STUDIES TOWARD THE ASYMMETRIC SYNTHESIS OF (+)-DICTYOXETANE

By

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Abstract

Dictyoxetane is a diterpene natural product isolated in 1985 along the coast of India, and it has not been found since. The structure consists of a *trans*-hydrindane unit, and the dioxatricyclic core which contains an oxetane moiety. There have been several publications demonstrating the synthesis of the dioxatricyclic core or similar structures, and a single report of the *trans*-hydrindane unit featuring a ketone for further elaboration. Despite this, the total synthesis of dictyoxetane has only been achieved once in the last 36 years, and as such further investigation is warranted. The literature surrounding dictyoxetane and methods to synthesise structurally similar fragments are critically reviewed in Chapter 1.

Chapter 2 contains studies toward the asymmetric synthesis of (+)-dictyoxetane *via* a cycloaddition approach, which require a key furan intermediate. The synthesis of this intermediate *via* haloformylation and enynol cyclisation-isomerisation is detailed. An investigation of the reviewed [4+3] and [4+2] cycloaddition methods to construct the oxabicyclo[3.2.1]octane base of the dioxatricyclic core was undertaken. One of the methods failed to yield an isolable oxabicycle, while the other three were either poorly selective or the resulting products could not be advanced toward (+)-dictyoxetane.

The final section of chapter 2 describes the use of a chiral auxiliary in a Diels-Alder reaction with the furan intermediate, resulting in a pair of regioisomeric oxanorbornenones. The ring-expansion of these strained ketones to the oxabicyclo[3.2.1]octane substructure is examined but remains inconclusive as a route to synthesising (+)-dictyoxetane.

Chapter 3 contains a conclusion of the work, and suggestions for further work should the project be continued past the work in this thesis. Chapter 4 details the experimental procedures and data for all compounds reported as part of the work. Chapter 5 contains all the cited references. Finally, following the references are the appendices, which contain all the characterisation data for synthesised compounds including NMR, MS, IR, and X-ray data.

Acknowledgements

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Contents

Abbreviations

Ac – acetyl

ACCN – 1,1'-azobis(cyclohexanecarbonitrile)

AIBN – azobisisobutyronitrile

ASAP – atmospheric solids analysis probe

ATR – attenuated total reflectance

BHT – butylated hydroxytoluene

Bn – benzyl

Bu – butyl (superscript *n* for *normal* or *t* for *tert*)

COSY – correlation spectroscopy

Cy – cyclohexyl

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE – 1,2-dichloroethane

DET – diethyl tartrate

DIBAL – diisobutylaluminium hydride

DIPA – diisopropylamine

DIPEA – diisopropylethylamine

DMA – dimethylacetamide

DMAP – 4-dimethylaminopyridine

DME – dimethyl ether

DMF – dimethylformamide

DMP – Dess-Martin periodinane

DMPU – *N,N'*-dimethylpropyleneurea

DMSO – dimethyl sulfoxide

dppp – 1,3-bis(diphenylphosphino)propane

d.r. – diastereomeric ratio

EDTA – ethylenediaminetetracetic acid

e.e. – enantiomeric excess

EI – electron impact

eqv. – equivalents

e.r. – enantiomeric ratio

ES – electrospray ionisation

FDA – Federal Drug Administration

FTIR – Fourier transform infrared

GC – gas chromatography

HCA – hexachloroacetone

Hex – hexyl

HFIP – 1,1,1,3,3,3-hexafluoroisopropan-2-ol

HMBC – heteronuclear multi-bond correlation

HPK – Hajos-Parrish ketone

HPLC – high performance liquid chromatography

HRMS – high resolution mass spectrometry

HSQC – heteronuclear single quantum correlation

Im – imidazole

IR – infrared

KHMDS – potassium hexamethyldisilazide

LDA – lithium diisopropylamide

LiHMDS – lithium hexamethyldisilazide

LRMS – low resolution mass spectrometry

*m*CPBA – *meta*-chloroperoxybenzoic acid

mp – melting point

Ms – methanesulfonyl

MS – mass spectrometry (or spectrum)

MTBE – methyl *tert*-butyl ether

MVK – methyl vinyl ketone

Naph – 2-naphthyl

NBS – *N*-bromosuccinimide

NIS – *N*-iodosuccinimide

NMO – *N*-methyl morpholine *N*-oxide

NMR – nuclear magnetic resonance

nOe – nuclear Overhauser effect

NOESY – nuclear Overhauser effect spectroscopy

PCA – pentachloroacetone

PCC – pyridinium chlorochromate

Ph – phenyl

PIFA – bis(trifluoroacetoxy)iodobenzene

ppm – parts per million

*p*TSA – *para*-toluenesulfonic acid

py – pyridine

RCM – ring-closing metathesis

R_f – retention factor

sym-TCA – 1,1,3,3-tetrachloroacetone

TBAF – tetrabutylammonium fluoride

TBCP – tetrabromocyclopropene

TBDMS – *tert*-butyldimethylsilyl

TBS – tetrabromosilyl

TCA – 1,1,3-trichloroacetone

TCCP – tetrachlorocyclopropene

TES – triethylsilyl

Tf – trifluoromethanesulfonyl

TFAA – trifluoroacetic anhydride

TFE – 2,2,2-trifluoroethanol

THF – tetrahydrofuran

TIPS – triisopropylsilyl

TLC – thin layer chromatography

TMEDA – tetramethylethylenediamine

TMS – trimethylsilyl

TOF – time of flight

TPAP – tetrapropylammonium perruthenate

TPP – tetraphenylporphyrin

Ts – *para*-toluenesulfonyl

UI – universal indicator

WHO – World Health Organisation

XPhos – 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1. Introduction

1.1. Natural Products

Natural products and their analogues have formed the basis of some of the most effective treatments for human disease in the world.[1–3] Examples include taxol,[4] a potent anti-cancer agent, the anti-microbial streptomycin,[5] and morphine,[6] a well-known pain medication (Figure 1). All three compounds are but a few that feature on the model list of essential medicines generated by the WHO, and a review of FDA-approved treatments by 2013 found that 38% of all approved drugs are natural products, or derivatives thereof.[3]

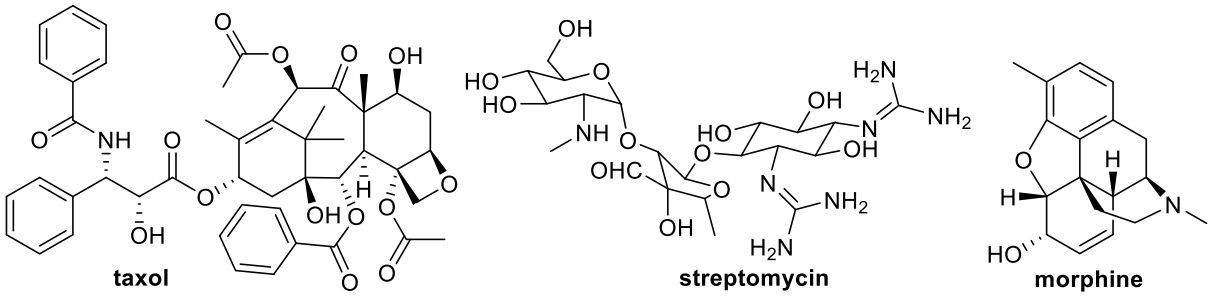


Figure 1: *Chemical structures of taxol,[4] streptomycin,[5] and morphine,[6] natural product-derived approved compounds found on the WHO's list of essential medicines.*

Despite over one third of FDA-approved medications being natural products or natural product-derived, Patridge *et al.* noted a decrease in the quantity of natural product-derived drugs since 1980.[3] High-throughput screening techniques and the prevalence of sp^2-rich molecules being selected from these processes, coupled with the quantification of molecular properties has driven the pharmaceutical industry in a different direction.[7] However, while these practices have generated effective molecules and new treatments, over the last decade it has become clear that medicinal chemistry is becoming pigeon-holed by this

approach.[8] The review suggested that there needs to be a return to molecules that have 3-dimensional shapes. Rodriguez *et al.* assert that 62% of natural products do not contain an aromatic moiety, and nearly 80% of known ring scaffolds have no drug equivalent.[9] Natural products offer a clear way back to molecular complexity either by their direct synthesis, or the inspiration they provide to fragment-based studies.[10]

1.2. Dictyoxetane

1.2.1. Isolation and Proposed Biosynthesis

Dictyoxetane (**1**) (Figure 2) is a naturally occurring diterpene obtained from the seaweed *Dictyota dichotoma*, found along the coast of India.[11]

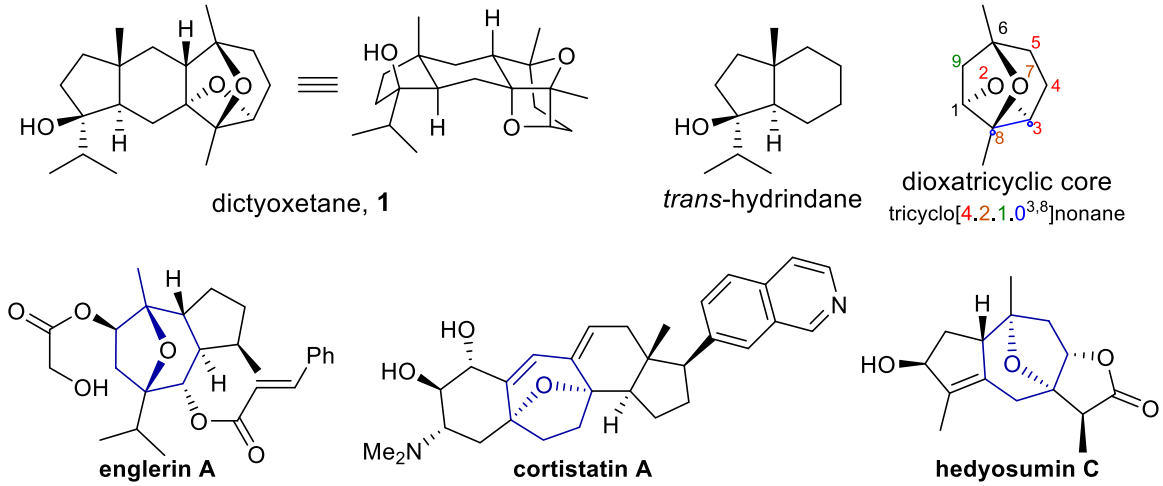
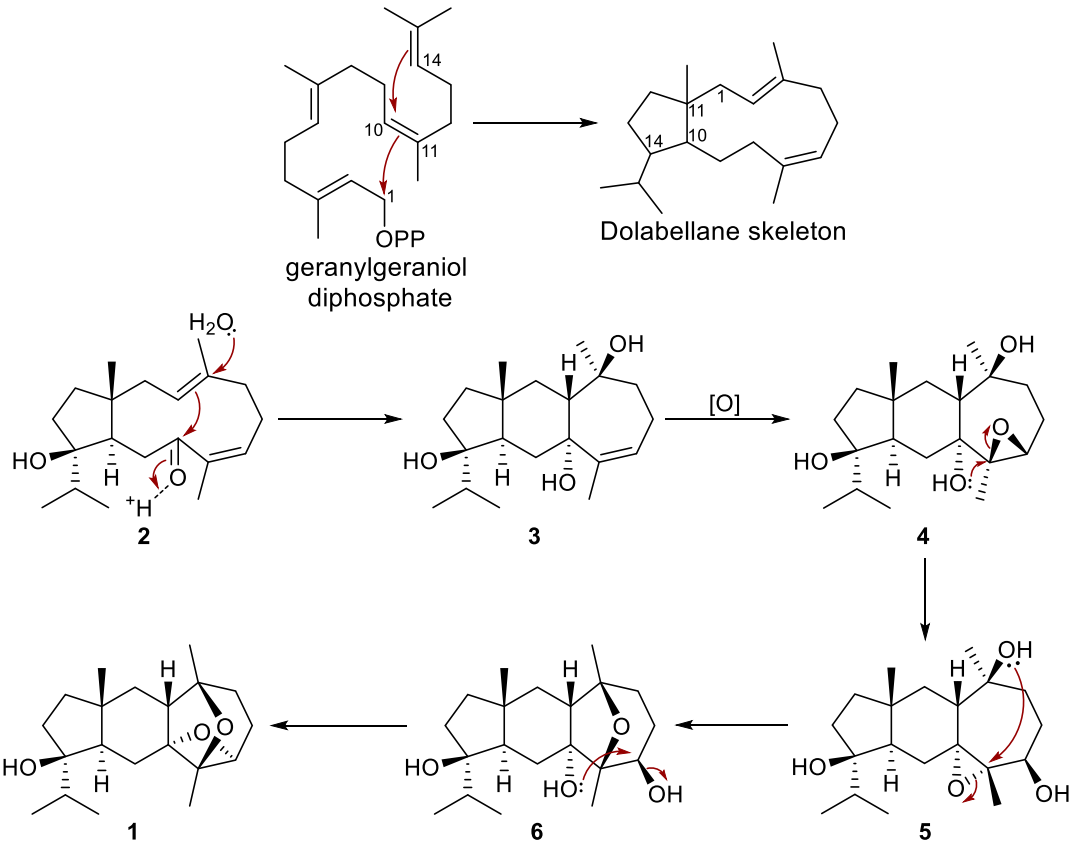


Figure 2: *Top: Chemical and geometric representations of (+)-dictyoxetane **1** (left), and chemical structures of the trans-hydrindane and dioxatricyclic core fragments of **1** (right).[11] Bottom: Chemical structures of englerin A, cortistatin A, and hedyosumin C which contain an oxabicyclo[3.2.1]octane ring system.[15-17]*

First reported in 1985, a crystal structure of dictyoxetane showed a unique carbon skeleton bearing resemblance to the dolabellane family of molecules, and as such is theorised to share a biosynthetic pathway (Scheme 1).[12–14] The pentacyclic framework of **1** consists of a *trans*-fused hydrindane and the dioxatricyclic core, formally a tricyclo[4.2.1.0^{3,8}]nonane, which

contains an oxetane moiety. Although the core has not been observed in any natural product before or since, the structure without the oxetane (oxabicyclo[3.2.1]octane) has been reported in several natural products such as englerin A, cortistatin A, and hedyosumin C.[15–17] There are eight stereocentres in dictyoxetane, but at the time of isolation the absolute configuration was unknown. No comment was made on the biological activity owing to a lack of material.



Scheme 1: *Hoffmann's proposed biosynthesis of dictyoxetane.[13,14] Top: Formation of the Dolabellane skeleton by C_{14}-C_{10} and C_{11}-C_1 ring closure of geranylgeraniol diphosphate. Bottom: A proposed mechanism for the transformation of Dolabellane derivative **2** into dictyoxetane **1** by hydration, oxidation, and a series of intramolecular cyclisations.*

Dictyoxetane and the dolabellane family likely share a biosynthetic pathway deriving from the C_{14}-C_{10}/C_{11}-C_1 cyclisation of geranylgeraniol diphosphate (Scheme 1). Hoffmann proposed, based on work by König and Wright, that the hydration of known intermediate **2** forms the C_2-

C_8 bond and establishes the 5-6-7 ring system of dictyoxetane.[18–20] Oxidation and intramolecular rearrangement then generate both the oxygen bridge and the oxetane ring. The biosynthetic proposal is supported by nOe analysis of **7** (Figure 3); here, the proton at the *trans* ring-junction experiences an nOe enhancement with respect to the C_3 methyl group, indicating that attack of the C_2-C_3 alkene onto the carbonyl is feasible. An H_2O molecule can then approach from one of two faces: the sterically hindered *endo*-face that points into the macrocycle, or the more open *exo*-face. The latter is more likely and delivers the stereochemistry found in **3**.

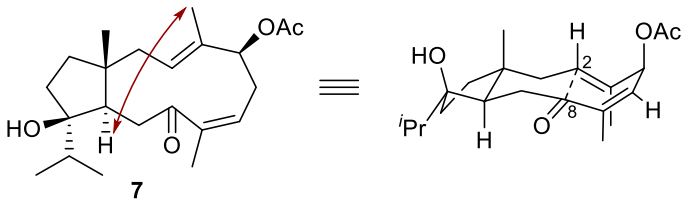


Figure 3: *Chemical and geometric representations of **7**, a proposed intermediate in the biosynthetic pathway toward **1**, and the observed nOe correlation that suggested the conformation of the macrocycle is favourable for C_2-C_8 transannular cyclisation.*[18]

1.2.2. Review of the Prior Art

As previously discussed, dictyoxetane is comprised of a *trans*-hydrindane unit and the dioxatricyclic core. The following sections will discuss the details and merits of the prior art relevant to a total synthesis of **1**; an overview of this work is provided by Figure 4.

Work exploring the synthesis of a racemic *trans*-hydrindane unit, in the form of a hydrindanone, has been published previously by the Grainger group and was adapted for the first total synthesis by Hugelshofer and Magauer in 2016 (Figure 4, I and II).[21,22] In further unpublished group work, the *trans*-hydrindanone synthesis was modified to make the bicycle in an asymmetric fashion.

While (+)-dictyoxetane has been synthesised once, there have also been reports detailing the construction of the dioxatricyclic core, or the structurally similar oxabicyclo[3.2.1]octane ring system (Figure 4, III-VI).[14,23–26] Since the majority of approaches to the dioxatricyclic core consist of a furan cycloaddition, relevant syntheses of furans will also be reviewed.[27–32]

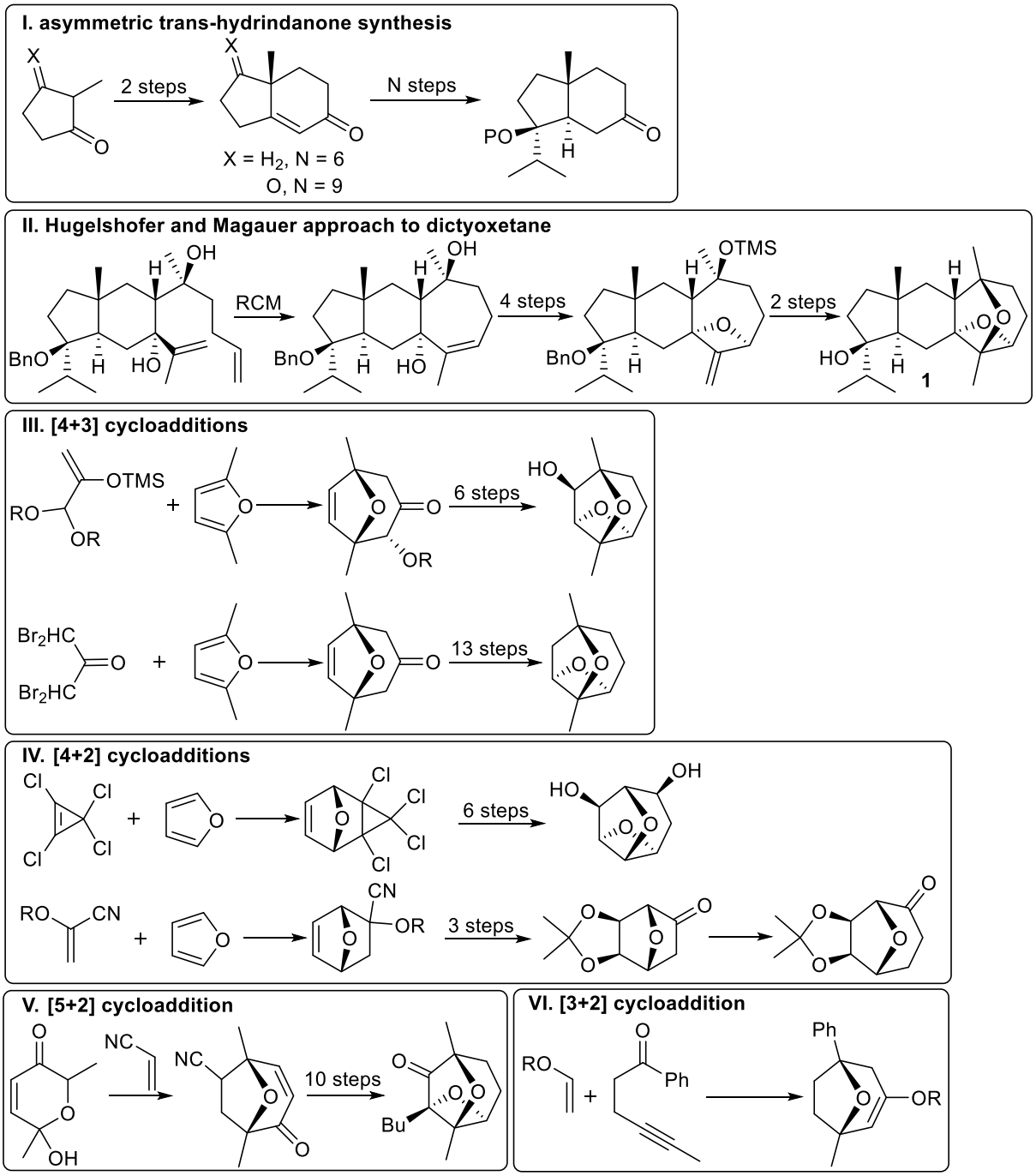
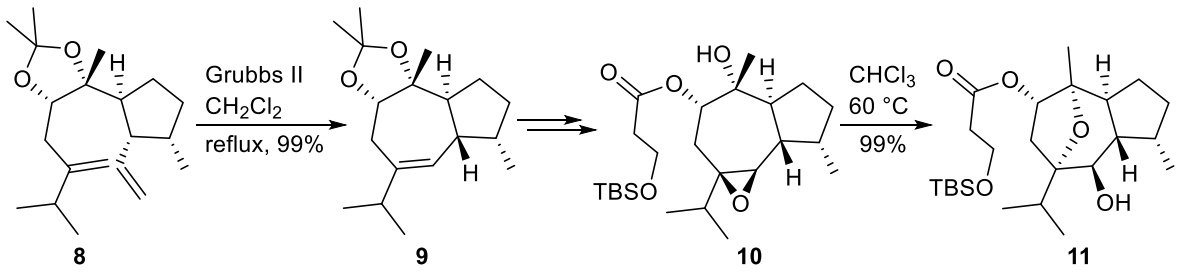


Figure 4: *Summary of previous methods used to construct the trans-hydrindane, the dioxatricyclic core, or oxabicyclo[3.2.1]octanes relevant to the synthesis of dictyoxetane.*
I. Asymmetric syntheses of the trans-hydrindanone fragment of ***1****.*[21,22] *II. Hugelshofer and Magauer's synthesis of* ***1****.*[21] *III: [4+3] furan cycloadditions that have led to the synthesis of an isolated dioxatricyclic ring system.*[14,35] *IV: [4+2] furan cycloadditions resulting in the construction of either an isolated dioxatricyclic ring system (top),*[43] *or the oxabicyclo[3.2.1]octane subunit (bottom).*[63] *V: A [5+2] pyrylium betaine cycloaddition approach to the dioxatricyclic core.*[26] *VI: A [3+2] platinum cascade method to assemble the oxabicyclo[3.2.1]octane subunit.*[55]

1.2.3. Synthesis of the Dioxatricyclic Core

1.2.3.1. Metathesis and Transannular Etherification

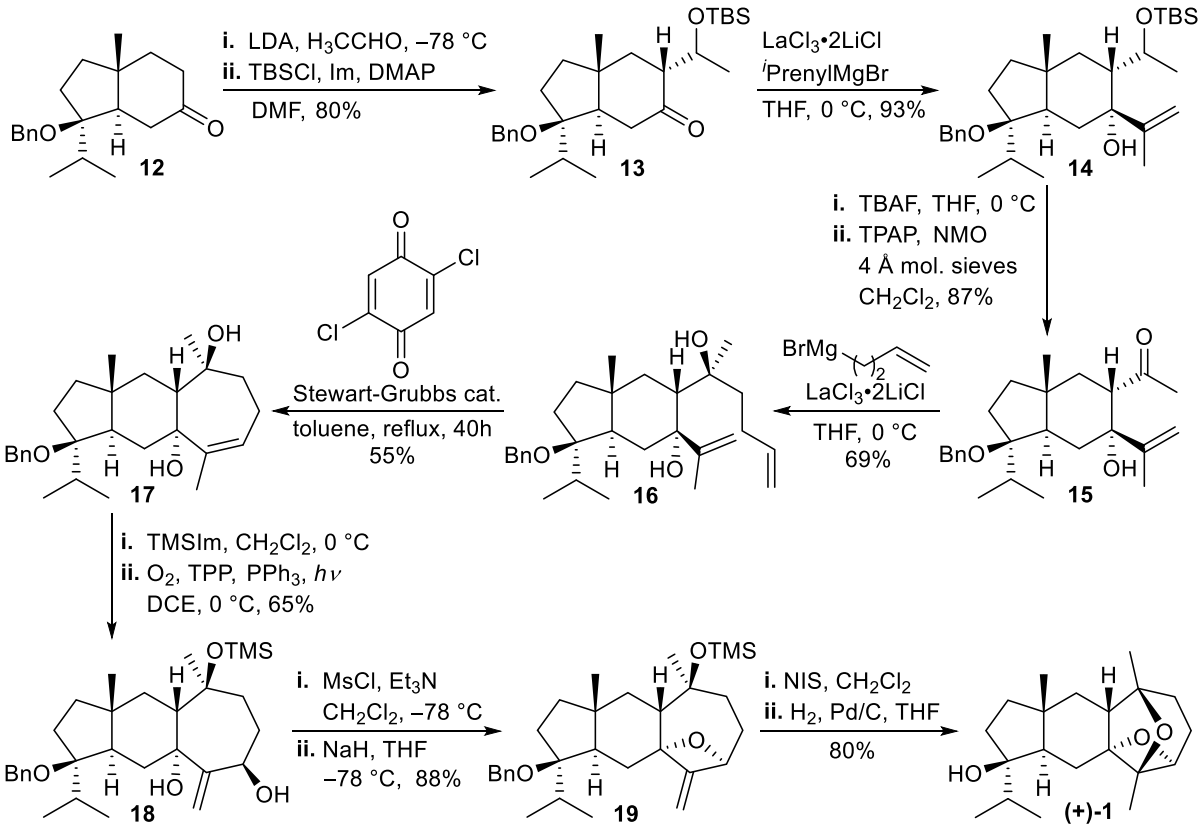
A metathesis approach to constructing the oxabicyclo[3.2.1]octane substructure was enlisted by Christmann for the synthesis of englerin A.[16] He used a RCM of diolefin **8** with 10 mol% of Grubbs' 2nd generation catalyst and obtained acetal **9** in 99% yield (Scheme 2). Heating alcohol **10** was sufficient for transannular alcohol attack to form the bridge and the synthesis was completed within two steps. Hatakeyama *et al.* adapted the protocol and noted that not protecting the diol caused the metathesis to be slow and poor-yielding.[33]



Scheme 2: *Christmann et al.'s construction of oxabicyclo[3.2.1]octane **11**, via RCM of **8** and transannular cyclisation of **10**, in the total synthesis of englerin A.*[16]

In their synthesis of (+)-dictyoxetane (Scheme 3), Hugelshofer and Magauer utilised a similar metathesis approach as Christmann *et al.* did for the synthesis of englerin A.[21] Following synthesis of benzyl-protected *trans*-hydrindanone **12**, they established a diene *via* sequential aldol and Grignard reactions to give **14** in a diastereocontrolled fashion. The RCM required substantial screening to obtain alkene **17** in 55% yield, despite high catalyst loading (25%), long reaction times, and the need for a quinone additive. They posited that the adjacent alcohol provides the challenge, presumably because of coordination and deactivation of the catalyst, echoing the findings of Hatakeyama in the synthesis of englerin A. The oxetane and oxygen bridge were both established by successive leaving group activation-elimination

reactions. Notably the oxygen bridge was formed late in the sequence, leaving the oxetane to survive hydrogenolytic dehalogenation and benzyl deprotection to complete the synthesis of dictyoxetane. The work of Hugelshofer and Magauer confirmed for the first time the absolute stereochemistry of the naturally-occurring (+)-isomer of **1**.

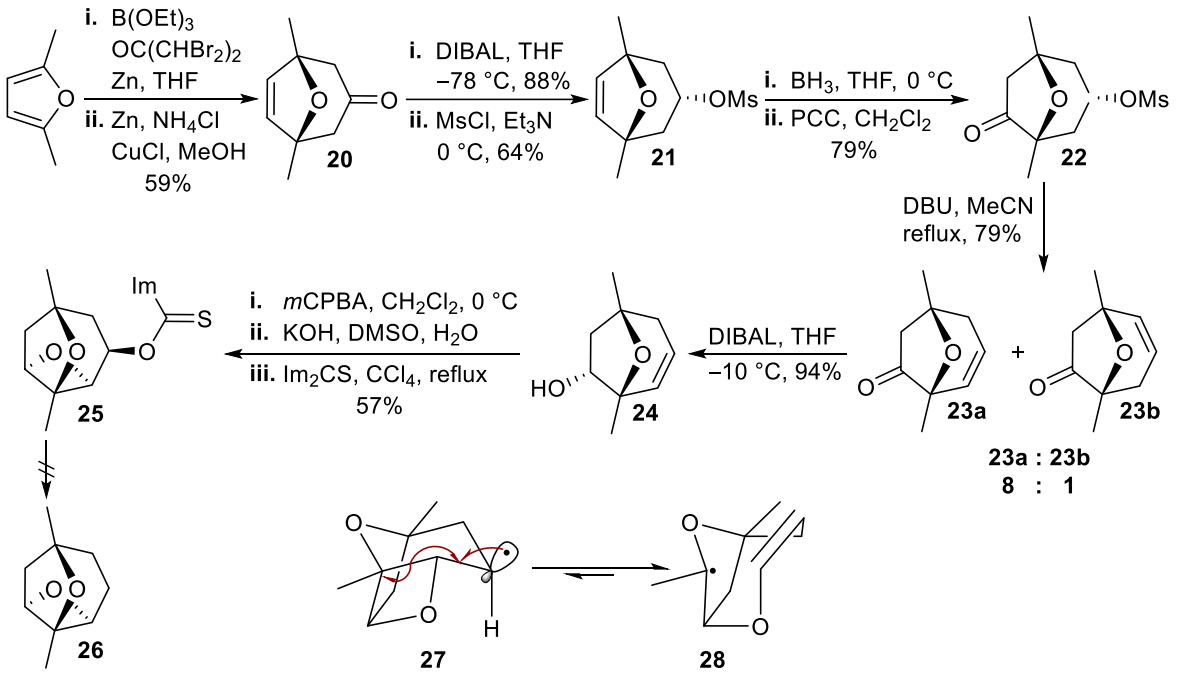


Scheme 3: *Hugelshofer and Magauer's synthesis of (+)-dictyoxetane **1** from trans-hydrindanone **12** via RCM of diolefin **16**, and sequential cyclisations of diol **18** and oxetane **19** to form the oxetane ring and oxygen bridge respectively.*[21]

1.2.3.2. Core Synthesis by [4+3] Cycloaddition of a Furan

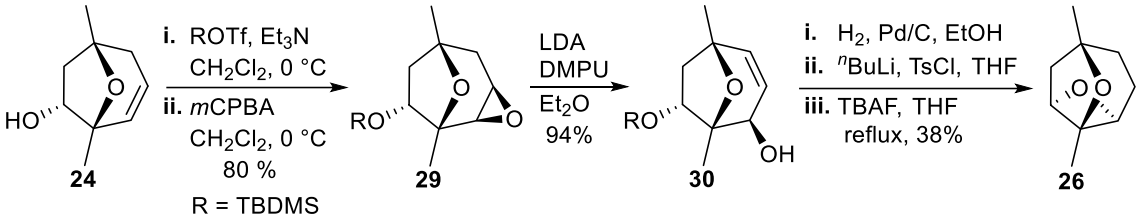
The first studies into the synthesis of (+)-dictyoxetane focused on constructing the dioxatricyclic core *via* a [4+3] cycloaddition (Scheme 4).[14] In 1995, Hoffmann and Reinecke established the oxabicyclic ring system from the cycloaddition of 2,5-dimethylfuran and 1,1,3,3-tetrabromoacetone, giving ketone **20** in 59% yield after zinc-mediated dehalogenation. Transformation of the ketone and olefin functionality delivered ketomesylate

22, which was then subjected to DBU in MeCN to deliver an 8:1 mixture of β-γ and γ-δ unsaturated ketones **23a** and **23b** respectively. Fortuitously, the isomers were separable so that **23a** could be reduced alone to homoallylic alcohol **24**, which was epoxidised and treated with a base to construct the oxetane ring. However, despite forming the thionocarbamate, Barton-McCombie deoxygenation to **26** failed which the authors proposed was the result of β-fragmentation of **27** to stabilised radical **28**.



Scheme 4: *Hoffmann and Reinecke's synthesis of thionocarbamate **25** from dimethylfuran via a [4+3] cycloaddition to give ketone **20**. Deoxygenation of **25** to desired dioxatricycle **26** could not be effected; inset is the proposed β-fragmentation of radical **27** to **28** to rationalise the failure to isolate **26**.*[14]

Alcohol **24** was instead transformed into the dioxatricyclic core subunit **26** *via* a 6-step process (Scheme 5). Elimination of the epoxide in **28** gave alcohol **29** in 94% yield, then following olefin hydrogenation and tosylation, the masked *trans*-diol was activated by TBAF to cyclise the oxetane, albeit in low yield. Despite the initial setbacks, this work represented the first synthesis of the dioxatricyclic core of dictyoxetane.

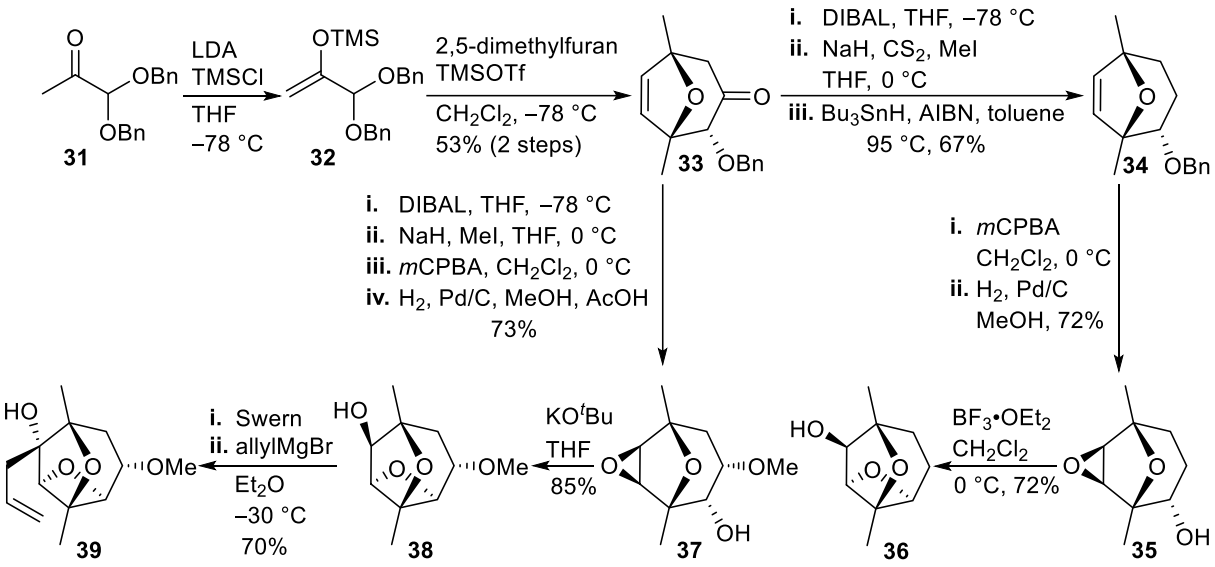


Scheme 5: *Hoffmann's successful synthesis of the dioxatricyclic ring system* ***26*** *from homoallylic alcohol* ***24****, via epoxidation-elimination to* ***30*** *which underwent cyclisation to form the oxetane ring.*[14]

In a later publication, Hoffmann *et al.* demonstrated a new route into the dioxatricyclic system and reported biological activities for some of the compounds (Scheme 6).[34] To overcome the issue of selectively installing oxygenation they used different cycloaddition conditions. Treatment of silyl enol ether **32** with 2,5-dimethylfuran in the presence of TMSOTf gave oxabicyclic ketone **33** in 53% yield over two steps, containing the required α-oxygenation *anti* to the oxygen bridge. To form a dictyoxetane-like core, the ketone was removed *via* a Barton-McCombie deoxygenation sequence to give **34**. The oxetane was then fashioned by attack of the alcohol onto the Lewis acid-activated epoxide to give oxatricycle **36** in 18% yield across 8 steps. Alternatively, ketone **33** was reduced and methylated and the oxetane formed by treatment of epoxyalcohol **37** with KO^{t}Bu in 85% yield. Further Swern oxidation and addition of allyl Grignard to the resulting ketone generated alcohol **39** in 23% yield over 9 steps. In contrast, the 1995 work gave the unfunctionalised dioxatricyclic core **26** in 6.3% yield across 14 steps. As such, either of the new routes represent a significant advancement in efficiency and functional utility.

As well as improving the route into the dioxatricyclic core structure, Hoffmann was able to obtain some bioactivity data for several of his compounds (Table 1). By comparison with *cis*-Platin and 5-fluorouracil, the test substrates showed moderate growth inhibition (GI_{50} and

TGI) of both HMO2 and HEP G2 tumour cells. These results demonstrate potential for the dictyoxetane framework, and analogues thereof, to be a new lead-like structure for medicinal investigation.

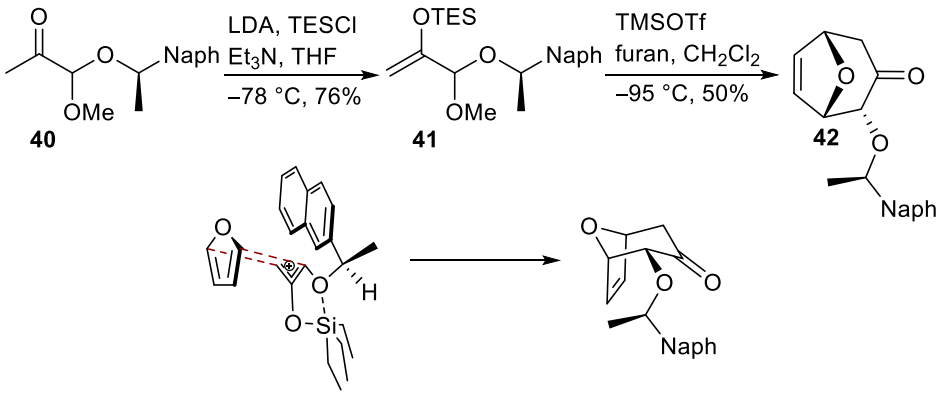


Scheme 6: *Hoffmann et al.'s synthesis of dioxatricycles **36** and **39**, both originating from oxabicyclic ketone **33** which was derived from the [4+3] cycloaddition of 2,5-dimethylfuran and the silyl enol ether of oxyallyl cation precursor **31**.*[34]

	GI_{50}		TGI		LC_{50}	
Compound	**HMO2**	**HEP G2**	**HMO2**	**HEP G2**	**HMO2**	**HEP G2**
36	4	0.1	50	30	>100	>50
37	3	< 0.1	57	45	>100	>50
38	< 1.0	< 0.1	72	35	>100	>50
39	< 1.0	< 0.1	54	30	>100	>50
5-fluorouracil	1.2	0.15	35	50	>50	>50
cis-Platin	0.1	0.5	2.5	30	40	>50

Table 1: *Antitumour activity (µL/mol) against HMO2 and HEP G2 cell lines for Hoffmann's intermediates GI_{50}: Drug concentration causing 50% growth inhibition; TGI: Drug concentration causing 100% growth inhibition; LC_{50}: Drug concentration causing 50% reduction of the cells present after 24 h.*

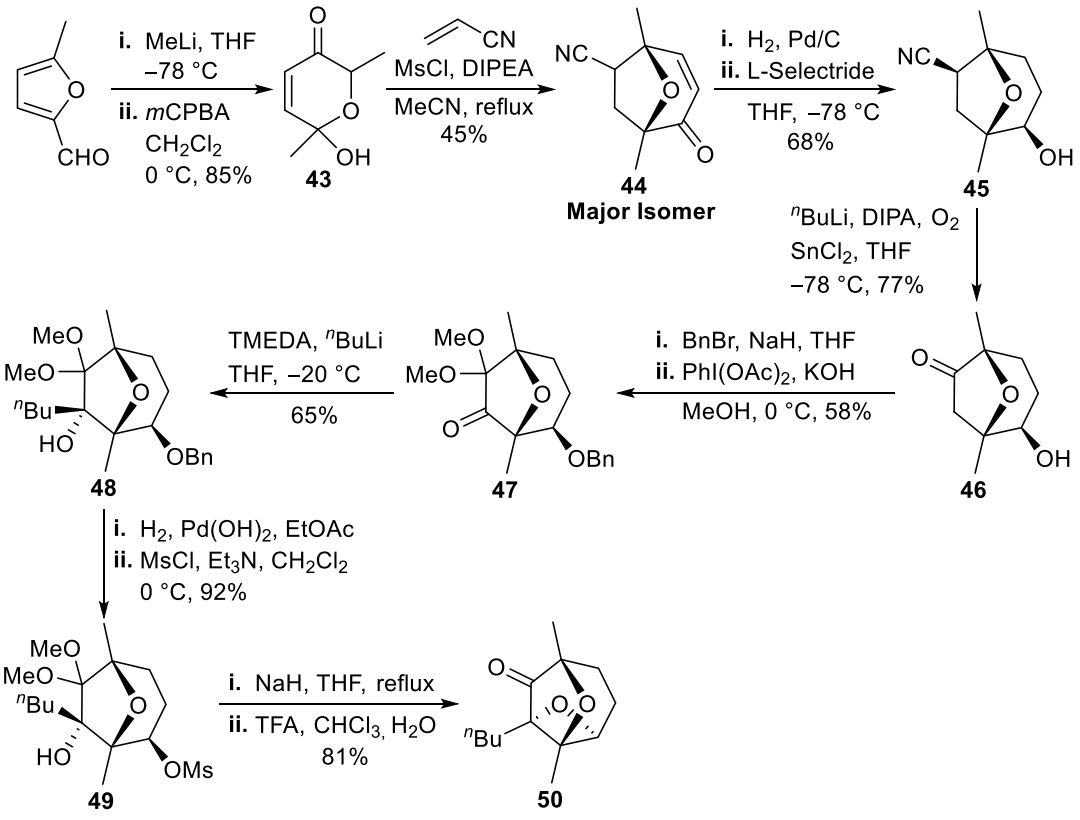
In 2000, Hoffmann published a further development of his methodology.[35] Previously, dibenzyl acetal **32** delivered benzyl ether **33** as a racemic mixture; however, using a chiral auxiliary in naphthyl ethanol derivative **41**, oxabicycle **42** was synthesised as a single enantiomer and diastereomer at −95 °C (Scheme 7). The disadvantage of this method is revealed in the real-world cost of enantiopure naphthyl ethanol, and the low temperature and dilution required to carry out the reaction effectively. The authors proposed a transition state where, following removal of methoxide by TMSOTf, the silicon coordinates to both the remaining oxygen atoms. The chelation fixes the position of the chiral naphthyl unit into blocking one face of the oxyallyl cation. They assumed an *endo* reaction profile owing to the low temperature. Evidence for this proposal is limited, but they note that with a similar auxiliary even slight increases in temperature, or ethereal solvents, decreased the observed diastereomeric ratio. Furthermore, changing the aromatic unit from phenyl to naphthyl made a significant difference, but changing the methyl group to bulkier substituents had little effect, suggesting a location on the outside of the reaction centre.



Scheme 7: *Top: Hoffmann's asymmetric [4+3] cycloaddition conditions using chiral oxyallyl cation precursor* ***41*** *to access oxabicyclic ketone* ***42****. Bottom: The proposed transition state model for the formation of* ***42*** *as a single isomer.*[35]

1.2.3.3. Core Synthesis by [5+2] Cycloaddition of Pyrylium Zwitterions

In 1996, Heathcock *et al.* constructed a similar ring system to the dioxatricyclic core of (+)-dictyoxetane derived from 5-methylfurfural (Scheme 8).[26] They utilised a ring-expansion of furfuranol by *m*CPBA to give enone **43**, followed by a [5+2] dipolar cycloaddition of the pyrylium salt generated *in situ* when **43** was treated with MsCl and a base. Acrylonitrile was found to be the most practical cycloaddition partner, giving the oxygen-bridged 7-membered ring in 45% yield as a mixture of isomers (10:1:1), of which **44** was the major isomer. For synthesis of the oxetane moiety, it would be desirable for the nitrile motif to be proximal to the ketone, but the major isomer instead favoured the distal position.



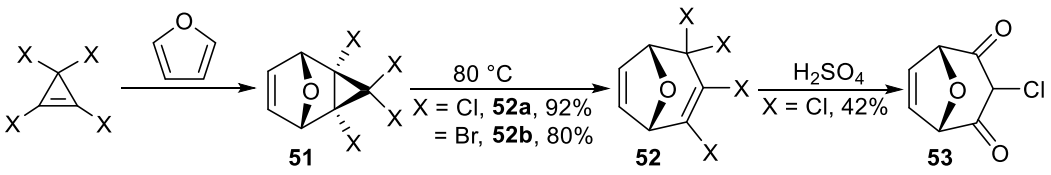
Scheme 8: *Heathcock's synthesis of the functionalised dioxatricyclic ring system* ***50****, via the ring expansion of commercially available furfural to alcohol* ***43****, the [5+2] cycloaddition of the pyrylium betaine generated in situ from* ***43*** *with acrylonitrile, and subsequent manipulation to oxetane precursor* ***49****.*[26]

The synthesis was continued *via* nitrile **45** which underwent chemoselective oxidation to

ketone **46** under basic conditions with $SnCl_2$. Following alcohol protection, an attempt at α-keto hydroxylation was made using Moriarty conditions which resulted in the 'migrated' dimethoxyketone **47**, whose regiochemistry was determined by 2D NMR analysis. Despite the unexpected outcome, synthesis of the oxetane was achieved through mesylate **49**, utilising a similar masked *trans*-diol system as Hoffmann. Subsequent deprotection of the dimethyl acetal gave dioxatricycle **50** in 5.6% yield over 13 steps. While this synthetic sequence was comparable to Hoffmann's first method (6.3%, 14 steps, Scheme 4/Scheme 5), it was overshadowed by Hoffmann's later work (Scheme 6).

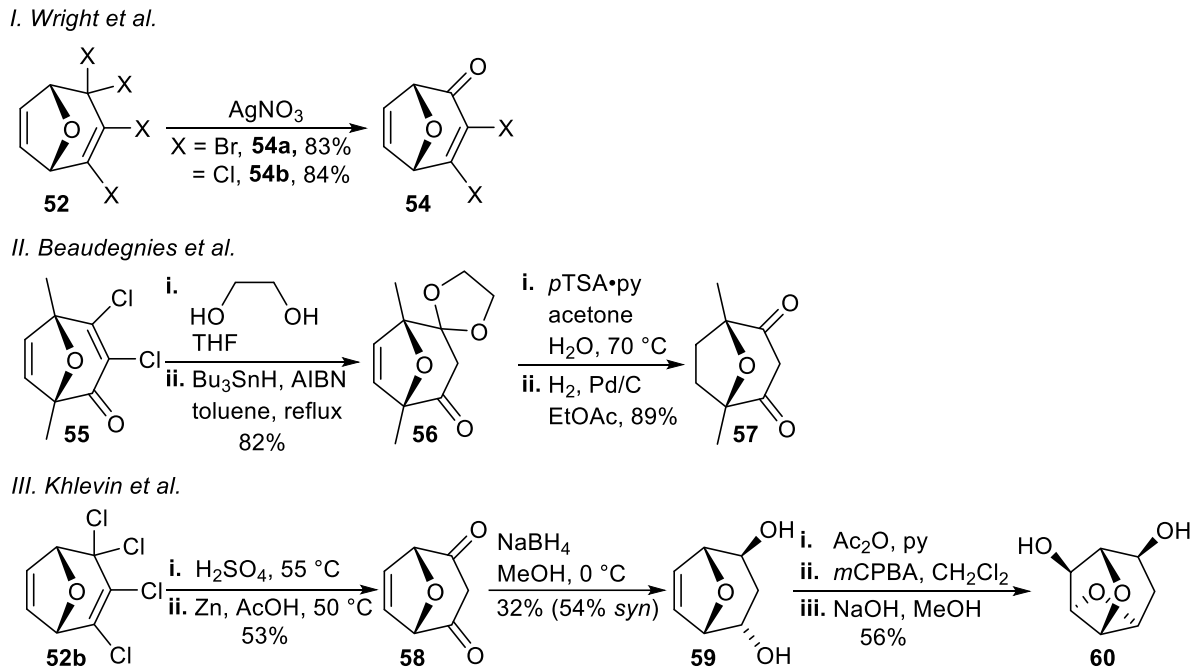
1.2.3.4. Core Synthesis by Ring-Expansion of Oxanorbornene Derivatives

In the 1960's, Tobey *et al.* published the synthesis and cycloaddition properties of tetrahalocyclopropenes (Scheme 9).[24,36] They reported that the cycloaddition of both tetrachloro- (TCCP) and tetrabromocyclopropene (TBCP) with furan obtained the corresponding tetrahalooxabicycles **52a** and **52b** in 92% and 80% yield respectively, proceeding through the cyclopropane intermediate **51**. Analysis by Wallerstein *et al.* showed that the cycloaddition proceeds through the adduct where the cyclopropane is *syn* to the oxygen bridge.[37] The only derivatisation Tobey *et al.* presented was treatment of the tetrachloride with H_2SO_4, which delivered diketone **53** in 42% yield.



Scheme 9: *Tobey's synthesis of oxabicyclo[3.2.1]octane **52** using the [4+2] cycloaddition of tetrahalocyclopropene and furan, followed by derivatisation to symmetrical diketone **53**.*[24,36]

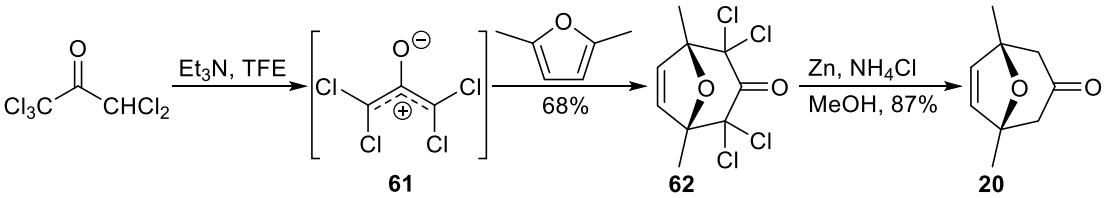
Wright *et al.* treated halooxabicycle **52** with $AgNO_3$ and H_2O to generate the corresponding dihaloenone **54** in >80% yield (Scheme 10, I).[38–40] They then applied the methodology to assemble a fragment of platensimycin and in the total synthesis of the frondosins.[41,42] Further work on the tetrahalide structures was presented by Beaudegnies *et al.* (Scheme 10, II) and Khlevin *et al.* (Scheme 10, III) and, the latter showing the most development of the ring structure where they synthesised the functionalised dioxatricyclic core mimic **60**.[43,44] It would be difficult to imagine **60** in a total synthesis of (+)-dictyoxetane, but Khlevin *et al.* demonstrated that the complex regioisomeric nature of the cycloaddition can be simplified *via* the symmetrical diketone **58**, and directed toward an asymmetric structure through reduction.



Scheme 10: *Advances upon Tobey's tetrahalocyclopropene chemistry. I. Wright et al.'s use of $AgNO_3$ to form enone **54** from oxabicycle **52**.[38-40] II. Beaudegnies et al.'s synthesis of diketone **57** from dichloroenone **55** via conversion to acetal **56**, then subsequent acetal hydrolysis and olefin hydrogenation.[44] III. Khlevin et al.'s synthesis of the dioxatricyclic ring system **60** from tetrachloride **52b** via transformation to diketone **58**, reduction to **59**, and oxetane formation.[43]*

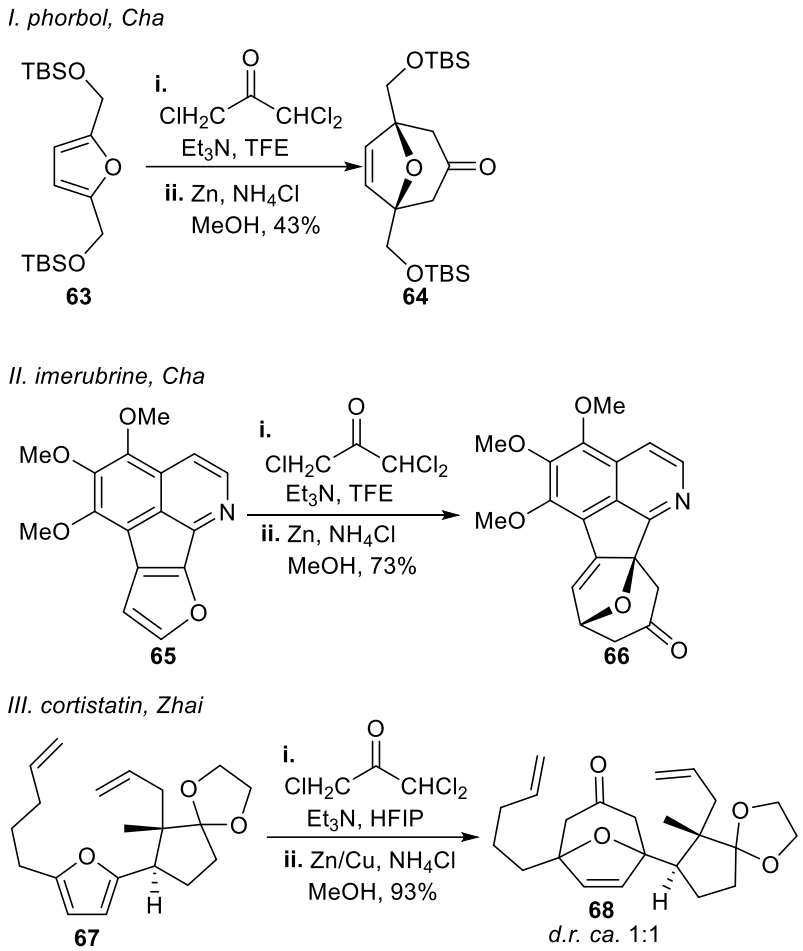
1.2.3.5. Synthesis of Oxabicyclo[3.2.1]octanes via Other Cycloadditions

While there are no further literature reports for the synthesis of the dioxatricyclic core of dictyoxetane, there are several methods that have been applied for the synthesis of oxabicyclo[3.2.1]octane ring systems. Föhlisch has shown that treatment of pentachloroacetone (PCA) with Et_3N in TFE generates oxyallyl cation **61**, which was then cycloadded to 2,5-dimethylfuran (Scheme 11).[25,45–47] Following dehalogenation by Zn, oxabicyclic ketone **20** was obtained in 87% yield.



***Scheme 11**: Föhlisch's synthesis of oxabiyclic ketone **20** via the [4+3] cycloaddition of 2,5-dimethylfuran and the oxyallyl cation **61**, generated in situ from pentachloroacetone, via the tetrachloride intermediate **62**.*[25]

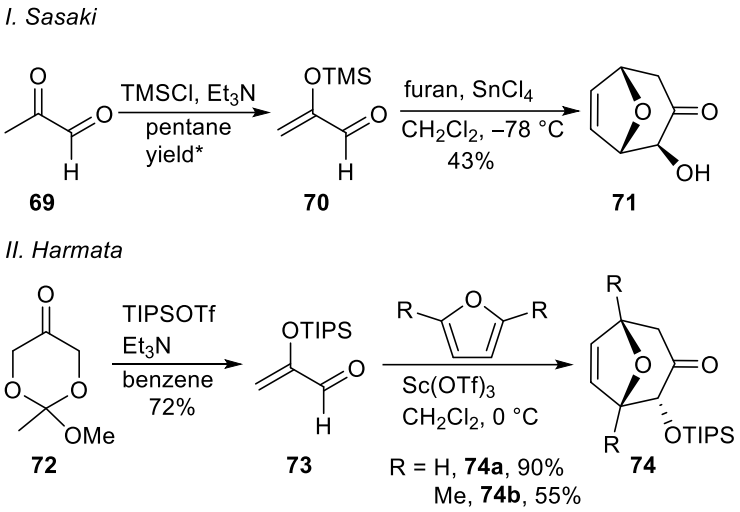
Föhlisch's chemistry has been applied in the synthesis of several natural products, notably by Cha *et al.* in the synthesis of phorbol and imerubrine (Scheme 12, I and II); further use was shown in Zhai's synthesis of the core of cortistatin (Scheme 12, III).[48–51] A key issue with this method is its lack of facial selectivity, evident from Zhai's work where a 1:1 mixture of diastereomers was obtained for ketone **67**.



Scheme 12: *Applications of the Fohlisch cycloaddition in natural product synthesis: I. Cycloaddition of **63** to **64** in Cha's synthesis of phorbol.[49] II. Cycloaddition of **65** to **66** in Cha's synthesis of imerubrine.[48] III. Cycloaddition of **67** to **68** in Zhai's synthesis of cortistatin, producing a 1:1 mixture of diastereomers.[51]*

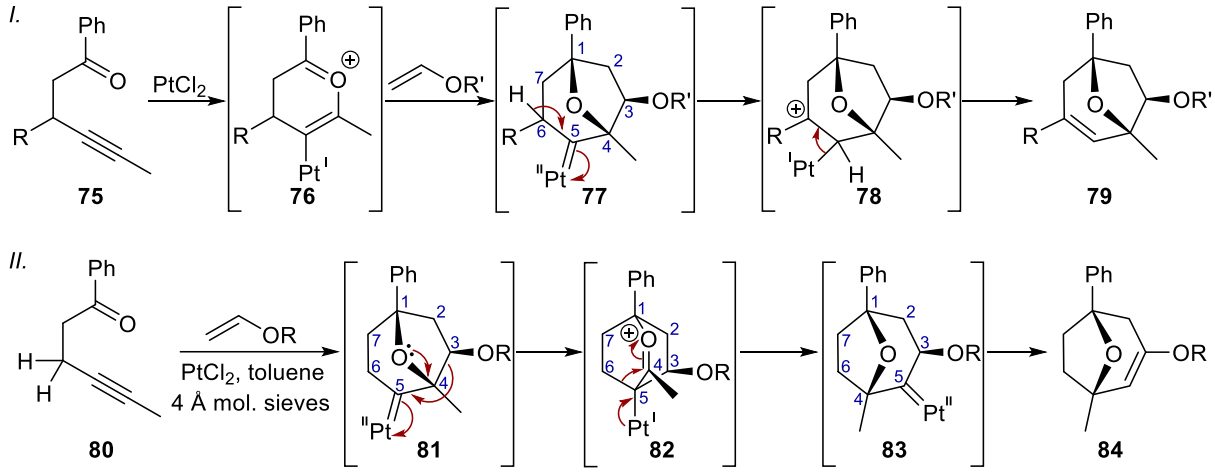
Another [4+3] cycloaddition method that affords α-keto oxygenation was first reported by Sasaki *et al.* in 1982.[52] Treatment of TMS acrolein **70** with furan and $SnCl_4$ gave oxabicycle **71** in 43% yield (Scheme 13, I). They observed that the stereochemistry of the alcohol was *syn* to the oxygen bridge based on NMR evidence. In 2000, Harmata adapted the method, improving the synthesis of the acrolein derivatives by the method of Funk *et al.*, then reaction of **73** with furan under $Sc(OTf)_3$ catalysis gave oxabicycle **74a** in 90% yield (Scheme 13, II).[53,54] Comparatively, 2,5-dimethylfuran afforded the corresponding oxabicycle **74b** in significantly reduced yield of 55%. In contrast to Sasaki, Harmata noted an *anti* relationship

between the oxygen bridge and the α-alkoxy group, again based on NMR evidence.



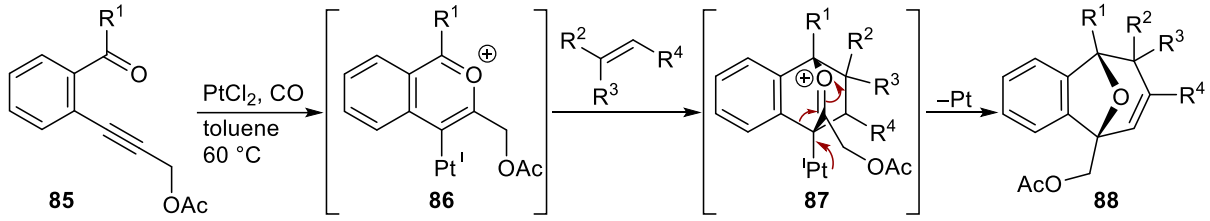
Scheme 13: *I. Sasaki's synthesis of oxabicycle **71** via the cycloaddition of the silyl enol ether of acrolein derivative **69** and furan.[52] II. Harmata's adaptation of Sasaki's conditions to synthesise oxabicycles **74a** and **74b** from silyl enol ether **73**, derived from dioxanone **72**, and either furan or 2,5-dimethylfuran respectively.[53] *No yield is given, but the report the synthesis is derived from quotes a 60% yield starting with diketones.*

Iwasawa *et al.* have reported a method for generating oxabicyclo[3.2.1]octane structures such as **79** and **84** (Scheme 14).[23,55] They proposed that formal 1,3-dipole **76**, formed by Pt^{II}-alkyne activation and cyclisation of **75**, undergoes a [3+2] cycloaddition with vinyl ethers to give platinocarbene **77**. The fate of **77** was subject to the nature of the substrate; when C_6 was populated with one alkyl or ether substituent (Scheme 14, I), a hydride migration and deplatination occurred through stabilised cation **78**. Alternatively, they proposed that when R = H (**80**, Scheme 14, II), the lack of stabilisation for cation **78** leads to C-C bond migration, promoted by the oxygen bridge (**81**). The oxocarbenium is quenched by a further migration as the platinum pushes electron density back into the ring. Deplatination then occurs *via* the C_3-hydride, producing enol ether **84**.



