mediated directed epoxidation of the resulting allylic alcohol was planned to provide the epoxide **310**. The A ring fragment **311** could be obtained after complete reduction of the anhydride **312**, silyl protection of both primary hydroxyl groups, and a Diels Alder reaction of maleic anhydride with the siloxydiene **313**, which should deliver the *endo* cycloaddition product **312**.

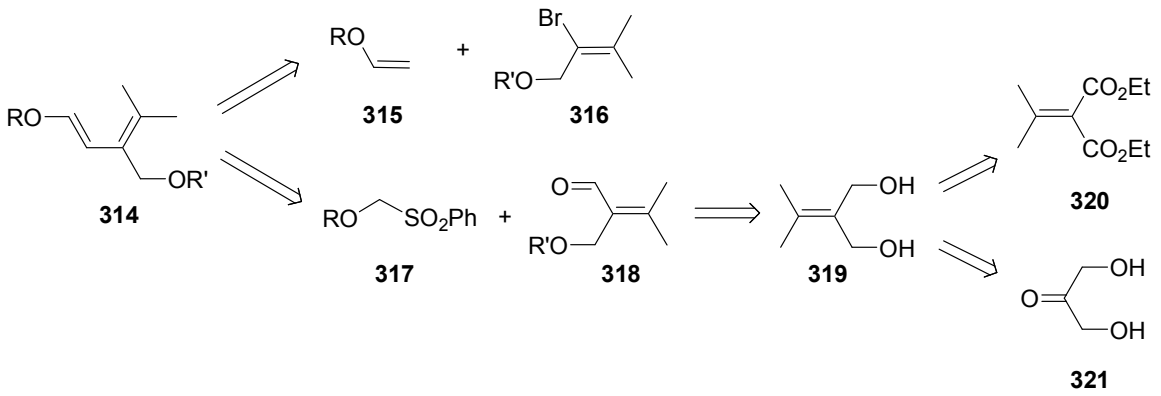


Scheme 93. Synthetic strategy of the core structure of Taxol **250**.

2.1.2. Synthesis of the siloxydiene

Our first target was to synthesise the siloxydiene **313**, and to do this, different routes were proposed (**Scheme 94**). First, it was anticipated that the diene **314** could be prepared using a Heck reaction of the alkene **315** and bromoalkene **316**. Alternatively, the diene **314** could be synthesised following the route described by Craig and co-workers[149] (who

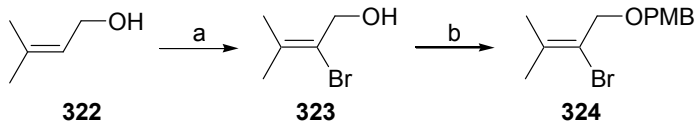
prepared a similar diene) by a Julia-Lythgoe type olefination, using the sulfone **317** and the aldehyde **318**. Several functional group manipulations reveal the diol **319**, which could be prepared either by reduction of isopropylidene malonate **320** or by a Wittig reaction with 1,3-dihydroxyacetone **321**.



Scheme 94. Synthetic strategies of the siloxydiene **314**.

2.1.2.1. Heck reaction attempts

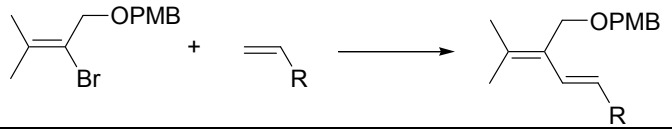
Initial attemps were made to prepare the desired siloxydiene **313** using a Heck reaction. The bromoalkene precursor **324** was prepared in two steps starting from the commercially available 3-methylbut-2-enol **322**, which upon bromination gave the bromoalcohol **323** in 64% yield (**Scheme 95**).[150] Different conditions for the protection of the alcohol **323** with a *p*-methoxybenzyl group were explored, and the best result (72% yield) was obtained with 4-methoxybenzyl-2,2,2-trichoroacetimidate in presence of a catalytic amount of pyridinium *p*-toluenesulfonate.



Scheme 95. a (i) Br_2, CH_2Cl_2, 0 °C, 1h, r.t., 3h. (ii) DBU, reflux, 4h, 64%. **b** PPTS, $PMBOC(=NH)CCl_3$, CH_2Cl_2, r.t., 3 days, 72%.

Following the synthesis of the bromovinyl precursor **324**, reactions with several alkenes and various conditions were explored (**Table 4**). The Heck reaction was first performed with a silyl enol ether (entry 1) and then methyl acrylate (entry 2) using palladium acetate as catalyst, but none of them gave the desired diene. Tetrakis(triphenylphosphine)palladium was then chosen as catalyst when ethyl vinyl ether

(entry 3) and vinyl acetate (entry 4) were used as precursors, but unfortunately these reactions failed to give any of the expected diene products.

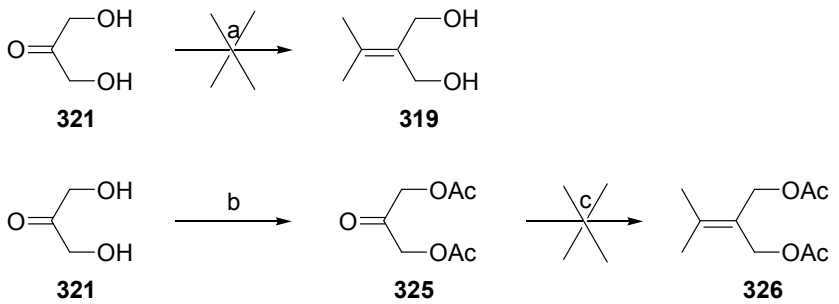


Entry	R	Conditions	Results
1	-OTBS	$Pd(OAc)_2$, LiCl, Bu_4NCl, K_2CO_3, DMF, 85 °C, 6 h	Only SM
2	$-CO_2Me$	$Pd(OAc)_2$, LiCl, Bu_4NCl, K_2CO_3, DMF, 85 °C, 16 h	Only SM
3	-OEt	$Pd(PPh_3)_4$, Et_3N, CH_3CN, 70 °C, 4 h	Only SM
4	-OAc	$Pd(PPh_3)_4$, Et_3N, CH_3CN, 95 °C, 4 days	Only SM

Table 4. Attempts of the Heck reaction.

2.1.2.2. Wittig reaction attempts

The failure of the Heck reaction to give the desired diene **313** meant that another strategy relying on the Julia-Lythgoe type reaction was explored. The synthesis of the alkenes **319** or **326** was required. After further functionalisation of the alkenes, they would react with the sulfone to deliver the expected diene **313**. It was proposed that both alkenes **319** and **326** would be prepared by a Wittig reaction of the commercially available 1,3-dihydroxyacetone dimer **321** (**Scheme 96**). However, treatment of 1,3-dihydroxyacetone **321** with isopropyltriphenylphosphonium bromide and base did not deliver the expected alkene **319**. So this diol **321** was treated, prior to the Wittig reaction, with acetic anhydride to afford the di-protected ketone **325** in 37% yield.[151] The Wittig reaction was then attempted using the same conditions but it failed to deliver the required product.

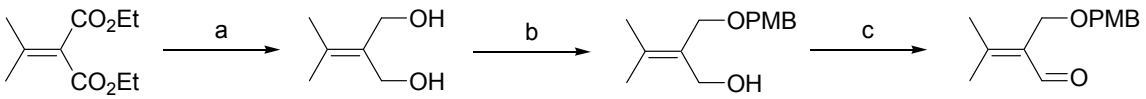


Scheme 96. a (i) $(CH_3)_2C{=}PPh_3^+Br^-$, KO^{t}Bu, benzene, reflux, 1 h. (ii) ketone **321**, toluene, reflux, 30 min. **b** Ac_2O, pyridine, –20 °C, 1 h, 37%. **c** (i) $(CH_3)_2C{=}PPh_3^+I^-$, KO^{t}Bu, benzene, reflux, 1 h. (ii) ketone **325**, toluene, r.t., 1 h, reflux, 1 day.

2.1.2.3. *First attempt of the Julia-olefination*

The synthesis of the desired alkene **319** by reduction of the isopropylidene malonate **320** had been previously described.[152] However, the procedures involving $LiAlH_4$ either in diethyl ether or benzene were not reproducible, and significant amounts of the product resulting from the reduction of the alkene were observed. The less reactive reducing agent, DIBAL-H was tested and proved to be better; the desired diol **319** was obtained in 89% yield (**Scheme 97**).

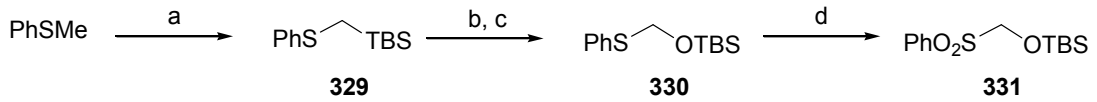
Various conditions were tested to mono-protect the diol **319** with a *p*-methoxybenzyl group. First the diol **319** was treated with KHMDS and PMBBr, as described previously, but the enol ether **327** was obtained in only 24% yield (28% BRSM). Diol **319** was also treated with sodium hydride and PMBCl in presence of a catalytic amount of tetra-*n*-butylammoniun iodide in THF to give product **327** in a very low yield (10%, 16% BRSM). The best result was obtained using sodium hydride and *p*-methoxybenzyl chloride in DMF/THF, which delivered the PMB-ether **327** in 33% yield. This alcohol **327** was then converted into the corresponding aldehyde **328** by Swern oxidation, and the product was used without further purification.



320 **319** **327** **328**

Scheme 97. a DIBAL-H, petroleum ether, 0 °C to r.t., overnight, 89%. **b** (i) NaH, DMF/THF, 0 °C to r.t., 1.5 h. (ii) PMBCl, THF, 0 °C to r.t., overnight, 33%. **c** (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1.5 h. (ii) Et_3N, r.t..

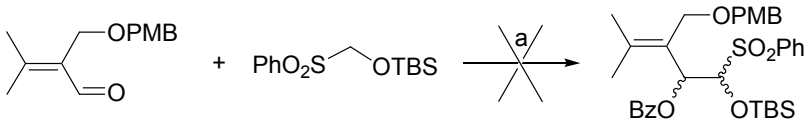
The sulfone **331**, required for the Julia-olefination reaction, was synthesised in four steps starting from the thioanisole (**Scheme 98**). Following a procedure described by Ager,[153] thioanisole was first deprotonated with *n*-butyllithium and then quenched with *tert*-butyldimethylsilyl chloride to the give sulfide **329**. This sulfide was immediately oxidised with *m*-chloroperbenzoic acid to give the corresponding sulfoxide, which rearranged when heated under reflux in carbon tetrachloride to give the sulfide **330** in 49% yield over 3 steps. This sulfide **330** was then converted into the desired sulfone **331** in 85% yield following a newly developed environmentally friendly protocol:[154] treatment with a catalytic amount of manganese sulfate monohydrate and 30% hydrogen peroxide in the presence of a buffer solution of $NaHCO_3$.



329 **330** **331**

Scheme 98. a (i) ^{n}Buli, Et_2O, reflux, 18 h. (ii) TBSCl, reflux, 27 h. **b** *m*-CPBA, CH_2Cl_2, –20 °C, 15 min, r.t., 1 h. **c** CCl_4, relux, 3 h, 49% over 3 steps. **d** H_2O_2 (30% wt), $MnSO_4.H_2O$ cat., 0.2 M $NaHCO_3$, CH_3CN, r.t., 3.5 h, 85%.

With these two precursors in hand, we then tried to perform Julia olefination. The sulfone **331** was first deprotonated with LDA, then treated with the aldehyde **328**, and *in situ* trapping with benzoyl chloride, which should have given the mixture of esters **332** (**Scheme 99**). However, the reaction failed and the ^{1}H NMR spectrum of the crude reaction mixture revealed that the starting aldehyde **328** remained unreacted whereas the starting sulfone **331** had decomposed, probably by undergoing Brook rearrangement.

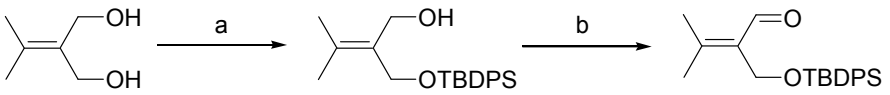


328 **331** **332**

Scheme 99. a (i) LDA, THF, -78 °C, 15 min. (ii) aldehyde **328**, –78 °C, 15 min. (iii) BzCl, –78 °C to r.t., 2 h.

2.1.2.4. Second attempt of the Julia-olefination

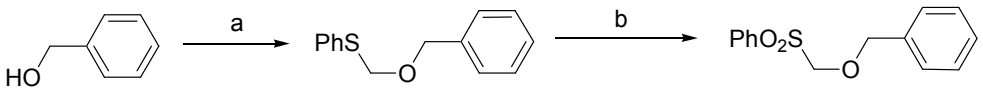
Following the unsatisfactory results of the Julia olefination, due to the incompatibility of the protecting group, it was decided to prepare the two precursors for the Julia-olefination by swapping the protecting groups. First, the aldehyde **334** bearing the *tert*-butyldiphenylsilyl protecting group was synthesised using the strategy described above. The diol **319** was mono-protected with TBDPSCl in 64% yield. The resulting alcohol **333** was then subjected to Swern oxidation giving the corresponding aldehyde **334** in 86% yield (**Scheme 100**).



319 **333** **334**

Scheme 100. a (i) NaH, THF, r.t., 1 h. (ii) TBDPSCl, r.t., 15 h, 64%. **b** (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h. (ii) Et_3N, r.t., 86%.

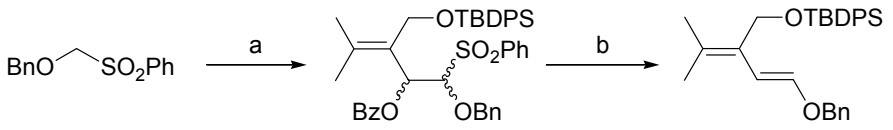
The other partner for the Julia olefination reaction, the sulfone **336** was prepared starting from benzyl alcohol (**Scheme 101**). It was first transformed into the corresponding sulfide **335** in 85% yield, which was prepared by reacting the anion from benzyl alcohol with chlorophenylmethyl sulfide in the presence of sodium iodide.[155] The sulfide **335** was then immediately oxidised using the same methodology as described above to afford the desired sulfone **336** in 72% yield.



335 **336**

Scheme 101. a (i) NaH, DME, 0 °C, 30 min. (ii) NaI, $PhSCH_2Cl$, 0 °C, 1 h, r.t., 2.5 h, 85%. **b** 30% H_2O_2, $MnSO_4.H_2O$ cat., 0.2 M $NaHCO_3$, CH_3CN, r.t., 3.5 h, 72%.

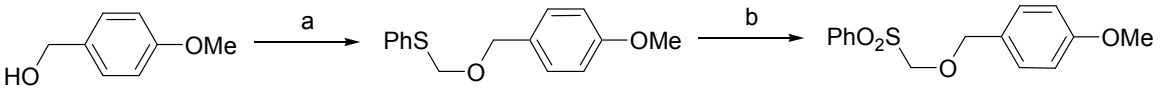
The diene **338** was prepared according to the procedure of Craig and co-workers, and was then used in the Diels Alder reaction (**Scheme 102**).[149a] The lithio-anion of sulfone **336** reacted with aldehyde **334**, *in situ* trapping with benzoyl chloride gave in this case the mixture of esters **337** in 76% yield. They were then exposed to samarium(II) diiodide to afford the diene **338** as a single regioisomer in 86% yield.



336 **337** **338**

Scheme 102. a (i) LDA, THF, –78 °C, 10 min. (ii) aldehyde **334**, THF, –78 °C, 10 min. (iii) BzCl, –78 °C to r.t., 45 min, 76% **b** SmI_2, DMPU, THF, r.t., 1 h, 86%.

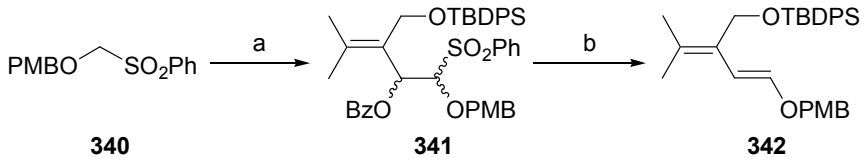
The diene **342** bearing a PMB group was then prepared in a way similar to the diene **338** bearing a Bn group so that it would be possible to deprotect the cycloadduct more easily. Sulfone **340** was prepared using the conditions described earlier starting from *p*-methoxybenzyl alcohol (**Scheme 103**). Sulfide **339** was obtained in 74% yield, and was then immediately oxidised to afford the desired sulfone **340** in 84% yield.



339 **340**

Scheme 103. a (i) NaH, DME, 0 °C, 30 min. (ii) NaI, $PhSCH_2Cl$, 0 °C, 1 h, r.t., 2.5 h, 74%. **b** 30% H_2O_2, $MnSO_4.H_2O$ cat., 0.2 M $NaHCO_3$, CH_3CN, r.t., 3.5 h, 84%.

The aldehyde **334** was then treated with the lithiated sulfone **340** to give epimeric benzoyl sulfones **341** upon benzoylation in 74% yield (**Scheme 104**). The mixture of esters **104** underwent a reductive elimination of 1,2-benzoyl sulfone when exposed to excess samarium(II) diiodide to afford the desired diene **342** with high stereoselectivity (*E:Z* ratio of 17:1) and in good 90% yield.

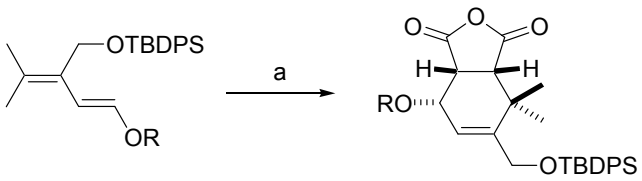


340 **341** **342**

Scheme 104. a (i) LDA, THF, -78 °C, 10 min. (ii) aldehyde **334**, THF, -78 °C, 10 min. (iii) BzCl, -78 °C to r.t., 45 min, 74% **b** SmI_2, DMPU, THF, r.t., 1 h, 90%.

2.1.3. Diels-Alder reactions

The dienes **338** and **342** were then subjected to the Diels-Alder reaction with maleic anhydride to give the desired cycloadducts **343** and **344** in 48% yield and 64% yield respectively (**Scheme 105**). In both cases, the Diels-Alder products were isolated as single stereoisomers. The anhydride **344** was a crystalline product, which enabled confirmation of the *endo*-stereochemistry by single crystal X-ray analysis (**Figure 19**).



R = Bn, **338** **343**, 48%

R = PMB, **342** **344**, 64%

Scheme 105. a maleic anhydride, toluene, 150 °C, 7 h.

Considering the previous results, it was decided that it would be more judicious to use the anhydride **344** rather than the anhydride **343**, first because the yields obtained for the preparation of the anhydride **344** were better, and also because removal of the PMB protecting group should be easier than the removal of a benzyl group in presence of the alkene functionality.

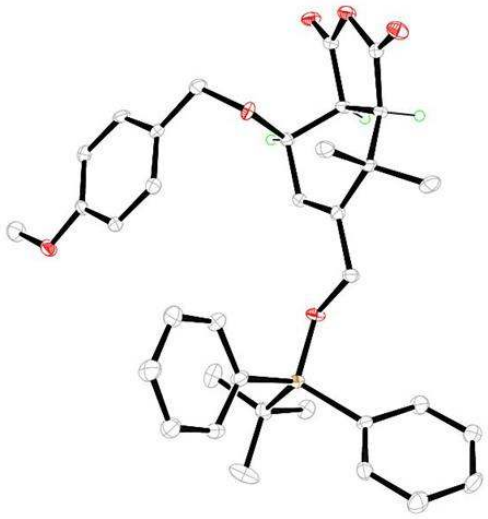
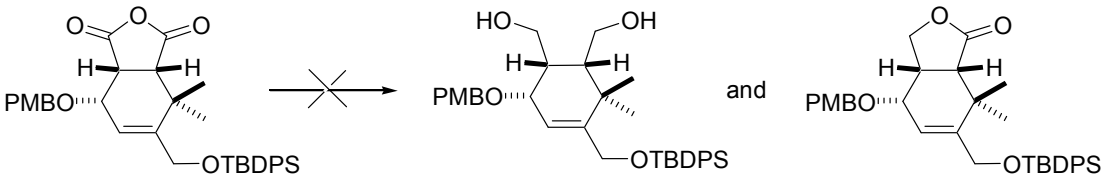


Figure 19. X-ray crystallography of the anhydride **344**.

Therefore, the reduction of the anhydride **344** into the corresponding diol **345** was investigated (**Table 5**). $LiAlH_4$ was initially employed as a reducing agent, and the reaction was carried out under different conditions. Unfortunately, either the starting material decomposed (entries 3 and 4), or the ^1H NMR spectra and the mass analysis of the crude reaction mixture revealed the formation of lactone **346** (entry 1). In one instance, traces of the diol **345** were observed in the ^1H NMR spectrum of the crude reaction mixture (entry 2). Since $LiAlH_4$ did not give reproducible results and did not deliver the expected diol **345**, DIBAL-H (entry 5) and RedAl® (entry 6) were used but gave the same negative results: decomposition of the starting anhydride **344**. Methanolysis (entry 7) of the anhydride **344** also failed, and reduction with sodium borohydride gave mixture of at least two products, with only traces of the lactone **346** visible in the ^1H NMR spectrum of the crude reaction mixture (entry 8). In other attempts involving two-step processes (entries 9 and 10), hydrolysis to form either the diacid or the acid ester followed by a reduction reaction failed and significative amounts of the diol **345** and the lactone **346** were not observed. Unfortunately, these results are only tentative because we have not been able to isolate either the diol **345** or the lactone **346** and therefore full characterisation was not possible.

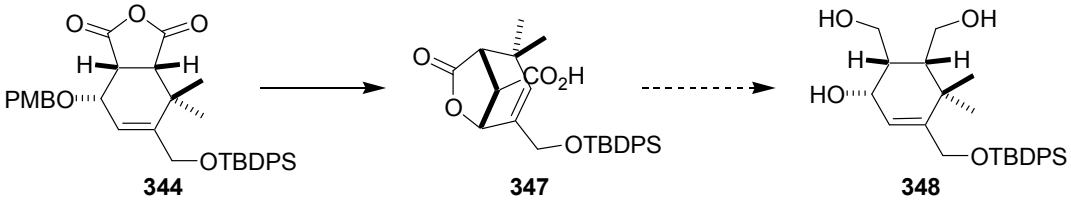


344 **345** **346**

Entry	Conditions	Results
1	$LiAlH_4$ (2 eq.), THF, 0 °C to r.t., overnight	trace of lactone
2	$LiAlH_4$ (2.1 eq.), THF, r.t., 1h	trace of diol
3	$LiAlH_4$ (3 eq.), THF, –78 °C, 1h	decomposition
4	$LiAlH_4$ (3 eq.), THF, 0 °C, 1h, reflux, 3h	decomposition
5	DIBAL-H, petroleum ether, –78 °C to r.t., overnight	decomposition
6	RedAl®, THF/toluene (1:1), reflux, 20 h	decomposition
7	MeOH, reflux, 18 h	decomposition
8	$NaBH_4$, THF, 0 °C, 10 min, r.t., 23 h	trace of lactone
9	**a.** NaOH, EtOH, r.t., 10 min **b.** $LiAlH_4$, THF, –78 °C, 1 h	complex mixture (trace of diol)
10	**a.** MeONa, MeOH, r.t., 30 min **b.** $LiAlH_4$, Et_2O, 0 °C to r.t., 1.5 h	trace of lactone

Table 5. Attempts of the reduction reaction.

As the reduction of the anhydride was not successful, another alternative was the removal of the PMB group with concomitant lactonisation to give the lactone **347**, which could then be transformed into the desired triol **348** (**Table 6**). Cleavage of the PMB group using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) resulted in 62% conversion (entry 1), whereas cerium(IV) ammonium nitrate (CAN) deprotection yielded the lactone **347** in 38% yield when 2 equivalents were used (entry 2), and 49% yield in the case of 1.1 equivalents (entry 3). The best result was found when the anhydride **344** was treated with trifluoroacetic acid (entry 4), which caused deprotection and concomitant lactonisation, to afford lactone **347** in 73% yield. Even though the transformation of the anhydride **344** into the corresponding lactone **347** was achieved in good yield, this route was abandoned in favour of a shorter one.



Entry	Conditions	Yield of 347
1	DDQ (1.5 eq.), DCM/H_2O (18:1), 0 °C to r.t., 2 h	62% conversion
2	CAN (2 eq.), MeCN, H_2O, 0 °C to r.t., 3.5 h	38%
3	CAN (1.1 eq.), MeCN, H_2O, 0 °C to r.t., 5 h	49%
4	CF_3CO_2H (10 eq.), DCM, 0 °C, 30 min, r.t., 1 h	73%

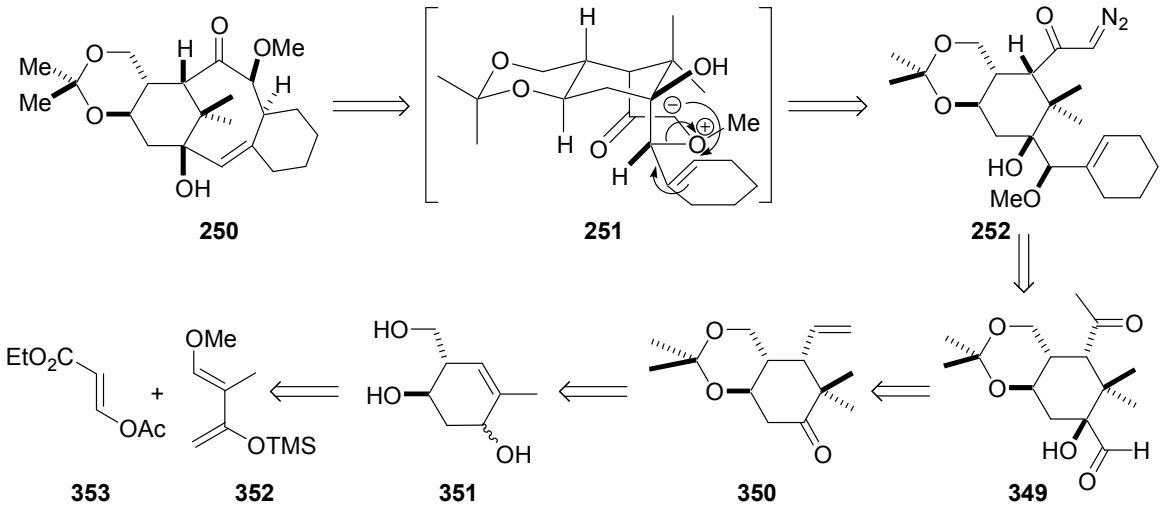
Table 6. Attempts of the deprotection reaction.

In summary, lactone **347** was successfully prepared from the commercially available isopropylidene malonate **320** in seven steps *via* a route involving sequential Julia-Lythgoe type olefination and Diels-Alder reactions.

2.2. Second route towards the tricyclic core of Taxol

2.2.1. Retrosynthetic analysis

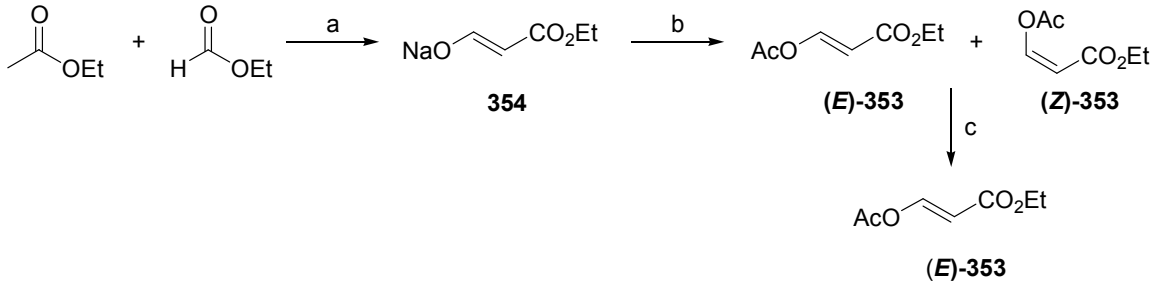
An alternative strategy was required in order to synthesise the tricyclic core of Taxol **250**, which demanded fewer steps as shown in **Scheme 106**. The cyclisation precursor **252** would be synthesised from the methyl ketone **349** by introduction of the C-ring, protection of the resulting secondary hydroxyl group and then diazo transfer. Simplification of the aldehyde **349** reveals the ketone **350**, which could undergo a Wittig reaction, a Wacker oxidation and a dihydroxylation to deliver the methyl ketone **349**. The ketone **350** could be prepared by 1,4-addition followed by methylation of the enone resulting from the oxidation of the acetonide-protected alcohol **351**. Diels-Alder reaction of the acetoxyacrylate **353** and the butadiene **352**, followed by reduction, would afford the A ring skeleton **351**.



Scheme 106. Synthetic strategy of the core structure of Taxol **250**: second route.

2.2.2. Synthesis of the key intermediate ketone 350

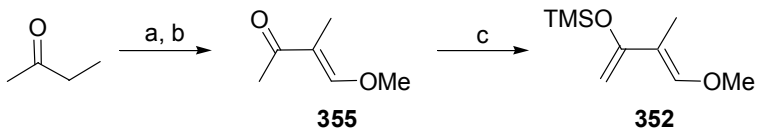
The syntheses of dienophile (*E*)-**353** and the diene **352** for the Diels-Alder reaction are presented in **Scheme 107** and **Scheme 108**. Ethyl (*E*)-3-acetyloxy-2-propenoate **353** was easily obtained on a multigram scale by formylation of ethyl acetate, followed by acetylation of the resulting sodium salt of the α-formyl ester **354** using acetyl chloride.[156] However, when the temperature during reaction and distillation was not well controlled, a mixture of (*E*)-**353** and (*Z)*-**353** was obtained. But this problem was overcome, by conversion of the (*Z*)-**353** isomer into (*E*)-**353** *via* treatment of the mixture with thiophenol in the presence of 2,2'-azobis(2-methylpropionitrile) (AIBN), as previously described by Herdewijn.[156a]



Scheme 107. a Na, Et_2O, 0 °C to r.t., 6 h, 46%. **b** AcCl, Et_2O, 0 °C to r.t., 6 h. **c** PhSH, AIBN, 80 °C, 3 h, 46% over 2 steps.

1-Methoxy-2-methy-3-trimethylsilyloxybuta-1,3-diene[157] **352**, a known compound that has often been used in Diels-Alder reaction, was prepared by the modified procedure shown in **Scheme 108**, as described by Miyashita.[157b] The starting material butan-2-one

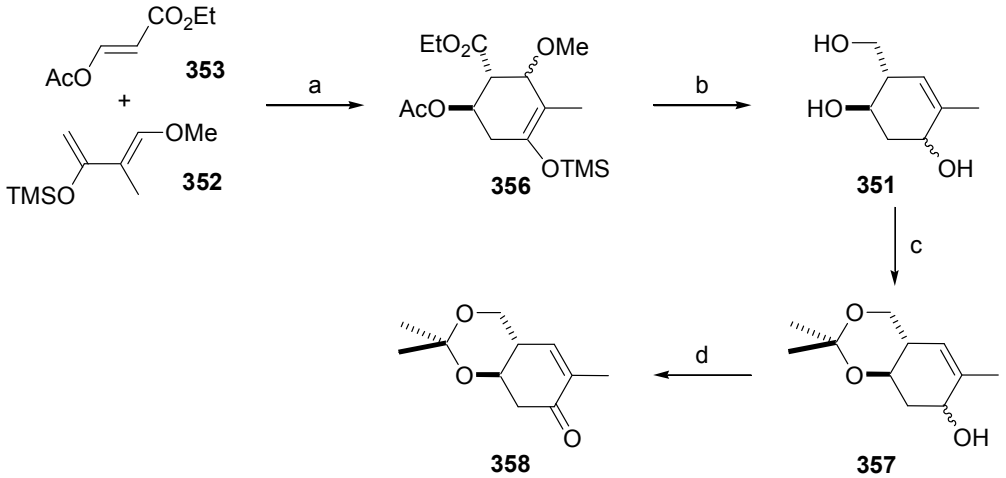
was treated with sodium hydride and methyl formate to give the sodium enolate, which was treated with dimethyl sulfate to give (*E*)-4-methoxy-3-methylbut-3-en-2-one **355** in 53% yield. The butenone **355** was then transformed into the siloxy diene **352** in 87% yield, by treatment with LDA in THF followed by addition of chlorotrimethyl silane.



355 **352**

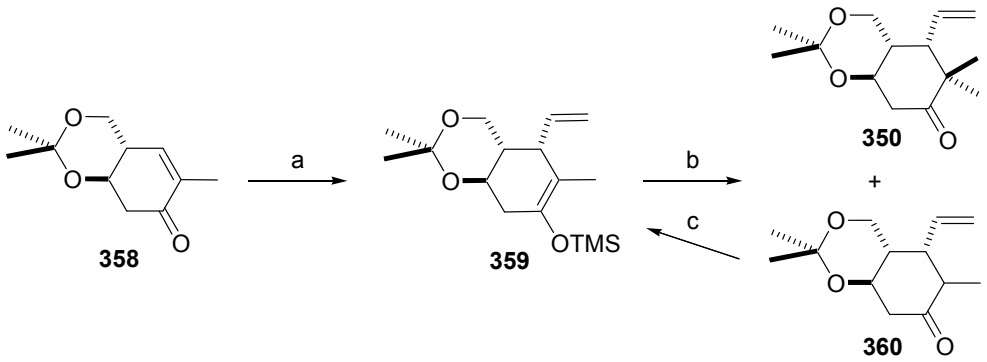
Scheme 108. a NaH, HCO_2Me, THF, r.t., 3h. **b** $(MeO)_2SO_2$, DMF, r.t., 2.5 h, 53% over 2 steps. **c** (i) LDA, THF, –78 °C, 30 min. (ii) TMSCl, –78 °C to r.t., 1 h, 87%.

The key Diels-Alder reaction was carried out by heating a mixture of the neat diene **352** and the neat dienophile **353** in the presence of a catalytic amount of hydroquinone at 180 °C in a sealed tube to produce a 2.4:1 mixture of the *endo* and *exo* adducts **356** (**Scheme 109**). Reduction of the mixture **356** with an excess of lithium aluminium hydride, according to the procedure of Fraser-Reid,[158] gave the triol **351** in 74% yield. This reaction involved the reduction of two esters groups and concomitant rearrangement of the silyloxyenol ether to the enone intermediate, which was then further reduced to alcohol **351**. The *trans*-fused dioxadecalin was constructed at this stage, to establish the rigidity of the rings and therefore ensure the correct conformation was adopted by the diazoketone **252**. Thus, the triol **351** was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in DMF to give the acetonide **357** in 79% yield. The allylic alcohol **357** was then oxidised with manganese dioxide to give the corresponding enone **358** in 90% yield.



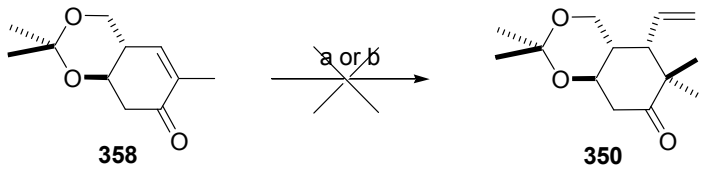
Scheme 109. a hydroquinone, 180 °C, 1.5 h, 98%. **b** $LiAlH_4$, THF, 0 °C, 2 h, r.t., 20 h, 74%. **c** 2,2-dimethoxypropane, *p*TsOH, DMF, r.t., 1 h, 79%. **d** MnO_2, DCM, r.t., overnight, 90%.

Following the procedure described by Clark and co-workers,[159] the axial conjugate addition of the vinyl Normant reagent was performed. Vinylmagnesium bromide in presence of copper(I)bromide-dimethyl sulfide complex, chlorotrimethylsilane and HMPA attacked the enone axially **358** to give the expected TMS-enol ether **359** (**Scheme 110**). It is well known that TMSCl is added before the ketone in order to trap the resulting enolate immediately and to enhance the rate of the conjugate addition reaction.[160] Indeed, the ^{1}H NMR spectrum of the crude reaction mixture showed that the expected TMS-enol ether **359** is the only identifiable product of the reaction, and that no 1,2-addition and equatorial-1,4-addition products were observed. The resulting silyl enol ether **359** was then subjected to a methylation following a methodology developed by Nakamura and Kuwajima.[161] The treatment of the enol ether **359** with methyl iodide and benzyltrimethylammonium fluoride gave the ketone **350** in a moderate 36% yield over two steps and the product **360** resulting from the proton transfer in 33% yield. We were disappointed by this result, since Clark and co-workers had reported the isolation of the dimethylketone **350** in 53% yield over two steps. Nevertheless, we managed to convert the α-monomethyl ketone **360** back into the silyl enol ether **359** in quantitative yield, by treating it with chlorotrimethylsilane in the presence of sodium iodide and triethylamine.



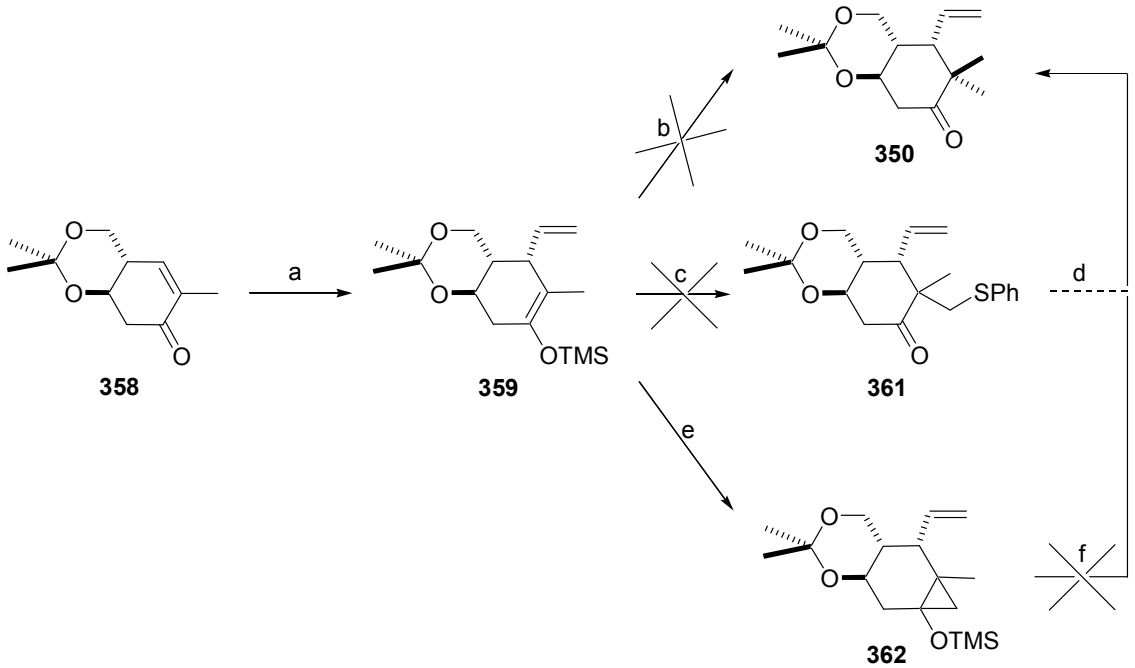
Scheme 110. a (i) CuBr-SMe_2, vinylmagnesium bromide, THF, –78 °C, 1 h. (ii) TMSCl, HMPA, THF, –78 °C, 15 min. (iii) ketone **358**, THF, –78 °C to r.t., overnight. **b** $PhCH_2NMe_3^+F^-$, MeI, THF, 4Å MS, r.t., overnight, 36% **350** and 33% **360** over 2 steps. **c** TMSCl, NaI, Et_3N, MeCN/hexane, r.t., 3 h, quant.

Attempts were made to improve the yield for the formation of the ketone **350** from the enone **358**, and methylation of the silyl enol ether **359** was investigated. First, the 1,4-addition of divinylcuprate to enone **358** was undertaken. Vinyllithium and vinylmagnesium bromide were used as precursors of the organocopper reagent, and 1,4-addition was then followed by a regioselective alkylation of the copper enolate intermediate with methyl iodide. Unfortunately, this approach did not succeed; in both cases analysis of the ^{1}H NMR spectra of the crude reaction mixture revealed a mixture of at least three products (**Scheme 111**).



Scheme 111. a (i) CuI, vinyllithium, Et_2O, THF, –35 °C to 0°C, 1 h. (ii) MeI, DME, 0 °C, 15 min. **b** CuI, vinylmagnesium bromide, THF, –78 °C, 1 h. (ii) MeI, HMPA, r.t., overnight.

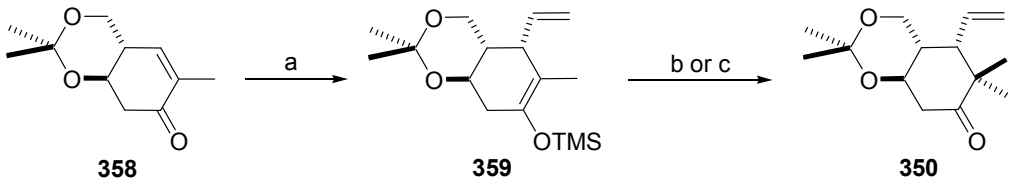
It was proved that the enone **358** was totally converted into the corresponding enol ether **359** by analysis of the ^{1}H NMR spectrum of the crude reaction mixture, and because the silyl enol ether **359** has been successfully isolated in 78% yield, by careful work up and column chromatography (**Scheme 112**). This result proved that the low yield obtained for the preparation of the dimethyl ketone **350** must be due to the methylation reaction. And so it was decided to concentrate on improving the yield of this particular step. Methodology developed by Yamamoto using methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) for primary α-alkylation of carbonyl compounds was first examined.[162] This method involves the organoaluminum-promoted alkylation of an enol silyl ether in combination with a primary alkyl triflate. Unfortunately, treatment of our TMS enol ether **359** with methyl triflate under the influence of MABR resulted in the decomposition of the starting material (**Scheme 112**).



Scheme 112. a (i) CuBr-SMe_2, vinylmagnesium bromide, THF, –78 °C, 1 h. (ii) TMSCl, HMPA, THF, –78 °C, 15 min. (iii) enone **358**, THF, –78 °C to r.t., overnight. 78% isolated once. **b** (i) MABR, MeOTf, DCM, –40 °C, 1 h. **c** chloromethylphenyl sulfide, $TiCl_4$, DCM, –23 °C, 1 h. **d** Raney Ni **e** Et_2Zn, CH_2I_2, toluene, 0 °C, 1 h, r.t., 2 h. **f** *p*TsOH, $CHCl_3$, r.t., 1.5 h.

An alternative possible method was the phenylthioalkylation of *O*-silylated enolate followed by reductive sulphur removal by Raney nickel, as shown by Paterson.[163] It was therefore necessary to prepare the corresponding α-phenylthiomethylketone **361**, which after reduction with Raney nickel would deliver the desired ketone **350**. Treatment of the crude silyl enol ether **359** with chloromethylphenyl sulfide in presence of the Lewis acid $TiCl_4$ was not successful and did not deliver the α-phenylthiomethylketone **361** (**Scheme 112**). Another basic approach for the indirect α-methylation of the ketone is the Simmons-Smith cyclopropanation of a silyl enol ether followed by hydrolysis leading to cyclopropane ring opening.[164] Cyclopropanation of the crude silyl enol ether **359** was performed with diethylzinc and diiodomethane and this crude material **362** was then treated with *p*-toluenesulfonic acid. However, the desired ketone **350** was not obtained from this reaction (**Scheme 112**).

Methylation of the silyl enol ether **359** was also performed by treatment with methyllithium and methyl iodide but this gave the product in only 21% yield (**Scheme 113**). Luckily, it was found that by drying the commercially available benzyltrimethylammonium fluoride under high vacuum at 65 °C for 24 h and then stirring it in a solution in THF with 3Å molecular sieves for an additional day dramatically improved the yield of the reaction (**Scheme 113**). Indeed, addition of methyl iodide to this mixture, followed by a solution of the silyl enol ether **359** afforded the expected ketone **350** in 60% yield over two steps.



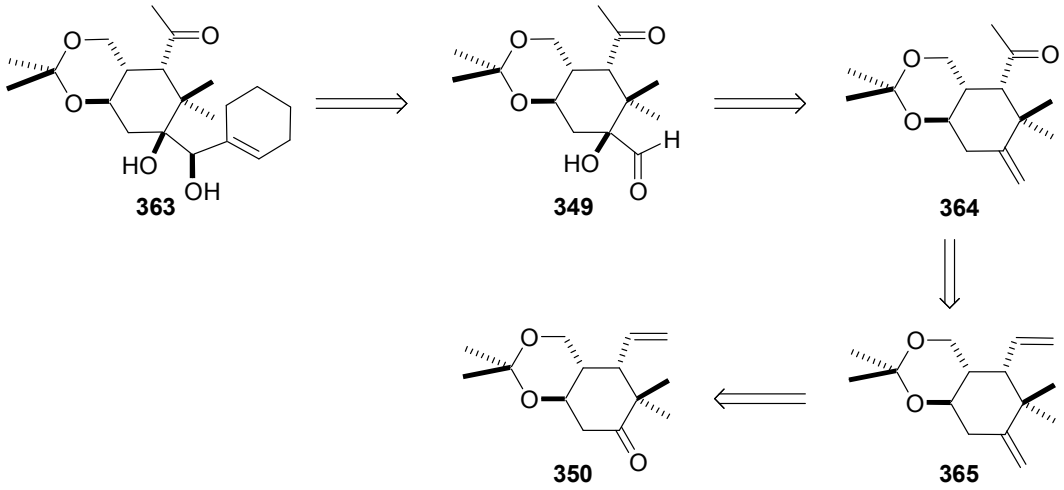
358 **359** **350**

Scheme 113. a (i) CuBr-SMe_2, vinylmagnesium bromide, THF, –78 °C, 1 h. (ii) TMSCl, HMPA, THF, –78 °C, 15 min. (iii) enone **358**, THF, –78 °C to r.t., overnight, (78 % isolated once). **b** (i) MeLi, THF, 0 °C, 15 min (ii) MeI, HMPA, –78 °C to r.t., 1 h, 21%. **c** (i) $PhCH_2NMe_3^+F^-$, high vacum, 65 °C, 24 h. (ii) THF, 3Å MS, r.t., 24 h. (iii) MeI, enol silyl ether **359**, THF, overnight, 60% over 2 steps (or 70% from **359** when isolated).

2.2.3. Attempts towards the synthesis of methyl ketone 363

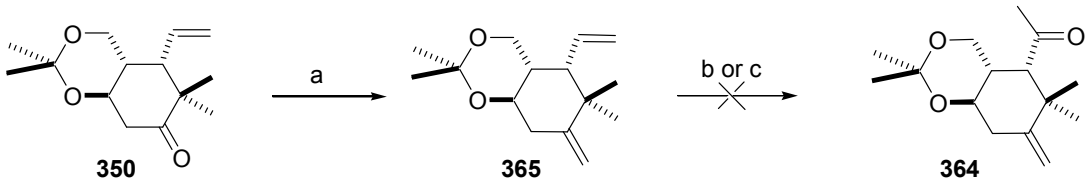
With an optimised synthesis of the ketone **350** in hand, it was then planned to transform it into the corresponding alkene **365** in order to construct the methyl ketone **364** *via* a Wacker oxidation. Stereoselective dihydroxylation of the alkene **364** would give the desired diol, which would be then oxidised to deliver the aldehyde **349**. A coupling

reaction could then be performed with the cyclohexenyl unit to yield the substrate **363** as shown in **Scheme 114**.



Scheme 114. Retrosynthetic analysis towards the diol **363**.

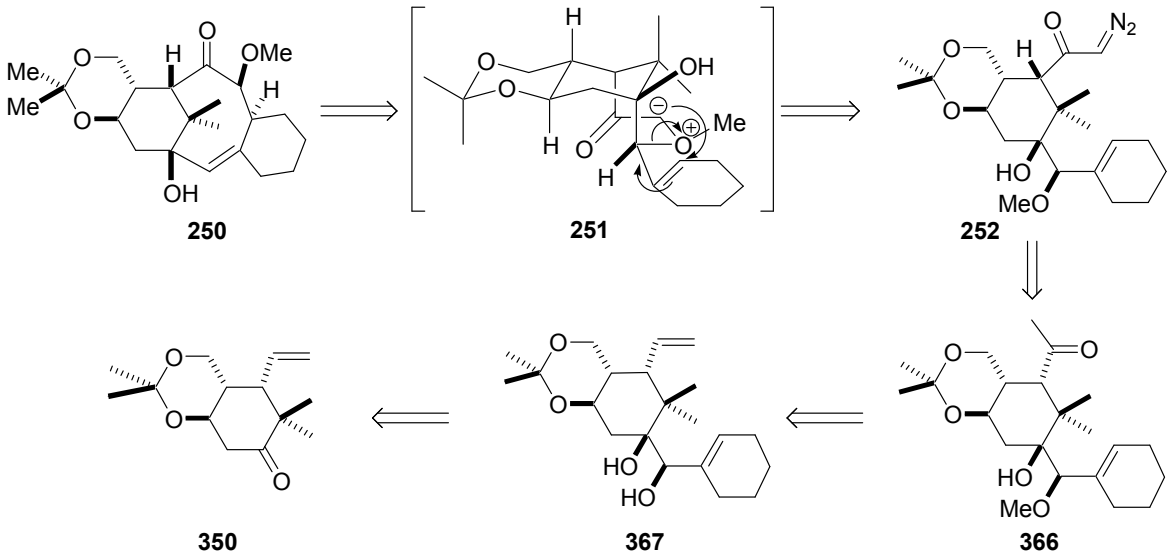
The Wittig methylenation of the ketone **350** proceeded smoothly using methyltriphenylphosphonium bromide yielding the alkene **365** in 70% (**Scheme 115**). This substrate **365** was then subjected to palladium-catalysed Wacker oxidation in an attempt to synthesise the methyl ketone **364**. To our disappointment, the standard Wacker oxidation[165] [2 mol % $PdCl_2$, 1 eq. CuCl, O_2, DMF/H_2O (10:1)] of the terminal alkene **365** did not reach completion, even when the reaction mixture was heated at 60 °C overnight. Moreover, it appeared that deprotection of the acetonide had occurred. A modified Wacker oxidation has been developed by Smith and co-workers;[166] only sub-stoichiometric amounts of $Cu(OAc)_2$ are necessary, and substrates containing an acetonide were oxidised in high yield by suppressing the acidic hydrolysis. Unfortunately, when these conditions were applied to our system [10 mol % $PdCl_2$, 2 eq. $Cu(OAc)_2$, O_2, $AcNMe_2$/ H_2O (7:1)], the starting terminal alkene **365** did not react.



Scheme 115. a Ph_3PCH_3Br, KO^{t}Bu, toluene, reflux, 1 h, 70%. **b** $PdCl_2$, CuCl, O_2, DMF/H_2O (10:1), r.t., 1 h, 60 °C, overnight. **c** $PdCl_2$, $Cu(OAc)_2$, O_2, $AcNMe_2$/ H_2O (7:1), r.t., 1 week.

2.2.4. Attempts towards a straightforward synthesis of diol

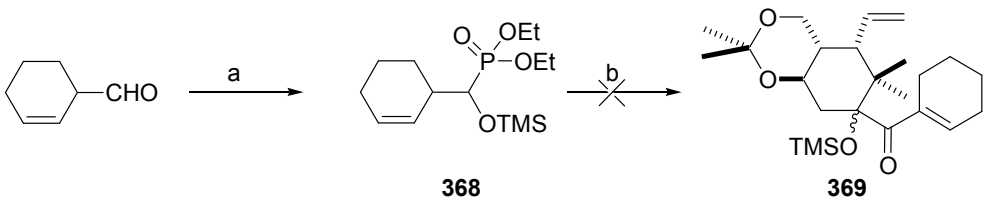
As a consequence of the problems encountered with Wacker oxidation, a new retrosynthetic analysis had to be designed to prepare diazoketone **252** from ketone **350** (**Scheme 116**). It was decided to first functionalise the southern part of the substrate and then finish the northern part. The cyclisation precursor **252** would be synthesised from the methyl ketone **366** *via* a diazo transfer reaction. Wacker oxidation and further functionalisation of the terminal alkene **367** would yield the required intermediate **366**. Disconnection of the C ring reveals the ketone **350**, which should be transformed into diol **367** by α-heterosubstituted phosphonate carbanion,[167] reductive coupling mediated by SmI_2,[168] or using Still α-alkoxylithium methodology.[169] This would result in the introduction of the C ring in one step from ketone **350**; such a convergent A + C approach to the taxoid ABC framework would be very efficient.



Scheme 116. Synthetic strategy of the core structure of Taxol **250**.

We first concentrated on the use of the α-heterosubstituted phosphonate carbanion strategy, introduced by Zimmer.[167] The targeted diol **367** could be synthesised *via* an α-*O*-protected ketone such as **369** by reaction of the ketone **350** with the designed trimethylsiloxymethane phosphonate carbanion **368**, an effective acyl anion equivalent (**Scheme 117**). Diethyl 1-cyclohexenyl-1-(trimethylsiloxy)methane phosphonate **368** was prepared in quantitative yield by treatment of 1-cyclohexene-1-carboxaldehyde with chlorotrimethylsilane and triethylphosphite. Subsequent deprotonation with lithium diisopropylamine at –78 °C should have afforded the corresponding anion which would

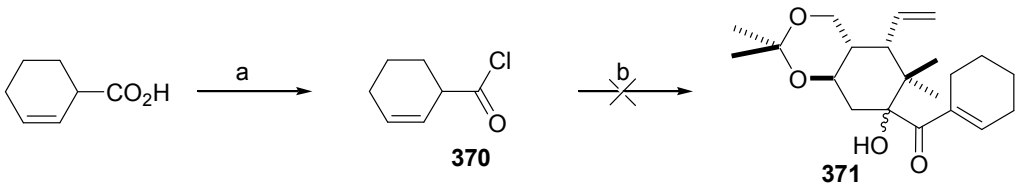
have then reacted with the ketone **350** to give the desired protected α-hydroxy ketone **369**. Unfortunately, the reaction did not proceed and only starting material was recovered.



368 **369**

Scheme 117. a $P(OEt)_3$, TMSCl, 120 °C, 1 h, quant. **b** (i) LDA, THF, –78 °C, 30 min. (ii) ketone **350**, –78 °C, 30 min, r.t., overnight.

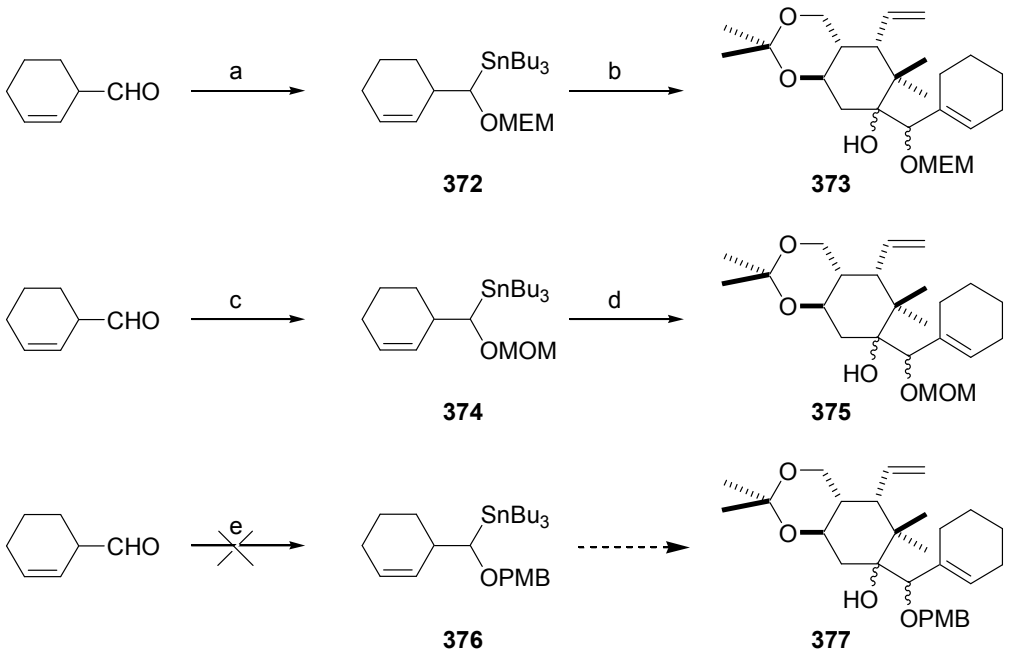
Another suitable convergent approach was a reductive coupling mediated by SmI_2.[168] Indeed, Kagan has reported the possible reductive coupling of acid chlorides with aldehydes and ketones in the presence of an excess of SmI_2 to produce α-hydroxy ketones. The acid chloride **370** was prepared quantitatively from 1-cyclohexene-1-carboxylic acid when treated with oxalyl chloride (**Scheme 118**). But the diiodosamarium-promoted coupling of the acid chloride **370** and ketone **350** failed to give the desired α-hydroxy ketone **371**.



370 **371**

Scheme 118. a $(COCl)_2$, DMF, 0 °C to r.t., 3.5 h, quant. **b** ketone **350**, SmI_2, THF, r.t., 24 h.

Finally, a strategy to incorporate the C-ring, based on Still α-alkoxylithium methodology,[169] and deliver the desired A-C fragment, by coupling of ketone **350** and α-alkoxyorganostannanes **372**, **374** and **376**, was investigated (**Scheme 119**). The acetal precursors **372** and **374** bearing a MEM and a MOM protecting group respectively were prepared following the literature procedures[169a] from the commercially available 1-cyclohexene-1-carboxaldehyde. Treatment of the aldehyde with lithium tributylstannylate followed by protection of the resulting alcohol with MEMCl and MOMBr in the presence of the Hünig's base gave the two products **372** and **374** respectively in 53% yield and 52% yield. We also attempted to prepare the cyclohexenyl derivative **376** bearing a PMB protecting group. The crude alcohol, obtained by treatment of 1-cyclohexene-1-carboxaldehyde with lithium tributylstannylate, was then treated with sodium hydride in presence of PMBCl, but unfortunately the material decomposed under these conditions.



Scheme 119. a (i) Bu_3SnH, LDA, THF, –78 °C, 45 min. (ii) MEMCl, $^{i}Pr_2NEt$, DMAP, DCM, r.t., overnight, 53%. **b** (i) $^{n}BuLi$, THF, –78 °C, 5 min. (ii) ketone **350**, –78 °C, 2.5 h, 57% (major isomer **373a** isolated in 28%). **c** (i) Bu_3SnH, LDA, THF, –78 °C, 45 min. (ii) MOMBr, $^{i}Pr_2NEt$, DMAP, DCM, r.t., overnight, 52%. **d** (i) $^{n}BuLi$, THF, –78 °C, 5 min. (ii) ketone **350**, –78 °C, 2.5 h, 76% (major isomer **375a** isolated in 37%). **e** (i) Bu_3SnH, LDA, THF, –78 °C, 1 h. (ii) NaH, 0 °C to r.t., 1h, then PMBCl, r.t., overnight.

Reactions between the ketone **350** and α-alkoxyorganolithiums derived from **372** and **374** *via* transmetallation were then carried out and proceeded in good yield (**Scheme 119**). Mixtures of diastereoisomeric products were obtained in both cases. The major isomers **373a** and **375a** resulting from these coupling reactions were successfully separated by column chromatography and characterised by comparison of the ^{1}H NMR spectra with those of the products **384** and **389** (described later in this thesis). The three other diastereoisomers were inseparable, and were not prepared in large enough quantities to be interesting for the purposes of our synthesis. To our disappointment, the major diastereoisomers **373a** and **375a** turned out not to have the desired configuration at the hydroxyl bearing carbon atom (**Figure 20**).

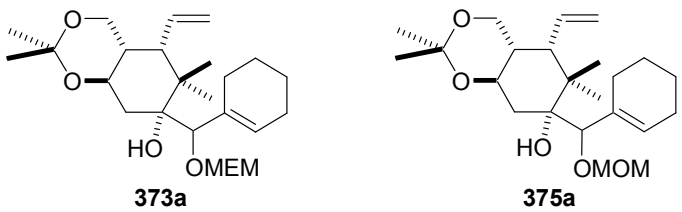
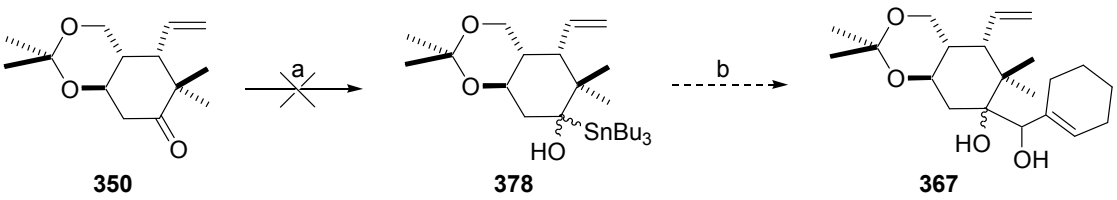


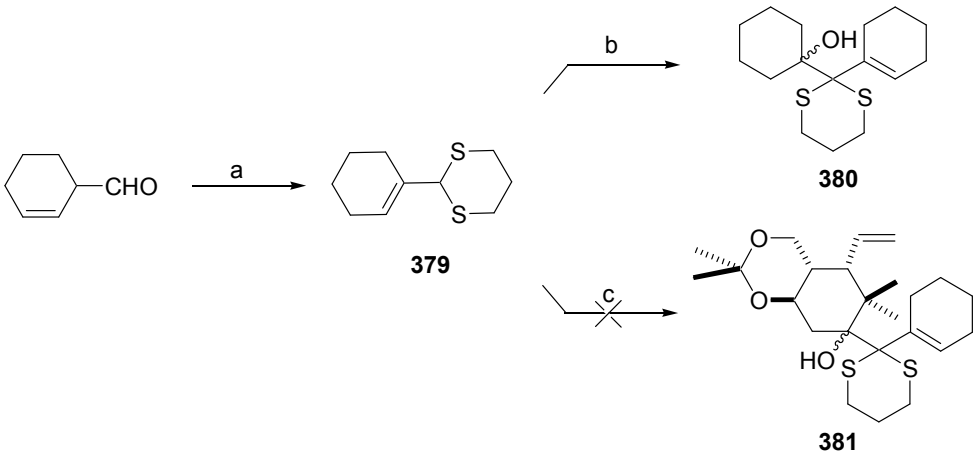
Figure 20. Major isomers **373a** and **375a** isolated from the Still reaction.

Instead of performing a coupling reaction between the ketone **350** and an organostannane, another possibility was coupling the organostannane **378**, derived from ketone **350**, with 1-cyclohexene-1-carboxaldehyde. This reaction would then deliver the desired diol **367**. The established conditions described above were used to transform the ketone **350** into the corresponding organostannane **378**. Disappointingly, the reaction did not furnish the desired α-alkoxyorganostannane **378** and the starting material **350** remained unreacted (**Scheme 120**).



Scheme 120. a (i) Bu_3SnH, LDA, THF, 0 °C to r.t., overnight. **b** (i) LDA, THF, 0 °C, 15 min. (ii) 1-cyclohexene-1-carboxaldehyde, THF, -78 °C.

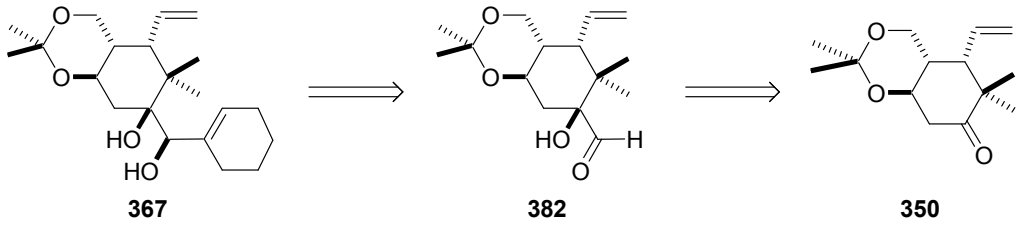
At this stage, a new method for the preparation of diol **367** was required. 2-Lithio-1,3-dithiane derivatives are the most successful of the sulfur-stabilised acyl anion equivalents, having been widely used as masked nucleophilic acylating agents since the pioneering work of Corey and Seebach.[170] These systems are easily prepared by deprotonation of the corresponding dithianes with alkyllithiums and show reverse reactivity of the carbonyl group. This approach towards the synthesis of the diol **367** appeared to be attractive. The C-ring unit would be added by reaction of cyclohexenyl-1,3-dithiane **379** to the ketone **350** to form the alcohol **381**, which should be easily transformed into the required diol **367**. Cyclohexenyl-1,3-dithiane **379** was first prepared by treatment of the 1-cyclohexene-1-carboxaldehyde with 1,3-propanedithiol and boron trifluoride etherate in 99% yield (**Scheme 121**). Unfortunately, the reaction between the cyclohexenyl-1,3-dithiane **379** and ketone **350** did not afford the desired product **381**. In contrast, a model system established the viability of the reaction: the cyclohexenyl-1,3-dithiane **379** reacted with cyclohexanone to give dithiane **380** in 46% yield without optimizing the reaction conditions.



Scheme 121. a 1,3-propanedithiol, $BF_3.OEt_2$, $CHCl_3$, 0 °C, 15 min, r.t., 30 min, 99 %. **b** (i) ^{t}BuLi, THF, –78 °C, 2.5 h. (ii) cyclohexanone, –78 °C to –20 °C, 2 h, 46%. **c** (i) ^{t}BuLi, THF, –78 °C, 2.5 h. (ii) ketone **350**, –78 °C to –20 °C, 2 h.

2.2.5. Synthesis of α-hydroxyaldehyde

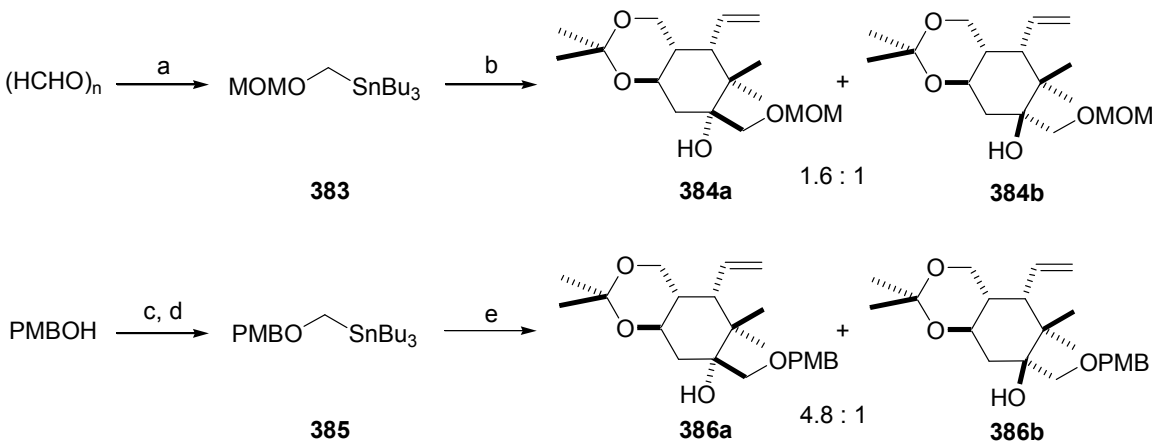
Since these convergent A + C approaches to the tricyclic core ABC were not as successful as expected, another approach was designed. Our synthetic plan involved the preparation the α-hydroxyaldehyde **382** *via* either Still α-alkoxylithium methodology, or by use of popular masked acyl anions such as the *O*-protected cyanohydrins and the dithioacetals. The α-hydroxyaldehyde **382** would then undergo a coupling with the C-ring to give the diol **367**, instead of integrating the fully functionalised C-ring in one step from the ketone **350** (**Scheme 122**).



Scheme 122. Synthetic strategy for the synthesis of **382**.

First, it was decided to employ the previous strategy elaborated, relying on the use of Still methodology, to prepare the desired monoprotected diols **384b** and **386b**, which would be easily converted into aldehyde **382**. The two organostannanes **383** and **385** required for the reaction were prepared (**Scheme 123**). First, the MOM-stannane **383** precursor was obtained as reported by Danheiser[169a,171] from the commercially available paraformaldehyde. The PMB-stannane **385** was prepared from *p*-methoxybenzyl alcohol, which was first converted into methylthiomethylether in 68% yield by alkylation with

chloromethyl methyl sulfide. The resulting sulfide was treated with sulfuryl chloride to give chloromethylether, which was converted into the corresponding organostannane **385** in 65% yield when treated with tributylstannyl lithium.[172]



Scheme 123. a (i) Bu_3SnH, LDA, THF, 0 °C, 15 min. (ii) $(HCHO)_n$, THF, –78 °C to r.t., 1.5 h (iii) $MeOCH_2OMe$, $BF_3.OEt_2$, 4Å MS, DCM, r.t., overnight, 26 %. **b** (i) ^nBuLi, THF, –78 °C, 5 min. (ii) ketone **350**, –78 °C, 30 min, 61% (**384a** 24%, **384b** 16%, and unseparable mixture of **384a** and **384b** 21%). **c** (i) NaH, NaI, THF, r.t., 5 min. (ii) $ClCH_2SMe$, 0°C to r.t., overnight, 68%. **d** (i) SO_2Cl_2, DCM, r.t., 30 min. (ii) Bu_3SnH, LDA, 0 °C to r.t. , overnight, 65%. **e** (i) ^nBuLi, THF, –78 °C, 5 min. (ii) ketone **350**, –78 °C, 20 min, 76% (**386a** 62%, **386b** 13%).

The coupling reactions of the ketone **350** with the α-alkoxylithiums derived from the corresponding α-alkoxyorganostannanes **383** and **385** were examined (**Scheme 123**). In the case of the MOM-organostannane **383**, the coupling reaction proceeded in 61% yield affording a mixture of two diastereoisomers in a ratio of 1.6:1. The relative configuration of the major isomer **384a** was determined by nOe experiments (**Figure 21**). Irradiation of the hydroxyl proton gave a nOe enhancement (0.35%) to the internal alkenyl proton, and a nOe enhancement (0.43%) to the α-ether methine. To confirm this result, the irradiation of the alkenyl proton showed a clear nOe enhancement (1.82%) to the α-ether methine. These results indicated that these three protons were on the same face of the molecule and the hydroxyl group was assigned as shown in the diagram.

