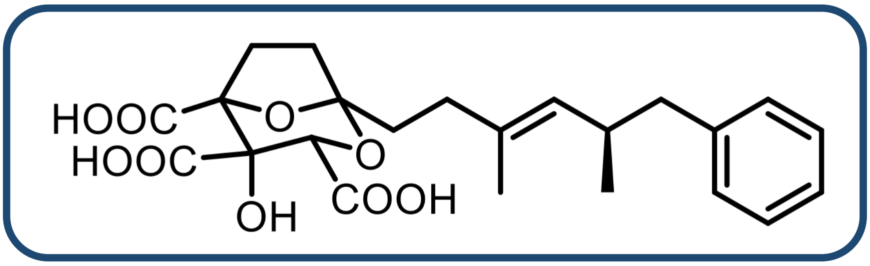
Total Synthesis of (–)-6,7-Dideoxysqualestatin H5 by Carbonyl Ylide Cycloaddition and Cross–Electrophile Coupling



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A thesis submitted to the

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In partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Chemistry Research Laboratory Hilary 2018

Dedicated to my parents

''We have met the enemy and they are ours'' R. B. Woodward

A telegram (1954) sent by Woodward to his fellow researchers on the completion of the strychnine synthesis.

Contents

Abstract

Total Synthesis of (–)-6,7-Dideoxysqualestatin H5 by Carbonyl Ylide Cycloaddition and Cross–Electrophile Coupling

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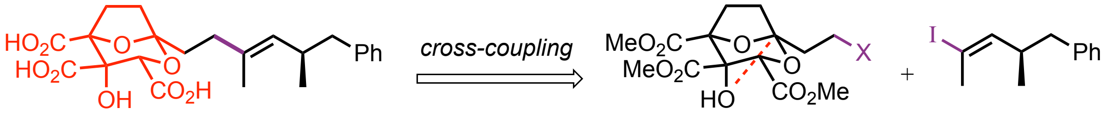
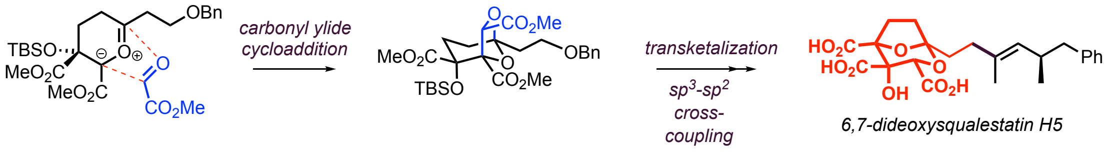
Oriel College, Hilary 2018

The work presented in this thesis focuses on the total synthesis of (–)-6,7-Dideoxysqualestatin H5. Particular emphasis was the development of a cross–coupling strategy for direct delivery of the side chain towards the end of the synthesis.



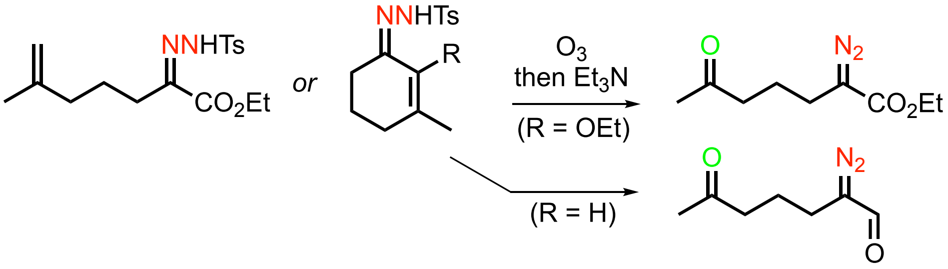
Scheme A1: cross–coupling strategy to assemble natural product.

Various methods investigated to perform the key Csp^3–Csp^2 coupling initially led to the Fu variant of the Negishi coupling at elevated temperatures and subsequent cross–electrophile coupling at rt. Key features of the asymmetric synthesis of (–)-6,7-dideoxysqualestatin H5, include: (1) highly diastereoselective *n*-alkylation of a tartrate acetonide enolate and subsequent oxidation-hydrolysis to provide an asymmetric entry to a *β*-hydroxy-*α*-ketoester motif; (2) facilitation of Rh(II)-catalysed cyclic carbonyl ylide formation-cycloaddition by cogeneration of keto and diazo functionality through ozonolysis of an unsaturated hydrazone; and (3) stereoretentive Ni-catalysed Csp^3–Csp^2 cross–electrophile coupling between tricarboxylate core and unsaturated side-chain to complete the natural product.



Scheme A2: Carbonyl ylide cycloaddition and Sp^3– Sp^2 cross–coupling.

Following completion of the natural product, further work was carried out on the ozonolysis of unsaturated tosylhydrazones as a direct approach to diazocarbonyls. The scope and limitations of reacting unsaturated tosylhydrazones with O_3 followed by Et_3N for the generation of 1,4- and 1,5-diazocarbonyl systems were explored. Tosylhydrazones, from tosylhydrazide condensation with readily available *δ*- and *ε*-unsaturated *α*-ketoesters, led in the former case to a 2-pyrazoline whereas the latter cases led to *α*-diazo-*ε*-ketoesters, although a terminal alkene produced a tetrahydropyridazinol. Tosylhydrazones from cyclic enones also allowed access to 1,4- and 1,5-diazocarbonyl systems using the ozonolysis–Et_3N strategy.



Scheme A3: Ozonolysis of unsaturated tosylhydrazones as a direct approach to diazocarbonyls.

Acknowledgements

Firstly, I would like to offer my sincere gratitude and appreciation to Professor David Hodgson for giving me the opportunity to work in his group, for his guidance and support throughout my D.Phil. His supervision towards organic chemistry has been supreme in guiding me become a competent chemist I am now. I have thoroughly enjoyed my research (even through all the hard times) in his group and am privileged to have worked under his supervision and grow as a synthetic organic chemist. I hope that your training will help me make a difference at some point in my life.

I also thank the EPSRC for funding and to the staff in the CRL, the NMR, Mass Spec and X-ray team (John Jolliffe and Steven Mansfield) who have helped along the way.

Specific thanks go to the Hodgson and the Smith group members both past and present, for their friendship and many laughs in the lab. There are many moments that I will never forget. I would like to thank Hassanain Al-Mohseni for being so pure (bureee just as he says it), Pascal Delany for always losing to me in every challenge we've had (though I'm not sure if I can beat him in fencing), Aubert Ribaucourt for being the most French person I know and Faisal Ebrahim for many moments of laughter and the opportunity to supervise his part II year.

Special thanks go to Antti Lahdenperä because if I wasn't going to hell already, I for sure will be joining him on the express bus on the highway to hell. He has been a true friend and I appreciate him being there for me and encourage when chemistry goes sideways (more then a few times). I'd like to thank Benji Franklin for being strong

(not a weak character) through all the Friday songs we've played in the lab and breaking world records, Shuyu Chu for being the most talented crazy chemist, Owen Snakey Smith for growing to be one hell of a Black Mamba (proud), Tudor Balan for his unforgiving point systems, and Richard Surgenor for being the tallest person in F4. Alex Cavell for the Friday playlist, Phil Gerkin for being the most politically correct person I know and Roly Armstrong for all his advice and funny stories. A special thanks also goes to Jonny Lockett for helping out proof reading my thesis, being a great football teammate (lobbed) and for all the mocha times comparing footballers salaries.

Once F4, always F4 (snake pit)

Furthermore, a special mention goes to all the QM and Whitefield guys because without them, it's just not the same.

Finally, I would like to extend my upmost gratitude to my parents, family and Sabiyah for their encouragement, support, patience and endless love throughout my biggest and proudest accomplishment.

Statement of Authorship

The work described in this thesis is entirely my own, with the following exceptions:

- X–ray analyses and data (performed and provided by John Jolliffe and Steven Mansfield)
- NOE studies on diazocarbonyls (performed by NMR staff)
- Where reference is given to a published source or thesis

Signature:

Name: Younes Fegheh-Hassanpour **Date:**

Abbreviations

Ac – Acetyl

acac – Acetylacetonate

Ar – Aryl

aq. – Aqueous

Bn – Benzyl

Boc – *tert*-Butyloxycarbonyl

b.p. – Boiling point

Bpy – 2,2'-Bipyridine

brsm – Based on recovered starting material

Bu – Butyl

Bz – Benzoyl

Cat. – Catalytic

CoA – Co-enzyme A

Cy – Cyclohexyl

Cyp – Cyclopentyl

δ – Chemical shift

d – Doublet

dba – Dibenzylideneacetone

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

DCC – N,N'-Dicyclohexylcarbodiimide

DIBAL-H – Diisobutylaluminium hydride

6,7-DDSQ H5 – 6,7-Dideoxysqualestatin

DMA – *N,N*-Dimethylacetamide

DMAD – Dimethyl acetylenedicarboxylate

DMAP – 4-Dimethylaminopyridine

m – Multiplet

Me – Methyl

mg – Milligram(s)

min – Minute(s)

mL – Millilitre(s)

mmol – Millimole(s)

MoOPH – MoO_5•Py•HMPA

m.p. – Melting point

MVK – Methyl vinyl ketone

^{n}Bu – *n*-Butyl

NMI – 1-Methylimidazole

NMP – N-Methyl-2-pyrrolidone

NMR – Nuclear magnetic resonance

Nu^- – Nucleophile

PCC – Pyridinium chlorochromate

PG – Generic protecting group

Ph – Phenyl

Pin – Pinacol

Piv – Pivalyl

PP – Pyrophosphate

ppm – Parts per million

PPTS – Pyridinium p-toluenesulfonate

Py – Pyridine

q – Quartet

R_f – Retention factor

DMF – *N*,*N*-Dimethylformamide

DMPU – 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*) - pyrimidinone

dr – Diastereomer ratio

DTBMS – Di-*tert*-butylmethylsilyl

E^{+} – Electrophile

eq. – Equivalent(s)

er – Enantiomer ratio

Et – Ethyl

g – Gram(s)

h – Hour(s)

HMDS – Hexamethyldisilazane

HMG – 3-Hydroxy-3-methylglutaryl

HMPA – Hexamethylphosphoramide

HMTA – Hexamethylenetetramine

HPLC – High-performance liquid chromatography

HRMS – High resolution mass spectrometry

Hz – Hertz

^{i}**Pr** – Isopropyl

IR – Infrared

J – Coupling constant

LDA – Lithium diisopropylamide

LHDMS – Lithium bis(trimethylsilyl)amide

Lit. – literature

M – Molarity

rt – Room temperature

LRMS – Low resolution mass spectrometry

s – Singlet

Sat. – Saturated

SM – Starting material(s)

t – Triplet

TBAF – Tetrabutylammonium fluoride

TBS/TBDMS – *tert*-Butyldimethylsilyl

TBDPS – *tert*-Butyldiphenylsilyl

^{t}**Bu –** *tert*-Butyl

TEBACl – Benzyltriethylammonium chloride

tert – Tertiary

TFA – Trifluoroacetic acid

Tf$_2$O – Trifluoromethanesulfonic anhydride

THF – Tetrahydrofuran

THP – Tetrahydropyran

TLC – Thin layer chromatography

TMAF – Tetramethylammonium fluoride

TMEDA – Tetramethylethylenediamine

TMS – Trimethylsilyl

tRNA – transfer Ribonucleic Acid

Ts – p-Toluenesulfonyl

υ_{max} – Infrared absorption maxima

Chapter 1

Introduction and Aims

1. Introduction

1.1 6,7-Dideoxysqualestatin H5 Background

Compounds with complex molecular architecture and multiple functional groups provide opportunities for devising new strategies and methodologies, as well as evaluating the applicability of known methods and reactions.

Coronary heart disease is the major cause of mortality in industrialised countries. In a study carried out by the World Health Organisation, it is estimated that every year cardiovascular disease kills approximately 15 million people, reflecting 54% of deaths worldwide. Cardiovascular disease has remained the leading causes of death globally in the last 15 years.[1]

Statins are effective in preventing cardiovascular disease by inhibiting HMG–CoA reductase, the rate-determining enzyme of the cholesterol biosynthetic pathway (**Figure 1**).[2] In 2011, global sales of statins and other lipid-regulating drugs had reached a new high of $39.1b a year. Pfizer's Lipitor was the world's top-selling drug with annual sales of over $12b. Although statin therapy is commonly well tolerated and has been used for the past 20 years, serious side effects have been reported (muscle pain, liver inflammation, increased risk of type 2 Diabetes and potential neurological damage). It is postulated that some statins side effects may be due to the fact that statins suppress all post-mevalonate biosynthesis steps including non-steroidal isoprenoids (**Figure 1**).[3] The inhibition of HMG–CoA reductase, a key regulator of the mevalonic acid pathway, causes not only decrease in cholesterol biosynthesis, but also disrupts the synthesis of other important molecules in the pathway (**Figure 1**).[4]

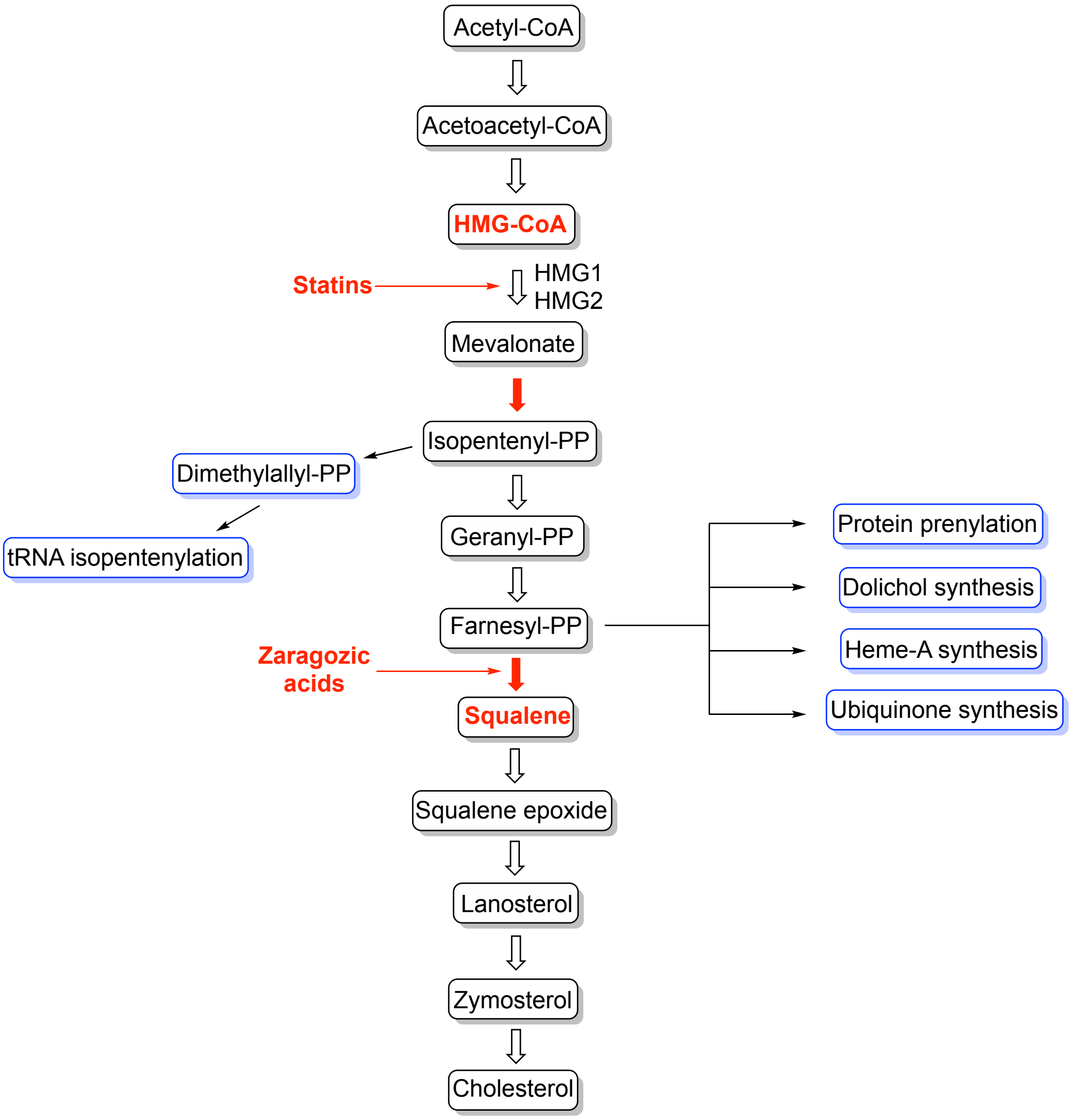
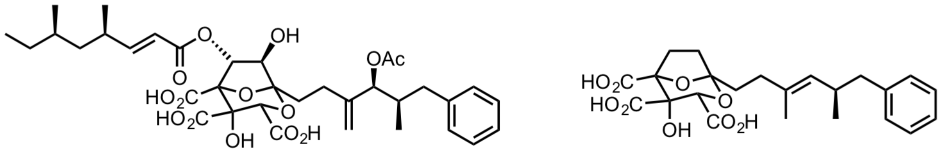


Figure 1. The biosynthesis of cholesterol.[4]

Therefore, there is a need for new medicines to lower cholesterol levels, without any serious adverse reactions and also effective against hypercholesterolemia. The zaragozic acids/squalestatins have been the focus of considerable interest ever since reports of their isolation appeared in the early 1990s.[5] Potent mammalian squalene synthase inhibition originally propelled these natural products into the limelight as lead structures for cholesterol lowering therapeutics.[6] Squalene synthase is involved in the reductive dimerisation of two farnesyl pyrophosphate molecules to form squalene implicated in the first committed step of cholesterol biosynthesis (**Figure 1**). The zaragozic acids (competitive inhibitor of sterol synthesis, also called squalestatins, eg. **2**)[7] offer a potential alternative to statins in reducing high levels of cholesterol; the latter being strongly associated with cardiovascular disease.[7]



1 **2**

Figure 2. The structure of zaragozic acid A (squalestatin S1) **1** and 6,7-Dideoxysqualestatin H5 (**2**).

The biological activity of squalestatins also extends to antifungal properties, as well as inhibition of farnasyl transferase.[8] More recent studies include potential application in retinal degenerative disorders,[9] antimalarials,[10] hepatitis C activity,[11] and as antitumor agents.[12]

This project entails the synthesis of 6,7-dideoxysqualestatin H5 (**2**) (**Figure 2**), a member of this class of fungal metabolites, which are therapeutic leads for the treatment of both hypercholesterolemia and fungal infections. The squalestatins possess a heavily oxygenated spiroketal 2,8-dioxabicyclo[3.1.0]octane core (**Figure 2 and 3**), proven to be synthetically challenging and part of a family of privileged scaffolds. Their biological activity combined with their structural challenges and novelty have made them compelling targets for synthetic studies, and many inventive strategies have been investigated resulting in several full, partial and model syntheses of members of the zaragozic acid/squalestatin family with the added benefit of introducing modifications at various stages, giving access to a large library of targets.[13] To put our current approach in perspective, an overview of key features of these syntheses is presented in **section 1.2**. Knowledge gained from previous studies was used as inspiration and motivation towards developing our synthetic route towards the natural product 6,7-DDSQ H5.

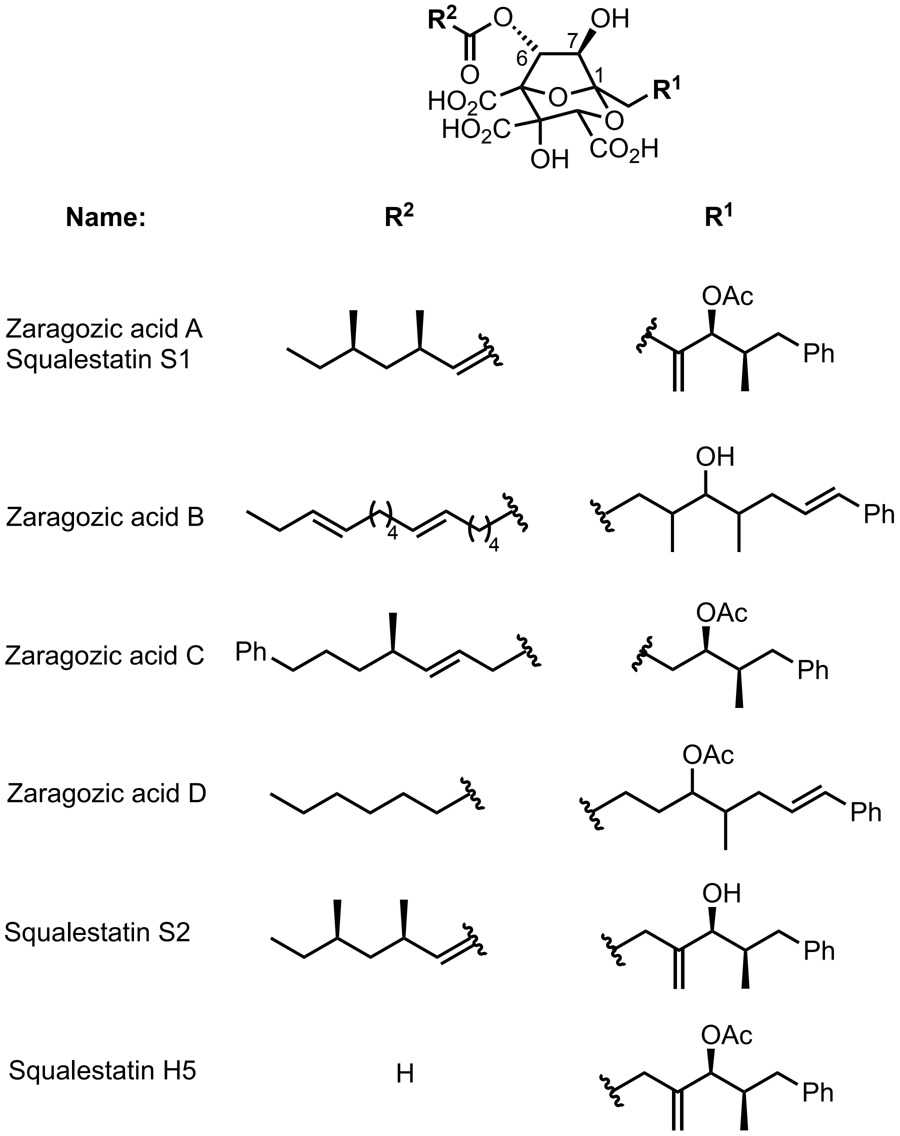
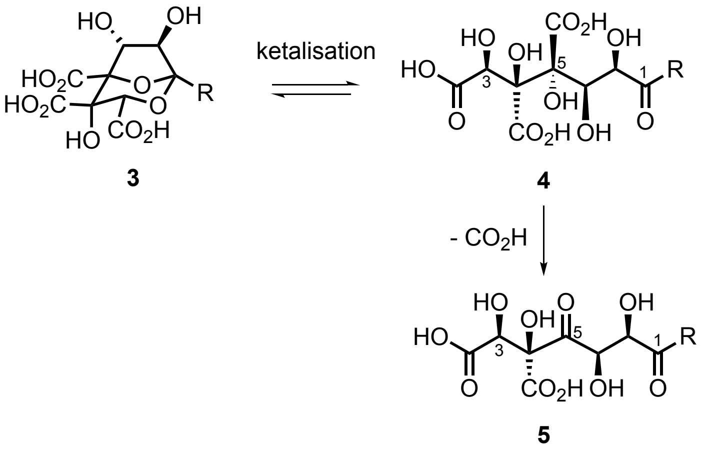


Figure 3. The different examples of the zaragozic acid/squalestatin family.

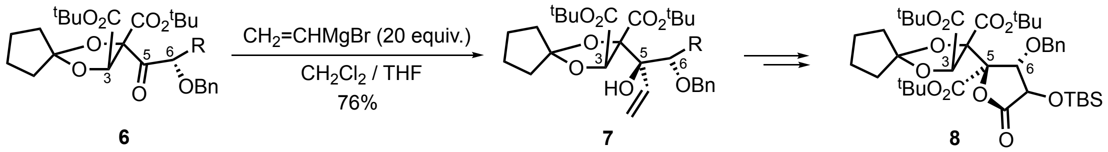
1.2 Previous Total Syntheses

In 1994, Evans[14] reported a total synthesis of zaragozic acid C, in which a key internal acid-catalysed transketalisation (TFA:CH_2Cl_2:H_2O, 10:20:1) led to the desired ketal **3** (**Scheme 1**).



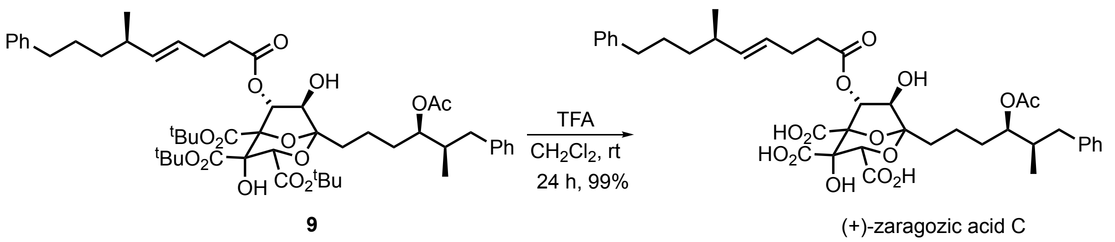
Scheme 1. Evans internal ketalisation.[14]

In another critical step, the introduction of C5 carboxylate fragment took place through chelate-controlled Grignard addition with stereocontrol (10:1 selectivity) evolving from C6 oxygen (**Scheme 2**).



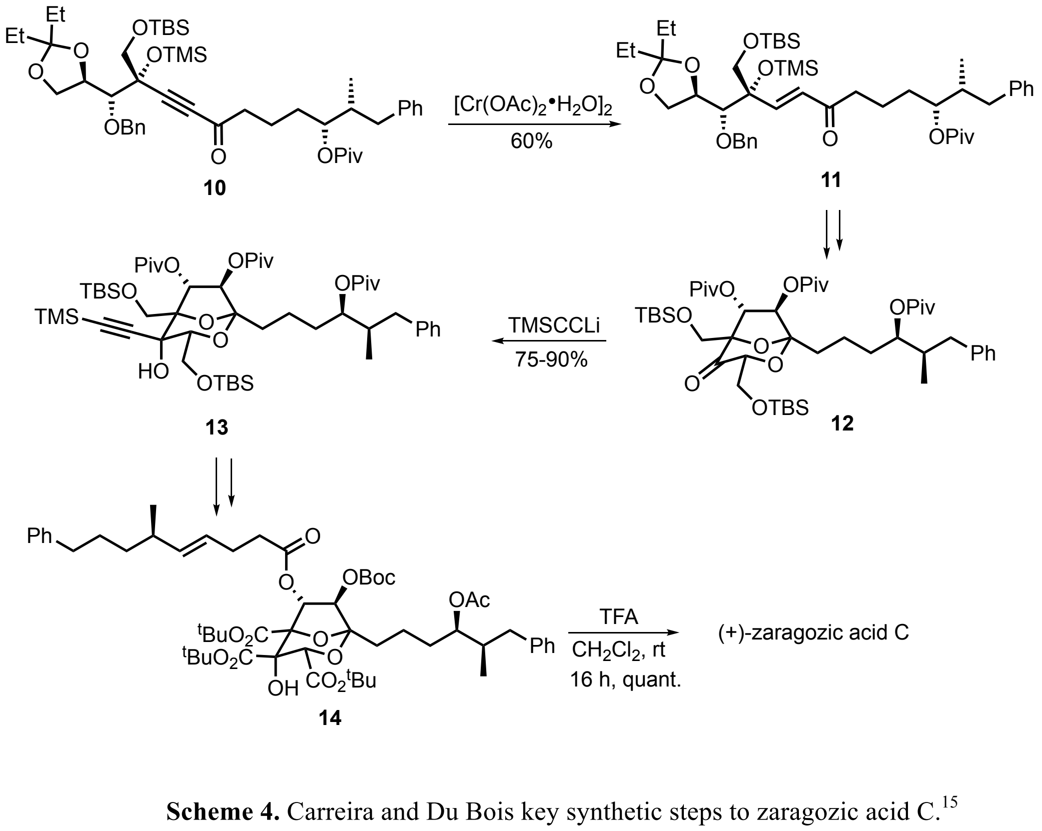
Scheme 2. Stereoselective carboxylate introduction *via* Grignard addition.[14]

The target compound was synthesised *via* TFA-catalysed hydrolysis of *t*-butyl esters (**Scheme 3**). The isolation of the natural product took place without the need for silica gel purification.



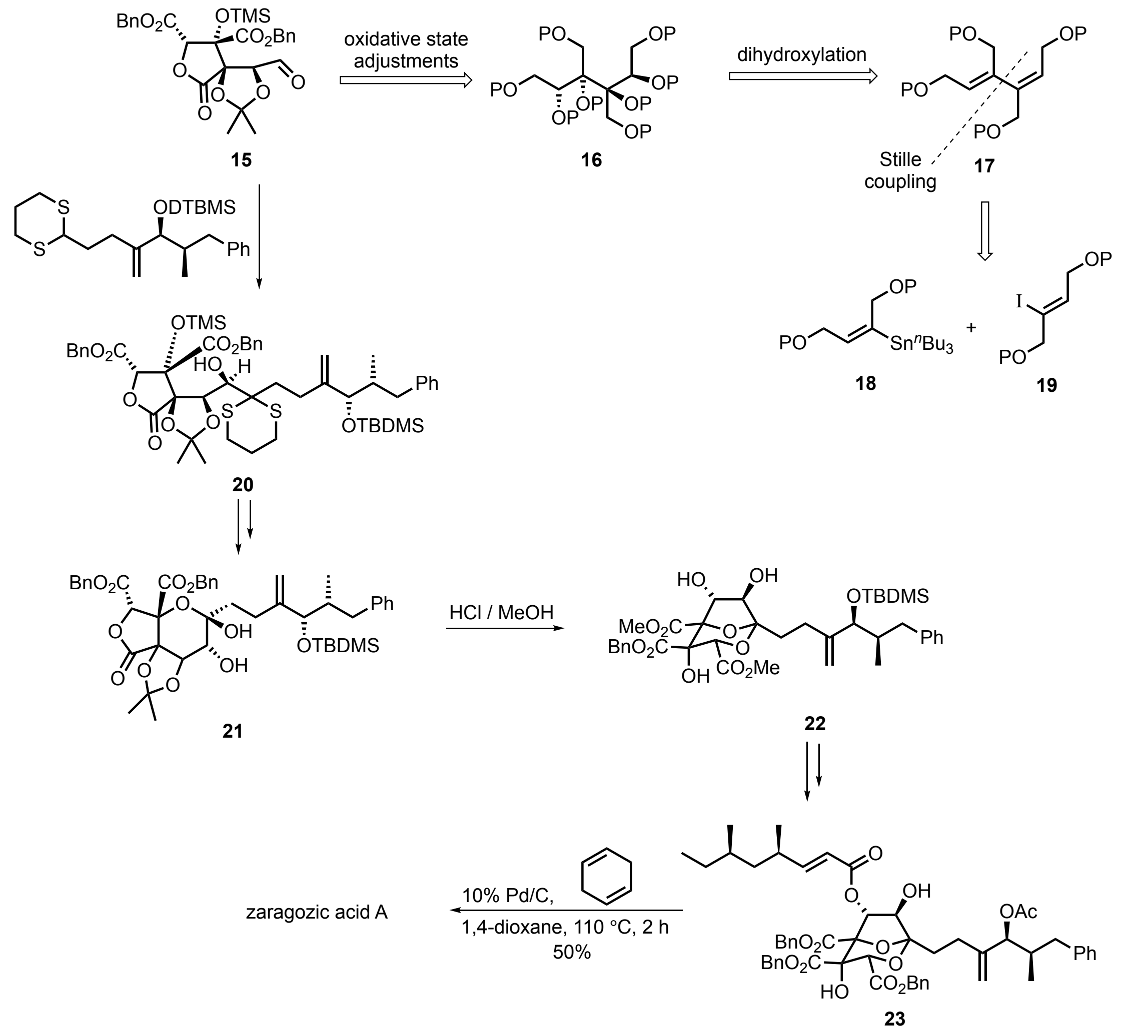
Scheme 3: Final step of Evans synthesis of zaragozic acid C.[14]

Carreira and Du Bois[15] total synthesis of zaragozic acid C in 1995 features the use of $[Cr(OAc)_2{\bullet}H_2O]_2$ for the diastereoselective reduction of an *α,β*–ynone **10** to furnish the *trans* enone **11** (**Scheme 4**). Nucleophilic addition of TMSC≡CLi to ketone **12**, gave alcohol **13** in 6:1 diastereoselectivity. Carreira found that the diastereoselection in the addition of TMSC≡CLi to ketone **12** depended on the aggregation state of the acetylide. The advanced intermediate was further elaborated into zaragozic acid C *via* TFA-catalysed hydrolysis of *t*-butyl esters accompanied with Boc removal at C7.



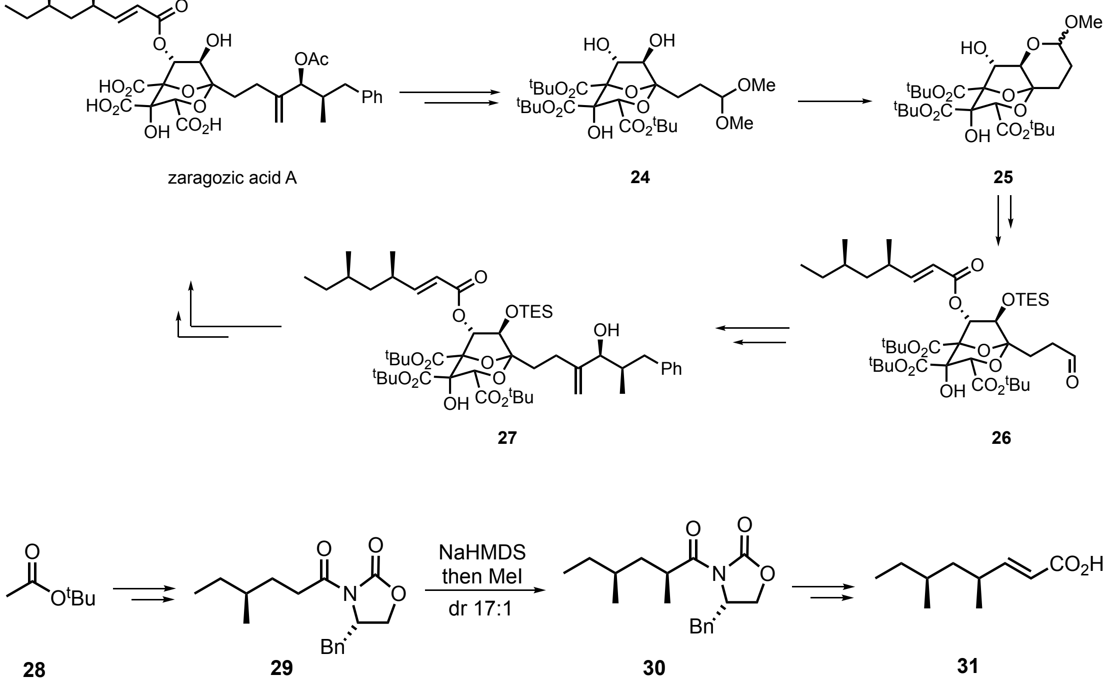
Scheme 4. Carreira and Du Bois key synthetic steps to zaragozic acid C.[15]

In 1995, Nicolaou[16] used a relay approach to complete a synthesis of zaragozic acid A. The total synthesis features several key steps including the use of dithiane chemistry to form functionalised alcohol **20** from aldehyde **15** which in turn is synthesised using Stille coupling (from stannane **18** and alkenyl iodide **19**) and double dihydroxylation (diene **17** to saturated protected alcohol **16**). An internal ketalisation from unrearranged diol **21** to rearranged diol **22** assembles the bicyclic core of the natural product. In the last step, transfer hydrogenolysis of tribenzyl triester **23** using Pd/C and 1,4-cyclohexadiene gave zaragozic acid A[16] in 70% crude yield; 50% after reverse phase HPLC purification (**Scheme 5**).



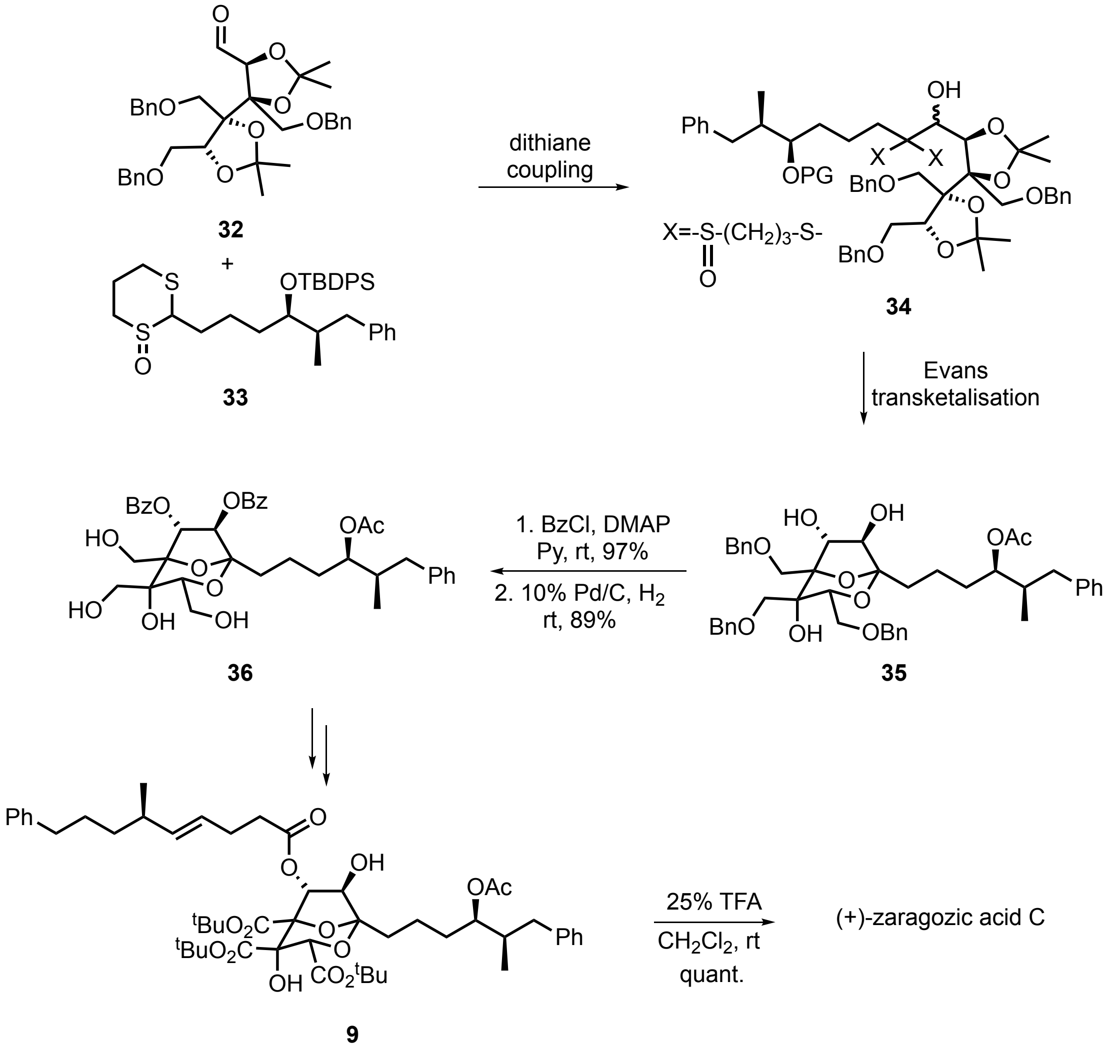
Scheme 5. Nicolaou's key steps in a synthesis of zaragozic acid A.[16]

The synthesis of zaragozic acid A by Heathcock[17] in 1996 was also a relay synthesis *via* relay compound acetal **24**[17b] as the key intermediate. Initially, the two side-chains were cleaved to form acetal **24** in a series of steps, which was further manipulated into cyclic methyl acetal **25**. Further to that, reconstruction began with hydrolysis of the diastereoisomers into aldehyde **26** and formation of the side-chain. A series of functional group interconversion *via* Evans[18] asymmetric enolate methylation was used as key step (from imide **29** to imide **30**) to form the side-chain **31** from bulk butyl acetate **28**. Heathcock obtained the final product using the method of Carreira (TFA, CH_2Cl_2, rt, 11 h) to hydrolyse *t*-butyl esters. However, the final product was then purified by semipreparative reverse phase HPLC to give zaragozic acid A in 74% yield (**Scheme 6**).



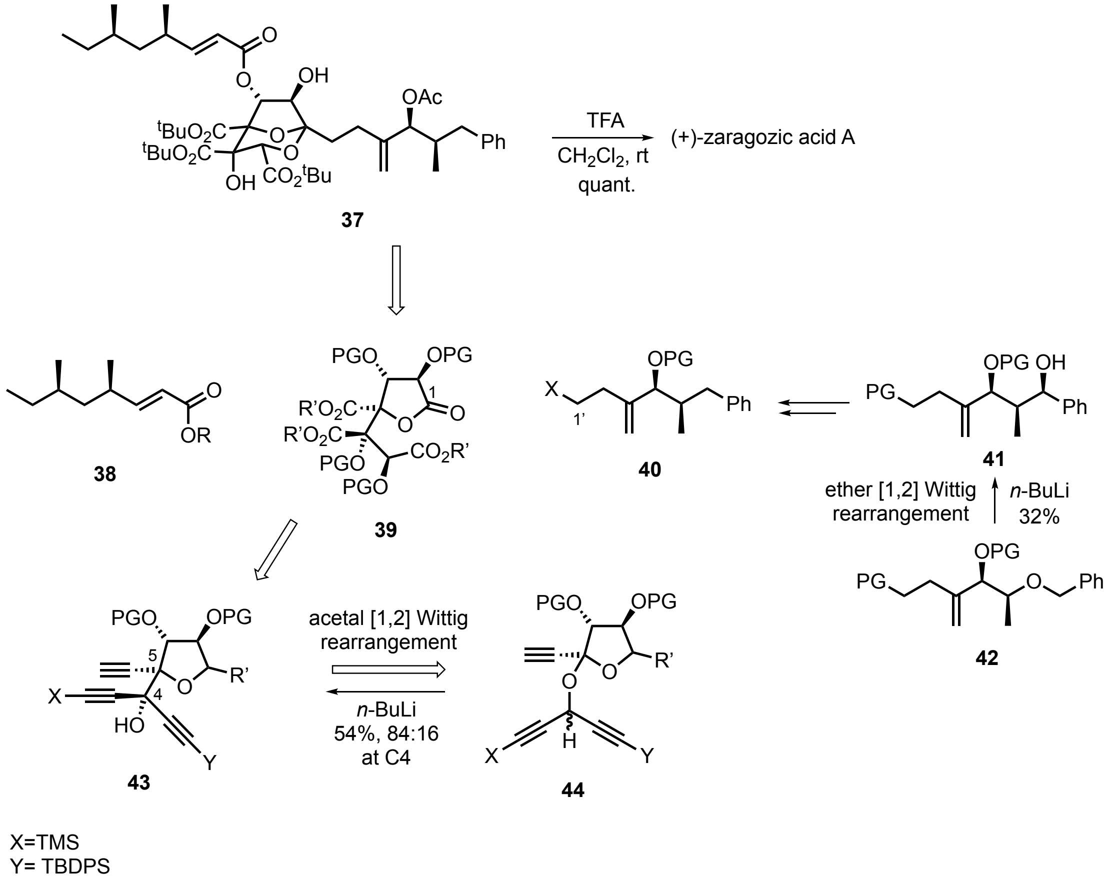
Scheme 6. Heathcock's key steps in a synthesis of zaragozic acid A.[17]

Armstrong[19] in 1998 accomplished a total synthesis of zaragozic acid C where a key reaction was the introduction of the C1 side-chain. The use of dithiane monosulfoxide coupling between aldehyde **32** and monosulfoxide **33** produced alcohol **34** as a mixture of diastereomers. Furthermore, the ketalisation conditions previously employed by Evans were used to assemble the bicyclic core **35** of zaragozic acid C. With positions C3, C4 and C5 all initially protected as benzyl ethers, hydrogenolysis of **35** led to the corresponding tetrol **36**. Functional group manipulations led to the triacids, protected as the *t*-butyl esters analogous to Carreira's approach. Lastly, acid hydrolysis led to formation of the target in quantitative yield (**Scheme 7**).



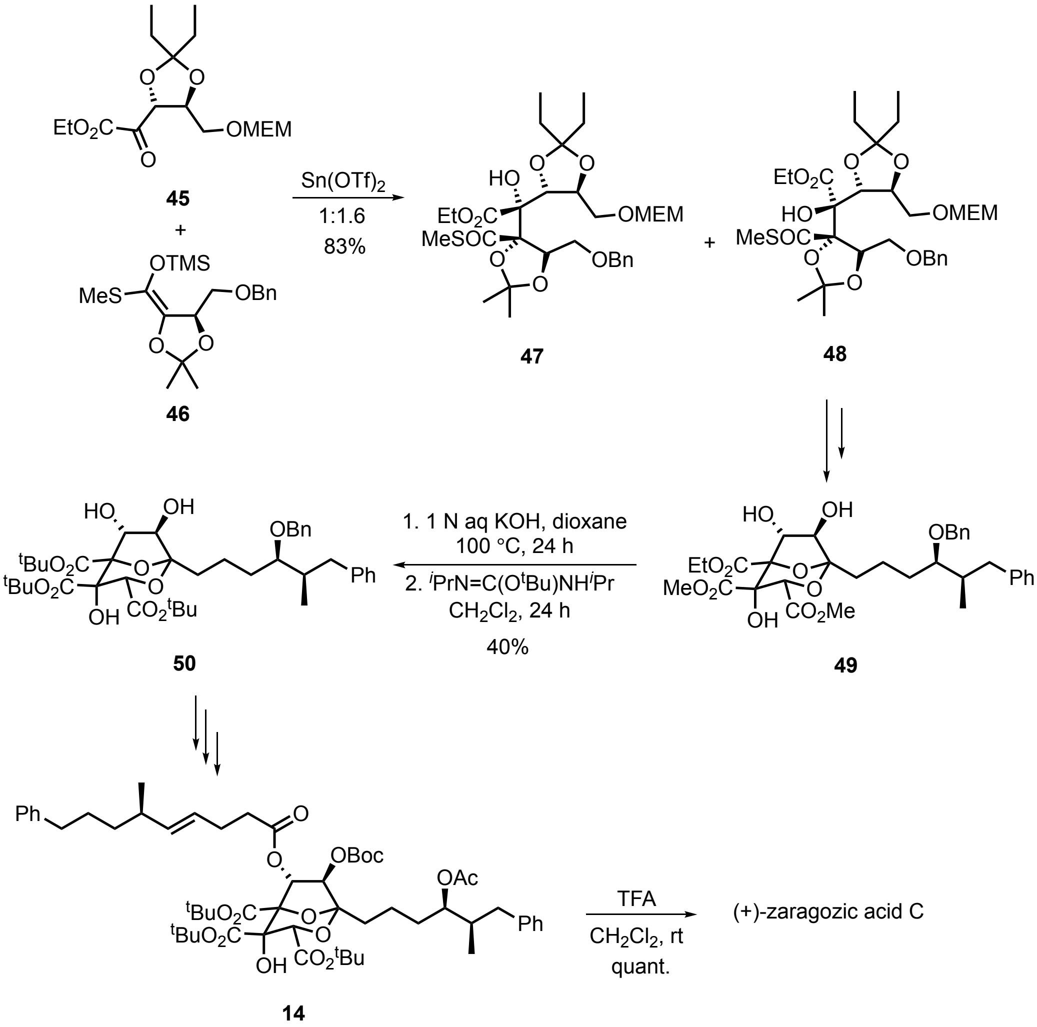
Scheme 7. Key steps in Armstrong's total synthesis of zaragozic acid C.[19]

In 2000, Tomooka[20] completed a stereoselective total synthesis of zaragozic acid A based on an acetal [1,2] Wittig rearrangement. The reaction of *O*-glycoside **44**, exclusively afforded the desired [1,2] Wittig product *C*-glycoside **43** with high diastereoselectivity >95% with 84% dr. at C4 in 54% yield (formation of C4-C5 bond). The side-chain (C1–C1') was then installed by reacting lactone **39** and alkyl halide **40** *via* carbanion chemistry; the latter was formed *via* an ether [1,2] Wittig rearrangement of ether **42** to alcohol **41** in 32% yield (**Scheme 8**). Finally, the synthesis was completed utilising the hydrolysis method of Carreira (TFA, CH_2Cl_2, rt, 73%), the synthesis was completed from *t*-butyl ester **37**. There appeared to be no signs of cyclisation of the Ph group onto the olefin moiety under the relatively acidic conditions employed (cf. see section 1.3.1 Sintim approach).



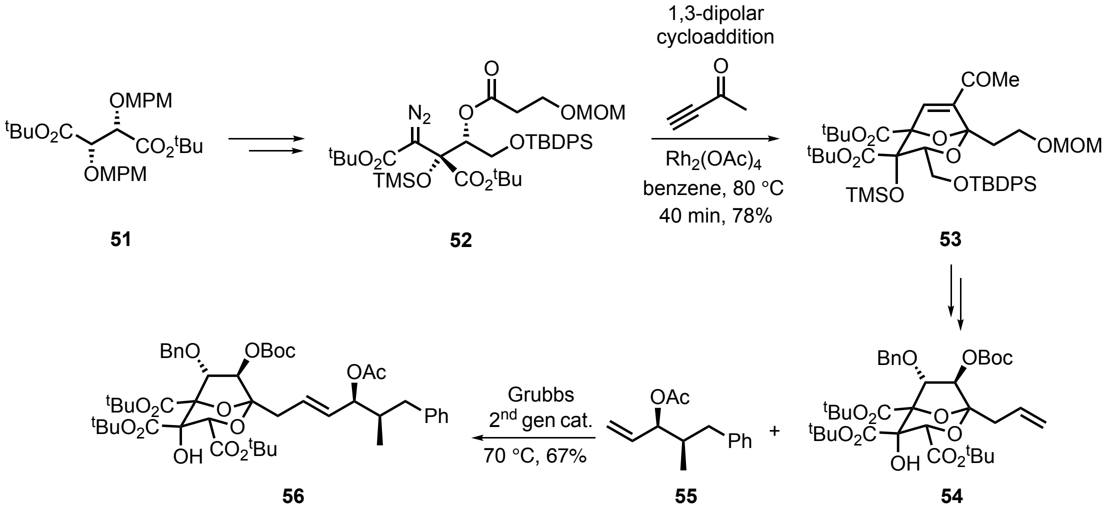
Scheme 8. Wittig rearrangement in Tomooka's total synthesis of zaragozic acid A.

Hashimoto[21] synthesised zaragozic acid C twice in 2005 and 2006 *via* an aldol reaction and tandem carbonyl ylide-formation/1,3-dipolar cycloaddition approaches with a key olefin cross-metathesis towards the end of synthesis. In the aldol approach, $Sn(OTf)_2$ is used in the coupling of α–ketoester **45** and thioacetal **46** to form the thioesters **47** and α-hydroxy thioester **48** in a 1:1.6 ratio respectively (**Scheme 9**). Hashimoto fully hydrolysed a mixture of methyl and ethyl esters of **49** to the corresponding triacid and immediately re–protected with *t*-butyl groups, to give **50** in a modest yield of 40% over the two steps. During the final step, Carreira's method (TFA) was used for global deprotection at rt to give zaragozic acid C in quantitative yield.



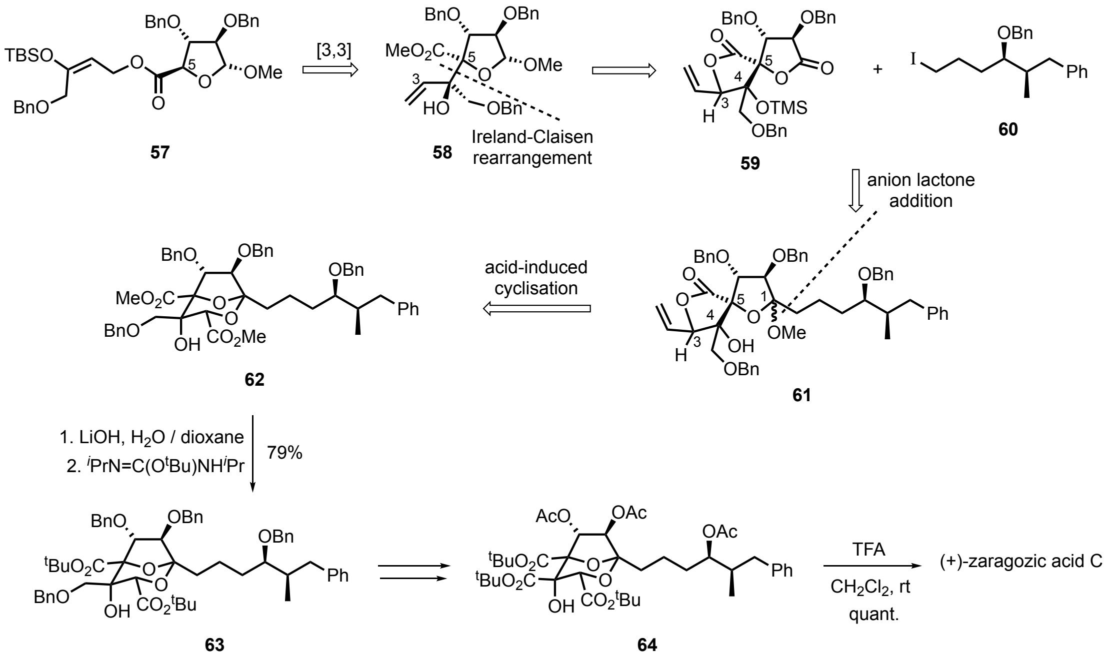
Scheme 9. Hashimoto's first approach using Aldol chemistry.[21]

In the second-generation approach (**Scheme 10**), the synthesis began with a protected D-tartrate **51** that was transformed into diazo substrate **52** in a series of reactions. The key cycloaddition step was treatment of diazo **52** with $Rh_2(OAc)_4$ to generate a carbonyl ylide which underwent 1,3-dipolar cycloaddition with 3-butyn-2-one in a completely regioselective and diastereoselective manner in 78% yield (**53**). Finally, olefin cross-metathesis using 2nd-generation Grubbs' catalyst gave cross-coupled product **56** as entirely the *E*-isomer, in 67% yield and 8% of homodimer from alkene **55** (**Scheme 10**).



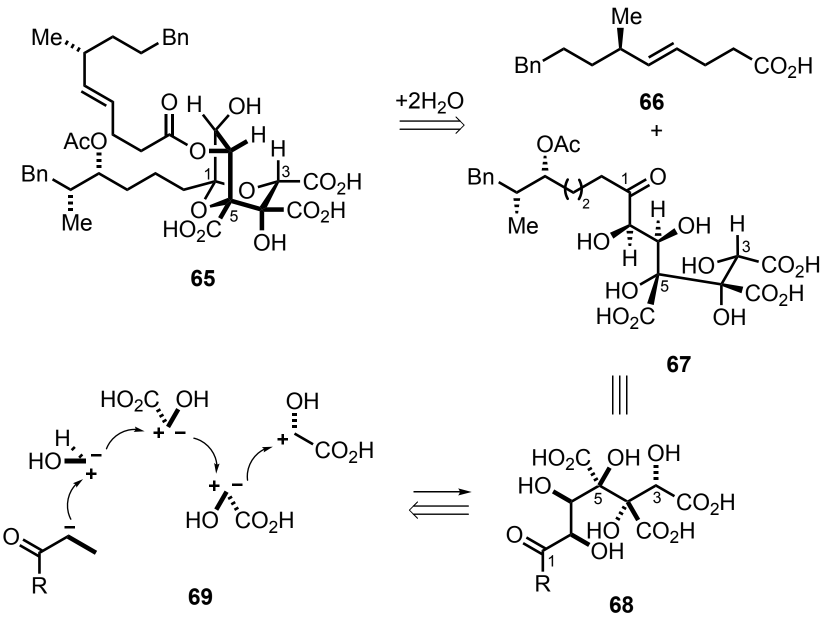
Scheme 10. Hashimoto's second approach using dipolar cycloaddition chemistry.[21]

In 2006 Rizzacasa[22] reported a formal synthesis of (+)-zaragozic acid C through an Ireland–Claisen rearrangement (**58**) in the presence of a *β*-leaving group of the sensitive allylic ester **57** derived from L-arabinose (**Scheme 11**). The acetal **61** is formed by regioselective addition of the alkyl lithium derived from the side-chain iodide **60** to the less-hindered C1 carbonyl group of the spirobislactone **59**. After acid-induced cyclisation (HCl/MeOH), the bicyclic core **62** of the product is formed. Hydrolysis of methyl esters at C3 and C5 using LiOH in dioxane/water followed by re–protection as *t*-butyl esters (**63**) were performed. After functional group manipulation at C4, it was eventually also protected as the *t*-butyl ester **64**; global deprotection in the final step used TFA (Carreira's method) to give the desired natural product (**Scheme 11**).



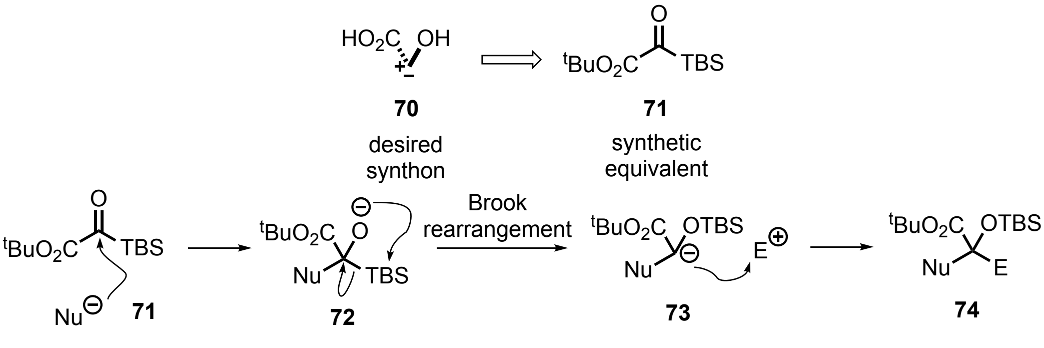
Scheme 11: Rizzacasa's synthesis of zaragozic acid C.

Syntheses of the zaragozic acid family continued in the last decade with the synthesis of zaragozic acid C *via* controlled oligomerisation. Johnson[23] in 2008 utilised a method of stereoselective polymerisation (**69**) generally applied in materials chemistry in the total synthesis (**Scheme 12**).



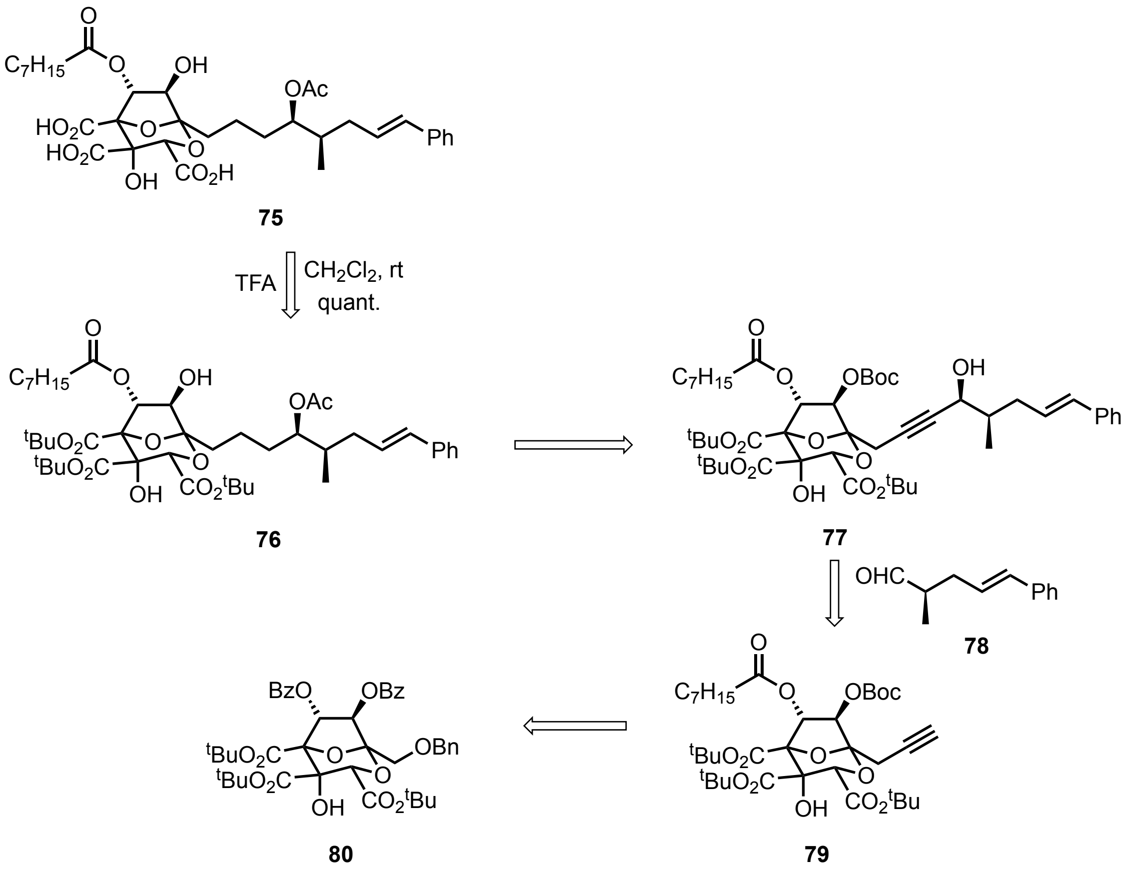
Scheme 12. Stereoselective polymerisation (**69**) to form the carbon skeleton **68**.[23]

Silyl glyoxylate **71** was used as a glycolic acid synthon (**70**) providing complementary Nu$^-$ and E$^+$ to form the backbone of the natural product. Nucleophilic attack on the silyl glyoxylate **71** facilitates Si migration in a Brook rearrangement[24] to form a stabilised carbanion (**72** to **73**), which then reacts with electrophiles (**73**) to give rise to a product where two new bonds have been formed (**74**, **Scheme 13**). The method assembled three contiguous stereogenic centers required for the natural product in the correct oxidation state. Johnson approached the end of the synthesis by converging to Carreira's substrate, which was then hydrolysed using TFA to obtain to the triacid.



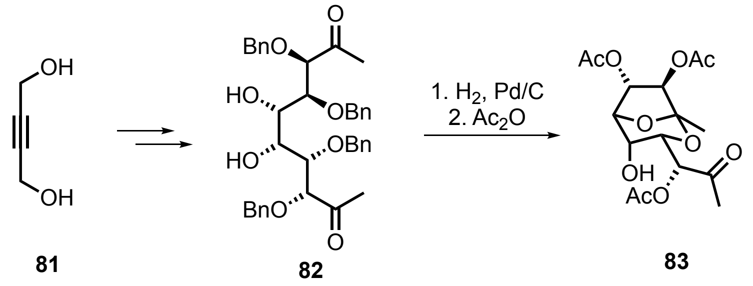
Scheme 13. The reactivity of silyl glyoxylate **71** as a building block.[23, 24]

In 2011, Metz achieved a total synthesis of zaragozic acid D with additional formal syntheses of zaragozic acids A and C.[25] The building block **80** previously published *via* intramolecular acetalisation[25b] provided a general functionalised core to access terminal alkyne **79**. Reaction of the alkyne **79** with the side-chain aldehyde **78** provided a diastereomeric mixture of internal alkyne **77** (1:2 epimer mixture at OH) which was later manipulated *via* a Dess-Martin oxidation and an asymmetric Ru transfer hydrogenation to the resultant alkynone **77** with excellent stereoselectivity (d.r. 20:1). Further functional group manipulations resulted in zaragozic acid D (**Scheme 14**) with zaragozic acids A and C also accessed.[26]



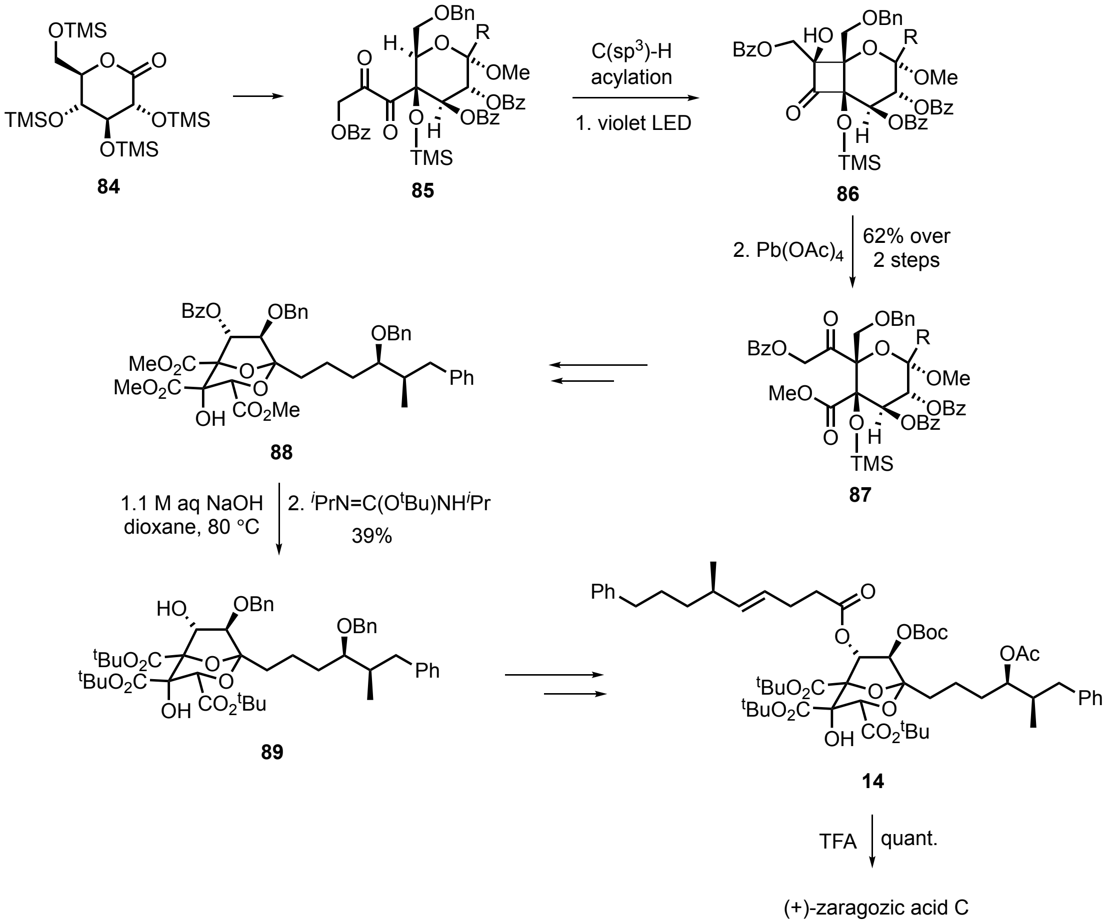
Scheme 14. Zaragozic acid D synthesis by Metz.[25]

As key steps, the symmetrical tetrabenzyl ether **82** was readily accessed from alkyne **81** through Sharpless asymmetric dihydroxylation (**Scheme 15**).[27] Furthermore, the heavily oxygenated **82** underwent a chemoselective intramolecular acetalisation to give the desired cyclisation product **83** on treatment with Ac_2O.