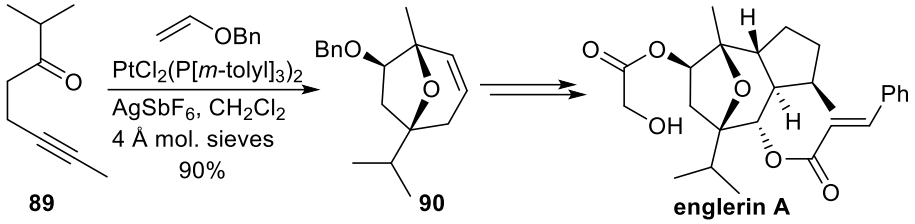
Scheme 14: *Iwasawa's platinum cascade cycloaddition of ynones **75** (I.) and **80** (II.) with a vinyl ether, and the proposed mechanisms, for the assembly of oxabicycles **79** (I.) and **84** (II.) respectively.*[23]

In 2009, Liang *et al.* published the use of aromatic substrates and found that good yields of oxabicycles were produced (Scheme 15).[56] They reported a need for higher temperatures and the addition of atmospheric carbon monoxide. They proposed a slightly different mechanism where the cycloaddition occurs through a [4+2] mode rather than a [3+2], eliminating one of the migration steps.



Scheme 15: *Platinum-mediated cascade of aromatic substrates, such as **85**, to produce aromatic-fused oxabicyclic ring systems such as **88** when cycloadded to trisubstituted olefins.*[56]

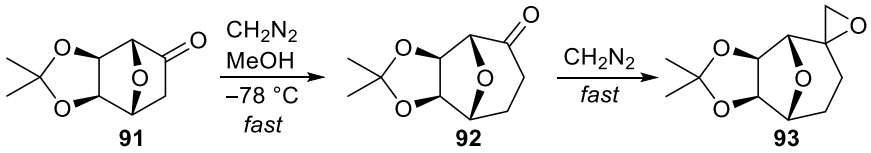
A year later, Iwasawa *et al.* published an asymmetric modification using chiral phosphine ligands and demonstrated that a silver salt effected a product shift from **84** to **79** (Scheme 14), despite the presence of a methylene unit adjacent to the Pt-carbene.[55] The conditions were applied to the synthesis of englerin A to give **90** in 90% yield as a single diastereomer (Scheme 16).[57]



Scheme 16: *Iwasawa et al.'s synthesis of oxabicycle* ***90,*** *via a platinum cycloaddition cascade of* ***89*** *and benzyl vinyl ether, for the preparation of englerin A.*[55]

1.2.3.6. Synthesis of Oxabicyclo[3.2.1]octanes via the Ring-Expansion of Cyclic Ketones

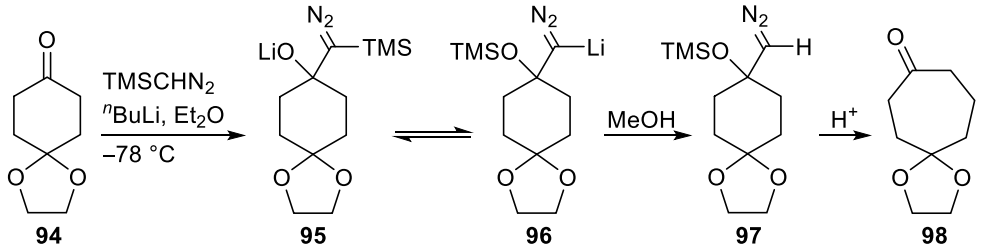
In 1991 Vogel *et al.* investigated the ring-expansion of norcamphors, and the oxygen-bridged derivatives obtained from Diels-Alder reactions with furan (Scheme 17).[58] They discovered that treating oxanorbornenone **91** with diazomethane at low temperature gave a mixture of starting material and epoxide **93**, produced from over reaction of the ring-expanded ketone **92**. When diazomethane was used in excess epoxide **93** was obtained in >90% yield. Their work suggested the exclusive migration of the α-methylene unit, for which they proposed that the oxygen bridge inductively deactivates the bridgehead carbon to migration, in contrast to the norbornene derivatives, where bridgehead migration was observed.



Scheme 17: *Vogel's diazomethane-induced ring expansion of oxanorbornenone* ***91*** *to epoxide* ***93*** *via oxabicyclic ketone* ***92****.*[58]

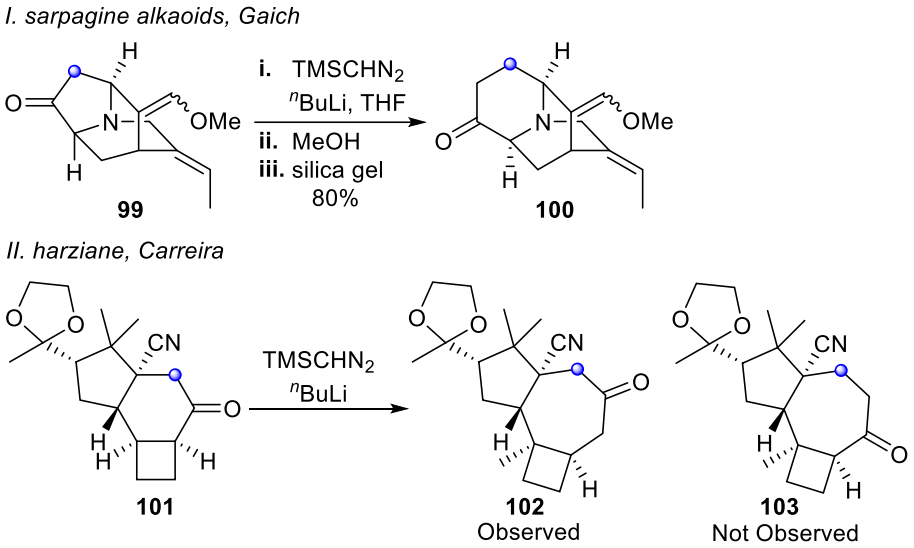
An advancement of the diazomethane-mediated ring-expansion was published by Lee *et al.* in 2012.[59] They discovered that using TMS-diazomethane resulted in the formation of cyclic ketones without the risk of over-reaction (Scheme 18). They proposed that the TMS-diazomethanyl anion adds to ketone **94** and the resulting alkoxide **95** undergoes an

equilibrium with TMS ether **96**. Using a soft acid such as MeOH, protonation occurred exclusively through **96** to silyl ether **97**. Exposure to a stronger acid or silica gel promotes the ring-expansion; in the case of **94**, cycloheptanone **98** was obtained in 84% yield. The advantage of this method is the need for an acidic work-up to trigger rearrangement and thus no further reaction of **97** can occur until work-up, at which point excess reagent has been quenched. Lee *et al.* also noted that in steroidal ketones, the migration preference was for methylene units over higher order carbon centres. They hypothesised that the minimisation of strain in the TMSO-C-C-N_2^+ interactions determines the migration outcome.



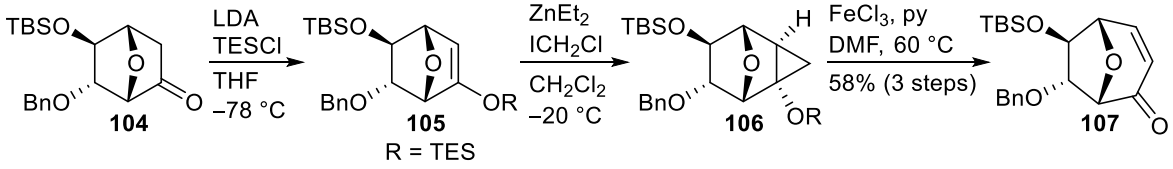
Scheme 18: *Lee et al.'s proposed mechanism for the one carbon ring-expansion of cyclohexanone **94** to cycloheptanone **98** using TMS-diazomethane.*[59]

Applications of Lee *et al.'*s chemistry in natural product synthesis are found in Gaich's work on the sarpagine alkaloids (Scheme 19, I), and an attempted use in Carreira's synthesis of harziane (Scheme 19, II).[60,61] In the former, the use of TMS-diazomethane gave ring-expanded ketone **100** as the only isomer, implying exclusive migration of the α-methylene unit. In contrast, when Carreira *et al.* observed the more substituted carbon centre migrate to deliver the undesired product **102**. It is unclear as to why there is a discrepancy in these observations, but it is possible that Gaich benefitted from the inductive deactivating effect of the nitrogen adjacent to the tertiary centre, as was posited by Vogel in the early work.



Scheme 19: *Attempted applications of Lee's ring-expansion method. I. Gaich's successful ring-expansion of* ***99*** *to* ***100*** *for the synthesis of sarpagine alkaloids.*[60] *II. Carreira's attempted ring-expansion of* ***101*** *for the synthesis of harziane.*[61]

Alternative ring-expansion conditions were reported by Vogel and Gerber utilising Saegusa's method to synthesise oxabicycle **107** in a yield of 58% over three steps (Scheme 20).[62,63] Starting from the oxanorbornenone **104**, formation of the silyl enol ether and reaction with diethylzinc in a Simmons-Smith fashion delivered cyclopropane **106**. Treatment with $FeCl_3$ then gave ring-expanded enone **107**, which Saegusa proposed occurs through the alkoxy-iron radical that then undergoes rapid cyclopropane fragmentation.



Scheme 20: *Vogel and Gerber's one carbon ring-expansion of oxanorborneone* ***104****, via the cyclopropanation of silyl enol ether* ***105*** *and subsequent radical ring-opening to give oxabicyclo[3.2.1]octane* ***107****.*[63]

1.2.3.7. Furan Synthesis

Up to this point, many of the reviewed cycloaddition methods rely on a furan as a substrate and so the synthesis of furans will be reviewed here. While there are a number of reviews in

the area,[64–67] appreciating the necessary substitution pattern of the furan limits the applicable methods (Figure 5). The required furan would need to be attached at positions 3 and 4 to the *trans*-hydrindane, preventing those carbons from being sourced from an alkyne. Furthermore, the oxygen must end up at position 1, not 2 or 5. Many literature reports contain furans that are synthesised as part of a polyaromatic system with no alkyl only examples, these reports have been omitted.

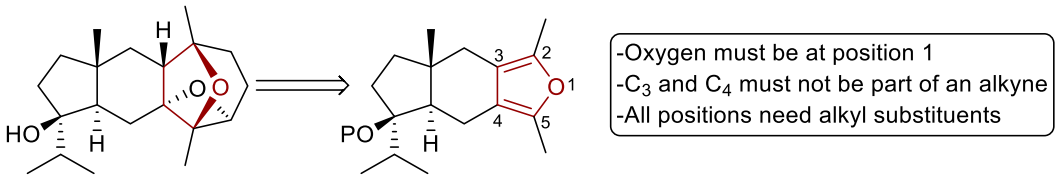
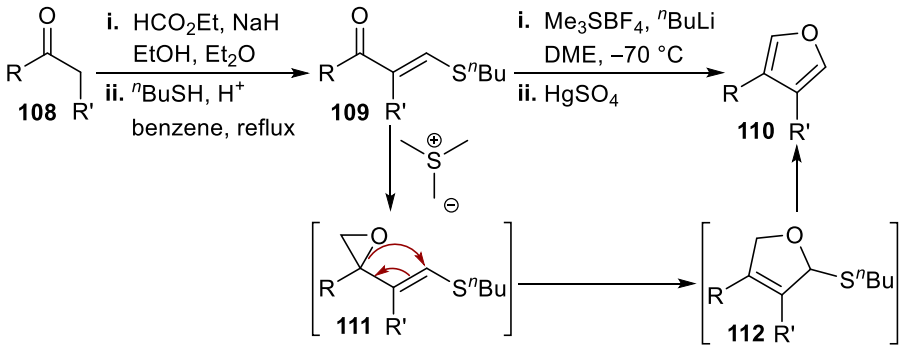


Figure 5: *Schematic showing the required regiochemistry of furan that would be necessary to correctly synthesise dictyoxetane via a cycloaddition approach.*

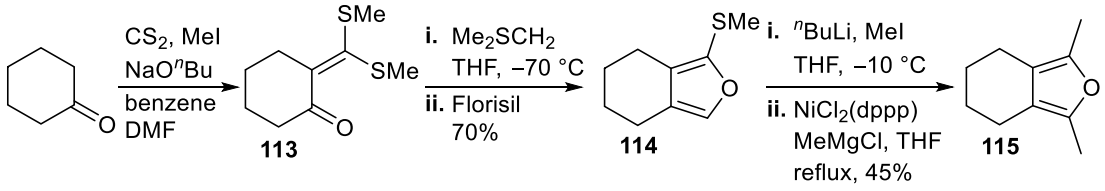
1.2.3.7.1. Epoxidation-Ring-expansion of Ketene Dithioacetals

In 1973, Garst and Spencer adapted the work of Ireland and Marshal for a new method of assembling furans from ketones.[68,69] They began by making vinyl sulfide **109** through an aldol reaction with ethyl formate, and then subsequent displacement of H_2O by ^{n}BuSH under azeotropic distillation (Scheme 21). Treatment of **109** with trimethylsulfonium ylide generated *in situ*, followed by $HgSO_4$ gave furan **110** with the only reported impurity being unreacted **109**. The authors proposed that the ylide epoxidises the ketone to give **111**, which then ring-expands to hydrofuran **112**. Treatment with a mild Brönsted acid or a mercury salt aids aromatisation by removal of ^{n}BuSH.



Scheme 21: *Garst and Spencer's synthesis of furan **110** via the epoxidation-ring expansion of ketone **109**, itself derived from ketone **108** and ethyl formate.*[69]

A decade later, Inamoto *et al.* expanded upon Garst and Spencer's work by replacing sulfide **109** with ketene dithioacetals such as **113** (Scheme 22).[32] The dithioacetals are readily available from the corresponding free ketone and CS_2/MeI in the presence of a base. Treatment of **113** with a sulfonium ylide followed by aromatisation with Florisil gave hydrofuran **114** in 70% yield. Inamoto *et al.* then showed derivatisations such as Kumada coupling and alkylation which gave dimethylfuran **115** in 45% yield across two steps.

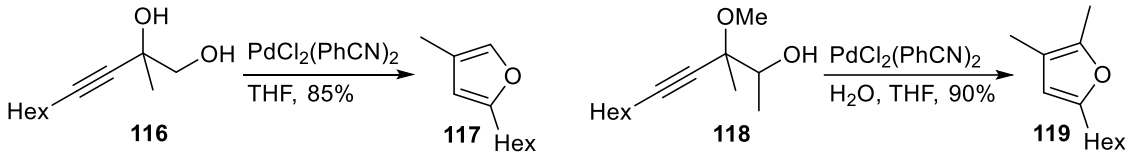


Scheme 22: *Inamoto et al.'s synthesis of dimethylfuran **115** from cyclohexanone, using ketene dithioacetal **113** in an adaptation of the Garst-Spencer furan synthesis with sulfonium ylides.*[32]

1.2.3.7.2. Alkynol Cyclisation-Isomerisation Reactions

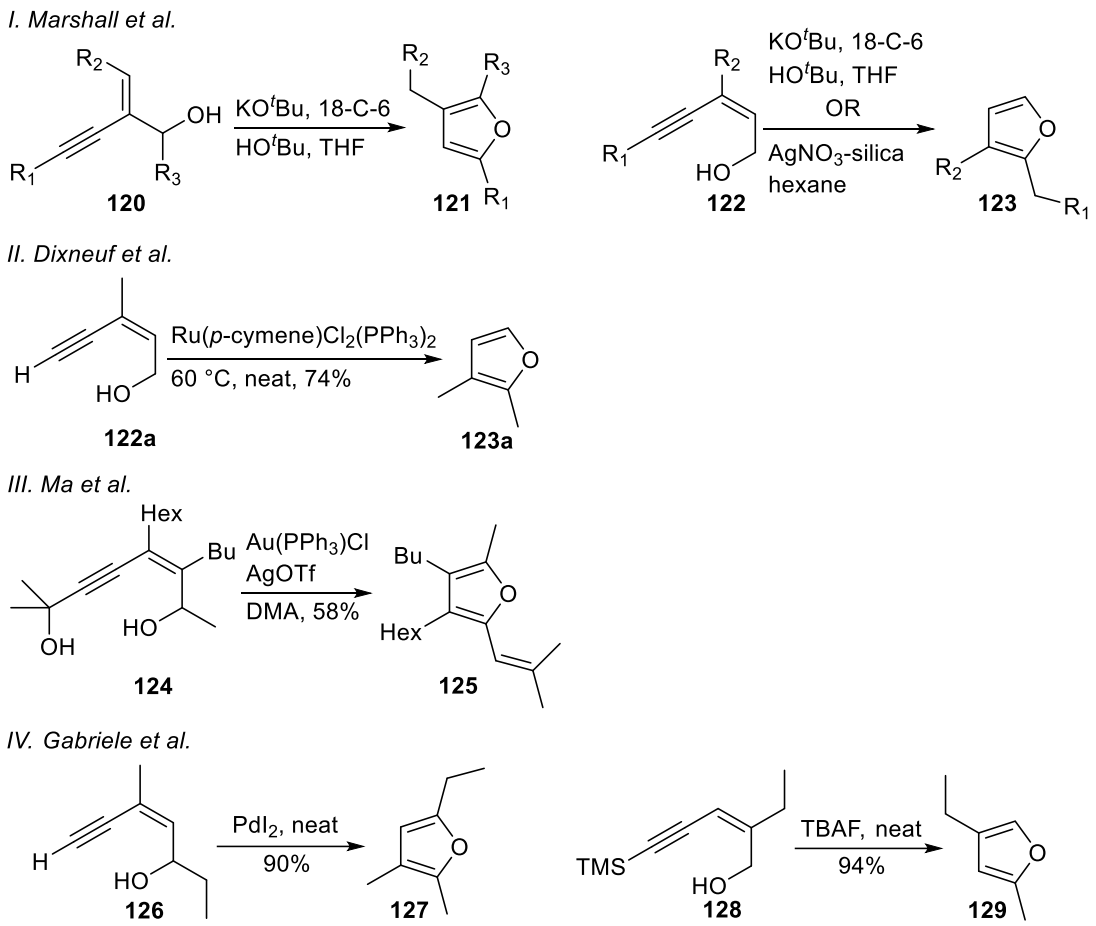
Another method for highly substituted furan synthesis is located within alkynol chemistry. Some of the early work was performed by Nozaki *et al.* who demonstrated that diols such as **116** were susceptible to cyclisation under mild Pd^{II} conditions (Scheme 23).[70] Methyl ether derivative **118** was cyclised with additional H_2O in the reaction mixture to facilitate loss of MeOH during aromatisation. The reaction is thought to proceed through π-activation of the

alkyne and attack of the distal alcohol, then loss of H_2O or MeOH affords aromaticity. In a further publication, Nozaki showed that these conditions could be used for β,γ-ynones in correspondingly good yields.[71]



Scheme 23: *Nozaki et al.'s synthesis of furans **117** and **119** from alkynols **116** and **118** respectively via Pd-catalysed cyclisation-isomerisation.*[70]

Marshall and DuBay expanded on alkynol cyclisations in several ways (Scheme 24).[27] They demonstrated that enynols such as **120** and **122** could be used, promoting the cyclisation under basic conditions with a crown ether to produce yields from 70–95%. With enynol **122**, there was a requirement for the allylic alcohol and alkyne moieties to be *cis* across the alkene, otherwise decomposition was observed. Notably, **122** offers two modes of cyclisation: *5-exo-dig* or *6-endo-dig*; yet the only observed product was the furan despite both cyclisations being formally 'allowed' by Baldwin's rules. No terminal acetylenes were investigated. In further work, Marshall established the use of $AgNO_3$ supported on silica gel to effect the transformation, again reporting yields >85% for several substrates.

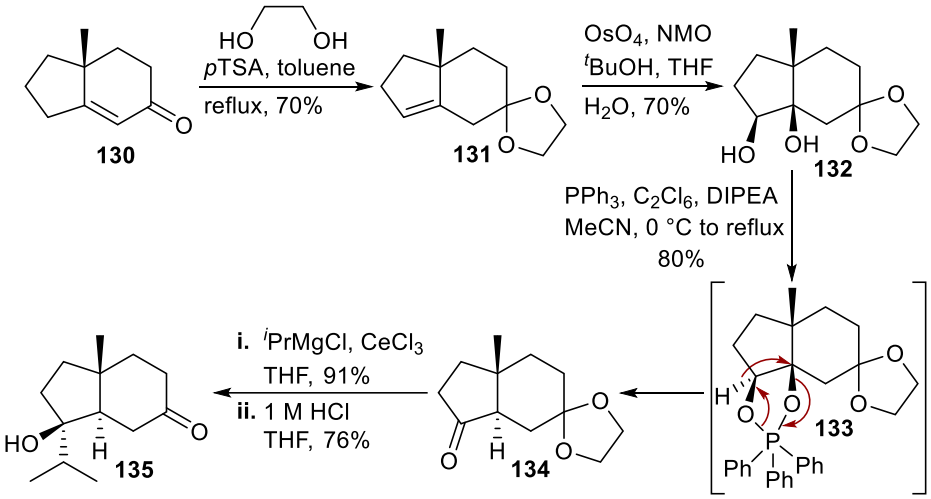


Scheme 24: *Notable conditions for making furans from enynol systems: I. Marshal et al.'s base-induced cyclisation-isomerisation of enynols **120** and **122** to give furans **121** and **123** respectively.[27] Furan **123** can also be synthesised from **122** using $AgNO_3$ on silica gel. II. Dixneuf et al.'s synthesis of furan **123a** using ruthenium catalysis.[31] III. Ma et al.'s gold-catalysed synthesis of furan **125** from the acetone-protected enynol **124**.[72] IV: Gabriele et al.'s synthesis of furan **127** by palladium catalysis (left), and furan **129** using TBAF (right) from enynols **126** and **128** respectively.[73]*

There have been additional conditions contributed to the area by several groups (Scheme 24).[31,72,73] In particular, Dixneuf *et al.* showed terminal acetylenes could be used under ruthenium catalysis, while Ma *et al.* have used gold to make tetrasubstituted furan **125** in 58% yield from the acetone-protected 'terminal' alkyne **124**. Gabriele *et al*. demonstrated excellent yields for up to trisubstituted furans using palladium, and have also reported that silyl-terminated alkyne **128** cyclised to **129** in the presence of TBAF.

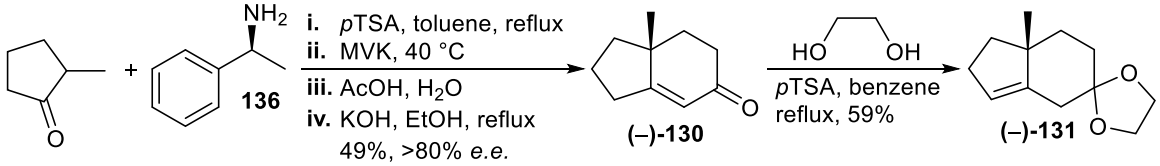
1.2.4. Synthesis of the Trans-Hydrindane

In 2012, the first synthesis of the *trans*-hydrindane unit was published by the Grainger group (Scheme 25).[22] From racemic enone **130**, acetalisation and Upjohn dihydroxylation gave diol **132** as a single diastereomer. Pinacol-like rearrangement, using Ph_3PCl_2 generated *in situ*, occurred with stereospecific migration of the hydride across the lower face of the hydrindane (**133**), generating only small traces of the *cis* compound that were easily separated from **134**. Examples of this rearrangement are sparse in the literature.[74,75]



Scheme 25: *Grainger et al.'s synthesis of racemic trans-hydrindanone **135** from known enone **130** via the phosphorus-mediated pinacol-like rearrangement of diol **132** to ketone **134**.*[22]

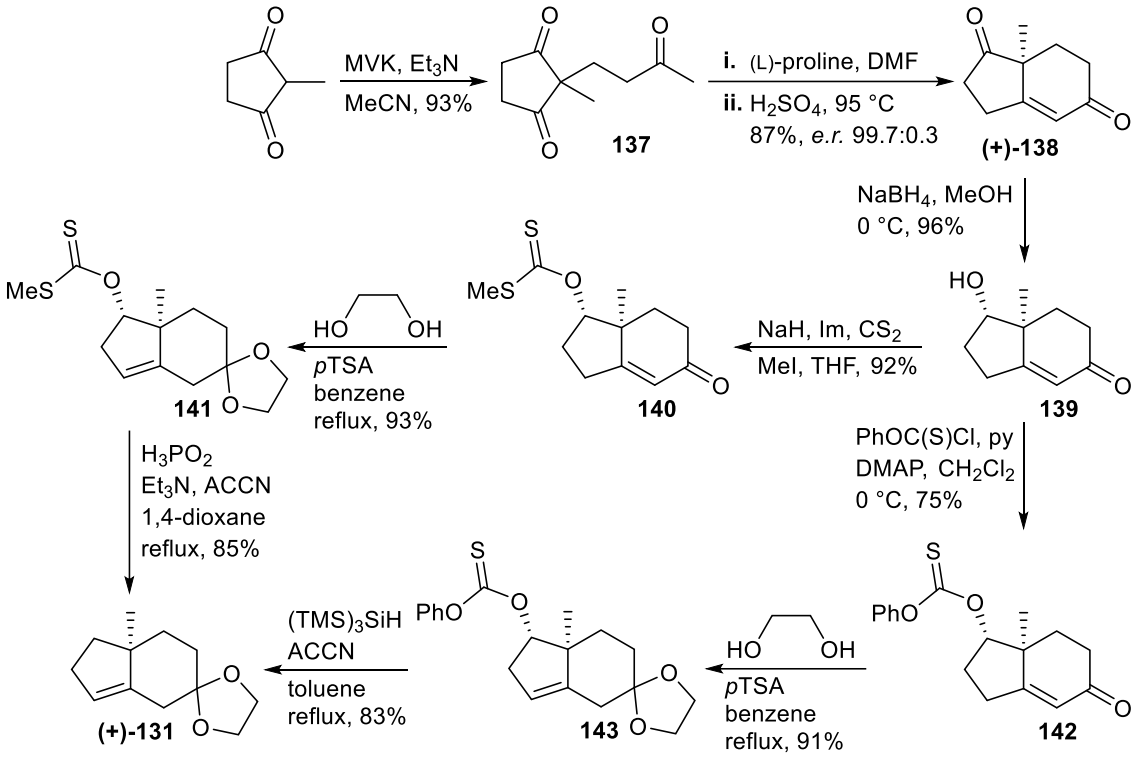
Completion of the synthesis by cerium-guided alkylation and deprotection of the acetal proceeded smoothly to give *trans*-hydrindanone **135**. The sequence was adapted by Hugelshofer and Magauer in the first synthesis of (+)-dictyoxetane in 2016.[21] Using a chiral auxiliary, they reported **(–)-130** in >80% *e.e.* as measured by optical rotation (Scheme 26).



Scheme 26: *Hugelshofer and Magauer's chiral auxiliary approach to access enantioenriched **131**, using commercially-available 2-methylcyclopentanone and chiral amine **136** to afford **130** in >80% e.e.*[21]

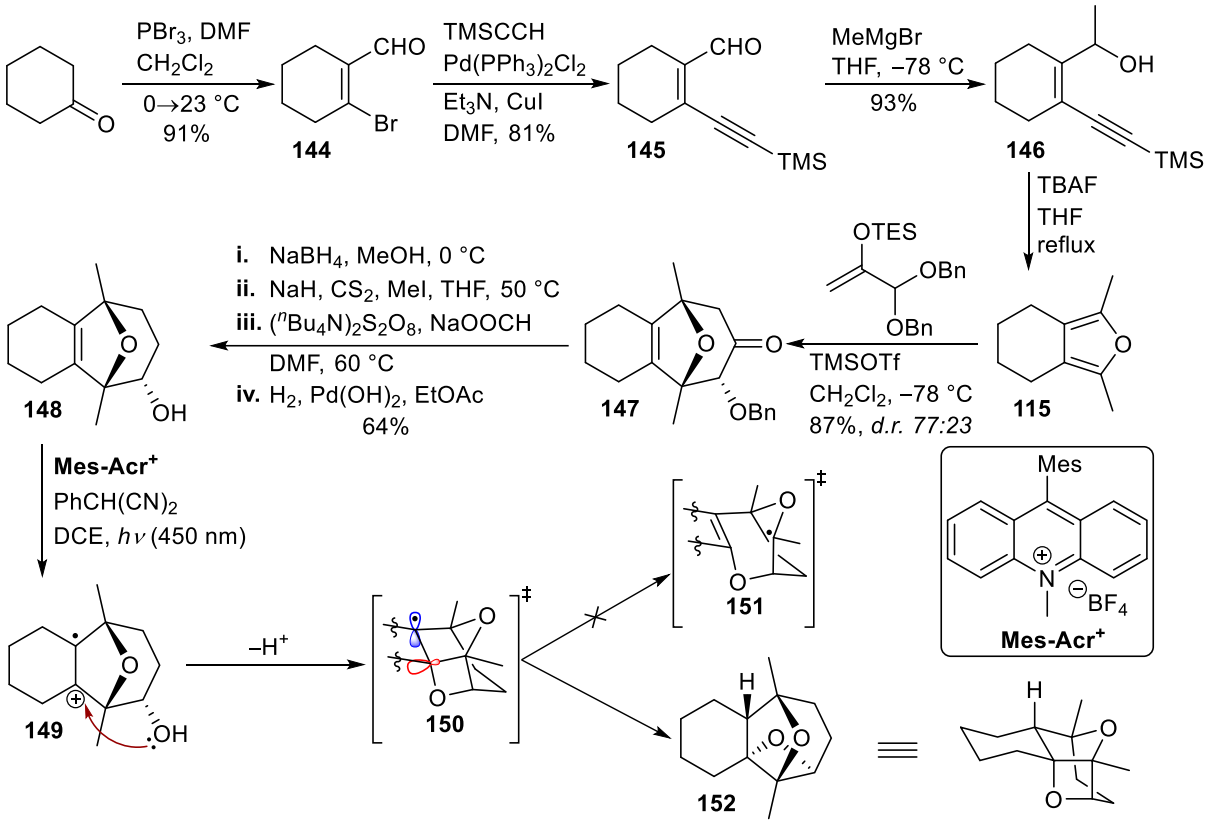
1.2.5. Unpublished Group Work

Following the 2012 publication, the group developed an asymmetric route to **131** using (L)-proline (Scheme 27).[76,77] 2-methylcyclopentane-1,3-dione was alkylated with MVK to give **137**, which then underwent an asymmetric Robinson annelation to afford the (+)-Hajos-Parrish ketone (**138**) in >99% *e.e*. To remove the extra ketone, a Barton-McCombie deoxygenation protocol was undertaken *via* the chemo- and diastereoselective reduction of the non-conjugated carbonyl, followed by derivatisation to either the methyl xanthate **140** or the *O*-phenyl thionocarbonate **142**. Acetalisation prior to radical deoxygenation gave higher yields, but the best method for deoxygenation varied for each precursor; xanthate **141** was most compatible with Barton's hypophosphorus acid,[78] whilst Chatgilialoglu *et al.*'s $(TMS)_3SiH$ was used for thionocarbonate **143**. Proceeding *via* the xanthate pathway established **(+)-131** in 56% over 6 steps, compared with Magauer's 29%.



Scheme 27: *Unreported group work asymmetrically synthesising acetal* ***(+)-131*** *from 2-methylcyclopentane-1,3-dione via Hajos-Parrish ketone* ***(+)-138*** *and subsequent radical deoxygenation through either methyl xanthate* ***140****, or the O-phenyl thionocarbonate* ***142****.*[76,77]

To assess an approach to the dioxatricyclic core, a model study was undertaken using cyclohexanone (Scheme 28).[76,77] To begin, haloformylation of cyclohexanone to bromoacraldehyde **144**, followed by Sonogashira coupling and Grignard addition afforded enynol **145** in excellent yield across three steps.[79] Subjecting **145** to TBAF delivered furan **115** which proved difficult to purify by silica gel, and so the crude reaction mixture was advanced without further treatment.[80] A [4+3] cycloaddition of furan **115** using Hoffmann's conditions gave a pair of diastereomers, of which **147** was determined to be the major (Scheme 6). Confirmation of the stereochemistry of **147** came from a crystal structure of a later compound, affording the desired *anti* relationship between the benzyl ether and oxygen bridge. The ketone was removed *via* a deoxygenation sequence and subsequent hydrogenolysis gave alcohol **148**.



Scheme 28: *Unreported group work studying the assembly of dioxatricyclic ring system **152** from cyclohexanone, using Hoffmann's conditions in the [4+3] cycloaddition of furan **115** to give predominantly ketone **147**, and Nicewicz's conditions for the hydroetherification of **148** to **152**.*[77]

Although many conditions to construct the oxetane ring were tested; only Nicewicz's photo-catalysed hydroetherification conditions showed promise in a novel application of the method (Scheme 28).[81–84] Irradiation of **148** should generate radical cation **149** which is then preferentially trapped as oxetane **150**; hydrofuran formation from attack of alcohol on the distal carbon in **149** was thought to be disfavoured by the atom-atom distance. In contrast to Hoffmann's initial work (Scheme 4), β-fragmentation of the oxetane in **150** to give **151** is likely infeasible due to poor orbital overlap, resulting in the abstraction of a hydrogen atom from the most accessible face to give dioxatricyclic core mimic **152**. Using 9-mesityl-10-methylacridinium tetrafluoroborate (**Mes-Acr$^+$**) as a photocatalyst in the presence of blue light (450 nm), alcohol **148** was fully consumed and the appearance of a single product observed. However, analysis of NMR data, while consistent with **152**, was inconclusive.

With the possibility of oxetane formation *via* this methodology, the next step was to begin testing the *trans*-hydrindanone, given that the asymmetric nature of the substrate would invariably affect the results of the model study anyway. Preliminary studies to synthesise (+)-dictyoxetane highlighted that the benzyl protecting group, used previously by both the group and Hugelshofer and Magauer, was unable to survive the haloformylation conditions. As such a new method for annelation to the tetrasubstituted furan will be needed.

1.3. Summary of the Prior Art

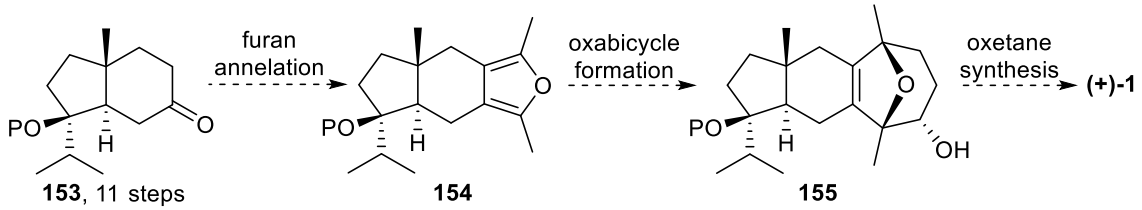
There is only one method in the literature for constructing the *trans*-hydrindane motif of (+)-dictyoxetane, albeit with minor variations to establish enantiopure **131**, which features a ketone for further elaboration. There has been one successful synthesis of dictyoxetane by

Hugelshofer and Magauer based upon this method, where RCM was used to build the 7-membered ring. The dioxatricyclic core was then completed with the oxygen bridge being installed after the oxetane, contrary to other core syntheses as well as the proposed biosynthesis. Literature reports over the last 36 years have delivered dioxatricyclic core-like structures four times, all from cycloadditions, of which three were derived from a furan. There has also been a plethora of syntheses aimed at constructing oxabicyclo[3.2.1]octanes that give a synthetic handle for elaboration to dictyoxetane *via* the same or similar cycloaddition processes. A review of furan syntheses suggests that for the desired substitution pattern, there are two approaches to consider: the Garst-Spencer method, and alkynol cyclisation-isomerisation reactions. There is literature precedent for synthesising Garst-Spencer substrates from cyclic ketones, while unpublished group work has developed a method for synthesising enynols from the same substrates as part of a model study. This study has shown not only a successful furan annelation sequence, but a potential route to constructing the entire dioxatricyclic subunit.

1.4. Project Aims and Objectives

The aim of the project is to complete the asymmetric synthesis of (+)-dictyoxetane based on the literature described up to this point (Scheme 29). The most compelling approach is to use the group's model study as a guide to annelate *trans*-hydrindanone **153**, available in 11 steps, to furan **154** *via* enynol cyclisation. Asymmetric synthesis of **153**, *via* the Hajos-Parrish ketone **138**, may require a new protection strategy or adoption of a different route given that initial tests with the benzyl protecting group have been unsuccessful. Upon synthesis of **154**, the oxabicyclo[3.2.1]octane will be established *via* cycloaddition. While in previous

group work Hoffmann's approach has worked well, given the chiral nature of furan **154**, potential methods will need to be evaluated for: i) facial selectivity, ii) regioselectivity of α-oxygenation, and iii) stereoselectivity of α-oxygenation. All three factors will be discussed further in section 2.3.1. To complete the synthesis, manipulation of the cycloaddition product to alcohol **155** will be performed, followed by application of Nicewicz's photoetherification reaction to construct the oxetane moiety. Deprotection of the tertiary alcohol will then complete the synthesis of (+)-dictyoxetane.



Scheme 29: *Proposed synthesis of (+)-dictyoxetane **1** from trans-hydrindanone **153**.*

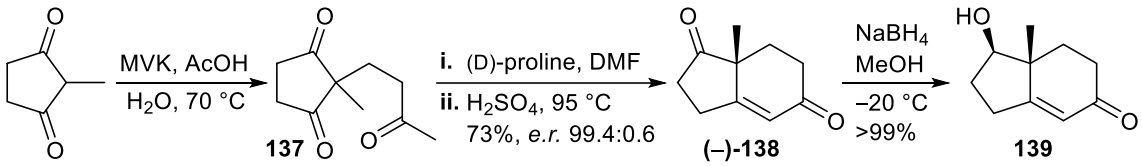
To efficiently investigate the late-stage transformations many of the early steps will need to be upscaled having been previously described at 1 g scale or less, and there will undoubtedly be challenges to performing this chemistry at >10 g scale that need to be overcome.

2. Results and Discussion

2.1. Asymmetric Synthesis of the Trans-Hydrindanone

2.1.1. First Steps

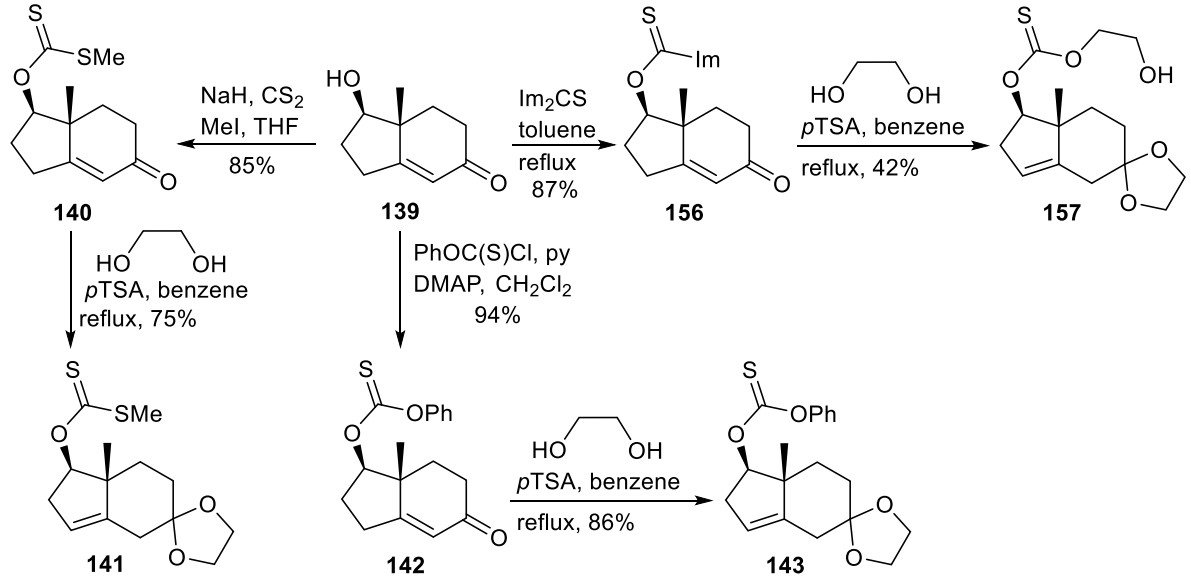
The first stage of the project was to synthesise **(–)-138** in an asymmetric fashion based on previous group methods. As such, 2-methylcyclopentane-1,3-dione was treated with MVK and AcOH in H_2O at 70 °C to give triketone **137** in 82% yield on 30 g scale (Scheme 30).[85] The AcOH method was chosen in preference to the Et_3N conditions used previously because of the precedent for larger scale reactions and the relative toxicity of stoichiometric Et_3N and catalytic AcOH. Triketone **137** was then subjected to Robinson annelation with 3 mol% (D)-proline serving as an organocatalyst to generate **(–)-138** in 78% yield on 25 g scale, or in 73% yield over the two steps at 100 g (0.9 mol). HPLC analysis showed an *e.r.* of 99.4:0.6 for the (*R*)-isomer. Chemoselective reduction of the non-conjugated ketone occurred with complete diastereoselectivity and essentially quantitative yield.[86]



Scheme 30: *Asymmetric synthesis of* ***(–)-138*** *in two steps from commercially-available 2-methylcyclopentane-1,3-dione, and subsequent diastereoselective reduction to give alcohol* ***139****.*

With alcohol **139** in hand, the deoxygenation sequence was examined (Scheme 31). Despite the precedent from previous group work, forming the xanthate radical precursor initially proved a challenge. Early work could only achieve a 49% yield and the purity was poor, with several side products by TLC. As a result, two other radical precursors, thionocarbonate **142**

and thionocarbamate **156**, were synthesised in contrastingly excellent yield.[87,88] Thionocarbonate **142** offered slightly more challenge in purification; removing the CH_2Cl_2 before work-up, then filtering and extracting with Et_2O made a substantial difference to the resulting quality. A further enhancement was observed by performing the acetalisation on crude thionocarbonate and recrystallising acetal **143**; the reason for this is discussed below. Xanthate **140** was later synthesised in 85% yield (and excellent purity) based on modifications to allow for CS_2 capture over a much longer period than was suggested (>12 h as opposed to 30 min) and in much higher eqv.'s; two variables that were changed independently in the original investigation but are both required for effective synthesis. The revelation came after working on ketene dithioacetal formation at a later stage in the synthesis, where the same type of problems occurred.

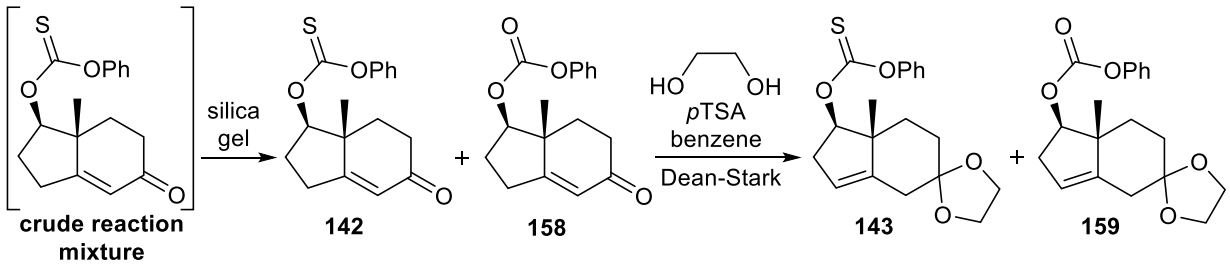


Scheme 31: *Synthesis of radical precursors **140**, **142**, and **156** from alcohol **139**, and the result of subjecting each precursor to acetalisation conditions, which for xanthate **140** and thionocarbonate **142** generated the desired products **141** and **143** respectively, whilst thionocarbamate **156** gave **157** in low yield.*

All three thiono derivatives were then subjected to acetalisation conditions which worked well for xanthate **140** and thionocarbonate **142**, yielding the corresponding acetals in 75%

and 86% respectively. Thionocarbamate **156** lost the imidazole unit under the acidic conditions to produce glycol-substituted acetal **157** in 42% yield with other products, a mixture that likely contained some glycol-substituted enone.

Whilst the yield of thionocarbonate **142** were initially high, as the scale increased a new product appeared after purification with a similar R_f. A mixture of thionocarbonate **142** and the side product was obtained following purification on silica gel (Scheme 32), for which ^{13}C NMR data suggested a resemblance to the desired compound, with only two notable peak shifts (see appendix): the 195 ppm peak which occurred at 152 ppm, and the 90 ppm peak which exhibited a shift to 86 ppm, both suggesting a change in the thionocarbonate fragment of the molecule. IR spectroscopy showed an additional stretch at 1758 cm^{-1}, and MS data gave a peak 16 mass units less than the desired compound's molecular ion. The data indicated the replacement of the sulfur atom for oxygen, giving carbonate **158**.



Scheme 32: *Purification of the thionocarbonation reaction mixture on silica gel leading to the desired compound **142** and side-product **158**, which upon subsequent acetalisation gave the corresponding acetal products **143** and **159**. Carbonate **159** was isolated from **143** which allowed for its structural elucidation.*

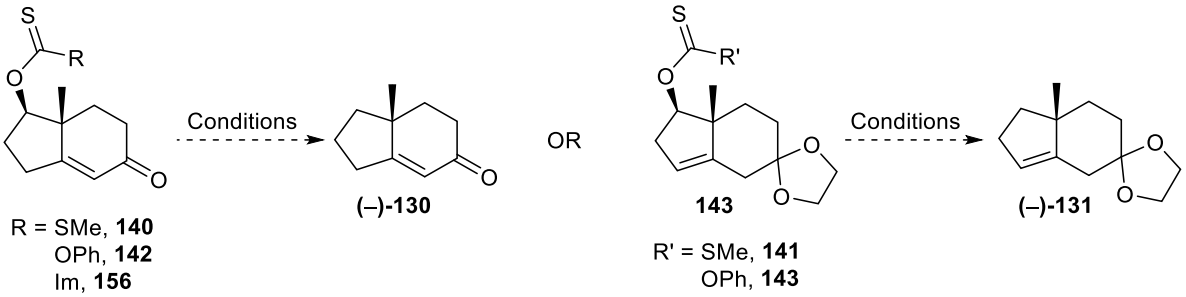
For a better understanding, the mixture was acetalised which resulted in a pure sample of a new compound (Scheme 32); in this instance, NMR data (see appendix) showed striking similarity to acetal **143** with three key peak shifts once again suggesting a change in the thionocarbonate moiety; in the IR spectrum the enone C=O peak at 1667 cm^{-1} disappeared,

whilst the 1756 cm^{-1} peak remained, and MS again showed a peak at 16 mass units below the desired $[M+H]^+$. The data strongly indicated the substitution of the sulfur atom in the thionocarbonate group, giving **159**, a phenomenon which did not occur before exposure to silica gel, and which appeared after both the thionocarbonate formation reaction, and the acetalisation. Interestingly, the acetalisation was performed in strongly acidic conditions but did not give rise to the impurity before column chromatography. There exists only one report of the transformation in the literature,[89] which mentions a silica sensitivity in the experimental section without further discussion. The side-reaction represented a significant obstacle since the trivial polarity difference between **142**/**143** and the side-products **158**/**159** led to overlap in chromatography fractions. Serendipitously, acetal **143** was a solid and was recrystallised to circumvent the issue. In later study, xanthate acetal **141** could not be purified by recrystallisation and this led to problems in the deoxygenation sequence.

2.1.2. Investigation of Conditions for the Radical Deoxygenation of Compounds 140, 141, 142, 143, and 156

To continue the synthesis, deoxygenation of one of the radical precursors (**140**, **141**, **142**, **143**, and **156**) needed to be achieved (Scheme 33). At first, a focus was placed on using tetrabutylammonium peroxydisulfate ($(Bu_4N)_2S_2O_8$, NaOOCH, DMF, 60 °C, method A)[90] and hypophosphorus acid (H_3PO_2, Et_3N, ACCN, dioxane, 100 °C, method B)[91] because these conditions facilitate purification by generating byproducts that are easily sequestered in an aqueous wash (Table 2). Method B appears frequently in the literature, whereas method A has been relatively unused, but both have been effective in previous group work.

$(TMS)_3SiH$,[92–94] $^nBu_3GeH$,[88] and $^nBu_3SnH$[87] (with ACCN/toluene/110 °C, methods C, D and E respectively) were also investigated.



Scheme 33: *Investigation of deoxygenation conditions on radical precursors **140**, **142**, **156**, and the acetalised precursors **141** and **143**, to access either enone **130** or acetal **131** for continuation of the synthesis.*

Entry	Substrate	Method	Start Mass (g)	Scale (mmol)	Yield (%)	Comment
1	**140**	A	0.021	0.082	0	Multiple products
2	**140**	B	0.011	0.043	0	Multiple products
3	**156**	A	0.099	0.358	11	Poor recovery
4	**156**	B	0.068	0.246	0	Poor starting material consumption
5	**156**	C	0.050	0.181	85	
6	**156**	C	0.200	0.724	62	
7	**156**	D	0.100	0.362	98	Impure
8	**142**	A	0.060	0.198	47	Multiple products
9	**142**	C	0.053	0.175	23	Silicon byproducts
10	**142**	C	0.052	0.172	58	
11	**142**	C	0.053	0.175	61	
12	**143**	A	0.088	0.254	0	Product formed by TLC
13	**143**	B	0.101	0.292	60	Poor starting material consumption
14	**143**	B	0.199	0.574	67	Impure
15	**143**	C	0.104	0.300	201	Silicon byproducts
16	**143**	C	0.030	0.087	71	New work-up
17	**143**	C	0.500	1.443	97	
18	**143**	C	1.001	2.889	88	
19	**143**	C	4.997	14.424	89	
20	**143**	C	5.421	15.647	82	
21	**143**	C	9.780	28.230	52	Purified in two batches
22	**143**	C	4.160	12.008	93	First vacuum distillation
23	**143**	D	0.153	0.442	97	Impure
24	**143**	E	0.051	0.147	42	Impure

Table 2: *Key results in attempting to deoxygenate compounds **140**, **142**, **156**, and the acetalised compounds **141** and **143** with the highlighted conditions. The data show that method C with thionocarbonate **143** was most effective, particularly when purifying by vacuum distillation. Methods: A = $(Bu_4N)_2S_2O_8$, NaOOCH, DMF, 60 °C;[90] B = H_3PO_2, Et_3N, ACCN, dioxane, 100 °C;[91] C = $(TMS)_3SiH$, ACCN, toluene, 110 °C;[92-94] D = $^nBu_3GeH$, ACCN, toluene, 110 °C;[88] E = $^nBu_3SnH$, ACCN, toluene, 110 °C.[87]*

Initially the idea was to use xanthate **140** as the precursor, but due to the previously described synthetic limitations only a few tests could be performed. Entries 1 and 2 describe how neither method A nor B delivered reasonable outcomes, both forming multiple products by TLC. In small amounts of isolated material, spectroscopic analysis was unable to confirm the presence of enone **130**.

Thionocarbamate **156** was the more easily accessed precursor and so conditions were tested on this substrate next. Entry 3 shows that while method A did give enone **130** as a product, the recovery was extremely poor and often there were many products. In contrast, method B generated a single product by TLC, but this method failed to consume **156** and again little could be isolated after purification (entry 4). The first success utilised $(TMS)_3SiH$ (method C, entries 5 and 6). At first a yield of 85% was obtained, but upon increasing the scale from 50 mg to 200 mg the yield diminished to *ca.* 60% consistently despite little change in experimental conditions. Finally, use of $^{n}Bu_3GeH$ effected complete consumption of **156**, however there was significant impurity from the germanium residues that could not be removed from the isolated oil by ^{1}H NMR (entry 7).

Thionocarbonate **142** produced similar observations to thionocarbamate **156** in many reactions, the differences are outlined here. Method A was slightly more effective on **142**, but enone **130** was only obtained as a mixture with an unknown side-product, and the yield of this mixture was still poor (entry 8). Method C initially afforded **130** in poor yield, but this was quickly optimised to 60% (entries 9–11). However, the purity of enone **130** was an issue because silicon-containing byproducts co-eluted from column chromatography. A hexane-

MeCN partition was effective in trapping the byproducts in the hexane, while **130** had a high affinity for MeCN. Following column chromatography, most of the silicon residues had been removed. Frustratingly, the yield of **130** could not be advanced above 60% and mirrored thionocarbamate **156** in this respect.

In previous group work, it was found that acetalisation of the radical precursor before deoxygenation generally led to overall higher yields across the sequence, and so acetal **143** was synthesised and tested in each method. However, methods A and D offered no difference in the reaction profile from previous substrates (entries 12 and 23). Method E performed similarly to Method D, but the isolated yield was lower for the same level of impurity (entry 24). As a result, methods D and E were discarded from further trial. Interestingly, method B now appeared viable and delivered acetal **131** in 60–67% yield (entries 13 and 14). Unfortunately, acetal **143** was never fully consumed even with fresh reagents, changes to eqv.'s, concentration, and reaction length. Frequently a yellow residue crept up the reaction condenser and a pungent odour was noticed, especially if the reaction ran for more than 12 h; the identity of this was not established and rinsing it back into solution made no apparent difference.

Deoxygenation of acetal **143** with $(TMS)_3SiH$ gave the most consistent results, consuming all the starting material, generating a single product, and producing acetal **131** in seemingly high yield. Method C did offer impurity problems like $^{n}Bu_3GeH$ and $^{n}Bu_3SnH$, but $(TMS)_3SiH$ was either cheaper or less toxic. As such method C underwent substantial trialling (entries 15–22). Others do not frequently report the impurity issues that were experienced here; in

fact, only one report from the literature appeared to address this problem.[95] They found that treating the crude reaction mixture with an acid wash, followed by TBAF in THF left the byproducts as a thick layer that would not pass through silica gel. Initially, this procedure worked well and provided a 97% yield of acetal **131** with minimal silicon residue (entries 16 and 17). Attempts to use KF as a cheaper alternative were fruitless, likely owing to the poor solubility of KF in organic solvents, and the poor solubility of the silicon byproducts in H_2O.

As the scale of the deoxygenation increased, the modified work-up procedure became less effective. Yields dropped below 90% and fell as low as 52% (entry 21). The problem with this purification method is that the silicon residues, having been treated with the TBAF solution, form a viscous layer which is insoluble under standard work-up conditions. When loaded onto silica gel it has a significant volume at 10 g scale and traps **131** within. This had two negative effects: recovery dropped, and as the product was slow to escape the residue layer the chromatographic band was wider, which in turn allowed other byproducts to co-elute and reduce the purity. At this point it was discovered that acetal **131** could be distilled under high vacuum, which significantly reduced the waste of silica, solvent, TBAF, and time spent on the purification and proved to be reliably better than the TBAF method at scale. Thus, as much as 20 g of acetal **143** was reacted in this procedure as part of a batch that went from alcohol **139** to diol **132** in 62% yield (84 mmol of **139**, 4 steps, averages to 89% per step).

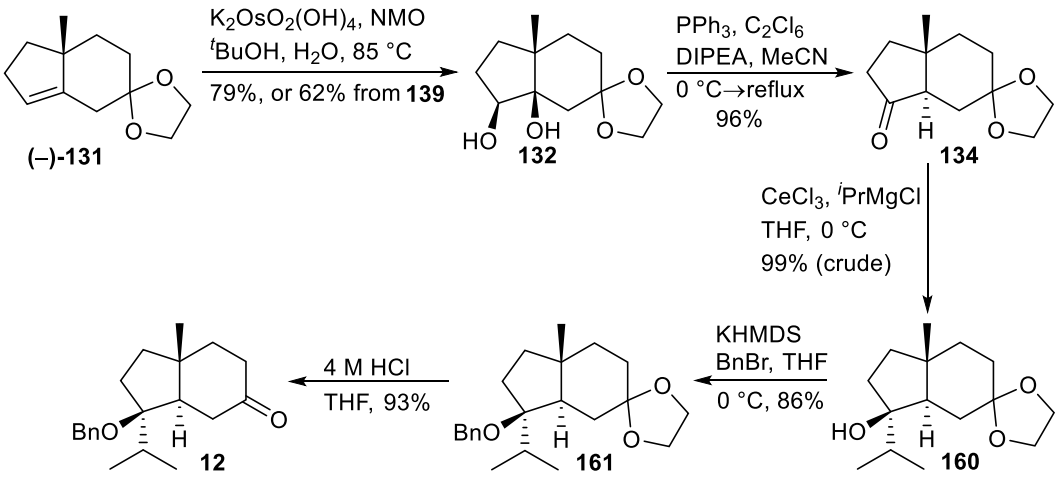
Xanthate acetal **141**, produced at a later stage, did not readily undergo the same 3- or 4-step deoxygenation process. While pure **141** was deoxygenated with $(TMS)_3SiH$ to give acetal **131** in yields of 75–85%, when a 3-step procedure from alcohol **139** without purification was

tested, the deoxygenation failed outright. The outcome suggested a conflict with the impurities being carried through; either the mineral oil from the NaH dispersion, or the remnants of CS_2 that are not volatile enough to be removed under reduced pressure. Since xanthate **140** also experiences mild silica sensitivity, purifying **140** and **141** to allow the deoxygenation to work would be less efficient in many ways and was deemed a worse route to acetal **131**.

To summarise the findings of the deoxygenation investigation: method A was completely incompatible with substrates **140**, **142**, **156**, and **143**, despite results observed in previous group work; it is unclear why this was the case. Method B only worked with acetal **143** but failed to completely consume starting material and produce yields above 60%. $^{n}Bu_3GeH$ (method D) and $^{n}Bu_3SnH$ (method E) produced byproducts that were inseparable even after chromatography; since these reagents are either more expensive or more toxic than $(TMS)_3SiH$ (method C), they were not optimised further. Method C produced the best yield for acetal **143** and was optimised to use vacuum distillation to purify **131**, providing excellent multistep yields. Substrates prior to acetalisation could not be deoxygenated in high yield or purity. Despite the low synthesis cost of xanthate **140**, impurities from the reaction meant that purification of both **140** and **141** before deoxygenation were necessary for success, which conflicts with the observation that silica gel causes transformation of the thiocarbonyl group, reducing isolated yields. Thus, acetal **143** had a higher multistep process efficiency and was the best substrate despite the relatively high cost of PhOC(S)Cl.

2.1.3. Completion of the Benzyl-Protected Trans-Hydrindanone

Having found a scalable solution to the deoxygenation problem, the synthesis of the *trans*-hydrindanone could once again be pursued (Scheme 34). Upjohn dihydroxylation of **131** was performed at 85 °C which reduced the reaction time from several days at room temperature to 5 h, without the need for a third solvent such as acetone or THF, and was completely diastereoselective.[22] However, the issue with the procedure was product purity; all previous reports purify **132** by flash chromatography which has impacted the purity at larger scale, with Hugelshofer and Magauer reporting a brown oil.[21] In this work, attempts to improve the outcome by filtration through either celite or charcoal, or subtle changes to the extraction sequence failed to remedy this problem. By recrystallising the crude residue instead, diol **132** was obtained as colourless to tan crystals which allowed for scale-up to >10 g. The synthesis even tolerated contaminants brought through from the deoxygenation without impacting the resulting crystals, and as such completed a 4-step protocol from alcohol **139** in 62% yield over 4 steps (averaging an 89% yield per step), or 79% yield in a standalone process.



Scheme 34: *Synthesis of the benzyl-protected trans-hydrindanone **12** from **131** over 5 steps, via diastereoselective Upjohn dihydroxylation, pinacol-like rearrangement, Grignard addition, benzyl protection and acetal deprotection. Diol **132**, ketone **134**, and alcohol **160** were all afforded as single isomers at the limit of detection by ^{1}H NMR analysis.*

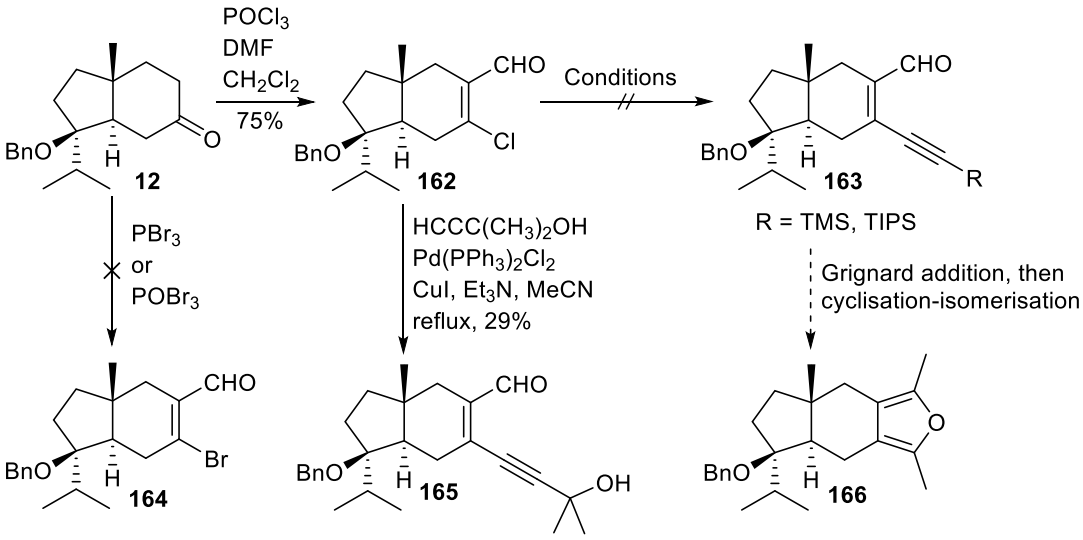
Continuing the sequence with a phosphorus-mediated pinacol-like rearrangement furnished ketone **134** in 99% yield at 1 g scale (Scheme 34). The yield fell slightly on 4.5 g scale to 96%, and lower still on further scale-up which highlights an issue with column chromatography and the significant amount of Ph_3PO present in the crude mixture. Subsequent addition of ^{i}PrMgCl to **134** gave alcohol **160** as the only product when the ketone and anhydrous $CeCl_3$ are mixed beforehand. When the Grignard reagent and $CeCl_3$ were stirred together first, no reaction was observed despite precedent for this order of addition.[96] Upon completion, it was necessary to add AcOH to the mixture and stir until the solution became clear to chelate the cerium residues which otherwise complicated separation. Alcohol **160** was obtained in a near quantitative yield without the need for purification on 10 g scale. Finally, KHMDS-mediated benzylation proceeded in 86% yield, followed by acidic deprotection to give *trans*-hydrindanone **12** in 93% yield. As such, the first objective of the project, to asymmetrically synthesise *trans*-hydrindanone **12**, was achieved.

2.2. Furan Synthesis

2.2.1. Investigation into Furan Annelation via Haloformylation of Trans-Hydrindanone 12

For the second objective of the project, access to furan **166** was required; as such ketone **12** was investigated in the haloformylation reaction with PBr_3 in accordance with the group's model synthesis using cyclohexanone (Scheme 28). Bromoacraldehyde **164** was expected as the single or predominant regioisomer based on comparison with other thermodynamically-controlled reactions under both basic and acidic conditions (Scheme 35).[97–100] Several attempts showed only consumption of **12** by TLC, while switching to the lesser-used $POBr_3$

yielded multiple products. Addition of 2,6-lutidine, a sterically congested base, served to stall all reaction with either phosphorus-species. However, use of $POCl_3$ did afford chloroacraldehyde **162** in 75% yield without much optimisation. The regiochemistry was suggested by analysis of 2D NMR data.