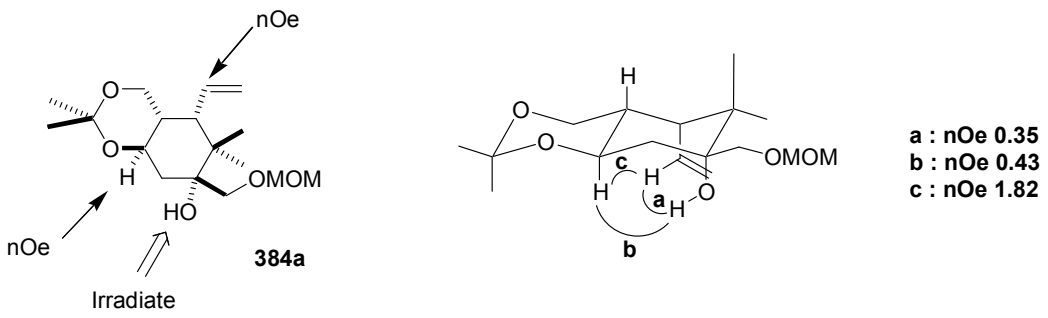


Figure 21. nOe experiments

In the case of the substrate **385**, the products **386a** and **386b** were obtained in 76% yield as a mixture of diastereoisomers in a ratio of 4.8:1. The major isomer **386a** was determined to have the same relative configuration as the major isomer **384a**, by comparison of the ^{1}H NMR spectrum. Indeed, the chemical shift of the internal alkenyl proton of the major isomer **386a** is 6.27 pm whereas the chemical shift of the internal alkenyl proton of the minor isomer **386b** is 5.46 pm, which are similar values to those of the MOM product **384** (6.28 ppm for **384a** and 5.68 ppm for **384b**).

In an effort to reverse the diastereoselectivity of the coupling reaction, the use of the MAD reagent, developed by Maruoka and Yamamoto, was explored.[173] This reagent is known to enhance axial attack of organolithium nucleophiles to cyclohexanones by blocking the equatorial face (**Figure 22**). However, the addition of MAD to our system (ketone **350** and organostannane **383**) led to the decomposition of both starting materials.

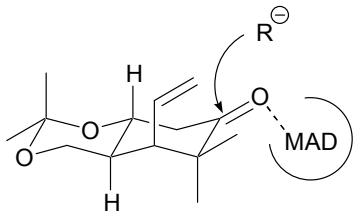
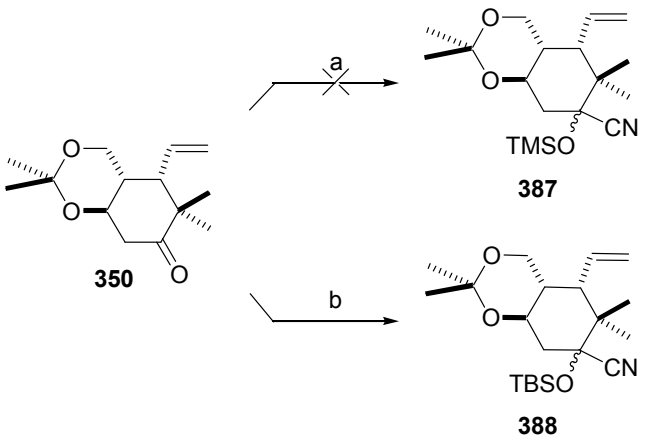


Figure 22. Hypothetical MAD-mediated reaction.

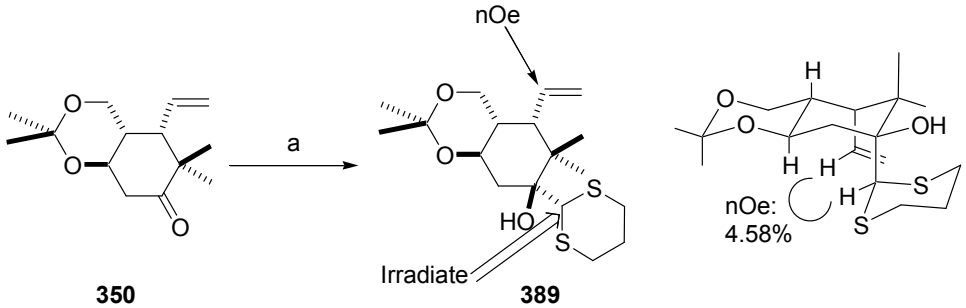
In addition to the Still α-alkoxylithium methodology, we were interested in using one of the most straightforward entries to α-*O*-protected aldehyde, proceeding *via* a cyanohydrin.[174] Cyanosilylation of the ketone **350** should afford the silyl-protected cyanohydrins **387** or **388**, which could be converted into α-hydroxyaldehyde **382**, via reduction and hydrolysis,[175] or even into α-hydroxyketone **371**, via Grignard addition and hydrolysis.[176] The preparation of cyanohydrins by addition of silyl cyanide (TMSCN and TBSCN) to sterically hindered ketones under Lewis acid (ZnI_2) catalysis, has been reported by Watt and co-workers,[177] and this strategy was applied to our system (**Scheme 124**). Treatment of the ketone **350** with TMSCN resulted in the formation of many products as shown by ^{1}H NMR analysis of the crude reaction mixture, and the desired product **377** was not isolated. The use of TBSCN gave also a mixture of products and the reaction did not reach completion. However, the desired *tert*-butyldimethyldimethylsilyl-protected cyanohydrin **388** was successfully isolated in 21% yield (27% BRSM).



Scheme 124. a TMSCN, ZnI_2 cat., DCM, r.t., 20 h. **b** TBSCN, ZnI_2 cat., DCM, r.t., overnight, 21% (27% BRSM).

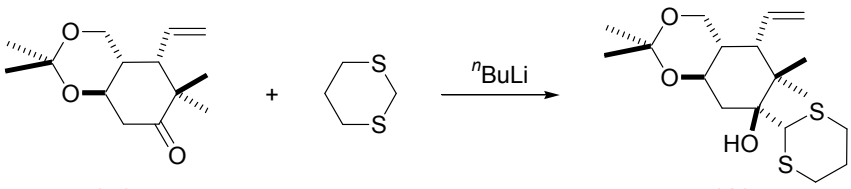
These very disappointing results prompted us to reconsider the use of 2-lithio-1,3-dithiane derivatives as masked nucleophilic acylating agents in our synthesis of the α-hydroxyaldehyde **382**. The alcohol **389** would be first prepared hopefully with the correct diastereoselectivity by treatment of the ketone **350** with 2-lithio-1,3-dithiane, which could then be converted into the corresponding aldehyde **382**.

In a first attempt, 1,3-dithiane was deprotonated with ^{n}BuLi in THF at low temperature to form 2-lithio-1,3-dithiane, which was then added to the carbonyl functionality of ketone **350** with high diastereoselectivity and good yield delivering alcohol **389** (**Scheme 125**). We were delighted to find that the alcohol **389** was obtained as a single diastereomer; we then undertook nOe studies which revealed that the dithiane functionality was situated on the same face of the ring as the vinyl group. Irradiation of the dithiane methine proton gave a clear nOe enhancement (4.58%) to the internal alkenyl proton. This result indicated that these two protons were on the same face of the molecule, and thus it was recognised that the product **389** had the required stereochemistry.



Scheme 125. a (i) 1,3-dithiane, ^{n}Buli, THF, 0 °C, 30 min, r.t., 30 min. (ii) ketone **350**, THF, –78 °C to r.t., overnight, 58%

As a consequence of this successful result, attention was then directed to improving the yield of the coupling reaction (**Table 7**). Indeed, the desired alcohol **389** was isolated in 58% yield when the 2-lithio-1,3-dithiane was prepared by deprotonation of 1.5 equivalents of 1,3-dithiane with 1.3 equivalents of ^{n}BuLi in THF at low temperature (entry 1). The conditions were investigated and it appeared that a competing reaction took place when ^{n}BuLi was used in excess, and that this reduced the yield of the desired alcohol **389** (entries 2-4). The optimal conditions were established as 3 equivalents of 1,3-dithiane and 2.5 equivalents of ^{n}BuLi, resulting in the formation of the product **389** in 81% yield (entry 5).



350 **389**

Entry	Conditions	Yield
1	1.5 eq dithiane + 1.3 eq ^{n}BuLi	58%
2	2.7 eq dithiane + 3.4 eq ^{n}BuLi	54%
3	3.0 eq dithiane + 3.5 eq ^{n}BuLi	45%
4	5.4 eq dithiane + 6.8 eq ^{n}BuLi	53%
5	3.0 eq dithiane + 2.5 eq ^{n}BuLi	81%

Table 7. Optimisation of conditions for the preparation of alcohol dithiane **389**.

It is worth noting the difference in diastereoselectivity between the reaction of an α-alkoxyorganostannane with the ketone **350** and the reaction of 1,3-dithiane with the ketone **350**. We can attribute this discrepancy to electronic and steric effects (**Figure 23**), indeed the dithiane exhibited preferential attack of the ketone **350** from an axial trajectory, since it can be considered as a small nucleophile and in this case the 1,2-interaction with the geminal dimethyl is avoided. In contrast, the α-alkoxyorganostannanes can be viewed as large nucleophiles, which are known to favour equatorial attack. In this case, 1,3 interaction with the vinyl group is also avoided.

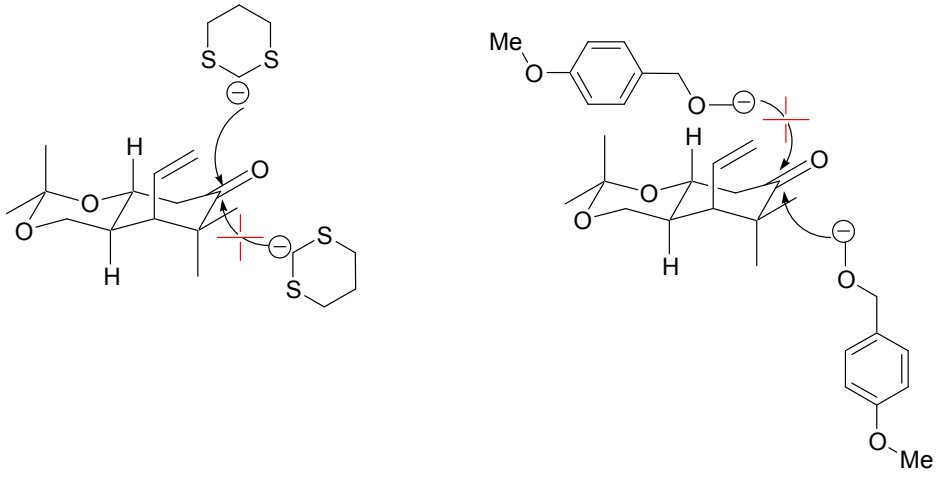


Figure 23.

Following the successful formation of the alcohol dithiane **389**, it was necessary to protect the hydroxyl group prior to the removal of the dithiane protecting group to afford the desired aldehyde. Protection of alcohol **389** proved to be difficult, and various reaction conditions were tested as summarised in **Table 8**.

389 **390**, **391** and **392**

Entry	Condition	Results
1	TBSCl, imidazole, DMAP, THF, r.t., 2 days	Only SM
2	TBSCl, imidazole, DMF, r.t., overnight	Only SM
3	TESCl, imidazole, r.t., 2 days	Only SM
4	(i) NaH, THF, r.t., 1h. (ii) TESCl, r.t., overnight.	Only SM
5	TBSOTf, 2,6-lutidine, DCM, reflux, 5 days.	65% (**390**)
6	TMSOTf, 2,6-lutidine, DCM, r.t., 1 h.	57% (**391**)
7	TESOTf, 2,6-lutidine, DCM, reflux, overnight.	89% (**392**)

Table 8. Optimisation of conditions for the silyl protection of alcohol dithiane **389**.

Routine treatment of the alcohol **389** with imidazole or sodium hydride as base and TBSCl or TESCl were unsuccessful (entries 1-4). However, use of silyltriflate reagents in the presence of 2,6-lutidine proved to be successful (entries 5-7). Indeed, treatment of the alcohol **389** with TBSOTf gave the product **390** in 65% yield, but the reaction took five

days under reflux in order to reach completion (entry 5). The TMS ether **391** was also produced in 57% yield when the alcohol **389** was treated with TMSOTf at room temperature (entry 6). Finally, the use of TESOTf gave the best result and the product **392** was isolated in 89% yield in this case (entry 7).

389-392 **393** and **394**

Entry	Substrate	Condition	Results
1	**389** (R = H)	NCS, DCM/H_2O, r.t., 30 min.	decomposition
2	**389** (R = H)	MeI, CH_3CN/H_2O, r.t., 2h.	only SM
3	**389** (R = H)	HgO, $BF_3.OEt_2$, THF/H_2O, r.t., 24h	decomposition
4	**390** (R = TBS)	MeI, $NaHCO_3$, MeCN/H_2O, r.t. 24h	only SM
5	**390** (R = TBS)	NBS, 2,6-lutidine, MeCN/H_2O, r.t., 15 min	decomposition
6	**390** (R = TBS)	CAN, MeCN/H_2O, r.t., 5 min.	decomposition
7	**391** (R = TMS)	$Hg(OAc)_2$, THF/H_2O, $NaBH_4$, NaOH, r.t., 1h	42% (**393**)
8	**392** (R = TES)	$Hg(OAc)_2$, MeCN/H_2O, r.t., 2h	15% (**394**)
9	**392** (R = TES)	$Hg(ClO_4)_2.xH_2O$, THF, r.t., 2h	decomposition
10	**392** (R = TES)	$Hg(OAc)_2$, THF, pH7 buffer, r.t., 2h	15% (**394**)
11	**392** (R = TES)	$Hg(ClO_4)_2.xH_2O$, $CaCO_3$, THF/H_2O, 0 °C, 1.5h	88% (**394**)

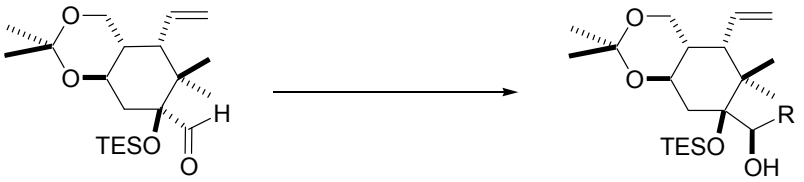
Table 9. Optimisation of conditions for the dithiane deprotection.

In addition to attempting to protect the alcohol, deprotection of the dithiane to afford the corresponding aldehyde was investigated (**Table 9**). The cleavage reaction was first attempted on the free alcohol **389**, the use of *N*-chlorosuccinimide and the mercuric oxide resulted in the decomposition of the starting material (entries 1 and 3), while iodomethane in acetonitrile did not react at all and the starting material was recovered (entry 2). With the TBS-protected dithiane **390**, the reaction with iodomethane was reconducted but once again the starting material was recovered (entry 4). Treatment of **390** with *N*-chlorosuccinimide or CAN resulted in decomposition (entries 5 and 6). The TMS-protected dithiane **391** reacted with mercuric acetate and sodium borohydride under oxymercuration conditions affording the expected product **393** in 42% yield, and no product resulting from the oxymercuration was observed (entry 7). The TES-protected

dithiane **392** was treated with mercuric acetate in acetonitrile to deliver aldehyde **394** in 15% yield, but when the substrate **392** was treated with mercuric perchlorate, it just decomposed (entries 8 and 9). It was believed that the low yield obtained was due to the acid released during the reaction, which had opened the acetonide. However, when pH7 buffer was added in the reaction mixture with mercuric acetate, the yield did not increase (entry 10). In contrast, addition of calcium carbonate to the reaction involving mercuric perchlorate made a huge difference and the desired aldehyde **394** was produced in 88% yield (entry 11).

2.2.6. Completion of the synthesis of the target diazoketone 252

The next stage was to install the C-ring unit (**Table 10**). 1-Bromocyclohexene was first transformed into the Grignard reagent and reacted with the aldehyde. The reaction was unsuccessful, and no consumption of the starting material was observed (entry 1). Both MeMgBr and MeLi were used to define which reagent would be the most appropriate. This study revealed that the Grignard reagent was not reactive towards the aldehyde **394** but the organolithium reagent gave the desired product **395** in 21% yield (entries 2 and 3). Thus, 1-bromocyclohexene was converted into the corresponding 1-lithiumcyclohexene when treated with ^{t}BuLi and reacted with the aldehyde **394** to afford the product **396** in an excellent 91% yield and moreover as a single diastereoisomer.



394 **395** and **396**

Entry	Condition	Results
1	1-bromocyclohexene, ^{t}BuLi, THF, –78 °C, $MgBr_2$	Only SM
2	MeMgBr,THF, r.t., 1.5 h	Only SM
3	MeLi, THF, –78 °C, 2 h	21% (**395**)
4	1-bromocyclohexene, ^{t}BuLi, THF, –78 °C, 1 h	91% (**396**)

Table 10. Installation of the C-ring unit.

To our surprise, the ^{1}H NMR data revealed a migration of the TES group had taken place during the formation of **396**, whereas this had not been the case for the Me-product

derivative **395**. This result was confirmed by X-ray analysis, which also enabled assignment of the relative stereochemistry of the product **396** (**Figure 24**). We were absolutely delighted to see that the diastereomer produced was the one required for the synthesis of the diazoketone **252**.

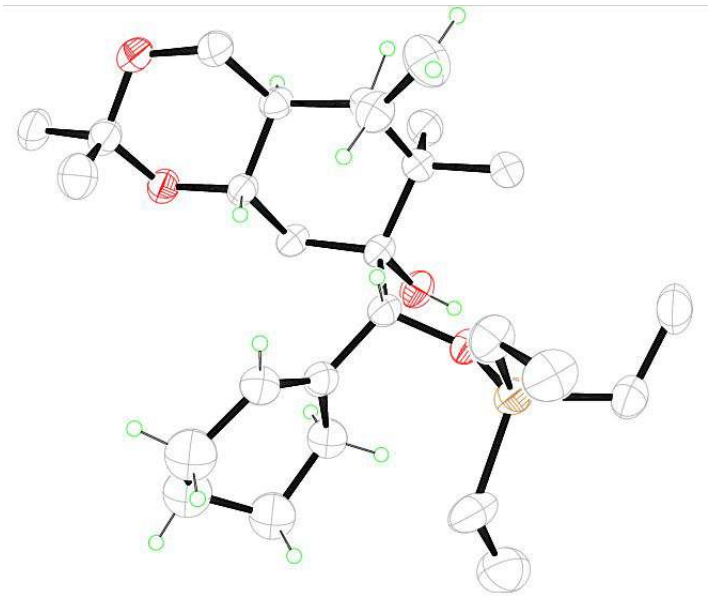
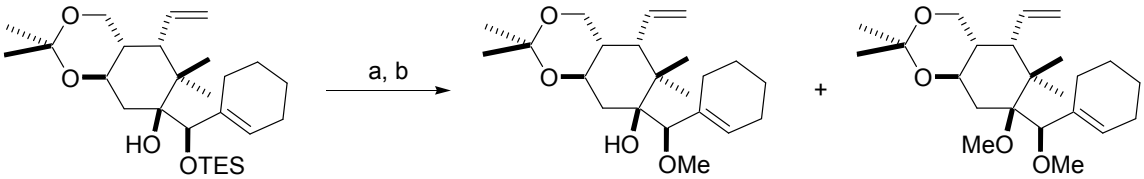


Figure 24. X-ray crystallography of the product **396**, some protons were omitted for clarity.

As a consequence of the migration of the silyl group, desilylation with TBAF was necessary, giving the diol **367** in 94% yield (**Scheme 126**). Selective methylation of the secondary alcohol **367** was then performed to define the optimized conditions. These studies established that the use of 2 equivalents of sodium hydride and 1.5 equivalents of iodomethane gave optimum yields. The expected product **397** was obtained in 64% yield (74% BRSM) along with a small amount of the dimethyl ether **398** (13% yield).

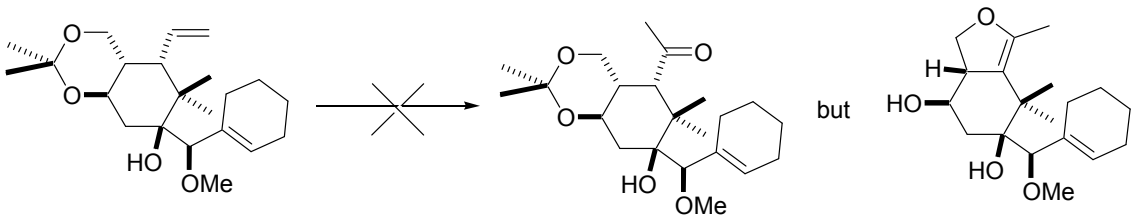


396 **397** **398**

Scheme 126. a TBAF, THF, r.t., 4 h, 94%. **b** (i) NaH, THF, r.t., 30 min, reflux, 30 min. (ii) MeI, 0 °C, 2 h, 64% **397** (82% BRSM) and 13% **398**.

With this late stage intermediate **397** in hand, its transformation into the corresponding methyl ketone **366** was required prior to conversion into the desired diazoketone **252** using a standard diazo transfer reaction (**Table 11**). In the first attempt, the standard condition of

the Wacker oxidation were used, but it did not result in the formation of the desired methyl ketone **366**. However, the product **399** presumably formed by reaction of the methyl ketone with the deprotected acetal was obtained in 36% yield (entry 1). The ^{13}C NMR spectrum proved that there is no carbonyl functionality but instead an additional alkene. Moreover, the LRMS data of the product (322.2) is consistent with the assumed structure **399**. Nevertheless, this product could not be fully characterized. When a scavenger such as $NaHCO_3$ and $CaCO_3$ was added, it inhibited the reaction completely (entries 2 and 3).



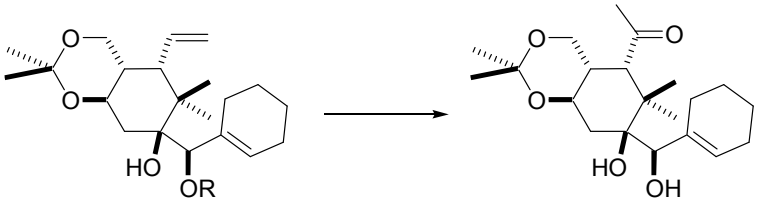
397 **366** **399**

Entry	Condition	Results
1	$PdCl_2$, CuCl, DMF/H_2O, O_2	36%
2	$PdCl_2$, CuCl, $NaHCO_3$, DMF, O_2	Only SM
3	$PdCl_2$, CuCl, $CaCO_3$, THF/H_2O, O_2	Only SM
4	$PdCl_2$, DMF, H_2O	Only SM
5	$PdCl_2$, $Cu(OAc)_2.H_2O$, DMA/H_2O, O_2.	Only SM
6	$Pd(OAc)_2$, $Cu(OAc)_2.H_2O$, DMA/H_2O, O_2	Only SM
7	$Pd(OAc)_2$, pyridine, toluene, propan-2-ol	Only SM
8	$Pd(OAc)_2$, H_2O_2, ^{t}BuOH	19%
9	(i) $Hg(OAc)_2$, THF/ H_2O (ii) LiCl, $PdCl_2$, $CuCl_2$, THF/H_2O	27%

Table 11. Optimisation of conditions for the Wacker oxidation.

The forced Wacker oxidation conditions, used by Mukaiyama for the total synthesis of Taxol,[86] were applied to our system but did not deliver the desired product (entry 4). As already mentioned, the use of copper acetate instead of copper chloride, to avoid the cleavage of the acetonide, was tested but did not furnish the methyl ketone (entry 5). The palladium source was also changed to palladium acetate in the presence of either copper acetate or pyridine and propan-2-ol, but only the starting material was recovered (entries 6 and 7).[178] When hydrogen peroxide and *tert*-butanol were added to the reaction mixture along with palladium acetate,[179] the only product obtained was **399** in 19% yield (entry 8). The addition of mercury acetate followed by palladium chloride and copper chloride also gave the product **399** in 27% yield (entry 9).[180]

As the Wacker oxidation of the methyl ether **397** did not deliver the required product, the standard conditions were applied to the silyl ether **396**, but led to decomposition (**Table 12**, entry 1). The forced conditions were tested and fortunately afforded the desired methyl ketone **363** with concomitant removal of the silyl group in 44% yield (entry 2). The rest of the material seemed to be the acetonide deprotected product. This promising result suggested it might worth applying these conditions to the diol **367**, and this proved to be very successful: the methyl ketone **363** was isolated in 76% yield when using four equivalents of $PdCl_2$ (entry 3). Then the reaction was tested with only two equivalents of $PdCl_2$, the reaction time was longer but it was as efficient (74% yield, 86% BRSM) as when four equivalents were used.



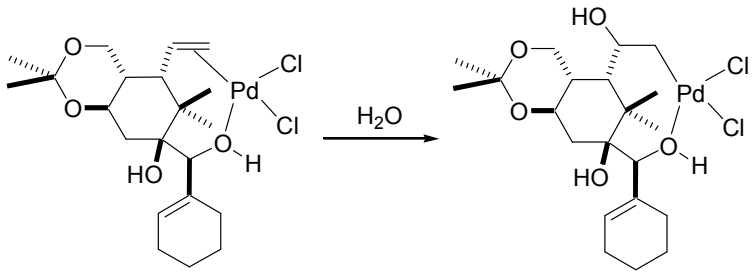
367 and **396** **363**

Entry	Substrate	Condition	Results
1	**396** (R = TES)	$PdCl_2$ (cat.), CuCl, DMF/H_2O, O_2	decomposition
2	**396** (R = TES)	$PdCl_2$ (4 eq.), DMF/H_2O, r.t., overnight	44%
3	**367** (R = H)	$PdCl_2$ (4 eq.), DMF/H_2O, r.t., 2 h	76%
4	**367** (R = H)	$PdCl_2$ (2 eq.), DMF/H_2O, r.t., overnight	74%, 86% BRSM

Table 12. Optimisation of conditions for the Wacker oxidation.

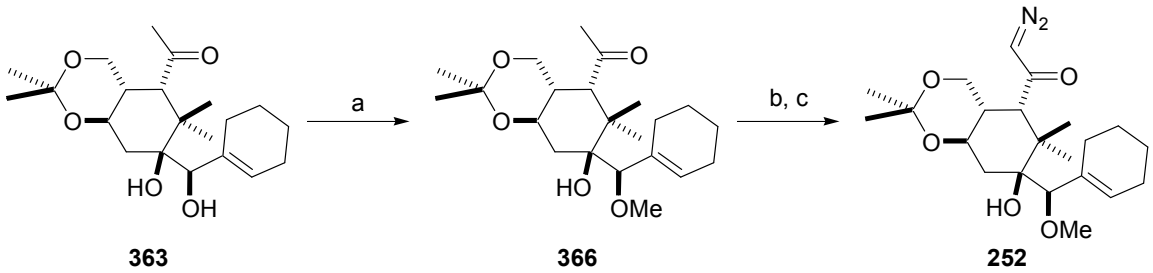
These extreme conditions [use of a stoichiometric amounts of Pd(II)] were also required for the total synthesis of Taxol[86] and macrosphelide H.[181] In the case of the total synthesis of Taxol, it was claimed that the Wacker reaction did not take place under the standard conditions, whereas it worked in the model systems.[182] Luckily, it was found that under forced Wacker conditions, the oxidation to form the desired methyl ketone proceeded smoothly, but no explanation was given. To achieve the total synthesis of macrosphelide H,[181] Kobayashi and co-workers attempted to perform the standard Wacker oxidation reaction but conversion was slow and the regioselectivity (methyl ketone : aldehyde) was poor. Fortunately, it was found that the use of stoichiometric amounts of $PdCl_2$ afforded the desired methyl ketone selectively. In our case, formation of aldehydes was not observed when the standard conditions were applied. The most surprising result of this study is that the forced Wacker oxidation reaction provides the expected product in the

cases where the substrates bear a free hydroxyl group **367** or a TES group **396**, but does not when the secondary alcohol is protected as a methyl ether **397**. The reason for the selectivity is not clear, but Kang and co-workers[183] reported the preparation of the expected methyl ketone starting with a diol and terminal olefin whereas the terminal aldehyde was obtained when the diol was protected. Moreover, Pellissier and co-workers[184] reported regioselective Wacker oxidation of a vinyl group: the methyl ketone was obtained when the lactonic bridge was situated on the β-face, but when it was located on the α-face the aldehyde was obtained preferentially. In these studies it was presumed that the chelation of the palladium with oxygen groups induces the regioselectivity (anti-Markovnikov). We assumed that the hydroxyl group must be free, avoiding any steric hindrance[185] and allowing intramolecular coordination of the palladium complex to the oxygen atom, in order to transform the vinyl group into the corresponding methyl ketone **(Scheme 127)**.



Scheme 127. Possible chelation of the palladium with the oxygen atom during the forced Wacker oxidation.

The conversion of the diol **363** into the methyl ether **366**, using the previously optimized conditions, was found to be problematic and resulted in the decomposition of the diol. Luckily, the use of methyl triflate in presence of 2,6-di-*tert*-butyl-4-methylpyridine in chloroform under reflux provided a good alternative and gave the desired methyl ether **366** in 65% yield (74% BRSM) (**Scheme 128**). The reaction had to be monitored carefully, and stopped before reaching completion, in order to avoid the formation of the dimethyl ether. The methyl ketone **366** was then converted into the diazoketone **252** by diazo transfer reaction in 33% yield over two steps.

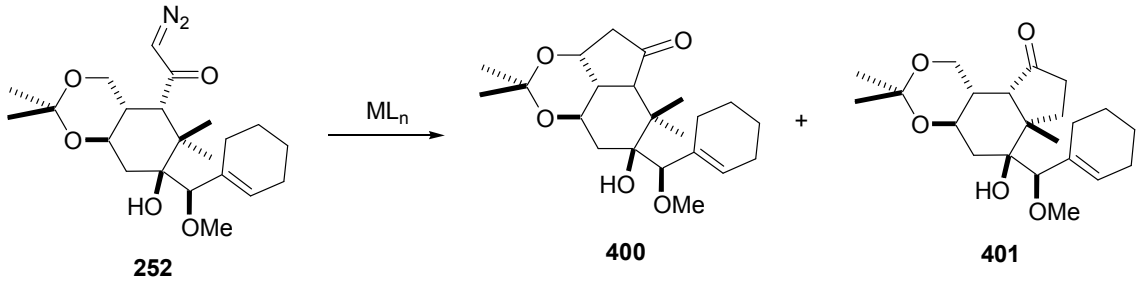


363 **366** **252**

Scheme 128. a MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, $CHCl_3$, reflux, 3.5 h, 65%, (74% BRSM). **b** (i) LiHMDS, THF, -78 °C, 1 h, r.t, 30 min. (ii) $CF_3CO_2CH_2CF_3$, r.t., 20 min. **c** *p*-ABSA, DBU, MeCN, r.t., 3 days. 33% from **366**.

2.2.7. Catalytic decomposition of the diazoketone 252

The successful synthesis of the diazoketone **252** allowed the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction to be explored. Several sets of reaction conditions were tested but they did not afford the expected tricyclic core of Taxol **250**, and instead delivered two C-H insertion products (**Scheme 129**). Indeed, treatment of the diazoketone **252** with the rhodium catalysts $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$ delivered mainly the product **401** resulting from geminal methyl C-H insertion of the intermediate carbenoid. This situation is rather unusual but this case is not isolated. Insertion reactions into the methyl C-H bond have been reported by several groups, but they mostly occur by the activation of a C-H bond adjacent to a heteroatom (oxygen or nitrogen).[186] However, Sonawane and co-workers has published a rare example describing a methyl C-H insertion without activation.[187] He claimed that the favourable geometrical disposition of the carbenoid centre and the primary C-H bond might be responsible, and we also think that the close proximity of the carbenoid and the methyl group favour this insertion reaction.



252 **400** **401**

$Rh_2(OAc)_4$, CH_2Cl_2, r.t.	30%	46%
$Rh_2(tfa)_4$,CH_2Cl_2, r.t.	-	61%
$Cu(hfacac)_2$, CH_2Cl_2, reflux	21%	14%
$Cu(hfacac)_2$, DCE, reflux	50%	43%

Scheme 129. Decomposition of diazoketone **252**.

In contrast, the copper-mediated reaction of the diazoketone **252** in dichloromethane under reflux was sluggish, even after reaction under reflux overnight, 64% of the starting diazoketone **252** was recovered. The methyl C-H insertion product **401** was isolated in 14% yield along with another C-H insertion product **400** in 21% yield. It was decided to change the reaction solvent and to heat at a higher temperature. Performing the reaction in dichoroethane resulted in consumption of the starting material **252** and delivered the acetonide C-H insertion product **400** in 50% yield along with the methyl C-H insertion product **401** in 43% yield. The methyl C-H insertion product **401** was a crystalline product and X-ray analysis enabled us to determine the relative configuration of the product (**Figure 25**). In contrast, the acetonide C-H insertion product **400** is suggested as a possible structure, but this product has not been fully characterised. The ^{1}H and ^{13}C NMR spectrum are not conclusive, but the exact mass [m/z = 379.2484 for $C_{22}H_{35}O_5$ ($[M+H]^+$)] and the IR spectra (1735 cm^{-1} for C=O) confirm the structure proposed. In the ^{1}H NMR spectrum, the CH_2 protons of the acetonide (H-5 usually at 3.7 to 3.5 ppm) disappeared suggesting a possible C-H insertion. In addition, the appearance of protons in the regions of 2.85-2.75 ppm and 2.45-2.35 ppm are probably the protons in α-position of the carbonyl group inserted in the acetonide. Full assignment was not possible since only half of the carbons are detectable in the ^{13}C NMR spectrum. In spite of this partial data we strongly believe that the product **400** possesses the proposed structure.

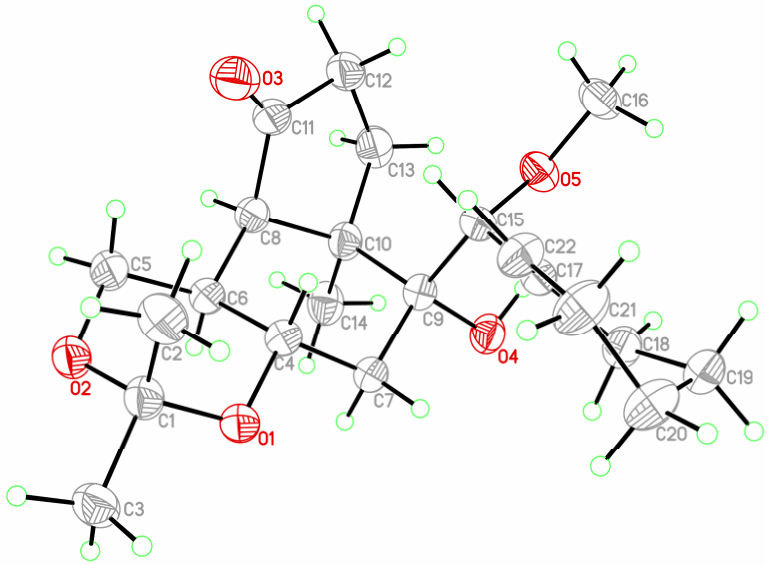
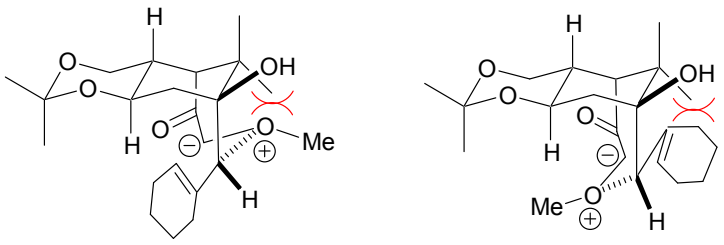


Figure 25. X-ray crystal structure of product **401**.

These results were disappointing, because no ylide-derived products were isolated at all. The carbenoid formed from diazoketone **252** did not generate the expected oxonium

ylide **402** but instead underwent various C-H insertion reactions. The formation of the oxonium ylide is disfavoured probably due to steric hindrance by the geminal dimethyl, this can be observed by constructing a model system of the oxonium ylide **402** (**Figure 26**). The model system of the diastereomeric oxonium ylide **403** was also constructed, and both models **402** and **403** were compared. This study proved to be informative, indeed the only possible interaction between the geminal methyl group and the cyclohexene unit in the oxonium ylide **403** indicated that oxonium ylide generation would not be disfavoured in this case and that [2,3]-rearrangement should be efficient. Consequently, it was decided to prepare the diastereomeric diazoketone **404** to test the reaction. Although in the previous studies, the rearrangement reactions of the diazoketones (**168**, **253** and **257**) having the same relative configuration as the designed diazoketone **404** did not give satisfactory results, we were still optimistic that this reaction would be possible.

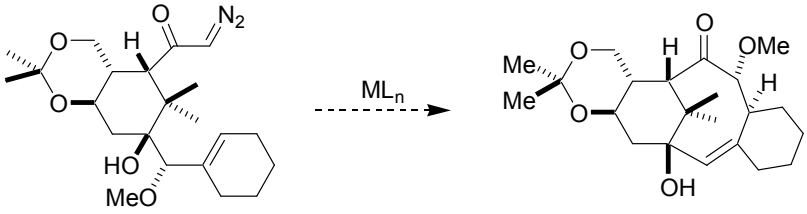


402 **403**

Figure 26. Model systems of oxonium ylides **402** and **403.**

2.2.8. Towards the synthesis of the target diazoketone 404

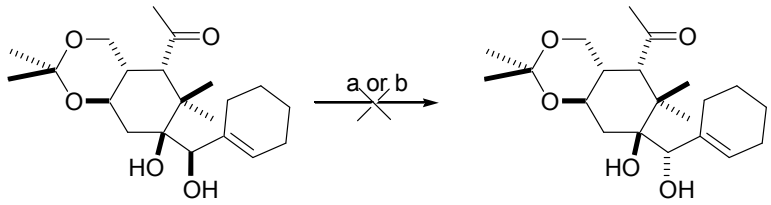
Since the catalytic decomposition of diazoketone **252** did not furnish the desired [2,3] sigmatropic rearrangement product **250**, preparation of the diastereomeric diazoketone **404** was required in order to discover whether the oxonium ylide formation followed by the [2,3] sigmatropic rearrangement would take place and deliver the tricyclic core system of Taxol **405** as shown in **Scheme 130**.



404 **405**

Scheme 130. New targeted diazoketone **404** and tricyclic core of Taxol **405**.

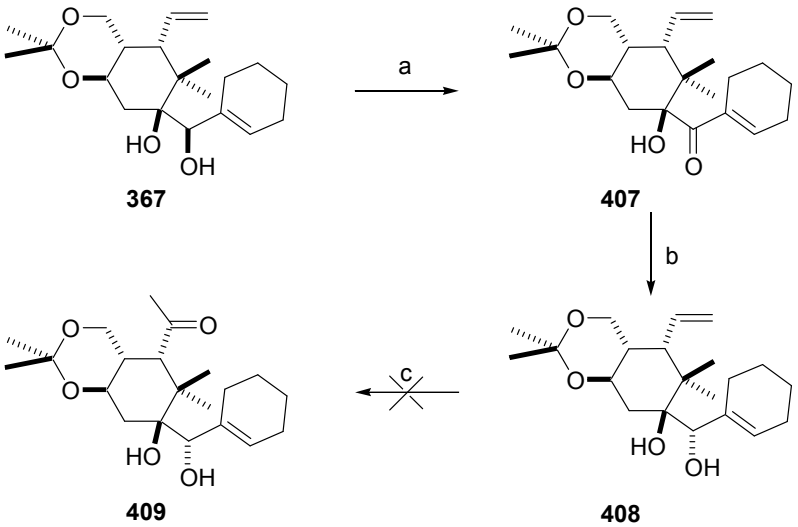
Initially, the Mistunobu reactions of the alcohol **363** were investigated (**Scheme 131**). Two typical protocols were attempted, the first using formic acid and the second employing *p*-nitrobenzoic acid in the presence of triphenylphosphine and an azocompound (DEAD or DIAD). These reactions should have yielded the corresponding formate ester and *p*-nitrobenzoate ester respectively as intermediates, but unfortunately the starting material **363** did not react in either cases.



363 **406**

Scheme 131. a (i) HCO_2H, PPh_3, DIAD, THF, r.t., 24 h. (ii) $NaHCO_3$, MeOH/H_2O. **b** (i) p-nitrobenzoic acid, PPh_3, DEAD, benzene, r.t, 24 h.

It was then decided to prepare the diastereomeric alcohol **406** by successive oxidation and reduction of alcohol **367**, subsequent Wacker oxidation would then deliver the required ketone **406**. The alcohol **367** was first treated with DMP, but no reaction occurred. When the alcohol was treated with PCC or TPAP/NMO, we observed cleavage of the 1,2-diol to give ketone **350** and 1-cyclohexene-1-carboxaldehyde. A standard Swern oxidation reaction gave the α-hydroxyketone **407** in 84% yield, but the best yield (92%) was obtained when the diol **367** was treated with SO_3.pyridine complex, Hunig's base and DMSO (**Scheme 132**).

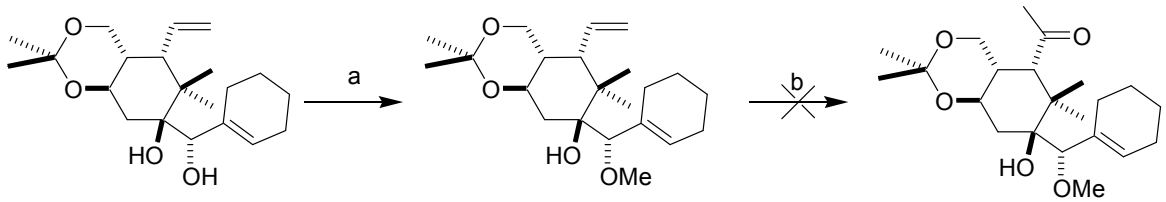


367 **407** **409** **408**

Scheme 132. a SO_3.pyridine complex, DIPEA, DMSO, CH_2Cl_2, 0°C to r.t., 1.5 h, 92%. **b** $NaBH_4$, THF/MeOH, r.t., 1h, 56% **408** (*anti*) and 43% **367** (*syn*). **c** $PdCl_2$, DMF, H_2O, 0°C to r.t.

The α-hydroxyketone **407** was then reduced in a stereoselective manner to deliver the desired alcohol **408** (**Scheme 132**). First, reduction of the α-hydroxyketone **407** with L-selectride was attempted but failed to deliver the diol **408**. In another attempt, the reduction with sodium borohydride in presence of cerium chloride heptahydrate gave the *syn*-diol **367** as major product but fortuitously the reduction without $CeCl_3.7H_2O$ furnished the *anti*-diol **408** preferentially. The desired diol **408** was then separated by column chromatography and isolated in 56% yield, and the *syn*-diol **367** was also isolated in 43% yield and then recycled by re-subjecting it to the oxidation/reduction process.

The optimised Wacker conditions were then applied to the alkene **408**, but did not prove to be successful. In this case, we thought it may be necessary to protect the secondary alcohol **408** with a methyl group prior to Wacker oxidation (**Scheme 133**). The diol **408** was converted into the corresponding methyl ether **409** using methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine in a moderate 40% yield (50% BRSM). We also found that treatment of the diol **409** with sodium hydride and methyl iodide gave a better result (49% yield, 72% BRSM). Once again, when optimised Wacker conditions were applied to the alkene **409**, they resulted in decomposition of the starting material.



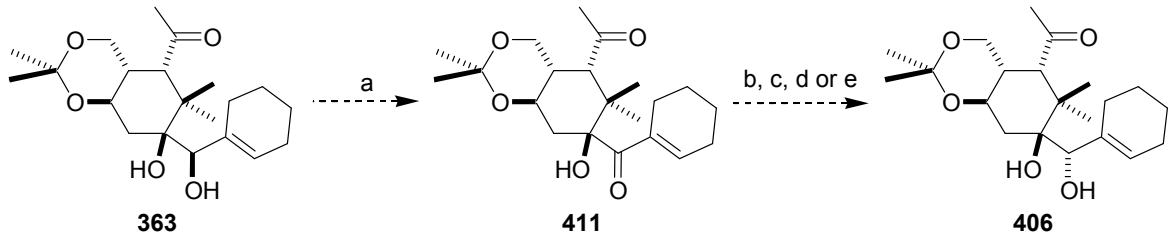
408 **409** **410**

Scheme 133. a (i) NaH, THF, r.t, 30 min, reflux, 30 min. (ii) MeI, r.t, 2h, reflux, 1 h. 49% (72% BRSM). **b** $PdCl_2$, DMF, H_2O, 0 °C to r.t.

3. *Conclusion and future work*

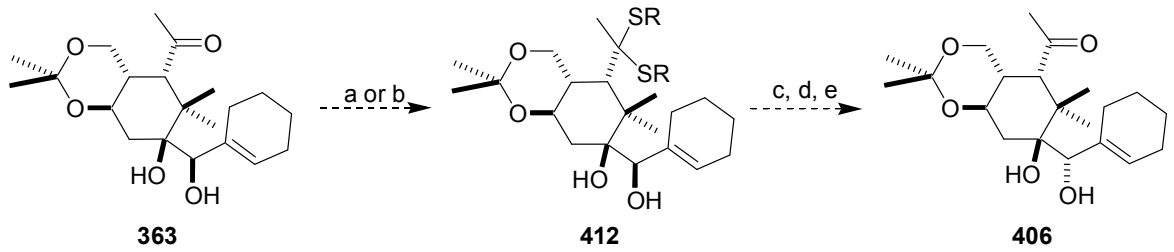
In summary, in the first part of this thesis we have shown that it is possible to construct fused bicyclic and tricyclic systems containing a seven-membered ring, such as **254**, **256**, **258** and **260**, *via* carbenoid generation, ylide formation and [2,3]-sigmatropic rearrangement. Unfortunately, this methodology has not yet proved to be successful for the synthesis of the tricyclic core of Taxol, though the targeted diazoketone **252** has been efficiently synthesised to test the viability of the key reaction. After abandoning the first route, the key reactions used to construct the required diazoketone **252** were a Diels-Alder reaction, an organocuprate conjugate addition and an Umpolung sequence. To our disappointment, the expected carbenoid generation, ylide formation and [2,3]-sigmatropic rearrangement did not occur, and only C-H insertion products **400** and **401** were obtained. However, we believe that the relative configuration in the substrate is crucial for the success of the reaction and so it is necessary to synthesise the diastereomeric diazoketone **404** to verify our strategy. At this stage, the preparation of the diazoketone **404** has proved troublesome due to an ineffective Wacker oxidation reaction. Future efforts will focus on alternative approaches to diazoketone **404**: either a selective reduction of the unprotected α-hydroxyketone **411** (**Scheme 134**) or a reduction of the protected α-hydroxyketone **412** (**Scheme 135**).

It is thought that a selective reduction of the hydroxyketone **411** could potentially lead to the *anti*-diol **406** (**Scheme 134**). First, the diol **363** would be converted into the hydroxyketone **411** by Swern oxidation, and this would then undergo Luche reduction to deliver the desired diol **406**. In the event that this latest reduction failed, the reaction with sodium borohydride/zinc chloride,[188] Red-Al,[189] indium hydride reagent,[190] or $BF_3.OEt_2$[191] would be performed.



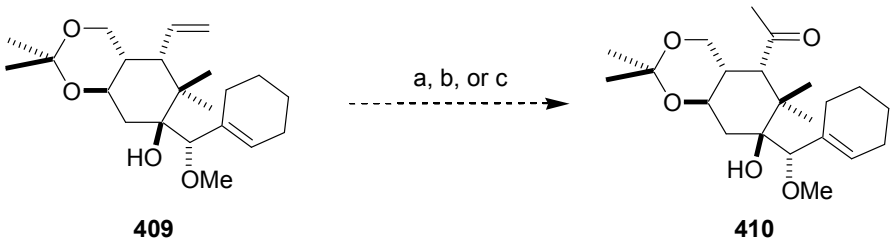
Scheme 134. a SO_3.pyridine complex, DIPEA, DMSO, CH_2Cl_2, 0 °C to r.t.. **b** (i) $CeCl_3.7H_2O$, MeOH, r.t. (ii) $NaBH_4$. **c** $NaBH_4$, $ZnCl_2/Et_2O$, THF, 0 °C. **d** $LiInH_4$, Et_2O, r.t.. **e** $BF_3.OEt_2$, Bu_3SnH, toluene, -78°C.

In the event that the diol **406** could not be obtained using these strategies, the methyl ketone **363** would be protected prior to reduction. The carbonyl functionality could be first protected as a thioacetal **412**, the secondary alcohol would then be oxidised, and reduction of the resulting α-hydroxyketone, as mentioned above, followed by the deprotection would deliver the desired *anti*-diol **406** (**Scheme 135**).



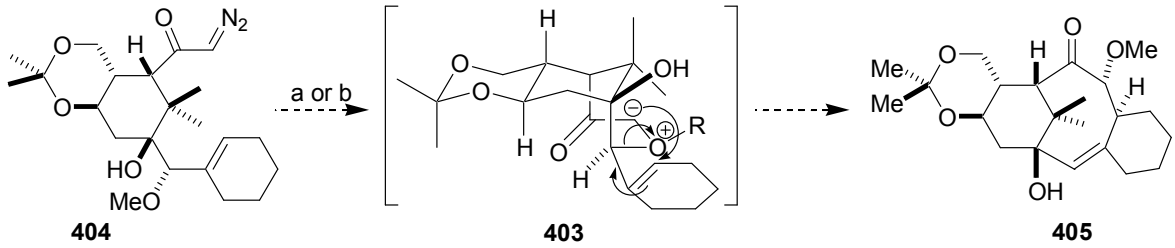
Scheme 135. a 1,3-propanedithiol, $BF_3.OEt_2$, $CHCl_3$, 0 °C. **b** $TMSSCH_2CH_2STMS$, ZnI_2, Et_2O, 0 °C. **c** SO_3.pyridine complex, DIPEA, DMSO, CH_2Cl_2, 0°C to r.t.. **d** reduction. **e** $Hg(ClO_4)_2.xH_2O$, $CaCO_3$, THF/H_2O, 0 °C.

In another approach, the vinyl group in **409** would be converted into the methyl ketone **410** by an epoxidation/epoxide opening sequence, followed by an oxidation reaction (**Scheme 136**). It is also possible, from the same alkene **409**, to prepare the methyl ketone **410** through Lemieux-Johnson cleavage of the alkene, followed by addition of methylmagnesium bromide to the aldehyde and subsequent oxidation of the intermediate secondary alcohol to the ketone **410**. Finally, the oxymercuration protocol[192] and subsequent oxidation could be applied to convert the terminal olefin **409** to the methyl ketone **410** if necessary.



Scheme 136. a (i) ^tBuOOH, $Mo(CO)_6$, DCE. (ii) $LiAlH_4$, THF. (iii) Swern oxidation **b** (i) OsO_4, $NaIO_4$, H_2O, THF. (ii) MeMgBr, THF. (iii) Swern oxidation. **c** (i) $Hg(OAc)_2$, THF. (ii) Swern oxidation.

The proposed routes, amongst many others not cited here, should deliver the desired methyl ketone **410**, which would be converted into the diazoketone **404**. Finally, the key cyclisation reaction should proceed and afford the tricyclic core of Taxol **405**, as discussed earlier, the relative configuration of the ether-bearing stereogenic centre will ensure that the cyclohexenyl group participates in the [2,3]-rearrangement reaction (**Scheme 137**). In the event that the cyclisation of the model substrate **404** delivers the required product **405** in high yield, subsequent studies would focus on the total synthesis of Taxol and related natural products.



404 **403** **405**

Scheme 137. a $Rh_2(OAc)_4$, DCM, r.t.. **b** $Cu(hfacac)_4$, DCM, reflux.

Experimental section

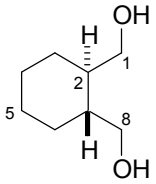
General comments

Air and/or moisture sensitive reactions were performed under an atmosphere of nitrogen or argon in oven or flame dried apparatus. Organic solvents and reagents were dried and distilled using standard methods: THF by distillation from sodium/benzophenone ketyl, dichloromethane by distillation from calcium hydride. All other solvents and reagents were used as supplied unless otherwise stated.

All reactions were moniored by thin layer chromatography Merck Kieselgel 60 F_{254}. Thin layer chromatography plates were viewed under UV light or visualised using either permanganate potassium solution, acidic ethanolic anisaldehyde solution, ethanolic phosphomolybdic acid solution or acidic cerium ammonium molybdate solution. Flash column chromatography was perfomed with silica gel (Fluorochem LC60A, 35-70 micron). Petroleum ether used for column chromatography was the 40-60 °C fraction.

IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument as chloroform solutions at ambient temperature and a JASCO FT/IR using NaCl plates or KBr plates. ^{1}H NMR spectra were recorded on a Bruker AV 400 (400MHz) spectrometer at ambient temperature. Data are reported as follows; chemical shifts in ppm relative to $CHCl_3$ (7.26) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = mutiplet), coupling constant(s) *J* (Hz), integration and assignment. ^{13}C NMR spectra were recorded on a Bruker AV 400 (100 MHz) spectrometer at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follows; chemical shifts in ppm relative to $CHCl_3$ (77.0) on the δ scale and assignment. High resolution mass spectra (HRMS) were obtained under EI, FAB, CI and ES conditions by the analytical services of the University of Nottingham and the analytical services of the University of Glasgow. Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus.

(1*R,2*R**)-*Trans*-cyclohexane-1,2-dimethanol (267)** [128c,193]



Trans-cyclohexane-1,2-dicarboxylic anhydride (5.80 g, 37.6 mmol) in THF (65 mL) was added dropwise to a suspension of $LiAlH_4$ (2.93 g, 78.8 mmol) in THF (47 mL) stirred under nitrogen. After stirring at room temperature for 30 min and under reflux for 2.5 h, the mixture was cooled in an ice-bath and sodium sulfate decahydrate (25 g) followed by water was carefully added to it. The mixture was then filtered on celite (8 g) and the residue washed with diethyl ether. The combined filtrate and washings were washed with water (40 mL). The organic layer was separated; the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield (2-hydroxymethyl-cychohexyl)methanol **267** (5.10 g, 94%) as a white powder.

R_f = 0.35 (diethyl ether / petroleum ether, 1:4).

ν_{max} (KBr) 3303, 2916, 2848, 1439 cm^{-1}.

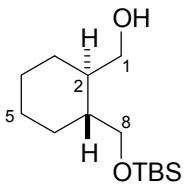
^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (d, 2H, *J* = 10.9 Hz, H-1 and H-8), 3.55 (dd, 2H, *J* = 6.0, 10.9 Hz, H-1 and H-8), 2.78 (b, 2H, O*H*), 1.81-1.68 (m, 2H, CH_2), 1.67-1.57 (m, 2H, CH_2), 1.40-1.28 (m, 2H, CH_2), 1.27-1.16 (m, 2H, H-2 and H-7), 1.12-0.98 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 67.9 (CH_2), 44.7 (CH), 29.9 (CH_2), 26.1 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_8H_{16}O_2Na$ 167.1048 ($[M+Na]^+$), found 167.1043.

The spectroscopic data is identical to that published by Maddaluno and Nicolaou.[128c,193]

[(1*R,2*R**)-2-(*tert*-Butyldimethylsilanyloxymethyl)-cyclohexyl]methanol (268)** [141,194]



A solution of the diol **267** (1.85 g, 12.8 mmol) and imidazole (1.40 g, 20.5 mmol) in THF (75 mL) was stirred at room temperature under an atmosphere of argon. A solution of *tert*-butyldimethyl chlorosilane (1.55 g, 10.3 mmol) in THF (20 mL) was added and the mixture was left to stir for 18 h. After this time the reaction mixture was washed with water (100 mL) and the organic layer removed. The aqueous layer was extracted with

diethyl ether (75 mL). The organic extracts were washed with brine (200 mL) and then dried over magnesium sulfate then filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:4) gave the expected mono-protected alcohol **268** as a colourless oil (2.02 g, 61%). The column was then flushed with neat diethyl ether to recover starting material (458 mg, 25%).

R_f = 0.63 (diethyl ether / petroleum ether, 1:1).

ν_{max} (KBr) 3375, 2926, 1471 cm^{-1}.

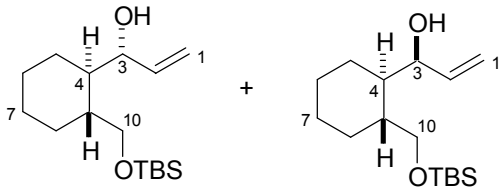
^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (dd, *J* = 5.4, 8.3 Hz, 1H, O*H*), 3.61-3.54 (m, 3H, H-1 and 2H-8), 3.46 (ddd, 1H, *J* = 5.4, 5.5, 11.3 Hz, H-1), 1.76-1.69 (m, 2H, CH_2), 1.65-1.53 (m, 2H, CH_2), 1.36-1.15 (m, 4H, H-2, H-7 and CH_2), 1.13-0.92 (m, 2H, CH_2), 0.90 (s, 9H, C{CH_3}$_3$), 0.08 (s, 3H, Si{CH_3}$_2$), 0.08 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 68.7 (CH_2), 67.5 (CH_2), 45.7 (CH), 44.2 (CH), 30.1 (CH_2), 29.8 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 25.8 (CH_3), 18.2 (C), -5.4 (CH_3), -5.6 (CH_3).

HRMS ESI (*m/z*) mass calc. for $C_{14}H_{31}O_2Si$ 259.2093 ($[M+H]^+$), found 259.2099.

The spectroscopic data is identical to that published by Jones and Friestad.[141,194]

(*R)-1-[(1*R**,2*R**)-2-*tert*-Butyldimethylsilanyloxymethyl)-cyclohexyl]-prop-2-en-1-ol (269) and (*S**)-1-[(1*R**,2*R**)-2-*tert*-Butyldimethylsilanyloxymethyl)-cyclohexyl]-prop-2-en-1-ol (270)**[109]



A stirred solution of oxalyl chloride (3.52 mL, 41.6 mmol) in CH_2Cl_2 (65 mL) was cooled to –78 °C and then DMSO (6.89 mL, 96.9 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **268** (4.47 g, 17.3mmol) in CH_2Cl_2 (45 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h, then triethylamine (35 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (110 mL) and then washed with saturated ammonium chloride solution (400 mL). The aqueous layer was extracted with CH_2Cl_2 (220 mL) and the combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the crude aldehyde **265** as a yellow oil.

Anhydrous cerium(III) chloride (5.71 g, 25.9 mmol) was added to a stirred solution of crude aldehyde **265** in THF (160 mL) at room temperature under an atmosphere of argon. The mixture was stirred at room temperature for 2 h then cooled to –78 °C and treated with vinyl magnesium bromide (40 mL, 1.0 M solution in THF, 40 mmol). The reaction mixture was warmed to room temperature over 21 h then quenched with saturated aqueous ammonium chloride (130 mL) and extracted with diethyl ether (2 × 150 mL). The combined organic extracts were washed with brine (300 mL), dried over magnesium sulfate and then concentrated *in vacuo* to a crude yellow oil. ^{1}H NMR showed a 2:1 mixture of diastereomeric alcohols. Separation by column chromatography (diethyl ether / petroleum ether, 3:97) gave the major alcohol **269** as a colourless oil (2.61 g, 53% over 2 steps), the minor alcohol **270** as a colourless oil (618 mg, 13%) and mixed fractions (531 mg).

Major alcohol 269

R_f = 0.48 (diethyl ether / petroleum ether, 1:4).

ν_{max} ($CHCl_3$) 3388, 2926, 2857, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 5.6, 10.5, 17.2 Hz, 1H, H-2), 5.23 (ddd, *J* = 1.7, 1.7, 17.2 Hz, 1H, H-1), 5.13 (ddd, *J* = 1.7, 1.7, 10.5 Hz, 1H, H-1), 4.25 (bs, 1H, H-3), 3.66 (dd, *J* = 3.2, 10.2 Hz, 1H, H-10), 3.56 (dd, *J* = 5.9, 10.2 Hz, 1H, H-10), 3.32 (b, 1H, O*H*), 1.75-1.69 (m, 2H, CH_2), 1.67-1.56 (m, 2H, CH_2), 1.53-1.37 (m, 2H, H-4 and H-9), 1.28-1.04 (m, 4H, CH_2), 0.90 (s, 9H, C{CH_3}$_3$), 0.08 (s, 6H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (CH), 114.5 (CH_2), 74.6 (CH), 67.9 (CH_2), 47.2 (CH), 41.1 (CH), 30.5 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 25.9 (CH_3), 18.3 (C), -5.4 (CH_3), -5.5 (CH_3).

HRMS ESI (*m/z*) mass calc. for $C_{16}H_{32}O_2SiNa$ 307.2069 ([M+Na]$^+$), found 307.2064.

Minor alcohol 270

R_f = 0.41 (diethyl ether / petroleum ether, 1:4).

ν_{max} ($CHCl_3$) 33872, 2925, 2857, 1063 cm^{-1}.

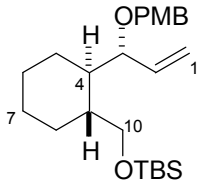
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 6.9, 10.4, 17.2 Hz, 1H, H-2), 5.21 (ddd, *J* = 1.3, 1.3, 17.2 Hz, 1H, H-1), 5.13 (ddd, *J* = 1.3, 1.3, 10.4 Hz, 1H, H-1), 4.14 (dd, *J* = 6.2, 6.3 Hz 1H, H-3), 3.62 (d, *J* = 4.7 Hz, 2H, H-10), 3.30 (b, 1H, O*H*), 1.79-1.59 (m, 4H, CH_2), 1.47-1.39 (m, 1H, H-4), 1.35-1.27 (m, 1H, H-9), 1.25-1.11 (m, 3H, CH_2), 0.99-0.93 (m, 1H, CH_2), 0.90 (s, 9H, C{CH_3}$_3$), 0.07 (s, 3H, Si{CH_3}$_2$), 0.06 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (CH), 115.2 (CH_2), 75.5 (CH), 67.3 (CH_2), 46.8 (CH), 43.4 (CH), 30.5 (CH_2), 27.6 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_3), 18.3 (C), -5.4 (CH_3), -5.5 (CH_3).

HRMS ESI (*m/z*) mass calc. for $C_{16}H_{32}O_2SiNa$ 307.2069 ([M+Na]$^+$), found 307.2061.

The spectroscopic data is identical to that published by Walls.[109]

tert-Butyl-{(1*R,2*R**)-2-[(*R**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexymethoxy}dimethylsilane (271)**



To a solution of alcohol **269** (1.02 g, 3.59 mmol) in DMF (40 mL) at 0 °C was added *p*-methoxybenzyl bromide (4.24 g, 21.1 mmol) followed by a solution of KHMDS (40 mL, 0.5 M in toluene, 20 mmol). The reaction mixture was stirred at room temperature for 2 days then the reaction mixture was quenched with saturated aqueous ammonium chloride (150 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate and concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography (treated with 1% Et_3N / petroleum ether, eluant diethyl ether / petroleum ether, 2:98) gave the title compound **271** as a pale yellow oil (1.36g, 96%).

R_f = 0.75 (diethyl ether / petroleum ether, 4:6).

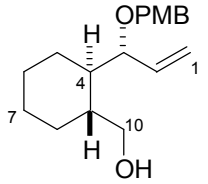
ν_{max} ($CHCl_3$) 2929, 2856, 1612, 1513 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.84 (ddd, *J* = 7.2, 10.5, 17.4 Hz, 1H, H-2), 5.24 (dd, *J* = 1.0, 10.5 Hz, 1H, H-1), 5.19 (dd, *J* = 1.0, 17.4 Hz, 1H, H-1), 4.53 (d, *J* = 11.6 Hz, 1H, C*H*HAr), 4.23 (d, *J* = 11.6 Hz, 1H, CH*H*Ar), 3.91 (dd, *J* = 2.8, 7.2 Hz, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.49 (dd, *J* = 3.1, 10.0 Hz, 1H, H-10), 3.35 (dd, *J* = 5.7, 10.0 Hz, 1H, H-10), 1.71-1.62 (m, 4H, CH_2), 1.59-1.52 (m, 1H, H-9), 1.47-1.40 (m, 1H, H-4), 1.36-1.12 (m, 4H, CH_2), 0.86 (s, 9H, C{CH_3}$_3$), –0.02 (s, 3H, Si{CH_3}$_2$), –0.04 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C), 138.3 (CH), 131.1 (C), 129.3 (CH), 116.7 (CH_2), 113.6 (CH), 79.7 (CH), 69.8 (CH_2), 65.0 (CH_2), 55.2 (CH_3), 43.3 (CH), 40.0 (CH), 29.7 (CH_2), 26.1 (CH_2), 26.0 (CH_3), 25.8 (CH_2), 25.3 (CH_2), 18.3 (C), -5.5 (CH_3).

HRMS (ESI) calcd. for $C_{24}H_{40}O_3SiNa$ 427.2639 ([M+Na]$^+$), found 427.2641.

{(1*R,2*R**)- 2-[(*R**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-methanol (272)**



A stirred solution of silyl ester **271** (1.01 g, 2.50 mmol) in THF (15 mL) was treated with TBAF (3.5 mL, 1.0 M solution in THF, 3.5 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (80 mL) then extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 2:8) gave the title compound **272** as a yellow oil (710 mg, 98%).

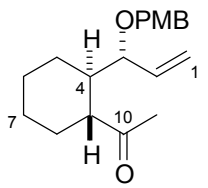
R_f = 0.22 (diethyl ether / petroleum ether, 4:6).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.93 (ddd, *J* = 8.2, 10.4, 17.2 Hz, 1H, H-2), 5.32 (dd, *J* = 1.7, 10.4 Hz, 1H, H-1), 5.22 (d, *J* = 17.2 Hz, 1H, H-1), 4.56 (d, *J* = 11.4 Hz, 1H, C*H*HAr), 4.29 (d, *J* = 11.4 Hz, 1H, CH*H*Ar), 3.80 (s, 3H, OCH_3), 3.74 (dd, *J* = 2.6, 8.2 Hz, 1H, H-3), 3.71-3.65 (m, 1H, H-10), 3.41-3.35 (m, 1H, H10), 3.34-3.29 (m, 1H, O*H*), 1.72-1.67 (m, 2H, CH_2), 1.63-1.51 (m, 3H, H-4 + CH_2), 1.44-1.34 (m, 1H, H-9), 1.25-1.07 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 135.4 (CH), 130.0 (C), 129.2 (CH), 119.1 (CH_2), 113.8 (CH), 85.3 (CH), 70.1 (CH_2), 67.2 (CH_2), 55.2 (CH_3), 44.6 (CH), 41.0 (CH), 30.5 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{18}H_{26}O_3Na$ 313.1785 ($[M+Na]^+$), found 313.1779.

1-{(1*R,2*R**)- 2-[(*R**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-ethanone] (273)**



A stirred solution of oxalyl chloride (640 µL, 7.56 mmol) in CH_2Cl_2 (18 mL) was cooled to –78 °C and then DMSO (1.25 mL, 17.6 mmol) was added dropwise. After stirring the mixture for 5 min, a solution of the alcohol **272** (911 mg, 3.14 mmol) in CH_2Cl_2 (13 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (6.6 mL) was added and the reaction mixture warmed to room temperature.

The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with saturated ammonium chloride solution (120 mL). The aqueous layer was extracted with CH_2Cl_2 (120 mL) and the combined organic extracts were washed with brine (250 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the aldehyde as a yellow oil.

A stirred solution of crude aldehyde in THF (30 mL) was cooled to –78°C, and then treated with methyl magnesium bromide (4.6 mL, 1.3M in THF/toluene, 6 mmol). The reaction mixture was warmed to room temperature overnight, and then diluted with water (200 mL), extracted with diethyl ether (2 × 200 mL). The combined organics extracts were washed with brine (400 mL), dried over magnesium sulfate and concentrated *in vacuo* to a crude yellow oil.

A stirred solution of oxalyl chloride (640 µL, 7.56 mmol) in CH_2Cl_2 (18 mL) was cooled to –78 °C and then DMSO (1.25 mL, 17.6 mmol) was added dropwise. After stirring for 5 min a solution of the crude alcohol in CH_2Cl_2 (13 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (6.6 mL) was added and the reaction mixture was warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with saturated ammonium chloride solution (120 mL). The aqueous layer was extracted with CH_2Cl_2 (120 mL) and the combined organic extracts were washed with brine (250 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 9:1) gave the methyl ketone **273** as a yellow oil (677 mg, 71% over 3 steps).

R_f = 0.52 (diethyl ether / petroleum ether, 4:6).

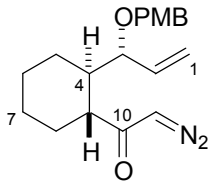
ν_{max} ($CHCl_3$) 2933, 2857, 1698, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 5.81 (ddd, *J* = 7.3, 10.5, 17.4 Hz, 1H, H-2), 5.25 (ddd, *J* = 0.8, 1.8, 10.5 Hz, 1H, H-1), 5.21 (ddd, *J* = 1.1, 1.8, 17.4 Hz, 1H, H-1), 4.45 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.13 (d, *J* = 11.5 Hz, 1H, CH*H*Ar), 3.80 (s, 3H, OCH_3), 3.66 (dd, *J* = 3.4, 7.3 Hz, 1H, H-3), 2.54 (dt, *J* = 3.6, 11.0 Hz, 1H, H-9), 1.98 (s, 3H, H-11), 1.94-1.88 (m, 1H, H-4), 1.83-1.78 (m, 1H, CH_2), 1.74-1.70 (m, 3H, CH_2), 1.27-1.19 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0 (C), 159.0 (C), 136.9 (CH), 130.8 (C), 129.3 (CH), 117.7 (CH_2), 113.6 (CH), 81.6 (CH), 69.9 (CH_2), 55.2 (CH_3), 52.6 (CH), 43.2 (CH), 29.8 (CH_2), 29.2 (CH_3), 25.6 (CH_2), 25.5 (CH_2), 25.4 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{19}H_{26}O_3Na$ 325.1774 ($[M+Na]^+$), found 325.1761.

2-Diazo-1-{(1*R,2*R**)-2-[(*R**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-ethanone (253)**



A solution of the methyl ketone **273** (763 mg, 2.52 mmol) in THF (10 mL) was added over 1 h to a solution of LHMDS (7.6 mL of a 1.0 M solution in THF, 7.6 mmol) at –78 °C. After stirring for 1.5 h, 2,2,2-trifluoroethyl trifluoroacetate (600 µL, 4.48 mmol) was added in one portion and the reaction mixture warmed to room temperature then stirred for 1 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (80 mL) and then extracted with diethyl ether (2 × 80 mL). The combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate then concentrated *in vacuo* to a crude yellow oil. The oil was dissolved in acetonitrile (12 mL), then DBU (600 µL, 4.01 mmol) and *p*-acetamidobenzenesulfonyl azide (911 mg, 3.79 mmol) were added, and the reaction mixture was stirred for four days. The reaction mixture was treated with a 10% solution of aqueous sodium hydroxide (35 mL) then the reaction mixture was extracted with diethyl ether (3 × 35 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated to a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9) gave the title compound **253** as a yellow oil (399 mg, 48%).

R_f = 0.42 (diethyl ether / petroleum ether, 1:1).