Scheme 15. Sharpless asymmetric dihydroxylation of alkyne **81** and key intramolecular acetalisation.[27]

In the most recent total synthesis of zaragozic acid C in 2017, Inoue[28] approached the synthesis *via* a two-step photochemical $C(sp^3)$−H acylation (**Scheme 16**). After conversion of silylated D-gluconolactone **84** into diketone **85**, Norrish−Yang cyclisation[29] under violet LED irradiation followed by oxidative opening of the resultant α-hydroxycyclobutanone (**86**) in a regio- and stereoselective manner transformed $C(sp^3)$−H bond at C4 into a $C(sp^3)$−C (**87**). Towards the last steps of the synthesis; Inoue illustrates another example of methyl ester hydrolysis followed by re–protection with *t*–butyl groups (**88** to **89**). Subsequent TFA catalysed hydrolysis gave the triacid in quantitative yield.

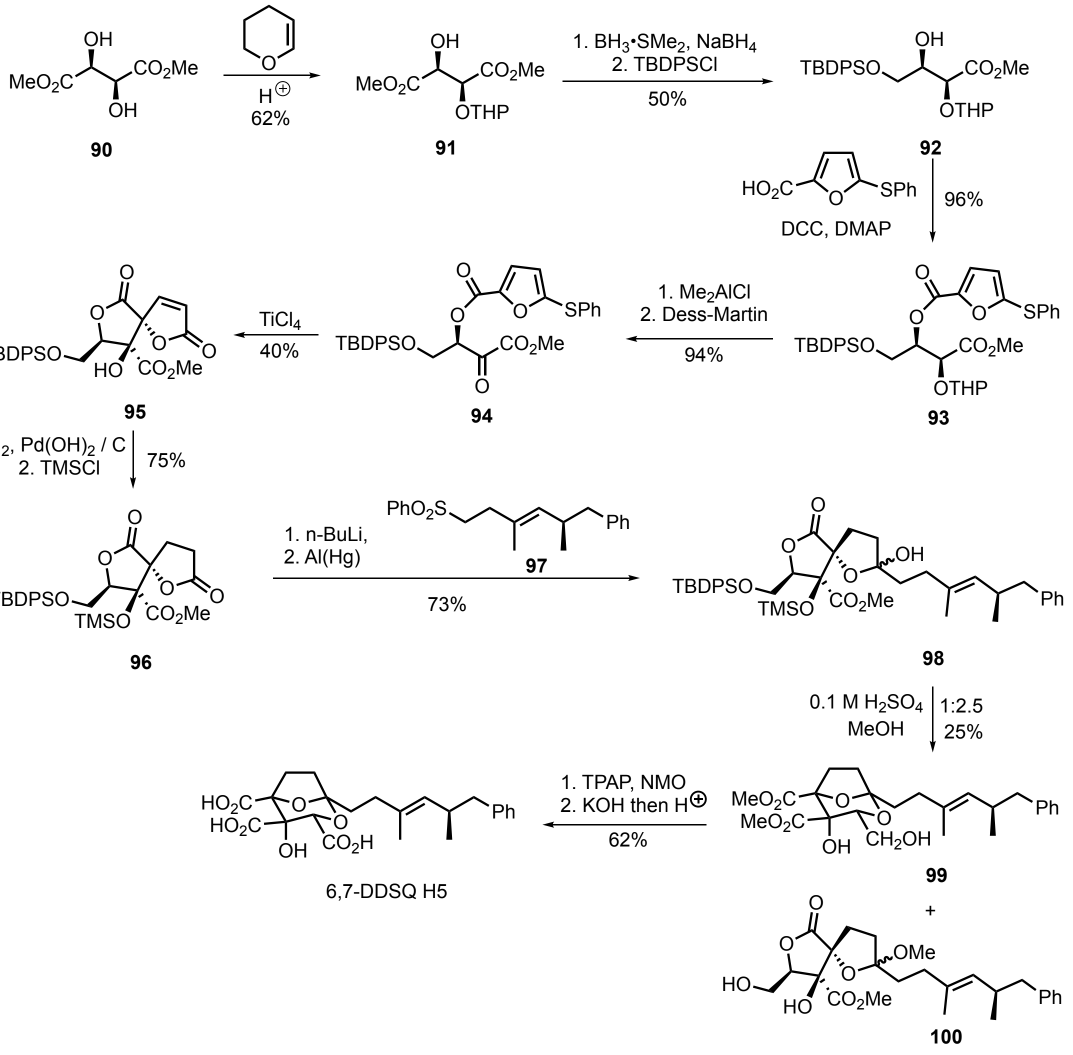


Scheme 16. Total synthesis of zaragozic acid C *via* photochemical acylation.[28]

1.3 Martin's Total Synthesis

Prior to our studies, Martin had carried out the only total synthesis of the least oxygenated member of the zaragozic acid family, 6,7-DDSQ H5 (**Scheme 17**).[30] The synthesis commenced with mono THP protection of readily available dimethyl tartrate **90** followed by regioselective reduction and primary alcohol TBDPS protection to give alcohol **92** in 50% yield. Alcohol **92** was then esterified to produce furoic ester **93**. After THP cleavage using Me_2AlCl, the resulting alcohol was oxidised with Dess-Martin periodinane to give ketoester **94** (**Scheme 17**). A key feature of Martin's synthesis was an intramolecular vinylogous aldol reaction using

$TiCl_4$, converting ketoester **94** to alcohol **95**, featuring the diastereoselective generation of stereochemistry required in 6,7-DDSQ H5 (less than 5% of the other three diastereomeric adducts were obtained under these conditions).



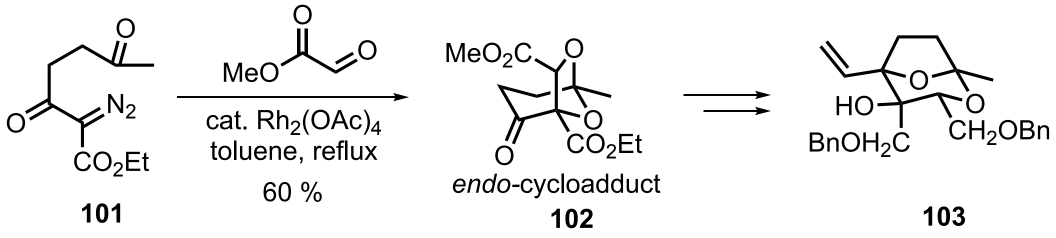
Scheme 17: Martin's total synthesis of 6,7-dideoxysqualestatin H5.[30]

Hydrogenation followed by silylation resulted in the formation of lactone **96**. The C1 side-chain was introduced to the lactone by the addition of the anion of sulfone **97** followed by reductive desulfonylation, to give alcohol **98**. Rearrangement of alcohol

98 with methanolic H_2SO_4 gave the desired bicyclic core **99** in a 1:2.5 mixture with lactone **100** that was separated by silica gel chromatography and the latter was recycled to generate more of the desired bicyclic core. The total synthesis was completed after initial oxidation of C3 alcohol using TPAP, leading to the monoacid **(Scheme 17)**. With the C4 and C5 acids initially protected as methyl esters, they were subsequently hydrolysed under basic conditions. Martin used KO^tBu in a mixture of dioxane/water to produce 'naked' hydroxide ions [31] for smooth hydrolysis. Acidification of the resulting K-salt led to formation of the natural product, in 62% yield over the 2 steps. Overall, 6,7-DDSQ H5 was formed in 14 steps from dimethyl tartrate (**Scheme 17**).

1.4 Hodgson's Previous Approaches

Historically in the Hodgson group, investigating the feasibility of using a tandem carbonyl ylide formation–1,3-dipolar cycloaddition to construct the 2,8-dioxabicyclo[3.2.1]octane core of the squalestatins has been a key feature.[32] Initially, Bailey's approach involved the reaction of diazoester **101** with methyl glyoxylate using catalytic $Rh_2(OAc)_4$ in toluene to afford *endo*–cycloadduct **102** (60%) as a single regio– and stereoisomer, albeit with the incorrect stereochemistry required for elaboration to the zaragozic acid family (**Scheme 18**).



Scheme 18: Synthesis of 6,8-dioxabicyclo[3.2.1]octane core by Bailey.[32]

The *endo*- selectivity was attributed to a favourable secondary orbital overlap interaction between the ester carbonyl of the glyoxylate and the ketone group of the ylide (**Figure 4**).[33] In order to obtain any of the desired *exo*- cycloadduct, it was believed that changing the ketone of the ylide or the ester carbonyl of the dipolarophile would suppress the secondary orbital overlap effect, therefore driving the reaction towards the desired *exo*–cycloadduct.

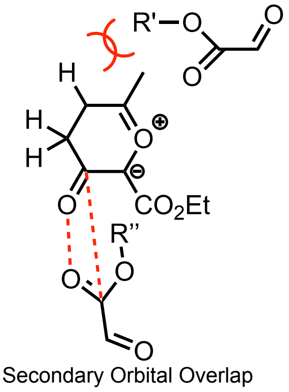
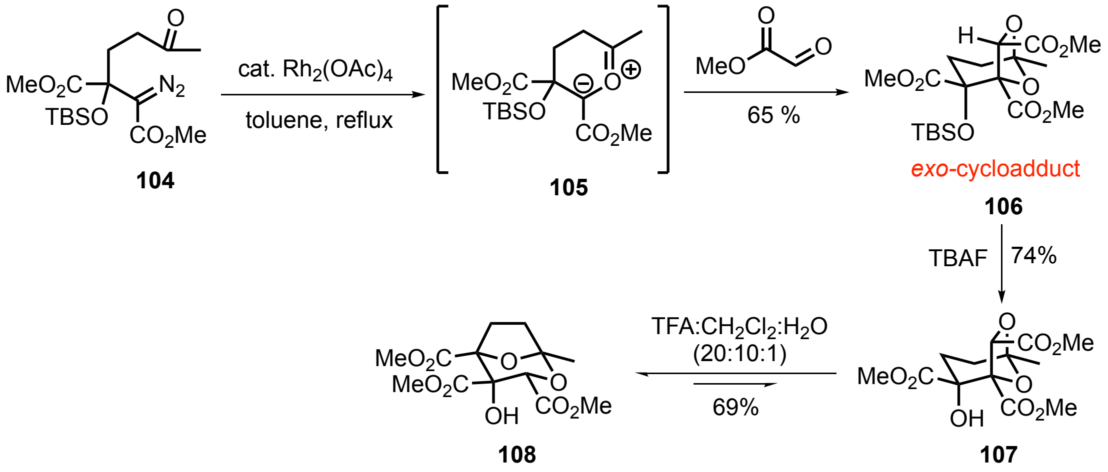


Figure 4: Secondary orbital overlap leading to *endo*- cycloadduct formation.

Villalonga–Barber then continued the studies, aiming to achieve conditions that would favour the formation of the desired *exo*–cycloadduct (**Scheme 19**). After extensive investigations, replacing the *β*-keto group in the diazoester **101** with the more sterically demanding *α*–siloxy ester moiety in racemic diazodiester **104** resulted in the formation of preferred *exo*–cycloadduct (**106**, *via* carbonyl ylide **105**, **Scheme**

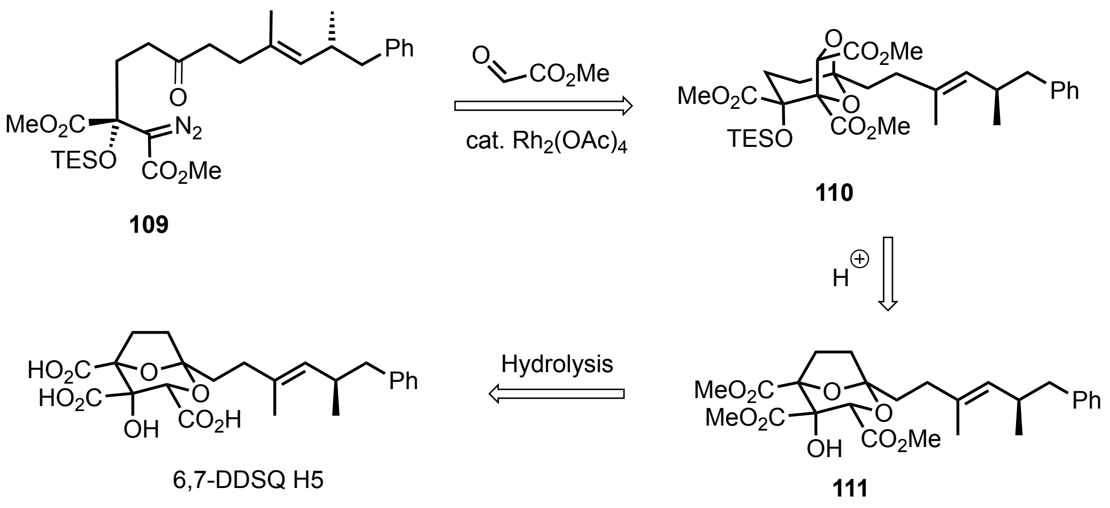
19).[34] The cycloaddition proceeded with methyl glyoxylate on the less hindered face, minimizing steric interaction with the ester subunit; this resulted in the predominant formation of 1 out of 8 possible cycloadducts. Subsequent TBAF-induced deprotection of siloxyester **106** to alcohol **107** and application of Evans acid–catalysed transketalisation conditions[14] resulted in the rearranged core **108** analogous to the natural product. These studies showed that, 1,3–dipolar cycloaddition followed by rearrangement chemistry could be used to successfully assemble the tricarboxylate core of 6,7-DDSQ H5, with the correct stereochemistry and tricarboxylic acid oxidation level.



Scheme 19: *Exo*–cycloadduct formation with respect to ring and subsequent rearrangement.[34]

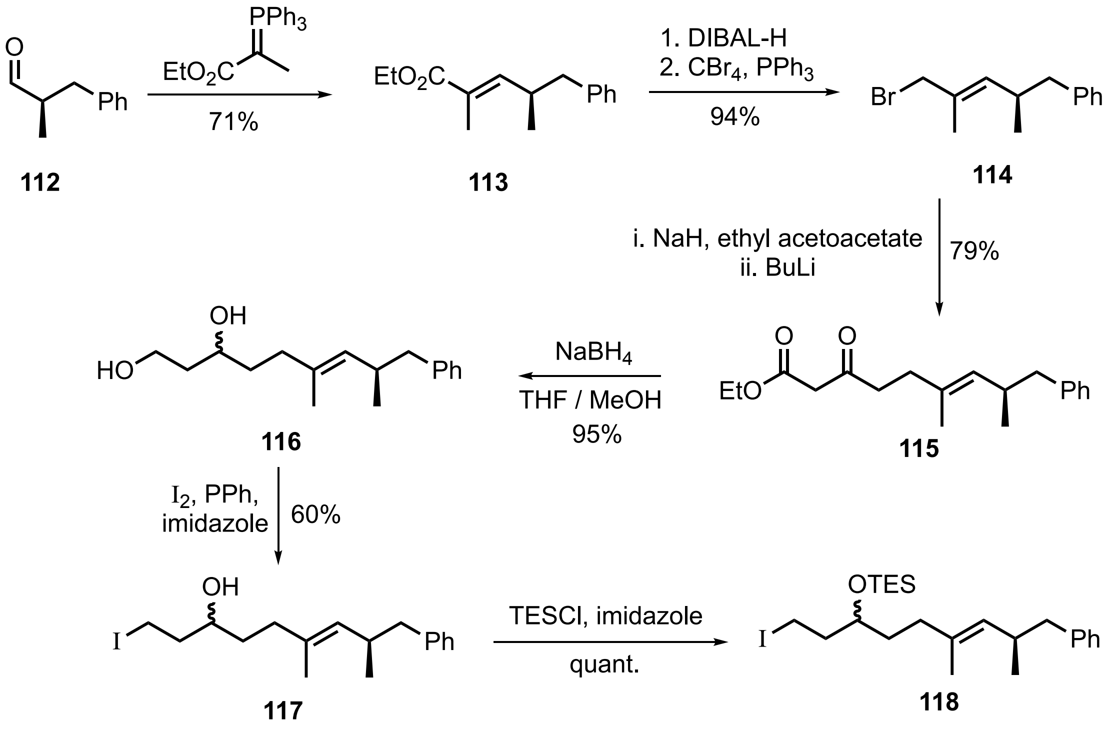
1.4.1 Sintim's Attempted Synthesis

Sintim attempted the total synthesis of 6,7-DDSQ H5 (**2**) *via* a Rh–catalysed 1,3–dipolar cycloaddition (**109**) as the key step (**Scheme 20**), as developed by Villalonga-Barber. The cycloaddition proceeded well to give the desired *exo*– cycloadduct **110**. It was anticipated that subsequent acid-catalysed rearrangement **111** followed by global hydrolysis would complete the total synthesis.



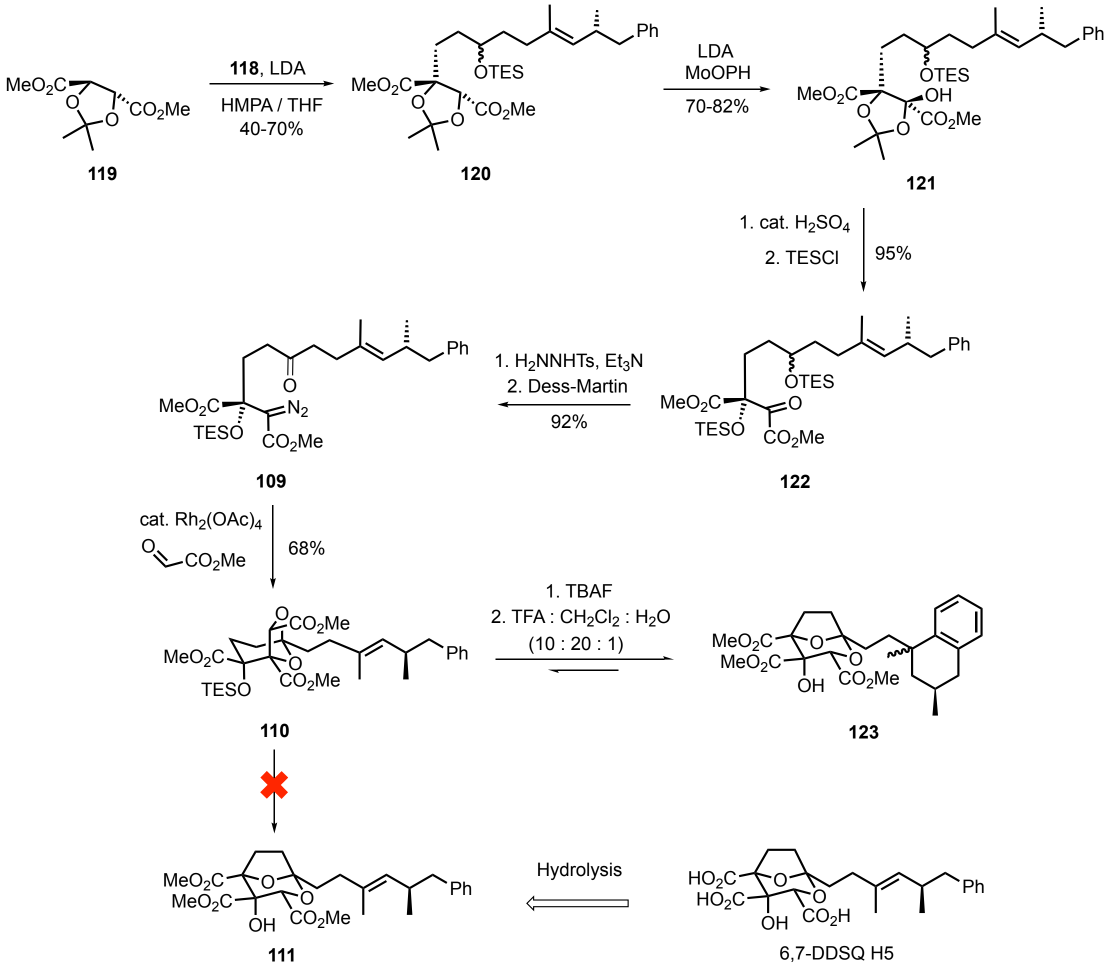
Scheme 20: Sintim's retrosynthesis to the natural product.

Sintim's sequence began with a synthesis of the squalestatin side-chain **118** from (*R*)-2-methyl-3-phenylpropanal (**112**) (**Scheme 21**). Aldehyde **112** was made by the well-established method of Myers.[35] The side-chain **118** was successfully synthesised in 11% overall yield in 11 steps from pseudoephedrine.[36]



Scheme 21: Sintim's side-chain synthesis.[36]

The side-chain **118** underwent alkylation with the anion of dimethyl L-tartrate acetonide **119** to form alkylated tartrate **120** in 40–70% yield (Scheme **22**).[37] After extensive investigation, hydroxylation of alkylated tartrate **120** was achieved using MoOPH, to give hydroxylated acetonide **121** in 70–82% yield. The hydroxylated acetonide **121** was then treated with methanolic H_2SO_4 to give a crude hydroxy ketone that was reacted with TESCl, giving TES ether **122** in 95% yield over the two steps. Transformation into a diazo compound **109** was achieved by treatment with $TsNHNH_2$ and Et_3N, followed by Dess-Martin periodinane oxidation (92% over two steps). The diazoketone **109** then underwent Rh–catalysed cycloaddition with methyl glyoxylate to give the desired *exo*-cycloadduct **110** in an excellent 68% yield (**Scheme 22**). Desilylation of the TES group using TBAF and subsequent acid-catalysed transketalisation using the already established Evans conditions [CH_2Cl_2:TFA:H_2O (20:10:1)][14] was anticipated to achieve the key rearrangement to give the bicyclic core of the natural product (**111**). Unfortunately, when **110** was subjected to Evans conditions after TES deprotection, the presence of relatively acidic TFA presumably induced the formation of a stabilised tertiary carbocation (at trisubstituted olefin in side-chain) and concomitant attack of the aromatic ring onto the acid-labile trisubstituted olefin could not be prevented under a number of different conditions. Cyclisation of the phenyl group gave **123**, instead of the desired rearranged product **111** (**Scheme 22**).

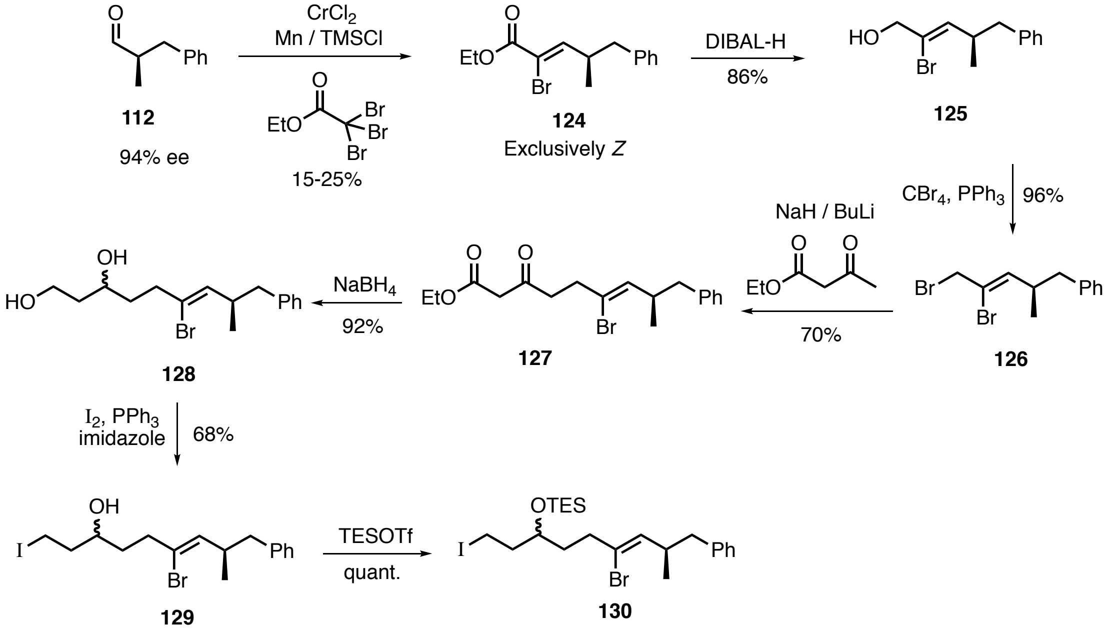


Scheme 22: Sintim's attempted synthesis of 6,7-DDSQ H5.[36]

1.4.2 Al Mamari's Attempted Synthesis

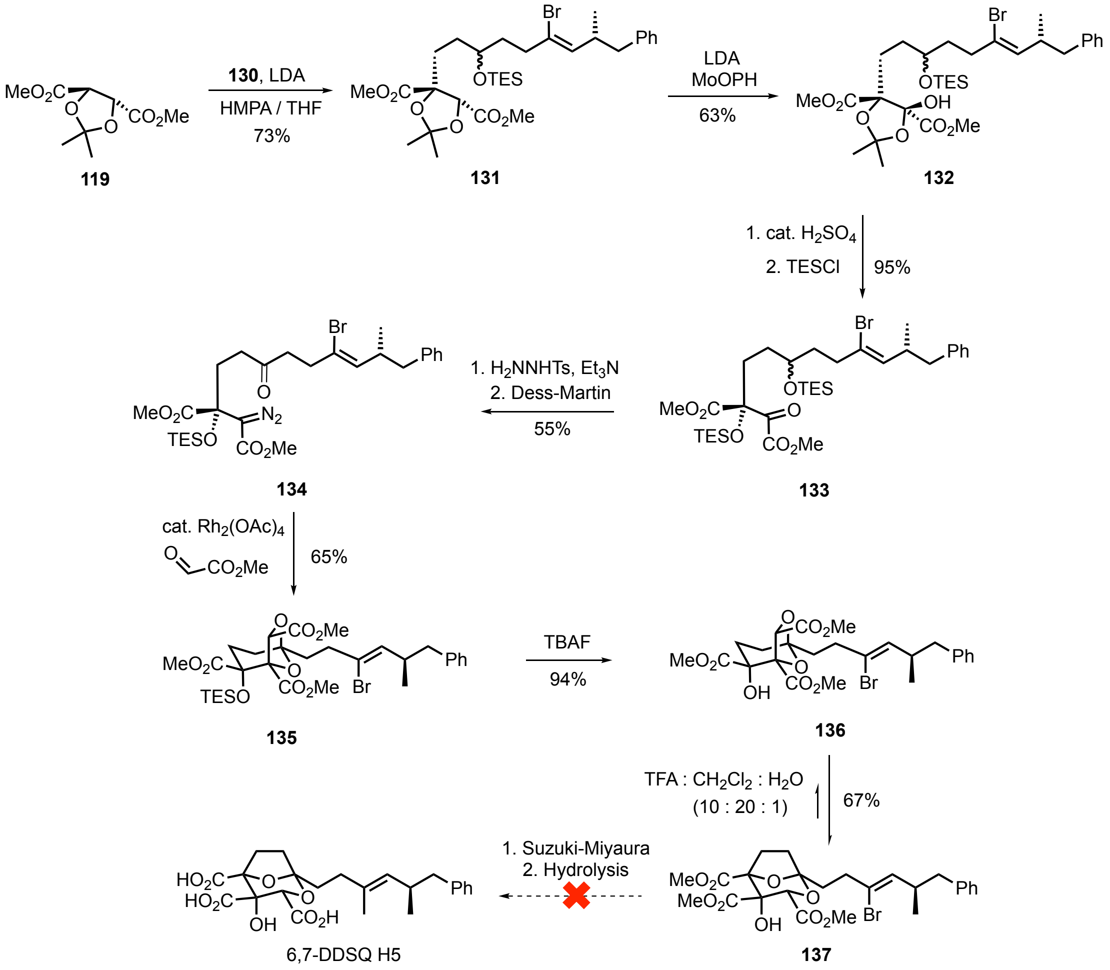
In light of the results obtained by Sintim, Al Mamari proposed that the undesired cyclisation of the phenyl group on to the electron-rich double bond in the side-chain under the acidic conditions of the rearrangement (**Scheme 22**) could be avoided by masking the trisubstituted olefin.[38] Therefore, the introduction of bromine in place of the methyl group was selected. It was anticipated that the electronegative Br substituent could deactivate the alkene to protonation/cyclisation. Finally, the methyl group could then be installed after an acid-catalysed rearrangement, by a boron-alkyl Suzuki-Miyaura[39] coupling reaction (**Scheme 24**).

Al Mamari began the synthesis of the side-chain akin to Sintim's work, by the established method of Myers to reach (*R*)-2-methyl-3-phenylpropanal (**112**) in very good overall yield. Unfortunately, olefination of **112** catalysed by chromium(II) proved to be a synthesis bottle–neck step, giving very poor yields between 15–25% (**Scheme 23**). Despite several attempts to optimise the reaction and many alternative routes investigated, the side-chain **130** could not be accessed in appreciably high overall yields.



Scheme 23: Al Mamari's synthesis of side chain **130** *via* 'bottle-neck' chromium chemistry.

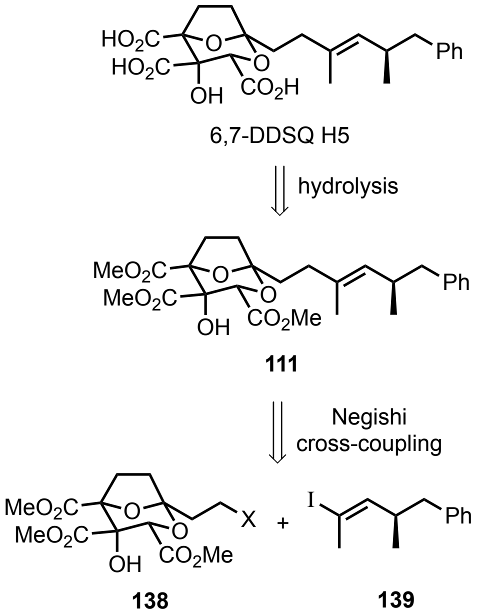
Nevertheless, Al Mamari continued towards the total synthesis with alkylation using tartrate acetonide **119** and subsequent hydroxylation and hydrolysis/protection to obtain silyl ether **133**, ready for diazo formation (**134**, **Scheme 24**). After appropriate functional group manipulation, the reaction sequence progressed with the Rh–catalysed cycloaddition giving cycloadduct **135** with the required *exo*-stereochemistry in 65% yield. In the key acid-catalysed rearrangement after TBAF-mediated desilylation (**136**), the desired rearranged core of squalestatin **137** was formed (67%) without any Ph-cyclisation onto the side-chain alkene (**Scheme 24**). Having solved the problems faced by Sintim with an excellent strategic use of Br masking the electron richness of the olefin, the final steps of the total synthesis were planned to be a one-pot tandem boron-alkyl Suzuki-Miyaura alkylation and ester hydrolysis. The reaction conditions led to consumption of all the starting material, but unfortunately no evidence of squalestatin H5 was observed, despite repeated attempts at purification of the crude mixture by reverse phase HPLC (**Scheme 24**). A combination of lack of material as well as time constraints meant that at this stage the one-pot cross–coupling and hydrolysis could not be investigated any further.



Scheme 24: Al Mamari's attempted synthesis of 6,7-DDSQ H5.

1.4.3 Arif's Attempted Synthesis

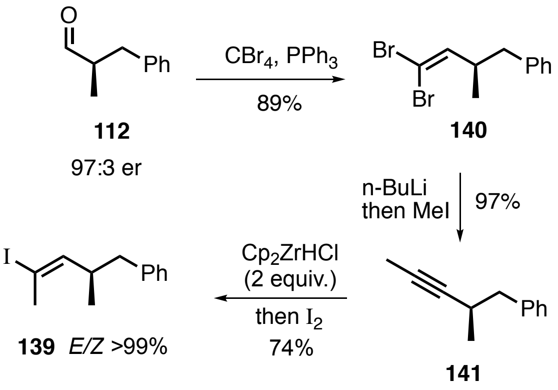
With the previous work by Sintim and Al Mamari as inspiration, Arif proposed that in order to investigate the problems with the Al Mamari's route, it would be necessary to begin with a large amount of material and avoid the bottle-neck chromium-catalysed olefination in the synthesis of the side-chain **130** (**Scheme 23**), as well as having sufficient amounts of rearranged core at hand to attempt late stage cross–coupling. Therefore, as this was a major problem in the Al-Mamari route, Arif proposed a more convergent strategy to synthesise 6,7-DDSQ H5 (**Scheme 25**). Alkyl halide **138** could be coupled with an alkenyl iodide **139** in an efficient and stereoselective fashion, utilising Pd–catalysed Negishi cross–coupling chemistry. The following retrosynthesis of the target was proposed (**Scheme 25**).[40]



Scheme 25: Arif's proposed retrosynthesis to 6,7-DDSQ H5 utilising Negishi cross–coupling.[40]

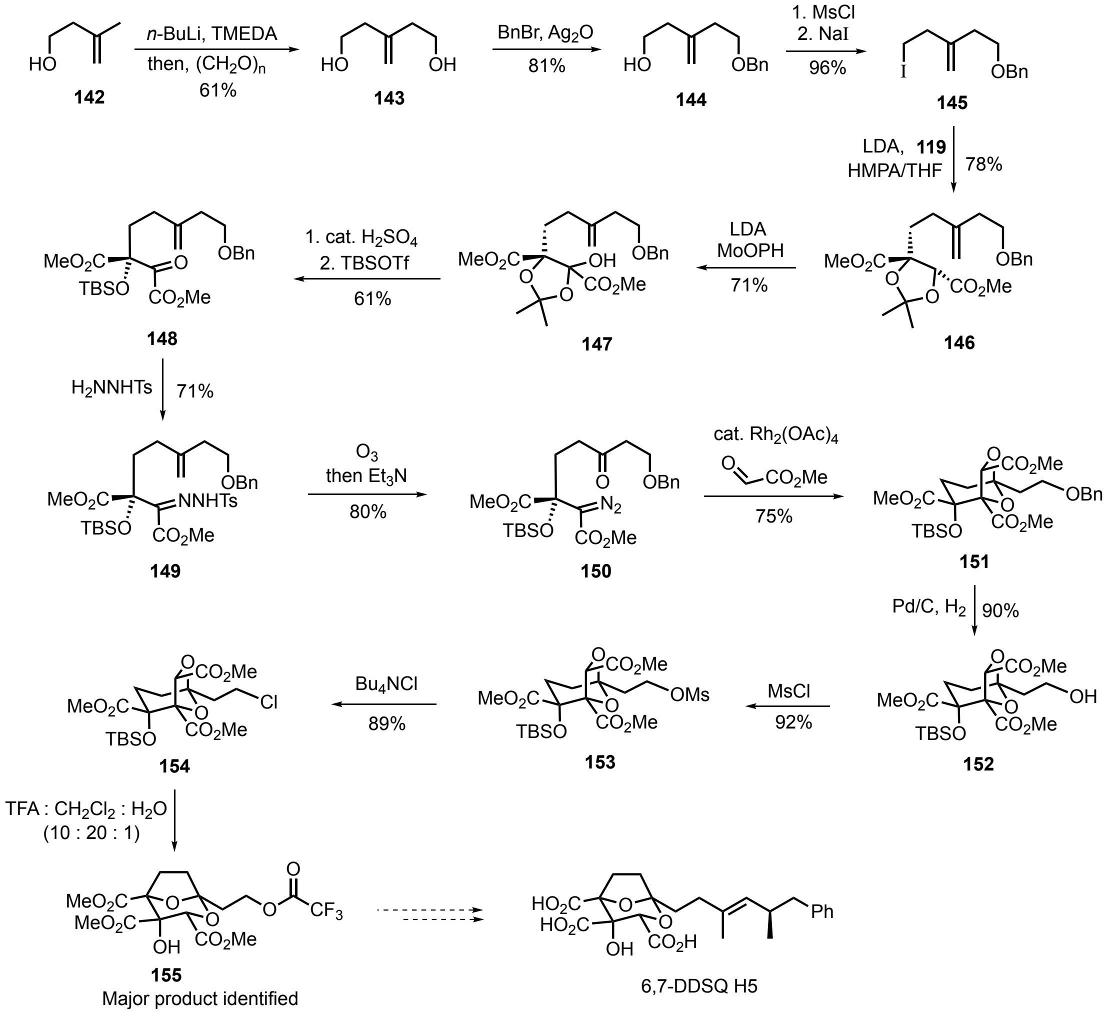
Synthesis of enantiopure alkenyl iodide partner **139** again started with Myers chemistry to reach (*R*)-(–)-aldehyde **112**. The freshly synthesised enantiopure (*R*)-(–)-

aldehyde **112** was then subjected to Corey-Fuchs olefination[41] to afford the dibromoalkene **140** in 89% yield (**Scheme 26**). Subsequent internal alkyne **141** formation (97%) was carried out before hydrozirconation[42] *via* an excess Schwartz's reagent (Cp_2ZrHCl).[43] Subsequent trapping of the intermediate alkenylzirconium with I_2 gave the *E*-alkenyl iodide **139** in high overall yield (74%) from alkyne **141** and with complete control of regio and stereoselectivity (**Scheme 26**).



Scheme 26: Arif's enantiopure synthesis of side-chain **139**.[40]

Towards the synthesis of bicyclic core, Arif started with readily available alcohol **142** where in a 2-carbon homologation produced diol **143** (61%, **Scheme 27**). Utilising Ag_2O, mono-benzyl protection of the diol **143** took place to give benzyl ether **144** that was converted to the alkyl iodide **145** *via* the mesylate (81% and 96% respectively, **Scheme 27**).[44] Following alkylation with tartrate acetonide **119** (78%), hydroxylation using MoOPH (71%) and hydrolysis/silyl protection to afford silyl ether **148** (61%), a 1–pot ozonolysis/Bamford–Stevens[45] process *via* the corresponding hydrazone **149** (71%) was carried out to obtain diazoketone **150** in good overall yield (80%). After the Rh–catalysed cycloaddition gave the desired bicyclic core **151** (75%), functional group manipulation led to the formation of alkyl chloride **154** (*via* primary alcohol **152** and mesylate **153**). In an attempt to achieve acid-catalysed rearrangement, the only major product identified was the rearranged trifluoroacetate **155**, presumably formed on prolonged contact with TFA in a relatively strong acidic environment at elevated temperatures (**Scheme 27**).[40] Unfortunately, due to lack of material as well as difficulty in isolation of the rearranged material and time constraints, no further progress with the project was achieved.



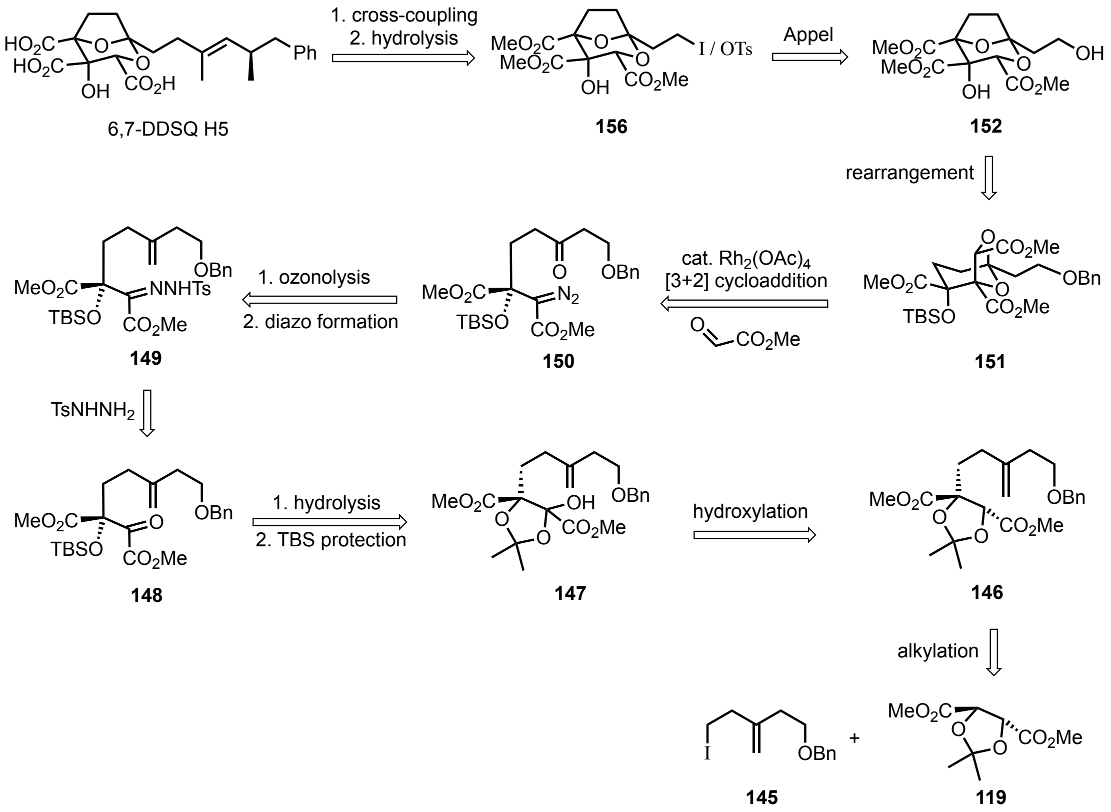
Scheme 27: Arif's attempted synthesis of 6,7-DDSQ H5.[40]

1.5 Project Objectives

The primary aim of the project was the total synthesis of 6,7-dideoxysqualestatin H5, while building on previous work in the group as inspiration and motivation in devising an elegant strategy to accomplish the target synthesis. According to research by Arif, a convergent route to the natural product should provide a better opportunity to eliminate problems faced by previous members of the group (**Scheme 25**). Knowledge gained from Arif's work suggested operating the acid-catalysed transketalisation prior to formation of alkyl halide **154** on the highly oxygenated core (**Scheme 27**) would be desirable. Moreover, upon successful rearrangement to bicyclic core of the natural product, a suitable chromatographic system needs to be developed in order to separate rearranged and unrearranged material, thus, enabling recycling to the rearranged core. Additionally, a suitable sp^3–sp^2 cross–coupling strategy would need to be developed to successfully deliver attachment of the desired side-chain towards the end of the total synthesis.

1.5.1 Project Strategy

The strategy to the asymmetric synthesis of 6,7-dideoxysqualestatin H5 began with highly diastereoselective *n*-alkylation of a tartrate acetonide enolate **119** and subsequent oxidation (**146**) to provide an asymmetric entry to a β-hydroxy-α-ketoester motif **147**. Facilitation of Rh–catalysed cyclic carbonyl ylide formation-cycloaddition by cogeneration of keto and diazo functionality through ozonolysis of an unsaturated hydrazone **149** would ultimately lead to bicyclic core of the natural product (**151**, **Scheme 28**). Using the already established Evans' acid-catalysed transketalisation conditions, (*vide supra*) the rearrangement will be carried out to obtain rearranged core **152** at the correct oxidation level. Finally, after substrate activation **156**, a stereoretentive Csp^3–Csp^2 cross–coupling between tricarboxylate core and unsaturated side-chain **139** followed by global hydrolysis to complete the natural product would be established.



Scheme 28: Retrosynthetic analysis of 6,7-DDSQ H5.

Chapter 2

Results and Discussion

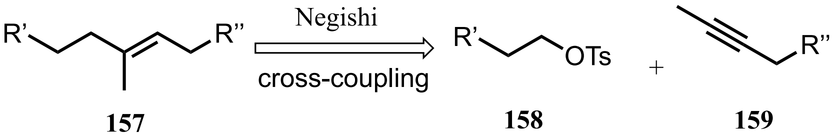
(Model Cross–Couplings and Synthesis of Oxygenated Core)

2. Results and Discussion

One of the main aspects of the project was to achieve an efficient cross–coupling process that would introduce the side-chain of 6,7-DDSQ H5 in a concise and stereo-controlled manner. Based on the retrosynthetic analysis (**Scheme 25**, p.40) and previous work by Arif,[40] a Negishi cross–coupling was identified to be most appropriate for the Csp^3–Csp^2 bond forming step.

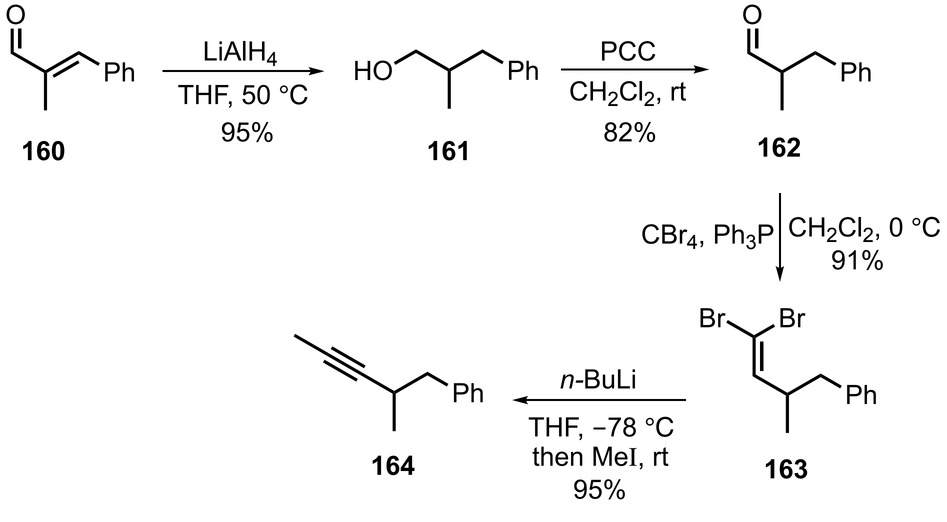
2.1 Model Substrate Synthesis

The Negishi cross–coupling reaction of an alkyl tosylate **158** and an alkyne **159** *via* a hydrozirconated[42] intermediate would be a rare application of this methodology in total synthesis.[46]



Scheme 29: Proposed Negishi cross-coupling.

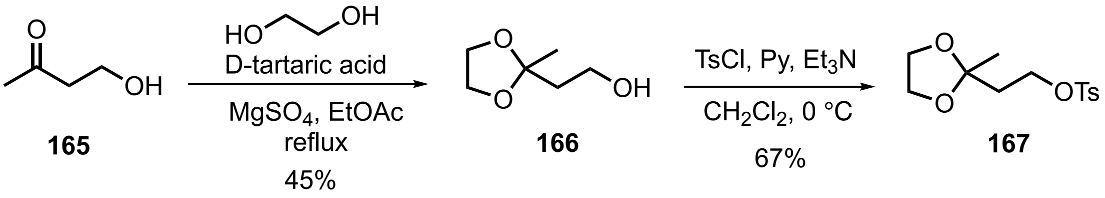
In order to check the feasibility of a Negishi cross–coupling, the racemic side–chain **164** Csp^2 partner was synthesised **(Scheme 30)**.



Scheme 30: Racemic alkyne **164** synthesis.

The reduction of commercially available *α*-methyl-*trans*-cinnamaldehyde **160** using LiAlH$_4$ proceeded in a clean and efficient manner (95%) to give saturated alcohol **161**.[38] PCC oxidation then yielded 82% of the aldehyde **162**. In a Corey–Fuchs olefination,[38] aldehyde **162** was reacted with CBr$_4$ and Ph$_3$P, giving dibromoalkene **163** in 91% yield (**Scheme 30**). Early attempts to synthesise dibromoalkene **163** were problematic due to inefficient extraction (30–50%) from the triphenylphosphine oxide by-product. To prevent potential loss of material during extraction, the crude residue was purified directly by silica gel chromatography. Finally, dibromoalkene **163** was reacted with *n*-BuLi (2 equiv.) at –78 °C in a Li/halogen exchange followed by Fritsch-Buttenberg-Wiechell (FBW)[47] rearrangement and the resulting lithio alkyne intermediate was trapped with excess MeI to give methylated alkyne **164** in 95% yield (**Scheme 30**).

As a mimic for the highly functionalised oxygenated core (**156**, **Scheme 28**, p.44) of the natural product in the cross coupling, it was considered important to have a substrate bearing 2 methylene groups with additional acetal functionality. Therefore, commercially available hydroxy ketone **165** was refluxed with ethylene glycol to form hydroxy acetal **166**[48] in moderate yield (45%, **Scheme 31**). The alcohol was then reacted with TsCl to produce the desired model tosylate **167**, in 67% yield.[49]

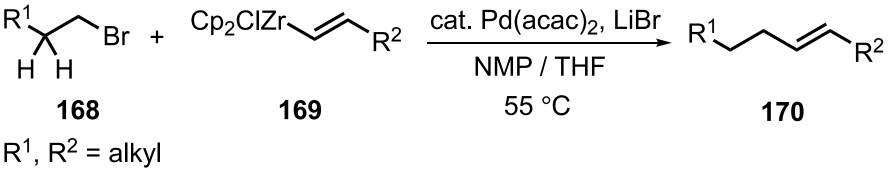


Scheme 31: Model tosylate for the oxygenated core.[48, 49]

2.2 Model Cross–Coupling

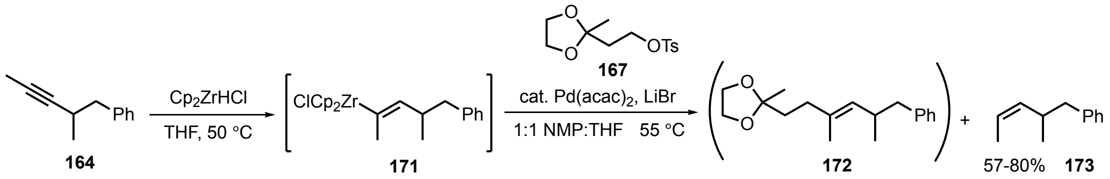
2.2.1 Hydrozirconation Strategy

With the two models at hand, it was time to test the key cross–coupling step. Historically, there have been major challenges in Csp^3–Csp^2 cross-coupling and the number of examples in the literature were limited.[50] Where regioselectivity and stereoselectivity are major issues, one of the most fundamental problems arising from Csp^3–Csp^2 cross-coupling is complications with *β*-hydride elimination. Bulky, electron-rich ligands such as trialkylphosphines, diaminophosphines, and carbenes are typically used to achieve such coupling reactions.[46] More recently, Fu reported 'ligandless' palladium complexes can catalyse zirconium-Negishi reactions (**Scheme 32**).[46]



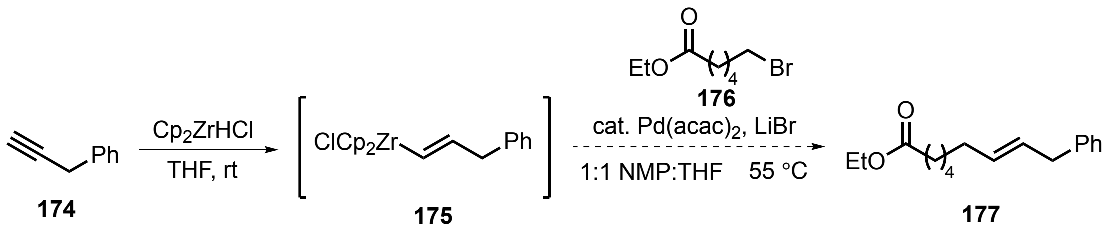
Scheme 32: Fu's variant of Negishi cross–coupling.[46]

The Fu chemistry above also benefits from avoiding pre-formation of an alkenyl halide partner. Methylated alkyne **164** was initially reacted with Schwartz's reagent [prepared by standard methods from zirconocene dichloride,[51] 81%] to produce a hydrozirconated intermediate followed by treatment with Pd(acac)$_2$, LiBr and tosylate **167** (**Scheme 33**). It was important to use slightly more than one equivalent of Schwartz's reagent to promote formation of *E*–zirconium species.[52] Additionally, the reaction was carried out in the dark, and monitored by TLC using anisaldehyde stain; the latter clearly differentiates between alkynes (red) and hydrozirconated species (blue). Although Fu carries out all the reactions in a glove–box, there is an experimental protocol available to conduct the reaction outside a glove–box if not available. Therefore, all the required starting materials and reagents were weighed in air and flushed with argon. However, the only product isolated from the reaction was disubstituted *Z*–alkene **173** (**Scheme 33**, 57–80%, J = 9 Hz), likely derived from protonation of the *in situ* formed hydrozirconated species **171**; no signs of the desired cross–coupled alkene **172** were detected.



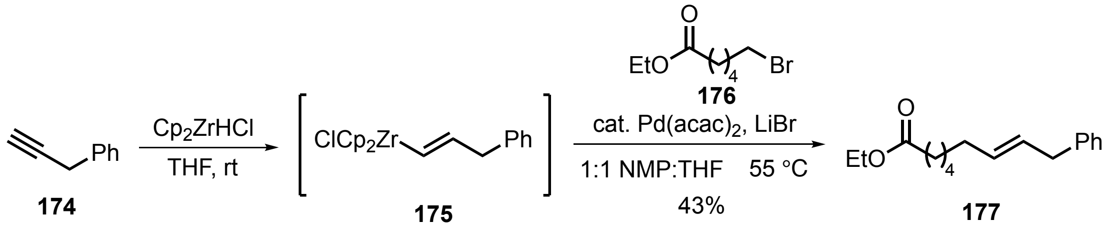
Scheme 33: Model cross–coupling with internal alkyne **164** and tosylate **167**.

Lack of success with the model substrates above suggested that an exact literature reaction described by Fu should be examined to pinpoint possible problems faced during our reaction. Therefore, terminal alkyne **174**, which readily undergoes hydrozirconation, and bromoester **176** were selected to probe areas that would be influential in determining successful reaction outcome.[46] Terminal alkyne **174** underwent smooth hydrozirconation as judged by TLC, however, the latter part of the reaction resulted in a complex mixture by ^{1}H NMR analysis, with no indications of any signals (δ_H = 5.6–5.4 ppm for olefinic region) from the desired product (**177**, **Scheme 34**).[46]



Scheme 34: Attempted literature cross–coupling with terminal alkyne **174** and bromoester **176**.

After various trials (sparging the solvent, distillation of starting materials and distillation of NMP from CaH_2), the target product **177** was eventually successfully synthesised in 43% yield (lit.[46] 99%), albeit containing slight impurities. It was found that the quality of the co-solvent (NMP) plays a key role in the outcome of the reaction: it was vital to distill this solvent to observe any cross–coupling.



Scheme 35: Repeat of literature cross–coupling with terminal alkyne **174** and bromoester **176**.

Unfortunately, on repeating the reaction on the same scale as before (0.39 mmol of **176**), the region of impurities in the ^{1}H NMR δ_H 2.90 ppm and δ_H 6.49–5.95 ppm almost doubled in intensity (**Figure 5**). This was also the case in further runs of the same reaction.

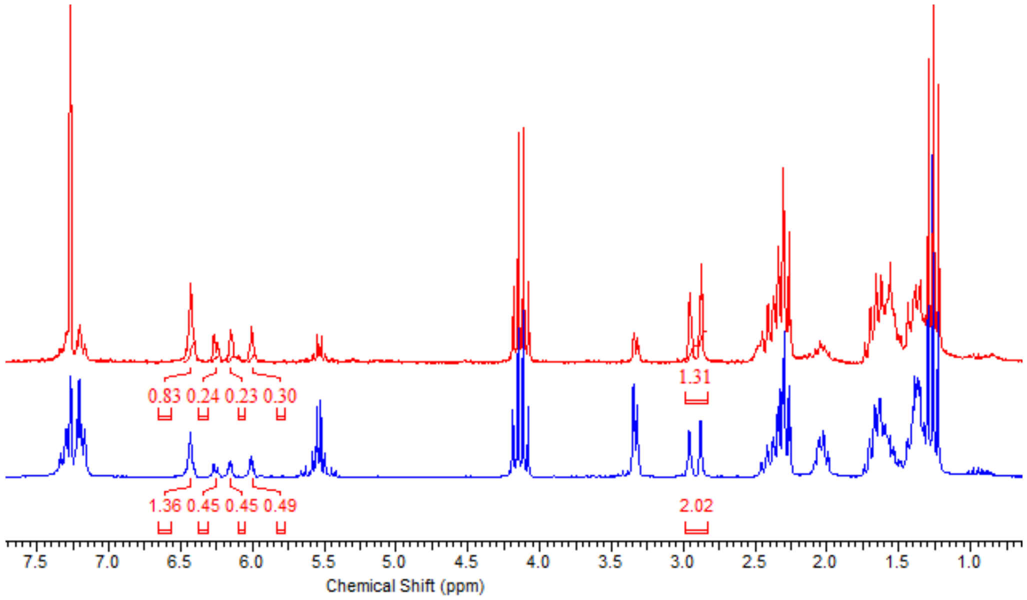
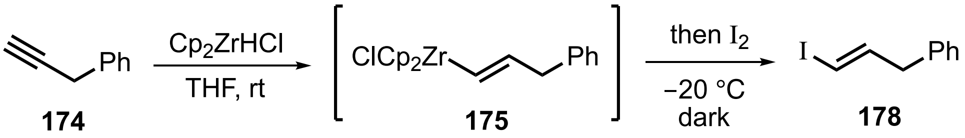


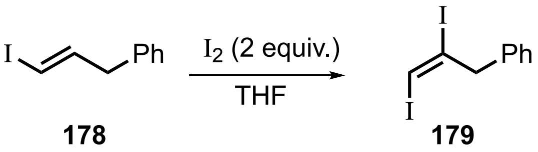
Figure 5. ^{1}H NMR spectra of cross–coupled compound with different intensities of impurity after chromatography.

To rationalise the increased level of impurities, it was proposed that the 'quality' of the air- and moisture-sensitive Schwartz's reagent and/or Pd(acac)$_2$ had deteriorated. In order to test the quality of reagents, terminal alkyne **174** was initially reacted with Schwartz's reagent, forming hydrozirconated intermediate **175** and was then trapped with iodine forming alkenyl iodide **178** (**Scheme 36**).[53] However, the alkenyl iodide **178** formed contained impurities (~16% of desired product in the mixture by NMR). Unfortunately, due to impure sample, the quality of Schwartz's reagent synthesised could not be determined.



Scheme 36: Model alkenyl iodide **178** formation.[53]

Despite formation of desired *E*–alkenyl iodide **178**,[53] another compound co-eluted possessing *two* singlet peaks at δ_H 7.0 ppm and δ_H 3.9 ppm by ^{1}H NMR (**Figure 6**). After careful spectroscopic analysis, it was proposed that once alkenyl iodide **178** is formed, it then undergoes a further iodination to form a novel compound, *E*-2,3-diiodoallylbenzene **(179)**. To test whether the second iodination had occurred, the mixture of alkenyl iodide **178** was treated with iodine (2 equiv.) in THF and stirred for 1 h at rt. ^{1}H NMR analysis found the monoiodide had indeed undergone further iodination where the integral intensities of the relevant peaks increased: at δ_H 3.9 ppm: (8.50 => 10.68) and at δ_H 7.0 ppm: (3.21 => 4.12) relative to CH_2Ph protons. Additionally, *m/z* (M+Na$^+$) was found as 370.8768 $C_9H_9{}^{127}I_2Na$ corresponding to di-iodo species **179**.



Scheme 37: Further iodination of the starting mono alkenyl iodide.

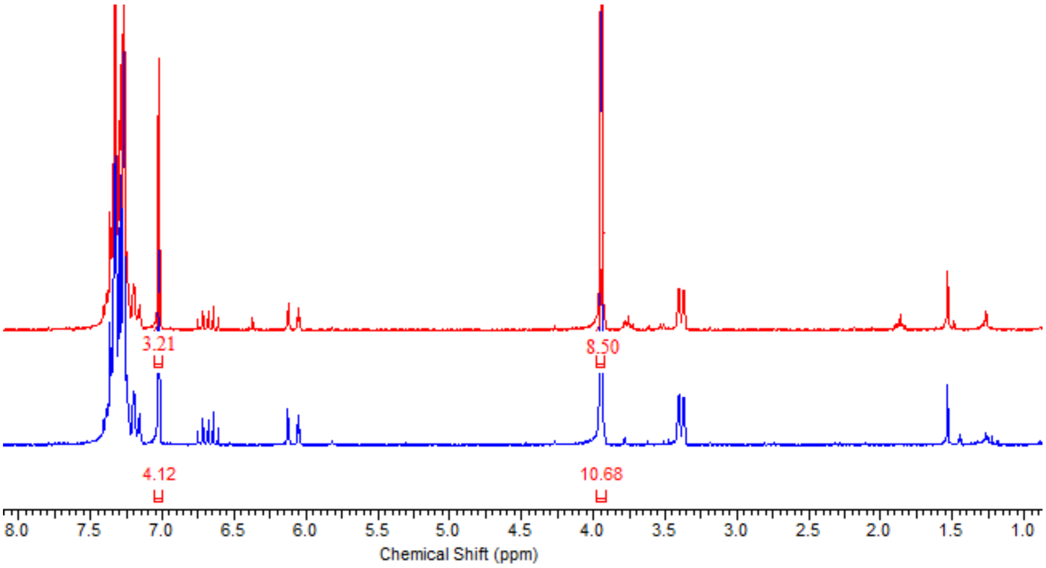
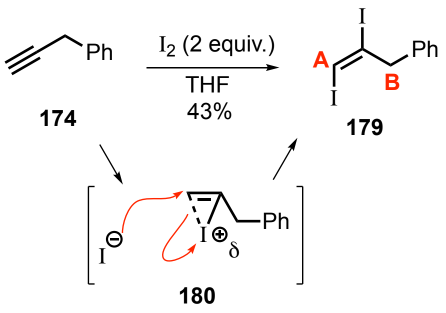


Figure 6. ^{1}H NMR spectra of alkenyl iodide **178** (red) with increased intensity of di-iodo species **179** after further treatment with I_2 (blue).

Additionally, it was proposed that if the initial alkyne was treated with iodine directly, the same outcome would be observed. For di-iodination, the internal alkyne **174** was reacted with iodine (2 equiv.) in THF for 1 h at rt giving di-iodide **179** in 43% yield (**Scheme 38**). NOE experiments to establish the *E/Z* isomer showed minor correlation. In the *E*- configuration, the protons A and B are far apart from each other thus resulting in no or very weak coupling (**Figure 7**). If the *cis* isomer were to be dominant, then there would be a strong through-space coupling between protons A and B, which were not observed in the present case. Therefore, it can be assumed on the basis of NOE experiments that the lack of coupling between the two protons mean the *trans* configured di-iodo species was obtained. Furthermore, such di-iodides have been previously postulated,[54] where it is assumed the reaction occurs through an iodonium ion intermediate **180** followed by nucleophilic attack resulting in formation of *E*-di-iodides. It has been reported on similar di-iodo compounds that proton A in the *Z*–isomer has a chemical shift in the region of δ_H 6.2–6.3 ppm[55] whereas in the *E*–isomer, the proton has a chemical shift in the region of δ_H 6.7–6.9 ppm;[56] this data provides further evidence that the product isolated in the current reaction is of *E*–configuration.



Scheme 38: Di-iodination of the terminal alkyne.

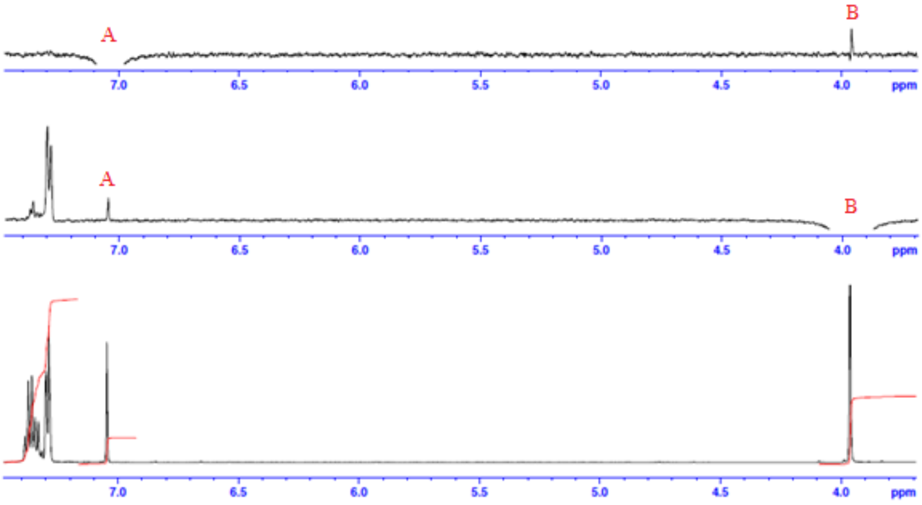
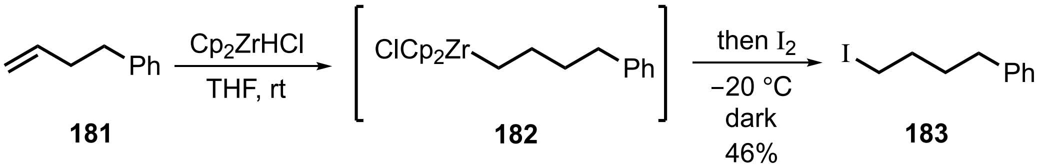


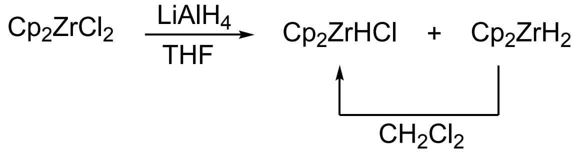
Figure 7. NOE spectra of *trans* di-iodide **179**.