Scheme 35: *Attempts to annelate trans-hydrindanone **12** to furan **166**, resulting in the synthesis of chloroacraldehyde **162** in good yield, and the acetone-protected enynal **165** in poor yield.*

There are a wide array of conditions in which aryl chlorides have been coupled to alkynes in the literature,[101–105] as well as vinyl chlorides.[106–108] The use of bromoacraldehydes[109–111] and chloroacraldehydes[112] are documented, although it should be noted that with the chloroacraldehydes, no silicon-terminated alkyne example is listed. As such, coupling of chloroacraldehyde **162** to TMS-acetylene was not envisaged to be a problem. However, despite significant effort, Sonogashira coupling failed under standard conditions ($Pd(PPh_3)_2Cl_2$ or Pd/C-PPh_3, Et_3N, THF/DMF, with and without CuI), or utilising Buchwald's adapted method ($Pd(MeCN/PhCN)_2Cl_2$, XPhos, K_2CO_3/Cs_2CO_3, MeCN) with variable catalyst-ligand loadings, reaction temperatures, and reaction times.[102]

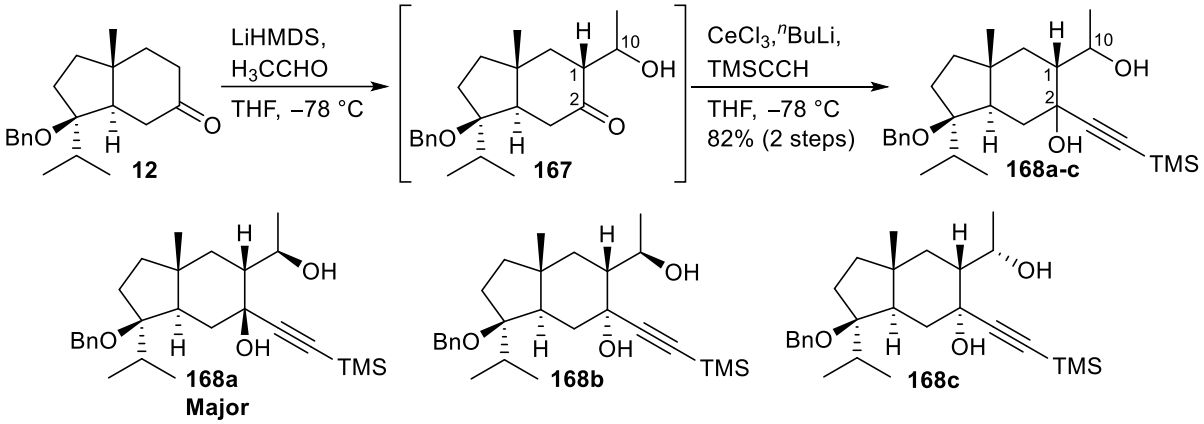
Under the standard conditions reported by Sonogashira, chloride **162** was typically not consumed by TLC. Buchwald observed a lack of reactivity in his investigations with aryl chlorides, especially if copper was used.[102] As such, Buchwald's copper-free conditions were attempted and generated new products by TLC, but did not fully consume starting material. The reactions generated significant quantities of an organic-insoluble brown semisolid, and ^{1}H NMR analysis of crude reaction mixtures showed no sign of the coupled product **163**. Separately, both Buchwald and Novak have noted an inability to couple TMS-acetylene under their conditions, showing that TES- and TIPS-acetylene were more successful.[102,104] However, experiments involving TIPS-acetylene and any of the catalytic systems listed failed to generate the corresponding TIPS-terminated product. The only progress was the coupling of the "acetone-protected" acetylene to give enynal **165**, with the idea being that the free alkyne could be returned after heating at reflux with a base. However, the yield and purity of **165** was so poor without sign of improvement that the route was considered infeasible.

2.2.2. Attempted Furan Annelation via 1,3-Diol Cyclisation-Isomerisation

Unable to adequately continue the annelation sequence beyond chloroacraldehyde **162**, the annelation precursor was reimagined as the yne-1,3-diol **168** (Scheme 36), which was in principle easily accessible from ketone **12**, and was structurally similar to Nozaki's early furan annelation substrates (Scheme 23).[70] Adopting Hugelshofer and Magauer's aldol reaction with acetaldehyde gave hydroxyketone **167** which did not purify well by flash chromatography, and so was used as a crude mixture in the alkyne addition chemistry. In this work, **167** was isolated as a single isomer, yet the literature reports a 10:1 *d.r.* at C_{10} with

the (*R*)-stereochemistry preferred.[21] Later in the synthesis of **168**, a product of the C_{10} (*S*)-stereochemistry was identified; it is unclear whether the presence or absence of this isomer is a consequence of scale or a subtle variation in conditions.

Following a procedure from Baran *et al.*, treatment of **167** with anhydrous $CeCl_3$ and TMS-ethynyllithium, generated *in situ* from the corresponding alkyne and ^{n}BuLi, gave three 1,3-diols (**168a-c**) in a combined 82% yield over 2 steps.[113] The exact ratio was difficult to discern because it seemed to change from experiment to experiment, suggesting a susceptibility to addition rate and concentration, and isomer **168c** was not observed until the scale advanced past 100 mg. The most biased isolated ratio was 1 **a** : 0.08 **b :** 0.05 **c**. Thankfully, the isomers were isolable and crystal structures were obtained (Figure 6, see appendix for full details) for all three to elucidate their absolute stereochemistry. The crystal structure of the major compound **168a** confirmed both the C_1-(*R*) and C_{10}-(*R*) stereochemistry that Hugelshofer and Magauer reported from the aldol reaction. Alkyne addition to the lower face of ketone **167** was favoured, resulting in an equatorial alcohol at C_2, while **168b** contains the axial alcohol derived from alkyne addition to the top face.



Scheme 36: *Synthesis of 1,3-diols **168a-c** from benzyl-protected trans-hydrindanone **12** via sequential aldol and TMS-acetylene addition reactions.*

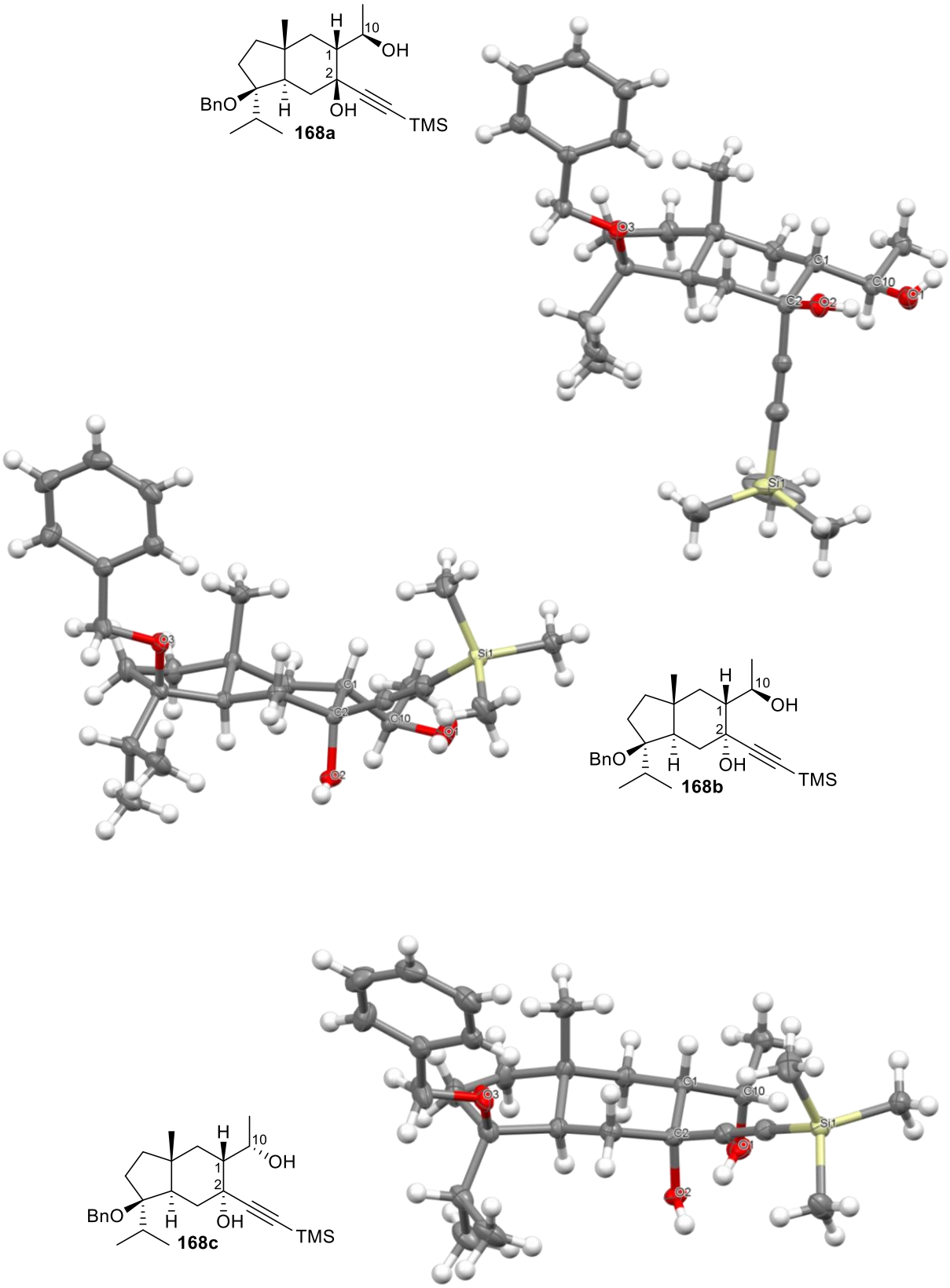
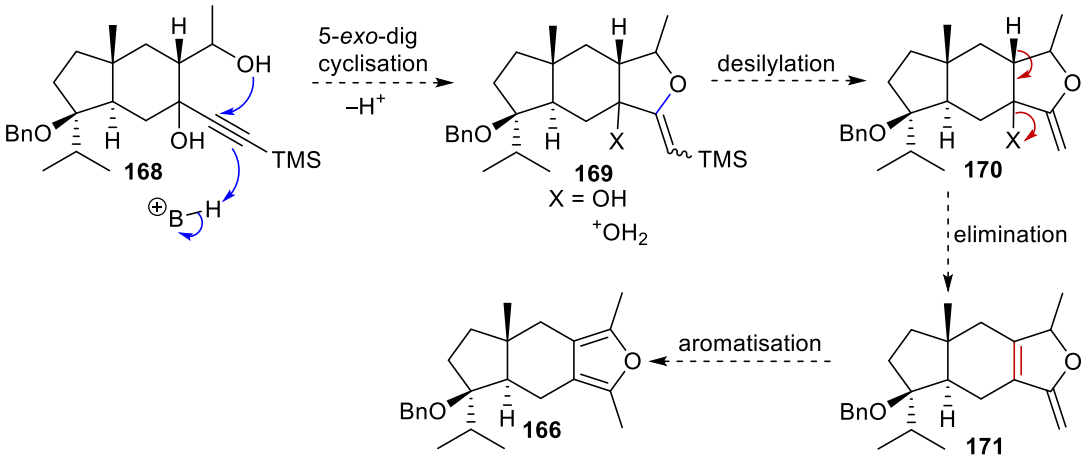


Figure 6: *Crystal structures of 1,3-diols* ***168a***, ***168b***, *and* ***168c***, *pictured next to their respective geometric representation. Ellipsoids are drawn at the 50% probability level. Top:* ***168a*** *[C_2-(S) C_{10}-(R)], Middle:* ***168b*** *[C_2-(R) C_{10}-(R)], Bottom:* ***168c*** *[C_2-(R) C_{10}-(S)]*

The final isomer **168c** is the minor product of the aldol reaction, containing the C_{10}-(*S*) stereochemistry, which explains why it was difficult to detect at small reaction scales. However, it does not follow the preferred addition trajectory found in **168a**, but rather contains a C_2-(*R*) centre like **168b**. This is most likely a result of using $CeCl_3$ to mediate the addition, where the C_{10}-(*S*) alcohol forms a different chelation complex which blocks the lower face of ketone **167**.

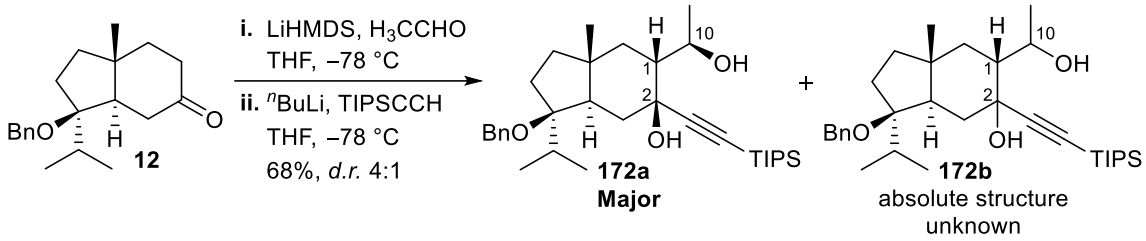
For annelation of the 1,3-diols to furan **166**, the C_{10} stereochemistry was envisaged to be inconsequential and as such the minor isomer of the aldol transformation was not a problem (Scheme 37). However, it was thought that a mixture of stereochemistry at C_2 could be a problem when considering mechanisms by which the C_2-OH could be eliminated. In the proposed mechanism, the removal of the TMS group could happen at any stage prior to aromatisation.



Scheme 37: *Proposed mechanism for the cyclisation-isomerisation of 1,3-diols such as **168** to furan **166**, via a 5-exo-dig cyclisation, elimination of water, and subsequent aromatisation.*

To address the issue of multiple C_2-stereoisomers from the addition of TMS-acetylene to

ketone **167**, it was hypothesised that a larger silicon group might provide a more selective nucleophile. As such, the corresponding TIPS-acetylene derivatives were synthesised in 68% combined yield in one pot as a pair of isomers with a *d.r. ca.* 4:1 (Scheme 38); **172a** crystallised and the structure was confirmed by X-ray diffraction (Figure 7) to have both -OH groups on the same face, or C_2-(*S*) C_{10}-(*R*), as found in the TMS-derived **168a**. The absolute structure of the minor isomer (**172b**) was unknown and could not be inferred by comparison with **168a-c**; it may be derived from the minor stereochemistry produced from the aldol reaction, but this would represent a significant decrease in selectivity from that process. Hence, **172b** is more likely to be the result of alkyne addition from the upper face of **167**, giving a C_2-(*R*) centre, with the minor aldol product not observed. Although the combined yield was lower than for **168a-c**, reproducibly higher selectivity and the potential for optimisation meant that this was not a route-breaking problem.



Scheme 38: *Synthesis of 1,3-diols **172a/b** from benzyl-protected trans-hydrindanone **12** via sequential aldol and TIPS-acetylene addition reactions. The absolute structure of **172b** was not elucidated.*

Conditions were then investigated to induce the 5-*exo*-dig cyclisation of the C_{10}-OH onto the alkyne (Scheme 39). The cyclisation conditions were first tested on the major TMS yne-1,3-diol **168a**. Treatment of **168a** with AgOTf, Ag_2CO_3, or Ag_2O in either CH_2Cl_2, hexane, or MeOH led to partial desilylation and many other new products by TLC, possibly due to issues with competing single-electron, oxidation-type processes.[29,114] Use of $CuCl_2$ in MeOH effected no

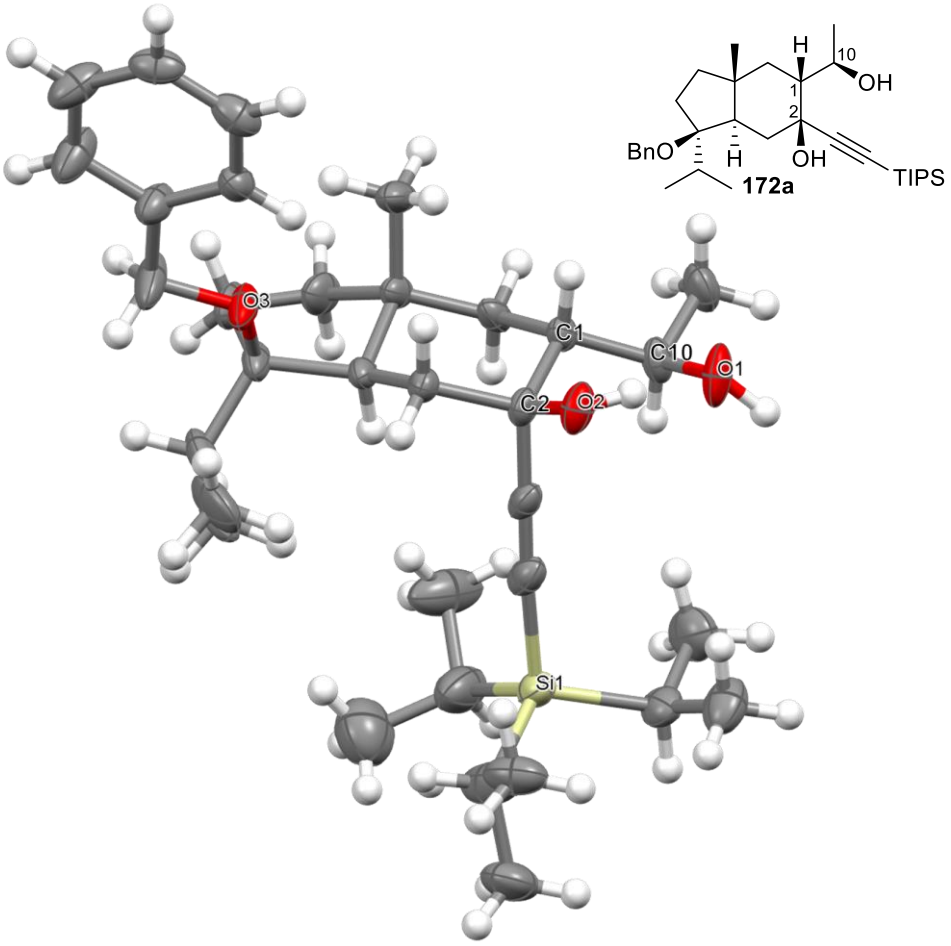
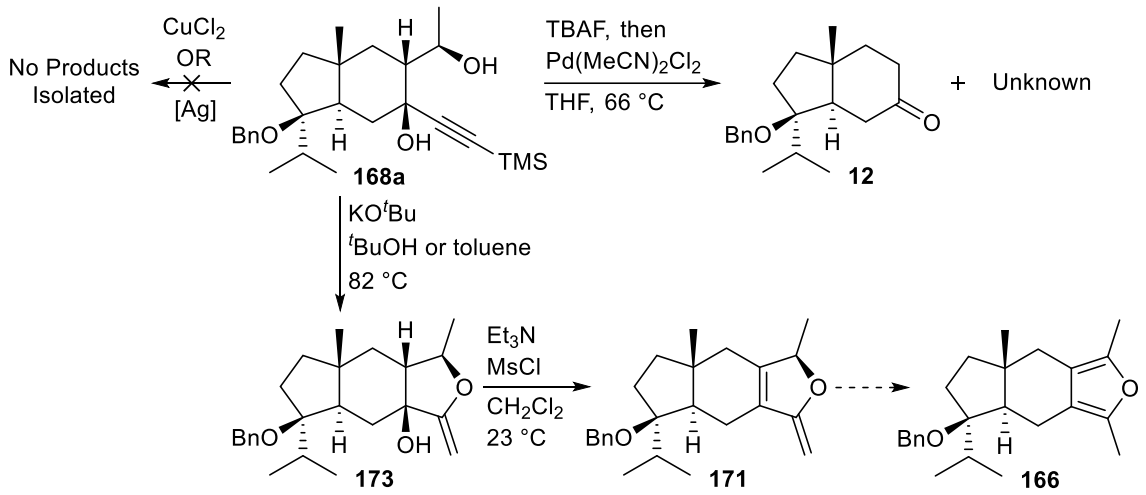


Figure 7: *Crystal structure and geometric representation of 1,3-diol* ***172a*** *showing the same C_2-(S) C_{10}-(R) stereochemistry observed for the TMS-derived 1,3-diol* ***168a****. The unit cell of the crystal structure contained two molecules of* ***172a*** *(see appendix), for which only one is represented here, pictured with ellipsoids at the 50% probability level.*

transformation at all.[28] Reaction of **168a** with TBAF in THF at room temperature gave only the desilylated alkyne; there was no change with heating in THF, but at 100 °C in 1,4-dioxane a similar result to KO^{t}Bu (described below) was observed. In a subsequent reaction, addition of a small amount of $Pd(MeCN)_2Cl_2$ after reaction of **168a** with TBAF generated two new products by TLC; spectroscopic analysis confirmed one of these products to be *trans*-hydrindanone **12**.[70] Spectroscopic analysis of the second product suggested the presence of a monosubstituted alkene, and the loss of the 2° alcohol and TMS group. Further analysis was hindered by poor mass recovery.



Scheme 39: *A summary of the findings in attempting to synthesise furan **166** from 1,3-diol **168a**: use of $CuCl_2$ or Ag^I salts did not lead to isolable products, while treatment with TBAF then $Pd(MeCN)_2Cl_2$ returned ketone **12** and an unknown product. Some evidence was collected to support the synthesis of exocyclic enol ether **173** and diolefin **171** as intermediates toward **166**.*

Use of Marshall's KO^{t}Bu in ^{t}BuOH (section 1.2.3.7.2., Scheme 24, I) at 82 °C consumed **168a** and delivered a new product by TLC (Scheme 39).[27] Again, mass recovery was poor but a ^{1}H NMR spectrum was obtained showing new chemical shifts at 4.42, 4.31 and 4.09 ppm, with normalised integrals of 2, 1 and 2 respectively (see Appendix). Burton *et al.* have reported exocyclic enol ether **175** (Figure 8, I),[115] identifying the chemical shifts of the olefinic protons as 4.33 and 3.87 ppm, both as broad singlets. Given the literature chemical shifts, the compound produced by the application of Marshall's conditions was tentatively assigned as enol ether **173** (Figure 8, II)**.** Although the literature did not report coupling constants, the observed coupling constants of <5 Hz supported the presence of an exocyclic enol ether. Furthermore, Burton *et al.* noted that **175** was prone to hydrolysis, producing ketoalcohol **176**; NMR data for a sample of **173** acquired less than 24 h later showed new chemical shifts of 4.35 and 3.86 ppm, with normalised integrals of 2 and 1 respectively, which may suggest hydrolysis of **173** to keto alcohol **174**. Given the possibility of instability, it was deemed that **173** must be used crude, or better *in situ*.

It was thought that protonation of the enol ether in **173** would be facile, but unproductive, in a protic solvent such as ^{t}BuOH; a reaction of **168a** with KO^{t}Bu in toluene was performed. Two new products were observed by TLC at a higher R_f, but **173** was not fully consumed. One of the new products was formed exclusively when the crude reaction mixture was treated with MsCl and Et_3N in CH_2Cl_2 (Scheme 39). After isolation, a MS peak of 353 [**173**−OH]$^{+}$ was obtained for the new product, suggesting the 3° alcohol had been eliminated as in **171**. It is unclear why at the compound did not aromatise spontaneously if, or perhaps the MsCl conditions were just too harsh to isolate furan **166** from, potentially accounting for the poor mass recovery. Heating of crude **173** with TsCl and pyridine produced several new products by TLC, but the identity of these was not established due to poor mass recovery.

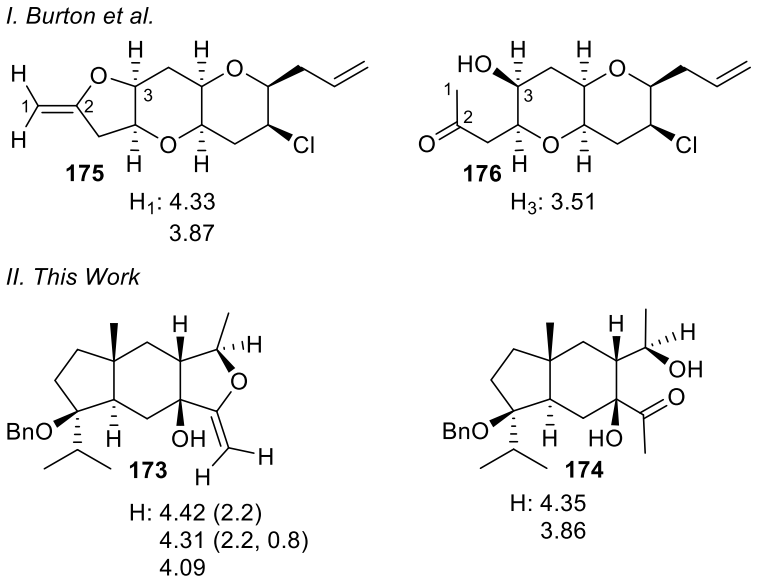
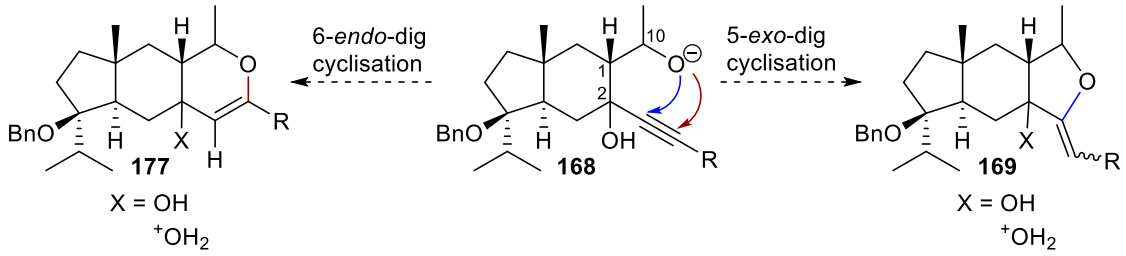


Figure 8: *Structures of I. Burton et al.'s[115] unstable exocyclic enol ether **175** and the product of hydrolysis **176** and II. theorised product **173** of the application of Marshall's conditions[27] in the 1,3-diol cyclisation-isomerisation reaction, and the potential hydrolysis product **174**. Under each compound are the relevant chemical shifts observed in ppm; bracketed numbers are coupling constants in Hz.*

In reactions where enol ether **173** was generated, there was another product by TLC whose identity was unknown. It was thought that alkoxide **167** might undergo a competitive 6-

endo-dig cyclisation to give **177** alongside the desired 5-*exo*-dig process (Scheme 40). As such, TIPS-protected alkyne **172a** was employed because the increased size of the TIPS group should disfavour hydropyran formation. When **172a** was treated with KO^{t}Bu in toluene, the side product was not observed by TLC.



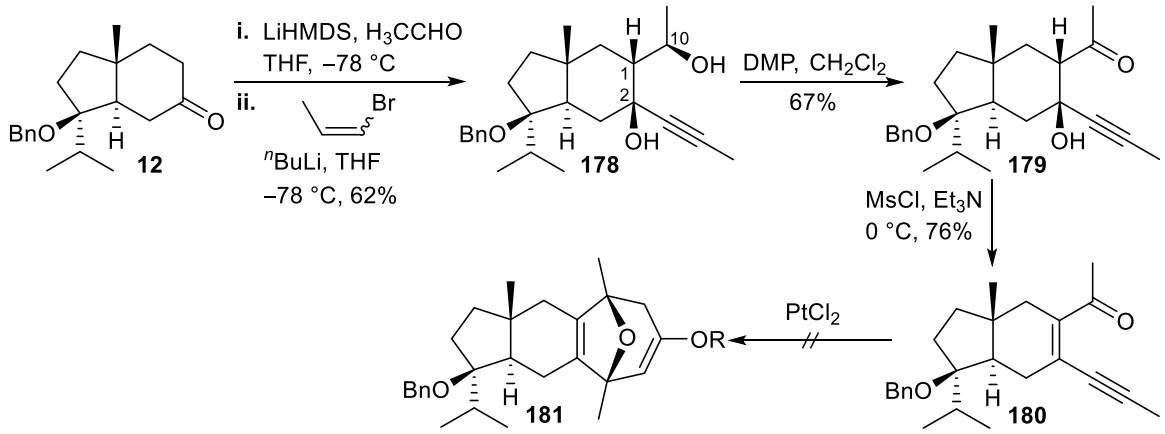
Scheme 40: *Possible cyclisation pathways for diol **168** to give either hydrofuran **169** or hydropyran **177**.*

In summary, the synthesis of benzyl-protected 1,3-diols **168a**–**c** and **172a** has been achieved *via* an aldol reaction with acetaldehyde and subsequent alkyne addition. Confirmation of four of the product structures by X-ray diffraction showed that the preferred approach trajectory of both the TMS- and TIPS-acetylide was from the lower face of ketone **167** to give the C_2-(*S*) stereocentre. Reaction of **167** with TIPS-acetylide appeared to be more selective, but the isomer ratios could not be determined with certainty because they varied between reactions. Treatment of diols **168a** and **172a** with a myriad of literature conditions reported to trigger annelation did not deliver furan **166**, and in some cases ketone **12** was returned instead. Use of KO^{t}Bu in toluene seemed to provide the most progress toward **166**, with acquired data suggesting a potential cyclisation to enol ether **173** from comparison with similar motifs in the literature. Further treatment of **173** with MsCl and Et_3N gave a new product with data that suggested diolefin **177**, but mass recovery throughout was poor and the synthesis of **177** could not be confirmed. Use of the TIPS group in **172a** was shown to reduce the number of products by TLC compared with the TMS equivalent **168a**, which may

imply an increased selectivity in the mode of cyclisation. Ultimately, furan **166** was not synthesised by a 1,3-diol cyclisation-isomerisation approach.

2.2.3. Adaptation of the 1,3-Diol Synthesis for Use in Iwasawa's Pt-Mediated Cyclisation-Cascade

Iwasawa's platinum cycloaddition cascade is a method that could be used to construct the oxabicyclo[3.2.1]octane subunit (section 1.2.3.5., Scheme 14).[23] To access enynone **180**, the 1,3-diol synthesis was adapted to add a propyne group following the aldol reaction of ketone **12** with acetaldehyde, using the *in situ* rearrangement of *cis/trans*-1-bromoprop-1-ene when treated with ^{n}BuLi (Scheme 41).[116] After purification, propyne diol **178** was isolated in 62% yield over two steps as a single diastereomer, although another compound was detected by TLC that could be a second isomer. Given that the aldol reaction had previously produced a mixture at C_{10}, the lack of a quantifiable minor isomer on 400 mg scale might suggest that the aldol reaction can be performed at a higher selectivity. A crystal structure of **178** showed the preferred C_2-(*S*) stereochemistry for the alkyne addition reaction (Figure 9).



Scheme 41: *Attempt to construct oxabicyclo[3.2.1]octane **181** via Iwasawa's cyclisation cascade[23] of enynone **180**, synthesised by adapting the 1,3-diol synthesis from trans-hydrindanone **12** to give **178** which then oxidised and dehydrated.*

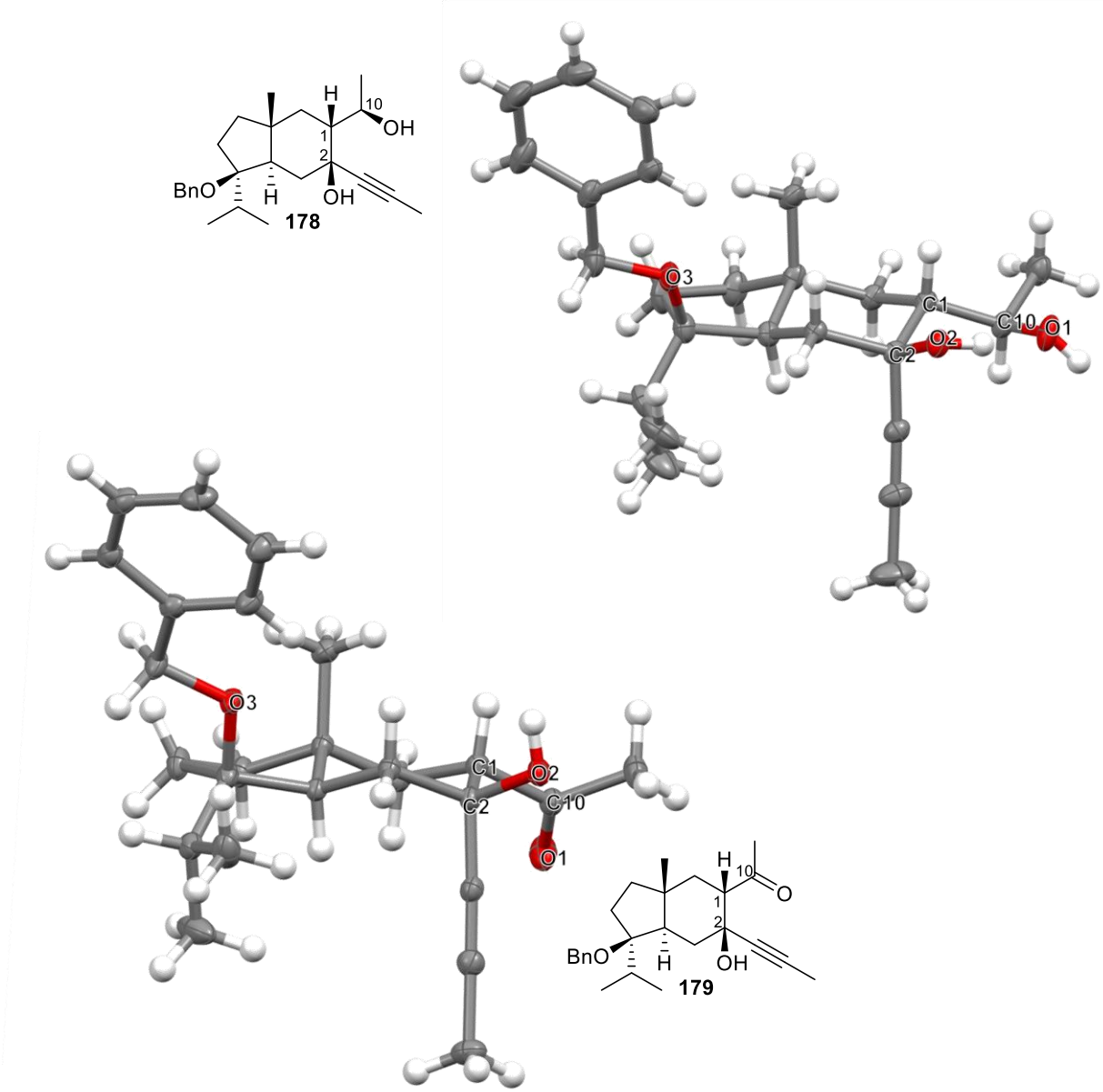


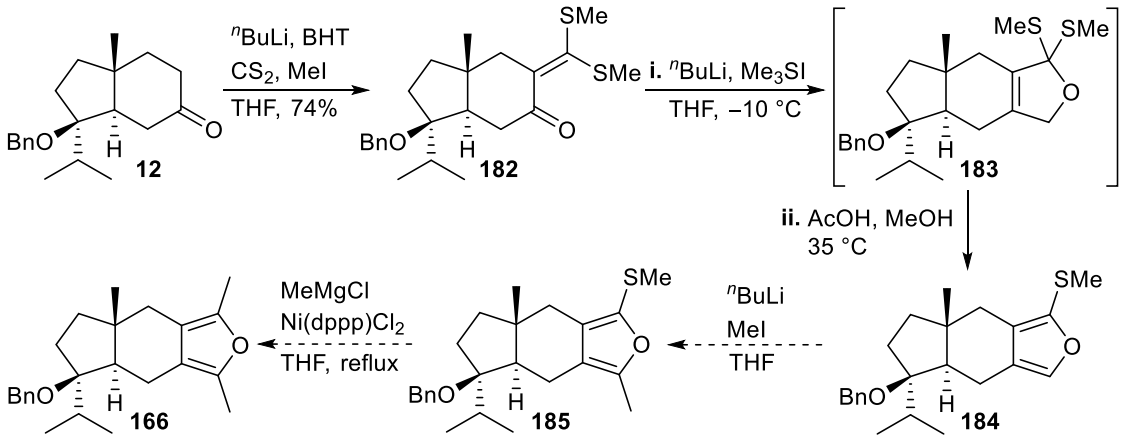
Figure 9: *Crystal and geometric structures of propyne 1,3-diol **178** (top) and subsequent ketone **179** (bottom), drawn with ellipsoids at the 50% probability level. The crystal structure of diol **178** showed three molecules in the unit cell (see appendix), only one has been represented here.*

Diol **178** was oxidised with DMP at room temperature to give ketone **179** in 67% yield. A single crystal of **179** was acquired and the crystal structure determined (Figure 9). Finally, the 3° alcohol was eliminated *via* the use of MsCl and Et_3N to give enynone **180** in 76% yield, a potential substrate for Iwasawa's platinum cascade chemistry. However, subjecting **180** to $PtCl_2$ and butyl vinyl ether at room or elevated temperature did not give **181** or provide any

spectroscopic evidence to suggest the cycloaddition takes place. Vanillin-staining TLC plates that had been spotted with the reaction mixture showed a single bright pink spot, which were observed in work on a Garst-Spencer approach (below, section 2.2.4), and were observed again in later synthesis (section 2.2.5.2.), where they corresponded to furan derivatives. The TLC data therefore suggested that the reaction was forming a furan, and no cycloaddition of that species was occurring.

2.2.4. Furan Annelation via Sulfonium Ylide Ring-expansion

With the failure of the desired route to furan **166**, an investigation of the Garst-Spencer method described previously was performed using Inamoto's dithioacetal modification (section 1.2.3.7.1., Scheme 22).[69] Attempts to form ketene dithioacetal **182** from KO^{t}Bu were plagued with the same issues that affected the synthesis of xanthate **140** (section 2.1.1, Scheme 31); several side-products that were difficult to remove completely, poor starting material consumption and mass recovery (Scheme 42). New conditions from the literature were sought out and featured the use of lithiated BHT as the base, high equivalents of CS_2 and MeI, and long reaction times.[117,118] After optimising under the new conditions it became clear that the eqv.'s of CS_2 were the key variable; while at 4–5 eqv. of CS_2 side products were formed to some degree, a 74% yield of **182** on 20 mg scale was obtained. With 10 eqv.'s, side-product formation was suppressed completely. However, after purification by column chromatography a portion of the product material co-eluted with a close-running impurity that was seemingly not present before, reducing the yield on 200 mg scale to 62%. The appearance of side-products after exposure to silica gel was reminiscent of the radical deoxygenation precursor studies and may well be a similar phenomenon.



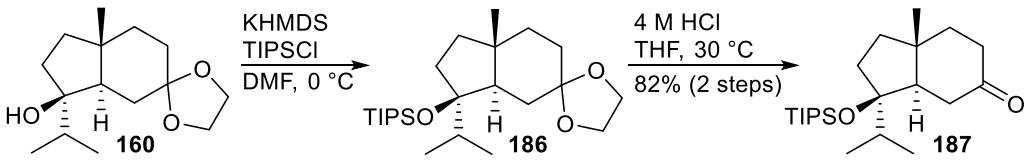
Scheme 42: *Attempted synthesis of furan **166** via ring-expansion and aromatisation of dithioacetal **182**, accessed through reaction of trans-hydrindanone **12** with CS_2 and MeI. Some evidence for thiofuran **184** was obtained, but subsequent products proved difficult to isolate and characterise.*

Ketene dithioacetal **182** was reacted with trimethylsulfonium ylide at −10 °C to generate hydrofuran **183** *in situ*. Addition of MeOH and AcOH with mild warming then delivered a new product with a peak in the MS of 371 ($[M]^+$) for thiofuran **184**, but the yield and subsequent purity by NMR were quite poor. Previous group experience suggested that purification of the furans could be problematic, the route was continued on the basis that taking crude reaction mixtures forward with a purification at the end of the four steps should suffice, since most of the conditions were relatively trivial in terms of byproducts. Crude thiofuran **184** was treated with ^{n}BuLi and MeI at room temperature and by TLC nothing changed, owing to the similarity of starting material and product. NMR analysis of crude reaction mixtures suggested methyl incorporation, and so the Kumada coupling was tested. By TLC, the starting material was consumed. However, a small difference in the R_f of the products prevented confirmation of success by NMR analysis, and the yield of the mixture was poor. Needing significant optimisation of the synthesis of thiofuran **184**, an investigation into the side products in the Kumada reaction, and a method for consolidating the steps together put this approach on hold in light of other results discussed below.

2.2.5. Modification of the Protection Strategy

2.2.5.1. Synthesis of the TIPS-Protected Trans-Hydrindanone and Reinvestigation of the Haloformylation Reaction

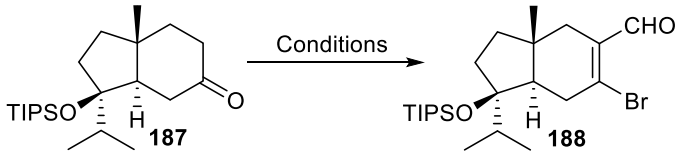
Despite extensive exploration of methods to construct furan **166** from benzyl-protected *trans*-hydrindanone **12**, success was elusive and at best was going to require significant optimisation. It was thought that the benzyl function was the cause of the failure in the haloformylation reaction, given that the group's model study had no issue with this transformation. Based on a comprehensive literature review the TIPS group was selected as a replacement, being the most robust group that could be added with a high confidence in its eventual removal.[119] Substituting TIPSCl in place of BnBr in the previously-used protection conditions allowed silylation of **160** to proceed smoothly with DMF as the solvent. Silyl ether **186** was generally not isolated, instead acetal deprotection afforded the corresponding *trans*-hydrindanone **187** in 82% yield on 500 mg (Scheme 43). It was difficult to completely consume **186**, even after adding more acid. As a result, on a 10 g scale the purification method had to be changed to recrystallisation to avoid chromatography fraction overlap. However, the change resulted in a reduction of the yield to 69% which reflects the high solubility of ketone **187** in standard organic solvents, and the practical difficulty faced in obtaining the small needle crystals produced by this method.



Scheme 43: *Protection of tertiary alcohol **160** as the TIPS-ether in the synthesis of trans-hydrindanone **187**.*

Having protected the *trans*-hydrindanone with a silicon group the haloformylation reaction

was tested anew (Scheme 44). Treatment of ketone **187** with PBr_3 and DMF gave bromoacraldehyde **188** as the only product, albeit in a very poor yield (Table 3, entry 1). Again, only a single regioisomer was detected and the outcome inferred from 2D NMR analysis.[97–100] Considering that benzyl ether **12** failed to produce anything at all, this was taken as a success and an extensive optimisation was performed. Suspecting that silica gel may be a problem for product isolation, some of the reactions were studied pseudo-quantitatively using ^{1}H NMR. The purpose of using NMR analysis was not to determine yields absolutely, but to monitor relative changes in the crude mass and then apparent NMR yield with respect to the internal standard mesitylene.



Scheme 44: *Haloformylation of ketone **187** to bromoacraldehyde **188**.*

Entry	T (°C)	PBr_3 Eqv.	Time (h)	Conc (M)	Additive	Quench	Quench T (°C)	SM Mass (g)	Scale (mmol)	Yield (%)
1	23	3	16	-	-	$NaHCO_3$	0	0.023	0.063	7
2	13	5	24	-	K_2CO_3	H_2O	13	0.020	0.055	28*
3	60	10	1	0.05	Mol. sieves	$NaHCO_3$	23	0.020	0.055	56*
4	60	5	0.83	0.1	Mol. sieves	$NaHCO_3$	23	0.100	0.273	79*
5	60	3	0.75	0.2	Mol. sieves	H_2O	23	0.100	0.273	77*
6	60	2.5	0.83	0.2	Mol. sieves	$NaHCO_3$	23	0.100	0.273	78*
7	60	2	0.75	0.03	Mol. sieves	$NaHCO_3$	0	0.050	0.136	71*
8	60	3	0.75	0.05	-	$NaHCO_3$	23	0.050	0.136	74*
9	60	1.4	0.67	0.05	-	$NaHCO_3$	0	0.275	0.750	89*
10	60	1.4	1.5	0.1	-	NaOH	23	0.100	0.273	59
11	80	3	1	0.08	-	$NaHCO_3$	23	0.200	0.545	69
12	80	3	0.5	0.1	-	$NaHCO_3$	80	0.200	0.545	65
13	100	3	0.5	0.1	-	H_2O	30	0.100	0.273	62
14	100	3	0.33	0.1	-	$NaHCO_3$	23	0.250	0.682	71
15	100	3	0.83	0.12	-	$NaHCO_3$	100	0.750	2.045	66
16	80	3	0.66	0.13	-	$NaHCO_3$	23	2.000	5.455	71
17	80	3	0.83	0.13	-	$NaHCO_3$	23	3.329	9.079	70
18	80	3	0.58	0.13	-	$NaHCO_3$	23	4.000	10.909	75

Table 3: *Key results in the optimisation of the haloformylation reaction conditions, showing that higher temperatures (ca. 80 °C) and higher scales resulted in higher yields, while additives made little difference. Starred yields were estimated by ^{1}H NMR analysis, comparing proton peak integrals with a known quantity of an internal standard (mesitylene)*

Initially, bromoacraldehyde **188** was thought to be relatively unstable, and so K_2CO_3 was added to the reaction mixture before the addition of the PBr_3 which did improve the isolated yield (entry 2). A single report in the literature commented on acid-sensitive functionality in the reaction, and proposed the addition of molecular sieves to moderate this *in situ*, even at 70 °C.[120] As such, ketone **187** was added to the Vilsmeier reagent mixture which contained activated 4 Å molecular sieves and the flask was heated at 60 °C until completion of the reaction by TLC (entry 3). Mass recovery after work-up was good and analysis by ^{1}H NMR showed little impurity. As such, the next steps in the annelation sequence were tested on crude **188** with some success. However, as the procedures began to scale the purity and yield of subsequent compounds diminished, and it became apparent that the haloformylation reaction needed to be optimised further.

Entries 4–7 show that changes to the eqv. of PBr_3 and quench conditions had little effect on the estimated crude yield. Removal of the molecular sieves in entries 8 and 9 showed that they served no purpose in the reaction despite the precedent. At this stage, the crude residue was purified by column chromatography on silica gel without Et_3N to afford a 59% yield of bromoacraldehyde **188** (entry 10). Entries 11–15 showed that reaction temperatures up to 100 °C provide higher yields, and that elevated quench temperatures did not compromise the reaction. These results implied a much higher stability of **188**, or the corresponding dimethyl iminium, within the reaction and during the quench than had been assumed up to this point. Testing the reaction mixture with UI paper indicated a pH of 5 or 6 initially, only turning red after several minutes of exposure to air. When the reaction mixture was quenched, UI paper showed the acidity was quickly neutralised, suggesting that $NaHCO_3$

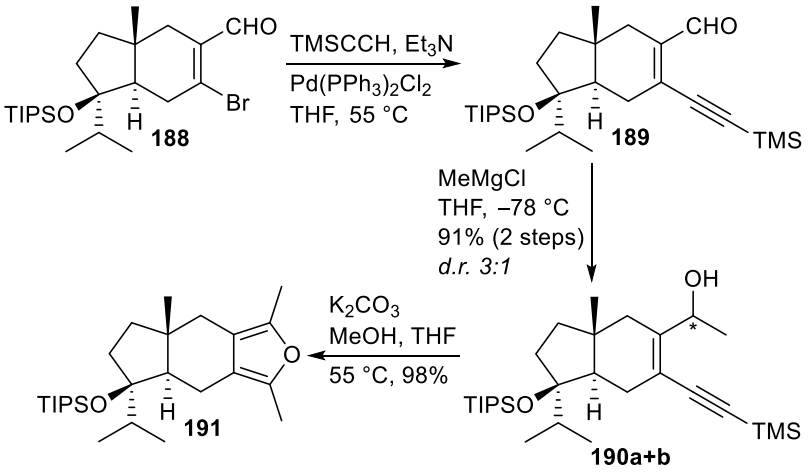
had been over-added which caused issues with the extraction process. When the reaction mixture was not neutralised at all a yield of 62% was recorded, only a slight decrease from the average isolated yield (entry 13). As the quantity of $NaHCO_3$ was reduced, and the extractant changed from Et_2O to CH_2Cl_2, better and more reproducible yields were obtained resulting in a 75% yield for the largest scale reaction (entries 16–18).

Although no clear point of failure was found in modifying the conditions of the haloformylation reaction, it appeared that the use of additives to the reaction mixture served no benefit here. The most significant factors were higher temperature (80 °C vs 23 °C), less $NaHCO_3$ in the quench and the use of pH paper to monitor that effectively, and increasing scale. Upon reflection, the observed success of the TIPS-protecting group confirms that the benzyl group in ketone **12** must be incompatible with these reaction conditions, presumably being susceptible to acid-mediated elimination.

2.2.5.2. Furan Annelation by Enynol Cyclisation-Isomerisation

Having synthesised bromoacraldehyde **188**, the rest of the annelation sequence was investigated (Scheme 45). The Sonogashira reaction with TMS-acetylene was found to work either with CuI at room temperature, or without at 55 °C; thus omission of the CuI was preferred. Purification of enynal **189** on silica gel produced an impure brown oil and so the crude aldehyde was taken forward instead. Addition of MeMgCl at −78 °C gave enynols **190a** and **190b** as a diastereomeric mixture with a ratio *ca.* 3:1. Purity over the sequence became a problem with scale and in part contributed to the review of the haloformylation protocol. To further address the purity issues the Sonogashira work-up was interrogated. After partial

removal of the solvent, the residues were filtered through celite eluting with hexane, followed by partition with MeCN. It was found that enynal **189** had a strong preference for hexane, whilst the MeCN captures aromatic and aminic impurities. Further washing of the hexane with H_2O and concentration under reduced pressure gave an orange oil containing **189**, which was then subjected to MeMgCl to generate a 91% yield over two steps of enynols **190a** and **190b** at 3.5 g scale with excellent purity, although still orange.



Scheme 45: *Synthesis of furan **191**, via sequential Sonogashira and Grignard reactions of **188** to afford enynols **190a/b**, which were then both underwent cyclisation-isomerisation to **191**.*

To cyclise to the furan, the model study from previous group work suggested the use of TBAF in THF at reflux (section 1.2.5., Scheme 28). While the TMS-group could be selectively removed at low temperature, when the reaction was heated at reflux multiple products (by TLC) appeared and based on their polarity were hypothesised to be the result of TIPS-deprotection. Marshall's KO^{t}Bu in ^{t}BuOH (section 1.2.3.7.2., Scheme 24, I) gave a single product by TLC, but ^{13}C NMR analysis showed a duplication of all environments and the presence of a peak at −1.3 ppm.[27] It was posited that the conditions were not sufficient to completely remove the TMS-group from the alkyne before triggering cyclisation, and may be

incapable of removing it after, meaning it was experimentally difficult to determine an endpoint even if the conditions could convert everything to furan **191**.

To guarantee removal of the TMS group, enynols **190a** and **190b** were treated with K_2CO_3 in MeOH, conditions which are used to remove TMS groups where a fluoride source cannot be used. THF was added to the mixture as the resulting furan was not soluble in MeOH. These changes swiftly afforded furan **191** in 98% yield from 280 mg of **190a/b**. However, it was difficult to maintain a high yield as the scale increased, causing decreases of 10% or more; this is most likely the result of purification with silica gel, although it is unclear why, or what a good alternative would be. Despite the yield issues, synthesis of furan **191** constituted completion of the second objective of the project: to annelate the *trans*-hydrindanone to a tetrasubstituted furan suitable for testing a cycloaddition approach to the oxabicyclo[3.2.1]octane substructure of dictyoxetane.

2.3. Studies Toward Synthesis of the Dioxatricyclic Core

2.3.1. Considerations for Applying the Cycloaddition Literature

With furan **191** in hand, the third objective of the project was to investigate access to oxabicyclo[3.2.1]octane **155**, required for oxetane synthesis (Figure 10). Prior literature review has suggested that there are several possible methods to achieve this.[24,25,35,53] To successfully synthesise (+)-dictyoxetane, these methods need to deliver a top-facing oxygen bridge and possess oxygenation at C_3. To establish the oxetane moiety, the alcohol at C_3 needs to be *anti* to the oxygen bridge. Finally, as C_1 and C_2 are methylene groups in the final product, steps will need to be performed to remove any functionality at these positions.

Given the pseudo-symmetric nature of furan **191**, it may be difficult to select between C_1 and C_3 with some of these methods.

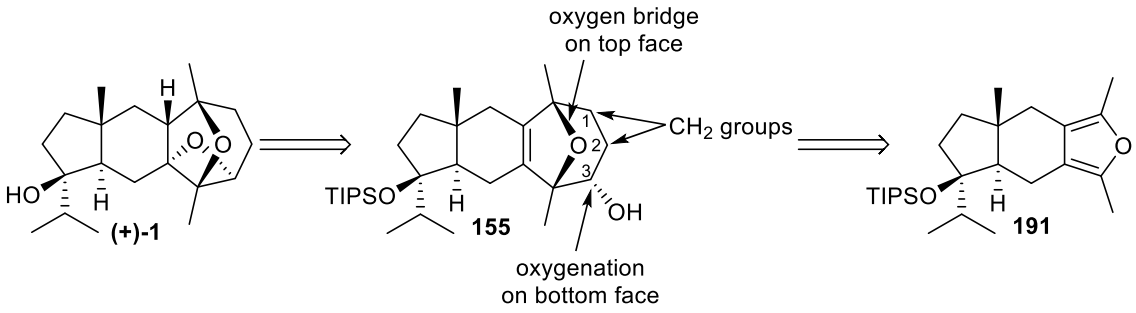
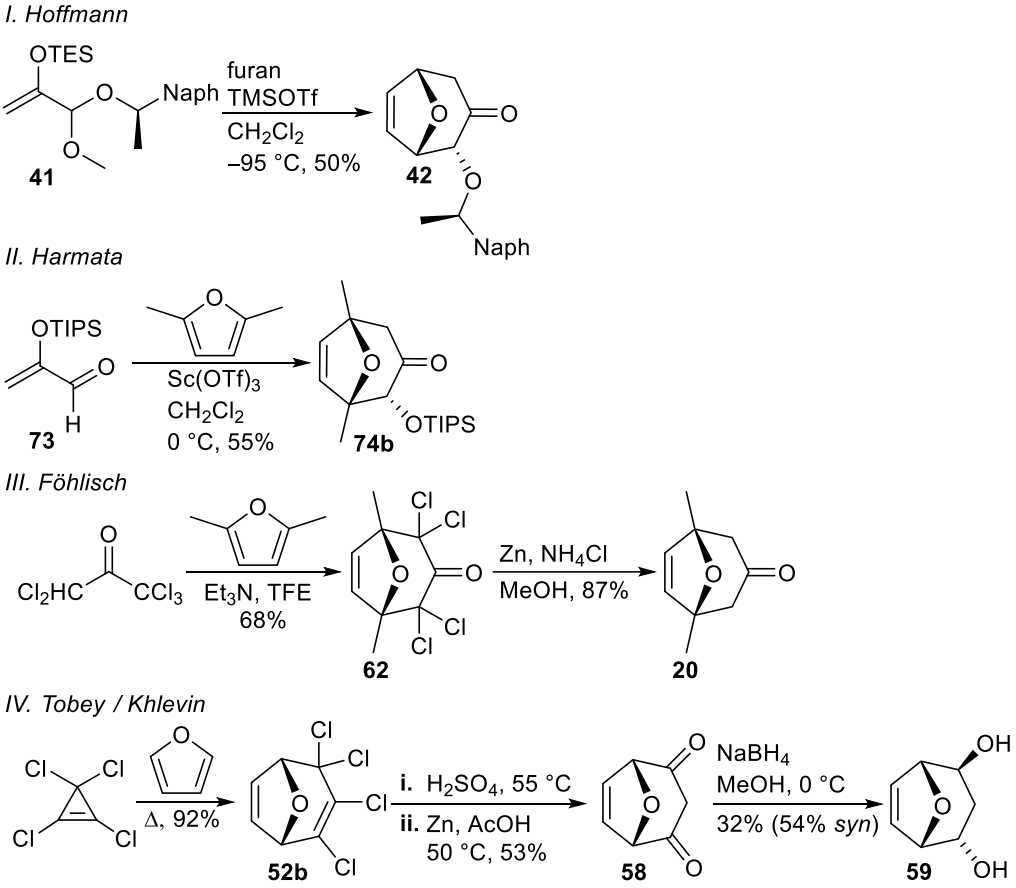


Figure 10: *Considerations for the cycloaddition sequence to produce oxabicyclic alcohol* ***155****.*

The most appropriate method was Hoffmann's (section 1.2.3.2); using chiral acetal **41**, oxabicyclic ketone **42** was synthesised as a single diastereomer (Scheme 46, I).[35] The method establishes the C_3-oxygenation with the correct stereochemistry and offers selectivity between C_1 and C_3 with reagent control – at least starting from a symmetrical furan. While furan **191** is not symmetrical, it does possess some elements of symmetry in proximity to the reaction centre, and thus the chiral nature of **191** should not affect the reagent control in Hoffmann's method. The ketone generated at C_2 will likely need to be removed before formation of the oxetane; previous group work on a model system has demonstrated this (section 1.2.5., Scheme 28).

Harmata's method (section 1.2.3.5.), using siloxyacrolein **73**, also delivers the correct C_3-oxygenation stereochemistry and creates a ketone function at C_2 in **74b** (Scheme 46, II).[53] However, the milder conditions provide less reason for selectivity of C_3 over C_1, and so a mixture would be expected here. Whereas in the Föhlisch cycloaddition (section 1.2.3.5.), no

C_3-oxygenation is created in ketone **20** and would therefore require extra steps to install successfully.[25]



Scheme 46: *Literature cycloaddition methods for constructing the oxabicyclo[3.2.1]octane subunit of dictyoxetane: I. Hoffmann et al.'s chiral oxyallyl cation precursor* ***42****,*[35] *II. Harmata's use of siloxyacrolein* ***73****,*[53] *and III. Föhlisch's haloacetone*[25] *work for the synthesis of oxabicyclo[3.2.1]octanes* ***42****,* ***74b****, and* ***20*** *respectively; and IV. Tobey's/Khlevin's synthesis of diol* ***59*** *from tetrachlorocyclopropene.*[24,43]

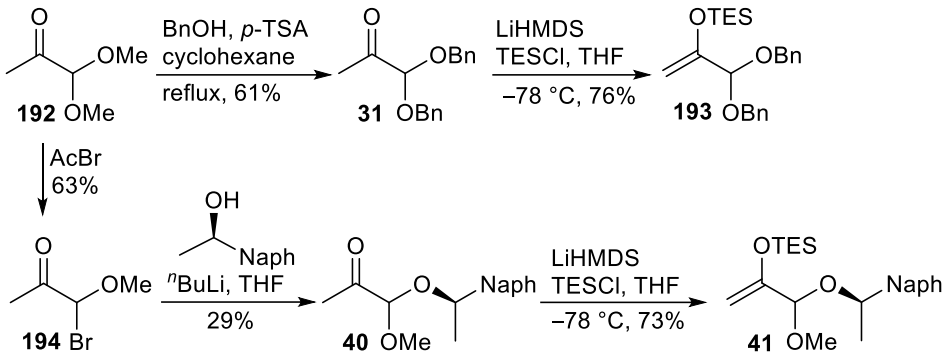
Tobey's cycloaddition (section 1.2.3.4) with TCCP provides completely different functionality in the oxabicycle, generating **52b** as a pair of regioisomers.[24] Khlevin's adaptation demonstrated a way to converge these regioisomers to diketone **58**, and then desymmetrise using carbonyl reduction to give diol **59**.[43] As such, the halocyclopropene chemistry could be used to distinguish C_3 from C_1 and establish the oxygenation needed for oxetane synthesis.

The one outstanding issue is that none of the above methods offer a strong reason for selectivity between the two faces of furan **191**, having been reported on achiral furans. However, there is precedent from Hugelshofer and Magauer's synthesis of dictyoxetane for the methyl group at the hydrindane ring fusion to direct the selectivity of transformations. They proposed that this was the reason for the high selectivity in the aldol reaction of *trans*-hydrindanone **12** with acetaldehyde, the results of which have been reproduced in this work. The key to this effect is likely a low reaction temperature, which allows the subtle steric influence provided by the methyl group to select between competing transition states. Thus, Hoffmann's method, being the only one reported at −78 °C or below, provides the best chance of utilising the methyl group as a facial discriminator in a cycloaddition.

2.3.2. Oxabicyclo[3.2.1]octane Synthesis via [4+3] Cycloaddition

2.3.2.1. Hoffmann's Method

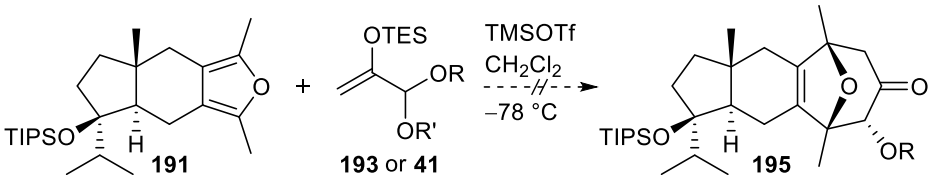
With the considerations outlined above, the [4+3] cycloaddition of furan **191** using the Hoffmann conditions was investigated.[34,35,121] Synthesis of acetal **193** was achieved by performing an acetal exchange on glyoxal **192** in 61% yield, followed by enolisation and trapping with TESCl to furnish **193** in 76% yield (Scheme 47). Meanwhile, the naphthyl derivative **41** was made by bromination of **192** with AcBr in 63% yield.[122] Subsequent displacement of the bromide by the lithium anion of (*R*)-2-naphthyl ethanol gave mixed acetal **40** in 29% yield, with unconsumed starting material accounting for much of the remainder. Silyl enol ether **41** was formed in 73% yield from the same enolisation and trapping conditions used previously.