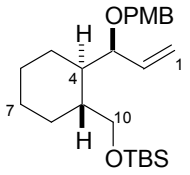
ν_{max} ($CHCl_3$) 2929, 2856, 2103, 1632, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.85-5.76 (m, 1H, H-2), 5.26 (bs, 1H, H-1), 5.23 (m, 1H, H-1), 4.87 (s, 1H, H-11), 4.50 (d, *J* = 11.6 Hz, 1H, C*H*HAr), 4.16 (d, *J* = 11.6 Hz, 1H, CH*H*Ar), 3.80 (s, 3H, OCH_3), 3.80-3.78 (m, 1H, H-3), 2.40-2.31 (m, 1H, H-9), 1.88-1.83(m, 1H, H-4), 1.82-1.70 (m, 4H, CH_2), 1.41-1.13 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6 (C), 159.1 (C), 137.4 (CH), 130.9 (C), 129.6 (CH), 117.1 (CH_2), 113.6 (CH), 80.0 (CH), 70.0 (CH_2), 55.2 (CH_3), 44.0 (CH), 30.5 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 24.4 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{19}H_{24}O_3N_2Na$ 351.1679 ($[M+Na]^+$), found 351.1680.

tert-Butyl-{(1*R,2*R**)-2-[(*S**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexymethoxy}dimethylsilane (275)**



To a solution of alcohol **270** (608 mg, 2.14 mmol) in DMF (25 mL) at 0°C was added *p*-methoxybenzylbromide (2.45 g, 12.2 mmol) followed by a solution of KHMDS (26 mL, 0.5 M in toluene, 12 mmol). The reaction mixture was stirred at room temperature for 1 h then the reaction mixture was quenched with saturated aqueous ammonium chloride (150 mL) and extracted with diethyl ether (3 ×150 mL). The combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate and concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography (treated with 1% Et_3N / petroleum ether, eluant diethyl ether / petroleum ether, 2:98) gave the title compound **275** as a pale yellow oil (751 mg, 87%).

R_f = 0.49 (diethyl ether / petroleum ether, 1:9).

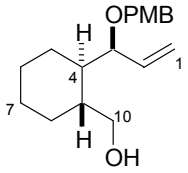
ν_{max} (neat) 2927, 2855, 1613, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.82 (ddd, *J* = 7.6, 10.5, 17.6 Hz, 1H, H-2), 5.30-5.22 (m, 2H, H-1), 4.51 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.32 (d, *J* = 11.5 Hz, 1H, CH*H*Ar), 4.02 (dd, *J* = 4.7, 7.6 Hz, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.58 (dd, *J* = 3.8, 10.0 Hz, 1H, H-10), 3.53 (dd, *J* = 5.9, 10.0 Hz, 1H, H-10), 1.95-1.92 (m, 1H, CH_2), 1.78-1.68 (m, 4H, H-4 and CH_2), 1.39-1.31 (m, 1H, CH_2), 1.25-1.18 (m, 3H, H-9 and CH_2), 1.11-1.01 (m, 1H, CH_2), 0.90 (s, 9H, C{CH_3}$_3$), 0.03(s, 6H, Si{CH_3}$_2$).

^{13}C NMR (400 MHz, $CDCl_3$) δ 158.9 (C), 136.1 (CH), 131.2 (C), 129.0 (CH), 117.6 (CH_2), 113.7 (CH), 80.6 (CH), 69.6 (CH_2), 65.6 (CH_2), 55.2 (CH_3), 42.9 (CH), 40.9 (CH), 29.7 (CH_2), 26.0 (CH_3), 25.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 18.3 (C), -5.4 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_{24}H_{41}O_3Si$ 405.2825 ($[M+H]^+$), found 405.2822.

{(1*R,2*R**)- 2-[(*S**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-methanol (276)**



A stirred solution of silyl ester **275** (701 mg, 1.73 mmol) in THF (10 mL) was treated with TBAF (2.4 mL, 1.0 M solution in THF, 2.4 mmol) then stirred at room temperature overnight. The reaction was not completed by TLC, and so further TBAF (0.7 mL) was added. After 3h, the reaction mixture was diluted with water (60 mL) then extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 2:8) gave the title compound **276** as a yellow oil (241 mg, 48%).

R_f = 0.27 (diethyl ether / petroleum ether, 4:6).

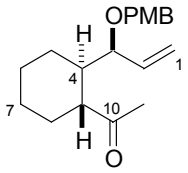
ν_{max} ($CHCl_3$) 3506, 3008, 2927, 2856, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 5.73 (ddd, *J* = 8.5, 10.3, 17.2 Hz, 1H, H-2), 5.31 (dd, *J* = 1.5, 10.3 Hz, 1H, H-1), 5.21 (dd, *J* = 1.5, 17.2 Hz, 1H, H-1), 4.51 (d, *J* = 11.0 Hz, 1H, C*H*HAr), 4.25 (d, *J* = 11.0 Hz, 1H, CH*H*Ar), 3.80 (s, 3H, OCH_3), 3.76-3.72 (m, 2H, H-3 and H-10), 3.46-3.40 (m, 1H, H-10), 2.31-2.26 (m, 1H, O*H*), 1.80-1.75 (m, 1H, CH_2), 1.73-1.59 (m, 3H, H-4 and CH_2), 1.41-1.13 (m, 2H, H-9 and CH_2), 0.97-0.83 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 137.0 (CH), 130.1 (C), 129.6 (CH), 118.3 (CH_2), 113.8 (CH), 84.0 (CH), 69.7 (CH_2), 66.0 (CH_2), 55.2 (CH_3), 44.1 (CH), 42.7 (CH), 30.6 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{18}H_{26}O_3Na$ 313.1780 ($[M+Na]^+$), found 313.1774.

1-{(1*R,2*R**)- 2-[(*S**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-ethanone] (277)**



A stirred solution of oxalyl chloride (700 µL, 8.30 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C and then DMSO (1.37 mL, 19.4 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **276** (1.0 g, 3.5 mmol) in CH_2Cl_2 (10 mL) was added

dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (6.8 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with saturated ammonium chloride solution (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the crude aldehyde as a yellow oil.

A stirred solution of aldehyde in dry diethyl ether (30 mL) was cooled to –78 °C, then treated with methyl magnesium bromide (4.9 mL, 1.4 M in THF/toluene, 6.9 mmol). The reaction mixture was warmed to room temperature overnight, then diluted with water (100 mL) and extracted with diethyl ether (2 × 100 mL). The combined organics extracts were washed with brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the crude alcohol as a yellow oil.

A stirred solution of oxalyl chloride (700 μL, 8.30 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C and then DMSO (1.37 mL, 19.4 mmol) was added dropwise. After stirring for 5 min a solution of the alcohol in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (6.8 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with saturated ammonium chloride solution (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate, then concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 9:1) gave the methyl ketone **277** as a yellow oil (814 mg, 78% over 3 steps).

R_f = 0.46 (diethyl ether / petroleum ether, 4:6).

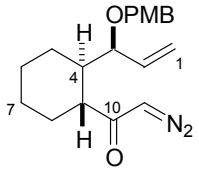
ν_{max} ($CHCl_3$) 3009, 2933, 2858,1696, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.66 (ddd, *J* = 8.2, 10.2, 17.2 Hz, 1H, H-2), 5.29 (dd, *J* = 1.6, 10.2 Hz, 1H, H-1), 5.15 (dd, *J* = 1.6, 17.2 Hz, 1H, H-1), 4.39 (d, *J* = 11.0 Hz, 1H, C*H*HAr), 4.14 (d, *J* = 11.0 Hz, 1H, CH*H*Ar), 3.79 (s, 3H, OCH_3), 3.41 (dd, *J* = 8.2, 8.2 Hz, 1H, H-3), 2.18 (dt, *J* = 3.2, 11.1 Hz, 1H, H-9), 1.97 (s, 3H, H-11), 1.96-1.89 (m, 1H, H-4), 1.83-1.70 (m, 3H, CH_2), 1.34-1.14 (m, 4H, CH_2), 0.95-0.83 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9 (C), 158.9 (C), 137.0 (CH), 130.3 (C), 129.6 (CH), 118.8 (CH_2), 113.5 (CH), 84.2 (CH), 69.7 (CH_2), 55.9 (CH_3), 55.2 (CH), 43.2 (CH), 29.6 (CH_2), 27.6 (CH_3), 27.3 (CH_2), 25.5 (CH_2), 25.2 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{19}H_{26}O_3$ 302.1882 ($[M]^+$), found 302.1881.

2-Diazo-1-{(1*R,2*R**)-2-[(*R**)-1-(4-methoxybenzyloxy)-allyl]-cyclohexyl}-ethanone (255)**



A solution of the methyl ketone **277** (793 mg, 2.62 mmol) in THF (10 mL) was added over 1 h to a solution of LHMDS (7.9 mL of a 1.0 M solution in THF, 7.9 mmol) at –78 °C. After stirring for 1.75 h, 2,2,2-trifluoroethyl trifuoroacetate (600 μL, 4.48 mmol) was added in one portion and the reaction mixture warmed to room temperature then stirred for 1 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (80 mL) and then extracted with diethyl ether (2 × 80 mL). The combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate then concentrated *in vacuo* to a crude yellow oil. The oil was dissolved in acetonitrile (12 mL), then DBU (600 μL, 4.01 mmol) and *p*-acetamidobenzenesulfonyl azide (945 mg, 3.93 mmol) were added, and the reaction mixture was stirred for four days. The reaction mixture was treated with a 10% solution of aqueous sodium hydroxide (35 mL) then the reaction mixture was extracted with diethyl ether (3 × 35 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated to a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9) gave the title compound **255** as a yellow oil (404 mg, 65%).

R_f = 0.34 (diethyl ether / petroleum ether, 1:1).

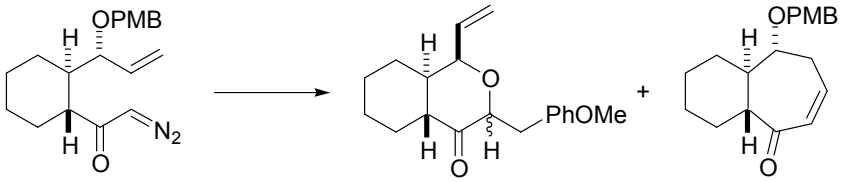
ν_{max} ($CHCl_3$) 2928, 2856, 2104, 1634, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.72 (ddd, *J* = 8.3, 10.3, 17.2 Hz, 1H, H-2), 5.29 (dd, *J* = 1.5, 10.3 Hz, 1H, H-1), 5.19 (dd, *J* = 1.5, 17.2 Hz, 1H, H-1), 5.08 (bs, 1H, C*H*=N_2), 4.45 (d, *J* = 11.3 Hz, 1H, C*H*HAr), 4.22 (d, *J* = 11.3 Hz, 1H, C*H*HAr), 3.79 (s, 3H, OCH_3), 3.62 (dd, *J* = 5.1, 8.3 Hz, 1H, H-3), 2.12-1.99 (m, 2H, H-4 and H-9), 1.94-1.88 (m, 1H, CH_2), 1.82-1.69 (m, 3H, CH_2), 1.40-1.33 (m, 1H, CH_2), 1.25-1.10 (m, 2H, CH_2), 1.04-0.94 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (C), 158.9 (C), 136.4 (CH), 130.8 (C), 129.2 (CH), 118.7 (CH_2), 113.6 (CH), 82.9 (CH), 69.9 (CH_2), 55.2 (CH_3), 43.0 (CH), 30.7 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 25.1 (CH_2).

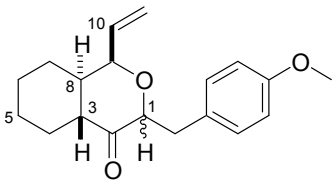
HRMS ESI (*m/z*) mass calc. for $C_{19}H_{24}O_3N_2Na$ 351.1685 ($[M+Na]^+$), found 351.1679.

Rhodium (II) Acetate Catalysed Rearrangement of Diazoketone 253



A solution of the diazoketone **253** (190 mg, 0.579 mmol) in CH_2Cl_2 (80 mL) was added dropwise over 1.25 h to a stirred solution of rhodium(II) acetate dimer (5.0 mg, 12 μmol) in CH_2Cl_2 (60 mL) at room temperature under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 5:95 to 2:8). This gave the pyranone **278** as a yellow oil (15 mg, 8%), the cycloheptenone **279** (19 mg, 10%) and an inseparable mixture of several cyclopropane adducts (60 mg, 34%).

(3*R**,5a*R**,9a*R**)-3-(4-Methoxyphenyl)-1-vinyloctahydrobenzo[*c*]oxepin-5-one (278)



R_f = 0.44 (diethyl ether / petroleum ether, 1:1).

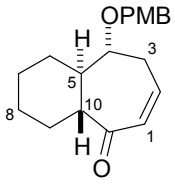
ν_{max} ($CHCl_3$) 2927, 2855, 1719, 1611 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.15 (ddd, *J* = 6.1, 10.7, 17.0 Hz, 1H, H-10), 5.36 (ddd, *J* = 1.6, 1.6, 10.7 Hz, 1H, H-11), 5.27 (ddd, *J* = 1.6, 1.6, 17.0 Hz, 1H, H-11), 4.34-4.31 (m, 2H, H-1 and H-9), 3.78 (s, 3H, OC*H*$_3$), 3.17 (dd, *J* = 4.2, 14.6 Hz, 1H, C*H*HAr), 2.75 (dd, *J* = 7.9, 14.6 Hz, 1H, CH*H*Ar), 2.19-2.13 (1H, m, H-3), 2.09-1.90 (2H, m, H-9 and C*H*$_2$), 1.88-1.73 (3H, m, C*H*$_2$), 1.62-1.58 (1H, m, C*H*$_2$), 1.28-1.11 (3H, m, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C), 158.0 (C), 131.4 (CH), 130.5 (C), 130.4 (CH), 120.4 (CH_2), 113.5 (CH), 77.2 (CH), 77.1 (CH), 55.2 (CH_3), 48.0 (CH), 46.2 (CH), 34.9 (CH_2), 28.5 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 24.6 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{19}H_{24}O_3Na$ 323.1623 ($[M+Na]^+$), found 323.1618.

(4a*R,6*Z*,9*R**,9a*R**)-9-(4-Methoxybenzyloxy)-1,2,3,4,4a,8,9,9a-octahydrobenzocyclohepten-5-one (279)**



R_f = 0.30 (diethyl ether / petroleum ether, 1:1).

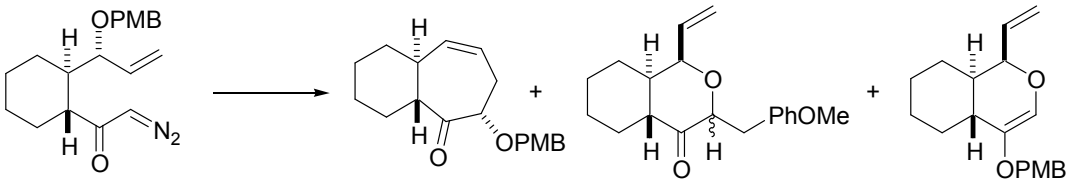
ν_{max} ($CHCl_3$) 3011, 2932, 2857, 1671, 1613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.84 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.41 (ddd, *J* = 3.0, 8.3, 11.4 Hz, 1H, H-2), 6.18 (dd, *J* = 3.1, 11.4 Hz, 1H, H-1), 4.31 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.22 (d, *J* = 11.5 Hz, 1H, CH*H*Ar), 3.78 (s, 3H, OCH_3), 3.53 (d, *J* = 6.0 Hz, 1H, H-4), 2.79 (ddd, *J* = 6.0, 8.3, 17.7 Hz, 1H, H-3), 2.53 (ddd, *J* = 2.4, 2.8, 17.7 Hz, 1H, H-3), 2.32-2.26 (dt, *J* = 2.4, 11.6 Hz, 1H, H-10), 1.82-1.67 (m, 4H, CH_2), 1.70-1.64 (m, 1H, H-5), 1.62-1.52 (m, 1H, CH_2),1.38-1.08 (m, 3H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2 (C), 159.0 (C), 138.5 (CH), 135.0 (CH), 130.3 (C), 128.8 (CH), 113.7 (CH), 81.0 (CH), 69.0 (CH_2), 55.2 (CH_3), 54.3 (CH), 47.2 (CH), 31.7 (CH_2), 30.5 (CH_2), 29.7 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 25.1 (CH_2).

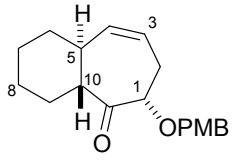
HRMS EI (*m/z*) mass calc. for $C_{19}H_{24}O_3$ 300.1725 ($[M]^+$), found 300.1727.

Copper (II) Hexafluoroacetylacetonate Catalysed Rearrangement of Diazoketone 253



A solution of the diazoketone **253** (45 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 25 min to a stirred solution of copper(II) hexafluoroacetylacetonate (1.3 mg, 2.7 μmol) in CH_2Cl_2 (15 mL) heated under reflux under an atmosphere of argon. After addition was complete, the reaction mixture was stirred for a further 10 min. Then the reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 1:9). This gave the cyloheptenone **254** (14 mg, 33%), the pyranone **278** (10 mg, 23%) and the pyrane **280** as a colourless oil (14 mg, 33%).

(4a*R,6*S**,8*Z*,9a*S**)-6-(4-Methoxybenzyloxy)-1,2,3,4,4a,6,7,9a-octahydrobenzocyclohepten-5-one (254)**



R_f = 0.47 (diethyl ether / petroleum ether, 1:1).

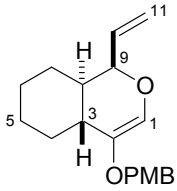
ν_{max} ($CHCl_3$) 3012, 2928, 2856, 1715, 1612 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.63 (dddd, *J* = 2.5, 4.8, 7.1, 11.8 Hz, 1H, H-3), 5.47 (d, *J* = 11.8 Hz, 1H, H-4), 4.63 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.39 (d, *J* = 11.5 Hz, 1H, CH*H*Ar), 4.01 (dd, *J* = 5.0, 7.8 Hz, 1H, H-1), 3.80 (s, 3H, OCH_3), 2.66 (ddddd, *J* = 1.2, 1.2, 5.0, 6.9, 16.4 Hz, 1H, H-2), 2.38-2.30 (m, 1H, H-10), 2.24 (ddddd, *J* = 2.1, 2.1, 4.7, 7.8, 16.4 Hz, 1H, H-2), 2.02 (bt, *J* = 10.7 Hz, 1H, H-5), 1.94-1.88 (m, 1H, CH_2), 1.81-1.66 (m, 3H, CH_2), 1.35-1.10 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (C), 159.3 (C), 137.0 (CH), 129.8 (C), 129.5 (CH), 124.0 (CH), 113.7 (CH), 83.3 (CH), 71.4 (CH_2), 55.2 (CH_3), 53.4 (CH), 39.5 (CH), 34.3 (CH_2), 31.2 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 24.8 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{19}H_{24}O_3Na$ 300.1623 ($[M+Na]^+$), found 323.1618.

(1*R,3*E*,4a*R**,8a*R**)-4-(4-Methoxybenzyloxy)-1-vinyl-4a,5,6,7,8,8a-hexahydro-1*H*-isochromene (280)**



R_f = 0.68 (diethyl ether / petroleum ether, 4:6).

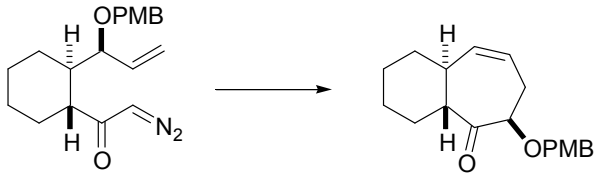
ν_{max} ($CHCl_3$) 2929, 2857, 1613, 991, 908 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.12 (d, *J* = 2.0 Hz, 1H, H-1) 5.49 (ddd, *J* = 6.4, 10.6, 17.1 Hz, 1H, H-10), 5.24-5.19 (m, 2H, H-11), 4.58 (d, *J* = 11.0 Hz, 1H, C*H*HAr), 4.50 (d, *J* = 11.0 Hz, 1H, CH*H*Ar), 4.27 (dd, *J* = 4.4, 6.4 Hz, 1H, H-9), 3.81 (s, 3H, OCH_3), 2.25-2.219 (m, 1H, CH_2), 1.98 (dddd, *J* = 2.0, 3.2, 11.2, 13.8 Hz, 1H, H-3), 1.82-1.79 (m, 2H, CH_2), 1.76-1.69 (m, 1H, H-8), 1.63-1.59 (m, 1H, CH_2), 1.37-1.18 (m, 2H, CH_2), 1.11-1.00 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 140.8 (C), 132.9 (CH), 129.8 (C), 129.0 (CH), 123.9 (CH), 117.2 (CH_2), 113.7 (CH), 78.4 (CH), 70.1 (CH_2), 55.2 (CH_3), 42.1 (CH), 35.9 (CH), 28.0 (CH_2), 27.8 (CH_2), 26.3 (CH_2), 25.8 (CH_2).

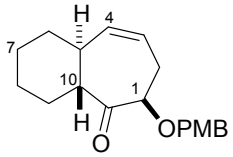
HRMS ESI (*m/z*) mass calc. for $C_{19}H_{24}O_3Na$ 323.1623 ($[M + Na]^+$), found 323.1618.

Rhodium (II) Acetate Catalysed Rearrangement of Diazoketone 255



A solution of the diazoketone **255** (150 mg, 0.46 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 1.25 h to a stirred solution of rhodium (II) acetate dimer (4.0 mg, 9 μmol) in CH_2Cl_2 (45 mL) at room temperature under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 5:95). This gave the cycloheptenone **256** as a yellow oil (109 mg, 79%).

(4a*R**,6*R**,8*Z*,9a*S**)-6-(4-Methoxybenzyloxy)-1,2,3,4,4a,6,7,9a-octahydrobenzocyclohepten-5-one (256)



R_f = 0.40 (diethyl ether / petroleum ether, 1:1).

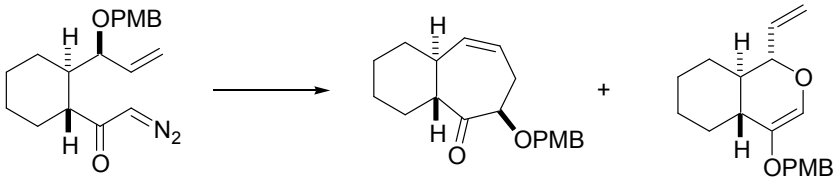
ν_{max} ($CHCl_3$) 3011, 2936, 2857, 1712, 1613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.49 (dddd, *J* = 2.3, 4.8, 4.8, 11.7 Hz, 1H, H-3), 5.41-5.36 (m, 1H, H-4), 4.53 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.45 (dd, *J* = 6.0, 9.7 Hz, 1H, H-1), 4.29 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 3.80 (s, 3H, OCH_3), 2.55-2.38 (m, 3H, H-2 and H-10), 2.22-2.12 (m, 1H, H-5), 1.91-1.84 (m, 1H, CH_2), 1.82-1.72 (m, 3H, CH_2), 1.42-1.12 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4 (C), 159.3 (C), 135.6 (CH), 129.6 (C), 129.6 (CH), 124.3 (CH), 113.8 (CH), 79.8 (CH), 71.3 (CH_2), 55.3 (CH_3), 53.9 (CH), 38.9 (CH), 33.3 (CH_2), 33.0 (CH_2), 28.5 (CH_2), 25.8 (CH_2), 25.1 (CH_2).

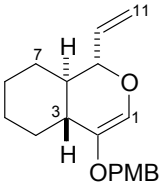
HRMS EI (*m/z*) mass calc. for $C_{19}H_{24}O_3$ 300.1725 ($[M]^+$), found 300.1727.
Found: C, 75.47; H, 8.08 $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%.

Copper (II) Hexafluoroacetylacetonate Catalysed Rearrangement of Diazoketone 255



A solution of the diazoketone **255** (150 mg, 0.46 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 1 h to a stirred solution of copper (II) hexafluoroacetylacetonate (4.4 mg, 9 μmol) in CH_2Cl_2 (45 mL) heated under reflux under an atmosphere of argon. After addition was complete, the reaction mixture was stirred for a further 30 min. Then the reaction mixture was concentrated in vacuo to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 5:95). This gave the cycloheptenone **256** as a yellow oil (22 mg, 16%) and the pyrane **282** as a white powder (52 mg, 38%).

(1*S,3*E*,4a*R**,8a*R**)-4-(4-Methoxybenzyloxy)-1-vinyl-4a,5,6,7,8,8a-hexahydro-1*H*-isochromene (282)**



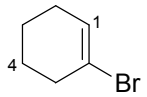
R_f = 0.45 (diethyl ether / petroleum ether, 1:1).
ν_{max} ($CHCl_3$) 3012, 2935, 2857, 1614, 991 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.21 (d, *J* = 2.0 Hz, 1H, H-1) 5.79 (ddd, *J* = 7.7, 10.3, 17.3 Hz, 1H, H-10), 5.30 (dd, *J* = 1.5, 17.3 Hz 1H, H-11), 5.26 (dd, *J* = 1.5, 10.3 Hz 1H, H-11), 4.58 (d, *J* = 10.9 Hz, 1H, C*H*HAr), 4.50 (d, *J* = 10.9 Hz, 1H, CH*H*Ar), 3.84 (dd, *J* = 7.9, 9.9 Hz, 1H, H-9), 3.81 (s, 3H, OCH_3), 2.23-2.09 (m, 2H, H-3 and CH_2), 1.86-1.76 (m, 2H, CH_2), 1.73-1.66 (m, 1H, CH_2), 1.44-1.18 (m, 3H, H-8 and CH_2), 1.02 (dq, *J* = 3.2, 12.6 Hz, 1H, CH_2), 0.91 (dq, *J* = 3.6, 12.5 Hz 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 141.9 (C), 136.4 (CH), 129.8 (C), 128.9 (CH), 124.6 (CH), 118.4 (CH_2), 113.8 (CH), 80.7 (CH), 69.8 (CH_2), 55.3 (CH_3), 43.4 (CH), 41.1 (CH), 28.0 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 25.7 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{19}H_{24}O_3$ 300.1725 ($[M]^+$), found 300.1723

Found: C, 76.09; H, 8.05 $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%.

1-bromocyclohexene (284)[143,195]



A suspension of sodium amide (50 g, 1.3 mol) in THF (500 mL) was cooled to stirred at –40 °C. *tert*-Butanol (67 mL, 0.7 mol) was added dropwise and then stirred for 45 min. Then, 1,2-dibromocyclohexane (23 mL, 0.17 mol) in THF (150 mL) was added dropwise. The mixture was stirred for 1h at –40 °C, and leave to warm to room temperature over 2.5 h. The precipitated salts were filtered on celite and washed with diethyl ether, then the solvent was removed in *vacuo*. The residue was diluted with diethyl ether (200 mL), washed with water (3 × 100 mL) and brine (2 × 100 mL), dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Distillation (b.p. 21°C at 3 mbar) provided 1-bromocyclohexene **284** as a colourless oil (8 g, 28%).

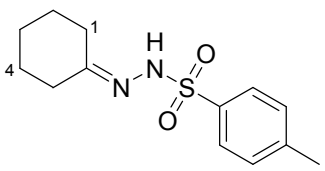
ν_{max} (neat) 2934, 2860, 2838, 1650, 1436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05-6.02 (m, 1H, H-1), 2.44-2.39 (m, 2H, CH_2), 2.10-2.04 (m, 2H, CH_2), 1.76-1.70 (m, 2H, CH_2), 1.63-1.57 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8 (CH), 122.3 (C), 35.2 (CH_2), 27.4 (CH_2), 24.5 (CH_2), 21.2 (CH_2).

The spectroscopic data is identical to that published by Billups and Paquette.[143,195]

***p*-Toluenesulfonylhydrazone of cyclohexanone (286)** [145,196]



Distilled cyclohexanone (10 mL, 0.95 mol) was added to a stirred solution of *p*-toluenesulfonhydrazide (20 g, 0.11 mol) in absolute ethanol (240 mL). The reaction mixture was heated under reflux for 3h and then allowed to cool down to 0°C in an ice

bath, and filtered to collect the crystals. Recrystallisation from absolute ethanol gave the product as a white powder (19.5 g, 73%).

m.p. 151-153 °C

ν_{max} (KBr) 3250, 2935, 2860, 2852, 1596, 1168 cm^{-1}.

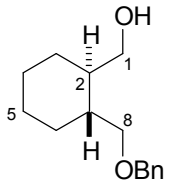
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.23 (bs, 1H, N*H*), 2.43 (s, 3H, Ar-C*H*$_3$), 2.25-2.18 (m, 4H, H-1 and H-5), 1.68-1.53 (m, 6H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (C), 143.9 (C), 135.4 (C), 129.5 (CH), 128.1 (CH), 35.3 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 21.6 (CH_3).

HRMS ESI (*m/z*) mass calc. for $C_{13}H_{19}N_2O_2S$ 267.1167 ($[M+H]^+$), found 267.1162.

The spectroscopic data is identical to that published by Cuevas-Yañez and Lambert.[145,196]

[(1*R, 2*R**)-2-benzyloxycyclohexyl]-methanol (287)**[128c]

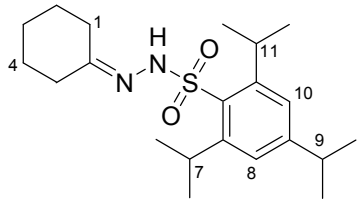


Potassium hydride (186 mg, 1.39 mmol, 30% in oil) was washed with heptane, suspended in THF (0.5 mL) at 0 °C and treated with a solution of the diol (200 mg, 1.39 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 1h. A solution of benzylbromide (166 µL, 1.39 mmol) in THF (1 mL) was added dropwise and the reaction mixture was stirred for 2.5 h. After dilution with diethyl ether (3 mL), the reaction mixture was quenched with saturated ammonium chloride aqueous solution (1 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 3 mL). The combined organic extracts were washed with water (2 × 2 mL), brine (2 mL) and then dried over magnesium sulfate then filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether / petroleum ether, 3:7) gave the expected mono-protected alcohol as a yellow oil (190 mg, 59%). The column was then flushed with neat diethyl ether to recover the starting material (56 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H, Ar-*H*), 4.52 (s, 2H, C*HH*Ph), 3.62 (dd, *J* = 3.8, 11.5 Hz, 1H, H-1), 3.50-3.44 (m, 2H, H-1 and H-8), 3.40 (dd, = 3.4, 9.4 Hz, 1H, H-8), 1.76-1.70 (m, 2H, C*H*$_2$), 1.69-1.60 (m, 2H, C*H*$_2$), 1.57-1.48 (m, 1H, H-7), 1.32-0.99 (m, 5H, H-2 and C*H*$_2$).

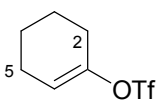
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (C), 128.5(CH), 127.8 (CH), 75.9 (CH_2), 73.4 (CH_2), 67.1 (CH_2), 45.3 (CH), 40.8 (CH), 30.2 (CH_2), 30.1 (CH_2), 26.1 (CH_2), 26.1 (CH_2).
The spectroscopic data is identical to that published by Nicolaou.[128c]

Cyclohexanone ((2,4,6-triisopropylphenyl)sulfonyl)-hydrazone (289)[197]



To a stirred suspension of 2,4,6-triisopropylbenzenesulfonylhydrazide (1.0 g, 3.3 mmol) in MeOH (10 mL) was added cyclohexanone (0.35 mL, 3.3 mmol). Few drops of HCl were added, then the reaction mixture was stored in the freezer overnight, then filtered to collect the crystals. The product was washed with cold methanol and dried *in vacuo* to give white cystals (525 mg, 42%).
m.p. 129-130 °C.
ν_{max} (KBr) 3245, 2956, 2932, 2865, 1644, 1171 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H, Ar-*H*), 4.23 (sept, *J* = 6.8 Hz, 2H, H-7 and H-11), 2.90 (sept, *J* = 6.9 Hz, 1H, H-9), 2.21 (dt, *J* = 5.5, 11.5 Hz, 4H, H-1 and H-5), 1.67-1.54 (m, 6H, C*H*$_2$), 1.27 (d, *J* = 2.3 Hz, 9H, C*H*$_3$), 1.25 (d, *J* = 2.5 Hz, 9H, C*H*$_3$).
^{13}C NMR (400 MHz, $CDCl_3$) δ 153.0 (C), 151.2 (C), 131.4 (C), 123.7 (CH), 35.3 (CH_2), 34.1 (CH), 29.9 (CH), 26.6 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 24.8(CH_3), 21.6 (CH_3).
HRMS ESI (*m/z*) mass calc. for $C_{21}H_{35}N_2O_2S$ 379.2419 ($[M+H]^+$), found 379.2414.
The spectroscopic data is identical to that published by Paquette.[197]

1-Cyclohexenyl trifluoromethanesulfonate (291)[198]



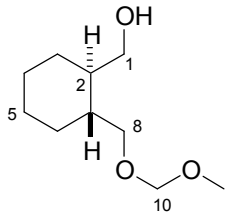
To a solution of diisopropylamine (2.1 mL, 15 mmol) in THF (15 mL) at –78 °C was added a solution of ^{n}BuLi (7.8 mL, 15 mmol, 1.9 M in hexane). The solution was stirred for 30 min at –78 °C and for 15 min at room temperature. A solution of cyclohexanone (1.39 mL, 13.5 mmol) in THF (10 mL) was added at –78 °C. After being stirred for 1.5 h, a solution of N-phenylbis(trifluoromethanesulfonimide) (5.1 g, 14 mmol) in THF (10 mL)

was added at –78 °C. After 15 min at –78 °C and 1 h at 0 °C, water (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate and carefully concentrated *in vacuo*. Purification by flash column chromatography (neat petroleum ether) gave the expected product as a colourless oil (1.73 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77-5.74 (m, 1H, H-2), 2.34-2.29 (m, 2H, CH_2), 2.21-2.15 (m, 2H, CH_2), 1.81-1.75 (m, 2H, CH_2), 1.64-1.57 (m, 2H, CH_2).

The spectroscopic data is identical to that published by Fallis and Fürstner.[198]

[(1*R, 2*R**)-2-Methoxymethoxymethylcyclohexyl]-methanol (292)**



Sodium hydride (35 mg, 0.89 mmol, 60% in oil) was suspended in THF (1 mL) and treated with a solution of the diol (270 mg, 1.87 mmol) in THF (2 mL). The reaction mixture was heated under reflux for 2.5h, then cooled to 0 °C to add chloromethylmethyl ether (69 μL, 0.91 mmol). The reaction mixture was left to warm to room temperature overnight, filtered and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether / petroleum ether, 3:7) gave the expected mono-protected alcohol **292** as a yellow oil (137 mg, 39%). The column was then flushed with neat diethyl ether to recover starting material (117 mg, 43%).

R_f = 0.47 (diethyl ether / petroleum ether, 7: 3)

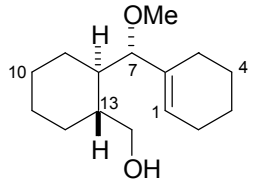
ν_{max} (KBr) 3419, 2923, 2854, 1448 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (s, 2H, H-10), 3.64 (dd, *J* = 4.2, 11.3 Hz, 1H, H-1), 3.54-3.49 (m, 2H, H-1 and H-8), 3.46 (dd, *J* = 4.1, 9.8 Hz, 1H, H-8), 3.36 (s, 3H, OCH_3), 2.48 (bs, 1H, O*H*), 1.75-1.64 (m, 4H, CH_2), 1.53-1.44 (m, 1H, H-7), 1.34-1.03 (m, 5H, H-2 and CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 96.7 (CH_2), 72.7 (CH_2), 66.7 (CH_2), 55.5 (CH_3), 44.3 (CH), 40.3 (CH), 30.1 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 26.0 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{10}H_{20}O_3Na$ 211.1310 ([M+Na]$^+$), found 211.1305.

[(1*R,2*R**)-2-((*R**)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-methanol (295)**



A stirred solution of oxalyl chloride (3.15 mL, 37.2 mmol) in CH_2Cl_2 (60 mL) was cooled to –78 °C and then DMSO (6.16 mL, 86.8 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **268** (4.00 g, 15.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 2.5 h, then triethylamine (32 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and then washed with saturated ammonium chloride solution (400 mL). The aqueous layer was extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the crude aldehyde **265** as a yellow oil.

To a solution of 1-bromocyclohexene **284** (4.9 g, 31 mmol) in dry diethyl ether (100 mL) at –78 °C was added ^{t}BuLi (40 mL, 1.7 M in pentane, 68 mmol). The resulting solution was stirred at –78 °C for 1 h and room temperature for 40 min. After cooling to –78 °C, $MgBr_2$ solution (33 mL, 1.0 M in Et_2O/benzene 3:1, 33 mmol)[199] was added dropwise. The reaction mixture was stirred at –78 °C for 30 min and a solution of the crude aldehyde **265** (15.5 mmol) in dry diethyl ether (120 mL) was added dropwise over 30 min. After stirring at –78 °C for 1 h, the reaction mixture was quenched with saturated ammonium chloride solution (250 mL) and extracted with diethyl ether (3 × 250 mL). The organic extracts were combined, washed with brine (750 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the crude of mixture of two diastereoisomers **285** (ratio 9:1) as a yellow oil.

A solution of the two diastereoisomers **285** in THF (190 mL) was added to a flask charged with NaH (3.7 g, 60% in mineral oil, 93 mmol). The suspension was stirred at room temperature for 30 min and then under reflux for 50 min. Methyl iodide (3.9 mL, 62 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 30 min, at 40 °C for 40 min, under reflux for 30 min then stirred at room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride solution (500 mL) then extracted with diethyl ether (3 × 500 mL). The combined organic extracts

were washed with brine (1 L), dried over magnesium sulfate, and then concentrated *in vacuo* to give the ether **294** as an orange oil.

A stirred solution of the crude silyl ether **294** in THF (120 mL) was treated with TBAF (23 mL, 1 M in THF, 23 mmol) then stirred overnight. The reaction mixture was diluted with water (500 mL) then extracted with diethyl ether (3 × 500 mL). The combined organic extracts were washed with brine (1 L), dried over magnesium sulfate, and then concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 85:15) gave a mixed fraction as a yellow oil (543 mg, 15% over 4 steps, ratio 1: 1) and the major alcohol **295** as a yellow oil (2.40 g, 65% over 4 steps).

R_f = 0.16 (diethyl ether / petroleum ether, 2:8).

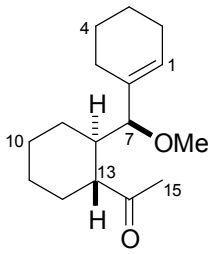
ν_{max} ($CHCl_3$) 3486, 2924, 2856, 1448 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.61-5.57 (m, 1H, H-1), 3.71 (dd, *J* = 4.7, 10.9 Hz, 1H, H-14), 3.59 (d, *J* = 3.5 Hz, 1H, H-7), 3.57 (dd, *J* = 3.9, 10.9 Hz, 1H, H-14), 3.23 (s, 3H, OCH_3), 2.10-2.03 (m, 2H, H-2), 1.97-1.75 (m, 3H, C*H*$_2$), 1.70-1.49 (m, 10H, H-8, H-13 and C*H*$_2$), 1.31-1.18 (m, 3H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (C), 124.7 (CH), 86.6 (CH), 66.3 (CH_2), 56.9 (CH_3), 41.2 (CH), 40.2 (CH), 29.0 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 22.8 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{15}H_{26}O_2Na$ 261.1830 ($[M+Na]^+$), found 261.1821.

1-[(1*R,2*R**)-2-((*R**)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-ethanone (299)**



A stirred solution of oxalyl chloride (1.11 mL, 12.9 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C and then DMSO (2.14 mL, 30.1 mmol) was added dropwise. After stirring for 5 min a solution of the alcohol **295** (1.28 g, 5.37 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (11 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with water (150 mL) and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extracts were washed with

brine (300 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the crude aldehyde **297** as a yellow oil.

A stirred solution of the crude aldehyde **297** in THF (25 mL) was cooled to –78 °C, then treated with methyl magnesium bromide (7.71 mL, 1.4 M in THF/toluene, 10.8 mmol). The reaction mixture was warmed to room temperature overnight, then diluted with water (200 mL), extracted with diethyl ether (3 × 100 mL). The combined organics extracts were washed with brine (300 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the crude alcohol as a yellow oil which was used without further purification.

A stirred solution of oxalyl chloride (1.11 mL, 12.9 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C and then DMSO (2.14 mL, 30.1 mmol) was added dropwise. After stirring for 5 min, a solution of the crude alcohol in CH_2Cl_2 (12 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, then triethylamine (11 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with water (200 mL) and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 9:1) gave the methyl ketone **299** as a yellow oil (900 mg, 66% over 3 steps).

R_f = 0.61 (diethyl ether / petroleum ether, 4:6)

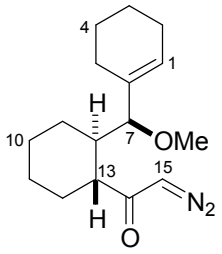
ν_{max} ($CHCl_3$) 2931, 2857, 2836, 1703, 1449 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.52-5.47 (m, 1H, H-1), 3.21 (d, *J* = 5.0 Hz, 1H, H-7), 3.17 (s, 3H, OC*H*$_3$), 2.55 (dt, *J* = 3.6, 10.5 Hz, 1H, H-13), 2.13 (s, 3H, H-15), 2.08-1.989 (m, 2H, H-2), 1.96-1.87 (m, 1H, H-8), 1.84-1.68 (m, 6H, C*H*$_2$), 1.62-1.52 (m, 4H, C*H*$_2$), 1.29-1.15 (m, 3H, C*H*$_2$), 1.14-1.04 (m, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5 (C), 135.3 (C), 124.0 (CH), 87.0 (CH), 57.0 (CH_3), 52.9 (CH), 40.9 (CH), 29.8 (CH_2), 29.6 (CH_3), 25.6 (CH_2), 25.3 (CH_2 x 2), 25.0 (CH_2), 24.9 (CH_2), 22.7 (CH_2), 22.5 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{16}H_{26}O_2Na$ 273.1830 ($[M+Na]^+$), found 273.1825.

2-Diazo-1-[(1*R,2*R**)-2-((*R**)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-ethanone (257)**



A solution of the methyl ketone **299** (630 mg, 2.52 mmol) in THF (10 mL) was added over 1 h to a solution of LHMDS (7.5 mL of a 1.0 M solution in THF, 7.5 mmol) at –78 °C. After stirring for 2 h, 2,2,2-trifluoroethyl trifuoroacetate (600 μL, 4.03 mmol) was added in one portion and the reaction mixture warmed to room temperature then stirred for 1 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (80 mL) and then extracted with diethyl ether (2 × 80 mL). The combined organic extracts were washed with brine (160 mL), dried over magnesium sulfate then concentrated *in vacuo* to a crude yellow oil. The oil was dissolved in acetonitrile (12 mL), then DBU (600 μL, 3.78 mmol) and *p*-acetamidobenzenesulfonyl azide (908 mg, 3.78 mmol) were added, and the reaction mixture was stirred for four days. The reaction mixture was treated with a 10% solution of aqueous sodium hydroxide (35 mL) then the reaction mixture was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (75 mL), dried over magnesium sulfate and concentrated to a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9) gave the title compound **257** as a yellow oil (437 mg, 63%).

R_f = 0.42 (diethyl ether / petroleum ether, 3:7).

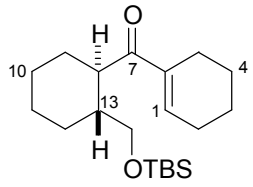
ν_{max} ($CHCl_3$) 2931, 2857, 2102, 1634, 1450 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.56-5.51 (m, 1H, H-1), 5.26 (bs, 1H, H-15), 3.33 (d, *J* = 2.4 Hz, 1H, H-7), 3.21 (s, 3H, OC*H*$_3$), 2.45-2.31 (m, 1H, H-13), 2.04-1.90 (m, 2H, C*H*$_2$), 1.90-1.76 (m, 4H, H-8 and C*H*$_2$), 1.74-1.66 (m, 3H, C*H*$_2$), 1.62-1.52 (m, 4H, C*H*$_2$), 1.47-1.37 (m, 1H, C*H*$_2$), 1.25-1.14 (m, 2H, C*H*$_2$), 1.13-1.03 (m, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 134.6 (C), 124,4 (CH), 122.8 (CH), 85.8 (CH), 57.4 (CH_3), 41.8 (CH), 30.4 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 22.6 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{16}H_{24}O_2N_2Na$ 299.1735 ($[M+Na]^+$), found 299.1730.

(1*R,2R*)-[2-(*tert*-Butyldimethylsilanoxymethyl)-cyclohexyl]-cyclohex-1-enylmethanone (300)**



A stirred solution of oxalyl chloride (2.36 mL, 27.9 mmol) in CH_2Cl_2 (40 mL) was cooled to –78 °C and then DMSO (4.62 mL, 65.1 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **268** (3.00 g, 11.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (22 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and then washed with saturated ammonium chloride solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 (150 mL) and the combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate, then concentrated *in vacuo* to give a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the crude aldehyde **265** as a yellow oil.

To a solution of 1-bromocyclohexene (3.74 g, 23.2 mmol) in dry diethyl ether (70 mL) at –78 °C was added ^{t}BuLi (30 mL, 1.7 M in pentane, 51 mmol). The resulting solution was stirred at –78 °C for 1 h and room temperature for 40 min. After cooling to –78 °C, $MgBr_2$ solution (23 mL, 1.0 M in Et_2O/benzene, 3:1, 23 mmol)[8] was added dropwise. The reaction mixture was stirred at –78 °C for 30 min and a solution of the crude aldehyde **265** in dry diethyl ether (90 mL) was added dropwise over 30 min. After stirring at –78 °C for 1 h, the reaction mixture was quenched with saturated ammonium chloride solution (200 mL) and extracted with diethyl ether (3 × 200 mL). The organic layer were combined, washed with brine (500 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a crude mixture of two diastereoisomers **285** (ratio 9:1) as a yellow oil.

To a stirred solution of the crude alcohol **285** in dichloromethane (150 mL) was added Dess-Martin periodinane (4.97 g, 11.7 mmol) in one portion. The solution was stirred for 2 h at room temperature and then quenched with sodium thiosulfate (150 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 × 150 mL). The combined organic extracts were washed with saturated Na_2CO_3 solution (150 mL) and brine (150 mL), then dried over magnesium sulfate and concentrated to give a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 4:96) gave the title compound **300** as a yellow oil (3.09 g, 79% over 3 steps).

R_f = 0.47 (diethyl ether / petroleum ether, 1:9).

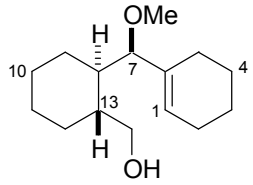
ν_{max} ($CHCl_3$) 3011, 2930, 2858, 1654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.97-6.93 (m, 1H, H-1), 3.31 (d, *J* = 3.9 Hz, 2H, H-14), 3.05 (dt, *J* = 3.2, 11.2 Hz, 1H, H-8), 2.27-2.17 (m, 4H, CH_2), 1.86-1.79 (m, 1H, H-13), 1.77-1.66 (m, 4H, CH_2), 1.64-1.55 (m, 4H, CH_2), 1.32-1.18 (m, 4H, CH_2), 0.84 (s, 9H, C{CH_3}$_3$), –0.04 (s, 3H, Si{CH_3}$_2$), –0.07 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5 (C), 139.2 (CH), 139.1 (C), 65.6 (CH_2), 44.6 (CH), 41.3 (CH) , 31.1 (CH_2), 28.8 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.9 (CH_3), 25.7 (CH_2), 23.2 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 18.2 (C), -5.6 (CH_3), -5.6 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_{20}H_{37}O_2Si$ 337.2563 ($[M+H]^+$), found 337.2562.

[(1*R,2*R**)-2-((*S*)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-methanol (296)**



To a solution of ketone **300** (5.98 g, 17.8 mmol) in methanol at –78 °C was added $CeCl_3.7H_2O$ (26.5 g, 71.2 mmol) and then sodium borohydride (2.69 g, 71.2 mmol). The suspension was left to stir and warm to room temperature overnight. The reaction mixture was quenched with water (300 mL) then extracted with diethyl ether (3 × 300 mL). The combined organic extracts were washed with brine (600 mL), dried over magnesium sulfate, and then concentrated *in vacuo* to give the crude of mixture of two diastereoisomers **285** (ratio 19:1) as a yellow oil.

A solution of the crude two diastereoisomers **285** in THF (200 mL) was added to a flask charged with NaH (4.25 g, 60% in mineral oil, 107 mmol). The suspension was stirred at room temperature for 30 min and then under reflux for 50 min. Methyl iodide (4.43 mL, 71.2 mmol) was then added at room temperature. The reaction mixture was stirred at room temperature for 30 min, at 40 °C for 30 min, under reflux for 30 min then stirred at room temperature for one hour. The reaction mixture was quenched with saturated ammonium chloride solution (300 mL) and then extracted with diethyl ether (3 × 300 mL). The combined organic extracts were washed with brine (500 mL), dried over magnesium sulfate, and then concentrated *in vacuo* to an orange oil.

A stirred solution of the crude silyl ester in THF (150 mL) was treated with TBAF (26.7 mL, 1 M in THF, 26.7 mmol) then stirred overnight. The reaction mixture was diluted with

water (300 mL) then extracted with diethyl ether (3 × 300 mL). The combined organic extracts were washed with brine (500 mL), dried over magnesium sulfate, and then concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 9:1) gave the major alcohol **296** as a yellow oil (1.93 g, 40% over 3 steps).

R_f = 0.13 (diethyl ether / petroleum ether, 2:8).

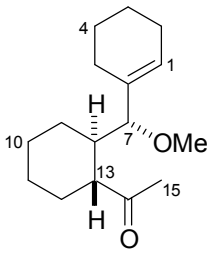
ν_{max} ($CHCl_3$) 3493, 3005, 2926, 2856, 1447 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.55-5.51 (m, 1H, H-1), 3.76 (dd, *J* = 3.1, 11.0 Hz, 1H, H-14), 3.32 (d, *J* = 11.0 Hz, 1H, H-14), 3.23 (d, *J* = 8.9 Hz, 1H, H-7), 3.14 (s, 3H, OC*H*$_3$), 2.10-1.98 (m, 2H, H-2), 1.96-1.86 (m, 1H, C*H*$_2$), 1.78-1.52 (m, 7H, C*H*$_2$), 1.50-1.37 (m, 3H, H-8 and C*H*$_2$), 1.27-1.09 (m, 4H, H-13 and CH_2), 0.75 (dq, *J* = 12.2, 3.3 Hz, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (C), 127.5 (CH), 91.7 (CH), 66.7 (CH_2), 55.0 (CH_3), 46.6 (CH), 40.7 (CH), 31.4 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.5 (CH_2).

HRMS CI (*m/z*) mass calc. for $C_{15}H_{27}O_2$ 239.2011 ($[M+H]^+$), found 239.2013.

1-[(1*R,2*R**)-2-((*S*)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-ethanone (301)**



A stirred solution of oxalyl chloride (853 µL, 10.1 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C and then DMSO (1.67 mL, 23.5 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **296** (1.0 g, 4.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (8.6 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with dichloromethane (30 mL) and then washed with saturated ammonium chloride solution (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Trituration in diethyl ether and removal of the solid gave the aldehyde as a yellow oil.

A stirred solution of the crude aldehyde in THF (20 mL) was cooled to –78 °C, then treated with methyl magnesium bromide (6.0 mL, 1.4 M in THF/toluene, 8.4 mmol). The

reaction mixture was warmed to room temperature overnight, then diluted with water (100 mL), extracted with diethyl ether (2 × 100 mL). The combined organics extracts were washed with brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo* to a yellow oil which was used without further purification.

A stirred solution of oxalyl chloride (853 μL, 10.1 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C and then DMSO (1.67 mL, 23.5 mmol) was added dropwise. After stirring for 5 min a solution of the crude alcohol in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (8.6 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with dichloromethane (30 mL) and then washed with saturated ammonium chloride solution (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate, then concentrated *in vacuo* to a crude yellow oil. Purification by flash column chromatography with as eluant (petroleum ether / diethyl ether, 9:1) gave the methyl ketone **301** as a yellow oil (595 mg, 56% over 3 steps).

R_f = 0.48 (diethyl ether / petroleum ether, 1:1).

ν_{max} ($CHCl_3$) 3009, 2933, 2857, 1693, 1448 cm^{-1}.

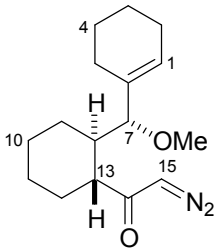
^1H NMR (400 MHz, $CDCl_3$) δ 5.56-5.52 (m, 1H, H-1), 3.00 (s, 3H, OCH_3), 2.96 (d, J = 9.5 Hz, 1H, H-7), 2.15-2.09 (m, 1H, H-13), 2.08 (s, 3H, H-15), 2.06-2.01 (m, 2H, H-2), 1.98-1.84 (m, 2H, H-8 and CH_2), 1.81-1.61 (m, 6H, CH_2), 1.59-1.48 (m, 3H, CH_2), 1.38-1.27 (m, 1H, CH_2), 1.25-1.13 (m, 2H, CH_2), 0.83-0.71 (m, 1H, CH_2).

^{13}C NMR (400 MHz, $CDCl_3$) δ 211.9 (C), 135.1 (C), 127.6 (CH), 91.8 (CH), 56.8 (CH_3), 55.2 (CH), 41.5 (CH), 29.5 (CH_2), 28.4 (CH_2), 27.7 (CH_3), 25.5 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 22.4 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{16}H_{27}O_2$ 250.1933 ($[M+H]^+$), found 250.1934.

Found: C, 76.61; H, 10.56 $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%.

2-Diazo-1-[(1*R,2*R**)-2-((*S*)-cyclohex-1-enylmethoxymethyl)-cyclohexyl]-ethanone (259)**



A solution of the methyl ketone **301** (500 mg, 2.00 mmol) in THF (8 mL) was added over 1 h to a solution of LHMDS (6 mL of a 1.0 M solution in THF, 6 mmol) at –78 °C. After stirring for 1.5 h, 2,2,2-trifluoroethyl trifuoroacetate (500 μL, 3.20 mmol) was added in one portion and the reaction mixture warmed to room temperature then stirred for 1 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (80 mL) and then extracted with diethyl ether (2 × 80 mL). The combined organic extracts were washed with brine (150 mL), dried over magnesium sulfate then concentrated *in vacuo* to give a crude yellow oil. The oil was dissolved in acetonitrile (10 mL), then DBU (450 μL, 3.00 mmol) and *p*-acetamidobenzenesulfonyl azide (720 mg, 3.00 mmol) were added, and the reaction mixture was stirred for four days. The reaction mixture was treated with a 10% solution of aqueous sodium hydroxide (30 mL) then the reaction mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated to a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9) gave the title compound **259** as a yellow oil (352 mg, 63%).

R_f = 0.42 (diethyl ether / petroleum ether, 1:1).

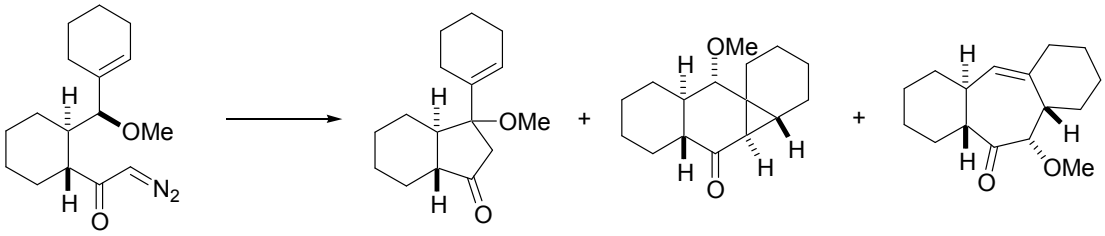
ν_{max} (neat) 3077, 2928, 2855, 2096, 1643, 1448 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.56-5.40 (m, 1H, H-1), 5.12 (bs, 1H, H-15), 3.07 (s, 3H, OC*H*$_3$), 3.03 (d, *J* = 8.7 Hz, 1H, H-7), 2.10-1.92 (m, 5H, H-8 and H-13 and C*H*$_2$), 1.82-1.72 (m, 3H, C*H*$_2$), 1.70-1.51 (m, 6H, C*H*$_2$), 1.48-1.37 (m, 1H, C*H*$_2$), 1.27-1.13 (m, 2H, C*H*$_2$), 0.89-0.77 (m, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 135.2 (C), 127.2 (CH), 91.6 (CH), 55.8 (CH_3), 40.9 (CH), 30.2 (CH_2), 28.5 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 22.5 (CH_2).

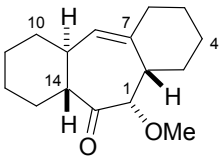
HRMS CI (*m/z*) mass calc. for $C_{16}H_{25}O_2N_2$ 277.1916 ($[M+H]^+$), found 277.1914.

Rhodium (II) Acetate Catalysed Rearrangement of Diazo Ketone 257



A solution of the diazoketone **257** (200 mg, 0.724 mmol) in CH_2Cl_2 (80 mL) was added dropwise over 1.15 h to a stirred solution of rhodium(II) acetate dimer (6.4 mg, 14 μmol) in CH_2Cl_2 (60 mL) at room temperature under an atmosphere of argon. After addition was complete, the reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 1:99 to 6:94). This gave the cyclopentanone **302** as a yellow oil (64 mg, 36%), the cyclopropane adduct **303** as colourless needles (49 mg, 27%) and the cycloheptenone **258** as a yellow oil (5 mg, 3%).

(4a*Z*,5a*S,9a*R**,11*S**,11a*S**)-11-Methoxy-1,2,3,4,5a,6,7,8,9,9a,11,11a-dodecahydrodibenzo[*a*,d]cyclohepten-10-one (258)**



R_f = 0.33 (diethyl ether / petroleum ether, 1:9).

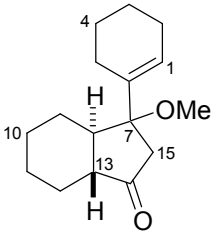
ν_{max} ($CHCl_3$) 2933, 2857, 1693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.17-5.13 (m, 1H, H-8), 3.59 (d, *J* = 3.6 Hz, 1H, H-1), 3.46 (s, 3H, OC*H*$_3$), 3.11-3.02 (m, 1H, H-9), 2.26-2.19 (m, 1H, H-2), 2.18-2.12 (m, 1H, C*H*$_2$), 2.08 (ddd, *J* = 3.3, 11.3, 12.4 Hz, 1H, H-14), 1.95-1.89 (m, 2H, C*H*$_2$), 1.87-1.80 (m, 2H, C*H*$_2$), 1.79-1.70 (m, 3H, C*H*$_2$), 1.64-1.54 (m, 2H, C*H*$_2$), 1.49-1.19 (m, 5H, C*H*$_2$), 1.06 (dq, *J* = 3.4, 12.6 Hz, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2 (C), 138.9 (C), 128.0 (CH), 93.0 (CH), 60.2 (CH_3), 58.0 (CH), 45.4 (CH), 39.0 (CH_2), 34.4 (CH), 33.8 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 26.1 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{16}H_{24}O_2$ 248.1776 ($[M]^+$), found 248.1775.

(3a*R,7a*R**)-3-Cyclohex-1-enyl-3-methoxyoctahydroinden-1-one (302)**



R_f = 0.36 (petroleum ether / diethyl ether, 8: 2)

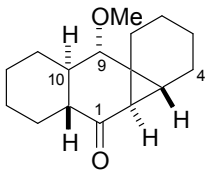
ν_{max} ($CHCl_3$) 3008, 2936, 2856, 1733, 1686, 1448 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$)) δ 5.72-5.69 (m, 1H, H-1), 3.05 (s, 3H, OC*H*$_3$), 2.53 (d, *J* = 1.2, 18.9 Hz, 1H, H-15), 2.30-2.23 (m, 2H, H-8 and H-15), 2.12-2.05 (m, 3H, H-2 and C*H*$_2$), 1.96-1.87 (m, 3H, H-12 and C*H*$_2$), 1.82-1.58 (m, 4H, C*H*$_2$), 1.55-1.45 (m, 3H, H-8 and C*H*$_2$), 1.24-1.00 (m, 3H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9 (C), 135.6 (C), 124.5 (CH), 84.8 (C), 51.9 (CH), 51.5 (CH), 51.4 (CH_3), 44.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 23.0 (CH_2), 22.2 (CH_2).

HRMS ESI (*m/z*) mass calc. for $C_{16}H_{24}O_2Na$ 271.1674 ($[M+Na]^+$), found 271.1669.

(4a*R,4b*R**,5a*R**,9a*R**,10*S**,10a*S**)-10-Methoxydodecahydrobenzo[1,3]cyclopropa[1,2-*b*]naphthalen-5(5a*H*)-one (303)**



R_f = 0.25 (petroleum ether / diethyl ether, 8:2).

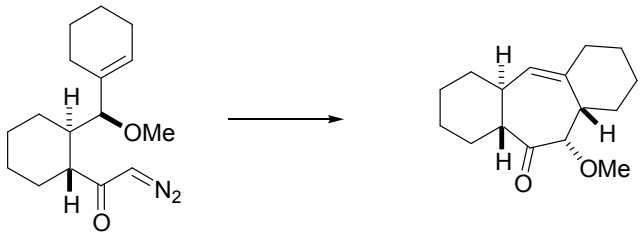
ν_{max} (neat) 2924, 2856, 1668, 1439, 1127, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, OC*H*$_3$), 3.00 (d, *J* = 9.6 Hz, 1H, H-9), 2.21-2.13 (m, 1H, C*H*$_2$), 2.11-2.02 (m, 1H, C*H*$_2$), 2.01-1.91 (m, 2H, C*H*$_2$), 1.82-1.71 (m, 3H, C*H* and C*H*$_2$), 1.70-1.62 (m, 3H, C*H* and C*H*$_2$), 1.59-1.43 (m, 3H, H-10, C*H*, C*H*$_2$), 1.35-1.20 (m, 4H, C*H*$_2$), 1.19-1.03 (m, 2H, C*H*$_2$), 1.01-0.91 (m, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8 (C), 87.1 (CH), 60.8 (CH_3), 48.1 (CH), 44.6 (CH), 39.0 (CH), 34.3 (C), 31.8 (CH), 31.4 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.0 (CH_2), 23.1 (CH_2), 21.0 (CH_2), 20.7 (CH_2).

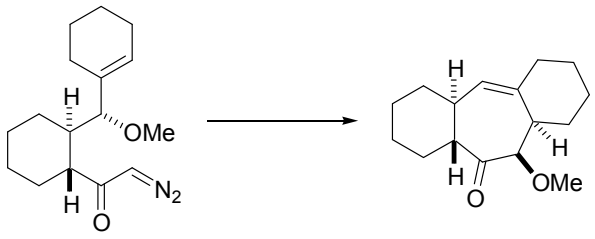
HRMS ESI (*m/z*) mass calc. for $C_{16}H_{24}O_2Na$ 271.1674 ($[M+Na]^+$), found 271.1669.

Copper (II) Hexafluoroacetylacetonate Catalysed Rearrangement of Diazo Ketone 257



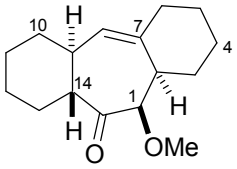
A solution of the diazoketone **257** (200 mg, 0.724 mmol) in CH_2Cl_2 (80 mL) was added dropwise over 1.2 h to a stirred solution of copper(II) hexafluoroacetylacetonate (6.9 mg, 14 μmol) in CH_2Cl_2 (60 mL) heated under reflux under an atmosphere of argon. After addition was complete, the reaction mixture was hetated under reflux for a further 2 h. Another portion of the catalyst (8 mg, 16 μmol) was added and the reaction mixture was heated under reflux overnight. The reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 1:99 to 6:94). This gave the cycloheptenone **258** as a yellow oil (50 mg, 28%).

Rhodium (II) Acetate Catalysed Rearrangement of Diazoketone (259)



A solution of the diazoketone **259** (150 mg, 0.543 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 1h to a stirred solution of rhodium(II) acetate dimer (4.8 mg, 10 μmol) in CH_2Cl_2 (45 mL) at room temperature under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 1:9). This gave the cycloheptenone **260** as a white powder (121 mg, 90%).

(4a*Z*,5a*S,9a*R**,11*R**,11a*R**)-11-Methoxy-1,2,3,4,5a,6,7,8,9,9a,11,11a-dodecahydrodibenzo[*a*,d]cyclohepten-10-one (260)**



R_f = 0.47 (diethyl ether / petroleum ether, 1:1).

ν_{max} ($CHCl_3$) 3011, 2932, 2856, 1710, 1447 cm^{-1}.

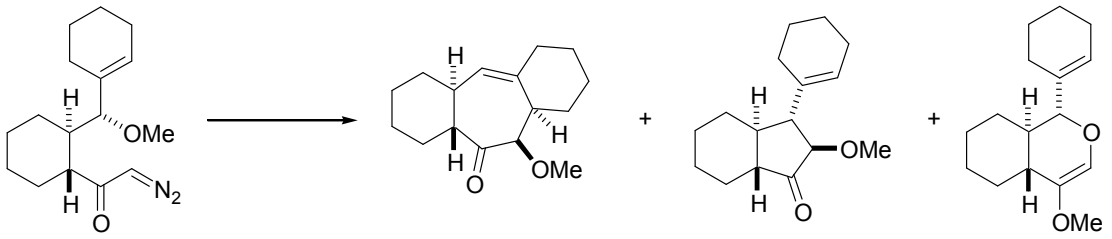
^1H NMR (400 MHz, $CDCl_3$) δ 5.08-5.04 (m, 1H, H-8), 4.81 (d, *J* = 5.3 Hz, 1H, H-1), 3.29 (s, 3H, OC*H*$_3$), 2.63-2.56 (m, 1H, H-2), 2.55-2.45 (m, 1H, H-9), 2.18-2.12 (m, 1H, C*H*$_2$), 2.08-1.95 (m, 4H, H-14 and C*H*$_2$), 1.89-1.72 (m, 5H, C*H*$_2$), 1.39-1.06 (m, 6H, C*H*$_2$), 0.80 (dq, 1H, *J* = 12.8, 3.6 Hz, H-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (C), 140.6 (C), 126.9 (CH), 83.2 (CH), 57.5 (CH_3), 56.7 (CH), 45.8 (CH), 38.6 (CH_2), 35.9 (CH), 34.0 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.6 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{16}H_{24}O_2$ 248.1776 ($[M]^+$), found 248.1775.

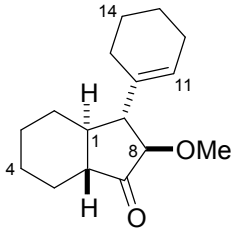
Found: C, 77.38; H, 9.79 $C_{16}H_{24}O_2$ requires C, 77.38; H, 9.74%.

<u>Copper (II) Hexafluoroacetylacetonate Catalysed Rearrangement of Diazo Ketone 259</u>



A solution of the diazoketone **259** (150 mg, 0.543 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 1h to a stirred solution of copper(II) hexafluoroacetylacetonate (5.2 mg, 10 μmol) in CH_2Cl_2 (45 mL) heated under reflux under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to a green oil and then purified by flash column chromatography (diethyl ether / petroleum ether, 1:9). This gave the cycloheptenone **260** as a white solid (13 mg, 10%), the cyclopentanone **305** as a yellow oil (46 mg, 34%) and the pyrane **306** (38 mg, 28%) as a pale yellow oil.

(2*R,3a*S**,7a*R**)-3-Cyclohex-1-enyl-2-methoxyoctahydroinden-1-one (305)**



R_f = 0.47 (diethyl ether / petroleum ether, 1:1).

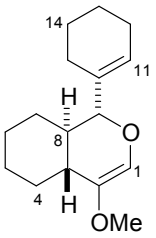
ν_{max} ($CHCl_3$) 2933, 2856, 1742, 1447 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.62-5.59 (m, 1H, H-11), 3.52 (s, 3H, OC*H*$_3$), 3.49 (d, *J* = 9.6 Hz, 1H, H-8), 2.21 (dd, *J* = 9.6, 11.5 Hz, 1H, H-9), 2.13-2.08 (m, 1H, C*H*$_2$), 2.07-2.02 (m, 2H, H-12), 1.97-1.87 (m, 3H, C*H*$_2$), 1.84-1.77 (m, 2H, C*H*$_2$), 1.74-1.70 (m, 1H, H-6), 1.69-1.57 (m, 4H, C*H*$_2$), 1.32-1.08 (m, 4H, H-1 and C*H*$_2$), 1.07-0.97 (m, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8 (C), 134.5 (C), 124.8 (CH), 84.8 (CH), 58.7 (CH_3), 55.8 (CH), 54.0 (CH), 39.8 (CH), 30.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.9 (CH_2), 22.6 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{16}H_{24}O_2$ 248.1776 ($[M]^+$), found 248.1774.

(1*R,4a*R**,8a*R**)-1-Cyclohex-1-enyl-4-methoxy-4a,5,6,7,7,8a-hexahydro-1*H*-isochromene (306)**



R_f = 0.74 (diethyl ether / petroleum ether, 1:1).

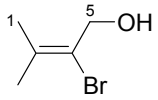
ν_{max} ($CHCl_3$) 2926, 2855, 1738, 1447 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 2.5 Hz, 1H, H-1), 5.72 (m, 1H, H-11), 3.96 (d, *J* = 10.3 Hz, 1H, H-9), 3.41 (s, 3H, OC*H*$_3$), 2.52-2.45 (m, 1H, C*H*$_2$), 2.24 (dddd, *J* = 2.5, 2.9, 11.5, 11.5 Hz, 1H, H-3), 2.09-1.98 (m, 3H, H-12 and C*H*$_2$), 1.93-1.85 (m, 1H, C*H*$_2$), 1.81-1.48 (m, 7H, H-8 and C*H*$_2$), 1.36-1.18 (m, 4H, C*H*$_2$), 1.06 (dq, *J* = 12.0, 3.1 Hz, 1H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7 (C), 134.9 (C), 126.6 (CH), 125.4 (CH), 88.6 (CH), 60.8 (CH_3), 48.3 (CH), 46.6 (CH), 27.9 (CH_2), 27.1 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 23.4 (CH_2), 22.5 (CH_2), 22.4 (CH_2).

HRMS EI (*m/z*) mass calc. for $C_{16}H_{24}O_2$ 248.1776 ($[M]^+$), found 248.1778.

2-Bromo-3-methylbut-2-en-1-ol (323)[150]



A solution of 3-methyl-but-2-enol (1.00 g, 11.6 mmol) in CH_2Cl_2 (20 mL) was treated with a solution of bromine (1.95 g, 12.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, allowed to warm to room temperature and stirred for another 3 hours. Then the reaction mixtue was treated, in dropwise fashion, with DBU (2.64 g, 17.4 mmol). The resulting mixture was stirred under reflux for 4 hours, allowed to cool to room temperature and treated dropwise with saturated aqueous sodium thiosulfate (30 mL). The reaction mixture was then partitioned between diethyl ether (20 mL) and 1M HCl (5 mL). The aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography with as eluant (petroleum ether / ethyl acetate, 8:2) gave alkene **323** as a colourless oil (1.23 g, 64%).

R_f = 0.50 (diethyl ether / petroleum ether, 1:1).

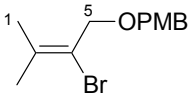
ν_{max} ($CHCl_3$) 3348, 2999, 2918, 1654, 1442, 1237 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (s, 2H, H-5), 1.91 (s, 3H, H-1), 1.87 (s, 3H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (C), 121.0 (C), 64.6 (CH_2), 25.4 (CH_3), 20.5 (CH_3).