After determination of the *E/Z* structure of the di-iodo species, it was time to return to the problems faced during cross–coupling of the model substrates (p.50, **Scheme 35**). The quality of Schwartz's reagent was checked using another model terminal olefin. Alkene **181** was initially hydrozirconated followed by trapping with I_2, forming the saturated iodide **183** (46%), albeit in a slightly impure state (**Scheme 39**).



Scheme 39: Hydrozirconation–iodination of alkene **181**.

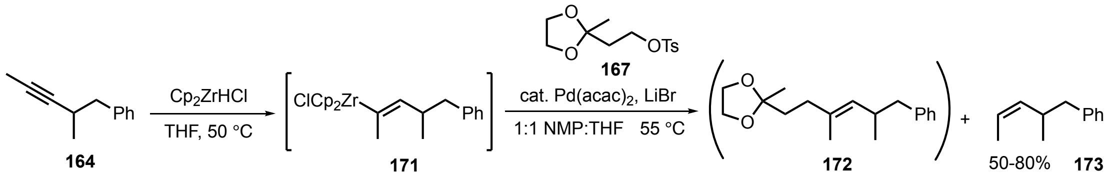
To determine whether the impurities could be reduced, Schwartz's reagent was resynthesised, this time washing the final product thoroughly with CH_2Cl_2 to reduce the amount of zirconocene dihydride byproduct.



Scheme 40: Formation of Schwartz's reagent.[51]

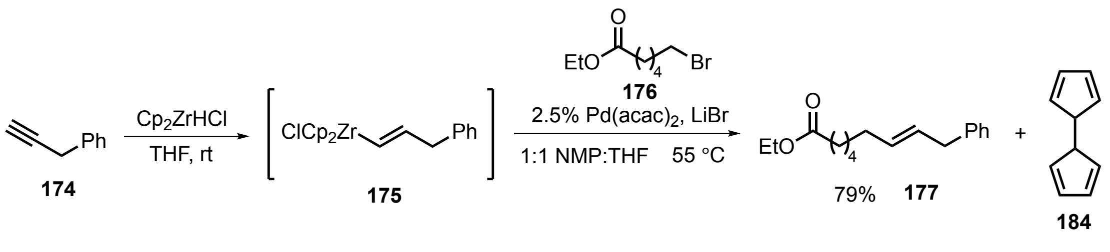
The quality of Schwartz's reagent was checked by repeating the synthesis of saturated iodide **183** (**Scheme 39**) giving slightly better yield (67%). Also, there were no indications of contaminant peaks in the ^{1}H NMR spectrum; therefore, it could be concluded that the Schwartz's reagent synthesised was of adequate quality.

Having earlier reproduced the literature cross–coupling (p.50), albeit obtaining the product in lower yield than reported, the new Schwartz's reagent was examined on the model racemic methylated alkyne **164**. However, once again the only product isolated was due to protonation of the vinyl zirconium **171**, alkene **173** (50–80% yield, **Scheme 41**).



Scheme 41: Attempted cross–coupling on model alkyne **164** and tosylate **167**.

Reconsideration of the only time where successful cross–coupling was achieved but with impurities, led to the conclusion that the impurities were due to excess Schwarz's reagent on heating (in the presence of Pd catalyst) undergoing formation of dihydrofulvene **184** (**Scheme 42** and p.51, **Figure 5**).[57]



Scheme 42: Literature cross–coupling and determination of the impurities.

If dihydrofulvene **184** was a major impurity, then if the mixture were placed under high vacuum (>0.75 mmHg) overnight, it was considered likely that the intensity of the contaminant peaks would reduce significantly. To our delight, this was the case and where the impurities[58] minimised considerably yielding the coupled product in 79% yield (**Figure 8**).

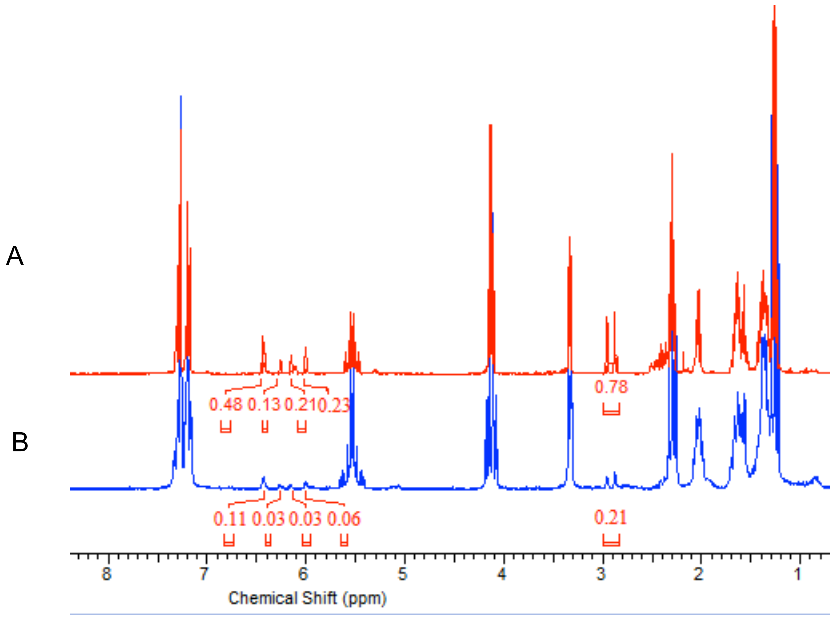
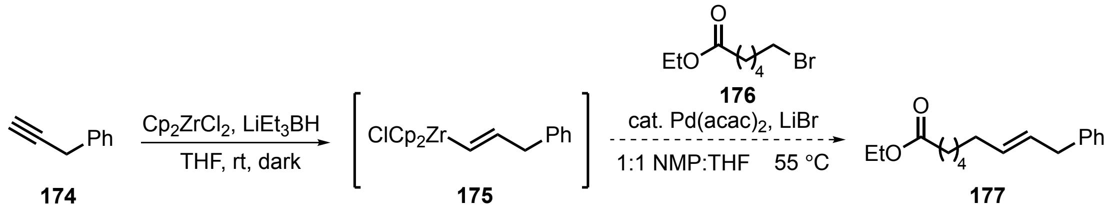


Figure 8. ^{1}H NMR spectra of cross–coupled compound with significantly reduced A =>B intensity of impurity peaks after being under high vacuum overnight.

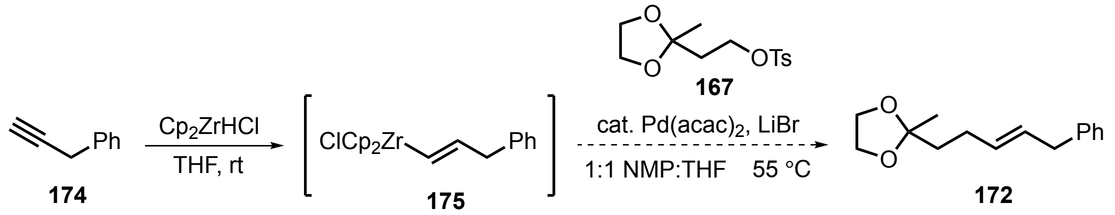
Having successfully synthesised alkene **177** in 79% yield, further effort to try and make the yield more comparable with literature cross–coupling (98%)[46] was undertaken. In one attempt, Schwartz's reagent was formed *in situ*, hoping to increase the yield of the reaction. *In situ* formed Schwartz's reagent could potentially contain minimal amounts of zirconocene dihydride compared to Schwartz's reagent prepared and isolated. Zirconocene dihydride, which is an intermediate in the formation of Schwartz's reagent, would provide a viable route to prevent formation of the vinyl zirconium intermediate. This in turn prevents any chances of cross–coupling.

Therefore, a suspension of Cp_2ZrCl_2 in THF was initially treated with super hydride solution in the dark for 1 h followed by reaction with alkyne **174** to produce the hydrozirconated species **175** (**Scheme 43**).[42] The intermediate formed was then taken on to attempted cross–coupling, which unfortunately did not yield any alkene.[46]



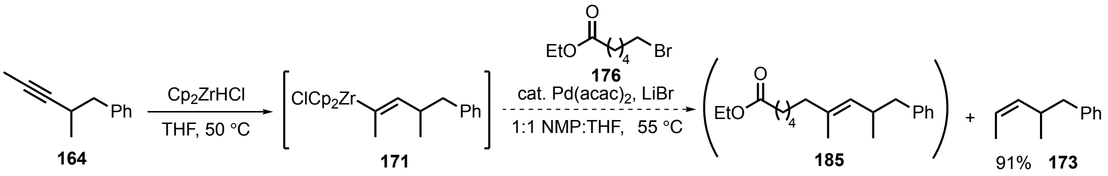
Scheme 43: Attempted literature cross–coupling using *in situ* formed Schwartz's reagent.

The highly oxygenated core of the natural product was originally envisaged to be functionalised as a tosylate for coupling to the side-chain. As such, it was deemed necessary to examine relevant couplings with model tosylate **167** and terminal alkyne **174** (terminal alkynes are known to undergo hydrozirconation easier with respect to internal alkynes). This reaction could potentially provide a platform to find out whether the problem of cross–coupling between the model systems arises from the tosylate part or the internal alkyne counterpart. However, unfortunately no coupling was observed (**Scheme 44**). This suggested that this particular tosylate might not be an ideal coupling partner to undergo cross–coupling with the terminal alkyne.



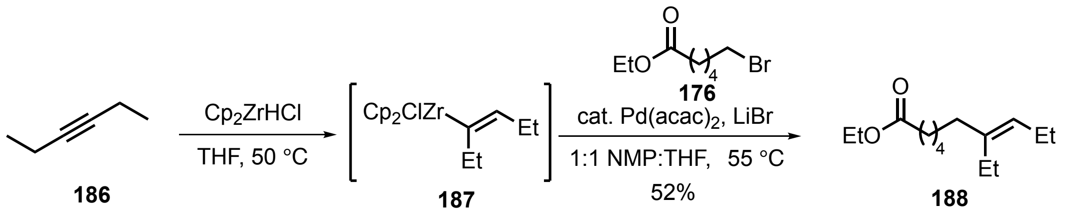
Scheme 44: Attempted cross–coupling using model tosylate **167** and terminal alkyne **174**.

Having established that tosylate cross–coupling was difficult to achieve (in our hands), a separate experiment where internal alkyne **164** was reacted with bromide **176** was attempted, but once again the only product isolated was alkene **173** (91% yield, **Scheme 45**). From this latter experiment it could be concluded that internal alkyne **164** readily undergoes hydrozirconation since alkene **173** is formed but the problem lies in the coupling stage, where it is believed this particular hydrozirconated intermediate protonates rapidly, therefore quenching the reaction before formation of coupled product **185**. Having moved to a glove–box to rigorously ensure an inert atmosphere, the cross–coupling was again unsuccessful.



Scheme 45: Attempted cross–coupling using model alkyne **164** and alkyl bromide **176**.

A literature reaction bearing a simpler and less sterically demanding internal alkyne **186** was now examined (**Scheme 46**), to see if the coupling problem persisted and if any protonation of the intermediate would be evident. The cross–coupling to form alkene **188** was achieved in 52% yield (lit.[46] 85%). ^{1}H NMR analysis of the crude residues ($\delta_H = 5.36$ ppm) also suggested that the alkyne underwent hydrozirconation but then partially protonated to form some of the internal alkene, which due to volatility was not isolated. This reaction indicated that our model internal alkyne **164** is an intrinsically difficult substrate for the cross–coupling *via* hydrozirconated species.



Scheme 46: Cross–coupling using simple internal alkyne **186** and alkyl bromide **176**.

2.2.2 Vinyl Zinc Strategy

To achieve cross–coupling in a more reliable and synthetically useful yields, it was decided to revert back to a strategy described by Fu in his earlier studies, involving organozinc species (**Scheme 47**).[59] Fu investigated the utility of Pd catalysts in the Negishi cross–coupling, a process of particular interest due to its high functional-group tolerance and the availability of organozinc complexes.

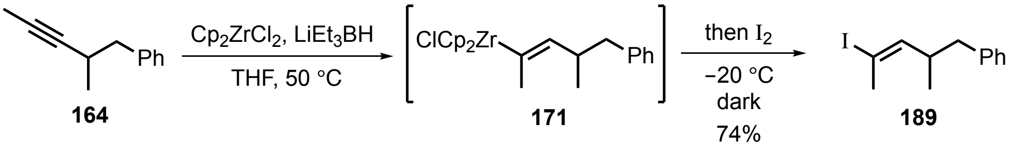
$$R^1CH_2X \quad + \quad R^2ZnX \xrightarrow[\text{THF:NMP (2:1)}\\ 80\ ^\circ\text{C}]{\text{cat. } Pd_2(dba)_3\text{, } PCyp_3\text{, NMI}} R^1CH_2R^2$$

X = I, Br, Cl, OTs

R^2 = alkyl, alkenyl, aryl

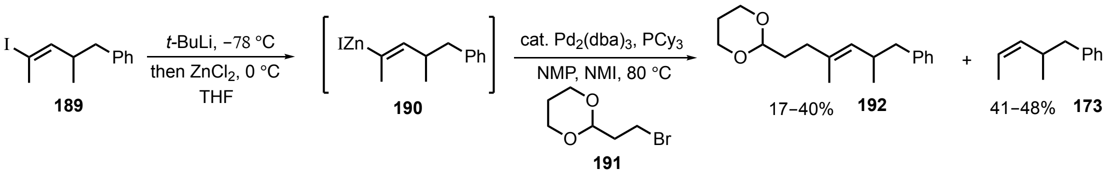
Scheme 47: General outline for Negishi cross–coupling using organozincs.[59]

It was necessary to revert to a sequential strategy (although not favourable with one additional step) through the intermediacy of an *E*–alkenyl iodide **189** (**Scheme 48**). Iodide **189** was prepared from internal alkyne **164** *via in situ* generated Schwartz's reagent and then hydrozirconation, followed by iodination in good overall yield and with complete control with respect to regio- and stereoselectivity.



Scheme 48: Formation of *E*-alkenyl iodide **189**.

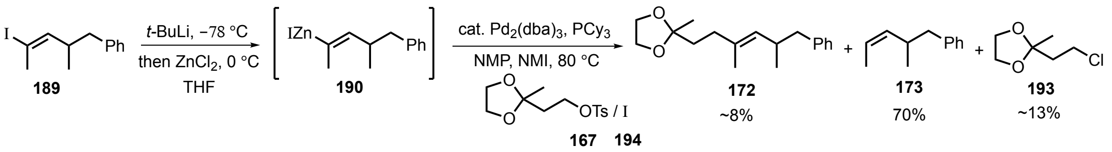
Following on from Arif's work (p.40–41) as a backup strategy, the model cross–couplings continued with attempts to couple *in situ* formed alkenyl zinc iodide **190**, synthesised from vinyl iodide **189**, with commercially available bromoethyl dioxane **191** (**Scheme 49**). Having the organozinc complex in hand, it was anticipated that the cross–coupling reaction utilising Pd chemistry would be more promising and efficient. Prior to the reaction, THF, NMP and NMI were thoroughly sparged with argon. The desired coupled product **192** was synthesised in ~20% yield in a mixture with unreacted bromoethyl dioxane **191** (20%). Additionally, the reaction produced 48% of *Z*-alkene **173** from protonation of the intermediate **190** (**Scheme 49**). While the reaction formed some (~20%) of the desired adduct for the first time, one of the major issues with the coupling was the consistent low yield. When the reaction was repeated, the desired product **192** was formed in ~17% yield as a 1:1 mixture with bromide **191**; 41% of *Z*-alkene **173** was also isolated. The best yield managed for the coupling was ~40%. Therefore, more work was required to optimise the conditions for a robust protocol.



Scheme 49: Cross-coupling *via* organozinc complex **190**.

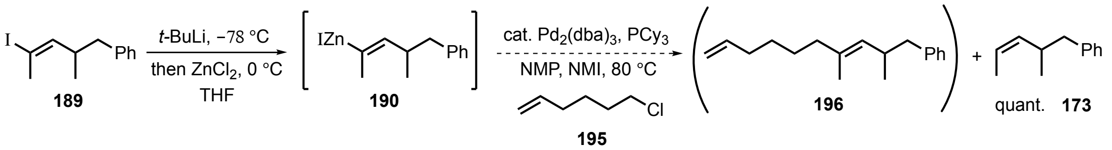
With some, albeit modest, coupling success utilising alkenyl zinc species **190**, coupling to tosylate **167** was attempted. Previously (**Scheme 41**, p.45), no successful coupling was observed with tosylates, however, this time the desired adduct **172** was formed in ~8% yield by ^{1}H NMR analysis, contaminated with alkyl chloride **193** (13%) by ^{1}H NMR and MS. analysis; **193** presumably being derived from excess

$ZnCl_2$ (**Scheme 50**). Additionally, the reaction gave 70% of *Z*-alkene **173**. No successful cross–coupling was seen when alkyl iodide (**194**, I instead of OTs) was used instead of the tosylate.



Scheme 50: Cross–coupling of alkenyl zinc iodide with alkyl tosylate.

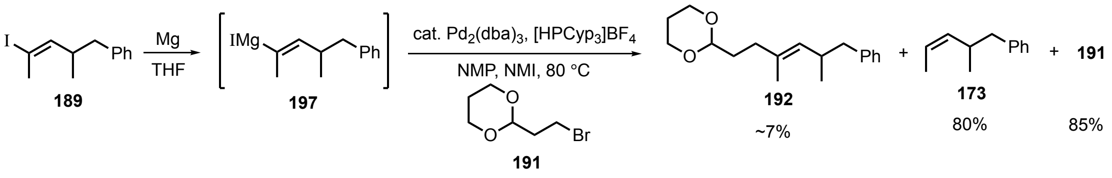
When alkyl chloride **195** was used as coupling partner, the reaction yielded no desired diene **196** and returned all protonated starting material alkene **173** (**Scheme 51**).



Scheme 51: Attempted cross–coupling of alkenyl zinc iodide **190** with alkyl chloride **195**.

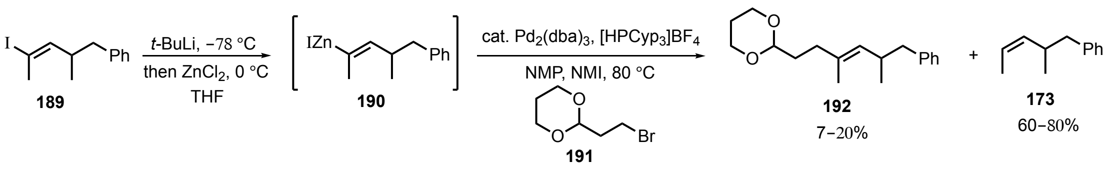
With little or no success with the above reagents and conditions, it was considered that the commercial $ZnCl_2$ solution used in the reaction could be a proton source thereby quenching the organozinc complex and returning mainly protonated material. Therefore, solid $ZnCl_2$ was dried by melting under high vacuum and allowing to cool to rt under vacuum. This procedure was repeated 3 times, and during the last cycle it was cooled to rt under argon. The dried $ZnCl_2$ was used directly in the reaction. Solubility of the solid $ZnCl_2$ proved problematic in the specific amount of THF (0.46 M) used, thus it required more solvent (from 0.46 M to 0.15 M) to fully dissolve. This meant additional NMP was used to maintain the relative ratio of THF:NMP for the cross–coupling. Unfortunately, with the dried $ZnCl_2$ only ~9% of desired adduct **192** was produced along with 67% of protonated *Z*-alkene **173**.

In another attempt, the exact conditions of Fu's chemistry were applied,[59] where the corresponding Grignard **197** was formed from alkenyl iodide **189** and used directly in the coupling reaction (**Scheme 52**). Mg turnings were initially activated under nitrogen for 5 h,[60] followed by addition of the starting iodide **189** in THF. A few drops of 1,2-dibromoethane were added and a slight temperature rise was observed, indicative of Grignard formation. Monitoring (TLC) the formation of Grignard was carried out by quenching a small amount of the reaction mixture, to observe protonated alkene **173**. There were slight difficulties in transferring the thick Grignard suspension *via* cannula to the reaction flask containing the palladium catalyst, [HPCyp$_3$]BF$_4$ and ZnCl$_2$ solution in THF. Fu and Zhou indicate that the order of addition of reagents is important, therefore after the above sequence of addition the halide coupling partner, NMI and NMP (both sparged under argon for 2 h) were successively added and the mixture heated at 80 °C overnight. ~7% of the desired product was formed with the rest of the material being protonated *Z*-alkene **173** and recovered bromoethyl dioxane **191** (**Scheme 52**).



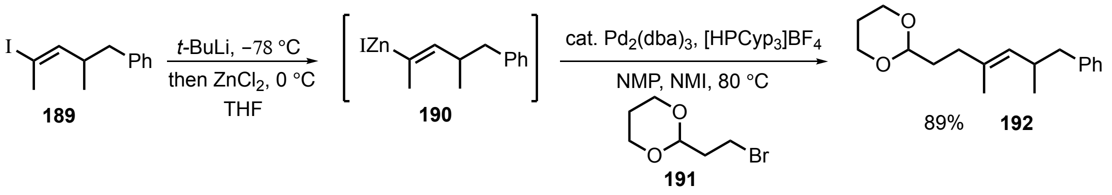
Scheme 52: Cross–coupling of alkenyl Grignard **197** with bromoethyl dioxane **191**.

The original organozinc reaction conditions were examined again with the only difference being the use of [HPCyp$_3$]BF$_4$ ligand instead of PCy$_3$. The salt is air and moisture stable thus, much easier to handle. The reaction yielded the desired product **192** in a range between 7–20% yield, but again returned significant protonated *Z*-alkene **173** (**Scheme 53**).



Scheme 53: Cross–coupling of alkenyl zinc species **190** with new ligand [HPCyp$_3$]BF$_4$.

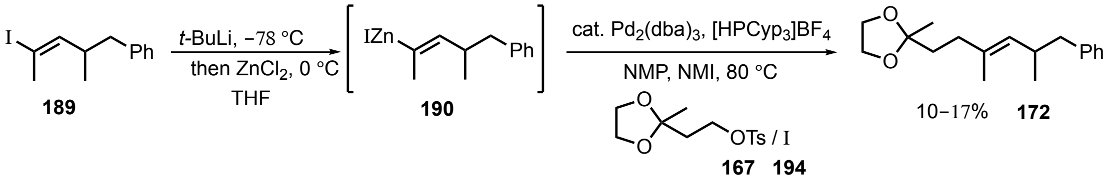
The model cross–couplings continued with attempts to couple *in situ* formed alkenyl zinc iodide **190**, synthesised from the vinyl iodide **189** with bromoethyl dioxane **191** (**Scheme 54**). Previously, no or little success was achieved with the cross–coupling reaction using the reagents and conditions employed. In an alternative approach trying to dry ZnCl$_2$, this time, ZnCl$_2$ (0.7M in THF) solution was added to a flame-dried flask containing activated molecular sieves (4Å) and stored at rt for 2 days before use. Additionally, NMP and NMI were distilled and sparged under argon. The desired coupled alkene **192** was then, finally, successfully synthesised in 89% yield (**Scheme 54**). Earlier lack of success was indicative of wet ZnCl$_2$ solution; therefore, it was imperative to use dry ZnCl$_2$ solution for successful cross–coupling to take place.



Scheme 54: Successful cross–coupling of alkenyl zinc species **190** with bromodioxane **191**.

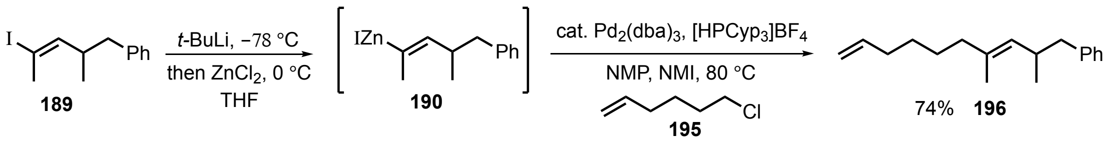
The reaction was repeated several times to ensure reliability and reproducibility of the conditions employed, before committing to the precious bicyclic core of the natural product (*vide infra*). The cross–coupling reaction was found to be reproducible with an average yield of 81% (3 runs). The same reaction was performed again this time on a small scale (0.0159 mmol *vs* 0.328 mmol), approximately comparable to the scale at which the coupling would potentially be carried out on the bicyclic core of the natural product. The cross–coupling yielded 67% of the desired adduct, providing confidence that the yield of the reaction would also be comparable with ones at larger scale (eg: 0.328 mmol).

In another attempt, the coupling partner was changed back to the original model tosylate **167**. Where previously no successful coupling was seen with this particular substrate (p.45), this time the desired adduct **172** was formed in ~17% yield, albeit with slight impurities (**Scheme 55**). Additionally, when iodoacetal **194**, (I instead of OTs) was used instead of the tosylate, there was ~10% of cross–coupled product in a mixture with traces of starting iodoacetal **194**. One explanation for the poor yields obtained in the reactions was the relatively labile acetal group (no recovery of starting material after cross-coupling) that potentially could decompose at higher temperatures.



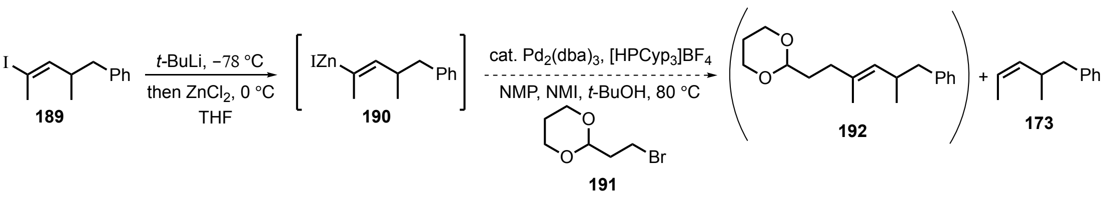
Scheme 55: Cross–coupling of alkenyl zinc iodide **190** with model alkyl tosylate **167** and iodide **194**.

When alkyl chloride **195** was used with a dry ZnCl$_2$ solution, diene **196** was formed in 74% yield (**Scheme 56**).



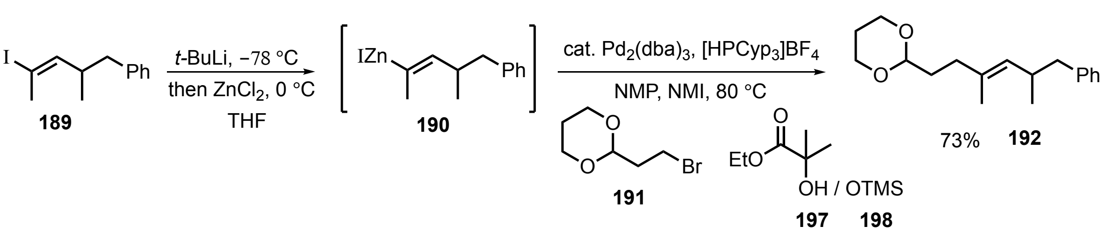
Scheme 56: Cross–coupling of alkenyl zinc halide with alkyl chloride **195**.

Cognisant of the free tertiary alcohol functionality at C–4 in the main core of the natural product (**Figure 2**, p.16) and sensitivity of the coupling reaction towards proton sources, a model cross–coupling in the presence of 1 equiv. of *t*-BuOH was performed, to indicate whether the coupling could be carried out without temporary protection of the alcohol. No cross–coupling was observed and the reaction returned almost all protonated alkene **173** and starting bromoethyl dioxane **191** (**Scheme 57**).



Scheme 57: Cross–coupling of alkenyl zinc halide in the presence of *t*-BuOH.

Similarly, when α-hydroxy ethyl isobutyrate **197** (a more closely relevant substrate structurally) was tested, no desired product was observed. However, with TMS-protected isobutyrate **198** (94%)[61] cross–coupling gave 73% of the desired adduct **192** (**Scheme 58**). It was therefore concluded that cross–coupling on the bicyclic system to be successful it would require temporary TMS protection at C–4 of the tertiary alcohol.



Scheme 58: Cross-coupling in the presence of silylated ethyl isobutyrate **198**.

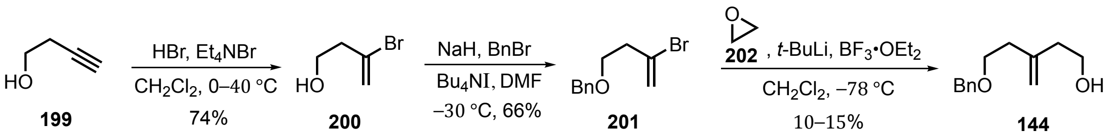
Efforts were also made to see if the reaction would proceed at milder reaction temperatures. Therefore, the bromoethyl dioxane **191** model system was re–

examined, but this time carrying out the reaction at ambient temperature rather than 80 °C. Monitoring the reaction by TLC revealed no product formation after 24 h. The same reaction was then heated to 40 °C and left stirring overnight. A ~1:1 ratio of product **192** to bromide **191** was observed. With this knowledge, it was considered that if the catalyst loading were increased (such as from 2 to 10 mol%), the formation of desired product might also increase. Unfortunately, the cross–coupling carried out with increased catalyst and ligand loading (10%) at 40 °C again yielded a 1:1 mixture of the desired adduct **192** to starting bromide **191**. These studies indicated that for full conversion of bromoethyl dioxane **191**, higher reaction temperatures (80 °C) are required.

2.3 Synthesis of Target Iodide (Bicyclic Core)

2.3.1 Ethylene Oxide Route

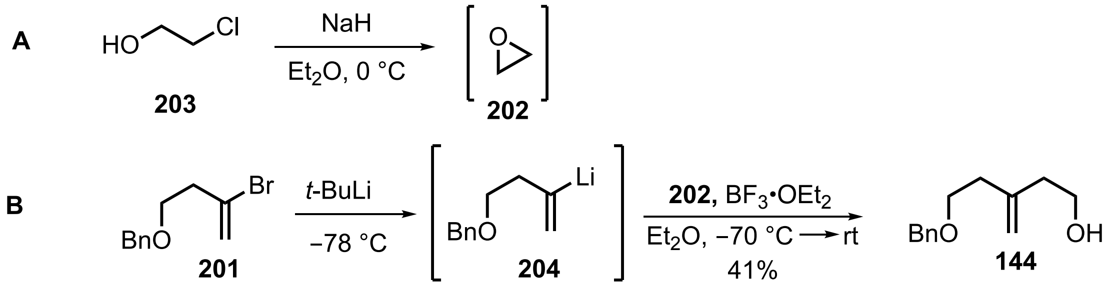
With suitable cross–coupling conditions developed on model systems, synthesis of the oxygenated core (see Arif's previous work **Scheme 27**, p.42) commenced with regioselective hydrobromination of commercially available 3-butyn-1-ol (**199**) with HBr, the latter being generated by bubbling PBr_3 through water at 0 °C, to give 2-bromoalkene (**200**) (2-bromo:1-bromo, 96:4) in 74% yield after vacuum distillation (**Scheme 59**).[62] Bromoalkene **200** was then benzylated in DMF at –30 °C, to form benzyl ether **201** (66%). When the benzylation was carried out at 0 °C or rt, the reaction yielded no desired product and led to the decomposition of starting bromide **200**. The next stage involved homologation using ethylene oxide,[63] however due to inefficient absorption of ethylene oxide gas (reaction flask was weighted out before and after gas was absorbed) on small scale (1.0 mmol), this only yielded ~10–15% of the desired alcohol **144**.



Scheme 59. Attempted ethylene oxide route form alkyne **199**.

Performing the reaction on larger scale (8.3 mmol) meant absorption of ethylene oxide in CH_2Cl_2 was more practical and gave alcohol **144** in a much more acceptable 59% yield.

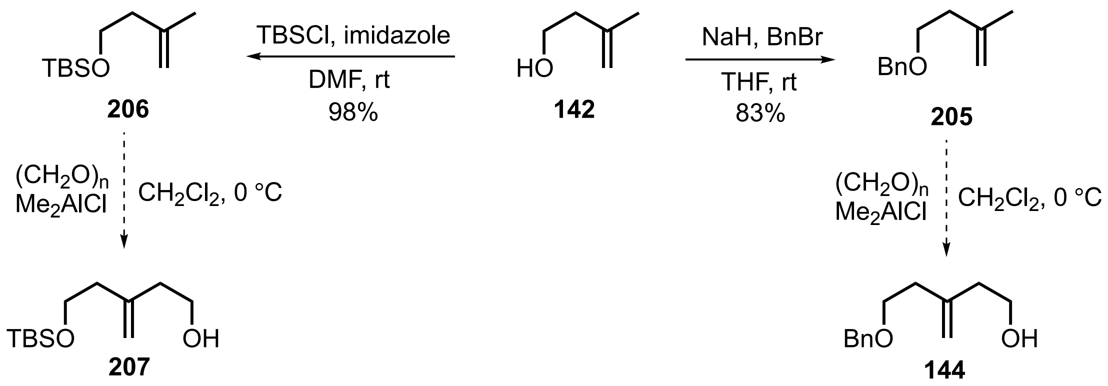
From a safety aspect, due to toxicity of ethylene oxide gas and its high cost (£91/mol), an alternative method to form the epoxide *in situ* was examined to lead to the corresponding alcohol **144**. Chloroethanol **203** was added dropwise to a solution of NaH in Et_2O and stirred at 0 °C for 2.5 h to form ethylene oxide **202**.[64] It is essential to ensure that chloroethanol is dried over 4Å MS prior to use. The ethereal ethylene oxide solution was in turn added to organolithium **204**, previously prepared by dropwise addition of *t*-BuLi to alkenyl bromide **201** at –78 °C. Finally, $BF_3 \cdot OEt_2$ was added to the mixture and the alcohol **144** was isolated in 41% yield (0.83 mmol of **201**, **Scheme 60**). The reaction was also carried out at larger scale (4.6 mmol of **201**), but unfortunately no alcohol **144** was observed. There were significant issues with cannula transfer of the ethylene oxide solution, due to the large quantity of NaCl by-product generated. An alternative method to prepare ethylene oxide *in situ* uses *n*-BuLi instead of NaH to achieve deprotonation and subsequent ring-closure,[65] but unfortunately this procedure showed no promise in forming the desired alcohol **144**.



Scheme 60: *In situ* formation of ethylene oxide **202**[64] for 2–carbon homologation.

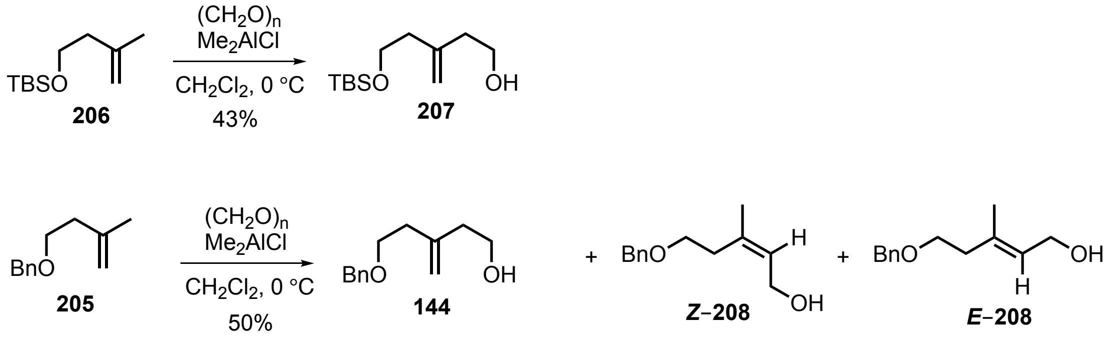
2.3.2 Carbonyl–Ene Route

Cognisant of the practical issues of using *t*-BuLi and ethylene oxide, particularly on scale, an alternative synthetic route was examined using an ene reaction as a key C–C bond-forming step. Following benzyl protection of 3-methyl-3-buten-1-ol **(142)** to produce benzyl ether **205** in 83% yield (**Scheme 61**), installation of the key hydroxymethyl group was attempted *via* a Lewis acid–activated carbonyl–ene reaction with paraformaldehyde.[66], [67] Benzyl ether **205** was reacted with paraformaldehyde and stoichiometric Me_2AlCl, however only starting material was recovered. Therefore, a literature reaction[67] was carried out in order to validate the quality of chemicals used. Alcohol **142** was initially TBS protected to yield 98% of silyl ether **206**. The ene reaction was then re-attempted, but again only traces of the desired product was observed with almost full mass recovery of the starting silyl ether; it was considered essential to use better quality Lewis acid.



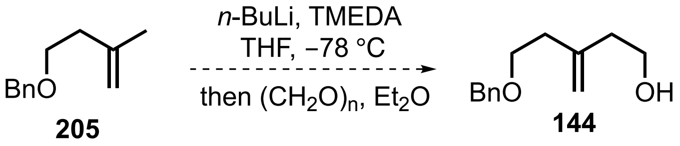
Scheme 61. Attempted hydroxymethyl homologation.

With high quality reagent acquired, the carbonyl–ene reaction with TBS ether **206** was successfully carried out, giving homoallylic alcohol **207** in moderate yield (43%, lit.[67] 72%) without any traces of internal alkenes (**Scheme 62**). However, performing the reaction with benzyl ether **205** returned 23% of starting material, together with 50% of an inseparable mixture of desired product **144** along with *Z*–**208** and *E*–**208** (**144**:*Z*-**208**:*E*-**208**, 51:26:23 respectively).



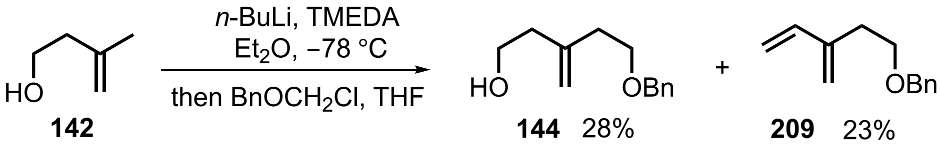
Scheme 62. Hydroxymethyl homologation with silyl ether **206** and benzyl ether **205**.

In an attempt to reach the target motif in a more direct fashion without a protection/deprotection strategy, benzyl ether **205** was lithiated with *n*-BuLi in freshly distilled TMEDA and THF overnight (**Scheme 63**).[47, 68] The intermediate organolithium was then trapped with paraformaldehyde to hopefully give alcohol **144**, but after several attempts, no desired product was observed and no starting material was recovered.



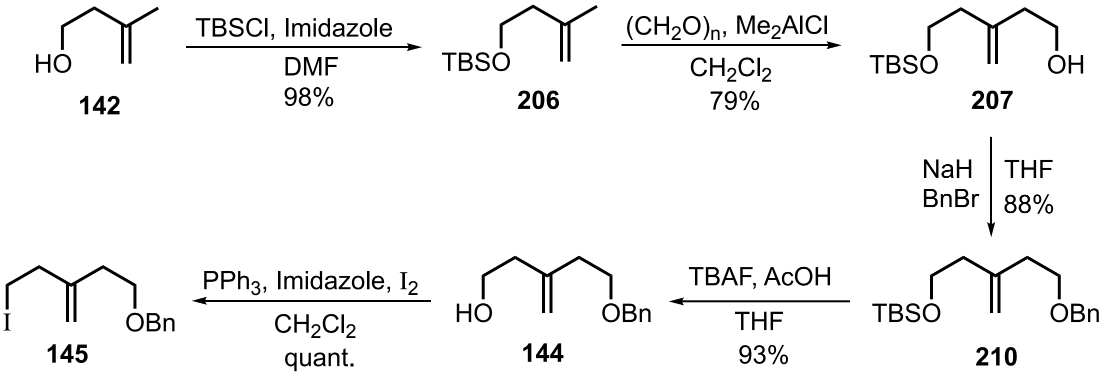
Scheme 63. Attempted dianion approach to alcohol **144**.

Benzyl chloromethyl ether[69] was used in an alternative attempt to trap the intermediate anion; however, there were severe problems (multiple products with very similar *R*f's complicated reaction mixture purification), with only 28% of desired alcohol **144** isolated. Additionally, 23% of diene **209** was isolated in a slightly impure state, along with a 19% mixture of the two products (**Scheme 64**). It was proposed that, once the product is formed, the excess anion facilitates elimination, forming a stable conjugated diene system.



Scheme 64. Benzyl chloromethyl ether[69] approach to alcohol **144**.

As the more direct approach was low yielding and inefficient, it was decided to pursue the route originally planned. Alcohol **142** was initially TBDMS protected[70] to yield 98% of silyl ether **206** (**Scheme 56**). The carbonyl-ene reaction on the TBS ether **206** gave alcohol **207** in much better yield (79%, 25 mmol) when the rate of addition of Me_2AlCl was slowed (61 mL over 1 h, compared to 30 min).[67] The only downside of the reaction was on scale-up; the yield of alcohol **207** was slightly compromised to an average of 40–60% (40 mmol scale). With the alcohol **207** in hand, benzyl protection yielded 88% of benzyl ether **210** (**Scheme 65**). Separation at this stage was slightly problematic due to co-elution of unreacted BnBr with the desired product, **210**. However, on repeating the experiment, purification was not carried out and crude material was reacted with TBAF to deprotect the silyl group, directly generating alcohol **144** in 93% yield.[71] Finally, the iodide **145** was formed in a clean and concise Appel reaction with Ph_3P, iodine and imidazole, in quantitative yield (**Scheme 65**).[72]

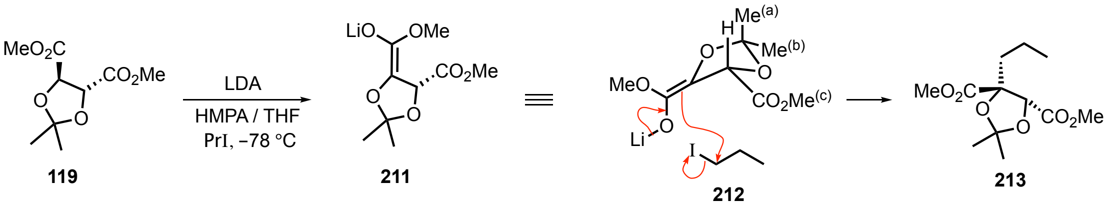


Scheme 65. Formation of iodide **145** *via* carbonyl–ene reaction.

2.4 Towards Cycloaddition Precursor

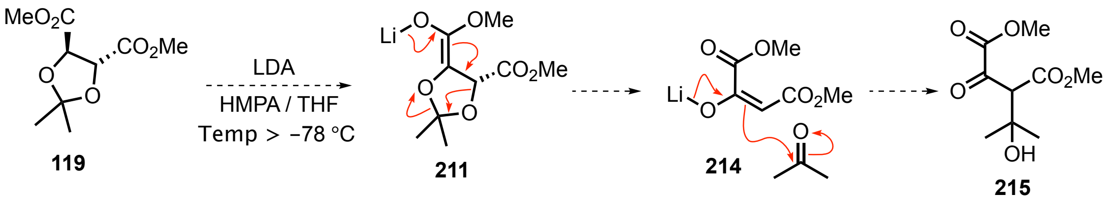
2.4.1 Alkylation

As a first committed step towards the bicyclic core of 6,7-dideoxysqualestatin H5, attempts were made to alkylate dimethyl-2,3-*O*-isopropylidine-*L*-tartrate (**119**) with iodide **145** following Seebach's procedure[73] Seebach originally reported alkylation of tartrate with several reactive alkyl halides,[73] and he established that alkylation occurred *cis* to the neighboring ester substituent of the dioxolane group; this is refered to as *"contra-steric"* alkylation.[74] An enolate conformation **211–212** (**Scheme 66**) was proposed by Ladner to help rationalise the stereochemical outcome.[74a] The Me(b) and CO_2Me position themselves pseudo-equatorial to minimise diaxial interactions. Alkyl iodide then approaches the enolate from the diastereotopic face away from the axial $Me^{(a)}$ in a "*contra-steric*" fashion, *cis* to the unenolised ester group.



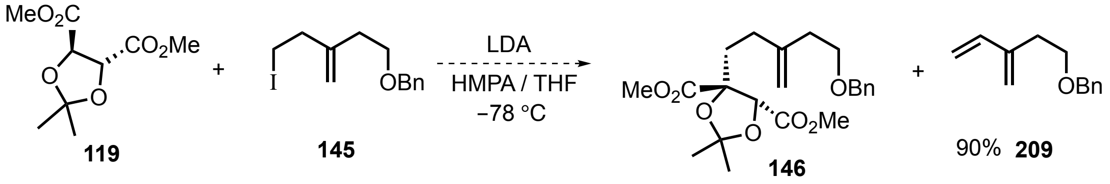
Scheme 66. 'Contra-steric' alkylation electrophile approach.

Low temperature alkylation is considered necessary, as the intermediate enolate is susceptible to *β*–elimination in the absence of reactive electrophiles.[73,74] A possible decomposition pathway is by collapse of lithium enolate **211** resulting in ring opening and loss of acetone. The newly formed enolate **214** could potentially react with the acetone to produce undesired tertiary alcohol **215** (**Scheme 67**).



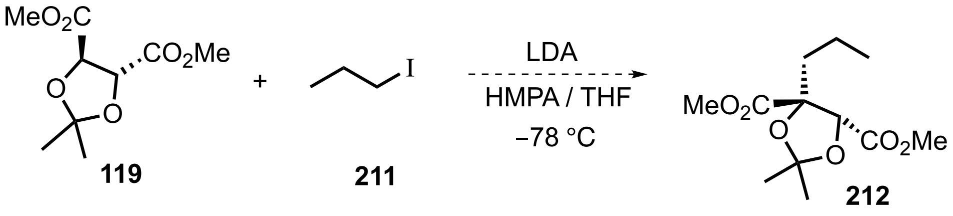
Scheme 67. Possible *β*–elimination decomposition pathway.

In the first experiment, a mixture of alkyl iodide **145** in THF/HMPA and tartrate **119** (2 equiv.) was reacted with LDA (2 equiv.) at –78 °C to generate the corresponding lithium enolate for *in situ* alkylation (**Scheme 68**). However, this initial attempt did not yield product, with only 52% tartrate recovered. Additionally, significant elimination of iodide **145** was observed, to give diene **209**. A particular practical problem was the uncontrolled rate of LDA addition (high pressure of argon inlet during cannula transfer). Presumably, the reaction requires slow addition of LDA to form the enolate needed for alkylation. This potentially increases chances of alkylation (instability of enolate) and reduces the possibility of elimination of iodide **145** to diene **209**. The reaction was therefore repeated, this time with full control over the rate of addition of base (cannula transfer of LDA to reaction mixture was regulated using argon filled balloon). However, once again the desired product was not observed, only tartrate (80%) and clean diene **209** (90%) were recovered.



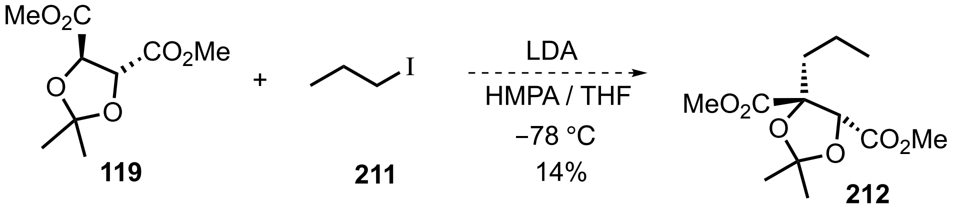
Scheme 68. Attempted alkylation with iodide **145**.

To ensure the precious iodide **145** (p.71) did not go to waste (through elimination), trial alkylation experiments were carried out using electrophiles that have previously been successfully used, such as 1-iodopropane (**211**).[38] The reaction was carried out with careful monitoring of internal reaction temperature. It was considered that, on enolate formation, coupling with the iodide might require warmer temperatures. However, it is vital that the temperature does not reach a level where the tartrate undergoes irreversible *β*–elimination (**Scheme 67**, p.72).[73,74] However, two temperature-controlled reactions (one at –78 °C and one at –60 °C) showed no difference to the outcome of the reaction and no desired product was observed, with tartrate (68–74%) recovered (**Scheme 69**). Since the alkyl iodide was somewhat volatile under reduced pressure (b.p. 101 °C at rt), no unreacted iodide was isolated at the end of the reactions.



Scheme 69. Attempted alkylation with 1–iodopropane **211**.

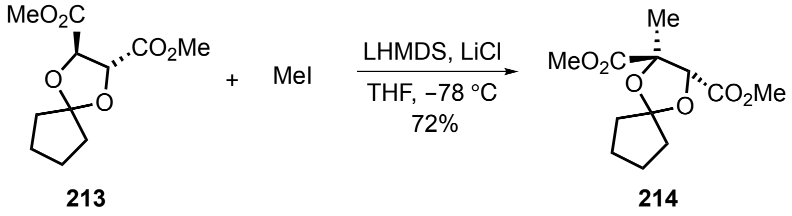
In an alternative experiment, DMPU[75,76] was substituted for HMPA, although the cation coordination ability of DMPU is likely lower compared with HMPA, and could lead to potentially lower yields. DMPU was used in a 1:2 mixture with THF and, pleasingly, the desired *n*-propylated product was finally synthesised successfully, albeit in low yield (14%, **Scheme 70**).



Scheme 70. Alkylation with iodopropane with DMPU as co-solvent.

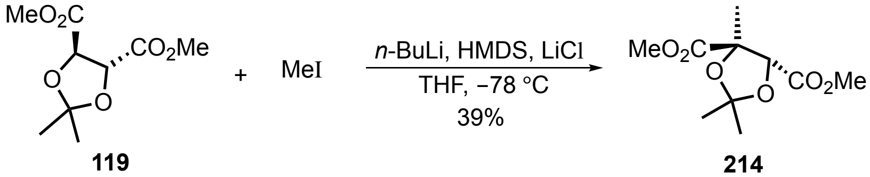
It was believed that one of the reasons why the reaction using HMPA yielded no alkylated tartrate was due to potentially significant water content in the HMPA. It therefore became a necessity to distill HMPA, as it is a very hygroscopic co-solvent. However, HMPA is a class A carcinogen and distillation was preferably avoided if alternative methods were available.

Prior to distilling HMPA, further effort was made to find a substitute for HMPA. Lipton *et al.*, performed a tartrate alkylation using LiHMDS and MeI in the presence of LiCl at –78 °C, yielding 72% of the alkylated tartrate **214** as a single diastereomer (**Scheme 71**).[77] In comparison, Seebach's studies contain an example of undesired dimethylation.



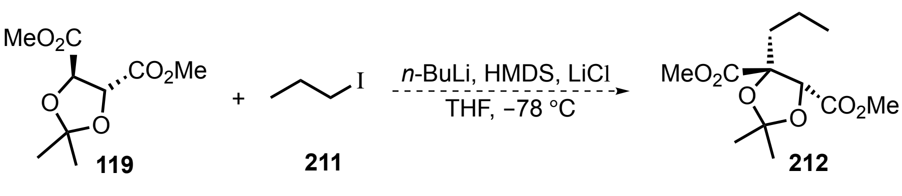
Scheme 71. Lipton *et al.* alkylation using LHMDS.[77]

The literature reaction of Lipton was carried out with the only variable being using tartrate acetonide **119** compared to its ketal form **213**; this was to ensure whether the same transformation could be achievable on the particular tartrate in hand. LiHMDS was generated from slow addition of *n*-BuLi to HMDS in THF and was then transferred at –78 °C to the reaction flask containing the tartrate, MeI and dry LiCl at –78 °C (**Scheme 72**). Monomethylation (**214**) was achieved in moderate yield (39%).



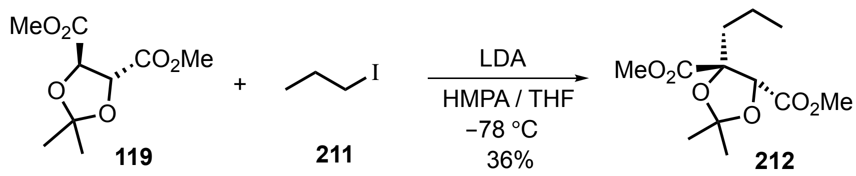
Scheme 72. Alkylation using LiHMDS on desired tartrate.

With knowledge gained from the above reaction with regard to formation of desired product on the preferred tartrate, the same transformation was carried out now using less activated 1-iodopropane **211** as a more realistic model in comparison to the actual alkyl iodide **145** that needed to be alkylated. Unfortunately, alkylation did not occur and only ~ 25% of tartrate was recovered, in an impure state (**Scheme 73**).



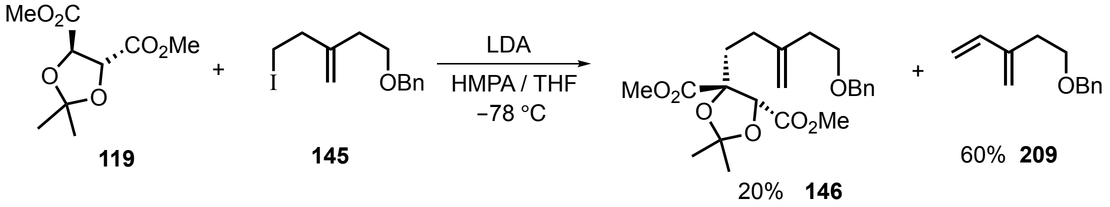
Scheme 73. Attempted alkylation using LiHMDS with 1-iodopropane **211**.

Despite efforts to alkylate tartrate acetonide **119** without using HMPA, the possible alternatives tested did not give sufficient yields with the model substrates in order to start with the target iodide. As such, HMPA was distilled using standard method[78,79] and the reaction with tartrate **119** and 1-iodopropane **211** was performed again. After 24 h, monoalkylation was achieved in 36% yield (**212**, **Scheme 74**). It could therefore be assumed the reason why alkylation was not achieved in earlier experiments was due to 'wet' HMPA, quenching the LDA and/or any enolate generated.



Scheme 74. Alkylation of 1-iodopropane **211** using distilled HMPA.

Having successfully achieved alkylation using distilled HMPA, the reaction was repeated with desired homoallylic iodide **145**. The alkylated tartrate **146** was obtained (~20%) in a mixture with unreacted tartrate (68%, **Scheme 75**). Additionally, 60% of diene **209** was isolated.



Scheme 75. Alkylation of target iodide **145** using distilled HMPA.

In a further attempt to isolate the desired product pure, the enolate of tartrate **119** was initially generated *via* slow addition of LDA in THF/HMPA followed by trapping with iodide **145**, to yield 48% of pure alkylated tartrate **146** (after repeated silica gel chromatography) and as a single diastereomer.

A detailed study was then carried out in order to try and increase the yield of alkylation, in a series of temperature-controlled reactions as well as control over the rate of addition of LDA with different substrates. A summary of the conditions investigated is displayed in **Table 1**. Initial reaction of iodide **145** using HMPA (from commercially available bottle) yielded no alkylated product (entries 1-2). The investigation continued by trying to find a replacement for HMPA that ultimately proved to be inefficient with the desired substrate. Experiments using freshly distilled HMPA and model iodide **145** proved to be promising and consistent in producing alkylated tartrate with slow rate of LDA addition (entries 3-7).

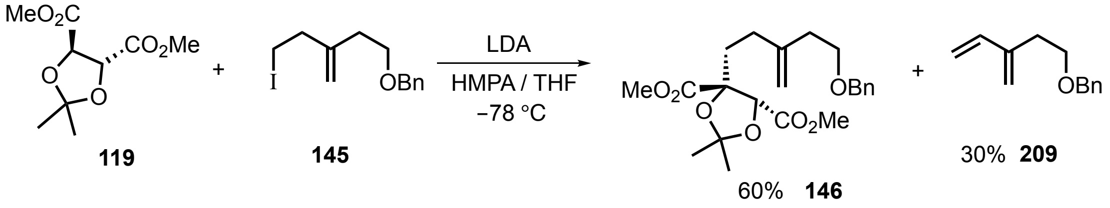
However, where the reaction was carried out at –60 °C (entry 5), a relatively low yield was obtained with significant elimination of iodide **145** to diene **209**. Finally, the alkylation yield was improved when iodide had minimum contact with HMPA at lower temperatures (entries 8-14), as well as slow addition of LDA to the mixture. The former observation is presumably indicative of iodide elimination to diene on prolonged contact time with HMPA.

Entry	**Iodide 145 (mmol)**	**Temperature (°C)**	**Duration of LDA (min)**	**Isolated yield (146) (%)**	**Iodide 145: diene 209 recovery**
1	0.791	–78	20	–	1:6
2	0.791	–78	60	–	1:3
3	0.791	–78	60	20	1:3
4	0.949	–78	60	24	1:3
5	0.949	–60	60	14	1:10
6	1.90	–78	90	34	3:1
7	3.16	–78	110	35	3:1
8	0.949	–78	60	–	1:10
9	1.58	rt to –78	70	–	All diene

10	1.58	rt to –60	70	Trace	All diene
Iodide added just before enolate formation at –78 °C					
11	1.58	–78	70	36	1:1
12	3.16	–78	90	45	1:1
13	6.32	–78	120	47	1:1
14	9.48	–78	150	48	1:1

Table 1: Summary of conditions examined to increase yield of tartrate alkylation.

While employing the optimised conditions (**Table 1**, entry 14) to increase yield of alkylation, purification remained as a fundamental issue after the alkylation reaction. To circumvent this problem, the crude residue was passed through a short pad of silica to obtain a mixture of unreacted tartrate **119** and the desired alkylated tartrate **146**. Once the mixture was free from toxic HMPA, a short path distillation was carried out under reduced pressure (0.2 mbar at ~160 °C) to remove unreacted tartrate. The desired product was then isolated in 60% yield. On average, the alkylation (2–20 mmol) yields between 50–60% of alkylated tartrate **146** and returns 30–40% of eliminated iodide, diene **209** (**Scheme 76**).

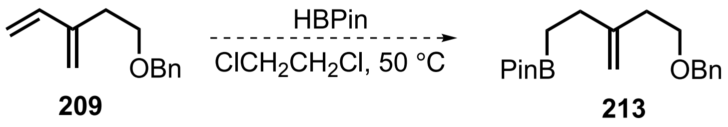


Scheme 76. Alkylation of target iodide **145** using distilled HMPA.

The optimum conditions for the formation of desired alkylated tartrate are the use of freshly distilled HMPA with slow addition of LDA to the reaction mixture at –78 °C. Additionally, minimum contact time of iodide with HMPA at lower temperatures prior to the start of LDA addition, seemed to reduce formation of unwanted diene

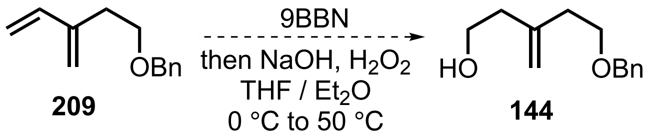
209. Furthermore, formation of LDA with 1.6 M *n*-BuLi gave an increase in yield as opposed to the use of 2.5 M *n*-BuLi. Finally, distillation to remove unreacted tartrate provides a more convenient method of purification.

In an attempt to recycle diene **209** from iodo elimination, by regioselective mono hydroboration–oxidation, it was reacted with HBPin[80] in $ClCH_2CH_2Cl$ at 50 °C. After 24 h, TLC showed significant amount of starting material. Therefore, the temperature was increased to 100 °C for a further 24 h (**Scheme 77**). Unfortunately, no desired product **213** was formed and all of the starting diene was recovered.



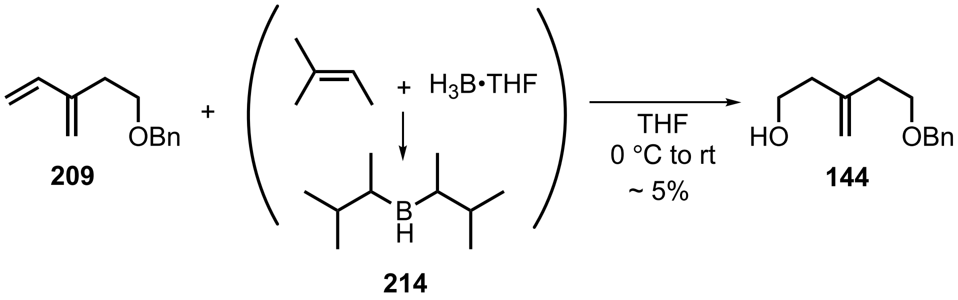
Scheme 77. Attempted recycling of diene **209** *via* HBPin.

Similarly, an attempt to form the corresponding 9BBN[81] complex followed by oxidation to form the alcohol **144**, yielded no desired product and returned only starting diene **209** (**Scheme 78**).



Scheme 78. Attempted recycling of diene **209** *via* 9BBN.

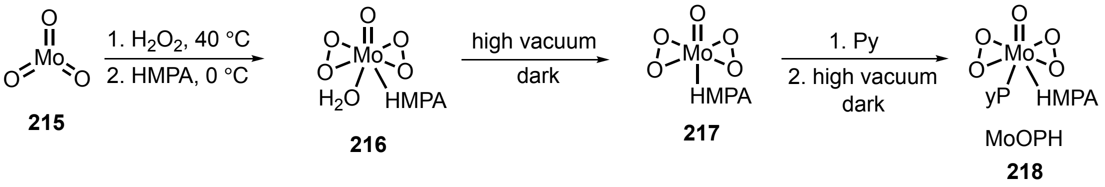
Lastly, disiamylborane[82] **214** (formed from H_3B•THF and amylene) was used in an attempt to form alcohol **144** after oxidation; however, only ~ 5% of the desired alcohol **144** was observed (**Scheme 79**). As attempts to recycle the diene were not successful, focus shifted back to the rest of the synthesis on the oxygenated core.



Scheme 79. Attempted recycling of diene **209** *via* disiamylborane **214**.

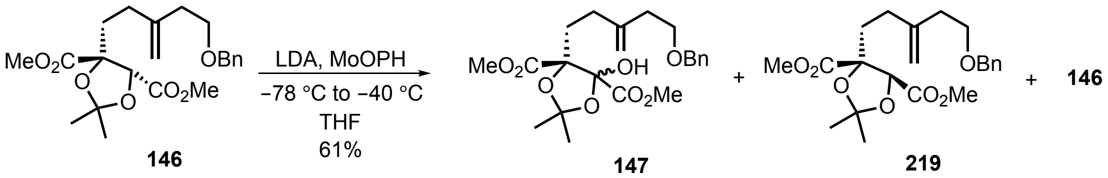
2.4.2 MoOPH Hydroxylation

In the next step towards the cycloadduct precursor, the lithium enolate of alkylated tartrate **146** was hydroxylated with MoOPH reagent **218** (MoO_5.Py.HMPA) (**Scheme 27**, p.42). The MoOPH reagent was prepared by the literature procedure.[83]The intermediate $MoO_5.H_2O$.HMPA **216** was dried under high vacuum for 48 h in the dark (**Scheme 80)**. After crystallisation of MoOPH, it was further dried under high vacuum (>0.75 mmHg) for a further 24 h in the dark and then stored in a freezer under argon.



Scheme 80. Preparation of MoOPH for hydroxylation.

A THF solution (–78 °C) of alkylated tartrate **146** was added slowly to an LDA solution in THF (–78 °C). To ensure maximum formation of the enolate, the mixture was stirred for an additional 30 min. at the same temperature. At this stage, the strong oxidising agent MoOPH (1.5 equiv.) was added in one portion to the enolate and the reaction allowed to warm to –40 °C and further stirred for 24 h. The material was hydroxylated to afford hemiketal **147** in 61% yield (76% brsm), as a 2:1 mixture of diastereomers (**Scheme 81**). Additionally, the reaction returned 10–15% of a mixture of (1:1) starting material along with the corresponding epimer **219** [^{1}H NMR: δ 4.95 (1H, s, C*H*CO_2Me) for starting material **146** and δ 4.84 (1H, s, C*H*CO_2Me) for epimer **219**] that was recycled when the experiment was repeated. Both diastereomers were useful (stereocentre destroyed in the next step), and thus were not separated after purification. Yields between 50–61% were typically obtained for the hydroxylation step.

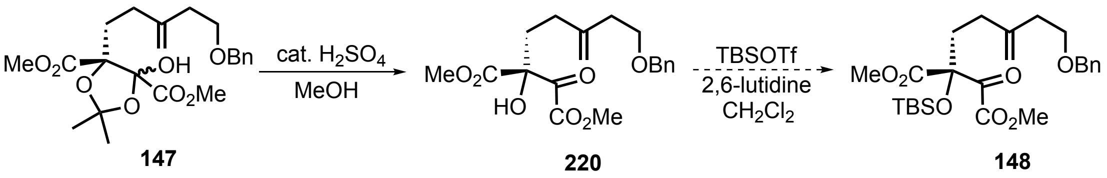


Scheme 81: MoOPH hydroxylation of alkylated tartrate **146**.

2.4.3 Hydrolysis and TBS Protection

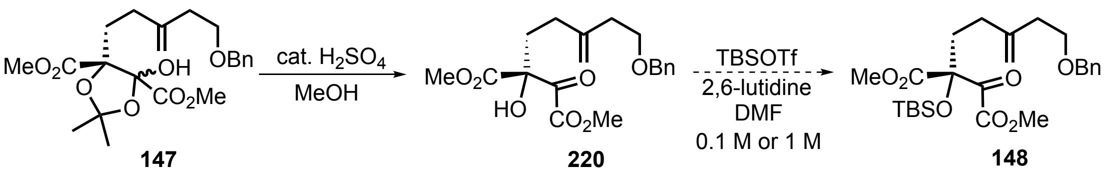
To cleave the acetonide protecting group in hemiketal **147**, the mixture of diastereomers were reacted with methanolic H_2SO_4 to give crude hydroxy-ketoester **220** (**Scheme 82**), as judged by ^{1}H NMR analysis showing the *gem*-dimethyl group loss at δ 1.5 ppm, as well as the appearance of a carbonyl group signal at δ 188.3 ppm in the ^{13}C NMR spectrum. Interestingly, full hydrolysis was not achieved after 12 h, therefore the reaction was left to stir at rt for an additional 12 h for full conversion. Possibly one of the diastereomers takes longer to hydrolyse. After neutralisation with pyridine, it is important to wash the pyridinium sulphate salts formed with Et_2O while stirring to fully extract the ketoester as it can potentially get trapped between the solids and make extraction difficult. The hydrolysis yielded between 80–90% of crude hydroxy-ketoester **220**.