Scheme 47: *Synthesis of oxyallyl cation precursors **193** and **41** via replacement of the methoxide substituents in commercially-available glyoxal **192**.*

Treatment of furan **191** and silyl enol ether **193** with TMSOTf in CH_2Cl_2 at −78 °C returned only the starting materials (Scheme 48). A higher temperature of *ca.* −40 °C for between 1 and 2 h was required and gave full consumption of the starting materials, which was extremely sluggish when compared with Hoffmann's report that simple furans react in minutes, if not seconds.[35] The observed reaction was particularly poor, with low (<20%) mass recovery of several products that were inseparable by column chromatography. Analysis of ^{1}H and ^{13}C NMR spectra suggested that **195** could be present but was likely occurring in a 1:1 ratio with another isomer, but there were other side products as well. A second structure was observed and could have been the debenzylated compound, again as a 1:1 mixture, but the data were unclear. It was hypothesised that the more sterically congested naphthyl ethanol substituent in **41** might be more resilient, however the same outcome was observed with this coupling partner. Hoffmann, nor previous group work, comment on any complication with the protocol that would lead to debenzylation or other side-products, but never performed the reaction at higher temperatures. Thus, the

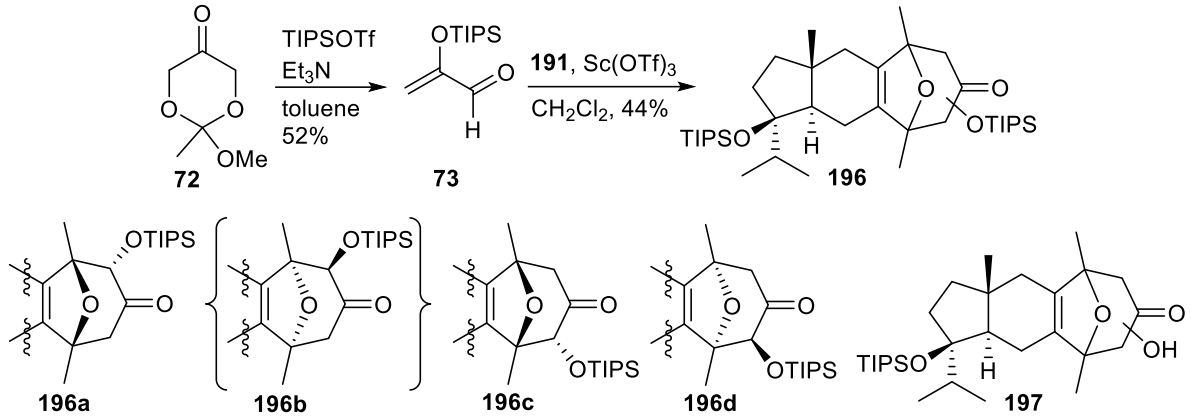
requirement of higher temperature appears to be a limitation of this methodology.



Scheme 48: *Attempted synthesis of the oxabicyclo[3.2.1]octane framework **195** via application of Hoffmann's [4+3] cycloaddition between furan **191** and either **193** or **41**.*[35]

2.3.2.2. Harmata's Method

Harmata's siloxyacrolein chemistry was the next most appropriate cycloaddition method given the mild synthesis temperature and Lewis acid, whilst delivering the C_3-oxygenation required for completion of the natural product (Scheme 46).[52,53] Dioxanone **72** was treated with TIPSOTf to give siloxyacrolein **73** in 52% yield (Scheme 49). The cycloaddition of **73** with furan **191** was then carried out at room temperature with catalytic $Sc(OTf)_3$ in CH_2Cl_2. A complex mixture was formed with three products by TLC; two were relatively apolar and close in R_f to each other and the starting materials, while another lay near the baseline. Upon purification by column chromatography, it was found that the first two product fractions each contained two compounds, accounting for 44% of the yield. The first two isomers **196a** and **196b** were isolated in an NMR ratio of 4:1 from one experiment, and 9:1 from another. The second set of isomers, **196c** and **196d**, were initially obtained as a mixture in a ratio of 5:3, however in a further experiment they were partially separated to give 51 mg of oxabicycle **196c** and 43 mg of a 1:5 mixture of **196c** and **196d**, which also conforms to an approximate 5:3 ratio. Whilst the ratio of **196c** and **196d** appeared consistent, the relative amount of **196a/b** to **196c/d** changed between reactions and so a meaningful mechanistic interpretation cannot be made.



Scheme 49: *Synthesis of siloxyacrolein **73** from dioxanone **72**, and subsequent use in a cycloaddition with furan **191** to produce the four α-oxygenated oxabicyclic ketones **196a-d**. The structures of **196a**, **196c**, and **196d** were elucidated through 2D NMR experiments, whilst **196b** was inferred. Alcohol **197** is a theorised side-product structure that may have been formed from the reaction.*

The absolute structures of **196a**, **196c**, and **196d** have been strongly inferred from analysis of HMBC and NOESY correlations (see appendix); not every correlation has been mapped in these diagrams (Figure 11). The thesis for the analysis was two-fold: firstly, as the oxabicycle is asymmetric it should be possible to map the structure once one side has been connected to a known environment in the *trans*-hydrindane. Secondly, the stereochemistry of the bridging oxygen will bend the oxabicycle in one of two ways relative to the rest of the framework. The change in shape will expose H-6 and H-8 to different faces of the *trans*-hydrindane which should be discernible from a NOESY spectrum if those resonances are discrete. As such, NMR analysis of the 9:1 mixture suggested that **196a** contained the desired bridge and α-oxygenation stereochemistry, but the incorrect α-keto regiochemistry (Scheme 49). **196c** was inferred as the desired outcome for the synthesis of (+)-dictyoxetane, with the most supporting correlations. **196d** differs from **196c** in the bridging oxygen stereochemistry only, as the -OR group occupies the *anti*-position relative to the bridge in

both structures, as expected from the literature.[53] Given that all three structures contain an *anti*-relationship between the oxygen bridge and the OTIPS group, it is likely that this exists in isomer **196b** also, for which there is only one remaining structure.

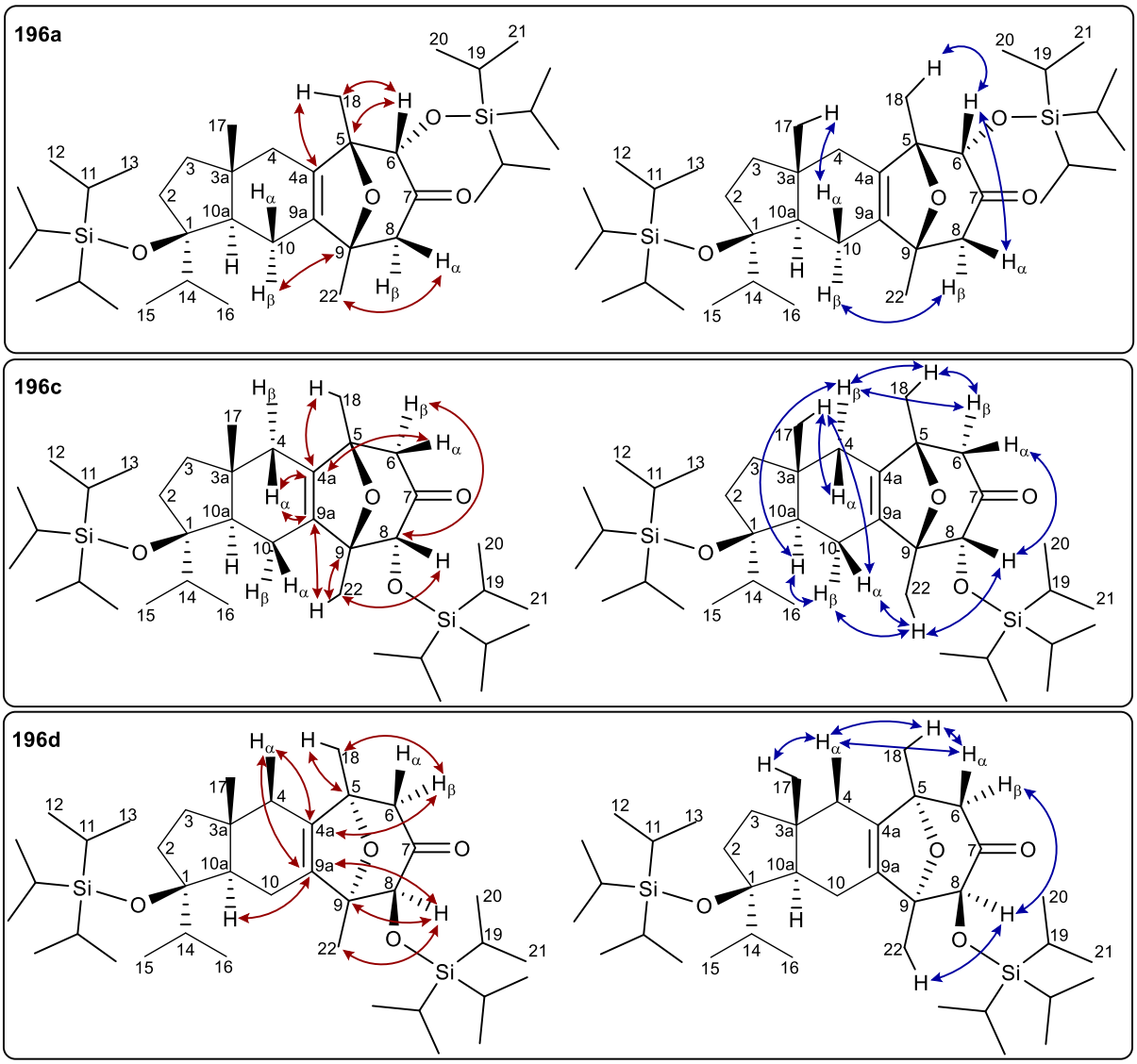


Figure 11: *HMBC (red, left) and NOESY (blue, right) maps showing the key correlations used to infer the absolute structure of three of the oxabicyclic ketones* ***196a***, ***196c***, *and* ***196d****.*

The final product fraction accounted for *ca.* 40% of the yield, and NMR analysis suggested that this fraction contained four compounds and that the only difference from **196** was the lack of the TIPS group derived from siloxyacrolein **73**, resulting in alcohol **197** (Scheme 49). The outcome was reminiscent of the Hoffmann chemistry (section 2.3.2.1). Due to the

complex nature of the data, and the inability to separate these compounds apart, it was unclear if the side-products were merely mono-desilylated versions of **196a**–**d** or if they were stereochemically different.

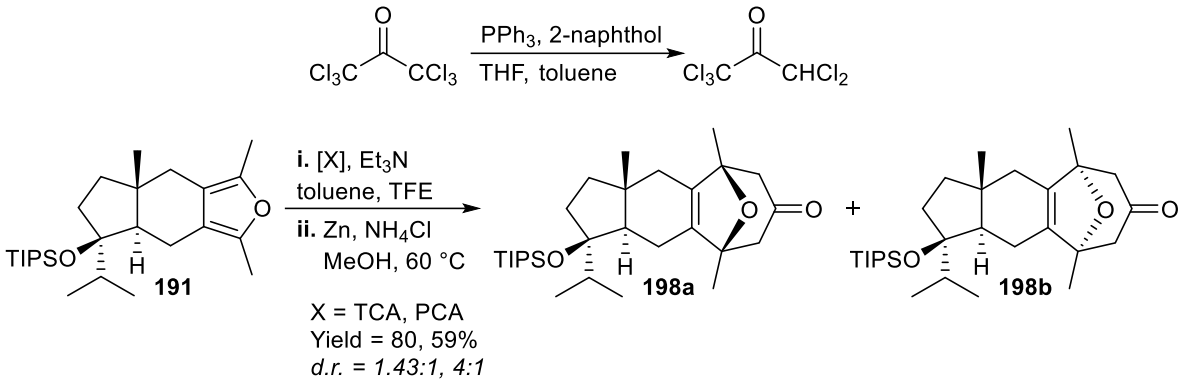
There was no precedent for the use of other Lewis acids to allow for lowering of the reaction temperature or use of a chiral catalyst to induce greater selectivity. Despite **196c** containing all the correct stereochemical information for progression to (+)-dictyoxetane, without a way to simplify the mixture or increase the yield of **196c**, Harmata's method was not appropriate for continuation of the synthesis.

2.3.2.3. Föhlisch's Method

Having attempted two sets of cycloaddition conditions without much success, it was thought that attempting to install the C_3-oxygenation was complicating the cycloaddition, resulting in poor conversion and selectivity in the product framework. By trialling the simpler Föhlisch cycloaddition, a single oxygen bridge stereochemistry might be afforded which would be easier to work with on a practical level, with the C_3-oxygenation established separately.[48,51]

Initially, treatment of furan **191** with commercially available 1,1,3-trichloroacetone (TCA) in 2,2,2-trifluoroethanol (TFE) and Et_3N was met with poor starting material consumption and the production of a brown semi-solid (Scheme 50, bottom). Unpublished group work suggested the need to add the base and the chloroacetone solutions simultaneously and slowly.[123] Furthermore, it was found that **191** was insoluble in TFE, and as such toluene was

required. Applying both modifications with the aid of a syringe pump delivered an improvement in purity, but still failed to completely consume the starting material.



Scheme 50: *Top: Synthesis of PCA from HCA; Bottom: Synthesis of ketones **198a** and **198b** via cycloaddition of furan **191** and either TCA or PCA, showing a significant difference in diastereoselectivity between the two.*

In contrast, the dehalogenation step required less optimisation. The two prevailing methods involve Zn dust and either a Cu source to make the Zn-Cu couple (typically CuI), or an acidic species such as NH_4Cl.[48,51] Experiments showed that copper was less effective, and that mild heating was necessary (Scheme 50). It was discovered that *ca.* 10 eqv.'s of Zn dust per halogen and 15 eqv.'s of NH_4Cl were optimal, as too much solid led to practical issues such as the stirrer bar stalling. No activation of the Zn dust was performed. An EDTA solution was employed at the work-up stage to chelate the zinc, which made a significant difference to the purity after column chromatography. At best, 50 mg of furan **191** was treated with three eqv.'s of TCA and Et_3N in equal volumes of TFE over 4 h to give an 80% yield of ketones **198a** and **198b** after dehalogenation, although the yields of these reactions had a high standard deviation. The facial selectivity of the cycloaddition using TCA was low, giving a *ca.* 1.4:1 inseparable mixture of isomers produced from addition to each face of furan **191**; the absolute stereochemistry of the major compound could not be determined.

In an attempt to improve the facial selectivity of the cycloaddition, PCA was synthesised by the method of Gilheany *et al*. (Scheme 50, top), chosen in strong preference to Föhlisch's use of chlorine gas.[47,124] Following the procedure, distillation of the crude residue gave mixtures of PCA and 1,1,3,3-tetrachloroacetone (*sym*-TCA) in a ratio of 1:0.24 by integral in the ^{1}H NMR spectrum; as *sym*-TCA has two protons, the molar ratio of PCA to *sym*-TCA is 8.3:1 (Scheme 50). Analysis of the ^{13}C NMR spectrum of these mixtures showed that HCA was also in the distillate. HCA should not react in the cycloaddition process, since there is no abstractable proton, but *sym*-TCA could be influencing the facial selectivity. By using only half of the reagents with respect to HCA, an integral ratio of 1:0.05 PCA:*sym*-TCA was obtained, implying a molar ratio of 40:1. However, the reduction in *sym*-TCA in the mixture made no appreciable difference to the *d.r.* of ketone **198**. The synthesis of PCA requires further optimisation for total synthesis adaptation, but was sufficient to proceed with.

Despite the issues involved in the synthesis of PCA, use of the HCA-PCA distillate in the cycloaddition with furan **191** gave oxabicyclic ketones **198a** and **198b** in 59% yield, but the *d.r.* improved significantly to 4:1. In the approach of the oxyallyl cation to furan **191**, there are two or three 'choices' that will determine the stereochemical outcome: which face of the furan the oxyallyl species reacts with, whether the reaction occurs through an *endo* or *exo* profile, and for TCA only, the orientation of the chlorides with respect to the framework of **191** (Figure 12). As PCA has four chlorides, they must occupy all available positions and there is thus no 'choice', leaving only the facial approach and *endo*/*exo* profiles to determine selectivity. Evaluating both factors for PCA (Figure 12, **II**, **IV**, **VI**, **VIII**), it is difficult to appreciate a preference, but it seems that less severe clashes would be experienced when

PCA reacts through the lower face of furan **191**, because the methyl group at the *trans* ring-junction exerts more steric influence on reagents approaching the top face than the proton at the *trans* ring-junction does for the lower face (Figure 12, **II** and **VI** vs **IV** and **VIII**).

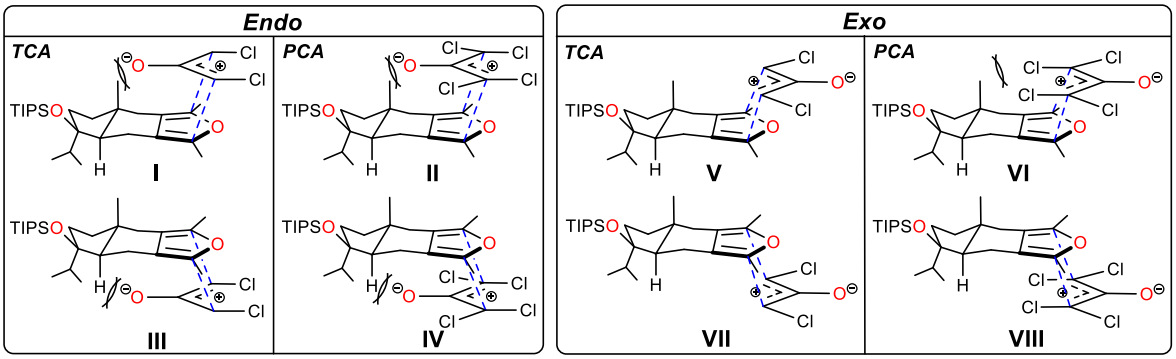


Figure 12: *Evaluation of the steric interactions experienced by both TCA and PCA when approaching furan* ***191*** *from the top and bottom faces, in both the endo and exo reactions modes, with the chlorides of TCA oriented for the least steric interactions for that configuration.*

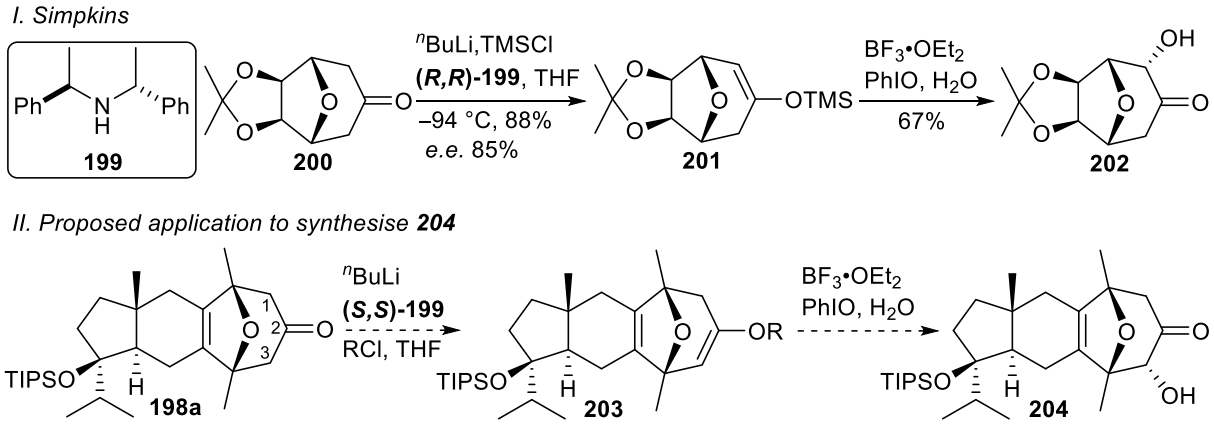
In examining the possible transition states for TCA, the chlorides have been positioned to experience the minimum steric interaction, since this should provide the strongest discrepancy between TCA and PCA, and provide a basis for understanding the differences. For the *endo* reaction mode, reaction between TCA and either face of furan **191** appears to lead to a steric clash between the oxyallyl oxygen and the framework of **191** (Figure 12, **I** and **III**). Meanwhile, for the *exo* mode of reaction there appears to be little steric clash from approach to either face of the furan (Figure 12, **V** and **VII**). The analysis would suggest then that for TCA, the *exo* mode of reaction is preferred as it leads to less steric clashes; here there appears to be no discrimination between the faces of the furan and that fits with the low selectivity observed experimentally (1.4:1) and higher yield (80% vs. 59% using PCA).

Although analysis of some of the potential transition states for the reaction of furan **191** and either TCA or PCA does not unambiguously resolve the mechanism, it is hard to envisage

that reaction of PCA through the top face of **191** would be preferred. As such, it is more likely that the major isomer experimentally was ketone **198a**.

2.3.2.3.1. Attempts to Regioselectively Install α-Keto Oxygenation

With the bridge stereochemistry unknown, methods to regioselectively install oxygen functionality next to the ketone were investigated. Promising literature precedent came from Simpkins *et al.* who used a chiral lithium amide derived from **199** to asymmetrically deprotonate **200**, which after trapping with TMSCl gave enol ether **201** in 88% yield and excellent *e.e.* (Scheme 51, I).[125,126] Subsequent oxidation of **201** under Moriarty conditions generated **202** with the alcohol group positioned *anti* to the oxygen bridge. Assuming that ketone **198a** was the major product of the Föhlisch cycloaddition, it was thought that **(*S,S*)-199** would be required to effect deprotonation of the C_3 position.



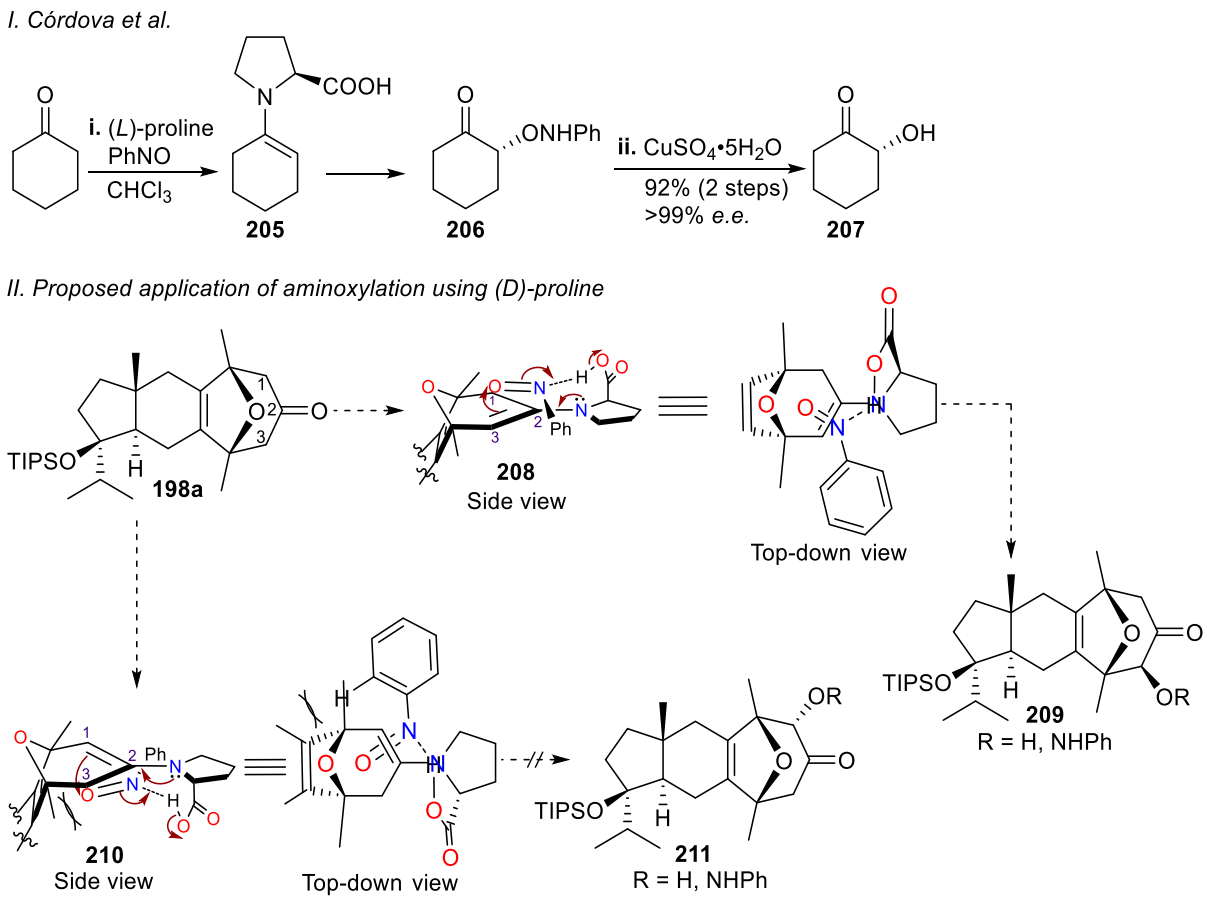
Scheme 51: *I. Simpkins et al.'s asymmetric deprotonation of **200**, using homochiral amine **199**, and subsequent oxidation of **201** to oxabicyclic alcohol **202**.[125,126] II. Proposed application of homochiral lithium amide chemistry to synthesise alcohol **204** from **198**.*

As such, the inseparable mixture of ketones **198a** and **198b** was subjected to the asymmetric deprotonation conditions, using the hydrochloride salt of **(*S,S*)-199** in the presence of TESCl at low temperature which generated two new spots by TLC, but **198** remained largely

unconsumed. ^{1}H NMR analysis of the crude reaction mixture suggested a silyl enol ether had been formed. A variety of experimental changes were made including: increased base and TESCl eqv.'s, distillation of the silyl chloride, use of both the internal and external quench methods used in the literature report,[125] longer reaction time, increased reaction temperature to −40 °C, and neutralised silica gel for purification. However, none of these gave acceptable conversion rates and isolated yields were extremely poor. In case the lithium enolate was not sufficiently reactive, both TMSCl and TIPSOTf were trialled as electrophiles. No reaction was observed with TIPSOTf, but TMSCl appeared to give higher starting material consumption than TESCl. However, after column chromatography ketone **198** was the exclusive product, presumably because of the instability of the corresponding enol ether **203** on silica gel with or without Et_3N in the eluent; and **203** needed to be purified from unconsumed **198**.

The issue with the application of Simpkins' conditions appeared to be a diminished reactivity of the framework to forming an enolate in the oxabicyclic ring system, presumably because of the extra rigidity imposed by the bridgehead methyl groups and the fusion of the oxabicyclic ring to a cyclohexene. It was thought that a higher temperature method might be more amenable, such as the aminoxylation of ketones using PhNO and catalytic proline, reported almost simultaneously by several groups in 2004.[127–132] In the method, cyclohexanone was converted to aminoxylated product **206** *via* enamine **205** (Scheme 52, I). The selectivity for the reaction was proposed to originate from hydrogen bonding between proline and the nitrogen of nitrosobenzene. Using a single enantiomer of proline lowers the energy of reaction from one face of the enamine leading to effectively enantiopure **206**.

Based on the mechanistic proposals,[127,131] it was envisaged that ketone **198a**, presumed to be the major stereoisomer, would need to interact with (D)-proline (Scheme 52, II). Reaction through the lower face of the oxabicycle, as in **210**→**211**, would likely be disfavoured due to clashes with the *trans*-hydrindane framework, preventing access to the desired *anti* relationship between the oxygen bridge and the resulting -OR group. Thus, the -OR group at C_3 must be accessed on the top face (*syn* to the oxygen bridge, **209**), for which (D)-proline is needed; in contrast, use of (L)-proline would give the *syn* -OR group at C_1.



Scheme 52: *I. Literature aminoxylation of cyclohexanone using PhNO and (L)-proline to afford α-hydroxyketone* ***207*** *across two steps.*[129] *II. Proposed application of the aminoxylation method and a model, based on mechanistic suggestions from the literature,*[127,131] *for why (D)-proline is needed and should deliver selectively* ***209*** *from ketone* ***198a****.*

Attempting the aminoxylation of ketone **198a/b** with the literature conditions gave no

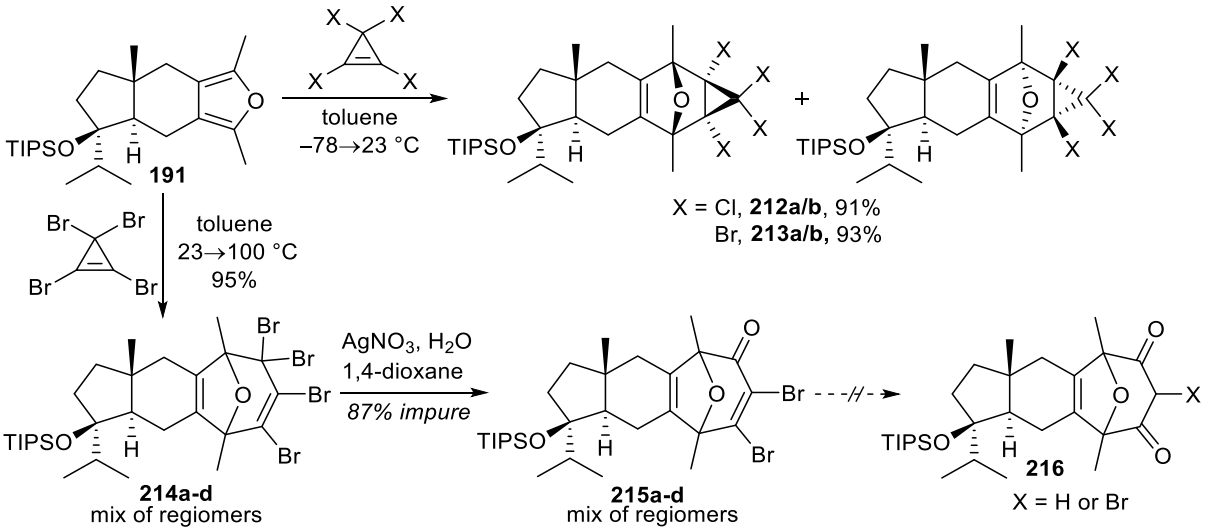
reaction. It was posited that the most likely reason was failure to form the enamine. To test the theory, ketones **198a/b** were heated at reflux in the presence of proline alone with a Dean-Stark trap, returning no detectable trace of enamine. Further interrogation with pyrrolidine also gave no trace of the corresponding enamine. The results describe why the aminoxylation did not proceed, but may also provide insight into why the homochiral lithium amide method failed as well, if the carbonyl is not particularly susceptible to enolate formation in the first place.

Despite good progress, and potentially selectivity, in the Föhlisch cycloaddition reaction of furan **191** and PCA, ketone **198a** could not be developed into alcohol **204** to complete the synthesis of (+)-dictyoxetane.

2.3.3. Oxabicyclo[3.2.1]octane Synthesis via [4+2] Cycloaddition

With the previous cycloadditions giving mixed results and a general problem of selectively installing oxygenation in the oxabicyclo[3.2.1]octane for oxetane synthesis, it was decided that Tobey's chemistry might offer a way forward (Scheme 46).[24,36,43,44] Furan **191** was treated with TCCP at room temperature which gave an inseparable mixture of the two cyclopropanes **212a** and **212b** in 91% yield, in a ratio of 1:1 (Scheme 53). Based on the literature precedent that with furan a single cycloadduct is formed derived from the *exo* mode of reaction, it was believed that **212a** and **212b** were derived from the *exo* reaction profile of TCCP with each face of furan **191**.[37] The more sterically demanding TBCP, made in 79% yield from treatment of TCCP with BBr_3, gave **213a** and **213b** in 93% yield with the same selectivity. Although the reaction was initiated at −78 °C and warmed to room temperature

slowly, product was only formed *ca.* −20 °C suggesting that the selectivity cannot be improved. The outcome was unsurprising given Tobey's observation that reaction between furan and TBCP is faster than with TCCP; they proposed that the bromides provide a significant electronic activation of the cyclopropene, which counteracts the increased steric hinderance of the larger halides. Once furan **191** had been fully consumed, heating at 100 °C for several hours delivered the ring-expanded tetraoxabicycles **214a-d** as a mixture in 95% yield. The four compounds are the result of each facial isomer being able to ring-expand into two regioisomeric olefins.



Scheme 53: *Reaction of furan **191** with halocyclopropenes initially generated cyclopropanes **212a/b** and **213a/b** which upon heating ring-expanded to oxabicycles **214a-d**, and the synthesis of dibromoenones **215a-d** in an attempt to access diketone **216**.*

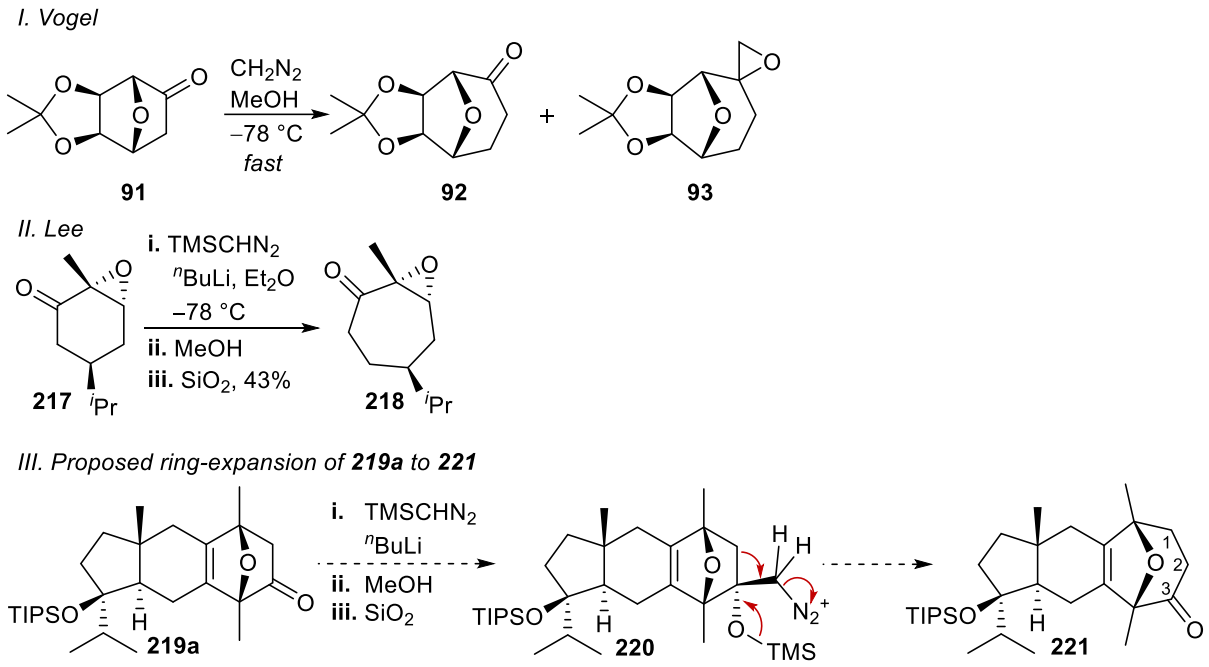
Treatment of **214a-d** with $AgNO_3$ in a mixture of 1,4-dioxane and H_2O gave four new products by TLC, with the reaction mixture precipitating a yellow solid over an hour. However, after isolation of the products NMR analysis showed significant impurity and was hindered by division over many inseparable isomers; despite this, peaks at *ca.* 185 ppm in the ^{13}C NMR spectrum suggested a conjugated ketone, and the *C*Br_2 resonance at 70 ppm disappeared (see appendix). Additionally, an IR peak at 1708 cm^{-1} and a MS peak at 631

([**215**+H]$^+$) restored some confidence that the chemistry had worked, but purification remained a challenge owing to the low polarity of the products. Regardless, a route to **216** was pursued on the basis that purification would be achieved across several steps.

Extensive effort was made to generate diketone **216** using KOH at reflux, or treatment with H_2SO_4 either from enones **215a-d** or tetrabromide **214a-d**.[24,44] All reactions produced either no new products, or far too many. Isolation of new products failed to deliver convincing data, mostly due to low mass recovery which, when divided among several isomers, made it difficult to understand if transformations had occurred. In retrospect, there is not enough data to brand this route as unsuccessful. However, the combination of low material availability, high attrition rate, and the presence of multiple isomers, meant that the route was set aside in favour of a new Diels-Alder approach.

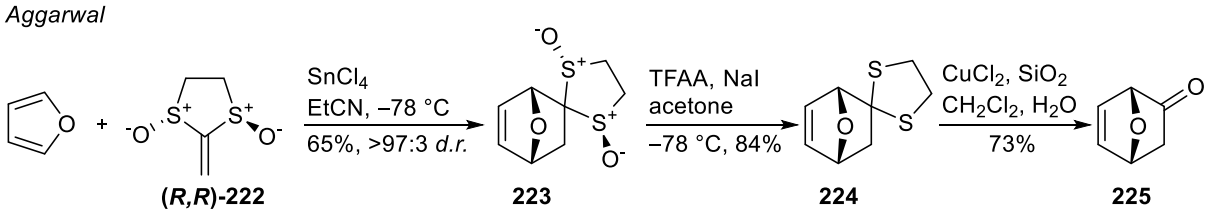
2.3.4. Synthesis of Oxanorbornenones via a Diels-Alder Reaction

At this point in the synthesis, the cycloaddition methods that were identified to synthesise dictyoxetane had been investigated with limited success. Selectivity for a single oxygen bridge stereochemistry had not been demonstrated, and installing the oxygenation in the correct position for oxetane synthesis was proving a challenge. To overcome the problems, a new approach was considered based on Vogel's early work on the ring-expansion of oxanorbornenones in combination with Lee's (section 1.2.3.6.) TMS-diazomethane chemistry (Scheme 54).[58,59] The precedent for the ring-expansion of oxanorbornenone **91** to ketone **92** was encouraging; if the process could be replicated on **219a** it would also eliminate the need to remove functionality from C_1 and C_2 of **221**, as previous methods may have required.



Scheme 54: *I. Vogel's diazomethane-mediated ring-expansion of oxanorbornenone* ***91*** *to oxabicyclic ketone* ***92****.*[58] *II. Lee's use of TMS-diazomethane in the ring-expansion of cyclohexanone* ***217****.*[59] *III. Proposed ring-expansion of norbornenone* ***219a*** *based on a combination of Vogel and Lee's work to give ketone* ***221****.*

With a new approach there was also an opportunity to establish the oxygen bridge stereochemistry with higher selectivity. A cycloaddition method that could achieve this was taken from Aggarwal's ketene-equivalent work using chiral bis-sulfoxides.[133–135] Treatment of furan with sulfoxide **222** in the presence of $SnCl_4$ at low temperature gave cycloadduct **223** in 65% yield and excellent diastereoselectivity (Scheme 55). The sulfoxide auxiliary was then removed *via* a TFAA/NaI-mediated reduction, followed by dithiane hydrolysis with $CuCl_2$ and SiO_2 in 84% and 73% yields respectively to give oxanorbornenone **225**.



Scheme 55: *Aggarwal's use of chiral ketene eqv.* ***222*** *in a Diels-Alder reaction with furan to synthesise oxanorbornenone* ***225****.*[133-135]

The theoretical basis for how many compounds can occur from the Diels-Alder reaction of sulfoxide **222** and furan **191** is evaluated in Figure 13. There are eight possible isomers that can be formed from a reaction containing racemic **222**. The sulfoxide imparts selectivity from steric interactions between the sulfinyl groups and the framework of the coupling partner. Using this idea, some approach trajectories appear unfavourable; namely **A**, **D**, **F**, and **G**, two from each sulfoxide stereochemistry. Both **G** and **H** could be used for the synthesis of (+)-dictyoxetane but **H**, derived from **(*S,S*)-222**, appears more favourable on steric grounds.

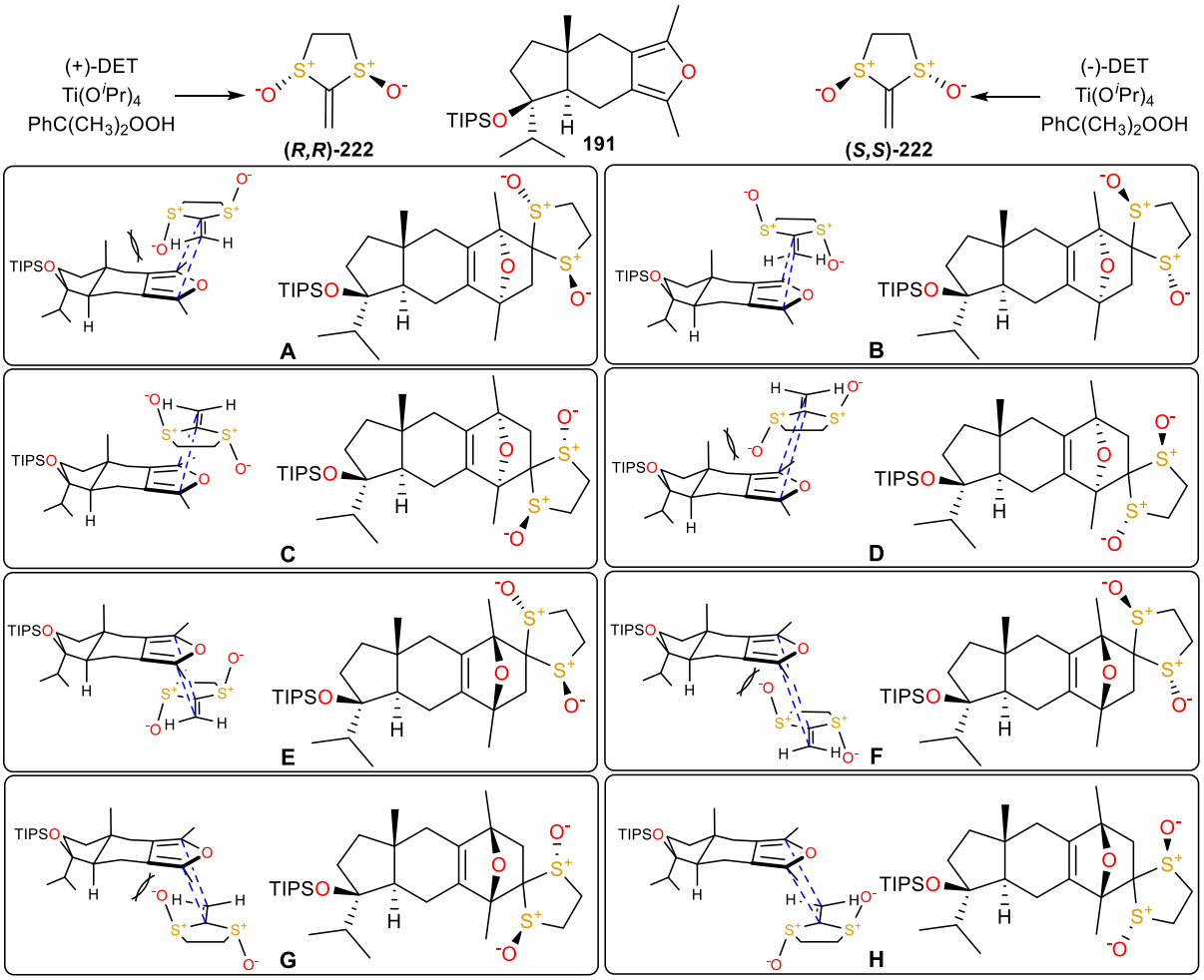
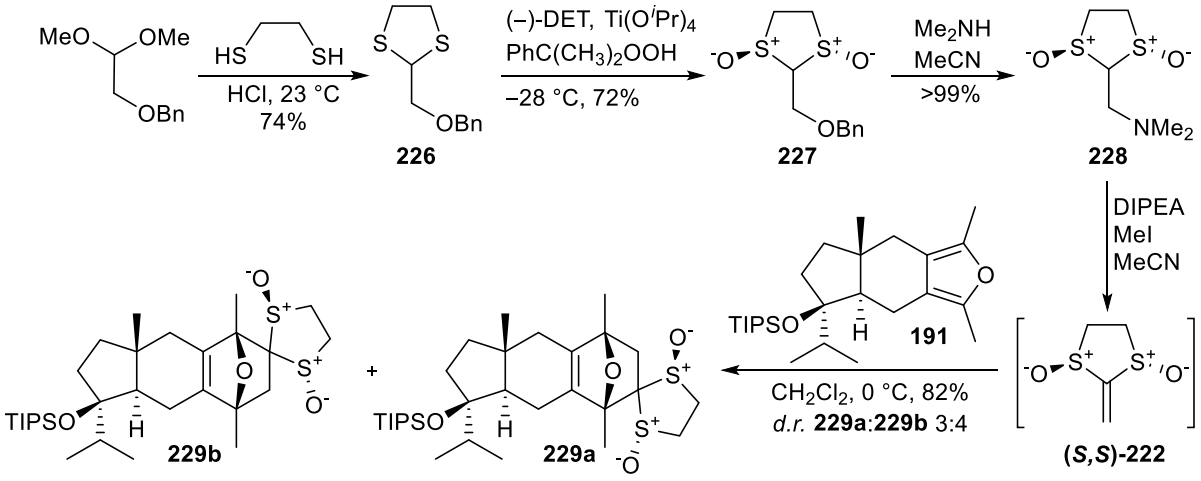


Figure 13: *Possible transition states and resulting cycloadducts from reaction of furan **191** and each isomer of sulfoxide **222**.*

To evaluate the new approach, synthesis of **(*S,S*)-222** was pursued starting with thioacetal

formation using ethanedithiol and HCl to give dithiane **226** in 74% yield (Scheme 56). Asymmetric oxidation was performed using (−)-DET to give (*S,S*)-sulfoxide **227** in 72% yield; the racemic oxidation was performed in 82% yield using *m*CPBA in Et_2O at 0 °C (see experimental). The enantiopurity of **227** was evaluated by optical rotation, giving a rotation of −108° after flash chromatography, compared with +125° for the (*R,R*)-isomer in the literature. Following recrystallisation, a rotation of −116° was obtained but in the next reaction, the same value was recorded from the chromatographed material without the need for recrystallisation; this was deemed to be sufficient for the Diels-Alder reaction. The benzyl ether of **227** was substituted for a dimethylamino group to give **228** in effectively quantitative yield, which was then subjected to a Hofmann elimination using DIPEA and MeI. The ketene equivalent was reported to be sensitive to silica gel and so in line with Gaich's report, the solvent and excess reagents were removed and the remaining residue was used crude.[60,136] At a later stage, the crude material was purified with silica gel but did not result in pure **222**, although it did remove some of the leftover salts, and requires further optimisation.



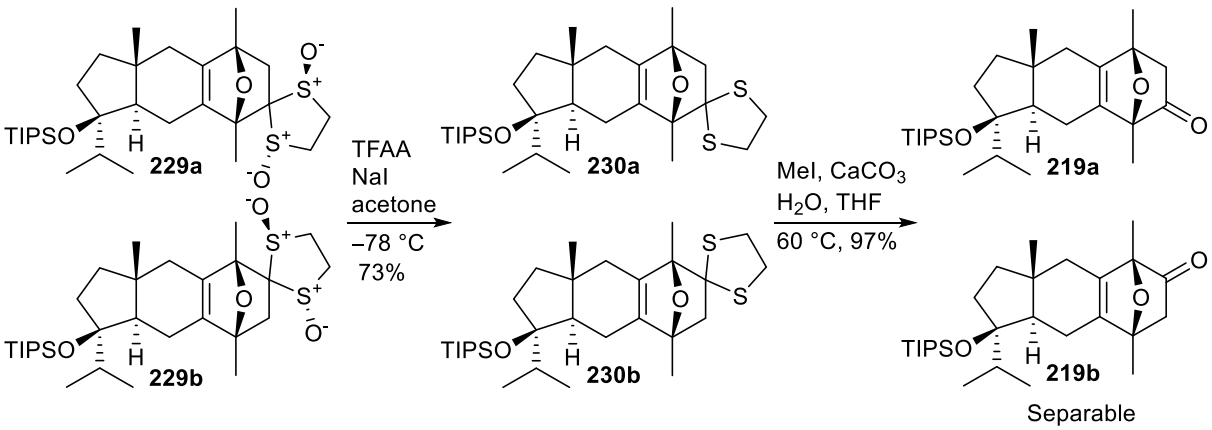
Scheme 56: *Synthesis of chiral ketene equivalent* ***(S,S)-222*** *from commercially-available benzyloxyacetaldehyde dimethylacetal, and subsequent Diels-Alder reaction with furan* ***191*** *to produce regioisomeric oxanorbornenes* ***229a*** *and* ***229b****.*

Furan **191** was treated with racemic **222** at 23 °C in CH_2Cl_2, resulting in four products by TLC. Three of the products were isolated, with one occurring as a mixture. Mass recovery was good, and analysis of spectroscopic data confirmed that the compounds were stereochemical isomers. However, their absolute structure was not determined, partly on account of mild impurities likely leftover from the use of crude **222**. Use of $SnCl_4$ at low temperature resulted in a brown solid that clogged the reaction vessel. By TLC, the reaction consumed starting material, but did not generate the same products. Further attempts with 4 eqv.'s **222** and 8 eqv.'s of either $SnCl_4$ or $BF_3{\cdot}OEt_2$ failed to consume starting material even as the reaction vessel was warmed to room temperature. It is unclear why the Lewis acids failed to generate cycloadducts when compared to the literature; it may be that impurities from the synthesis of **222** poison the Lewis acids.

To pursue higher selectivity, **(*S,S*)-222** was trialled in the cycloaddition which resulted in an 82% yield of **229a** and **229b** as an inseparable mixture with a *d.r.* of 3:4 (Scheme 56). Most (13%) of the remaining yield was accounted for by the two other isomers. The absolute structures of **229a** and **229b** were not able to be determined by NMR analysis, and were inferred from the crystal structures of later ketones **219a** and **219b** (Scheme 57). The crystal structures showed that **219a** and **219b** both contained the desired top-facing oxygen bridge, and were regioisomers with respect to the ketone position in the oxanorbornene ring system (Figure 14). The oxygen bridge stereochemistry was determined in the cycloaddition and while the ketone function was obtained by conversion of the sulfoxide moiety, the sulfoxide regiochemistry was also put in place as part of the cycloaddition. Therefore, the relationship between **219a/b** implied that the approach trajectory of sulfoxide **222** favoured

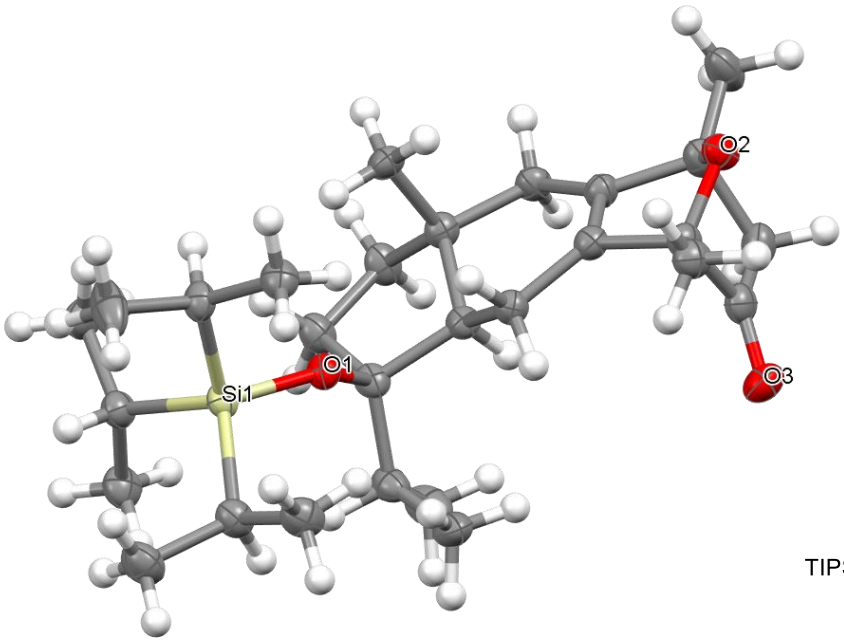
reaction with the lower face of furan **191** (**F** and **H**, Figure 13), despite trajectory **F** appearing sterically unfavourable. The suggestion is that the sulfoxide can distinguish between the faces of the furan, presumably based on a steric clash with the methyl group on the top face of **191** (**D** vs **H**), yet trajectory **B** does not appear to have this clash. It is unclear whether contaminants left over from the synthesis of sulfoxide **222** are affecting the outcome. The process requires more investigation as the question of using Lewis acids to impart higher selectivity in the transformation has not been sufficiently answered.

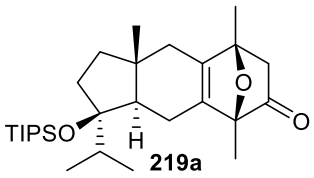
With the cycloadduct mixture of **229a** and **229b** in hand, removal of the bis-sulfoxide auxiliary was undertaken. Using literature conditions for the sulfoxide reduction, dithiolanes **230a** and **230b** were obtained in 73% yield as an inseparable mixture (Scheme 57).[134] Small quantities of furan **191** were detected in the reaction that did not come from the starting material, suggesting a susceptibility to cycloelimination. Attempting the hydrolysis of **230a** and **230b** with $CuCl_2$ and SiO_2 at room temperature resulted in no reaction, and with mild heating (40 °C) gave furan **191** as the sole product.[134]



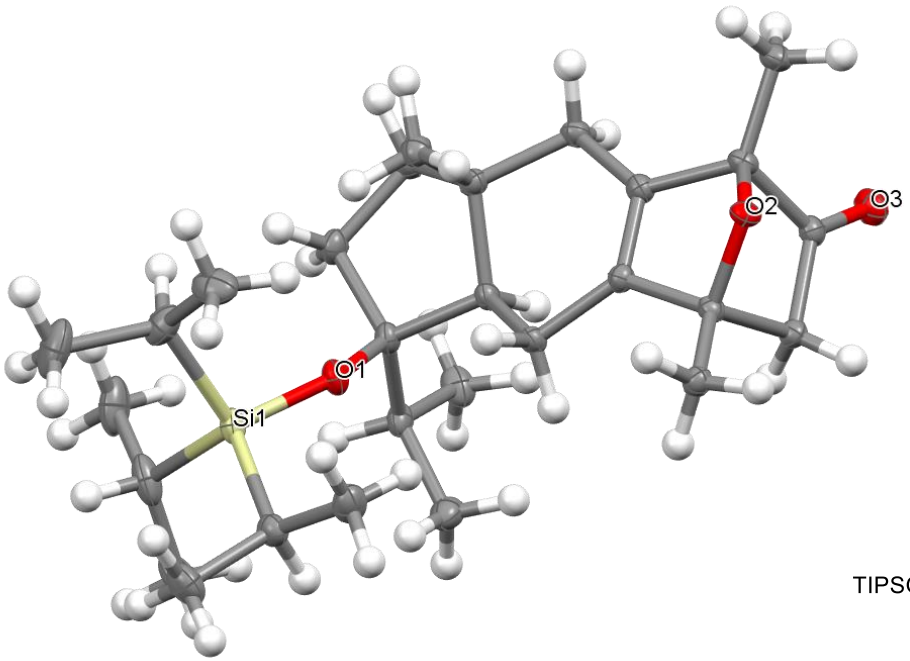
Scheme 57: *Removal of the bis-sulfoxide auxiliary from **229a** and **229b**, via sulfoxide reduction and thioacetal hydrolysis, to give separable norbornenones **219a** and **219b**.*

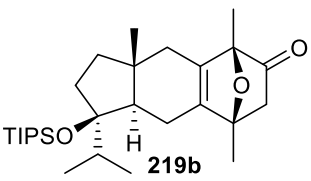
Other procedures that either did not involve heating, or contained a base were sought out, leading to five sets of conditions: PIFA (with and without $NaHCO_3$),[137] $I_2/CaCO_3$,[138] $AgNO_3$/NBS/$CaCO_3$,[139] and MeI/$CaCO_3$.[140] Use of PIFA without $NaHCO_3$ generated two new spots by TLC that looked promising from initial analysis, but the mass recovered of both crude material and post-purification was abysmal. It was hypothesised that the resulting ketones could be acid-sensitive rather than heat-sensitive, with silica gel being the problem from the Aggarwal conditions.[134] Adding $NaHCO_3$ to the reaction mixture either from the start or to quench produced a different outcome by TLC. The I_2 and $AgNO_3$/NBS conditions both showed only traces of the same two products as the original PIFA reaction suggesting these conditions were too harsh. The MeI conditions had been due to requiring heating and large amounts of MeI; however, at 60 °C this method delivered a 97% yield of regioisomeric ketones **219a** and **219b** on 620 mg scale. The ketones were separable with only 12% of the yield occurring in mixed fractions, and there was no trace of furan **191**. Column chromatography of the compounds on silica gel was not a problem and so previous issues with synthesis probably stem from both silica gel and heat. Crystal structures of both ketones were acquired and determined their absolute structures, which were resolved from analysis of NMR data (Figure 14, see appendix). The X-ray data confirms both the regiochemistry of the ketone function within the oxanorbornene ring system, and the top-facing stereochemistry of the oxygen bridge which resulted from the cycloaddition of **(*S*,*S*)-222** and furan **191**.





219a



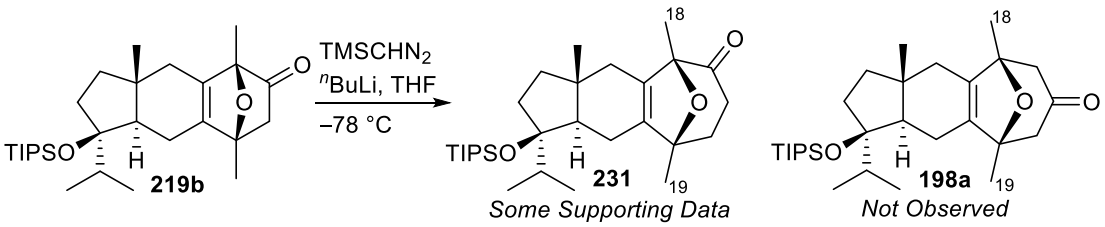


219b

Figure 14: *Crystal and geometric structures of oxanorbornenones* ***219a*** *(top) and* ***219b*** *(bottom), drawn with ellipsoids at the 50% probability level. The crystal structure of* ***219a*** *showed four molecules in the asymmetric unit, while there were two for* ***219b****, but only one for each compound has been represented here (full details in appendix).*

2.3.5. Investigation of Oxabicyclo[3.2.1]octane Synthesis via Ring-Expansion

With desired ketone **219a** in hand, the next step was to expand the norbornene ring system by one carbon to deliver an oxabicyclo[3.2.1]octanone, completing the carbon skeleton of (+)-dictyoxetane (Scheme 58). Initial attempts were performed on ketone **219b** because the absolute structures had not been determined at this time. Using Lee's TMS-diazomethane chemistry, 20 mg of ketone **219b** was subjected to five eqv.'s of the reagent and stirred for 1 h at −78 °C before being quenched with MeOH and warmed to room temperature.[59] After stirring with silica gel and flash chromatography, two products were isolated, A and B, with masses of 7 mg and 3 mg respectively. Product A gave an IR peak at 1731 cm^{-1}, and a peak in the ^{13}C NMR spectrum at 205.6 ppm (see appendix for all spectroscopic data). In the ^{1}H NMR spectrum, 50 protons can be found easily, and the C_{18} and C_{19} methyl signals at *ca.* 1.4 ppm and 1.3 ppm are separated significantly, whereas in pseudosymmetrical ketone **198a** these environments overlapped; the data suggested that the oxabicyclo[3.2.1]octane substructure was not symmetrical and thus could be ketone **231**.

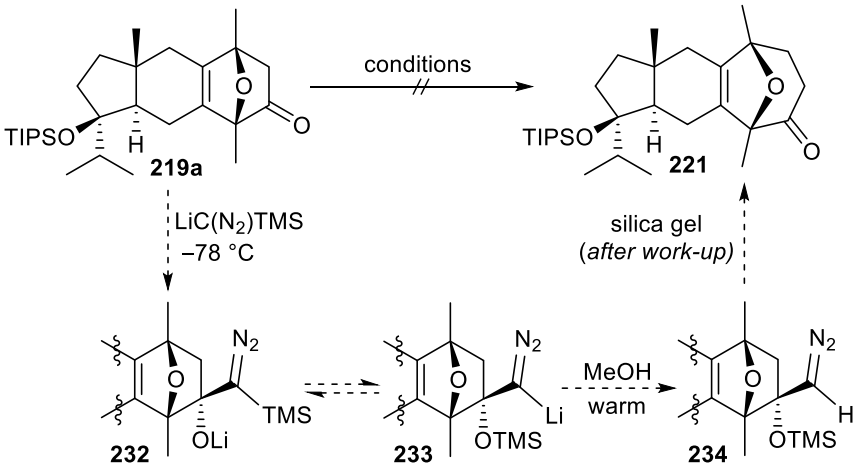


Scheme 58: *Attempted ring-expansion of **219b** using Lee's TMS-diazomethane chemistry,[59] and the two possible regioisomeric products ketone **231**, for which there is some supporting data, and ketone **198a** which was not observed.*

Less data was obtained for product B with only one notable feature in the ^{1}H NMR spectrum: a peak at *ca.* 0 ppm indicative of a TMS group, but the rest of the spectrum was poorly

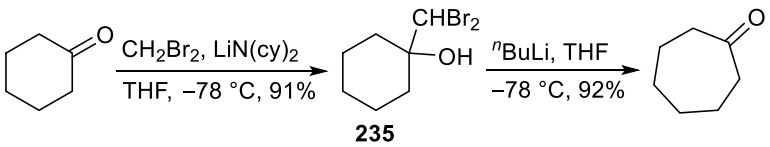
resolved. The hypothesis for the appearance of multiple products with low recovery was a failure of the MeOH to fully protonate the C-Li bond; instead partial protonation of the O-Li before the TMS migration (see section 1.2.3.6., Scheme 18) could be leading to the corresponding alcohol, caused by a lack of MeOH. Since the data from product A seemed to support the desired ring-expansion to ketone **231**, a further reaction with increased MeOH (10 → 20 eqv.) was performed which removed one of the extra products by TLC, but seemed to bias the result toward product B with an isolated mass ratio of 4:5. Despite the higher recovery of B, NMR data did not elucidate its nature, although a peak at 217 ppm was observed in the ^{13}C spectrum which would suggest a ketone function, it was neither the chemical shift observed for **198a** (or **198b** in case the assignment was incorrect), nor that of **231**. Other attempts to investigate the reaction on **219b** returned large proportions of starting material, which was difficult to separate from either A or B.

At this time, the absolute structures of **219a** and **219b** were established, and so rather than optimising the reaction on ketone **219b**, the investigation switched to the desired isomer **219a** (Scheme 59). However, **219a** did not behave like **219b** and failed to produce any isolable product. It was found that adding the silica gel directly after the MeOH, and then warming to room temperature negates the reaction, suggesting that the MeOH is not quenching the reaction at −78 °C. Further attempts to isolate the pre-silica gel intermediates resulted only in complex NMR spectra that could not be interpreted. A predominant outcome from both isomers in the final tests of the TMS-diazomethane chemistry suggested that ketone **198a** was present, despite early data on ketone **219b** indicating otherwise.