The spectroscopic data is identical to that published by Jacobi.[150]

1-(2-Bromo-3-methylbut-2-enyloxymethyl)-4-methoxybenzene (324)



A solution of alcohol **323** (0.1 g, 0.6 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of pyridinium *p*-toluenesulfonate (17 mg, 70 μmol) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (291 mg, 1.03 mmol) in CH_2Cl_2 (2.5 mL) under Argon. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with petroleum ether, and the precipitate was filtrated. The filtrate was washed with a saturated solution of sodium carbonate (10 mL), water (10 mL), brine (10 mL), dried over magnesium sulfate and then concentrated *in vacuo*. Purification by flash column

chromatography with as eluant (petroleum ether / diethyl ether, 95:5) gave alkene **324** as a colourless oil (125 mg, 72%).

R_f = 0.53 (diethyl ether / petroleum ether, 1:1).

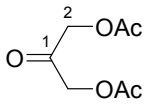
ν_{max} (neat) 2998, 2912, 2857, 1612, 1586, 1514, 1301, 1249 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 4.46 (s, 2H, C*H*$_2$Ar), 4.27 (s, 2H, H-5), 3.81 (s, 3H, OC*H*$_3$), 1.93 (s, 3H, H-1), 1.80 (s, 3H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 136.8 (C), 130.1 (C), 129.5 (CH), 117.5 (C), 113.8 (CH), 71.1 (CH_2), 71.0 (CH_2), 55.3 (CH_3), 25.5 (CH_3), 20.8 (CH_3).

HRMS EI (*m/z*) mass calc. for $C_{13}H_{17}BrO_2$ 284.0412 ($[M]^+$), found 284.0408.

2-Oxo-1,3-propanediol 1,3-diacetate (325)[151]



1,3-Dihydroxyacetone (1.00 g, 11.1 mmol) was dissolved in pyridine (3.2 mL) and acetic anhydride (3.2 mL). After 1 hour at room temperature, the solvents were removed as completely as possible *in vacuo*. The residue, dissolved in ethyl acetate (30 mL), was washed with water (30 mL), 3% aqueous HCl (30 mL), water (30 mL), and brine (30 mL) and then dried over magnesium sulfate. Evaporation and crystallisation from toluene-hexane gave the diacetate **325** (722 mg, 37%) as long colourless needles.

R_f = 0.55 (methylene chloride/ methanol, 95:5).

m.p. 44-46 °C.

ν_{max} (neat) 2936, 1742, 1419, 1375, 1232 cm^{-1}.

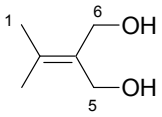
^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 4H, H-2), 2.15 (s, 6H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9 (C), 170.0 (C), 66.2 (CH_2), 20.3 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_7H_{10}O_5$ 175.0606 ($[M+H]^+$), found 175.0608.

The spectroscopic data is identical to that published by Bentley and Bates.[151]

2-Isopropylidene-propane-1,3-diol (319) [152a]



A solution of DIBAL-H (1 M in cyclohexane, 360 mL, 360 mmol) was added to a solution of diethylisopropylmalonate (12 g, 60 mmol) in petroleum ether (200 mL) at –60 °C. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was then diluted with diethyl ether and water at 0 °C, and a precipitate were formed. A solution of Rochelle salt and the resulting mixture was stirred for 1 hour, extracted with methylene chloride and ethyl acetate, dried over $MgSO_4$, and concentrated *in vaccuo* to afford crude diol **319** as a colourless solid (6.18 g, 89%).

R_f = 0.17 (neat ethyl acetate).

m.p. 38-40 °C.

ν_{max} (KBr) 3303, 2886, 1665, 1443 cm^{-1}.

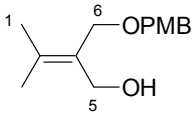
^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 4H, H-5 and H-6), 2.68 (bs, 2H, O*H*), 1.77 (s, 6H, H-1 and H-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7 (C), 130.7 (C), 62.0 (CH_2), 20.3 (CH_3).

HRMS EI (*m/z*) mass calc. for $C_6H_{12}O_2$ 116.0837 ($[M]^+$), found 116.0840.

The spectroscopic data is identical to that published by Gleiter.[152a]

2-(4-methoxybenzyloxymethyl)-3-methylbut-2-en-1-ol (327)



A solution of diol **319** (200 mg, 1.72 mmol) in DMF (0.5 mL) was slowly added to a flask containing NaH (60% in mineral oil, 68.5 mg, 1.72 mmol) in THF (1 mL) at 0 °C. After stirring for 1.5 h at room temperature, the reaction mixture was cooled to 0 °C and a solution of *p*-methoxybenzylchloride (156 µL, 1.15 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with ice-cold water, extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography with as eluant (diethyl ether / petroleum ether, 7:3) afforded alcohol **327** as a colourless oil (133 mg, 33%).

R_f = 0.20 (diethyl ether / petroleum ether, 7:3).

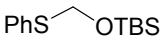
ν_{max} (neat) 3418, 2997, 2933, 1612, 1514, 1465, 1302, 1249, 1174 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.46 (s, 2H, C*H*$_2$Ar), 4.24 (s, 2H, H-5), 4.14 (s, 2H, H-6), 3.80 (s, 3H, OC*H*$_3$), 2.19 (b, 1H, O*H*), 1.79 (s, 3H, H-1), 1.73 (s, 3H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 134.8 (C), 130.2 (C), 129.4 (CH), 128.7 (C), 113.8 (CH), 72.2 (CH_2), 69.1 (CH_2), 62.0 (CH_2), 55.2 (CH_3), 20.5 (CH_3), 20.4 (CH_3).

HRMS EI (*m/z*) mass calc. for $C_{14}H_{20}O_3$ 236.1412 ($[M]^+$), found 236.1414.

tert-Butyldimethylphenylsulfanylmethoxysilane (330)[200]



Thioanisole (4.73 mL, 40.2 mmol) was added to ^{n}BuLi (1.6 M in hexane, 25.4 mL, 40.7 mmol) in diethyl ether (12 mL), and the resulting solution was heated under reflux for 18 h. *tert*-Butyldimethylchlorosilane (7.17 g, 47.6 mmol) was added and the mixture heated under reflux for 27 h. The reactionmixture was then poured into saturated aqueous ammonium chloride (20 mL), extracted with diethyl ether (3 × 20 mL), washed with water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude phenylthio-*tert*-butyldimethylsilylmethane **329** (10.39 g).

m-Chloroperoxybenzoic acid (901 mg, 4.02 mmol) in dichloromethane (20 mL) was added to a solution of crude phenylthio-*tert*-butyldimethylsilylmethane **329** (4.02 mmol, 1/10 of the crude previously obtained) in dichloromethane (20 mL), under argon at –23 °C, over 15 min.The reaction mixture was allowed to warm to room temprature over 1 h and poured into saturated aqueous sodium hydrogen carbonate (20 mL). The organic layer was separated, washed with saturated aqueous sodium choride (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was taken up in carbon tetrachloride (20 mL), and heated under reflux for 3h. The solution was then evaporated under reduced pressure. Purification by flash column chromatography with neat petroleum ether afforded sulfide **330** as a colourless oil (498 mg, 49%).

R_f = 0.73 (diethyl ether / petroleum ether, 1:1).

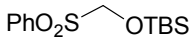
ν_{max} (neat) 2954, 2929, 2857, 1585, 1471, 1439, 1315, 1257, 1072 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.31-7.19 (m, 3H, Ar-*H*), 5.11 (s, 2H, H-1), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.07 (s, 6H, Si(C*H*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (C), 130.2 (CH), 128.8 (CH), 126.6 (CH), 69.0 (CH_2), 25.7 (CH_3), 18.1 (C), -5.1 (CH_3).

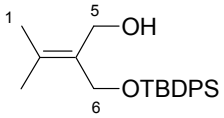
HRMS EI (*m/z*) mass calc. for $C_{13}H_{22}OSSi$ 254.1161 ($[M]^+$), found 254.1157.
The spectroscopic data is identical to that published by Kersey.[200]

Benzenesulfonylmethoxy-*tert*-butyldimethylsilane (331)



To a stirred solution of sulfide **330** (254 mg, 1.00 mmol) and $MnSO_4.H_2O$ (1.69 mg, 0.01 mmol) in acetonitrile (23 mL) was added at room temperature an aqueous mixture comprised by H_2O_2 (30% wt, 0.5 mL, 5.0 mmol) and 0.2 M solution of $NaHCO_3$ (17 mL) previously prepared at 0 °C. After 3.5 h, the reaction mixture was quenched with saturated aqueous sodium choride (20 mL), extracted with ethyl acetate (3 × 20 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography with as eluant (diethyl ether / petroleum ether, 1:1) afforded sulfone **331** as a colourless oil (244 mg, 85%).
R_f = 0.41 (diethyl ether / petroleum ether, 1:1).
ν_{max} (neat) 2929, 2887, 2857, 1471, 1439, 1315, 1257, 1072 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.63 (m, 2H, Ar-*H*), 7.53-7.51 (m, 3H, Ar-*H*), 4.63 (d, *J* = 8.9 Hz, 1H, H-1), 4.44 (d, *J* = 8.9 Hz, 1H, H-1), 0.86 (s, 9H, SiC{CH_3}$_3$), 0.06 (s, 3H, Si{CH_3}$_2$), 0.03 (s, 3H, Si{CH_3}$_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (C), 131.3 (CH), 129.0 (CH), 124.8 (CH), 84.6 (CH_2), 25.6 (CH_3), 18.2 (C), -5.3 (CH_3), -5.1 (CH_3).
HRMS CI (*m/z*) mass calc. for $C_{13}H_{23}O_3SSi$ 287.1137 ($[M+H]^+$), found 287.1134.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylbut-2-en-1-ol (333)



To a suspension of sodium hydride (60% in mineral oil, 1.00 g, 25.1 mmol) in THF (100 mL) was added dropwise a solution of diol **319** (2.89 g, 24.9 mmol) in THF (250 mL). The mixture was stirred at room temperature for 1 h, then *tert*-butyldiphenylchlorosilane (6.47 mL, 24.9 mmol) was added and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched with water (200 mL) at 0 °C, and the mixture was extracted with diethyl ether (3 × 200 mL), washed with saturated aqueous sodium choride (500 mL), dried over magnesium sulfate and concentrated under reduced pressure.

Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9 to 3:7) afforded ether **333** as a colourless oil (5.66 g, 64%).

R_f = 0.46 (diethyl ether / petroleum ether, 1:1).

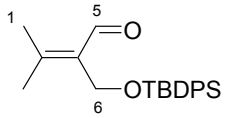
ν_{max} (neat) 3425, 2930, 2857, 1472, 1428, 1112, 1050 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H, Ar-*H*), 7.45-7.38 (m, 6H, Ar-*H*), 4.36 (s, 2H, H-6), 4.33 (d, *J* = 5.9 Hz, 2H, H-5), 2.50 (t, *J* = 5.9 Hz, 1H, O*H*), 1.77 (s, 3H, H-1), 1.48 (s, 3H, H-2), 1.05 (s, 9H, SiC{CH_3}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (CH), 133.0 (C), 132.0 (C), 130.2 (C), 129.8 (CH), 127.8 (CH), 64.0 (CH_2), 61.8 (CH_2), 26.8 (CH_3), 20.4 (CH_3), 20.2 (CH_3), 19.1 (C).

HRMS FAB (*m/z*) mass calc. for $C_{22}H_{30}O_2SiNa$ 377.1913 ([M+ Na]$^+$), found 377.1916.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylbut-2-enal (334)



A stirred solution of oxalyl chloride (246 μL, 2.91 mmol) in CH_2Cl_2 (6 mL) was cooled to –78 °C and then DMSO (483 μL, 6.79 mmol) was added dropwise. After stirring for 5 min, a solution of the alcohol **333** (500 mg, 1.41 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1.5 h, then triethylamine (2.4 mL) was added and the reaction mixture warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous ammonium chloride (20 mL), extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were washed with brine (40 mL), dried over magnesium sulfate, then concentrated *in vacuo*. Trituration in diethyl ether and removal of the solid gave the crude aldehyde. Purification by flash column chromatography with as eluant (diethyl ether / petroleum ether, 2:8) afforded aldehyde **334** as a pale yellow oil (428 mg, 86%).

R_f = 0.23 (diethyl ether / petroleum ether, 2:8).

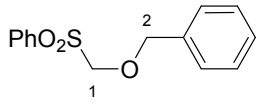
ν_{max} (neat) 2931, 2857, 1723, 1667, 1635, 1472, 1428, 1112, 1070 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H, H-5), 7.70-7.67 (m, 4H, Ar-*H*), 7.43-7.36 (m, 6H, Ar-*H*), 4.40 (s, 2H, H-6), 2.20 (s, 3H, H-1), 2.02 (s, 3H, H-2), 1.03 (s, 9H, SiC(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (CH), 159.6 (C), 135.7 (CH), 133.6 (C), 130.6 (C), 129.6 (CH), 127.6 (CH), 56.4 (CH_2), 26.8 (CH_3), 23.6 (CH_3), 19.7 (CH_3), 19.3 (C).

HRMS CI (*m/z*) mass calc. for $C_{22}H_{29}O_2Si$ 353.1937 ([M+ H]$^+$), found 353.1934.

[{(Phenylmethoxy)methyl}sulphonyl]benzene (336)[201]



Sodium hydride (60% dispersion in oil, 497 mg, 12.5 mmol) was suspended in distilled 1,2-dimethoxyethane (19 mL) at 0 °C under argon. Benzylalcohol (0.96 mL, 9.25 mmol) in 1,2-dimethoxyethane (9 mL) was slowly added by cannula. When the evolution of hydrogen was complete (*c.* 30 min), sodium iodide (1.87 g, 12.5 mmol) was added followed by chloromethyl phenyl sulfide (1.55 ml, 11.5 mmol). The reaction mixture was stirred at 0 °C for 1 h and 1.5 h at room temperature, before the reaction was quenched with water, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, then concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether / petroleum ether, 5:95) afforded sulfide **335** as a colourless oil (1.79 g, 85%).

To a stirred solution of sulfide **335** (1.52 g, 6.60 mmol) and $MnSO_4.H_2O$ (11 mg, 65 μmol) in acetonitrile (150 mL) was added at room temperature an aqueous mixture comprising 30% H_2O_2 (3.7 g, 33 mmol) and 0.2 M solution of $NaHCO_3$ (110 mL) previously prepared at 0 °C. After 3.5 h, the reaction was quenched with saturated aqueous sodium chloride (150 mL), and the mixture was extracted with ethyl acetate (3 × 150 mL). The organic extracs were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 4:6) afforded sulfone **336** as a white powder (1.25 g, 72%).

R_f= 0.39 (diethyl ether / petroleum ether, 1:1).

m.p. 66-68 °C.

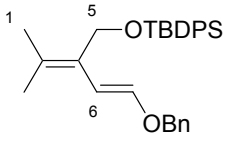
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H, Ar-*H*), 7.71-7.66 (m, 1H, Ar-*H*), 7.61-7.55 (m, 2H, Ar-*H*), 7.36-7.31 (m, 3H, Ar-*H*), 7.30-7.25 (m, 2H, Ar-*H*), 4.91 (s, 2H, H-1), 4.58 (s, 2H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (C), 135.8 (C), 134.0 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 84.6 (CH_2), 74.5 (CH_2).

HRMS CI (*m/z*) mass calc. for $C_{14}H_{15}O_3S$ 263.0742 ($[M+ H]^+$), found 263.0747.

The spectroscopic data is identical to that published by Taylor.[201]

[2-(2*E*-Benzyloxyvinyl)-3-methylbut-2-enyloxy]-*tert*-butyldiphenylsilane (338)



LDA (0.41 mL, 0.41 mmol) was added to a solution of sulfone **336** (108 mg, 0.412 mmol) in THF (4.1 mL) at –78 °C, the reaction mixture was stirred for 10 min. Then a solution of aldehyde **334** (169 mg, 0.479 mmol) in THF (4 mL) was added dropwise, and the reaction mixture was stirred for 10 min before the addition of benzoylchloride (55 μL, 0.41mmol). The resulting mixture was warmed to room temperature for 45 min, quenched with saturated aqueous ammonium choride (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9) afforded a racemic mixture of esters **337** as a white foam (223 mg, 76%).

A solution of esters **337** (223 mg, 0.310 mmol) and DMPU (560 μL, 4.65 mmol) in THF (3 mL) was treated with SmI_2 (15.5 mL, 0.1 M in THF, 1.55 mmol). The resulting mixture was stirred at room temperature for 1 h, and the reaction was then quenched with saturated aqueous ammonium choride (60 mL). The reaction mixture was extracted with diethyl ether (3 × 150 mL) and the combined organic extracts were washed with 10% solution of aqueous sodium thiosulfate (150 mL), water (150 mL), brine (150 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:99) afforded diene **338** as a colourless oil (122 mg, 86%).

R_f = 0.77 (diethyl ether / petroleum ether, 2:8).

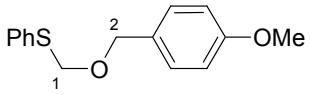
ν_{max} (neat) 2929, 2857, 1428, 1160, 1106, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 4H, Ar-*H*), 7.44-7.29 (m, 11H, Ar-*H*), 6.81 (d, *J* = 12.5 Hz, 1H, H-7)), 5.94 (d, *J* = 12.5 Hz, 1H, H-6), 4.78 (s, 2H, C*H*$_2$Ph), 4.31 (s, 2H, H-5), 1.70 (s, 3H, H-1), 1.49 (s, 3H, H-2), 1.02 (s, 9H, SiC{C*H*$_3$}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5 (CH), 137.3 (C), 135.8 (CH), 133.9 (C), 129.6 (C), 129.5 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.2 (C), 105.8 (CH), 72.2 (CH_2), 61.3 (CH_2), 26.9 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 19.3 (C).

HRMS EI (*m/z*) mass calc. for $C_{30}H_{36}O_2Si$ 456.2485 ($[M]^+$), found 456.2487.

{[*p*-Methoxy-(phenylmethoxy)methyl]thio}benzene (339)



Sodium hydride (60% dispersion in oil, 389 mg, 9.77 mmol) was suspended in distilled 1,2-dimethoxyethane (15 mL) at 0 °C under argon. Benzylalcohol (1.0 g, 7.2 mmol) in 1,2-dimethoxyethane (7 mL) was slowly added *via* a cannula. When the evolution of hydrogen was complete (*c.* 30 min), sodium iodide (1.46 g, 9.77 mmol) was added followed by chloromethyl phenyl sulfide (1.21 ml, 9.05 mmol). The reaction mixture was stirred at 0 °C for 1 h and 2.5 h at room temperature, before being quenched with water, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, then concentrated *in vacuo*. Purification by flash column chromatography with as eluant (diethyl ether / petroleum ether, 2:98) afforded sulfide **339** as a colourless oil (1.38 g, 74%).

R_f = 0.64 (diethyl ether / petroleum ether, 1:1).

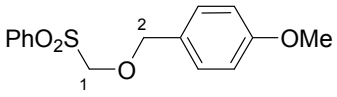
ν_{max} (neat) 2905, 2835, 1612, 1584, 1513, 1480, 1440, 1303, 1249, 1174, 1061 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (m, 2H, Ar-*H*), 7.33-7.20 (m, 5H, Ar-*H*), 6.90-6.86 (m, 2H, Ar-*H*), 5.03 (s, 2H, H-1), 4.65 (s, 2H, H-2), 3.81 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C), 136.0 (C), 130.0 (CH), 129.9 (CH), 129.1 (C), 128.9 (CH), 126.6 (CH), 113.8 (CH), 74.7 (CH_2), 69.3 (CH_2), 55.3 (CH_3).

HRMS EI (*m/z*) mass calc. for $C_{15}H_{16}O_2S$ 260.0871 ($[M]^+$), found 260.0870.

{[*p*-Methoxy-(phenylmethoxy)methyl]sulphonyl}benzene (340)



To a stirred solution of sulfide **339** (520 mg, 2.00 mmol) and $MnSO_4.H_2O$ (3 mg, 0.02 mmol) in acetonitrile (50 mL) was added at room temperature an aqueous mixture comprising30% H_2O_2 (1.13 g, 10.0 mmol) and 0.2 M solution of $NaHCO_3$ (35 mL) previously prepared at 0 °C. After 1.5 h, the reaction was quenched with saturated aqueous sodium chloride (40 mL) and the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:1) afforded sulfone **340** as a white powder (488 mg, 84%).

R_f = 0.27 (diethyl ether / petroleum ether, 1:1).

m.p. 97-99 °C.

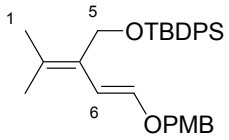
ν_{max} (KBr) 2962, 2892, 1614, 1584, 1446, 1330, 1290, 1144, 1073, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H, Ar-*H*), 7.70-7.65 (m, 1H, Ar-*H*), 7.60-7.54 (m, 2H, Ar-*H*), 7.22 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 4.83 (s, 2H, H-1), 4.54 (s, 2H, H-2), 3.81 (s, 3H, OC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (C), 137.4 (C), 134.0 (CH), 130.1 (CH), 129.2 (CH), 128.8 (CH), 127.7 (C), 114.0 (CH), 84.2 (CH_2), 74.1 (CH_2), 55.3 (CH_3).

HRMS EI (*m/z*) mass calc. for $C_{15}H_{16}O_4S$ 292.0769 ($[M]^+$), found 292.0771.

Tert-Butyl-{2-[2*E*-(4-methoxybenzyloxy)-vinyl]-3methylbut-2-enyloxy}-diphenylsilane (342)



LDA (226 µL, 0.22 mmol) was added to a solution of sulfone **340** (66 mg, 0.22 mmol) in THF (2.2 mL) at −78 °C, the reaction mixture was stirred for 10 min. A solution of aldehyde **334** (93 mg, 0.3 mmol) in THF (2.3 mL) was added dropwise, and the reaction mixture was stirred for 10 min before benzoylchloride (30 µL, 0.2 mmol) was added. The resulting mixture was warmed to room temperature for 45 min, quenched with saturated aqueous ammonium chloride (10 mL), extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:9 to 3:7) afforded a racemic mixture of esters **341** as a white foam (121 mg, 74%).

A solution of esters **341** (3.23 g, 4.31 mmol) and DMPU (7.8 mL, 65 mmol) in THF (43 mL) was treated with SmI_2 (215 mL, 0.1 M in THF, 21.5 mmol). The resulting mixture was stirred at room temperature for 1 h, and the reaction was then quenched with saturated aqueous ammonium choride (400 mL). The mixture was extracted with diethyl ether (3 × 500 mL) and the combined organic extracts were washed with 10% solution of aqueous sodium thiosulfate (800 mL), water (500 mL), brine (500 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography with as eluant (diethyl ether / petroleum ether, 5:95) afforded diene **342** as a pale yellow oil (1.91 g, 90%).

R_f = 0.54 (diethyl ether / petroleum ether, 2:8).

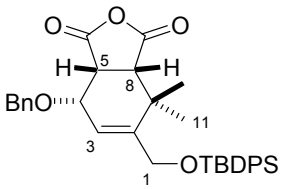
ν_{max} (neat) 2930, 2857, 1613, 1514,1250, 1172, 1105, 1039 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H, Ar-*H*), 7.45-7.34 (m, 6H, Ar-*H*), 7.28 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.89 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 12.5 Hz, 1H, H-7), 5.93 (d, *J* = 12.5 Hz, 1H, H-6), 4.71 (s, 2H, C*H*$_2$Ar), 4.31 (s, 2H, H-5), 3.81 (s, 3H, OC*H*$_3$), 1.70 (s, 3H, H-1), 1.49 (s, 3H, H-2), 1.03 (s, 9H, SiC{C*H*$_3$}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 147.4 (CH), 135.8 (CH), 135.6 (CH), 133.9 (C), 129.5 (CH), 129.3 (CH), 128.7 (C), 127.5 (CH), 127.2 (C), 113.9 (CH), 105.7 (CH), 71.9 (CH_2), 61.3 (CH_2), 55.3 (CH_3), 26.9 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 19.3 (C).

HRMS EI (*m/z*) mass calc. for $C_{31}H_{38}O_3Si$ 486.2590 ($[M]^+$), found 486.2589.

(3a*R,5*E*,7*S**,7a*S**)-7-Benzyloxy-5-*tert*-butyldiphenylsilanyloxymethyl-4,4-dimethyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (343)**



A degassed solution of diene **338** (100 mg, 0.219 mmol) and maleic anhydride (43 mg, 0.44 mmol) in toluene (0.2 mL) was heated in a sealed tube at 150 °C for 7 h. The reaction mixture was diluted with dichloromethane and then concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 2:8) afforded cycloadduct **343** as a pale yellow oil (58 mg, 48%).

R_f = 0.30 (diethyl ether / petroleum ether, 1:1).

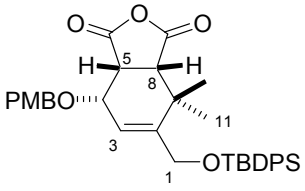
ν_{max} (neat) 2930, 2857, 1780, 1740, 1428, 1219, 1113, 1074 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H, Ar-*H*), 7.48-7.27 (m, 11H, Ar-*H*), 6.23 (ddd, *J* = 1.6, 1.6, 5.8 Hz, 1H, H-3), 4.60 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.53 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.46 (dd, *J* = 5.8, 5.8 Hz, 1H, H-4), 4.30 (d, *J* = 1.6 Hz, 2H, H-1), 3.44 (dd, *J* = 5.8, 10.9 Hz, 1H, H-5), 3.07 (d, *J* = 10.9 Hz, 1H, H-8), 1.37 (s, 3H, H-10), 1.22 (s, 3H, H-11), 1.11 (s, 9H, SiC{C*H*$_3$}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 169.8 (C), 150.8 (C), 137.3 (C), 135.4 (CH), 135.4 (CH), 133.1 (C), 132.9 (C), 130.0 (CH), 129.9 (CH), 128.4 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 119.1 (CH), 70.7 (CH_2), 66.8 (CH), 62.9 (CH_2), 49.9 (CH), 46.2 (CH), 35.0 (C), 28.1 (CH_3), 26.8 (CH_3), 25.4 (CH_3), 19.2 (C).

HRMS FAB (*m/z*) mass calc. for $C_{34}H_{38}O_5SiNa$ 577.2386 ($[M+Na]^+$), found 577.2395.

(3a*R, 5E, 7*S**, 7a*S**)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-7-(4-methoxybenzyloxy)-4,4-dimethyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (344)**



A degassed solution of diene **342** (200 mg, 0.411 mmol) and maleic anhydride (81 mg, 0.83 mmol) in toluene (0.3 mL) was heated in a sealed tube at 150 °C for 4 h. The reaction mixture was diluted with dichloromethane and then concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether / petroleum ether, 3:7) afforded cycloadduct **344** as a white solid (154 mg, 64%).

R_f = 0.39 (diethyl ether / petroleum ether, 1:1).

m.p. 126-129 °C.

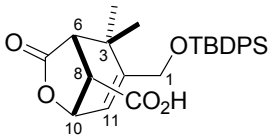
ν_{max} (KBr) 2930,1772, 1612, 1514, 1248, 1111, 1072, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H, Ar-*H*), 7.48-7.36 (m, 6H, Ar-*H*), 7.20 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.20 (ddd, *J* = 1.6, 1.6, 5.8 Hz, 1H, H-3), 4.52 (d, *J* = 11.5 Hz, 1H, C*H*HAr), 4.44 (d, *J* = 11.5 Hz, 1H, CH*H*Ar), 4.41 (dd, *J* = 5.8, 5.8 Hz, 1H, H-4), 4.28 (d, *J* = 1.6 Hz, 2H, H-1), 3.80 (s, 3H, OCH_3), 3.40 (dd, *J* = 5.8, 10.8 Hz, 1H, H-5), 3.04 (d, *J* = 10.8 Hz, 1H, H-8), 1.35 (s, 3H, H-10), 1.20 (s, 3H, H-11), 1.09 (s, 9H, SiC{CH_3}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 169.8 (C), 159.2 (C), 150.7 (C), 135.4 (CH), 135.4 (CH), 133.1 (C), 132.9 (C), 130.0 (CH), 129.9 (CH), 129.3 (C), 129.3 (CH), 127.8 (CH), 127.8 (CH), 119.3 (CH), 113.8 (CH), 70.3 (CH_2), 66.4 (CH), 62.9 (CH_2), 55.2 (CH_3), 50.0 (CH), 46.2 (CH), 35.0 (C), 28.1 (CH_3), 26.8 (CH_3), 25.4 (CH_3), 19.2 (C).

HRMS FAB (*m/z*) mass calc. for $C_{35}H_{41}O_6Si$ 585.2672 ($[M+H]^+$), found 585.2675.

(1*S,3*E*,5*R**,8*R**)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethyl-7-oxo-6-oxa-bicyclo[3.2.1]oct-3-ene-8-carboxylic acid (347)**



Trifluoroaetic acid (32 μL, 0.4 mmol) was added slowly to a solution of anhydride **344** (50 mg, 80 μmol) in dichloromethane (3 mL) at 0 °C. After being stirred for 30 min at 0 °C

and 1 h at room temperature, trifluroacetic acid (40 μL, 0.54 mmol) was added, the reaction mixture turned pink and was stirred overnight at room temperature. Another portion of trifluoroacetic acid was added (50 μL, 0.67 mmol), and after a further 4 h, the reaction mixture was poured into a saturated solution of sodium hydrogen carbonate (6 mL). The mixture was extracted with dichloromethane (3 × 6 mL) and the combined organic extracts were washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure. Purification by flash column chromatography (dichloromethane / methanol, 95:5) afforded carboxylic acid **347** as a pale yellow foam (29 mg, 73%).

R_f = 0.11 (diethyl ether / petroleum ether, 1:1).

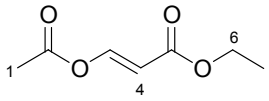
ν_{max} (neat) 3525, 3071, 3015, 2961, 2931, 2858, 1782, 1730, 1428, 1218, 1114, 1074 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H, Ar-*H*), 7.47-7.37 (m, 6H, Ar-*H*), 6.44 (ddd, *J* = 1.8, 1.8, 6.0 Hz, 1H, H-11), 5.04 (d, *J* = 6.0 Hz, 1H, H-10), 4.19 (dd, *J* = 1.8, 15.3 Hz, 1H, H-1), 4.13 (dd, *J* = 1.8 15.3 Hz, 1H, H-1), 3.20 (s, 1H, H-6), 2.71 (d, *J* = 1.0 Hz, 1H, H-8), 1.12 (s, 3H, H-4), 1.10 (s, 3H, H-5), 1.06 (s, 9H, SiC{C*H*$_3$}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C), 174.9 (C), 149.3 (C), 135.5 (CH), 135.4 (CH), 133.0 (C), 132.7 (C), 130.0 (CH), 129.9 (CH), 127.8 (CH), 127.8 (CH), 120.7 (CH), 74.5 (CH), 61.4 (CH_2), 53.0 (CH), 49.0 (CH), 38.2 (C), 26.8 (CH_3), 26.6 (CH_3), 26.4 (CH_3), 19.2 (C).

HRMS FAB (*m/z*) mass calc. for $C_{27}H_{33}O_5Si$ 465.2097 ($[M+H]^+$), found 465.2095.

Ethyl (*E*)-3-acetyloxy-2-propenoate (353)[156a,202]



In a 1L–three-necked flask equipped with reflux condenser, and an addition funnel, was added dry diethyl ether (200 mL) and sodium pieces (11.5 g, 500 mmol). A mixture of ethyl acetate (49 mL, 0.50 mmol) and ethyl formate (40 mL, 0.50 mmol) was added dropwise over a period of 2 h; a copious amount of hydrogen gas was given off and a pale yellow precipitate was formed in the reaction. The reaction mixture was allowed to stir for an additional 3 h. The product was collected by vacuum filtration and washed several times with diethyl ether. Vacuum drying gave a light brown powdery product **354** (32 g, 46% yield). Utilizing the same set-up described above, the product **354** (32 g, 232 mmol) was added to dry diethyl ether (450 mL) and cooled to 0 °C, and acetyl chloride (15 mL, 237 mmol) was added dropwise. The reaction was stirred at room temperature overnight. Water

(250 mL) was added, the mixture neutralized with sodium hydrogen carbonate, and extracted with diethyl ether (3 × 300 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated *in vacuo* to give a mixture of (*Z*)-**353** and (*E*)-**353** (2:1, 17.30 g). This mixture of (*Z*)-**353** and (*E*)-**353** (17.3 g, 109 mmol) was treated with thiophenol (5.6 mL, 55 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN), (2.7 g, 16 mmol) at 80 °C for 3 h. The reaction mixture was cooled to room temperature and taken up in ethyl acetate (150 mL) that was washed with a 0.01 N aqueous solution of sodium hydroxide (150 mL). The organic layer was dried over sodium sulfate and concentrated to leave a brown oil. Distillation under vacuum (65 °C, 7 mbar) afforded pure (*E*)-**353** (13.4 g, 36% over two steps), slightly contaminated with an aromatic thiol product.

R_f = 0.54 (diethyl ether / petroleum ether, 4: 6).

ν_{max} (neat) 3093, 2984, 1782, 1720, 1659, 1371, 955 cm^{-1}.

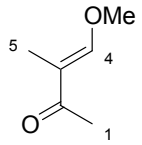
^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 12.5 Hz, 1H, H-3), 5.71 (d, *J* = 12.5 Hz, 1H, H-4), 4.21 (q, *J* = 7.1 Hz, 2H, H-6), 2.21 (s, 3H, H-1), 1.29 (t, *J* = 7.1 Hz, 3H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 166.1 (C), 149.3 (CH), 105.8 (CH), 60.4 (CH_2), 20.5 (CH_3), 14.2 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_7H_{11}O_4$ 159.0657 ($[M+H]^+$), found 159.0656.

The spectroscopic data is identical to that published by Herdewijn and Freeman.[156a,202]

(*E*)-4-methoxy-3-methylbut-3-en-2-one (355)[157c]



To a suspension of sodium hydride (60% dispersion in oil, 16.6 g, 416 mmol) in dry THF (500 mL) and methyl formate (51.3 mL, 832 mmol) under argon, was added dropwise butan-2-one (24.8 mL, 277 mmol). When half of it was added, the reaction mixture was initiated by heating. A copious amount of hydrogen gas was given off and a pale yellow precipitate was formed in the reaction. The reaction mixture was allowed to stir for an additional 1 h. The product was collected by vacuum filtration. Vacuum drying gave a light yellow powdery product (31.8 g). To sodium enolate (31.8 g, 260 mmol) in DMF (200 mL) was added dropwise dimethylsulfate (52.5 mL, 554 mmol). When half of it was added, the reaction mixture was cooled to 0 °C. After complete addition the ice-bath was removed and the reaction solution was allowed to stir for an additional 2 h. The reaction mixture was quenched at 0 °C by the addition of a 1 M aqueous solution of potassium

carbonate (500 mL) and methanol (500 mL) and the mixture was stirred at room temperature for 5 h. The mixture was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether / diethyl ether, 1:1 to 3:7) gave butenone **355** as a colourless oil (16.85 g, 53 % over two steps).

R_f = 0.19 (diethyl ether / petroleum ether, 1:1).

ν_{max} (neat) 2942, 2853, 1640, 1457 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (q, *J* = 1.2 Hz, 1H, H-4), 3.86 (s, 3H, OCH_3), 2.20 (s, 3H, H-1) 1.71 (d, *J* = 1.2 Hz, 3H, H-5).

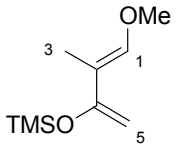
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4 (C), 160.2 (CH), 117.7(C), 61.3 (CH_3), 25.3 (CH_3), 8.2 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_6H_{11}O_2$ 115.0759 ($[M+H]^+$), found 115.0755.

CHN calc. for $C_6H_{10}O_2$: C 63.14; H 8.83. found C 63.14; H 8.95.

The spectroscopic data is identical to that published by Clive.[157c]

(*E*)-1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene (352)[157c,157e]



LDA freshly prepared (10.4 mL, 10.4 mmol, 1 M in THF) was added dropwise to a solution of butenone **355** (1.08 g, 9.4 mmol) in THF at –78 °C. The solution was stirred for 30 min and then TMSCl (1.45 mL, 11.4 mmol) was added dropwise. After a further 10 min, the cooling bath was removed. The reaction mixture was allowed to stir at room temperature for 1 h and then diluted with diethyl ether (25 mL), filtered through Florisil, and concentrated. Distillation under high vacuum (40 °C, 4 mbar) afforded pure **352** (1.31 g, 87%).

R_f = 0.83 (diethyl ether / petroleum ether, 1:1).

ν_{max} (neat) 2958, 2839, 1656, 1591 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H, H-1), 4.24 (d, *J* = 1.2 Hz, 1H, H-5), 4.13 (d, *J* = 1.2 Hz, 1H, H-5), 3.68 (s, 3H, OCH_3), 1.70 (s, 3H, H-3), 0.24 (s, 9H, OSi(CH_3)$_3$).

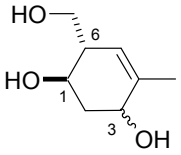
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (C), 147.1 (CH), 111.3 (C), 89.1 (CH_2), 60.1 (CH_3), 10.0 (CH_3), 0.1 (CH_3).

HRMS CI (*m/z*) mass calc. for $C_9H_{19}O_2Si$ 187.1154 ($[M+H]^+$), found 187.1158.

CHN calc. for $C_9H_{18}O_2Si$: C 58.02; H 9.74. found C 57.92; H 9.87.

The spectroscopic data is identical to that published by Clive[157c] and Danishefsky.[157e]

(1*R,6*S**)-6-Hydroxymethyl-4-methylcyclohex-4-ene-1,3-diol (351)**[159]



A mixture of diene **352** (6.94 g, 37.2 mmol) and dienophile **353** (3.69 g, 23.3 mmol) in the presence of a small amount of hydroquinone (25.0 mg, 0.02 mmol) was heated at 180 °C in a sealed tube for 1.5 h. The volatile materials were removed *in vacuo* at 80 °C to give a mixture of *endo* and *exo* adducts **356** (7.11 g, 89 % crude).

To a mixture of $LiAlH_4$ (7.05 g, 186 mmol) in dry THF (61 mL) at 0 °C under argon was added dropwise a solution of **356** (7.11 g, 20.6 mmol) in dry THF (24 mL). The reaction was allowed to warm to room temperature overnight. The viscous reaction mixture was diluted with dry THF (40 mL), then cooled in an ice bath and carefully treated with water (7.5 mL) for 15 min, a 15 % aqueous solution of sodium hydroxide (7.5 mL) for 10 min, and finally water (23 mL). After being stirred at room temperature for 1 h, the resulting mixture was filtered on Büchner and the slurry was washed with water (5 × 40 mL) and EtOAc (3 × 40 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 40 mL). The organic layer was extracted with water (3 × 40 mL). The combined aqueous layers were evaporated to dryness to give a brown gummy residue, which was purified by column chromatography (ethyl acetate / methanol, 98:2 to 9:1) to give **351** (2.62 g, 71 % over two steps) as a yellow syrup.

R_f = 0.12 (ethyl acetate / methanol, 98:2).

ν_{max} (neat) 3365, 2943, 2881, 1655, 1451, 1360 cm^{-1}.

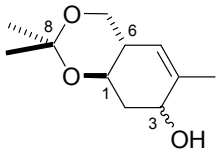
1H NMR (400 MHz, DMSO-*d*6) δ 5.25 (d, *J* = 1.6 Hz, 1H, H-5), 4.65 (d, *J* = 6.6 Hz, 1H, O*H*-3), 4.61 (d, *J* = 4.6 Hz, 1H, O*H*-1), 4.47 (m, 1H, O*H*-7), 3.91 (m, 1H, H-3), 3.57 (m, 1H, H-7), 3.36 (m, 1H, H-1), 3.26 (m, 1H, H-7), 2.06 (ddd, *J* = 3.3, 5.8, 11.7 Hz, 1H, H-2), 1.98 (m, 1H, H-6), 1.63 (s, 3H, CH_3), 1.45 (ddd, *J* = 10.0, 11.7,11.7 Hz, 1H, H-2).

13C NMR (100 MHz, DMSO-*d6*) δ 137.7 (C), 123.1 (CH), 67.9 (CH), 66.4 (CH), 62.4 (CH_2), 47.3 (CH), 42.0 (CH_2), 19.2 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_8H_{15}O_3$ ($[M+H]^+$) 159.1021, found 159.1024.

The spectroscopic data is identical to that published by Clark. [159]

(4a*S,8a*R**)-2,2,6-Trimethyl-4a,7,8,8a-tetrahydro-4*H*-benzo[1,3]-dioxin-7-ol (357)** [159]



To a mixture of triol **351** (12.3 g, 79.9 mmol) in DMF (180 mL) and 2,2-dimethoxypropane (95.0 mL, 767 mmol) was added *p*-toleuenesulfonic acid (304 mg, 1.59 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then diluted with DCM (800 mL). The mixture was washed with saturated aqueous sodium hydrogen carbonate (3 x 400 mL), and brine (500 mL), dried over sodium sulfate, and concentrated. Purification by flash column chromatography (petroleum ether / diethyl ether, 8:2 to 1:1) gave acetonide **357** as a colourless oil (12.47 g, 80 %).

R_f = 0.26 (diethyl ether / petroleum ether, 2:8).

ν_{max} (neat) 3420, 2945, 2872, 1453, 1384, 1270, 1197 cm^{-1}.

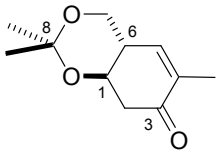
^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, *J* = 1.5 Hz, 1H, H-5), 4.34-4.26 (m, 1H, H-3), 3.80 (dd, *J* = 4.8, 11.1 Hz, 1H, H-7), 3.67 (ddd, *J* = 3.0, 9.7, 12.4 Hz, 1H, H-1), 3.57 (dd, *J* = 11.1, 11.7 Hz, 1H, H-7), 2.39-2.30 (m, 2H, H-2 and H-6), 1.77-1.76 (m, 3H, C*H*$_3$), 1.65 (ddd, *J* = 9.7, 11.9, 11.9 Hz, 1H, H-2), 1.48 (s, 3H, C{C*H*$_3$}$_2$), 1.43 (s, 3H, C{C*H*$_3$}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 120.8 (CH), 99.2 (C), 70.7 (CH), 69.8 (CH), 64.3 (CH_2), 40.5 (CH), 39.3 (CH_2), 29.8 (CH_3), 19.4 (CH_3), 19.0 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{11}H_{19}O_3$ ($[M+H]^+$) 199.1334, found 199.1337.

The spectroscopic data is identical to that published by Clark. [159]

(4a*S,8a*R**)-2,2,6-Trimethyl-4,4a,8,8a-tetrahydrobenzo[1,3]-dioxin-7-one (358)** [159]



A solution of allylic alcohol **357 (**12.4 g, 62.6 mmol) and activated manganese dioxide (81.0 g, 940 mmol) in DCM (300 mL) was stirred at room temperature overnight. The black slurry was filtered through Celite and concentrated under reduced pressure to give enone **358** (11.17 g, 91 %) as a white powder.

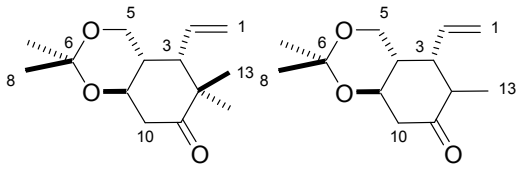
R_f = 0.47 (diethyl ether / petroleum ether, 1:1).

m.p. 94-96 °C.

ν_{max} (KBr) 2997, 2860, 1668, 1388, 1369, 1274, 1203, 1126 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29-6.27 (m, 1H, H-5), 4.02 (ddd, *J* = 4.3, 9.1, 12.4 Hz, 1H, H-1), 3.98 (dd, *J* = 4.9, 11.2 Hz, 1H, H-7), 3.74 (dd, *J* = 11.2, 11.7 Hz 1H, H-7), 2.77 (dd, *J* = 4.3, 16.3 Hz, 1H, H-2), 2.62-2.53 (m, 1H, H-6), 2.46 (dd, *J* = 12.4, 16.3 Hz, 1H, H-2), 1.79 (dd, *J* = 1.5 , 2.6 Hz, 3H, C*H*$_3$), 1.49 (s, 3H, C{C*H*$_3$}$_2$), 1.44 (s, 3H, C{C*H*$_3$}$_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (C), 140.3 (CH), 138.5 (C), 99.1 (CH), 70.1 (CH), 63.0 (CH_2), 44.8 (CH_2), 40.5 (CH), 29.6 (CH_3), 19.2 (CH_3), 15.6 (CH_3).
HRMS CI (*m*/*z*) calcd for $C_{11}H_{17}O_3$ ([M+H]$^+$) 197.1778, found 197.1777.
CHN calc. for $C_6H_{10}O_2$: C 67.32; H 8.22. found C 67.49; H 8.30.
The spectroscopic data is identical to that published by Clark. [159]

(4a*S,5*S**,8a*R**)-2,2,6,6-Tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-one (350)** [159] **and (4a*S**,5*S**,8a*R**)-2,2,6-trimethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-one (360)**



Method A from ketone **358**

To dimethyl sulfide-copper bromide complex (2.10 g, 10.2 mmol) in THF (26 mL) at –78 °C under argon was added dropwise over a period of 20 min a solution of vinylmagnesium bromide (20.4 mL of a 1 M solution in THF, 20.4 mmol, diluted in THF (6.4 mL)). The resulting heterogeneous brown-green solution was stirred at –78 °C for 20 min. A solution of chlorotrimethylsilane (3.33 mL, 25.5 mmol) and HMPA (1.77 mL, 10.2 mmol) in THF (10 mL) was added over a period of 4 min. This was immediately followed by a solution of enone **358** (1.0 g, 5.1 mmol) in THF (10 mL). The reaction was stirred at –78 °C, and the bath was allowed to warm slowly to room temperature. After being stirred for 16.5 h, the reaction mixture was diluted with petroleum ether (200 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure, the residue was triturated with petroleum ether. The supernatant was dried over anhydrous and concentrated under reduced pressure to give the silyl enol ether **359** (1.65 g).

A suspension of benzyltrimethylammonium fluoride (1.38 g, 8.15 mmol, pre-dried in *vaccuo* at 65 °C for 24 h) and activated 3Å molecular sieves (7.9 g) in THF (12 mL) was stirred under argon at room temperature for 24 h. To this mixture was added methyl iodide (3.19 mL, 51.0 mmol). After 15 min stirring, a solution of crude silyl enol ether **359** (1.65 g) in THF (10 mL) was added and the reaction mixture was stirred at room temperature for

15 h. The mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 9:1) gave ketone **350** as a white solid (739 mg, 60 % over 2 steps) and ketone **360** as a white solid (94 mg, 8%).

Method B from ketone **360**

To a solution of ketone **360** (200 mg, 0.893 mmol) in petroleum ether (0.7 mL), under argon, were added triethylamine (250 µL, 1.79 mmol), chlorotrimethylsilane (235 µL, 1.79 mmol) followed by a solution of sodium iodide (269 mg, 1.79 mmol) in acetonitrile (2 mL). The reaction mixture was stirred at room temperature for 3 h. The upper organic layer was transferred into a dry flask. The remaining mixture was extracted with petroleum ether, and the combined petroleum ether phases were concentrated to give silyl enol ether **359** (261 mg 98%). The silyl enol ether was transformed into the corresponding ketone **350** as previously described.

Tetramethyl ketone 350

R_f = 0.33 (diethyl ether / petroleum ether, 2:8).

m.p. 86-88 °C.

ν_{max} (KBr) 2985, 2969, 2939, 1708, 1468, 1386, 1275, 1199 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (ddd, *J* = 10.5, 10.5, 16.7 Hz, 1H, H-2), 5.12 (dd, *J* = 1.2, 10.5 Hz, 1H, H-1), 4.99 (dd, *J* = 1.2, 16.7 Hz, 1H, H-1), 4.02 (ddd, *J* = 5.5, 11.8, 11.8 Hz, 1H, H-9), 3.79 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.70 (dd, *J* = 4.8, 11.5 Hz, 1H, H-5), 2.76 (dd, *J* = 11.8, 13.7 Hz, 1H, H-10), 2.57 (dd, *J* = 5.5, 13.7 Hz, 1H, H-10), 2.46-2.38 (m, 1H, H-4), 2.19 (dd, *J* = 4.1, 10.5 Hz, 1H, H-3), 1.41 (s, 6H, H-7 and H-8), 1.34 (s, 3H, H-13), 0.95 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1 (C), 134.3 (CH), 118.9 (CH_2), 98.6 (C), 68.1 (CH), 63.5 (CH_2), 52.9 (CH), 48.6 (C), 44.3 (CH_2), 38.3 (CH), 29.7 (CH_3), 26.8 (CH_3), 22.9 (CH_3), 19.4 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{14}H_{22}O_3$ ($[M+H]^+$) 239.1647, found 239.1650.

CHN calc. for $C_{14}H_{22}O_3$: C 70.56; H 9.30. found 70.65; H 9.37.

The spectroscopic data is identical to that published by Clark. [159]

Trimethyl ketone 360

R_f = 0.19 (diethyl ether / petroleum ether, 2:8).

m.p. 79-82 °C.

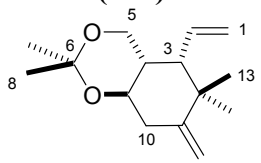
ν_{max} (KBr) 2994, 2976, 2911, 1709, 1389, 1276, 1194 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.29 (ddd, *J* = 10.3, 10.3, 16.5 Hz, 1H, H-2), 5.17 (dd, *J* = 1.5, 10.3 Hz, 1H, H-1), 5.06 (dd, *J* = 1.5, 16.5 Hz, 1H, H-1), 4.04 (ddd, *J* = 5.2, 11.4, 11.4 Hz, 1H, H-9), 3.85-3.73 (m, 2H, H-5), 2.74-2.62 (m, 2H, H-10 and H-12), 2.59-2.44 (m, 2H, H-3 and H-4), 2.21-2.12 (m, 1H, H-10), 1.42 (s, 3H, H-7), 1.41 (s, 3H, H-8), 0.94 (dd, *J* = 6.7 Hz, 3H, H-13).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6 (C), 132.8 (CH), 120.2 (CH_2), 98.6 (C), 68.0 (CH), 63.0 (CH_2), 48.6 (CH), 48.0 (CH_2), 47.2 (CH), 43.5 (CH), 29.7 (CH_3), 19.3 (CH_3), 11.9 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{13}H_{21}O_3$ ($[M+H]^+$) 225.1491, found 225.1488.

(4a*S,5*S**,8a*R**)-2,2,6,6-Tetramethyl-7-methylene-5-vinylhexahydrobenzo[1,3]-dioxine (365)**



Methyltriphenylphosphonium bromide (450 mg, 1.26 mmol) was added to a suspension of potassium *tert*-butoxide (141 mg, 1.26 mmol) in dry toluene (15 mL) under argon, the yellow solution was stirred under reflux for 1 h. A solution of ketone **350** (100 mg, 0.420 mmol) in dry toluene (15 mL) was added at room temperature. After 30 min, acetone (6 mL) was added to quench the reaction mixture, then water (30 mL) was added, and the reaction mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure, the residue was triturated with petroleum ether. Purification by flash column chromatography (petroleum ether / diethyl ether, 95:5) gave alkene **365** as a pale yellow oil (70 mg, 70%).

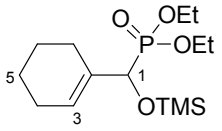
R_f = 0.71 (diethyl ether / petroleum ether, 2:8).

ν_{max} (neat) 2990, 2876, 1639, 1456, 1382 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (ddd, *J* = 10.4, 10.4, 17.0 Hz, 1H, H-2), 5.03 (dd, *J* = 2.1, 10.4 Hz, 1H, H-1), 4.92 (dd, *J* = 2.1, 17.0 Hz, 1H, H-1), 4.88 (dd, *J* = 1.4, 1.4 Hz, 1H, H-15), 4.75 (dd, *J* = 1.4, 1.4 Hz, 1H, H-15), 3.78 (ddd, *J* = 5.9, 11.2, 11.2 Hz, 1H, H-9), 3.72 (dd, *J* = 11.2, 11.3 Hz, 1H, H-5), 3.55 (dd, *J* = 4.7, 11.3 Hz, 1H, H-5), 2.47-2.36 (m,

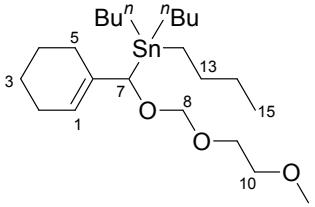
2H, H-10), 2.16 (dddd, J = 4.7, 4.7, 11.2, 11.2 Hz, 1H, H-4), 1.91 (dd, J = 4.7, 10.4 Hz, 1H, H-3), 1.41 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.22 (s, 3H, H-13), 0.97 (s, 3H, H-14).
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 136.1 (CH), 117.1 (CH_2), 110.7 (CH_2), 98.6 (C), 69.7 (CH), 64.0 (CH_2), 53.2 (CH), 39.3 (C), 38.9 (CH_2), 38.6 (CH), 29.9 (CH_3), 28.1 (CH_3), 26.5 (CH_3), 19.5 (CH_3).
HRMS CI (m/z) calcd for $C_{15}H_{25}O_2$ ($[M+H]^+$) 237.1855, found 237.1853.

(Cyclohex-2-enyltrimethylsilanyloxymethyl)-phosphonic acid diethyl ester (368)



To a mixture of 1-cyclohexene-1-carboxaldehyde (500 mg, 4.54 mmol) and triethylphosphite (0.8 mL, 5 mmol) in a sealed tube was added chlorotrimethylsilane (0.6 mL, 5 mmol). The reaction mixture was heated at 120 °C for 5 h. Then the reaction mixture was concentrated under reduced pressure, and dried under high vacuum to give **368** (1.6 g, quantitative) as a brown oil.
ν_{max} (neat) 3293, 2981, 2931, 2858, 1685, 1440, 1392, 1252, 1164, 1033 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.76 (m, 1H, H-3), 4.28 (d, J_{PH} = 14.0 Hz, 1H, H-1), 4.20-4.07 (m, 4H, OCH_2CH_3), 2.26-2.18 (m, 1H, CH_2), 2.15-2.03 (m, 3H, CH_2), 1.71-1.51 (m, 4H, CH_2), 1.30 (dt, J_{PH} = 3.8 Hz, J = 7.0 Hz, 6H, OCH_2CH_3), 0.13 (s, 9H, $SiCH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4 (C), 126.6 (d, CH), 74.2 (d, CH), 62.9 (d, CH_2), 62.4 (d, CH_2), 25.3 (CH_2), 25.0 (d, CH_2), 22.6 (CH_2), 22.4 (CH_2), 16.6 (d, CH_3), 16.5 (d, CH_3), -0.11 (CH_3).
^{31}P NMR (161 MHz, $CDCl_3$) δ 21.4.

Tributyl-[cylohex-2-enyl-(2-methoxyethoxymethoxy)-methyl]stannane (372)[203]



To a magnetically stirred solution of diisopropylamine (1.1 mL, 7.7 mmol) in dry THF (3.5 mL) under an argon atmosphere at 0 °C, ^{n}BuLi (2.5 M hexane solution, 2.9 mL, 7.3 mmol) was added dropwise. The solution was stirred for 30 min at 0 °C and then at room

temperature for 30 min, $^{n}Bu_3SnH$ (1.7 mL, 6.4 mmol) was added, and stirring was continued for 40 min at 0 °C. The reaction mixture was chilled to –78 °C before a solution of 1-cyclohexene-1-carboxaldehyde (0.50 mL, 4.4 mmol) in dry THF (1 mL) was added dropwise. The mixture was stirred at –78 °C for 45 min and then quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and then concentrated under reduced pressure. This residue was dissolved in dichloromethane (8 mL) and cooled to 0 °C under an argon atmosphere. $^{i}Pr_2NEt$ (3.2 mL, 18 mmol) was added, followed by MEMCl (1 mL, 9 mmol) and few crystals of DMAP. The solution was stirred overnight at room temperature and then quenched with saturated aqueous solution of ammonium chloride (25 mL) at 0 °C. The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts were dried with magnesium sulfate and then concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether / triethylamine, 90:10:1) gave the α-alkoxyorgano stannane **372** (1.18 g, 53%) as a colourless oil.

R_f = 0.47 (diethyl ether / petroleum ether, 1:9).

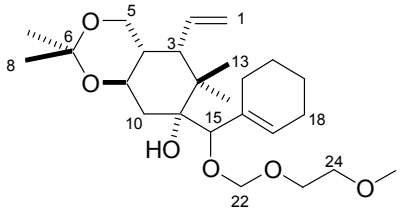
ν_{max} (neat) 2925, 1458, 1015 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (m, 1H, H-1), 4.65 (d, *J* = 6.4 Hz, 1H, H-8), 4.56 (d, *J* = 6.4 Hz, 1H, H-8), 4.47 (s, 1H, H-7), 3.75 (ddd, *J* = 2.8, 5.1, 9.5 Hz, 1H, H-10), 3.60-3.53 (m, 3H, H-9 and H-10), 3.39 (s, 3H, H-11), 2.08-1.96 (m, 2H, H-2), 1.94-1.85 (m, 1H, C*H*$_2$), 1.83-1.73 (m, 1H, C*H*$_2$), 1.69-1.40 (m, 10H, H-13 and C*H*$_2$), 1.35-1.25 (m, 6H, H-14), 0.97-0.80 (m, 15H, H-12 and H-15).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 (C), 118.0 (CH), 93.9 (CH_2), 76.1 (CH), 71.8 (CH_2), 66.8 (CH_2), 59.0 (CH_3), 29.1 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 13.7 (CH_3), 9.5 (CH_2).

The spectroscopic data is identical to that published by Pancrazi.[203]

(4a*S,5*S**,7*R**,8a*R**)-7-Cyclohex-1-enyl-(2-methoxyethoxymethoxy)-methyl]-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (373a)**



To a magnetically stirred solution of the acetal **372** (244 mg, 0.499 mmol) in anhydrous THF (0.8 mL) cooled at –78 °C under argon, ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added and the mixture was stirred at this temperature for 5 min before a solution of ketone **350** (100 mg, 0.420 mmol) in dry THF (0.5 mL) was added dropwise. After stirring 2 h at –78 °C, a previously prepared solution of organostannane (244 mg, 0.499 mmol) in anhydrous THF (0.8 mL) with ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added dropwise. After 30 min, the reaction mixture was quenched with a saturated solution of ammonium chloride (1 mL), and then allowed to warm to room temperature. It was diluted with ethyl acetate (6 mL), and water (6 mL). The aqueous layer was extracted with ethyl acetate (2 × 6 mL), and the combined organic extracts were washed with brine (10 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 7:3 to 1:1) gave product **373a** as a single diastereoisomer (51 mg, 28%) as a colourless viscous oil and an inseparable mixture of the three other diastereoisomers (54 mg, 29%) as a colourless viscous oil.

R_f = 0.16 (diethyl ether / petroleum ether, 3:7).

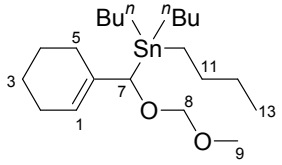
ν_{max} (neat) 3545, 2931, 1666, 1451, 1381, 1270 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (ddd, *J* = 10.0, 10.0, 17.0 Hz, 1H, H-2), 6.24 (bs, 1H, H-17), 4.90 (dd, *J* = 2.4, 10.0 Hz, 1H, H-1), 4.85 (s, 2H, H-22), 4.80 (dd, *J* = 2.4, 17.0 Hz, 1H, H-1), 4.23 (ddd, *J* = 4.8, 10.9, 10.9 Hz, 1H, H-9), 3.76-3.67 (m, 3H, H-5 and H-23), 3.55-3.52 (m, 2H, H-24), 3.46 (dd, *J* = 4.7, 11.6 Hz, 1H, H-5), 3.38 (s, 3H, H-25), 3.27-3.23 (m, 1H, H-15), 2.28 (s, 1H, O*H*), 2.06-1.93 (m, 5H, H-4, H-10 and H-18), 1.92-1.86 (m, 1H, CH_2), 1.82 (dd, *J* = 4.7, 10.0 Hz, 1H, H-3), 1.79-1.73 (m, 1H, CH_2), 1.72-1.65 (m, 1H, CH_2), 1.55-1.46 (m, 2H, CH_2), 1.44 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.29-1.20 (m, 1H, CH_2), 1.17 (s, 3H, H-13), 0.92 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (CH), 139.3 (CH), 118.6 (C), 116.0 (CH_2), 98.5 (C), 95.4 (CH_2), 78.8 (C), 71.5 (CH_2), 67.6 (CH_2), 67.1 (CH), 64.1 (CH_2), 59.0 (CH_3), 56.9 (CH), 42.8 (C), 39.4 (CH_2), 38.1 (CH), 38.0 (CH), 30.0 (CH_3), 28.7 (CH_2), 28.1(CH_2), 27.2 (CH_2), 27.1 (CH_3), 23.4 (CH_2), 23.0 (CH_3), 19.7 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{25}H_{43}O_6$ ($[M+H]^+$) 439.3060, found 439.3057.

Tributyl-(cylohex-2-enylmethoxymethoxymethyl)-stannane (374)



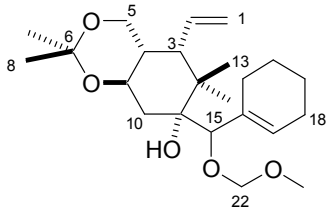
To a magnetically stirred solution of diisopropylamine (1.1 mL, 7.7 mmol) in dry THF (3.3 mL) under an argon atmosphere at –78 °C, ^{n}BuLi (2.5 M hexane solution, 2.9 mL, 7.3 mmol) was added dropwise. The solution was stirred for 30 min at –78 °C and then at room temperature for 30 min. Tributyltin hydride (1.7 mL, 6.4 mmol) was added at 0 °C, and stirring was continued for 40 min. The reaction mixture was chilled to –78 °C before a solution of 1-cyclohexene-1-carboxaldehyde (500 mg, 4.54 mmol) in dry THF (1 mL) was added dropwise. The mixture was stirred at –78 °C for 45 min and the reaction mixture was then quenched with saturated aqueous solution of ammonium chloride (20 mL). The mixture was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were dried with magnesium sulfate, and concentrated under reduced pressure. The residual material was dissolved in dichloromethane (8 mL) and cooled to 0 °C under an argon atmosphere. ^{i}Pr$_2$NEt (3.2 mL, 18 mmol) was added, followed by MOMBr (0.74 mL, 9.1 mmol) and few crystals of DMAP. The solution was stirred overnight at room temperature. The reaction was quenched with saturated aqueous solution of ammonium chloride (25 mL) at 0 °C, and the mixture was extracted with diethyl ether (3 × 25 mL). The organic phase was dried with magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 9:1) gave the α-alkoxyorgano stannane **374** (1.05 g, 52%) as a colourless oil.

ν_{max} (neat) 2925, 1463, 1016 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (m, 1H, H-1), 4.58 (d, *J* = 6.3 Hz, 1H, H-8), 4.49-4.40 (m, 2H, H-7 and H-8), 3.33 (s, 3H, H-9), 2.08-1.99 (m, 2H, H-2), 1.96-1.86 (m, 1H, C*H*$_2$), 1.83-1.72 (m, 1H, C*H*$_2$), 1.69-1.41 (m, 10H, C*H*$_2$ and H-11), 1.35-1.25 (m, 6H, H-12), 0.98-0.82 (m, 15H, H-10 and H-13).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (C), 118.1 (CH), 94.9 (CH_2), 76.1 (CH), 55.4 (CH_3), 29.1 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 25.0 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 13.7 (CH_3), 9.5 (CH_2).

(4a*S,5*S**,7*R**,8a*R**)-7-(Cyclohex-1-enylmethoxymethoxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (375a)**



To a magnetically stirred solution of the acetal **374** (222 mg, 0.499 mmol) in anhydrous THF (0.8 mL) cooled at –78 °C under argon, ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added and the mixture was stirred at this temperature for 5 min before a solution of ketone **350** (100 mg, 0.42 mmol) in dry THF (0.5 mL) was added dropwise. After stirring for 2 h at –78 °C, the previously prepared solution of organostannane (222 mg, 0.499 mmol) in anhydrous THF (0.8 mL) with ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added dropwise. After 30 min, the reaction was quenched with a saturated solution of ammonium chloride (1 mL), and the mixture was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (6 mL), and water (6 mL) and the aqueous layer was extracted with ethyl acetate (2 × 6 mL). The combined organic extracts were washed with brine (10 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 7:3) gave product **375a** as a single diastereoisomer (61 mg, 37%) as a pale yellow oil and an inseparable mixture of the three other diastereoisomers (65 mg, 39%) as a pale yellow oil.

R_f = 0.68 (diethyl ether / petroleum ether, 1:1).

ν_{max} (neat) 3548, 2953, 1666, 1448, 1381, 1269 cm^{-1}.

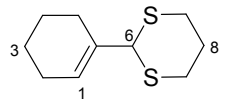
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (ddd, *J* = 10.3, 10.3, 17.0 Hz, 1H, H-2), 6.22 (d, *J* = 1.2 Hz, 1H, H-17), 4.92 (dd, *J* = 2.4, 10.3 Hz, 1H, H-1), 4.81 (dd, *J* = 2.4, 17.0 Hz, 1H, H-1), 4.78-4.74 (m, 2H, H-22), 4.24 (ddd, *J* = 4.8, 10.9, 10.9 Hz, 1H, H-9), 3.75 (dd, *J* = 11.6, 11.6 Hz, 1H, H-5), 3.48 (dd, *J* = 4.7, 11.6 Hz, 1H, H-5), 3.38 (s, 3H, H-23), 3.30-3.26 (m, 1H, H-15), 2.32 (s, 1H, O*H*), 2.10-1.95 (m, 5H, H-4, H-10 and H-18), 1.94-1.87 (m, 1H, CH_2), 1.84 (dd, *J* = 4.7, 10.3 Hz, 1H, H-3), 1.80-1.74 (m, 1H, CH_2), 1.73-1.64 (m, 1H, CH_2), 1.55-1.48 (m, 2H, CH_2), 1.46 (s, 3H, H-7), 1.41 (s, 3H, H-8), 1.30-1.25 (m, 1H, CH_2), 1.19 (s, 3H, H-13), 0.94 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (CH), 139.3 (CH), 118.7 (C), 116.1 (CH_2), 98.6 (C), 96.3 (CH_2), 78.9 (C), 67.1 (CH), 64.1 (CH_2), 56.9 (CH), 55.9 (CH_3), 42.9 (C), 39.4 (CH_2),

38.2 (CH), 38.0 (CH), 30.1 (CH_3), 28.8 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 27.1 (CH_3), 23.4 (CH_2), 23.0 (CH_3), 19.7 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{23}H_{39}O_5$ ($[M+H]^+$) 395.2797, found 395.2799.

2-Cyclohex-1-enyl-[1,3]-dithiane (379)



To a solution of 1-cyclohexene-1-carboxaldehyde (500 mg, 4.54 mmol) in chloroform (17 mL) was added 1,3-propanedithiol (0.48 mL, 4.8 mmol) under an atmosphere of argon. At 0 °C, boron trifluoride etherate (0.23 mL, 1.8 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and warmed to room temperature for 30 min. The stirred solution was treated with chloroform (5 mL) and washed with a 10% solution of aqueous sodium hydroxide (10 mL) at 0 °C and with water (30 mL). The combined aqueous layers were extracted with chloroform (2 × 50 mL), and the combined organic solutions were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give cyclohexenyl-1,3-dithiane **379** (905 mg, 99%) as a yellow oil.

R_f = 0.63 (diethyl ether / petroleum ether, 4:6)

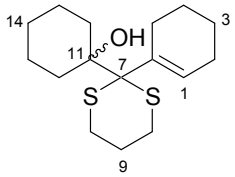
ν_{max} (neat) 2929, 2832, 1722, 1677, 1433, 1274 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.93-5.94 (m, 1H, H-1), 4.17 (s, 1H, H-6), 2.99-2.84 (m, 4H, H-7 and H-9), 2.18-2.04 (m, 5H, H-2, H-9 and C*H*$_2$), 1.89-1.82 (m, 1H, H-9), 1.67-1.63 (m, 2H, C*H*$_2$), 1.59-1.55 (m, 2H, C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (C), 126.6 (CH), 53.8 (CH), 31.7 (CH_2), 27.0 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 22.0 (CH_2).

HRMS EI (*m*/*z*) calcd for $C_{10}H_{16}S_2$ ($[M]^+$) 200.0693, found 200.0696.

1-(2-Cyclohex-1-enyl-[1,3]-dithian-2-yl)-cyclohexanol (380)



To a solution of cyclohexenyl-1,3-dithiane **379** (200 mg, 1.00 mmol) in THF (1 mL) at –78 °C was added ^{n}BuLi (1.6 M hexane solution, 1.25 mL, 2.00 mmol). The reaction mixture was allowed to warm to –20 °C over 2.5 h, then cyclohexanone (65 mg, 0.67 mmol) was

added at –78 °C and the reaction mixture allowed to warm to –20 °C over 2 h. The reaction was then quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether / diethyl ether, 8:2) gave product **380** (92 mg, 46%) as a white crystals.

R_f = 0.70 (diethyl ether / petroleum ether, 1:1).

m.p. 129-130 °C.

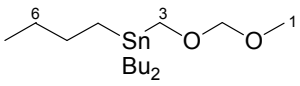
ν_{max} (KBr) 3464, 2934, 2850, 1445, 1372, 1257 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.43-6.42 (m, 1H, H-1), 2.76-2.64 (m, 4H, H-8 and H-10), 2.36-2.34 (m, 2H, H-5), 2.25-2.23 (m, 2H, H-2), 2.07 (s, 1H, O*H*), 1.97-1.92 (m, 1H, H-9), 1.86-1.79 (m, 3H, H-9 and CH_2), 1.63-1.58 (m, 11H, CH_2), 1.10-1.05 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8 (C), 132.8 (CH), 77.3 (C), 73.1 (C), 33.0 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 23.8 (CH_2), 22.0 (CH_2), 21.9 (CH_2).

HRMS CI (*m*/*z*) calcd for $C_{16}H_{27}OS_2$ ($[M+H]^+$) 299.1503, found 299.1499.

Tributylmethoxymethoxymethylstannane (383)[169a]



To a magnetically stirred solution of diisopropylamine (1.14 mL, 8.14 mmol) in dry THF (10 mL) under an argon atmosphere at 0 °C, *n*BuLi (1.4 M hexane solution, 5.3 mL, 7.4 mmol) was added dropwise. After 5 min, tributyltin hydride (2.0 mL, 7.4 mmol) was added at 0 °C, and stirring was continued for 15 min. The reaction mixture was chilled to –78 °C before a solution of paraformaldehyde (222 mg, 7.39 mmol) in dry THF (21 mL) was added. The mixture was stirred at room temperature for 1.5 h and then diluted with petroleum ether (30 mL) and water (30 mL). The aqueous phase was extracted with petroleum ether (15 mL). The combined organic layers were washed with brine (30 mL), dried with sodium sulfate, and concentrated under reduced pressure to afford approximately 2.5 g of (tributylstannyl)methanol as a colourless oil, which was used in the next step without further purification.