In an attempt to convert crude hydrolysed material **220** to siloxy ketoester **148**, no desired product was formed and only 49% of hydroxy-ketoester **220** was recovered (**Scheme 82**). The hydroxy-ketoester **220** is potentially susceptible to hydration; therefore, the crude material was not purified by silica gel chromatography.



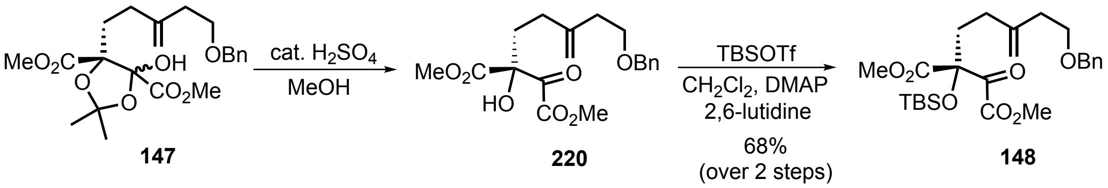
Scheme 82: Hydrolysis and attempted TBS protection.

When solvent in the protection step was changed to DMF from CH_2Cl_2, traces of the desired product were observed (**Scheme 83**). Concentrating the reaction mixture to 1 M from 0.1 M did not improve the yield of protection step.



Scheme 83: Hydrolysis and attempted TBS protection in DMF.

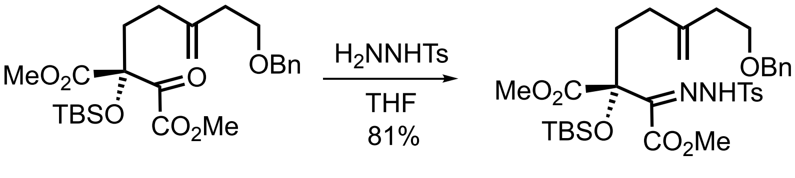
On the other hand, when DMAP (0.1 equiv.) was added to the silylation reaction mixture in CH_2Cl_2 and 2,6-lutidine, the desired siloxy ketoester **148** was obtained in 55% yield from hemiketal **147** (**Scheme 84**). Running the reaction for an additional 24 h improved the formation of siloxy ketoester **148** to 68%. The yields for the reaction under these conditions were typically between 45% and 68%.



Scheme 84: Hydrolysis and TBS protection to give siloxy ketoester **148**.

2.4.4 Diazoketone *via* Hydrazone Formation

With the carbon skeleton of the oxygenated core in place, further progress was made towards the bicyclic system, following the chemistry described by Arif.[40] Siloxy-ketoester **148** conversion to a diazo intermediate *via* hydrazone **149** was required (see **Scheme 27**, p.42). Initially, siloxy ketoester **148** was heated to 75 °C in the presence of $TsNHNH_2$ in THF, forming the desired hydrazone **149** in an excellent 81% yield after 24 h (**Table 2**, entry 1) (85% brsm). However, as the scale of the reaction was increased (from 0.23 mmol to 0.62 mmol), the yield reduced to 50% with ~ 46% of starting siloxy ketoester **148** returned (entry 2). As water is the byproduct of the condensation reaction, it was considered that its removal might improve the yield. Therefore, the reaction was carried out in the presence of activated molecular sieves (4 Å). However, the presence of the sieves significantly retarded the reaction and returned 66% starting material **148** with only 8% of hydrazone **149** (entry 3). Alternatively, siloxy ketoester **148** was re–subjected to the initial reaction conditions, but increasing the reaction temperature to 85 °C; under these conditions the hydrazone was formed in 60% yield with 23% recovered starting material (entry 4). In addition to running the reaction at 85 °C, leaving it for an extra 24 h, increased the yield to 73% (entry 5). On average, under these latter conditions the reaction yield ranged between 70–81% for the desired hydrazone **149** (**Scheme 85**).



148

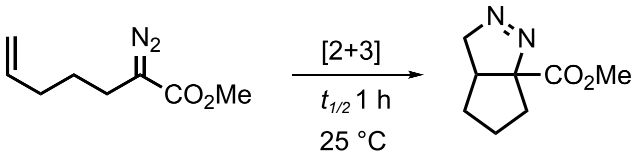
149

Scheme 85: Hydrazone formation.

Entry	**Siloxy-ketoester 148** (mmol)	**Time** (h)	**Temperature** (°C)	**Yield of hydrazone 149** (%)	**Recovered 148** (%)
1	0.23	24	75	81	–
2	0.62	24	75	50	46
3	0.79 (with 4Å MS)	24	75	8	66
4	0.88	24	85	60	23
5	0.67	48	85	73	–

Table 2: Summary of hydrazone **149** formation reactions.

Revealing the diazo functionality prior to double bond manipulation was anticipated to be problematic: decomposition of material from studies carried out by Arif and a, structurally related (but simpler) unsaturated *α*-diazoester has been observed to undergo spontaneous intramolecular dipolar cycloaddition to give a 1-pyrazoline (**Scheme 86**).[84]

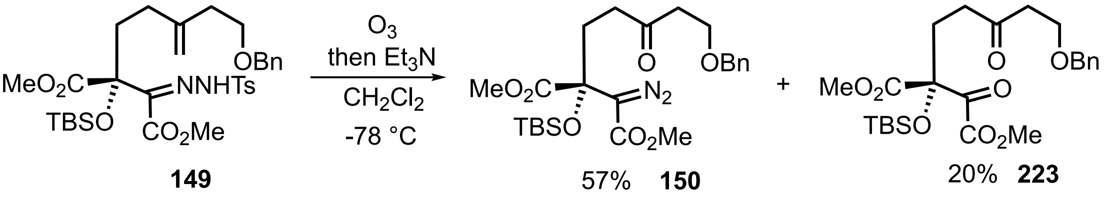


221

222

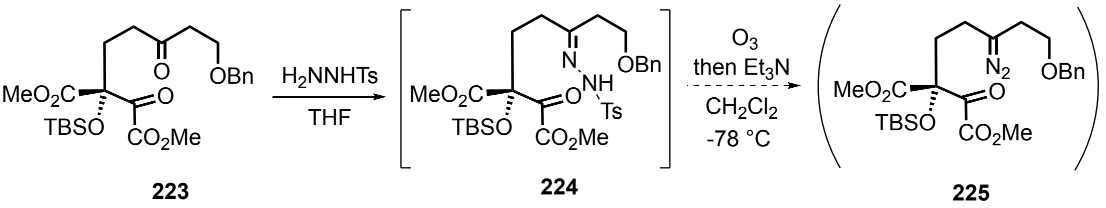
Scheme 86: Spontaneous cycloaddition at rt to form a 1-pyrazoline.[84]

Also, under ozonolytic conditions, hydrazones are known to transform to ketones,[85] but the rate of this currently undesired process was expected to be reduced by proximal electron deficiency[85a] (in the present case by the presence of the ester and Ts groups). Ozonolysis of unsaturated hydrazone **149** (deep blue colour indicated ozonolysis end-point) followed by addition of Et_3N produced diazoketone **150** (57% yield, **Scheme 87**); here, the Et_3N functions as a base in two processes; facilitating anionic cycloreversion of the intermediate ozonide to the ketone (and triethylammonium formate),[86] and in the Bamford-Stevens reaction.[45] A major byproduct identified from the reaction was undesired over oxidation of the hydrazone prior to conversion to the diazo group (**223**, ~ 20%).



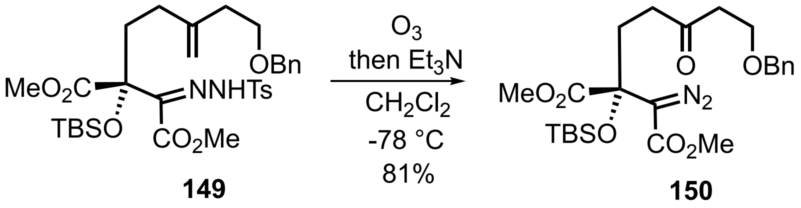
Scheme 87: ozonolysis to form diazoketone **150** and over oxidised byproduct **223**.

In an attempt to recycle the diketone **223** byproduct, (as it was a precious material), it was reacted with $TsNHNH_2$ to hopefully form the corresponding hydrazone from the α-ketoester substituent (**Scheme 88**). However, hydrazone formation only took place on the less hindered ketone in **223**. The hydrazone **224** formed could subsequently lead to formation of desired cycloadduct, however formation of an unstabilised diazo moiety **225** was of experimental concern from a safety aspect, thus it was not pursued.



Scheme 88: Formation of hydrazone **224** on the least hindered ketone.

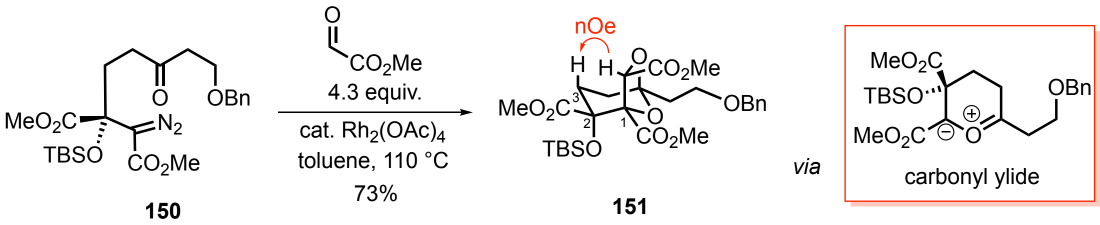
Ozonolysis of hydrazone **149** was very rapid (~1 min). To prevent over oxidation, it was terminated just before a deep blue colour appeared (when a very pale blue colour is apparent) and the intermediate ozonide was reacted with Et_3N to cleanly give diazoketone **150** in 81% yield (**Scheme 89**).



Scheme 89: Ozonolysis and Bamford-Stevens process in forming diazoketone **150**.

2.5 Key 1,3-Dipolar Cycloaddition

A key transformation in the total synthesis of 6,7-dideoxysqualestatin H5 was the $Rh_2(OAc)_4$–catalysed tandem carbonyl ylide formation–1,3-dipolar cycloaddition between diazoketone **150** and freshly distilled methyl glyoxylate (**Scheme 90**).[87] The cycloaddition chemistry, when performed at 110 °C in toluene, yielded 73% of cycloadduct **151**, which possessed the desired regio- and stereochemistry for squalestatin synthesis. The *exo*–stereoselectivity of the cycloaddition was supported by a nOe[40] between the C*H*CO_2Me and axial C^3 protons.

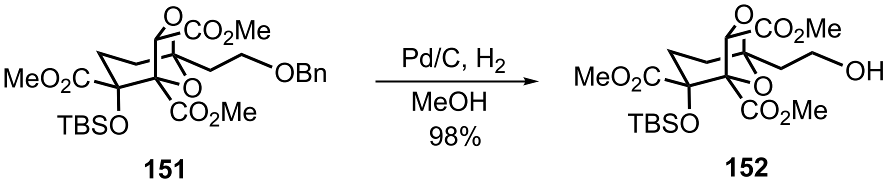


Scheme 90: Key [3+2] cycloaddition chemistry.

Close analysis of the ^{1}H NMR spectrum of the crude product indicated two other possible additional minor cycloadduct isomers in a ratio of 20:6:1, as judged by singlets assigned to the C*H*CO_2Me methines at δ 5.59, 4.84 and 4.58, respectively. However, these possible minor isomeric cycloadducts could not be subsequently isolated following chromatographic purification.

2.6 Rearrangement Chemistry

Cycloadduct **151** was initially debenzylated with Pd/C under a hydrogen atmosphere, to yield alcohol **152** (98%, **Scheme 91**) as a solid. A crystal structure of this alcohol **152** (**Figure 9**) was obtained (**Appendix 8.1.1**), which unambiguously confirmed the *exo*- incorporation of the ester group with respect to the carbonyl ylide-containing ring in the dipolar cycloaddition step. Debenzylations yields ranged between 80–98%.



Scheme 91: Debenzylation to alcohol **152**.

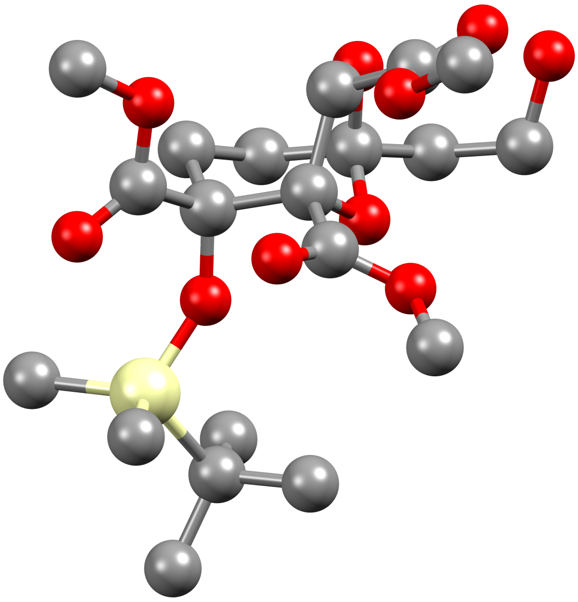
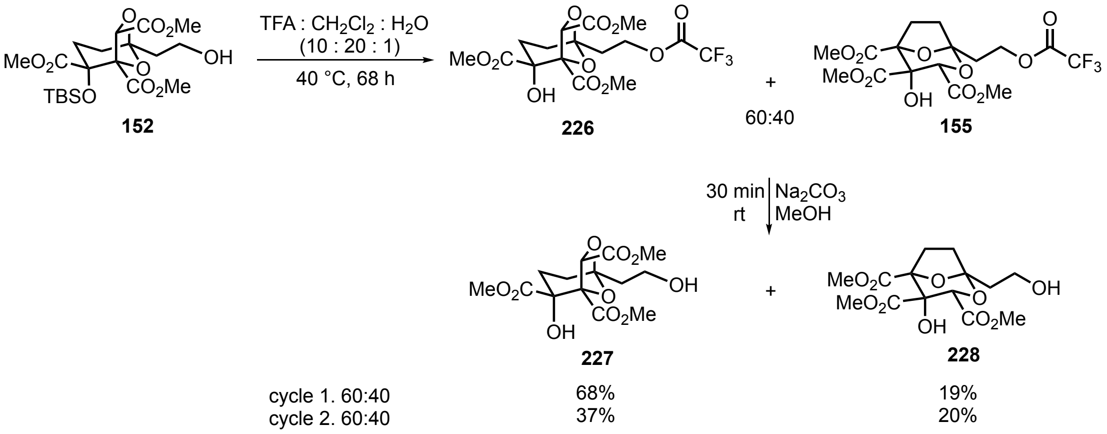


Figure 9: X–ray crystal structure of alcohol **152** (H's are omitted for clarity).

Acid–catalysed transketalisation conditions[14] to access the desired rearranged bicyclic core were then investigated. It was anticipated that the acidic conditions would be sufficient to cleave the TBS group (necessary for the rearrangement chemistry to occur).

Following heating in TFA/CH_2Cl_2/H_2O at 40 °C for 68 h (Evans' conditions,[14] **Scheme 1**, p.18), NMR and MS analyses indicated that rearrangement to the desired bicyclic core took place, in ~ 60:40 ratio of unrearranged to rearranged material, with trifluoroacetyl incorporation at the primary alcohol **226** and **155** (**Scheme 92**, **Figure 10**, spectrum A); the latter was assigned on the basis of a singlet at $\delta_H = 5.50$ for unrearranged and $\delta_H = 4.94$ for the rearranged material, as well as ^{19}F NMR analysis indicating $\delta_F = 75.1$ (COCF_3) for unrearranged and $\delta_F = 75.2$ (COCF_3) for rearranged material (**Scheme 92**).

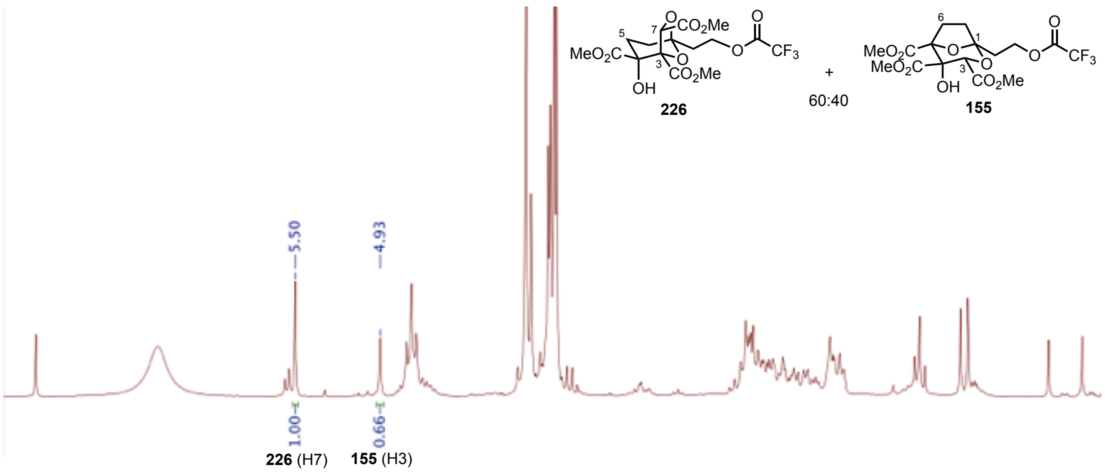


Scheme 92: Rearrangement chemistry.

One of the aims at this stage of the project was to advance beyond this point (the furthest point Arif had reached, p.42) by separating the desired rearranged product from the unrearranged material. The two trifluoroacetylated compounds **226** and **155** could be partially separated by column chromatography in 50% ethyl acetate in petrol

(R_f = 0.36 for unrearranged **226** and R_f = 0.34 for rearranged **155**); however, only a small amount of unrearranged **226** was obtained pure for full characterisation (spectrum B).

A (crude mixture)



B

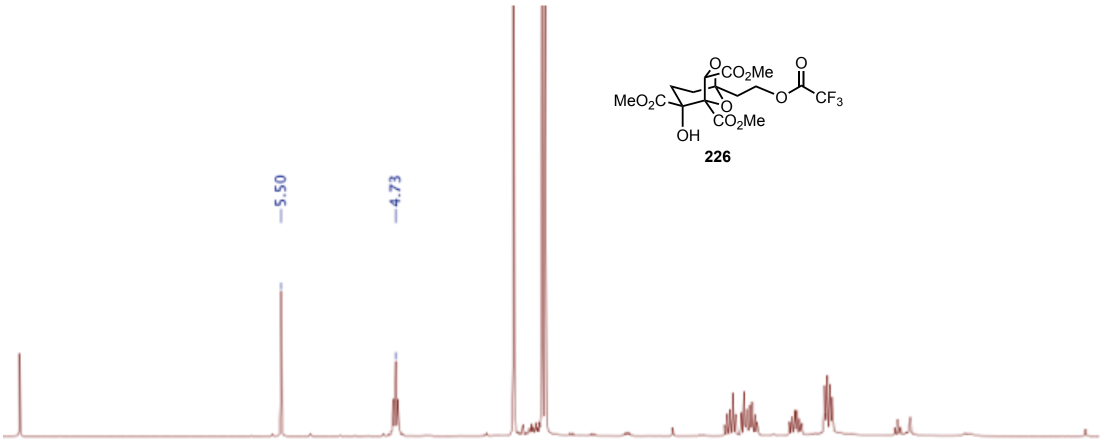
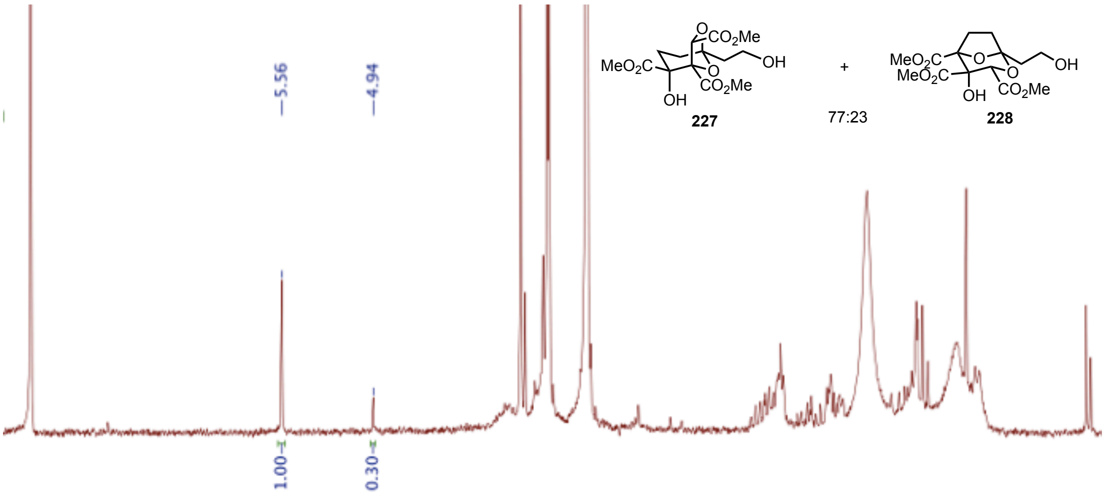


Figure 10: ^{1}H NMR spectra of trifluoroacetylated products **226** and **155**.

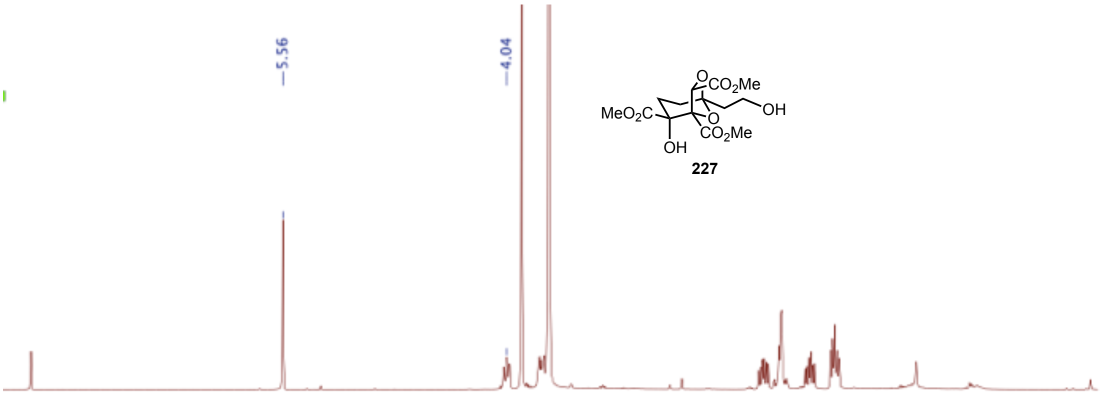
Unfortunately, mass recoveries of both products were poor following silica gel chromatography (below 40% in total). Therefore, the crude material was treated with Na_2CO_3 (1.5 eq.) in MeOH, to cleave the trifluoroacetate groups (**Scheme 92**). The crude ^{1}H NMR spectrum after hydrolysis indicated the formation of unrearranged **227**

(δ_H = 5.56), to rearranged **228** (δ_H = 4.94), diols in a 77:23 ratio (spectrum **A**). After extensive exploration of various solvent systems to separate the two diols, the best system found was 5% MeOH in CH_2Cl_2 (R_f = 0.37 for unrearranged and R_f = 0.34 for rearranged). Recycling desilylated unrearranged diol **227** under the same rearrangement (**Scheme 92**) reaction conditions gave 60:40 (unrearranged **227**:rearranged **228**). Spectra **B** and **C** show the pure unrearranged **227** and rearranged **228** diols respectively.

A (Crude mixture)



B (Unrearranged diol 227)



C (Rearranged diol 228)

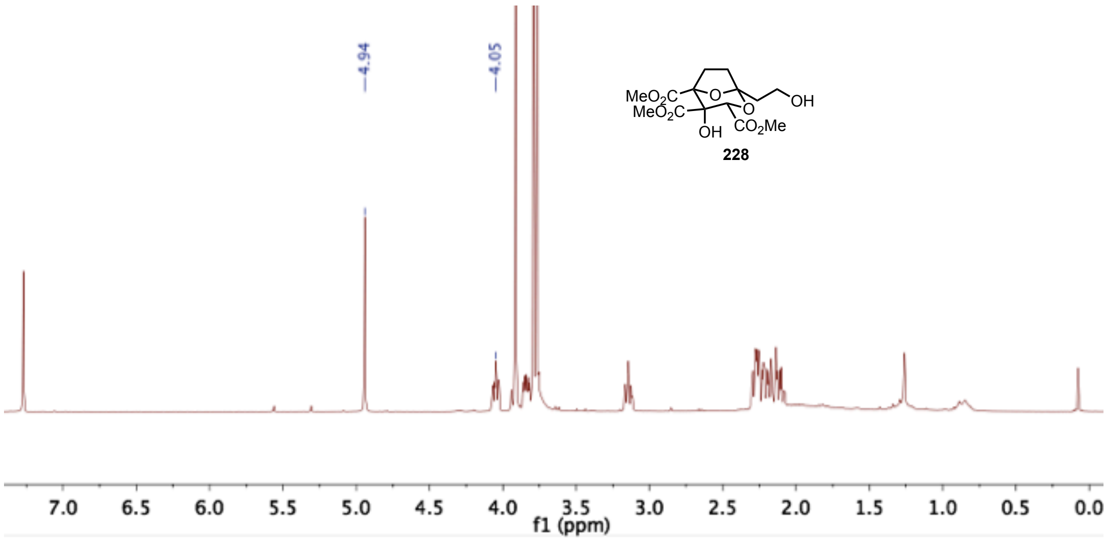
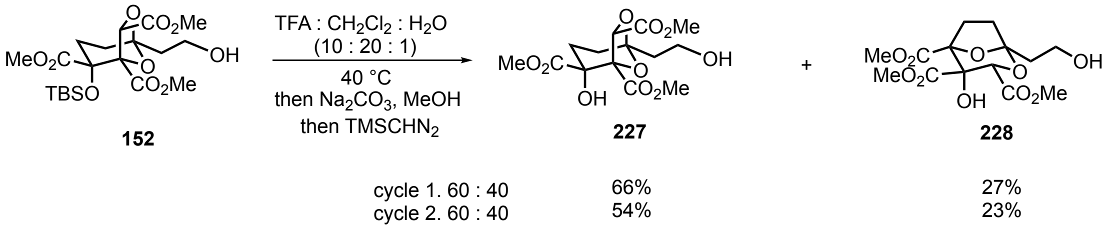


Figure 11: ^{1}H NMR spectra of rearrangement chemistry.

Rearranged diol **228** was resubmitted to the same reaction conditions to determine whether equilibrium has been reached. Crude ^{1}H NMR analysis indicated an approximate ratio of 57:43 (unrearranged:rearranged) suggesting within experimental error, that true equilibrium had been reached after exposure to Evans' conditions for 3 days.

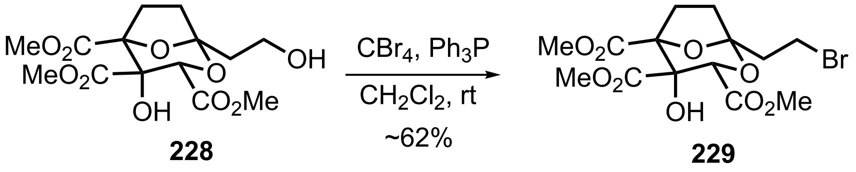
One of the major issues faced *en route* to the natural product was this rearrangement step, as it suffered from poor overall mass recovery, resulting in a synthesis bottleneck. Efforts to improve the overall yield of the key acid-catalysed rearrangement step starting from unrearranged alcohol **152** were investigated. It was considered that on prolonged contact with the strongly acidic environment in the presence of water, one or more of the methyl esters could be being hydrolysed to the corresponding acid; this would increase polarity of the resulting material hence leaving it on the baseline during chromatography leading to the observed poor mass recovery and overall yield. Therefore, once the trifluoroacetylated mixture was hydrolysed to the diols, toluene was added followed by dropwise addition of TMSCHN$_2$[88] (1.5 equiv.). The latter appeared to be successful in re-esterifying any carboxylic acids formed since, from the first and second cycles, the overall yield of materials were 93% and 77% respectively, which was a significant improvement on previous syntheses with less than 20% overall yield (**Scheme 93**).



Scheme 93: Synthesis of rearranged diol **228**.

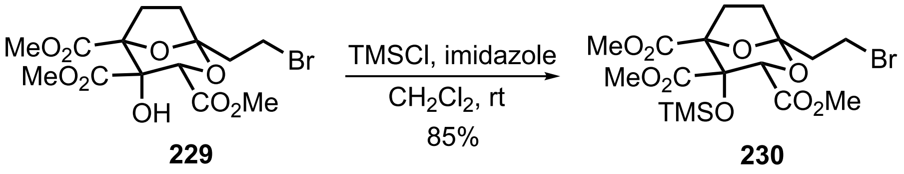
2.7 Alkyl Bromide and Cross–Coupling

With sufficient rearranged material **228** in hand, an Appel reaction was carried out to synthesise bromoalcohol **229** (**Scheme 94**). Initially, the reaction was carried out in Et_2O and resulted in formation of 27% of the desired bromide **229** along with ~ 6% recovery of starting material. The poor yield appeared due to solubility issues in combination with loss of solvent overnight. Additionally, there was a significant issue with respect to isolation of the alkyl bromide: thermal instability leading to decomposition. Bromoalcohol **229** was found to thermally decompose to a complex mixture under reduced pressure at 40 °C (water-bath). Therefore, from this point onwards in the bromide synthesis, heating under reduced pressure to remove solvent at the end of reaction was avoided. Instead, nitrogen was used to blow off the solvent to concentrate samples. With instability of the product in mind, the reaction was carried out again, this time in a more polar solvent, CH_2Cl_2, and in a sealed vial. The desired alkyl bromide was successfully synthesised in 62% yield, with slight impurities (**Scheme 94**).



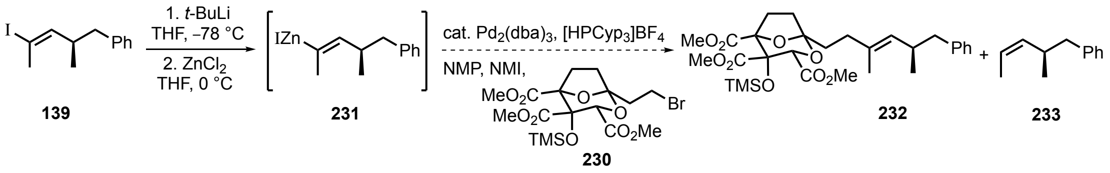
Scheme 94: Appel reaction to form bromoalcohol **229**.

Model studies on cross–coupling (*vide supra*, p.65) suggested that temporary TMS protection of the tertiary alcohol was required for successful cross–coupling to take place. Therefore, bromoalcohol **229** was treated with TMSCl and imidazole to form silyl ether **230** (solvent removed under nitrogen) (**Scheme 95**). With the relatively labile TMS group installed, the crude material was taken to next step without further purification, carrying minor impurities from previous steps.



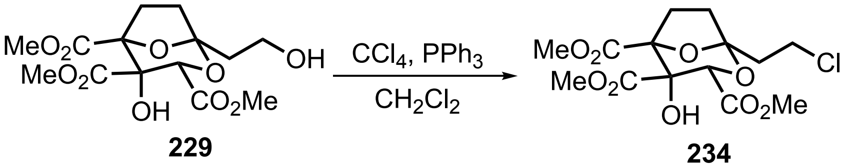
Scheme 95: TMS protection of bromoalcohol **229**.

With alkyl bromide **230** in hand, it was time to test the key cross–coupling using the conditions developed earlier (p.65). Previously synthesised enantiopure alkenyl iodide **139** (synthesised by Arif,[40] p.41) underwent Li–iodide exchange, followed by transmetallation with $ZnCl_2$. In a separate Schlenk tube, $Pd_2(dba)_3$ and $[HPCyp_3]BF_4$ were placed under high vacuum for 3–4 h before NMP (freshly distilled) and the previously prepared alkenyl zinc halide **231** solution was added (**Scheme 96**). Finally, NMI and the alkyl bromide **230** was added and the flask sealed and heated at 80 °C overnight. Disappointingly, ^{1}H NMR analysis of the crude showed no indication of desired coupled adduct **232**. Also, no starting bromide **230** was recovered (likely due to decomposition). It was considered that unanticipated thermal instability of the alkyl bromide **230** prevented formation of cross–coupled product. Also, all protonated alkene **233** was returned.



Scheme 96: Attempted cross–coupling of enantiopure side chain **139** and alkyl bromide **230**.

With the failure of cross–coupling of alkyl bromide **230** likely due to decomposition of the latter at high temperatures, alkyl chloride **234** was synthesised to hopefully increase stability despite likely loss of reactivity under the same reaction conditions (**Scheme 97**). However, and akin to the bromoalcohol **229**, the chloroalcohol **234** was also found prone to partial decomposition at 40 °C (water-bath), and was isolated in an impure state.



Scheme 97: Synthesis of chloroalcohol **234**.

Lack of success in the cross–coupling reaction and decomposition meant more material needed to be synthesised so as to investigate this particular step in greater detail. Importantly, particular emphasis was now placed on devising a cross–coupling strategy on model systems that would occur at ambient temperature or below, due to the thermal instability of one of the coupling partners.

Chapter 3

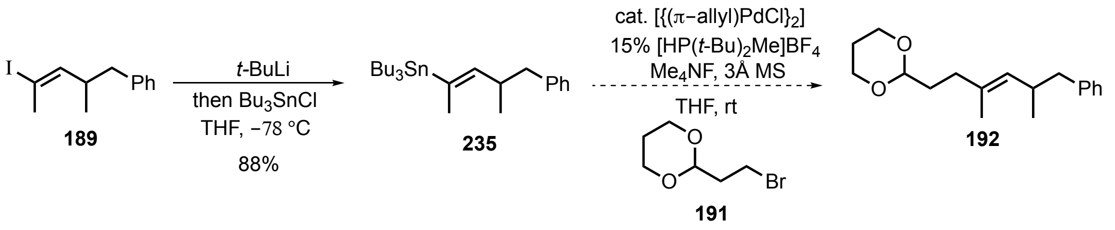
Results and Discussion

(Model Cross–Couplings Continued)

3. Results and Discussion – Model Cross-Couplings Continued

3.1 Stille Coupling

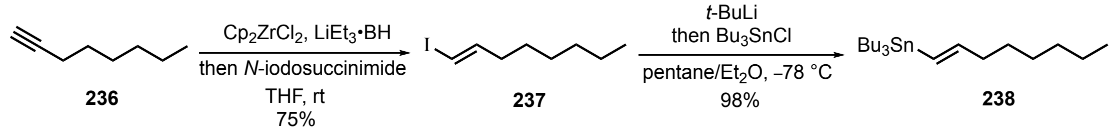
As the model Negishi cross–coupling conditions (p.65) proved unsuitable for the desired C–C bond formation on the highly oxygenated core of the natural product (p.29), an alternative strategy needed to be devised, initially through less precious model systems. Cross–coupling of the corresponding vinyl stannane **235** from vinyl iodide **189** was therefore investigated to hopefully achieve a rt palladium–catalysed Stille coupling[89] with bromoethyl dioxane **191** (**Scheme 98**).



Scheme 98: Formation of vinyl stannane **235** and attempted Stille cross–coupling.

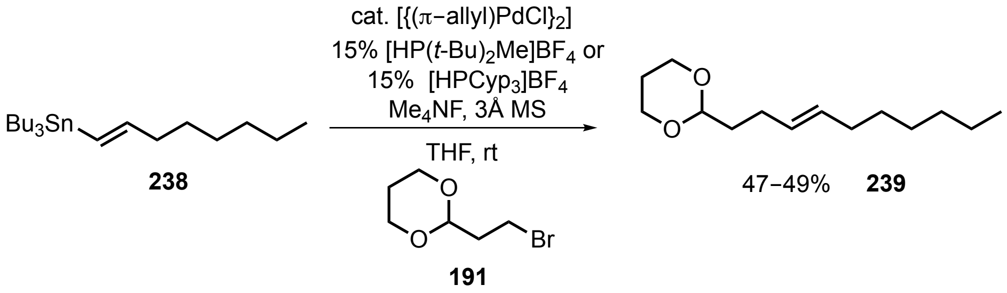
Vinyl iodide **189** initially underwent Li/Hal exchange and the intermediate organolithium was trapped with Bu_3SnCl, to form the corresponding vinyl stannane **235** in 88% yield. However, efforts to cross–couple vinyl stannane **235** and bromoethyl dioxane **191** both inside and outside of a glove–box gave no desired product (**Scheme 98**).

It was decided to simplify the test reaction by using an alternative alkenylstannane. Terminal alkyne **236** was initially hydrozirconated, followed by trapping with *N*-iodosuccinimide to form the corresponding *E*–alkenyl iodide **237**[90] in 75% yield (**Scheme 99**). The vinyl iodide **237** was then reacted with *t*-BuLi to form the corresponding organolithium, which was quenched with Bu_3SnCl to give the desired *E*-alkenylstannane **238** in 98% yield.



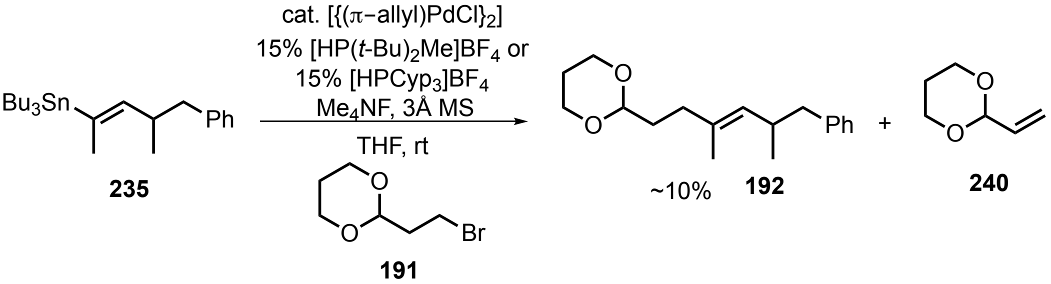
Scheme 99: Synthesis of model *E*–alkenylstannane **238**.

Alkenylstannane **238** was then used in an attempted Stille cross–coupling with bromoethyl dioxane **191** (**Scheme 100**). Unfortunately, only traces of the desired product were observed. It was anticipated that the dryness of the highly hygroscopic TMAF, which is an essential component of the coupling, might be detrimental to the reaction outcome. Therefore, a new batch of TMAF (from Alfa Aesar) was purchased and only opened in a glove–box. The coupling was re–attempted, and this time 47% of the desired coupled product **239** was obtained. When the ligand was changed from $[HP(t\text{-}Bu)_2Me]BF_4$ to $[HPCyp_3]BF_4$, alkene **239** was formed in a similar yield (49%). No unreacted stannane **238** was recovered at the end of the reaction.



Scheme 100: Model *E*–alkenylstannane Stille coupling.

The model reactions indicated that the couplings take place in moderate yields, provided the TMAF used is dry. Additionally, there appears to be no significant difference between the two ligands used for the coupling. With this in mind, the target vinyl stannane **235** was re–examined, this time yielding ~10% of the coupled alkene **192** (**Scheme 101**). In addition to the desired adduct, the majority of the starting bromoethyl dioxane **191** along with the 2-vinyl 1,3-dioxane (**240**),[91] a by-product from *β*–hydride elimination [δ_H 5.95–5.76 (1H, m, C*H*CH$_2$) and 5.54–5.24 (2H, m, CHC*H*$_2$)], was recovered as a mixture (~ 1:8, *β*–hydride elimination : bromoethyl dioxane).



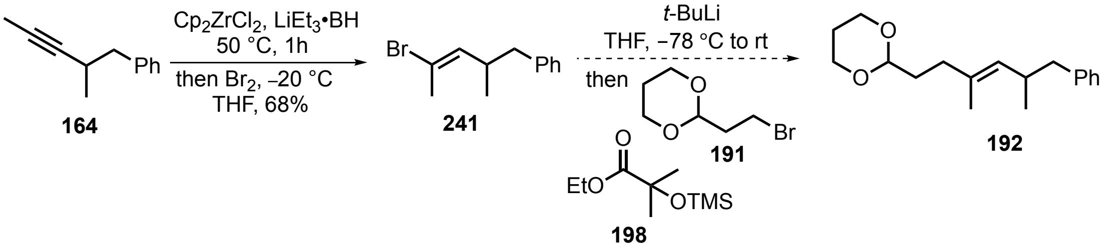
Scheme 101: Target *E*–alkenylstannane Stille coupling.

To increase the yield, the catalyst and ligand loading were doubled to 5% and 30%, respectively. ^{1}H NMR analysis showed that the formation of the desired product **192** increased to ~20% but the amount of *β*–hydride elimination **240** increased to a 1:1 ratio with the starting bromide **191**. Alternatively, TMAF, implicated in forming the active catalyst species by generating the free phosphine ligand which can complex to the Pd, as well as forming an ate complex with the stannane to increase transmetallation rate, was increased from 1.9 equiv. to 4 equiv.[92] Unfortunately, this change did not bias the formation of the desired product, and large amounts of *β*–hydride elimination was still observed.

In retrospect, the use of potentially more reactive trimethyl stannane (Me$_3$Sn instead of Bu$_3$Sn in **235**) from vinyl iodide **189** could have been an alternative substrate to utilise in the Stille coupling to form the desired product. However, with no success in the Stille coupling, other coupling methods were investigated.

3.2 Other Organometallics

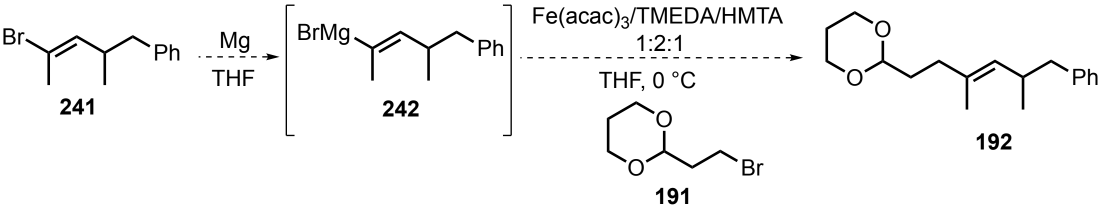
Other alkenyl organometallics were now considered. Internal alkyne **164** was initially hydrozirconated, followed by trapping with Br_2 to form *E*–alkenylbromide **241** in 68% yield (**Scheme 102**). Bromide **241** was then reacted with *t*-BuLi followed by addition of bromoethyl dioxane **191** and siloxy-isobutyrate **198**. The reaction showed that addition to the ester did not take place, however, only traces of the desired product were observed. Additionally, almost all of the starting vinyl bromide **241** was converted to the protonated alkene.



Scheme 102: Attempted synthesis of alkene **192** using vinyl bromide **241** with *t*-BuLi.

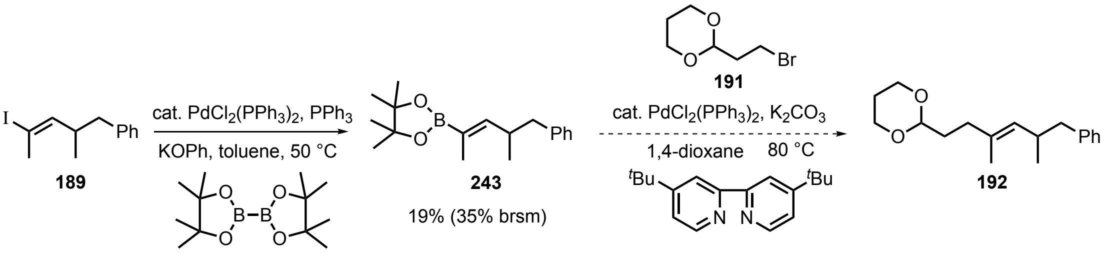
In a separate experiment, alkenyl iodide **189** (I instead of Br) was reacted with *s*-BuLi, and to the resulting organolithium was added bromoethyl dioxane **191**, and siloxy-isobutyrate **198**. Unfortunately, and similarly to the reaction with alkenyl bromide **241** only traces of the desired product were observed with large amounts of protonation and almost full recovery of the starting electrophile.

Formation of the corresponding Grignard **242** from alkenylbromide **241** using Mg was attempted, and was then reacted with bromoethyl dioxane **191** in the presence of Fe(acac)$_3$ as a catalyst and TMEDA/HMTA (2:1) in THF at 0 °C (**Scheme 103**).[93] However, crude ^{1}H NMR analysis indicated that both starting materials were unchanged; revealing that generation of the vinyl Grignard was unsuccessful.



Scheme 103: Attempted synthesis of coupled adduct from Grignard reagent.

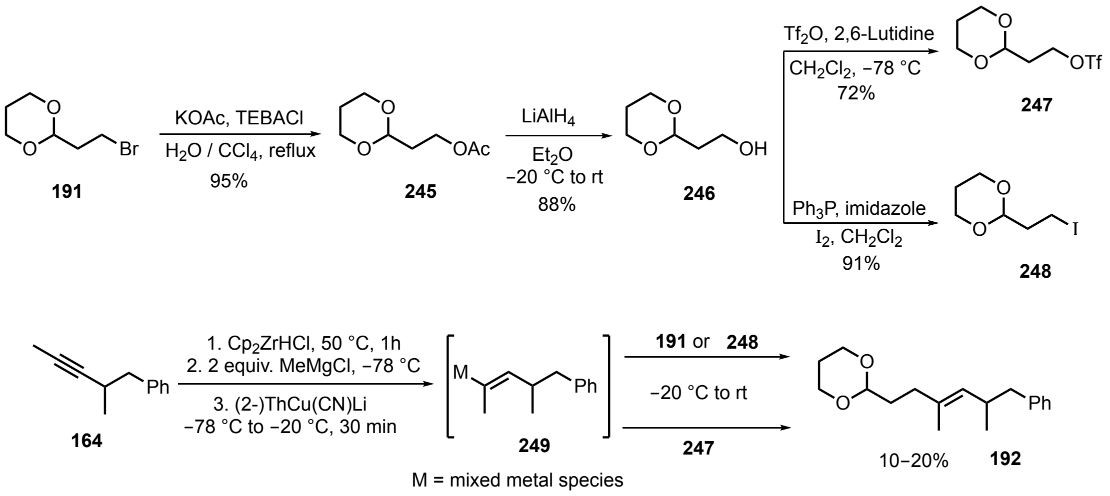
For an attempted Suzuki cross–coupling reaction, alkenyl iodide **189** was initially converted to the pinacol boronic ester **243** using B_2Pin_2 catalysed by $PdCl_2(PPh_3)_2$ in the presence of potassium phenoxide, albeit in only 19% yield (35% brsm) (**Scheme 104**).[94] With the pinacol ester in hand, the Suzuki coupling[95] was examined with bromoethyl dioxane **191**, but no coupled product was observed and the reaction returned both starting materials (**Scheme 104**). No protonation of starting material was seen. It was anticipated that the boronic ester partner is difficult to hydrolyse *in situ* therefore hindering the cross–coupling. In hindsight, while there are stability issues with regards to alkenyl boronic acids, it is believed that if the acid was used instead, this cross–coupling may have been more productive.



Scheme 104: Attempted Suzuki cross–coupling with pinacol ester **243**.

3.3 Higher Order Cyanocuprates

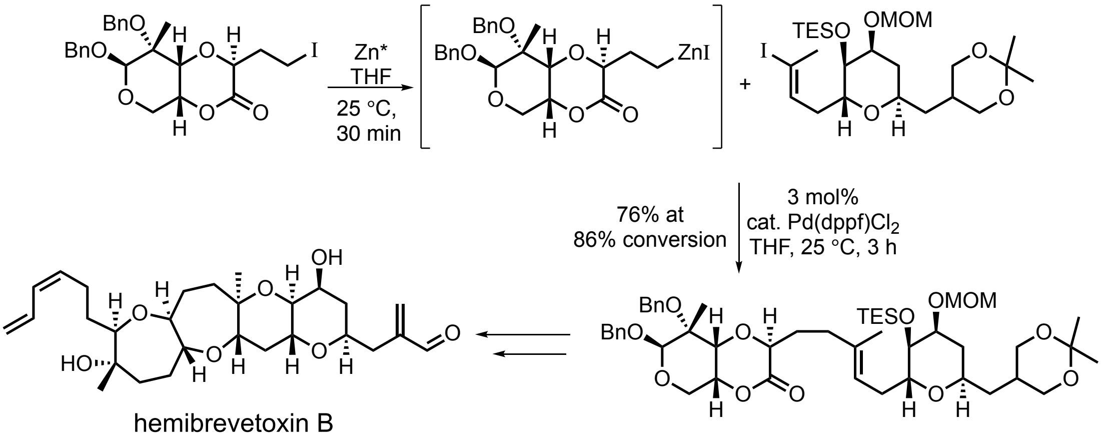
In an alkylation reaction utilising higher order mixed lithio/magnesio cyanocuprates, internal alkyne **164** was initially hydrozirconated at 50 °C (to ensure equilibration to the less–hindered alkenyl zirconium), followed by reaction with MeMgCl at –78 °C (**Scheme 105**). Vinylic zirconium species are reported to rapidly transmetallate at low temperatures with higher order cyanocuprates.[96,97] In a separate reaction flask, thiophene was reacted with *n*-BuLi to form the organolithium, which was then added to a solution of CuCN in THF to form the higher order cyanocuprate. The copper complex was then added to the mixed metal species **249** initially formed at –78 °C and stirred for 30 min at –20 °C. The non–transferable thiophene ligand (dummy) group allows selective delivery of the olefinic residue to accomplish an alkylation reaction.[98] Finally, the electrophile was added to the mixture and the reaction stirred at –20 °C overnight, before warming to rt for a further 1 h. Lipshutz and Kato found that the reaction does not proceed with even simple unactivated alkyl bromides or iodides (unactivated halide under investigation). However, where a mixed metal cuprate is generated using MeMgCl, alkylation can be achieved with primary alkyl triflates **247**.[98] When performing the reaction with both bromoethyl dioxane **191** (and the corresponding iodide **248**) and alkyl triflate **247** (**Scheme 105**), only a minor amount of the desired product (10–20%) was synthesised (~ 1:4, product:starting bromide/triflate) as judged by crude ^{1}H NMR analysis. The triflate **247** used in the alkylation reaction was prepared by phase transfer catalysed substitution of bromoethyl dioxane **191** using KOAc in the presence of triethylbenzylammonium chloride refluxed for 120 hours to give acetate **245** in 95% yield.[99] Subsequent reduction using $LiAlH_4$ gave alcohol **246** (88%) that was triflated using triflic anhydride in 2,6-lutidine/CH_2Cl_2 to give alkyl triflate **247** in 72% yield, after purification through a short pad of silica (**Scheme 105**).[100]



Scheme 105: Higher order mixed lithio-/magnesio- cyanocuprates with alkyl triflate/bromide.

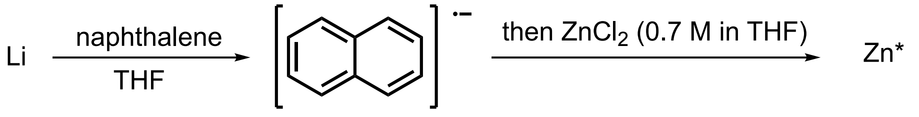
3.4 Rieke Zinc

In a total synthesis of hemibrevetoxin B (**Scheme 106**), Holton and co-workers carried out coupling of an unactivated primary alkyl iodide utilising highly activated Rieke zinc (Zn*) with a trisubstituted alkenyl iodide.[101]



Scheme 106: Total synthesis of hemibrevetoxin B using a Zn* cross–coupling.[101]

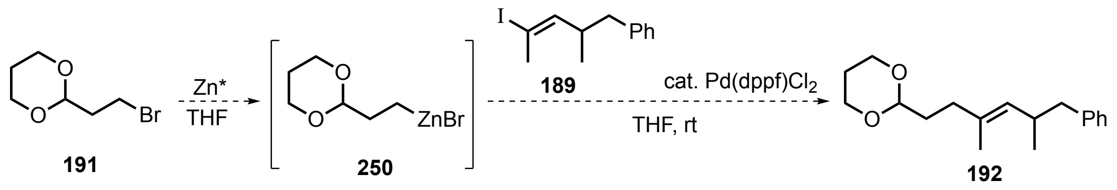
The advantage of this method in the context of our chemistry is the high reactivity of the intermediate with good conversion and reliability also comprising arguably even more sensitive functional groups (lactones and epimerisable centres) in comparison to our highly oxygenated core of dideoxysqualestatin H5 (containing acetal and methyl esters **2**). Additionally, the coupling is performed at ambient temperature, which is ideal due to the likely thermal instability of the halide precursor **230** in our case (p.93). Rieke zinc was synthesised from Li metal mixed with naphthalene in THF.[101] In a slight modification to Holton's protocol for the formation of Zn* (stirring at room temperature for 5 h), the reaction was initiated and maintained ultrasonically for ~30 min with the characteristic dark green/black colour of lithium naphthalenide radical anion **249** appearing almost instantly. Then, previously dried $ZnCl_2$ (0.7 M in THF) was added dropwise and the reaction mixture stirred for an additional 15 min at rt. Stirring was then stopped and the finely powered black Rieke zinc was diluted with THF and allowed to settle at the bottom of the flask for 2–3 h (**Scheme 107**).



249

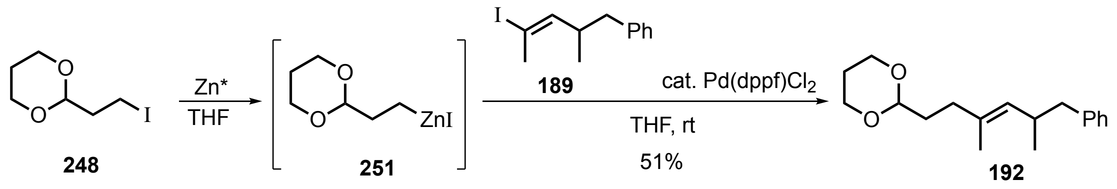
Scheme 107: Rieke zinc (Zn*) formation.

In a model cross–coupling using the highly reactive Rieke zinc (formed *in situ*) and Pd(dppf)Cl_2, bromoethyl dioxane **191** was reacted with the Zn* (**Scheme 108**) and the reaction was monitored by TLC for consumption of starting material. The bromide used was not consumed after several hours at rt, therefore, it was allowed to stir at rt overnight. TLC analysis showed no consumption of the staring material; and the materials were recovered at the end of the reaction.



Scheme 108: Attempted cross–coupling using Rieke zinc (Zn*) with bromoethyl dioxane **191**.

Since Holton's substrate, a primary alkyl iodide, was fully consumed in ~20 min,[101] the corresponding alkyl iodide **248** from alcohol **246** was synthesised in 91% yield *via* an Appel reaction (**Scheme 105**, p.103).[102] Using the alkyl iodide **248** as starting material with the Zn* (**Scheme 109**), TLC analysis showed full consumption of the material in ~10 min. The solid Zn* suspension was then left to hopefully settle at the bottom of the flask. But after several hours, the finely powdered Zn* had not fully settled, therefore, the entire suspension (including the Zn*) was transferred *via* syringe to a flask containing the Pd(dppf)Cl_2 and alkenyl iodide **189**. Monitoring the reaction after 3 h suggested that formation of the desired product had taken place, albeit with some alkenyl iodide **189** still present. Therefore, the mixture was stirred at rt overnight. The desired C–C bond formation was successful giving **192** in 51% yield (**Scheme 109**).

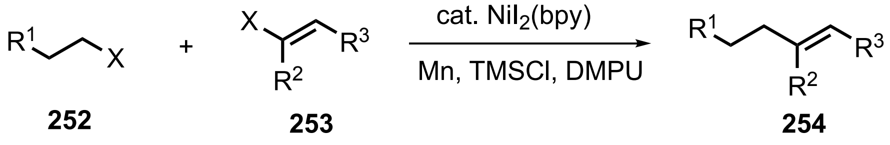


Scheme 109: Cross–coupling using Rieke zinc (Zn*) and alkyl iodide **248**.

Applying Holton's conditions, the model primary alkyl iodide **248** (1 equiv.) was reacted with highly active Rieke zinc (Zn*) and was fully consumed in ~10 min. In a variation of above, the suspension was then centrifuged (5000 rpm for 5 min) to settle unreacted Zn* followed by transferring the supernatant to a flask containing Pd(dppf)Cl_2 (0.025 mol%) and alkenyl iodide **189** (1 equiv.). After 3 h, TLC analysis of the reaction mixture suggested that formation of the desired alkene **192** had taken place at rt, and the latter was isolated in 49–51% yield (**Scheme 109**). The chemistry was repeated on many occasions, to ensure reliability and reproducibility, but unfortunately there were significant issues with this regard, especially at smaller scales (from 0.35 mmol to 0.018 mmol) comparable to ones that would be carried out in the real bicyclic system. The most important problem faced with this system was the consistency in formation of the alkylzinc species **251**, as well as forming the active Zn*. As a result, it was decided to seek an alternative strategy to form the C–C bond.

3.5 Cross–Electrophile Coupling

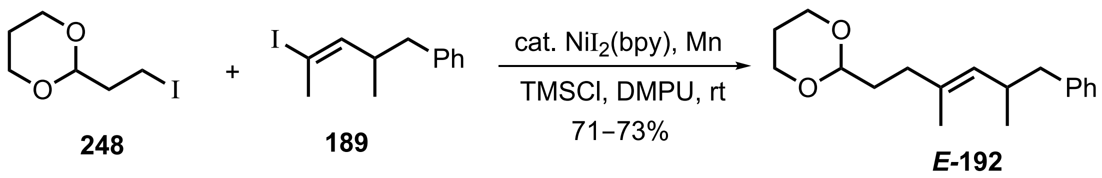
As studies up to this point showed no or limited success in the Csp^3–Csp^2 cross-coupling of alkyl iodide **252** and alkenyl iodide **253** at rt, focus shifted to the relatively new area of cross–electrophile coupling. The development of cross–electrophile coupling provides a unique alternative to traditional cross–couplings where there is a need for prior generation of carbon nucleophiles.[103] Alkyl halide **252** and alkenyl halide **253** are reacted together under Ni catalysis in DMPU with Mn and TMSCl to form coupled product **254** (**Scheme 110**).



Scheme 110: Cross-electrophile coupling.[103]

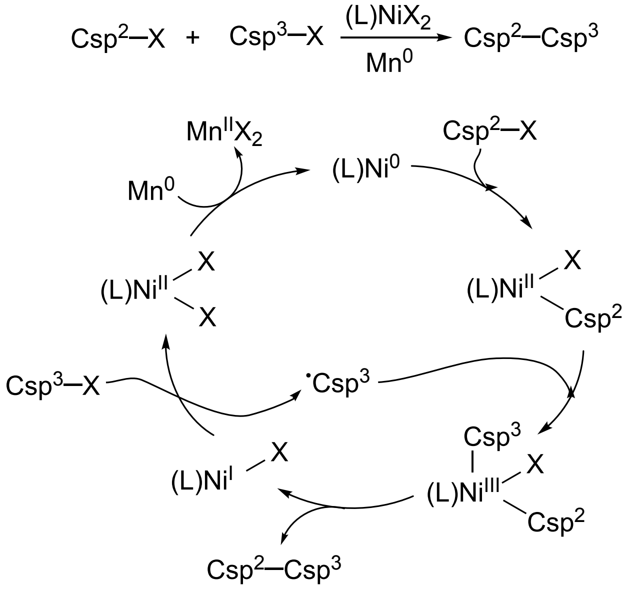
In the cross–electrophile coupling approach two electrophiles are directly used as coupling partners. A downside of the transformation is that it often leads to dimerisation of one of the electrophiles; however, the slight differences in reactivity of electrophiles in the presence of a Ni complex, allows for selective cross–coupling.[103]

In an attempt using Ni in a catalyst system, NiI_2 was first refluxed with bipyridine in THF to form the catalyst NiI_2(bpy), in 93% yield.[104] Using the freshly synthesised catalyst, in combination with Mn and freshly distilled TMSCl, cross–electrophile coupling between iodoethyl dioxane **248** and vinyl iodide **189** (2:1 ratio respectively) in DMPU at rt gave alkene **192** in 42% yield (**Scheme 111**). Repeating the experiment several times (no change in conditions) gave improved yields of between 71–73%. Interestingly, the product was entirely *E*–configured and no signs of stereochemical degradation were ever observed.



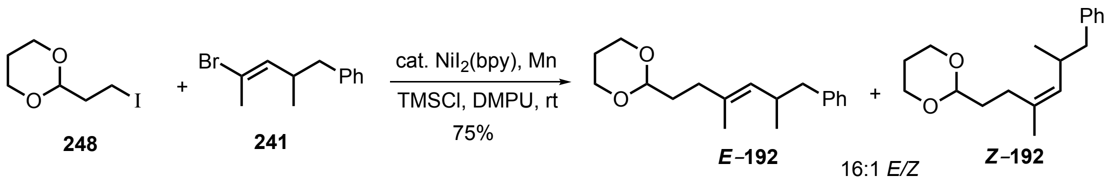
Scheme 111: Cross–electrophile coupling under Ni catalysis with alkenyl iodide **189**.

A series of studies by Weix have showed that the reaction likely entails a rather unusual radical chain mechanism in the presence of a Ni catalyst.[103] Weix's studies indicated that an oxidative addition is likely to preferentially occur with an alkenyl or an aryl electrophile in the presence of an alkyl electrophile. Steric hindrance of the alkenyl/aryl electrophile dictates the possibility or the extent of dimerisation at this stage. Additionally, the likelihood of an alkyl electrophile to undergo self–radical initiation is of greater possibility compared to both alkenyl/aryl electrophiles. Thus, it could be presumed that an initial insertion of Ni(0) into the Csp^2–X occurs to form an alkenyl nickel(II) species (**Scheme 112**), which then undergoes addition to alkyl free radical (presumably generated under self–radical initiation in the presence of the Ni species) to form another Ni(II) species. The resulting Ni(III) intermediate then efficiently forms, through reductive elimination, a new C–C bond. Where *E/Z* selectivity could potentially be of particular importance (as in my work), steric hindrance of the alkyl partner likely plays a vital role in dictating the levels of selectivity achieved. At this stage, a Ni(I) species is generated which subsequently can form another alkyl radical (chain carrier) from another molecule of the alkyl electrophile. Finally, the stoichiometric reductant present (Mn), will reduce the Ni(II) back down to Ni(0), ready to undergo another catalytic cycle.



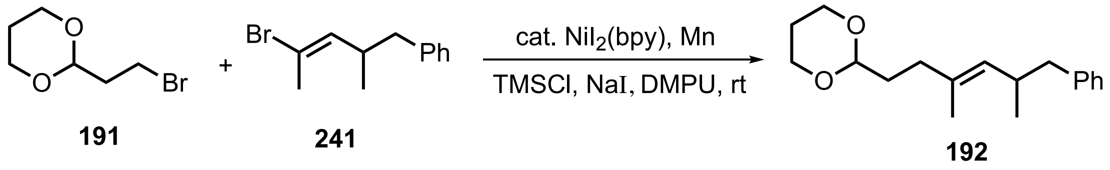
Scheme 112: Mechanism of cross–electrophile coupling.[103]

Performing the reaction with iododethyl dioxane **248** and vinyl bromide **241** (2:1 ratio respectively) produced alkene **192** in 75% isolated yield (16:1 *E/Z* ratio by crude ^{1}H NMR analysis, **Scheme 113**).



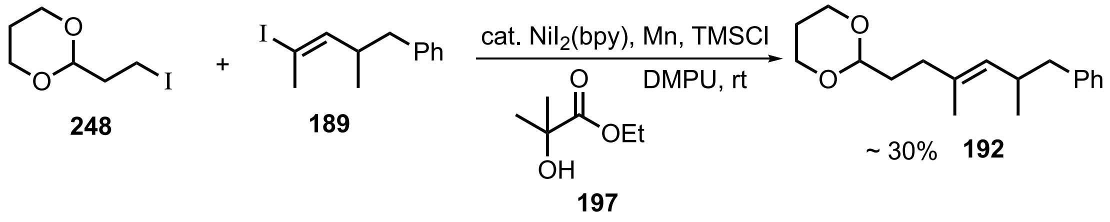
Scheme 113: Cross–electrophile coupling under Ni catalysis with alkenyl bromide **241**.

When bromoethyl dioxane **191** was cross–coupled with vinyl bromide **241** (2:1 ratio respectively) with the addition of NaI,[105] possibly forming the alkyl iodide **248** *in situ*, cross–coupling was again observed, albeit in a 1:1.3 mixture of product to starting material (**Scheme 114**). Repeating the experiment several times consistently showed that the conversion of bromoethyl dioxane **191** to the corresponding iodide **248** *in situ* is inefficient, thus it was decided to use iodoethyl dioxane **248** for further studies.



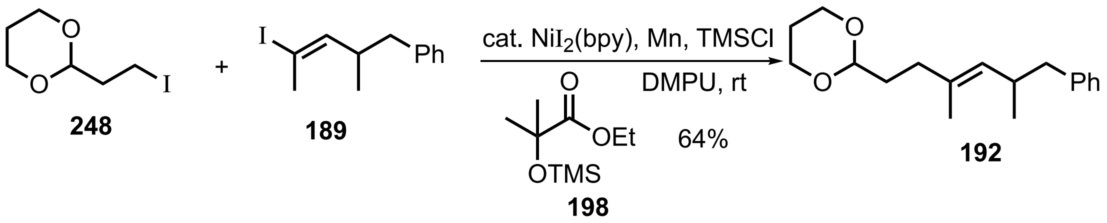
Scheme 114: Cross–electrophile coupling with bromoethyl dioxane **191** and vinyl bromide **241**.

An experiment with the two iodides **248** and **189** (2:1 ratio respectively) but with an additional equiv. of hydroxy isobutyrate **197** only led to ~ 30% desired product, in a mixture with starting materials (**Scheme 115**).



Scheme 115: Cross–electrophile coupling with an equiv of hydroxy isobutyrate **197**.