Scheme 59: *Attempted ring-expansion of **219a** to oxanorbornenone **221** using Lee's TMS-diazomethane chemistry,[59] via addition of the TMS-diazomethanyl anion to the ketone of **219a** and silica gel-mediated ring-expansion of TMS ether **234**.*

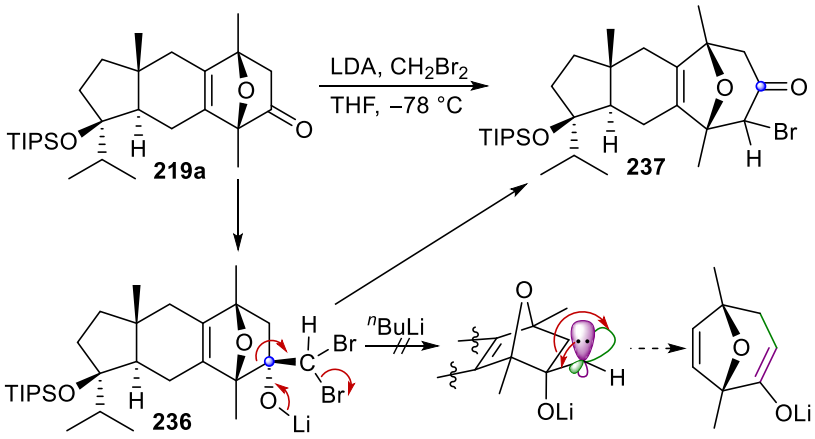
Lee's method was abandoned because of a strong lack of clear outcome or predictability from both isomers, and instead the method of Yamamoto *et al.* using dihalomethyllithium addition was adopted (Scheme 60).[141,142] This procedure utilises the dibromomethanyl anion to add into the ketone, similar to Lee's TMS-diazomethanyllithium species. The intermediate dibromo alcohol **235** can be isolated allowing for a more stepwise investigation of the ring-expansion, which may elucidate the problems with applying Lee's conditions. Following addition of ^{n}BuLi to **235**, ring-expansion to the cycloheptanone was observed in 92% yield.



Scheme 60: *Yamamoto's dibromomethane-mediated ring-expansion of cyclohexanone to cycloheptanone via alcohol **235**.[141,142]*

There was no precedent for the regioselectivity of Yamamoto's ring-expansion chemistry on the oxanorbornenone, but despite this ketone **219a** was subjected to CH_2Br_2 and LDA at −78 °C,[143] affording two products by TLC (Scheme 61). The major compound showed a 1732 cm^{-1}

stretch in the IR spectrum, a peak at 198 ppm in the ^{13}C NMR spectrum suggesting a ketone, and a >0.2 ppm difference between the two methyl signals of the oxabicyclic subunit in the ^{1}H NMR spectrum (see appendix). However, the appearance of a single proton at 4.6 ppm was concerning, and the 1:1 ratio of peaks at 553 and 555 in the MS ($[M]^+$ for ^{79}Br and ^{81}Br) showed that it was bromide **237**; this compound is likely the result of a rearrangement of intermediate **236** *in situ*, promoted by the -OLi and nucleofugality of the adjacent bromides. As such, the structure does not generate the carbene from ^{n}BuLi and progress along the expected path, nor can it be trapped as the dibromo alcohol by addition of a proton source. Moreover, the rearrangement appears to have exclusively favoured migration of the more substituted bridgehead carbon, not the α-methylene unit.



Scheme 61: *Application of Yamamoto's dibromomethane ring-expansion chemistry[141,142] on ketone **219a** preferentially generating bromide **237** via rearrangement of **236** before the addition of ^{n}BuLi.*

The appearance of **237** as a major product suggested that oxanorbornenone **219a** was highly susceptible to rearrangement, which may explain why Lee's TMS-diazomethane chemistry failed to adequately ring-expand successfully as well, and may also tie into why furan **191** was so readily reformed from either the cycloadducts **229a** and **229b**, or the subsequent dithianes. Yamamoto's conditions were tested at *ca.* −100 °C using a liquid nitrogen/MeOH

cooling bath to try and control the ring-expansion. Several new products were observed by TLC, but NMR and IR analysis of the isolated fractions did not elucidate the desired ketone or the dibromo alcohol intermediate formed from quenching of **236**. It may be that **236** was too unstable to be isolated, and conditions that allow for rearrangement *in situ* should be pursued.

3. Conclusions and Further Work

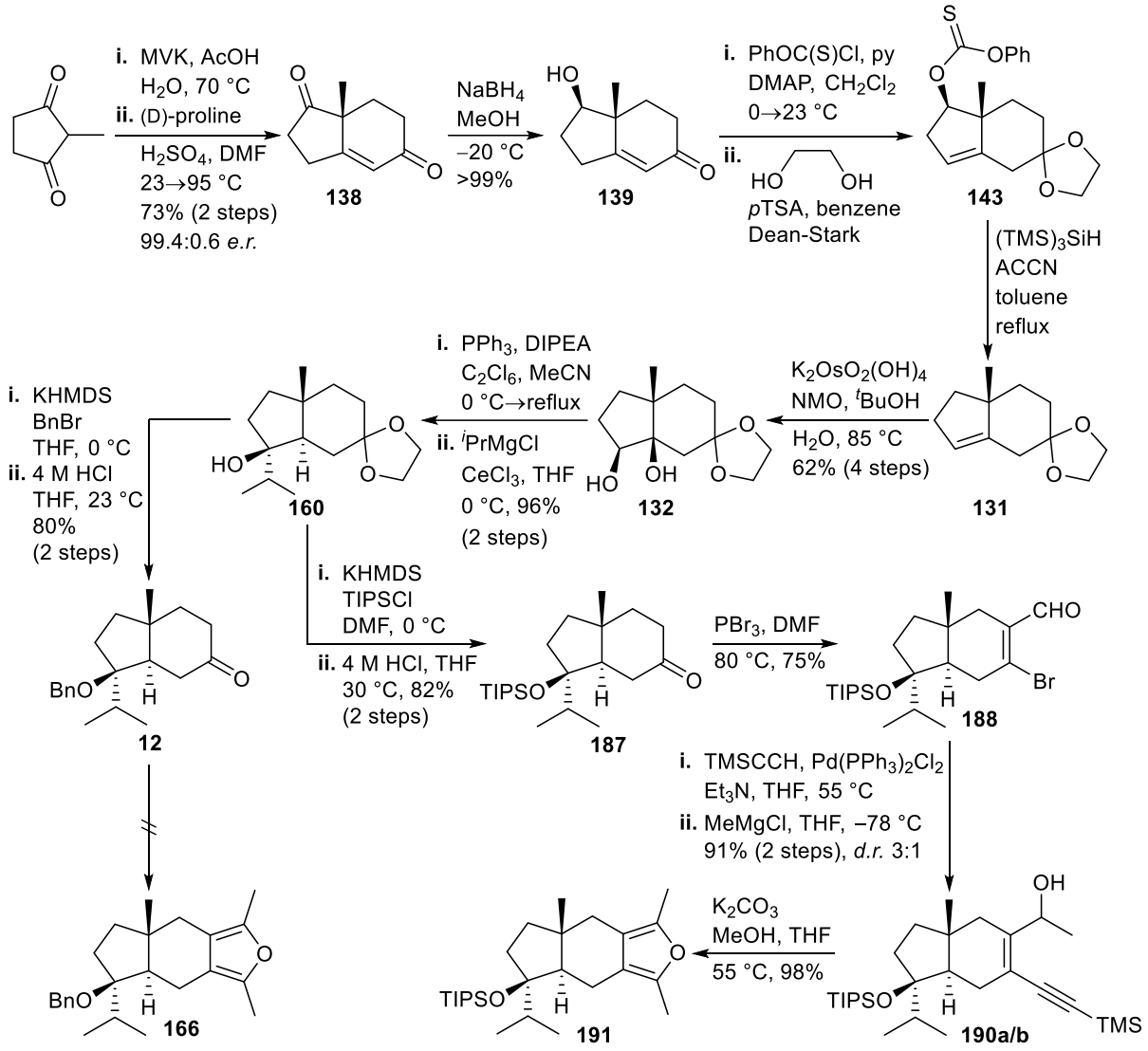
3.1. Project Summary

The first objective was to asymmetrically synthesise a protected trans-hydrindanone, which began by accessing the Hajos-Parrish ketone **138** in 73% yield over two steps from the commercially-available 2-methylcyclopentane-1,3-dione, and with an *e.r.* of 99.4:0.6 (Scheme 62). Deoxygenation of **138** was performed *via* a Barton-McCombie protocol to synthesise acetal **131**, ultimately using a four-step process from alcohol **139** to diol **132** with an overall yield of 62% on *ca.* 50 mmol. By applying the group's previously published hydrindane synthesis,[22] *trans*-hydrindanone **12** was obtained in 35% yield across 11 steps, compared with Hugelshofer and Magauer's 23% yield (8 steps).[21] The improvement in yield reflected the higher process efficiency of synthesising **131** from 2-methylcyclopentane-1,3-dione (56% yield over 6 steps, producing *ca.* 60 mmol / 13 g), rather than starting from 2-methylcyclopentanone (28% over 3 steps, producing 36 mmol / 7 g).

The second objective of the project was to annelate *trans*-hydrindanone **12** to furan **166** (Scheme 62), initially by using the group's model study work (section 1.2.5.). However, haloformylation of **12** failed to provide access to **166**, as did a variety of other approaches based on 1,3-diol cyclisation-isomerisation, and the Garst-Spencer annelation.

Tertiary alcohol **160** was protected with a TIPS group in place of benzyl and, following acetal hydrolysis, the haloformylation reaction was retried and bromoacraldehyde **188** successfully synthesised in 75% yield on 4 g scale (Scheme 62). Annelation of furan **191** was then

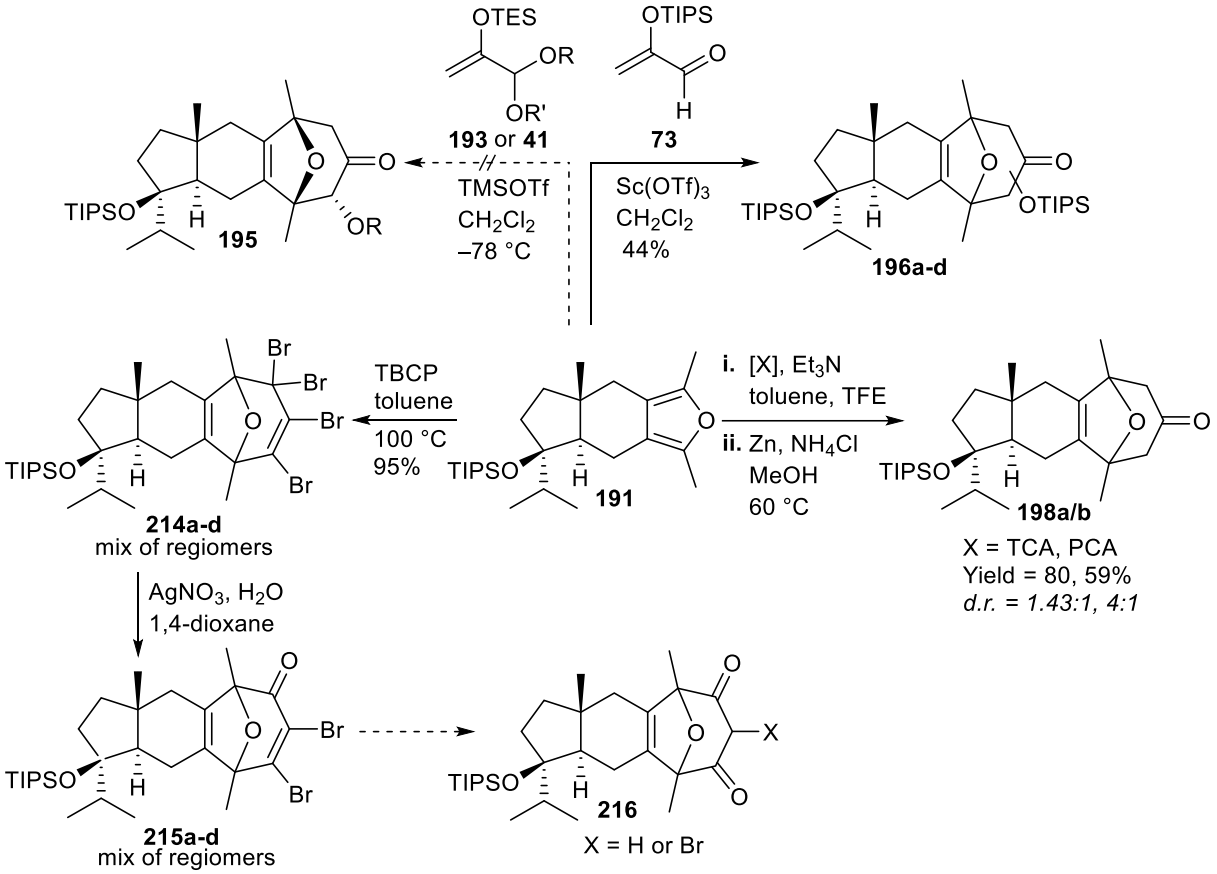
achieved in 89% yield across three steps, *via* Sonogashira coupling with TMS-acetylene, MeMgCl addition, and enynol cyclisation-isomerisation.



Scheme 62: *A summary of the steps and conditions used in the synthesis of furan **191** from commercially available 2-methylcyclopentane-1,3-dione, via Barton-McCombie deoxygenation of thionocarbonate **143** to give acetal **131**, and subsequent protection of alcohol **160** as a TIPS ether. Protection of **160** as a benzyl ether did afford known trans-hydrindanone **12**, but this was unable to be annelated to the corresponding furan **166**.*

The third objective of the project was to investigate the relevant cycloaddition methodologies for construction of the oxabicyclo[3.2.1]octane subunit of dictyoxetane from tetrasubstituted furan **191** (Scheme 63). Treatment of **191** with either **193** or **41** (Hoffmann's conditions)[144] failed to generate the corresponding oxabicycle **195**, despite the success

experienced in the group's cyclohexanone-derived model system. Meanwhile, reaction of **191** with siloxyacrolein **73** (Harmata's conditions)[53] generated four new compounds **196a-d**, all isomers of the desired empirical structure. Although the desired isomer **196c** was one of two predominantly formed from the reaction, the combined yield was low and separation from other constituents difficult, preventing further study.



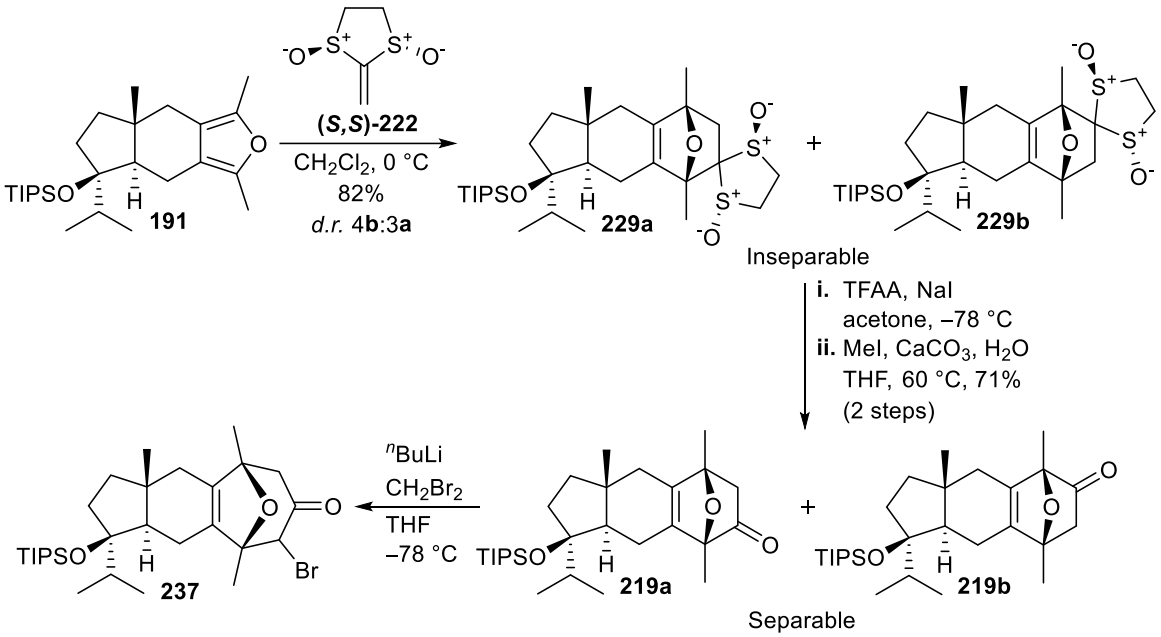
Scheme 63: *A summary of the results from attempted cycloaddition of furan **191** with the oxyallyl cation precursors **193/41** (Hoffmann[35]), **73** (Harmata[53]), and TCA/PCA (Föhlisch[25]), as well as with TBCP (Tobey[24]), to access oxabicyclic ring systems **195**, **196a-d**, **198a/b**, or **216** via **214a-d**, respectively.*

Use of either TCA or PCA (Föhlisch conditions)[25] afforded an inseparable mixture of oxabicyclic ketones **198a/b** from reaction of furan **191** in 80% and 59% combined yield respectively (Scheme 63). Significantly, the observed *d.r.* changed from 1.4:1 using TCA to 4:1 using PCA. Attempts to develop ketones **198a/b** toward dictyoxetane were unsuccessful.

The final cycloaddition method investigated the use of halocyclopropenes (Tobey).[24] Reaction of TBCP with furan **191** generated four tetrabromooxabicycles **214a-d** in excellent yield (Scheme 63). However, while attempts to converge the regioisomers by applying the work of Khlevin *et al.* provided some evidence for the formation of enones **215a-d**, synthesis of diketone **216** was not achieved.[43]

Altogether, the investigation of cycloaddition conditions has highlighted several flaws in the application of current methodology for the construction of oxabicyclo[3.2.1]octane ring systems from chiral furans such as **191**, particularly where substrate control is required to impart selectivity.

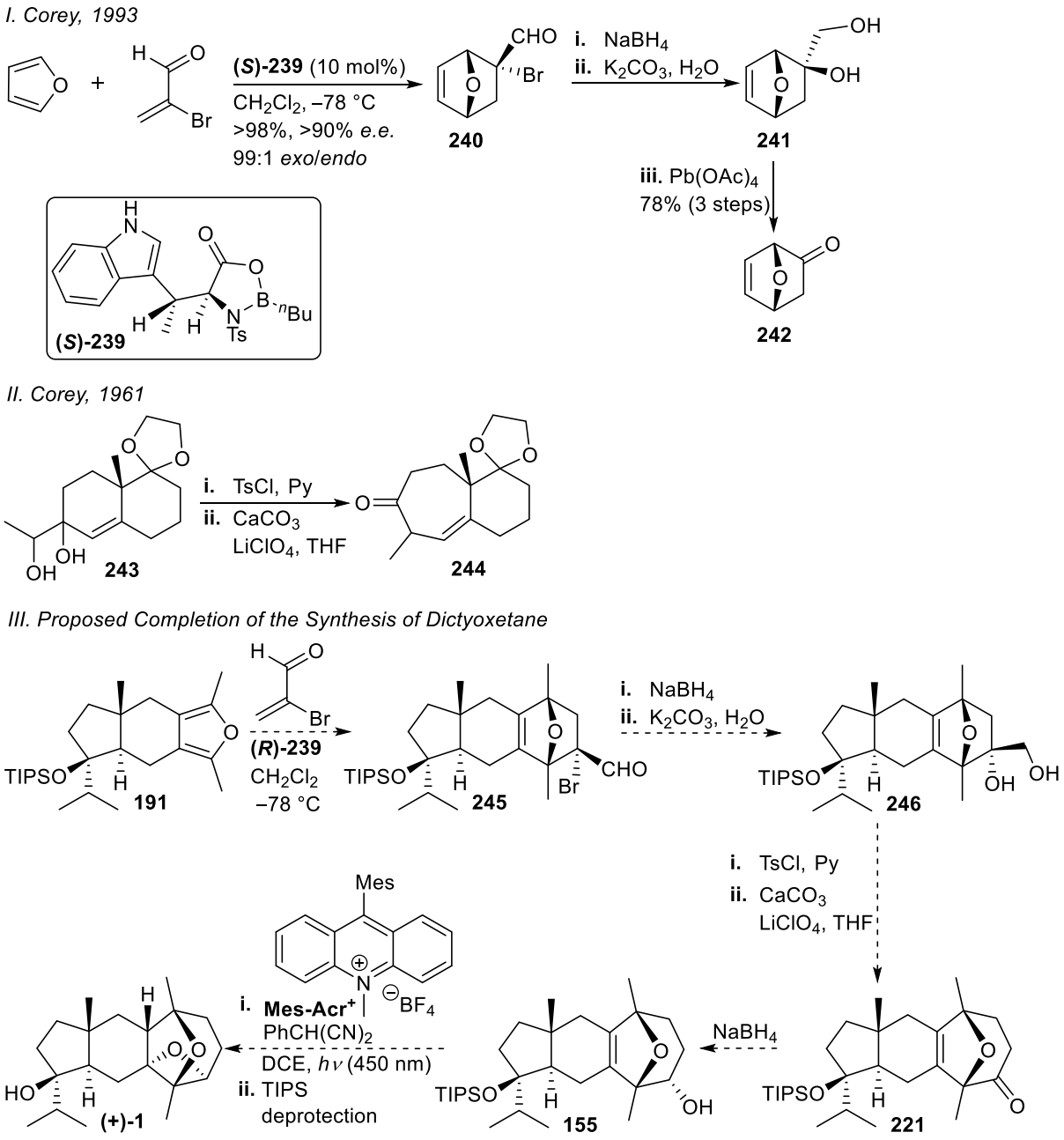
As part of a new approach, reaction of furan **191** with Aggarwal's chiral ketene equivalent **(*S*,*S*)-222** afforded a mixture of bissulfoxides **229a/b** in 82% combined yield (Scheme 64).[133] The absolute structures of **229a/b** were inferred from subsequent crystal structures of the separable oxanorbornenones **219a/b**, obtained from removal of the bissulfoxide auxiliary. The X-ray data showed a selectivity of **(*S*,*S*)-222** for reaction with the lower face of furan **191**. To access the oxabicyclic ring system, the ring-expansion of oxanorbornenone **219a** was attempted (Scheme 64). However, use of TMS-diazomethane, in a combination of Vogel and Lee's work,[58,59] was unsuccessful without a clear cause, while application of Yamamoto's dibromomethane ring-expansion of **219a** produced α-bromo ketone **237**,[141,142] resulting from ring-expansion prior to the addition of ^{n}BuLi.



Scheme 64: *Synthesis of oxanorbornenones **219a/b** from the cycloaddition of furan **191** with **(S,S)-222** and subsequent bissulfoxide auxiliary removal. Ring-expansion of **219a** using Yamamoto's[141,142] conditions afforded only undesired bromoketone **237**.*

3.2. Future Work

Further work should first focus on improving the synthesis of oxanorborneone **219a** by increasing the selectivity of the cycloaddition step. Purification of chiral sulfoxide **222**, either on alumina or florisil, to remove impurities may allow for compatibility with the use of Lewis acids in the cycloaddition with furan **191**, enabling access to lower temperatures, and thus higher selectivity. Alternatively, Corey *et al.* have reported the use of chiral oxazaborolidine **239**, derived from (*S*)-tryptophan, in the cycloaddition of furan and 2-bromoacrolein (Scheme 65, I).[145–147] The synthesis of oxanorbornene **240** was achieved in high yield and selectivity using 10 mol% of **239**, and in three further steps oxanorbornenone **242** was accessed. There is also literature precedent for the pinacol rearrangement of diol **243**, *via* the tosylate, to the ring-expanded ketone **244** from Corey's synthesis of longifolene (Scheme 65, II).[148] Using **(*R*)-239**, derived from (*R*)-tryptophan, in a cycloaddition of furan **191** and 2-

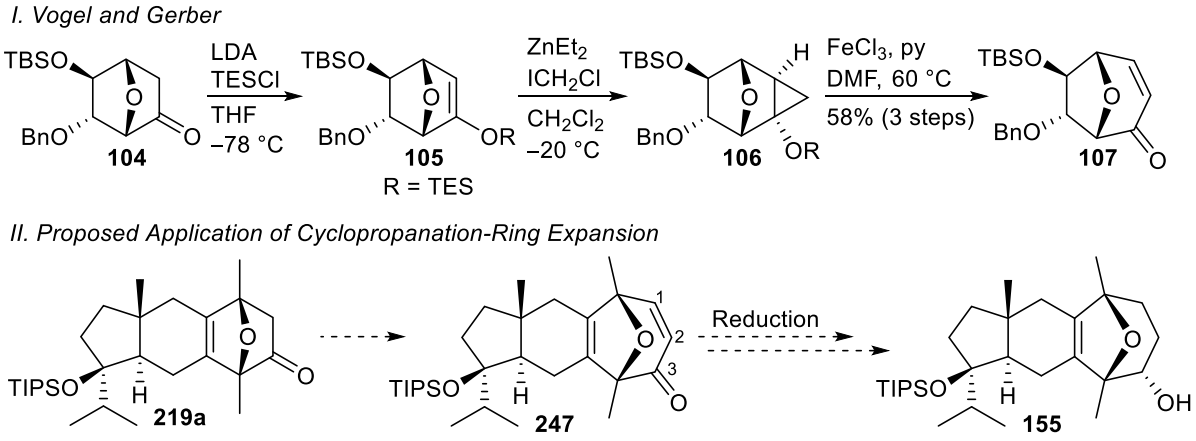


Scheme 65: *I. Corey et al.'s synthesis of oxanorborneone **242** via the Diels-Alder reaction of furan and 2-bromoacrolein, catalysed by **239**, and manipulation of the resulting bromoaldehyde by way of diol **241**.[145-147] II. Corey et al.'s pinacol rearrangement to induce ring-expansion of **243** to **244** in the total synthesis of longifolene.[148] III. Proposed application of Corey's Diels-Alder using **(R)-239** in the reaction of furan **191** with 2-bromoacrolein to access oxanorbornene **245**, which could in turn be transformed into diol **246** and undergo ring-expansion to ketone **221**. Completion of the synthesis from **221** would then require a ketone reduction, oxetane formation, and TIPS deprotection.*

bromoacrolein (Scheme 65, III) may effect a more selective transformation than previously observed for the synthesis of **229a/b**. Bromoaldehyde **245** could then be converted to diol

246, which could undergo a pinacol rearrangement to the ring-expanded ketone **221**. Reduction of **221** would then afford oxabicyclic alcohol **155**, a substrate for the Nicewicz hydroetherification conditions, previously trialled in the group's cyclohexanone model study (section 1.2.5.), to form the oxetane ring.[81,82] Upon successful installation of the oxetane, the synthesis of (+)-dictyoxetane would be completed by removal of the TIPS groups from the tertiary alcohol.

Should the pinacol rearrangement not work, or give the wrong selectivity, another ring-expansion protocol to the oxabicyclo[3.2.1]octane framework can be found in Vogel and Gerber's synthesis of oxabicyclo[3.2.1]octenone **107** *via* the cyclopropanation of silyl enol ether **105** to afford cyclopropane **106** (Scheme 66, I).[63] Vogel and Gerber's method has the advantage that the ketone function can only be produced at C_3 of the resulting oxabicyclo[3.2.1]octene, avoiding the issue observed with the formation of ketone **237** (Scheme 64), where the carbonyl is at the C_2 position. Reduction of **247** would then afford oxabicyclic alcohol **155**, which could complete the synthesis as described above.



Scheme 66: *I. Vogel and Gerber's one carbon ring-expansion of oxanorborneone **104**, via the cyclopropanation of silyl enol ether **105**, to give oxabicyclo[3.2.1]octane **107**.[63] II. Proposed application of the cyclopropanation ring-opening ring-expansion on ketone **219a** to oxabicyclic enone **243**, and subsequent transformation to oxabicyclic alcohol **155**.*

4. Experimental

4.1. General Experimental

4.1.1. Reagents and Solvents

All reagents were bought commercially from either Sigma-Aldrich (Merck), Alfa Aesar, Acros Organics, Fisher Scientific, VWR, or Fluorochem, and were used as sold unless stated. ^{i}PrMgCl was bought as a 2 M solution in THF and titrated against a solution of menthol (2.5 mmol) and 1,10-phenanthroline; MeMgCl was bought as a 3 M in THF, and titrated the same way.[149] ^{n}BuLi was bought as a 2.5 M in hexanes and titrated with menthol and the indicator 'blue'.[150] PPh_3 was recrystallised via a two-step process: 20 g dissolved in 150 mL conc. HCl and precipitated using 150 mL H_2O, the filter cake was then recrystallised from 1:1 EtOH-Et_2O to give the purified material, stored in a dessicator cabinet with silica as the dessicant. *m*CPBA was purified by a phosphate buffer: *m*CPBA (5 g) was dissolved in Et_2O (25 mL) and washed with buffer (3 × 25 mL, [2.5 g NaOH, 27 g KH_2PO_4, 250 mL H_2O]), then dried over $MgSO_4$, filtered and concentrated under reduced pressure [**CAUTION! Detonation Risk**]. MeI, TESCl, TIPSCl, TMSCl, and AcBr were passed through either basic alumina or K_2CO_3 immediately prior use. All solvents were bought from one of the above suppliers and used without further drying or purification unless stated below. Any solvents that were dried were stored under argon in a round-bottom flask sealed with a rubber septum. Before and after every use the flask was flushed with argon gas. MeOH, toluene, THF, CH_2Cl_2, Et_2O, and DMF were dried over 3 Å molecular sieves for at least 24 h before use to ensure low-water content.[151] MeCN was distilled from CaH_2 onto 3 Å molecular sieves and stored for at least 24 h before use. Et_3N, 2,6-lutidine, and pyridine were distilled from CaH_2 and stored over KOH. Acetone and MVK were

distilled freshly from K_2CO_3. H_2O was used in a deionised state as provided by a water deioniser. Petroleum ether refers to the fraction with boiling point 40–60 °C. All aqueous solutions are saturated unless stated otherwise. All mol/mmol amounts of reagents supplied as solutions or suspensions refer to the intended stoichiometry; this mostly pertains to the use of mineral dispersions such as NaH.

4.1.2. Analysis

Silica gel on aluminium-backed TLC plates were used for reaction monitoring, supplied from Merck (60F254). The plates were visualised by UV (254 nm) and standard laboratory agents: $KMnO_4$, anisaldehyde, vanillin, iodine powder. Purification by flash column chromatography was performed on Sigma-Aldrich/Fluorochem silica gel, pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size.[152] Infra-red spectra were recorded neat (oil), thin-film, or with the aid of an ATR-attachment (solid) on a Perkin Elmer Spectrum 100 FT-IR spectrometer, only selected absorbances ($\tilde{\nu}_{max}$, cm^{-1}) are reported. The following abbreviations are used when describing the data: w (weak), m (medium), st (strong), n (narrow), br (broad), sh (sharp). Melting points were recorded using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected, with three data points recorded and averaged. Samples for melting points were obtained by recrystallising a small portion of the bulk material from the solvent in brackets. Optical activities were recorded on polarimeter PolAAr 2001 and are calculated according to the following equation:

$$[\alpha]_D^{25} = \frac{[\alpha] \cdot 100}{c \cdot l}$$

Where c is concentration (g 100 mL^{-1}), l is path length (mm), and [α] is the measured optical rotation. MS data are reported as m/z (%) (relative intensity except in cases where only the parent ion is observed), from the following instruments: Bruker MicroTOF QII, Waters Xevo G2-XS, Waters GCT, and Waters LCT. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII300, Bruker AVIII400, and Bruker NEO400 in the solvents indicated. The solvent signals were used as references: residual $CHCl_3$ (^{1}H, 7.26 ppm), $CDCl_3$ (^{13}C, 77.16 ppm), residual CH_2Cl_2 (^{1}H, 5.32 ppm), CD_2Cl_2 (^{13}C, 53.84 ppm), residual C_6H_6 (^{1}H, 7.16 ppm) and C_6D_6 (^{13}C, 128.06 ppm). Coupling constants (*J*) are reported in Hz, and are reported as observed, not averaged between the two environments that share them. The following abbreviations are used to describe multiplicity in ^{1}H-NMR: m (multiplet), st (stack), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sept (septet), *ap.* (apparent) and in ^{13}C-NMR: C (quaternary), CH (tertiary), CH_2 (secondary) and CH_3 (primary). The distinction between multiplet and stack: a multiplet is a single environment that is too convoluted to establish its multiplicity correctly, a stack is where multiple environments overlap and their fidelity is lost. 1D ^{13}C NMR spectra were recorded using UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. 2D ^{1}H-^{13}C HSQC, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY and ^{1}H-^{13}C HMBC NMR spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova version 10.[153] Where data is ambiguous and absolute assignment cannot be made from the data, generic assignments are given (e.g. CH_2, 2 × 1H of CH_2), otherwise compound structures are numbered fully, not necessarily in accordance with their naming scheme, and this numbering is used to assign environments. In cases of diastereotopic protons H-#’ and H-#’’ are used when an absolute assignment cannot be made. Analytical chiral HPLC

was performed by REACH separations in Nottingham, UK, using a Lux C4 (4.6 mm × 250 mm × 5 µm); chiral column-conditions will be stated where necessary.

4.1.3. Reaction Setup

All reaction flasks were stored and dried in an oven (150 °C); reactions should be assumed to be carried out using dry glassware unless they contain or are removing H_2O. Flasks were cooled under vacuum and backfilled with argon for use. Argon gas was the chosen inert gas, lines were dried by passing the gas through drying silica, and needles were stored in a rubber septum over drying silica contained within a conical flask. Degassing refers to inserting a syringe needle into the middle of a solution and bubbling argon through at more than one bubble per second for the time stated. Reactions requiring heating were carried out using hotplates and an appropriately-sized heating block. A digital thermometer was used to establish the temperature of the hotplate and infer the temperature of the reaction flask. The following cooling baths were used: 0 °C (H_2O-ice), −40 °C (dry ice-MeCN), −78 °C (dry ice-acetone), −95 °C (N_2/MeOH). Typically, −10 to −20 °C was established by adding dry ice to acetone gently until the desired temperature was reached, monitored by thermometer, and careful maintenance of this state by further addition of dry ice as opposed to typical ice-salt-water mixtures. All reactions were stirred with Teflon-coated magnetic stirrer bars of appropriate size for the reaction volume unless stated otherwise. Filtration of the drying agent ($MgSO_4$ or Na_2SO_4) was performed under suction through glass or cotton wool. In cases where the solid was required, Whatman filter paper of an appropriate size was placed over a sintered glass funnel and the filtrate was pulled through under suction. Solvent removal was achieved using a pressure-controlled rotary evaporator at the minimum pressure required to remove

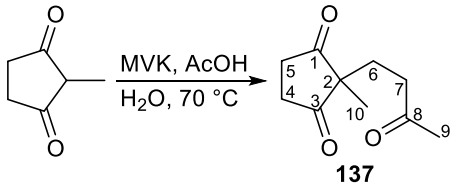
solvent until complete removal was achieved, using a typical temperature of 40-50 °C unless otherwise specified. Ultimate solvent removal was achieved under high vacuum (<10^{-2} mbar, as measured by a digital manometer) using a rotary vane pump and glass manifold setup. Flash column chromatography on silica gel was performed using a standard glass column, (or in test-scale cases a syringe) either with a sinter or using sand as a levelling-agent. Silica gel was loaded as a slurry and compacted under pressure from either a set of bellows or a fish tank pump. Fractions were collected in appropriately-sized test tubes and interrogated by TLC analysis.

4.1.4. X-Ray Diffraction Data

Suitable single crystals were selected and diffracted on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at 100.01(10) K during data collection. Using Olex2,[154] the structure was solved with the ShelXT structure solution program using intrinsic phasing and refined with the ShelXL refinement package using least squares minimisation.[155,156]

4.2. Procedures

Compound 137: 2-Methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione



Procedure adapted from a literature report.[157] 2-Methyl-1,3-cyclopentanedione (101.7 g, 0.907 mol), MVK (102 mL, 1.26 mol), and glacial AcOH (2.60 mL, 45.4 mmol) were dissolved in deionised H_2O (202 mL). The reaction vessel was shielded from light and the mixture heated at 70 °C, over which time the solution turns a reddish brown. Upon completion, the reaction mixture was cooled to 23 °C and extracted with CH_2Cl_2 (6 extracts, total volume *ca.* 1 L). The combined extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a dark brown oil. The crude material was taken forward without further purification. An analytically pure sample was obtained by vacuum distillation (<1 mbar, 120 °C) to give triketone **137** as a yellow oil.

TLC: EtOAc, R_f = 0.53 UV / $KMnO_4$

IR (neat): $\tilde{\nu}_{max}$ 2930 w (C-H), 1764 w (C=O), 1712 st (C=O)

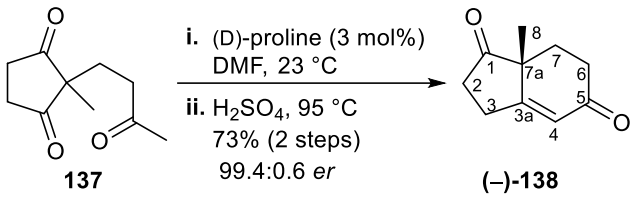
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89−2.66 (st, 4H, H-4 and 5), 2.43 (t, *J* 7.2, 2H, H-7), 2.07 (s, 3H, H-9), 1.86 (t, *J* 7.2, 2H, H-6), 1.08 (s, 3H, H-10)

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.9 (C, C-1 and 3), 207.9 (C, C-8), 55.2 (C, C-2), 37.5 (CH_2, C-7), 34.8 (CH_2, C-4 and 5), 30.1 (CH_3, C-9), 27.9 (CH_2, C-6), 19.2 (CH_3, C-10)

LRMS [TOF-EI$^+$]: *m/z* 182 (35%, $[M]^+$), 164 (15, $[M-H_2O]^+$), 154 (30), 139 (20, $[M-OCCH_3]^+$), 125 (100, $[M-H_3CCOCH_2]^+$), 97 (100, $[C_5H_5O_2]^+$), 69 (80), 55 (80)

These data are in agreement with literature reported values.[157]

Compound (−)-138: (*R*)-7a-Methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5-(*6H*)-dione



Procedure adapted from a literature report.[157]

(D)-Proline (3.13 g, 27.0 mmol) was dissolved in DMF (*ca.* 250 mL, transferred *via* cannula), and the resulting solution stirred for 1 h at 23 °C, having shielded the system from light with foil. A solution of crude triketone **137** (assume 0.907 mol) in DMF (*ca.* 110 mL) was added and the resulting mixture stirred for 6 d. Upon consumption of the starting material (50% EtOAc-petroleum ether, R_f (triketone) = 0.26, R_f (ketol) = 0.13) the reaction was heated at 95 °C. Starting at 75 °C, an aliquot of an H_2SO_4-DMF solution (20 mL, 20 mL H_2SO_4 in 60 mL DMF, kept at −20 °C) was added. After 90 min, TLC indicated full conversion and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (400 mL) and washed with $H_2SO_{4\,(aq.)}$ (2 M, 2 × 150 mL), and then $NaHCO_{3\,(aq.)}$ (2 × 180 mL). Furthermore, each aqueous wash was re-extracted with EtOAc (3 × 150 mL). All organic extracts were combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude material as a dark brown oil. Purification by flash column chromatography (50% EtOAc-petroleum ether) gave *ca.* 160 g of an orange oil that solidified. The solid was then recrystallised from Et_2O in a single batch using a seed crystal, to give **(–)-138** (108.6 g, 73% over 2 steps) as pale orange plate crystals.

TLC: 50% EtOAc-petroleum ether, R_f = 0.21 UV / Vanillin

MP: 60−62 °C (Et_2O-hexane); *Lit.*[157] 66 °C (Et_2O-hexane)

Optical Rotation: $[\alpha]_D^{25}$ = −341°, (c = 1.0, toluene); Lit.[157] $[\alpha]_D^{25}$ = +347.5−349°, (c = 1.0, toluene, opposite enantiomer)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2957 w (C-H), 2878 w (C-H), 1741 st (C=O), 1699 w (C=C), 1650 st (C=O)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (d, *J* 2.5, 1H, H-4), 2.93 (dddd, *J* 17.0, 11.0, 9.9, 2.4, 1H, H-3'), 2.83−2.66 (st, 2H, H-2' and 3''), 2.55−2.34 (st, 3H, H-2'', 6' and 6''), 2.07 (ddd, *J* 13.5, 5.2, 2.2, 1H, H-7'), 1.81 (*ap.* td, *J* 13.7, 5.4, 1H, H-7''), 1.32 (s, 3H, H-8)

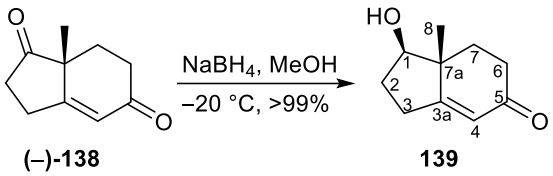
^{13}C NMR (101 MHz, $CDCl_3$): δ 216.6 (C, C-1), 198.2 (C, C-5), 169.8 (C, C-3a), 123.9 (CH, C-4), 48.8 (C, C-7a), 35.9 (CH_2, C-2), 33.0 (CH_2, C-6), 29.3 (CH_2, C-7), 26.9 (CH_2, C-3), 20.6 (CH_3, C-8)

LRMS [TOF-ES$^+$]: m/z 165 (20%, $[M+H]^+$), 123 (100, $[M-H_2CCO]^+$)

HPLC: ratio of enantiomers = 99.4:0.6 (20% MeOH: 80% CO_2, 4 mL/min, 40 °C, T_r = 1.58 min [T_r (+)-isomer = 1.74 min])

These data are in agreement with literature reported values.[157]

Compound 139: (1*R*,7a*R*)-1-Hydroxy-7a-methyl-1,2,3,6,7,7a-hexahydro-*5H*-inden-5-one



(–)-138 **139**

Procedure adapted from a literature report.[158]

(−)-138 (10.0 g, 6.09 mmol) was dissolved in MeOH (61 mL) and the resulting solution cooled to −20 °C, as measured by an internal thermometer. $NaBH_4$ (693 mg, 18.3 mmol) was added portionwise (1 portion per 5 min) over 42 min such that the internal temperature did not exceed −20 °C. The solvent was removed under reduced pressure, and the residue taken up in EtOAc (40 mL) and H_2O (30 mL). The resulting solution was brought to neutral pH (universal indicator paper) by the addition of 1 M $HCl_{(aq.)}$, turning from orange to yellow. The aqueous phase was separated, saturated with NaCl, and further extracted with EtOAc (6 × 60 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (70% → 100% EtOAc-petroleum ether) to give alcohol **139** (10.1 g, >99%) as a cream solid.

TLC: 80% EtOAc-petroleum ether, R_f = 0.22 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −73°, (c = 1.0, $CHCl_3$); *Lit.*[86] $[\alpha]_D^{25}$ = +90°, (c = 1.0, C_6H_6, opposite enantiomer)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3341 br (O-H), 2963 w (C-H), 2936 w (C-H), 1633 st (C=O), 1076 st (C-O)

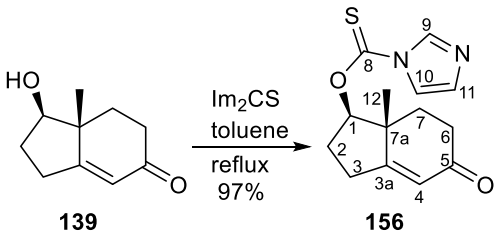
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (s, 1H, H-4), 3.83 (ddd, *J* 10.2, 7.4, 4.6, 1H, H-1), 2.69 (*ap.* ddtd, *J* 19.7, 11.6, 2.4, 0.7, 1H, H-3'), 2.58−2.28 (st, 4H, H-3'', 6', 6'' and O*H*), 2.16−2.05 (st, 2H, H-2' and 7'), 1.89−1.69 (st, 2H, H-2'' and 7''), 1.12 (d, *J* 0.7, 3H, H-8)

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6 (C, C-5), 175.6 (C, C-3a), 123.5 (CH, C-4), 80.7 (CH, C-1), 45.3 (C, C-7a), 34.2 (CH_2, C-7), 33.4 (CH_2, C-6), 29.2 (CH_2, C-2), 26.6 (CH_2, C-3), 15.2 (CH_3, C-8)

LRMS [TOF-EI$^+$]: *m/z* 166 (40%, $[M]^+$), 109 (100, $[M-HOCHCH_2CH_2]^+$)

The data are in agreement with previously recorded values.[159]

Compound 156: *O*-((1*R*,7a*R*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl) 1*H*-imidazole-1-Carbothioate



139 **156**

Procedure adapted from a literature report.[88]

Alcohol **139** (101 mg, 0.61 mmol) and thiocarbonyldiimidazole (129 mg, 0.72 mmol) were dissolved in toluene (6 mL) and the resulting mixture stirred for 5 min at 23 °C. The solution was then heated at reflux for 2 h, turning from yellow to orange. Upon completion, the reaction mixture was cooled to 23 °C and the solvent removed under reduced pressure. The crude material was purified directly by flash column chromatography (90% EtOAc-petroleum ether) to give thionocarbamate **156** (163 mg, 97%) as a yellow solid.

TLC: 80% EtOAc-petroleum ether, R_f = 0.08 UV / $KMnO_4$

MP: 86−88 °C (EtOAc-petroleum ether)

Optical Rotation: $[\alpha]_D^{25}$ = −48°, (c = 1.0, $CHCl_3$)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3142 w (C-H), 2962 w (C-H), 2927 w (C-H), 1760 w, 1667 st (C=O)

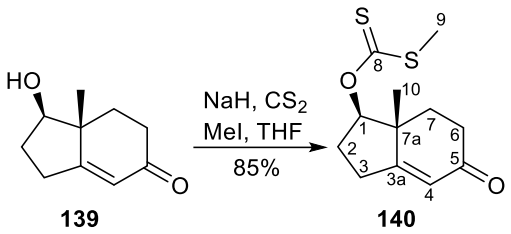
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.32 (s, 1H, H-9, 10 or 11), 7.61 (*ap.* t , *J* 1.4, 1H, H-9, 10 or 11), 7.09 (dd, *J* 1.6, 0.8, 1H, H-9, 10 or 11), 5.85 (s, 1H, H-4), 5.52 (dd, *J* 10.0, 7.3, 1H, H-1), 2.96−2.78 (m, 1H), 2.64−2.46 (st, 3H, H-6' and 2H of CH_2), 2.40 (ddd, *J* 17.9, 5.0, 2.1, 1H, H-6''), 2.13 (ddd, *J* 13.1, 5.3, 2.2, 1H, H-7'), 2.04−1.93 (st, 2H, H-7'' and 1H of CH_2), 1.35 (s, 3H, H-12)

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9 (C, C-5), 183.6 (C, C-8), 170.7 (C, C-3a), 136.8 (CH, C-9, 10 or 11), 131.2 (CH, C-9, 10 or 11), 124.2 (CH, C-4), 117.9 (CH, C-9, 10 or 11), 89.4 (CH, C-1), 45.4 (C, C-7a), 34.5 (CH_2, C-7), 33.1 (CH_2, C-6), 26.7 (CH_2, C-2 or 3), 25.8 (CH_2, C-2 or 3), 17.8 (CH_3, C-12)

LRMS [TOF-ES$^+$]: *m/z* 277 (100%, $[M+H]^+$), 217 (40), 149 (28, $[M-C_4H_3N_2OS]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{14}H_{17}N_2O_2S$): 277.1011, found: 277.1019

Compound 140: *S*-Methyl *O*-((1*R*,7a*R*)-7a-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl) carbonodithioate



139 **140**

Procedure adapted from a literature report.[76,160]

A suspension of NaH (189 mg, 3.91 mmol, 60% mineral oil dispersion) in THF (8 mL) was cooled to 0 °C, and a solution of alcohol **139** (501 mg, 3.01 mmol) in THF (7 mL) was added. The flask was raised from the cooling bath immediately after, followed by the addition of CS_2 (2.2 mL, 36.1 mmol). After 20 h, MeI (0.56 mL, 9.03 mmol) was added and the resulting solution was stirred until TLC indicated completion. Notably, the solution turns from a pale, cloudy yellow to bright red after the addition of CS_2, then to brown overnight, and back to red after the addition of MeI. Upon completion, the reaction mixture was quenched by the addition of H_2O (**Careful! Exotherm**), then partitioned with Et_2O (25 mL). The organic phase was washed with H_2O (3 × 15 mL), then the combined aqueous layers were re-extracted with Et_2O (1 × 25 mL). The organic layers were then washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (40% Et_2O-petroleum ether) to give xanthate **140** (659 mg, 85%) as an orange oil.

TLC: 50% EtOAc-petroleum ether, R_f = 0.56 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −4.1°, (c = 1.0, $CHCl_3$)

IR (neat): $\tilde{\nu}_{max}$ 2925 w (C-H), 1666 st (C=O), 1200 st, 1063 st

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dt, *J* 2.1, 1.1, 1H, H-4), 5.63−5.57 (m, 1H, H-1), 2.87−2.75

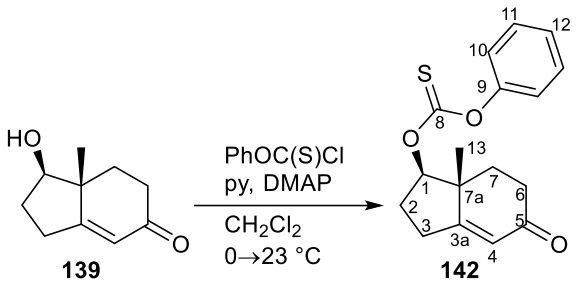
(m, 1H, H-6'), 2.57 (s, 3H, H-9), 2.55−2.43 (st, 3H, H-2', H-3', and H-6''), 2.37 (dddd, *J* 17.9, 5.2, 2.1, 0.8, 1H, H-3''), 2.10 (ddd, *J* 13.1, 5.3, 2.1 , 1H, H-7'), 1.99−1.87 (st, 2H, H-2'' and H-7''), 1.29 (d, *J* 0.7, 3H, H-10)

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.9 (C, C-8), 198.6 (C, C-5), 172.1 (C, C-3a), 123.9 (CH, C-4), 89.3 (CH, C-1), 45.6 (C, C-7a), 34.5 (CH_2, C-7), 33.3 (CH_2, C-6), 26.9 (CH_2, C-3), 26.0 (CH_2, C-2), 19.4 (CH_3, C-9), 17.5 (CH_3, C-10)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{12}H_{17}O_2S_2$): 257.0670, found: 257.0674

The data are in agreement with previously unpublished values.[76,77]

Compound 142: *O*-((1*R*,7a*R*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl) *O*-phenyl carbonothioate



Procedure adapted from a literature report.[87]

Alcohol **139** (14.00 g, 84.23 mmol) was dissolved in CH_2Cl_2 (*ca*. 168 mL, transferred *via* cannula), followed by the addition of DMAP (1.00 g, 8.40 mmol) and pyridine (27 mL, 337 mmol). The solution was cooled to 0 °C and *O*-phenyl chlorothionoformate (14.0 mL, 101 mmol) was added *via* syringe pump over 1 h, causing the solution to turn yellow from colourless. The reaction mixture was allowed to warm in the cooling bath to 23 °C. After 4 h, the solvent was removed under reduced pressure, and the residue taken up in Et_2O (100 mL) then washed with H_2O (3 × 50 mL). The aqueous phases were re-extracted with Et_2O (4 × 50 mL) and the combined organic layers were then washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an orange oil. The crude thionocarbonate was used without further purification.

An analytically pure sample was obtained by flash column chromatography (10 → 20% EtOAc-petroleum ether) to give thionocarbonate **142** as a viscous orange oil.

TLC: 80% EtOAc-petroleum ether, R_f = 0.69 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = +39°, (c = 1.0, $CHCl_3$), *Lit.*[76] $[\alpha]_D^{25}$ = −51°, (c = 1.0, $CHCl_3$, opposite enantiomer)

IR (neat): $\tilde{\nu}_{max}$ 2934 w (C-H), 1667 sh (C=O), 1189 st

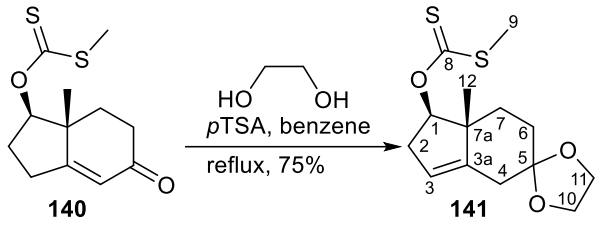
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45−7.39 (m, 2H, H-10), 7.33−7.27 (m, 1H, H-12), 7.14−7.08 (m, 2H, H-11), 5.83 (*ap.* t, *J* 1.6, 1H, H-4), 5.34−5.28 (m, 1H, H-1), 2.90−2.77 (m, 1H, H-3'), 2.62−2.46 (st, 3H, H-2',3'' and 6'), 2.41 (dddd, *J* 17.9, 5.3, 2.1, 0.9, 1H, H-6''), 2.17 (ddd, *J* 13.1, 5.3, 2.1, 1H, H-7'), 2.07−1.92 (st, 2H, H-2'' and 7''), 1.28 (d, *J* 0.7, 3H, H-13)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 198.3 (C, C-5), 194.7 (C, C-8), 171.7 (C, C-3a), 153.4 (C, C-9), 129.7 (CH, C-10), 126.8 (CH, C-12), 123.9 (CH, C-4), 121.9 (CH, C-11), 90.1 (CH, C-1), 45.2 (C, C-7a), 34.3 (CH_2, C-7), 33.2 (CH_2, C-6), 26.7 (CH_2, C-3), 25.6 (CH_2, C-2), 17.2 (CH_3, C-13)

LRMS [TOF-ES$^+$]: *m/z* 303 (85%, $[M+H]^+$), 209 (50, $[M-OPh]^+$), 149 (100, $[M-PhOCSO]^+$)

These data are in agreement with previously unpublished values.[76,77]

Compound 141: *S*-Methyl *O*-((1*R*,7a*R*)-7a-methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1',3']dioxolan]-1-yl) carbonodithioate



140 **141**

Procedure adapted from a literature report.[22]

Enone **140** (659 mg, 2.57 mmol) was dissolved in benzene (17 mL) with ethylene glycol (0.72 mL, 12.9 mmol) and *p*TSA (73 mg, 0.39 mmol). A Dean-Stark apparatus was fitted, and the trap filled with benzene. The reaction mixture was heated at reflux for 2 h at which point TLC indicated completion. The reaction mixture was cooled, neutralised with $NaHCO_{3\ (aq.)}$, and partitioned between Et_2O (20 mL) and H_2O (20 mL). The aqueous layer was re-extracted with Et_2O (1 × 20 mL), then the combined organic layers were washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (10% EtOAc-petroleum ether) to give acetal **141** (578 mg, 75%) as a pale orange oil that solidifies on standing.

TLC: 25% EtOAc-petroleum ether, R_f = 0.50 UV / Vanillin

MP: 69−72 °C (EtOAc-petroleum ether)

Optical Rotation: $[\alpha]_D^{25}$ = −32°, (c = 1.0, $CHCl_3$)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2963 n (C-H), 2938 n (C-H), 2859 n (C-H), 2888 n (C-H), 1447 w, 1422 w, 1207 m, 1091 m (C-O), 1062 st (C-O), 1043 m (C-O), 798 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (*ap.* t, *J* 7.7, 1H, H-1), 5.29−5.26 (m, 1H, H-3), 3.99−3.90 (st, 4H, H-10 and H-11), 2.95−2.86 (m, 1H, H-2'), 2.56 (s, 3H, H-9), 2.45−2.35 (st, 3H, H-2'' and 2H

of CH_2), 1.91−1.78 (st, 2H, H-7' and 1H of CH_2), 1.73−1.64 (st, 2H, H-7'' and 1H of CH_2), 1.14 (d, *J* 0.6, 3H, H-12)

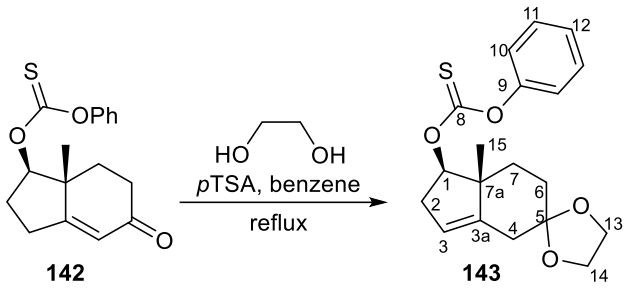
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 215.8 (C, C-8), 145.0 (C, C-3a), 119.1 (CH, C-3), 109.1 (C, C-5), 91.3 (CH, C-1), 64.64** (CH_2, C-10 or 11), 64.59** (CH_2, C-10 or 11), 47.6 (C, C-7a), 36.8 (CH_2, C-4 or 6), 36.2 (CH_2, C-7), 35.7 (CH_2, C-2), 31.3 (CH_2, C-4 or 6), 19.1 (CH_3, C-9), 16.7 (CH_3, C-12)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

HRMS [TOF-ES$^+$]: *m/z* calculated for ($[M+H]^+$, $C_{14}H_{20}O_3S_2$): 301.0932, found: 301.0938

These data are in agreement with previously unpublished values.[76,77]

Compound 143: *O*-((1*R*,7a*R*)-7a-Methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1',3']-dioxolan]-1-yl) *O*-phenyl carbonothioate



Procedure adapted from a literature report.[22]

Crude enone **142** (assumed 84.2 mmol) was dissolved in benzene (250 mL), followed by the addition of ethylene glycol (23.0 mL, 420 mmol) and *p*TSA (2.50 g, 13.2 mmol). A Dean-Stark trap and condenser were fitted, and the solution was heated at reflux for 3 d. After 1.5 d, an additional portion of ethylene glycol (6.0 mL, 108 mmol) and *p*TSA (0.50 g, 2.64 mmol) was added. Upon completion, the mixture was concentrated under reduced pressure and poured into a separating funnel with Et_2O (100 mL), then washed with $NaHCO_{3\,(aq.)}$ (3 × 50 mL). The aqueous phase was further extracted with Et_2O (1 × 50 mL) and the combined organic layers were washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude acetal as an orange solid which was used without further purification. An analytically pure sample was obtained by a series of recrystallisations (Et_2O-hexane) to give acetal **143** as cream crystals.

TLC: 20% EtOAc-petroleum ether, R_f = 0.33 UV / Vanillin

MP: 93–94 °C (Et_2O); *Lit.*[76] 84–87 °C

Optical Rotation: $[\alpha]_D^{25}$ = −7.7°, (c = 1.0, $CHCl_3$); *Lit.*[76] $[\alpha]_D^{25}$ = −128°, (c = 1.0, $CHCl_3$, opposite enantiomer)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2949 w (C-H), 2931 w (C-H), 2880 w (C-H), 1296 m, 1201 st

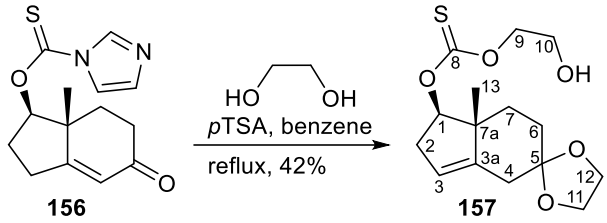
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.44−7.38 (m, 2H, H-10), 7.31−7.26 (m, 1H, H-12), 7.14−7.09 (m, 2H, H-11), 5.57 (*ap.* t, *J* 8.0, 1H, H-1), 5.31−5.28 (m, 1H, H-3), 3.96 (*ap.* qd, *J* 4.9, 2.1, 4H, H-13 and 14), 3.02−2.93 (m, 1H, H-2'), 2.51−2.38 (st, 3H, H-2'', 4' and 4''), 1.96−1.89 (m, 1H, H-7'), 1.84 (dd, *J* 14.8, 4.5, 1H, H-6'), 1.77−1.68 (st, 2H, H-6'' and 7''), 1.14 (s, 3H, H-15)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 195.1 (C, C-8), 153.6 (C, C-9), 145.0 (C, C-3a), 129.6 (CH, C-10), 126.6 (CH, C-12), 122.1 (CH, C-11), 118.9 (CH, C-3), 109.1 (C, C-5), 92.0 (CH, C-1), 64.7 (CH_2, C-13 or 14), 64.6 (CH_2, C-13 or 14), 47.2 (C, C-7a), 36.8 (CH_2, C-2 or 4), 36.2 (CH_2, C-7), 35.4 (CH_2, C-2 or 4), 31.3 (CH_2, C-6), 16.5 (CH_3, C-15)

LRMS [TOF-ES$^+$]: *m/z* 369 (80%, $[M+Na]^+$), 347 (100, $[M+H]^+$), 325 (20, $[M-OCH_2CH_2]^+$), 193 (80, $[M-PhOCSO+H]^+$)

These data are in agreement with previously unpublished values.[76,77]

Compound 157: *O*-(2-Hydroxyethyl) *O*-((*1R*,7a*R*)-7a-methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1',3']-dioxolan]-1-yl) carbonothioate (157):



Procedure adapted from a literature report.[22]

Thionocarbamate **156** (52 mg, 0.18 mmol) was dissolved in benzene (10 mL), followed by addition of ethylene glycol (0.10 mL, 1.8 mmol,) and *p*TSA (42 mg, 0.22 mmol). A Dean-Stark trap and condenser were fitted, and the solution was heated at reflux for 3 h, resulting in a pale-yellow solution. Upon completion, the solution was cooled to 23 °C and $NaHCO_{3\,(aq.)}$ (15 mL) was added while stirring for 5 min. The organic phase was separated, and the aqueous phase further extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (50% EtOAc-petroleum ether) to give thionocarbonate **157** (24 mg, 42%) as a cream solid.