This material was dissolved in dichloromethane (16.5 mL) under an argon atmosphere, with dimethoxymethane (24.3 mL, 275 mmol), 4Å molecular sieves (4.5 g). Boron trifluoride etherate (1.2 mL, 9.2 mmol) was then added dropwise. The resulting solution

was stirred overnight at room temperature, then filtered through celite and washed with dichloromethane. The combined filtrates were washed with saturated sodium bicarbonate solution (2 × 25 mL). The combined aqueous layers were extracted with dichloromethane (25 mL), and the combined organic phases were then washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. Purification by flash chromatography on alumina with as eluant (petroleum ether / diethyl ether, 9:1) gave product **383** (707 mg, 26%) as a colourless oil.

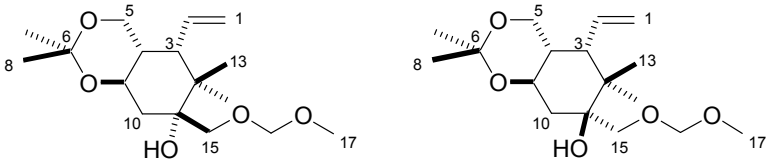
ν_{max} (neat) 2956, 2925, 2872, 1464, 1146, 1094, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (s, 2H, H-2), 3.73 (s, 2H, H-3), 3.33 (s, 3H, H-1), 1.55-1.47 (m, 6H, H-5), 1.35-1.25 (m, 6H, H-6), 1.00-0.82 (m, 15H, H-4 and H-7).

^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4 (CH_2), 57.6 (CH_2), 54.9 (CH_3), 29.1 (CH_2), 27.3 (CH_2), 13.7 (CH_3), 8.9 (CH_2).

The spectroscopic data is identical to that published by Danheiser. [169a]

(4a*S,5*S**,7*R**,8a*R**)-7-Methoxymethoxymethyl-2,2,6,6-tetramethyl-5-vinylhexahydro-benzo[1,3]-dioxin-7-ol (384a) and (4a*S**,5*S**,7*S**,8a*R**)-7-methoxymethoxymethyl-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (384b)**



To a solution of the acetal **383** (182 mg, 0.50 mmol) in anhydrous THF (0.7 mL) cooled at -78 °C under argon, was added dropwise ^{n}BuLi (1.6 M hexane solution, 0.30 mL, 0.49 mmol). After 5 min, ketone (100 mg, 0.420 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred at this temperature for 30 min, then quenched with a saturated solution of ammonium chloride (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 4 mL), and the combined organic extracts were washed with brine (2 mL), dried on anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography with as eluant (petroleum ether / diethyl ether, 7:3) gave the major diastereoismer **384a** (32 mg, 24%) as a colourless oil, the minor diastereoisomer **384b** (21 mg, 16%), and an inseparable mixture of diastereoisomers (28 mg, 21%).

Major diastereoisomer 384a

R_f = 0.41 (diethyl ether / petroleum ether, 1:1).

ν_{max} (KBr) 3483, 2990, 2958, 2882, 1630, 1384 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (ddd, *J* = 10.4, 10.4, 17.0 Hz, 1H, H-2), 4.97 (dd, *J* = 2.3, 10.4 Hz, 1H, H-1), 4.84 (dd, *J* = 2.3, 17.0 Hz, 1H, H-1), 4.63 (s, 2H, H-16), 4.20 (ddd, *J* = 4.6, 11.3, 11.3 Hz, 1H, H-9), 3.75 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.51-3.46 (m, 2H, H-5 and H-15), 3.37 (d, *J* = 9.3 Hz, 1H, H-15), 3.34 (s, 3H, H-17), 2.57 (s, 1H, O*H*), 2.05-1.95 (m, 2H, H-4 and H-10), 1.84 (dd, *J* = 4.6, 10.4 Hz, 1H, H-3), 1.62 (dd, *J* = 11.3, 13.1 Hz, 1H, H-10), 1.44 (s, 3H, H-7), 1.38 (s, 3H, H-8), 1.06 (s, 3H, H-13), 0.92 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (CH), 116.6 (CH_2), 98.5 (C), 96.9 (CH_2), 76.4 (C), 72.3 (CH_2), 66.3 (CH), 64.0 (CH_2), 56.0 (CH), 55.4 (CH_3), 38.9 (C), 38.2 (CH), 38.0 (CH_2), 29.9 (CH_3), 25.9 (CH_3), 23.0 (CH_3), 19.6 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{17}H_{31}O_5$ ($[M+H]^+$) 315.2171, found 315.2173.

Minor diastereoisomer 384b

R_f = 0.24 (diethyl ether / petroleum ether, 1:1).

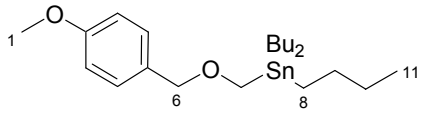
ν_{max} (KBr) 3487, 2948, 1702, 1632, 1460, 1383, 1269 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (ddd, *J* = 10.2, 10.2, 16.5 Hz, 1H, H-2), 5.09 (dd, *J* = 1.8, 10.2 Hz, 1H, H-1), 4.97 (dd, *J* = 1.8, 16.5 Hz, 1H, H-1), 4.68 (s, 1H, H-16), 4.67 (s, 1H, H-16), 3.81 (ddd, *J* = 4.3, 11.9, 11.9 Hz, 1H, H-9), 3.71-3.64 (m, 2H, H-5 and H-15), 3.51 (dd, *J* = 4.6, 11.7 Hz, 1H, H-5), 3.45 (dd, *J* = 1.3, 10.0 Hz, 1H, H-15), 3.39 (s, 3H, H-17), 2.64 (s, 1H, O*H*), 2.19 (dd, *J* = 4.3, 11.9 Hz, 1H, H-10), 2.16-2.03 (m, 2H, H-3 and H-4), 1.68 (ddd, *J* = 1.3, 11.9, 11.9 Hz, 1H, H-10), 1.43 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.23 (s, 3H, H-13), 0.86 (s, 3H, H-14).

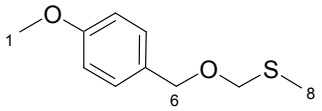
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (CH), 119.3 (CH_2), 98.4 (C), 96.9 (CH_2), 75.1 (C), 71.6 (CH_2), 66.9 (CH), 63.7 (CH_2), 55.6 (CH_3), 53.4 (CH), 40.1 (C), 37.9 (CH), 37.1 (CH_2), 29.9 (CH_3), 26.2 (CH_3), 22.1 (CH_3), 19.4 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{17}H_{31}O_5$ ($[M+H]^+$) 315.2171, found 315.2176.

Tributyl-(4-methoxybenzyloxymethyl)-stannane (385)[172,204,205]



p-Methoxybenzyl alcohol (2.00 g, 14.5 mmol) was added carefully dropwise to a mixture of sodium iodide (2.17 g, 14.5 mmol) and sodium hydride (60% dispersion in oil, 1.16 g, 29.0 mmol) in dry THF (16 mL) under argon at room temperature. When hydrogen evolution had ceased (~ 5 min), the solution was cooled to 0 °C, and choromethyl methylsufide (1.21 mL, 14.5 mmol) was added over 15 min. The reaction mixture was allowed to warm to room temperature overnight and water (40 mL) was then added carefully to the solution, followed by ethyl acetate (15 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were dried over magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 95:5) gave the product 1-methoxy-4-methylsulfanylmethoymetyl-benzene (1.94 g, 68%) as a colourless oil.



R_f = 0.58 (diethyl ether / petroleum ether, 4:6).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.89 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.66 (s, 2H, H-7), 4.55 (s, 2H, H-6), 3.81 (s, 3H, H-1), 2.18 (s, 3H, H-8).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C), 129.8 (CH), 129.5 (C), 113.9 (CH), 74.0 (CH_2), 69.0 (CH_2), 55.3 (CH_3), 13.9 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{10}H_{14}O_2S$ ($[M+H]^+$) 199.0793, found 199.0791.

The spectroscopic data is identical to that published by Gómez and Parry.[172,204]

To a solution of the above thioether (1.92 g, 9.68 mmol) in dichloromethane (16 mL) at –78 °C was added dropwise over 5 min, a solution of sulfuryl chloride (0.78 mL, 9.7 mmol) in dichloromethane (6 mL). The resulting orange solution was stirred for 30 min, after which time, the solvents were evaporated to give the crude chloromethylether (1.9 g, 100%). A solution of diisopropylamine (1.36 mL, 9.68 mmol) in THF (11.5 mL) was cooled to 0 °C, treated with ^{n}BuLi (2.5 M hexane solution, 3.90 mL, 9.76 mmol) and stirred for 15 min at 0 °C. Tributyltin hydride (2.17 mL, 8.07 mmol) was then added dropwise. The yellow solution was stirred for 15 min and a solution of the above crude

chloromethylether (1.9 g, 9.7 mmol) in THF (7.6 mL) was then added. The reaction mixture was allowed to warm to room temperature overnight, diluted with ethyl acetate (60 mL) and water (60 mL). The aqueous layer was extracted with ethyl acetate (30 mL) and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 98:2) gave the product **385** (2.34 g, 65%) as a colourless oil.

R_f = 0.50 (diethyl ether / petroleum ether, 6:94).

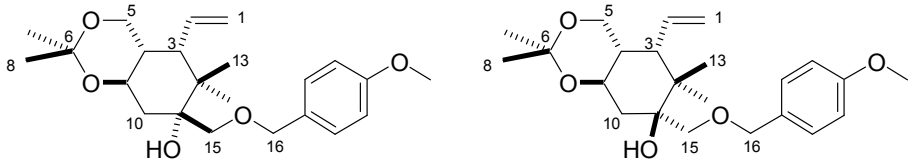
ν_{max} (neat) 2955, 2925, 2848, 1613, 1513, 1464, 1248 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 4.34 (s, 2H, H-6), 3.81 (s, 3H, H-1), 3.72 (s, 2H, H-6), 1.55-1.46 (m, 6H, H-9), 1.35-1.25 (m, 6H, H-10), 1.00-0.82 (m, 15H, H-8 and H-11).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4 (C), 131.0 (C), 129.1 (CH), 113.6 (CH), 76.8 (CH_2), 61.1 (CH_2), 55.2 (CH_3), 29.1 (CH_2), 27.3 (CH_2), 13.7 (CH_3), 9.0 (CH_2).

The spectroscopic data is identical to that published by Parry and Buchwald. [172,204]

(4a*S,5*S**,7*R**,8a*R**)-7-(4-Methoxybenzyloxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (386a) and (4a*S**,5*S**,7*S**,8a*R**)-7-(4-methoxybenzyloxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (386b)**



To a magnetically stirred solution of the acetal **385** (0.22 g, 0.50 mmol) in anhydrous THF (0.8 mL) cooled at –78 °C under argon, ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added and the mixture was stirred at this temperature for 5 min before a solution of ketone **350** (100 mg, 0.420 mmol) in dry THF (0.5 mL) was added dropwise. After stirring 2 h at –78 °C, a previously prepared solution of organostannane (0.22 g, 0.50 mmol) in anhydrous THF (0.8 mL) with ^{n}BuLi (2.5 M hexane solution, 0.20 mL, 0.49 mmol) was added dropwise. After 30 min, the reaction was quenched by the addition of a saturated solution of ammonium chloride (1 mL). The mixture was allowed to warm to room temperature and then diluted with ethyl acetate (6 mL) and water (6 mL). The aqueous layer was extracted with ethyl acetate (2 × 6 mL), and the combined organic extracts were washed with brine (10 mL), dried on anhydrous magnesium sulfate, and

concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 75:25 to 1:1) gave product **386a** (102 mg, 62%) as a colourless viscous oil and the product **386b** (22 mg, 13%) as a colourless viscous oil.

Major diastereoisomer 386a

R_f = 0.45 (diethyl ether / petroleum ether, 1:1).

ν_{max} (neat) 3546, 3069, 2941, 1613, 1586, 1514, 1464, 1382, 1248, 1198 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.27 (ddd, *J* = 10.3, 10.3, 17.0 Hz, 1H, H-2), 4.98 (dd, *J* = 2.3, 10.3 Hz, 1H, H-1), 4.84 (dd, *J* = 2.3, 17.0 Hz, 1H, H-1), 4.49 (d, *J* = 11.4 Hz, 1H, H-16), 4.43 (d, *J* = 11.4 Hz, 1H, H-16), 4.20 (ddd, *J* = 4.6, 11.3, 11.3 Hz, 1H, H-9), 3.81 (s, 3H, OC*H*$_3$), 3.76 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.51-3.46 (m, 2H, H-5 and H-15), 3.24 (d, *J* = 8.6 Hz, 1H, H-15), 2.64 (s, 1H, O*H*), 2.08 (dd, *J* = 4.6, 13.1 Hz, 1H, H-10), 2.00 (dddd, *J* = 4.6, 4.6, 11.3, 11.5 Hz, 1H, H-4), 1.84 (dd, *J* = 4.6, 10.3 Hz, 1H, H-3), 1.60 (dd, *J* = 11.3, 13.1 Hz, 1H, H-10), 1.45 (s, 3H, H-7), 1.39 (s, 3H, H-8), 1.03 (s, 3H, H-13), 0.92 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 138.6 (CH), 129.9 (C), 129.1 (CH), 116.5 (CH_2), 113.8 (CH), 98.5 (C), 76.6 (C), 74.0 (CH_2), 73.2 (CH_2), 66.4 (CH), 64.0 (CH_2), 56.0 (CH), 55.3 (CH_3), 38.9 (C), 38.3 (CH), 38.2 (CH_2), 30.0 (CH_3), 25.9 (CH_3), 23.1 (CH_3), 19.6 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{23}H_{35}O_5$ ($[M+H]^+$) 391.2484, found 391.2485.

Minor diastereoisomer 386b

R_f = 0.21 (diethyl ether / petroleum ether, 1:1).

ν_{max} (neat) 3528, 2935, 2876, 1612, 1586, 1514, 1461, 1382, 1301, 1249 cm^{-1}.

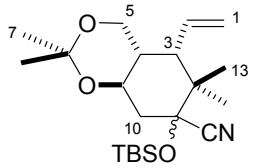
^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.89 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.46 (ddd, *J* = 10.4, 10.4, 16.5 Hz, 1H, H-2), 5.02 (dd, *J* = 1.8, 10.4 Hz, 1H, H-1), 4.93 (dd, *J* = 1.8, 16.5 Hz, 1H, H-1), 4.60 (d, *J* = 11.8 Hz, 1H, H-16), 4.42 (d, *J* = 11.8 Hz, 1H, H-16), 3.81 (s, 3H, OC*H*$_3$), 3.65-3.56 (m, 2H, H-5 and H-9), 3.47 (dd, *J* = 4.7, 11.7 Hz, 1H, H-5), 3.44 (d, *J* = 9.2 Hz, 1H, H-15), 3.38 (dd, *J* = 1.1, 9.2 Hz, 1H, H-15), 2.64 (s, 1H, O*H*), 2.20 (dd, *J* = 4.4, 12.2 Hz, 1H, H-10), 2.11-2.03 (m, 1H, H-4), 2.00 (dd, *J* = 5.1, 10.4 Hz, 1H, H-3), 1.65 (dd, *J* = 12.2, 12.2 Hz, 1H, H-10), 1.39 (s, 3H, H-7), 1.38 (s, 3H, H-8), 1.21 (s, 3H, H-13), 0.84 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 135.9 (CH), 130.0 (C), 129.2 (CH), 119.1 (CH_2), 113.8 (CH), 98.3 (C), 75.3 (C), 72.8 (CH_2), 72.5 (CH_2), 66.9 (CH), 63.7 (CH_2), 55.3

(CH), 53.7 (CH_3), 40.1 (CH_2), 37.9 (CH), 37.2 (C), 29.9 (CH_3), 26.1 (CH_3), 22.3 (CH_3), 19.5 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{23}H_{35}O_5$ ($[M+H]^+$) 391.2484, found 391.2487.

(4a*S,5*S**,8a*R**)-7-(*tert*-Butyldimethyldimethylsilanyloxy)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxine-7-carbonitrile (388)**



To a solution of ketone **350** (0.10 g, 0.42 mmol) and *tert*-butyldimethyldimethylsilyl cyanide (77 mg, 0.54 mmol) in dichloromethane (1 mL) was added zinc iodide (4.0 mg, 10 μmol). The reaction mixture was stirred at room temperature overnight, diluted with diethyl ether, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 8:2) gave product **388** (33 mg, 21%) as a colourless oil.

Rf = 0.78 (diethyl ether / petroleum ether, 1:1).

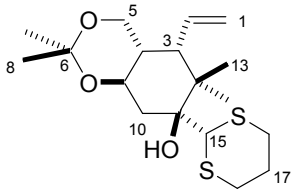
ν_{max} (neat) 2932, 2883, 2859, 1472, 1384, 1261 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (ddd, *J* = 10.0, 11.0, 16.5 Hz, 1H, H-2), 5.14 (dd, *J* = 2.0, 10.0 Hz, 1H, H-1), 4.99 (dd, *J* = 2.0, 16.5 Hz, 1H, H-1), 4.12 (ddd, *J* = 4.3, 11.5, 11.8 Hz, 1H, H-9), 3.70 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.51 (dd, *J* = 4.7, 11.5 Hz, 1H, H-5), 2.26 (dd, *J* = 4.3, 12.3 Hz, 1H, H-10), 2.13-1.99 (m, 2H, H-3 and H-4), 1.92 (dd, *J* = 11.8, 12.3 Hz, 1H, H-10), 1.46 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.13 (s, 3H, H-13), 1.10 (s, 3H, H-14), 0.88 (s, 9H, SiC{CH_3}$_3$), 0.26 (s, 3H, Si{CH_3}$_2$), 0.24 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3 (CH), 122.5 (C), 119.5 (CH_2), 98.8 (C), 74.1 (C), 66.5 (CH), 63.5 (CH_2), 52.6 (CH), 42.5 (C), 41.1 (CH_2), 37.6 (CH), 29.7 (CH_3), 25.5 (CH_3), 24.3 (CH_3), 23.5 (CH_3), 19.4 (CH_3), 18.2 (C), -3.06 (CH_3), -4.16 (CH_3).

HRMS FAB (*m*/*z*) calcd for $C_{21}H_{38}NO_3Si$ ($[M+H]^+$) 380.2621, found 380.2622.

(4a*S,5*S**,7*S**,8a*R**)-7-[1,3]Dithian-2-yl-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (389)**



To a stirred solution 1,3-dithiane (997 mg, 8.29 mmol) in THF (7.5 mL) was added dropwise ^{n}BuLi (1.6 M hexane solution, 4.32 mL, 6.91 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. Then a solution of ketone **350** (659 mg, 2.76 mmol) in THF (7.5 mL) was added dropwise at –78 °C. After 1.5 h, the reaction was quenched with ice-water (15 mL) and the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 75:25) gave product alcohol dithiane **389** (804 mg, 81%) as a white foam.

R_f = 0.12 (diethyl ether / petroleum ether, 3:7).

m.p. 87-89 °C.

ν_{max} (KBr) 3457, 2988, 2942, 2880, 1386, 1270, 1197, 1158, 1069 cm^{-1}.

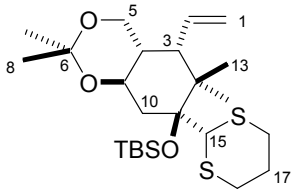
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 10.4, 10.5, 16.6 Hz, 1H, H-2), 5.16 (dd, *J* = 1.2, 10.5 Hz, 1H, H-1), 5.04 (d, *J* = 16.6 Hz, 1H, H-1), 4.20 (ddd, *J* = 4.3, 11.6, 11.6 Hz, 1H, H-9), 4.16 (s, 1H, H-15), 3.68 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.52 (dd, *J* = 4.7, 11.5 Hz, 1H, H-5), 3.00-2.91 (m, 2H, H-16 and H-18), 2.86-2.73 (m, 2H, H-16 and H-18), 2.68 (bs, 1H, O*H*), 2.28 (dd, *J* = 4.3, 13.3 Hz, 1H, H-10), 2.19-2.10 (m, 1H, H-4), 2.04 (dd, *J* = 4.9, 10.4 Hz, 1H, H-3), 2.00-1.86 (m, 3H, H-10 and H-17), 1.47 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.21 (s, 3H, H-13), 1.01 (s, 3H, H-14).

^{13}C NMR (400 MHz, $CDCl_3$) δ 134.7 (CH), 119.9 (CH_2), 98.5 (C), 77.8 (C), 66.8 (CH), 63.6 (CH_2), 54.7 (CH), 53.6 (CH), 43.6 (CH_2), 39.3 (CH), 37.2 (C), 29.8 (CH_3), 29.7 (CH_2), 29.6 (CH_2), 26.7 (CH_3), 25.0 (CH_2), 23.9 (CH_3), 19.6 (CH_3).

HRMS EI (*m*/*z*) calcd for $C_{18}H_{30}O_3S_2$ ($[M]^+$) 358.1636, found 358.1638.

CHN calc. for $C_{18}H_{30}O_3S_2$: C 60.29; H 8.43. found 60.44; H 8.58.

(4a*S,5*S**,7*S**,8a*R**)-*tert*-Butyl-(7-[1,3]Dithian-2-yl-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-yloxy)-dimethylsilane (390)**



A solution of alcohol **389** (0.17 g, 0.47 mmol) in CH_2Cl_2 (6 mL) was treated with 2,6-lutidine (276 μL, 2.35 mmol) and TBSOTf (436 μL, 1.88 mmol). The reaction mixture was heated under reflux for 6 days, quenched with saturated solution of ammonium chloride (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 95:5) gave product dithiane **390** (145 mg, 65%) as a white foam.

R_f = 0.57 (diethyl ether / petroleum ether, 4:6).

m.p. 127-130 °C.

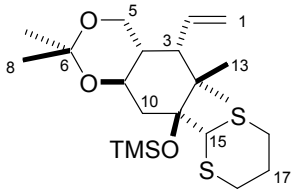
ν_{max} (KBr) 2926, 2855, 1630, 1472, 1386, 1253 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 10.2, 10.2, 16.8 Hz, 1H, H-2), 5.17 (dd, *J* = 1.6, 10.2 Hz, 1H, H-1), 5.06 (dd, *J* = 1.6, 16.8 Hz, 1H, H-1), 4.34 (ddd, *J* = 4.1, 11.4, 11.4 Hz, 1H, H-9), 4.25 (s, 1H, H-15), 3.68 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.51 (dd, *J* = 4.6, 11.5 Hz, 1H, H-5), 2.98-2.93 (m, 2H, H-16), 2.87-2.78 (m, 1H, H-18), 2.71 (td, *J* = 3.3, 14.2 Hz, 1H, H-18), 2.13-1.93 (m, 5H, H-3, H-4, H-10 and H-17), 1.85-1.72 (m, 1H, H-17), 1.46 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.16 (s, 3H, H-13), 1.10 (s, 3H, H-14), 0.95 (s, 9H, SiC{CH_3}$_3$), 0.36 (s, 3H, Si{CH_3}$_2$), 0.15 (s, 3H, Si{CH_3}$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1 (CH), 119.5 (CH_2), 98.5 (C), 80.3 (C), 67.0 (CH), 63.7 (CH_2), 61.9 (CH), 53.6 (CH), 45.1 (C), 39.4 (CH_2), 37.0 (CH), 33.9 (CH_2), 32.2 (CH_2), 29.8 (CH_3), 27.5 (CH_3), 26.8 (CH_3), 26.5 (CH_2), 24.6 (CH_3), 19.7 (CH_3), 19.6 (C), –0.77 (CH_3), –1.38 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{24}H_{45}O_3SiS_2$ ($[M+H]^+$) 473.2579, found 473.2576.

(4a*S,5*S**,7*S**,8a*R**)-(7-[1,3]Dithian-2-yl-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-yloxy)-trimethylsilane (391)**



A solution of alcohol **389** (0.10 g, 0.28 mmol) in CH_2Cl_2 (3.5 mL) was treated with 2,6-lutidine (130 μL, 1.12 mmol) and TMSOTf (0.15 mL, 0.84 mmol). The reaction was stirred at room temperature for 1 h, and quenched with saturated solution of ammonium chloride (4 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried on anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether/ triethylamine, 90:10:1) gave product dithiane **391** (68 mg, 57%) as a colourless oil.

R_f = 0.59 (diethyl ether / petroleum ether, 3:7).

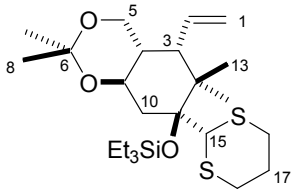
ν_{max} (neat) 2947, 1422, 1384, 1250 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 10.2, 10.2, 16.7 Hz, 1H, H-2), 5.16 (dd, *J* = 1.8, 10.2 Hz, 1H, H-1), 5.05 (dd, *J* = 1.8, 16.7 Hz, 1H, H-1), 4.35 (ddd, *J* = 4.2, 11.5, 11.5 Hz, 1H, H-9), 4.23 (s, 1H, H-15), 3.67 (dd, *J* = 11.6, 11.6 Hz, 1H, H-5), 3.51 (dd, *J* = 4.8, 11.6 Hz, 1H, H-5), 2.96-2.91 (m, 2H, H-16), 2.88-2.80 (m, 1H, H-18), 2.69 (td, *J* = 3.3, 14.0 Hz, 1H, H-18), 2.17 (dd, *J* = 4.2, 12.8 Hz, 1H, H-10), 2.12-1.99 (m, 3H, H-3, H-4 and H-17), 1.92-1.72 (m, 2H, H-10 and H-17), 1.45 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.12 (s, 3H, H-13), 1.04 (s, 3H, H-14), 0.23 (s, 9H, Si{C*H*$_3$}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1 (CH), 119.4 (CH_2), 98.5 (C), 80.0 (C), 66.9 (CH), 63.7 (CH_2), 61.5 (CH), 53.3 (CH), 44.5 (C), 38.9 (CH_2), 37.0 (CH), 33.8 (CH_2), 32.1 (CH_2), 29.8 (CH_3), 27.4 (CH_3), 26.5 (CH_2), 24.0 (CH_3), 19.7 (CH_3), 2.3 (CH_3).

HRMS EI (*m*/*z*) calcd for $C_{21}H_{39}O_3SiS_2$ ($[M+H]^+$) 431.2110, found 431.2105.

(4a*S,5*S**,7*S**,8a*R**)-(7-[1,3]Dithian-2-yl-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-yloxy)-triethylsilane (392)**



A solution of alcohol **389** (1.50 g, 4.18 mmol) in CH_2Cl_2 (45 mL) was treated with 2,6-lutidine (1.95 mL, 16.4 mmol) and TESOTf (2.84 mL, 12.5 mmol). The reaction mixture was heated under reflux overnight, quenched with saturated solution of ammonium chloride (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 95:5) gave product dithiane **392** (1.77 g, 89%) as a colourless solid.

R_f = 0.44 (diethyl ether / petroleum ether, 3:7).

m.p. 120-122 °C.

ν_{max} (KBr) 2986, 2946, 2873, 1458, 1421, 1377, 1266 cm^{-1}.

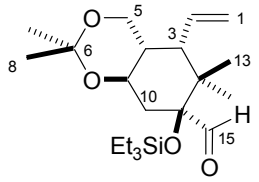
^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 10.2, 10.2, 16.7 Hz, 1H, H-2), 5.16 (dd, *J* = 1.6, 10.2 Hz, 1H, H-1), 5.06 (dd, *J* = 1.6, 16.7 Hz, 1H, H-1), 4.36 (ddd, *J* = 4.23, 11.5, 11.5 Hz, 1H, H-9), 4.24 (s, 1H, H-15), 3.68 (dd, *J* = 11.4, 11.4 Hz, 1H, H-5), 3.51 (dd, *J* = 4.6, 11.4 Hz, 1H, H-5), 2.96-2.92 (m, 2H, H-16), 2.90-2.84 (m, 1H, H-18), 2.69 (td, *J* = 3.3, 14.0 Hz, 1H, H-18), 2.13-1.99 (m, 4H, H-3, H-4, H-10 and H-17), 1.86-1.75 (m, 2H, H-10 and H-17), 1.45 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.13 (s, 3H, H-13), 1.07 (s, 3H, H-14), 1.00 (t, *J* = 7.8 Hz, 9H, Si{CH_2CH_3}$_3$), 0.84 (dt, *J* = 7.8, 15.8 Hz, 3H, Si{CH_2CH_3}$_3$), 0.72 (dt, *J* = 7.8, 15.8 Hz, 3H, Si{CH_2CH_3}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1 (CH), 119.4 (CH_2), 98.5 (C), 79.8 (C), 66.9 (CH), 63.7 (CH_2), 61.8 (CH), 53.5 (CH), 44.9 (C), 39.6 (CH_2), 37.0 (CH), 33.8 (CH_2), 32.1 (CH_2), 29.9 (CH_3), 27.6 (CH_3), 26.5 (CH_2), 24.2 (CH_3), 19.7 (CH_3), 7.5 (CH_3), 6.9 (CH_2).

HRMS EI (*m*/*z*) calcd for $C_{24}H_{44}O_3SiS_2$ ($[M]^+$) 472.2501, found 472.2503.

CHN calc. for $C_{24}H_{44}O_3SiS_2$ C 60.97; H 9.38. found 61.08; H 9.39.

(4a*S,5*S**,7*S**,8a*R**)-2,2,6,6-Tetramethyl-7-triethylsilanyloxy-5-vinylhexahydrobenzo[1,3]-dioxine-7-carbaldehyde (394)**



To a stirred solution of dithiane **392** (556 mg, 1.17 mmol) in THF (25 mL) and H_2O (12.5 mL) was added $CaCO_3$ (494 mg, 4.94 mmol) and $Hg(ClO_4)_2.xH_2O$ (986 mg, 2.47 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then warmed to room temperature for 1.5 h. The reaction mixture was diluted with EtOAc (100 mL) and saturated sodium hydrogen carbonate solution (25 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water brine (50 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 95:5) gave product aldehyde **394** (397 mg, 88%) as a colourless oil.

R_f = 0.50 (diethyl ether / petroleum ether, 3:7).

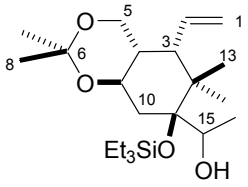
ν_{max} (neat) 2958, 2877, 1730, 1457 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 1.4 Hz, 1H, H-15), 5.49 (ddd, *J* = 10.3, 10.3, 16.6 Hz, 1H, H-2), 5.04 (dd, *J* = 1.6, 10.3 Hz, 1H, H-1), 4.93 (d, *J* = 16.6 Hz, 1H, H-1), 4.29 (ddd, *J* = 4.6, 11.5, 11.5 Hz, 1H, H-9), 3.65 (dd, *J* = 11.4, 11.4 Hz, 1H, H-5), 3.50 (dd, *J* = 4.3, 11.4 Hz, 1H, H-5), 2.10-1.99 (m, 3H, H-3, H-4 and H-10), 1.72 (dd, *J* = 11.5, 11.5 Hz, 1H, H-10), 1.46 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.20 (s, 3H, H-13), 1.04 (s, 3H, H-14), 0.94 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.66-0.53 (m, 6H, $Si(CH_2CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1 (CH), 134.9 (CH), 119.5 (CH_2), 98.7 (C), 81.2 (C), 66.2 (CH), 63.9 (CH_2), 53.2 (CH), 42.1 (C), 37.5 (CH), 36.4 (CH_2), 29.9 (CH_3), 25.9 (CH_3), 22.2 (CH_3), 19.6 (CH_3), 7.0 (CH_3), 6.5 (CH_2).

HRMS FAB (*m*/*z*) calcd for $C_{21}H_{39}O_4Si$ ($[M+H]^+$) 383.2618, found 383.2612.

(4a*S,5*S**,7*S**,8a*R**)-1-(2,2,6,6-Tetramethyl-7-triethylsilanyloxy-5-vinylhexahydrobenzo[1,3]-dioxin-7-yl)-ethanol (395)**



To a solution of aldehyde **394** (20 mg, 52 μmol) in THF (1 mL) was added dropwise at –78 °C MeLi (1.6 M in Et_2O, 65 μL, 0.10 mmol). The reaction mixture was stirred at –78 °C for 2 h, then quenched with saturated ammonium chloride solution (1 mL), extracted with Et_2O (3 × 2 mL). The combined organic solutions were washed with brine (2 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether / diethyl ether, 8:2) gave product alcohol **395** (9 mg, 21%) as a white solid.

R_f = 0.24 (diethyl ether / petroleum ether, 2:8).

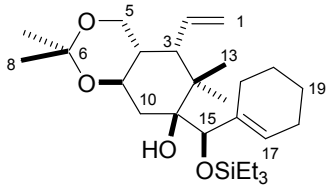
ν_{max} (neat) 3514, 2956, 2877, 1458, 1383, 1198 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 10.3, 10.6, 16.6 Hz, 1H, H-2), 5.09 (dd, *J* = 1.8, 10.3 Hz, 1H, H-1), 5.00 (dd, *J* = 1.8, 16.6 Hz, 1H, H-1), 4.07 (q, *J* = 6.2 Hz, 1H, H-15), 3.74-3.64 (m, 3H, O*H*, H-5 and H-9), 3.52 (dd, *J* = 4.8, 11.7 Hz, 1H, H-5), 2.20-2.11 (m, 1H, H-4), 2.06 (dd, *J* = 5.2, 10.6 Hz, 1H, H-3), 1.86 (dd, *J* = 13.0, 13.0 Hz, 1H, H-10), 1.76 (dd, *J* = 4.1, 13.0 Hz, 1H, H-10), 1.45 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.22 (d, *J* = 6.2 Hz, 3H, H-16), 1.17 (s, 3H, H-13), 0.96 (t, *J* = 7.9 Hz, 9H, Si{CH_2CH_3}$_3$), 0.86 (s, 3H, H-14), 0.62 (q, *J* = 7.9 Hz, 6H, Si{CH_2CH_3}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH), 118.8 (CH_2), 98.3 (C), 75.7 (C), 71.2 (CH), 66.3 (CH), 63.6 (CH_2), 53.5 (CH), 42.9 (C), 37.8 (CH), 37.3 (CH_2), 29.8 (CH_3), 27.0 (CH_3), 24.6 (CH_3), 19.5 (CH_3), 19.5 (CH_3), 6.9 (CH_3), 5.6 (CH_2).

HRMS CI (*m*/*z*) calcd for $C_{21}H_{43}O_4Si$ ($[M+H]^+$) 399.2931, found 399.2933.

(4a*S,5*S**,7*S**,8a*R**)-7-(Cyclohex-1-enyl-(*R**)-triethylsilanyloxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (396)**



To a solution of 1-bromocyclohexene (750 mg, 4.66 mmol) in Et_2O (12 mL) was added ^tBuLi (1.7 M in pentane, 6.0 mL, 10 mmol) under an atmosphere of argon at –78 °C. The resulting solution was stirred at –78 °C for 30 min and at room temperature for 30 min. A solution of aldehyde **394** (892 mg, 2.33 mmol) in THF (45 mL) was added dropwise at –78 °C. After 1 h, the reaction was quenched with saturated ammonium chloride solution (45 mL) and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic solutions were washed with brine (200 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 85:15) gave product alcohol **396** (1.02 g, 94%) as a white solid.

R_f = 0.35 (diethyl ether / petroleum ether, 2:8).

m.p. 98-100 °C.

ν_{max} (KBr) 3529, 2940, 2877, 1457cm^{-1}.

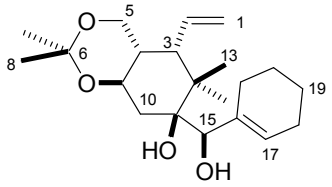
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 10.2, 10.2, 16.6 Hz, 1H, H-2), 5.64 (bs, 1H, H-17), 5.12 (dd, *J* = 1.8, 10.2 Hz, 1H, H-1), 5.01 (dd, *J* = 1.8, 16.6 Hz, 1H, H-1), 4.19 (s, 1H, H-15), 3.81 (ddd, *J* = 4.2, 12.2, 12.2 Hz, 1H, H-9), 3.76 (s, 1H, O*H*), 3.67 (dd, *J* = 11.6, 11.6 Hz, 1H, H-5), 3.52 (dd, *J* = 4.8, 11.6 Hz, 1H, H-5), 2.24-1.98 (m, 6H, H-3, H-4, H-18 and CH_2 × 3), 1.81 (dd, *J* = 12.2, 12.2 Hz, 1H, H-10), 1.73-1.58 (m, 4H, H-10 and CH_2 × 3), 1.55-1.46 (m, 1H, CH_2), 1.38 (s, 6H, H-7 and H-8), 1.16 (s, 3H, H-13), 0.95 (t, *J* = 8.0 Hz, 9H, Si{CH_2CH_3}$_3$), 0.86 (s, 3H, H-14), 0.62 (q, *J* = 8.0 Hz, 6H, Si{CH_2CH_3}$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (C), 136.1 (CH), 126.1 (CH), 118.9 (CH_2), 98.2 (C), 80.8 (CH), 76.1(C), 66.5 (CH), 63.7 (CH_2), 53.7 (CH), 43.1 (C), 37.2 (CH), 37.1 (CH_2), 29.8 (CH_3), 27.0 (CH_3), 25.3 (CH_2), 24.5 (CH_3), 23.9 (CH_2), 22.3 (CH_2), 22.2 (CH_2), 19.3 (CH_3), 7.0 (CH_3), 5.0 (CH_2).

HRMS FAB (*m*/*z*) calcd for $C_{27}H_{48}O_4SiNa$ ([M+Na]$^+$) 487.3220, found 487.3217.

CHN calc. for $C_{27}H_{48}O_4Si$: C 69.78; H 10.41. found 69.95; H 10.57.

(4a*S, 5*S**, 7*S**, 8a*R**)-7-(Cyclohex-1-enyl-(*R**)-hydroxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (367)**



A solution of alcohol **396** (1.67 g, 3.59 mmol) in THF (40 mL) was treated with TBAF (1M in THF, 5.39 mL, 5.39 mmol) and stirred at room temperature for 2 h. The reaction mixture was then quenched with water (65 mL) and the mixture was extracted with diethyl ether (3 × 65 mL). The combined organic extracts were washed with brine (65 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 6:4) gave diol **367** (1.19 g, 94%) as a white solid.

R_f = 0.50 (diethyl ether / petroleum ether, 1:1).

m.p. 171-173 °C.

ν_{max} (KBr) 3410, 2921, 1386, 1200, 1071, 1037, 1013 cm^{-1}.

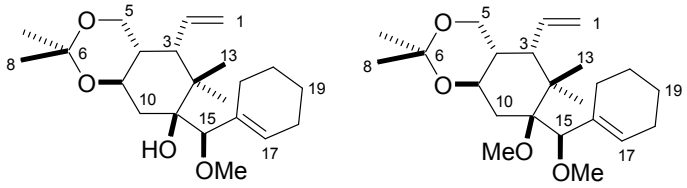
^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 10.2, 10.2, 16.6 Hz, 1H, H-2), 5.72-5.68 (m, 1H, H-17), 5.12 (dd, *J* = 1.8, 10.2 Hz, 1H, H-1), 5.01 (dd, *J* = 1.8, 16.6 Hz, 1H, H-1), 4.16 (d, *J* = 4.3 Hz, 1H, H-15), 3.83 (ddd, *J* = 4.3, 11.9, 11.9 Hz, 1H, H-9), 3.68 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.53 (dd, *J* = 4.7, 11.5 Hz, 1H, H-5), 3.06 (s, 1H, O*H*), 2.25-1.97 (m, 6H, H-3, H-4, H-18 and CH_2), 1.94 (d, *J* = 4.3 Hz, 1H, O*H*), 1.80 (dd, *J* = 11.9, 11.9 Hz, 1H, H-10), 1.73-1.56 (m, 5H, H-10 and CH_2), 1.39 (s, 3H, H-7), 1.38 (s, 3H, H-8), 1.18 (s, 3H, H-13), 0.95 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (C), 135.7 (CH), 126.5 (CH), 119.1 (CH_2), 98.2 (C), 79.3 (CH), 76.3 (C), 66.3 (CH), 63.7 (CH_2), 53.8 (CH), 42.9 (C), 38.2 (CH), 37.3 (CH_2), 29.8 (CH_3), 26.7 (CH_3), 25.2 (CH_2), 24.3 (CH_3), 23.9 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 19.3 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{21}H_{35}O_4$ ($[M+H]^+$) 351.2535, found 351.2538.

CHN calc. for $C_{21}H_{34}O_4$: C 71.96; H 9.78. found 71.99; H 9.91.

(4a*S,5*S**,7*S**,8a*R**)-7-(Cyclohex-1-enyl-(*R**)-methoxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (397) and (4a*S**,5*S**,7*S**,8a*R**)-7-(cyclohex-1-enyl-(*R**)-methoxymethyl)-7-methoxy-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxine (398)**



To a solution of diol **367** (100 mg, 286 μmol) in THF (6 mL) was added NaH (20 mg, 60% in mineral oil, 0.51 mmol). The suspension was stirred at room temperature for 30 min and then under reflux for 30 min. At room temperature, methyl iodide (24 μL, 0.38 mmol) was added. The mixture was stirred at room temperature for 2 h, and then the reaction was quenched with water (5 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate, and then concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 85:15 to 1:1) gave monomethyl prodcut **397** (67 mg, 64%) as a white solid, dimethyl product **398** (14 mg, 13%) as a white solid, and diol starting material (13 mg, 13%).

Monomethyl ether 397

R_f = 0.64 (diethyl ether / petroleum ether, 1:1).

m.p. 115-117 °C.

ν_{max} (KBr) 3476, 3003, 2978, 2925,1633, 1467, 1385, 1197 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 10.2, 10.2, 16.6 Hz, 1H, H-2), 5.70 (bs, 1H, H-17), 5.11 (dd, *J* = 1.8, 10.2 Hz, 1H, H-1), 5.00 (dd, *J* = 1.8, 16.6 Hz, 1H, H-1), 3.81 (ddd, *J* = 4.3, 12.0, 12.0 Hz, 1H, H-9), 3.67 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.52 (dd, *J* = 4.8, 11.5 Hz, 1H, H-5), 3.48 (s, 1H, H-15), 3.45 (s, 1H, O*H*), 3.13 (s, 3H, OCH_3), 2.22-1.99 (m, 5H, H-3, H-4, H-18 and CH_2), 1.98-1.88 (m, 1H, CH_2), 1.76 (dd, *J* = 12.0, 12.0 Hz, 1H, H-10), 1.72-1.55 (m, 5H, H-10 and CH_2), 1.39 (s, 3H, H-7), 1.38 (s, 3H, H-8), 1.16 (s, 3H, H-13), 0.84 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0 (CH), 135.8 (C), 128.3 (CH), 118.7 (CH_2), 98.2 (C), 87.9 (CH), 76.3 (C), 66.3 (CH), 63.7 (CH_2), 54.5 (CH_3), 53.8 (CH), 43.1 (C), 37.5 (CH_2), 37.2 (CH), 29.8 (CH_3), 26.9 (CH_3), 25.4 (CH_2), 23.8 (CH_3), 23.8 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 19.3 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{22}H_{37}O_4$ ([M+H]$^+$) 365.2692, found 365.2686.

CHN calc. for $C_{22}H_{36}O_4$: C 72.49; H 9.95. found 72.40; H 10.02.

Dimethyl ether 397

R_f = 0.58 (diethyl ether / petroleum ether, 1:1).

m.p. 76-79 °C.

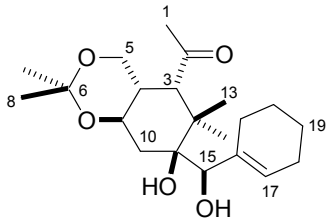
ν_{max} (KBr) 2920,1630, 1463, 1383, 1269, 1091 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 10.2, 10.2, 16.6 Hz, 1H, H-2), 5.68-5.63 (m, 1H, H-17), 5.11 (dd, *J* = 1.7, 10.2 Hz, 1H, H-1), 4.99 (dd, *J* = 1.7, 16.6 Hz, 1H, H-1), 3.89 (ddd, *J* = 3.9, 11.4, 11.5 Hz, 1H, H-9), 3.69 (dd, *J* = 11.6, 11.6 Hz, 1H, H-5), 3.52 (dd, *J* = 4.8, 11.6 Hz, 1H, H-5), 3.47 (s, 1H, H-15), 3.35 (s, 3H, OC*H*$_3$), 3.10 (s, 3H, OC*H*$_3$), 2.20-1.90 (m, 7H, H-3, H-4, H-10, H-18 and C*H*$_2$), 1.77-1.69 (m, 2H, H-10 and C*H*$_2$), 1.68-1.48 (m, 3H, C*H*$_2$), 1.42 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.20 (s, 3H, H-13), 0.99 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (CH), 136.0 (C), 128.2 (CH), 118.9 (CH_2), 98.3 (C), 90.6 (CH), 80.6 (C), 66.8 (CH), 63.6 (CH_2), 55.1 (CH_3), 54.1 (CH), 52.7 (CH_3), 45.2 (C), 37.5 (CH), 33.9 (CH_2), 29.8 (CH_3), 27.8 (CH_3), 25.4 (CH_2), 25.4 (CH_2), 24.7 (CH_3), 22.8 (CH_2), 22.6 (CH_2), 19.3 (CH_3).

HRMS EI (*m*/*z*) calcd for $C_{23}H_{38}O_4$ ([M]$^+$) 378.2770, found 378.2767.

(4a*S,5*S**,7*S**,8a*R**)-1-[7-(Cyclohex-1-enyl-(*R**)-hydroxymethyl)-7-hydroxy-2,2,6,6-tetramethylhexahydrobenzo[1,3]-dioxin-5-yl]-ethanone (363)**



To a suspension of palladium chloride (20 mg, 11 μmol) in degassed DMF (15 mL) and H_2O (2 mL) under argon was added the alkene **367** (20 mg, 57 μmol) at 0 °C. After being stirred at room temperature overnight, the reaction was quenched with pH = 7 buffer (20 mL) at 0 °C and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate and concentrated. Purification by flash column chromatography (petroleum ether / diethyl ether, 1:1) gave the alkene **367** starting material (2.8 mg) and methyl ketone **363** (15.4 mg, 74%, 86% BRSM) as a white solid.

R_f = 0.39 (diethyl ether / petroleum ether, 7:3).

m.p. 164-166 °C.

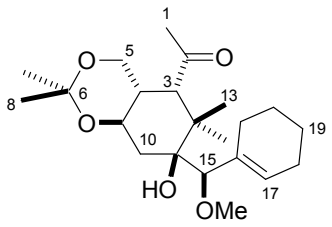
ν_{max} (KBr) 3414, 2925,1702, 1460, 1378 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (bs, 1H, H-17), 4.60 (d, *J* = 3.1 Hz, 1H, H-15), 4.38 (ddd, *J* = 4.6, 11.4, 11.4 Hz, 1H, H-9), 3.66 (dd, *J* = 11.0, 11.0 Hz, 1H, H-5), 3.56 (dd, *J* = 4.8, 11.0 Hz, 1H, H-5), 3.39 (s, 1H, O*H*), 2.84 (d, *J* = 5.5 Hz, 1H, H-3), 2.20 (s, 3H, H-1), 2.19-2.00 (m, 5H, H-4, H-18 and CH_2), 1.74-1.55 (m, 7H, H-10, O*H* and CH_2), 1.40 (s, 3H, H-7), 1.36 (s, 3H, H-8), 1.25 (s, 3H, H-13), 1.12 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0 (C), 137.9 (C), 127.3 (CH), 98.6 (C), 76.3 (C), 76.2 (CH), 65.3 (CH), 61.9 (CH_2), 59.7 (CH), 42.9 (C), 38.4 (CH), 37.8 (CH_2), 36.5 (CH_3), 29.6 (CH_3), 27.4 (CH_3), 25.2 (CH_2), 24.4 (CH_3), 23.7 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 19.6 (CH_3).

HRMS FAB (*m*/*z*) calcd for $C_{21}H_{34}O_5Na$ ($[M+Na]^+$) 389.2304, found 389.2303.

(4a*S,5*S**,7*S**,8a*R**)-1-[7-(Cyclohex-1-enyl-(*R**)-methoxymethyl)-7-hydroxy-2,2,6,6-tetramethylhexahydrobenzo[1,3]-dioxin-5-yl]-ethanone (366)**



A solution of diol **363** (162 mg, 442 µmol) in chloroform (12 mL) was treated with 2,6-di-*tert*-butyl-4-methyl pyridine (2.0 g, 9.7 mmol) and methyl triflate (1.75 mL, 15.5 mmol). The reaction mixture was stirred under reflux for 5 h, diluted with diethyl ether (50 mL) and a saturated solution of sodium hydrogen carbonate (30 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over magnesium sulfate and concentrated. Purification by flash column chromatography (petroleum ether / diethyl ether, 6:4) gave the methyl ether **366** (109 mg, 65%, 74% BRSM) as a white solid and diol **363** starting material (20 mg,).

R_f = 0.28 (diethyl ether / petroleum ether, 1:1).

m.p. 111-113 °C.

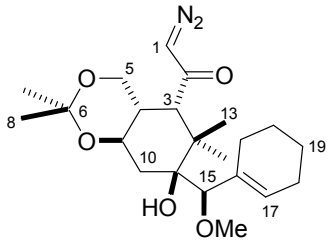
ν_{max} (KBr) 3552, 3507, 2939,1703, 1460, 1364 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (bs, 1H, H-17), 4.38-4.31 (m, 1H, H-9), 3.97 (s, 1H, H-15), 3.65 (dd, *J* = 11.2, 11.2 Hz, 1H, H-5), 3.58-3.54 (m, 2H, H-5 and O*H*), 3.09 (s, 3H, OCH_3), 2.83 (d, *J* = 5.5 Hz, 1H, H-3), 2.19 (s, 3H, H-1), 2.17-2.03 (m, 4H, H-4, H-18 and CH_2), 1.93-1.83 (m, 1H, CH_2), 1.72-1.51(m, 6H, H-10 and CH_2), 1.40 (s, 3H, H-7), 1.36 (s, 3H, H-8), 1.24 (s, 3H, H-13), 1.01 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0 (C), 134.9 (C), 129.1 (CH), 98.5 (C), 84.6 (CH), 76.3 (C), 65.2 (CH), 62.0 (CH_2), 59.8 (CH), 54.3 (CH_3), 42.9 (C), 38.3 (CH), 37.5 (CH_2), 36.5 (CH_3), 29.7 (CH_3), 27.5 (CH_3), 25.3 (CH_2), 23.8 (CH_3), 23.5 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 19.6 (CH_3).

HRMS FAB (*m*/*z*) calcd for $C_{22}H_{36}O_5Na$ ($[M+Na]^+$) 403.2460, found 403.2460.

(4a*S,5*S**,7*S**,8a*R**)-1-[7-(Cyclohex-1-enyl-(*R**)-methoxymethyl)-7-hydroxy-2,2,6,6-tetramethylhexahydrobenzo[1,3]-dioxin-5-yl]-2-diazoethanone (252)**



A solution of the methyl ketone **366** (99 mg, 0.26 mmol) in THF (0.27 mL) was added over 5 min to a solution of LHMDS (0.78 mL of a 1.0 M solution in hexane, 0.78 mmol) at –78 °C. After stirring for 1 h at –78 °C and 30 min at room temperature, 2,2,2-trifluoroethyl trifuoroacetate (56 μL, 0.42 mmol) was added in one portion and the reaction mixture stirred for 20 min. The reaction mixture was diluted with saturated aqueous ammonium chloride (4 mL) and then extracted with diethyl ether (3 × 6 mL). The combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate then concentrated *in vacuo* to give a yellowish solid.

The crude solid product was dissolved in acetonitrile (1.2 mL), then DBU (58 μL, 0.39 mmol) and *p*-acetamidobenzenesulfonyl azide (94 mg, 0.39 mmol) were added, and the reaction mixture was stirred for three days. The reaction mixture was treated with a 10% solution of aqueous sodium hydroxide (4 mL) then the reaction mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate and concentrated to a yellow oil. Purification by flash column chromatography (diethyl ether / petroleum ether, 1:1) gave the title compound **252** as a yellow solid (35 mg, 33%).

R_f = 0.23 (diethyl ether / petroleum ether, 8:2).

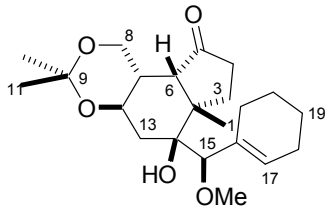
ν_{max} (KBr) 3525, 2940, 2103,1615, 1457, 1365 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (bs, 1H, H-17), 5.27 (s, 1H, H-1), 4.42 (ddd, *J* = 8.1, 8.1, 11.0 Hz 1H, H-9), 4.24 (s, 1H, H-15), 3.78 (dd, *J* = 11.2, 11.2 Hz, 1H, H-5), 3.57 (dd, *J* = 4.6, 11.2 Hz, 1H, H-5), 3.56 (s, 1H, O*H*), 3.11 (s, 3H, OCH_3), 2.29 (d, *J* = 5.7 Hz, 1H, H-3), 2.18-1.98 (m, 4H, H-4, H-18 and CH_2), 1.95-1.85 (m, 1H, CH_2), 1.71-1.54 (m, 6H, H-10 and CH_2), 1.42 (s, 3H, H-7), 1.37 (s, 3H, H-8), 1.22 (s, 3H, H-13), 1.00 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C), 134.9 (C), 129.2 (CH), 98.6 (C), 84.5 (CH), 76.3 (C), 65.7 (CH), 62.3 (CH_2), 58.9 (CH), 58.4 (CH), 54.3 (CH_3), 43.4 (C), 38.3 (CH), 37.5 (CH_2), 29.7 (CH_3), 27.6 (CH_3), 25.3 (CH_2), 24.0 (CH_3), 23.5 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 19.7 (CH_3).

HRMS FAB (*m*/*z*) calcd for $C_{22}H_{34}O_5N_2Na$ ($[M+Na]^+$) 429.2365, found 429.2363.

(3a*S,4*S**,6*R**,9*S**,10*S**)-4-(Cyclohex-1-enyl-(*R**)-methoxymethyl)-4-hydroxy-3a,7,7-trimethyloctahydro-6,8-dioxacyclopenta[*a*]naphthalen-1-one (401)**



A solution of the diazoketone **252** (17 mg, 42 μmol) in CH_2Cl_2 (3.5 mL) was added dropwise over 10 min to a stirred solution of rhodium(II) trifluoroacetate (1.4 mg, 2 μmol) in CH_2Cl_2 (5 mL) at room temperature under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to give a green oil which was then purified by flash column chromatography (diethyl ether / petroleum ether, 1:1) to afford the cyclopentanone **401** as a white powder (9.7 mg, 61%).

R_f = 0.40 (diethyl ether / petroleum ether, 8:2).

m.p. 150-152 °C.

ν_{max} (KBr) 3482, 2926,1724, 1468, 1383cm^{-1}.

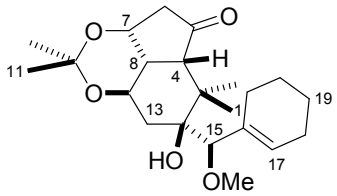
^1H NMR (400 MHz, C_6D_6) δ 5.46 (bs, 1H, H-17), 4.88 (dd, *J* = 11.0, 11.0 Hz, 1H, H-8), 3.90 (dd, *J* = 4.7, 11.0 Hz, 1H, H-8), 3.82 (ddd, *J* = 6.0, 9.9, 11.5 Hz, 1H, H-12), 3.20 (s, 1H, H-15), 3.06 (s, 1H, O*H*), 2.79 (s, 3H, OCH_3), 2.36-2.19 (m, 2H, H-7 and CH_2), 2.15-2.03 (m, 1H, H-4), 1.99-1.84 (m, 6H, H-3, H-13 and H-18), 1.79-1.69 (m, 1H, CH_2), 1.66

(d, *J* = 6.7 Hz, 1H, H-6), 1.53 (s, 3H, H-10), 1.47 (s, 3H, H-11), 1.45-1.24 (m, 4H, CH_2), 1.09 (ddd, *J* = 7.4, 10.8, 13.4 Hz, 1H, H-4), 1.04 (s, 3H, H-1).

^{13}C NMR (100 MHz, C_6D_6) δ 218.0 (C), 134.9 (C), 130.0 (CH), 96.6 (C), 87.7 (CH), 76.5 (C), 66.7 (CH), 61.6 (CH_2), 57.1 (CH), 54.9 (CH_3), 48.4 (C), 38.7 (CH_2), 37.0 (CH), 36.3 (CH_2), 30.8 (CH_2), 30.3 (CH_3), 25.8 (CH_3), 25.6 (CH_2), 24.5 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 19.6 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{22}H_{35}O_5$ ($[M+H]^+$) 379.2484, found 379.2486.

7-(Cyclohex-1-enylmethoxymethyl)-7-hydroxy-4,4,8,8-tetramethyloctahydro-3,5-dioxaacenaphthylen-1-one (400)



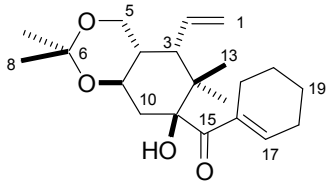
A solution of the diazoketone **252** (15 mg, 38 μmol) in 1,2-dichloroethane (5 mL) was added dropwise over 15 min to a stirred solution of copper(II) hexafluoroacetylacetonate (1 mg, 2 μmol) in 1,2-dichloroethane (4 mL) under reflux under an atmosphere of argon. After addition was complete, the reaction mixture was concentrated *in vacuo* to give a green oil which was then purified by flash column chromatography (diethyl ether / petroleum ether, 1:1) to afford the cyclopentanone **400** as a white powder (7 mg, 50%), and cyclopentanone **401** (6 mg, 43%).

R_f = 0.57 (diethyl ether / petroleum ether, 8:2).

ν_{max} (KBr) 3536, 2929,1735, 1460, 1371, 1243, 1163, 1090 cm^{-1}.

HRMS CI (*m*/*z*) calcd for $C_{22}H_{35}O_5$ ($[M+H]^+$) 379.2484, found 379.2480.

(4a*S,5*S**,7*S**,8a*R**)-Cyclohex-1-enyl-(7-hydroxy-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-yl)-methanone (407)**



To a solution of alcohol **367** (200 mg, 571 μmol) in dichloromethane (56 mL) was treated with DMSO (0.40 mL, 5.7 mmol) and diisopropylethylamine (0.49 mL, 2.8 mmol) at 0 °C. Sulfur trioxide pyridine complex (318 mg, 2.00 mmol) was then added in one-portion. After 1.5 h at room temperature, the reaction was quenched with a saturated solution of sodium thiosulfate (30 mL) and the mixture was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried on anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 75:25) gave hydroxyketone **407** (183 mg, 92%) as a white solid.

R_f = 0.23 (diethyl ether / petroleum ether, 4:6).

m.p. 57-60 °C.

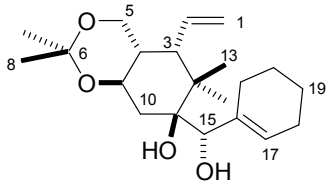
ν_{max} (KBr) 3435, 2935, 2870, 1652, 1627, 1384, 1200, 1161, 1071, 1013 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.07-7.03 (m, 1H, H-17), 6.05 (ddd, *J* = 10.2, 10.2, 16.8 Hz, 1H, H-2), 4.96 (dd, *J* = 2.3, 10.2 Hz, 1H, H-1), 4.85 (dd, *J* = 2.3, 16.8 Hz, 1H, H-1), 4.55 (ddd, *J* = 4.7, 10.9, 10.9 Hz, 1H, H-9), 3.73 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.51 (dd, *J* = 4.3, 11.5 Hz, 1H, H-5), 2.24-2.18 (m, 4H, H-18 and C*H*$_2$), 2.12-2.04 (m, 3H, H-3, H-4 and H-10), 2.00 (s, 1H, O*H*), 1.68-1.54 (m, 5H, H-10 and C*H*$_2$), 1.47 (s, 3H, H-7), 1.38 (s, 3H, H-8), 1.23 (s, 3H, H-13), 0.87 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8 (C), 139.1 (C), 138.9 (CH), 136.6 (CH), 117.8 (CH_2), 98.6 (C), 84.6 (C), 66.9 (CH), 64.0 (CH_2), 55.3 (CH), 41.7 (CH_2), 40.9 (C), 37.9 (CH), 29.9 (CH_3), 27.2 (CH_3), 25.9 (CH_2), 25.4 (CH_2), 25.3 (CH_3), 22.3 (CH_2), 21.3 (CH_2), 19.7 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{21}H_{33}O_4$ ($[M+H]^+$) 349.2379, found 349.2377.

(4a*S,5*S**,7*S**,8a*R**)-7-(Cyclohex-1-enyl-(*S**)-hydroxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (408)**



To a solution of hydroxyketone **407** (81 mg, 0.23 mmol) in THF (6.5 mL) and MeOH (0.65 mL) was added $NaBH_4$ (35 mg, 0.93 mmol). After 1 h at room temperature, the reaction mixture was diluted with ethyl acetate (30 mL), washed with water (25 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 75:25) gave *syn* diol **367** (35 mg, 43%) and *anti* diol **408** (46 mg, 56%) as a white foam.

R_f = 0.29 (diethyl ether / petroleum ether, 4:6).

m.p. 163-166 °C.

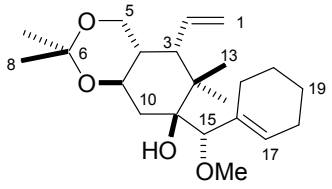
ν_{max} (neat) 3410, 2927, 1459, 1383, 1269, 1198, 1161, 1071, 1013 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 10.2, 10.2, 16.7 Hz, 1H, H-2), 5.79-5.73 (m, 1H, H-17), 5.03 (dd, *J* = 2.2, 10.2 Hz, 1H, H-1), 4.94 (dd, *J* = 2.2, 16.7 Hz, 1H, H-1), 4.20 (ddd, *J* = 5.0, 11.2, 11.2 Hz, 1H, H-9), 4.16 (d, *J* = 3.6 Hz, 1H, H-15), 3.68 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.52 (dd, *J* = 4.6, 11.5 Hz, 1H, H-5), 2.36 (dd, *J* = 5.0, 12.9 Hz, 1H, H-10), 2.23-2.12 (m, 3H, H-4 and C*H*$_2$), 2.10-2.01 (m, 3H, H-3, H-18 and C*H*$_2$), 1.88 (s, 1H, O*H*), 1.69-1.51 (m, 6H, H-10, O*H* and C*H*$_2$), 1.46 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.20 (s, 3H, H-13), 0.98 (s, 3H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (C), 136.9 (CH), 127.4 (CH), 117.9 (CH_2), 98.4 (C), 79.0 (CH), 78.5 (C), 67.2 (CH), 64.0 (CH_2), 54.0 (CH), 41.5 (C), 38.4 (CH_2), 37.8 (CH), 30.0 (CH_3), 27.5 (CH_3), 26.1 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 22.7 (CH_3), 22.2 (CH_2), 19.6 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{21}H_{35}O_4$ ($[M+H]^+$) 351.2535, found 351.2532.

(4a*S,5*S**,7*S**,8a*R**)-7-(Cyclohex-1-enyl-(*S**)-methoxymethyl)-2,2,6,6-tetramethyl-5-vinylhexahydrobenzo[1,3]-dioxin-7-ol (409)**



To a solution of diol **408** (88 mg, 0.25 mmol) in THF (5 mL) was added NaH (18 mg, 60% in mineral oil, 0.45 mmol). The suspension was stirred at room temperature for 30 min and then heated under reflux for 30 min. At room temperature, methyl iodide (17 μL, 0.28 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and reflux for 1 h, and then quenched with water (5 mL). The mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate, and then concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether / diethyl ether, 7:3) gave product **409** (45 mg, 49%, 72% BRSM) as a white solid, and diol starting material (28 mg).

R_f = 0.34 (diethyl ether / petroleum ether, 4:6).

m.p. 99-101 °C.

ν_{max} (KBr) 2925,1630 cm^{-1}.

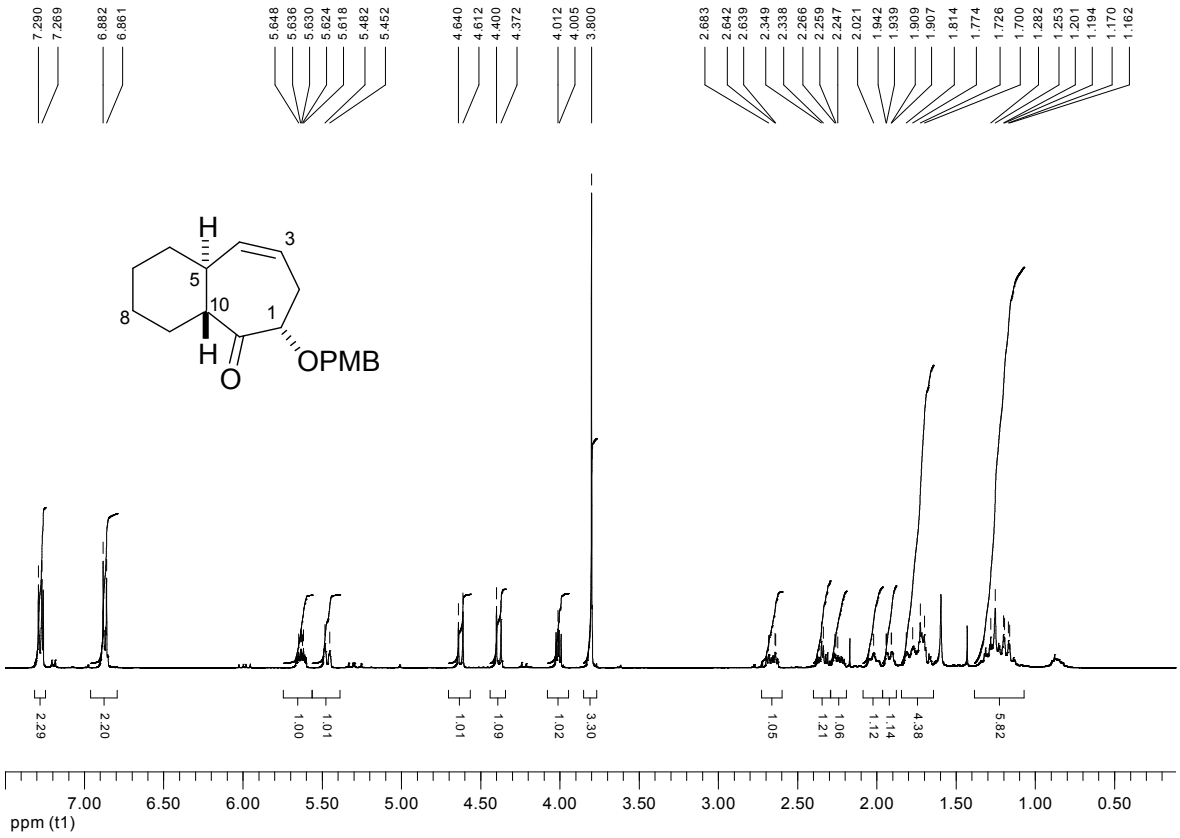
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 10.2, 10.2, 16.9 Hz, 1H, H-2), 5.74-5.69 (m, 1H, H-17), 5.01 (dd, *J* = 2.2, 10.2 Hz, 1H, H-1), 4.91 (dd, *J* = 2.2, 16.9 Hz, 1H, H-1), 4.26 (ddd, *J* = 5.1, 11.2, 11.2 Hz, 1H, H-9), 3.67 (dd, *J* = 11.5, 11.5 Hz, 1H, H-5), 3.55 (s, 1H, H-15), 3.50 (dd, *J* = 4.7, 11.5 Hz, 1H, H-5), 3.13 (s, 3H, OC*H*$_3$), 2.20 (dd, *J* = 5.1, 13.0 Hz, 1H, H-10), 2.17-2.04 (m, 6H, H-3, H-4, H-18 and C*H*$_2$), 1.88 (s, 1H, O*H*), 1.72-1.49 (m, 5H, H-10 and C*H*$_2$), 1.45 (s, 3H, H-7), 1.39 (s, 3H, H-8), 1.18 (s, 3H, H-13), 0.93 (s, 3H, H-14).

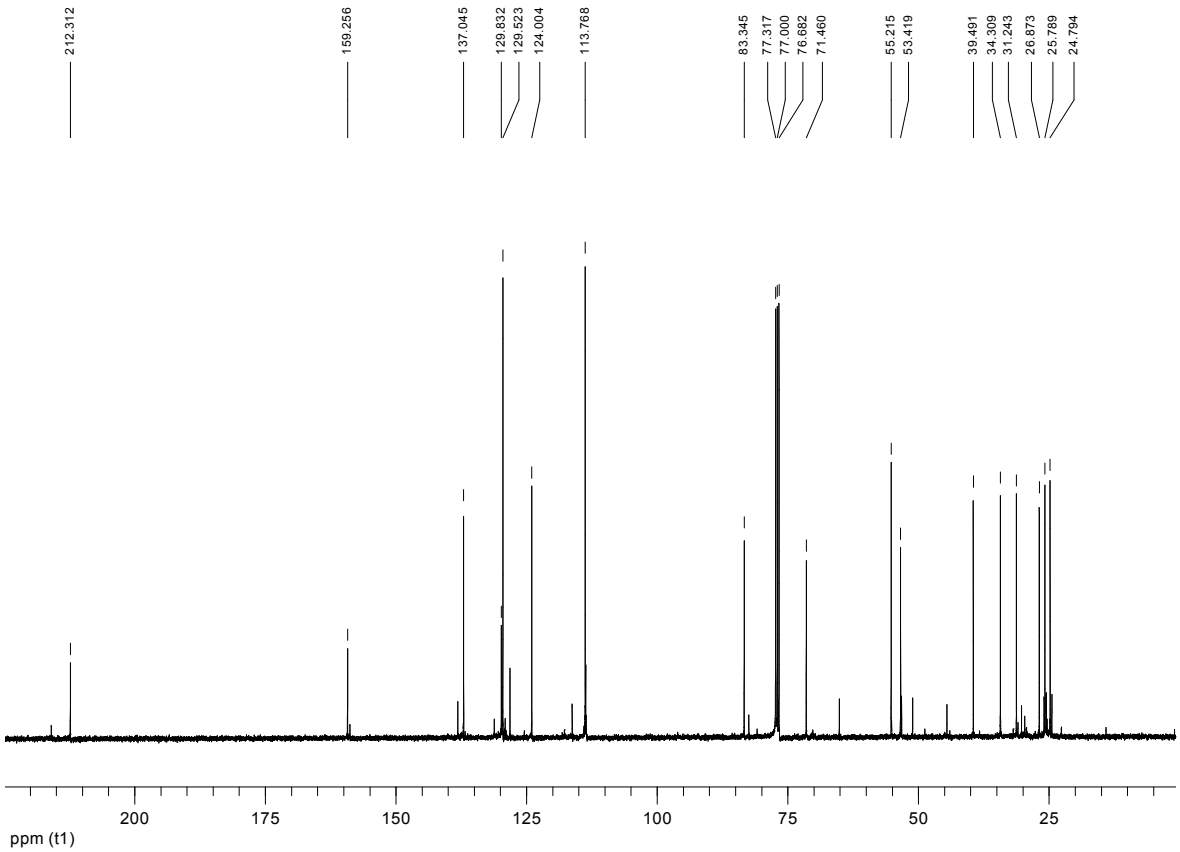
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (CH), 136.6 (C), 129.8 (CH), 117.3 (CH_2), 98.3 (C), 88.7 (CH), 77.2 (C), 67.1 (CH), 64.1 (CH_2), 55.9 (CH_3), 54.0 (CH), 41.5 (C), 38.6 (CH_2), 37.7 (CH), 30.0 (CH_3), 27.6 (CH_3), 25.6 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 22.6 (CH_3), 22.6 (CH_2), 19.6 (CH_3).