As only ~ 30% of alkene **192** was formed in the presence of free tertiary alcohol (**197**), it was considered necessary to temporarily TMS protect the hydroxy isobutyrate, so as to judge how the cross–coupling is affected in the presence of siloxy isobutyrate **198**. In the event, alkene **192** was formed in 64% yield (**Scheme 116**). This experiment confirmed that it would likely be necessary to TMS protect the tertiary alcohol present in the core of the natural product (**2**) prior to cross–coupling.

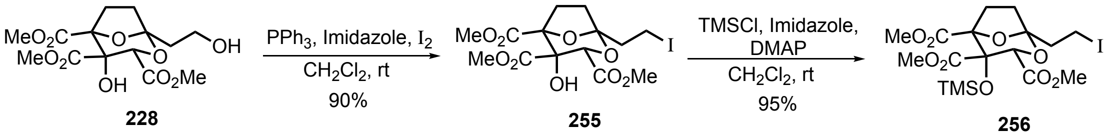


Scheme 116: Cross–electrophile coupling with an equiv. of siloxy isobutyrate **198**.

Finally, the cross–coupling was carried out on a small scale, comparable to scales at which it would be carried out on the real system (0.0151 mmol). The desired *E*–alkene **192** was formed in 65% yield. The only variable altered with respect to the literature conditions[105] was the concentration of the reaction (0.17 M compared to 0.25 M in literature). These model studies provided significant encouragement that cross–electrophile coupling on the real system could be successful.

3.6 Alkyl Iodide and Subsequent Cross–Electrophile Coupling

With necessary cross–coupling studies on model systems carried out and sufficient amounts of rearranged diol **228** in hand, an Appel reaction was carried out to form iodoalcohol **255** in 90% yield, followed by temporary TMS protection of the tertiary alcohol, forming siloxyiodide **256** in 95% yield (**Scheme 117**). In an attempt to iodinate and subsequently TMS protect diol **228** in one–pot, only 26% of the desired siloxyiodide **256** was formed, with 32% of intermediate iodoalcohol **255** recovered. These experiments indicated that a better overall yield is achieved if the two steps are carried out separately.



Scheme 117: Appel reaction to form iodoalcohol **255** followed by siloxyiodide **256**.

Additionally, a crystal structure of rearranged siloxy iodide **256** (**Figure 12**) was obtained (**Appendix 8.1.2**) which unambiguously confirmed the structure as comprising bicyclic core of the natural product with the desired stereochemistry.

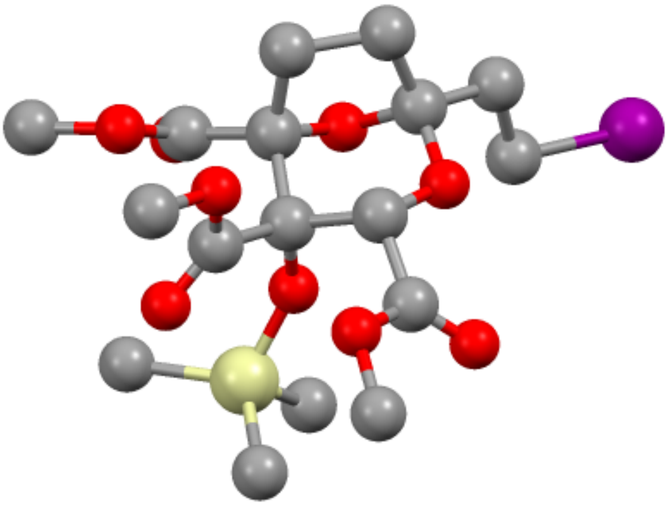
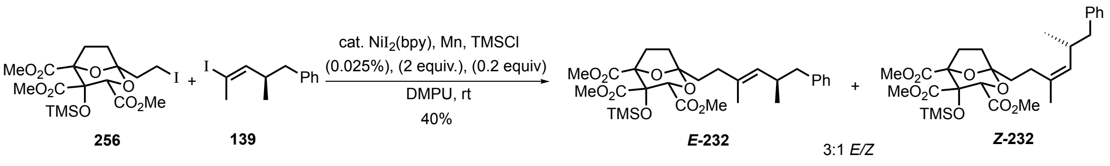


Figure 12: X–ray crystal structure of rearranged siloxy iodide **256** (H's are omitted for clarity).

With the oxygenated core siloxyiodide **256** of the natural product in hand, the previously optimised cross–electrophile coupling conditions[105] (p.110) were employed to form the key C–C bond with enantiopure alkenyl iodide **139** (**Scheme 118**).[40] First, $NiI_2(bpy)$ and the stoichiometric reductant Mn were placed in a Schlenk tube, which was then evacuated and refilled with argon three times. To the solid mixture was added DMPU as reaction solvent, followed by equimolar quantities of siloxyiodide **256** (0.0075 mmol) and alkenyl iodide **139** (0.0075 mmol). Finally, freshly distilled TMSCl (0.2 equiv.), used to activate the Mn,[106] was added and the mixture stirred vigorously at rt overnight.



Scheme 118: Cross–coupling of enantiopure side chain **139** and siloxy iodide **256**.

Under the above conditions, the key C–C bond was successfully achieved in 40% yield but unfortunately, as an inseparable 3:1, *E:Z* mixture (confirmed by nOe studies) (**Scheme 118**, **Figure 13**). Due to the small amounts of material used, to ensure that all the reagents were transferred to the reaction flask, more DMPU was used; this reduced the concentration of the reaction, from standard literature concentrations of 0.25 M to 0.025 M.

When the cross–coupling was re–attempted, with the only difference being running the reaction slightly more dilute (From 0.025 M to 0.018 M) in comparison to the first time (use of more solvent to transfer material to reaction flask), the relative ratio of *Z*–alkene significantly increased, to a ~ 1:1 ratio *E/Z.*

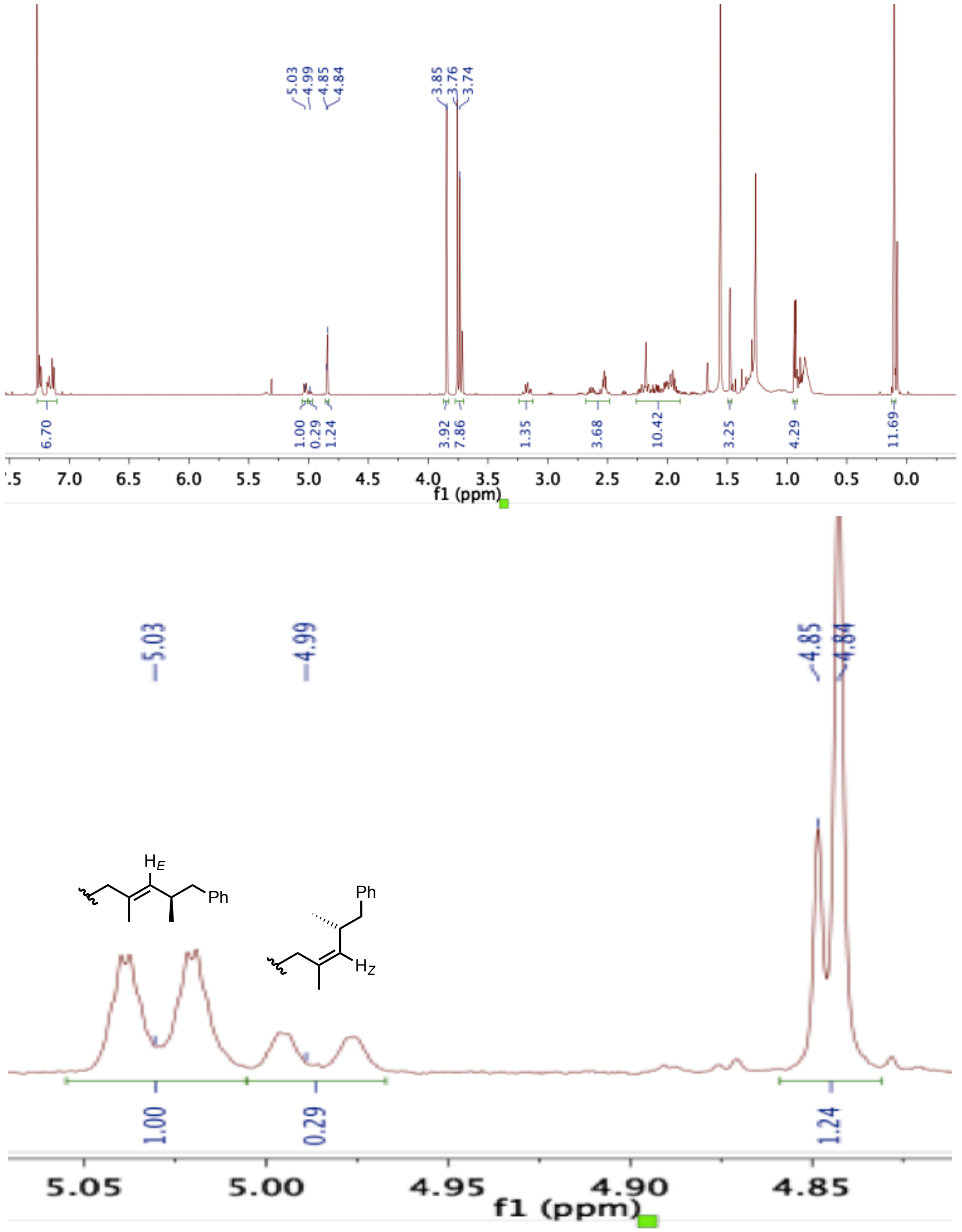
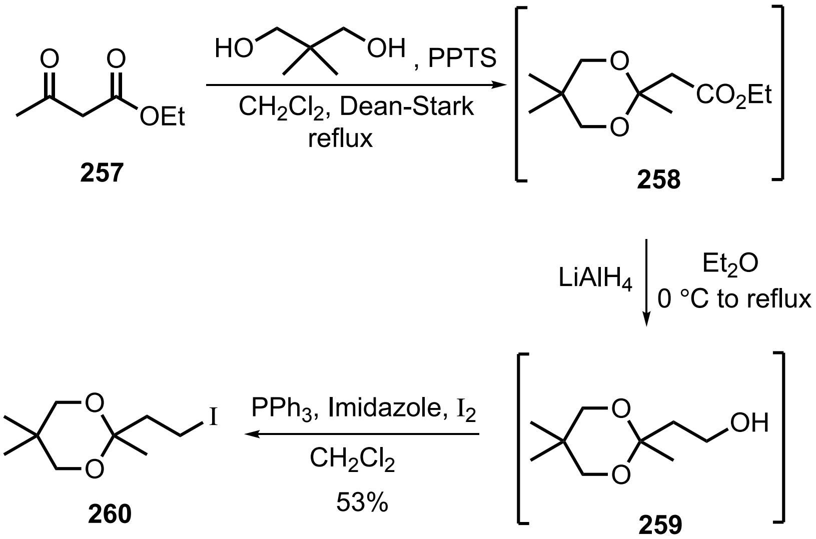


Figure 13: Crude ^{1}H NMR analysis of **232** showing expansion of 5.05–4.85 ppm region indicating ~ 3:1, *E*:*Z* ratio.

With the entire model cross–coupling studies indicating a much higher *E/Z* ratio, ~16:1 (p.109), the results of cross–coupling on the real system were surprisingly (and disappointingly) different. The model system used for cross–coupling was potentially not a reliable mimic for the real system; therefore, it was necessary to design a more relevant mimic of the oxygenated core and continue model studies before committing more precious material to cross–coupling.

3.7 Cross–Electrophile Coupling (New Model)

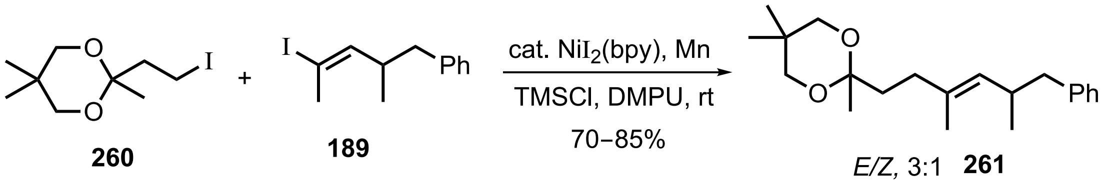
After the significant erosion in stereochemical integrity was observed in the real system (3:1, *E/Z*), a more hindered model alkyl iodide **260** was synthesised (**Scheme 119**). Ethyl acetoacetate **257** was initially ketalised and the crude ketal **258** was reduced using $LiAlH_4$, to give the corresponding hydroxy ketal **259** which, without further purification, was subjected to an Appel reaction to form the more sterically hindered alkyl iodide **260**, in 53% yield over 3 steps.[104, 107]



Scheme 119: New model substrate for cross–electrophile coupling.[104, 107]

With the new model substrate **260** in hand, the cross–electrophile coupling was re–attempted. The desired C–C bond was formed, giving alkene **261** in 68% yield, 3:1

E/Z (**Scheme 120**). Repeating the experiment to study reproducibility yielded alkene **261** in 70–85% yield and again as an ~ 3:1 *E/Z* mixture.



Scheme 120: Cross–coupling using new alkyl iodide **260** substrate.

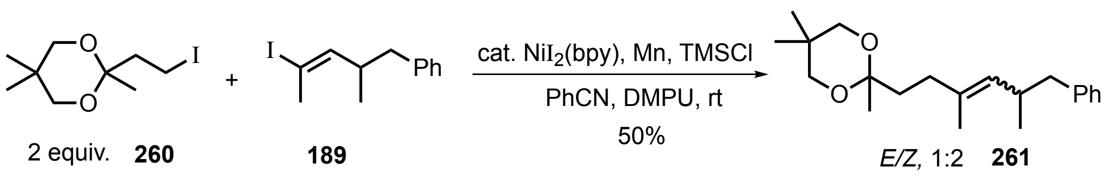
The result with alkyl iodide **260** indicated that this slightly more hindered system provided a better mimic of the real system: the fully–substituted ketal **260** (bearing Me instead of H as in iodide **248**) provided enough steric hindrance to significantly reduce the stereochemical integrity on cross–electrophile coupling with *E*–alkenyl iodide **189**. The new aim then became optimising the reaction conditions with this substrate, so as to minimise the formation of undesired *Z*–alkene.

The first variable examined was the use of new Mn with mesh size (–325) identical to that used in the lit.[102] Previously, a mesh size of –50 was used. However, the new Mn provided no change in the stereochemical outcome of the reaction (**Table 3**, entry 1). Interestingly when the reaction was diluted (0.047 M rather than 0.14 M) the *E/Z* ratio worsened ~ 1.4:1 (**Table 3**, entry 2). As this was a major influence on *E/Z* selectivity, the remainder of the reactions were performed on a 0.14 M concentration due to practicality aspects and ensuring all reagents were in solution (0.014 mmol scale reactions). As the transformation potentially proceeds *via* an alkyl radical (**Scheme 112**, p.110), it was considered that if the alkyl iodide were used in excess, then the *E/Z* selectivity could potentially improve. When the quantity of the alkyl iodide **260** was doubled relative to alkenyl iodide **189**, alkene **261** was formed in 77% yield with improved *E/Z* selectivity (6:1). Although increasing the ratio of the more valuable alkyl iodide partner is undesirable in the real system, a reaction with 4 equiv. of the alkyl iodide was performed and alkene **261** was formed an 11:1 *E/Z* mixture (**Table 3**, entries 3 and 4). In an attempt to improve the selectivity without varying the 1:1 stoichiometry, the reaction was carried out at –20 °C rather than rt, which led to consumption of the alkyl iodide but with only trace amounts of desired product formed (**Table 3**, entry 5).

Entry	**Alkyl iodide 260 equiv.**	**Alkenyl iodide 189 equiv.**	***E/Z* ratio**
1. New Mn used	1	1	3:1
2. Concentration effect (0.14 M to 0.047 M)	1	1	1.4:1
3. Changing starting material ratios	2	1	6:1
4. Changing starting material ratios	4	1	11:1
5. Temperature effect (–20 °C)	1	1	-

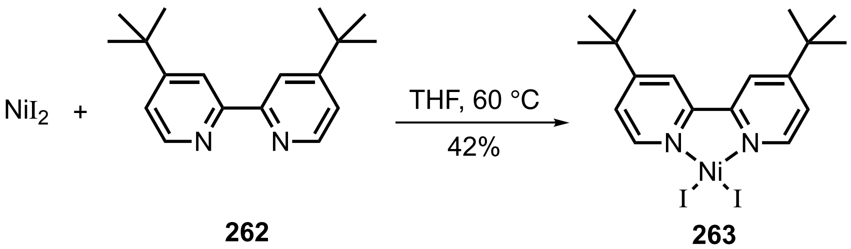
Table 3: Effects of various conditions on model cross–coupling.

In Weix's studies, addition of trace benzonitrile in DMA provided more consistent results in forming their intended *Z*–alkenes.[108] Although Weix used benzonitrile to minimise dimerisation of the terminal alkenyl partner, in our system we did not see this problem, as the alkenyl partner is presumably sufficiently hindered (internal alkene) and no dimerisation was ever observed. Therefore, benzonitrile was used to test whether the selectivity would be affected. Benzonitrile (0.05 equiv.) was added to the reaction mixture and the selectivity of the reaction was significantly decreased giving an ~ *E/Z*, 1.1:1 mixture in only 50% yield. When excess alkyl iodide **260** was used (2 equiv), with PhCN as additive, remarkably the selectivity was reversed to the undesired isomer, 1:2 *E/Z* (**Scheme 121**).



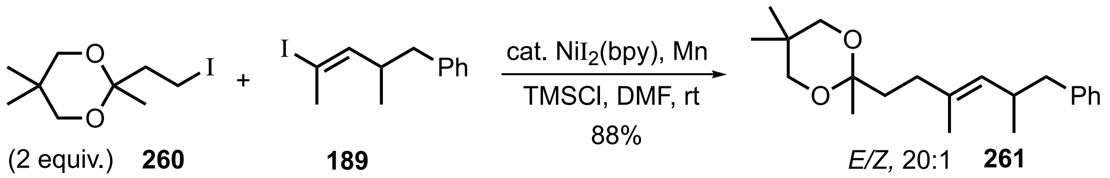
Scheme 121: Effect of PhCN as an additive on model cross–electrophile coupling.

As part of the optimisations, a different catalyst system was also synthesised for examination. NiI_2 was heated with 4,4-di-*tert*-butyl-2,2-dipyridyl (**262**) to furnish the Ni complex **263**, [42% yield] (**Scheme 122**).[105] The new catalyst was then examined in the coupling reactions under the standard reaction conditions (Mn, TMSCl in DMPU at rt), but no significant change was observed in terms of yield or *E/Z* selectivity.



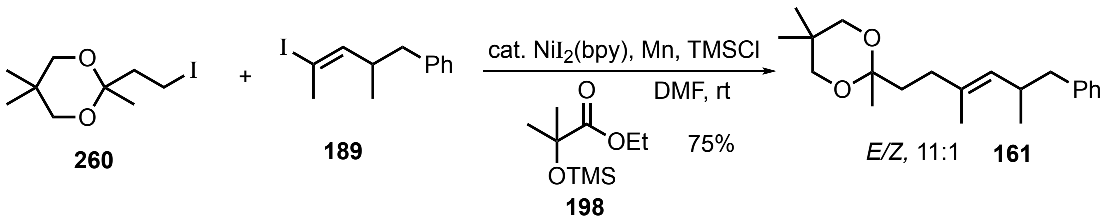
Scheme 122: A different catalyst for cross–electrophile coupling.

Changing the reaction solvent led to the use of DMA (also used in Weix's studies) instead of standard DMPU. The reaction consumed all of the starting alkyl iodide **260**, unfortunately no desired product was observed. However, in DMF, the reaction yielded alkene **261** in 86% yield with excellent *E/Z* selectivity (~17:1) by NMR analysis. DMF was originally used in Weix's aromatic systems to achieve cross–electrophile coupling of *Z*–alkenes.[103] When 2 equiv of alkyl iodide **260** was used, the selectivity ratio improved to ~ 20:1 *E/Z* (*Z* isomer now reaching the limits of NMR detection), in 88% yield (**Scheme 123**). It appeared that in addition to sterics, subtle differences in polar aprotic solvents such as DMPU, DMA and DMF played key roles in favouring formation of a particular isomer in the Ni species formed. Although not probed, the presence of traces of $HNMe_2$ in the DMF could potentially be playing a coordinating role at Ni to influence *E/Z* selectivity.



Scheme 123: Solvent effect on model cross–electrophile coupling.

To investigate functional groups that would be present in the real system, the cross–coupling reaction in DMF was carried out in the presence of ethyl *α*–hydroxy isobutyrate **197**: this yielded 57% of alkene **261** (11:1 *E/Z*). When siloxy isobutyrate **198** was used; the reaction gave 75% of the desired alkene **261** (11:1 *E/Z*, **Scheme 124**).



Scheme 124: Cross–electrophile coupling with an equiv. of siloxy isobutyrate **198**.

Following the investigations carried out on cross–electrophile coupling between alkyl iodide **260** and vinyl iodide **189**, the optimal conditions were use of a 1:1 mixture of starting materials, with temporary capping of the tertiary alcohol with TMS (likely to be done in the real system). Furthermore, the reaction should be carried out in DMF for optimum *E/Z* selectivity. Additionally, different catalysts did not alter the outcome of the reaction, thus NiI_2(bpy) would be used for cross–coupling in the real system.

Chapter 4

Results and Discussion

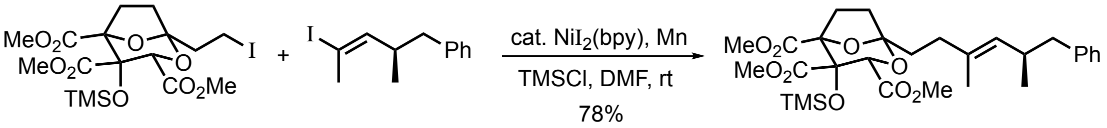
(Cross–Couplings and

Hydrolysis to DDSQ H5)

4. Results and Discussion – Cross-Coupling to 6,7-DDSQ H5

4.1 Cross–Electrophile Coupling to Natural Product

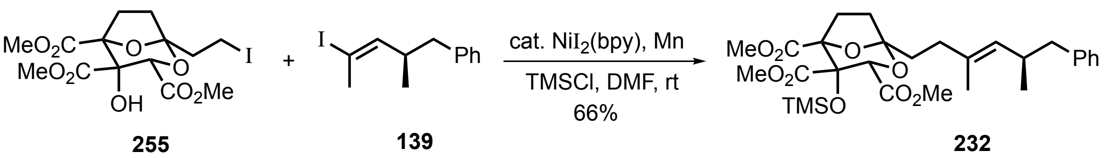
With model studies indicating that DMF is a more suitable reaction solvent than DMPU for our substrate (p.117), the cross–electrophile coupling on the precious material **256** was attempted again (*cf* first attempt, p.111). The coupling yielded 47% of the desired alkene, but most importantly as entirely *E*–isomer. The reaction was carried out several times (0.0075 mmol to 0.019 mmol scale) with more care in handling the reagents to ensure reproducibility and the desired *E*–alkene **232** was formed in up to 78% yield (**Scheme 125**).



256 **139** **232**

Scheme 125: Cross–coupling of enantiopure side chain **139** and siloxyiodide **256** in DMF.

It is anticipated that ~ 20% free bpy ligand is present in the catalyst system.[105] It was therefore anticipated that the presence of this base could potentially facilitate TMS protection of the free tertiary alcohol under the reaction conditions employed. To that extent, a test cross–electrophile coupling between hydroxy iodide **255** and enantiopure alkenyl iodide **139** was carried out. The desired C–C bond was formed in excellent 66% yield (**Scheme 126**). As anticipated, the presence of TMSCl and the free ligand in the reaction accompanied the cross–coupling with TMS protection at the tertiary alcohol.

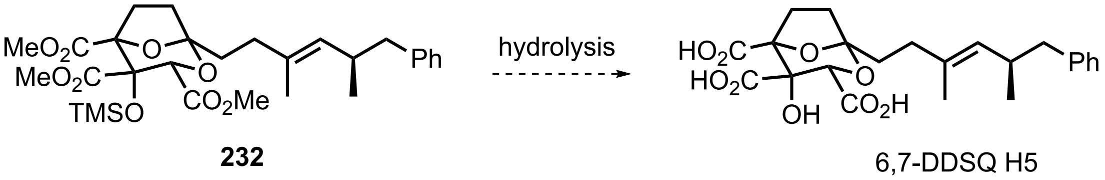


Scheme 126: Cross–coupling of enantiopure side chain **139** and hydroxy iodide **255** in DMF.

4.2 Hydrolysis

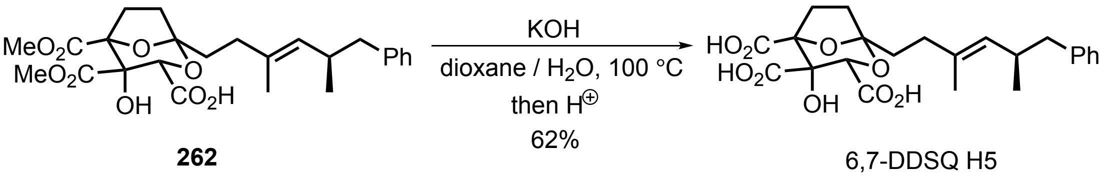
4.2.1 Hydrolysis to Natural Product

After achieving the first example (to the best of our knowledge) of cross–electrophile coupling in target synthesis, "all" that was left to do was hydrolyse the esters and cleave the temporary TMS group, to give the natural product (**Scheme 127**).[109] Due to the potentially aq acid labile acetal present in the advanced intermediate **232** and also the possibility of acid-catalysed retro–aldol decomposition, a based-induced hydrolysis was investigated.



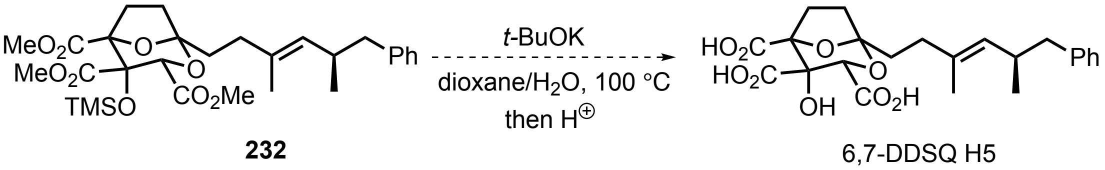
Scheme 127: Final chemistry to 6,7-dideoxysqualestatin H5 (**2**).

In an attempt at global hydrolysis, TMS triester **232** was subject to hydrolysis conditions previously carried out by Martin on a similar substrate (**Scheme 128**, see also chapter 1, p.32).[30] Martin's substrate **262** already 'benefited' from a free acid at C3 as well as a free tertiary alcohol at C4.



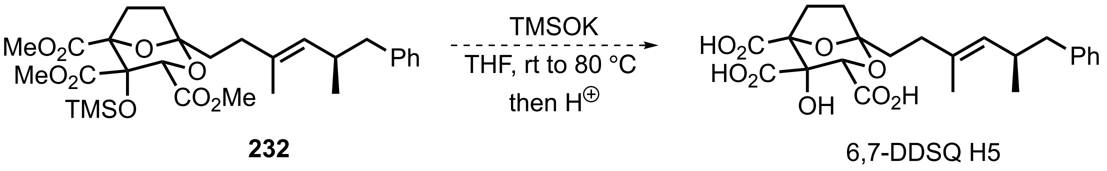
Scheme 128: Martin's ester hydrolysis to give 6,7-dideoxysqualestatin H5.[30]

Siloxytriester **232** was refluxed in dioxane/H_2O (0.25 mL / 58 μL) in the presence of *t*-BuOK (9 mg, 0.080 mmol, 15 equiv.) at 100 °C (**Scheme 129**). As monitoring the reaction was difficult to follow by TLC, the reaction was allowed to stir for 24 h. The reaction mixture was then acidified with HCl (2 mL, 0.1 M) but unfortunately no signs of the natural product could be detected. ^{1}H NMR analysis was unclear, possibly due to decomposition of the substrate. Attempting the reaction again on slightly larger scale (6 mg of starting material compared to previous 3 mg) also led to decomposition.



Scheme 129: Attempted hydrolysis to 6,7-dideoxysqualestatin H5 using *t*-BuOK.

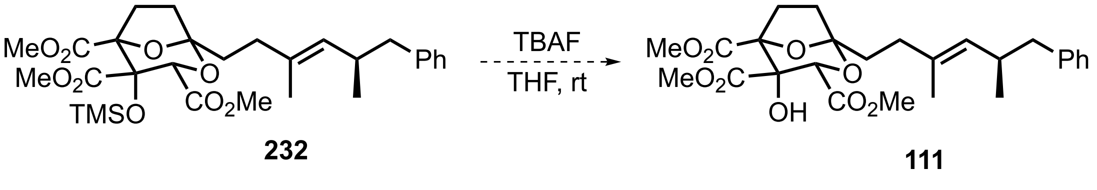
In another attempt to hydrolyse the esters under milder conditions, 1 equiv. of TMSOK[110] was used to desilylate and hydrolyse the least hindered ester (at C3)[111] and to complete a formal synthesis by intersecting with Martin's synthesis (**Scheme 130**). After 3 h at rt, TLC analysis showed significant quantities of starting material **232** present. Therefore, an extra equiv. of the TMSOK was added and the mixture was allowed to stir at rt for a further 3 h. Monitoring the reaction revealed starting material still present, thus, the reaction mixture was heated to 40 °C overnight. At this point, with no change in starting material judged by TLC, 10 equiv. of TMSOK was added to the mixture and heating continued at 40 °C for another 3 h in an attempt to drive the reaction to full hydrolysis. Unfortunately, this did not prove sufficient, so the reaction was heated to 80 °C overnight. Quenching the reaction by acidification using HCl (5 mL, 0.1 M) proved unsuccessful in obtaining any desired natural product.



Scheme 130: Attempted hydrolysis to 6,7-DDSQ H5 using TMSOK.

Monitoring the reaction proved difficult by TLC. The analysis showed the presence of significant amounts of starting material after 48 h. However, after acidification, no starting material was evident by TLC. It could be assumed that the problem of the reaction could be either during the hydrolysis step, owing to the very hindered ester at C4,[16] or during the acidification and isolation step.

In a separate experiment, the siloxytriester **232** was reacted with TBAF (2 equiv) to desilylate separately before undergoing ester hydrolysis (**Scheme 131**). Unfortunately, no product could be isolated, possibly due to very small scale of the reaction (~2 mg). Unfortunately, at this stage no more material was available for a further investigation of the ester hydrolyses to 6,7-DDSQ H5, therefore a resynthesis from the start was required.

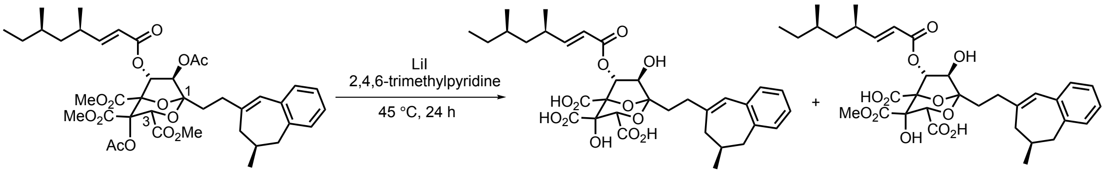


Scheme 131: Attempted TBAF deprotection.

Due to lack of success in global hydrolysis of the TMS triesters, it was considered necessary to conduct a thorough review of the literature on hydrolysis and isolation of the final triacid natural product.

4.2.2 Other Zaragozic Acid Hydrolyses Conditions

In addition to the hydrolysis conditions studied during the total synthesis of the zaragozic acid family (**Chapter 1**), a review of the other methods in the literature was carried out. In an attempt to hydrolyse methyl esters of analogue of zaragozic acid A **262** it was found by Procopiou in 1998, that full hydrolysis did not take place.[111] Excess LiI in 2,4,6-trimethylpyridine at 45 °C for 24 h partially removed not only the methyl esters, but also resulted in cleavage of the *O*-acetyl ester at C7, together with partial cleavage of the C6-ester side-chain (**Scheme 132**). Purification of this reaction mixture by preparative HPLC gave the tricarboxylic acid **263** (4%) and the 3,5-dicarboxylic acid-4-methyl ester **264** (10%, i.e., the C4 methyl ester was intact). Based on previous findings[112], the C4 ester was the most resistant ester to hydrolysis.

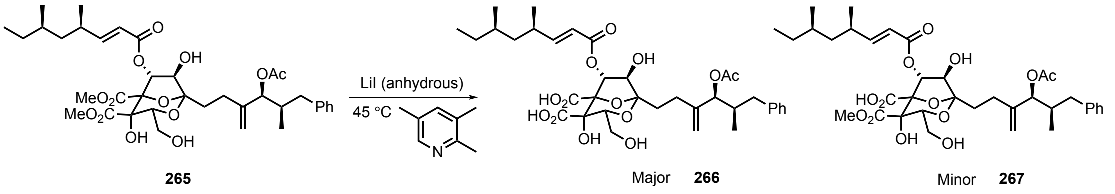


262 **263** **264**

Scheme 132: Procopiou’s hydrolysis of methyl esters.[111]

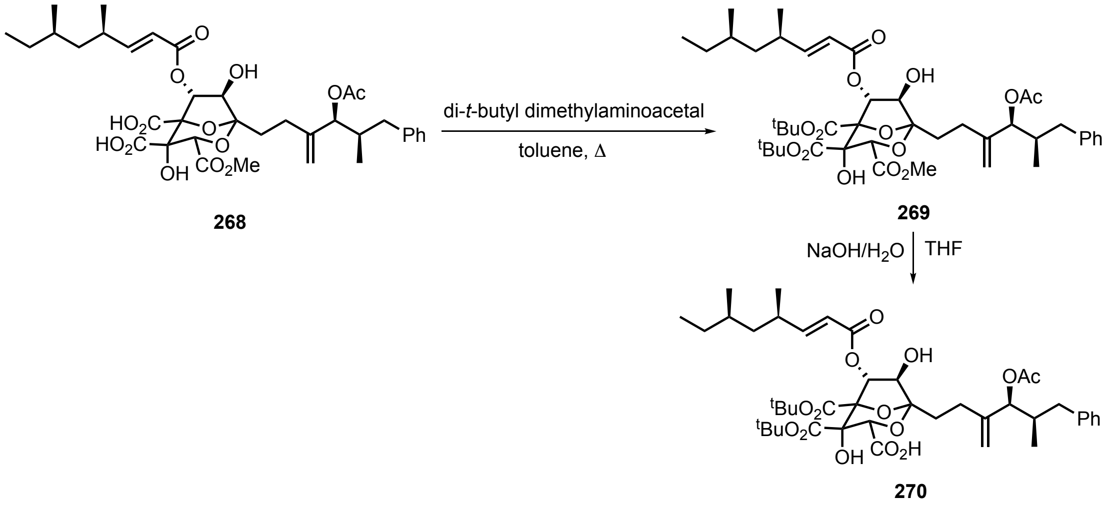
Following on from the previous result indicating difficulty in hydrolysing the C4 methyl ester, Cox in 1994 performed a series of studies investigating how different acid mixtures show different potencies towards the enzymes in the cholesterol biosynthesis.[113] Hydrolysis of di–methyl ester **265** using anhydrous LiI in *sym*-

collidine led to almost complete hydrolysis to the di–acid **266** and minor amounts of methyl ester at C4 (**267**, **Scheme 133**).



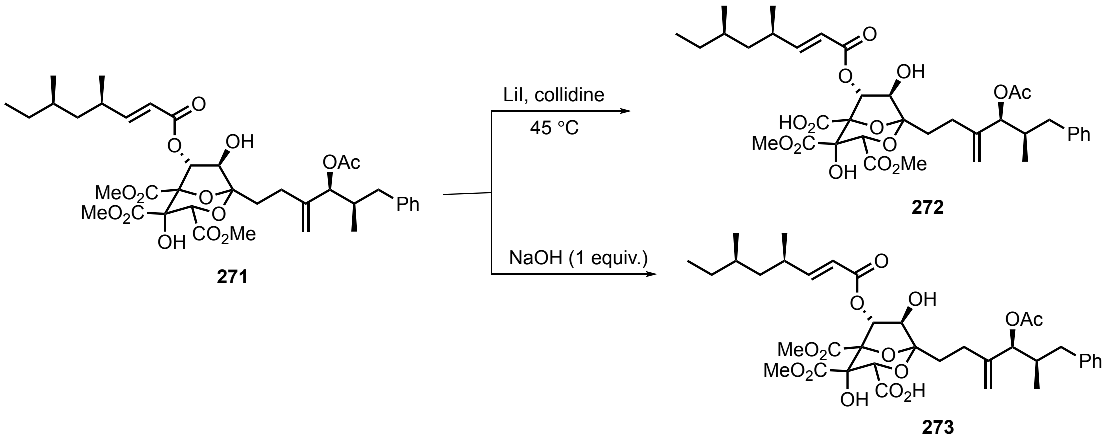
Scheme 133: Cox's hydrolysis of methyl esters.[113]

Cox also selectively hydrolysed C3 methyl ester in the presence of C4 and C5 protected as *t*-butyl esters **269** (**Scheme 134**). The mono methyl ester was treated with NaOH/H$_2$O in THF to give the monoacid.[113]



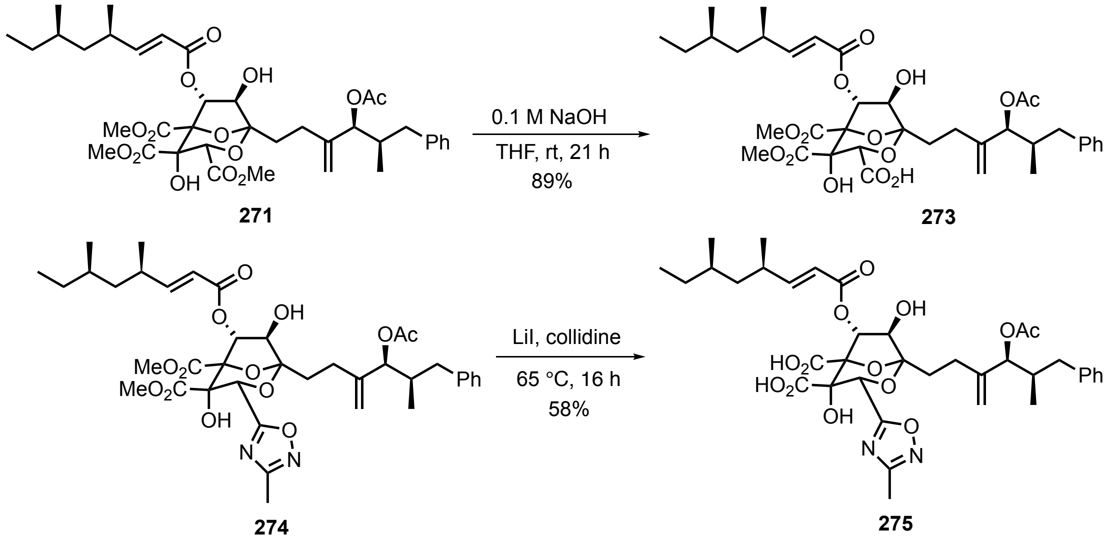
Scheme 134: Cox's hydrolysis of methyl ester in zaragozic acid A.[113]

In another study of the zaragozic acid A core, Watson[112] in 1993 treated the natural product (trimethyl ester) **271** with LiI in collidine to provide a route for the selective removal of the 5-methyl ester **272** (**Scheme 135**).[114] Reaction of the trimethyl ester **271** with 1 equiv. NaOH established a route to the 4,5-dimethyl ester with hydrolysis at C3 (**273**). The corresponding 5-monomethyl (C3 & C4 hydrolysis) and 3,5-dimethyl esters (C4 hydrolysis) were isolated following a reaction of triacid with 1 equiv. of MeI and $NaHCO_3$ in DMP followed by purification of the derived mixture by HPLC.



Scheme 135: Watson's hydrolysis of methyl esters in zaragozic acid A.[112, 114]

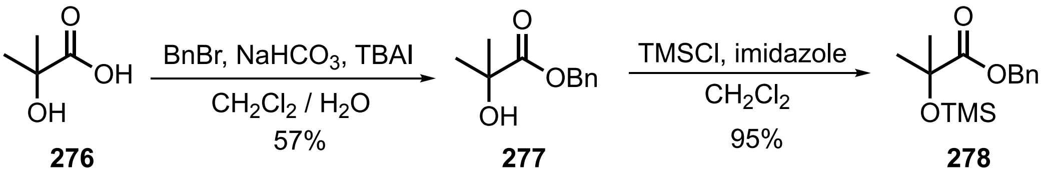
In 1995, Bamford[115] reported biological activity of zaragozic acid A derivatives at the triacid core. During the investigation, selective hydrolysis of the methyl esters took place using 0.1 M NaOH and LiI (**Scheme 136**). Procopiou[116] in 1996 performed the same transformations as Bamford to achieve selective hydrolysis on zaragozic acid A.



Scheme 136: Bamford's hydrolysis of methyl esters in zaragozic acid A derivatives.[116]

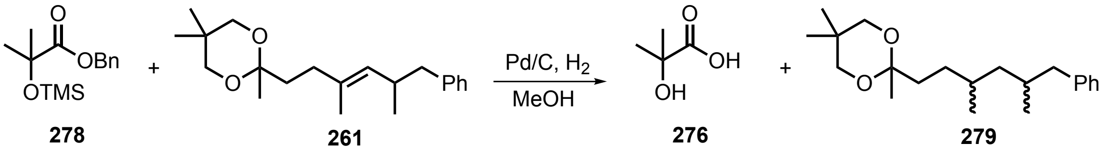
4.2.3 Hydrolysis Continued

A model system was set up to investigate whether the trisubstituted electron rich alkene in our system would survive Pd/C hydrogenolysis conditions. If the conditions showed any promise, the methyl esters in the real system would be converted to benzyl ethers, which would then be debenzylated in the last step of the synthesis avoiding hydrolysis conditions. Therefore *α*–hydroxyisobutyric acid **276** was benzyl-protected to give *α*–hydroxbenzyl ether **277** (57%) and then silylated to give *α*–siloxybenzyl ether **278** in 95% yield (**Scheme 137**).[117]



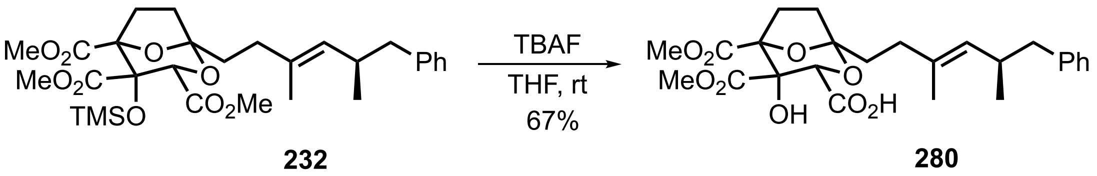
Scheme 137: Model substrate for hydrogenolysis.

With the model substrate **278** and previously synthesised model alkene **261** in hand, the hydrogenolysis was attempted with Pd/C in MeOH (**Scheme 138**). Monitoring the reaction after 3 h at rt showed no progress and all the starting materials were unreacted. Therefore, the reaction was left to stir at rt overnight. ^{1}H NMR analysis of the crude residue showed that successful benzyl deprotection had taken place. However, the alkene had been hydrogenated under the reaction conditions (loss of olefin at δ_H 5.20 ppm, HC=C). Additionally, the TMS ether was also cleaved during the reaction.



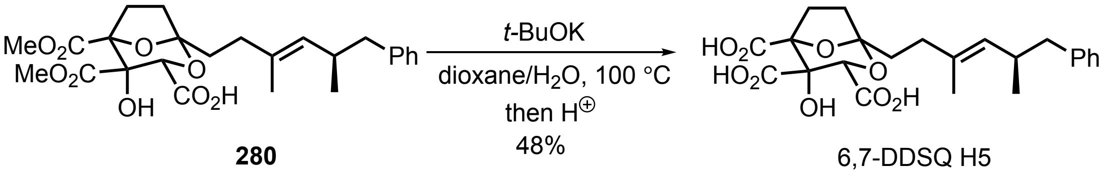
Scheme 138: Hydrogenolysis check to see if alkene **261** survives the conditions.

With hydrogenolysis proving incompatible with the model substrate **261**, it was considered necessary to revert back to previous options, where desilylation was a primary transformation to be achieved. With more cross–coupled material (**232**) in the real system now in hand, the TBAF desilylation was re-attempted. This was accompanied by hydrolysis[118] of the C–3 ester, to give dimethyl ester **280**, in 67% yield (**Scheme 139**).



Scheme 139: TBAF deprotection and simultaneous C–3 ester hydrolysis.

Finally, hydrolysis of the remaining more-hindered esters using anhydrous KOH gave the long-sought (–)-6,7-dideoxysqualestatin H5 (**2**) in 48% yield after reverse phase HPLC purification, possessing spectral data in complete agreement with that previously reported (**Scheme 140, Appendix 8.2**).[30]

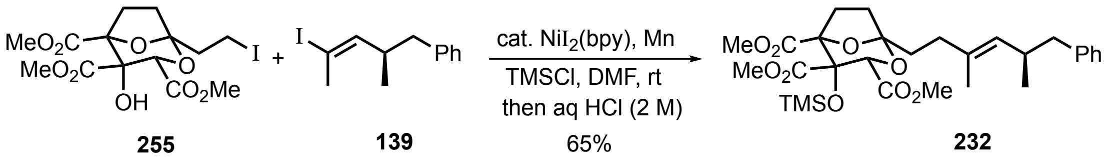


Scheme 140: Hydrolysis to the natural product.

4.2.4 Further Hydrolysis

With the major total synthesis goal achieved, further investigation focused on reducing the number of steps in the synthesis. In an attempt to obtain 6,7-DDSQ triester with free tertiary alcohol, TBAF desilylation was reattempted, this time quenching the reaction after 5 min. Crude product analysis still showed concomitant hydrolysis at C–3 (**Scheme 139**). This reaction showed that hydrolysis is a rapid transformation under the conditions; therefore an alternative approach was required.

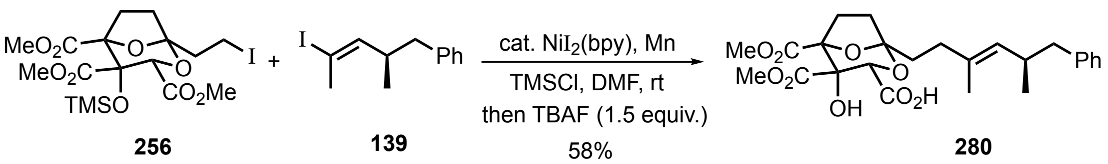
In an alternative approach, at the end of the cross–electrophile coupling, the mixture was treated with aq HCl (2 M) hoping that the TMS group would be cleaved. However, the substrate did not undergo desilylation and the coupled adduct **232** was isolated in 65% yield (**Scheme 141**).



Scheme 141: Attempted desilylation.

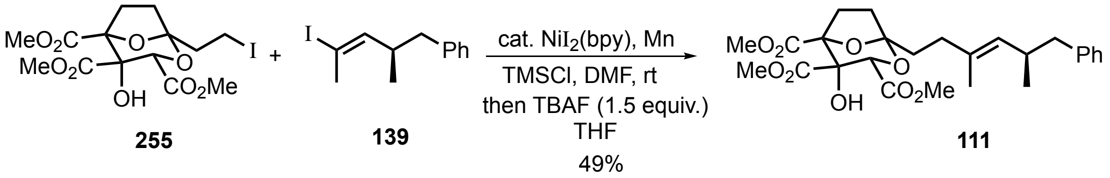
When the cross-coupling reaction mixture was treated with HCl (4 M) in dioxane and allowed to stir at rt, desilylation did not take place and again the cross–coupled material **232** was isolated in ~60% yield.

In another attempt to desilylate directly at the end of the cross–coupling, the mixture was treated with TBAF (1.5 equiv), As expected from the above studies, desilylation was accompanied with hydrolysis at C–3, to yield hydroxy acid **280** in 58% yield (**Scheme 142**).



Scheme 142: TBAF desilylation and hydrolysis at C–3 at the end of cross–coupling.

Alternatively, at the end of cross–coupling, the mixture was diluted with THF (4 x reaction solvent) and TBAF was added dropwise at rt. The desilylation took place in 49% yield (**Scheme 143**). However, the resulting product displayed thermal instability (decomposing above ambient) when it was concentrated under reduced pressure at 40 °C (water bath).



Scheme 143: TBAF desilylation in THF:DMF (4:1) to give hydroxy triester **111**.

As the hydroxy triester **111** showed partial thermal instability at 40 °C and above, the global ester hydrolysis under already established KOH conditions were not employed to obtain the natural product.

Chapter 5

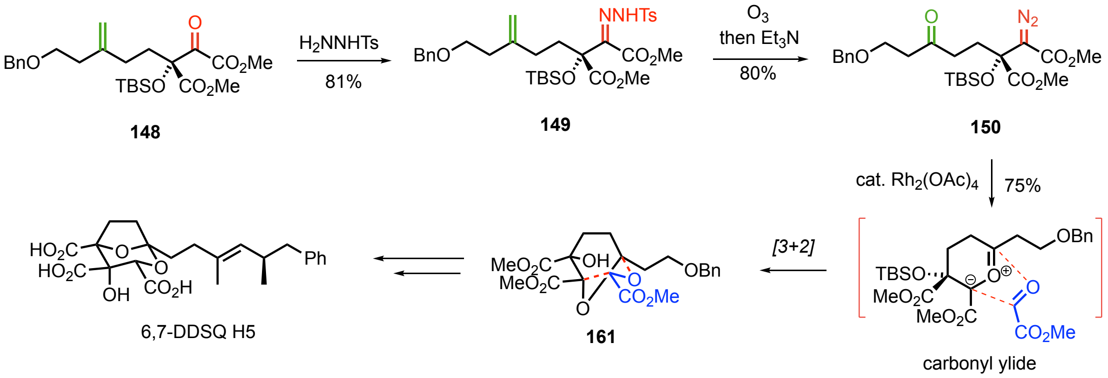
Post DDSQ H5

Diazoketone Formation

5. Results and Discussion – Diazoketone Formation

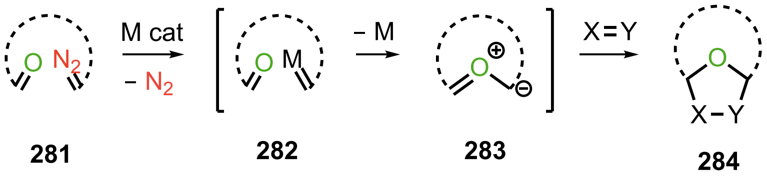
5.1 Diazoketone Background

A key transformation in my asymmetric synthesis of 6,7–dideoxysqualestatin H5 (Chapter 4) was (Rh–catalysed cyclic carbonyl ylide formation–cycloaddition *via*) cogeneration of keto and diazo functionality **150** through ozonolysis of an unsaturated hydrazone **149**.[119] The strategy ultimately led to bicyclic core of the natural product **151** and subsequent total synthesis (**Scheme 144**).



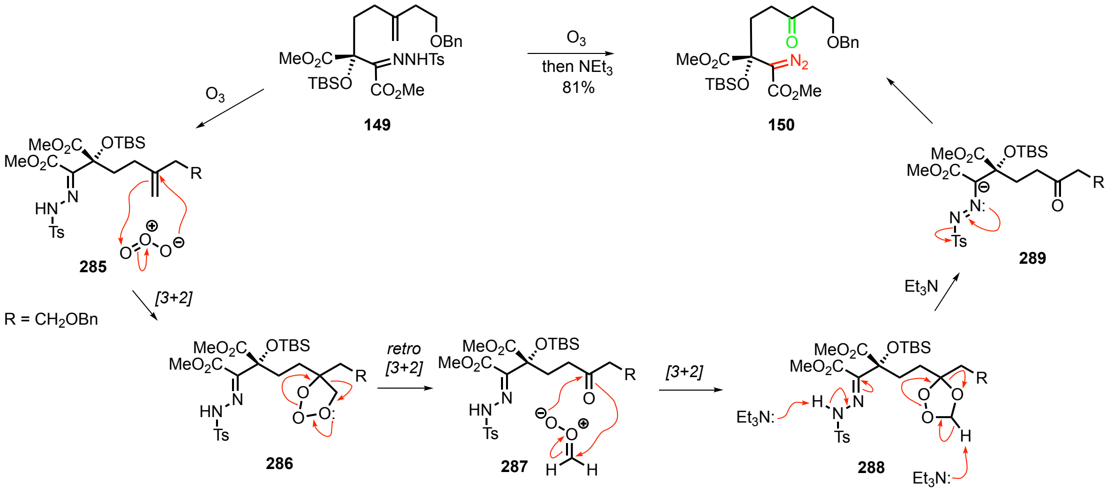
Scheme 144: Chemoselective formation of diazoketone **150** leading to formation of 6,7-DDSQ H5.

Transition metal-catalysed decomposition of diazo functionality in the presence of a carbonyl group provides one of the best ways of accessing carbonyl ylides for applications in 1,3-dipolar cycloaddition chemistry (**Scheme 145**).[120] It was therefore considered that a further exploration of the method, (**149** to **150** sequence) that simultaneously reveals the reactive diazo and ketone functionalities from more readily accessible and compatible functional groups, would be of value in the further development of this chemistry. Therefore, the scope and limitations of reacting unsaturated tosylhydrazones with O_3,[121] followed by decomposition with Et_3N (in Bamford–Stevens[45] reaction) for the direct generation of 1,4- and 1,5-diazocarbonyl systems was examined.



Scheme 145: Carbonyl ylide formation–cycloaddition from diazocarbonyls.

The mechanism of the diazoketone formation likely proceeds *via* standard ozonolysis to form the molozonide (**285** to **286**), followed by rearrangement to give the ozonide (**287** to **288**). Et_3N is then used to facilitate the decomposition of the ozonide **288** formed as well as formation of the diazo group (**288** to **289**, **Scheme 146**).

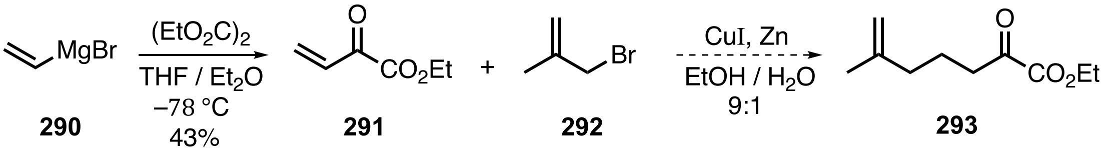


Scheme 146: Mechanism of diazoketone formation using Et_3N.

To test the generality of this chemistry, first it was proposed to strip down functionality *α*- to the diazo moiety to determine if sterics and/or electronic factors bias the transformation (only previous example was in my 6,7-DDSQ H5 total synthesis). Tosylhydrazide condensation with unsaturated ketoesters was considered the most appropriate route to the precursors; routes to the latter were then investigated.

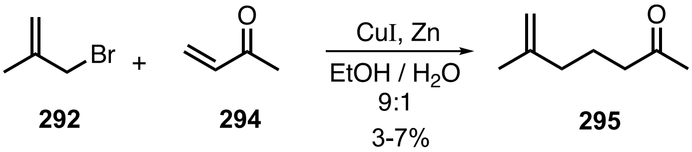
5.2 Ultrasound Promoted Conjugate Addition

Luche first investigated (1986) an ultrasound-promoted conjugate addition to *α,β*–unsaturated carbonyl compounds in aqueous media.[122] This was applied in the ultrasound-promoted synthesis of natural products in 2004.[122] So as to access the requisite ketoesters, vinyl magnesium bromide **290** was coupled with diethyl oxalate to form the heat and light sensitive vinyl ketone **291**, in 43% yield.[123] However, efforts to react vinyl ketone **291** with methallyl bromide (**292**) in the presence of a CuI/Zn complex under sonication yielded no desired ketoester **293** (**Scheme 147**).



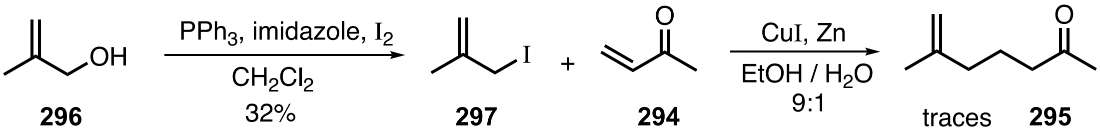
Scheme 147: Formation of vinyl ketone **291** and attempted *α*–ketoester **293** formation.[123]

In an attempt to check whether the reactions with simpler substrates are more productive, CuI and Zn were sonicated for 5 min to generate the required complex,[124] followed by addition of methyl MVK **294** and methallyl bromide **292** in EtOH/H_2O (9:1) (**Scheme 148**). However, only traces of desired product was formed. Purification of Zn and distillation of starting MVK **294** and bromide **292** did not make any difference to the outcome of the reaction and only ~ 3–7% of the unsaturated ketone **195** was obtained. Additionally, running the reaction more dilute (0.05 M rather than 0.5 M) did not improve the outcome of the reaction.



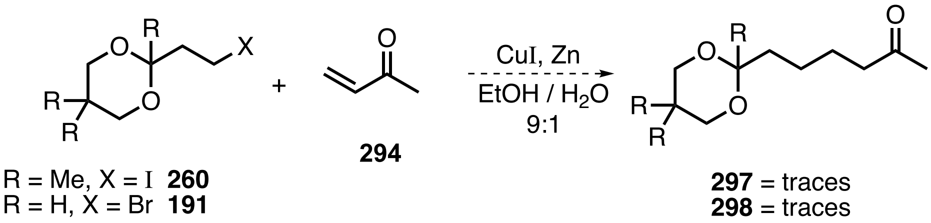
Scheme 148: Formation of unsaturated ketone **295** using CuI/Zn complex.

After synthesis of the corresponding volatile and light sensitive iodide **297** from methallyl alcohol **296**, coupling was studied, but yet again only traces of product were obtained (**Scheme 149**). However, by NMR analysis, the reaction mixture was cleaner in comparison to the methallyl bromide **292** counterpart.



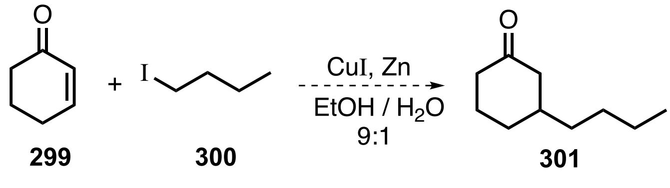
Scheme 149: Formation of methallyl iodide **297** and attempted unsaturated ketone **295** formation.

Utilising less volatile halides such as iododioxane **260** (p.116) and bromodioxane **191** (commercially available), resulted in no product formation and almost all the halide starting materials were recovered (**Scheme 150**).



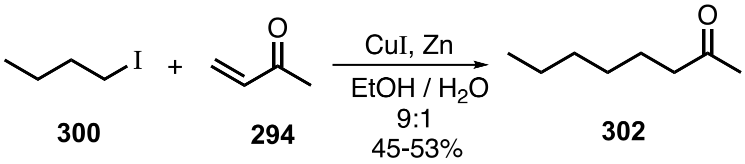
Scheme 150: Attempted ketone synthesis *via* dioxanes.

When cyclic enone **299** was tested with much simpler 1-iodobutane **300**, no product was observed (**Scheme 151**). In another attempt, the halide **300** and the cyclohexenone **299** were added dropwise over 30 min to the CuI/Zn complex, but this also resulted in no product formation (**301**).



Scheme 151: Attempted ketone synthesis using cyclohexenone **299** and iodide **300**.

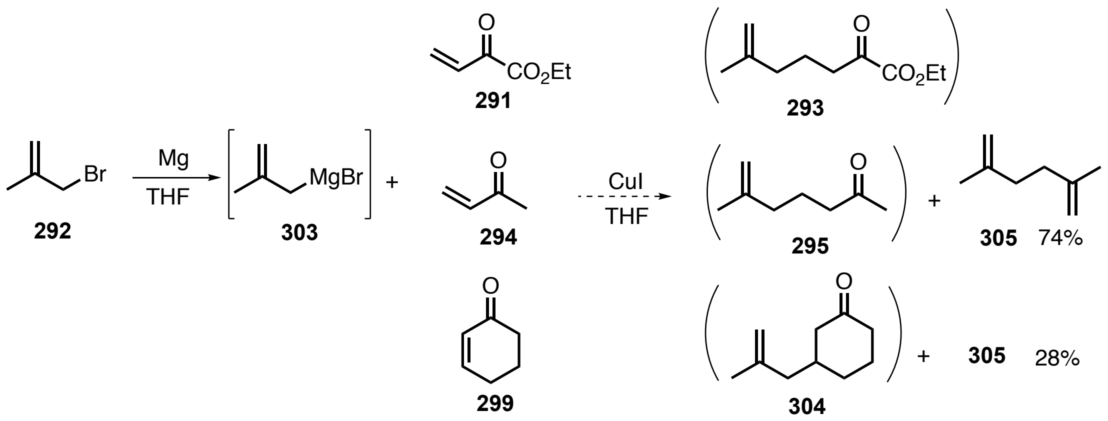
In a separate attempt, 1-iodobutane **300** was reacted with MVK **294** under the same reaction conditions (**Scheme 152**); this time the ketone **302** was successfully synthesised in 45% yield. When the reaction was repeated to test reproducibility, the ketone **302** was formed in 53% yield. Various efforts to perform the reaction with the previous substrates did not yield any desired product. However, when iododecane was used, the ketone was formed in 38% yield. In my hands, this reaction appears only viable for simple substrates, and as soon as there is slight structural variation only traces of products are formed.



Scheme 152: ketone **302** synthesis *via* 1-iodobutane (**300**) and MVK **294**.

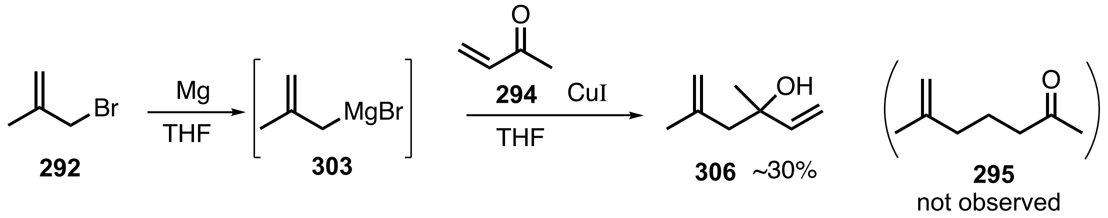
5.3 Cu, In and Grignard Mediated Ketoester Formation

If the corresponding Grignard could be generated from methallyl bromide **292** and subsequently reacted with vinyl ketones in the presence of a copper source, then ketoester formation might be viable (**Scheme 153**).[125] The Grignard reagent **303** was then reacted with vinyl ketones **291**, **294** and **299** in the presence of CuI, but this did not lead to ketoester formation. When the Grignard reagent **303** was reacted with MVK **294** or cyclohexenone (**299**), the only product identified was dimerised starting bromide **305**, (74% and 28% respectively), with the majority of the starting cyclohexenone recovered (**Scheme 153**).



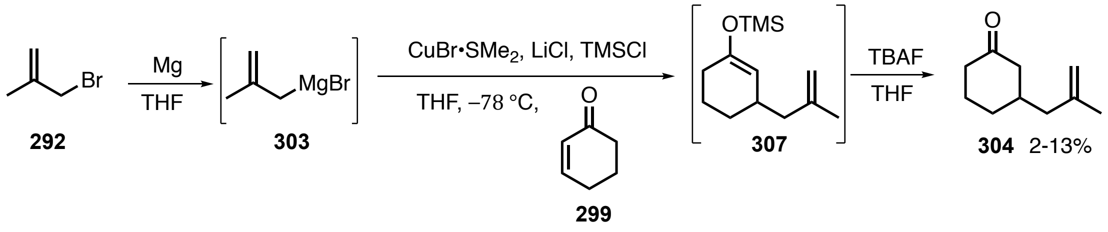
Scheme 153: Attempted ketoester and unsaturated ketone formation.

When the solvent was changed from THF to Et_2O, there were significant solubility issues of CuI and the only product identified with MVK **294** was hydroxy diene **306**,[126] arising from 1,2 addition (~30% yield, **Scheme 154**).



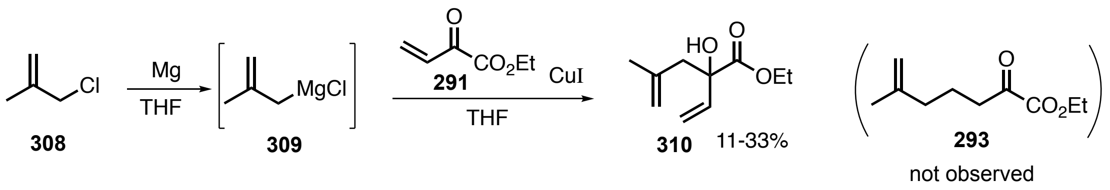
Scheme 154: Formation of hydroxy diene **306**.[126]

In an alternative attempt, CuBr•SMe_2 complex and TMSCl was used to initially form siloxyenol ether **307** that was desilylated to form unsaturated ketone **304**, in only ~2–13% yield and in an impure state (**Scheme 155**).[127]



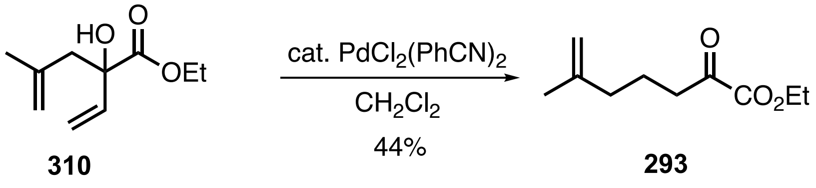
Scheme 155: Utilising CuBr•SMe_2 to form unsaturated ketone **304**.[127]

It was considered that the formation of the Grignard from methallyl bromide **292** could potentially be the point from which most of the complications arise. It was thought that the bromide might be too reactive, thus leading to (potential) dimerisation (*cf.* **Scheme 153**, p.136); therefore, if the relevant Grignard formed from methallyl chloride **308**, then the chances of product formation might rise.[128] To that extent, methallyl Grignard **309** was reacted with vinylketoester **291** in the presence of CuI, but the only product isolated was the product of a 1,2-addition, diene **310** in 11–33% yield (**Scheme 156**).