TLC: 80% EtOAc-petroleum ether, R_f = 0.58 UV / $KMnO_4$

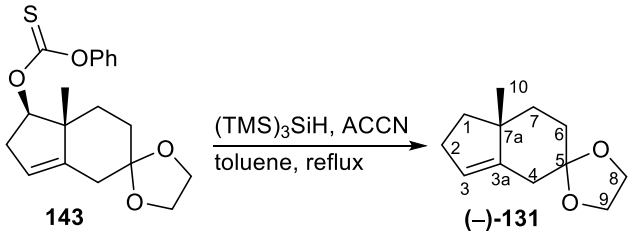
IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3391 br (O-H), 2935 n (C-H), 2887 n (C-H), 1806 w, 1775 w, 1746 w, 1454 w, 1231 m, 1088 st (C-O), 1062 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.55 (*ap.* t, *J* 7.9, 1H, H-1), 5.27 (dd , *J* 2.9, 1.4, 1H, H-3), 4.55 (ddd, *J* 6.0, 3.0, 1.2, 2H, H-9), 3.99−3.91 (st, 6H, H-10, 11, and 12), 2.89 (ddt, *J* 10.0, 7.0, 2.3, 1H, H-2'), 2.49−2.29 (st, 3H, H-2'' and 2H of CH_2), 1.97 (s, 1H, OH), 1.92−1.59 (st, 4H), 1.11 (s, 3H, H-13)

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.7 (C, C-8), 145.0 (C, C-3a), 119.0 (CH, C-3), 109.1 (C, C-5), 91.1 (CH, C-1), 74.2 (CH_2, C-9), 64.64** (CH_2, C-11 or 12), 64.58** (CH_2, C-11 or 12), 60.8 (CH_2, C-10), 47.1 (C, C-7a), 36.8 (CH_2), 36.1 (CH_2), 35.4 (CH_2, C-2), 31.3 (CH_2), 16.5 (CH_3, C-13)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

Compound (−)-131: (*R*)-7a-Methyl-1,2,4,6,7,7a-hexahydrospiro(indene-5,2'-(1',3')-dioxolane)



Procedure adapted from a literature report.[95]

Crude thionocarbonate **143** was divided between three flasks for practical reasons. A representative procedure for one of these batches follows:

Thionocarbonate **143** (*ca*. 28.9 mmol) was dissolved in wet toluene (290 mL), followed by the addition of $(TMS)_3SiH$ (10.5 mL, 34.7 mmol), and the resulting solution was degassed for 50 min. At this time ACCN (706 mg, 2.89 mmol) was added and the resulting mixture heated at reflux for 45 min. Upon cooling to 23 °C, the solvent was removed under reduced pressure and the residue taken up in Et_2O (80 mL) and washed with $HCl_{(aq.)}$ (1 M, 3 × 50 mL), then $NaOH_{(aq.)}$ (1 M, 3 × 50 mL). The aqueous phases were re-extracted with Et_2O (3 × 30 mL, 1 × 30 mL respectively) and then the combined organic extracts were washed with brine (3 × 80 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was distilled (60 °C, 10^{-1} mbar) to give acetal **(−)-131**, typically with minor silicon contaminants, as a yellowish oil (20.11 g total) which was used in the next step without further purification.

TLC: 20% EtOAc-petroleum ether, R_f = 0.33 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −27° (c = 1.0, CH_2Cl_2); *Lit.*[21] $[\alpha]_D^{20}$ = −18.7° (c = 0.83, CH_2Cl_2)

IR (neat): $\tilde{\nu}_{max}$ 2937 n (C-H), 1089 m (C-O)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (d, *J* 2.2, 1H, H-3), 3.99−3.89 (st, 4H, H-8 and 9), 2.42 (dd, *J*

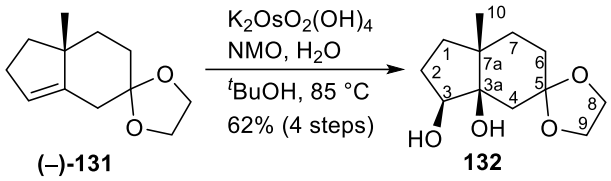
13.5, 2.5, 1H), 2.39−2.22 (st, 3H), 1.88−1.75 (st, 2H), 1.73−1.63 (st, 3H), 1.58−1.48 (m, 1H), 1.05 (s, 3H, H-10)

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.4 (C, C-3a), 122.6 (CH, C-3), 109.9 (C, C-5), 64.6 (CH_2, C-8 or 9), 64.5 (CH_2, C-8 or 9), 45.1 (C, C-7a), 40.3 (CH_2), 37.7 (CH_2), 36.2 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 22.3 (CH_3, C-10)

LRMS [TOF-EI$^+$]: *m/z* 194 (75%, $[M]^+$), 165 (40, $[M-CHO]^+$), 99 (100), 91 (85), 77 (80), 55 (35)

These data are in agreement with literature reported values.[22]

Compound 132: (3*S*,3a*R*,7a*R*)-7a-Methylhexahydrospiro(indene-5,2'-(1',3')-dioxolane)-3,3a-(4*H*)-diol



Procedure adapted from literature reports.[22]

Crude alkene **(–)-131** (assumed 60 mmol) was dissolved in ^{t}BuOH (90 mL) and H_2O (30 mL). NMO (14.8 mL, 72.0 mmol, 50 wt% aqueous solution) and $K_2OsO_2(OH)_4$ (221 mg, 0.600 mmol) were added, and the resulting solution was heated at 85 °C for 5 h. After 3 h, an additional portion of NMO (8.0 mL, 39.0 mmol) and $K_2OsO_2(OH)_4$ (50 mg, 0.14 mmol) were added. Upon completion, the solution was cooled to 23 °C, Na_2SO_3 (9.0 g, 71 mmol) and H_2O (15 mL) were added and the resulting mixture stirred for 10 min. The solution was extracted with EtOAc (150 mL, then 3 × 50 mL), saturating the aqueous phase with NaCl each time. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown oil. A solid was precipitated by glass-scratching and was purified by a series of recrystallisations (Et_2O-hexane) to give diol **132** (11.86 g, 62% over 4 steps) as tan crystals.

TLC: 50% EtOAc-petroleum ether, R_f = 0.14 Vanillin

MP: 97–99 °C (Et_2O-hexane); *Lit.*[22] 70–72 °C, *Lit.*[76] 80–84 °C

Optical Rotation: $[\alpha]_D^{25}$ = −4.6°, (c = 1.0, $CHCl_3$); *Lit.*[21] $[\alpha]_D^{20}$ = −61.8°, (c = 0.33, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3482 w br (O-H), 3344 br (O-H), 2940 w (C-H), 2888 w (C-H), 1067 m sh (C-O), 1013 m sh (C-O)

^{1}H NMR (400 MHz, C_6D_6): δ 4.33 (ddd, *J* 8.8, 5.2, 3.2, 1H, H-3), 3.55–3.34 (st, 4H, H-8 and 9), 3.02 (s, 1H, 3°-OH), 2.55 (d, *J* 3.6, 1H, 2°-OH), 1.92 (*ap.* dddd, *J* 14.1, 9.8, 8.5, 4.5, 1H, H-2'),

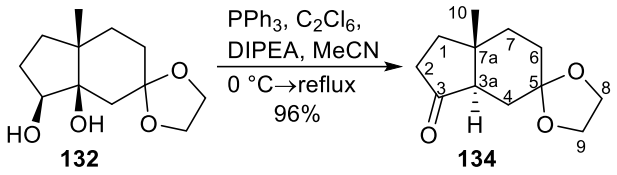
1.80−1.66 (st, 3H, H-2'' and H-4), 1.64−1.55 (st, 2H, H-1' and 1H of CH_2), 1.53−1.38 (st, 2H), 1.36−1.23 (st, 2H, H-1'' and 1H of CH_2), 1.07 (s, 3H, H-10)

^{13}C NMR (101 MHz, C_6D_6): δ 109.5 (C, C-5), 80.2 (C, C-3a), 76.5 (CH, C-3), 64.3 (CH_2, C-8 or 9), 64.0 (CH_2, C-8 or 9), 42.7 (C, C-7a), 40.5 (CH_2, C-4), 34.7 (CH_2, C-1), 32.9 (CH_2, C-6 or 7), 30.8 (CH_2, C-6 or 7), 29.2 (CH_2, C-2), 21.4 (CH_3, C-10)

LRMS [TOF-EI$^+$]: *m/z* 228 (15%, $[M]^+$), 170 (15), 99 (100)

These data are in agreement with literature reported values.[22]

Compound 134: (3a*R*,7a*R*)-7a-Methylhexahydrospiro(indene-5,2'-(1',3')-dioxolane)-3-(2*H*)-one



Procedure adapted from a literature report.[22]

A solution of PPh_3 (10.3 g, 39.4 mmol) and C_2Cl_6 (9.33 g, 39.4 mmol) in MeCN (40 mL) was stirred for 20 min. DIPEA (17.0 mL, 97.6 mmol) was added, and the resulting solution was cooled to 0 °C, followed by the addition of a solution of diol **132** (4.50 g, 19.7 mmol) in MeCN (30 mL) over 10 min. After 1 h, TLC (50% EtOAc-petroleum ether) indicated consumption of the starting diol (R_f = 0.14) and formation of the phosphorane intermediate (R_f = 0.55). The reaction mixture was heated at reflux until the intermediate spot had disappeared and a new spot (R_f = 0.50) was formed, at which time the reaction mixture was cooled to 23 °C. The solution was diluted with Et_2O (60 mL) and washed with H_2O (3 × 30 mL). The aqueous layers were further extracted with Et_2O (5 × 30 mL), and all organic extracts were combined and washed with brine (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (50% Et_2O-petroleum ether) to give ketone **134** (3.97 g, 96%) as a colourless oil that solidifies upon standing.

TLC: 50% EtOAc-petroleum ether, R_f = 0.50 Vanillin

MP: 61−63 °C (Et_2O); *Lit.*[22] 62−64 °C

Optical Rotation: $[\alpha]_D^{25}$ = −85° (c = 0.5, CH_2Cl_2), *Lit.*[21] $[\alpha]_D^{20}$ = −92.6° (c = 1.0, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2927 w (C-H), 2881 w (C-H), 2854 w (C-H), 1729 sh (C=O)

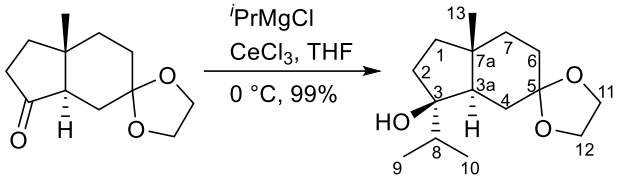
^{1}H NMR (400 MHz, C_6D_6): *δ* 3.54−3.38 (st, 4H, H-8 and 9), 2.21 (dd, *J* 12.5, 3.2, 1H, H-3a), 2.15 (*ap.* dt, *J* 13.1, 2.7, 1H, H-4'), 1.92 (*ap.* dt, *J* 9.6, 0.9, 1H, H-7'), 1.91 (*ap.* dd, *J* 9.8, 0.8, 1H, H-7''), 1.76 (*ap.* td, *J* 13.7, 4.9, 1H, H-6'), 1.63−1.46 (st, 3H, H-2', 4'' and 6''), 1.40−1.29 (st, 2H, H-1' and 2''), 1.14 (*ap.* dtd, *J* 12.2, 9.9, 1.0, 1H, H-1''), 0.51 (s, 3H, H-10)

^{13}C NMR (101 MHz, C_6D_6): *δ* 213.5 (C, C-3), 109.7 (C, C-5), 64.5 (CH_2, C-8 or 9), 64.2 (CH_2, C-8 or 9), 57.0 (CH, C-3a), 38.4 (C, C-7a), 36.0 (CH_2, C-7), 35.6 (CH_2, C-2), 35.4 (CH_2, C-1), 32.2 (CH_2, C-6), 30.6 (CH_2, C-4), 16.6 (CH_3, C-10)

LRMS [TOF-EI$^+$]: *m/z* 210 (15%, $[M]^+$), 181 (15), 154 (15), 139 (10), 112 (15), 99 (100), 86 (90), 79 (40), 67 (65)

These data are in agreement with literature reported values.[22]

Compound 160: (3*R*,3a*R*,7a*R*)-3-Isopropyl-7a-methyloctahydrospiro(indene-5,2'-(1',3')-dioxolane)-3-ol



134 **160**

Procedure adapted from literature reports.[22,96]

$CeCl_3 \cdot 7H_2O$ (25.3 g, 67.8 mmol) was placed in a Schlenk tube with a stirrer bar and heated at 160 °C under vacuum (<10^{-1} mbar) for 2.5 h. **Note:** powdered $CeCl_3$ is easily sucked through tubing, as such the Schlenk tube was angled to reduce this. The tube was cooled to 23 °C, backfilled with argon, and THF (30 mL) was added. The milky suspension was stirred overnight to form a thick slurry. At this time, ketone **134** (8.40g, 39.9 mmol) in THF (40 mL) was added and stirred for a further 30 min, causing a yellowing of the solution. The reaction mixture was then cooled to 0 °C and ^{i}PrMgCl (35 mL, 63.4 mmol, 1.81 M solution in THF) was added over 40 min. Immediately after addition, the cooling bath was removed, and the reaction mixture stirred for a further 20 min. Upon completion, Et_2O (50 mL) and H_2O (50 mL) were added to quench the reaction, then AcOH was added until the phases became clear. The organic phase was washed with H_2O (3 × 30 mL) and the aqueous layers extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (3 × 60 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give alcohol **160** (10.0 g, 99%) as cream crystals without a need for further purification.

TLC: 50% EtOAc-petroleum ether, R_f = 0.50 Vanillin

MP: 81−82 °C (Et_2O), *Lit.*[22] 62−64 °C

Optical Rotation: $[\alpha]_D^{25}$ = −13° (c = 0.5, CH_2Cl_2); *Lit.*[21] $[\alpha]_D^{20}$ = −12.6° (c = 1.0, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3508 br (O-H), 2948 (C-H), 2876 (C-H), 1087 m (C-O)

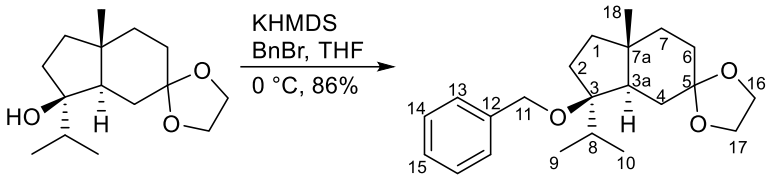
^{1}H NMR (400 MHz, C_6D_6): δ 3.62−3.56 (m, 2H, H-11 or 12), 3.55−3.50 (m, 2H, H-11 or 12), 1.93 (ddd, *J* 14.2, 11.3, 7.4, 1H), 1.88−1.78 (st, 3H, H-3a and 2H of CH_2), 1.74−1.65 (st, 3H), 1.58−1.46 (st, 4H, H-14, and 3H of CH_2), 1.13 (s, 3H, H-13), 1.04 (*ap.* qd, 1H), 0.91 (d, *J* 6.8, 3H, H-9 or 10), 0.85 (d, *J* 6.8, 3H, H-9 or 10), 0.62 (s, 1H, OH)

^{13}C NMR (101 MHz, C_6D_6): δ 110.9 (C, C-5), 82.9 (C, C-3), 64.5 (CH_2, C-11 or 12), 64.2 (CH_2, C-11 or 12), 51.2 (CH, C-3a), 41.8 (C, C-7a), 39.8 (CH_2), 37.7 (CH_2), 37.6 (CH, C-8), 36.7 (CH_2), 32.3 (CH_2), 32.0 (CH_2), 18.5 (CH_3, C-9 or 10), 18.4 (CH_3, C-13), 17.7 (CH_3, C-9 or 10)

LRMS [TOF-ES$^+$]: *m/z* 237 (100%, $[M-OH]^+$), 193 (10, $[M-OH-{}^{i}Pr]^+$)

These data are in agreement with literature reported values.[22]

Compound 161: (3*R*,3a*R*,7a*R*)-3-Benzyloxy-3-isopropyl-7a-methyloctahydrospiro(indene-5,2'-(1,3)-dioxolane)



Procedure adapted from a literature report.[21]

KHMDS (1 M in THF, 10 mL, 10 mmol) and BnBr (0.63 mL, 5.30 mmol) were added to a solution of alcohol **160** (1.12 g, 4.42 mmol) in THF (5.4 mL) at −78 °C. After 4 h, a further portion of BnBr (0.15 mL, 1.32 mmol) was added. Upon completion, the reaction mixture was quenched by the addition of $NH_4Cl_{(aq.)}$ (15 mL), diluted with Et_2O (30 mL) and washed with H_2O (3 × 15 mL), then brine (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil. The crude material was purified by flash column chromatography (10% Et_2O-petroleum ether) to give benzyl ether **161** (1.31 g, 86%) as a white solid.

TLC: 25% EtOAc-petroleum ether, R_f = 0.58 UV / Vanillin

MP: 91−92 °C (MTBE-acetone); L*it.*[76] 69−75 °C

Optical Rotation: $[\alpha]_D^{25}$ = +67° (c = 0.5, CH_2Cl_2); *Lit.*[21] $[\alpha]_D^{20}$ = +32.2° (c = 1.06, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2953 (C-H), 2876 (C-H), 1084 m (C-O)

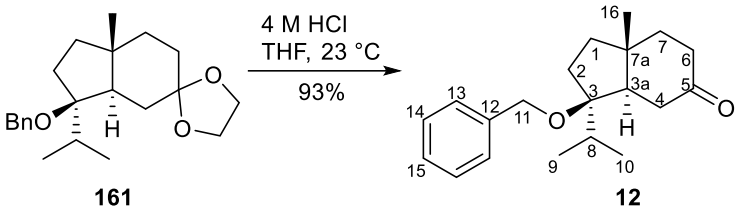
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.37−7.29 (st, 4H, H-13 and 14), 7.26−7.21 (m, 1H, H-15), 4.42 (d, *J* 1.4, 2H, H-11), 4.00−3.91 (st, 4H, H-16 and 17), 2.27 (*ap.* p, *J* 6.8, 1H, H-8), 2.18 (ddd, *J* 14.1, 11.8, 7.9, 1H), 1.97−1.78 (st, 5H, H-3a and 4H of CH_2), 1.67−1.55 (st, 3H), 1.42 (td, *J* 13.4, 4.5, 1H), 1.23−1.11 (m, 1H), 1.09 (s, 3H, H-18), 0.99 (d, *J* 6.8, 3H, H-9 or 10), 0.97 (d, *J* 6.9, 3H, H-9 or 10)

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3 (C, C-12), 128.2 (CH, C-13 or 14), 126.8 (CH, C-15), 126.7 (CH, C-13 or 14), 110.0 (C, C-5), 87.6 (C, C-3) 64.4 (CH_2, C-16 or 17), 64.3 (CH_2, C-16 or 17), 62.5 (CH_2, C-11), 48.3 (CH, C-3a), 41.8 (C, C-7a), 40.2 (CH_2), 36.9 (CH_2), 34.4 (CH_2), 33.8 (CH_2), 33.0 (CH, C-8), 31.7 (CH_2), 18.5 (CH_3, C-9 or 10), 18.2 (CH_3, C-9 or 10), 18.1 (CH_3, C-18)

LRMS [TOF-ES$^+$]: *m/z* 367 (100%, $[M+Na]^+$), 237 (50, $[M-OBn]^+$)

These data are in agreement with literature reported values.[21]

Compound 12: (3*R*,3a*R*,7a*R*)-3-Benzyloxy-3-isopropyl-7a-methyloctahydro-5*H*-inden-5-one



Procedure adapted from a literature report.[22]

Acetal **161** (10.27 g, 29.81 mmol) was dissolved in wet THF (15 mL) in air, and an aliquot of $HCl_{(aq.)}$ (15 mL of a freshly prepared 4 M solution) was added. The resulting solution was stirred vigorously overnight, with some additional portions of $HCl_{(aq.)}$ (total volume added 6 mL) added. Upon completion, the reaction was diluted with Et_2O (40 mL) washed with $NaHCO_{3\,(aq.)}$ (3 × 15 mL). The aqueous phase was re-extracted with Et_2O (3 × 40 mL), then the combined organics were washed with brine (3 × 30 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A solid was precipitated from solution by the addition of hexane (2 mL) and scratching. This was then recrystallised from hexane with a seed crystal to give ketone **12** (8.357 g, 93%) as white needle crystals.

TLC: 25% Et_2O-petroleum ether, R_f = 0.32 Vanillin

MP: 75−78 °C (hexane); *Lit.*[76] 68−71°C

Optical Rotation: $[\alpha]_D^{25}$ = +13° (c = 0.5, CH_2Cl_2); *Lit.*[21] $[\alpha]_D^{20}$ = +15.6° (c = 1.05, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2939 n (C-H), 2894 w (C-H), 2865 n (C-H), 1706 m (C=O), 1048 st (C-O)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.29 (st, 4H, H-13 and 14), 7.28−7.22 (m, 1H, H-15), 4.42 (s, 2H, H-11), 2.77 (dd, *J* 16.0, 14.5, 1H, H-4'), 2.53−2.21 (st, 5H, H-4'', H-8, and 3H of CH_2), 1.94−1.80 (st, 3H, H-3a, 2H of CH_2), 1.71 (dd, J 12.0, 7.7, 1H), 1.52 (*ap.* td, J 12.6, 5.6, 1H),

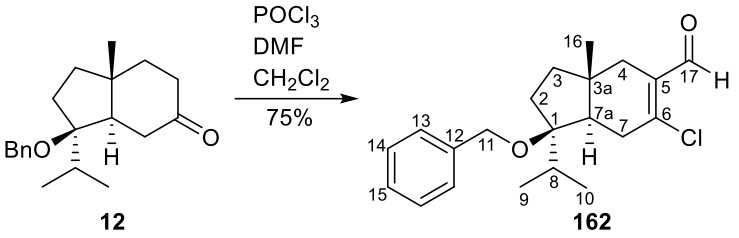
1.29−1.16 (m, 1H), 1.21 (s, 3H, H-16), 0.95 (d, J 6.8, 3H, H-9 or 10), 0.92 (d, J 6.9, 3H, H-9 or 10)

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.7 (C, C-5), 139.9 (C, C-12), 128.3 (CH, C-13 or 14), 127.1 (CH, C-15), 126.8 (CH, C-13 or 14), 87.4 (C, C-3), 62.6 (CH_2, C-11), 49.6 (CH, C-3a), 41.7 (C, C-7a), 41.6 (CH_2, C-4), 39.9 (CH_2), 37.7 (CH_2), 37.3 (CH_2), 35.1 (CH_2), 33.0 (CH, C-8), 18.3 (CH_3, C-9 or 10), 18.1 (CH_3, C-16), 17.8 (CH_3, C-9 or 10)

LRMS [TOF-ES$^+$]: *m/z* 323 (100%, $[M+Na]^+$), 207 (5), 193 (30, $[M-OBn]^+$)

These data are in agreement with literature reported values.[21]

Compound 162: (3*R*,3a*R*,7a*R*)-1-Benzyloxy-6-chloro-1-isopropyl-3a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-5-carbaldehyde



Procedure adapted from a literature report.[79]

DMF (0.12 mL, 1.5 mmol) and CH_2Cl_2 (1.2 mL) were cooled to 0 °C and $POCl_3$ (0.06 mL, 0.65 mmol) was added over 5 min. The cooling bath was removed upon complete addition, and the solution stirred for 20 min at 23 °C. At this time, ketone **12** (150 mg, 0.50 mmol) in CH_2Cl_2 (0.8 mL) was added over 5 min, causing a yellowing of the solution. After 24 h the reaction was quenched by addition of ice and solid $NaHCO_3$ until the effervescence ceased. The reaction mixture was partitioned with Et_2O (30 mL) and H_2O (20 mL). The aqueous phase was extracted with Et_2O (2 × 15 mL), and the organic layers were washed with brine (3 × 10 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The crude material was purified by flash column chromatography (10% Et_2O-petroleum ether) to give chloroacraldehyde **162** (130 mg, 75%) as a pale-yellow oil.

Notes: Removal of solvent at room temperature. This compound was stored in a freezer under argon until needed.

TLC: 25% Et_2O-petroleum ether, R_f = 0.60 UV / Vanillin

IR (neat): $\tilde{\nu}_{max}$ 2949 w (C-H), 2889 w (C-H), 2861 w (C-H), 1671 st (C=O), 1608 sh m (C=C) 1062 m (C-O), 697 m

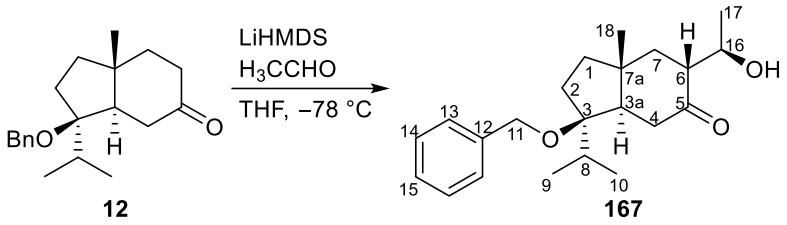
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.23 (s, 1H, H-17), 7.38−7.25 (st, 5H, H-13, 14 and 15), 4.46−4.39 (st, 2H, H-11), 3.04 (dddd, *J* 19.6, 12.2, 4.2, 2.0, 1H, H-7'), 2.55 (ddd, *J* 19.6, 5.2, 2.4, 1H, H-7''),

2.51 (dd, *J* 17.2, 2.0, 1H, H-4'), 2.32 (sept, *J* 6.8, 1H, H-8), 2.26−2.17 (m, 1H), 1.97 (d, *J* 16.9, 1H, H-4''), 1.91 (dd, *J* 13.8, 7.9, 1H), 1.76 (*ap.* ddd, *J* 12.1, 6.3, 3.0, 2H, H-7a and 1H of CH_2), 1.31−1.22 (m, 1H), 0.95 (*ap.* t, *J* 7.4, 9H, H-9, 10 and 16)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 192.0 (CH, C-17), 153.1 (C, C-6), 139.7 (C, C-12), 132.7 (C, C-5), 128.4 (CH, C-14), 127.2 (CH, C-15), 127.1 (CH, C-13), 87.3 (C, C-1), 62.9 (CH_2, C-11), 46.9 (CH, C-3a), 40.0 (C, C-7a), 39.7 (CH_2, C-2 or 3), 38.9 (CH_2, C-4), 36.7 (CH_2, C-7), 34.8 (CH_2, C-2 or 3), 33.1 (CH, C-8), 18.6 (CH_3, C-16), 18.1 (CH_3, C-9 or 10), 17.7 (CH_3, C-9 or 10)

LRMS [TOF-ES+]: *m/z* 552 (5%), 536 (5), 426 (5), 406 (25), 404 (100), 371 (15, $[M\{^{37}Cl\}+Na]^+$), 369 (50, $[M\{^{35}Cl\}+Na]^+$), 274 (55), 251 (85), 206 (95)

Compound 167: (3*R*,3a*R*,6*R*,7a*R*)-3-Benzyloxy-6-(1'-(*R*)-hydroxyethyl)-3-isopropyl-7a-methyloctahydro-5*H*-inden-5-one



This procedure was adapted from reported literature.[21,113]

A solution of ketone **12** (401 mg, 1.33 mmol) in THF (4 mL) was cooled to −78 °C and LiHMDS (1 M in THF, 1.50 mL, 1.50 mmol) was added over 2 min. After 1 h, acetaldehyde (0.22 mL, 4.0 mmol) in THF (1.3 mL) was added in two portions. After a further 85 min, the reaction mixture was allowed to warm via removal from the cooling bath, and $NH_4Cl_{(aq.)}$ (5 mL) was added. The mixture was diluted in Et_2O (10 mL) and washed with H_2O (1 × 10 mL). The aqueous phase was re-extracted with Et_2O (3 × 10 mL), and the combined organics were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was taken into the next step without further purification.

An analytically pure sample was obtained by flash column chromatography (40% Et_2O-petroleum ether) to give aldol product **167** as a pale-yellow oil.

Notes: In this instance, only a single isomer at C_{16} was detected. Later chemistry and the literature suggest there is an ca. 10:1 ratio here.

TLC: 50% Et_2O-petroleum ether, R_f = 0.26 Vanillin

IR (neat): $\tilde{\nu}_{max}$ 3459 br (OH), 2963 w (C-H), 2938 w (C-H), 2879 w (C-H), 1689 m (C=O), 1455 w (C=C), 1059 m (CO), 732 m, 697 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.30 (st, 4H, H-13 and 14), 7.28−7.23 (m, 1H, H-15), 4.42 (s, 2H, H-11), 4.13 (s, 1H, OH), 3.96 (*ap.* p, *J* 6.4, 1H, H-16), 2.77 (*ap.* td, *J* 14.8, 1.0, 1H, H-4'), 2.48

(dd, *J* 15.2, 3.5, 1H, H-4''), 2.40−2.20 (st, 3H, H-2', 6 and 8), 1.93 (t, *J* 6.4, 1H, H-7'), 1.92−1.85 (m, 1H, H-2''), 1.76−1.68 (st, 2H, H-1' and 3a), 1.26 (s, 3H, H-18), 1.26−1.17 (st, 2H, H-1'' and 8''), 1.15 (d, *J* 6.4, 3H, H-17), 0.93 (*ap.* dd, *J* 6.8, 4.3, 6H, H-9 and 10)*

**Note: this is actually a pair of doublets J 6.8 but they overlap. As such the 4.3 Hz coupling in artificial.*

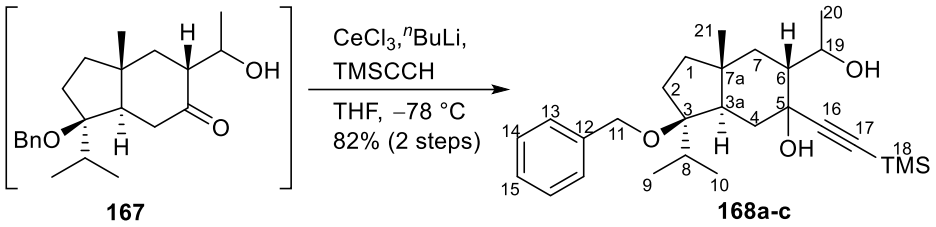
^{13}C NMR (400 MHz, $CDCl_3$): *δ* 217.5 (C, C-5), 139.7 (C, C-12), 128.4 (CH, C-13 or 14), 127.1 (CH, C-15), 126.9 (CH, C-13 or 14), 87.4 (C, C-3), 68.7 (CH, C-16), 62.6 (CH_2, C-11), 53.0 (CH, C-6), 50.4 (CH, C-3a), 42.3 (CH_2, C-4), 41.9 (C, C-7a), 41.4 (CH_2, C-7), 39.9 (CH_2, C-1), 34.9 (CH_2, C-2), 33.0 (CH, C-8), 20.2 (CH_3, C-17), 19.1 (CH_3, C-18), 18.3 (CH_3, C-9 or 10), 17.8 (CH_3, C-9 or 10)

LRMS [TOF-ES$^+$]: *m/z* 408 (100%, $[M+MeCN+Na]^+$), 367 (50, $[M+Na]^+$), 271 (50), 237 (30, $[M-OBn]^+$), 219 (30, $[M-OBn-H_2O]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{22}H_{32}O_3Na$): 367.2249, found: 367.2251

Although this compound has been reported in the literature, no data is reported for the free alcohol, only for the TBS ether.[21]

Compounds 168a-c: (3*R*,3a*R*,6*R*,7a*R*)-3-Benzyloxy-6-(1-hydroxyethyl)-3-isopropyl-7a-methyl-5-([trimethylsilyl]ethynyl)octahydro-1*H*-inden-5-ol

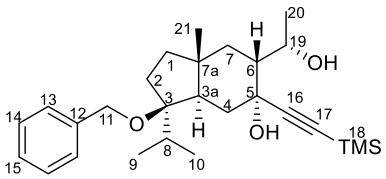


Procedure adapted from a literature report.[113]

A Schlenk tube containing $CeCl_3 \cdot 7H_2O$ (1.49 g, 3.99 mmol) was heated at 140 °C for 2 h under vacuum (<1 mbar) whilst stirring. A sintered adapter was used to prevent powdered $CeCl_3$ from being pulled through the tubing. Upon cooling, the tube was backfilled with argon, and THF (2.5 mL) was added to form a white slurry. This was left to stir under argon overnight in which time the slurry thickens. A solution of TMS-acetylene (0.55 mL, 3.99 mmol) in THF (2.4 mL) was cooled to −78 °C and ^{n}BuLi (2.0 M in hexanes, 2.0 mL, 4.0 mmol) was added over 2 min. After 20 min, the Ce slurry was cooled to −78 °C, and the Li-acetylide solution was added over 5 min, resulting in a yellow slurry. After 1 h, a solution of the crude aldol product **167** (assumed 1.33 mmol) in THF (4 mL) was added over 5 min. After 1 h, the mixture was warmed to room temperature via removal of the cooling bath and diluted with Et_2O (10 mL) and $NH_4Cl_{(aq.)}$ (3 mL). The organic layer was washed with H_2O (3 × 10 mL), the aqueous layers re-extracted with Et_2O (3 × 10 mL). Then the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (25% → 50% Et_2O-petroleum ether) to give first, diol **168c** (40 mg, 7%) as clear white crystals, then diol **168b** (45 mg, 8%) as a colourless oil that forms plate crystals on standing, and finally diol **168a** (252 mg, 43%) as a white crystalline solid. Furthermore, diols **168a** and **168b** co-eluted

to give a white solid (146 mg, 25%).

(3*R*,3a*R*,5*R*,6*R*,7a*R*)-3-Benzyloxy-6-((*S*)-1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((trimethylsilyl) ethynyl)octahydro-1*H*-inden-5-ol (168c):



TLC: 50% Et_2O-petroleum ether, R_f = 0.52 Vanillin

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3157 br (OH), 2958 n (C-H), 2903 w (C-H), 2874 w (C-H), 2169 n (C≡C), 1709 w, 1608 w (C=C), 840 st, 730 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.31 (st, 4H, H-13 and 14), 7.29−7.20 (m, 1H, H-15), 4.84−4.74 (m, 1H, H-19), 4.42 (s, 2H, H-11), 3.38 (s, 1H, 3°-OH), 2.47 (d, *J* 3.4, 1H, 2°-OH), 2.28 (sept, *J* 6.7, 1H, H-8), 2.15 (ddd, *J* 14.0, 11.7, 7.9, 1H), 2.05−1.99 (st, 2H), 1.95 (dd, *J* 10.9, 4.4, 1H, H-3a), 1.81 (dd, *J* 13.9, 8.4, 1H), 1.68 (ddd, *J* 11.8, 5.4, 1.3, 1H), 1.62 (dd, *J* 11.7, 7.8, 1H), 1.58−1.51 (st, 2H), 1.28−1.20 (m, 1H), 1.20 (d, *J* 6.5, 3H, H-20), 1.06 (s, 3H, H-21), 0.99 (d, *J* 6.9, 3H, H-9 or 10), 0.97 (d, *J* 6.7, 3H, H-9 or 10), 0.17 (s, 9H, H-18)

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3 (C, C-12), 128.3 (CH, C-13 or 14), 127.1 (CH, C-13 or 14), 127.0 (CH, C-15), 110.5 (C, C-16), 95.0* (C, C-17), 88.3 (C, C-3), 73.0 (C, C-5), 68.8 (CH, C-19), 62.9 (CH_2, C-11), 46.1 (CH, C-6), 44.2 (CH, C-3a), 41.7 (C, C-7a), 40.8 (CH_2, C-1 or 7), 38.8 (CH_2, C-4), 33.9 (CH_2, C-2), 33.2 (CH_2, C-1 or 7), 33.1 (CH, C-8), 21.7 (CH_3, C-20), 19.1 (CH_3, C-21), 18.5 (CH_3, C-9 or 10), 18.3 (CH_3, C-9 or 10), 0.2 (CH_3, C-18)

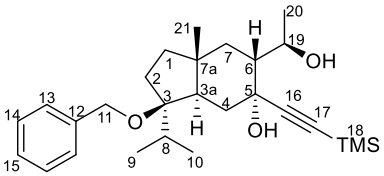
**Appeared on a JMOD experiment, but not on the ^{13}C UDEFT and as such assignment is tentative, and only assigned by comparison with the other isomers.*

LRMS [TOF-ES$^+$]: *m/z* 465 (100, $[M+Na]^+$), 317 (20, $[M-OBn-H_2O]^+$), 142 (5)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{27}H_{42}O_3SiNa$): 465.2801, found: 465.2800

(3*R*,3a*R*,5*R*,6*R*,7a*R*)-3-Benzyloxy-6-((*R*)-1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((trimethylsilyl) ethynyl)octahydro-1*H*-inden-5-ol (168b):

TLC: 50% Et_2O-petroleum ether, R_f = 0.49 Vanillin



MP: 125−128 °C (Et_2O-petroleum ether)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3347 br (OH), 2959 w (C-H), 2160 w (C≡C), 1455 w (C=C), 1249 n, 1056 m (C-O), 993 m, 840 st, 729 st

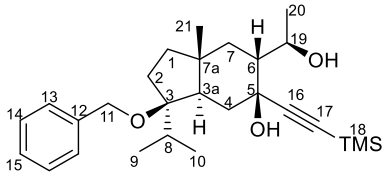
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38−7.31 (st, 4H, H-13 and 14), 7.28−7.23 (m, 1H, H-15), 4.41 (s, 2H, H-11), 4.00 (*ap.* p, *J* 6.4, 1H, H-11), 2.92 (br s, 1H, OH), 2.71 (br s, 1H, OH), 2.28 (sept, *J* 6.8, 1H, H-8), 2.20−2.00 (st, 3H, H-2' and 4), 1.93−1.76 (st, 3H, H-3a, 6 and H-2''), 1.59 (dd, *J* 11.7, 7.8, 1H, H-1'), 1.49 (dd, *J* 12.6, 4.5, 1H, H-7'), 1.39 (*ap.* d, *J* 12.7, 1H, H-7''), 1.33 (d, *J* 6.5, 3H, H-20), 1.20−1.11 (m, 1H, H-1''), 1.07 (s, 3H, H-21), 1.00 (d, *J* 6.9, 3H, H-9 or 10), 0.97 (d, *J* 6.7, 3H, H-9 or 10), 0.17 (s, 9H, H-18)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 140.2 (C, C-12), 128.3 (CH, C-13 or 14), 127.1 (CH, C-13 or 14), 127.0 (CH, C-15), 112.1 (C, C-16), 89.7 (C, C-17), 88.3 (C, C-3), 71.3 (CH, C-19), 69.2 (C, C-5), 62.9 (CH_2, C-11), 48.3 (CH, C-6), 44.0 (CH, C-3a), 42.0 (C, C-7a), 40.6 (CH_2, C-1), 40.5 (CH_2, C-7), 39.5 (CH_2, C-4), 34.0 (CH_2, C-2), 33.1 (CH, C-8), 22.8 (CH_3, C-20), 19.0 (CH_3, C-21), 18.5 (CH_3, C-9 or 10), 18.3 (CH_3, C-9 or 10), 0.0 (CH_3, C-18)

LRMS [TOF-ES$^+$]: *m/z* 907 (15%, $[2M+Na]^+$), 620 (10), 465 (100, $[M+Na]^+$), 333 (15, $[M-H_2O-Bn]^+$), 317 (50, $[M-OBn-H_2O]^+$), 245 (5, $[317-TMS]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{27}H_{42}O_3SiNa$): 465.2801, found: 465.2802

(3*R*,3a*R*,5*S*,6*R*,7a*R*)-3-Benzyloxy-6-((*R*)-1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((trimethylsilyl) ethynyl)octahydro-1*H*-inden-5-ol (168a):



TLC: 50% Et_2O-petroleum ether, R_f = 0.37 Vanillin

MP: 100−103 °C (acetone)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3382 br (OH), 3285 br (OH), 2963 w (C-H), 2942 w (C-H),

2851 w (C-H), 2160 n (C≡C), 1453 n (C=C), 1250 m, 1090 m (CO), 842 st, 729 st

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35−7.27 (st, 4H, H-13 and 14), 7.25−7.19 (m, 1H, H-15), 4.87 (s, 1H, 3°-OH), 4.44 (d, *J* 12.0, 1H, 11'), 4.38 (d, *J* 12.0, 1H, H-11''), 4.13 (dqd, *J* 9.3, 6.2, 3.6, 1H, H-19), 2.58 (d, *J* 3.6, 1H, 2°-OH), 2.28 *(*sept*, J* 6.8, 1H, H-8), 2.19−2.09 (st, 2H, H-2' and 4'), 1.98 (*ap.* t, *J* 12.8, 1H, H-4''), 1.86−1.75 (st, 3H, H-2'', 3a, and 6), 1.59 (dd, *J* 11.5, 7.9, 1H, H-7'), 1.53 (dd, *J* 12.7, 4.1, 1H, H-1'), 1.23 (d, *J* 6.2, 3H, H-20), 1.15−1.09 (m, 1H, H-7''), 1.08 (s, 3H, H-21), 1.00 (d, *J* 6.8, 3H, H-9 or 10), 0.98 (d, *J* 6.8, 3H, H-9 or 10), 0.94 (m, 1H, H-1''), 0.19 (s, 9H, H-18)

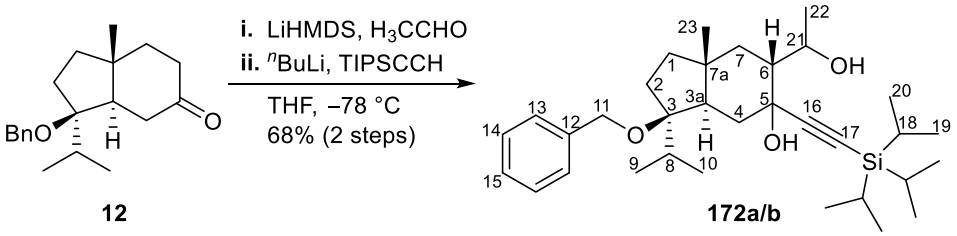
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 140.2 (C, C-12), 128.2 (CH, C-13 or 14), 126.8 (CH, C-15), 126.7 (CH, C-13 or 14), 108.2 (C, C-16), 90.1 (C, C-17), 87.6 (C, C-3), 75.2 (C, C-5), 72.6 (CH, C-19), 62.5 (CH_2, C-11), 49.5 (CH, C-6), 47.9 (CH, C-3a), 42.1 (C, C-7a), 40.8 (CH_2, C-1), 40.6 (CH_2, C-7), 38.1 (CH_2, C-4), 34.3 (CH_2, C-2), 32.9 (CH, C-8), 22.7 (CH_3, C-20), 19.8 (CH_3, C-21), 18.3 (CH_3, C-9 or 10), 18.0 (CH_3, C-9 or 10), 0.3 (CH_3, C-18)

LRMS [TOF-ES$^+$]: *m/z* 907 (40%, $[2M + Na]^+$), 465 (80, $[M+Na]^+$), 370 (100, $[M-TMS+H]^+$), 317 (60, $[M-OBn-H_2O]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{27}H_{42}O_3SiNa$): 465.2801, found: 465.2804

Single crystals of all three were obtained by slow evaporation of Et_2O. Crystal structures for **168a**, **168b**, and **168c** can be found in the appendix.

Compounds 172a/b: (3*R*,3a*R*,6*R*,7a*R*)-3-Benzyloxy-6-(1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((triisopropylsilyl)ethynyl)octahydro-1*H*-inden-5-ol



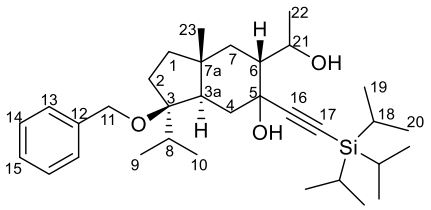
Procedure adapted from a literature report.[113]

A solution of ketone **12** (500 mg, 1.66 mmol) in THF (3.5 mL) was cooled to −78 °C and LiHMDS (1 M in THF, 1.8 mL, 1.8 mmol) was added over 2 min. After 1 h, acetaldehyde (0.14 mL, 2.49 mmol) in THF (0.5 mL) was added. After 1 h, an extra portion of acetaldehyde (0.02 mL, 0.36 mmol) was added neat. Meanwhile, TIPS-acetylene (0.82 mL, 3.65 mmol) was cooled to −78 °C and ^{n}BuLi (1.6 M in hexanes, 2.4 mL, 3.65 mmol) was added over 2 min, and the resulting solution was stirred at −78 °C for 1 h. The Li-acetylide solution was added to the aldol mixture *ca.* 1 h after the addition of acetaldehyde, over 10 min. After a further 20 min the solution was warmed by removal of the cooling bath, and diluted with Et_2O (20 mL), then washed with H_2O (2 × 15 mL). The aqueous phases were re-extracted with Et_2O (2 × 15 mL), then the combined organic layers were washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (10 → 30% Et_2O-petroleum ether) to give first, diol **172b** (123 mg, 14%) as a white solid, then diol **172a** (473 mg, 54%) as a white solid.

(3*R*,3a*R*,6*R*,7a*R*)-3-Benzyloxy-6-(1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((triisopropylsilyl)ethynyl)octahydro-1*H*-inden-5-ol (172b):

The absolute stereochemistry of this compound is unknown.

TLC: 50% Et_2O-petroleum ether, R_f = 0.50 Vanillin



MP: 130−132 °C (acetone)

Optical Rotation: $[\alpha]_D^{25}$ = +21°, (c = 0.5, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3288 br (OH), 3178 br (OH), 2941 n (C-H), 2864 n (C-H), 2161 w (C≡C), 1690 w, 1608 w, 1461 n (C=C), 1143 n, 994 m, 729 m, 665 m

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36−7.28 (st, 4H, H-13 and 14), 7.26−7.21 (m, 1H, H-15), 4.43 (d, *J* 2.2, 2H, H-11), 3.97 (*ap.* q, *J* 6.2, 1H, H-21), 2.93 (d, *J* 5.8, 1H, 2°-OH), 2.63 (s, 1H, 3°-OH), 2.28 (*ap.* p, *J* 6.8, 1H, H-8), 2.22−2.05 (m, 3H), 1.92 (ddd, *J* 12.7, 6.3, 4.5, 1H), 1.86 (dd, *J* 12.5, 3.3, 1H), 1.80 (dd, *J* 14.0, 8.4, 1H), 1.59 (dd, *J* 11.9, 7.9, 1H), 1.50 (dd, *J* 12.7, 8.1, 1H), 1.37 (d, *J* 12.6, 1H), 1.33 (d, *J* 6.4, 3H, H-22), 1.10−1.06 (st, 22H, H-18, 19, 20, and 1H of CH_2), 1.05 (s, 3H, H-23), 0.98 (*ap.* t, *J* 6.4, 6H, H-9 and 10)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 140.4 (C, C-12), 128.3 (CH, C-13 or 14), 126.8 (CH, C-15), 126.7 (CH, C-13 or 14), 114.6 (C, C-16), 88.1 (C, C-3), 85.9 (C, C-17), 71.3 (CH, C-21), 69.3 (C, C-5), 62.5 (CH_2, C-11), 48.8 (CH, C-6), 44.3 (C, C-3a), 42.0 (CH_2), 40.6 (CH_2), 40.1 (CH_2, C-4), 33.8 (CH_2), 33.0 (CH, C-8), 23.0 (CH_3, C-22), 18.9 (CH_3, C-23), 18.8 (CH_3, C-19 and 20), 18.5 (CH_3, C-9 or 10), 18.3 (CH_3, C-9 or 10), 11.3 (CH, C-18)

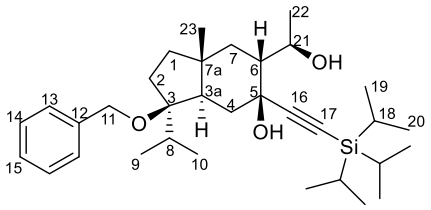
Note: C-7a was not observed.

LRMS [TOF-ES$^+$]: *m/z* 1075 (30%, $[2M+Na]^+$), 590 (100, $[M+Na+MeCN]^+$), 549 (50, $[M+Na]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{33}H_{54}O_3SiNa$): 549.3740, found: 549.3743

(3*R*,3a*R*,5*S*,6*R*,7a*R*)-3-Benzyloxy-6-((*R*)-1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-((triisopropylsilyl)ethynyl)octahydro-1*H*-inden-5-ol (172a):

TLC: 50% Et_2O-petroleum ether, R_f = 0.38 Vanillin



MP: 180−182 °C (acetone)

Optical Rotation: $[\alpha]_D^{25}$ = +78°, (c = 0.5, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3319 br (OH), 3217 br (OH), 2943 w (C-H), 2865 n (C-H), 2161 w (C≡C), 1456 w (C=C), 727 m

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35−7.27 (st, 4H, H-13 and 14), 7.25−7.20 (m, 1H, H-15), 4.79 (s, 1H, 3°-OH), 4.44 (d, *J* 12.0, 1H, H-11'), 4.38 (d, *J* 11.9, 1H, H-11''), 4.19 (*ap.* dtd, *J* 12.8, 6.4, 3.4, 1H, H-21), 2.46 (d, *J* 3.4, 1H, 2°-OH), 2.28 *(*sept*, J* 6.8, 1H, H-8), 2.25−2.08 (st, 2H, H-4' and 7'), 2.00 (*ap.* t, *J* 12.9, 1H, H-4''), 1.86−1.78 (st, 3H, H-3a, 6 and 7''), 1.59 (*ap.* dd, *J* 11.7, 7.8, 1H, H-1' or 2'), 1.53 (dd, *J* 12.8, 4.1, 1H, H-1' or 2'), 1.24 (d, *J* 6.2, 3H, H-22), 1.11−1.08 (st, 24H, H-18, 19, 20 and 23), 1.07−1.02 (st, 2H, H-1'' and 2''), 1.00 (d, *J* 6.9, 3H, H-9 or 10), 0.97 (d, *J* 6.8, 3H, H-9 or 10)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 140.2 (C, C-12), 128.2 (CH, C-13 or 14), 126.8 (CH, C-15), 126.7 (CH, C-13 or 14), 110.3 (C, C-16), 87.7 (C, C-3), 86.1 (C, C-17), 75.2 (C, C-5), 72.7 (CH, C-21), 62.5 (CH_2, C-11), 49.8 (CH, C-6), 48.1 (CH, C-3a), 42.1 (C, C-7a), 40.9 (CH_2, C-1 or 2), 40.5 (CH_2, C-1 or 2), 37.9 (CH_2, C-4), 34.1 (CH_2, C-7), 33.0 (CH, C-8), 22.7 (CH_3, C-22), 19.8 (CH_3, C-10), 18.88** (CH_3, C-19 or 20), 18.85** (CH_3, C-19 or 20), 18.3 (CH_3, C-17 or 19), 18.1 (CH_3, C-17 or 19), 11.4 (CH, C-15)

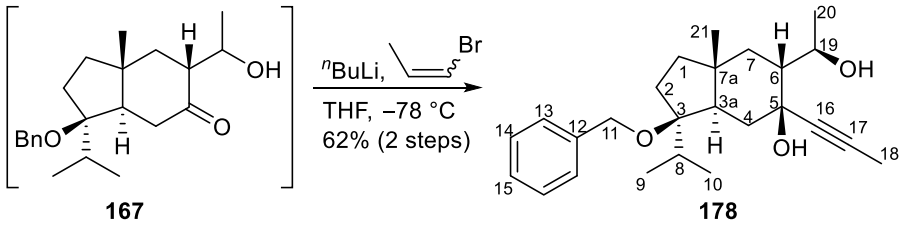
***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

LRMS [TOF-ES$^+$]: *m/z* 1075 (80%, $[2M+Na]^+$), 590 (100, $[M+MeCN+Na]^+$), 549 (50, $[M+Na]^+$), 393 (5, $[M-TIPS+H]^+$), 349 (5), 305 (5)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{33}H_{54}O_3SiNa$): 549.3740, found: 549.3743

A single crystal of **172a** was obtained by slow evaporation of acetone. The crystal structure can be found in the appendix.

Compound 178: (3*R*,3a*R*,5*S*,6*R*,7a*R*)-3-Benzyloxy-6-((*R*)-1'-hydroxyethyl)-3-isopropyl-7a-methyl-5-(prop-1-yn-1-yl)-octahydro-1*H*-inden-5-ol



Procedure adapted from a literature report.[116]

A solution of ^{n}BuLi (1.76 M in hexanes, 4.6 mL, 8.1 mmol) was added over 12 min to a solution of *trans/cis*-1-bromoprop-1-ene (0.37 mL, 4.3 mmol) in THF (10 mL) at −78 °C, monitored by an internal thermometer such that addition did not cause the solution temperature to rise above −60 °C. After 2 h, a solution of crude ketone **167** (assume 1.66 mmol) in THF (6.5 mL) was added over 80 min to maintain −78 °C throughout. After 20 min the solution was warmed by removal of the cooling bath and NH_4Cl (5 mL) added. The mixture was diluted with Et_2O (30 mL) and washed with H_2O (3 × 20 mL) and then brine (2 × 20 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (40% Et_2O-petroleum ether) to give diol **178** (398 mg, 62%) as a white solid.

Traces of one other compound, which could be an isomer, were detected by TLC but not isolated in any significant quantity or quality.

TLC: 50% Et_2O-petroleum ether, R_f = 0.2 Vanillin

MP: 145−147 °C (acetone-MTBE)

Optical Rotation: $[\alpha]_D^{25}$ = +100°, (c = 0.5, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3325 br (OH), 2962 n (C-H), 2245 w (C≡C), 1454 n (C=C), 1377 n, 1059 m (C-O), 1027 m (C-O), 907 st, 728 st

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36−7.25 (st, 4H, H-13 and 14), 7.26−7.17 (m, 1H, H-15), 4.73 (s, 1H, 3°-OH), 4.44 (d, *J* 11.9, 1H, H-11'), 4.39 (d, *J* 12.0, 1H, H-11''), 4.13 (dq, *J* 9.2, 6.2, 1H, H-19), 2.86 (s, 1H, 2°-OH), 2.28 (*ap.* p, *J* 6.8, 1H, H-8), 2.19−2.08 (st, 2H, H-2' and 4'), 1.96 (*ap.* t, *J* 12.7, 1H, H-4''), 1.90 (s, 3H, H-18), 1.87−1.71 (st, 3H, H-2'', 3a and 6), 1.59 (dd, *J* 11.7, 7.8, 1H, H-1' or 7'), 1.51 (dd, *J* 12.7, 4.1, 1H, H-1' or 7'), 1.21 (d, *J* 6.2, 3H, H-20), 1.14−1.09 (m, 1H, H-1'' or 7''), 1.08 (s, 3H, H-21), 1.00 (d, *J* 6.9, 3H, H-9 or 10), 0.96 (d, *J* 6.7, 3H, H-9 or 10)*

**A partial HSQC spectrum has been included in the appendix that shows that behind the ^{i}Pr doublets is an extra proton that cannot be determined but could be either H-1'' or 7'' by process of elimination.*

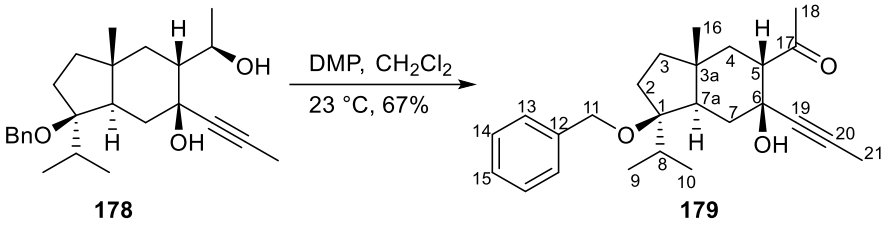
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 140.2 (C, C-12), 128.2 (CH, C-13 or 14), 126.8 (CH, C-15), 126.7 (CH, C-13 or 14), 87.7 (C, C-3), 81.7 (C, C-16 or 17), 81.4 (C, C-16 or 17), 75.4 (C, C-5), 72.6 (CH, C-19), 62.5 (CH_2, C-11), 49.6 (CH, C-6), 47.9 (CH, C-3a), 42.1 (C, C-7a), 40.8 (CH_2, C-1 or 7), 40.5 (CH_2, C-1 or 7), 38.6 (CH_2, C-4), 34.2 (CH_2, C-2), 32.8 (CH, C-8), 22.6 (CH_3, C-20), 19.8 (CH_3, C-21), 18.4 (CH_3, C-9 or 10), 18.0 (CH_3, C-9 or 10), 3.70 (CH_3, C-18)

LRMS [TOF-ES^{+}]: *m/z* 791 (15%, $[2M+Na]^{+}$), 453 (25), 407 (100, $[M+Na]^{+}$), 259 (10, $[M-H_2O-OBn]^{+}$), 247 (5)

HRMS [TOF-ES^{+}]: calculated for ($[M+Na]^{+}$, $C_{25}H_{36}O_3Na$): 407.2562, found: 407.2561

A single crystal of **178** was obtained by slow evaporation of acetone-MTBE. The crystal structure has been included in the appendix.

Compound 179: 1'-((1*R*,3a*R*,5*S*,6*S*,7a*R*)-1-Benzyloxy-6-hydroxy-1-isopropyl-3a-methyl-6-(prop-1-yn-1-yl)octahydro-1*H*-inden-5-yl)ethan-1'-one



178 **179**

Procedure adapted from a literature report.[161]

DMP (168 mg, 0.39 mmol) was added to solution of diol **178** (126 mg, 0.33 mmol) in CH_2Cl_2 (3.3 mL) and the resulting mixture stirred overnight. Upon completion, $NaHCO_{3\,(aq.)}$ (3 mL) was added and the resulting solution stirred for 5 min then poured into a separating funnel. Et_2O (20 mL) was added, and the organic layer was washed with $NaHCO_{3\,(aq.)}$ (2 × 10 mL), then brine (2 × 10 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (33% Et_2O-petroleum ether) to give ketone **179** as a white solid (81 mg, 67%).

TLC: 50% Et_2O-petroleum ether, R_f = 0.35 Vanillin

MP: 153−155 °C (acetone)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3421 br (OH), 3067 w (C-H), 2963 n (C-H), 2950 n (C-H), 2871 n (C-H), 2187 w (C≡C), 1689 sh (C=O), 1607 w, 1088 m (C-O), 733 st

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.33−7.29 (st, 4H, H-13 and 14), 7.25−7.20 (m, 1H, H-15), 4.43 (d, *J* 11.8, 1H, H-11'), 4.39 (d, *J* 11.9, 1H, H-11''), 4.29 (s, 1H, OH), 2.65 (dd, *J* 13.2, 3.9, 1H, H-5), 2.29 (*ap.* p, *J* 6.8, 1H, H-8), 2.21 (s, 3H, H-18), 2.19−2.10 (st, 2H), 2.01−1.86 (st, 4H), 1.85 (s, 3H, H-21), 1.70−1.58 (st, 2H), 1.25−1.17 (m, 1H), 1.09 (s, 3H, H-16), 0.98 (dd, *J* 8.1, 6.8, 6H)*

**This is actually two doublets (J 6.8) stacked and as such the 8.1 coupling is artificial.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.6 (C, C-17), 140.1* (C, C-12), 128.3 (CH, C-13 or 14), 126.9 (CH, C-15), 126.7 (CH, C-13 or 14), 87.6 (C, C-1), 81.5 (C, C-19 or 20), 80.9 (C, C-19 or 20), 72.1 (C, C-6), 62.6 (CH_2, C-11), 56.3 (CH, C-5), 47.8 (CH, C-7a), 42.2 (C, C-3a), 40.3 (CH_2), 40.2 (CH_2), 38.2 (CH_2), 34.2 (CH_2), 32.8 (CH, C-8), 29.8 (CH_3, C-18), 19.2 (CH_3, C-16), 18.4 (CH_3, C-9 or 10), 18.0 (CH_3, C-9 or 10), 3.7 (CH_3, C-21)

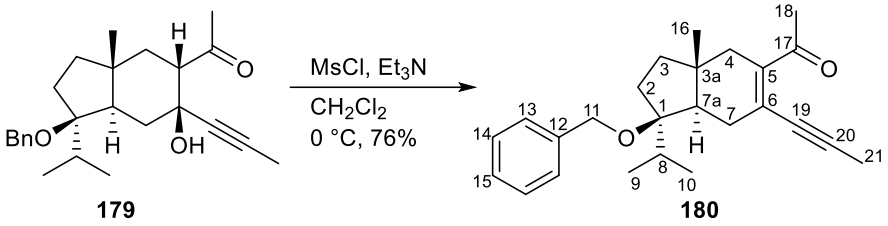
**Appears on ^{13}C UDEFT but not on the JMOD experiment, as such assignment is tentative*

LRMS [TOF-ES$^+$]: *m/z* 405 (100%, $[M+Na]^+$), 259 (10, $[M-H_2O-OBn]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{25}H_{34}O_3Na$): 405.2406, found: 405.2408

A single crystal of **179** was obtained by the slow evaporation of acetone. The crystal structure has been included in the appendix.

Compound 180: 1'-((1*R*,3a*R*,7a*R*)-1-(Benzyloxy)-1-isopropyl-3a-methyl-6-(prop-1-yn-1-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl)ethan-1'-one



Procedure adapted from a literature report.[161]

Alcohol **179** (84 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2.2 mL) with Et_3N (0.18 mL, 1.32 mmol), and the resulting solution was cooled to 0 °C. MsCl (0.04 mL, 0.51 mmol) was added dropwise over several minutes, causing the solution to turn yellow. After 20 min, TLC confirmed consumption of starting material and the reaction was quenched by the addition of solid $NaHCO_3$. The reaction mixture was taken up in Et_2O (15 mL), then washed with $NaHCO_{3\,(aq.)}$ (2 × 10 mL). The aqueous phase was further extracted with Et_2O (10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (25% Et_2O-petroleum ether) to give enynone **180** as a colourless oil (61 mg, 76%).