HRMS CI (*m*/*z*) calcd for $C_{22}H_{37}O_4$ ($[M+H]^+$) 365.2692, found 365.2687.

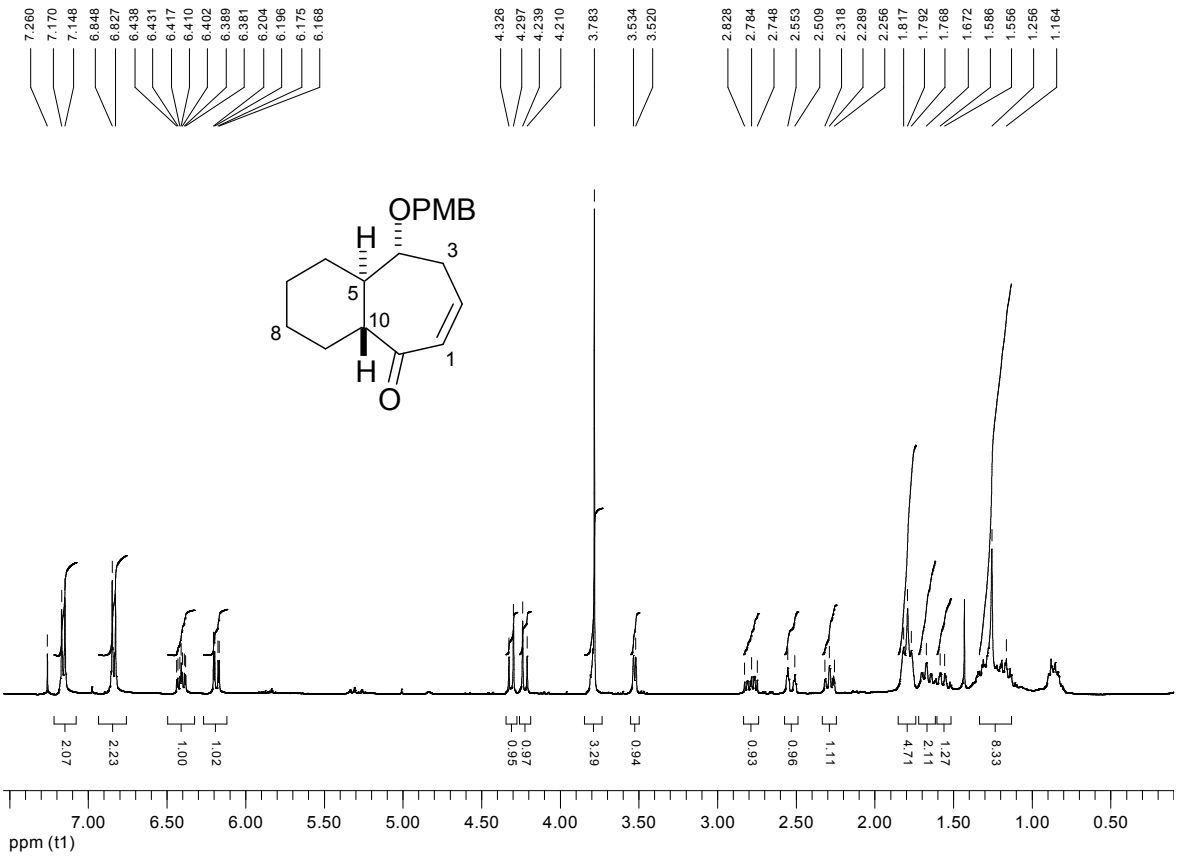
Appendices

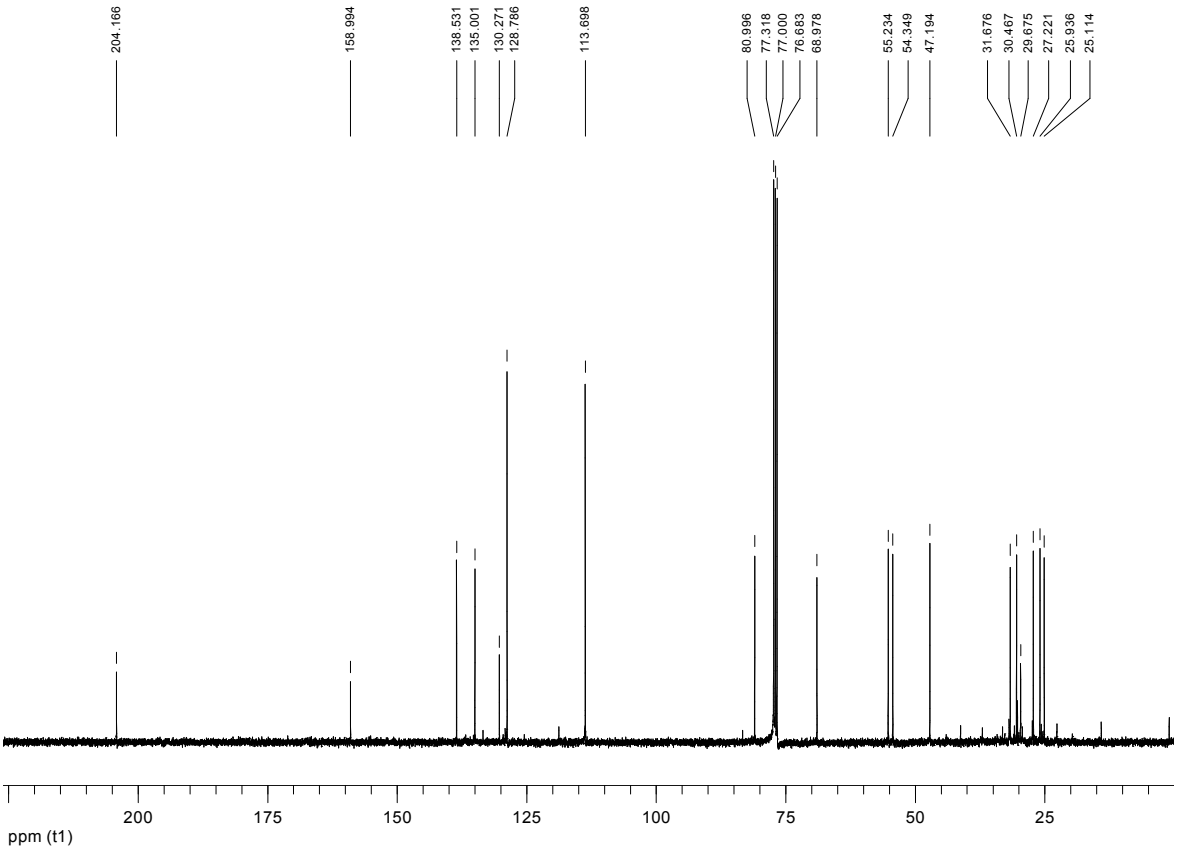
Appendix 1: ^{1}H and ^{13}C NMR spectra of 254



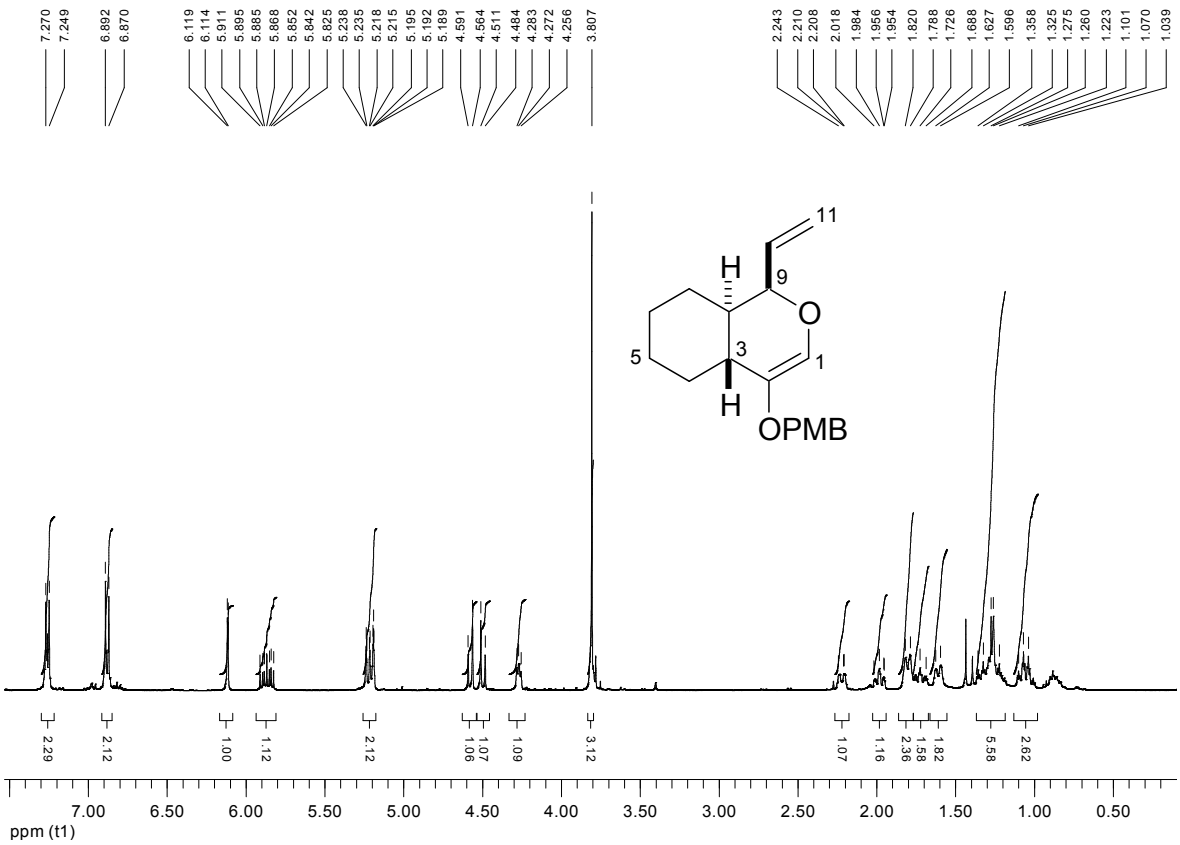


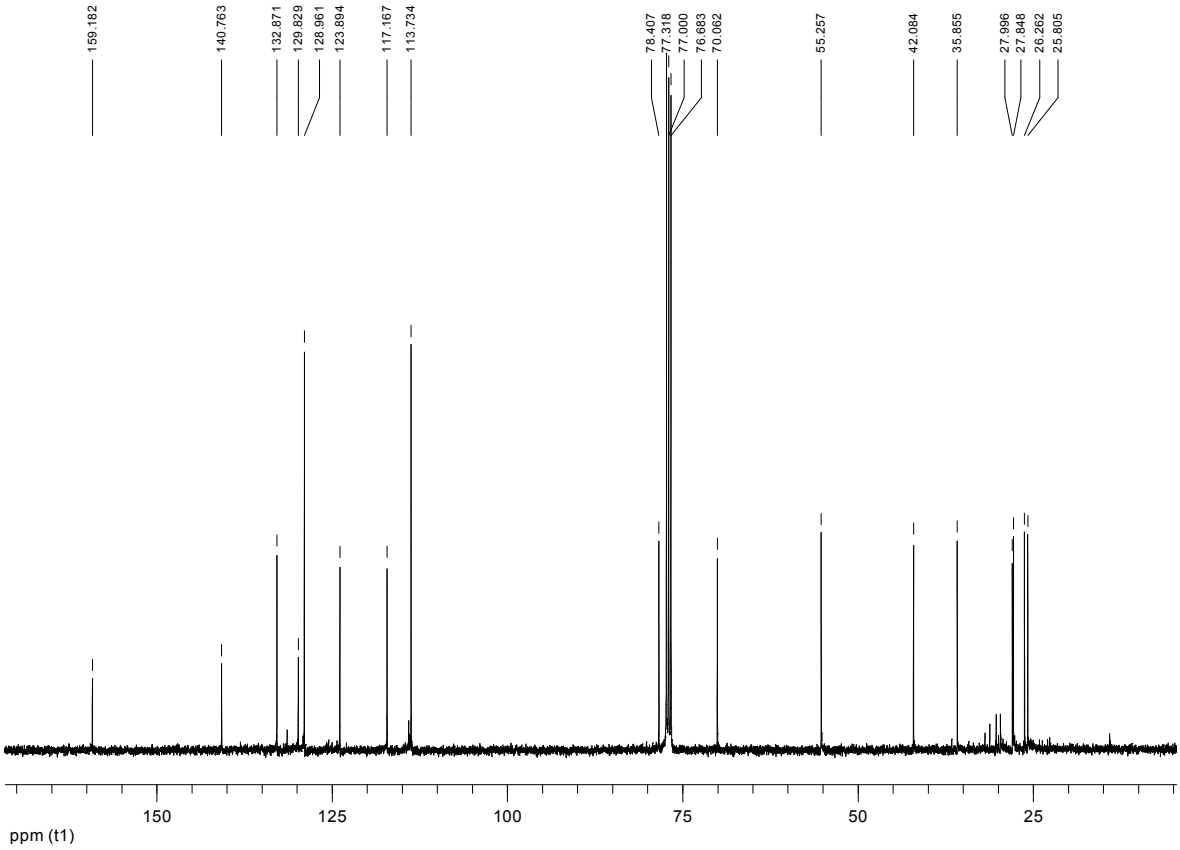
Appendix 2: ^{1}H and ^{13}C NMR spectra of 279



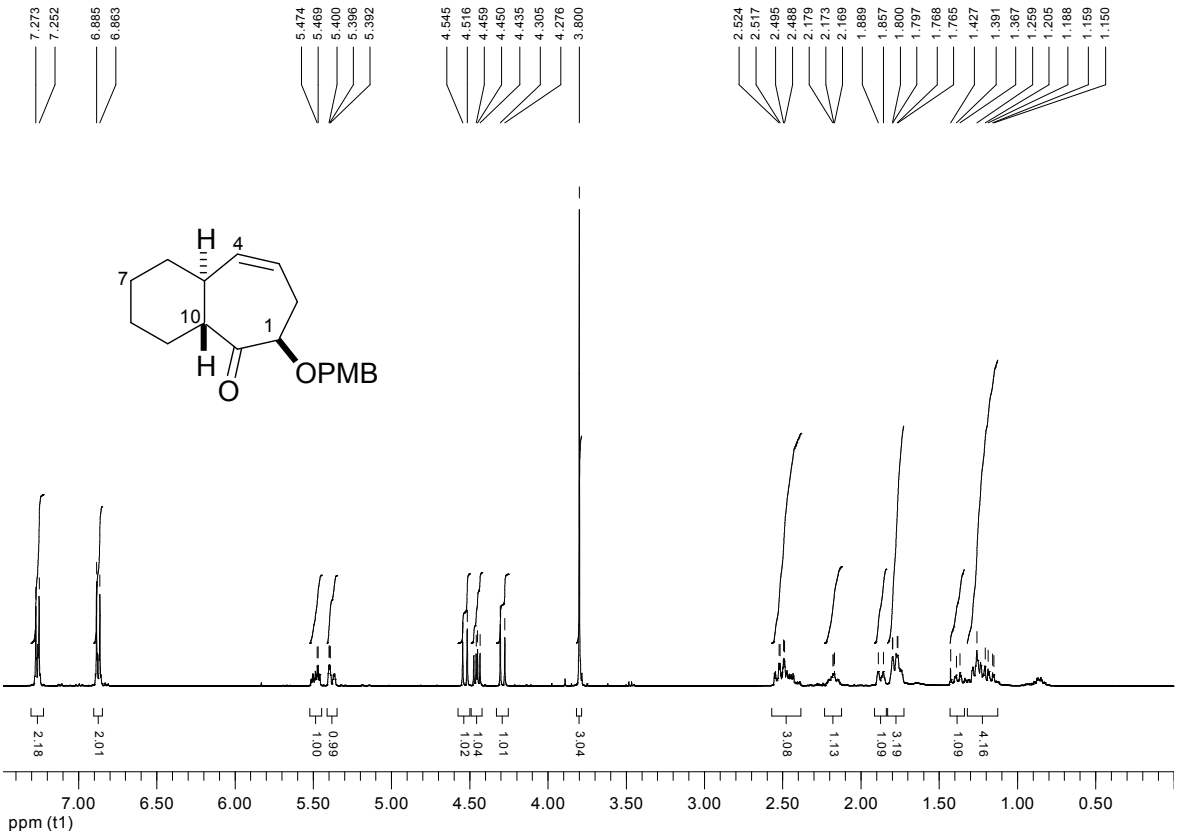


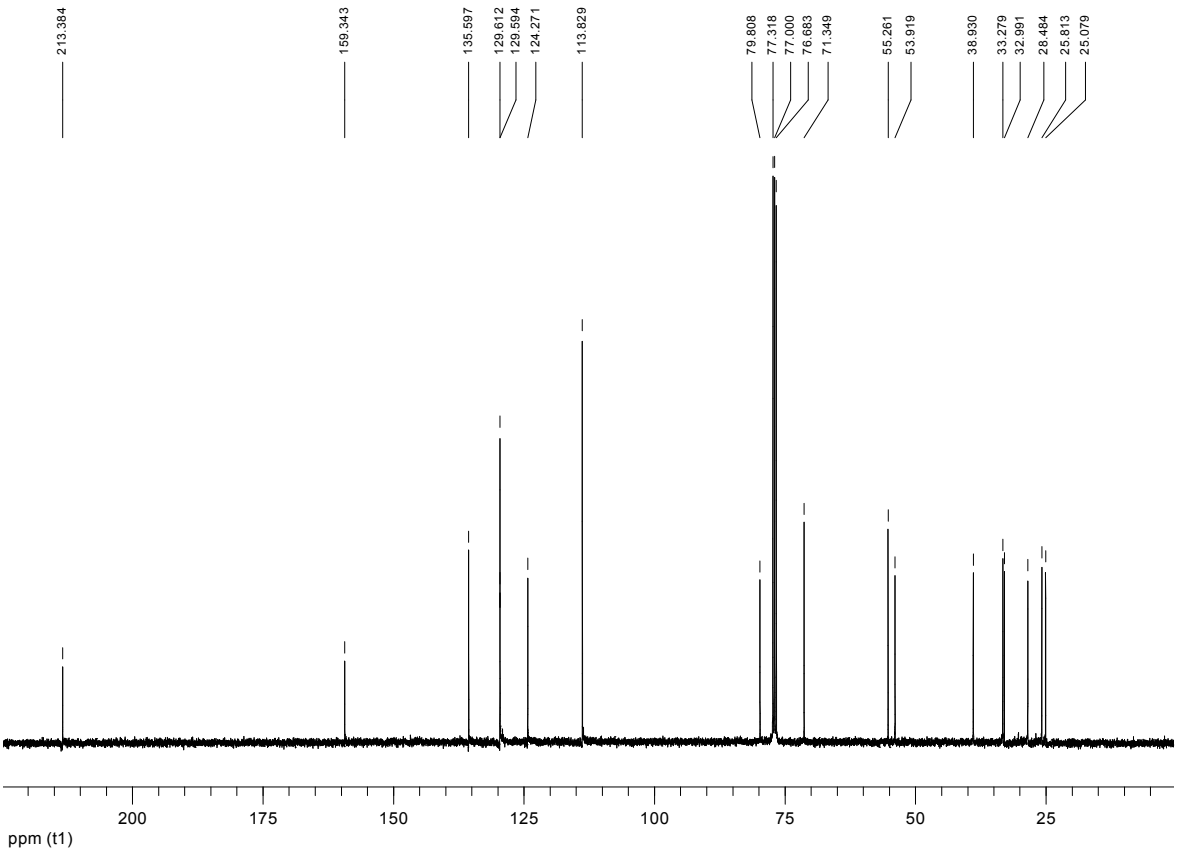
Appendix 3: ^{1}H and ^{13}C NMR spectra of 280



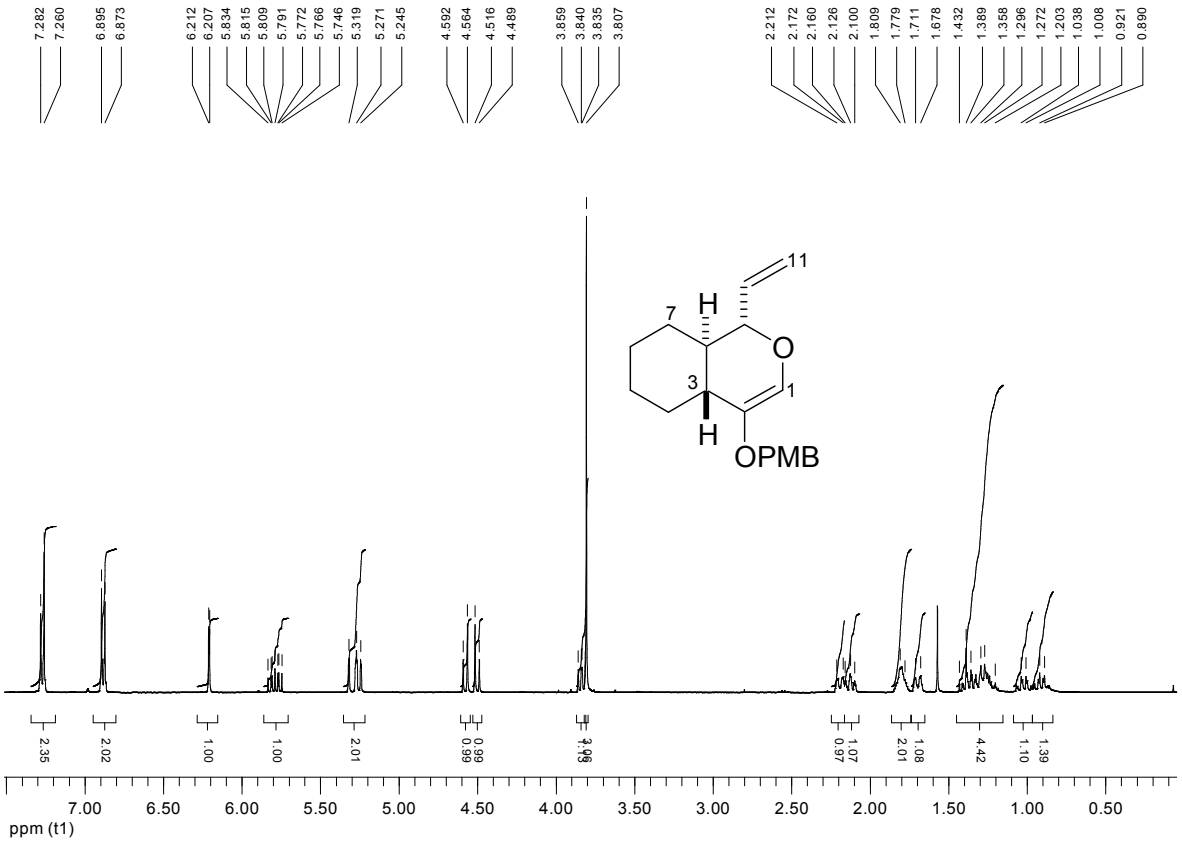


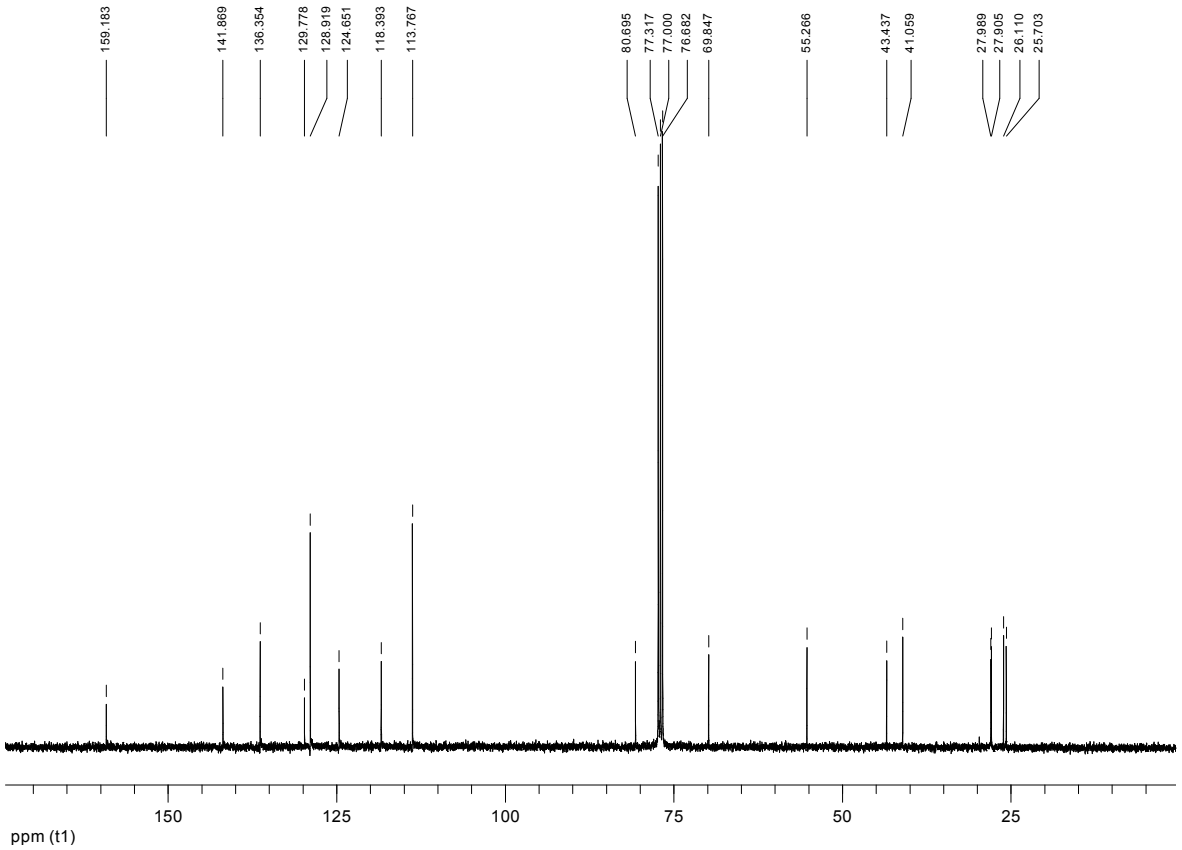
Appendix 4: ^{1}H and ^{13}C NMR spectra of 256



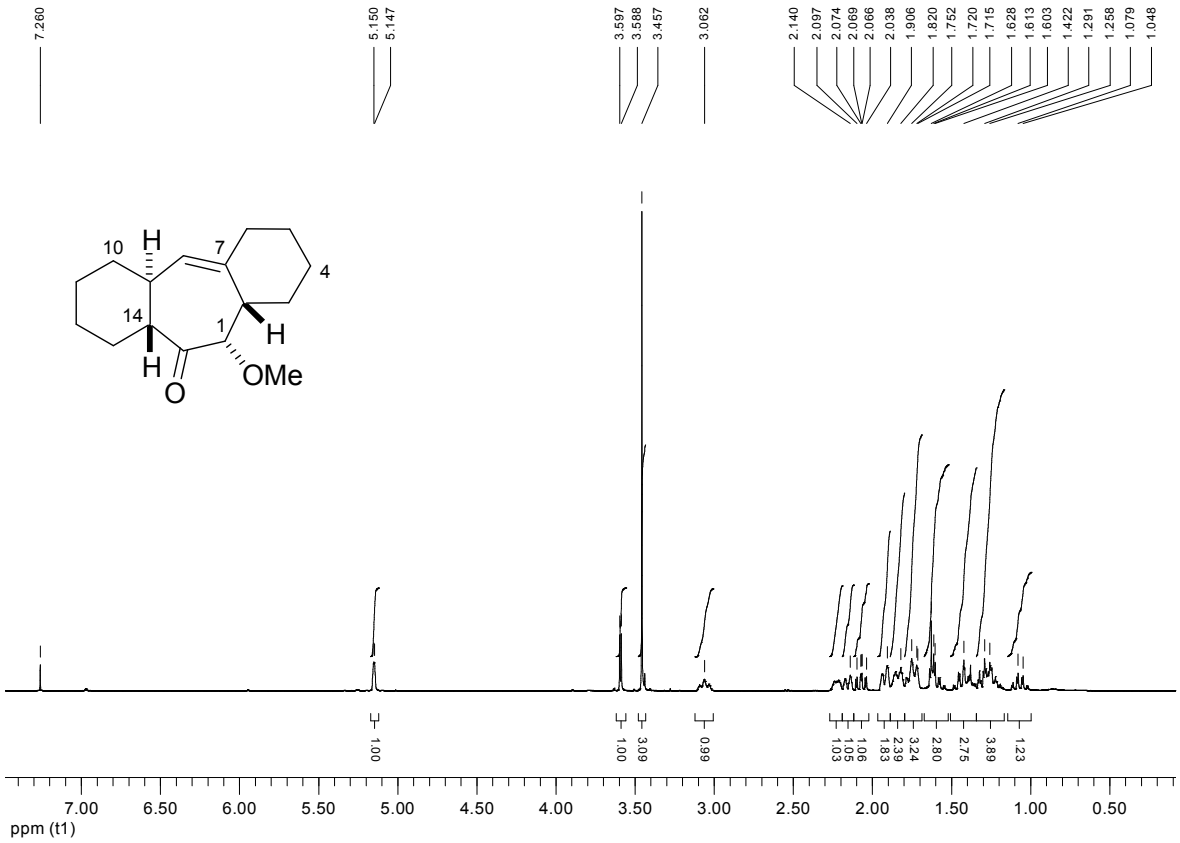


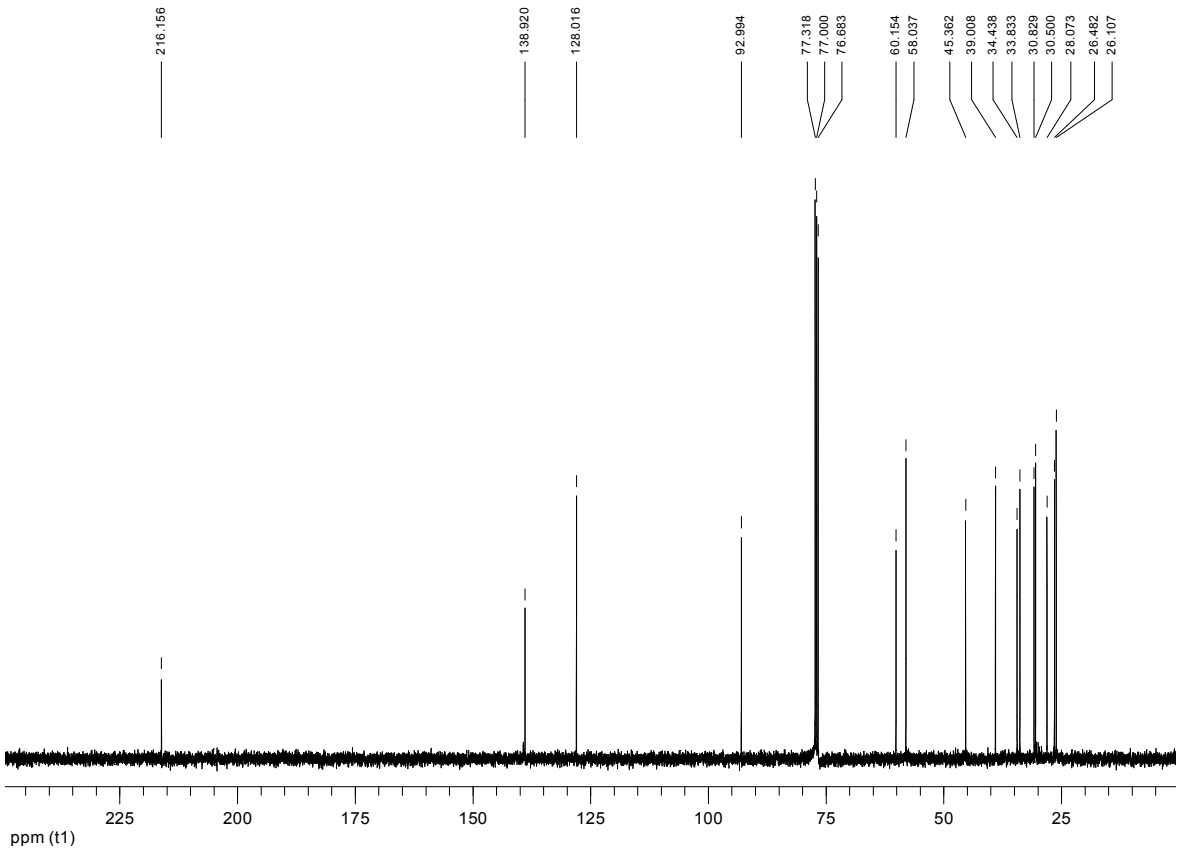
Appendix 5: ^{1}H and ^{13}C NMR spectra of 282



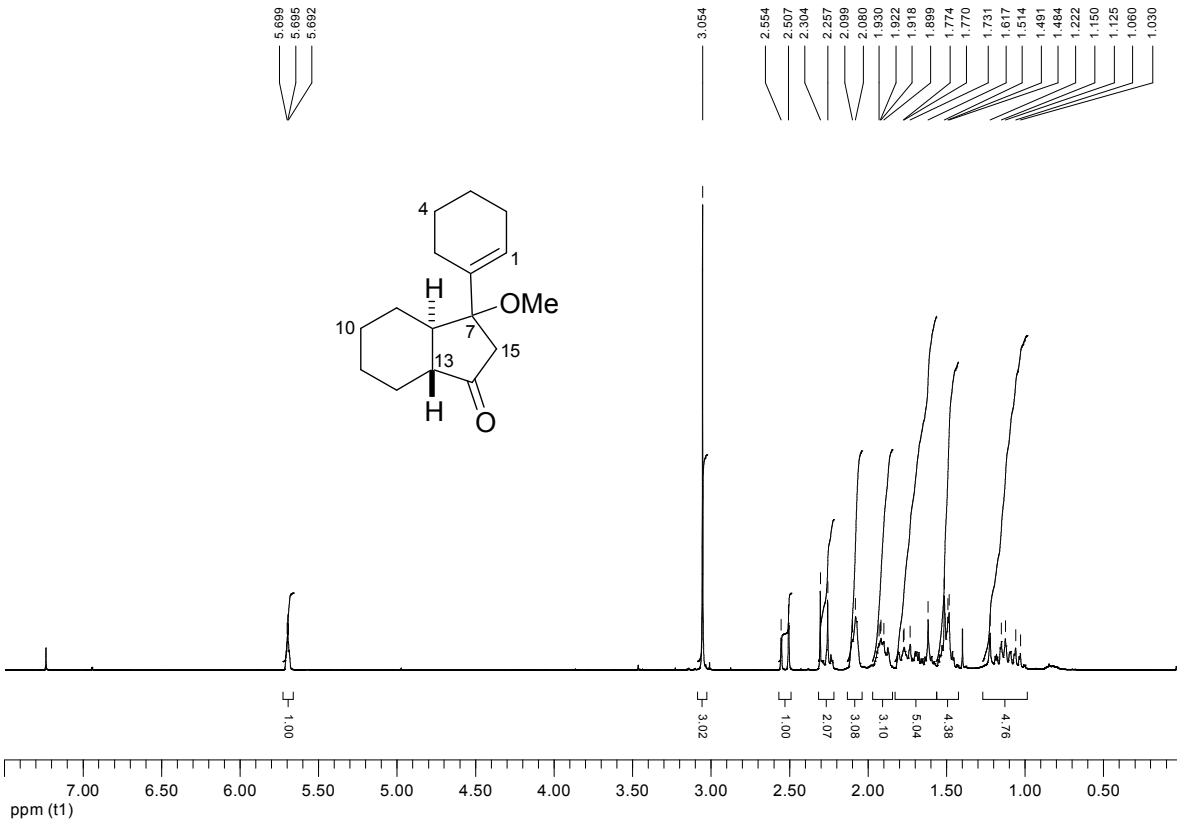


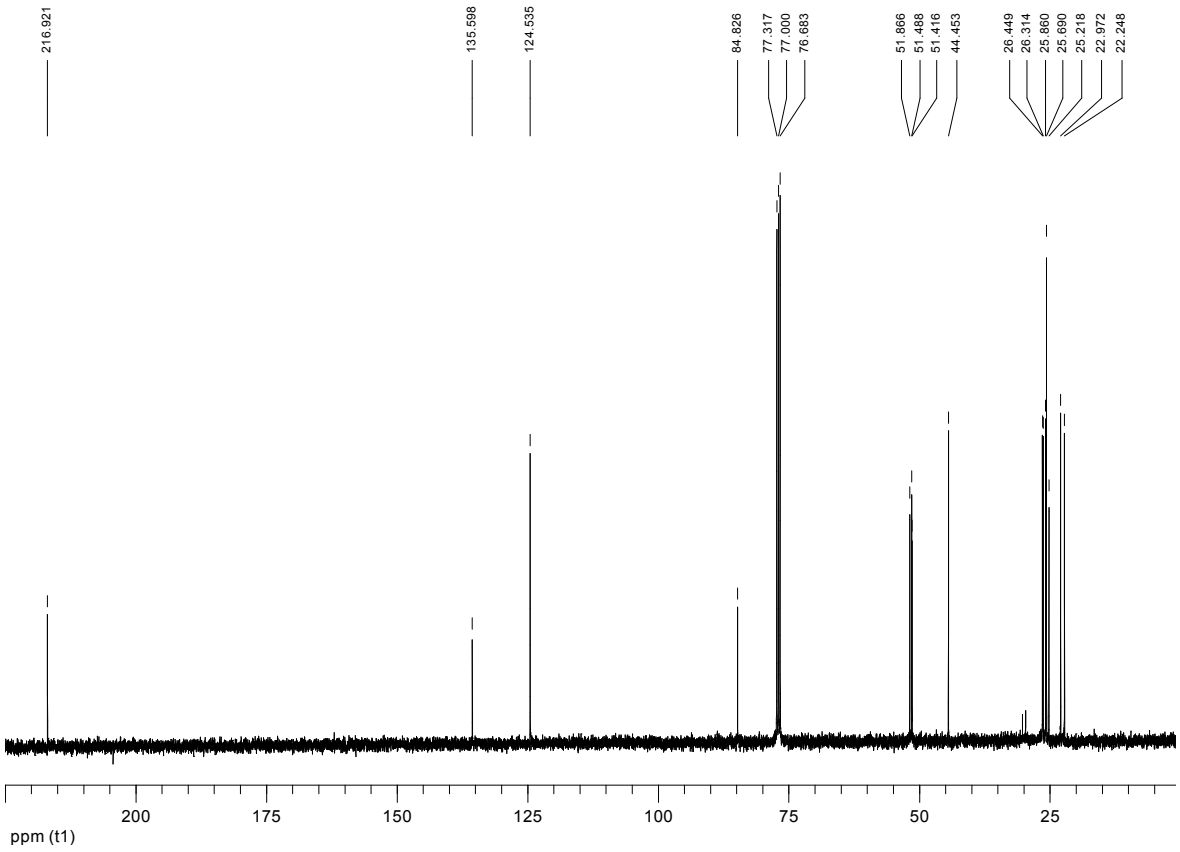
Appendix 6: ^{1}H and ^{13}C NMR spectra of 258



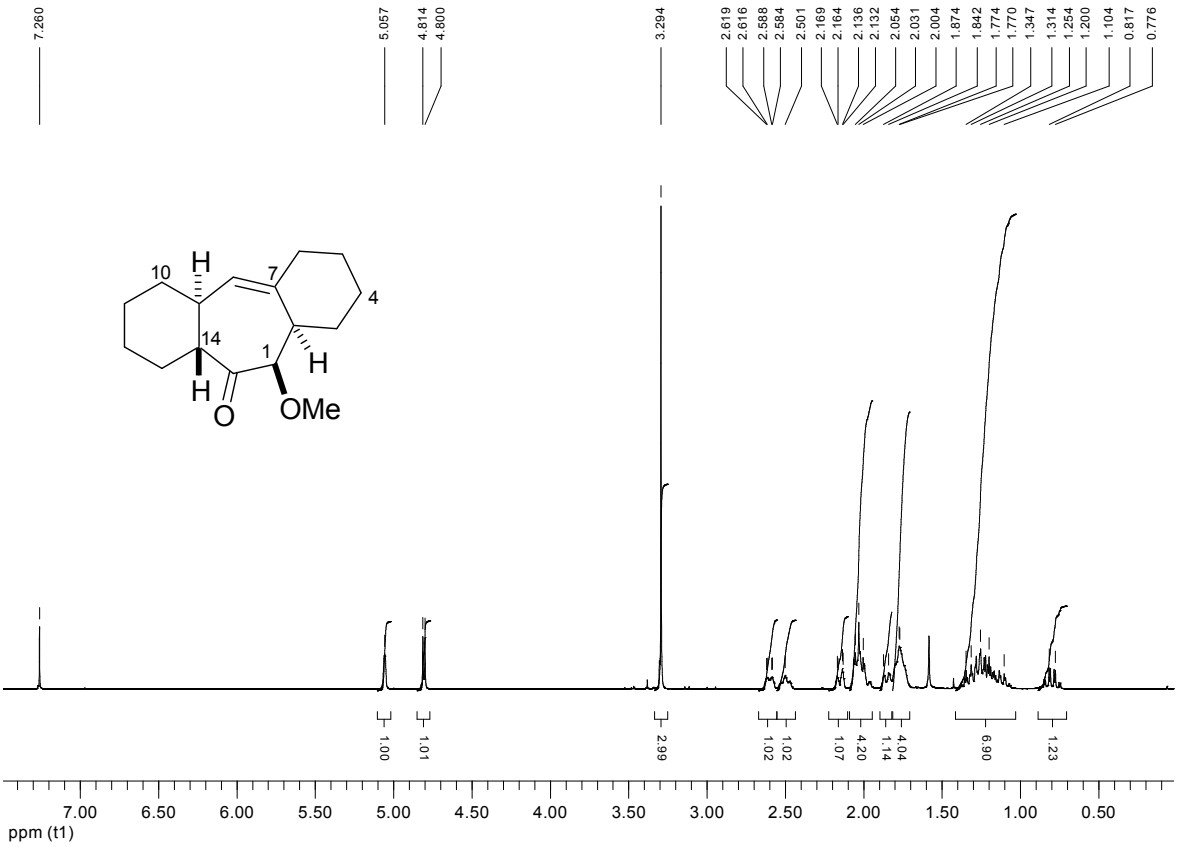


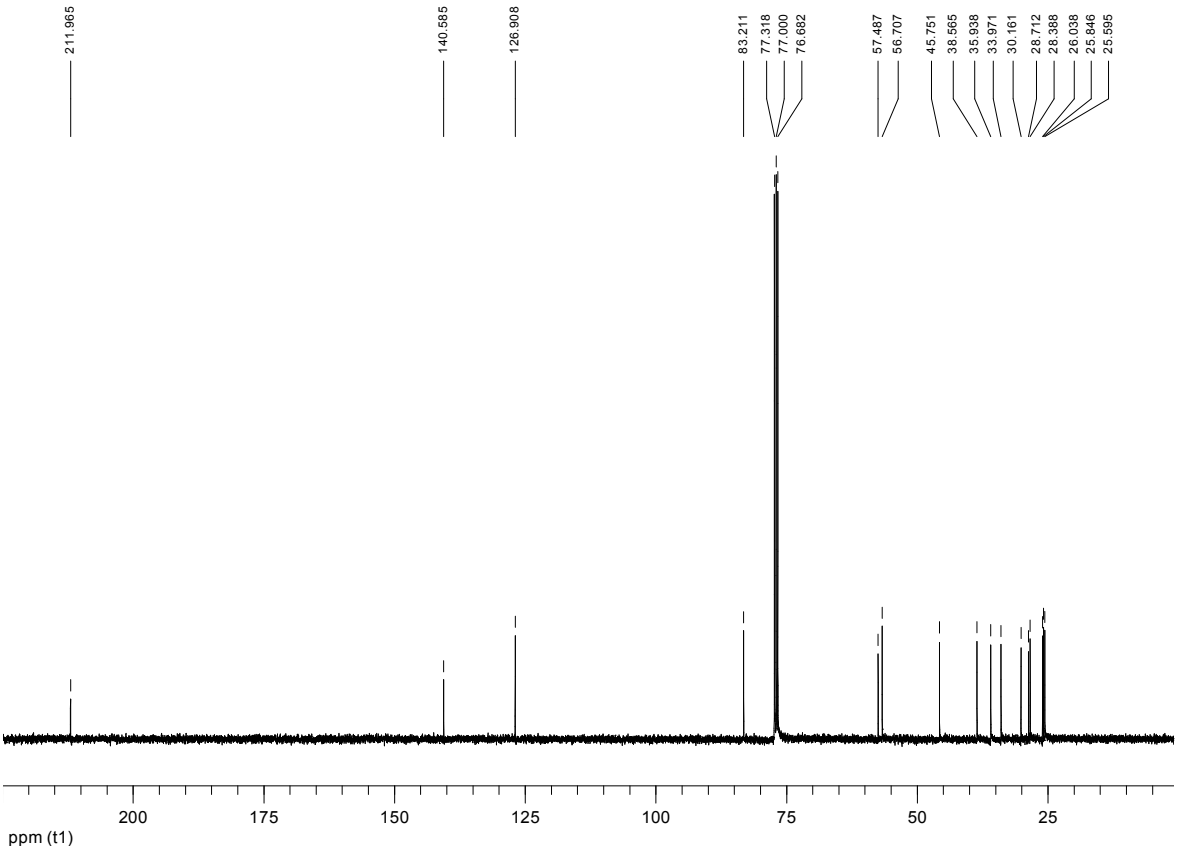
Appendix 7: ^{1}H and ^{13}C NMR spectra of 302



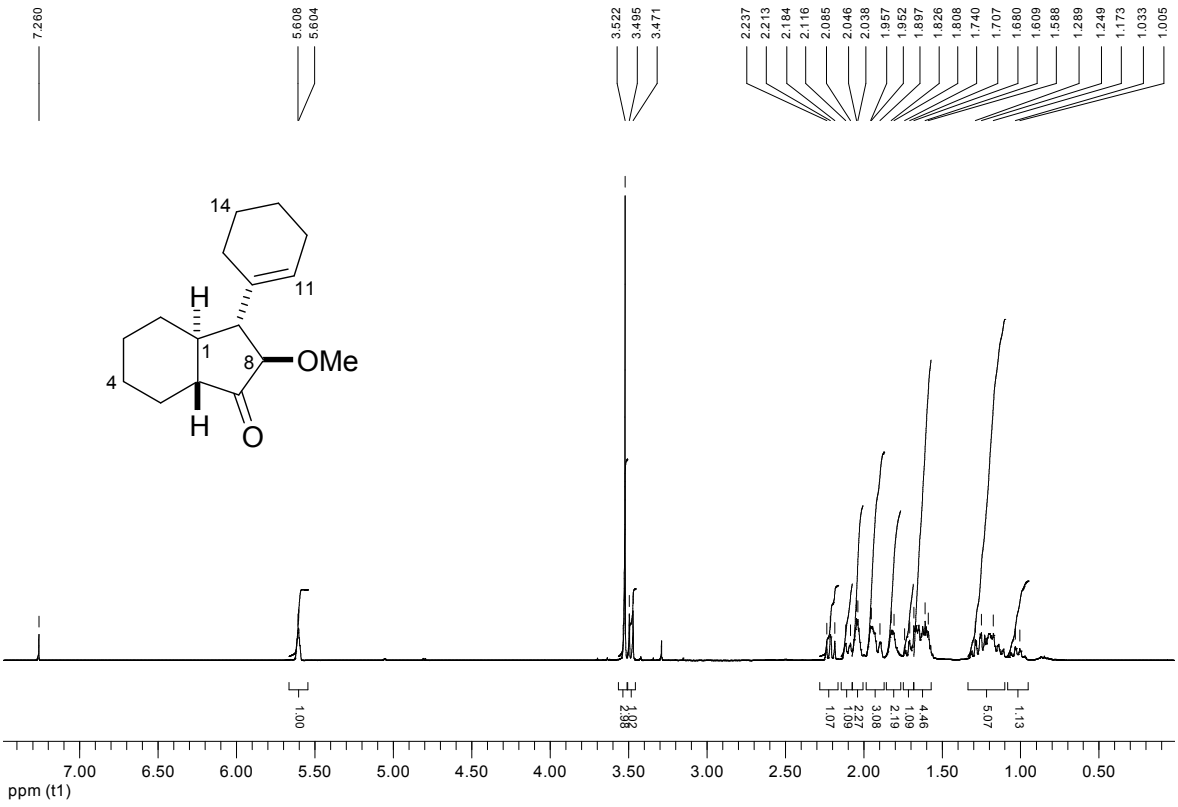


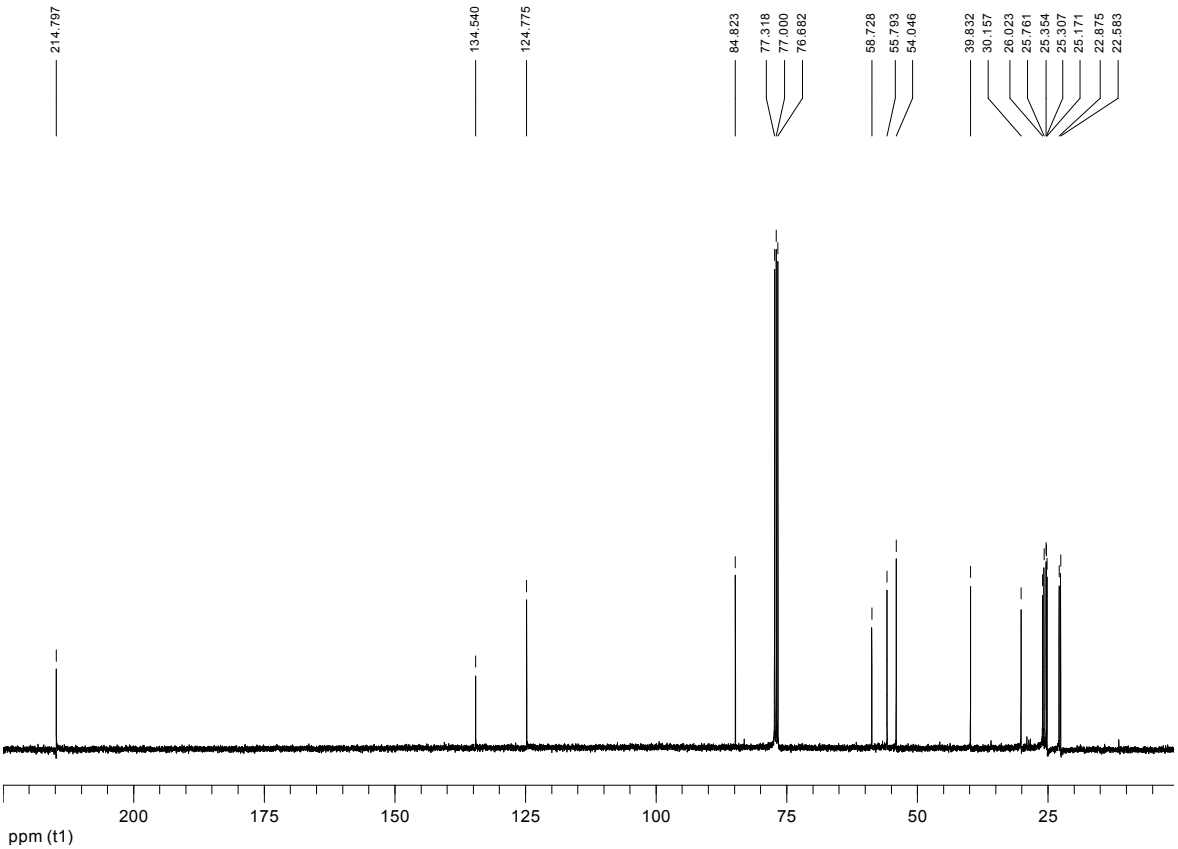
Appendix 9: ^{1}H and ^{13}C NMR spectra of 260



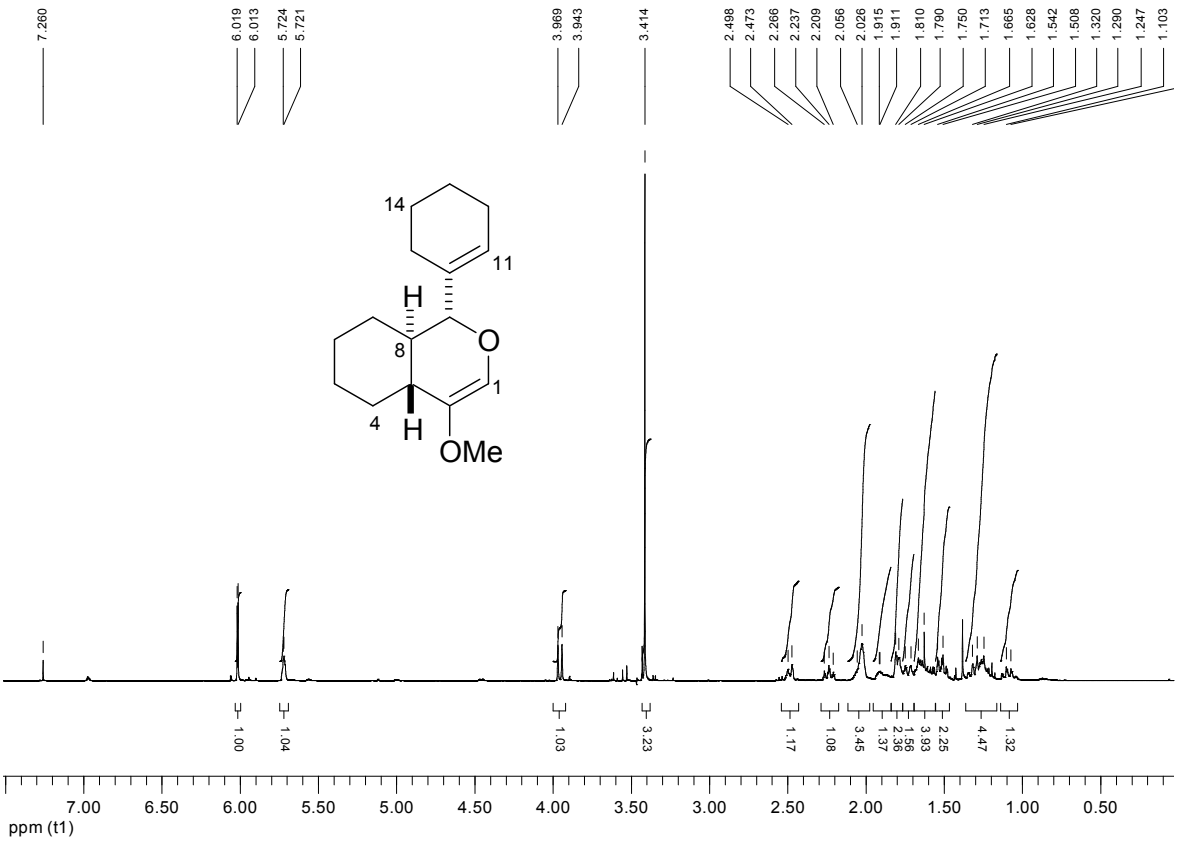


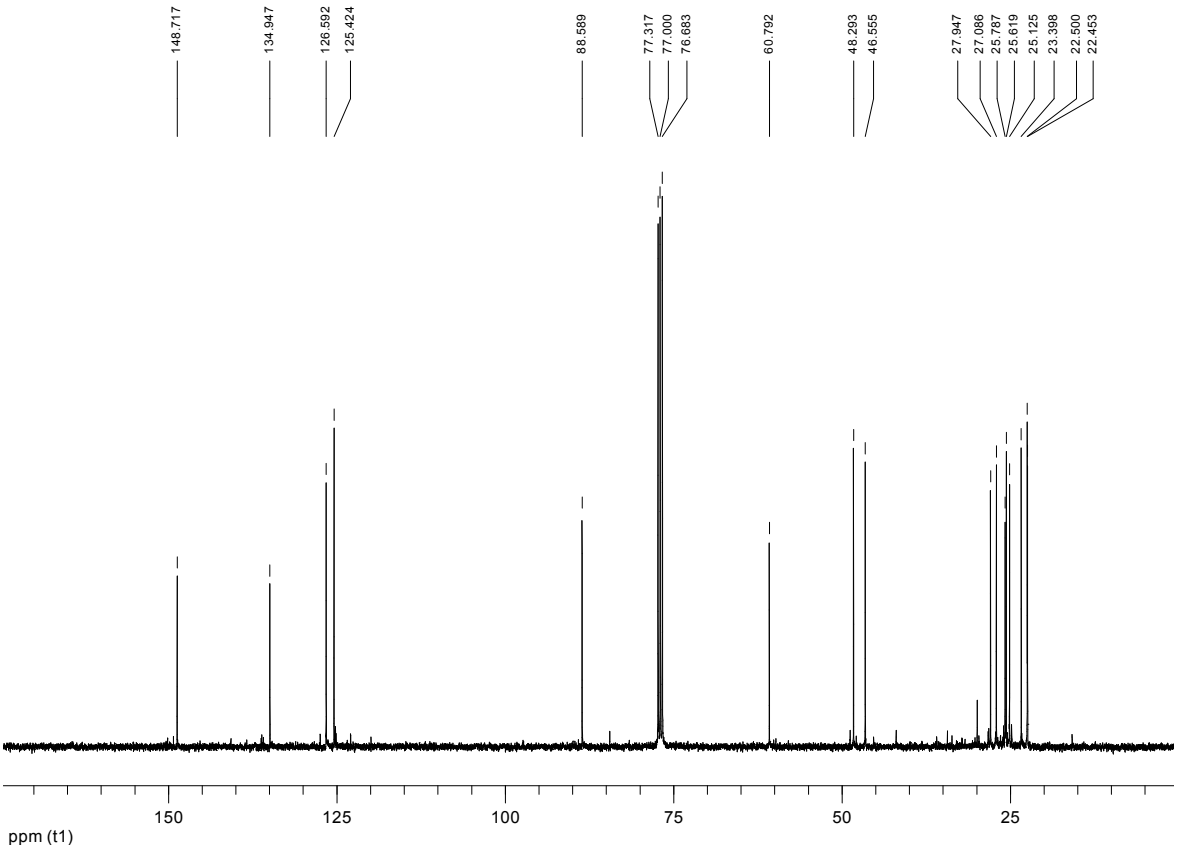
Appendix 10: ^{1}H and ^{13}C NMR spectra of 305



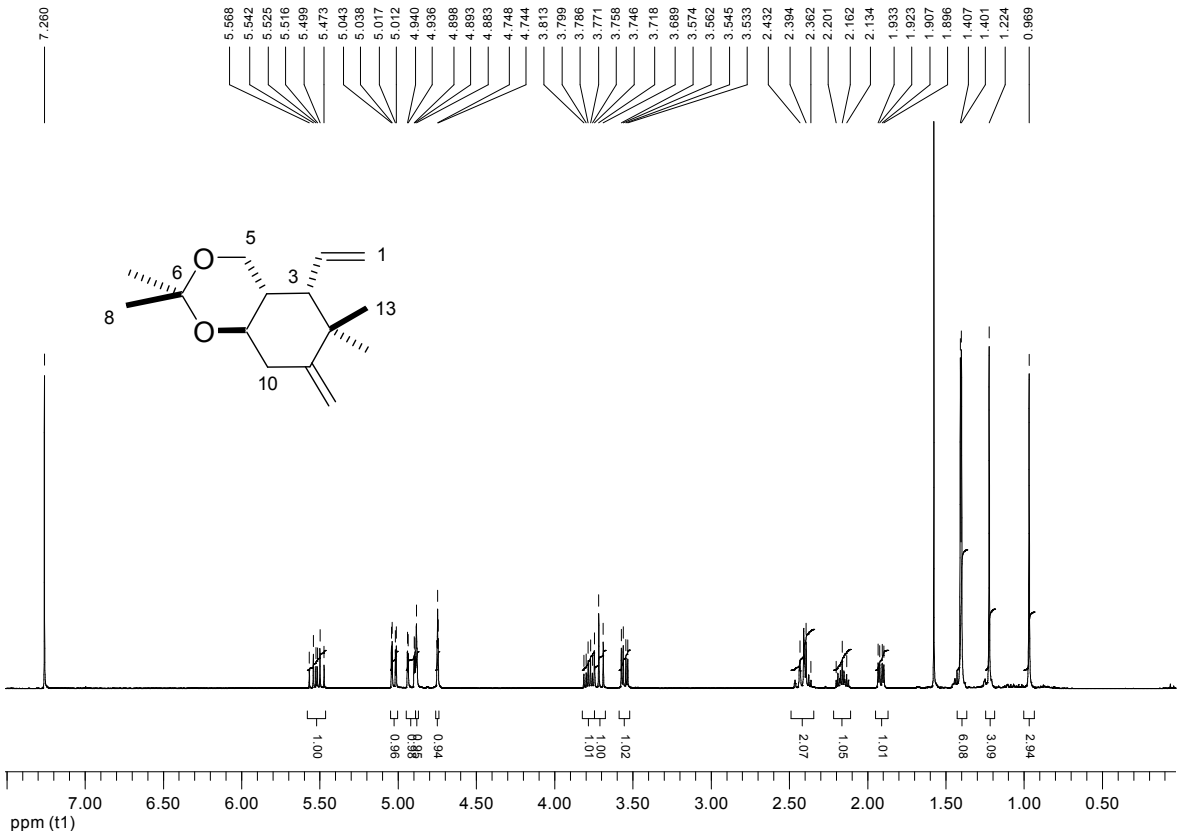


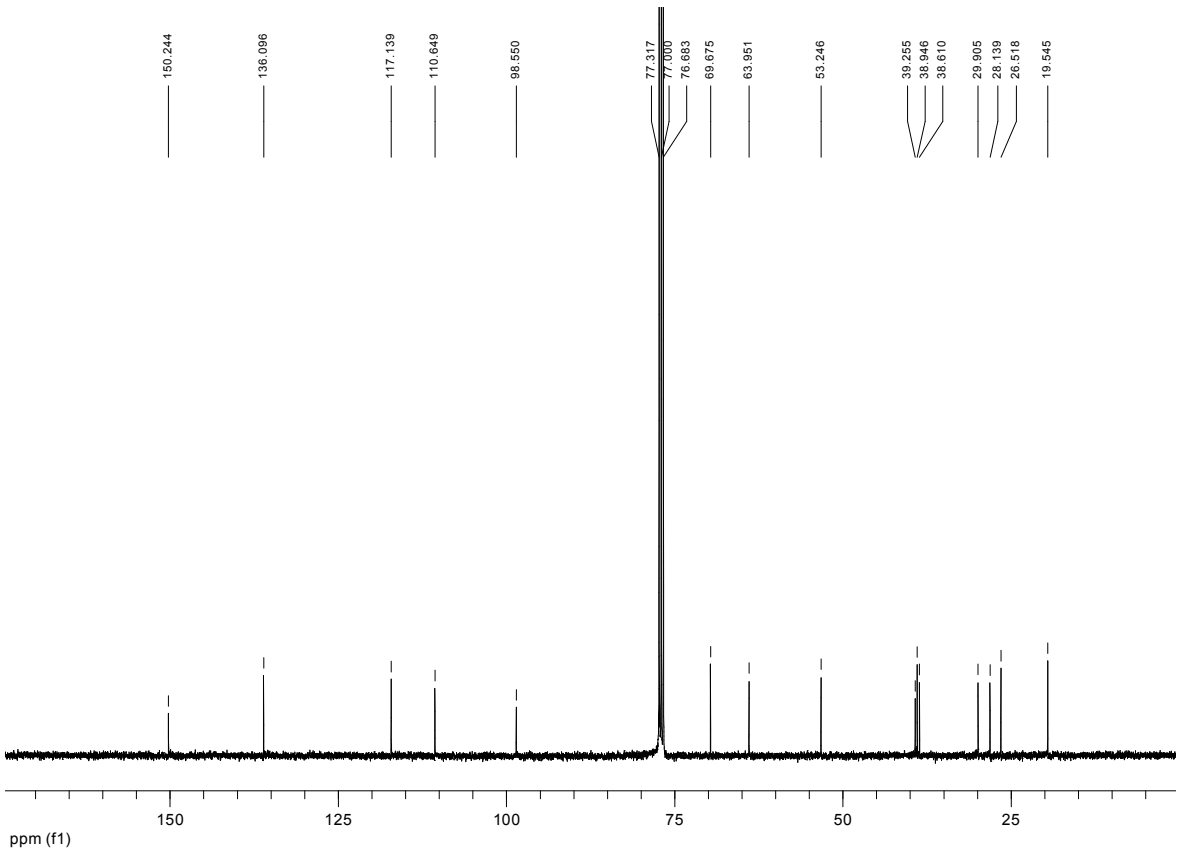
Appendix 11: ^{1}H and ^{13}C NMR spectra of 306



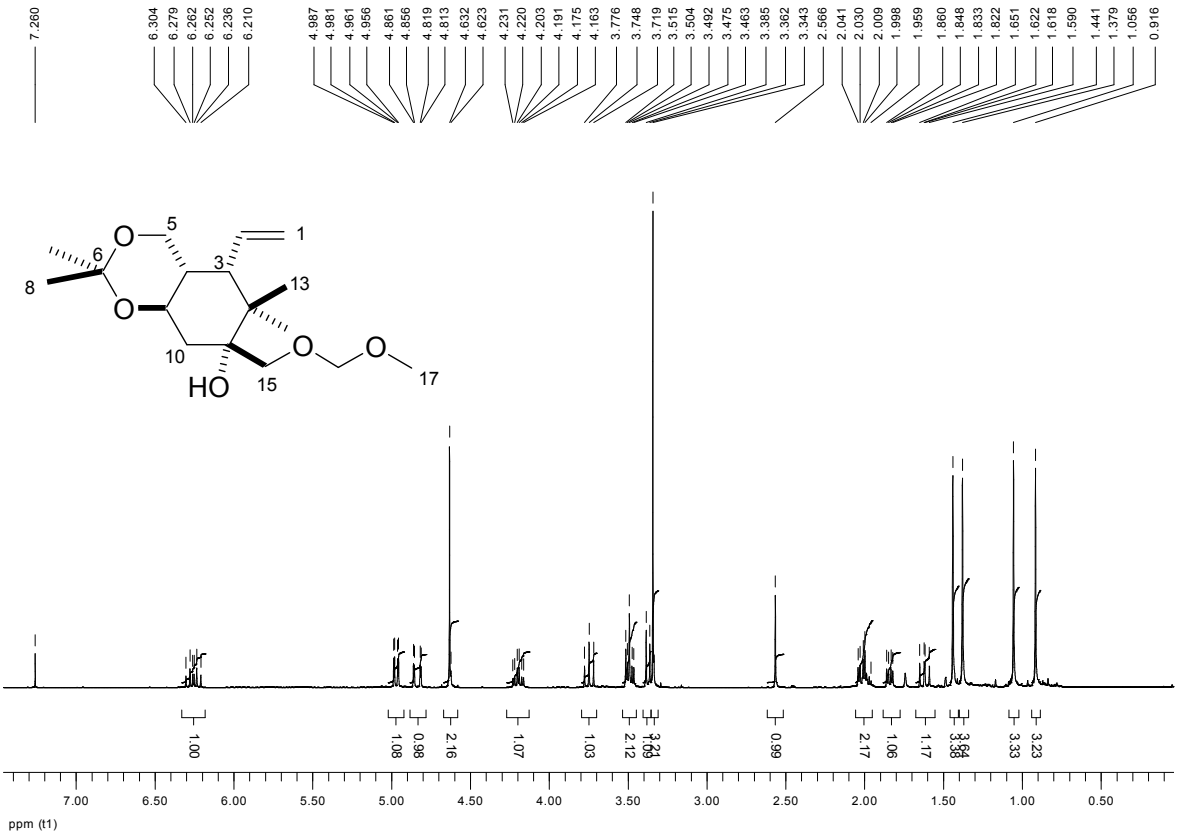


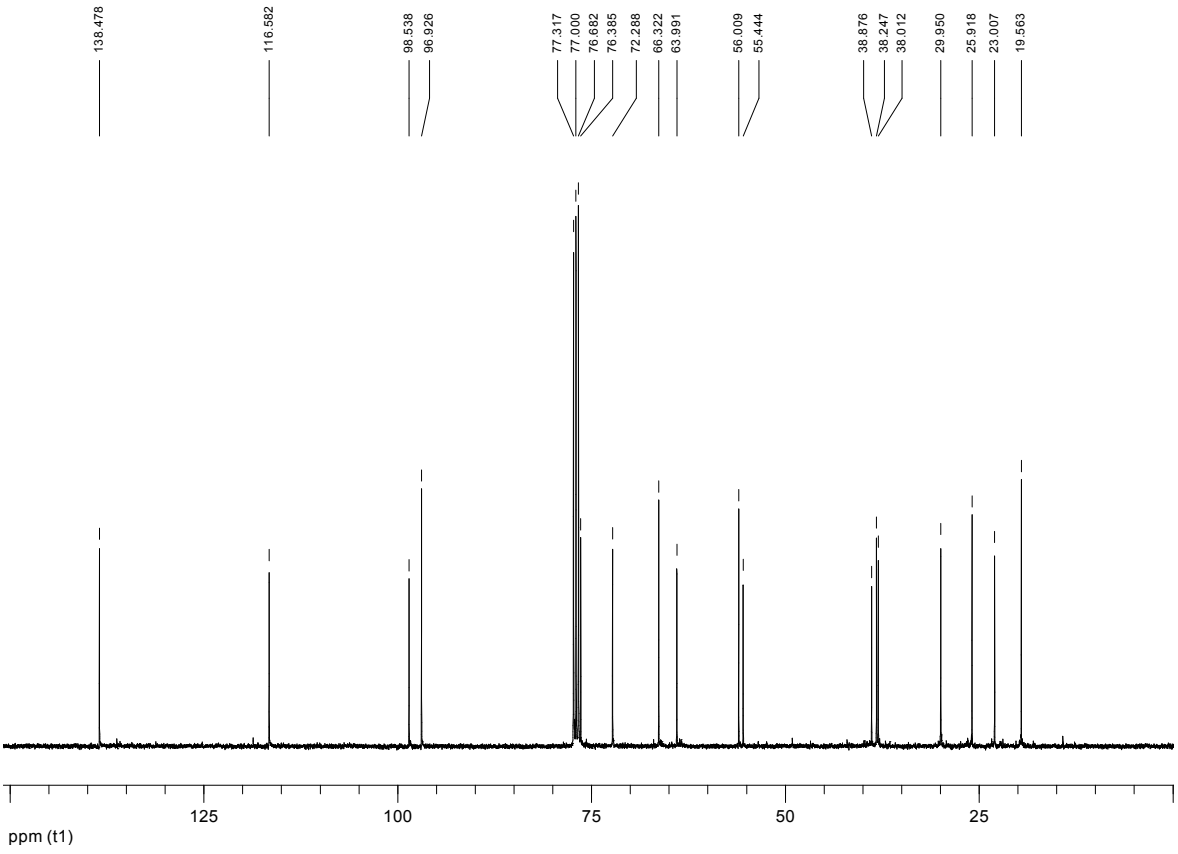
Appendix 12: ^{1}H and ^{13}C NMR spectra of 365