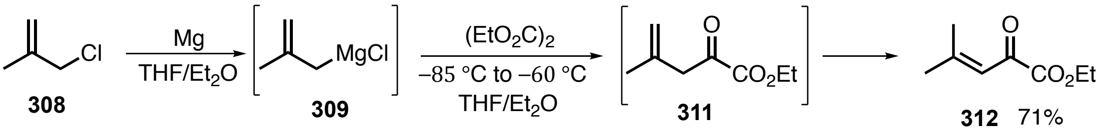
Scheme 156: Attempted Grignard **309** reaction to form ketoester **293**.

To convert diene **310** to the desired ketoester **293**, a Pd–mediated oxy-Cope rearrangement[129] was examined, and the ketoester **293** was isolated in 44% yield (**Scheme 157**). However, the 3-step sequence to obtain the desired ketoester **293** was overall somewhat inefficient and low yielding.



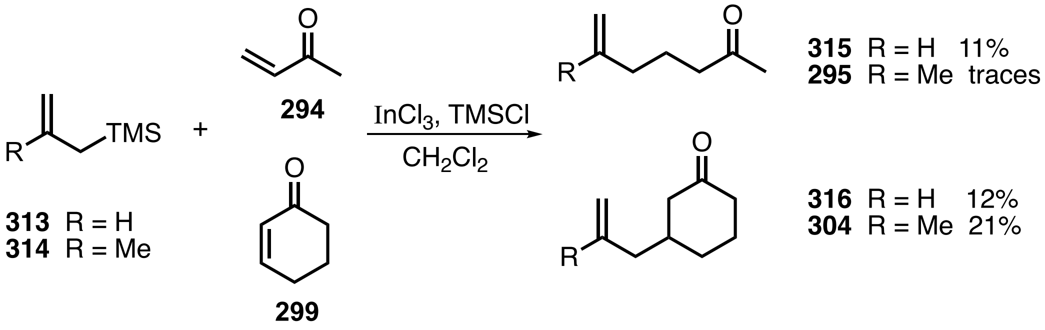
Scheme 157: Oxy-Cope rearrangement to ketoester **293**.[129]

In order to generate the desired ketoester in a more direct fashion, methallyl magnesium chloride **309** was added to diethyl oxalate at –78 °C, but unfortunately terminal alkene **311** was not observed. However, when the temperature was further reduced to –85 °C during Grignard addition and then warmed to –60 °C for 1 h, addition took place and an addition product was isolated in 71% yield, however, isomerisation to the more stable conjugated internal alkene **312**[130] had occurred (**Scheme 158**).



Scheme 158: Formation of conjugated enone **312**.[130]

As the Grignard additions were proving inefficient, alternative allylations were examined. Allylic silanes **313** or **314** were reacted with MVK **294** using $InCl_3$ in a Hosomi-Sakurai reaction.[131] But this led to formation of the desired products in only 11% yield (**Scheme 159**). When In was used in the reaction,[132] there were severe solubility issues, thus only traces of the desired product was observed. Additionally, when cyclohexenone **299** was replaced with MVK **294**, only ~12–21% of the corresponding products **316** and **304** were observed.

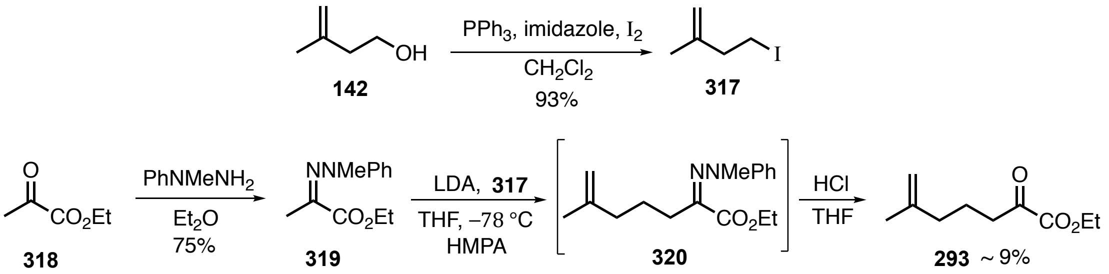


Scheme 159: Utilising allylTMS **313**/**314** to form unsaturated ketones.

5.4 Hydrazone Alkylation

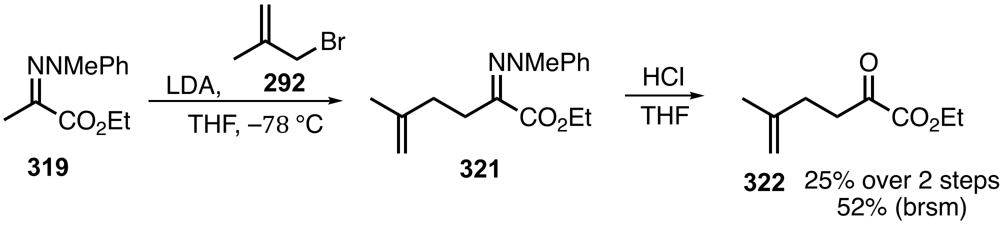
In an alternative approach involving homoallylation of a pyruvate hydrazone as an enolate (**Scheme 160**), iodide **317**[133] (93%) was initially formed from alcohol **142**. Concurrently, ethyl pyruvate **318** was condensed with $PhNMeNH_2$ in 75% yield.

When the hydrazone **319**[134] was reacted with LDA and subsequently trapped with iodide **317**, the alkylated hydrazone was hydrolysed back to the ketoester **293** in only trace amounts, with minor amounts of starting hydrazone recovered. When HMPA was used as co-solvent to hopefully assist breakdown of aggregates, the yield improved to ~9% (**Scheme 160**);[135] this was not efficient enough to merit further investigations.



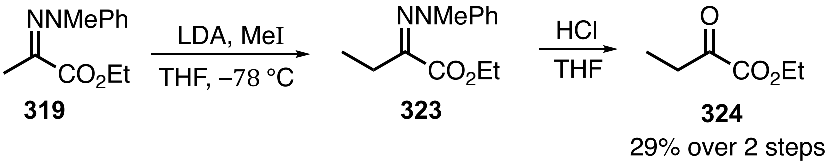
Scheme 160: Attempted ketoester formation from alkyl iodide **317** and hydrazone **319**.[133, 134, 135]

Methallyl bromide **292**, a more reactive electrophile in comparison to iodide **317**, was coupled with hydrazone **319** to give the required ketoester **322** in a slightly better 25% yield (52% brsm, **Scheme 161**).



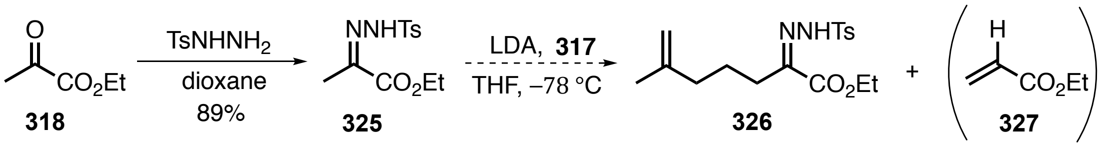
Scheme 161: ketoester formation from methallyl bromide **292** and hydrazone **319**.

The literature reaction, with MeI, yielded 29% of desired ketoester **324** over the 2 steps (**Scheme 162**, lit.[136] 57%).



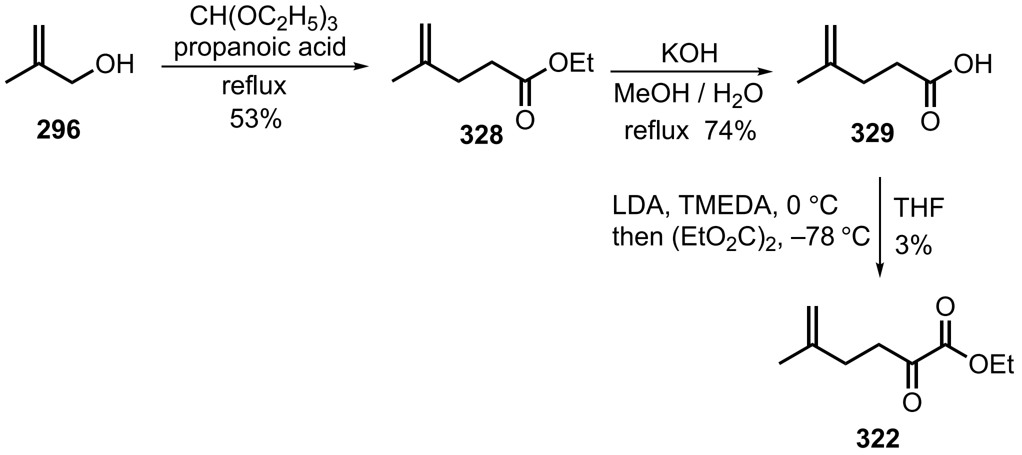
Scheme 162: Ketoester **324** formation from hydrazone **319** and MeI.[136]

Alternatively, using the potentially more reactive dianion from tosylhydrazone **325**[137] (89% from **318**, **Scheme 163**) and subsequently trapping with alkyl iodide **317** (p.143) was examined, but no traces of product or the starting materials were observed, nor the potential by-product **327** arising from Shapiro reaction.[138] The use of additives (TMEDA), different rates of addition, order of addition of reagents or temperature control (–85 ºC to rt), did not provide any desired product.



Scheme 163: Tosylhydrazone **325** formation and subsequent attempted alkylation with iodide **317**.

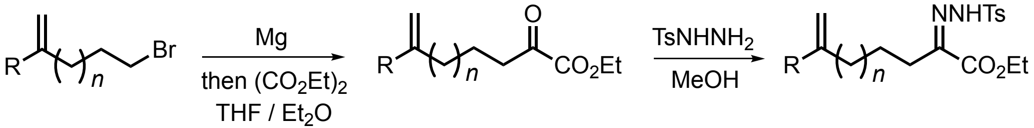
Alternatively, methallyl alcohol **296** was reacted with $CH(OC_2H_5)_3$ in a Johnson–Claisen[139] orthoester rearrangement to obtain ester **328** (53%) and the latter subsequently hydrolysed to the acid **329** using KOH in 74% yield.[140] Finally, ketoester formation was attempted with excess LDA (2 equiv.) and diethyl oxalate, but this only led to ~ 3% of the desired ketoester **322** (**Scheme 164**).



Scheme 164: Johnson–Claisen orthoester rearrangement, hydrolysis and ketoester formation.[139, 140]

5.5 Ketoester Formation *via* Grignard Reagents

Various methods to access unsaturated ketoesters had been examined (Section 5.4); however, the most general method to ketoesters was found to be the reaction of the relevant Grignard with diethyl oxalate.[141] Therefore, unsaturated tosylhydrazones **326** and **337–339**, lacking the *β*-siloxy and *β*-ester functionality that could be providing additional steric and/or electronic "protection" of the hydrazone to ozonolysis (**149**, **Scheme 144**, p.131), were made by tosylhydrazide condensation with *δ*- and *ε*-unsaturated *α*-ketoesters **293** and **334–336** (**Scheme 165**). The latter were readily prepared by addition to diethyl oxalate of the relevant Grignard reagents available from the corresponding unsaturated bromides **330–333**.[142]



330 (R = Me, n = 1)
331 (R = Me, n = 0)
332 (R = H, n = 1)
333 (R = H, n = 0)

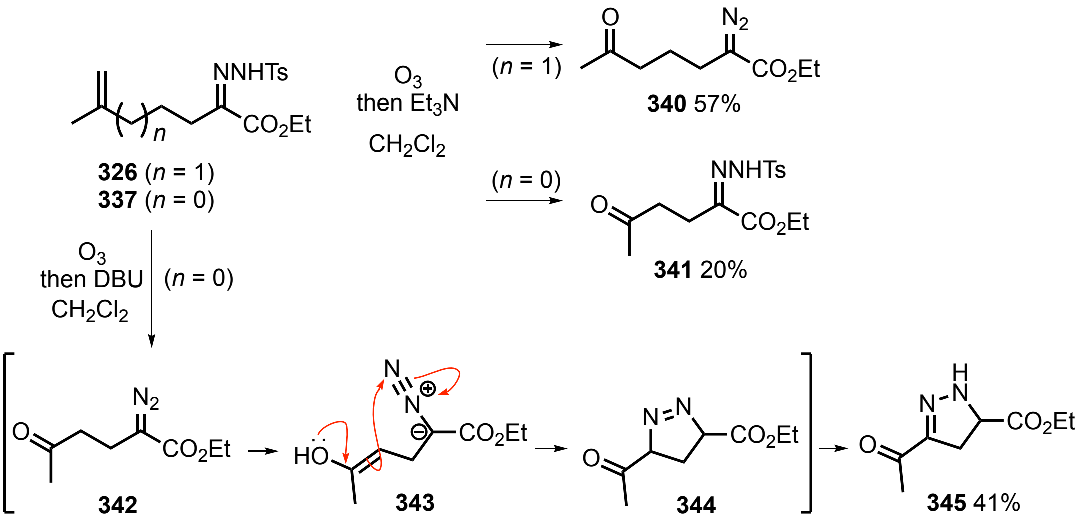
293 (R = Me, n = 1) 63%
334 (R = Me, n = 0) 37%
335 (R = H, n = 1)
336 (R = H, n = 0)

326 (R = Me, n = 1) 66%
337 (R = Me, n = 0) 84%
338 (R = H, n = 1) 80% (from **332**)
339 (R = H, n = 0) 71% (from **333**)

Scheme 165: Synthesis of unsaturated tosylhydrazones **326** and **337–339**.

5.6 Diazocarbonyl Formation

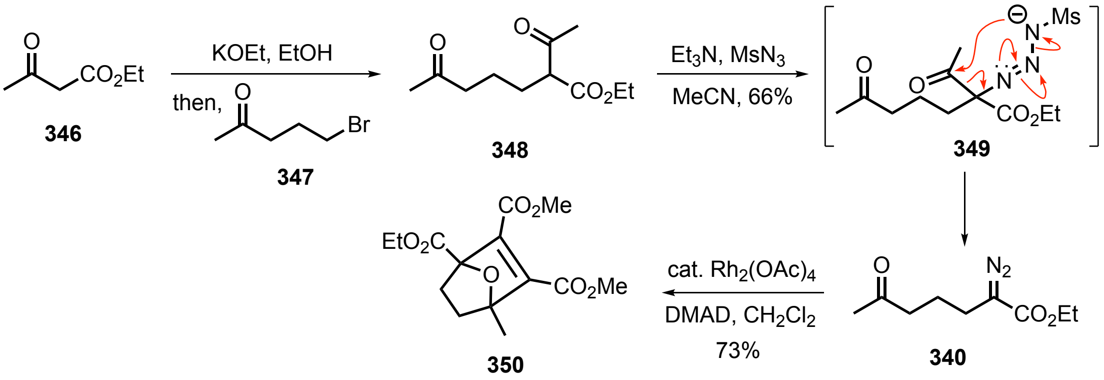
Of the unsaturated tosylhydrazones **326** and **337–339**, only **326** could be successfully converted to the corresponding diazocarbonyl **340** though the ozonolysis/Bamford-Stevens process (**Scheme 166**). Surprisingly, following ozonolysis and addition of Et_3N, unsaturated tosylhydrazone **337** was only converted as far as the keto hydrazone **342**, in low yield (20%, **Scheme 166**). Switching to DBU[143] as a stronger base after ozonolysis of tosylhydrazone **337** led to the 2-pyrazoline **345** (41%). Presumably, DBU does facilitate generation of the anticipated diazoketone **342**, but under the reaction conditions the corresponding enol **343** undergoes cyclisation with the proximal diazo functionality followed by regioselective tautomerisation from 1-pyrazoline **344**.[144]



Scheme 166: Ozonolysis followed by base treatment of unsaturated tosylhydrazones **326** and **337**.

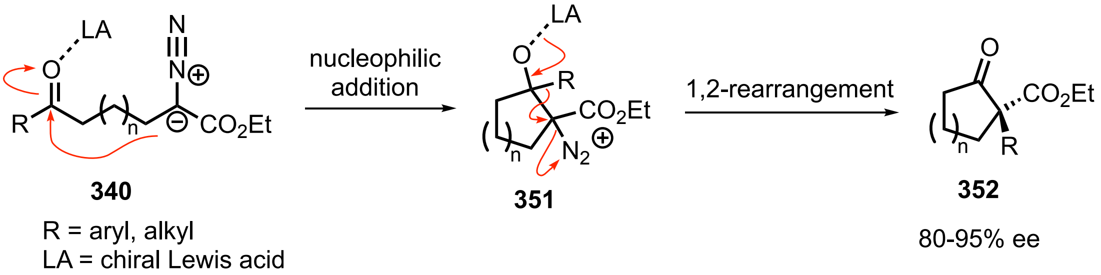
Formation of α-diazocarbonyl compounds *via* direct diazo transfer has been widely reported, with proton removal being the rate-limiting step.[145] For comparison with above, and as an example of viability in cycloaddition chemistry diazocarbonyl **340**

(57%) has previously been prepared by Padwa and co-workers using this method (**Scheme 167**), and shown to be a viable substrate for carbonyl ylide formation – cycloaddition chemistry (for example with DMAD as the dipolarophile, in 73% yield).[146]



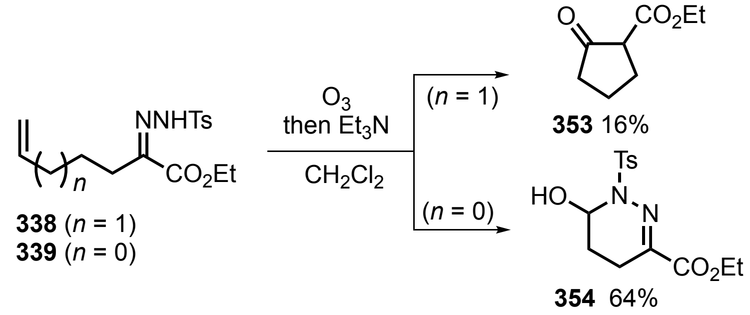
Scheme 167: Diazo transfer method followed by DMAD cycloaddition.[146]

Additionally, diazocarbonyl **340** and structurally related substrates also undergo chiral Lewis acid-catalysed cyclisation / 1,2-shift (**351**) in the enantioselective formation of α-substituted cyclic β-ketoesters **352** (**Scheme 168**).[147]



Scheme 168: Chiral Lewis acid-catalysed cyclisation / 1,2-shift.[147]

Terminal alkene-containing hydrazones **338** and **339** (**Scheme 169**) were anticipated to lead to diazoaldehydes following ozonolysis and base treatment. However, in both cases the greater reactivity of the aldehyde group, compared to ketone functionality earlier, led to cyclisation chemistry at the aldehyde. With hydrazone **338**, only β-ketoester **352** was isolated (16%), likely arising from intramolecular aldolisation of the diazoaldehyde followed by 1,2-hydride shift with expulsion of N_2.[147b] For hydrazone **339**, tetrahydropyridazinol **354** was obtained (64%, structure confirmed by X-ray crystallographic analysis (**Figure 14**, **Appendix 8.1.3**). The latter proved recalcitrant to conversion to the corresponding diazoaldehyde, being inert to separate treatment with Et_3N or NaOEt whereas significant decomposition was observed on exposure to DBU.



Scheme 169: Ozonolysis followed by base treatment of unsaturated tosylhydrazones **338** and **339**.

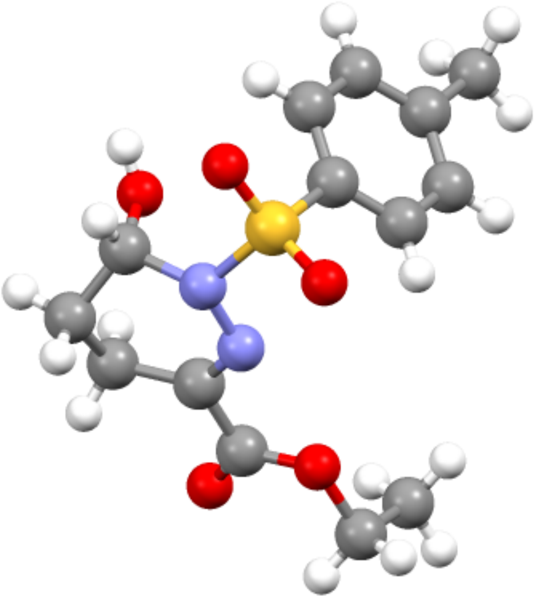
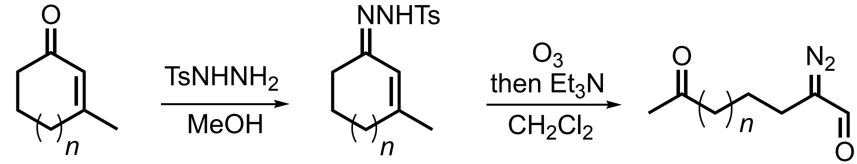


Figure 14. X–ray crystal structure of tetrahydropyridazinol **354**.

α,β-Unsaturated hydrazones **357** and **358** from 3-methylcyclohexenone (**355**) and 3-methylcyclopentenone (**356**) allow access to 1,5- and 1,4-diazoketones **359** and **360** using the ozonolysis–Et_3N strategy in 63% and 64% yields respectively (**Scheme 170**).



355 (n = 1) **356** (n = 0)

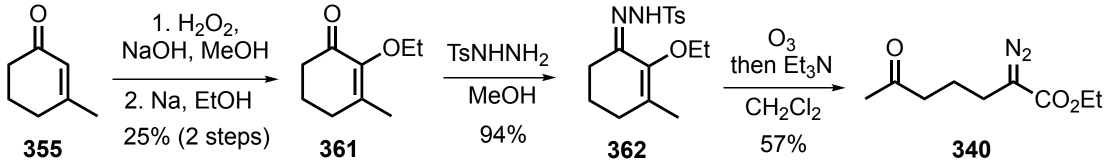
357 (n = 1) 89% **358** (n = 0) 78%

359 (n = 1) 63% **360** (n = 0) 64%

Scheme 170: Formation of diazoaldehydes **359** and **360** from cyclic enones.

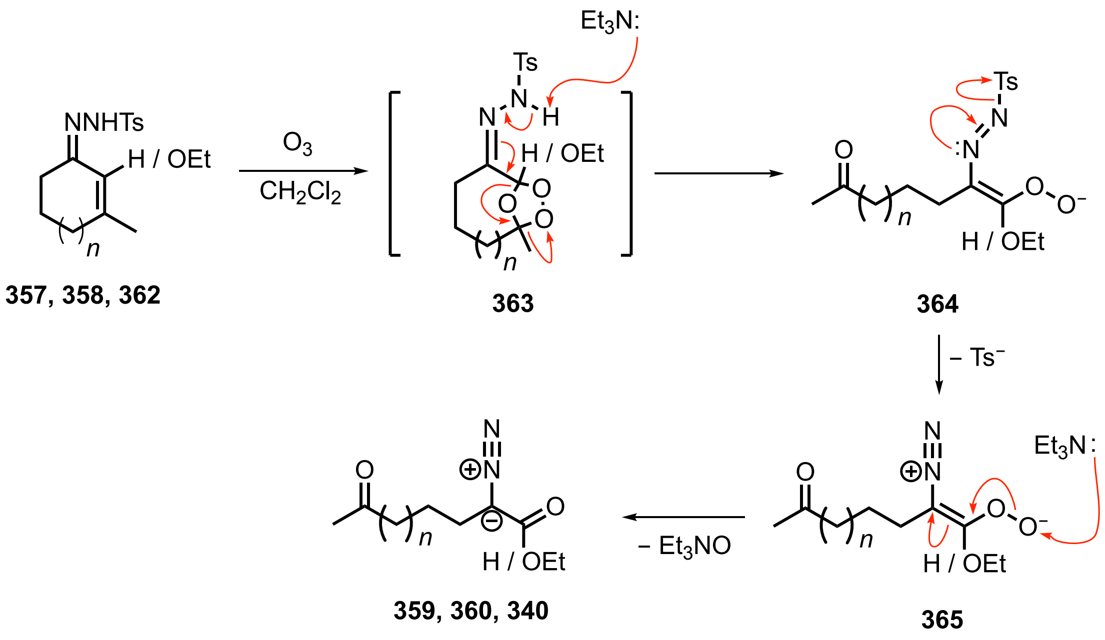
The α-diazoaldehydes **359** and **360** display *s-cis*/*trans* isomerism, arising from partial double bond character in the N_2C-CHO bond. This phenomenon has been observed for diazoacetaldehyde (the simplest α-diazoaldehyde), α-diazoketones and other α-diazo carbonyl compounds.[145c,148] In solution, diazoacetaldehyde and monosubstituted *α*-diazoketones ($RCOCHN_2$) prefer the *Z*-form, whereas disubstituted open-chain *α*-diazo carbonyl compounds exist exclusively as, or prefer, the *E*-form. NOE studies (by NMR staff members) on α-diazoaldehyde **359** recorded at –40 °C (to eliminate exchange between isomers) indicated that the predominant form was *E*- (analogously for **360**; *E*-:*Z*- both ~85:15). Stabilisation by weak hydrogen bonding between *β*- C–H on the (*cis*-) alkyl chain and the aldehyde may contribute to the preference for the *E*-form.[149] Variable temperature ^1H NMR studies in $CDCl_3$ and 1D EXSY analyses were used to obtain exchange rate constants and hence estimate rotational activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$), from which the activation energy ($\Delta G^\ddagger$) barrier to rotation was calculated as 74 $kJmol^{-1}$ at 25 °C (**Appendix 8.3**). The latter value lies at the upper end of the range of barriers so far determined for α-diazo carbonyl compounds, and likely reflects greater electron delocalisation into the aldehyde compared with α-diazo-ketone (and -ester) systems.

The *α*-diazo-*ε*-ketoester **340** (57%), made earlier (**Scheme 166**, p.142), was also accessible *via* 2-ethoxy-3-methylcyclohexenone (**361**, prepared from the epoxide of 3-methylcyclohexenone (**355**) by α-ring-opening / *β*-elimination using NaOEt[150] in 25% over the two steps, **Scheme 171**).



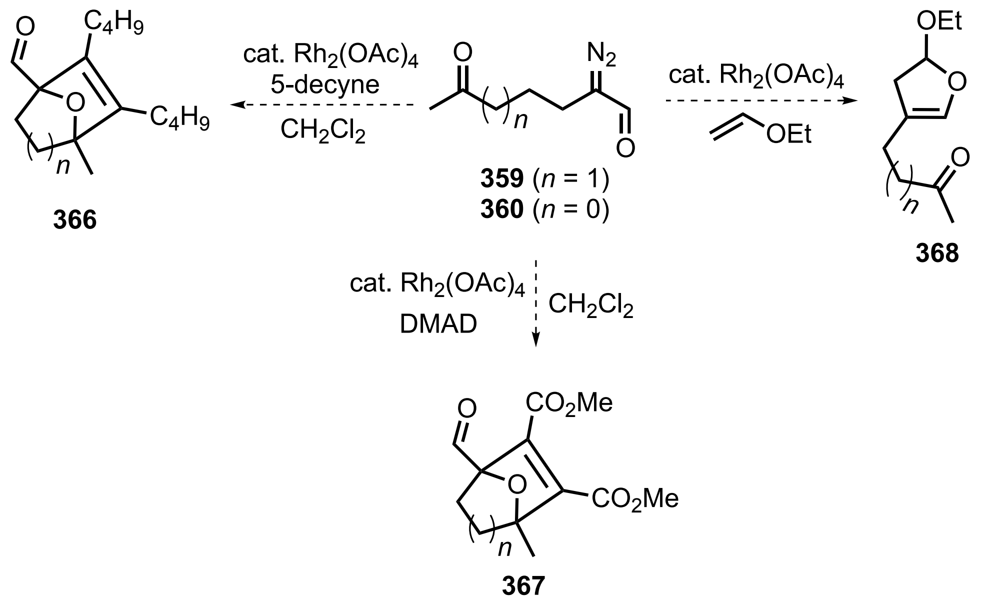
Scheme 171: Formation of 1,5diazoketone **340** from cyclic enones.[150]

Generation of diazo carbonyl compounds **359**, **360** and **340** from the corresponding, *α,β*-unsaturated hydrazones **357**, **358**, and **362** indicates that, if the reactions were to proceed through ozonoide **363** formation (**Scheme 172**), then the Et_3N acts as a reductant, although for the potential ozonides derived from **359** and **360** bridgehead deprotonation might be expected on the basis of direct analogy with previous studies on simple (cyclo)alkenes,[86] leading to carboxylic acid functionality through anionic cycloreversion, rather than the aldehyde functionality observed. However, in these systems, the proximity of the adjacent hydrazone functionality, aside from likely dictating (through stabilisation) carbonyl oxide generation on the proximal, rather than distal carbon in the first formed molozonoide, could also lead, through NH deprotonation to intermediate **364**. The latter, following elimination of Ts^-, could undergo reduction by Et_3N (**365**) to the desired diazocarbonyls.



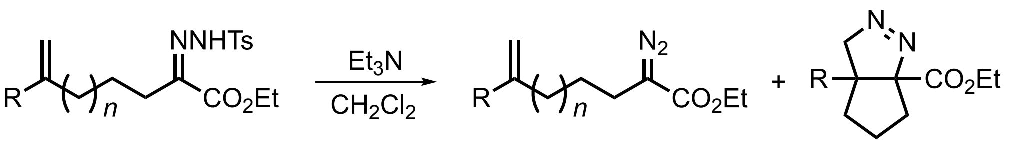
Scheme 172 Proposed pathway to diazocarbonyls **359**, **360** and **340**.

An attempt to utilise the diazoaldehydes **359** and **360** in carbonyl ylide cycloadditions in the presence of $Rh_2(OAc)_4$ with DMAD or 5-decyne – symmetrical dipolarophiles to avoid regioselectivity issues, led to no cycloadducts being isolated (**366**, **367**, **Scheme 173**).[151] Visually, Rh insertion into the diazo compound seemed to have occurred as gas evolution was observed, however, the presence of α-aldehyde and/or the remote ketone possibly complicated carbonyl ylide formation, thus preventing formation of cycloadducts. When the diazoaldehydes **359** and **360** were mixed with DMAD or 5-decyne in the absence of the catalyst, no reaction took place and the starting materials were recovered. Additionally, treating the diazoaldehydes with cat. $Rh(OAc)_4$ in neat ethyl vinyl ether (as dipolarophile and as solvent)[152] showed no success in forming any cycloadduct **368**. The rate of N_2 evolution was much slower when carried out in ethyl vinyl ether compared to CH_2Cl_2, however complete decomposition took place and no starting material was recovered.



Scheme 173: Attempted cycloadditions with ethyl vinyl ether, DMAD and 5-decyne.[151, 152]

Dauben and co-workers reported that unsaturated diazo substrate **221**, underwent spontaneous intramolecular dipolar cycloaddition to give a 1-pyrazoline **222** (**Scheme 86**, p.84).[84] Therefore, in a test to establish if the diazo group would be functionally compatible with the proximal olefins, the requisite hydrazones prepared previously (p.141) (**326** and **337–339)** were treated with Et_3N in CH_2Cl_2 at rt (**Scheme 174**). As anticipated from Dauben's studies,[87] hydrazone **338** underwent intramolecular cycloaddition to form 1-pyrazoline (**374**, ethyl ester) in 89% yield. However, it was believed that further substitution about the olefin would minimise this intramolecular cycloaddition. When hydrazone **326** was treated with Et_3N, the presence of the methyl group significantly reduced the cycloaddition to give majority diazo **369** (44%) and minor amounts of bicycle **373** in ~8% yield. When the carbon chain was reduced by one methylene group, the diazo alkenes **370** and **372** were fully formed in 63% and 71% yield respectively, as expected without any traces of the fused cyclobutane from intramolecular cycloaddition.



326 (R = Me, *n* = 1)
337 (R = Me, *n* = 0)
338 (R = H, *n* = 1)
339 (R = H, *n* = 0)

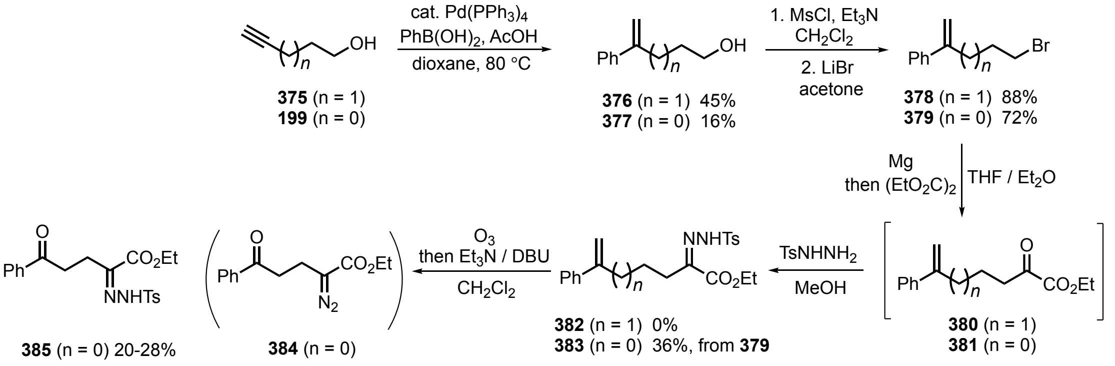
369 (R = Me, *n* = 1), 44%
370 (R = Me, *n* = 0), 63%
371 (R = H, *n* = 1), 0%
372 (R = H, *n* = 0), 71%

373 8%

374 89%

Scheme 174: Diazo group compatibility with terminal olefins.

So as to synthesise phenyl variants of the 5- and 6-membered hydrazones (**Scheme 175**), terminal alkynes **375** and **199** were reacted with phenylboronic acid in the presence of cat. $Pd(PPh_3)_4$[153] to give regioisomerically pure alkenes **376** and **377** in 45% and 16% yield, respectively. Activation as the bromides **378** and **379** *via* the mesylates (88% and 72%, respectively) and subsequent Grignard reaction with diethyl oxalate only led to hydrazone **383** *via* ketoester **381** in poor yield (36% from **379**, **Scheme 175**). Attempted bromide formation *via* an Appel reaction using PPh_3 and CBr_4 led to contamination with side product bromoform, hence why the 2-step formation was pursued. Attempts to form ketoester **380** from bromide **378** (n = 1) led to no product formation. It was assumed that Grignard formation at this stage was the limiting factor.



375 (n = 1)
199 (n = 0)

376 (n = 1) 45%
377 (n = 0) 16%

378 (n = 1) 88%
379 (n = 0) 72%

380 (n = 1)
381 (n = 0)

382 (n = 1) 0%
383 (n = 0) 36%, from **379**

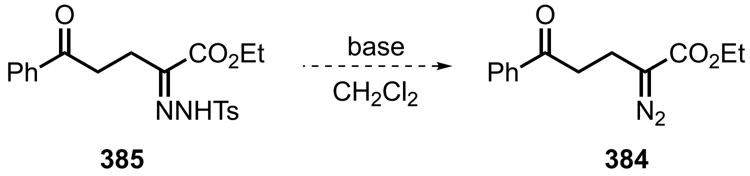
384 (n = 0)

385 (n = 0) 20-28%

Scheme 175: Hydrazone formation with phenyl variant systems.

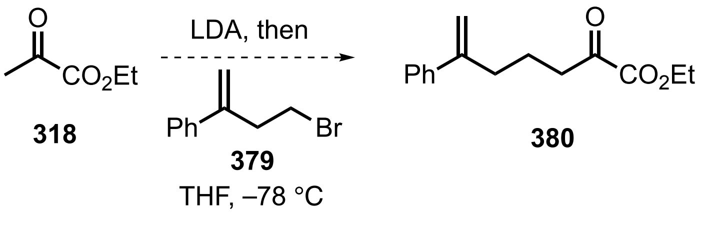
When the ozonolysis / Et_3N (or DBU) conditions were applied to hydrazone **383**, the product obtained (20-28%) indicated that only alkene ozonolysis (**385**) had taken place and no hydrazone conversion to the diazo (**384**) was achieved using Et_3N or DBU (**Scheme 175**).

Treating the keto-hydrazone **385** separately with various bases showed no improvement in the conversion to the diazo **384** and returned starting material using Et_3N, whereas DBU and NaOMe led to complete decomposition of the starting material (**Scheme 176**).



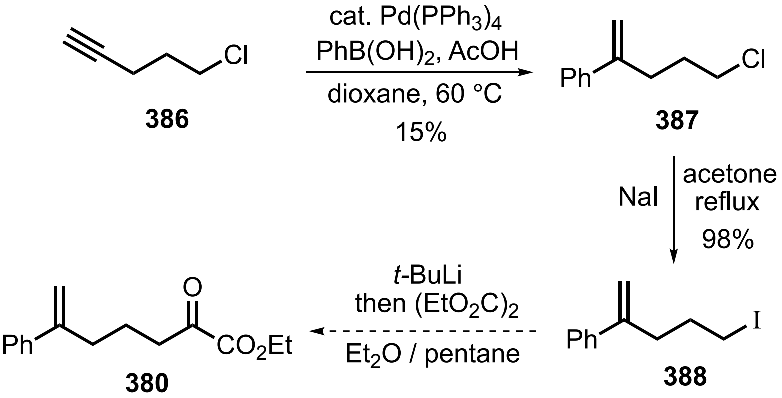
Scheme 176: Attempted diazo formation from keto-hydrazone **385**.

In another attempt to form ketoester **380**, methyl pyruvate **318** was reacted with LDA, and then bromide **379** added (**Scheme 177**). However, the desired ketoester **380** did not form – even when 1 equiv. of NaI was used to form the corresponding alkyl iodide *in situ*; the only compound recovered was starting bromide **379**.



Scheme 177: Attempted ketoester **380** formation from methyl pyruvate **318** and bromide **379**.

In a Li/hal exchange, bromide **379** was reacted with *t*-BuLi and trapped with diethyl oxalate but this did not lead to any product (**380**) and nor was any starting material recovered. It was believed that the chances of smoother Li/hal exchange with an appropriate solvent system from an alkyl iodide would lead to greater chances of ketoester formation.[154] Therefore, chloro-alkyne **386** was reacted with phenylboronic acid (15%) and the resulting alkene **387** was converted to the alkyl iodide **388** in a Finkelstein reaction in 98% yield.[155] Li/hal exchange was then attempted, but the resulting organolithium did not react with diethyl oxalate to form the ketoester **380**. Additionally, attempted transmetallation to the corresponding Grignard or organozinc using $MgCl_2$ or $ZnCl_2$ from the organolithium did not lead to any desired product.



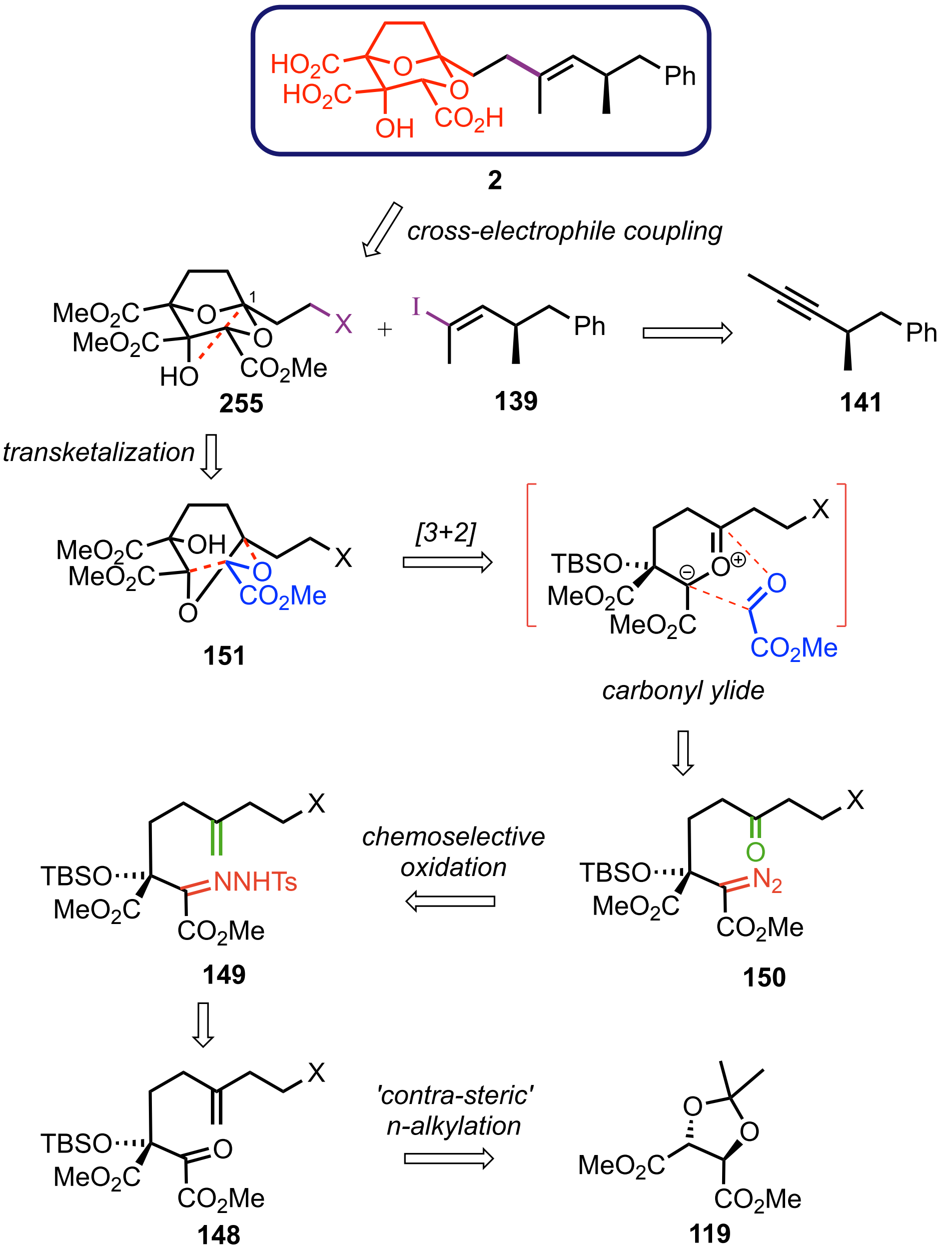
Scheme 178: Attempted ketoester **380** formation *via* alkyl iodide **388**.

Chapter 6

Conclusions

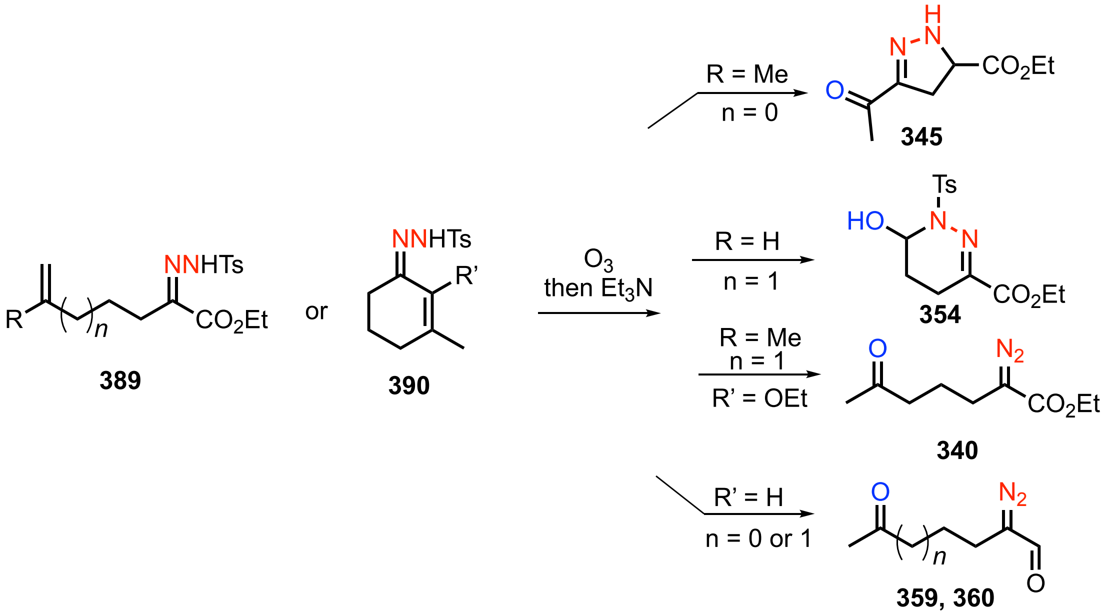
6. Conclusions

The total synthesis of the natural product (−)-6,7-dideoxysqualestatin H5 (**2**) was completed from commercially available starting materials; the 16-step sequence compares favorably with Martin's[30] previous 14- and 17-step routes. Noteworthy features include improvement in alkylation scope and stereochemical efficiency from the enolate of a commercially available tartrate acetonide **119**, leading to a new entry to the *β*-hydroxy-*α*-ketoester motif in an asymmetric manner. Also, the direct ozonolytic conversion of an unsaturated hydrazone **149** to a diazoketone **150** illustrates a new strategic entry to substrates for cyclic carbonyl ylide formation−cycloaddition chemistry. The current synthesis showcases the power of the latter pericyclic process to deliver high levels of stereocontrol from functional group rich precursors. Finally, a late-stage ester and alcohol functional group-tolerant Ni-catalysed Mn-mediated Csp^3−Csp^2 cross-electrophile coupling involving equimolar quantities of the halide **139** and **255** partners and occurring at rt with geometrical integrity at the internal alkenyl halide demonstrates the utility of this emerging technology in complex natural product synthesis.



Scheme 179: Overview of the total synthesis of 6,7-dideoxysqualestatin H5 (**2**).

During post 6,7-DDSQ H5 investigations, the scope and limitations of reacting unsaturated tosylhydrazones **389** and **390** with O_3 followed by Et_3N for the direct generation of diazocarbonyl systems were examined. The chemistry is viable to α-diazo-ε-ketoesters, but an α-diazo-δ-ketoester underwent cyclisation to a 2-pyrazoline (**345**) under the basic reaction conditions following ozonolysis. Terminal alkene hydrazones did not produce diazoaldehydes, as the later proved too reactive in the presence of tethered hydrazone or diazo functionality, although the chemistry did provide an interesting route to a tetrahydropyridazine (**354)** ring system. Finally, cyclic *α,β*-unsaturated hydrazones **390** were shown to undergo ozonolytic ring-cleavage and Bamford–Stevens reaction to give 2,5- and 2,6-diazoketones with aldehyde or ester functionality at the 1-position, **340**, **359** and **360**. The *α*-diazoaldehydes prefer the *s-trans* conformation, with a rotation barrier of 74 kJmol^{-1} at 25 °C as determined by NMR studies.



Scheme 180: Overview of the ozonolysis of unsaturated tosylhydrazones as a direct approach to diazocarbonyls.

Chapter 7

Experimental

7. Experimental

7.1 General Techniques

All reactions requiring anhydrous conditions were carried out under an atmosphere of argon in flame-dried glassware. Tetrahydrofuran (THF), dichloromethane (DCM), ether (Et_2O) and ethyl acetate (EtOAc) were obtained from Grubbs' drying towers.[156] MeOH was dried over 4Å MS for at least 24 h. Petrol (petroleum ether) 30–40 °C was used in flash column chromatography. Flash column chromatography was carried out using silica gel (VWR chemicals, BDH) and monitored by thin layer chromatography (TLC) (Merck 60 F_{254}) plates. TLC plates were viewed using ultraviolet light (λ_{max} = 254/365 nm) and immersion in $KMnO_4$, anisaldehyde or vanillin stains, followed by heating. Reverse phase HPLC was carried out using Phenomenex - Luna 5u C18(2)100A (column 250 x 10 mm). Except where stated otherwise, commercially available reagents were used as received. "Freshly distilled" refers to distillation over CaH_2 using a short-path distillation apparatus under a nitrogen atmosphere. Melting points (m.p.) were obtained using an Electrothermal melting point apparatus to the nearest 1 °C and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, with a path length of 10 cm in $CHCl_3$ or MeOH. $[\alpha]_D^{25}$ values are given in 10^{-1} deg cm^2 g^{-1}. Concentrations (*c*) are given in grams/cm^3. Infrared spectra were obtained using a PerkinElmer FT–IR spectrometer (Universal ATR Sampling Accessory), with absorption maxima quoted in wavenumbers (cm^{-1}). Peak intensities are described as broad (br), weak (w), medium (m) or strong (s). NMR (^1H NMR and ^{13}C NMR) spectra were recorded on Bruker Avance UltraShield AVC 500 and AVX 500 (500 MHz) spectrometers in $CDCl_3$, referenced to residual $CHCl_3$ singlet at δ 7.27 and CD_3OD quintet at δ 3.31 for ^1H NMR spectra, and to the central line of

$CDCl_3$ triplet at 77.16 as well as the central line of CD_3OD heptet at 49.0 for ^{13}C NMR spectra. Chemical shifts are quoted in ppm. Coupling constants (*J*) are measured to the nearest 0.5 Hertz (Hz). The splittings are quoted as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). The ^{13}C NMR peaks were assigned by standard methods using HSQC. Stereochemical assignments were based on NOE studies and X-ray crystallography. Low resolution mass spectra were obtained using electrospray ionization (ESI). High resolution mass spectra were obtained by electrospray ionization (ESI) using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass.

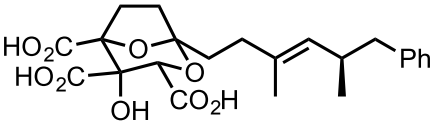
The MoOPH reagent was prepared by the literature procedure.[83]

General procedure A for the formation of hydrazones. (i) Mg turnings (50.6 mmol) were flame-dried under vacuum for 15 min and then allowed to cool to rt under argon. A mixture of THF/Et_2O (0.88 mL/mmol, 1:1) was added, followed by dropwise addition of bromoalkene (16.9 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of diethyl oxalate (11.3 mmol) in THF/Et_2O (0.88 mL/mmol, 1:1) at –78 °C. After 2 h at –78 °C, the reaction was quenched with sat. aq NH_4Cl (15 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give α-ketoester as colourless oil, which was used in the next step without further purification. **(ii)** A mixture of crude α-ketoester (11.2 mmol) and $TsNHNH_2$ (13.4 mmol) in MeOH (1.3 mL/mmol of α-ketoester) was heated to 45 °C for 16h. The mixture was then cooled to rt, concentrated under reduced pressure and purified by column chromatography to give the hydrazone.

General procedure B for ozonolysis/Bamford-Stevens process

A solution of hydrazone (1.48 mmol) in CH_2Cl_2 (115 mL/mmol) was cooled to –78 °C. A stream of O_3 in oxygen was bubbled through the solution. Ozone treatment was terminated when the colour of the reaction mixture changed from colourless to light blue. The excess O_3 was removed by bubbling N_2 through the reaction mixture. After 10 min, Et_3N (5.91 mmol) was added and the reaction mixture was warmed to rt. After stirring for 3 h, the reaction mixture was passed through a pad of silica, evaporated under reduced pressure and purified by column chromatography to give the diazocarbonyl.

(1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-Dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid (2)[30]

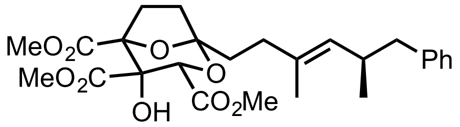


To a solution of 6,7-dideoxysqualestatin H5 dimethyl ester **280** (6.0 mg, 0.013 mmol) in dioxane (0.6 mL) was added H_2O (0.91 mg, 0.050 mmol), and KO*t*-Bu (14.1 mg, 0.13 mmol). The reaction mixture was heated at 110 °C for 24 h. The solvent was evaporated, and H_2O (5 mL) was added. The aq mixture was washed with Et_2O (1x5 mL), acidified with 0.1 M HCl (2 mL), and extracted with EtOAc (2x10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by reverse phase (C18) HPLC eluting with MeOH/H_2O/AcOH (850:150:2, t_R = 10:00 min) to give 6,7-dideoxysqualestatin H5 (**2**)[30] (2.7 mg 48%) as a colourless glass; $[\alpha]_D^{25} = -50.6$ (*c* 0.13, MeOH); IR (film, υ_{max} cm^{-1}) 3381 br, 2957 w, 2490 br, 1732 s, 1452 w, 1119 s, 972 s; ^1H NMR (500 MHz;

CD_3OD) δ 7.24–7.11 (5H, m, ArCH), 5.04 (1H, d, *J* 9.0, HC=C), 4.87 (1H, s, C*H*CO_2Me), 3.22–3.15 (1H, m, H_{endo} of C^6H_2), 2.68–2.62 (1H, m, C*H*CH_3), 2.59 (1H, dd, *J* 13.0, *J* 6.0, CH_2Ph), 2.48 (1H, d, *J* 13.0, 8.5, CH_2Ph), 2.23–2.11 (2H, m, C^7H_2), 2.09–1.93 (4H, m, CH_2CH_2C=C), 1.90–1.83 (1H, m, 1H_{exo} of C^6H_2), 1.43 (3H, d, *J* 1.0, CCH_3), 0.96 (3H, d, *J* 6.5, CHCH_3); ^{13}C NMR (125 MHz; CD_3OD) δ 173.5 (CO_2H), 172.4 (CO_2H), 171.1 (CO_2H), 142.4 (*C*=CH), 135.0 (ArC), 131.7 (C=*C*H), 130.3 (2x ArCH), 129.0 (2xArCH), 126.7 (ArCH), 109.8 (O–C^1–O), 89.5 (C^5CO_2Me), 76.2 (C^4CO_2Me), 75.9 (*C*HCO_2Me), 45.1 (*C*H_2Ph), 36.5 (*C*HCH_3), 35.9 (C^6H_2), 34.7 (C^7H_2), 32.2 (CCH_2CH_2CMe), 30.3 (CH_2), 21.4 ($CHCH_3$), 16.1 (C=CCH_3); HRMS *m/z* $(M–H)^+$ found 447.1660, $C_{23}H_{27}O_9$ requires 447.1661.

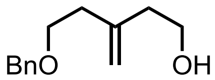
Data comparisons with natural isolate in **Appendix 8.2** p.259

Trimethyl (1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (111)



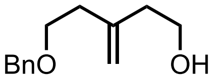
To a Schlenk tube was added Mn dust (4.8 mg, 0.087 mmol), NiI_2(bpy)[105] (0.5 mg, 0.0011 mmol, 2.5 mol%), hydroxy iodide **255** (20 mg, 0.044 mmol) and (*R*-)–alkenyl iodide **139** (12.5 mg, 0.044 mmol) and the flask evacuated and refilled with argon (x3). DMF (0.2 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (1.1 µL, 0.0087 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. The mixture was then diluted with THF (1 mL) and TBAF (0.4 mL, 0.40 mmol, 1 M in THF) was added dropwise and stirred at rt for 2 h. H_2O (5 mL) was then added and the aq layer extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under constant stream of nitrogen and the residue purified by column chromatography (30% EtOAc in petrol) to give hydroxy triester **111** (10.5 mg, 49%) as colourless oil, $R_f = 0.28$ (30% EtOAc in petrol); $[\alpha]_D^{25} = -37.9$ (*c* 0.53, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3078 br, 2956 s, 2925 s, 2854 s, 1768 s, 1739 s, 1439 s, 1266 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.28–7.22 (2H, m, ArCH), 7.19–7.12 (3H, m, ArCH), 5.03 (1H, d, *J* 9.0, HC=C), 4.87 (1H, s, C*H*CO_2Me), 3.90 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.68 (1H, s, OH), 3.16–3.05 (1H, m, H_{endo} of C^6H_2), 2.69–2.25 (1H, m, C*H*CH_3), 2.52 (2H, dd, *J* 7.5, *J* 4.0, CH_2Ph), 2.23–2.07 (3H, m, $1H_{exo}$ of C^6H_2 and 2H, C^7H_2), 2.05–1.97 (4H, m, CH_2CH_2), 1.47 (3H, d, *J* 1.0, CCH_3), 0.94 (3H, d, *J* 7.0, CHCH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.0 (*C*O_2Me), 168.9 (*C*O_2Me), 167.6 (*C*O_2Me), 141.2 (*C*=CH), 133.2 (C=*C*H), 130.8 (ArC), 129.4 (2xArCH), 128.1 (2xArCH), 125.8 (ArCH), 109.3 (O-C^1-O), 88.1 (C^5CO_2Me), 75.2 (C^4CO_2MeOH), 75.0 (*C*HCO_2Me), 53.4 (CO_2Me), 53.0 (CO_2Me), 52.8 (CO_2Me), 44.1 (*C*H_2Ph), 35.2 (*C*HCH_3), 34.6 (C^6H_2), 33.5 (C^7H_2), 31.2 (CCH_2CH_2CMe), 29.2 (CCH_2CH_2CMe), 21.0 (CH*C*H_3), 16.3 (C=C*C*H_3); HRMS *m/z* ($M+Na^+$) found 513.2100, $C_{26}H_{34}NaO_9$ requires 513.2106.

5-(Benzyloxy)-3-methylenepentan-1-ol (144)



A solution of alkenyl bromide **201** (2.00 g, 8.29 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C and *t*-BuLi (9.76 mL, 1.7 M in hexanes, 16.6 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 30 min and a pre-cooled (–78 °C) solution of ethylene oxide[63] (0.630 g, 14.3 mmol) in CH_2Cl_2 (12 mL) was transferred to the reaction mixture *via* cannula. Then $BF_3•Et_2O$ (1.54 mL, 12.4 mmol) was added dropwise over 30 min. After stirring at –78 °C for 2 h, the reaction mixture was slowly warmed to rt (over 1h) and quenched with sat. aq NH_4Cl (50 mL). The aq layer was extracted with Et_2O (2x100 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give alcohol **144**[71] (1.01 g, 59%) as pale yellow oil, R_f = 0.43 (40% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3339 br, 2935 m, 2861 s, 2360 m, 2341 w, 1645 m, 1099 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.37–7.28 (5H, m, 5xArC*H*), 4.94 (2H, d, *J* 9.0, CH_2=C), 4.53 (2H, s, C*H*$_2$Ph), 3.73 (2H, t, *J* 6.0, C*H*$_2$OH), 3.62 (2H, t, *J* 7.0, C*H*$_2$OBn), 2.38 (2H, t, *J* 7.0, C*H*$_2$$CH_2$OH), 2.33 (2H, t, *J* 6.0, C*H*$_2$$CH_2$OBn), 1.82 (1H, br. s, O*H*); ^{13}C NMR (125 MHz; $CDCl_3$) δ 143.5 (CH_2=*C*), 138.3 (Ar*C*), 128.5 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 113.6 (*C*H_2=C), 73.2 (*C*H_2Ph), 69.1 (*C*H_2OBn), 60.6 (CH_2OH), 39.8 (CH_2), 35.8 (CH_2); HRMS *m/z* (M+Na^+) found 229.1196, $C_{13}H_{18}NaO_2$ requires 229.1199.

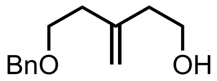
5-(Benzyloxy)-3-methylenepentan-1-ol (144)



A solution of alkenyl bromide **201** (200 mg, 0.83 mmol) in Et_2O (6 mL) was cooled to –78 °C and *t*-BuLi (0.98 mL, 1.7 M in hexanes, 1.7 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 30 min and a previously prepared (–78 °C) solution of ethylene oxide [To a dispersion of NaH (530 mg, 60% in mineral oil, 13.3 mmol) in Et_2O (9 mL) was added dropwise chloroethanol **203** (0.5 mL, 7.5 mmol) over 5 min and stirred at 0 °C for 2.5 h][64] was transferred to the reaction mixture *via* cannula. Then $BF_3•Et_2O$ (0.43 mL, 3.32 mmol) was added dropwise over 10 min. After stirring at –78 °C for 2 h, the reaction mixture was slowly warmed to rt (over 1 h) and quenched with sat. aq NH_4Cl (10 mL). The aq layer was extracted with Et_2O (2x20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give alcohol **144**[71] (70 mg, 41%) as pale yellow oil, $R_f = 0.21$ (20% EtOAc in petrol).

Analytical data identical to that previously reported.

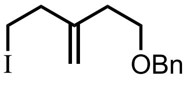
5-(Benzyloxy)-3-methylenepentan-1-ol (144)



A solution of ((5-(Benzyloxy)-3-methylenepentyl)oxy)(tert-butyl)dimethylsilane (**210**) (230 mg, 0.72 mmol) in THF (2 mL) was added TBAF[71] (2.0 mL, 2.0 mmol, 1 M in THF) at 0 °C. The reaction mixture was allowed to warm to rt. After stirring at rt for 30 min, the mixture was poured into sat. aq $NaHCO_3$ (30 mL) and extracted with Et_2O (3x40 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography to give allylic alcohol 5-(benzyloxy)-3-methylenepentan-1-ol (**144**) (138 mg, 93% yield) as colourless oil, $R_f = 0.20$ (5% EtOAc in petrol)

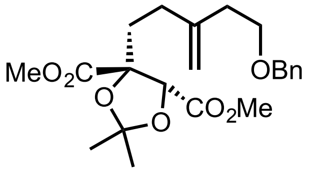
Analytical data identical to that previously reported.

(((5-Iodo-3-methylenepentyl)oxy)methyl)benzene (145)



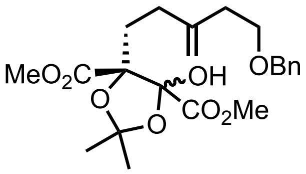
To a solution of PPh_3 (2.30 g, 8.77 mmol) and imidazole (1.66 g, 24.4 mmol) in CH_2Cl_2 (37 mL) was added iodine (3.10 g, 12.2 mmol) at 0 °C. After 15 min, benzyl ether **144** (2.30 g, 11.1 mmol) in $\mathrm{CH_2Cl_2}$ (6 mL) was added dropwise. The ice bath was removed and the suspension was stirred for 2 h at rt. $\mathrm{H_2O}$ (30 mL) was then added and the aq layer extracted with $\mathrm{CH_2Cl_2}$ (2x30 mL), the combined organic layers were dried ($\mathrm{MgSO_4}$), evaporated under reduced pressure and the residue purified by column chromatography (20% $\mathrm{CH_2Cl_2}$ in petrol) to give iodide **145** (3.50 g, quant.) as a colourless oil, $R_f = 0.21$ (20% $\mathrm{CH_2Cl_2}$ in petrol); IR (film, υ_{max} $\mathrm{cm^{-1}}$) 2826 s, 1645 m, 1595 m, 1495 m, 1453 s, 1361 s, 1098 s; ^{1}H NMR (500 MHz; $\mathrm{CDCl_3}$) δ 7.38–7.25 (5H, m, Ar*H*), 4.91 (2H, d, *J* 12.0, $\mathrm{C{=}CH_2}$), 4.53 (2H, s, CH_2Ph), 3.59 (2H, t, *J* 7.0, CH_2OBn), 3.26 (2H, t, *J* 8.0, $C\mathrm{H_2I}$), 2.63 (2H, t, *J* 8.0, $\mathrm{ICH_2}CH_2$), 2.36 (2H, t, *J* 7.0, $\mathrm{OBnCH_2}CH_2$); ^{13}C NMR (125 MHz; $\mathrm{CDCl_3}$) δ 145.3 ($C\mathrm{{=}CH_2}$), 138.4 (Ar*C*), 128.5 (ArCH), 127.8 (Ar*C*H), 127.75 (Ar*C*H), 113.0 ($\mathrm{C{=}}C\mathrm{H_2}$), 73.2 ($C\mathrm{H_2Ph}$), 68.9 ($C\mathrm{H_2OBn}$), 40.7 ($\mathrm{ICH_2}C\mathrm{H_2}$), 35.7 ($C\mathrm{H_2CH_2OBn}$), 3.54 ($\mathrm{ICH_2}$); HRMS *m/z* ($\mathrm{M{+}Na^+}$) found 339.0215, $\mathrm{C_{13}H_{17}INaO}$ requires 339.0216.

(*4R,5R*)-Dimethyl 4-{5-(benzyloxy)-3-methylenepentyl}-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (146)



A stirred solution of dimethyl-2,3-*O*-isopropylidine-*L*-tartrate (**119**) (6.90 g, 31.6 mmol), iodide **145** (5.00 g, 15.8 mmol) and freshly distilled HMPA (21.2 mL) in THF (50 mL) was cooled to –78 °C. To this reaction mixture was added dropwise a pre-cooled (–78 °C) solution of LDA [31.6 mmol, freshly prepared by adding dropwise *n*-BuLi (20.3 mL, 1.6 M in hexanes, 31.6 mmol) to a solution of freshly distilled *i*-$\mathrm{Pr_2NH}$ (3.30 g, 31.6 mmol) in THF (50 mL) at 0 °C] over 1 h. The reaction mixture was further stirred for 48 h at –78 °C, and then quenched at the same temperature with sat. aq NH_4Cl (100 mL), extracted with EtOAc (3x100 mL), washed with sat. aq $CuSO_4$ (100 mL), The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by column chromatography (40% Et_2O in petrol) to give a mixture of alkylated tartrate **146** and tartrate **119** (~12 g) which was then distilled under reduced pressure (0.2 mbar at ~160 °C) to give alkylated tartrate **146** (3.85 g, 60%) as colourless oil; $R_f = 0.48$ (40% Et_2O in petrol); $[\alpha]_D^{25} = -61.4$ (*c* 0.07, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3066 w, 2991 m, 2858 w, 1756 s, 1739 s, 1647 w, 1453 m, 1382 m, 1209 s, 1103 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.39–7.28 (5H, m, 5xArCH), 4.95 (1H, s, C*H*CO_2Me), 4.78 (2H, d, *J* 16.0, H_2C=C), 4.51 (2H, s, C*H*$_2$Ph), 3.80 (3H, s, CO_2Me), 3.80 (3H, s, CO_2Me), 3.56 (2H, t, *J* 7.0, C*H*$_2$OBn), 2.32 (2H, t, *J* 7.0, C*H*$_2$$CH_2$OBn), 2.21–2.11 (1H, m, 1H of CH_2C*H*$_2$C=C), 2.03–1.91 (2H, m, C*H*$_2$$CH_2$C=C), 1.81–1.74 (1H, m, 1H of CH_2C*H*$_2$C=C), 1.61 (3H, s, CH_3C), 1.45 (3H, s, CH_3C); ^{13}C NMR (125 MHz; $CDCl_3$) δ 172.3 (*C*O_2Me), 168.8 (*C*O_2Me), 145.5 (CH_2=*C*), 138.5 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 112.8 (*C*H_2=C), 111.0 (*C*Me_2), 85.6 (*C*CO_2Me), 80.2 (*C*HCO_2Me), 72.9 (*C*H_2Ph), 68.9 (*C*H_2OBn), 53.0 (CO_2*Me*), 52.5 (CO_2*Me*), 36.4 (*C*$H_2$$CH_2$OBn), 32.7 ($CCH_2$*C*$H_2$C=O), 30.4 (C*Me*), 27.8 (C*Me*), 26.1 (C*C*$H_2$$CH_2$C=O); HRMS *m/z* (M+$Na^+$) found 429.1886, $C_{22}H_{30}NaO_7$ requires 429.1884.