TLC: 50% Et_2O-petroleum ether, R_f = 0.54 UV/Vanillin

IR (neat): $\tilde{\nu}_{max}$ 2959 n (C-H), 2872 n (C-H), 2221 w (C≡C), 1655 sh (C=O), 1584 w, 1454 w, 1356 w, 1060 m (C-O), 729 m, 696 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.30 (st, 4H, H-13 and 14), 7.28−7.22 (m, 1H, H-15), 4.42 (s, 2H, H-11), 2.73 (dddd, *J* 18.5, 12.1, 4.3, 1.8, 1H, H-7'), 2.54 (s, 3H, H-18), 2.48 (dd, *J* 17.4, 1.7, 1H, H-4'), 2.36 (ddd, *J* 18.7, 5.3, 2.7, 1H, H-7''), 2.31−2.05 (st, 3H, H-4'', 8, and either H-2' or 3'), 2.03 (s, 3H, H-21), 1.86 (dd, *J* 13.7, 8.0, 1H, either H-2'' or 3''), 1.73 (dd, *J* 11.9, 7.6, 1H,

either H-2’ or 3’), 1.56 (dd, *J* 12.3, 4.9, 1H, H-7a), 1.21 (*ap.* dd, *J* 12.2, 8.1, 1H, either H-2’’ or 3’’), 0.96 (d, *J* 6.9, 3H, H-9 or 10), 0.92 (d, *J* 6.8, 6H, H-9 or 10 and 16*)

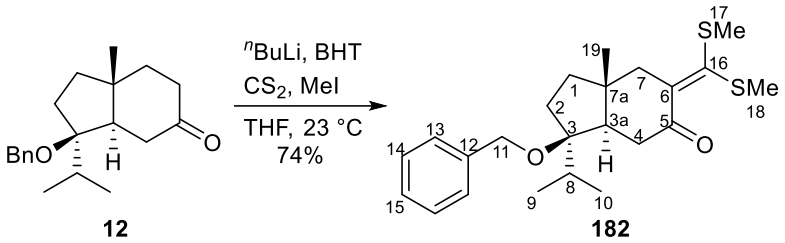
**A partial HSQC spectrum has been included in the appendix which shows the C-16 methyl signal is also here, reflected by the increased integral and peak height of half the doublet.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4 (C, C-17), 142.0 (C, C-5), 140.1 (C, C-12), 129.2 (C, C-6), 128.3 (CH, C-14), 127.0* (CH, C-13), 95.8 (C, C-19 or 20), 87.6 (C, C-1), 81.0 (C, C-19 or 20), 62.8 (CH_2, C-11), 45.7 (CH, C-7a), 41.8 (CH_2, C-4), 40.3 (CH_2, C-2 or 3), 40.0 (C, C-3a), 34.6 (CH_2, C-2 or 3), 33.4 (CH_2, C-7), 33.2 (CH, C-8), 30.6 (CH_3, C-18), 18.7 (CH_3, C-16), 18.2 (CH_3, C-9 or 10), 17.7 (CH_3, C-9 or 10), 4.9 (CH_3, C-21)

**There is one missing aromatic carbon; this peak is larger than expected and may contain two signals, see HSQC in the appendix which shows this peak correlating to two different ^{1}H environments, suggesting a co-incidence of two aromatic peaks.*

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{25}H_{32}O_2Na$): 387.2300, found: 387.2304

Compound 182: (3*R*,3a*R*,7a*R*)-3-Benzyloxy-6-(bis(methylthio)methylene)-3-isopropyl-7a-methyloctahydro-5*H*-inden-5-one



Procedure adapted from a literature report.[117,118]

A solution of BHT (33 mg, 0.15 mmol) dissolved in THF (0.35 mL) was cooled to −20 °C and ^{n}BuLi (1.76 M in hexanes, 0.09 mL, 0.15 mmol) was added. The flask was raised from the bath and a solution of ketone **12** (21 mg, 0.07 mmol) in THF (0.35 mL) was added, followed by CS_2 (0.02 mL, 0.27 mmol). The resulting solution was stirred overnight, at which point MeI (0.02 mL, 0.27 mmol) was added. After 3 h, the solution was diluted with Et_2O (10 mL), washed with H_2O (2 × 10 mL), then brine (2 × 10 mL). The organic layers were then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (10% Et_2O-petroleum ether) to give dithioacetal **182** (20 mg, 74%) as a yellow oil.

TLC: 25% Et_2O-petroleum ether, R_f = 0.4 UV/Vanillin

IR (neat): $\tilde{\nu}_{max}$ 2959 n (C-H), 2924 n (C-H), 2901 n (C-H), 1644 w sh (C=O), 1453 n (C=C), 1386 n, 1234 m, 1058 m (C-O)

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.36−7.29 (st, 4H, H-13 and H-14), 7.26−7.21 (m, 1H, H-15), 4.47−4.37 (st, 2H, H-11), 3.10 (d, *J* 16.0, 1H, H-3a), 2.82 (dd, *J* 18.2, 13.6, 1H), 2.47−2.38 (st, 2H), 2.38 (s, 3H, H-17 or 18), 2.37 (s, 3H, H-17 or 18), 2.34−2.20 (st, 2H, H-8 and 1H of CH_2),

2.00−1.92 (st, 2H), 1.76 (dd, *J* 12.0, 7.7, 1H), 1.36 (*ap.* td, *J* 2.2, 8.1, 1H), 1.01 (d, *J* 0.8, 3H, H-19), 0.96 (d, *J* 6.8, 3H, H-9 or 10), 0.92 (d, *J* 6.8, 3H, H-9 or 10)

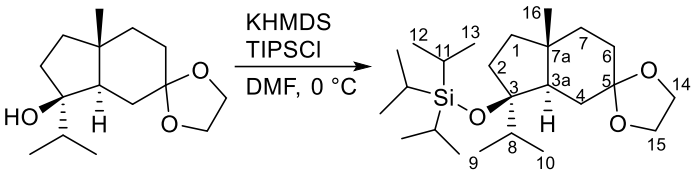
^{13}C NMR (101 MHz, CD_2Cl_2): *δ* 199.7 (C, C-5), 151.8 (C, C-16), 140.3 (C, C-12), 137.1 (C, C-6), 128.5 (CH, C-13 or 14), 127.30** (CH, C-13 or 14), 127.26** (CH, C-15), 87.9 (C, C-3), 63.1 (CH_2, C-11), 46.9 (CH_2) 46.8 (CH, C-3a), 42.3 (C, C-7a), 40.4 (CH_2), 39.5 (CH_2), 35.3 (CH_2), 33.3 (CH, C-8), 19.4 (CH_3, C-19), 18.9 (CH_3, C-17 or 18), 18.7 (CH_3, C-17 or 18), 18.2 (CH_3, C-9 or 10), 17.7 (CH_3, C-9 or 10)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

LRMS [TOF-ES$^+$]: *m/z* 427 (100%, $[M+Na]^+$), 405 (100, $[M+H]^+$), 297 (20, $[M-OBn]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{23}H_{33}O_2S_2$): 405.1922, found: 405.1920

Compound 186: Triisopropyl(((3*R*,3a*R*,7a*R*)-3-isopropyl-7a-methyloctahydrospiro(inden-5,2'-(1',3')-dioxolan)-3-yl)oxy)silane



160 **186**

Procedure adapted from the benzylation protocol detailed previously.

KHMDS (1 M in THF, 3.00 mL, 3.00 mmol) was added to a solution of alcohol **160** (500 mg, 1.97 mmol) in DMF (5 mL) and the resulting solution was cooled to 0 °C. TIPSCl (0.46 mL, 2.2 mmol) was added and the flask was raised from the cooling bath. Upon completion, the reaction mixture was diluted with Et_2O (20 mL) and washed with HCl (1 M, 3 × 15 mL). The aqueous layer was re-extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (3 × 15 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used without further purification.

An analytically pure sample was obtained by flash column chromatography (5% Et_2O-petroleum ether) to give silyl ether **186** as a colourless oil.

TLC: 50% Et_2O-petroleum ether, R_f = 0.68 Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = +28°, (c = 0.55, CH_2Cl_2)

IR (neat): $\tilde{\nu}_{max}$ 2944 n (C-H), 2866 n (C-H), 1462 w, 1079 m (C-O), 882 n, 670 m

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.99−3.89 (st, 4H, H-14 and 15), 2.12−1.95 (st, 2H), 1.91 (*ap.* p, *J* 6.8, 1H, H-8), 1.87−1.71 (st, 3H), 1.68−1.47 (st, 5H, H-3a and 4H of CH_2), 1.35 (*ap.* td, *J* 13.1, 4.4, 1H), 1.12−1.01 (st, 24H, H-11, 12, 13 and 16), 0.95 (d, *J* 6.8, 3H, H-9 or 10), 0.93 (d, *J* 6.7, 3H, H-9 or 10)

**There is an impurity at ca. 0 ppm that is difficult to remove at this stage*

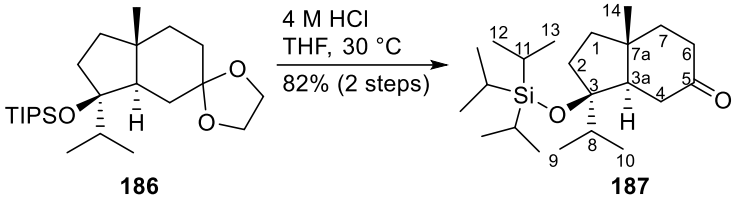
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 111.3 (C, C-5), 86.1 (C, C-3), 64.4 (CH_2, C-14 or 15), 64.3 (CH_2, C-14 or 15), 48.7 (CH, C-3a), 41.6 (CH_2), 41.5 (C, C-7a), 40.5 (CH_2), 40.1 (CH, C-8), 36.8 (CH_2), 34.3 (CH_2), 31.8 (CH_2), 19.0 (CH_3, C-16), 18.9 (CH_3, C-12 or 13), 18.8* (CH_3, C-12 or 13), 18.3 (CH_3, C-9 or 10), 14.5 (CH, C-11)

**Note: Either C-9 or 10 was not observed most likely because it co-incides with the signals for the TIPS group and in fact a shoulder can be seen at 18.8 ppm.*

LRMS [TOF-ES$^+$]: *m/z* 411 (1%, $[M+H]^+$), 237 (100, $[M-OTIPS]^+$), 193 (10, $[M-OTIPS-C_2H_4O]^+$), 175 (5)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{24}H_{47}O_3Si$): 411.3289, found: 411.3262

Compound 187: (3*R*,3a*R*,7a*R*)-3-Isopropyl-7a-methyl-3-((triisopropylsilyl)oxy)octahydro-5*H*-inden-5-one



Procedure adapted from a literature report.[22]

$HCl_{(aq.)}$ (4 M, 6.6 mL) was added to a solution of acetal **186** (assumed 1.97 mmol) in wet THF (13 mL), in air, and the resulting solution was heated at 30 °C. After 3 h, the reaction mixture was extracted with petroleum-ether (5 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (5 → 10% Et_2O-petroleum ether) to give ketone **187** (590 mg, 82% over two steps) as a colourless oil that solidifies white over time.

TLC: 25% Et_2O-petroleum ether, R_f = 0.46 Vanillin

MP: 39−41 °C (acetone)

Optical Rotation: $[\alpha]_D^{25}$ = −3.6°, (c = 0.5, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2945 n (C-H), 2866 n (C-H), 1704 st (C=O), 1463 n, 1067 m (C-O), 882 m, 675 st, 623 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (dd, *J* 15.8, 14.4, 1H, H-4'), 2.52−2.30 (st, 3H, H-4'' and H-6), 2.22−2.07 (st, 2H, H-2), 1.93 (sept, *J* 6.8, 1H, H-8), 1.84 (ddd, *J* 12.8, 7.2, 1.8, 1H, H-7'), 1.71−1.61 (st, 2H, H-1' and 3a), 1.54 (*ap.* td, *J* 12.4, 6.3, 1H, H-7''), 1.21 (s, 3H, H-14), 1.09 (st, 22H, H-11, 12, 13 and 1''), 0.91* (dd, *J* 6.8, 1.6, 6H)

**This is a pair of doublets almost completely stacked (J 6.8) and as such the 1.6 Hz coupling is unreal.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.8 (C, C-5), 86.1 (C, C-3), 50.0 (CH, C-3a), 42.3 (CH_2, C-4), 42.0 (CH_2, C-2), 41.3 (C, C-7a), 40.2 (CH_2, C-1), 39.8 (CH, C-8), 37.7 (CH_2, C-6), 37.3 (CH_2, C-7), 18.84** (CH_3, C-12 or 13), 18.79** (CH_3, C-12 or 13), 18.5 (CH_3, C-9 or 10), 18.3 (CH_3, C-14), 14.4 (CH, C-11)

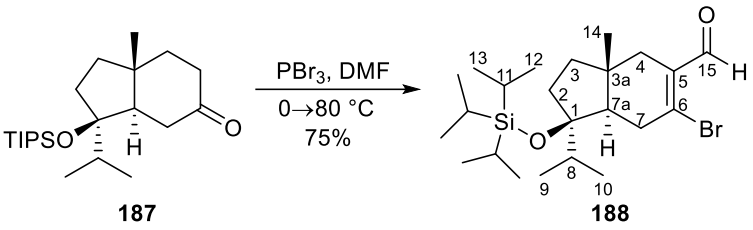
***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

Note: only one peak was observed for C-9 and 10 but 2D shows both ^{i}Pr correlate with this signal.

LRMS [TOF-ES$^+$]: *m/z* 733 (90%, $[2M+H]^+$), 559 (40, $[M+H]^+$), 407 (20, $[M+MeCN]^+$), 384 (20, $[M+H_2O]^+$), 367 (5, $[M+H]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{22}H_{42}O_2Si$): 367.3027, found: 367.3035

Compound 188: (1*R*,3a*R*,7a*R*)-6-Bromo-1-isopropyl-3a-methyl-1-((triisopropylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-indene-5-carbaldehyde



Procedure adapted from a literature report.[120]

PBr_3 (3.10 mL, 33.0 mmol) was added [**Carefully!**] to an ice-cooled solution of DMF (70 mL) over 10 min. After addition, the cooling bath was removed and the reaction mixture was stirred at 23 °C for 30 min, over which time a white slurry formed. At this time, a solution of ketone **187** (4.00 g, 10.9 mmol) in DMF (18 mL) was added and the resulting solution was heated at 80 °C for 35 min, at which time the vessel was cooled to 23 °C and $NaHCO_{3\,(aq.)}$ was added until the pH of the solution was 7, followed by H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed with H_2O (3 × 100 mL). Following a final re-extraction with CH_2Cl_2 (50 mL), the organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (2.5% Et_2O-petroleum ether) to give bromoacraldehyde **188** (3.72 g, 75%) as a white solid.

Note: solvent removal was done at ambient temperature (ca. 23 °C) as the compound is thermally unstable.

TLC: 10% Et_2O-petroleum ether, R_f = 0.53 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −81.6°, (c = 1.0, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2925 n (C-H), 2866 n (C-H), 1678 st (C=O), 1602 m (C=C), 1463 m, 1077 m (C-O), 882 m, 670 st

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.06 (s, 1H, H-15), 3.02 (dddd, *J* 19.7, 12.1, 4.2, 2.0, 1H), 2.69 (ddd, *J* 19.7, 4.9, 2.2, 1H), 2.49 (dd, *J* 16.8, 1.9, 1H), 2.14 (dd, *J* 13.7, 7.8, 1H), 2.06−1.87 (m, 3H, H-8 and 2 × 1H of CH_2), 1.68 (dd, *J* 12.1, 7.3, 1H, 1H of CH_2), 1.62 (dd, *J* 12.1, 4.9, 1H, H-7a), 1.19−1.07 (st, 22H, H-11, 12, 13, and 1H of CH_2), 0.96−0.91 (st, 6H, H-14 and either H-16 or 18), 0.88 (d, *J* 6.8, 3H, H-16 or 18)

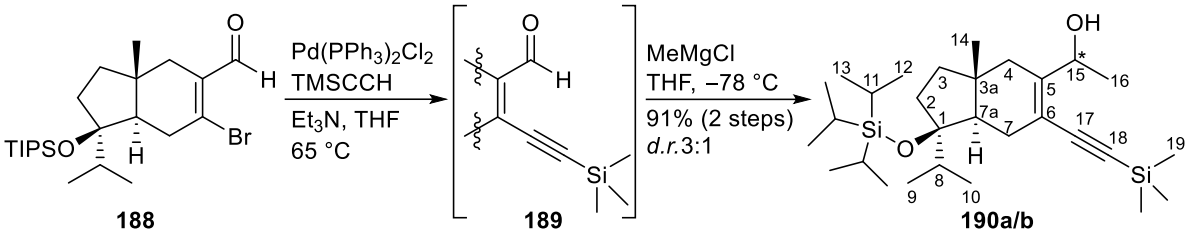
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 194.4 (CH, C-15), 145.1 (C, C-6), 134.6 (C, C-5), 85.9 (C, C-1), 48.4 (CH, C-7a), 41.4 (CH_2), 40.5 (CH_2), 40.4 (CH_2), 39.8 (CH, C-8), 39.7 (CH_2), 39.5 (C, C-3a), 18.84** (CH_3, C-12 or 13), 18.79†** (CH_3, C-12 or 13), 18.6 (CH_3, C-9, 10 or 14), 18.5 (CH_3, C-9, 10 or 14), 14.3 (CH, C-11)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†This is peak is slightly taller than the 18.84 ppm peak, and there is a ^{13}C environment missing. It has been seen in other compounds that this peak often merges into the TIPS-signals and it is likely that this is occurring here.

HRMS [TOF-ES^{+}]: calculated for ([M{^{79}Br}–OTIPS]$^{+}$, $C_{14}H_{20}O^{79}Br$): 283.0692, found: 283.0691

Compounds 190a/b: 1-([1*R*,3a*R*,7a*R*]-1-isopropyl-3a-methyl-1-[{triisopropylsilyl]oxy}-6-[{trimethylsilyl}ethynyl]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl)ethan-1-ol



Procedure adapted from a literature report.[162]

Bromide **188** (3.72 g, 8.14 mmol) was dissolved in THF (24 mL) with Et_3N (3.40 mL, 24.3 mmol) and $Pd(PPh_3)_2Cl_2$ (284 mg, 0.41 mmol). The resulting solution was degassed for 25 min, then TMSCCH (1.20 mL, 8.91 mmol) was added and the resulting mixture was heated at 65 °C. Upon completion (^{1}H NMR*), the solution was allowed to cool to 23 °C and the solvent removed under reduced pressure. The residue was taken up in hexane (30 mL) and filtered through celite to remove all solids, washing with portions of hexane. The filtrate was poured into a separating funnel and washed with MeCN (50 + 25 mL). The MeCN-phase was re-extracted with hexane (3 × 40 mL) using TLC to monitor extraction, and the combined hexane layers were washed with H_2O (3 × 40 mL), then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was used in the next step without further purification.

TLC: 10% Et_2O-petroleum ether, R_f = 0.53 UV / Vanillin*

**Starting material and product have the same R_f and dip sensitivity-as such this reaction was monitored by ^{1}H NMR of reaction aliquots taken from solution and concentrated under reduced pressure, before being taken up in the NMR solvent: CHO_{sm} 10.06 ppm, CHO_{pr} 10.26 ppm ($CDCl_3$).*

Crude enynal **189** (assumed 8.14 mmol) was dissolved in THF (18 mL) and the resulting solution cooled to −78 °C. After 10 min at this temperature, MeMgCl (5.60 mL, 12.2 mmol, 2.17 M solution in THF) was added. Upon completion, the reaction mixture was allowed to warm to 23 °C, then quenched with H_2O/NH_4Cl and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (10 → 20% Et_2O-petroleum ether) to give an isomeric mix of enynols **190a** and **190b** (3.63 g, 91% over two steps, crude *d.r.* 1:3) as an orange solid.

The isomers can be partially separated under these conditions, and as such the data is given individually.

190a:

TLC: 25% Et_2O-petroleum ether, R_f = 0.42 UV / Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −46°, (c = 0.5, CH_2Cl_2)

IR (thin film, CH_2Cl_2): $\tilde{\nu}_{max}$ 3388 br (OH), 2944 n (C-H), 2867 n (C-H), 2138 w (C≡C), 1464 w, 1249 m, 1063 m (C-O), 840 m

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.94 (qd, *J* 6.5, 4.5, 1H, H-15), 2.42 (dddd, *J* 16.8, 12.2, 4.3, 2.0, 1H), 2.25 (dd, *J* 17.4, 1.9, 1H), 2.16−2.05 (st, 2H), 2.02−1.86 (st, 4H, H-8, OH, and 2H of CH_2), 1.64 (dd, *J* 11.9, 7.3, 1H), 1.36 (dd, *J* 12.2, 4.9, 1H, H-7a), 1.27 (d, *J* 6.5, 3H, H-15), 1.14−1.05 (st, 22H, H-11, 12, 13, and 1H of CH_2), 0.95 (d, *J* 6.8, 3H, H-9 or 10), 0.93 (s, 3H, H-14), 0.87 (d, *J* 6.8, 3H, H-9 or 10), 0.20 (s, 9H, H-19)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 148.7 (C, C-5), 116.9 (C, C-6), 105.2 (C, C-17), 98.1 (C, C-18), 86.2 (C, C-1), 69.3 (CH, C-15), 46.5 (CH, C-7a), 41.3 (CH_2), 40.4 (CH_2), 40.04** (CH, C-8), 40.01**

(CH_2), 39.8 (C, C-3a), 31.2 (CH_2), 20.2 (CH_3, C-16), 18.92** (CH_3, C-14), 18.87** (CH_3, C-12 or 13), 18.8 (CH_3, C-12 or 13), 18.7 (CH_3, C-9 or 10), 18.5 (CH_3, C-9 or 10), 14.4 (CH, C-11), 0.20 (CH_3, C-19)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

LRMS [TOF-ES$^+$]: *m/z* 491 (5%, $[M+H]^+$), 327 (5, $[M-H_2O-TIPS+H]^+$), 299 (100, $[M-OTIPS-H_2O]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{29}H_{55}O_2Si_2$): 491.3735, found: 491.3725

190b:

TLC: 25% Et_2O-petroleum ether, R_f = 0.34 UV/Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −42°, (c = 0.5, CH_2Cl_2)

IR (thin film, CH_2Cl_2): $\tilde{\nu}_{max}$ 3326 br (OH), 2943 w (C-H), 2867 n (C-H), 2136 w (C≡C), 1464 w, 1249 n, 1060 m (C-O), 855 m, 840 sh

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.10 (dd, *J* 6.7, 3.0, 1H, H-15), 2.37 (tdd, *J* 14.0, 5.2, 2.7, 1H, H-7'), 2.18−1.88 (st, 6H, H-4', 4'', 7'', 8, and either H-2 or 3), 1.68−1.58 (st, 2H, OH and H-2' or 3'), 1.40 (dd, *J* 12.1, 4.9, 1H, H-7a), 1.25 (d, *J* 6.5, 3H, H-16), 1.14−1.05 (st, 22H, H-2'' or 3'', and H-11, 12, 13), 0.94 (d, *J* 6.8, 3H, H-9 or 10), 0.90 (s, 3H, H-14), 0.86 (d, *J* 6.8, 3H, H-9 or 10), 0.20 (s, 9H, H-19)

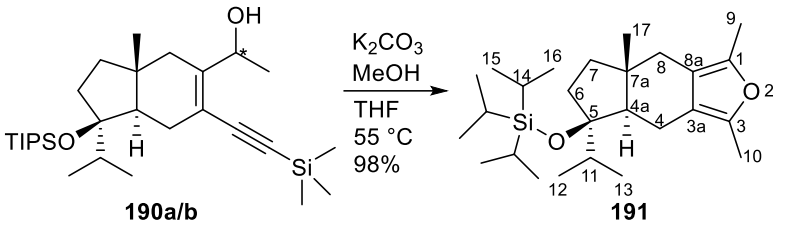
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 149.1 (C, C-5), 115.9 (C, C-6), 105.0 (C, C-17), 98.2 (C, C-18), 86.3 (C, C-1), 69.9 (CH, C-15), 46.5 (CH, C-7a), 41.2 (CH_2), 40.4 (CH_2), 40.1 (CH, C-8), 39.64** (CH_2), 39.59** (C, C-3a), 30.9 (CH_2, C-7), 21.1 (CH_3, C-16), 18.87** (CH_3, C-12 or 13), 18.85** (CH_3, C-14), 18.8 (CH_3, C-12 or 13), 18.7 (CH_3, C-9 or 10), 18.5 (CH_3, C-9 or 10), 14.4 (CH, C-11), 0.23 (CH_3, C-19)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

LRMS [TOF-ES$^+$]: *m/z* 491 (5%, $[M+H]^+$), 299 (100, $[M-OTIPS-H_2O]^+$)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{29}H_{55}O_2Si_2$): 491.3735, found: 491.3739

Compound 191: Triisopropyl(((4a*R*,5*R*,7a*R*)-5-isopropyl-1,3,7a-trimethyl-4a,5,6,7,7a,8-hexahydro-4*H*-indeno(5',6'-c)furan-5-yl)oxy)silane



Enynols **190a/b** (279 mg, 0.569 mmol) and K_2CO_3 (787 mg, 5.69 mmol) were dissolved in THF (0.95 mL) and MeOH (1.90 mL). The resulting solution was heated at 55 °C for 6 h, with an additional portion of K_2CO_3 (50 mg, 0.36 mmol) being added after 5 h. Upon completion, the reaction mixture was allowed to cool to 23 °C and was then filtered, partitioned with Et_2O (10 mL), H_2O (10 mL) and $NH_4Cl_{(aq.)}$ (1 mL). The aqueous layer was further extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (3% Et_2O-petroleum ether) to give furan **191** (234 mg, 98%) as a yellow oil.

TLC: 10% Et_2O-petroleum ether, R_f = 0.78 Vanillin

Optical Rotation: $[\alpha]_D^{25}$ = −23°, (c = 0.6, CH_2Cl_2)

IR (neat): $\tilde{\nu}_{max}$ 2939 n (C-H), 2867 n (C-H), 1603 w (C≡C), 1463 w, 1064 m (C-O), 881 m, 670 m

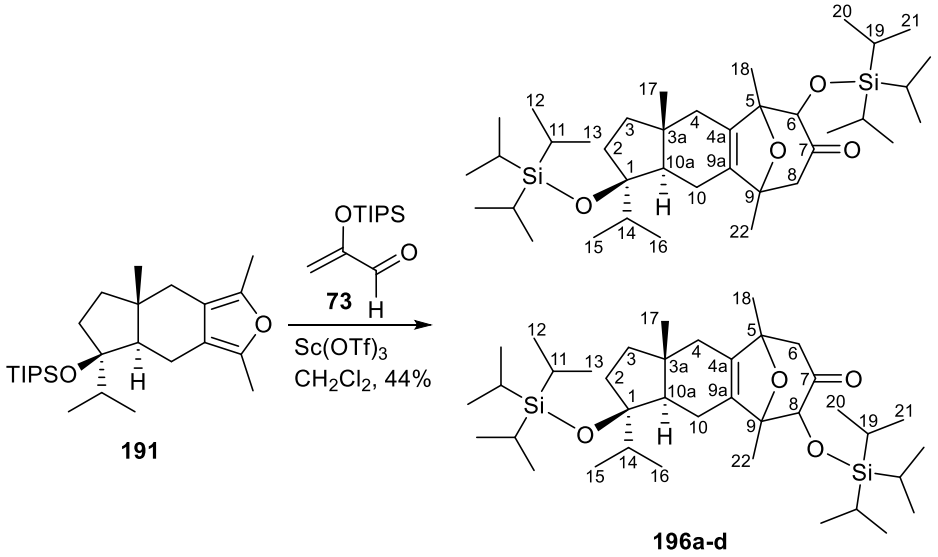
^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.49 (dddd, *J* 14.3, 12.8, 2.9, 1.5, 1H, H-4'), 2.39 (d, *J* 14.2, 1H, H-8'), 2.35 (dd, *J* 15.6, 4.9, 1H, H-4''), 2.19−2.03 (st, 3H, H-8'' and either H-6' or 7'), 2.11 (s, 3H, H-9 or 10), 2.09 (s, 3H, H-9 or 10), 1.97 (*ap*. p, *J* 6.8, 1H, H-11), 1.64 (dd, *J* 12.0, 6.8, 1H, H-6' or 7'), 1.60 (dd, *J* 12.8, 5.0, 1H, H-4a), 1.21 (dd, *J* 12.2, 4.4, 1H, H-6'' or 7''), 1.14−1.10 (st, 21H, H-14, 15 and 16), 0.97 (d, *J* 6.8, 3H, H-12 or 13), 0.96 (s, 3H, H-17), 0.91 (d, *J* 6.8, 3H, H-12 or 13)

^{13}C NMR (101 MHz, CD_2Cl_2): *δ* 143.4 (C, C-1), 143.1 (C, C-3), 118.0 (C, C-3a), 117.6 (C, C-8a), 86.1 (C, C-5), 49.0 (CH, C-4a), 42.3 (C, C-7a), 42.1 (CH_2, C-6 or 7), 40.6 (CH, C-11), 40.2 (CH_2, C-6 or 7), 36.5 (CH_2, C-8), 20.9 (CH_2, C-4), 19.3 (CH_3, C-17), 18.93** (CH_3, C-15 or 16), 18.89** (CH_3, C-15 or 16), 18.7 (CH_3, C-12 or 13), 18.4 (CH_3, C-12 or 13), 14.7 (CH, C-14), 11.7 (CH_3, C-9 or 10), 11.6 (CH_3, C-9 or 10)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{26}H_{47}O_2Si$): 419.3340, found: 419.3336

Compounds 196a-d: (1*R*,3a*R*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1,6-bis((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one
and
(1*R*,3a*R*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1,8-bis((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one



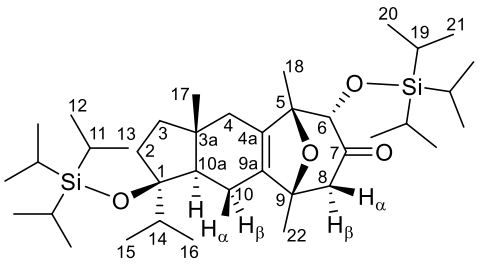
This procedure was adapted from a literature report.[53]

$Sc(OTf)_3$ (30 mg, 61 µmol) was placed in a flask with a stirrer bar and heated at 300 °C under vacuum (10^{-1} mbar) for *ca.* 2 h. Upon cooling to 23 °C, the flask was backfilled with argon, and a solution of furan **191** (257 mg, 0.61 mmol) in CH_2Cl_2 (0.6 mL) was added. The resulting mixture was stirred for 5 min, then a solution of **73** (135 mg, 0.59 mmol) in CH_2Cl_2 (0.6 mL) was added, turning the resulting mixture brown. After 22 h, the reaction mixture was washed with H_2O (15 mL) and re-extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2% → 25% Et_2O-petroleum ether) to give a mixture of ketones **196a** and **196b** (75 mg, 20%) as a

yellow oil, followed by **196c** (51 mg, 13%) as a yellow oil, and finally a mixture of **196c** and **196d** (43 mg, 11%) as a yellow oil.

(1*R*,3a*R*,5*R*,6*S*,9*R*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1,6-bis((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one (196a):

196a+b:
*Note: The pictured structure is for the major isomer "**196a**".*



TLC: 5% Et_2O-petroleum ether, R_f = 0.35 Vanillin

IR (thin film, CH_2Cl_2): $\tilde{\nu}_{max}$ 2943 n (C-H), 2866 n (C-H), 1728 sh (C=O), 1464 w, 1150 n, 1113 n, 1065 n (C-O), 670 m

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.29/**4.23** (s, 1H, H-6), 2.56/**2.54** (d, *J* 14.9, 1H, H-8$_\alpha$), 2.47/**2.41** (d, *J* 14.8, 1H, H-8$_\beta$), 2.26 (dddd, *J* 16.2, 11.8, 4.3, 2.8, 1H, H-10$_\alpha$), 2.11−1.94 (st, 4H, H-4, and either H-2 or 3), 1.88 (sept, *J* 6.8, 1H, H-14), 1.66 (ddd, *J* 17.4, 4.8, 2.1, 1H, H-10$_\beta$), 1.58 (dd, *J* 11.9, 7.2, 1H, H-2' or 3'), 1.50/**1.48** (s, 3H, H-18), 1.37/**1.36** (s, 3H, H-22),1.33 (dd, *J* 11.6, 7.0, 1H, H-10a), 1.19 (*ap.* ddt, *J* 14.1, 8.3, 6.9, 3H, H-19), 1.09 (s, 21H, H-11, 12, and 13), 1.05 (d, *J* 5.6, 10H, H-20 or 21, and either H-2'' or 3''), 1.03 (d, *J* 6.2, 9H, H-20 or 21), 0.96 (s, 3H, H-17), 0.88 (d, *J* 6.8, 3H, H-15 or 16), 0.81 (d, *J* 6.8, 3H, H-15 or 16)

**Minor compound signals have been included where possible; in this case the chemical shift in bold indicates the major compound signal, and the integrals throughout reflect the number of major-compound protons per environment; this may alter the order of peaks. **There is an aromatic impurity contributing peaks around the solvent ca. 7.26 ppm (see appendix for spectra).*

^{13}C NMR (126 MHz, $CDCl_3$): δ **206.2**/205.9 (C, C-7), 141.8/**140.6** (C, C-9a), **139.7**/139.2 (C, C-4a), **86.7**/85.8 (C, C-5), 85.2/**85.1** (C, C-1), 84.1/**83.9** (C, C-9), 84.0/**83.8** (CH, C-6), 51.4/**50.8** (CH_2, C-8), **48.7**/47.8 (CH, C-10a), **41.63**** (CH_2), 41.55/41.5** (C/CH_2), **41.1** (C, C-3a), 40.2/**40.1** (CH, C-14), 39.9/**39.8** (CH_2, C-2 or 3), **39.1**/38.2 (CH_2), **22.02**/21.97** (CH_2, C-10), **21.4**/21.2 (CH_3, C-22), **19.8**† (CH_3, C-18), 19.1/**19.0** (CH_3, C-17), 18.9/**18.83**/**18.78**** (CH_3, C-12 and 13), 18.7/**18.53**/18.47/**18.42****† (CH_3, C-20, 21 and either 15 or 16), **18.36**** (CH_3, C-15 or 16), **14.4**† (CH, C-11), **13.3**/13.0 (CH, C-19)

**Where possible, sister signals are paired together with the chemical shift in bold denoting the major compound, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

****There are peaks ca. 130 ppm contributed by an aromatic impurity (see appendix for spectra).*

†This peak has a distinct shoulder, or a higher amplitude, and likely contains one of the missing signals.

HRMS [TOF-ES$^+$]: calculated for ([M+H]$^+$, $C_{38}H_{71}O_4Si_2$): 647.4885, found: 647.4910

196c+d:

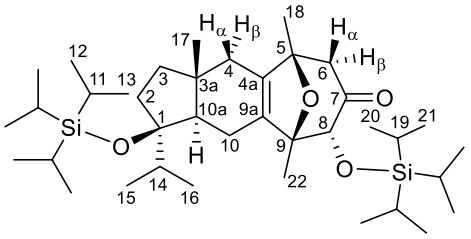
Note: In initial experiments, isomers C and D were isolated together and as such the IR and MS data that follows refers to that mixture. However, in the quoted experimental C was partially isolated allowing the NMR data to be given for C and D specifically – this pertains to the suggested absolute structural assignment of both.

TLC: 5% Et_2O-petroleum ether, R_f = 0.30 Vanillin

IR (thin film, CH_2Cl_2): $\tilde{\nu}_{max}$ 2942 n (C-H), 2866 n (C-H), 1730 sh (C=O), 1464 w, 1065 n

HRMS [TOF-ES$^+$]: calculated for ([M+Na]$^+$, $C_{38}H_{70}O_4Si_2Na$): 669.4705, found: 669.4717

(1*R*,3a*R*,5*S*,8*R*,9*S*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1,8-bis((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one (196c):

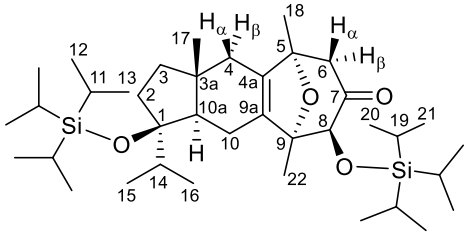


^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.28 (s, 1H, H-8), 2.57 (d, *J* 14.9, 1H, H-6$_\alpha$), 2.41 (d, *J* 14.9, 1H, H-6$_\beta$), 2.34−2.21 (m, 1H, H-10$_\alpha$), 2.17−2.10 (m, 1H, H-10$_\beta$), 2.09−1.83 (st, 4H, H-4$_\alpha$, 14, and either H-2 or 3), 1.76−1.67 (m, 1H, H-4$_\beta$), 1.58 (*ap.* q, *J* 6.7, 1H, H-2' or 3'), 1.50 (s, 3H, H-22), 1.43−1.36 (m, 1H, H-10a), 1.33 (s, 3H, H-18), 1.23−1.13 (m, 3H, H-19), 1.11−1.03 (st, 40H, H-11, 12, 13, 20, 21, and H-2'' or 3''), 0.96 (s, 3H, H-17), 0.87 (d, *J* 6.8, 3H, H-15 or 16), 0.82 (d, *J* 6.8, 3H, H-15 or 16)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 205.9 (C, C-7), 140.5 (C, C-9a), 139.7 (C, C-4a), 86.2 (C, C-9), 85.5 (C, C-1), 84.1 (CH, C-8), 83.9 (C, C-5), 51.7 (CH_2, C-6), 48.2 (CH, C-10a), 41.65** (CH_2, C-2 or 3), 40.9 (C, C-3a), 39.87** (CH, C-14), 39.7 (CH_2, C-2 or 3), 37.0 (CH_2, C-4), 23.2 (CH_2, C-10), 22.0 (CH_3, C-18), 19.5 (CH_3, C-22), 19.1 (CH_3, C-17), 18.8 (CH_3, C-12 and 13), 18.68/18.54** (CH_3, C-15 and 16), 18.46/18.35** (CH_3, C-20 and 21), 14.4 (CH, C-11), 12.90** (CH, C-19)

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

(1*R*,3a*R*,5*R*,8*S*,9*R*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1,8-bis((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one (196d):



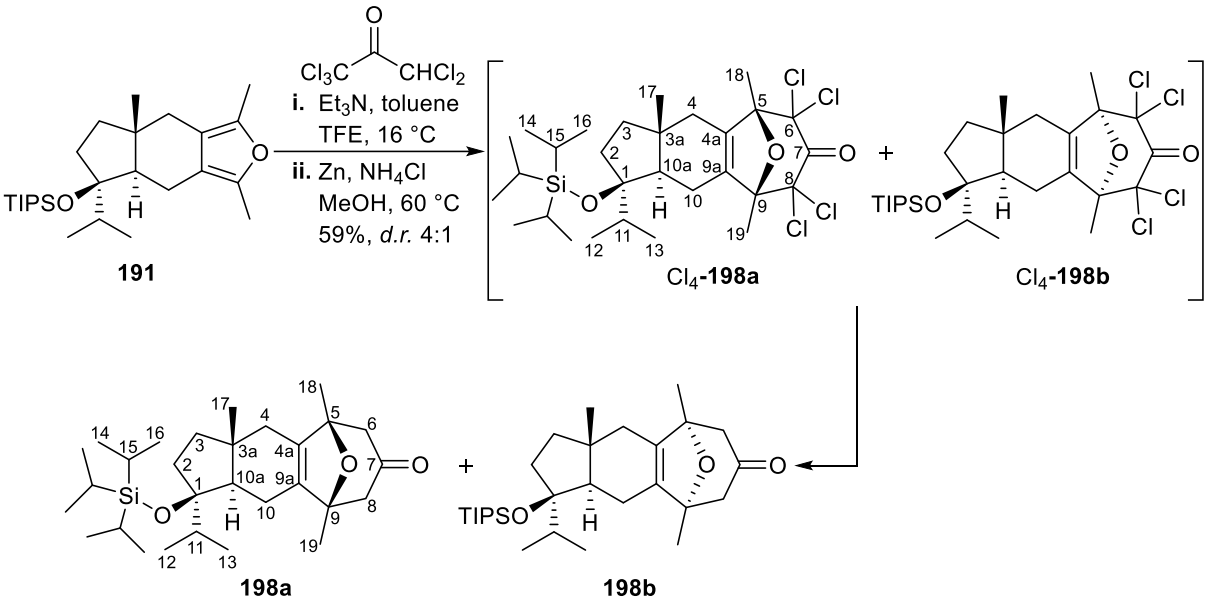
^{1}H NMR (500 MHz, $CDCl_3$): *δ* 4.24 (s, 1H, H-8), 2.53 (d, *J* 15.1, 1H, H-6_β), 2.39 (d, *J* 15.1, 1H, H-6_α), 2.25−1.83 (st, 6H, H-4_β, 10, 14, and either H-2 or 3), 1.66 (dd, *J* 16.8, 2.3, 1H, H-4_α), 1.61−1.58 (m, 1H, H-2' or 3'), 1.52 (s, 3H, H-22), 1.39 (dd, *J* 11.7, 4.3, 1H, H-10a), 1.34 (s, 3H, H-18), 1.17 (*ap.* td, *J* 8.3, 6.8, 3H, H-19), 1.14−0.99 (st, 40H, H-11, 12, 13, 20, 21, and either H-2'' or 3''), 0.93 (d, *J* 6.7, 3H, H-15 or 16), 0.87 (d, *J* 6.8, 3H, H-15 or 16), 0.79 (s, 3H, H-17)

^{13}C NMR (126 MHz, $CDCl_3$): *δ* 206.1 (C, C-7), 141.2 (C, C-9a), 140.2 (C, C-4a), 87.0 (C, C-9), 85.1 (C, C-1), 83.8 (CH, C-8), 83.3 (C, C-5), 50.6 (CH_2, C-6), 48.3 (CH, C-10a), 41.69** (CH_2), 41.2 (C, C-3a), 40.3 (CH, C-14), 39.9 (CH_2), 37.5 (CH_2, C-4), 23.6 (CH_2, C-10), 21.5 (CH_3, C-18), 20.1 (CH_3, C-22), 19.0 (CH_3, C-17), 18.88/18.87** (CH_3, C-12 and 13), 18.68** (CH_3, C-15 or 16), 18.47/18.42** (CH_3, C-20 and 21), 18.33** (CH_3, C-15 or 16), 14.2 (CH, C-11), 12.93** (CH, C-19)

**Note: these data were taken from a sample with an isomer ratio of 1 C : 5 D, but having partially isolated C (data above), only peaks corresponding to isomer D are reported here.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.; in some cases, where isomer C has a peak within the 1 d.p. range.*

Compounds 198a/b: (1*R*,3a*R*,10a*R*)-1-Isopropyl-3a,5,9-trimethyl-1-((triisopropylsilyl)oxy)-2,3,3a,4,5,6,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-7(1*H*)-one



The stereochemistry of C_5 and C_9 of the major product are tentatively assigned as (S) and (R) respectively, see main text.

Procedure adapted from a literature report.[25]

Furan **191** (220 mg, 0.53 mmol) was dissolved in toluene (0.26 mL) and 2,2,2-trifluoroethanol (1.0 mL) and the resulting solution was stirred vigorously. Solutions of PCA (444 mg, 1.93 mmol) in TFE (3 mL), and Et_3N (total 0.27 mL, 1.93 mmol) in TFE (3 mL) were added simultaneously *via* a syringe pump over 9 h, and the resulting mixture was stirred overnight. Note: lab temperature began at 14 °C and warmed to 18 °C across addition time. The reaction mixture was poured into Et_2O (20 mL), washed with H_2O (3 × 15 mL), and then re-extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over $MgSO_4$, filtered, and finally concentrated under reduced pressure to give a cream solid. This material was used without further purification.

Note: The intermediate tetrachlorides can be purified, but not separated, by flash column chromatography (2.5% Et_2O-petroleum ether) to give a mixture as a white solid.

The crude chlorides were dissolved in MeOH (2.7 mL) with zinc dust (2.07 g, 31.6 mmol) and NH_4Cl (422 mg, 7.89 mmol) and the resulting suspension was heated at 60 °C for 2.5 h. At this time, the reaction mixture was cooled to ambient temperature and filtered through celite to remove the excess solid, eluting with Et_2O (20 mL). The filtrate was washed with a solution of EDTA (0.5 M, pH 8, 3 × 15 mL), re-extracted with Et_2O (15 mL), and the combined organic extracts were washed with brine (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (25% Et_2O-petroleum ether) to give oxabicyclic ketones **198a/b** (147 mg, 59%, *ca.* 4:1 isomer ratio) as a yellow oil.

TLC: Intermediate chlorides, 10% Et_2O-petroleum ether, R_f = 0.61 Vanillin

Ketone, 25% Et_2O-petroleum ether, R_f = 0.30 Vanillin

IR (neat): $\tilde{\nu}_{max}$ 2928 n (C-H), 2892 n (C-H), 2867 n (C-H), 1715 sh (C=O), 1464 w, 1375 w, 1295 w, 1064 m, 882 m, 670 m

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (d, *J* 15.7, 1H, H-6' or 8'), 2.37 (d, J 16.0, 1H, H-6' or 8'), 2.35−2.24 (st, 3H, H6'', 8'', H-10'), 2.11 (dd, *J* 13.7, 7.7, 1H), 2.03 (dd, *J* 13.3, 7.3, 1H), 2.00−1.87 (st, 2H, H-11 and 1H of CH_2), 1.71−1.64 (st, 2H, H-10'' and 1H of CH_2), 1.64−1.57 (dd, *J* 12.0, 7.1, 1H), 1.40/**1.37**/**1.36** (s, 2 × 3H, H-18 and 19), 1.56−1.48/**1.31** (m/dd, *J* 11.6, 4.6, 1H, H-10a), **1.09**/1.07 (s/s, 22H, H-14, 15, 16, and 1H of CH_2), **0.99**/0.74 (s, 3H, H-17), 0.93/0.90/**0.88**/**0.83** (d, *J* 6.9, 2 × 3H, H-12 and 13)

**Minor compound signals have been included where possible; in this case the chemical shift in bold indicates the major compound signal, and the integrals throughout reflect the number of major-compound protons per environment; this may alter the order of peaks.*

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.9/**207.8** (C, C-7), 141.5/**140.7** (C, C-9a), **139.7**/139.4 (C, C-4a), 85.2/**85.1** (C, C-1), 82.98/**82.97****/**82.9/**82.4 (C, C-5 and 9), **49.8**/**49.5**/49.2 (CH_2, C-6 and 8), **48.9**/47.8 (CH, C-10a), **41.5**/41.38** (CH_2), **41.36**/41.0** (C, C-3a), 40.1/**40.0** (CH, C-11), **39.8**/39.6 (CH_2), **37.0**/36.9 (CH_2), **22.3**/22.2 (CH_3, C-18 or 19), 21.79/**21.77**** (CH_2, C-10), 21.7/**21.6** (CH_3, C-18 or 19), **19.2**/18.9 (CH_3, C-17), **18.82**†/18.79/**18.78**** (CH_3, C-14 and 16), 18.67/**18.65**** (CH_3, C-12 or 13), **18.50**/18.48** (CH_3, C-12 or 13), **14.4**/14.3 (CH, C-15)

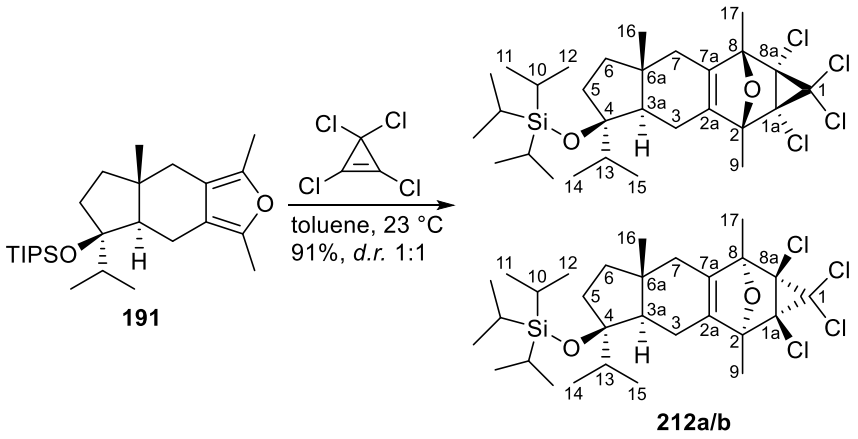
**Where possible, sister signals are paired together with the frequency in bold denoting the major compound, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†There are two missing signals for the minor isomer. This peak has a distinct shoulder and likely contains one of the missing signals.

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{29}H_{51}O_3Si$): 475.3607, found: 475.3619

Compounds 212a/b: Triisopropyl(((1a*R/S*,2*R/S*,3a*R*,4*R*,6a*R*,8*R/S*,8a*R/S*)-1,1,1a,8a-tetrachloro-4-isopropyl-2,6a,8-trimethyl-1,1a,2,3,3a,4,5,6,6a,7,8,8a-dodecahydro-2,8-epoxycyclopenta[b]cyclopropa[g]naphthalen-4-yl)oxy)silane



Procedure adapted from a literature report.[38]

A solution of furan **191** (27 mg, 65 µmol) in toluene (0.65 mL) was treated with TCCP (0.01 mL, 85 µmol) and the resulting solution was stirred at 23 °C for 3 h. At this time, the solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (1% Et_2O-petroleum ether) to give a mixture of chlorocyclopropanes **212a/b** (35 mg, 91%, isolated *d.r.* 1:1) as a white solid.

TLC: 5% Et_2O-petroleum ether, R_f = 0.52, 0.50 Vanillin

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2940 n (C-H), 2867 n (C-H), 1464 w, 1382 n, 1247 w, 1152 n, 1113 n, 1064 m (C-O), 882 m, 735 m, 671 m, 644 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45−2.26 (st, 2H), 2.24−1.85 (st, 12H), 1.66/1.65/1.63/1.61 (s, 4 × 3H, H-9 and 17), 1.67−1.60 (m, 2 × 1H), 1.51/1.41 (dd, *J* 11.3/11.7, 4.9/4.8, 2 × 1H, H-3a), 1.12−1.05 (st, 44H, H-10, 11, 12, and 2 × 1H of CH_2), 0.97−0.83 (st, 18H, H-14, 15, and 16)

**Where possible, sister signals are paired together, this may alter the order of peaks. Note: Integral values sum to 92H (the sum of both isomers protons).*

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0/149.0/148.2/148.0 (C, C2a and 7a), 90.7/90.5/90.1/90.0 (C, C-2 and 8), 85.3/84.9 (C, C-4), 67.4/67.14/67.09/67.05** (C, C1a and 8a), 48.7/47.6 (CH, C-3a), 41.9/41.3 (C, C-6a), 41.6/41.5 (CH_2), 40.2/40.1 (CH, C-13), 39.8/39.5/39.0/38.1 (CH_2), 23.8/23.5 (CH_2, C-3), 19.3/19.1 (CH_3, C-16), 18.84/18.80/18.76** (CH_3, C-11 and 12), 18.71/18.65/18.5/18.3** (CH_3, C-14 and 15), 14.4 (CH, C-10), 12.9/12.8/12.7/12.4 (CH_3, C-9 and 17)

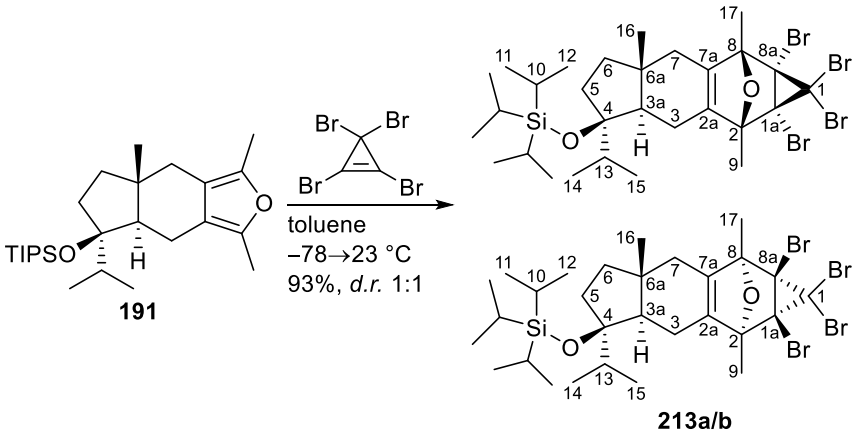
**Where possible, sister signals are paired together, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

Note: C-1 of both isomers was not observed.

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_{29}H_{47}O_2Si^{35}Cl_4$): 595.2094, found: 595.2074

Compounds 213a/b: Triisopropyl(((1a*R/S*,2*R/S*,3a*R*,4*R*,6a*R*,8*R/S*,8a*R/S*)-1,1,1a,8a-tetrabromo-4-isopropyl-2,6a,8-trimethyl-1,1a,2,3,3a,4,5,6,6a,7,8,8a-dodecahydro-2,8-epoxycyclopenta[b]cyclopropa[g]naphthalen-4-yl)oxy)silane



Procedure adapted from a literature report.[38]

A solution of furan **191** (115 mg, 0.28 mmol) in toluene (0.7 mL) was cooled to −78 °C and a solution of TBCP (109 mg, 0.31 mmol) in toluene (0.7 mL) was added dropwise over 5 min. The reaction mixture was allowed to warm over several hours to ambient temperature. After 6 h, TBCP (2 drops, neat) was added and the reaction mixture was stirred for 15 h. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (2% Et_2O-petroleum ether) to give a mixture of bromocyclopropanes **213a/b** (197 mg, 93%, isolated *d.r.* 1:1) as a white solid.

TLC: 5% Et_2O-petroleum ether, R_f = 0.56, 0.50 Vanillin

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2934 n (C-H), 2866 n (C-H), 1464 w, 1381 n, 1064 n (C-O), 880 n, 672 n, 654 n

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42−2.25 (m, 1H, H-10'), 2.21−1.97 (st, 5H, H-10'' and 4H of CH_2), 1.69/1.68/1.67/1.65 (s, 4 x 3H, H-9 and 17), 1.61 (*ap.* dd, *J* 7.1, 4.4, 1H), 1.49/1.40 (dd, *J* 11.6/11.4, 4.6/4.8, 1H, H-3a), 1.96−1.88 (m, 1H, H-13), 1.22−0.98 (st, 22H, H-10, 11, 12, and 1H of CH_2), 0.98−0.84 (st, 9H, H14, 15, and 16)

**Where possible, sister signals are paired together, this may alter the order of peaks.*

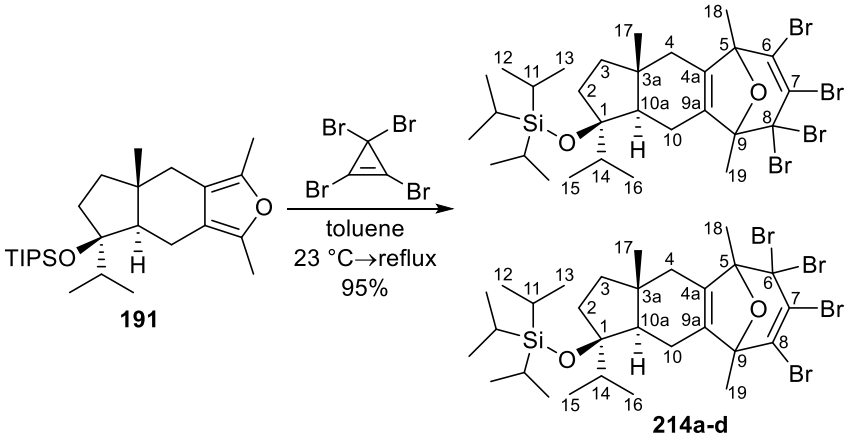
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.8/149.9/149.0/148.8 (C, C-2a and 7a), 91.5/91.3/90.82/90.79** (C, C-2 and 8), 85.3/84.9 (C, C-4), 61.7/61.3/61.1/61.0 (C, C-1a and 8a), 48.4/47.7 (CH, C-3a), 48.3/48.2 (C, C-1), 42.0/41.3 (C, C-6a), 41.6/41.5 (CH_2), 40.18/40.15** (CH, C-13), 39.8/39.5/39.2/38.2 (CH_2), 24.0/23.7 (CH_2, C-3), 19.4/19.3 (CH_3, C-16), 18.9/18.80** (CH_3, C-11 and 12), 18.75/18.7/18.5/18.4** (CH_3, C-14 and 15), 14.39/14.36** (CH, C-10), 13.2/13.1/12.9/12.7 (CH_3, C-9 and 17)

**Where possible, sister signals are paired together, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

HRMS [TOF-ASAP$^+$]: calculated for ($[M+H]^+$, $C_{29}H_{47}O_2{}^{79}Br_3{}^{81}BrSi$): 773.0058, found: 773.0038

Compounds 214a-d: Triisopropyl(((1*R*,3a*R*,10a*R*)-6,7,8,8-tetrabromo-1-isopropyl-3a,5,9-trimethyl-1,2,3,3a,4,5,8,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-1-yl)oxy)silane
and
Triisopropyl(((1*R*,3a*R*,10a*R*)-6,6,7,8-tetrabromo-1-isopropyl-3a,5,9-trimethyl-1,2,3,3a,4,5,6,9,10,10a-decahydro-5,9-epoxycyclohepta[f]inden-1-yl)oxy)silane



Note: Each regioisomer drawn above exists as a pair of facial isomers.

Procedure adapted from a literature report.[38]

A solution of TBCP (273 mg, 0.77 mmol) in toluene (1 mL) was added to a solution of furan **191** (281 mg, 0.67 mmol) in toluene (2.4 mL) and the resulting mixture was stirred at ambient temperature for 1 h (until starting material consumption by TLC), then heated at reflux for 5 h*. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (2% Et_2O-petroleum ether) to give a mixture of oxabicycles **214a-d** (492 mg, 95%, isolated *d.r.* 1:1:1:1) as a white solid.

**Note: there is no R_f change from the cyclopropanes to the oxabicycles.*

TLC: 5% Et_2O-petroleum ether, R_f = 0.56, 0.50 Vanillin

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2940 n (C-H), 2866 n (C-H), 1566 w, 1464 w, 1376 n, 1063 m (C-O), 741 m, 671 m, 652 m

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (dddd, *J* 17.6, 11.6, 4.6, 2.7, 1H), 2.66−2.56 (st, 2H), 2.50-

2.26 (st, 4H), 2.20−1.89 (st, 21H), 1.87/1.86/1.82/1.79 (s, 12H, H-18 or 19), 1.69−1.59 (st, 4H), 1.58/1.56/1.55/1.53 (s, 12H, H-18 or 19), 1.56−1.41 (m, 4H, H-10a), 1.16−1.02 (st, 88H, H-11, 12, 13, and 1H of CH_2), 0.98−0.81 (st, 36H, H-15, 16, and 17)

**Where possible, sister signals are paired together, this may alter the order of peaks.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.9/150.7/149.1/148.8 (C, C-4a or 9a), 137.2/137.1/136.0/135.75/135.73/135.6/135.4/135.2** (C, C-4a or 9a, and either C-6/8 or 7), 127.6†/127.5/126.8 (C, C-6/8 or 7), 92.8/92.7/91.5/91.4 and 88.8/88.6/88.1/88.0 (C, C-5 and 9), 85.3/85.2† (C, C-1), 71.9/71.6/71.1/71.0 (C, *C*Br_2, C-8/6), 48.24/48.19/47.9/47.6** (CH, C-10a), 42.0/41.5/41.33/40.8** (C, C-3a), 41.7/41.4/41.28/40.7** (CH_2,), 40.2/40.1/40.0† (CH, C-14), 39.6/39.4/39.33/39.29/39.0/38.0/37.4** (CH_2), 25.7/24.9/23.13/23.09** (CH_2), 23.2/23.0/22.3†† (CH_3, C-18 or 19), 21.2/20.7/20.4/20.2 (CH_3, C-18 or 19), 19.4/18.72/18.68/18.65/18.6/18.5/18.4** (CH_3, C-15, 16, and 17), 18.83/18.79** (CH_3, C-12 and 13), 14.4†/14.3 (CH, C-11)

**Where possible, sister signals are paired together, this may alter the order of peaks.*

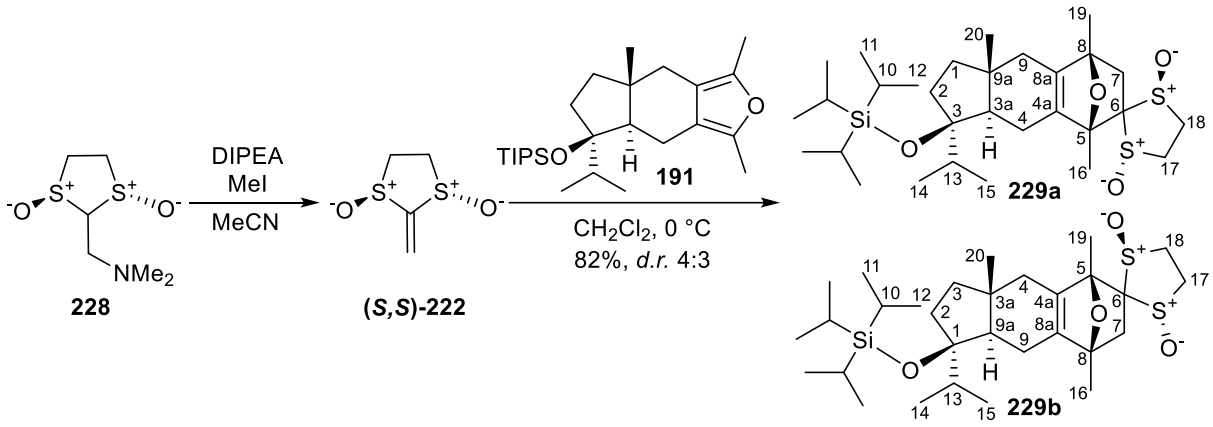
***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†This peak is suspected of containing more than one signal owing to either a visible shoulder or an enhanced amplitude.

††2D data shows that this peak correlates with 2-CH_3 ^{1}H environments. An HSQC spectrum has been provided in the appendix to show the correlation.

HRMS [TOF-ASAP$^+$]: calculated for ([M+H]$^+$, $C_{29}H_{47}O_2{}^{79}Br_3{}^{81}BrSi$): 773.0058, found: 773.0040

Compounds 229a/b: (1'*S*,3*R*,3'*S*,3a*R*,5*S*,8*S*,9a*R*)-3-Isopropyl-5,8,9a-trimethyl-3-((triisopropylsilyl)oxy)-1,2,3,3a,4,5,7,8,9,9a-decahydrospiro[[1',3']dithiolane-2',6-[5,8]epoxycyclopenta[b]naphthalene] 1',3'-dioxide
and
(1'*S*,1*R*,3'*S*,3a*R*,5*R*,8*R*,9a*R*)-1-Isopropyl-3a,5,8-trimethyl-1-((triisopropylsilyl)oxy)-1,2,3,3a,4,5,7,8,9,9a-decahydrospiro[[1',3']dithiolane-2',6-[5,8]epoxycyclopenta[b]naphthalene] 1',3'-dioxide



Procedure adapted from a literature report.[134]

DIPEA (0.88 mL, 5.08 mmol) and MeI (0.79 mL, 12.7 mmol) were added to a solution of amine **225** (495 mg, 2.53 mmol) in MeCN (5 mL). The reaction vessel was shielded from light and stirred overnight. In the morning, an aliquot of the reaction mixture was taken to determine completion by ^{1}H NMR spectroscopy. Upon completion, the reaction mixture was concentrated to dryness to give a white solid. This material was used without further purification.

Crude sulfoxide **(*S,S*)-222** (1.28 g, *nominally* 8.66 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and the resulting suspension was cooled to 0 °C, then a solution of furan **191** (358 mg, 0.856 mmol) in CH_2Cl_2 (2 mL) was added. An additional portion of **(*S,S*)-222** (64 mg, 0.43 mmol) was added after 1.3 h, and following a further 15 min the reaction was considered complete by TLC. The reaction mixture was filtered to remove solids, eluting with EtOAc, and the filtrate concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc → 3% MeOH-EtOAc) to give cycloadducts **229a** and **229b**

(400 mg, 82%, isolated *d.r.* 4:3) as a white solid.