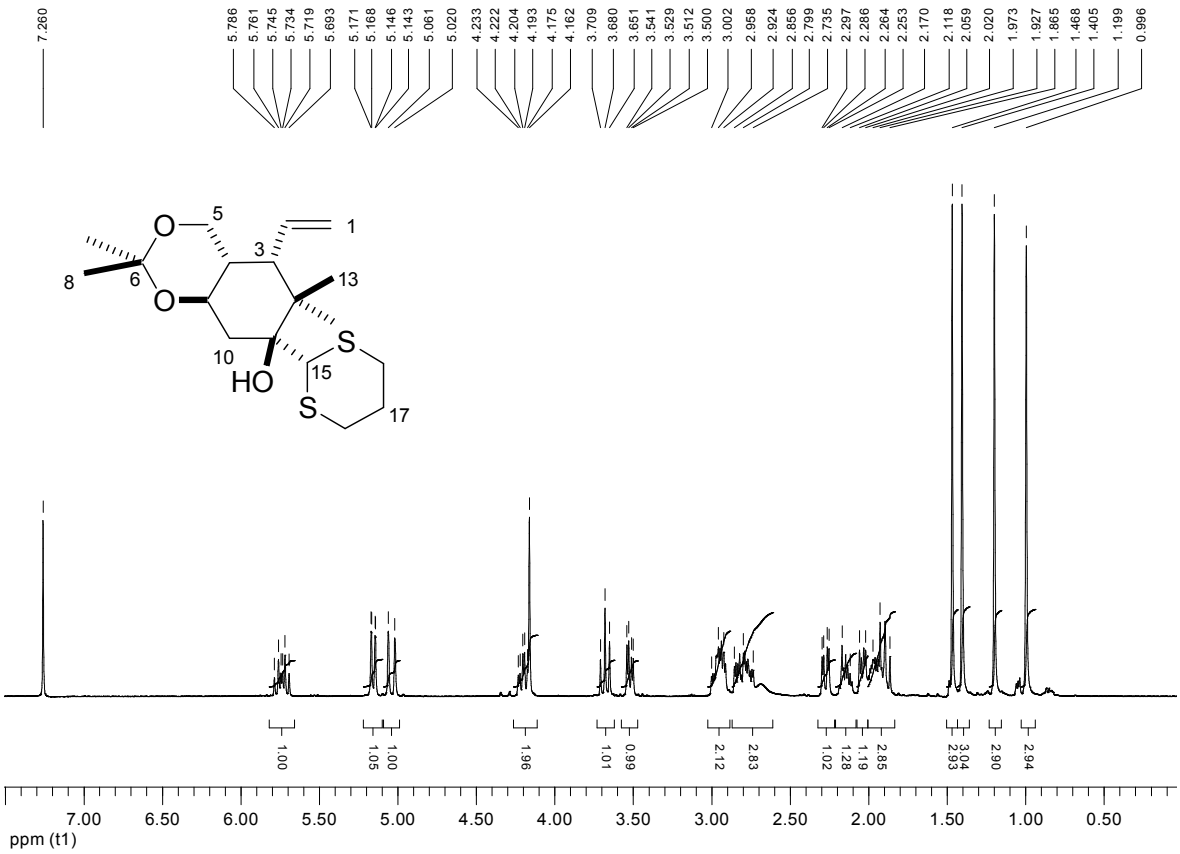


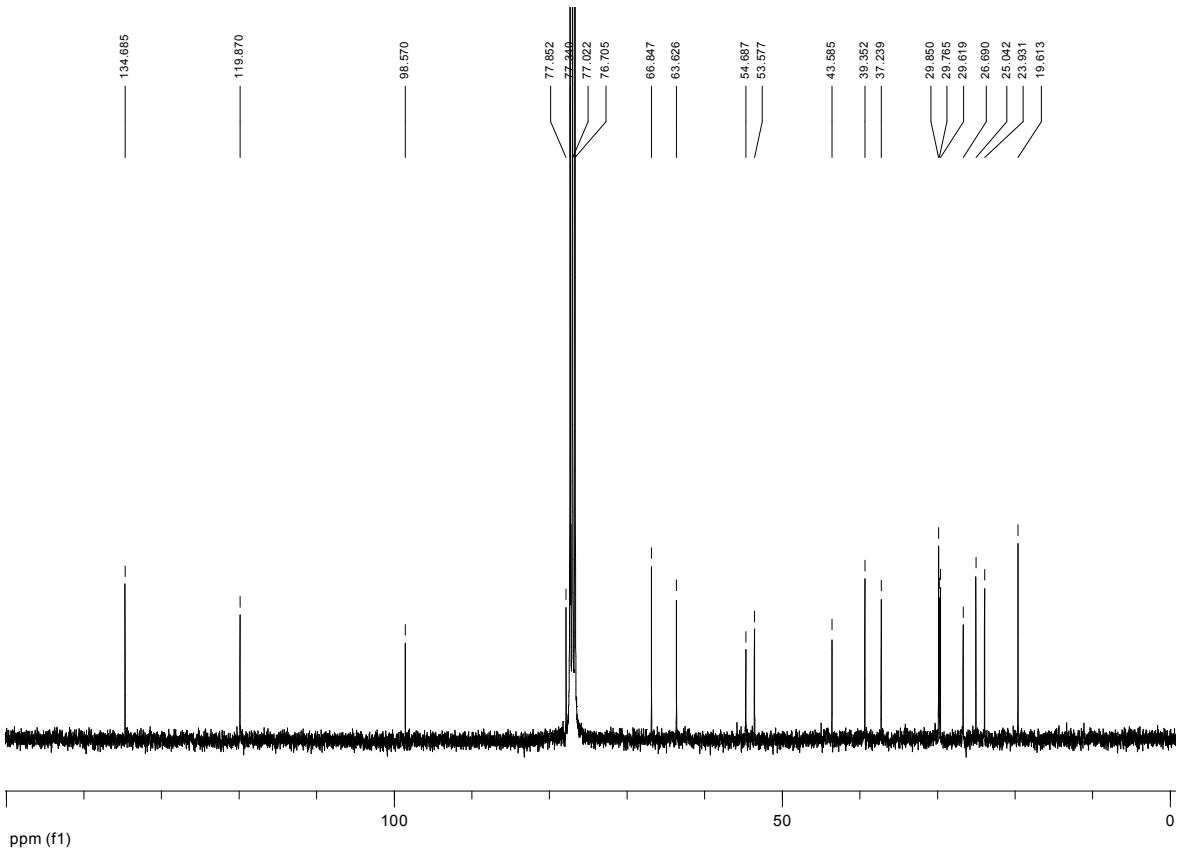
Appendix 13: ^{1}H and ^{13}C NMR spectra of 384a



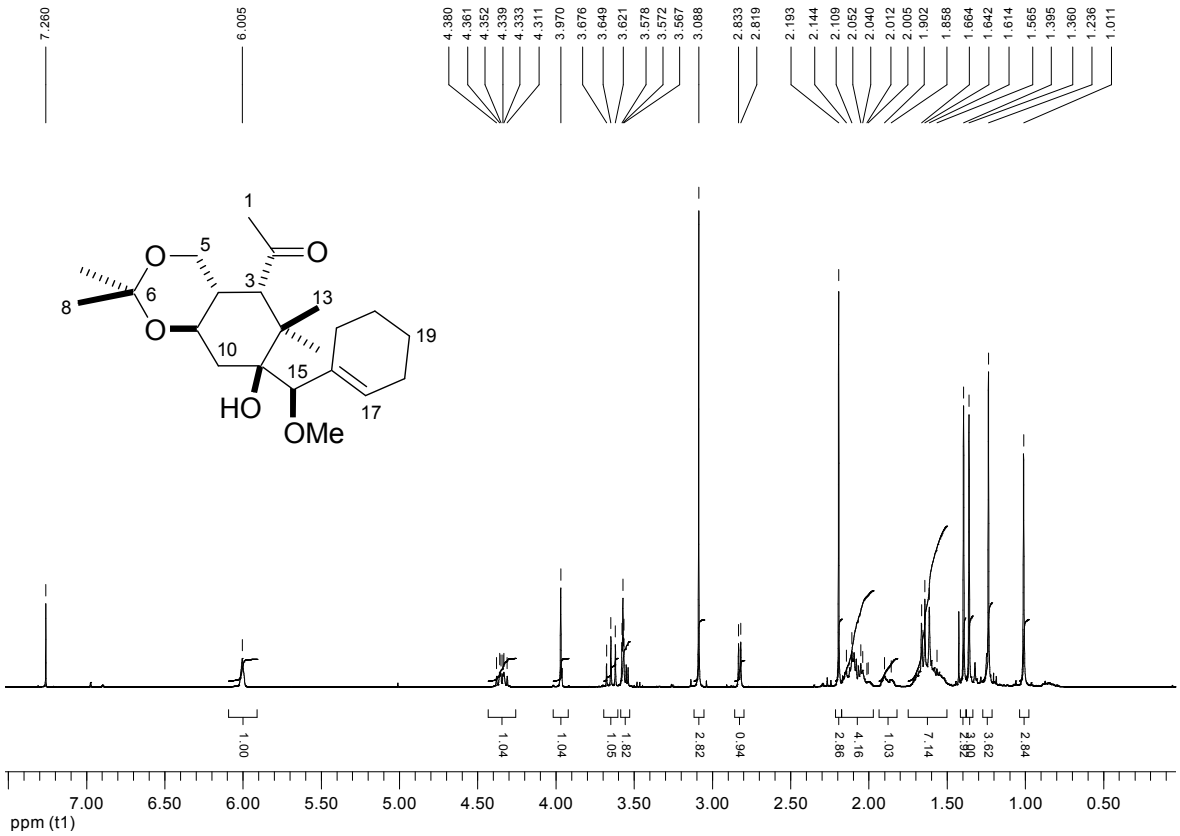


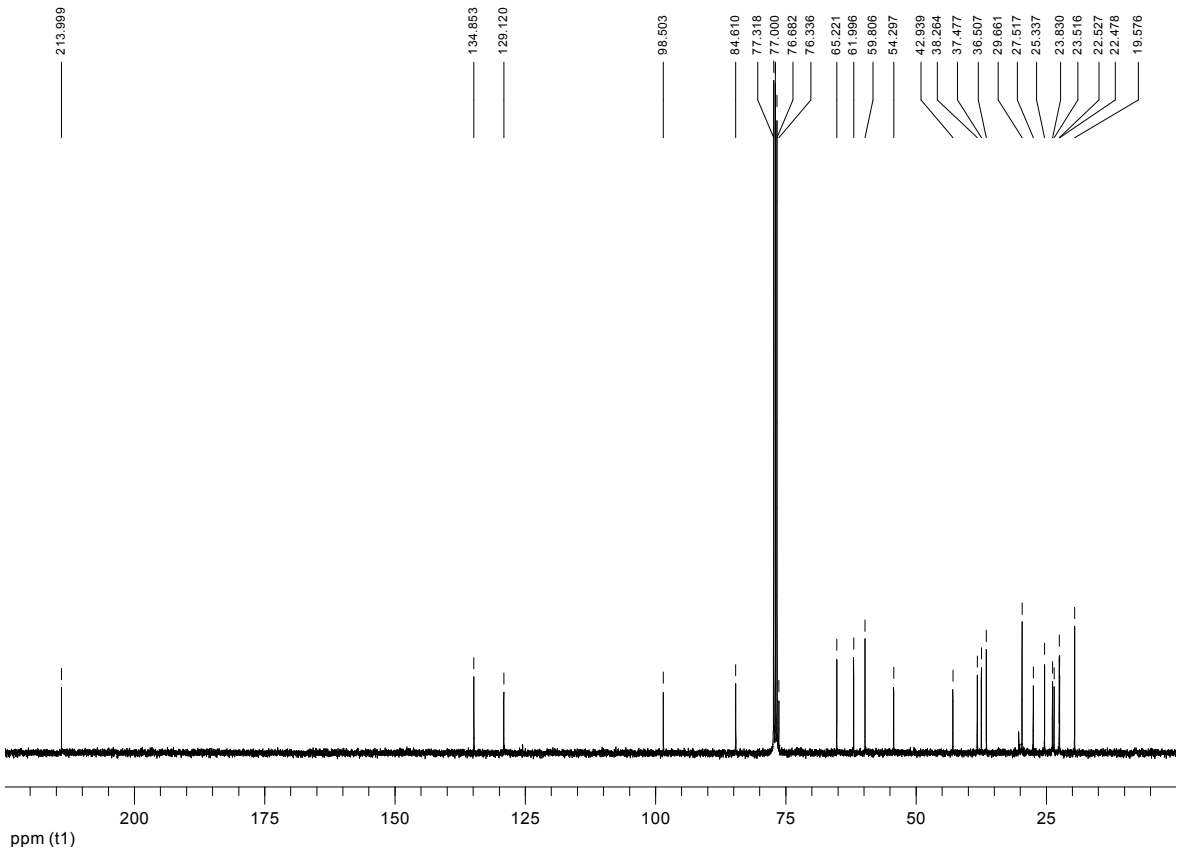
Appendix 14: ^{1}H and ^{13}C NMR spectra of 389



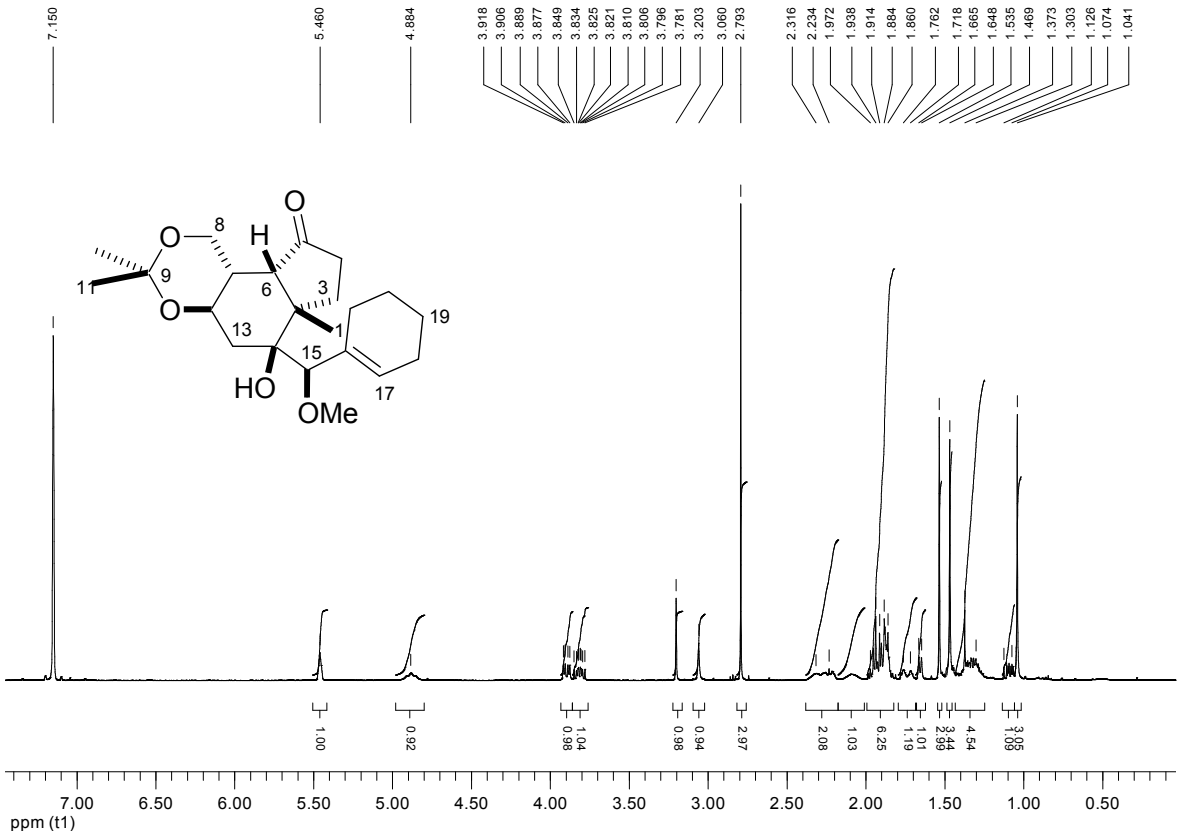


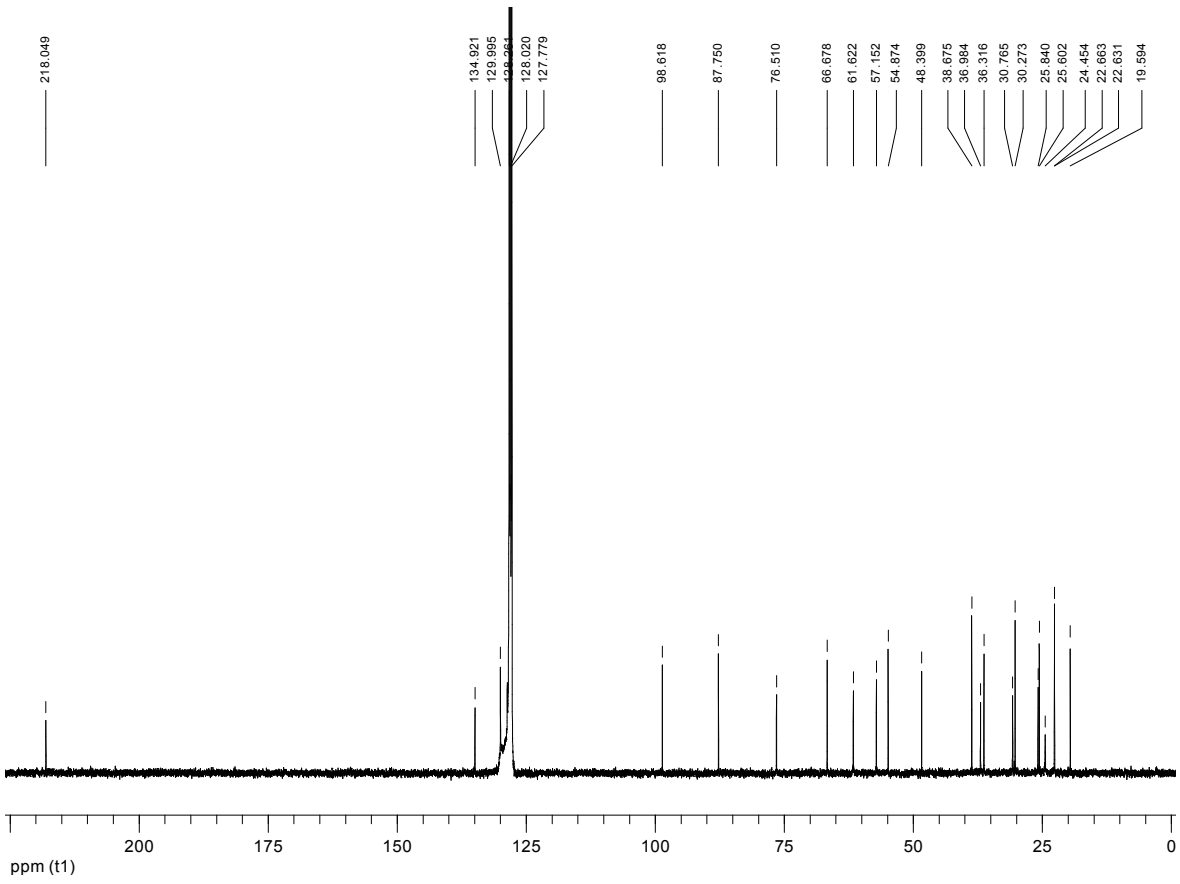
Appendix 15: ^{1}H and ^{13}C NMR spectra of 366



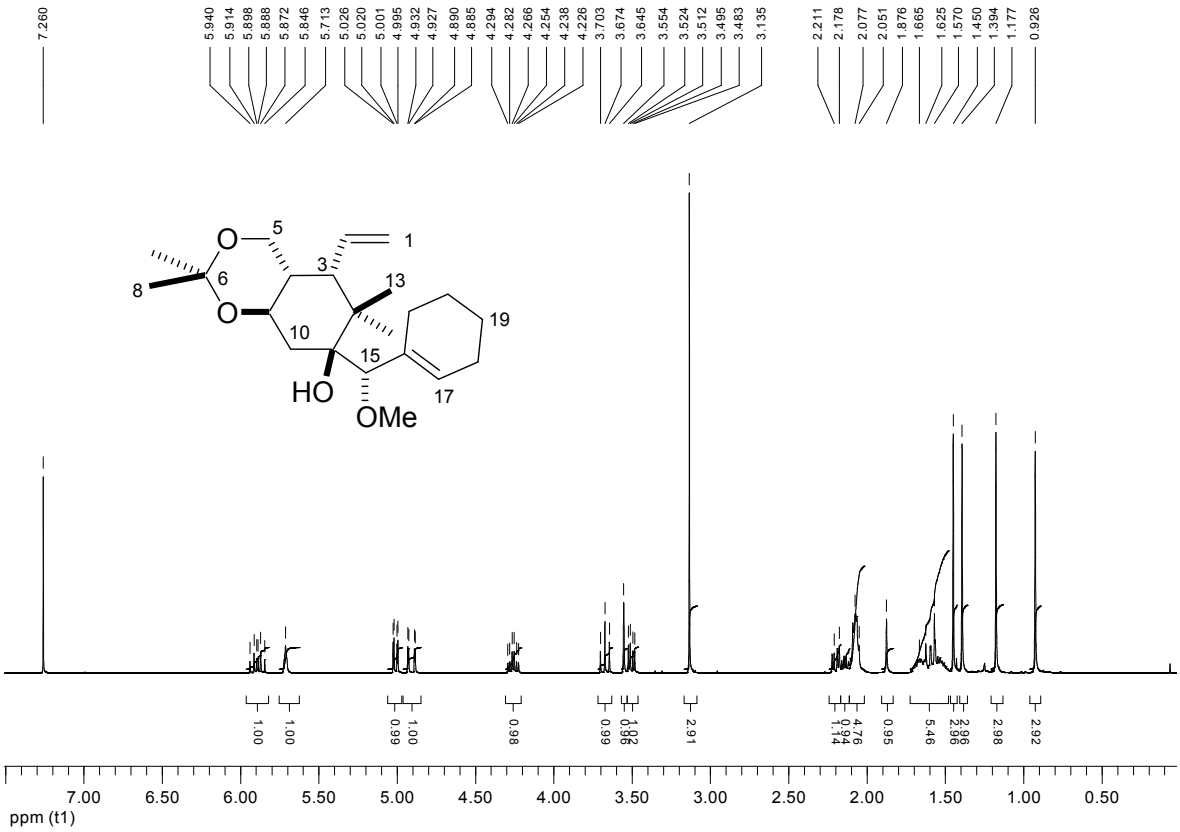


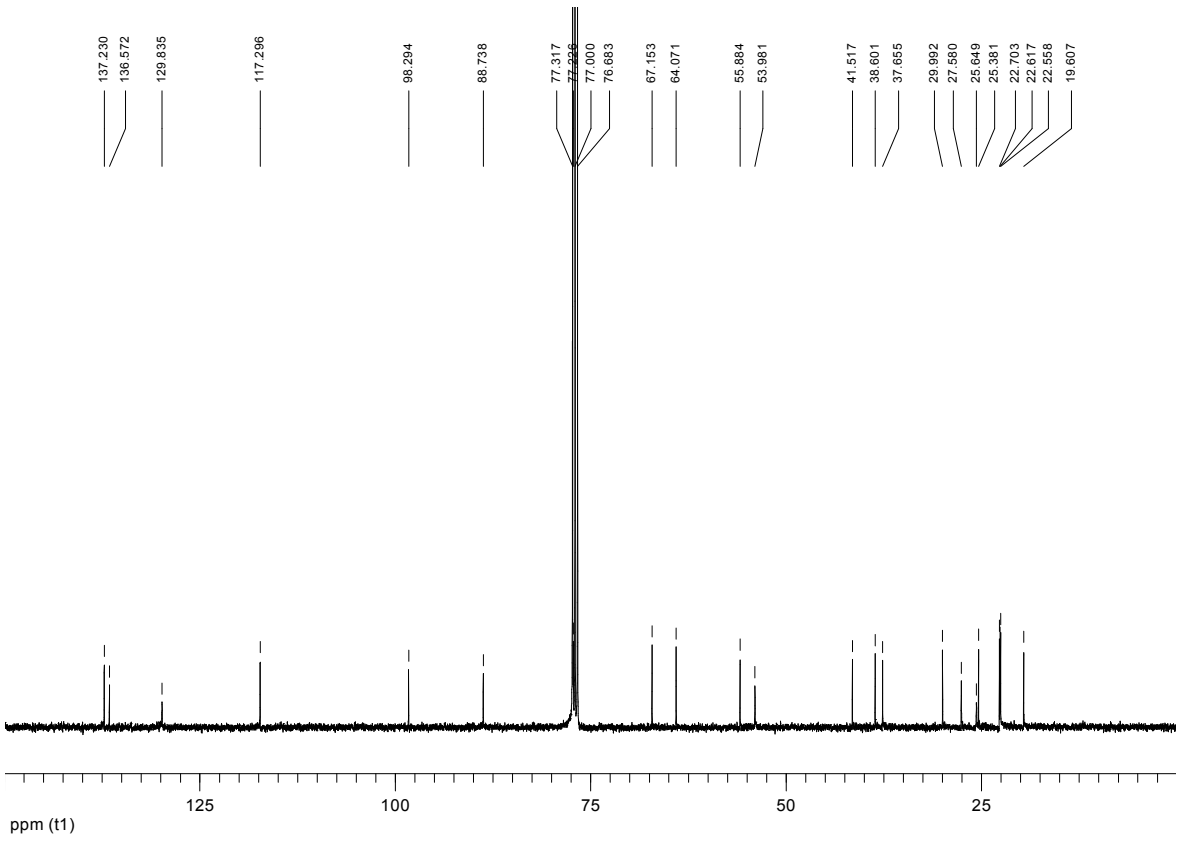
Appendix 16: ^{1}H and ^{13}C NMR spectra of 401





Appendix 17: ^{1}H and ^{13}C NMR spectra of 409





Appendix 18: X-ray crystal structure of the [1,4]-shift product 282

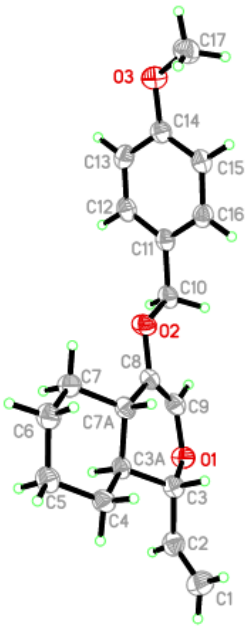


Table 1. Crystal data and structure refinement for mebzqu.

Identification code	mebzqu	
Empirical formula	C19 H24 O3	
Formula weight	300.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.4027(6) Å	α= 97.311(2)°.
	b = 11.2344(13) Å	β= 95.227(2)°.
	c = 13.4933(16) Å	γ = 91.841(2)°.
Volume	808.16(16) Å^3	
Z	2	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	324	
Crystal size	0.41 x 0.16 x 0.03 mm^3	
Theta range for data collection	2.23 to 27.52°.	
Index ranges	-6<=h<=6, -14<=k<=14, -17<=l<=17	
Reflections collected	6346	
Independent reflections	3546 [R(int) = 0.038	
Completeness to theta = 27.50°	95.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3546 / 0 / 199	
Goodness-of-fit on F^2	0.938	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.0870	
R indices (all data)	R1 = 0.0704, wR2 = 0.0933	
Largest diff. peak and hole	0.205 and -0.184 e.Å^{-3}	

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

	x	y	z	U(eq)
O(1)	3776(2)	2861(1)	6549(1)	32(1)
C(1)	8255(3)	2030(2)	4948(1)	44(1)
O(2)	2789(2)	2509(1)	9164(1)	34(1)
C(2)	6195(3)	1887(1)	5362(1)	34(1)
O(3)	291(2)	4013(1)	13554(1)	41(1)
C(3A)	5590(3)	1001(1)	6958(1)	26(1)
C(3)	5921(3)	2129(1)	6456(1)	29(1)
C(4)	7697(3)	142(1)	6838(1)	33(1)
C(5)	7229(3)	-974(1)	7344(1)	38(1)
C(6)	6727(3)	-666(1)	8438(1)	36(1)
C(7A)	5308(3)	1339(1)	8069(1)	28(1)
C(7)	4663(3)	222(1)	8554(1)	34(1)
C(8)	3546(3)	2337(1)	8207(1)	27(1)
C(9)	2900(3)	3001(1)	7486(1)	29(1)
C(10)	1200(3)	3490(1)	9377(1)	30(1)
C(11)	924(3)	3651(1)	10477(1)	27(1)
C(12)	-1100(3)	3165(1)	10876(1)	31(1)
C(13)	-1278(3)	3311(1)	11899(1)	33(1)
C(14)	603(3)	3943(1)	12549(1)	30(1)
C(15)	2615(3)	4454(1)	12167(1)	32(1)
C(16)	2739(3)	4303(1)	11138(1)	31(1)
C(17)	2407(3)	4449(2)	14238(1)	47(1)

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

O(1)-C(9)	1.3817(16)	C(5)-C(6)	1.524(2)
O(1)-C(3)	1.4482(17)	C(6)-C(7)	1.526(2)
C(1)-C(2)	1.304(2)	C(7A)-C(8)	1.4983(19)
O(2)-C(8)	1.3817(16)	C(7A)-C(7)	1.5317(19)
O(2)-C(10)	1.4357(16)	C(8)-C(9)	1.3286(19)
C(2)-C(3)	1.4893(19)	C(10)-C(11)	1.4945(19)
O(3)-C(14)	1.3738(17)	C(11)-C(16)	1.3863(19)
O(3)-C(17)	1.4337(18)	C(11)-C(12)	1.3879(19)
C(3A)-C(4)	1.5218(19)	C(12)-C(13)	1.381(2)
C(3A)-C(7A)	1.5219(18)	C(13)-C(14)	1.393(2)
C(3A)-C(3)	1.5245(19)	C(14)-C(15)	1.3837(19)
C(4)-C(5)	1.527(2)	C(15)-C(16)	1.3846(19)
C(9)-O(1)-C(3)	115.39(11)	C(6)-C(7)-C(7A)	109.57(12)
C(8)-O(2)-C(10)	116.27(10)	C(9)-C(8)-O(2)	124.95(13)
C(1)-C(2)-C(3)	125.34(15)	C(9)-C(8)-C(7A)	122.37(13)
C(14)-O(3)-C(17)	116.40(13)	O(2)-C(8)-C(7A)	112.62(12)
C(4)-C(3A)-C(7A)	109.38(11)	C(8)-C(9)-O(1)	124.39(14)
C(4)-C(3A)-C(3)	113.74(12)	O(2)-C(10)-C(11)	108.16(11)
C(7A)-C(3A)-C(3)	110.13(11)	C(16)-C(11)-C(12)	117.75(13)
O(1)-C(3)-C(2)	105.95(11)	C(16)-C(11)-C(10)	119.77(13)
O(1)-C(3)-C(3A)	110.44(11)	C(12)-C(11)-C(10)	122.48(13)
C(2)-C(3)-C(3A)	114.06(12)	C(13)-C(12)-C(11)	121.08(14)
C(3A)-C(4)-C(5)	110.97(12)	C(12)-C(13)-C(14)	120.05(14)
C(6)-C(5)-C(4)	112.54(13)	O(3)-C(14)-C(15)	124.38(14)
C(5)-C(6)-C(7)	111.66(12)	O(3)-C(14)-C(13)	115.77(14)
C(8)-C(7A)-C(3A)	109.93(11)	C(15)-C(14)-C(13)	119.85(14)
C(8)-C(7A)-C(7)	115.28(12)	C(14)-C(15)-C(16)	118.94(14)
C(3A)-C(7A)-C(7)	110.56(12)	C(15)-C(16)-C(11)	122.29(14)

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	31(1)	31(1)	7(1)	4(1)	9(1)
C(1)	46(1)	48(1)	40(1)	10(1)	8(1)	4(1)
O(2)	43(1)	28(1)	32(1)	3(1)	8(1)	14(1)
C(2)	37(1)	31(1)	35(1)	7(1)	1(1)	2(1)
O(3)	47(1)	43(1)	33(1)	5(1)	6(1)	0(1)
C(3A)	25(1)	23(1)	31(1)	3(1)	2(1)	2(1)
C(3)	27(1)	27(1)	33(1)	3(1)	1(1)	3(1)
C(4)	35(1)	29(1)	34(1)	2(1)	6(1)	6(1)
C(5)	44(1)	28(1)	44(1)	6(1)	7(1)	11(1)
C(6)	43(1)	29(1)	39(1)	8(1)	3(1)	9(1)
C(7A)	29(1)	24(1)	29(1)	3(1)	0(1)	5(1)
C(7)	41(1)	31(1)	33(1)	8(1)	6(1)	9(1)
C(8)	31(1)	22(1)	29(1)	0(1)	2(1)	2(1)
C(9)	29(1)	24(1)	33(1)	-1(1)	2(1)	4(1)
C(10)	28(1)	22(1)	38(1)	2(1)	4(1)	7(1)
C(11)	26(1)	19(1)	35(1)	3(1)	3(1)	6(1)
C(12)	28(1)	25(1)	40(1)	2(1)	-1(1)	2(1)
C(13)	28(1)	29(1)	43(1)	8(1)	7(1)	1(1)
C(14)	35(1)	23(1)	33(1)	5(1)	6(1)	8(1)
C(15)	32(1)	26(1)	36(1)	2(1)	1(1)	0(1)
C(16)	27(1)	28(1)	39(1)	5(1)	7(1)	1(1)
C(17)	60(1)	43(1)	35(1)	3(1)	-3(1)	-1(1)

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

	x	y	z	U(eq)
H(1A)	9741	2310	5353	53
H(1B)	8269	1855	4241	53
H(2A)	4751	1606	4930	41
H(3AA)	4016	564	6641	32
H(3A)	7427	2605	6797	35
H(4A)	9285	556	7139	39
H(4B)	7845	-100	6115	39
H(5A)	5784	-1450	6973	46
H(5B)	8697	-1477	7309	46
H(6A)	8270	-316	8835	43
H(6B)	6245	-1411	8707	43
H(7AA)	6972	1664	8394	33
H(7A)	4475	455	9275	41
H(7B)	3066	-158	8228	41
H(9A)	1760	3613	7623	35
H(10A)	-449	3315	8992	35
H(10B)	1937	4234	9181	35
H(12A)	-2384	2726	10439	37
H(13A)	-2684	2980	12159	39
H(15A)	3892	4900	12603	38
H(16A)	4115	4659	10876	37
H(17A)	1979	4460	14929	70
H(17B)	2899	5264	14124	70
H(17C)	3791	3920	14127	70

Table 6. Torsion angles [°] for mebzqu.

C(9)-O(1)-C(3)-C(2)	168.19(11)	C(7)-C(7A)-C(8)-C(9)	-141.67(14)
C(9)-O(1)-C(3)-C(3A)	44.21(15)	C(3A)-C(7A)-C(8)-O(2)	166.73(11)
C(1)-C(2)-C(3)-O(1)	130.74(16)	C(7)-C(7A)-C(8)-O(2)	40.98(16)
C(1)-C(2)-C(3)-C(3A)	-107.58(18)	O(2)-C(8)-C(9)-O(1)	176.36(12)
C(4)-C(3A)-C(3)-O(1)	176.40(11)	C(7A)-C(8)-C(9)-O(1)	-0.7(2)
C(7A)-C(3A)-C(3)-O(1)	-60.41(15)	C(3)-O(1)-C(9)-C(8)	-14.17(19)
C(4)-C(3A)-C(3)-C(2)	57.23(17)	C(8)-O(2)-C(10)-C(11)	-171.04(11)
C(7A)-C(3A)-C(3)-C(2)	-179.59(12)	O(2)-C(10)-C(11)-C(16)	82.70(16)
C(7A)-C(3A)-C(4)-C(5)	57.23(15)	O(2)-C(10)-C(11)-C(12)	-97.12(15)
C(3)-C(3A)-C(4)-C(5)	-179.18(12)	C(16)-C(11)-C(12)-C(13)	-1.0(2)
C(3A)-C(4)-C(5)-C(6)	-53.51(17)	C(10)-C(11)-C(12)-C(13)	178.79(14)
C(4)-C(5)-C(6)-C(7)	52.46(18)	C(11)-C(12)-C(13)-C(14)	-0.6(2)
C(4)-C(3A)-C(7A)-C(8)	170.50(11)	C(17)-O(3)-C(14)-C(15)	-12.0(2)
C(3)-C(3A)-C(7A)-C(8)	44.80(16)	C(17)-O(3)-C(14)-C(13)	168.18(13)
C(4)-C(3A)-C(7A)-C(7)	-61.10(15)	C(12)-C(13)-C(14)-O(3)	-178.33(13)
C(3)-C(3A)-C(7A)-C(7)	173.20(11)	C(12)-C(13)-C(14)-C(15)	1.8(2)
C(5)-C(6)-C(7)-C(7A)	-54.80(16)	O(3)-C(14)-C(15)-C(16)	178.88(13)
C(8)-C(7A)-C(7)-C(6)	-174.82(12)	C(13)-C(14)-C(15)-C(16)	-1.3(2)
C(3A)-C(7A)-C(7)-C(6)	59.75(15)	C(14)-C(15)-C(16)-C(11)	-0.5(2)
C(10)-O(2)-C(8)-C(9)	-0.4(2)	C(12)-C(11)-C(16)-C(15)	1.6(2)
C(10)-O(2)-C(8)-C(7A)	176.82(11)	C(10)-C(11)-C(16)-C(15)	-178.23(13)
C(3A)-C(7A)-C(8)-C(9)	-15.91(19)		

Appendix 19: X-ray crystal structure of the cyclopropane 303

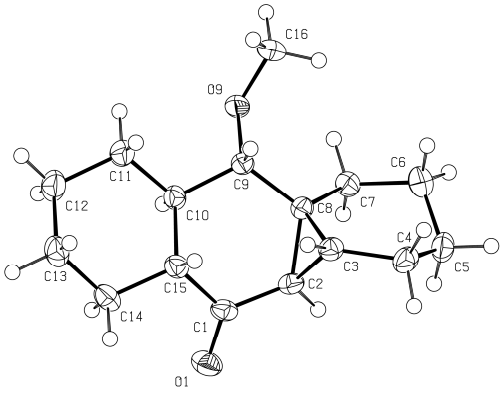


Table 1. Crystal data and structure refinement for TRIHXO at 150(2)K.

Empirical formula	C16 H24 O2
Formula weight	248.35
Crystal description	colourless needle
Crystal size	1.12 x 0.08 x 0.06 mm
Crystal system	Orthorhombic
Space group	F d d 2
Unit cell dimensions	a = 31.128(11) Å α = 90 deg. b = 33.904(12) Å β = 90 deg. c = 5.139(2) Å γ = 90 deg.
Volume	5424(5) $Å^3$
Reflections for cell refinement	2197
Range in theta	2.6 to 24.5 deg.
Z	16
Density (calculated)	1.217 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	2176
Diffractometer type	Bruker SMART1000 CCD area detector
Wavelength	0.71073 Å
Scan type	omega
Reflections collected	8550
Theta range for data collection	1.78 to 27.59 deg.
Index ranges	-39<=h<=38, -31<=k<=43, -6<=l<=6
Independent reflections	1731 [R(int) = 0.101]
Observed reflections	1354 [II>2\s(I)]
Absorption correction	None
Decay correction	None
Structure solution by	direc methods
Hydrogen atom location	geometrically placed
Hydrogen atom treatment	riding model
Data / restraints / parameters	1731/1/164 (least-squares on F^2)
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0876
Final R indices (all data)	R1 = 0.0559, wR2 = 0.0936
Goodness-of-fit on F^2	0.94
Absolute structure parameter	not reliably determined: Friedel opposites merged
Extinction coefficient	0.0008(2)
Final maximum delta/sigma	0.001
Weighting scheme	calc w=1/[\s^2^(Fo^2^)+(0.047P)^2^] where P=(Fo^2^+2Fc^2^)/3
Largest diff. peak and hole	0.18 and -0.18 $e.A^{-3}$

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

	x	y	z	U(eq)
C(1)	781(1)	9880(1)	6910(5)	25(1)
O(1)	759(1)	10113(1)	5102(3)	35(1)
C(2)	454(1)	9572(1)	7247(5)	25(1)
C(3)	285(1)	9455(1)	9924(5)	25(1)
C(4)	-188(1)	9358(1)	10301(5)	31(1)
C(5)	-354(1)	9045(1)	8415(5)	34(1)
C(6)	-47(1)	8696(1)	8322(6)	38(1)
C(7)	388(1)	8812(1)	7191(6)	28(1)
C(8)	579(1)	9177(1)	8537(5)	22(1)
C(9)	1038(1)	9147(1)	9720(5)	23(1)
O(9)	1229(1)	8773(1)	9240(3)	30(1)
C(10)	1356(1)	9454(1)	8717(5)	24(1)
C(11)	1769(1)	9438(1)	10330(5)	32(1)
C(12)	2096(1)	9751(1)	9492(7)	38(1)
C(13)	1898(1)	10160(1)	9717(6)	36(1)
C(14)	1492(1)	10192(1)	8075(5)	31(1)
C(15)	1160(1)	9874(1)	8768(5)	25(1)
C(16)	1156(1)	8496(1)	11283(6)	39(1)

Table 3. Bond lengths [Å], angles and torsions [deg] for TRIHXO.

C(1)-O(1)	1.223(3)	C(9)-C(10)	1.526(3)
C(1)-C(2)	1.470(3)	C(9)-H(9)	1.0000
C(1)-C(15)	1.517(3)	O(9)-C(16)	1.426(3)
C(2)-C(3)	1.525(3)	C(10)-C(11)	1.532(3)
C(2)-C(8)	1.542(3)	C(10)-C(15)	1.551(3)
C(2)-H(2)	1.0000	C(10)-H(10A)	1.0000
C(3)-C(8)	1.495(3)	C(11)-C(12)	1.529(3)
C(3)-C(4)	1.522(3)	C(11)-H(11A)	0.9900
C(3)-H(3)	1.0000	C(11)-H(11B)	0.9900
C(4)-C(5)	1.527(3)	C(12)-C(13)	1.522(3)
C(4)-H(4A)	0.9900	C(12)-H(12A)	0.9900
C(4)-H(4B)	0.9900	C(12)-H(12B)	0.9900
C(5)-C(6)	1.522(3)	C(13)-C(14)	1.523(3)
C(5)-H(5A)	0.9900	C(13)-H(13A)	0.9900
C(5)-H(5B)	0.9900	C(13)-H(13B)	0.9900
C(6)-C(7)	1.526(3)	C(14)-C(15)	1.534(3)
C(6)-H(6A)	0.9900	C(14)-H(14A)	0.9900
C(6)-H(6B)	0.9900	C(14)-H(14B)	0.9900
C(7)-C(8)	1.539(3)	C(15)-H(15)	1.0000
C(7)-H(7A)	0.9900	C(16)-H(16C)	0.9800
C(7)-H(7B)	0.9900	C(16)-H(16D)	0.9800
C(8)-C(9)	1.554(3)	C(16)-H(16A)	0.9800
C(9)-O(9)	1.422(2)		

O(1)-C(1)-C(2)	120.8(2)	C(3)-C(2)-C(8)	58.33(15)
O(1)-C(1)-C(15)	121.9(2)	C(1)-C(2)-H(2)	115.1
C(2)-C(1)-C(15)	117.14(19)	C(3)-C(2)-H(2)	115.1
C(1)-C(2)-C(3)	122.0(2)	C(8)-C(2)-H(2)	115.1
C(1)-C(2)-C(8)	119.40(17)	C(8)-C(3)-C(4)	121.18(19)

C(8)-C(3)-C(2)	61.43(15)	C(9)-C(10)-C(11)	109.87(18)
C(4)-C(3)-C(2)	120.31(19)	C(9)-C(10)-C(15)	111.49(16)
C(8)-C(3)-H(3)	114.6	C(11)-C(10)-C(15)	110.60(18)
C(4)-C(3)-H(3)	114.6	C(9)-C(10)-H(10A)	108.3
C(2)-C(3)-H(3)	114.6	C(11)-C(10)-H(10A)	108.3
C(3)-C(4)-C(5)	113.37(19)	C(15)-C(10)-H(10A)	108.3
C(3)-C(4)-H(4A)	108.9	C(12)-C(11)-C(10)	112.5(2)
C(5)-C(4)-H(4A)	108.9	C(12)-C(11)-H(11A)	109.1
C(3)-C(4)-H(4B)	108.9	C(10)-C(11)-H(11A)	109.1
C(5)-C(4)-H(4B)	108.9	C(12)-C(11)-H(11B)	109.1
H(4A)-C(4)-H(4B)	107.7	C(10)-C(11)-H(11B)	109.1
C(6)-C(5)-C(4)	110.4(2)	H(11A)-C(11)-H(11B)	107.8
C(6)-C(5)-H(5A)	109.6	C(13)-C(12)-C(11)	109.92(18)
C(4)-C(5)-H(5A)	109.6	C(13)-C(12)-H(12A)	109.7
C(6)-C(5)-H(5B)	109.6	C(11)-C(12)-H(12A)	109.7
C(4)-C(5)-H(5B)	109.6	C(13)-C(12)-H(12B)	109.7
H(5A)-C(5)-H(5B)	108.1	C(11)-C(12)-H(12B)	109.7
C(5)-C(6)-C(7)	111.62(19)	H(12A)-C(12)-H(12B)	108.2
C(5)-C(6)-H(6A)	109.3	C(12)-C(13)-C(14)	111.0(2)
C(7)-C(6)-H(6A)	109.3	C(12)-C(13)-H(13A)	109.4
C(5)-C(6)-H(6B)	109.3	C(14)-C(13)-H(13A)	109.4
C(7)-C(6)-H(6B)	109.3	C(12)-C(13)-H(13B)	109.4
H(6A)-C(6)-H(6B)	108.0	C(14)-C(13)-H(13B)	109.4
C(6)-C(7)-C(8)	112.3(2)	H(13A)-C(13)-H(13B)	108.0
C(6)-C(7)-H(7A)	109.1	C(13)-C(14)-C(15)	112.37(19)
C(8)-C(7)-H(7A)	109.1	C(13)-C(14)-H(14A)	109.1
C(6)-C(7)-H(7B)	109.1	C(15)-C(14)-H(14A)	109.1
C(8)-C(7)-H(7B)	109.1	C(13)-C(14)-H(14B)	109.1
H(7A)-C(7)-H(7B)	107.9	C(15)-C(14)-H(14B)	109.1
C(3)-C(8)-C(7)	118.97(17)	H(14A)-C(14)-H(14B)	107.9
C(3)-C(8)-C(2)	60.24(14)	C(1)-C(15)-C(14)	111.67(19)
C(7)-C(8)-C(2)	114.02(19)	C(1)-C(15)-C(10)	107.82(18)
C(3)-C(8)-C(9)	114.74(19)	C(14)-C(15)-C(10)	112.10(16)
C(7)-C(8)-C(9)	118.46(17)	C(1)-C(15)-H(15)	108.4
C(2)-C(8)-C(9)	117.32(17)	C(14)-C(15)-H(15)	108.4
O(9)-C(9)-C(10)	106.14(16)	C(10)-C(15)-H(15)	108.4
O(9)-C(9)-C(8)	112.08(18)	O(9)-C(16)-H(16C)	109.5
C(10)-C(9)-C(8)	114.69(17)	O(9)-C(16)-H(16D)	109.5
O(9)-C(9)-H(9)	107.9	H(16C)-C(16)-H(16D)	109.5
C(10)-C(9)-H(9)	107.9	O(9)-C(16)-H(16A)	109.5
C(8)-C(9)-H(9)	107.9	H(16C)-C(16)-H(16A)	109.5
C(9)-O(9)-C(16)	113.13(18)	H(16D)-C(16)-H(16A)	109.5

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	31(1)	19(1)	25(1)	1(1)	4(1)	5(1)
O(1)	45(1)	30(1)	31(1)	9(1)	-3(1)	-2(1)
C(2)	26(1)	25(1)	25(1)	3(1)	-4(1)	4(1)
C(3)	25(1)	27(1)	23(1)	1(1)	0(1)	3(1)
C(4)	24(1)	39(1)	29(1)	4(1)	5(1)	6(1)
C(5)	22(1)	45(2)	33(1)	7(1)	1(1)	-5(1)
C(6)	33(1)	35(1)	48(2)	2(1)	-1(1)	-10(1)
C(7)	27(1)	24(1)	33(1)	-1(1)	0(1)	-1(1)
C(8)	21(1)	23(1)	24(1)	2(1)	2(1)	2(1)
C(9)	21(1)	20(1)	28(1)	2(1)	4(1)	3(1)
O(9)	25(1)	19(1)	47(1)	5(1)	5(1)	4(1)
C(10)	22(1)	23(1)	28(1)	0(1)	5(1)	-1(1)
C(11)	26(1)	26(1)	43(2)	0(1)	-2(1)	-1(1)
C(12)	26(1)	33(1)	55(2)	-5(1)	1(1)	-4(1)
C(13)	31(1)	28(1)	48(2)	-6(1)	5(1)	-7(1)
C(14)	37(1)	22(1)	35(2)	2(1)	5(1)	-5(1)
C(15)	26(1)	21(1)	27(1)	0(1)	4(1)	1(1)
C(16)	37(1)	26(1)	54(2)	16(1)	-7(1)	0(1)

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

	x	y	z	U(eq)
H(2)	241	9550	5798	30
H(3)	420	9600	11408	30
H(4A)	-359	9602	10072	37
H(4B)	-233	9264	12105	37
H(5A)	-641	8954	8981	40
H(5B)	-382	9160	6655	40
H(6A)	-175	8484	7246	46
H(6B)	-6	8591	10104	46
H(7A)	355	8867	5310	34
H(7B)	590	8588	7381	34
H(9)	1012	9180	11647	28
H(10A)	1429	9387	6875	29
H(11A)	1698	9478	12188	38
H(11B)	1901	9174	10152	38
H(12A)	2354	9734	10610	45
H(12B)	2185	9702	7671	45
H(13A)	2109	10359	9132	43
H(13B)	1827	10214	11560	43
H(14A)	1569	10166	6214	37
H(14B)	1363	10455	8334	37
H(15)	1051	9928	10564	30
H(16C)	1295	8245	10847	59
H(16D)	847	8454	11497	59
H(16A)	1277	8598	12909	59

Table 6. Torsion angles [°] for TRIHXO.

O(1)-C(1)-C(2)-C(3)	-140.6(2)	C(7)-C(8)-C(9)-O(9)	3.1(3)
C(15)-C(1)-C(2)-C(3)	43.8(3)	C(2)-C(8)-C(9)-O(9)	-140.1(2)
O(1)-C(1)-C(2)-C(8)	150.4(2)	C(3)-C(8)-C(9)-C(10)	-86.9(2)
C(15)-C(1)-C(2)-C(8)	-25.2(3)	C(7)-C(8)-C(9)-C(10)	124.2(2)
C(1)-C(2)-C(3)-C(8)	-107.1(2)	C(2)-C(8)-C(9)-C(10)	-19.0(3)
C(1)-C(2)-C(3)-C(4)	141.5(2)	C(10)-C(9)-O(9)-C(16)	141.45(18)
C(8)-C(2)-C(3)-C(4)	-111.4(2)	C(8)-C(9)-O(9)-C(16)	-92.6(2)
C(8)-C(3)-C(4)-C(5)	-19.8(3)	O(9)-C(9)-C(10)-C(11)	-65.0(2)
C(2)-C(3)-C(4)-C(5)	53.1(3)	C(8)-C(9)-C(10)-C(11)	170.7(2)
C(3)-C(4)-C(5)-C(6)	47.5(3)	O(9)-C(9)-C(10)-C(15)	172.02(19)
C(4)-C(5)-C(6)-C(7)	-65.2(3)	C(8)-C(9)-C(10)-C(15)	47.7(3)
C(5)-C(6)-C(7)-C(8)	51.3(3)	C(9)-C(10)-C(11)-C(12)	-177.7(2)
C(4)-C(3)-C(8)-C(7)	7.3(3)	C(15)-C(10)-C(11)-C(12)	-54.2(3)
C(2)-C(3)-C(8)-C(7)	-102.7(2)	C(10)-C(11)-C(12)-C(13)	58.0(3)
C(4)-C(3)-C(8)-C(2)	110.0(2)	C(11)-C(12)-C(13)-C(14)	-57.8(3)
C(4)-C(3)-C(8)-C(9)	-141.4(2)	C(12)-C(13)-C(14)-C(15)	55.8(3)
C(2)-C(3)-C(8)-C(9)	108.6(2)	O(1)-C(1)-C(15)-C(14)	0.3(3)
C(6)-C(7)-C(8)-C(3)	-22.5(3)	C(2)-C(1)-C(15)-C(14)	175.83(19)
C(6)-C(7)-C(8)-C(2)	-90.5(2)	O(1)-C(1)-C(15)-C(10)	-123.3(2)
C(6)-C(7)-C(8)-C(9)	125.1(2)	C(2)-C(1)-C(15)-C(10)	52.3(2)
C(1)-C(2)-C(8)-C(3)	111.5(2)	C(13)-C(14)-C(15)-C(1)	-173.3(2)
C(1)-C(2)-C(8)-C(7)	-137.6(2)	C(13)-C(14)-C(15)-C(10)	-52.2(3)
C(3)-C(2)-C(8)-C(7)	110.9(2)	C(9)-C(10)-C(15)-C(1)	-63.5(2)
C(1)-C(2)-C(8)-C(9)	7.2(3)	C(11)-C(10)-C(15)-C(1)	173.97(18)
C(3)-C(2)-C(8)-C(9)	-104.3(2)	C(9)-C(10)-C(15)-C(14)	173.2(2)
C(3)-C(8)-C(9)-O(9)	152.04(18)	C(11)-C(10)-C(15)-C(14)	50.7(3)

Appendix 20: X-ray crystal structure of the tricyclic product 260

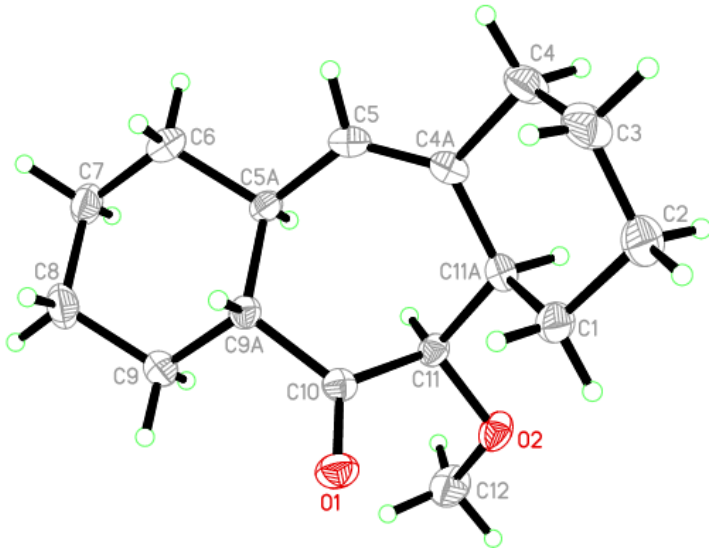


Table 1. Crystal data and structure refinement for hxhepo.

Identification code	hxhepo
Empirical formula	C16 H24 O2

Formula weight	248.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.2434(5) Å	α= 90°.
	b = 9.3200(9) Å	β= 90°.
	c = 28.332(3) Å	γ = 90°.
Volume	1384.5(2) $Å^3$	
Z	4	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	544	
Crystal size	0.53 x 0.17 x 0.15 mm^3	
Theta range for data collection	2.30 to 27.61°.	
Index ranges	-6<=h<=6, -10<=k<=12, -18<=l<=36	
Reflections collected	7674	
Independent reflections	1893 [R(int) = 0.064]	
Completeness to theta = 27.50°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1893 / 0 / 163	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2sigma(I)]	R1 = 0.0406, wR2 = 0.0997	
R indices (all data)	R1 = 0.0457, wR2 = 0.1021	
Largest diff. peak and hole	0.333 and -0.186 e.$Å^{-3}$	

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

	x	y	z	U(eq)
O(1)	4210(2)	671(1)	574(1)	27(1)
O(2)	7556(3)	-1579(1)	527(1)	26(1)
C(1)	4853(4)	-1767(2)	1415(1)	26(1)
C(2)	4613(4)	-2577(2)	1882(1)	33(1)
C(3)	5256(4)	-1598(2)	2296(1)	34(1)
C(4A)	8209(3)	-179(2)	1765(1)	21(1)
C(4)	7919(4)	-937(2)	2238(1)	30(1)
C(5)	8940(4)	1190(2)	1751(1)	23(1)
C(5A)	9316(3)	2171(2)	1330(1)	19(1)
C(6)	9967(4)	3696(2)	1500(1)	26(1)
C(7)	10395(4)	4724(2)	1090(1)	28(1)
C(8)	8074(4)	4770(2)	765(1)	32(1)
C(9A)	6979(3)	2226(2)	1002(1)	19(1)
C(9)	7416(4)	3269(2)	590(1)	27(1)
C(10)	6180(3)	786(2)	793(1)	18(1)
C(11A)	7564(3)	-1149(2)	1353(1)	21(1)
C(11)	7973(3)	-487(2)	861(1)	19(1)
C(12)	8503(4)	-1186(2)	71(1)	32(1)

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

O(1)-C(10)	1.210(2)	C(5)-C(5A)	1.515(2)
O(2)-C(11)	1.4084(19)	C(5A)-C(6)	1.538(2)
O(2)-C(12)	1.430(2)	C(5A)-C(9A)	1.540(2)
C(1)-C(2)	1.530(2)	C(6)-C(7)	1.522(2)
C(1)-C(11A)	1.543(2)	C(7)-C(8)	1.526(3)
C(2)-C(3)	1.525(3)	C(8)-C(9)	1.525(3)
C(3)-C(4)	1.535(3)	C(9A)-C(10)	1.525(2)
C(4A)-C(5)	1.332(3)	C(9A)-C(9)	1.536(2)
C(4A)-C(11A)	1.514(2)	C(10)-C(11)	1.526(2)
C(4A)-C(4)	1.522(2)	C(11A)-C(11)	1.539(2)
C(11)-O(2)-C(12)	111.62(13)	C(9)-C(8)-C(7)	110.55(15)
C(2)-C(1)-C(11A)	110.95(15)	C(10)-C(9A)-C(9)	107.65(13)
C(3)-C(2)-C(1)	110.66(15)	C(10)-C(9A)-C(5A)	115.05(14)
C(2)-C(3)-C(4)	111.00(17)	C(9)-C(9A)-C(5A)	111.20(14)
C(5)-C(4A)-C(11A)	127.82(15)	C(8)-C(9)-C(9A)	111.49(15)
C(5)-C(4A)-C(4)	119.94(16)	O(1)-C(10)-C(9A)	120.74(16)
C(11A)-C(4A)-C(4)	112.24(14)	O(1)-C(10)-C(11)	121.47(15)
C(4A)-C(4)-C(3)	111.85(15)	C(9A)-C(10)-C(11)	117.78(14)
C(4A)-C(5)-C(5A)	129.70(16)	C(4A)-C(11A)-C(11)	115.26(13)
C(5)-C(5A)-C(6)	109.92(13)	C(4A)-C(11A)-C(1)	110.00(14)
C(5)-C(5A)-C(9A)	113.07(14)	C(11)-C(11A)-C(1)	112.32(14)
C(6)-C(5A)-C(9A)	109.55(14)	O(2)-C(11)-C(10)	112.40(13)
C(7)-C(6)-C(5A)	112.07(14)	O(2)-C(11)-C(11A)	107.37(12)
C(6)-C(7)-C(8)	111.12(16)	C(10)-C(11)-C(11A)	109.89(13)

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	23(1)	30(1)	27(1)	-2(1)	-6(1)	-3(1)
O(2)	36(1)	20(1)	21(1)	-5(1)	6(1)	-4(1)
C(1)	29(1)	25(1)	24(1)	2(1)	1(1)	-5(1)
C(2)	34(1)	32(1)	31(1)	7(1)	6(1)	-8(1)
C(3)	37(1)	43(1)	22(1)	8(1)	6(1)	-4(1)
C(4A)	19(1)	28(1)	17(1)	3(1)	-1(1)	1(1)
C(4)	33(1)	35(1)	20(1)	7(1)	-2(1)	-2(1)
C(5)	22(1)	30(1)	17(1)	-3(1)	-3(1)	0(1)
C(5A)	20(1)	19(1)	19(1)	-3(1)	-1(1)	-1(1)
C(6)	28(1)	25(1)	25(1)	-7(1)	-2(1)	-3(1)
C(7)	30(1)	18(1)	37(1)	-1(1)	-3(1)	-3(1)
C(8)	32(1)	20(1)	45(1)	6(1)	-8(1)	0(1)
C(9A)	19(1)	17(1)	21(1)	-2(1)	-1(1)	3(1)
C(9)	31(1)	22(1)	27(1)	4(1)	-7(1)	-1(1)
C(10)	18(1)	21(1)	16(1)	1(1)	2(1)	-2(1)
C(11A)	21(1)	19(1)	22(1)	3(1)	1(1)	1(1)
C(11)	22(1)	17(1)	18(1)	-2(1)	2(1)	-1(1)
C(12)	44(1)	32(1)	22(1)	-6(1)	9(1)	-4(1)

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

	x	y	z	U(eq)
H(1A)	3595	-975	1406	31
H(1B)	4471	-2426	1150	31
H(2A)	2849	-2942	1917	39
H(2B)	5784	-3410	1881	39
H(3A)	5194	-2156	2593	41
H(3B)	3970	-823	2317	41
H(4A)	8222	-240	2496	35
H(4B)	9220	-1702	2263	35
H(5A)	9277	1613	2049	28
H(5AA)	10797	1803	1143	23
H(6A)	8556	4060	1699	31
H(6B)	11526	3661	1697	31
H(7A)	11908	4413	907	34
H(7B)	10736	5698	1214	34
H(8A)	6600	5175	938	39
H(8B)	8437	5402	492	39
H(9AA)	5510	2599	1190	23
H(9A)	8824	2906	389	32
H(9B)	5857	3314	393	32
H(11A)	8756	-1984	1374	25
H(11B)	9776	-147	835	23
H(12A)	8183	-1967	-153	49
H(12B)	10341	-1005	91	49
H(12C)	7634	-315	-37	49

Table 6. Torsion angles [°] for hxhepo.

C(11A)-C(1)-C(2)-C(3)	57.7(2)	C(9)-C(9A)-C(10)-O(1)	-63.9(2)
C(1)-C(2)-C(3)-C(4)	-55.6(2)	C(5A)-C(9A)-C(10)-O(1)	171.57(15)
C(5)-C(4A)-C(4)-C(3)	125.21(19)	C(9)-C(9A)-C(10)-C(11)	114.87(15)
C(11A)-C(4A)-C(4)-C(3)	-54.3(2)	C(5A)-C(9A)-C(10)-C(11)	-9.7(2)
C(2)-C(3)-C(4)-C(4A)	53.8(2)	C(5)-C(4A)-C(11A)-C(11)	4.1(3)
C(11A)-C(4A)-C(5)-C(5A)	0.6(3)	C(4)-C(4A)-C(11A)-C(11)	-176.34(15)
C(4)-C(4A)-C(5)-C(5A)	-178.83(17)	C(5)-C(4A)-C(11A)-C(1)	-124.1(2)
C(4A)-C(5)-C(5A)-C(6)	175.39(19)	C(4)-C(4A)-C(11A)-C(1)	55.43(19)
C(4A)-C(5)-C(5A)-C(9A)	52.6(3)	C(2)-C(1)-C(11A)-C(4A)	-57.17(19)
C(5)-C(5A)-C(6)-C(7)	179.34(16)	C(2)-C(1)-C(11A)-C(11)	173.00(14)
C(9A)-C(5A)-C(6)-C(7)	-55.8(2)	C(12)-O(2)-C(11)-C(10)	73.78(18)
C(5A)-C(6)-C(7)-C(8)	56.7(2)	C(12)-O(2)-C(11)-C(11A)	-165.25(15)
C(6)-C(7)-C(8)-C(9)	-56.0(2)	O(1)-C(10)-C(11)-O(2)	20.1(2)
C(5)-C(5A)-C(9A)-C(10)	-59.07(18)	C(9A)-C(10)-C(11)-O(2)	-158.66(14)
C(6)-C(5A)-C(9A)-C(10)	177.95(15)	O(1)-C(10)-C(11)-C(11A)	-99.45(17)
C(5)-C(5A)-C(9A)-C(9)	178.23(14)	C(9A)-C(10)-C(11)-C(11A)	81.83(18)
C(6)-C(5A)-C(9A)-C(9)	55.25(18)	C(4A)-C(11A)-C(11)-O(2)	173.60(14)
C(7)-C(8)-C(9)-C(9A)	56.1(2)	C(1)-C(11A)-C(11)-O(2)	-59.34(18)
C(10)-C(9A)-C(9)-C(8)	176.66(15)	C(4A)-C(11A)-C(11)-C(10)	-63.86(18)
C(5A)-C(9A)-C(9)-C(8)	-56.5(2)	C(1)-C(11A)-C(11)-C(10)	63.20(18)

Appendix 21: X-ray crystal structure of the anhydride 344

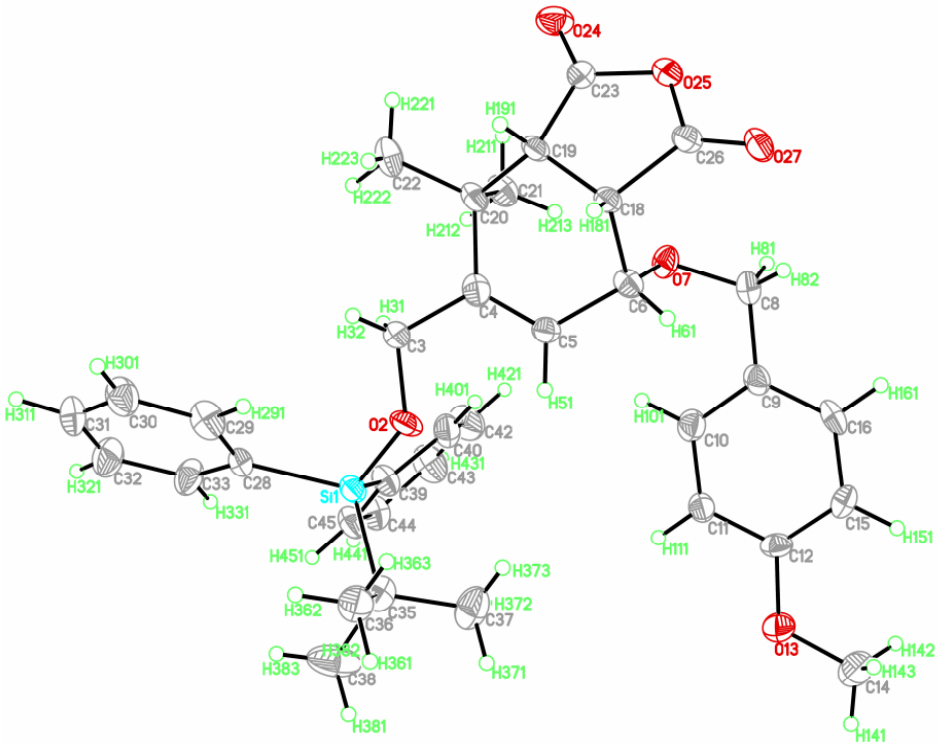


Table 1. Crystal data and structure refinement for sx142..

Identification code	sx142	
Empirical formula	C35 H40 O6 Si1	
Formula weight	584.78	
Temperature	293 K	
Wavelength	0.68840 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.492(5) Å	α= 86.454(8)°.
	b = 9.468(7) Å	β= 89.545(8)°.
	c = 23.187(16) Å	γ = 70.197(8)°.
Volume	1544.4(19) Å^3	
Z	2	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	624	
Crystal size	0.4 x 0.2 x 0.02 mm^3	
Theta range for data collection	2.326 to 26.551°.	
Index ranges	-9<=h<=9, -12<=k<=12, 0<=l<=30	
Reflections collected	6861	
Independent reflections	6861 [R(int) = 0.000]	
Completeness to theta = 25.224 °	97.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6861 / 0 / 380	
Goodness-of-fit on F^2	1.0050	
Final R indices [I>2sigma(I)]	R1 = 0.1455, wR2 = 0.4074	
R indices (all data)	R1 = 0.1751, wR2 = 0.4164	
Largest diff. peak and hole	0.95 and -0.98 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sx142. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	5470(3)	4969(3)	3441(1)	21
O(2)	5690(8)	4927(7)	2732(2)	26
C(3)	7447(11)	4766(10)	2437(3)	24
C(4)	7065(12)	5467(9)	1829(3)	25
C(5)	5316(11)	6115(9)	1608(3)	21
C(6)	4959(12)	6830(9)	1002(3)	21
O(7)	5188(8)	8291(6)	970(3)	24
C(8)	3613(12)	9506(10)	726(4)	29
C(9)	1884(12)	9925(9)	1105(3)	24
C(10)	2057(12)	9654(10)	1706(4)	27
C(11)	432(12)	10059(9)	2041(3)	23
C(12)	-1351(11)	10761(9)	1780(4)	24
O(13)	-2872(9)	11085(7)	2153(3)	30
C(14)	-4713(14)	11799(12)	1895(5)	39
C(15)	-1532(11)	11083(9)	1188(4)	25
C(16)	108(13)	10659(9)	855(3)	27
C(18)	6453(11)	5810(9)	616(3)	20
C(19)	8509(11)	5379(9)	842(3)	20
C(20)	8850(12)	5498(9)	1502(3)	22
C(21)	9129(13)	7015(10)	1628(4)	27
C(22)	10637(14)	4201(11)	1680(4)	34
C(23)	9395(12)	6259(9)	434(3)	24
O(24)	10945(9)	6330(8)	431(3)	32
O(25)	8130(8)	6969(7)	-24(2)	26
C(26)	6465(12)	6676(9)	34(3)	23
O(27)	5280(9)	7082(7)	-332(2)	28
C(28)	7439(12)	3322(10)	3792(3)	26
C(29)	8250(14)	2042(10)	3489(4)	32
C(30)	9741(15)	822(11)	3732(4)	37
C(31)	10453(15)	857(11)	4282(5)	41
C(32)	9651(14)	2116(12)	4588(4)	39
C(33)	8210(14)	3342(11)	4338(4)	35
C(35)	3036(13)	4924(10)	3579(4)	28
C(36)	2834(13)	3488(10)	3348(4)	32
C(37)	1565(14)	6274(11)	3266(5)	40
C(38)	2576(17)	4916(16)	4227(4)	50
C(39)	5665(13)	6772(9)	3679(4)	27
C(40)	5863(13)	7900(10)	3273(4)	32
C(42)	6099(16)	9225(11)	3437(5)	43
C(43)	6069(16)	9473(11)	4014(4)	39
C(44)	5801(14)	8435(11)	4421(4)	34
C(45)	5606(14)	7107(10)	4259(4)	31

Table 3. Bond lengths [Å] and angles [°] for sx142.