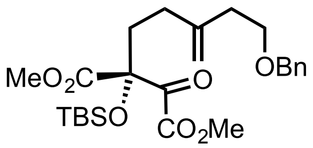
(*4R*)-Dimethyl 4-{5-(benzyloxy)-3-methylenepentyl}-5-hydroxy-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (147)



A pre-cooled (–78 °C) solution of alkylated tartrate **146** (1.0 g, 2.42 mmol) in THF (12 mL) was added dropwise over 1 h to a stirred solution of LDA [3.69 mmol, freshly prepared by adding dropwise *n*-BuLi (2.3 mL, 1.6 M in hexanes, 3.69 mmol) to a solution of freshly distilled *i*-Pr_2NH (373 mg, 3.69 mmol) in THF (6 mL) at 0 °C] at –78 °C. After 30 min stirring at –78 °C, MoOPH (1.6 g, 3.69 mmol) was added in one portion (by solid addition funnel) and the reaction mixture warmed to –40 °C over 15 min. The reaction was stirred at –40 °C for 24 h, then warmed to –20 °C and stirred for a further 3 h. The reaction mixture was quenched by adding sat. aq Na_2SO_3 solution and warmed to rt. The reaction mixture was diluted with Et_2O (50 mL) and H_2O (25 mL). The layers were separated and the aq layer extracted with Et_2O (3x50 mL). The combined organic layers were washed with sat. aq $CuSO_4$ (25 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (5–30% EtOAc in petrol) to give a 2:1 mixture of diastereomers of hydroxyacetonide **147** (624 mg, 61%) as a colourless oil; $R_f = 0.32$ and 0.25 (30% EtOAc in petrol); $[\alpha]_D^{25} = -5.2$ (*c* 0.11, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3453 br, 2990 m, 2952 s, 2858 m, 1751 s, 1093 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.36–7.28 (5H, m, ArCH), 4.81 (2H, d, *J* 6.0, $CH_2=C$), 4.59 (1H, s, OH), 4.51 (2H, s, CH_2Ph), 3.81 (3H, s, CO_2Me), 3.69 (3H, s, CO_2Me), 3.56 (2H, t, *J* 7.0, CH_2OBn), 2.35 (2H, t, *J* 7.0, CH_2CH_2OBn), 2.24–2.03 (3H, m, CH_2, 1H of CH_2), 1.84 (1H, td, *J* 14.0, *J* 7.0, 1H of CH_2CCO_2Me), 1.60 (3H, s, CH_3C), 1.57 (3H, s, CH_3C); ^{13}C NMR

(125 MHz; $CDCl_3$) δ 171.6 (*C*O_2Me), 170.3 (*C*O_2Me), 145.7 (CH_2=*C*), 138.6 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 113.7 (*C*H_2=C), 110.9 (*C*(CH_3)$_2$), 101.9 (HO–*C*–CO_2Me), 91.0 (*C*CO_2Me), 73.1 (*C*H_2Ph), 68.9 (*C*H_2OBn), 54.1 (CO_2*Me*), 52.6 (CO_2*Me*), 36.4 (*C*$H_2$$CH_2$OBn), 34.0 ($CCH_2$*C*$H_2$C=O), 30.9 (C*Me*), 29.3 (C*Me*), 27.5 (C*C*$H_2$$CH_2$C=O); HRMS *m/z* ($M+Na^+$) found 445.1825, $C_{22}H_{30}NaO_8$ requires 445.1833.

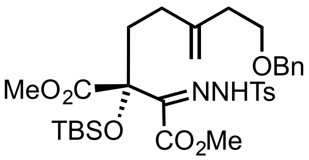
(*R*)-Dimethyl 2-{5-(benzyloxy)-3-methylenepentyl}-2-{(*tert*-butyldimethylsilyl)oxy}-3-oxosuccinate (148)



A mixture of hydroxyacetonide **147** (537 mg, 1.27 mmol) and H_2SO_4 (100 mL, 0.1 M in MeOH) was stirred at rt for 48 h. Pyridine (1.0 mL, 12.7 mmol) was then added dropwise, the mixture was concentrated under reduced pressure and the residue diluted with Et_2O (200 mL) and filtered through a pad of Na_2SO_4. The filtrate was concentrated under reduced pressure to give crude hydroxyketone as a yellow oil, which was used in the next step without further purification. DMAP (15.5 mg, 0.13 mmol) was added to the above crude hydroxyketone, followed by a solution of 2,6-lutidine (0.44 mL, 3.82 mmol) in CH_2Cl_2 (3 mL). Finally, TBSOTf (0.87 mL, 3.81 mmol) was added. After 24 h at rt, H_2O (10 mL) was added and the aq layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% EtOAc in petrol) to give unsaturated ketone **148** (411 mg, 68%) as colourless oil; R_f = 0.43 (10% EtOAc in petrol); $[\alpha]_D^{25} = -2.6$ (*c* 0.30, $CHCl_3$);

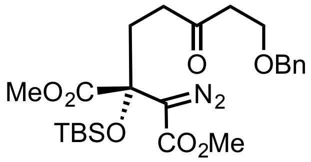
IR (film, υ_{max} cm^{-1}) 3465 br, 2954 s, 2929 s, 2857 m, 1744 s, 1452 m, 1256 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 7.36–7.28 (5H, m, ArCH), 4.82 (2H, s, CH$_2$=C), 4.52 (2H, s, C*H*$_2$Ph), 3.84 (3H, s, CO$_2$Me), 3.76 (3H, s, CO$_2$Me), 3.57 (2H, t, *J* 7.0, C*H*$_2$OBn), 2.35 (2H, t, *J* 7.0, C*H*$_2$CH$_2$OBn), 2.27–2.20 (1H, m, 1 H of CH$_2$C*H*$_2$C=C), 2.19–1.98 (3H, m, 1 H of CH$_2$C*H*$_2$C=C and C*H*$_2$CH$_2$C=C), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.17 (3H, s, SiCH$_3$), 0.17 (3H, s, SiCH$_3$); ^{13}C NMR (125 MHz; CDCl$_3$) δ 190.1 (C=O), 169.8 (*C*O$_2$Me), 162.7 (*C*O$_2$Me), 145.5 (CH$_2$=*C*), 138.5 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 111.3 (*C*H$_2$=C), 83.8 (*C*CO$_2$Me), 73.1 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 53.6 (CO$_2$*Me*), 52.9 (CO$_2$*Me*), 36.4 (*C*H$_2$CH$_2$OBn), 34.9 (CCH$_2$*C*H$_2$C=O), 29.8 (*C*(CH$_3$)$_3$), 25.9 (C(*C*H$_3$)$_3$), 18.9 (C*C*H$_2$CH$_2$C=O), –3.0 (SiCH$_3$), –3.3 (SiCH$_3$); HRMS *m/z* (M+Na$^+$) found 501.2228, C$_{25}$H$_{38}$SiNaO$_7$ requires 501.2279.

(*R*)-Dimethyl 2-{5-(benzyloxy)-3-methylenepentyl}-2-{(*tert*-butyldimethylsilyl)oxy}-3-(2-tosylhydrazono)succinate (149)



A mixture of unsaturated ketone **148** (3.2 g, 6.69 mmol) and TsNHNH$_2$ (1.87 g, 10.0 mmol) in THF (70 mL) was heated at 75 °C under reflux. After 24 h the mixture was concentrated under reduced pressure and purified by column chromatography (20% EtOAc in petrol) to give hydrazone **149** (3.48 g, 81%, 85% brsm) as a colourless glass; R_f = 0.45 (20% EtOAc in petrol); $[\alpha]_D^{25} = -6.8$ (*c* 0.51, CHCl$_3$); IR (film, υ_{max} cm^{-1}) 3215 br, 2952 m, 2929 m, 2856 s, 2360 m, 1757 s, 1702 s, 1170 s, 1086 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 11.63 (1H, s, NH), 7.84 (2H, d, *J* 8.0, 2xArCH), 7.34 (4H, m, 4xArCH), 7.32−7.28 (3H, m, 3xArCH), 4.84 (1H, s, 1H of CH_2=C), 4.80 (1H, s, 1H of CH_2=C), 4.54 (2H, s, C*H*$_2$Ph), 3.75 (3H, s, CO_2Me), 3.64 (3H, s, CO_2Me), 3.59 (2H, t, *J* 7.0, C*H*$_2$OBn), 2.40 (3H, s, *C*H_3Ar), 2.34 (2H, t, *J* 7.0, C*H*$_2$$CH_2$OBn), 2.05−1.97 (3H, m, C*H*$_2$$CH_2$C=C and 1H CH_2C*H*$_2$C=C), 1.93–1.86 (1H, m, 1 H of CH_2C*H*$_2$C=C), 0.79 (9H, s, SiC(CH_3)$_3$), −0.10 (3H, s, SiCH_3), −0.24 (3H, s, SiCH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 172.3 (*C*O_2Me), 161.8 (*C*O_2Me), 146.0 (CH_2=*C*), 144.8 (ArC), 138.6 (ArC), 136.9 (Ar*C*Me), 135.3 (N=*C*CO_2Me), 129.8 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 110.5 (*C*H_2=C), 80.2 (*C*CO_2Me), 73.1 (*C*H_2Ph), 69.0 (*C*H_2OBn), 52.5 (CO_2*Me*), 52.3 (CO_2*Me*), 36.7 (*C*$H_2$$CH_2$OBn), 35.6 (C$CH_2$*C*$H_2$C=O), 30.2 (*C*($CH_3$)$_3$), 25.7 (C(*C*$H_3$)$_3$), 21.7 (Ar*CH$_3$*), 18.5 (C*C*$H_2$$CH_2$C=O), –3.1 (Si$CH_3$), –3.2 (Si$CH_3$); HRMS *m/z* (M+Na$^+$) found 669.2642, $C_{32}H_{46}N_2NaO_8SSi$ requires 669.2642.

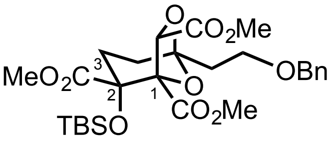
(*R*)-Dimethyl 2-{5-(benzyloxy)-3-oxopentyl}-2-{(*tert*-butyldimethylsilyl)oxy}-3-diazosuccinate (150)



Following the general procedure **B** using hydrazone **149** (110 mg, 0.17 mmol) in CH_2Cl_2 (20 mL) and Et_3N (0.1 mL, 0.68 mmol) gave diazoketone **150** (67 mg, 80%) as a bright yellow oil; R_f = 0.54 (50% Et_2O in petrol); $[\alpha]_D^{25}$ = +1.4 (*c* 0.50, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 2954 m, 2857 m, 2360 s, 2341 m, 2098 s, 1748 m, 1710 s, 1135 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.36–7.30 (5H, m, ArCH), 4.50 (2H, s, C*H*$_2$Ph), 3.74–3.72 (8H, m, 2xCO_2Me, C*H*$_2$OBn), 2.70 (2H, t, *J* 6.0, C*H*$_2$$CH_2$OBn), 2.76–2.61 (1H, m, 1H of CC*H*$_2$$CH_2$C=O), 2.52–2.46 (1H, m, 1H of CC*H*$_2$$CH_2$C=O), 2.27–2.23 (2H, m, CCH_2C*H*$_2$C=O), 0.87 (9H, s, SiCCH_3), 0.10 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3); ^{13}C

NMR (125 MHz; $CDCl_3$) δ 207.7 (C=O), 171.3 (*C*O_2Me), 165.2 (N_2C*C*O_2Me), 138.2 (ArC), 128.5 (ArCH), 127.83 (ArCH), 127.82 (ArCH), 75.4 (TBSO-*C*-CO_2Me), 73.4 (*C*H_2Ph), 65.4 (*C*H_2OBn), 52.9 (CO_2*Me*), 52.1 (CO_2*Me*), 43.2 (*C*H_2CH_2OBn), 37.8 (CCH_2*C*H_2C=O), 32.1 (*C*$(CH_3)_3$), 25.8 (C(*C*$H_3)_3$), 18.6 (C*C*H_2CH_2C=O), –3.5 ($SiCH_3$), –3.9 (Si CH_3); HRMS *m/z* ($M+Na^+$) found 515.2185, $C_{24}H_{36}N_2NaO_7Si$ requires 515.2184.

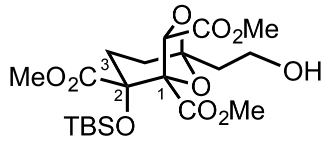
Trimethyl-(*1S,2R,5R,7S*)- 5-(2-(benzyloxy)ethyl)-2-{(*tert*-butyldimethylsilyl)oxy}-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate (151)



$Rh_2(OAc)_4$ (~2 mg, cat.) was added to a stirred solution of diazoketone **150** (100 mg, 0.20 mmol) and freshly distilled methyl glyoxylate[87] (77 mg, 0.87 mmol) in toluene (0.8 mL) and heated to 110 °C. After 1 h, the reaction mixture was allowed to cool to rt, diluted with Et_2O (10 mL), filtered through Celite and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in petrol) gave the major cycloadduct **151** (81 mg, 73%) as colourless oil; $R_f = 0.47$ (50% Et_2O in petrol); $[\alpha]_D^{25} = +36.5$ (*c* 0.21, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 2952 s, 2855 s, 1753 s, 1436 s, 1258 m, 1093 s, 831 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.35–7.26 (5H, m, ArCH), 5.59 (1H, s, C*H*CO_2Me), 4.51 (2H, d, *J* 6.0, C*H*$_2$Ph), 3.82 (3H, s, CO_2Me), 3.77 (2H, ddd, *J* 10.0, *J* 10.0, *J* 5.5, C*H*$_2$OBn), 3.70 (3H, s, CO_2Me), 3.66 (3H, s, CO_2Me), 2.39 (1H, ddd, *J* 14.0, *J* 13.0, *J* 6.0, $1H_{endo}$ of $C^{(3)}H_2$), 2.30 (2H, t, *J* 7.0, C*H*$_2CH_2$OBn), 2.01 (1H, td, *J* 13.0, *J* 6.0, 1H of $C^{(4)}H_2$), 1.81–1.75 (2H, m, $1H_{exo}$ of $C^{(3)}H_2$, 1H of $C^{(4)}H_2$), 0.89 (9H, s, SiC(C*H*$_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$); *NOE experiment:* irradiation at δ 5.59 (C*H*CO_2Me) saw enhancement at δ

2.39 ($1H_{endo}$ of $C^{(3)}H_2$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 173.3 (*C*O_2Me), 169.6 (*C*O_2Me), 166.8 (*C*O_2Me), 138.5 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 111.2 (O–$C^{(5)}$–O), 90.4 ($C^{(1)}CO_2Me$), 77.4 (*C*HCO_2Me) 77.2 ($C^{(2)}CO_2Me$), 73.2 (*C*H_2Ph), 65.9 (*C*H_2OBn), 52.7 (CO_2*Me*), 52.54 (CO_2*Me*), 52.52 (CO_2*Me*), 37.5 (*C*H_2CH_2OBn), 30.0 ($C^{(4)}H_2$), 29.8 ($C^{(3)}H_2$), 26.0 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$), –2.7 ($SiCH_3$), –2.9 ($SiCH_3$); HRMS *m/z* ($M+Na^+$) found 575.2286, $C_{27}H_{40}NaO_{10}Si$ requires 575.2283.

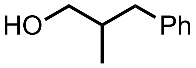
Trimethyl (*1S,2R,5R,7S*)-2-{(*tert*-butyldimethylsilyl)oxy}-5-(2-hydroxyethyl)-6,8-dioxabicyclo [3.2.1]octane-1,2,7-tricarboxylate (152)



To a solution of cycloadduct **151** (87 mg, 0.16 mmol) in MeOH (14 mL) was added a spatula tip of 10% Pd/C. The reaction mixture was stirred overnight under H_2 (balloon) at rt. The reaction mixture was then filtered through a pad of Celite (under N_2), evaporated under reduced pressure and the residue purified by column chromatography (80% Et_2O in petrol) to give alcohol **152** (71 mg, 98%) as a white solid; R_f = 0.20 (80% Et_2O in petrol); m.p. 111–113 °C; $[\alpha]_D^{25}$ = +26.9 (*c* 0.0013, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3528 br, 2954 w, 2928 w, 2854 w, 1753 s, 1726 s, 1438 w, 1262 s, 1096 s; ^1H NMR (500 MHz; $CDCl_3$) δ 5.69 (1H, s, C*H*CO_2Me), 4.01–3.97 (1H, m, 1H of C*H*$_2$OH), 3.88–3.85 (1H, m, 1H of C*H*$_2$OH), 3.84 (3H, s, CO_2Me), 3.73 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.57 (1H, t, *J* 7.0, CH_2O*H*), 2.35 (1H, ddd, *J* 14.0, *J* 13.0, *J* 6.0, $1H_{endo}$ of $C^{(3)}H_2$), 2.16–2.13 (2H, m, C*H*$_2CH_2OH$), 1.94 (1H, td, *J* 13.5, *J* 6.0, 1H of $C^{(4)}H_2$), 1.83–1.72 (2H, m, $1H_{exo}$ of $C^{(3)}H_2$, 1H of $C^{(4)}H_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.14 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$); ^{13}C NMR (125

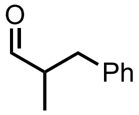
MHz; $CDCl_3$) δ 173.3 (CO_2Me), 170.3 (CO_2Me), 166.6 (CO_2Me), 112.1 (O–$C^{(5)}$–O), 90.0 ($C^{(1)}CO_2Me$), 77.6 ($CHCO_2Me$), 57.3 (CH_2OH), 52.9 (CO_2Me), 52.8 (CO_2Me), 52.6 (CO_2Me), 38.8 (CH_2CH_2OH), 30.8 ($C^{(4)}H_2$), 29.7 ($C^{(3)}H_2$), 25.9 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$), –2.6 ($SiCH_3$), –2.9 ($SiCH_3$); HRMS *m/z* ($M+Na^+$) found 485.1813, $C_{20}H_{34}NaO_{10}Si$ requires 485.1813.

2-Methyl-3-phenylpropan-1-ol (161)[38]



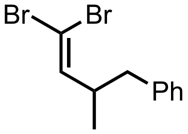
$LiAlH_4$ (1.95 g, 51.4 mmol) was cooled to 0 °C and THF (68 mL) were added slowly over 5 min. (*E*)-2-Methyl-3-phenylpropenal (**160**) (4.78 mL, 34.2 mmol) in THF (15 mL) was then added dropwise. After 30 min the reaction mixture was warmed to rt and then stirred at 50 °C for 24 h. The mixture was then quenched with sat. aq NH_4Cl (80 mL), extracted with EtOAc (3×25 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (30% EtOAc in petrol) to give 2-methyl-3-phenylpropan-1-ol (**161**) (4.90 g, 95%) as a colourless oil, $R_f = 0.34$ (30% EtOAc in petrol); ^1H NMR (200 MHz; $CDCl_3$) δ 7.40–7.14 (5H, m, ArH), 3.42–3.62 (2H, m, CH_2OH), 2.77 (1H, dd, *J* 13.5, 6.5, 1H of CH_2Ph), 2.43 (1H, dd, *J* 13.5, 8.0, 1 H of CH_2Ph), 1.91–2.01 (1H, m, $CHCH_3$), 0.93 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 140.7 (ArC), 129.6 (ArCH) 128.7 (ArCH), 126.3 (ArCH), 68.1 (CH_2OH), 40.2 (CH_2Ph), 38.3 ($CHCH_3$), 16.9 (CH_3).

2-Methyl-3-phenylpropanal (162)[38]



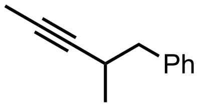
To a solution of PCC (4.31 g, 20 mmol) in CH_2Cl_2 (30 mL) with 3 Å MS (8.0 g) was added 2-methyl-3-phenyl-1-propanol (**161**) (2.00 g, 13.3 mmol) in CH_2Cl_2 (30 mL). After 2 h, Et_2O (100 mL) was added and supernatant was decanted from the black slurry. The insoluble residue was washed with Et_2O (3x25 mL). The combined organic layers were passed through a short pad of Florisil® and evaporated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in petrol) to give 2-methyl-3-phenylpropanal (**162**) (1.61 g, 82%) as a colourless oil, R_f = 0.39 (5% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3080 s, 3067 s, 3026 m, 1716 s, 1452 s, 1373 m, 1160 m; ^{1}H NMR (200 MHz; $CDCl_3$) δ 9.73 (1H, d, *J* 1.5, CHO), 7.38–7.12 (5H, m, ArH), 3.16–3.06 (1H, m, $CHCH_3$), 2.54–2.77 (2H, m, CH_2Ph), 1.10 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 204.8 (CHO), 140.7 (ArC), 129.6 (ArCH) 128.7 (ArCH), 126.3 (ArCH), 48.2 (CH_2Ph), 37.1 ($CHCH_3$), 13.6 (CH_3).

(4,4-Dibromo-2-methylbut-3-en-1-yl)benzene (163)[38]



A solution of CBr_4 (10.7 g, 32.3 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and a solution of PPh_3 (16.9 g, 64.6 mmol) in CH_2Cl_2 (25 mL) was then added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 10 min before a solution of 2-methyl-3-phenylpropanal (**162**) (2.39 g, 16.0 mmol) in CH_2Cl_2 (35 mL) was added over 10 min. After 1 h at 0 °C, H_2O (100 mL) was added and the aq layer extracted with CH_2Cl_2 (2x100 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. To the residue was added CH_2Cl_2 (10 mL) and silica (~5 g) and the resulting residue was purified by column chromatography (Petrol) to give (4,4-dibromo-2-methylbut-3-enyl)benzene (**163**) (4.44 g, 91%) as a colourless oil, $R_f = 0.54$ (Petrol); IR (film, υ_{max} cm^{-1}) 3085 w, 3062 m, 3026 s, 2963 s, 2926 s, 2869 m, 1944 w, 1614 m, 1495 s, 1374 m, 1089 m; ^1H NMR (200 MHz; $CDCl_3$) δ 7.38–7.12 (5H, m, ArH), 6.27 (1H, d, *J* 8.0, $CHCBr_2$), 2.79–2.71 (2H, m, CH_2Ph), 2.60–2.56 (1H, m, $CHCH_3$), 1.02 (3H, d, *J* 6.5, CH_3); ^{13}C NMR (50 MHz; $CDCl_3$) δ 143.0 (*C*H=C), 139.7 (ArC), 129.6 (ArCH) 128.8 (ArCH), 126.7 (ArCH), 88.1 (CH=CBr_2), 42.3 (CH_2Ph), 40.4 (*C*HCH_3), 18.9 (CH_3); HRMS *m/z* (M^+) found 301.9309, $C_{11}H_{14}{}^{79}Br_2$ requires 301.9306.

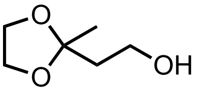
(2-Methylpent-3-yn-1-yl)benzene (164)[38]



To a solution of dibromoalkene (**163**) (4.14 g, 13.6 mmol) in THF (40 mL) was added *n*-BuLi (12.5 mL, 2.5 M in hexanes, 31.3 mmol) at –78 °C. The resulting mixture was warmed to rt and allowed to stir for 30 min. MeI (2.54 mL, 40.8 mmol) was then added and the mixture was allowed to stir at rt for 1 h. The mixture was quenched with sat. aq NH_4Cl (40 mL) and the aq layer was extracted with Et_2O (3x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue by purified by column chromatography (Petrol) to give alkyne **164** (2.05 g, 95%) as a colourless oil, $R_f = 0.22$ (Petrol); IR (film, υ_{max} cm^{-1}) 3028 m, 2968 s, 2919 s, 2360 m, 1726 m, 1603 m, 1495 s, 1086 s; ^1H NMR (200 MHz; $CDCl_3$) δ 7.37–7.20 (5H, m, ArH), 2.91–2.80 (2H, m, CH_2Ph), 2.73–2.62 (2H, m, $CHCH_3$ and 1H of CH_3), 1.80 (3H, d, *J* 4.0, $CH_3C\equiv C$), 1.15 (3H, d, *J* 6.5, CH_3);

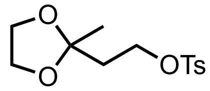
^{13}C NMR (50 MHz; $CDCl_3$) δ 140.4 (ArC), 129.7 (ArCH) 128.6 (ArCH), 126.6 (ArCH), 83.9 (*C*≡CCH_3), 76.8 (C≡*C*CH_3), 43.9 (*C*H_2Ph), 28.4 (*C*HCH_3), 21.3 (CH_3), 3.98 (*C*H_3C≡C); HRMS *m/z* (M+Na^+) found 181.0982, $C_{12}H_{14}Na$ requires 181.0988.

2-(2-Methyl-1,3-dioxolan-2-yl)ethan-1-ol (166)[48]



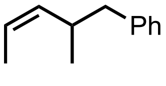
A solution of 4-hydroxybutan-2-one (**165**) (2.00 g, 22.7 mmol) in EtOAc (30 mL) was added D-tartaric acid (0.018 g, 0.118 mmol) and $MgSO_4$ (0.765g 6.36 mmol). Ethylene glycol (2.15 mL, 38.6 mmol) was then added over 10 min. The reaction flask was then equipped with a Dean-Stark, with a small amount of $MgSO_4$ (0.5 g) placed at the bottom of the Dean-Stark. The mixture was then allowed to reflux for 16 h before cooling to rt and neutralising with $NaHCO_3$ (0.076 g, 0.91 mmol), with further stirring at rt for 30 min. The reaction was filtered and the filter cake washed with EtOAc (3x10 mL). The combined organic layers were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with sat. aq $NaHCO_3$ (5 mL). The aq layer was back-extracted with CH_2Cl_2 (3x10 mL), and the combined organic layers dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue distilled by Kugelrohr (b.p. 140 °C at 20 mbar) to give 2-(2-methyl-1,3-dioxolan-2-yl)ethan-1-ol (**166**) (1.34 g, 40%) as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.00 (4H, m, OC*H*$_2$-C*H*$_2$O), 3.75 (2H, t, *J* 8.0, C*H*$_2$OH), 3.73 (1H, s, OH), 1.95 (2H, t, *J* 8.0, C*H*$_2$$CH_2OH$), 1.36 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 110.5 (*C*CO_2), 64.6 (O*C*H_2-CH_2O), 59.0 (*C*H_2OH), 40.3 (*C*H_2CH_2OH), 23.9 (CH_3).

2-(2-Methyl-1,3-dioxolan-2-yl)ethyl 4-methylbenzenesulfonate (167)[49]



2-(2-Methyl-1,3-dioxolan-2-yl)ethan-1-ol (**166**) (1.172 g, 8.87 mmol) was added to a mixture of pyridine (2.73 mL, 0.034 mmol) and Et_3N (0.79 mL, 0.0057 mmol) at 0 °C. TsCl (1.97 g, 10.3 mmol) was then added to the reaction mixture. After 2 h, ice-water (50 mL) and CH_2Cl_2 (50 mL) was added and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give 2-(2-methyl-1,3-dioxolan-2-yl)ethyl 4-methylbenzenesulfonate (**167**) (1.70 g, 67%) as a yellow oil, R_f = 0.30 (20% EtOAc in petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.80 (2H, d, *J* 8.0, 2xArCH), 7.35 (2H, d, *J* 8.0, 2xArCH), 4.15 (2H, t, *J* 8.0, CH_2OTs), 3.97–3.80 (4H, m, OCH_2-CH_2O), 2.46 (3H, s, $ArCH_3$), 2.05 (2H, t, *J* 8.0, CH_2CH_2OTs), 1.29 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 144.7 (ArC), 133.2 ($ArCCH_3$), 129.8 (2xArCH), 127.9 (2xArCH), 108.5 (CH_3CCH_2), 66.6 (OCH_2-CH_2O), 64.7 (OCH_2-CH_2O), 37.9 ($CH_3CCH_2CH_2$), 26.8 (CH_3CCH_2), 24.3 (CH_3), 21.7 ($ArCH_3$).

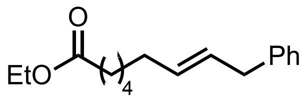
(*Z*)-(2-Methylpent-3-en-1-yl)benzene (173)



In air, Cp_2ZrHCl[51] (150 mg, 0.78 mmol) was added to a vial that was evacuated and refilled with argon x3. THF (1 mL) and then (2-methylpent-3-yn-1-yl)benzene **164** (92 mg, 0.58 mmol) were added. The mixture was allowed to stir at 50 °C for 1 h, then diluted with NMP (1 mL) and transferred to a vial containing $Pd(acac)_2$ (2.2 mg, 0.0073 mmol) and LiBr (40 mg, 0.58 mmol). Finally, ethyl-6-bromohexanoate **175**

(51.8 μL, 0.29 mmol) was added and the vial purged with argon. The reaction mixture was heated at 55 °C for 24 h. The mixture was passed through a short pad of silica (Et_2O), the filtrate was concentrated under reduced pressure and the residue purified by column chromatography (2% Et_2O in petrol) to give (*Z*)-(2-methylpent-3-en-1-yl)benzene (**173**)[46, 157] (85 mg, 91%) as a colourless oil, R_f = 0.82 (2% Et_2O in petrol); IR (film, υ_{max} cm^{-1}); 3027 w, 2958 w, 2924 w, 2869 w, 1452 s, 698 s; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.9–7.14 (5H, m, Ar*H*), 5.41–5.32 (1H, m, $CH_3HC{=}C$*H*), 5.27–5.20 (1H, m, CH_3*H*C=CH), 2.56 (2H, d, *J* 8.0, *CH*$_2$Ph), 1.45 (3H, dd, *J* 7.5, *J* 2.0, *CH*$_3$HC=CH), 0.98 (3H, d, *J* 7.0, $PhCH_2CH$*CH*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 141.0 (ArC), 136.1 ($CH_3HC{=}$*C*H), 129.2 (ArCH), 128.0 (ArCH), 125.6 (ArCH), 122.8 (CH_3H*C*=CH), 43.7 (*C*H_2Ph), 33.4 (*C*HCH_2Ph), 20.6 (*C*H_3CHCH_2Ph), 12.8 (*C*H_3HC=CH); HRMS *m/z* (M^+) found 160.1254, $C_{12}H_{16}$ requires 160.1252.

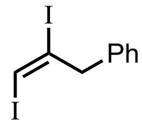
Ethyl (*E*)-6-phenylhex-4-enoate (177)[46]



In a glove-box, Cp_2ZrHCl[51] (200 mg, 0.78 mmol) was added to a vial in THF (1 mL). 3-Phenyl-1-propyne (**174**) (96.5 μL, 0.78 mmol) was then added. The mixture was allowed to stir at rt for 1 h, then diluted with NMP (1 mL) and transferred to a vial containing $Pd(acac)_2$ (3 mg, 0.0097 mmol) and LiBr (53 mg, 0.78 mmol). Finally, ethyl 6-bromohexanoate **176** (69 μL, 0.39 mmol) was added. The reaction mixture was heated in the dark at 55 °C for 24 h, then allowed to cool to rt, removed from glove-box and passed through a short pad of silica (Et_2O). The filtrate was evaporated under reduced pressure and residue purified by column chromatography (2% Et_2O in petrol) to give ethyl (*E*)-6-phenylhex-4-enoate **177** (67 mg, 79%) as colourless oil, R_f

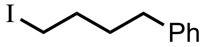
= 0.34 (2% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.32–7.17 (5H, m, ArH), 5.63–5.44 (2H, m, *H*C=C*H*), 4.13 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.3 (2H, d, *J* 6.5, C*H*$_2$Ar), 2.29 (2H, t, *J* 4.0, COC*H*$_2$), 2.04 (2H, q, *J* 7.0, C*H*$_2$C=C), 1.69–1.54 (2H, m, C*H*$_2$), 1.43–1.31 (4H, m, C*H*$_2$), 1.26 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.8 (*C*O$_2$Et), 141.0 (ArC), 131.7 (HC=*C*H), 128.9 (H*C*=CH), 128.4 (ArCH), 128.3 (ArCH), 136.3 (ArCH), 60.2 (CO$_2$*C*H$_2$CH$_3$), 39.0 (*C*H$_2$Ph), 34.3 (C=O*C*H$_2$), 32.3 (*C*H$_2$C=C), 29.1 (CH$_2$), 28.7 (CH$_2$), 24.8 (CH$_2$), 14.3 (CO$_2$CH$_2$*C*H$_3$).

(*E*)-(2,3-Diiodoallyl)benzene (179)



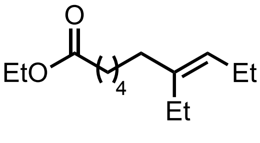
To a mixture of prop-2-yn-1-ylbenzene (**174**) (50.0 μL, 0.40 mmol) in THF (1 mL) was added iodine (203 mg, 0.80 mmol) in THF (0.5 mL) at –20 °C. The mixture was warmed to rt and left to stir for 1 h before it was poured into sat. aq $NaHCO_3$ (10 mL) and the aq layer was extracted with Et_2O (3x30 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give di-iodoallyl benzene **179** (64 mg, 43%) as red oil, R_f = 0.72 (petrol); IR (film, υ_{max} cm^{-1}) 3065 w, 3027 w, 2970 w, 1739 s, 1217 s, 697 s; ^1H NMR (400 MHz; $CDCl_3$) δ 7.39–7.26 (5H, m, ArCH), 7.03 (1H, s, CHI), 3.95 (2H, s, CH$_2$Ph); ^{13}C NMR (100 MHz; $CDCl_3$) δ 136.5 (ArC), 128.9 (ArCH), 128.6 (ArCH), 127.2 (ArCH), 102.7 (IC=*C*ICH$_2$), 80.5 (CI*C*=CICH$_2$), 50.6 (CH$_2$Ph); HRMS *m/z* (M+Na$^+$) found 370.8768, $C_9H_9{}^{127}I_2Na$ requires 370.8788.

(4-Iodobutyl)benzene (183)



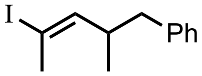
To a mixture of Cp_2ZrHCl[51] (150 mg, 0.58 mmol) in THF (1 mL) and shielded from light was added but-3-en-1-ylbenzene **(181)** (58.3 µL, 0.39 mmol), and stirred at rt for 1 h. The reaction mixture was then cooled to –20 °C and a solution of I_2 (170 mg, 0.78 mmol) in THF (0.5 mL) were added dropwise. The reaction was warmed to rt and stirred for 30 min and then poured into sat. aq $NaHCO_3$ (10 mL). The aq layer was extracted with Et_2O (3x30 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (Petrol) to give saturated iodide (**183**)[158] (68 mg, 67%) as colourless oil R_f = 0.78 (Petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.33–7.17 (5H, m, ArCH), 3.21 (2H, t, *J* 7, CH_2I), 2.65 (2H, t, *J* 7.5 CH_2Ph), 1.86 (2H, q, *J* 8.0, *J* 7.0, $\mathit{CH_2}CH_2I$), 1.76 (2H, q, *J* 7.0, *J* 7.0, $PhCH_2\mathit{CH_2}$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 141.9 (ArC), 128.5 (ArCH), 128.4 (ArCH), 126.0 (ArCH), 34.7 ($Ph\mathit{CH_2}$), 32.9 ($PhCH_2\mathit{CH_2}$), 32.2 ($\mathit{C}H_2CH_2I$), 6.75 ($\mathit{C}H_2I$).

Ethyl 7-ethyl-7-*E*-decenoate (188)[46]



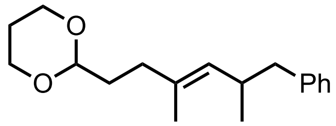
In air, Cp_2ZrHCl[51] (150 mg, 0.58 mmol) was added to a vial that was evacuated and refilled with argon x3. THF (1 mL) and then hex-3-yne **186** (66.1 µL, 0.58 mmol) were added. The mixture was allowed to stir at rt for 1 h, then diluted with NMP (1 mL) and transferred to a vial containing, $Pd(acac)_2$ (2 mg, $0.0073x10^{-3}$ mmol) and LiBr (40 mg, 0.78 mmol). Finally, ethyl 6-bromohexanoate **176** (51.8 µL, 0.29 mmol) was added and the vial purged with argon. The reaction mixture was heated in the dark at 55 °C for 24 h, then allowed to cool to rt, and passed through a short pad of silica (Et_2O). The filtrate was evaporated under reduced pressure and purified by column chromatography (2% Et_2O in petrol) to give ethyl 7-ethyl-7-*E*-decenoate **188** (28 mg, 52%) as colourless oil, $R_f = 0.62$ (2% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 5.07 (1H, t, *J* 7.0, Et*C*=*CH*Et), 4.13 (2H, q, *J* 7.0, $COCH_2CH_3$), 3.30 (2H, d, *J* 8.0, CH_2CO_2Et), 2.06–1.92 (6H, m, CH_2), 1.68–1.56 (2H, m, CH_2), 1.40–1.20 (7H, m, CH_2), 0.94 (6H, t, *J* 8.0, $(CH_3)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.8 (CO_2Et), 140.2 (Et*C*=CHEt), 126.0 (EtC=*C*HEt), 60.2 (CH_2O), 36.8 (CH_2), 34.3 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 24.8 (CH_2), 23.1 ($CH_3CH_2C=CHEt$), 21.0 ($EtC=CHCH_2CH_3$), 14.8 (CH_3), 13.5 (CH_3).

(*E*)-(4-Iodo-2-methylpent-3-en-1-yl)benzene (189)[40]



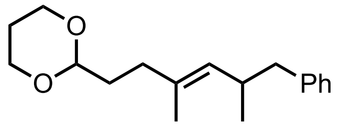
To a solution of Cp_2ZrCl_2 (195 mg, 0.76 mmol) in THF (1.5 mL) cooled to 0 °C was added a solution of $LiEt_3BH$ (0.76 mL, 1.0 M in THF) dropwise. The reaction mixture was shielded from light and left to stir at rt for 1 h, then (2-methylpent-3-yn-1-yl)benzene (**164**) (60 mg, 0.38 mmol) in THF (0.4 mL) was added dropwise. The reaction mixture was stirred at 50 °C for 1 h, and then allowed to reach rt. The mixture was then cooled to –20 °C and a solution of I_2 (192 mg, 0.76 mmol) in THF (0.4 mL) were added dropwise. The reaction was warmed to rt and stirred for 30 min and then poured into sat. aq $NaHCO_3$ (10 mL). The aq layer was extracted with Et_2O (3x30 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give alkenyl iodide (±)–**189** (81 mg, 74%) as colourless oil, R_f = 0.60 (petrol); IR (film, υ_{max} cm^{-1}); 3026 w, 2959 s, 2924 s, 2360 s, 2341 m, 1452 s, 1039 m; ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.35–7.09 (5H, m, ArCH), 6.01 (1H, dq, *J* 10.5, *J* 2.0, CHCI), 2.70–2.58 (1H, m, C*H*CH$_3$), 2.57–2.53 (2H, m, CH$_2$Ph), 2.10 (3H, d, *J* 2.0, CICH$_3$), 1.01 (3H, d, *J* 12.0, CHC*H*$_3$); ^{13}C NMR (100 MHz; CDCl$_3$) δ 146.0 (H*C*=CI), 140.0 (ArC), 129.2 (ArCH), 128.2 (ArCH), 126.1 (ArCH), 93.5 (C=*C*I), 43.2 (*C*H$_2$Ph), 38.1 (*C*HCH$_3$), 27.5 (CI*C*H$_3$), 20.1 (CH*C*H$_3$); HRMS *m/z* (M+Na$^+$) found 309.00109, $C_{12}H_{15}INa$ requires 309.0111.

(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (192) from ZnCl$_2$



To a solution of alkenyl iodide (±)–(**189**) (150 mg, 0.52 mmol) in THF (3 mL) at –78 °C was added dropwise *t*-BuLi (0.58 mL, 1.7 M in hexanes, 1.10 mmol) over 10 min. The reaction mixture was stirred for 30 min and then allowed to warm to 0 °C. A solution of anhydrous ZnCl$_2$ (0.77 mL, 0.7 M in THF, 0.54 mmol) was added and the reaction mixture warmed to rt. The reaction mixture was stirred for further 30 min and the resulting alkenylzinc iodide was directly used in the next step. In a Schlenk flask, Pd$_2$(dba)$_3$ (6 mg, 0.0065 mmol, 2 mol%), [HPCyp$_3$]BF$_4$ (7.4 mg, 0.026 mmol, 8 mol%) and freshly distilled NMP (0.66 mL, 1.6 mL/mmol) were stirred at rt for 5 min. To this reaction mixture was added the previously prepared alkenylzinc iodide and stirred for 5 min. Then NMI (31.4 μL, 0.39 mmol) and 2-(2-bromoethyl)-1,3-dioxane **176** (44.6 μL, 0.33 mmol) were added and the Schlenk flask sealed under argon. The reaction mixture was stirred at 80 °C, then after 12 h cooled to rt, diluted with Et$_2$O (10 mL), passed through a pad of silica, solvent evaporated under reduced pressure and the residue purified by column chromatography (10% Et_2O in petrol) to give alkene **192** (81 mg, 89%) as colourless oil. R_f = 0.52 (10% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 2957 s, 2925 s, 2849 s, 2360 w, 1452 m, 1378 m, 1144 s; ^1H NMR (400 MHz; $CDCl_3$) δ 7.26–7.23 (2H, m, ArCH), 7.17–7.12 (3H, m, ArCH), 4.99 (1H, dd, *J* 9.5, *J* 1.5, CH=C), 4.42 (1H, t, *J* 5.5, O-CH-O), 4.11–4.08 (2H, m, CH_2), 3.75–3.69 (2H, m, CH_2), 2.67–2.60 (1H, m, C*H*CH_3), 2.57–2.49 (2H, m, C*H*$_2$Ph), 2.13–1.98 (3H, m, 1H of CH_2, CH_2), 1.64 (2H, td, *J* 8.0, *J* 5.5, C*H*$_2$CHO), 1.41 (3H, s, CCH_3), 1.35–1.31 (1H, m, 1H of CH_2), 0.95 (3H, d, *J* 7.0, CHC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 141.1 (ArC), 133.2 (CH=*C*), 130.5 (ArCH), 129.2 (ArCH), 127.9 (ArCH), 125.5 (*C*H=C), 102.0 (O-CH-O), 66.8 (2xCH_2-O), 43.9 (*C*H_2Ph), 34.4 (*C*HCH_3), 33.8 (CH_2), 33.5 (CH_2), 25.8 (CH_2), 20.8 (CH*C*H_3), 15.9 (C*C*H_3); HRMS *m/z* (M+Na^+) found 297.1821, $C_{18}H_{26}NaO_2$ requires 297.1825.

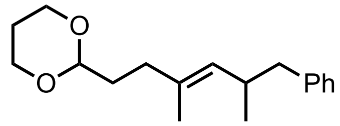
(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (192) from stannane



In a glove-box, either [P(*t*-Bu)$_2$Me]BF_4 (15 mg, 0.061 mmol) or [HPCyp$_3$]BF_4 (21.8 mg, 0.067 mmol) and anhydrous TMAF (71.7 mg, 0.77 mmol) was added to a vial containing a yellow solution of [(π-allyl)PdCl]$_2$ (3.7 mg, 0.010 mmol) in THF (4 mL, 0.10 M). The heterogeneous mixture was stirred for 5 min before alkenylstannane **235** (200 mg, 0.45 mmol), activated powdered 3Å MS (202 mg) and alkyl bromide **191** (78.9 mg, 0.41 mmol) were added. The vial was sealed, removed from the glove-box and the mixture stirred vigorously at rt. After 24 h, aq KF (4 mL, 10%) was added. After 30 min, the aq layer was extracted with Et_2O (3x10 mL), and the combined organic layers were dried ($MgSO_4$), evaporated, evaporated under reduced pressure and the residues purified by column chromatography to give alkene **192** (10–20%) as colourless oil; *R_f* = 0.52 (10% Et_2O in petrol).

Analytical data identical to that previously reported

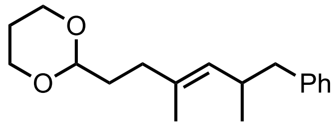
(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (192) from cyanocuprate



To a solution of Cp_2ZrHCl[51] (326 mg, 1.27 mmol) in THF (7.5 mL) was added alkyne **164** (200 mg, 1.27 mmol) and the mixture heated at 50 °C for 1 h. The mixture was then cooled to –78 °C and MeMgCl (0.84 mL, 3 M in THF, 2.53 mmol) added. Simultaneously, a solution of thiophene (0.10 mL, 1.28 mmol) in THF (2.5 mL) was cooled to –20 °C. *n*-BuLi (0.5 ml, 2.5 M in hexanes, 1.24 mmol) was added dropwise and the mixture was allowed to stir for 1 h at –20 °C. The solution was then transferred *via* cannula to a pre-cooled (–78 °C) suspension of CuCN (113 mg, 1.27 mmol) in THF (2.5 mL). The suspension was then warmed to rt to obtain a clear orange solution which was cooled again to –78 °C and transferred *via* cannula to the solution containing the vinyl zirconate. The mixture was warmed to –20 °C and stirred for 30 min, before alkyl bromide/iodide **191/248** (123 mg, 0.63 mmol) or alkyl triflate **247** (167 mg, 0.63 mmol) was added. The reaction was stirred at –20 °C overnight and then warmed to rt for 3 h. The reaction mixture was quenched using 10% NH_4OH in sat. aq NH_4Cl (10 mL). The aq layer was extracted with Et_2O (3x10 mL), and the combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by column chromatography to give, alkenyl iodide **192** (10–15 %) as colourless oil.

Analytical data identical to that previously reported.

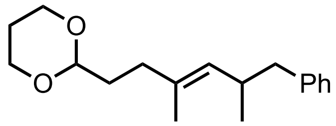
(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (192) from Rieke zinc



Lithium (12 mg, 6.94 mmol, 5 equiv.) cleaned by successive dipping in hexanes, methanol, and ether, was stirred with naphthalene (224 mg, 1.75 mmol) in THF (0.7 ml) using a glass-coated stirring bar and under sonication for 30 min. A solution of $ZnCl_2$ in THF (1.25 ml, 0.7 M in THF, 0.87 mmol) was then added slowly dropwise during a 10 min period, while the reaction mixture was kept at 25 °C (water bath). After stirring at rt for 15 min, the Rieke zinc suspension was diluted with THF (2 mL) and allowed to settle for 2–3 h. The THF solution was removed with a syringe, and then freshly distilled dry THF (0.7 ml) was added. To the stirring suspension of Rieke zinc was added a solution of alkyl iodide **248** (93 mg, 0.38 mmol) in THF (0.5 ml), and stirring was continued at rt until TLC indicated that the alkyl iodide was consumed (~15 min). The solution of the organozinc reagent was then transferred to a mixture of alkenyl iodide **189** (100 mg, 0.35 mmol) and Pd(dppf)Cl_2 (13 mg, 0.017 mmol, 5 mol%) in THF (0.5 ml) at –30 °C. The solution was allowed to stir at rt overnight. The solution was poured into a separatory funnel containing EtOAc (10 ml) and water (10 ml), the aq layer was extracted with EtOAc (3x10 ml), and the combined organic layers were washed with brine (10 ml), dried ($MgSO_4$), evaporated under reduced pressure and the residue purified by column chromatography (10 % Et_2O petrol) to give alkenyl iodide **192** (49 mg, 51%) as colourless oil.

Analytical data identical to that previously reported

(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (192) cross–electrophile coupling



To a Schlenk tube under argon was added Mn dust (38 mg, 0.70 mmol) and $NiI_2(bpy)$[105] (4.1 mg, 0.0087 mmol) and the flask evacuated and refilled with argon (x3). DMPU (1.4 mL) was added and allowed to stir for 2 min. Alkyl iodide **248** (84 mg, 0.35 mmol) and alkenyl iodide **189** (100 mg, 0.35 mmol) were dissolved in DMPU (0.6 mL) and added to the reaction mixture followed by freshly distilled TMSCl (8.9 μL, 0.070 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (5 mL) was then added and the aq layer extracted with Et_2O (3x10 mL). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by column chromatography (10% Et_2O in petrol) to give *E*–alkene **192** (70 mg, 73%) as colourless oil, $R_f = 0.52$ (10% Et_2O in petrol).

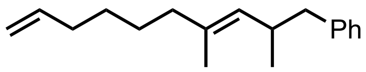
Analytical data identical to that previously reported.

When alkenyl bromide **241** used instead of alkenyl iodide **189**: alkene **192** (72 mg, 75%) was formed as a 16:1 *E:Z* mixture; *E* isomer: ^1H NMR (500 MHz; C_6D_6) δ 4.99 (1H, dd, *J* 9.0, 1.5, CH=C); *Z* isomer: ^1H NMR (500 MHz; C_6D_6) δ 5.02 (1H, d, *J* 4.0, 1.5, CH=C).

When hydroxy isobutyrate **197** (46.3 mg, 0.35 mmol) was used as additive: alkene **192** (29 mg, 30%) was formed as entirely *E*-isomer.

When siloxy isobutyrate **198** (71.5 mg, 0.35 mmol) was used as additive: alkene **192** (61 mg, 64%) was formed as entirely *E*-isomer.

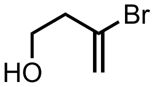
(*E*)-(2,4-Dimethyldeca-3,9-dien-1-yl)benzene (196)



To a solution of alkenyl iodide (±)–**189** (150 mg, 0.52 mmol) in THF (1.3 mL) at –78 °C was added dropwise *t*-BuLi (0.58 mL, 1.9 M in hexanes, 1.10 mmol) over 10 min. The reaction mixture was stirred for 30 min and then allowed to warm to 0 °C. A solution of anhydrous $ZnCl_2$ (0.77 mL, 0.7 M in THF, 0.54 mmol) was added and the reaction mixture was warmed to rt over 10 min. The reaction mixture was stirred for further 30 min and the resulting alkenylzinc iodide was directly used in the next step. In a Schlenk flask, $Pd_2(dba)_3$ (6 mg, 0.0065 mmol, 2 mol%), $[HPCyp_3]BF_4$ (7 mg, 0.026 mmol, 8 mol%) and freshly distilled NMP (0.66 mL, 1.6 mL/mmol) were stirred at rt for 5 min. To this reaction mixture was added the previously prepared alkenylzinc iodide and the reaction mixture stirred for 5 min before NMI (31.4 μL, 0.39 mmol) and 6-chloro-1-hexene **195** (43.3 μL, 0.33 mmol) were added and the Schlenk flask sealed under argon. The reaction mixture was stirred at 80 °C, then after 12 h cooled to rt, diluted with Et_2O (10 mL), passed through a pad of silica, solvent evaporated under reduced pressure and the residue was purified by column chromatography (petrol) to give diene **196** (59 mg, 74%) as colourless oil; $R_f = 0.72$

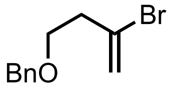
(petrol); IR (film, υ_{max} cm^{-1}) 3027 w, 2926 s, 2855 m, 1640 w, 1603 w, 1495 w, 1452 m, 909 s; ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.26–7.13 (5H, m, ArCH), 5.85–5.77 (1H, m, C*H*=CH$_2$), 5.02–4.93 (3H, m, C*H*=C, CH=C*H$_2$*), 2.68–2.57 (1H, m, C*H*CH$_3$), 2.55–2.51 (2H, m, C*H$_2$*Ph), 2.06–2.02 (2H, m, CH$_2$), 1.94–1.91 (2H, m, CH$_2$), 1.44–1.26 (7H, m, 2xCH$_2$ and CCH$_3$), 0.94 (3H, d, *J* 7.0, CHC*H$_3$*); ^{13}C NMR (100 MHz; CDCl$_3$) δ 141.2 (ArC), 139.1 (*C*H=CH$_2$), 134.1 (CH=*C*), 130.1 (ArCH), 129.2 (ArCH), 127.9 (ArCH), 125.5 (*C*H=C), 114.1 (CH=*C*H$_2$), 44.0 (*C*H$_2$Ph), 39.4 (CH$_2$), 34.5 (CH$_2$), 33.7 (*C*HCH$_3$), 28.4 (CH$_2$), 27.3 (CH$_2$), 20.8 (CH*C*H$_3$), 15.8 (C*C*H$_3$). HRMS *m/z* (M+NH$_4^+$) found 260.2377, $C_{18}H_{30}N$ requires 260.2373.

3-Bromobut-3-en-1-ol (200)



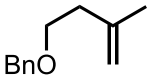
To a 2-necked flask containing H$_2$O (0.3 mL, 16.5 mmol) was added dropwise PBr$_3$ (0.517 mL, 5.50 mmol) to generate HBr gas. The HBr gas generated was bubbled through to another 2-necked flask containing a vigorously stirred solution of Et$_4$N$^+$Br$^-$ (3.15 g, 15.0 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C. The reaction mixture was weighed before and after addition of HBr to find HBr (1.08 g, 13.3 mmol) absorbed. Then 3-butyn-1-ol (**199**) (0.95 mL, 12.5 mmol) was added and the reaction mixture was heated at 40 °C for 5 h. The reaction mixture was then cooled to 0 ºC and diluted with Et$_2$O (30 mL). The resulting suspension was filtered and solvent evaporated under reduced pressure. Distillation under reduced pressure (70 °C at 13 mbar) gave 3-bromo-3-buten-1-ol (**200**)[62] (2-bromo:1-bromo, 96:4 regioisomer as detected by ^{1}H NMR) (1.40 g, 74%,) as a colourless oil. IR (film, υ_{max} cm^{-1}); 3030 br, 2949 w, 2885 w, 1629 s, 1419 m, 1205 m, 1126 s, 888 s; ^{1}H NMR (400 MHz; CDCl$_3$) δ 5.71 (1H, s, C=CH$_2$), 5.54 (1H, d, *J* 1.5, C=CH$_2$), 3.82 (2H, t, *J* 8.0, CH$_2$OH), 2.67 (2H, t, *J* 8.0, C*H$_2$*CH$_2$OH), 1.85 (1H, s, OH); ^{13}C NMR (100 MHz; CDCl$_3$) δ 130.5 (*C*=CH$_2$), 119.4 (C=*C*H$_2$), 60.1 (CH$_2$OH), 44.4 (*C*H$_2$CH$_2$OH); HRMS *m/z* (M+NH$_4^+$) found 168.0024, $C_4H_{11}{}^{79}BrNO$ requires 168.0019.

(((3-Bromobut-3-en-1-yl)oxy)methyl)benzene (201)



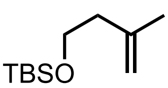
A solution of 3-bromo-3-buten-1-ol (**200**) (5.00 g, 33.1 mmol) in DMF (90 mL) was cooled to –30 °C. To this mixture was added NaH (1.32 g, 33.1 mmol, 60% suspension in mineral oil) portion–wise and then stirred at –30 °C for 1 h. Then BnBr (4.72 mL, 39.7 mmol) and $Bu_4N^+I^-$ (0.122 g, 0.331 mmol) were added and the reaction mixture was stirred for 6 h. The reaction was then quenched with sat. aq NH$_4$Cl (50 mL). The aq layer was extracted with Et$_2$O (3x100 mL), the combined organic layers were washed with sat. aq LiCl (3x10 mL), dried (MgSO$_4$), filtered, solvent evaporated under reduced pressure and the residue purified by flash column chromatography (20% CH$_2$Cl$_2$ in petrol) to give (((3-bromobut-3-en-1-yl)oxy)methyl)benzene (**201**) (5.24 g, 66%) as a yellow oil, R_f = 0.51 (20% CH$_2$Cl$_2$ in petrol); IR (film, υ_{max} cm^{-1}) 3030 w, 2861 w, 1720 s, 1631 m, 1273 s, 1097 s, 890 m; ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.32–7.20 (5H, m, ArCH), 5.69 (1H, q, *J* 1.5, C=CH$_2$), 5.50 (1H, d, *J* 2.0, C=CH$_2$), 4.56 (2H s, CH$_2$Ph), 3.67 (2H, t, *J* 8.0, CH$_2$O), 2.74 (2H, td, *J* 6.5, *J* 1.5, C*H$_2$*CH$_2$O); ^{13}C NMR (100 MHz; CDCl$_3$) δ 138.2 (ArC), 130.7 (*C*=CH$_2$), 128.4 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 118.4 (C=*C*H$_2$), 73.1 (*C*H$_2$Ph), 67.7 (CH$_2$O), 41.7 (*C*H$_2$CH$_2$O); HRMS *m/z* (M$^+$) found 240.0140, $C_{11}H_{13}{}^{79}BrO$ requires 240.0144.

(((3-Methylbut-3-en-1-yl)oxy)methyl)benzene (205)[159]



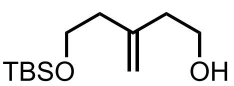
To a solution of NaH (1.58 g, 39.6 mmol, 60% suspension in mineral oil) in THF (80 mL) at 0 °C was added 3-methyl-buten-1-ol **(142)** (2.00 mL, 19.8 mmol) dropwise. Then BnBr (2.35 mL, 19.8 mmol) was added to the mixture. The reaction mixture was warmed to rt and stirred for 12 h. The mixture was then cooled to 0 °C and quenched with sat. aq NH_4Cl (20 mL) and water (20 mL). The aq layer was extracted with EtOAc (2x50 mL), washed with brine (50 mL), dried ($NaSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (Petrol) to give (((3-methylbut-3-en-1-yl)oxy)methyl)benzene **(205)** (2.88 g, 83 %) as pale yellow oil, R_f = 0.72 (Petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39–7.26 (5H, m, ArCH), 4.79 (2H, d, *J* 8.0, C=CH_2), 4.55 (2H, s, CH_2Ph), 3.61 (2H, t, *J* 8.0, CH_2OBn), 2.37 (2H, t, *J* 8.0, C$H_2$$CH_2$OBn), 1.77 (3H, s, CH_3); ^{1}H NMR (100 MHz; $CDCl_3$) δ 143.3 (*C*=CH_2), 139.0 (ArC), 128.8 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 111.9 (C=*C*H_2), 73.4 (*C*H_2Ph), 69.2 (*C*H_2OBn), 38.3 (*C*$H_2$$CH_2$OBn), 23.2 ($CH_3$).

tert-Butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (206)[70]



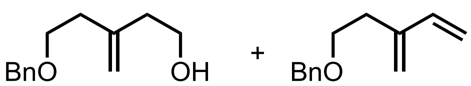
Imidazole (4.41 g, 64.8 mmol) and TBSCl (4.88 g, 32.5 mmol) was dissolved in DMF (25 mL). After 5 min, 3-methyl-buten-1-ol (**142**) (2.00 mL, 19.8 mmol) was added and the mixture was left to stir at rt. After 4 h, H_2O (10 mL) and Et_2O (10 mL) were added and the aq layer was extracted with Et_2O (3x20 mL), washed with HCl (10 mL, 1 M), sat. aq $NaHCO_3$ (10 mL) and H_2O (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue was passed through a short pad of silica then purified by column chromatography (10% Et_2O in petrol) to give *tert*-butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (**206**) (3.87 g, 98%) as colourless oil, $R_f = 0.74$ (10% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 4.70 (1H, m, $C{=}CH_2$), 4.64 (1H, m, $C{=}CH_2$), 3.72 (2H, t, *J* 8.0, CH_2O), 2.25 (2H, t, *J* 8.0, $C\mathit{H}_2CH_2O$), 1.75 (3H, s, CH_3), 0.90 (9H, s, $C(C\mathit{H}_3)_3$), 0.06 (6H, s, $Si(C\mathit{H}_3)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.1 ($\mathit{C}{=}CH_2$), 111.5 ($C{=}\mathit{C}H_2$), 62.2 (CH_2O), 41.2 ($\mathit{C}H_2CH_2O$), 26.0 ($((CH_3)_3)$), 22.9 (CH_3), 18.3 ($Si(C(\mathit{C}H_3)_3)$), –5.28 ($Si(CH_3)_2$).

5-((*tert*-Butyldimethylsilyl)oxy)-3-methylenepentan-1-ol (207)[67]



To a solution of isopentenyl silyl ether **206** (5.0 g, 25.0 mmol) and $(CH_2O)_n$ (0.749 g, 25.0 mmol) in CH_2Cl_2 (125 mL) cooled to 0 °C was slowly added Me_2AlCl (61 mL, 0.9 M in hexanes, 54.9 mmol). The reaction was then warmed to rt and left to stir for 2 h. Then sat. aq NaH_2PO_4 (100 mL) was slowly added followed by Et_2O (200 mL). The dropwise addition of HCl (15 mL, 10%) dissolved the precipitated aluminium. The organic layer was separated by decantation and the aq layer was extracted with Et_2O (3x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and purified by column chromatography (10 % EtOAc in petrol) to give 5-((*tert*-butyldimethylsilyl)oxy)-3-methylenepentan-1-ol (**207**) (4.55 g, 79%) as colourless oil, $R_f = 0.30$ (10 % EtOAc in petrol). ^1H NMR (400 MHz; $CDCl_3$) δ 4.92 (2H, s, $C{=}CH_2$), 3.76 (2H, t, *J* 8.0, $C\mathit{H}_2OH$), 3.73 (2H, t, *J* 4.0, CH_2OSi) 2.33 (2H, t, *J* 8.0, $C\mathit{H}_2CH_2OSi$), 2.28 (2H, t, *J* 8.0, $C\mathit{H}_2CH_2OH$), 0.90 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.7 (*C*=CH_2), 113.7 (C=*C*H_2), 62.4 (CH_2OH), 60.6 (CH_2OSi), 39.7 (*C*H_2CH_2OH), 38.8 (*C*H_2CH_2OSi), 25.9 ($(CH_3)_3$), 18.4 (Si(C(*C*H_3)$_3$)), –5.3 ($Si(CH_3)_2$).

5-(Benzyloxy)-3-methylenepentan-1-ol (144) and **(((3-methylenepent-4-en-1-yl)oxy)methyl)benzene (209)**



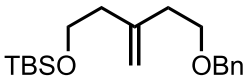
To a solution of TMEDA (2.97 mL, 19.8 mmol) in Et_2O (5 mL) at 0 °C was added *n*-BuLi (7.92 mL, 2.5 M in hexanes, 19.8 mmol) dropwise over 5 min. The reaction mixture was stirred for 15 min before a solution of alcohol **142** (1.00 mL, 9.90 mmol) in Et_2O (3 mL) was added dropwise over 5 min. After 15 min, the mixture was warmed to rt and stirred vigorously for 15 h. The mixture was then diluted with THF (5 mL) and cooled to –78 °C before addition of $BnOCH_2Cl$[69] (1.45 mL, 10.4 mmol). The mixture was warmed to rt and stirred vigorously overnight. To the mixture was then added sat. aq NH_4Cl (10 mL), the aq layer was extracted with $CHCl_3$/*i*-PrOH (3x20 mL, 8:2) and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10-20% EtOAc in petrol) first eluted to give diene **209** (311 mg, 23%), second eluted alcohol **144** (382 mg, 28%) and a mixture of both (266 mg, 19%) all as pale yellow oils.

Alcohol **144:** Analytical data identical to that previously reported.

Diene **209**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.31–7.24 (5H, m, ArCH), 6.32 (1H, dd, *J* 18.0, *J* 11.0, CC*H*=CH_2), 5.18 (1H, d, *J* 18.0, 1H of CCH_2), 5.01 (3H, d, *J* 11.0, 1H of

CCH$_2$ and CHC*H$_2$*), 4.46 (2H, s, C*H$_2$*Ph), 3.57 (2H, t, *J* 7.0, CH$_2$OBn), 2.51 (2H, t, *J* 7.0, C*H$_2$*CH$_2$OBn); ^{13}C NMR (100 MHz; CDCl$_3$) δ 143.0 (*C*=CH$_2$), 138.8 (*C*HCH$_2$), 138.5 (ArC), 128.4 (2xArCH), 127.6 (2xArCH), 127.6 (ArCH), 117.1 (C=*C*H$_2$), 113.5 (CH*C*H$_2$), 73.0 (*C*H$_2$Ph), 69.0 (*C*H$_2$OBn), 31.7 (*C*H$_2$CH$_2$OBn).