Notes: All solvent removal was done at ca. 25 °C. When the purified cycloadducts had been dissolved in a chlorinated solvent for several hours the solution turned green.

TLC: EtOAc, R_f = 0.30 and 0.23 UV/Vanillin

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2933 n (C-H), 2867 n (C-H), 1463 w, 1383 w, 1151 n, 1064 m (C-O), 1038 m (C-O), 671 n

^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.19−3.96/3.56−3.20 (st, 2H/6H, H-17 and 18), 2.56/2.36 (d, *J* 13.0/12.4, 1H, H-7'), 2.51−2.38 (st, 2H), 2.27−2.19 (m, 1H), 2.16−1.84 (st, 10H, H-13 and 8H of CH_2), 1.78-1.72 (m, 1H), 1.76/1.61/1.50/1.47 (s, 3H, H-16 and 19), 1.68−1.57 (st, 3H, H-3a/9a, and 2H of CH_2), 1.49−1.46 (m, 1H, H-3a/9a), 1.37/1.28 (d, *J* 13.0/12.5, 1H, H-7''), 1.20−1.08 (st, 44H, H-10, 11, 12 and 2H of CH_2), 1.01−0.97 (st, 9H, H-20 and either 14 or 15), 0.93 (d, *J* 6.7, 3H, H-14 or 15), 0.88 (*ap.* dd, *J* 7.8, 6.8, 6H, 2 × H-14 or 15)

**Where possible, sister signals are paired together, this may alter the order of peaks.*

^{13}C NMR (101 MHz, CD_2Cl_2): δ 149.7/147.6/142.3/141.7 (C, C-4a and 8a), 101.1/97.1 (C, C-6), 91.3/90.1/87.3/86.7 (C, C-5 and 8), 85.52/85.45** (C, C-3/1), 52.5/52.4/51.1/50.1 (CH_2, C-17 and 18), 49.0/47.9 (CH, C-3a/9a), 41.9/41.8 (CH_2), 41.7/41.22** (C, C-9a/3a), 40.6/40.3 (CH, C-13), 40.0 (CH_2), 39.9 (CH_2), 38.3 (CH_2), 36.7 (CH_2), 36.4/36.1 (CH_2, C-7), 23.1/22.2 (CH_2), 19.7/19.2 (CH_3, C-20), 18.89/18.85**† (CH_3, C-11 and 12), 18.7/18.54/18.46** (CH_3, C-14 and 15), 17.1/16.4/15.8/15.4 (CH_3, C-16 and 19), 14.6 (CH, C-13)

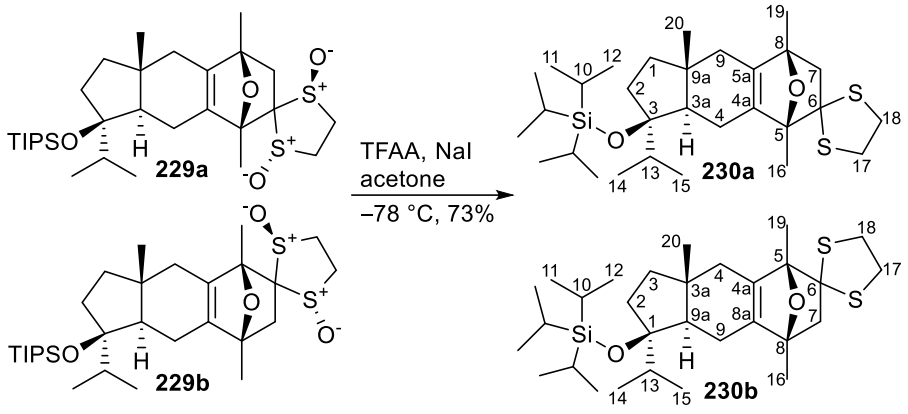
**Where possible, sister signals are paired together, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†2D data shows that this peak/s correlates with more ^{1}H environments than expected.

HRMS [TOF-ES$^+$]: calculated for ([M+H]$^+$, $C_{30}H_{53}O_4SiS_2$): 569.3155, found: 569.3156

Compounds 230a/b: Triisopropyl(((3*R*,3a*R*,5*S*,8*S*,9a*R*)-3-isopropyl-5,8,9a-trimethyl-1,2,3,3a,4,5,7,8,9,9a-decahydrospiro[[1,3]dithiolane-2',6-[5,8]epoxycyclopenta[b]naphthalen]-3-yl)oxy)silane
and
Triisopropyl(((1*R*,3a*R*,5*R*,8*R*,9a*R*)-1-isopropyl-3a,5,8-trimethyl-1,2,3,3a,4,5,7,8,9,9a-decahydrospiro[[1,3]dithiolane-2',6-[5,8]epoxycyclopenta[b]naphthalen]-1-yl)oxy)silane



Procedure adapted from a literature report.[134]

A solution of bis-sulfoxides **229a** and **229b** (131 mg, 0.230 mmol) in acetone (2.3 mL) was cooled to −78 °C. NaI (172 mg, 1.15 mmol) was added to the reaction mixture, followed by the addition of TFAA (0.19 mL, 1.38 mmol) over 10 min. An additional portion of NaI (89 mg, 0.59 mmol) and TFAA (0.10 mL, 0.71 mmol) after 80 min was required for full starting material consumption. After a further 10 min, $Na_2S_2O_{3\,(aq.)}$ and $NaHCO_{3\,(aq.)}$ were added and the solution allowed to warm to 23 °C. The amount of $Na_2S_2O_3$ added should be sufficient to turn the solution colourless. The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (2 × 20 mL), then dried over $MgSO_4$, filtered, and finally concentrated under reduced pressure. The crude material was purified by flash column chromatography (5% Et_2O-petroleum ether) to give a mixture of thioacetals **230a** and **230b** (90 mg, 73%) as a colourless oil.

TLC: 10% Et_2O-petroleum ether, R_f = 0.47 UV/Vanillin

IR (thin film, CH_2Cl_2): $\tilde{\nu}_{max}$ 2927 n (C-H), 2866 n (C-H), 1464 w, 1375 w, 1151 n, 1063 m (C-O),

998 n, 880 n, 670 m

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.32−3.17/3.09−2.99 (st, 6H/2H, H-17 and 18), 2.44−2.24 (st, 6H, H-7 and 2 × 1H of CH_2), 2.22−1.97 (st, 8H), 1.95−1.86 (st, 2H, H-13), 1.80−1.67 (st, 2H), 1.64−1.57 (st, 2H, H-1/3' or 2'), 1.56/1.53/1.41/1.38 (s, 4 × 3H, H-16 and 19), 1.51−1.43 (st, 2H, H-3a/9a), 1.11−1.04 (st, 44H, H-10, 11, 12, and either H-1/3'' or 2''), 0.99/0.96 (s, 2 × 3H, H-20), 0.96 (d, *J* 6.6, 3H, H-14 or 15)/0.92−0.85 (st, 9H, H-14 and 15)

**Where possible, sister signals are paired together, this may alter the order of peaks*

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 146.0/144.6/143.2/142.5 (C, C-4a and 5a/8a), 91.7/90.7/85.0/84.9 (C, C-5 and 8),85.2/85.1 (C, C-3/1), 75.3/75.2 (C, C-6), 56.21/56.17** (CH_2, C-7), 48.81/48.75** (CH, C-3a/9a), 41.59/41.5** (CH_2), 41.55/41.1** (C, C-9a/3a), 40.84/40.77** (CH_2, C-17 or 18), 40.4 (CH_2), 40.3/40.18** (CH, C-13), 40.24/40.1** (CH_2, C-17 or 18), 40.0/39.9 (CH_2), 36.9 (CH_2), 24.2/21.8 (CH_2, C-9/4), 19.8/19.2 (CH_3, C-20), 18.80/18.77/18.75/18.7**† (CH_3, C-11, 12, and either C-14 or 15), 18.52/18.47** (CH_3, C-14 or 15), 17.4/16.7 (CH_3, C-16 or 19), 14.4/14.3 (CH, C-10), 12.4/11.9 (CH_3, C-16 or 19)

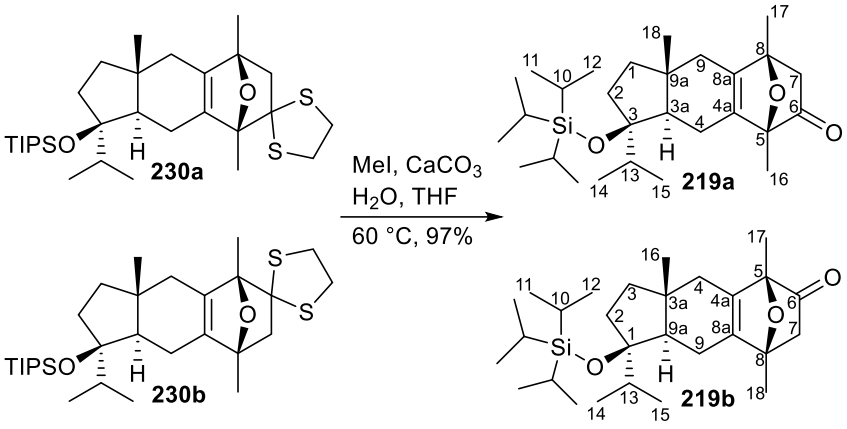
**Where possible, sister signals are paired together, this may alter the order of peaks.*

***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†2D data shows that this peak/s correlates with more ^{1}H environments than expected.

HRMS [TOF-ES^{+}]: calculated for ($[M+H]^+$, $C_{30}H_{53}O_2S_2Si$): 537.3256, found: 537.3270

Compounds 219a/b: (3*R*,3a*R*,5*S*,8*S*,9a*R*)-3-Isopropyl-5,8,9a-trimethyl-3-((triisopropylsilyl)oxy)-1,2,3,3a,4,5,7,8,9,9a-decahydro-6*H*-5,8-epoxycyclopenta[*b*]naphthalen-6-one
and
(1*R*,3a*R*,5*R*,8*R*,9a*R*)-1-Isopropyl-3a,5,8-trimethyl-1-((triisopropylsilyl)oxy)-1,2,3,3a,4,5,7,8,9,9a-decahydro-6*H*-5,8-epoxycyclopenta[*b*]naphthalen-6-one



Procedure adapted from a literature report.[140]

Thioacetals **230a** and **230b** (620 mg, 1.15 mmol) were dissolved in THF (8.6 mL) with H_2O (2.9 mL), $CaCO_3$ (1.15 g, 11.5 mmol) and MeI (7.25 mL, 115 mmol). The resulting solution was heated at 60 °C for 4 d. Upon completion, the reaction mixture was cooled to ambient temperature and filtered through celite, eluting with Et_2O, and washed with H_2O (3 × 30 mL). The aqueous layers were re-extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was then purified by flash column chromatography (10% Et_2O-petroleum ether) to give first **219b** (233 mg, 44%) as a cream solid, then **219a** (219 mg, 41%) as a cream solid. An additional 62 mg (12%) of isomerically-mixed fractions were also obtained.

219b:

TLC: 10% Et_2O-petroleum ether, R_f = 0.28 UV/Vanillin

MP: 91−94 °C (Et_2O-petroleum ether)

Optical Rotation: $[\alpha]_D^{25}$ = +223°, (c = 0.5, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2960 n (C-H), 2941 n (C-H), 2888 n (C-H), 2864 n (C-H), 1755 sh (C=O), 1659 w (C=C), 1463 w, 1380 n, 1077 m (C-O), 1064 m (C-O), 882 m, 672 st

^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 2.50−2.40 (m, 1H, H-9'), 2.17−2.00 (st, 3H, H-4' and 2H of H-2 or 3), 1.99 (br s, 2H, H-7' and 7''), 1.93 (*ap.* p, *J* 6.8, 1H, H-13), 1.82−1.68 (st, 2H, H-4'' and H-9''), 1.62 (dd, *J* 12.1, 6.9, 1H, either H-2' or 3'), 1.51 (s, 3H, H-18), 1.37−1.33 (m, 1H, H-9a), 1.32 (s, 3H, H-17), 1.11 (s, 22H, H-10, 11, 12, and either H-2'' or 3''), 1.02 (s, 3H, H-16), 0.89 (d, *J* 6.8 Hz, 3H, H-14 or 15), 0.84 (d, *J* 6.8 Hz, 3H, H-14 or 15)

^{13}C NMR (101 MHz, CD_2Cl_2): *δ* 210.9 (C, C-6), 151.3 (C, C-8a), 138.0 (C, C-4a), 89.3 (C, C-5), 85.3 (C, C-1), 84.9 (C, C-8), 49.3 (CH, C-9a), 41.9 (C, C-3a), 41.8 (CH_2, C-2 or 3), 40.9 (CH_2, C-7), 40.3 (CH, C-13), 39.8 (CH_2, C-2 or 3), 36.8 (CH_2, C-4), 23.2 (CH_2, C-9), 19.3 (CH_3, C-16), 18.87* (CH_3, C-11 or 12), 18.83* (CH_3, C-11 or 12), 18.6 (CH_3, *both* C-14 and 15**), 17.4 (CH_3, C-18), 14.6 (CH, C-10), 11.0 (CH_3, C-17)

**2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

***in 2-D NMR experiments, both H-14 and H-15 correlate with this peak, and the peak itself is noticeably broad.*

HRMS [TOF-ES$^+$]: calculated for ($[M+OH]^+$, $C_{28}H_{49}O_4Si$): 477.3400, found: 477.3386

Note: The molecular ion was not observed under mass spectrometry conditions; however, a mass corresponding to the ionised hydrate was and the ketone is inferred from this.

219a:

TLC: 10% Et_2O-petroleum ether, R_f = 0.23 UV/Vanillin

MP: 90−92 °C (Et_2O-petroleum ether)

Optical Rotation: $[\alpha]_D^{25}$ = −267°, (c = 0.33, CH_2Cl_2)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 2929 n (C-H), 2866, n (C-H), 1753 sh (C=O), 1649 w (C=C), 1391 n, 1062 m (C-O), 676 m

^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 2.36 (dddd, *J* 17.2, 11.6, 4.9, 2.7, 1H, H-4'), 2.17−2.10 (st, 2H, H-9', and either H-1' or 2'), 2.06 (dd, *J* 13.1, 7.2, 1H, H-1'' or H-2''), 2.01 (br. s, 2H, H-7' and 7''), 1.92 (sept, *J* 6.8, 1H, H-13), 1.79 (ddd, *J* 17.6, 4.9, 2.6, 1H, H-4''), 1.69−1.61 (st, 2H, H-9'', and either H-1' or 2'), 1.49 (s, 3H, H-17), 1.35 (s, 3H, H-16), 1.31 (dd, *J* 11.6, 4.9, 1H, H-3a), 1.10 (s, 22H, H-10, 11, 12, and either H-1'' or 2''), 1.02 (s, 3H, H-18), 0.87 (d, *J* 6.8, 3H, H-14 or 15), 0.84 (d, *J* 6.8, 3H, H-14 or 15)

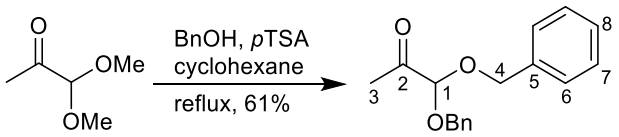
^{13}C NMR (101 MHz, CD_2Cl_2): *δ* 210.2 (C, C-6), 150.5 (C, C-8a), 138.5 (C, C-4a), 89.2 (C, C-5), 85.4 (C, C-3), 84.8 (C, C-8), 49.4 (CH, C-3a), 41.8 (CH_2, C-1 or 2), 41.5 (C, C-9a), 41.1 (CH_2, C-7), 40.2 (CH, C-13), 39.8 (CH_2, C-1 or 2), 38.2 (CH_2, C-9), 21.6 (CH_2, C-4), 19.5 (CH_3, C-18), 18.9 (CH_3, C-11 or 12), 18.8 (CH_3, C-11 or 12), 18.6 (CH_3, C-14 or 15), 18.5 (CH_3, C-14 or 15), 17.9 (CH_3, C-17), 14.6 (CH, C-10), 10.5 (CH_3, C-16)

HRMS [TOF-ES$^+$]: calculated for ($[M+OH]^+$, $C_{28}H_{49}O_4Si$): 477.3400, found: 477.3403

Note: The molecular ion was not observed under mass spectrometry conditions; however, a mass corresponding to the ionised hydrate was and the ketone is inferred from this.

Single crystals of both **219a** and **219b** were obtained by the slow evaporation of acetone. The crystal structures of both compounds can be found in the appendix.

Compound 31: **1,1-Bis(benzyloxy)propan-2-one**



31

Procedure adapted from a literature report.[163]

Methylglyoxal-1,1-dimethyl acetal (0.59 mL, 5.0 mmol) was dissolved in cyclohexane (12.5 mL) with BnOH (1.1 mL, 11 mmol), and *p*TSA (47 mg, 0.25 mmol), then the resulting mixture was heated at reflux for 90 min using Dean-Stark apparatus. At this time, the solution was cooled and neutralised by the addition of $NaHCO_{3\,(aq.)}$ (20 mL). The organic layer was further washed with $NaHCO_{3\,(aq.)}$ (2 × 20 mL) and brine (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown oil. The crude material was purified by flash column chromatography (15% Et_2O-petroleum ether) to give dibenzyl acetal **31** (820 mg, 61%) as a colourless oil.

TLC: 25% Et_2O-petroleum ether, R_f = 0.42 Vanillin

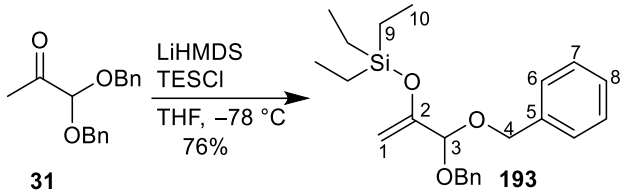
IR (neat): $\tilde{\nu}_{max}$ 3033 w (C-H), 2876 w (C-H), 1728 sh (C=O), 1455 n (C=C), 1048 m (C-O), 1025 m (C-O)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.29 (st, 10H, H-6, 7 and 8), 4.73 (s, 1H, H-3), 4.68 (d, *J* 11.8, 2H, H-4'), 4.59 (d, *J* 11.8, 2H, H-4''), 2.25 (s, 3H, H-1)

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.0 (C, C-2), 137.0 (C, C-5), 128.7 (CH), 128.2 (CH), 101.1 (CH, C-3), 69.4 (CH_2, C-4), 25.2 (CH_3, C-1)

These data are in agreement with literature reported values, with the exception of one carbon environment being unobserved *ca.* 127 ppm.[163]

Compound 193: ((3,3-Bis(benzyloxy)prop-1-en-2-yl)oxy)triethylsilane



31 **193**

Procedure adapted from a literature report.[163]

Ketone **31** (377 mg, 1.40 mmol) and TESCl (0.35 mL, 2.09 mmol) were dissolved in THF (7 mL) and the resulting solution was cooled to −78 °C. LiHMDS (1 M in THF, 1.70 mL, 1.70 mmol) was added to over 20 min, resulting in a yellow solution. After 45 min, the reaction mixture was quenched by the addition of $NaHCO_{3\,(aq.)}$ (3 mL), then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were washed with brine (3 × 15 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (95:4:1 petroleum ether-Et_2O-Et_3N) to give silyl enol ether **193** (406 mg, 76%) as a colourless oil.

TLC: 25% Et_2O-petroleum ether, R_f = 0.32 Vanillin

IR (neat): $\tilde{\nu}_{max}$ 3031 w (C-H), 2955 w (C-H), 2912 w (C-H), 2877 w (C-H), 1640 w (C=C-O), 1455 w (C=C), 1055 m (C-O), 1018 m (C-O), 729 st, 695 st

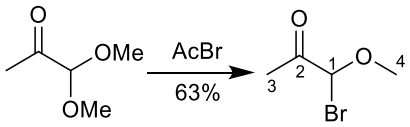
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.27 (st, 10H, H-8, 9 and 10), 4.93 (s, 1H, H-3), 4.73 (t, *J* 1.0, 1H, H-1'), 4.67 (d, *J* 11.9, 2H, H-6'), 4.59 (d, *J* 11.9, 2H, H-6''), 4.41 (d, *J* 1.2, 1H, H-1''), 0.98 (t, *J* 7.9, 9H, H-5), 0.76−0.68 (m, 6H, H-4)

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (C), 138.3 (C), 128.4 (CH, C-8), 127.9 (CH, C-9), 127.6 (CH, C-10), 99.2 (CH, C-3), 92.4 (CH_2, C-1), 67.7 (CH_2, C-6), 6.8 (CH_3, C-5), 5.0 (CH_2, C-4)

LRMS [TOF-ES$^+$]: *m/z* 407 (100%, $[M+Na]^+$)

These data are in agreement with literature reported values.[163]

Compound 194: **1-Bromo-1-methoxypropan-2-one**



194

Procedure adapted from a literature report.[122]

AcBr (0.81 mL, 11.0 mmol) was added to methylglyoxal 1,1-dimethyl acetal (1.20 mL, 10.0 mmol) at 0 °C and the resulting solution stirred at 23 °C for 1 h. At this time, the mixture was distilled (*ca.* 170 mbar, 50 °C) to give bromide **194** (1.06 g, 63%) as a pale-yellow oil.

Note: It was found that the oil fumes in air and turns yellow fairly rapidly at room temperature. It was stored in a freezer under argon when not in use, but better results were obtained using it immediately after distillation.

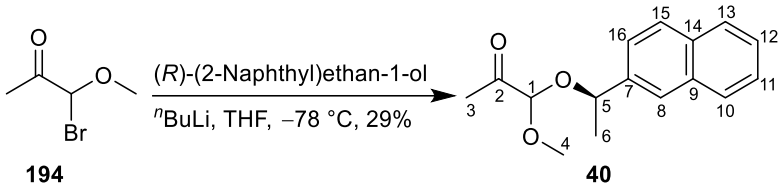
IR (neat): $\tilde{\nu}_{max}$ 2941 w (C-H), 2843 w (C-H), 1727 st (C=O), 1356 m, 1224 m, 1090 st (C-O), 626 st

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 (s, 1H, H-1), 3.59 (s, 3H, H-4), 2.37 (s, 3H, H-3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.4 (C, C-2), 92.4 (CH, C-1), 59.0 (CH_3, C-4), 23.0 (CH_3, C-3)

These data are in agreement with literature reported values.[122]

Compound 40: **1-Methoxy-1-((*R*)-1-(naphthalen-2-yl)ethoxy)propan-2-one**



Procedure adapted from a literature report.[35]

(*R*)-(2-Naphthyl)ethan-1-ol (491 mg, 2.85 mmol) in THF (6 mL) was cooled to 0 °C, at which point ^{n}BuLi (2.39 M in hexanes, 1.43 mL, 3.42 mmol) was added resulting in a yellow solution. After 15 min, bromide **194** (520 mg, 3.13 mmol, prepared earlier that day) in THF (5 mL) was added over 5 min and the cooling bath was removed. After 3 h, the reaction mixture was quenched by the addition of $NaHCO_{3\,(aq.)}$ (2 mL), then diluted with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were washed with brine (3 × 25 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (15% Et_2O-petroleum ether) to give a 1:1 mixture of diastereomers of acetal **40** (213 mg, 29%) as a yellow oil.

Note: 128 mg of naphthylethanol was returned, the adjusted yield of the mixed acetal was therefore 39%.

TLC: 25% Et_2O-petroleum ether, R_f = 0.32 UV / Vanillin

IR (neat): $\tilde{\nu}_{max}$ 3056 w (C-H), 2976 w (C-H), 2930 w (C-H), 2834 w (C-H), 1728 m (C=O), 1602 w (C=C), 1102 m, 1059 st (C-O), 1032 st (C-O)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.74 (st, 8H, Ar), 7.57−7.45 (st, 6H, Ar), 4.99/4.80 (q, *J* 6.6, 1H, H-5), 4.46/4.41 (s, 1H, H-1), 3.36/3.21 (s, 3H, H-4), 2.23/2.18 (s, 3H, H-3), 1.63/1.58 (d, *J* 6.6, H-5)

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4/204.0 (C, C-2), 140.0/139.4 (C, C-7), 133.4 (C, C-9 or 14), 133.29** (C, C-9 or 14), 133.26**† (C, C-9 or 14), 128.9 (CH, Ar), 128.6 (CH, Ar), 128.1 (CH, Ar), 128.0 (CH, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 126.5 (CH, Ar), 126.4 (CH, Ar), 126.3 (CH, Ar), 126.2 (CH, Ar), 126.1 (CH, Ar), 125.7 (CH, Ar), 124.3 (CH, Ar), 124.2 (CH, Ar), 102.5/100.9 (CH, C-1), 76.0/75.5 (CH, C-5), 55.5/54.0 (CH_3, C-4), 25.2 (CH_3), 24.3 (CH_3), 23.8 (CH_3), 23.4 (CH_3)

**Compound exists as a pair of diastereomers, as such sister signals have been paired where possible.*

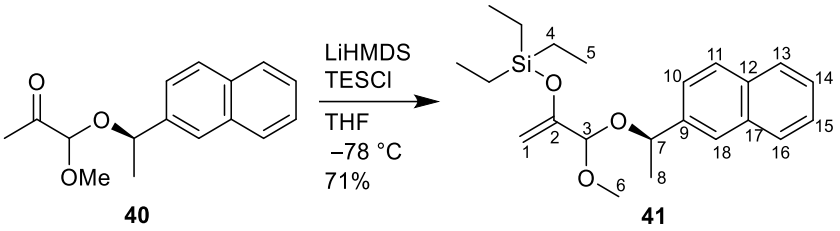
***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†Peak is twice as high and close inspection shows a shoulder, it is likely that the missing C-9/14 environment is here.

LRMS [TOF-ES$^+$]: *m/z* 313 (90%, $[M+Na+MeOH]^+$), 281 (100, $[M+Na]^+$), 155 (25, $[NaphCH_2CH_3]^+$)

These data are in agreement with literature reported values.[35]

Compound 41: Triethyl((3-methoxy-3-((*R*)-1-(naphthalen-2-yl)ethoxy)prop-1-en-2-yl)oxy)silane



Procedure adapted from a literature report.[35]

Ketone **40** (52 mg, 0.20 mmol) was dissolved in THF (0.95 mL) and cooled to −78 °C. TESCl (0.05 mL, 0.29 mmol), then LiHMDS (1 M in THF, 0.23 mL, 0.23 mmol) were added. After 45 min, the reaction mixture was quenched by the addition of $NaHCO_{3\,(aq.)}$ (2 mL), then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were washed with brine (2 × 10 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (95:4:1 petroleum ether-Et_2O-Et_3N) to give a diastereomeric mixture of silyl enol ethers **41** (53 mg, 71%) as a colourless oil.

TLC: 25% Et_2O-petroleum ether, R_f = 0.65 UV / Vanillin

IR (neat): $\tilde{\nu}_{max}$ 3057 w (C-H), 2955 n (C-H), 2911 n (C-H), 2877 n (C-H), 1640 sh (C=O), 1510 w (C=C), 1050 m (C-O), 1018 m (C-O), 747 st

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.87−7.81 (st, 6H, Ar), 7.79 (dd, *J* 1.8, 0.7, 1H, Ar), 7.77 (*ap.* dt, *J* 1.8, 0.7 Hz, 1H, Ar), 7.56 (dd, *J* 8.5, 1.7, 1H, Ar), 7.52−7.43 (st, 5H, Ar), 4.99/4.83 (q, *J* 6.6, 1H, H-7), 4.61/4.49 (d, *J* 0.7, 1H, H-3), 4.59/4.58 (dd, *J* 1.2, 0.6, 1H, H-1), 4.35/4.33 (d, *J* 1.2, 1H, H-1'), 3.26/3.16 (s, 3H, H-6), 1.55/1.53 (d, *J* 2.3, 3H, H-8), 1.01−0.96/0.95−0.90 (st, 9H, H-5), 0.75−0.63 (st, 12H, H-4)

^{13}C NMR (101 MHz, CD_2Cl_2): δ 154.9/154.6 (C, C-2), 141.8/141.2 (C, C-9), 133.69/133.65** (C,

C-12 or 17), 133.5/133.4 (C-12 or 17), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.24** (CH, Ar), 128.20** (CH, Ar), 127.99** (CH, Ar), 127.98** (CH, Ar), 126.42** (CH, Ar), 126.41** (CH, Ar), 126.13* (CH, Ar), 126.11** (CH, Ar), 125.7 (CH, Ar), 125.4 (CH, Ar), 125.0 (CH, Ar), 124.9 (CH, Ar), 101.0/99.2 (CH, C-3), 92.2/92.0 (CH_2, C-1), 75.0/74.4 (CH, C-7), 54.1†/52.5 (CH_3, C-6), 24.3/23.4 (CH_3, C-8), 6.80/6.75** (CH_3, C-5), 5.16/5.13** (CH_2, C-4)

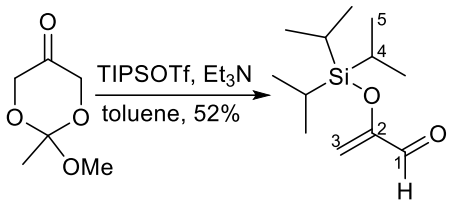
***2 d.p. provided to distinguish peaks that would otherwise be the same at 1 d.p.*

†signal merges with solvent in UDEFT, but JMOD shows a signal here, as such assignment is tentative

LRMS [TOF-ES$^+$]: *m/z* 767 (70%, $[2M+Na]^+$), 395 (100, $[M+Na]^+$)

These data are in agreement with literature reported values.[35]

Compound 73: 2-((Triisopropylsilyl)oxy)acrylaldehyde



72 **73**

Procedure adapted from a literature report.[53]

Dioxanone **72**[†] (256 mg, 1.75 mmol) was dissolved in toluene (3.4 mL) with Et_3N (0.48 mL, 3.42 mmol) and TIPSOTf (0.51 mL, 1.88 mmol), and the resulting solution was stirred for 1 d. At this time, the flask was heated at 40 °C for 1 h, at which point NMR analysis determined completion. H_2O (10 mL) was added, and the mixture was extracted with Et_2O (2 × 10 mL). The organic layers were washed with brine (2 × 10 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (2% Et_2O-petroleum ether) to give acrylaldehyde **73** (208 mg, 52%) as a colourless oil.

TLC: 2% Et_2O-petroleum ether, R_f = 0.39 Vanillin

IR (neat): $\tilde{\nu}_{max}$ 2945 m (C-H), 2894 n (C-H), 2868 m (C-H), 1703 sh (C=O), 1615 sh (C=C), 1464 w, 1304, sh, 1036 sh, 881 st, 678 st

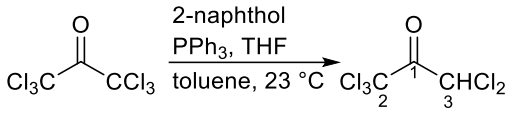
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.32 (s, 1H, H-1), 5.49 (d, *J* 1.7, 1H, H-3'), 5.24 (d, *J* 1.7 Hz, 1H, H-3''), 1.28−1.18 (m, 3H, H-4), 1.09 (d, *J* 7.1, 18H, H-5)

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 189.6 (CH, C-1), 156.4 (C, C-2), 112.2 (CH_2, C-3), 18.0 (CH_3, C-5), 12.8 (CH, C-4)

These data are in agreement with literature reported values.[53]

[†]*Was supplied by group member I. Barker.*

Pentachloroacetone



Procedure adapted from a literature report.[124]

A solution of HCA (9.00 mL, 49.0 mmol) and 2-naphthol (3.60 g, 25.0 mmol) in THF (10 mL) and toluene (20 mL) was added to a solution of PPh_3 (6.56 g, 25.0 mmol) in toluene (19 mL) at 0°C over 5 min. A purple solid crashed out almost immediately, and the cooling bath was removed after addition. After 20 min, the solution was filtered and washed with toluene (30 mL total). The filtrate was concentrated under reduced pressure, and then distilled (160 °C, 80-100 mbar) to give a colourless oil (4.15 g, 80-100 mbar). Other fractions totalling 5.49 g were obtained, but were deemed less pure by NMR.

Note: See results and discussion for details; the obtained oil was not pure and could not be made so on any occasion and as such a yield is not given. The mixture was used in any relevant cycloaddition.

IR (neat): $\tilde{\nu}_{max}$ 3016 w (C-H), 1780 sh (C=O), 894 sh, 831 s, 643 st

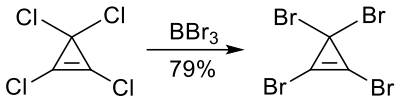
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H)

Note: the 6.45 ppm impurity with an integral of 0.05 relative to the 6.74 ppm peak is likely trace sym-TCA, using integrals there is 1:0.025 or 2.4%.

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.7 (C, C-1), 92.6 (C, C-2), 61.9 (CH, C-3)

Note: peaks for HCA can be seen at 175.7 ppm and 90.1 ppm.

Tetrabromocyclopropene



Procedure adapted from a literature report.[36]

TCCP (0.74 mL, 6.00 mmol) was treated with BBr_3 (0.86 mL, 9.01 mmol) dropwise over 5 min. **CAUTION!** A potent exotherm ensued, joined by vigorous effervescence. The crude material was subjected to vacuum distillation (115 °C, 0.1 mbar) to give TBCP (1.68 g, 79%) as a colourless oil.

Note: the oil freezes to a white solid when stored at/below −25 °C.

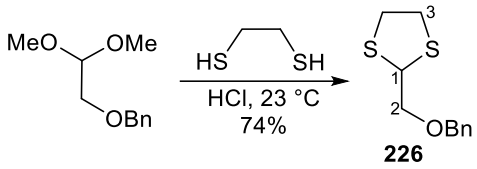
IR (neat): $\tilde{\nu}_{max}$ 1761 sh (C=C), 1117 st, 992 st, 651 st, 581 m

^{13}C NMR (101 MHz, $CDCl_3$): δ 121.1 (C, C=C), 24.1 (C, CBr_2)

MS [GCMS-EI$^+$]: *m/z* 356 [$C_3Br^{79}{}_2\,Br^{81}{}_2$], 275 [$C_3Br^{79}{}_2\,Br^{81}{}_1$], 196 [$C_3Br^{79}{}_1\,Br^{81}{}_1$], 115 [$C_3Br^{79}{}_1$]

These data are in agreement with literature reported values.[36]

Compound 226: 2-((Benzyloxy)methyl)-1,3-dithiolane



226

Procedure adapted from a literature report.[133,134]

Ethanedithiol (4.80 mL, 57.0 mmol) and HCl (37.5%, 3.60 mL) were cooled to 0 °C and benzyloxyacetaldehyde dimethyl acetal (10.92 g, 55.6 mmol) was added dropwise over 2 h *via* a syringe pump, causing the solution to cloud. The cooling bath was removed after addition, and after a further 45 min TLC indicated completion. The reaction mixture was poured (**Careful! Exotherm**) into H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were washed with H_2O (2 × 25 mL), $NaHCO_{3\,(aq.)}$ (2 × 25 mL), and brine (1 × 20 mL), then were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (8% Et_2O-petroleum ether) to give dithiane **226** (9.37 g, 74%) as a colourless oil.

TLC: 10% Et_2O-petroleum ether, R_f = 0.33 UV / $KMnO_4$

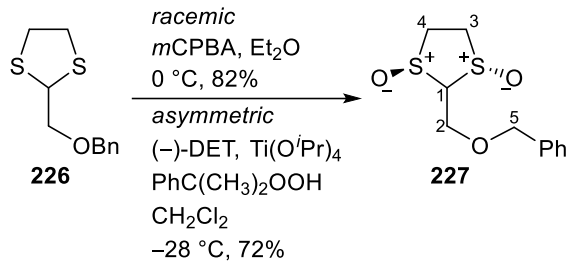
IR (neat): $\tilde{\nu}_{max}$ 3028 w (C-H), 2923 w (C-H), 2852 w (C-H), 1495 w (C=C), 1096 st (C-O), 734 st, 696 st

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.33 (st, 4H, Ar), 7.33−7.27 (m, 1H, Ar), 4.63 (t, *J* 7.0, 1H, H-1), 4.60 (s, 2H, OBn), 3.57 (d, *J* 7.0, 2H, H-2), 3.20 (s, 4H, H-3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1 (C, Ar), 128.6 (C, Ar), 127.9 (C, Ar), 127.8 (C, Ar), 75.3 (CH_2, C-2), 73.4 (CH_2, OBn), 51.9 (CH, C-1), 38.2 (CH_2, C-3)

These data are in agreement with literature reported values.[133,134]

Compound 227: (1*S*, 3*S*)-2-((Benzyloxy)methyl)-1,3-dithiolane 1,3-dioxide



**stereochemistry drawn for the asymmetric reaction product*

Procedure adapted from a literature report.[133,134]

Racemic Synthesis:

A solution of *m*CPBA (3.94 g, 22.8 mmol) in Et_2O (57 mL) was added to a solution of thioacetal **226** (2.05 g, 9.06 mmol) in Et_2O (24 mL) over 90 min *via* a syringe pump. Approximately 20 min into addition, a white solid began to precipitate from solution. Upon completion, the solid was obtained by filtration and purified by recrystallisation from EtOAc, being careful to cool from reflux to −28 °C (freezer) over 4 h. The racemic sulfoxide **227** (1.86 g, 82%) was obtained as white plate crystals.

Asymmetric Synthesis of the (S,S) or (−)-Isomer:

$Ti(O^iPr)_4$ (1.30 mL, 4.42 mmol) was added to a solution of (−)-DET (3.00 mL, 17.7 mmol) in CH_2Cl_2 (20 mL) and the resulting yellow solution was stirred for a further 30 min. At this point, thioacetal **226** (2.02 g, 8.92 mmol) was added with the aid of CH_2Cl_2 (15 mL) and the resulting solution was cooled to −40 °C using a carefully managed dry ice-acetone bath. After stirring at this temperature for 1 h, cumyl hydroperoxide (3.30 mL, 17.7 mmol, 80% technical grade) was added over 5 min, and following 20 min of further stirring, the reaction vessel was transferred to a freezer (−28 °C, no stirring) for 3 d. Upon completion, H_2O (1.50 mL) was

added and the reaction mixture was stirred vigorously as it warmed to 23 °C over 2 h. After this period, the reaction mixture was filtered through celite (4 cm by 3.5^2 cm) washing with CH_2Cl_2. It should be noted that the initial gel was reluctant to filter until it was mechanically stirred into the celite, at which point fluid rushed through. The filtrate was concentrated under reduced pressure to give *ca.* 9 g of crude material, that purified by flash column chromatography (5% → 10% MeOH-EtOAc) to give the (*S,S*)-bis-sulfoxide **227** (1.65 g, 72%) as a white crystalline solid.

TLC: 10% MeOH-EtOAc, R_f = 0.62 UV / $KMnO_4$

Optical Rotation: $[\alpha]_D^{25}$ = −116°, (c = 1.0, $CHCl_3$); *Lit.*[134] $[\alpha]_D^{25}$ = +125.4°, (c = 1.0, $CHCl_3$, for the (*R,R*)-isomer)

IR (neat, ATR attachment): $\tilde{\nu}_{max}$ 3059 w (C-H), 2976 n (C-H), 2861 w (C-H), 1453 n (C=C), 1015 st, 732 st, 696 st

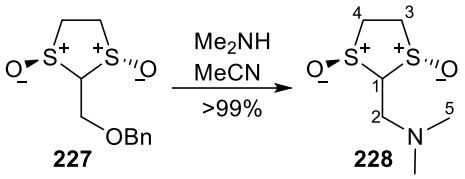
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.29 (st, 5H, Ar), 4.66 (d, *J* 12.0, 1H, H-5'), 4.60 (d, *J* 11.9, 1H, H-5''), 4.14−4.05 (st, 2H, H-2), 4.04−3.96 (m, 1H, H-1), 3.83−3.61 (st, 4H, H-3 and 4)

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.0 (C, Ar), 128.7 (C, Ar), 128.3 (C, Ar), 128.1 (C, Ar), 90.1 (CH, C-1), 74.1 (CH_2, C-2 or 5) , 62.0 (CH_2, C-2 or 5), 51.9 (CH_2, C-3 or 4), 51.5 (CH_2, C-3 or 4)

HRMS [TOF-ES$^+$]: calculated for ($[M+Na]^+$, $C_{11}H_{14}O_3S_2Na$): 281.0282, found: 281.0287

These data are in agreement with literature reported values.[133,134]

Compound 228: (1*S*, 3*S*)-2-((Dimethylamino)methyl)-1,3-dithiolane 1,3-dioxide



Procedure adapted from a literature report.[133,134]

Me_2NH (18.0 mL, 36.0 mmol, 2 M in THF) was added to a solution of benzyl ether **227** (1.86 g, 7.20 mmol) in MeCN (28 mL) and the flask was protected from light. After 16 h, a further portion of Me_2NH (18.0 mL, 36.0 mmol) was added. After stirring for 4 d, the solvent and excess reagent were removed under reduced pressure, and the resulting residue was purified by flash column chromatography (EtOAc → 10% MeOH-EtOAc, only 6 cm of silica gel) to give amine **228** (1.41 g, >99%) as a white solid.

TLC: 10% MeOH-EtOAc, R_f = 0.08 UV / $KMnO_4$

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (t, J 8.8, 1H, H-1), 3.81−3.59 (st, 4H, H-3 and 4), 2.95 (d, J 8.6, 2H, H-2), 2.41 (s, 6H, H-5)

^{13}C NMR (101 MHz, $CDCl_3$): δ 90.7 (CH, C-1), 52.3 (CH_2, C-2), 51.5 (CH_2, C-3 or 4), 51.0 (CH_2, C-3 or 4), 45.7 (CH_3, C-5)

HRMS [TOF-ES$^+$]: calculated for ($[M+H]^+$, $C_6H_{14}O_2S_2N$): 196.0466, found: 196.0462

5. References

1 S. E. Rossiter, M. H. Fletcher and W. M. Wuest, *Chem. Rev.*, 2017, **117**, 12415–12474.

2 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, I. E. Orhan, M. Banach, J. M. Rollinger, D. Barreca, W. Weckwerth, R. Bauer, E. A. Bayer, M. Majeed, A. Bishayee, V. Bochkov, G. K. Bonn, N. Braidy, F. Bucar, A. Cifuentes, G. D'Onofrio, M. Bodkin, M. Diederich, A. T. Dinkova-Kostova, T. Efferth, K. El Bairi, N. Arkells, T. P. Fan, B. L. Fiebich, M. Freissmuth, M. I. Georgiev, S. Gibbons, K. M. Godfrey, C. W. Gruber, J. Heer, L. A. Huber, E. Ibanez, A. Kijjoa, A. K. Kiss, A. Lu, F. A. Macias, M. J. S. Miller, A. Mocan, R. Müller, F. Nicoletti, G. Perry, V. Pittalà, L. Rastrelli, M. Ristow, G. L. Russo, A. S. Silva, D. Schuster, H. Sheridan, K. Skalicka-Woźniak, L. Skaltsounis, E. Sobarzo-Sánchez, D. S. Bredt, H. Stuppner, A. Sureda, N. T. Tzvetkov, R. A. Vacca, B. B. Aggarwal, M. Battino, F. Giampieri, M. Wink, J. L. Wolfender, J. Xiao, A. W. K. Yeung, G. Lizard, M. A. Popp, M. Heinrich, I. Berindan-Neagoe, M. Stadler, M. Daglia, R. Verpoorte and C. T. Supuran, *Nat. Rev. Drug Discov.*, 2021, **20**, 200–216.

3 E. Patridge, P. Gareiss, M. S. Kinch and D. Hoyer, *Drug Discov. Today*, 2016, **21**, 204–207.

4 B. A. Weaver, *Mol. Biol. Cell*, 2014, **25**, 2677–2681.

5 J. H. Grosset and T. Singer, *Brenner's Encycl. Genet. Second Ed.*, 2013, 568–569.

6 P. B. Murphy, S. Bechmann and M. J. Barrett, *Nat. Small Mol. Drugs from Plants*, 2020, 295–302.

7 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Deliv. Rev.*, 2012, **64**, 4–17.

8 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

9 T. Rodrigues, D. Reker, P. Schneider and G. Schneider, *Nat. Chem.*, 2016, **8**, 531–541.

10 B. Over, S. Wetzel, C. Grütter, Y. Nakai, S. Renner, D. Rauh and H. Waldmann, *Nat. Chem.*, 2013, **5**, 21–28.

11 K. C. Pullaiah, R. K. Surapaneni, C. B. Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, H. Cun-heng and J. Clardy, *J. Org. Chem.*, 1985, **50**, 3665–3666.

12 D. J. Faulkner, *Nat. Prod. Rep.*, 1984, **1**, 251–280.

13 A. D. Rodriguez, E. Gonzalez and C. Ramirez, *Tetrahedron*, 1998, **54**, 11683–11729.

14 J. Reinecke and H. M. R. Hoffmann, *Chem. Eur. J.*, 1995, **1**, 368–373.

15 K. C. Nicolaou, Y. P. Sun, X. S. Peng, D. Polet and D. Y. K. Chen, *Angew. Chem. Int. Ed.*, 2008, **47**, 7310–7313.

16 M. Willot, L. Radtke, D. Könning, R. Fröhlich, V. H. Gessner, C. Strohmann and M. Christmann, *Angew. Chem. Int. Ed.*, 2009, **48**, 9105–9108.

17 W. Bin Sun, X. Wang, B. F. Sun, J. P. Zou and G. Q. Lin, *Org. Lett.*, 2016, **18**, 1219–1221.

18 G. M. Konig and A. D. Wright, *Tetrahedron*, 1994, **50**, 8011–8018.

19 M. Piattelli, C. Tringali, P. Neri and C. Rocco, *J. Nat. Prod.*, 1995, **58**, 697–704.

20 C. B. Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, H. Cun-heng and J. Clardy, *J. Org. Chem.*, 1986, **51**, 2736–2742.

21 C. L. Hugelshofer and T. Magauer, *J. Am. Chem. Soc.*, 2016, **138**, 6420–6423.

22 B. Defaut, T. B. Parsons, N. Spencer, L. Male, B. M. Kariuki and R. S. Grainger, *Org. Biomol. Chem.*, 2012, **10**, 4926–4932.

23 H. Kusama, K. Ishida, H. Funami and N. Iwasawa, *Angew. Chem. Int. Ed.*, 2008, **47**, 4903–4905.

24 D. C. F. Law and S. W. Tobey, *J. Am. Chem. Soc.*, 1968, **90**, 2376–2386.

25 B. Föhlisch, E. Gehrlach and R. Herter, *Angew. Chemie Int. Ed. Engl.*, 1982, **21**, 137–137.

26 K. A. Marshall, A. K. Mapp and C. H. Heathcock, *J. Org. Chem.*, 1996, **61**, 9135–9145.

27 J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, 1993, **58**, 3435–3443.

28 B. Gabriele, P. Plastina, M. V Vetere, L. Veltri, R. Mancuso and G. Salerno, *Tetrahedron Lett.*, 2010, **51**, 3565–3567.

29 J. A. Marshall and C. A. Sehon, *J. Org. Chem.*, 1995, **60**, 5966–5968.

30 M. Kurosu, L. R. Marcin and Y. Kishi, *Tetrahedron Lett.*, 1998, **39**, 8929–8932.

31 B. Seiller, C. Bruneau and P. H. Dixneuf, *Tetrahedron*, 1995, **51**, 13089–13102.

32 R. Okazaki, Y. Negishi and N. Inamoto, *J. Org. Chem.*, 1984, **49**, 3819–3824.

33 K. Takahashi, K. Komine, Y. Yokoi, J. Ishihara and S. Hatakeyama, *J. Org. Chem.*, 2012, **77**, 7364–7370.

34 J. Wittenberg, W. Beil and H. M. R. Hoffmann, *Tetrahedron Lett.*, 1998, **39**, 8259–8262.

35 C. B. W. Stark, S. Pierau, R. Wartchow and H. M. R. Hoffmann, *Chem. Eur. J.*, 2000, **6**, 684–691.

36 S. W. Tobey and R. West, *J. Am. Chem. Soc.*, 1966, **88**, 2481–2488.

37 Y. Apeloig, D. Arad, M. Kapon and M. Wallerstein, *Tetrahedron Lett.*, 1987, **28**, 5917–5920.

38 R. S. Orugunty, D. L. Wright, M. A. Battiste and K. A. Abboud, *Org. Lett.*, 2002, **4**, 1997–2000.

39 R. S. Orugunty, I. Ghiviriga, K. A. Abboud, M. A. Battiste and D. L. Wright, *J. Org.*

Chem., 2004, **69**, 570–572.

40 R. S. Orugunty, D. L. Wright, M. A. Battiste, R. J. Helmich and K. Abboud, *J. Org. Chem.*, 2004, **69**, 406–416.

41 E. Z. Oblak and D. L. Wright, *Org. Lett.*, 2011, **13**, 2263–2265.

42 E. Z. Oblak, M. D. Vanheyst, J. Li, A. J. Wiemer and D. L. Wright, *J. Am. Chem. Soc.*, 2014, **136**, 4309–4315.

43 D. A. Khlevin, S. E. Sosonyuk, M. V. Proskurnina and N. S. Zefirov, *Tetrahedron*, 2012, **68**, 5785–5792.

44 M. Baalouch, A. De Mesmaeker and R. Beaudegnies, *Tetrahedron Lett.*, 2013, **54**, 557–561.

45 S. Sendelbach, R. Schwetzler-Raschke, A. Radl, R. Kaiser, G. H. Henle, H. Korfant, S. Reiner and B. Fohlisch, *J. Org. Chem.*, 1999, **64**, 3398–3408.

46 B. Föhlisch, H. Korfant, H. Meining and W. Frey, *Eur. J. Org. Chem.*, 2000, 1335–1344.

47 B. Föhlisch and H. Zinser, *Org. Prep. Proced. Int.*, 2004, **36**, 549–572.

48 J. C. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 3243–3246.

49 K. Lee and Jin Kun Cha, *J. Am. Chem. Soc.*, 2001, **123**, 5590–5591.

50 G. Kreiselmeier and B. Föhlisch, *Tetrahedron Lett.*, 2000, **41**, 1375–1379.

51 F. Yu, G. Li, P. Gao, H. Gong, Y. Liu, Y. Wu, B. Cheng and H. Zhai, *Org. Lett.*, 2010, **12**, 5135–5137.

52 T. Sasaki, Y. Ishibashi and M. Ohno, *Tetrahedron Lett.*, 1982, **23**, 1693–1696.

53 M. Harmata and U. Sharma, *Org. Lett.*, 2000, **2**, 2703–2705.

54 R. L. Funk and K. J. Yost, *J. Org. Chem.*, 1996, **61**, 2598–2599.

55 K. Ishida, H. Kusama and N. Iwasawa, *J. Am. Chem. Soc.*, 2010, **132**, 8842–8843.

56 X. Z. Shu, S. C. Zhao, K. G. Ji, Z. J. Zheng, X. Y. Liu and Y. M. Liang, *Eur. J. Org. Chem.*, 2009, 117–122.

57 H. Kusama, A. Tazawa, K. Ishida and N. Iwasawa, *Chem. Asian J.*, 2016, **11**, 64–67.

58 Y. Auberson, R. M. Bimwala and P. Vogel, *Tetrahedron Lett.*, 1991, **32**, 1637–1640.

59 H. Liu, C. Sun, N. K. Lee, R. F. Henry and D. Lee, *Chem. Eur. J.*, 2012, **18**, 11889–11893.

60 S. Krüger and T. Gaich, *Angew. Chem. Int. Ed.*, 2015, **54**, 315–317.

61 M. Hönig and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2020, **59**, 1192–1196.

62 Y. Ito, S. Fujii and T. Saegusa, *J. Org. Chem.*, 1976, **41**, 2073–2074.

63 P. Vogel and P. Gerber, *Helv. Chim. Acta*, 2001, **84**, 1363–1395.

64 W. J. Moran and A. Rodríguez, *Org. Prep. Proced. Int.*, 2012, **44**, 103–130.

65 A. Blanc, V. Bénéteau, J. M. Weibel and P. Pale, *Org. Biomol. Chem.*, 2016, **14**, 9184–9205.

66 A. L. Siva Kumari, A. Siva Reddy and K. C. K. K. Swamy, *Org. Biomol. Chem.*, 2016, **14**, 6651–6671.

67 A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084–3213.

68 R. E. Ireland and J. A. Marshal, *J. Org. Chem.*, 1962, **27**, 1615–1619.

69 M. E. Garst and T. A. Spencer, *J. Am. Chem. Soc.*, 1973, **95**, 250–252.

70 Y. Wakabayashi, Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki, *Tetrahedron*, 1985, **41**, 3655–3661.

71 Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki, *J. Org. Chem.*, 1991, **56**, 5816–5819.

72 X. Zhang, Z. Lu, C. Fu and S. Ma, *J. Org. Chem.*, 2010, **75**, 2589–2598.

73 B. Gabriele, G. Salerno and E. Lauria, *J. Org. Chem.*, 1999, **64**, 7687–7692.

74 A. E. DeCamp, S. G. Mills, A. T. Kawaguchi, R. Desmond, R. A. Reamer, L. DiMichele and R. P. Volante, *J. Org. Chem.*, 1991, **56**, 3564–3571.

75 S. A. Liu and D. Trauner, *J. Am. Chem. Soc.*, 2017, **139**, 9491–9494.

76 S. Ahmadipour, PhD Thesis, 2016.

77 A. Sembayeva, Masters Thesis, 2016.

78 D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *J. Org. Chem.*, 1993, **58**, 6838–6842.

79 Z. Arnold and A. Holy, *Collect. Czechoslov. Chem. Commun.*, 1961, **26**, 3059–3073.

80 K. Hiroya, R. Jouka, M. Kameda, A. Yasuhara and T. Sakamoto, *Tetrahedron*, 2001, **57**, 9697–9710.

81 D. S. Hamilton and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2012, **134**, 18577–18580.

82 J. M. M. Grandjean and D. A. Nicewicz, *Angew. Chem. Int. Ed.*, 2013, **125**, 4059–4063.

83 D. A. Nicewicz and D. S. Hamilton, *Synlett*, 2014, **25**, 1191–1196.

84 N. A. Romero and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2014, **136**, 17024–17035.

85 Z. G. Hajos and D. R. Parrish, *Org. Synth.*, 1985, **63**, 26.

86 R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott and P. A. Wehrli, *J. Org. Chem.*, 1975, **40**, 675–681.

87 H. Ohmiya, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2006, **128**, 1886–1889.

88 S. Mahapatra and R. G. Carter, *J. Am. Chem. Soc.*, 2013, **135**, 10792–10803.

89 J. Dressel, K. L. Chasey and L. A. Paquette, *J. Am. Chem. Soc.*, 1988, **110**, 5479–5489.

90 H. S. Park, H. Y. Lee and Y. H. Kim, *Org. Lett.*, 2005, 3187–3190.

91 D. H. R. Barton, D. Ok Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1992, **33**, 5709–5712.

92 C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188–194.

93 G. J. Rowlands, *Tetrahedron*, 2009, **65**, 8603–8655.

94 D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1990, **31**, 4681–4684.

95 P. Kraft, C. Weymuth and C. Nussbaumer, *Eur. J. Org. Chem.*, 2006, **2006**, 1403–1412.

96 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392–4398.

97 M. Qian and D. F. Covey, *Adv. Synth. Catal.*, 2010, **352**, 2057–2061.

98 E. J. Corey and A. X. Huang, *J. Am. Chem. Soc.*, 1999, **121**, 710–714.

99 U. Yunus, R. Iqbal and E. Winterfeldt, *J. Heterocycl. Chem.*, 2005, **42**, 1079–1084.

100 E. J. Corey, M. C. Desai and T. A. Engler, *J. Am. Chem. Soc.*, 1985, **107**, 4339–4341.

101 Z. Novák, A. Szabó, J. Répási and A. Kotschy, *J. Org. Chem.*, 2003, **68**, 3327–3329.

102 D. Gelman and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2003, **42**, 5993–5996.

103 Y. Luo, H. Gao, Y. Li, W. Huang, W. Lu and Z. Zhang, *Tetrahedron*, 2006, **62**, 2465–2470.

104 A. Komáromi and Z. Novák, *Chem. Commun.*, 2008, 4968–4970.

105 E. A. Reddy, D. K. Barange, A. Islam, K. Mukkanti and M. Pal, *Tetrahedron*, 2008, **64**, 7143–7150.

106 M. Alami and G. Linstrumelle, *Tetrahedron Lett.*, 1991, **32**, 6109–6112.

107 M. Alami, B. Crousse and F. Ferri, *J. Organomet. Chem.*, 2001, **624**, 114–123.

108 M. Gredičak and I. Jerić, *Synlett*, 2009, **2**, 1063–1066.

109 G. Bucher, A. A. Mahajan and M. Schmittel, *J. Org. Chem.*, 2008, **73**, 8815–8828.

110 Y. Hsu, C. Ting and R. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 2090–2091.

111 H. Takahashi, K. Yoshida and A. Yanagisawa, *J. Org. Chem.*, 2009, **74**, 3632–3640.

112 R. Bera, K. Swamy, G. Dhananjaya, J. M. Babu, P. R. Kumar, K. Mukkanti and M. Pal, *Tetrahedron*, 2007, **63**, 13018–13023.

113 S. J. Mckerrall, L. Jørgensen, C. A. Kuttru, F. Ungeheuer and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5799–5810.

114 P. Pale and J. Chuche, *Eur. J. Org. Chem.*, 2000, **2000**, 1019–1025.

115 H. M. Sheldrake, C. Jamieson, S. I. Pascu and J. W. Burton, *Org. Biomol. Chem.*, 2009, **7**, 238–252.

116 J. Suffert and D. Toussaint, *Org. Synth.*, 2014, **76**, 214.

117 E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1973, 3817–3820.

118 H. Xu, H. Tang, Z. Yang, H. Feng and Y. Li, *Tetrahedron*, 2014, **70**, 3107–3115.

119 C. Ruecker, *Chem. Rev.*, 1995, **95**, 1009–1064.

120 M. Utsugi, M. Miyano and M. Nakada, *Org. Lett.*, 2006, **8**, 2973–2976.

121 C. B. W. Stark, U. Eggert and H. M. R. Hoffmann, *Angew. Chem. Int. Ed.*, 1998, **37**, 1266–1268.

122 K. Schank and A. Weber, *Chem. Ber.*, 1972, **105**, 2188–2196.

123 T. B. Parsons and R. S. Grainger, Unreported Work.

124 K. V. Rajendran, D. J. Carr and D. G. Gilheany, *Tetrahedron Lett.*, 2011, **52**, 7113–7115.

125 B. J. Bunn, P. J. Cox and N. S. Simpkins, *Tetrahedron*, 1993, **49**, 207–218.

126 C. M. Cain, R. P. C. Cousins, G. Coumbarides and N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523–544.

127 Y. Hayashi, J. Yamaguchi, T. Sumiya and M. Shoji, *Angew. Chem. Int. Ed.*, 2004, **43**, 1112–1115.

128 S. P. Mathew, H. Iwamura and D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2004, **43**, 3317–3321.

129 A. Bøgevig, H. Sundén and A. Córdova, *Angew. Chem. Int. Ed.*, 2004, **43**, 1109–1112.

130 P. H. Y. Cheong and K. N. Houk, *J. Am. Chem. Soc.*, 2004, **126**, 13912–13913.

131 P. Merino and T. Tejero, *Angew. Chem. Int. Ed.*, 2004, **43**, 2995–2997.

132 N. Momiyama, H. Torii, S. Saito and H. Yamamoto, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5374–5378.

133 V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gultekin, M. Lightowler and P. L. Spargo, *J. Org. Chem.*, 1995, **60**, 4962–4963.

134 V. K. Aggarwal, Z. Gültekin, R. S. Grainger, H. Adams and P. L. Spargo, *J. Chem. Soc. - Perkin Trans. 1*, 1998, 2771–2781.

135 V. K. Aggarwal, G. Evans, J. Dowden and E. Moya, *J. Org. Chem.*, 1992, **57**, 6390–6391.

136 H. Rebmann, C. K. G. Gerlinger and T. Gaich, *Chem. Eur. J.*, 2019, **25**, 2704–2707.

137 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287–290.

138 S. Musulla, Y. Bharathi Kumari, M. Madala, A. Srinivasa Rao and V. N. Vema, *Nat. Prod. Res.*, 2019, **0**, 1–5.

139 T. Nakata, S. Nagao and T. Oishi, *Tetrahedron Lett.*, 1985, **26**, 75–78.

140 M. Fetizon and M. Jurion, *J. Chem. Soc. Chem. Commun.*, 1972, **0**, 382–383.

141 H. Taguchi, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 6510–6511.

142 H. Taguchi, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 3010–3011.

143 K. C. Nicolaou, R. L. Magolda and D. A. Claremon, *J. Am. Chem. Soc.*, 1980, **102**, 1404–1409.

144 C. B. W. Stark, S. Pierau, R. Wartchow and H. M. R. Hoffmann, 2000, **6**, 684–691.

145 E. J. Corey and T. P. Loh, *Tetrahedron Lett.*, 1993, **34**, 3979–3982.

146 E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966–8967.

147 E. J. Corey, T. Loh, T. D. Roper, M. D. Azimioara and M. C. Noe, *J. Am. Chem. Soc.*, 1992, **114**, 8290–8292.

148 E. J. Corey, M. Ohno, P. A. Vatakencherry and R. B. Mitra, *J. Am. Chem. Soc.*, 1961, **83**, 1251–1252.

149 H.-S. Lin and L. A. Paquette, *Synth. Commun.*, 1994, **24**, 2503–2506.

150 L. Duhamel, *J. Organomet. Chem.*, 1993, **448**, 1–3.

151 D. B. G. Williams and M. Lawton, *J. Org. Chem.*, 2010, **75**, 8351–8354.

152 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.

153 G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176–2179.

154 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

155 G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Crystallogr.*, 2015, **71**, 3–8.

156 G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.*, 2015, **71**, 3–8.

157 Z. G. Hajos and D. R. Parrish, *Org. Synth.*, 1985, **63**, 26.

158 J. N. Gardner, B. A. Anderson and E. P. Oliveto, *J. Org. Chem.*, 1969, **34**, 107–112.

159 H. Hioki, T. Hashimoto and M. Kodama, *Tetrahedron Asymmetry*, 2000, **11**, 829–834.

160 J. S. Yadav and V. Rajender, *Eur. J. Org. Chem.*, 2010, **7**, 2148–2156.

161 S. Arseniyadis, D. V. Yashunsky, R. P. de Freitas, M. M. Dorado, E. Toromanoff and P. Potier, *Tetrahedron Lett.*, 1993, **34**, 1137–1140.

162 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470.

163 M. Vidal-Pascual, C. Martinez-Lamenca and H. M. R. Hoffmann, *Org. Synth.*, 2006, **83**, 61–69.