Si(1)-O(2)	1.652(6)	C(21)-H(212)	0.950
Si(1)-C(28)	1.891(8)	C(21)-H(213)	0.950
Si(1)-C(35)	1.863(9)	C(22)-H(221)	0.950
Si(1)-C(39)	1.878(9)	C(22)-H(222)	0.950
O(2)-C(3)	1.444(9)	C(22)-H(223)	0.950
C(3)-C(4)	1.508(11)	C(23)-O(24)	1.186(10)
C(3)-H(31)	0.950	C(23)-O(25)	1.404(10)
C(3)-H(32)	0.950	O(25)-C(26)	1.371(10)
C(4)-C(5)	1.335(11)	C(26)-O(27)	1.182(10)
C(4)-C(20)	1.540(12)	C(28)-C(29)	1.390(12)
C(5)-C(6)	1.508(10)	C(28)-C(33)	1.400(12)
C(5)-H(51)	0.950	C(29)-C(30)	1.398(13)
C(6)-O(7)	1.448(9)	C(29)-H(291)	0.950
C(6)-C(18)	1.530(10)	C(30)-C(31)	1.393(14)
C(6)-H(61)	0.950	C(30)-H(301)	0.950
O(7)-C(8)	1.431(10)	C(31)-C(32)	1.378(15)
C(8)-C(9)	1.511(12)	C(31)-H(311)	0.950
C(8)-H(81)	0.950	C(32)-C(33)	1.388(13)
C(8)-H(82)	0.950	C(32)-H(321)	0.950
C(9)-C(10)	1.400(11)	C(33)-H(331)	0.950
C(9)-C(16)	1.387(12)	C(35)-C(36)	1.546(12)
C(10)-C(11)	1.393(12)	C(35)-C(37)	1.523(13)
C(10)-H(101)	0.950	C(35)-C(38)	1.539(12)
C(11)-C(12)	1.398(11)	C(36)-H(361)	0.950
C(11)-H(111)	0.950	C(36)-H(362)	0.950
C(12)-O(13)	1.386(10)	C(36)-H(363)	0.950
C(12)-C(15)	1.385(12)	C(37)-H(371)	0.950
O(13)-C(14)	1.431(11)	C(37)-H(372)	0.950
C(14)-H(141)	0.950	C(37)-H(373)	0.950
C(14)-H(142)	0.950	C(38)-H(381)	0.950
C(14)-H(143)	0.950	C(38)-H(382)	0.950
C(15)-C(16)	1.398(12)	C(38)-H(383)	0.950
C(15)-H(151)	0.950	C(39)-C(40)	1.425(12)
C(16)-H(161)	0.950	C(39)-C(45)	1.399(12)
C(18)-C(19)	1.541(11)	C(40)-C(42)	1.400(14)
C(18)-C(26)	1.537(10)	C(40)-H(401)	0.950
C(18)-H(181)	0.950	C(42)-C(43)	1.372(15)
C(19)-C(20)	1.571(10)	C(42)-H(421)	0.950
C(19)-C(23)	1.516(11)	C(43)-C(44)	1.383(13)
C(19)-H(191)	0.950	C(43)-H(431)	0.950
C(20)-C(21)	1.565(11)	C(44)-C(45)	1.388(13)
C(20)-C(22)	1.517(12)	C(44)-H(441)	0.950
C(21)-H(211)	0.950	C(45)-H(451)	0.950

O(2)-Si(1)-C(28)	108.7(3)	C(4)-C(5)-H(51)	119.1
O(2)-Si(1)-C(35)	104.6(3)	C(6)-C(5)-H(51)	118.9
C(28)-Si(1)-C(35)	114.5(4)	C(5)-C(6)-O(7)	111.0(6)
O(2)-Si(1)-C(39)	109.5(4)	C(5)-C(6)-C(18)	107.3(6)
C(28)-Si(1)-C(39)	109.4(4)	O(7)-C(6)-C(18)	108.0(6)
C(35)-Si(1)-C(39)	110.0(4)	C(5)-C(6)-H(61)	109.8
Si(1)-O(2)-C(3)	123.5(5)	O(7)-C(6)-H(61)	110.2
O(2)-C(3)-C(4)	110.7(6)	C(18)-C(6)-H(61)	110.6
O(2)-C(3)-H(31)	109.2	C(6)-O(7)-C(8)	115.4(6)
C(4)-C(3)-H(31)	109.2	O(7)-C(8)-C(9)	113.7(7)
O(2)-C(3)-H(32)	109.3	O(7)-C(8)-H(81)	108.2
C(4)-C(3)-H(32)	109.0	C(9)-C(8)-H(81)	108.2
H(31)-C(3)-H(32)	109.5	O(7)-C(8)-H(82)	108.4
C(3)-C(4)-C(5)	122.8(8)	C(9)-C(8)-H(82)	108.8
C(3)-C(4)-C(20)	114.3(7)	H(81)-C(8)-H(82)	109.5
C(5)-C(4)-C(20)	122.7(7)	C(8)-C(9)-C(10)	121.0(7)
C(4)-C(5)-C(6)	122.1(7)	C(8)-C(9)-C(16)	119.3(7)

C(10)-C(9)-C(16)	119.6(8)	Si(1)-C(28)-C(29)	119.4(7)
C(9)-C(10)-C(11)	119.4(8)	Si(1)-C(28)-C(33)	123.4(7)
C(9)-C(10)-H(101)	120.3	C(29)-C(28)-C(33)	117.1(8)
C(11)-C(10)-H(101)	120.3	C(28)-C(29)-C(30)	120.7(8)
C(10)-C(11)-C(12)	120.1(7)	C(28)-C(29)-H(291)	119.6
C(10)-C(11)-H(111)	120.0	C(30)-C(29)-H(291)	119.7
C(12)-C(11)-H(111)	119.9	C(29)-C(30)-C(31)	121.0(9)
C(11)-C(12)-O(13)	115.3(7)	C(29)-C(30)-H(301)	119.4
C(11)-C(12)-C(15)	120.9(7)	C(31)-C(30)-H(301)	119.6
O(13)-C(12)-C(15)	123.8(7)	C(30)-C(31)-C(32)	118.8(9)
C(12)-O(13)-C(14)	116.3(7)	C(30)-C(31)-H(311)	120.6
O(13)-C(14)-H(141)	109.8	C(32)-C(31)-H(311)	120.5
O(13)-C(14)-H(142)	109.8	C(31)-C(32)-C(33)	119.9(9)
H(141)-C(14)-H(142)	109.5	C(31)-C(32)-H(321)	120.4
O(13)-C(14)-H(143)	108.8	C(33)-C(32)-H(321)	119.7
H(141)-C(14)-H(143)	109.5	C(28)-C(33)-C(32)	122.3(9)
H(142)-C(14)-H(143)	109.5	C(28)-C(33)-H(331)	118.4
C(12)-C(15)-C(16)	118.4(7)	C(32)-C(33)-H(331)	119.3
C(12)-C(15)-H(151)	120.7	Si(1)-C(35)-C(36)	110.0(6)
C(16)-C(15)-H(151)	120.9	Si(1)-C(35)-C(37)	110.3(7)
C(15)-C(16)-C(9)	121.5(7)	C(36)-C(35)-C(37)	107.7(7)
C(15)-C(16)-H(161)	119.0	Si(1)-C(35)-C(38)	112.4(6)
C(9)-C(16)-H(161)	119.5	C(36)-C(35)-C(38)	107.3(8)
C(6)-C(18)-C(19)	114.5(6)	C(37)-C(35)-C(38)	108.9(9)
C(6)-C(18)-C(26)	108.8(6)	C(35)-C(36)-H(361)	110.1
C(19)-C(18)-C(26)	103.6(6)	C(35)-C(36)-H(362)	109.0
C(6)-C(18)-H(181)	109.7	H(361)-C(36)-H(362)	109.5
C(19)-C(18)-H(181)	110.2	C(35)-C(36)-H(363)	109.3
C(26)-C(18)-H(181)	109.8	H(361)-C(36)-H(363)	109.5
C(18)-C(19)-C(20)	118.6(6)	H(362)-C(36)-H(363)	109.5
C(18)-C(19)-C(23)	104.2(6)	C(35)-C(37)-H(371)	110.0
C(20)-C(19)-C(23)	115.1(7)	C(35)-C(37)-H(372)	108.7
C(18)-C(19)-H(191)	106.3	H(371)-C(37)-H(372)	109.5
C(20)-C(19)-H(191)	105.6	C(35)-C(37)-H(373)	109.7
C(23)-C(19)-H(191)	106.2	H(371)-C(37)-H(373)	109.5
C(4)-C(20)-C(19)	108.0(6)	H(372)-C(37)-H(373)	109.5
C(4)-C(20)-C(21)	106.6(6)	C(35)-C(38)-H(381)	109.9
C(19)-C(20)-C(21)	112.4(6)	C(35)-C(38)-H(382)	109.3
C(4)-C(20)-C(22)	114.1(7)	H(381)-C(38)-H(382)	109.5
C(19)-C(20)-C(22)	106.7(6)	C(35)-C(38)-H(383)	109.2
C(21)-C(20)-C(22)	109.2(7)	H(381)-C(38)-H(383)	109.5
C(20)-C(21)-H(211)	109.4	H(382)-C(38)-H(383)	109.5
C(20)-C(21)-H(212)	109.3	Si(1)-C(39)-C(40)	121.5(7)
H(211)-C(21)-H(212)	109.5	Si(1)-C(39)-C(45)	122.8(6)
C(20)-C(21)-H(213)	109.7	C(40)-C(39)-C(45)	115.6(8)
H(211)-C(21)-H(213)	109.5	C(39)-C(40)-C(42)	123.0(9)
H(212)-C(21)-H(213)	109.5	C(39)-C(40)-H(401)	118.4
C(20)-C(22)-H(221)	110.1	C(42)-C(40)-H(401)	118.6
C(20)-C(22)-H(222)	109.3	C(40)-C(42)-C(43)	118.5(9)
H(221)-C(22)-H(222)	109.5	C(40)-C(42)-H(421)	120.7
C(20)-C(22)-H(223)	109.1	C(43)-C(42)-H(421)	120.8
H(221)-C(22)-H(223)	109.5	C(42)-C(43)-C(44)	120.4(9)
H(222)-C(22)-H(223)	109.5	C(42)-C(43)-H(431)	119.5
C(19)-C(23)-O(24)	130.3(8)	C(44)-C(43)-H(431)	120.1
C(19)-C(23)-O(25)	110.0(7)	C(43)-C(44)-C(45)	121.1(9)
O(24)-C(23)-O(25)	119.5(7)	C(43)-C(44)-H(441)	119.3
C(23)-O(25)-C(26)	111.0(6)	C(45)-C(44)-H(441)	119.5
C(18)-C(26)-O(25)	110.1(7)	C(39)-C(45)-C(44)	121.3(8)
C(18)-C(26)-O(27)	129.0(8)	C(39)-C(45)-H(451)	119.2
O(25)-C(26)-O(27)	120.9(7)	C(44)-C(45)-H(451)	119.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sx142. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	24(1)	22(1)	17(1)	1(1)	1(1)	-8(1)
O(2)	28(3)	34(3)	17(3)	1(2)	6(2)	-14(3)
C(3)	21(4)	29(4)	19(4)	3(3)	1(3)	-5(3)
C(4)	31(4)	20(4)	19(4)	-3(3)	0(3)	-4(3)
C(5)	21(4)	21(4)	20(4)	-1(3)	4(3)	-6(3)
C(6)	27(4)	18(4)	18(3)	-3(3)	3(3)	-8(3)
O(7)	24(3)	15(3)	31(3)	2(2)	-3(2)	-3(2)
C(8)	28(4)	32(4)	22(4)	6(3)	-5(3)	-5(4)
C(9)	28(4)	17(4)	24(4)	4(3)	1(3)	-6(3)
C(10)	27(4)	24(4)	27(4)	0(3)	-1(3)	-4(3)
C(11)	25(4)	21(4)	20(3)	0(3)	0(3)	-5(3)
C(12)	21(4)	20(4)	28(4)	-4(3)	9(3)	-5(3)
O(13)	25(3)	33(3)	27(3)	-4(2)	5(2)	-5(3)
C(14)	28(5)	45(6)	41(5)	-3(4)	-1(4)	-8(4)
C(15)	19(4)	21(4)	31(4)	0(3)	-5(3)	-2(3)
C(16)	40(5)	24(4)	17(3)	6(3)	2(3)	-11(4)
C(18)	19(4)	27(4)	15(3)	1(3)	0(3)	-10(3)
C(19)	24(4)	21(4)	14(3)	0(3)	4(3)	-7(3)
C(20)	30(4)	22(4)	15(3)	1(3)	1(3)	-9(3)
C(21)	36(5)	28(4)	20(4)	-4(3)	0(3)	-14(4)
C(22)	40(5)	36(5)	23(4)	7(4)	-9(4)	-11(4)
C(23)	23(4)	23(4)	23(4)	1(3)	3(3)	-3(3)
O(24)	26(3)	43(4)	30(3)	-3(3)	6(2)	-17(3)
O(25)	25(3)	33(3)	19(3)	1(2)	2(2)	-9(2)
C(26)	25(4)	24(4)	20(4)	0(3)	4(3)	-7(3)
O(27)	30(3)	35(3)	19(3)	7(2)	-2(2)	-12(3)
C(28)	25(4)	28(4)	20(4)	7(3)	1(3)	-4(3)
C(29)	46(5)	23(4)	29(4)	-5(3)	0(4)	-15(4)
C(30)	49(6)	26(4)	31(5)	-1(4)	4(4)	-7(4)
C(31)	40(5)	28(5)	45(6)	15(4)	-2(4)	-3(4)
C(32)	32(5)	42(5)	38(5)	3(4)	-11(4)	-7(4)
C(33)	34(5)	35(5)	24(4)	-5(4)	-2(4)	6(4)
C(35)	30(4)	31(4)	23(4)	-8(3)	-3(3)	-7(4)
C(36)	30(5)	29(4)	39(5)	0(4)	-3(4)	-14(4)
C(37)	34(5)	28(5)	57(6)	0(4)	-10(4)	-8(4)
C(38)	51(6)	90(9)	28(5)	-18(5)	12(4)	-45(7)
C(39)	35(5)	23(4)	24(4)	2(3)	0(3)	-12(4)
C(40)	34(5)	27(4)	29(4)	5(3)	-2(4)	-5(4)
C(42)	56(6)	26(5)	43(5)	-2(4)	12(5)	-11(4)
C(43)	59(7)	27(5)	38(5)	-3(4)	-1(5)	-23(5)
C(44)	40(5)	30(5)	31(5)	-1(4)	-3(4)	-12(4)
C(45)	40(5)	29(4)	20(4)	2(3)	1(4)	-10(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for sx142.

	x	y	z	U(eq)
H(31)	8148	5248	2642	29
H(32)	8165	3728	2423	29
H(51)	4261	6120	1840	24
H(61)	3718	6921	877	25
H(81)	3994	10363	665	32
H(82)	3282	9228	366	32
H(101)	3273	9202	1884	31
H(111)	533	9859	2448	27
H(141)	-5654	11971	2184	44
H(142)	-4778	12731	1702	44
H(143)	-4927	11160	1623	44
H(151)	-2744	11570	1012	29
H(161)	0	10894	450	32
H(181)	6156	4931	556	23
H(191)	9114	4350	771	24
H(211)	10216	7084	1432	33
H(212)	9302	7043	2032	33
H(213)	8043	7835	1499	33
H(221)	11685	4284	1465	36
H(222)	10878	4222	2081	36
H(223)	10458	3280	1609	36
H(291)	7782	1995	3113	38
H(301)	10268	-47	3519	43
H(311)	11486	34	4441	45
H(321)	10084	2154	4969	47
H(331)	7701	4221	4546	0
H(361)	1594	3462	3419	44
H(362)	3742	2631	3538	44
H(363)	3057	3482	2944	44
H(371)	326	6246	3336	55
H(372)	1666	7167	3405	55
H(373)	1793	6261	2862	55
H(381)	1329	4888	4280	68
H(382)	2662	5799	4379	68
H(383)	3462	4055	4422	68
H(401)	5843	7740	2873	34
H(421)	6272	9936	3155	51
H(431)	6251	10358	4133	46
H(441)	5733	8643	4818	38
H(451)	5438	6408	4548	39

Appendix 22: X-ray crystal structure of the product 396

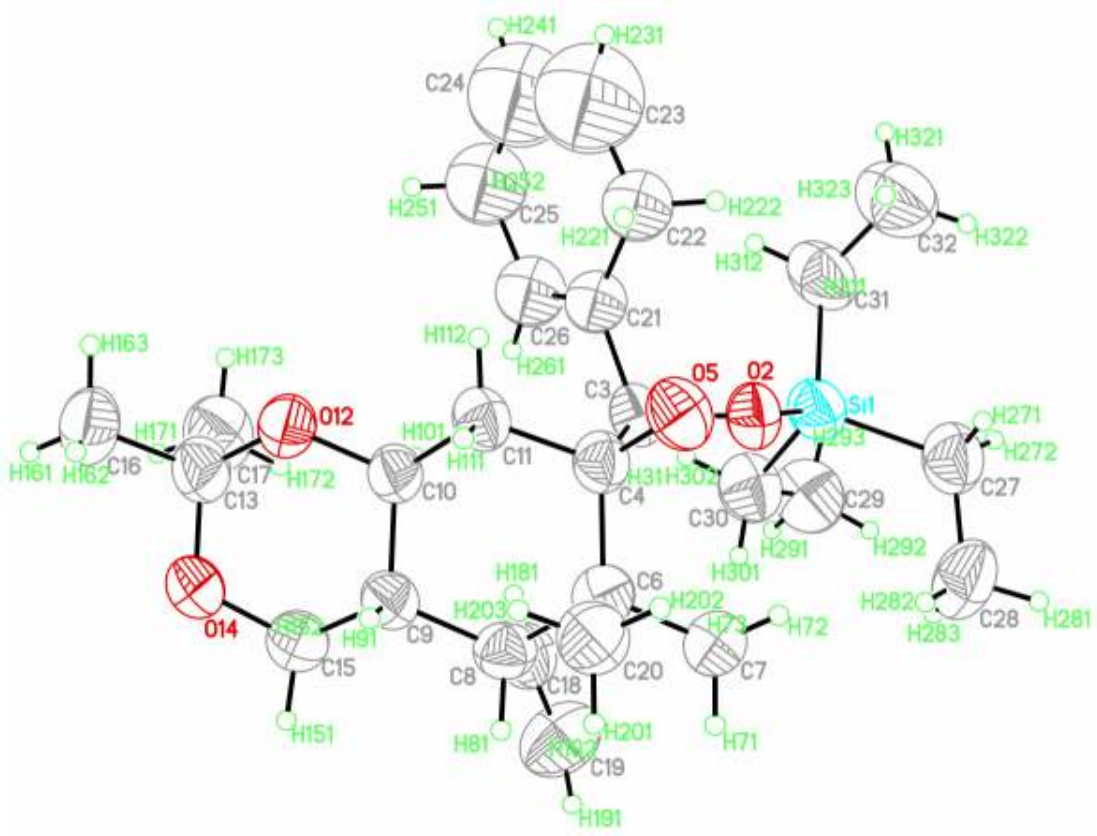


Table 1. Crystal data and structure refinement for sx174..

Identification code	sx174	
Empirical formula	C27 H48 O4 Si1	
Formula weight	464.76	
Temperature	293 K	
Crystal system	Monoclinic	
Space group	P 1 2_1/c 1	
Unit cell dimensions	a = 11.2020(4) Å	α= 90°.
	b = 19.5806(7) Å	β= 111.7873(18)°.
	c = 13.4973(5) Å	γ = 90°.
Volume	2749.04(18) Å^3	
Z	4	
Density (calculated)	1.12 Mg/m^3	
Absorption coefficient	0.967 mm^{-1}	
F(000)	1024	
Crystal size	0.20 × 0.10 × 0.05 mm^3	
Absorption correction	None	
Diffractometer	Rigaku R-axis/RAPID	
Scan type	2θ/ω scans	
Reflections measured	18762	
Independent reflections	4553	
Rint	0.0459	
θ_{max}	65.3708	
h =	-13 → 13	
k =	-23 → 23	
l =	-9 → 14	
$\Delta\rho_{min}$ =	-0.56 e Å^{-3}	
$\Delta\rho_{max}$ =	0.85 e Å^{-3}	
Reflections used	4553	

Cutoff: I >	-10.00σ(I)
Parameters refined	280
S =	1.03
R-factor	0.159
weighted R-factor	0.078
Δ/σ_{max}	0.0001
Refinement on	F^2
w =	$w' \times [1 - (\Delta F_{obs} / 6 \times \Delta F_{est})^2]^2$
w′ =	$[P_0T_0'(x) + P_1T_1'(x) + ...P_{n-1}T_{n-1}'(x)]^{-1}$,
	where P_i are the coefficients of a Chebychev series in $t_i(x)$, and $x = F_{calc}^2/F_{calc}^2{}_{max}$.
P_0 - P_{n-1} =	585. 686. 240.

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for sx174.

	x	y	z	U(iso/eq)
Si(1)	0.53811(13)	0.43578(7)	0.32894(12)	0.0631
O(2)	0.6134(3)	0.39971(14)	0.4472(2)	0.0568
C(3)	0.6563(4)	0.3296(2)	0.4616(3)	0.0532
C(4)	0.7600(4)	0.3218(2)	0.5781(3)	0.0512
O(5)	0.7152(3)	0.35977(16)	0.6490(3)	0.0633
C(6)	0.8990(4)	0.3472(2)	0.5919(3)	0.0513
C(7)	0.8970(4)	0.4194(2)	0.5466(4)	0.0653
C(8)	0.9710(4)	0.2970(2)	0.5414(4)	0.0547
C(9)	0.9664(4)	0.2226(2)	0.5777(3)	0.0526
C(10)	0.8285(4)	0.2015(2)	0.5574(3)	0.0503
C(11)	0.7673(4)	0.2472(2)	0.6159(3)	0.0526
O(12)	0.8272(3)	0.13304(15)	0.5958(2)	0.0566
C(13)	0.8839(5)	0.0833(2)	0.5488(4)	0.0636
O(14)	1.0120(3)	0.10234(16)	0.5636(3)	0.0723
C(15)	1.0248(5)	0.1696(3)	0.5260(4)	0.0703
C(16)	0.8961(5)	0.0187(2)	0.6139(4)	0.0829
C(17)	0.8017(5)	0.0723(3)	0.4306(4)	0.0828
C(18)	0.9353(5)	0.3040(2)	0.4232(4)	0.0641
C(19)	1.0026(5)	0.3386(3)	0.3778(4)	0.0901
C(20)	0.9814(4)	0.3522(2)	0.7132(4)	0.0696
C(21)	0.5407(4)	0.2834(2)	0.4392(4)	0.0616
C(22)	0.4538(5)	0.2942(3)	0.5010(4)	0.0768(16)
C(26)	0.5175(5)	0.2352(3)	0.3631(4)	0.0835
C(27)	0.5564(5)	0.5296(2)	0.3549(4)	0.0762
C(28)	0.6931(5)	0.5573(3)	0.3798(4)	0.0895
C(29)	0.5581(5)	0.4471(3)	0.1257(4)	0.0920
C(30)	0.6088(5)	0.4078(3)	0.2312(4)	0.0750
C(31)	0.3618(5)	0.4123(3)	0.2678(4)	0.0863
C(32)	0.2787(6)	0.4455(4)	0.3157(5)	0.1174

Table 3. Bond lengths [Å] and angles [°] for sx174.

Si(1)-O(2)	1.661(3)	C(22)-H(222)	0.944
Si(1)-C(27)	1.868(5)	C(22)-H(223)	0.942
Si(1)-C(30)	1.855(5)	C(22)-H(224)	0.951
Si(1)-C(31)	1.892(5)	C(26)-C(251)	1.536(7)
O(2)-C(3)	1.444(5)	C(26)-H(261)	0.994
C(3)-C(4)	1.578(5)	C(27)-C(28)	1.539(6)
C(3)-C(21)	1.515(6)	C(27)-H(271)	0.968
C(3)-H(31)	0.978	C(27)-H(272)	0.967
C(4)-O(5)	1.442(5)	C(28)-H(281)	0.956
C(4)-C(6)	1.579(6)	C(28)-H(282)	0.958
C(4)-C(11)	1.539(6)	C(28)-H(283)	0.972
O(5)-H(12)	0.781(17)	C(29)-C(30)	1.531(6)
C(6)-C(7)	1.537(6)	C(29)-H(291)	0.962
C(6)-C(8)	1.578(6)	C(29)-H(292)	0.950
C(6)-C(20)	1.556(5)	C(29)-H(293)	0.970
C(7)-H(71)	0.963	C(30)-H(301)	0.976
C(7)-H(72)	0.950	C(30)-H(302)	0.961
C(7)-H(73)	0.989	C(31)-C(32)	1.467(7)
C(8)-C(9)	1.544(6)	C(31)-H(311)	0.954
C(8)-C(18)	1.500(6)	C(31)-H(312)	0.959
C(8)-H(81)	0.976	C(32)-H(321)	0.983
C(9)-C(10)	1.522(5)	C(32)-H(322)	0.961
C(9)-C(15)	1.527(6)	C(32)-H(323)	0.975
C(9)-H(91)	0.979	C(230)-C(231)	0.859(17)
C(10)-C(11)	1.515(5)	C(230)-C(240)	1.405(17)
C(10)-O(12)	1.439(5)	C(230)-C(241)	1.558(14)
C(10)-H(101)	0.988	C(230)-H(2311)	1.156
C(11)-H(111)	0.961	C(230)-H(2301)	0.973
C(11)-H(112)	0.958	C(230)-H(2302)	0.920
O(12)-C(13)	1.433(5)	C(231)-C(240)	1.520(14)
C(13)-O(14)	1.422(5)	C(231)-C(241)	1.230(17)
C(13)-C(16)	1.518(6)	C(231)-H(2311)	0.928
C(13)-C(17)	1.533(6)	C(231)-H(2312)	1.010
O(14)-C(15)	1.438(5)	C(231)-H(2301)	1.187
C(15)-H(151)	0.969	C(240)-C(241)	0.75(2)
C(15)-H(152)	0.970	C(240)-C(251)	1.487(12)
C(16)-H(161)	0.971	C(240)-H(2412)	1.006
C(16)-H(162)	0.949	C(240)-H(2401)	0.982
C(16)-H(163)	0.971	C(240)-H(2402)	0.954
C(17)-H(171)	0.979	C(241)-C(251)	1.514(13)
C(17)-H(172)	0.962	C(241)-H(2411)	0.862
C(17)-H(173)	0.965	C(241)-H(2412)	0.944
C(18)-C(19)	1.321(6)	C(241)-H(2402)	1.139
C(18)-H(181)	0.931	C(251)-H(2511)	0.979
C(19)-H(191)	0.931	C(251)-H(2512)	0.957
C(19)-H(192)	0.937	C(251)-H(2513)	0.984
C(20)-H(201)	0.960	C(251)-H(2514)	0.943
C(20)-H(202)	0.968	H(2311)-H(2301)	0.564
C(20)-H(203)	0.950	H(2412)-H(2402	0.380
C(21)-C(22)	1.513(6)	H(2511)-H(2513)	0.432
C(21)-C(26)	1.347(6)	H(2512)-H(2514)	0.428
C(22)-C(230)	1.551(12)	H(221)-H(224)	0.550
C(22)-C(231)	1.576(11)	H(222)-H(223)	0.564
C(22)-H(221)	0.947		

O(2)-Si(1)-C(27)	104.9(2)°	C(27)-Si(1)-C(31)	110.2(3)°
O(2)-Si(1)-C(3)	111.04(19)°	C(30)-Si(1)-C(31)	105.7(2)°
C(27)Si(1)-C(30)	112.2(2)°	Si(1)-O(2)-C(3)	124.0(3)°
O(2)-Si(1)-C(31)	113.0(2)°	O(2)-C(3)-C(4)	108.1(3)°

O(2)-C(3)-C(21)	108.8(4)°	H(161)-C(16)-H(162)	110.043°
C(4)-C(3)-C(21)	113.6(4)°	C(13)-C(16)-H(163)	109.162°
O(2)-C(3)-H(31)	108.471°	H(161)-C(16)-H(163)	107.441°
C(4)-C(3)-H(31)	107.843°	H(162)-C(16)-H(163)	109.350°
C(21)-C(3)-H(31)	109.848°	C(13)-C(17)-H(171)	109.727°
C(3)-C(4)-O(5)	107.6(3)°	C(13)-C(17)-H(172)	111.918°
C(3)-C(4)-C(6)	114.6(4)°	H(171)-C(17)-H(172)	108.182°
O(5)-C(4)-C(6)	109.3(4)°	C(13)-C(17)-H(173)	109.708°
C(3)-C(4)-C(11)	110.5(4)°	H(171)-C(17)-H(173)	107.520°
O(5)-C(4)-C(11)	104.9(3)°	H(172)-C(17)-H(173)	109.675°
C(6)-C(4)-C(11)	109.4(3)°	C(8)-C(18)-C(19)	124.6(5)°
C(4)-O(5)-H(12)	102(3)°	C(8)-C(18)-H(181)	117.135°
C(4)-C(6)-C(7)	112.0(4)°	C(19)-C(18)-H(181)	118.281°
C(4)-C(6)-C(8)	113.1(4)°	C(18)-C(19)-H(191)	120.212°
C(7)-C(6)-C(8)	109.6(4)°	C(18)-C(19)-H(192)	120.938°
C(4)-C(6)-C(20)	108.5(4)°	H(191)-C(19)-H(192)	118.849°
C(7)-C(6)-C(20)	106.1(4)°	C(6)-C(20)-H(201)	107.560°
C(8)-C(6)-C(20)	107.2(4)°	C(6)-C(20)-H(202)	108.131°
C(6)-C(7)-H(71)	109.848°	H(201)-C(20)-H(202)	109.125°
C(6)-C(7)-H(72)	110.491°	C(6)-C(20)-H(203)	110.364°
H(71)-C(7)-H(72)	110.435°	H(201)-C(20)-H(203)	110.491°
C(6)-C(7)-H(73)	109.882°	H(202)-C(20)-H(203)	111.070°
H(71)-C(7)-H(73)	107.701°	C(3)-C(21)-C(22)	119.0(4)°
H(72)-C(7)-H(73)	108.428°	C(3)-C(21)-C(26)	118.6(5)°
C(6)-C(8)-C(9)	111.6(4)°	C(22)-C(21)-C(26)	122.4(5)°
C(6)-C(8)-C(18)	115.2(4)°	C(21)-C(22)-C(230)	113.2(7)°
C(9)-C(8)-C(18)	113.4(4)°	C(21)-C(22)-C(231)	112.5(6)°
C(6)-C(8)-H(81)	106.835°	C(230)-C(22)-C(23)	131.9(6)°
C(9)-C(8)-H(81)	105.610°	C(21)-C(22)-H(221)	108.324°
C(18)-C(8)-H(81)	103.153°	C(230)-C(22)-H(221)	132.091°
C(8)-C(9)-C(10)	110.5(4)°	C(231)-C(22)-H(221)	109.201°
C(8)-C(9)-C(15)	115.1(4)°	C(21)-C(22)-H(222)	109.241°
C(10)-C(9)-C(15)	108.1(4)°	C(230)-C(22)-H(222)	77.627°
C(8)-C(9)-H(91)	108.516°	C(231)-C(22)-H(222)	107.298°
C(10)-C(9)-H(91)	106.785°	H(221)-C(22)-H(222)	110.274°
C(15)-C(9)-H(91)	107.374°	C(21)-C(22)-H(223)	108.136°
C(9)-C(10)-C(11)	111.7(4)°	C(230)-C(22)-H(223)	109.275°
C(9)-C(10)-O(12)	109.5(3)°	C(231)-C(22)-H(223)	132.991°
C(11)-C(10)-O(12)	107.2(3)°	H(221)C(22)-H(223)	78.333°
C(9)-C(10)-H(101)	108.592°	H(222)-C(22)-H(223)	34.802°
C(11)-C(10)-H(101)	109.830°	C(21)-C(22)-H(224)	107.474°
O(12)-C(10)-H(101)	109.980°	C(230)-C(22)-H(224)	108.694°
C(4)-C(11)-C(10)	111.5(4)°	C(231)-C(22)-H(224)	79.272°
C(4)-C(11)-H(111)	108.105°	H(221)-C(22)-H(224)	33.689°
C(10)(C(11)-H(111)	108.619°	H(222)-C(22)-H(224)	136.149°
C(4)-C(11)-H(112)	109.513°	H(223)-C(22)-H(224)	110.077°
C(10)-C(11)-H(112)	108.915°	C(21)-C(26)-C(251)	122.2(5)°
H(111)-C(11)-H(112)	110.166°	C(21)-C(26)-H(261)	118.052°
C(10)-O(12)-C(13)	114.1(3)°	C(251)-C(26)-H(261)	119.708°
O(12)-C(13)-O(14)	110.4(4)°	Si(1)-C(27)-C(28)	114.8(4)°
O(12)-C(13)-C(16)	105.6(4)°	Si(1)-C(27)-H(271)	106.015°
O(14)-C(13)-C(16)	105.5(4)°	C(28)-C(27)-H(271)	108.360°
O(12)-C(13)-C(17)	111.3(4)°	Si(1)-C(27)-H(272)	107.459°
O(14)-C(13)-C(17)	111.6(4)°	C(28)-C(27)-H(272)	109.458°
C(16)-C(13)-C(17)	112.0(4)°	H(271)-C(27)-H(272)	110.739°
C(13)-O(14)-C(15)	114.7(4)°	C(27)-C(28)-H(281)	110.544°
C(9)-C(15)-O(14)	110.2(4)°	C(27)-C(28)-H(282)	109.998°
C(9)-C(15)-H(151)	109.310°	H(281)-C(28)-H(282)	109.714°
O(14)-C(15)-H(151)	107.972°	C(27)-C(28)-H(283)	108.737°
C(9)-C(15)-H(152)	110.154°	H(281)-C(28)-H(283)	109.372°
O(14)-C(15)-H(152)	109.850°	H(282)-C(28)-H(283)	108.435°
H(151)-C(15)-H(152)	109.351°	C(30)-C(29)-H(291)	111.053°
C(13)-C(16)-H(161)	109.712°	C(30)-C(29)-H(292)	110.253°
C(13)-C(16)-H(162)	111.055°	H(291)-C(29)-H(292)	109.580°

C(30)-C(29)-H(293)	108.925°	C(230)-C(240)-C(241)	87.1(17)°
H(291)-C(29)-H(293)	108.595°	C(231)-C(240)-C(241)	53.3(14)°
H(292)-C(29)-H(293)	108.373°	C(230)-C(240)-C(251)	123.6(12)°
Si(1)-C(30)-C(29)	113.8(4)°	C(231)-C(240)-C(251)	110.3(10)°
Si(1)-C(30)-H(301)	108.202°	C(241)-C(240)-C(251)	77.6(15)°
C(29)-C(30)-H(301)	108.504°	C(230)-C(240)-H(2412)	120.073°
Si(1)-C(30)-H(302)	108.116°	C(231)-C(240)-H(2412)	97.490°
C(29)-C(30)-H(302)	109.849°	C(241)-C(240)-H(2412)	63.134°
H(301)-C(30)-H(302)	108.195°	C(251)-C(240)-H(2412)	100.467°
Si(1)-C(31)-C(32)	115.5(4)°	C(230)-C(240)-H(2401)	68.070°
Si(1)-C(31)-H(311)	107.757°	C(231)-C(240)-H(2401)	101.862°
C(32)-C(31)-H(311)	106.866°	C(241)-C(240)-H(2401)	155.196°
Si(1)-C(31)-H(312)	110.896°	C(251)-C(240)-H(2401)	115.987°
C(32)-C(31)-H(312)	107.200°	H(2412)-C(240)-H(2401)	128.618°
H(311)-C(31)-H(312)	108.372°	C(230)-C(240)-H(2402)	115.121°
C(31)-C(32)-H(321)	108.816°	C(231)-C(240)-H(2402)	104.358°
C(31)-C(32)-H(322)	109.477°	C(241)-C(240)-H(2402)	83.009°
H(321)-C(32)-H(322)	109.952°	C(251)-C(240)-H(2402)	116.256°
C(31)-C(32)-H(323)	108.528°	H(2412)-C(240)-H(2402)	22.136°
H(321)-C(32)-H(323)	109.097°	H(2401)-C(240)-H(2402)	106.491°
H(322)-C(32)-H(323)	110.929°	C(230)-C(241)-C(231)	33.3(8)°
C(22)-C(230)-C(231)	75.6(12)°	C(230)-C(241)-C(240)	64.2(15)°
C(22)-C(230)-C(240)	118.5(11)°	C(231)-C(241)-C(240)	97.5(18)°
C(231)-C(230)-C(240)	80.5(13)°	C(230)-C(241)-C(251)	112.1(11)°
C(22)-C(230)-C(241)	103.9(10)°	C(231)-C(241)-C(251)	127.9(13)°
C(231)-C(230)-C(241)	51.9(12)°	C(240)-C(241)-C(251)	73.5(15)°
C(240)-C(230)-C(241)	28.6(8)°	C(230)-C(241)-H(2411)	113.316°
C(22)-C(230)-H(2311)	101.707°	C(231)-C(241)-H(2411)	81.152°
C(231)-C(230)-H(2311)	52.365°	C(240)-C(241)-H(2411)	168.451°
C(240)-C(230)-H(2311)	106.535°	C(251)-C(241)-H(2411)	98.168°
C(241)-C(230)-H(2311)	86.963°	C(230)-C(241)-H(2412)	111.589°
C(22)-C(230)-H(2301)	106.113°	C(231)-C(241)-H(2412)	124.574°
C(231)-C(230)-H(2301)	80.581°	C(240)-C(241)-H(2412)	71.888°
C(240)-C(230)-H(2301)	124.566°	C(251)-C(241)-H(2412)	101.719°
C(241)-C(230)-H(2301)	113.055°	H(2411)-C(241)-H(2412)	118.364°
H(2311)-C(230)-H(2301)	29.137°	C(230)-C(241)-H(2402)	94.833°
C(22)-C(230)-H(2302)	108.908°	C(231)-C(241)-H(2402)	113.853°
C(231)-C(230)-H(2302)	165.840°	C(240)-C(241)-H(2402)	56.305°
C(240)-C(230)-H(2302)	85.696°	C(251)-C(241)-H(2402)	103.190°
C(241)-C(230)-H(2302)	114.180°	H(2411)-C(241)-H(2402)	134.714°
H(2311)-C(230)-H(2302)	136.157°	H(2412)-C(241)-H(2402)	18.083°
H(2301)-C(230)-H(2302)	110.073°	C(26)-C(251)-C(240)	113.6(8)°
C(22)-C(231)-C(230)	72.5(12)°	C(26)-C(251)-C(241)	110.8(8)°
C(22)-C(231)-C(240)	110.4(10)°	C(240)-C(251)-C(241)	28.8(8)°
C(230)-C(231)-C(240)	65.7(13)°	C(26)-C(251)-H(2511)	108.872°
C(22)-C(231)-C(241)	121.1(12)°	C(240)-C(251)-H(2511)	83.797°
C(230)-C(231)-C(241)	94.8(16)°	C(241)-C(251)-H(2511)	111.133°
C(240)-C(231)-C(241)	29.2(9)°	C(26)-C(251)-H(2512)	110.516°
C(22)-C(231)-H(2311)	112.639°	C(240)-C(251)-H(2512)	128.079°
C(230)-C(231)-H(2311)	80.541°	C(241)-C(251)-H(2512)	108.980°
C(240)-C(231)-H(2311)	112.119°	H(2511)-C(251)-H(2512)	106.505°
C(241)-C(231)-H(2311)	121.694°	C(26)-C(251)-H(2513)	108.933°
C(22)-C(231)-H(2312)	110.959°	C(240)-C(251)-H(2513)	106.312°
C(230)-C(231)-H(2312)	169.550°	C(241)-C(251)-H(2513)	130.242°
C(240)-C(231)-H(2312)	104.063°	H(2511)-C(251)-H(2513)	25.402°
C(241)-C(231)-H(2312)	74.880°	H(2512)-C(251)-H(2513)	83.266°
H(2311)-C(231)-H(2312)	106.277°	C(26)-C(251)-H(2514)	110.561°
C(22)-C(231)-H(2301)	94.547°	C(240)-C(251)-H(2514)	109.883°
C(230)-C(231)-H(2301)	53.909°	C(241)-C(251)-H(2514)	85.522°
C(240)-C(231)-H(2301)	101.982°	H(2511)-C(251)-H(2514)	127.413°
C(241)-C(231)-H(2301)	124.124°	H(2512)-C(251)-H(2514)	26.037°
H(2311)-C(231)-H(2301)	27.622°	H(2513)-C(251)-H(2514)	107.248°
H(2312)-C(231)-H(2301)	133.705°	C(230)-H(2311)-C(231)	47.094°
C(230)-C(240)-C(231)	33.8(7)°	C(230)-H(2311)-H(2301)	57.066°

C(231)-H(2311)-H(2301)	102.668°	C(241)-H(2402)-H(2412)	50.510°
C(230)-H(2301)-C(231)	45.511°	C(251)-H(2511)-H(2513)	77.856°
C(230)-H(2301)-H(231)	193.797°	C(251)-H(2512)-H(2514)	75.189°
C(231)-H(2301)-H(231)	149.710°	C(251)-H(2513)-H(2511)	76.742°
C(240)-H(2412)-C(241)	44.978°	C(251)-H(2514)-H(2512)	78.773°
C(240)-H(2412)-H(2402)	71.330°	C(22)-H(221)-H(224)	73.586°
C(241)-H(2412)-H(2402)	111.407°	C(22)-H(222)-H(223)	72.399°
C(240)-H(2402)-C(241)	40.686°	C(22)-H(223)-H(222)	72.799°
C(240)-H(2402)-H(2412)	86.534°	C(22)-H(224)-H(221)	72.725°

Table 4. Anisotropic displacement parameters for sx174.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	0.0583(9)	0.0606(9)	0.0703(10)	0.0091(8)	0.0237(7)	0.0100(8)
O(2)	0.058(2)	0.0463(19)	0.063(2)	0.0059(16)	0.0183(17)	0.0080(16)
C(3)	0.050(3)	0.052(3)	0.055(3)	0.004(2)	0.016(2)	0.006(2)
C(4)	0.055(3)	0.048(3)	0.054(3)	0.004(2)	0.024(2)	0.010(2)
O(5)	0.075(2)	0.057(2)	0.064(2)	-0.0055(18)	0.032(2)	0.0107(19)
C(6)	0.054(3)	0.053(3)	0.047(3)	0.000(2)	0.020(2)	-0.001(2)
C(7)	0.058(3)	0.055(3)	0.080(4)	0.003(3)	0.023(3)	-0.004(3)
C(8)	0.051(3)	0.054(3)	0.062(3)	0.002(3)	0.024(3)	-0.001(2)
C(9)	0.053(3)	0.055(3)	0.056(3)	0.005(2)	0.027(3)	0.007(2)
C(10)	0.052(3)	0.045(3)	0.057(3)	0.005(2)	0.023(2)	0.007(2)
C(11)	0.055(3)	0.052(3)	0.053(3)	0.007(2)	0.023(2)	0.010(2)
O(12)	0.060(2)	0.0470(19)	0.068(2)	0.0038(17)	0.0305(18)	0.0042(16)
C(13)	0.067(4)	0.052(3)	0.079(4)	0.000(3)	0.036(3)	0.007(3)
O(14)	0.064(2)	0.056(2)	0.106(3)	0.003(2)	0.042(2)	0.0122(18)
C(15)	0.066(4)	0.058(3)	0.100(4)	0.001(3)	0.046(3)	0.004(3)
C(16)	0.093(4)	0.048(3)	0.120(5)	0.012(3)	0.054(4)	0.010(3)
C(17)	0.091(4)	0.074(4)	0.084(4)	-0.022(3)	0.033(3)	-0.002(3)
C(18)	0.075(4)	0.062(3)	0.059(3)	0.003(3)	0.030(3)	0.008(3)
C(19)	0.110(5)	0.095(5)	0.078(4)	-0.003(4)	0.051(4)	-0.024(4)
C(20)	0.065(3)	0.068(4)	0.067(4)	-0.010(3)	0.013(3)	-0.005(3)
C(21)	0.056(3)	0.055(3)	0.063(3)	-0.004(3)	0.010(3)	0.004(3)
C(26)	0.065(4)	0.072(4)	0.099(5)	-0.005(4)	0.014(3)	0.001(3)
C(27)	0.083(4)	0.059(3)	0.083(4)	0.010(3)	0.027(3)	0.008(3)
C(28)	0.104(4)	0.056(3)	0.098(4)	0.012(3)	0.025(4)	-0.006(3)
C(29)	0.098(4)	0.110(5)	0.075(4)	0.013(4)	0.040(4)	0.015(4)
C(30)	0.087(4)	0.078(4)	0.062(3)	0.011(3)	0.030(3)	0.009(3)
C(31)	0.074(4)	0.100(5)	0.095(4)	0.036(4)	0.044(3)	0.035(3)
C(32)	0.094(5)	0.128(6)	0.121(6)	0.028(5)	0.030(4)	0.009(5)

Appendix 23: X-ray crystal structure of the methyl C-H insertion product 401

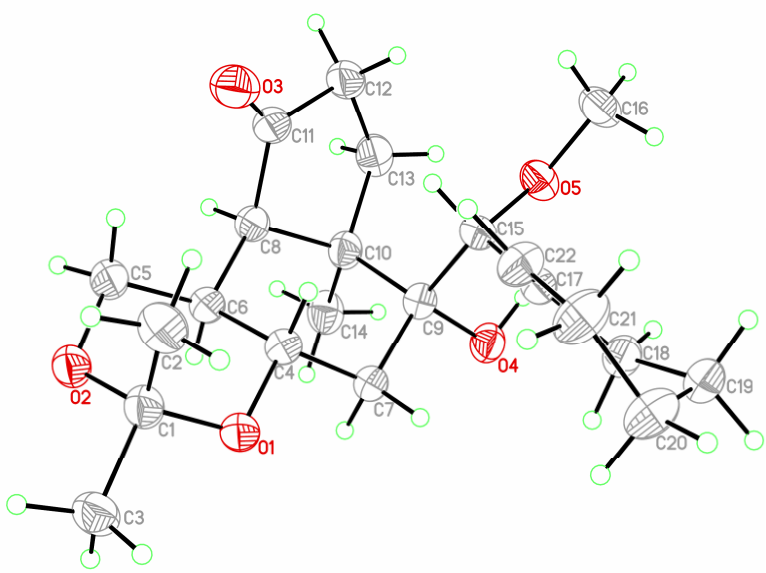


Table 1. Crystal data and structure refinement for CG656f2.

Identification code	**CG656f2**	
Empirical formula	C22 H34 O5	
Formula weight	378.49	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 16.2526(16)Å	α= 90°.
	b = 10.2359(11)Å	β= 91.053(4)°.
	c = 12.074(2)Å	γ = 90°.
Volume	2008.3(4) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	824	
Crystal size	0.54 x 0.23 x 0.03 mm^3	
Theta range for data collection	3.200 to 30.51°.	
Index ranges	-23<=h<=23, -14<=k<=14, -17<=l<=17	
Reflections collected	22757	
Independent reflections	6080 [R(int) 0.0848]	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6080 / 0 / 381	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0646, wR2 = 0.1408	
R indices (all data)	R1 = 0.1210, wR2 = 0.1714	
Largest diff. peak and hole	0.313 and -0.273 $e.Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for CG656f2.

	x	y	z	U(iso/eq)
O(1)	0.31103(8)	0.65147(14)	0.65931(12)	0.0314(3)
O(2)	0.22578(9)	0.78713(14)	0.55111(12)	0.0325(3)
O(3)	0.10047(11)	0.42487(17)	0.48273(14)	0.0436(4)
O(4)	0.20750(10)	0.32637(16)	0.90679(12)	0.0329(3)
O(5)	0.18020(9)	0.14720(14)	0.75790(12)	0.0318(3)
C(1)	0.30411(13)	0.7250(2)	0.55842(18)	0.0317(4)
C(2)	0.32040(16)	0.6407(3)	0.4572(2)	0.0393(5)
C(3)	0.36631(14)	0.8343(2)	0.5699(2)	0.0367(5)
C(4)	0.24810(12)	0.5532(2)	0.67010(17)	0.0283(4)
C(5)	0.15732(13)	0.6978(2)	0.55508(19)	0.0318(4)
C(6)	0.16365(12)	0.6161(2)	0.66002(17)	0.0281(4)
C(7)	0.25869(12)	0.4877(2)	0.78250(17)	0.0286(4)
C(8)	0.09755(12)	0.5113(2)	0.67216(17)	0.0283(4)
C(9)	0.19805(12)	0.37376(19)	0.79525(16)	0.0273(4)
C(10)	0.10688(12)	0.4256(2)	0.77833(17)	0.0292(4)
C(11)	0.08258(12)	0.4141(2)	0.57913(18)	0.0313(4)
C(12)	0.04033(14)	0.2958(2)	0.6288(2)	0.0356(5)
C(13)	0.04112(13)	0.3182(2)	0.7545(2)	0.0354(5)
C(14)	0.08210(15)	0.5020(2)	0.88225(19)	0.0364(5)
C(16)	0.19229(16)	0.0310(2)	0.6954(2)	0.0378(5)
C(15)	0.22331(12)	0.25864(19)	0.71707(17)	0.0270(4)
C(17)	0.31533(12)	0.23311(19)	0.71196(17)	0.0273(4)
C(18)	0.36131(13)	0.1898(2)	0.81535(18)	0.0322(5)
C(19)	0.44374(14)	0.1266(2)	0.7894(2)	0.0353(5)
C(20)	0.49088(14)	0.2094(3)	0.7070(2)	0.0423(6)
C(21)	0.44271(14)	0.2195(3)	0.5979(2)	0.0426(6)
C(22)	0.35252(13)	0.2421(2)	0.61500(19)	0.0344(5)

Table 3. Bond lengths [Å] and angles [°] for CG656f2.

O(1)-C(1)	1.435(3)	C(1)-C(3)	1.512(3)
O(1)-C(4)	1.442(2)	C(1)-C(2)	1.523(3)
O(5)-C(16)	1.424(3)	O(3)-C(11)	1.210(3)
O(5)-C(15)	1.431(2)	C(10)-C(14)	1.539(3)
O(4)-C(9)	1.437(2)	C(10)-C(13)	1.556(3)
O(4)-H(32)	0.89(4)	C(5)-H(11)	1.01(2)
O(2)-C(1)	1.424(2)	C(5)-H(12)	1.03(2)
O(2)-C(5)	1.442(2)	C(15)- C(17)	1.521(3)
C(9)-C(7)	1.537(3)	C(15)-H(17)	1.00(2)
C(9)-C(15)	1.569(3)	C(17)- C(22)	1.330(3)
C(9)-C(10)	1.583(3)	C(17)-C(18)	1.510(3)
C(8)-C(11)	1.517(3)	C(11)-C(12)	1.521(3)
C(8)-C(6)	1.527(3)	C(13)-C(12)	1.535(3)
C(8)-C(10)	1.558(3)	C(13)-H(16)	1.01(3)
C(8)-H(14)	0.99(2)	C(13)-H(34)	0.94(3)
C(6)-C(4)	1.519(3)	C(22)-C(21)	1.502(3)
C(6)-C(5)	1.520(3)	C(22)-H(7)	0.97(3)
C(6)-H(13)	1.00(2)	C(2)-H(23)	0.96(3)
C(7)-C(4)	1.521(3)	C(2)-H(21)	0.98(3)
C(7)-H(8)	0.99(2)	C(2)-H(22)	1.00(3)
C(7)-H(9)	0.98(2)	C(3)-H(20)	1.00(3)
C(4)-H(10)	1.05(2)	C(3)-H(18)	1.04(3)

C(3)-H(19)	0.95(3)	C(14)-H(26)	1.02(3)
C(18)-C(19)	1.526(3)	C(14)-H(25)	1.00(3)
C(18)-H(3)	0.97(3)	C(20)-C(19)	1.524(3)
C(18)-H(4)	1.00(3)	C(20)-H(31)	1.00(3)
C(21)-C(20)	1.524(3)	C(20)-H(30)	1.00(3)
C(21)-H(29)	0.98(3)	C(19)-H(6)	1.05(3)
C(21)-H(28)	0.99(3)	C(19)-H(5)	0.96(3)
C(12)-H(15)	0.98(3)	C(16)-H(2)	0.98(3)
C(12)-H(33)	1.01(3)	C(16)-H(1)	0.96(3)
C(14)-H(24)	0.99(3)	C(16)-H(27)	0.98(3)

C(1)-O(1)-C(4)	113.45(15)	O(5)-C(15)-C(17)	111.42(16)
C(16)-O(5)-C(15)	114.22(16)	O(5)-C(15)-C(9)	104.84(15) .
C(9)-O(4)-H(32)	106(2)	C(17)-C(15)-C(9)	114.96(16)
C(1)-O(2)-C(5)	113.84(15)	O(5)-C(15)-H(17)	107.4(12)
O(4)-C(9)-C(7)	107.00(16)	C(17)-C(15)-H(17)	107.3(12)
O(4)-C(9)-C(15)	106.60(16)	C(9)-C(15)-H(17)	110.7(13)
C(7)-C(9)-C(15)	109.53(16)	C(22)-C(17)-C(18)	121.47(18)
O(4)-C(9)-C(10)	108.52(15)	C(22)-C(17)-C(15)	119.13(18)
C(7)-C(9)-C(10)	109.46(16)	C(18)-C(17)-C(15)	119.28(17)
C(15)-C(9)-C(10)	115.37(16)	O(3)-C(11)-C(8)	127.90(19)
C(11)-C(8)-C(6)	119.56(17)	O(3)-C(11)-C(12)	124.8(2)
C(11)-C(8)-C(10)	104.59(17)	C(8)-C(11)-C(12)	107.33(18)
C(6)-C(8)-C(10)	114.60(16)	C(12)-C(13)-C(10)	106.35(17)
C(11)-C(8)-H(14)	101.9(13) .	C(12)-C(13)-H(16)	107.6(14)
C(6)-C(8)-H(14)	109.0(13)	C(10)-C(13)-H(16)	106.9(15)
C(10)-C(8)-H(14)	105.7(13)	C(12)-C(13)-H(34)	113.5(15)
C(4)-C(6)-C(5)	110.32(17)	C(10)-C(13)-H(34)	112.7(15)
C(4)-C(6)-C(8)	109.33(16)	H(16)-C(13)-H(34)	109(2)
C(5)-C(6)-C(8)	115.44(17)	C(17)-C(22)-C(21)	124.8(2)
C(4)-C(6)-H(13)	106.8(13)	C(17)-C(22)-H(7)	117.5(15)
C(5)-C(6)-H(13)	108.5(13)	C(21)-C(22)-H(7)	117.6(15)
C(8)-C(6)-H(13)	106.0(13)	C(1)-C(2)-H(23)	112.9(16)
C(4)-C(7)-C(9)	111.22(16)	C(1)-C(2)-H(21)	108.5(17)
C(4)-C(7)-H(8)	107.7(14)	H(23)-C(2)-H(21)	110(2)
C(9)-C(7)-H(8)	109.9(13)	C(1)-C(2)-H(22)	109.4(17)
C(4)-C(7)-H(9)	109.7(13)	H(23)-C(2)-H(22)	108(2)
C(9)-C(7)-H(9)	108.7(13)	H(21)-C(2)-H(22)	109(2)
H(8)-C(7)-H(9)	109.7(19)	C(1)-C(3)-H(20)	112.9(15)
O(1)-C(4)-C(6)	109.80(16)	C(1)-C(3)- H(18)	110.5(16)
O(1)-C(4)-C(7)	108.63(16)	H(20)-C(3)-H(18)	106(2)
C(6)-C(4)-C(7)	110.22(16)	C(1)-C(3)-H(19)	110.0(17)
O(1)-C(4)-H(10)	107.7(12)	H(20)-C(3)-H(19)	108(2)
C(6)-C(4)-H(10)	111.0(13)	H(18)-C(3)-H(19)	109(2)
C(7)-C(4)-H(10)	109.4(12)	C(17)-C(18)-C(19)	112.19(18)
O(2)-C(1)-O(1)	110.05(16)	C(17)-C(18)-H(3)	110.6(16)
O(2)-C(1)-C(3)	105.69(17)	C(19)-C(18)-H(3)	111.2(16)
O(1)-C(1)-C(3)	105.55(18)	C(17)-C(18)-H(4)	109.6(15)
O(2)-C(1)-C(2)	111.81(18)	C(19)-C(18)-H(4)	109.0(15)
O(1)-C(1)-C(2)	111.86(18)	H(3)-C(18)-H(4)	104(2)
C(3)-C(1)-C(2)	111.53(19)	C(22)-C(21)-C(20)	112.3(2)
C(14)-C(10)-C(13)	108.69(17)	C(22)-C(21)-H(29)	110.2(16)
C(14)-C(10)-C(8)	111.21(18)	C(20)-C(21)-H(29)	110.3(16)
C(13)-C(10)-C(8)	100.92(16)	C(22)-C(21)-H(28)	110.2(19)
C(14)-C(10)-C(9)	108.88(17)	C(20)-C(21)-H(28)	112.1(19)
C(13)-C(10)-C(9)	115.16(17)	H(29)-C(21)-H(28)	101(2)
C(8)-C(10)-C(9)	111.80(15)	C(11)-C(12)-C(13)	105.97(18)
O(2)-C(5)-C(6)	109.65(17)	C(11)-C(12)-H(15)	105.3(14)
O(2)-C(5)-H(11)	106.4(13)	C(13)-C(12)-H(15)	115.1(14)
C(6)-C(5)-H(11)	110.5(13)	C(11)-C(12)-H(33)	107.4(15)
O(2)-C(5)-H(12)	108.6(13)	C(13)-C(12)-H(33)	116.2(15)
C(6)-C(5)-H(12)	111.7(13)	H(15)-C(12)-H(33)	106(2)
H(11)-C(5)-H(12)	109.9(19)	C(10)-C(14)-H(24)	111.8(15)

C(10)-C(14)-H(26)	110.2(16)	C(20)-C(19)-H(6)	111.7(14)
H(24)-C(14)-H(26)	104(2)	C(18)-C(19)-H(6)	109.3(14)
C(10)-C(14)-H(25)	114.0(16)	C(20)-C(19)-H(5)	111.0(16)
H(24)-C(14)-H(25)	105(2)	C(18)-C(19)-H(5)	107.5(16)
H(26)-C(14)-H(25)	112(2)	H(6)-C(19)-H(5)	106(2)
C(21)-C(20)-C(19)	110.2(2)	O(5)-C(16)- H(2)	110.2(17)
C(21)-C(20)-H(31)	111.1(17)	O(5)-C(16)-H(1)	107.1(16)
C(19)-C(20)-H(31)	112.7(17)	H(2)-C(16)-H(1)	109(2)
C(21)-C(20)-H(30)	108.6(17)	O(5)-C(16)-H(27)	115.2(18)
C(19)-C(20)-H(30)	106.6(16)	H(2)-C(16)-H(27)	106(2)
H(31)-C(20)-H(30)	107(2)	H(1)-C(16)-H(27)	109(2)
C(20)-C(19)-C(18)	110.6(2)		

Table 4. Anisotropic displacement parameters ($Å^2$) for CG656f2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0271(7)	0.0272(8)	0.0398(8)	0.0025(6)	-0.0062(6)	-0.0029(6)
O(2)	0.0281(9)	0.0253(10)	0.0285(10)	0.0009(8)	-0.0031(7)	0.0017(8)
O(3)	0.0522(10)	0.0403(9)	0.0381(9)	-0.0036(7)	-0.0024(7)	-0.0070(8)
O(4)	0.0388(8)	0.0316(8)	0.0281(8)	0.0021(6)	-0.0026(6)	0.0054(7)
O(5)	0.0313(7)	0.0247(7)	0.0394(8)	-0.0013(6)	0.0033(6)	-0.0021(6)
C(1)	0.0288(10)	0.0272(10)	0.0391(11)	0.0027(9)	-0.0030(8)	0.0006(8)
C(2)	0.0417(13)	0.0346(12)	0.0417(13)	-0.0021(10)	0.0040(10)	-0.0001(11)
C(3)	0.0306(11)	0.0304(12)	0.0490(14)	0.0001(10)	-0.0012(10)	-0.0050(9)
C(4)	0.0268(9)	0.0261(10)	0.0319(10)	0.0005(8)	-0.0043(8)	-0.0004(8)
C(5)	0.0271(10)	0.0284(11)	0.0398(12)	0.0029(9)	-0.0046(8)	-0.0009(8)
C(6)	0.0262(9)	0.0254(10)	0.0324(10)	-0.0001(8)	-0.0038(8)	0.0004(8)
C(7)	0.0267(9)	0.0244(10)	0.0343(11)	-0.0003(8)	-0.0068(8)	0.0017(8)
C(8)	0.0241(9)	0.0263(10)	0.0343(10)	-0.0007(8)	-0.0028(7)	0.0024(8)
C(9)	0.0281(9)	0.0253(10)	0.0285(10)	0.0009(8)	-0.0031(7)	0.0017(8)
C(10)	0.0278(9)	0.0274(10)	0.0324(10)	0.0014(8)	-0.0007(8)	0.0035(8)
C(11)	0.0260(9)	0.0291(10)	0.0387(12)	-0.0009(9)	-0.0057(8)	-0.0003(8)
C(12)	0.0295(10)	0.0294(11)	0.0477(13)	-0.0005(10)	-0.0062(9)	-0.0023(9)
C(13)	0.0263(10)	0.0324(12)	0.0477(13)	0.0040(10)	0.0018(9)	-0.0004(9)
C(14)	0.0383(12)	0.0347(12)	0.0364(12)	-0.0003(10)	0.0047(9)	0.0096(10)
C(15)	0.0271(9)	0.0236(9)	0.0300(10)	-0.0007(8)	-0.0021(7)	-0.0022(8)
C(16)	0.0378(12)	0.0256(11)	0.0499(15)	-0.0076(10)	-0.0001(10)	-0.0011(10)
C(17)	0.0269(9)	0.0224(9)	0.0326(10)	-0.0020(8)	-0.0031(7)	0.0007(8)
C(18)	0.0313(10)	0.0327(11)	0.0325(11)	0.0026(9)	-0.0023(8)	0.0027(9)
C(19)	0.0316(10)	0.0360(12)	0.0381(12)	-0.0002(10)	-0.0073(9)	0.0050(9)
C(20)	0.0281(11)	0.0582(17)	0.0406(13)	0.0013(12)	-0.0042(9)	0.0017(11)
C(21)	0.0275(10)	0.0631(17)	0.0370(12)	0.0028(12)	0.0009(9)	0.0045(11)
C(22)	0.0286(10)	0.0411(13)	0.0334(11)	-0.0003(9)	-0.0040(8)	0.0024(9)

Table 5. Hydrogen coordinates and isotropic displacement parameters (Å^2) for CG656f2.

	x	y	z	U(eq)
H(1)	0.1536(17)	-0.033(3)	0.722(2)	0.046(7)
H(2)	0.2481(19)	-0.002(3)	0.707(2)	0.054(8)
H(3)	0.3274(16)	0.132(3)	0.859(2)	0.044(7)
H(4)	0.3711(16)	0.266(3)	0.865(2)	0.041(7)
H(5)	0.4325(16)	0.041(3)	0.760(2)	0.047(7)
H(6)	0.4775(16)	0.112(3)	0.863(2)	0.044(7)
H(7)	0.3185(16)	0.260(3)	0.550(2)	0.041(7)
H(8)	0.2487(14)	0.555(2)	0.840(2)	0.033(6)
H(9)	0.3151(14)	0.454(2)	0.7908(18)	0.026(5)
H(10)	0.2565(14)	0.484(2)	0.6075(19)	0.028(6)
H(11)	0.1060(15)	0.753(2)	0.5554(19)	0.032(6)
H(12)	0.1576(14)	0.641(2)	0.485(2)	0.034(6)
H(13)	0.1581(13)	0.675(2)	0.7252(19)	0.027(6)
H(14)	0.0430(14)	0.554(2)	0.6774(18)	0.030(6)
H(15)	0.0722(15)	0.220(3)	0.604(2)	0.036(6)
H(16)	-0.0141(16)	0.357(3)	0.775(2)	0.042(7)
H(17)	0.2031(13)	0.275(2)	0.6397(19)	0.025(5)
H(18)	0.3622(18)	0.897(3)	0.502(3)	0.058(8)
H(19)	0.3568(17)	0.883(3)	0.636(2)	0.052(8)
H(20)	0.4245(17)	0.802(3)	0.573(2)	0.043(7)
H(21)	0.3200(18)	0.697(3)	0.392(2)	0.056(8)
H(22)	0.3762(19)	0.599(3)	0.465(2)	0.057(8)
H(23)	0.2809(18)	0.572(3)	0.448(2)	0.048(7)
H(24)	0.0288(17)	0.547(3)	0.871(2)	0.043(7)
H(25)	0.1218(18)	0.573(3)	0.904(2)	0.053(8)
H(26)	0.0719(17)	0.439(3)	0.946(2)	0.053(8)
H(27)	0.1846(18)	0.040(3)	0.615(3)	0.060(9)
H(28)	0.465(2)	0.288(3)	0.549(3)	0.063(9)
H(29)	0.4509(17)	0.141(3)	0.553(2)	0.047(7)
H(30)	0.4958(18)	0.299(3)	0.740(2)	0.053(8)
H(31)	0.5477(19)	0.177(3)	0.695(2)	0.057(8)
H(32)	0.183(2)	0.249(4)	0.908(3)	0.082(12)
H(33)	-0.0158(18)	0.288(3)	0.592(2)	0.046(7)
H(34)	0.0505(15)	0.242(3)	0.796(2)	0.034(6)

Table 6. Torsion angles [°] for CG656f2.

		C(7)-C(9)-C(10)-C(8)	48.5(2)
C(11)-C(8)-C(6)-C(4)	-72.3(2)	C(15)-C(9)-C(10)-C(8)	-75.6(2)
C(10)-C(8)-C(6)-C(4)	53.0(2)	C(1)-O(2)-C(5)-C(6)	56.1(2)
C(11)-C(8)-C(6)-C(5)	52.7(3)	C(4)-C(6)-C(5)-O(2)	-52.1(2)
C(10)-C(8)-C(6)-C(5)	178.05(17)	C(8)-C(6)-C(5)-O(2)	-176.65(16)
O(4)-C(9)-C(7)-C(4)	-174.79(16)	C(16)-O(5)-C(15)-C(17)	-57.2(2)
C(15)-C(9)-C(7)-C(4)	70.0(2)	C(16)-O(5)-C(15)-C(9)	177.88(17)
C(10)-C(9)-C(7)-C(4)	-57.4(2)	O(4)-C(9)-C(15)-O(5)	47.95(19)
C(1)-O(1)-C(4)-C(6)	-56.1(2)	C(7)-C(9)-C(15)-O(5)	163.38(15)
C(1)-O(1)-C(4)-C(7)	-176.68(16)	C(10)-C(9)-C(15)-O(5)	-72.6(2)
C(5)-C(6)-C(4)-O(1)	52.3(2)	O(4)-C(9)-C(15)-C(17)	-74.7(2)
C(8)-C(6)-C(4)-O(1)	-179.71(16)	C(7)-C(9)-C(15)-C(17)	40.7(2)
C(5)-C(6)-C(4)-C(7)	171.94(17)	C(10)-C(9)-C(15)-C(17)	164.72(17)
C(8)-C(6)-C(4)-C(7)	-60.1(2)	O(5)-C(15)-C(17)-C(22)	120.6(2)
C(9)-C(7)-C(4)-O(1)	-175.11(16)	C(9)-C(15)-C(17)-C(22)	-120.3(2)
C(9)-C(7)-C(4)-C(6)	64.5(2)	O(5)-C(15)-C(17)-C(18)	-55.5(2)
C(5)-O(2)-C(1)-O(1)	-58.3(2)	C(9)-C(15)-C(17)-C(18)	63.6(2)
C(5)-O(2)-C(1)-C(3)	-171.85(18)	C(6)-C(8)-C(11)-O(3)	-20.8(3)
C(5)-O(2)-C(1)-C(2)	66.6(2)	C(10)-C(8)-C(11)-O(3)	-150.8(2)
C(4)-O(1)-C(1)-O(2)	58.2(2)	C(6)-C(8)-C(11)-C(12)	158.73(18)
C(4)-O(1)-C(1)-C(3)	171.82(17)	C(10)-C(8)-C(11)-C(12)	28.8(2)
C(4)-O(1)-C(1)-C(2)	-66.7(2)	C(14)-C(10)-C(13)-C(12)	150.97(18)
C(11)-C(8)-C(10)-C(14)	-153.22(18)	C(8)-C(10)-C(13)-C(12)	34.0(2)
C(6)-C(8)-C(10)-C(14)	73.9(2)	C(9)-C(10)-C(13)-C(12)	-86.6(2)
C(11)-C(8)-C(10)-C(13)	-38.07(18)	C(18)-C(17)-C(22)-C(21)	-3.9(4)
C(6)-C(8)-C(10)-C(13)	-170.90(17)	C(15)-C(17)-C(22)-C(21)	-180.0(2)
C(11)-C(8)-C(10)-C(9)	84.85(19)	C(22)-C(17)-C(18)-C(19)	-14.8(3)
C(6)-C(8)-C(10)-C(9)	-48.0(2)	C(15)-C(17)-C(18)-C(19)	161.22(19)
O(4)-C(9)-C(10)-C(14)	41.7(2)	C(17)-C(22)-C(21)-C(20)	-10.6(4)
C(7)-C(9)-C(10)-C(14)	-74.8(2)	O(3)-C(11)-C(12)-C(13)	172.5(2)
C(15)-C(9)-C(10)-C(14)	161.15(18)	C(8)-C(11)-C(12)-C(13)	-7.1(2)
O(4)-C(9)-C(10)-C(13)	-80.7(2)	C(10)-C(13)-C(12)-C(11)	-17.3(2)
C(7)-C(9)-C(10)-C(13)	162.88(18)	C(22)-C(21)-C(20)-C(19)	42.7(3)
C(15)-C(9)-C(10)-C(13)	38.8(2)	C(21)-C(20)-C(19)-C(18)	-62.1(3)
O(4)-C(9)-C(10)-C(8)	164.92(16)	C(17)-C(18)-C(19)-C(20)	47.2(3)

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