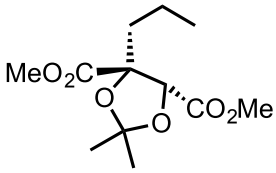
((5-(Benzyloxy)-3-methylenepentyl)oxy)(tert-butyl)dimethylsilane (210)



To a stirred solution of NaH (0.410 g, 60% suspension in mineral oil, 10.2 mmol) in THF (25 mL) at 0 °C was added 5-((*tert*-butyldimethylsilyl)oxy)-3-methylenepentan-1-ol (**206**) (1.18 g, 5.12 mmol) dropwise. Then BnBr (0.61 mL, 5.12 mmol) was added to the mixture. The reaction mixture was warmed to rt and stirred for 12 h. The mixture was then cooled to 0 °C and quenched with sat. aq NH$_4$Cl (30 mL) and water (30 mL). The aq layer was extracted with EtOAc (2x50 mL), washed with brine (20 mL), dried (NaSO$_4$), evaporated under reduced pressure and the residue purified by column chromatography (2% Et$_2$O in petrol) to give ((5-(Benzyloxy)-3-methylenepentyl)oxy)(tert-butyl)dimethylsilane (**210**) (1.45 g, 88%) as pale yellow oil, R_f = 0.41 (2% Et$_2$O in petrol); IR (film, υ_{max} cm^{-1}); 2928 w, 2856 w, 2361 w, 2341 w, 1097 s, 835 s; ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.31–7.19 (5H, m, ArCH), 4.76 (2H, d, *J* 5.0, C=CH$_2$), 4.46 (2H, s, CH$_2$Ph), 3.64 (2H, t, *J* 7.0, CH$_2$OTBS), 3.52 (2H, t, *J* 7.0, CH$_2$OBn), 2.30 (2H, t, *J* 7.0, C*H$_2$*CH$_2$OTBS), 2.20 (2H, t, *J* 7.0, C*H$_2$*CH$_2$OBn), 0.82 (9H, s, C(CH$_3$)$_3$), –0.02 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz; CDCl$_3$) δ 143.8 (*C*=CH$_2$), 138.4 (ArC), 128.4 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 112.2 (C=*C*H$_2$), 72.9 (*C*H$_2$Ph), 68.9 (*C*H$_2$OBn), 62.2 (CH$_2$OTBS), 39.6 (*C*H$_2$CH$_2$OTBS), 36.5

(CH$_2$CH$_2$OBn), 25.9 (C(CH$_3$)$_3$), 18.4 (C(CH$_3$)$_3$), –5.26 (Si(CH$_3$)$_2$); HRMS *m/z* (M+Na$^+$) found 343.2064, $C_{19}H_{32}SiNaO_2$ requires 343.2064.

Dimethyl (4*R*,5*R*)-2,2-dimethyl-4-propyl-1,3-dioxolane-4,5-dicarboxylate (212)

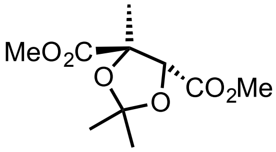


A solution of dimethyl 2,3-*O*-isopropylidine-L-tartrate (**119**) (1.1 mL, 5.44 mmol), 1-iodopropane (0.72 mL, 7.34 mmol) and freshly distilled DMPU (7.5 mL) in THF (25 mL) was cooled to –78 °C. To this reaction mixture was added dropwise a pre-cooled (–78 ºC) solution of LDA {freshly prepared by adding dropwise *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.65 mmol) to a solution of freshly distilled *i*-Pr$_2$NH (0.8 mL, 5.76 mmol) in THF (25 mL) at 0 °C} over 1 h. The reaction mixture was further stirred for 48 h at –78 °C, and then quenched at the same temperature with sat. aq NH$_4$Cl (20 mL), extracted with EtOAc (3 x 30 mL), washed with sat. aq CuSO$_4$ (30 mL), dried (MgSO$_4$), filtered, evaporated under reduced pressure and purified by column chromatography (10% EtOAc in petrol) to give propylated tartrate **212** (0.193 g, 14%) as colourless oil, R_f = 0.25 (10% EtOAc in petrol); ^{1}H NMR (400 MHz; CDCl$_3$) δ 4.94 (1H, s, CO$_2$Me*CH*), 3.83 (3H, s, CO$_2$Me), 3.82 (3H, s, CO$_2$Me), 1.81–1.20 (4H, m, *CH$_2$CH$_2$*CH$_3$), 1.62 (3H, s, C(CH$_3$)), 1.43 (3H, s, C(CH$_3$)), 0.90 (3H, t, *J* 7.0, CH$_2$CH$_2$*CH$_3$*); ^{13}C NMR (100 MHz; CDCl$_3$) δ 172.5 (*C*O$_2$Me), 169.0 (*C*O$_2$Me), 112.5 (CO$_2$Me*C*CH$_2$CH$_2$CH$_3$), 85.9 (*C*(CH$_3$)$_2$), 80.0 (CO$_2$Me*C*H), 52.7 (CO$_2$*Me*), 52.2 (CO$_2$*Me*), 36.4 (*C*H$_2$CH$_2$CH$_3$), 27.6 (C*C*H$_3$), 26.0 (C*C*H$_3$), 17.3 (CH$_2$*C*H$_2$CH$_3$), 14.3 (CH$_2$CH$_2$*C*H$_3$).

In another attempt with dimethyl 2,3-*O*-isopropylidine-L-tartrate (1.1 mL, 5.44 mmol), 1-iodopropane (0.50 mL, 5.13 mmol) and freshly distilled HMPA (5 mL) in THF (25 mL) with addition of LDA {freshly prepared by adding dropwise *n*-BuLi (2.7, 2.5 M in hexanes, 6.67 mmol) to a solution of freshly distilled *i*-Pr_2NH (1.1 mL, 7.49 mmol) in THF (25 mL) at 0 °C} stirred for 12 h yielded propylated tartrate **212** (0.474 g, 36%, lit: 66%) as colourless oil.

Analytical data identical to that previously reported.

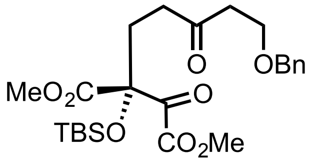
Dimethyl (4*R*,5*R*)-2,2,4-trimethyl-1,3-dioxolane-4,5-dicarboxylate (214)



A solution of dimethyl 2,3-*O*-isopropylidine-L-tartrate (**119**) (1.0 mL, 5.45 mmol), MeI (1.0 mL, 16.4 mmol) and anhydrous LiCl (1.39 g, 32.7 mmol) in THF (6 mL) was cooled to –78 °C. To this mixture was added dropwise a pre-cooled (–78 ºC) solution of LHMDS {freshly prepared by adding dropwise *n*-BuLi (2.6 mL, 2.5 M in hexanes, 6.54 mmol) to a solution of freshly distilled HMDS (1.5 mL, 7.09 mmol) in THF (4 mL) at 0 °C}. The reaction mixture was slowly warmed to rt and stirred for 16 h. The mixture was then poured into EtOAc (20 mL) and washed with H_2O (3x20 mL), brine (30 mL), dried (Na_2SO_4), filtered, evaporated under reduced pressure and purified by column chromatography (20 % EtOAc in petrol) to give methylated tartrate **214** (0.48 g, 39%) as colourless oil, $R_f = 0.47$ (20 % EtOAc in petrol); $[\alpha]_D^{25} = -66.6$ (*c* 1.00, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 2993 w, 2956 w, 1739 s, 1116 s; ^1H NMR (400 MHz; $CDCl_3$) δ 5.13 (1H, s, CH), 3.83 (3H, s, CO_2Me), 3.80 (3H, s, CO_2Me), 1.61 (3H, s, $CO_2MeCC\mathit{H_3}$), 1.42 (3H, s, $C(CH_3)$, 1.41 (3H, s, $C(CH)_3$); ^{13}C NMR (100

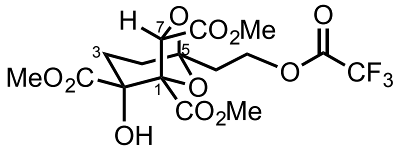
MHz; $CDCl_3$) δ 172.4 (*C*O_2Me), 169.0 (*C*O_2Me), 112.3 (*C*$(CH_3)_2$), 82.9 (CO_2Me*C*CH_3), 79.6 (CO_2Me*C*H), 53.0 (CO_2*Me*), 52.3 (CO_2*Me*), 27.7 (CO_2MeC*C*H_3), 26.0 (C*C*H_3), 20.6 (C*C*H_3); HRMS *m/z* ($M+Na^+$) found 255.0839, $C_{10}H_{16}NaO_6$ requires 255.0839.

Dimethyl (*R*)-2-(5-(benzyloxy)-3-oxopentyl)-2-((*tert*-butyldimethylsilyl)oxy)-3-oxosuccinate (223)



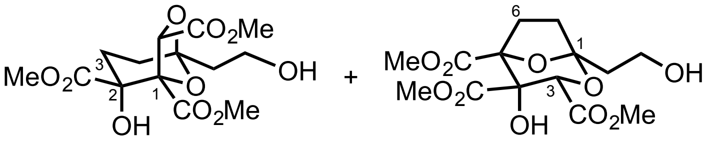
Following the general procedure **B** using hydrazone **149** (810 mg, 1.25 mmol) in CH_2Cl_2 (145 mL) and Et_3N (0.7 mL, 5.01 mmol) gave diketone **223** (120 mg, 20%) as yellow oil; R_f = 0.50 (50% Et_2O in petrol); $[\alpha]_D^{25}$ = +1.4 (*c* 0.50, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 2955 m, 2932 m, 2859 m, 1750 s, 1252 s, 839 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.32–7.22 (5H, m, ArCH), 4.45 (2H, s, C*H_2*Ph), 3.82 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.67 (2H, td, *J* 6.0, *J* 1.5, CH_2OBn), 2.63 (2H, td, *J* 6.0, *J* 4.0, C*H_2*CH_2OBn), 2.56 (2H, t, *J* 7.0, CCH_2C*H_2*C=O), 2.41–2.34 (1H, dt, *J* 15.0, *J* 7.0, 1H of CC*H_2*CH_2C=O), 2.27–2.20 (1H, dt, *J* 15.0, *J* 7.0, 1H of CC*H_2*CH_2C=O), 0.81 (9H, s, $SiCMe_3$), 0.12 (3H, s, SiMe), 0.09 (3H, s, SiMe); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.7 (C=O), 189.1 (O=*C*CO_2Me), 169.4 (*C*O_2Me), 162.0 (*C*O_2Me), 138.1 (ArC), 128.5 (ArCH), 127.77 (ArCH), 127.75 (ArCH), 82.9 (TBSO-*C*-CO_2Me), 73.3 (*C*H_2Ph), 65.3 (*C*H_2OBn), 53.0 (CO_2*Me*), 52.9 (CO_2*Me*), 43.0 (*C*H_2CH_2OBn), 37.0 (CCH_2*C*H_2C=O), 29.6 (*C*$(CH_3)_3$), 25.8 (C(*C*$H_3)_3$), 18.8 (C*C*H_2CH_2C=O), –3.2 (SiCH-$_3$), –3.3 ($SiCH_3$); HRMS *m/z* ($M+Na^+$) found 503.2061, $C_{24}H_{36}NaO_8Si$ requires 503.2074.

Trimethyl (1*S*,2*R*,5*R*,7*S*)-2-hydroxy-5-(2-(2,2,2-trifluoroacetoxy)ethyl)-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate (226)



To a solution of cycloadduct **152** (70 mg, 0.151 mmol) in CH_2Cl_2 (1.06 mL) was added TFA (558 µL) and H_2O (56 µL). The mixture was heated to 40 °C for 68 h. The mixture was concentrated under reduced pressure and purified by column chromatography (50% EtOAc in petrol) first eluted to give unrearranged trifluoroacetate **226** (11.9 mg, 23%) with a mixture of unrearranged and rearranged trifluoroacetate (6.6 mg, 13% mixture) last eluted all as colourless oils; R_f = 0.36 (50% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3490 br, 2958 w, 1748 s, 1439 w, 1361 w, 1220 s, 1165 s, 1089 s; ^1H NMR (500 MHz; $CDCl_3$) δ 5.50 (1H, s, C*H*CO_2Me), 4.77–4.69 (2H, ddd, *J* 7.0, *J* 2.0, *J* 1.5, *C*H_2OCOCF_3), 3.93 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 2.50–2.44 (1H, dt, *J* 14.0, *J* 7.0, *J* 1.5, 1H of C^8H_2), 2.39–2.30 (2H, m, 1H of C^8H_2, 1H *endo* C^3H_2), 2.06–2.00 (1H, m, 1H of C^4H_2), 1.83–1.79 (2H, m, 1H *exo* of C^3H_2, 1H of C^4H_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ 173.6 (*C*O_2Me), 168.9 (*C*O_2Me), 166.5 (*C*O_2Me), 158.1–157.0 (*C*OCF_3, *J* 42.0), 118.0–111.0 (CO*CF₃*, *J* 283.0), 110.7 (O-C^5-O), 89.5 (*C*$^1CO_2Me$), 77.8 (*C*HCO_2Me), 73.8 (*C*$^2CO_2MeOH$), 63.3 (C*H₂*$COCF_3$), 53.2 (CO_2*Me*), 53.0 (CO_2*Me*), 52.8 (CO_2*Me*), 34.7 (*C*$H_2CH_2COCF_3$), 30.5 (C^4H_2), 29.3 (C^3H_2); ^{19}F NMR (500 MHz; $CDCl_3$) δ_F 75.1 (CO*CF₃*); HRMS *m/z* (M+Na$^+$) found 467.0768, $C_{16}H_{19}NaO_{11}{}^{19}F_3$ requires 467.0772.

Trimethyl (1*S*,2*R*,5*R*,7*S*)-2-hydroxy-5-(2-hydroxyethyl)-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate (227) and **Trimethyl (1*R*,3*S*,4*S*,5*R*)-4-hydroxy-1-(2-hydroxyethyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (228)**



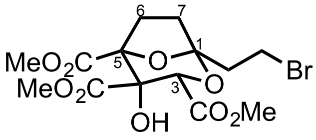
To a solution of alcohol **152** (20 mg, 0.043 mmol) in CH_2Cl_2 (0.32 mL) was added TFA (160 μL) and H_2O (16 μL). The mixture was heated to 40 °C for 68 h, then concentrated under reduced pressure. To the residue was added toluene (3x1 mL) to azeotrope traces of TFA and H_2O. To the residue was then added Na_2CO_3 (6.9 mg, 0.065 mmol) in MeOH (1.0 mL) and stirred at rt. After 1 h toluene (0.4 mL), and $TMSCHN_2$ (28 μL, 2 M in Et_2O, 0.056 mmol) was added dropwise. After 30 min, AcOH (50 μL) was added dropwise, and the mixture then evaporated under reduced pressure. Purification of the residue by column chromatography (1% MeOH in CH_2Cl_2) gave unrearranged diol **227** (10 mg, 67%) and rearranged diol **228** (4.1 mg, 27%), both as colourless oils.

Data for unrearranged diol **227**: R_f = 0.36 (5% MeOH in CH_2Cl_2): $[\alpha]_D^{25}$ = +60.7 (*c* 0.59, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3490 br, 2959 w, 1750 s, 1748 s, 1439 w, 1361 w, 1220 s, 1165 s, 1089 s; ^1H NMR (500 MHz; $CDCl_3$) δ 5.56 (1H, s, C*H*CO_2Me), 4.06–4.01 (1H, m, 1H of C*H*$_2$OH), 3.93 (3H, s, CO_2Me), 3.82–3.78 (1H, m, 1H of C*H*$_2$OH), 3.75 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 2.29 (1H, ddd, *J* 13.0, *J* 8.0, *J* 7.0, 1H of C*H*$_2$$CH_2OH$), 2.19–2.16 (2H, m, 1H of C*H*$_2$$CH_2OH$, 1H *endo* C^3H_2), 1.98 (1H, ddd, *J* 13.0, *J* 7.0, *J* 7.0, 1H of C^4H_2), 1.84–1.78 (2H, m, 1H *exo* of C^3H_2, 1H of C^4H_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ 173.8 (*C*O_2Me), 170.0 (*C*O_2Me), 166.7

(CO$_2$Me), 112.9 (O-C^5-O), 89.2 (C^1CO$_2$Me), 77.8 (CHCO$_2$Me), 73.8 (HOC^2CO$_2$Me), 56.9 (CH$_2$OH), 53.9 (CO$_2$*Me*), 53.3 (CO$_2$*Me*), 53.0 (CO$_2$*Me*), 38.6 (CH$_2$CH$_2$OH), 31.1 (C^{4}H$_2$), 29.3 (C^{3}H$_2$); HRMS *m/z* (M+Na$^+$); found 371.0945, $C_{14}H_{20}NaO_{10}$ requires 371.0949.

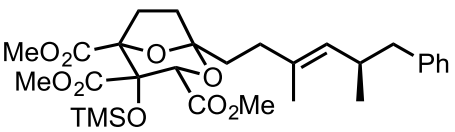
Data for rearranged diol **228**: R_f 0.34 (5% MeOH in CH$_2$Cl$_2$); $[\alpha]_D^{25} = -13.8$ (*c* 0.41, CHCl$_3$); IR (film, υ_{max} cm^{-1}) 3517 br, 2957 w, 1737 s, 1439 w, 1271 s, 1130 s, 1096 s, 1060 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 4.94 (1H, s, CHCO$_2$Me), 4.05 (1H, ddd, *J* 12.0, *J* 8.0, *J* 3.0, 1H of CH_2OH), 3.91 (3H, s, CO$_2$Me), 3.84 (1H, ddd, *J* 12.0, *J* 6.5, *J* 3.0, 1H of CH_2OH), 3.79 (3H, s, CO$_2$Me), 3.77 (3H, s, CO$_2$Me), 3.14 (1H, ddd, *J* 13.0, *J* 8.5, *J* 3.0, 1H *endo* of C^{6}H$_2$), 2.30–2.07 (5H, m, 1H *exo* of C^{6}H$_2$, 2H C^{7}H$_2$, CH_2CH$_2$OH), 1.92 (2H, br s, CH$_2$$OH$, C$OHCO_2$Me); ^{13}C NMR (125 MHz; CDCl$_3$) δ 170.0 (CO$_2$Me), 168.7 (CO$_2$Me), 167.4 (CO$_2$Me), 109.5 (O-C^1-O), 88.2 (C^5CO$_2$Me), 74.94 (C^4CO$_2$MeOH), 74.88 (CHCO$_2$Me), 58.9 (CH$_2$OH), 53.7 (CO$_2$*Me*), 53.1 (CO$_2$*Me*), 53.0 (CO$_2$*Me*), 38.9 (CH$_2$CH$_2$OH), 32.5 (C^{7}H$_2$), 29.1 (C^{6}H$_2$); HRMS *m/z* (M+Na$^+$): found 371.0948, $C_{14}H_{20}NaO_{10}$ requires 371.0949.

Trimethyl (1*R*,3*S*,4*S*,5*R*)-1-(2-bromoethyl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (230)



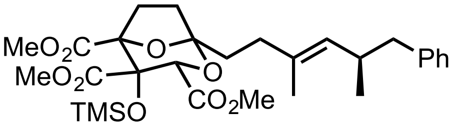
To a solution of diol **228** (6.0 mg, 0.017 mmol) was added Ph$_3$P (6.8 mg, 0.026 mmol) and CBr$_4$ (8.5 mg, 0.026 mmol) in CH$_2$ Cl$_2$ (0.2 mL) at 0 °C. The vial was sealed and the suspension stirred at 0 °C for 30 min, then warmed to rt overnight. The reaction mixture was then concentrated by blowing nitrogen and purified by column chromatography (5% MeOH in CH_2Cl_2) to give alkyl bromide **230** (4.4 mg, 62%) as colourless glass; $R_f = 0.56$ (5% MeOH in CH_2Cl_2); IR (film, υ_{max} cm^{-1}) 2980 s, 1766 s, 1739 s, 1271 s, 1220 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 4.91 (1H, s, C*H*CO_2Me), 3.91 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.66–3.61 (2H, ddd, *J* 9.0, *J* 6.0, *J* 1.5, CH_2Br), 3.17–3.12 (1H, ddd, *J* 13.0, *J* 9.0, *J* 4.0, 1H *endo* of C^6H_2), 2.66–2.60 (1H, ddd, *J* 15.0, *J* 9.0, *J* 6.0, 1H C*H*$_2$$CH_2$Br), 2.56–2.50 (1H, ddd, *J* 14.5, *J* 9.0, *J* 7.0, 1H C*H*$_2$$CH_2$Br), 2.29–2.23 (1H, ddd, *J* 14.5, *J* 9.0, *J* 5.5, 1H *exo* of C^6H_2), 2.22–2.16 (1H, td, *J* 14.5, *J* 13.0, *J* 4.0, 1H of C^7H_2), 2.13–2.06 (1H, td, *J* 13.5, *J* 13.0, *J* 5.5, 1H of C^7H_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.0 (*C*O_2Me), 168.6 (*C*O_2Me), 167.3 (*C*O_2Me), 107.5 (O-C^1-O), 88.1 (*C*^{5}CO_2Me), 75.0 (*C*HCO_2Me), 74.9 (*C*^{4}CO_2MeOH), 53.6 (CO_2*Me*), 53.1 (CO_2*Me*), 52.8 (CO_2*Me*), 40.4 (*C*H_2CH_2OH), 32.1 (C^7H_2), 29.1 (C^6H_2), 26.2 (CH_2Br); HRMS *m/z* (M+Na$^+$) found 433.0103, $C_{14}H_{19}O_9{}^{79}BrNa$ requires 433.0105 and found 435.0084, $C_{14}H_{19}O_9{}^{81}BrNa$ requires 435.0083.

Trimethyl (1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-dimethyl-6-phenylhex-3-en-1-yl)-4-((trimethylsilyl)oxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (232)



To a Schlenk tube was added Mn dust (4.1 mg, 0.075 mmol), NiI_2(bpy)[105] (0.4 mg, 0.00094 mmol, 2.5 mol%), siloxy iodide **256** (20 mg, 0.038 mmol) and (*R*-)–alkenyl iodide **139** (10.8 mg, 0.038 mmol) and the flask evacuated and refilled with argon (x3). DMF (0.1 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (0.96 μL, 0.0075 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (3 mL) was then added and the aq layer extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (30% EtOAc in petrol) to give *E*–alkene **232** (16.5 mg, 78%) as colourless oil, $R_f = 0.51$ (30% EtOAc in petrol); $[\alpha]_D^{25} = -42.10$ (*c* 0.073, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3025 s, 2956 s, 2920 s, 2850 s, 2358 w, 2342 w, 2331 w, 1770 s, 1739 s, 1453 s, 1274 s, 1204 s, 846 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.26–7.22 (2H, m, ArCH), 7.18–7.11 (3H, m, ArCH), 5.02 (1H, dq, *J* 9.0, *J* 1.5, HC=C), 4.84 (1H, s, C*H*CO_2Me), 3.85 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.20–3.14 (1H, m, H_{endo} of C^6H_2), 2.67–2.60 (1H, m, C*H*CH_3), 2.52 (2H, dd, *J* 7.0, *J* 4.0 CH_2Ph), 2.24–2.07 (3H, m, 1H_{exo} of C^6H_2 and 2H, C^7H_2), 2.02–1.93 (4H, m, CH_2CH_2), 1.47 (3H, d, *J* 1.0, CCH_3), 0.93 (3H, d, *J* 7.0, CHC*H*$_3$), 0.10 (9H, s, OTMS); ^{13}C NMR (125 MHz; $CDCl_3$) δ 171.3 (*C*O_2Me), 169.8 (*C*O_2Me), 168.0 (*C*O_2Me), 141.3 (*C*=CH), 133.4 (C=*C*H), 130.3 (ArC), 129.4 (2xArCH), 128.1 (2xArCH), 125.7 (ArCH), 108.8 (O-C^1-O), 88.4 (C^5CO_2Me), 78.5 (C^4CO_2MeOTMS), 75.8 (*C*HCO_2Me), 52.8 (CO_2*Me*), 52.7 (CO_2*Me*), 52.6 (CO_2*Me*), 44.1 (*C*H_2Ph), 35.3 (*C*HCH_3), 34.6 (C^6H_2), 33.3 (C^7H_2), 31.5 (CCH_2*C*H_2CMe), 30.3 (CH_2), 20.9 (CH*C*H_3), 16.5 (C=C*C*H_3), 2.34 (OTMS); HRMS *m/z* (M+Na^+) found 585.2489, $C_{29}H_{42}O_9NaSi$ requires 585.2490.

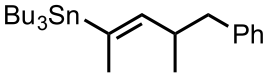
Trimethyl (1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-dimethyl-6-phenylhex-3-en-1-yl)-4-((trimethylsilyl)oxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (232)



To a Schlenk tube was added Mn dust (8.4 mg, 0.152 mmol), $NiI_2(bpy)^{105}$ (0.9 mg, 0.0019 mmol, 2.5 mol%), hydroxy iodide **255** (35 mg, 0.076 mmol) and (*R*-)–alkenyl iodide **139** (21.8 mg, 0.076 mmol) and the flask evacuated and refilled with argon (x3). DMF (0.2 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (1.9 μL, 0.015 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (3 mL) was then added and the aq layer extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue was purified by column chromatography to give *E*–alkene **232** (28.1 mg, 66%) as colourless oil, R_f = 0.51 (30% EtOAc in petrol).

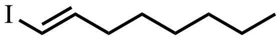
Analytical data identical to previously reported.

(*E*)-Tributyl(4-methyl-5-phenylpent-2-en-2-yl)stannane (235)



To a solution of alkenyl iodide (±)–**189** (200 mg, 0.70 mmol) in Et_2O (2 mL) and pentane (5 mL) at –78 °C was added *t*-BuLi (0.82 mL, 1.7 M in hexanes, 1.4 mmol) dropwise over 10 min. After 15 min, Bu_3SnCl (0.23 ml, 0.84 mmol) was added dropwise over 5 min and the mixture stirred at –78 °C for 6 h, then allowed to gradually warm to rt overnight. The reaction was quenched with sat. aq NH_4Cl (10 mL). The aq layer was extracted with Et_2O (3x20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give alkenyl stannane **235** (276 mg, 88%) as a clear oil R_f = 0.6 (petrol) IR (film, υ_{max} cm^{-1}) 2955 s, 2923 s, 2870 s, 2850 s, 1454 m, 1375 w, 697 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.26–7.22 (2H, m, ArCH), 7.17–7.13 (3H, m, ArCH), 5.35–5.30 (1H, dq, *J* 9.0, *J* 1.5, $J\ ^{119}{}_{Sn\text{-}H}$ 55.0, $J\ ^{117}{}_{Sn\text{-}H}$ 45.0, C*H*=$CSnBu_3$), 2.92–2.84 (1H, m, C*H*CH_3), 2.59–2.51 (2H, m, CH_2Ph), 1.63 (3H, d, *J* 1.5, *J* $^{119}{}_{\text{Sn-H}}$ 25.0, *J* $^{117}{}_{\text{Sn-H}}$ 20.0, $\mathrm{Bu_3SnCC}\mathit{H_3}$), 1.54–1.38 (6H, m, $\mathrm{SnC}\mathit{H_2}\mathrm{CH_2}$ x3), 1.34–1.27 (6H, sext, *J* 7.0, $\mathrm{SnCH_2C}\mathit{H_2}\mathrm{CH_2}$ x3), 0.97 (3H, d, *J* 7.0, $\mathrm{CHC}\mathit{H_3}$), 0.89 (9H, t, *J* 7.0, $\mathrm{SnCH_2CH_2C}\mathit{H_2}\mathrm{CH_3}$ x3 and 1H of $\mathrm{SnCH_2CH_2CH_2C}\mathit{H_3}$ x3), 0.84 (6H, t, *J* 7.0, $\mathrm{SnCH_2CH_2CH_2}\mathit{CH_3}$); ^{13}C NMR (125 MHz; $\mathrm{CDCl_3}$) δ 146.5 (*J* $^{119}{}_{\text{Sn-C}}$ 47.0, *C*=CSn), 141.3 (ArC), 136.4 (C=*C*Sn), 129.4 (ArCH), 128.1 (ArCH), 125.7 (ArCH), 43.9 ($\mathit{C}\mathrm{H_2Ph}$), 34.5 ($\mathit{C}\mathrm{HCH_3}$), 29.3 (*J* $^{119}{}_{\text{Sn-C}}$ 71.0, *J* $^{117}{}_{\text{Sn-C}}$ 39.0, $\mathrm{SnCH_2}\mathit{C}\mathrm{H_2}$ x3), 27.5 (*J* $^{119}{}_{\text{Sn-C}}$ 107.0, *J* $^{117}{}_{\text{Sn-C}}$ 105.0, $\mathrm{SnCH_2CH_2}\mathit{C}\mathrm{H_2Me}$ x3), 20.8 ($\mathrm{CH}\mathit{C}\mathrm{H_3}$), 19.1 ($\mathrm{C}\mathit{C}\mathrm{H_3}$), 13.9 ($\mathrm{SnCH_2CH_2CH_2}\mathit{Me}$ x3), 9.2 (*J* $^{119}{}_{\text{Sn-C}}$ 648.0, *J* $^{117}{}_{\text{Sn-C}}$ 619.0, $\mathrm{Sn}\mathit{C}\mathrm{H_2CH_2CH_2CH_3}$ x3); HRMS *m/z* ($\mathrm{M^+}$–Bu) found 393.1607, $\mathrm{C_{24}H_{42}}{}^{120}\mathrm{Sn}$ requires 393.1682.

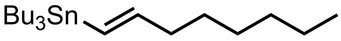
(*E*)-1-Iodooct-1-ene (237)[90]



To a solution of $\mathrm{Cp_2ZrCl_2}$ (10.6 g, 36.3 mmol) in THF (130 mL) cooled to 0 °C was added a solution of $\mathrm{LiEt_3BH}$ (21.4 mL, 1.70 M in THF, 36.3 mmol) dropwise. The reaction mixture was shielded from light and left to stir at rt for 1 h, then oct-1-yne (**236**) (2.0 g, 18.1 mmol) in THF (20 mL) was added dropwise and the mixture stirred at rt for 1 h. The mixture was then cooled to –20 °C and a solution of *N*-iodosuccinimide (8.96 g, 39.8 mmol) in THF (20 mL) was added dropwise. The reaction mixture was warmed to rt, followed by further stirring for 30 min and then poured into sat. aq $\mathrm{NaHCO_3}$ (40 mL). The aq layer was extracted with $\mathrm{Et_2O}$ (3x50 mL), and the combined organic layers were dried ($\mathrm{MgSO_4}$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give alkenyl iodide **237** (3.25 g, 75%) as colourless oil, R_f = 0.82 (petrol); ^{1}H NMR (400

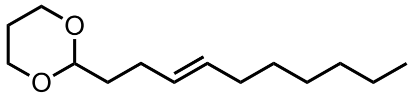
MHz; $CDCl_3$) δ 6.52 (1H, dt, *J* 14.0, *J* 7.0, *H*C=CHI), 5.97 (1H, dt, *J* 14.0, *J* 1.5, HC=C*H*I), 2.06 (2H, qd, *J* 7.0, *J* 1.5, C*H₂*HC=CHI), 1.47–1.21 (8H, m, CH_2), 0.89 (3H, t, *J* 7.0, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 146.9 (H*C*=CHI), 73.8 (HC=*C*HI), 36.1 (*C*H_2HC=CHI), 30.8 (CH_2), 28.1 (CH_2), 27.3 (CH_2), 22.5 (CH_2), 14.8 (CH_3).

(*E*)-Tributyl(oct-1-en-1-yl)stannane (238)[160]



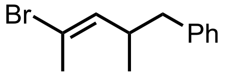
To a solution of alkenyl iodide **237** (3.2 g, 13.4 mmol) in Et_2O (45 mL) and pentane (100 mL) at –78 °C was added dropwise *t*-BuLi (15.8 mL, 1.7 M in hexanes, 26.9 mmol) over 60 min. After 15 min Bu_3SnCl (4.7 ml, 16.1 mmol) was added dropwise and the mixture stirred at –78 °C for 6 h, then allowed to gradually warm to rt overnight. The reaction was quenched with sat. aq NH_4Cl (100 mL). The aq layer was extracted with Et_2O (3x100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give stannane **238** (5.27 g, 98%) as clear oil, R_f = 0.71 (petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 6.01–5.86 (1H, m, *H*C=CHSn), 5.06–4.90 (1H, m, HC=C*H*Sn), 2.20–2.07 (2H, m, C*H₂*HC=CHSn), 1.59–1.24 (20H, m, CH_2), 0.97–0.80 (12H, t, *J* 7.0, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 145.2 (H*C*=CHSn), 130.5 (HC=*C*HSn), 38.6 (*C*H_2HC=CHI), 30.8 (CH_2), 29.2 (3xCH_2), 28.1 (CH_2), 27.3 (CH_2), 27.2 (3xCH_2), 22.5 (CH_2), 18.1 (3xCH_2), 14.9 (3xCH_3), 13.2 (CH_3).

(E)-2-(Dec-3-en-1-yl)-1,3-dioxane (239)



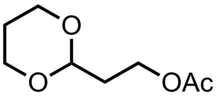
In a glove-box, either [P(*t*-Bu)$_2$Me]BF$_4$ (21 mg, 0.085 mmol) or [HPCyp$_3$]BF$_4$ (27.7 mg, 0.085 mmol) and anhydrous TMAF (100 mg, 1.08 mmol) was added to a vial containing a yellow solution of [(π-allyl)PdCl]$_2$ (5.2 mg, 0.014 mmol) in THF (5.6 mL, 0.10 M). The heterogeneous mixture was stirred for 5 min before alkenylstannane **238** (250 mg, 0.62 mmol), activated powdered 3Å MS (283 mg) and alkyl bromide **191** (110 mg, 0.57 mmol) were added. The vial was sealed, removed from the glove-box and the mixture stirred vigorously at rt. After 24 h, aq KF (5.6 mL, 10%) was added. After 30 min, the aq layer was extracted with Et$_2$O (3x10 mL), and the combined organic layers were dried (MgSO$_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% Et$_2$O in petrol) to give alkene **239** (63 mg, 49%) as colourless oil; R_f = 0.54 (10% Et$_2$O in petrol); IR (film, υ_{max} cm^{-1}) 2955 s, 2924 s, 2850 s, 1378 w, 1142 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 5.47–5.31 (2H, m, *H*C=C*H*), 4.50 (1H, t, *J* 5.0, OCHO), 4.10 (2H, dd, *J* 11.5, *J* 5.0, CH$_2$), 3.68 (2H, td, *J* 12.0, *J* 11.5, *J* 1.5, CH$_2$), 2.12–2.03 (2H, m, C*H*$_2$C=C), 1.96 (2H, q, *J* 7.0, *J* 6.5, C=CC*H*$_2$), 2.16–1.60 (2H, m, CHC*H*$_2$), 1.37–1.23 (10H, m, 4xCH$_2$ and OCH$_2$C*H*$_2$), 0.88 (3H, t, *J* 7.0, CH$_3$); ^{13}C NMR (125 MHz; CDCl$_3$) δ 131.2 (*C*=C), 129.4 (C=*C*), 102.0 (OCHO), 67.0 (2xOCH$_2$), 35.2 (CH*C*H$_2$), 32.7 (C=C*C*H$_2$), 31.9 (*C*H$_2$C=C), 29.6 (CH$_2$), 28.9 (CH$_2$), 27.1 (CH$_2$), 26.0 (OCH$_2$*C*H$_2$), 22.8 (*C*H$_2$CH$_3$), 14.2 (CH$_3$); HRMS *m/z* (M+H$^+$) found 227.2007, $C_{14}H_{27}O_2$ requires 227.2006.

(*E*)-(4-Bromo-2-methylpent-3-en-1-yl)benzene (241)



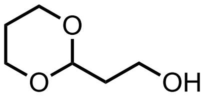
To a solution of Cp_2ZrCl_2 (1.85 g, 6.32 mmol) in THF (15 mL) cooled to 0 °C was added $LiEt_3$•BH (3.72 mL, 1.7 M in THF, 6.32 mmol) dropwise. The reaction mixture was shielded from light and left to stir at rt for 1 h, then (2-methylpent-3-yn-1-yl)benzene (**164**) (500 mg, 3.16 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at 50 °C for 1 h, and then allowed to reach rt. The mixture was then cooled to –20 °C and a solution of Br_2 (0.32 mL, 6.32 mmol) were added dropwise. The reaction was warmed to rt followed by further stirring for 30 min and then poured into sat. aq $NaHCO_3$ (30 mL). The aq layer was extracted with Et_2O (3x50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give *E*-alkenyl bromide **241** (517 mg, 68%) as colourless oil. R_f = 0.70 (petrol); IR (film, υ_{max} cm^{-1}) 3027 w, 2959 w, 2925 w, 2869 w, 1651 w, 1453 m, 698 s; ^1H NMR (400 MHz; $CDCl_3$) δ 7.39–7.19 (5H, m, ArCH), 5.77 (1H, d, *J* 8.0, CHCBr), 2.73–2.61 (3H, m, C*H*CH_3 and CH_2Ph), 2.02 (3H, d, *J* 1.5, CBrCH_3), 1.10 (3H, d, *J* 4.0, CHCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 140.0 (H*C*=CBr), 137.1 (ArC), 129.3 (ArCH), 128.3 (ArCH), 126.1 (ArCH), 119.1 (C=*C*Br), 43.4 (*C*H_2Ph), 37.2 (*C*HCH_3), 23.3 (CBr*C*H_3), 20.4 (CH*C*H_3); HRMS *m/z* ($M+H^+$) found 238.0346 and 240.0347, $C_{12}H_{15}{}^{79}Br$ and $C_{12}H_{15}{}^{81}Br$ requires 238.0357 and 240.0337.

2-(1,3-Dioxan-2-yl)ethyl acetate (245)[99]



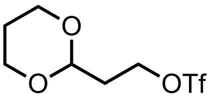
To a solution of KOAc (1.69 g, 17.2 mmol) and triethylbenzylammonium chloride (0.49 g, 2.15 mmol) in CCl_4 (3 mL) and H_2O (1.2 mL) was added alkyl bromide **191** (2.87 g, 4.30 mmol) and the mixture refluxed for 120 h. The reaction mixture was then cooled to rt and poured into ice-water (12 mL). The aq layer was extracted with Et_2O (3x20 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% Et_2O in petrol) to give acetate **245** (713 mg, 95%) as colourless oil $R_f = 0.54$ (10% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 4.66 (1H, t, *J* 5.5, CH), 4.22–4.05 (4H, m, 2xCH_2O), 3.77 (2H, td, *J* 12.0, *J* 1.5, CH_2OAc), 2.06 (3H, s, CH_3), 1.93 (2H, td, *J* 7.0, *J* 1.5, $CHCH_2$), 1.41–1.21 (2H, m, CH_2CH_2O); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.7 (C=O), 101.2 (O-CH-O), 74.9 ($CHCH_2$), 66.5 (2xCH_2O), 59.1 (CH_2OAc), 25.5 (OCH_2CH_2), 20.7 (CH_3).

2-(1,3-Dioxan-2-yl)ethan-1-ol (246)[99]



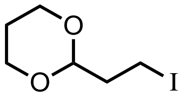
A solution of $LiAlH_4$ (201 mg, 5.3 mmol) in Et_2O (2 mL) was cooled to –20 °C. Alkyl acetate **245** (710 mg, 4.1 mmol) in Et_2O (2 mL) was then added dropwise to the mixture. After 5 min, the mixture was warmed to rt and stirred for 1 h. Fieser workup was performed and then solvent removed under reduced pressure. The residue was purified by column chromatography (80% EtOAc in petrol) to give alcohol **246** (475 mg, 88%) as colourless oil, R_f = 0.36 (80% EtOAc in petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.77 (1H, t, *J* 5.5, OCHO), 4.13 (2H, ddd, *J* 12.0, *J* 6.0, CH_2OH), 3.83–3.76 (4H, m, 2xCH_2O), 2.11 (1H, dtt, *J* 14.0, *J* 12.0, *J* 5.5, 1H of CHC*H*$_2$), 1.91–1.85 (2H, m, OCH_2C*H*$_2$), 1.37 (1H, dtt, *J* 14.0, *J* 12.0, *J* 5.5, 1H of CHC*H*$_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 100.5 (O-CH-O), 75.8 (*C*H_2CH_2OH), 65.9 (2x*C*H_2O), 48.1 (CH_2OH), 25.1 (OCH_2*C*H_2).

2-(1,3-Dioxan-2-yl)ethyl trifluoromethanesulfonate (247)



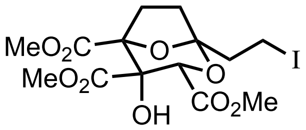
Alcohol **246** (200 mg, 1.51 mmol) in CH_2Cl_2 (1.5 mL, 1.0 M) and 2,6-lutidine (0.28 mL, 2.42 mmol) was cooled to –78 °C. Tf_2O (0.31 mL, 1.82 mmol) was added dropwise. After 1 h, the cold mixture was poured into hexanes (5 mL). The mixture was passed through a short silica plug and residues evaporated under reduced pressure to give alkyl triflate **247** (289 mg, 72%) as colourless oil. R_f = 0.48 (20% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 2760 w, 1450 s, 1100 s, 950 s; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.69 (1H, t, *J* 5.5, OCHO), 4.65 (2H, t, *J* 6.0, CH_2OTf), 4.09 (2H, dd, *J* 10.0, *J* 6.0, CH_2), 3.75 (2H, td, *J* 12.5, *J* 12.0, *J* 1.5, CH_2), 2.12–2.06 (2H, m, CHC*H*$_2$), 1.38–1.32 (2H, m, OCH_2C*H*$_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 118.6 (CF_3, Q), 97.9 (O-CH-O), 73.2 (*C*H_2CH_2OTf), 66.8 (2x*C*H_2O), 34.6 (CH_2OTf), 25.5 (OCH_2*C*H_2); ^{19}F NMR (100 MHz; $CDCl_3$) δ_F –74.9 (CF_3); HRMS *m/z* (M+NH$^+$) found 282.0607, $C_7H_{15}F_3NO_5{}^{32}S$ requires 282.0618.

2-(2-Iodoethyl)-1,3-dioxane (248)



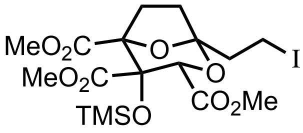
To a solution of Ph_3P (327 mg, 1.25 mmol) and imidazole (170 mg, 2.50 mmol) in CH_2Cl_2 (4 mL) was added I_2 (3.12 g, 1.25 mmol) at 0 °C. After 15 min, alcohol **246** (2.30 g, 9.99 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise and the suspension was stirred for 2 h at rt. The solvent was then removed under reduced pressure to give a dark yellow/orange slurry, which was then diluted with petrol (100 mL) and filtered through a pad of Celite®. The solvent was evaporated under reduced pressure and residue purified by column chromatography (2% Et_2O in petrol) to give iodide **248**[161] (2.21 g, 91%) as colourless oil, $R_f = 0.64$ (2% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 4.63 (1H, t, *J* 5.5, OCHO), 4.11 (2H, ddt, *J* 11.0, *J* 6.0, *J* 1.5, CH_2O), 3.87–3.72 (2H, m, CH_2O), 3.22 (2H, t, *J* 7.0, CH_2I), 2.12 (2H, td, *J* 7.0, *J* 5.5, $\mathit{CH_2}CH_2I$), 1.36 (2H, dsept, *J* 14.0, *J* 1.5, $OCH_2\mathit{CH_2}$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 101.6 (O-CH-O), 66.8 ($2xCH_2O$), 38.7 ($\mathit{C}H_2CH_2I$), 25.8 ($OCH_2\mathit{C}H_2$), –0.8 (CH_2I).

Trimethyl (1*R*,3*S*,4*S*,5*R*)-4-hydroxy-1-(2-iodoethyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (255)



A vial was charged with Ph_3P (4.0 mg, 0.014 mmol) and imidazole (2.0 mg, 0.028 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C. To the solution was added I_2 (4.0 mg, 0.014 mmol) and the vial was sealed. A solution of diol **228** (4.5 mg, 0.013 mmol) in CH_2Cl_2 (0.1 mL) was added to the mixture. After 12 h, H_2O (0.5 mL) was added to the reaction mixture and the aq layer extracted with CH_2Cl_2 (3x2 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated by blowing nitrogen and purified by column chromatography (70% EtOAc in petrol) to give iodide **255** (5.3 mg, 90%) as a colourless glass, R_f = 0.47 (70% EtOAc in petrol); $[\alpha]_D^{25} = -11.6$ (*c* 0.50, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 3469 br, 2955 w, 1765 s, 1738 s, 1439 s; ^1H NMR (500 MHz; $CDCl_3$) δ 4.90 (1H, s, C*H*CO_2Me), 3.90 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.67 (1H, s, OH), 3.38 (2H, ddd, *J* 10.0, *J* 5.0, *J* 5.0, CH_2I), 3.14 (1H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, 1H *endo* of C^6H_2), 2.59 (2H, ddd, *J* 10.0, *J* 10.0, *J* 5.0, C*H*$_2$$CH_2$I), 2.23 (1H, ddd, *J* 10.0, *J* 10.0, *J* 5.0, 1H *exo* of C^6H_2), 2.11 (2H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, C^7H_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.0 (*C*O_2Me), 168.6 (*C*O_2Me), 167.3 (*C*O_2Me), 108.6 (O-C^1-O), 88.2 (C^5CO_2Me), 75.0 (C^4CO_2MeOH), 74.9 (*C*HCO_2Me), 53.6 (CO_2*Me*), 53.1 (CO_2*Me*), 52.9 (CO_2*Me*), 41.9 (*C*H_2CH_2OH), 31.8 (C^6H_2), 29.0 (C^7H_2), –3.42 (CH_2I); HRMS *m/z* ($M+Na^+$): found 480.9965, $C_{14}H_{19}O_9INa$ requires 480.9966.

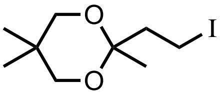
Trimethyl (1*R*,3*S*,4*S*,5*R*)-1-(2-iodoethyl)-4-((trimethylsilyl)oxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (256)



A vial was charged with iodoalcohol **255** (5.0 mg, 0.011 mmol), imidazole (1.3 mg, 0.019 mmol) and DMAP (0.1 mg, 0.0011 mmol) in CH_2Cl_2 (0.1 mL) and sealed. To the solution was added TMSCl (2.2 μL, 0.018 mmol) dropwise and allowed to stir at rt overnight. The mixture was then loaded directly onto a column and purified by column chromatography (80% Et_2O in petrol) to give alkyl iodide **256** (5.5 mg, 95%)

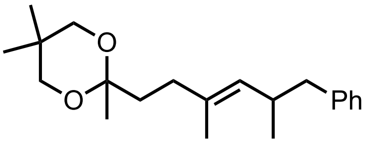
as colourless glass; R_f = 0.71 (80% Et_2O in petrol); $[\alpha]_D^{25}$ = –14.60 (*c* 0.273, $CHCl_3$); IR (film, υ_{max} cm^{-1}) 2955 w, 2917 s, 2850 s, 1767 s, 1739 s, 1438 s; ^1H NMR (500 MHz; $CDCl_3$) δ 4.85 (1H, s, C*H*CO_2Me), 3.84 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.73 (3H, s, CO_2Me), 3.42 (2H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, C*H*$_2$I), 3.18 (1H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, 1H *endo* of C^6H_2), 2.57 (2H, dd, *J* 10.0, *J* 1.5, C*H*$_2$$CH_2I$), 2.15 (1H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, 1H *exo* of C^6H_2), 2.00 (2H, ddd, *J* 15.0, *J* 10.0, *J* 5.0, C^7H_2), 0.08 (9H, s, OTMS); ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.8 (*C*O_2Me), 169.4 (*C*O_2Me), 167.7 (*C*O_2Me), 108.2 (O-C^1-O), 88.4 (*C*^{5}CO_2Me), 78.4 (*C*^{4}CO_2MeOH), 75.8 (*C*HCO_2Me), 52.78 (CO_2*Me*), 52.75 (CO_2*Me*), 52.6 (CO_2*Me*), 42.3 (*C*H_2CH_2OH), 32.3 (C^6H_2), 30.0 (C^7H_2), –2.25 (OTMS), –2.36 (CH_2I); HRMS *m/z* ($M+Na^+$): found 553.0359, $C_{17}H_{27}INaO_9Si$ requires 553.0361.

2-(2-Iodoethyl)-2,5,5-trimethyl-1,3-dioxane (260)



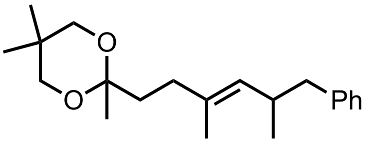
A solution of ethyl acetoacetate **257** (1.94 mL, 15.3 mmol), 2,2-dimethyl-1,3-propanediol (4.0 g, 38.3 mmol) pyridinium *p*-toluenesulfonate (PPTS) (190 mg, 0.77 mmol) in CH_2Cl_2 (40 ml) was refluxed on a Dean-Stark trap. After 72 h, the solvent was removed under reduced pressure. The residue was diluted with Et_2O (50 ml) and the organic layer was washed with H_2O (50 mL x 2), $NaHCO_3$ (20 ml) and brine (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and solvent evaporated under reduced pressure to give crude ester **258**.[107] To a suspension of $LiAlH_4$ in Et_2O (20 mL) at 0 °C was added dropwise ester **258** dissolved in Et_2O (50 mL). The crude mixture was then warmed to rt and then refluxed for 6 h. The reaction mixture was cooled to 0 °C, and the Feiser workup[162] performed. The organic layer was dried ($MgSO_4$), filtered, and solvent evaporated under reduced pressure to give alcohol **259**[108] as a clear liquid that was used without purification in the next steps. To a solution of Ph_3P (910 mg, 3.47 mmol) and imidazole (473 mg, 6.94 mmol) in CH_2Cl_2 (25 mL) was added iodine (880 mg, 3.47 mmol) at 0 °C. After 15 min, alcohol **259** (550 mg, 3.16 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the suspension was stirred for 2 h at rt. The solvent was evaporated under reduced pressure to give dark yellow/orange slurry, which was then diluted with petrol (100 mL) and filtered through a pad of celite. The solvent evaporated under reduced pressure and residue purified by column chromatography (2% Et_2O in petrol) to give alkyl iodide **260** (472 mg, 53%) as colourless oil, $R_f = 0.42$ (2% Et_2O in petrol); ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.59 (2H, d, *J* 12.0, CH_2O), 3.41 (2H, d, *J* 12.0, CH_2O), 3.34–3.23 (2H, m, CH_2I), 2.39–2.27 (2H, m, $C\mathit{H_2}CH_2I$), 1.37 (3H, s, CH_3), 1.04 (3H, s, CH_3), 0.86 (3H, s, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 120.2 (O-C-O), 65.9 (2xCH_2O), 42.7 ($\mathit{C}H_2CH_2I$), 30.1 ($\mathit{C}(CH_3)_2$), 25.8 ($C\mathit{C}H_3$), 25.1 ($C(\mathit{C}H_3)_2$), –0.7 (CH_2I).

(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-2,5,5-trimethyl-1,3-dioxane (261)



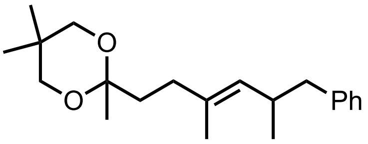
To a Schlenk tube was added Mn dust (1.5 mg, 0.027 mmol), NiI_2(bpy)[105] (0.13 mg, 0.00028 mmol), alkyl iodide **260** (4 mg, 0.014 mmol) and alkenyl iodide (±)–**189** (4 mg, 0.014 mmol) and the flask evacuated and refilled with argon (x3). DMPU (0.1 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (0.4 μL, 0.0028 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (2 mL) was then added and the aq layer extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (1% EtOAc in petrol) to give alkene (*E*)–**261** (3.8 mg, 85%, 3:1 *E/Z*) as a colourless oil; R_f 0.59 (1% EtOAc in petrol); **Major:** IR (film) 3027 s, 2954 s, 2925 s, 2864 s, 1495 m, 1252 m, 1121 s, 1089 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.27–7.22 (2H, m, ArCH), 7.19–7.14 (3H, m, ArCH), 5.20 (1H, dq, *J* 9.0, *J* 1.5, HC=C), 3.50 (2H, d, *J* 11.0, CH_2O), 3.45–3.37 (2H, m, CH_2O), 2.75–2.69 (1H, m, C*H*CH_3), 2.59–2.55 (2H, m, CH_2Ph), 2.46–2.42 (2H, m, H_2C=C), 2.05–2.01 (2H, m, CH_2), 1.52 (3H, d, *J* 1.5, C=CCH_3), 1.44 (3H, s, OCCH_3), 1.05 (3H, d, *J* 7.0, CHCH_3), 1.04 (3H, s, CH_3CCH_3), 0.72 (3H, s, CH_3CCH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 141.32 (*C*=CH), 134.2 (C=*C*H), 130.2 (ArC), 129.44 (2xArCH), 128.1 (2xArCH), 125.70 (ArCH), 99.1 (O-*C*Me-O), 70.6 (OCH_2), 70.50 (OCH_2), 44.2 (*C*H_2Ph), 36.5 (*C*HCH_3), 34.7 (CH_2), 33.4 (CH_2), 30.11 (OC*C*H_3), 26.0 (*C*H_3CCH_3), 22.9 (CH_3C*C*H_3), 21.1 (CH*C*H_3), 20.9 (C=C*C*H_3), 16.4 (CH_3*C*CH_3); HRMS *m/z* (M+H^+) found 317.2475, $C_{21}H_{33}O_2$ requires 317.2475; Discernible data for (*Z*)–**261**: ^{1}H NMR (500 MHz; $CDCl_3$) δ 5.14 (1H, d, *J* 9.0, HC=C), 1.97 (3H, d, *J* 1.5, C=CCH_3), 1.42 (3H, s, OCCH_3), 1.07 (3H, d, *J* 7.0, CHCH_3), 1.06 (3H, s, CH_3CCH_3), 0.71 (3H, s, CH_3CCH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 134.1 (C=*C*H), 131.3 (ArC), 125.8 (ArCH), 98.9 (O-*C*Me-O), 70.5 (OCH_2), 70.47 (OCH_2), 44.4 (*C*H_2Ph), 35.8 (*C*HCH_3), 23.6 (*C*H_3CCH_3), 22.7 (CH_3C*C*H_3), 21.0 (CH*C*H_3), 20.8 (C=C*C*H_3).

(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-2,5,5-trimethyl-1,3-dioxane (261)



To a Schlenk tube was added Mn dust (1.5 mg, 0.027 mmol), $NiI_2(bpy)$[105] (0.13 mg, 0.00028 mmol), alkyl iodide **260** (4 mg, 0.014 mmol), alkenyl iodide (±)–**189** (4 mg, 0.014 mmol) and PhCN (70 µL, 0.0007 mmol) and the flask evacuated and refilled with argon (x3). DMPU (0.1 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (0.4 µL, 0.0028 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (2 mL) was then added and the aq layer extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (1% EtOAc in petrol) to give alkene **261** (2.2 mg, 50%, 1:2 *E/Z*) as a colourless oil, $R_f = 0.59$ (1% EtOAc in petrol); ^1H NMR (500 MHz; C_6D_6) δ 5.10 (Minor 1H, dq, *J* 9.0, *J* 1.5, HC=C), 5.04 (Major 1H, d, *J* 9.0, HC=C). Other analytical data identical to that previously reported.

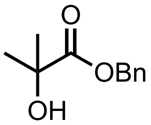
(*E*)-2-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-2,5,5-trimethyl-1,3-dioxane (261)



To a Schlenk tube was added Mn dust (1.5 mg, 0.027 mmol), $NiI_2(bpy)$[105] (0.13 mg, 0.00028 mmol), alkyl iodide **260** (7.9 mg, 0.028 mmol) and alkenyl iodide (±)–**189** (4 mg, 0.014 mmol) and the flask evacuated and refilled with argon (x3). DMF (0.1 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (0.4 µL, 0.0028 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. H_2O (2 mL) was then added and the aq layer extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by column chromatography (1% EtOAc in petrol) to give alkene **261** (3.9 mg, 88%, 20:1 *E/Z*) as a colourless oil; $R_f = 0.59$ (1% EtOAc in petrol).

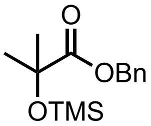
Analytical data identical to that previously reported.

Benzyl 2-hydroxy-2-methylpropanoate (277)[117]



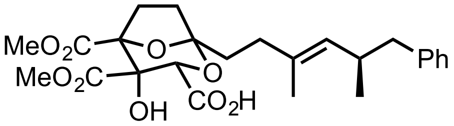
To a solution of α-hydroxyisobutyric acid **276** (2.00 g, 19.2 mmol) and $NaHCO_3$ (3.33 g, 19.5 mmol) in CH_2Cl_2 (36 mL) and H_2O (36 mL) were added BnBr (2.49 mL, 21.0 mmol) and tetrabutylammonium iodide (6.97 g, 18.9 mmol) and stirred at rt for 2 days. The mixture was then extracted with Et_2O (3x50 mL). The combined organic layers dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue was purified by column chromatography (20% EtOAc in petrol) to give benzyl ester **277** (2.13g, 57%) as colourless oil, $R_f = 0.43$ (20% EtOAc in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.25–7.18 (5H, m, ArCH), 5.21 (2H, s, CH_2Ph), 3.51 (1H, br s, OH), 1.46 (6H, s, $C(CH_3)_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.0 (C=O), 135.4 (ArC), 128.5 (2xArCH), 128.3 (ArCH), 127.9 (2xArCH), 72.0 ($\mathit{C}(CH_3)_2$), 67.1 (CH_2Ph), 27.0 ($C(\mathit{C}H_3)_2$).

Benzyl 2-methyl-2-((trimethylsilyl)oxy)propanoate (278)



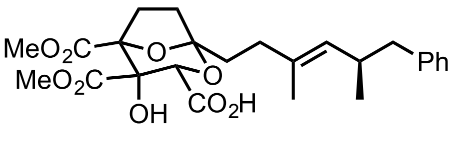
To a solution of benzyl ester **277** (1.50 g, 7.72 mmol) and imidazole (0.893 g, 13.1 mmol) in CH_2Cl_2 (37 mL) was added TMSCl (1.57 mL, 12.4 mmol) dropwise and allowed to stir at rt. After 2 h, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried (MgSO4), filtered, evaporated under reduced pressure and the residue was purified by column chromatography (20% Et2O in Petrol) to give siloxybenzyl ester **278** (1.95 g, 95%) as colourless oil, $R_f = 0.73$ (20% Et2O in Petrol); IR (film, υ_{max} cm^{-1}) 2957 w, 1744 s, 1138 s, 841 s; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.25–7.18 (5H, m, ArCH), 5.03 (2H, s, CH_2Ph), 1.36 (6H, s, C(CH$_3$)$_2$), 0.00 (9H, s, OTMS); ^{13}C NMR (100 MHz; $CDCl_3$) δ 175.6 (C=O), 135.9 (ArC), 128.6 (2xArCH), 128.3 (ArCH), 128.1 (2xArCH), 75.1 (*C*(CH_3)$_2$), 66.6 (CH_2Ph), 28.7 (C(CH$_3$)$_2$), 2.10 (OTMS); HRMS m/z (M+Na$^+$) found 289.1230, $C_{14}H_{22}NaO_3Si$ requires 289.1230.

(1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-Dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-4,5-bis(methoxycarbonyl)-2,8-dioxabicyclo[3.2.1]octane-3-carboxylic acid (280)



To a solution of siloxytriester **232** (18 mg, 0.032 mmol) in THF (0.1 mL) was added a solution of TBAF (60 μL, 1.0 M in THF, 0.064 mmol) at rt. After 4 h, H_2O (2 mL) was added and the aq layer was extracted with EtOAc (3x5 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% EtOAc in CH_2Cl_2) to give hydroxyacid **280**[30] (10.3 mg, 67%) as colourless glass, R_f = 0.37 (10% EtOAc in CH_2Cl_2); $[\alpha]_D^{25} = -96.4$ (*c* 0.1, MeOH); IR (film, υ_{max} cm^{-1}) 3437 br, 3026 s, 2954 s, 2919 s, 2850 s, 1739 s, 1690 s, 1625 s, 1438 s, 1204 w, 1124 w, 700 s; ^1H NMR (500 MHz; CD_3OD) δ 7.26–7.19 (2H, m, ArCH), 7.16–7.10 (3H, m, ArCH), 5.03 (1H, d, *J* 9.0, HC=C), 4.85 (1H, s, C*H*CO_2Me), 3.80 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.08–3.01 (1H, m, H_{endo} of C^6H_2), 2.69–2.57 (1H, m, C*H*CH_3 and 1H of CH_2Ph), 2.47 (1H, dd, *J* 7.0, 13.0, CH_2Ph), 2.20–2.09 (2H, m, C^7H_2), 2.08–1.93 (4H, m, CCH_2CH_2), 1.90–1.83 (1H, m, 1H_{exo} of C^6H_2), 1.43 (3H, d, *J* 1.0, CCH_3), 0.96 (3H, d, *J* 7.0, CHCH_3); ^{13}C NMR (125 MHz; CD_3OD) δ 171.8 (*C*O_2Me), 170.7 (*C*O_2Me), 169.5 (*C*O_2Me), 142.4 (*C*=CH), 134.9 (ArC), 131.8 (C=*C*H), 130.3 (2xArCH), 129.0 (2xArCH), 126.7 (ArCH), 110.0 (O–C^1–O), 89.4 ($C^5$$CO_2Me$), 76.6 ($C^4$$CO_2Me$), 75.7 (*C*H$CO_2$Me), 53.3 ($CO_2$*Me*), 52.9 ($CO_2$*Me*), 45.1 (*C*$H_2$Ph), 36.3 (*C*H$CH_3$), 35.9 ($C^6H_2$), 34.6 ($C^7H_2$), 31.9 ($CCH_2CH_2CMe$), 30.3 ($CH_2$), 21.4 (CH*C*$H_3$), 16.1 (C=C*C*$H_3$); HRMS *m/z* $(M–H)^+$ found 475.1973, $C_{25}H_{31}O_9$ requires 475.1974.

(1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-Dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-4,5-bis(methoxycarbonyl)-2,8-dioxabicyclo[3.2.1]octane-3-carboxylic acid (280)

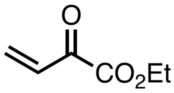


To a Schlenk tube was added Mn dust (2.9 mg, 0.528 mmol), $NiI_2(bpy)$[105] (0.3 mg, 0.0007 mmol, 2.5 mol%), siloxy iodide **256** (14 mg, 0.026 mmol) and (*R*-)–alkenyl iodide **139** (7.6 mg, 0.026 mmol) and the flask evacuated and refilled with argon (x3).

DMF (0.2 mL) was added to the reaction mixture, followed by freshly distilled TMSCl (0.67 µL, 0.0053 mmol). The reaction mixture was then allowed to stir vigorously at rt overnight. TBAF (40 µL, 0.04 mmol, 1 M in THF) was added and the mixture stirred at rt for 2 h. H_2O (3 mL) was then added and the aq layer extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue was purified by column chromatography to give hydroxy acid **280**[30] (8.6 mg, 69%) as colourless oil.

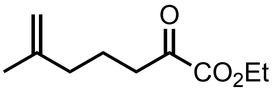
Analytical data identical to previously reported.

Ethyl 2-oxobut-3-enoate (291)[123]



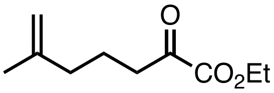
A solution of diethyl oxalate (0.93 mL, 6.85 mmol) in THF/Et_2O (60 mL, 1:1) was cooled to –78 °C and was slowly treated with a solution of vinyl magnesium bromide **290** (10.3 mL, 10.3 mmol, 1 M in THF). The solution was stirred for 30 min before it was quenched with HCl (2 mL, 2 M), warmed to rt, extracted with Et_2O (3x50 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% Et_2O in petrol) to give Ethyl 2-oxobut-3-enoate (**291**) (379 mg, 43%) as a colourless oil; $R_f = 0.29$ (20% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 6.89 (1H, dd, *J* 18.0, *J* 11.0, $H_2C{=}CH$), 6.54 (1H, d, *J* 18.0, 1H of $H_2C{=}CH$), 6.10 (1H, d, *J* 11.0, 1H of $H_2C{=}CH$), 4.35 (2H, q, *J* 7.0, CH_2CH_3), 1.37 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 183.8 (C=O), 161.8 (CO_2Et), 134.3 ($H_2C{=}CH$), 131.3 ($H_2C{=}CH$), 62.6 (CH_2CH_3), 14.1 (CH_2CH_3).

Ethyl 6-methyl-2-oxohept-6-enoate (293)



Following the general procedure **A(i)** using Mg turnings (206 mg, 8.46 mmol), 5-bromo-2-methylpent-1-ene **330**[163] (600 mg, 3.68 mmol) and diethyl oxalate (0.40 mL, 2.94 mmol) to give ethyl 6-methyl-2-oxohept-6-enoate **(293)** (542 mg, 63%) as colourless oil; $R_f = 0.79$ (20% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 2930 w, 1726 s, 1447 w, 1254 s, 1084 s, 1045 s; ^1H NMR (500 MHz; $CDCl_3$) δ 4.75 (1H, s, 1H of $H_2C{=}C$), 4.69 (1H, s, 1H of $H_2C{=}C$), 4.32 (2H, q, *J* 7.0, CH_2CH_3), 2.84 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.07 (2H, t, *J* 7.0, $CH_2C{=}CH_2$), 1.80 (2H, q, *J* 7.5, $CH_2CH_2CH_2C{=}O$), 1.71 (3H, s, $CH_3C{=}C$), 1.37 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.7 ($C{=}OCO_2Et$), 161.3 ($C{=}OCO_2Et$), 144.7 ($CH_3C{=}C$), 111.1 ($C{=}CH_2$), 62.5 (CH_2CH_3), 38.6 ($CH_2C{=}O$), 36.9 ($CH_2C{=}CH_2$), 22.2 ($CH_3C{=}CH_2$), 20.8 ($CH_2CH_2CH_2C{=}O$), 14.1 (CH_2CH_3); HRMS *m/z* ($M+Na^+$), found 185.1174, $C_{10}H_{17}O_3$ requires 185.1172.

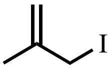
Ethyl 6-methyl-2-oxohept-6-enoate (293)



To a mixture of $PdCl_2(PhCN)_2$[129] (9.4 mg, 0.024 mmol) in CH_2Cl_2 (5 mL) was added alcohol **310** (90 mg, 0.49 mmol) at rt. After 2 h, and the mixture was evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give ketoester **293** (39.8 mg, 44%) as colourless oil.

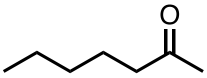
Analytical data identical to previously reported.

4-Iodo-2-methylbut-1-ene (297)[133]



To a solution of Ph_3P (5.72 g, 21.8 mmol) and imidazole (2.97 g, 43.6 mmol) in CH_2Cl_2 (30 mL) was added I_2 (5.53 g, 21.8 mmol) at 0 °C. After 10 min, alcohol **296** (2.00 mL, 19.8 mmol) was added dropwise and the suspension was stirred for 2 h at rt. The solvent was removed under reduced pressure to give dark yellow/orange slurry, which was then diluted with petrol (100 mL) and filtered through a pad of celite. The solvent evaporated under reduced pressure and residue purified by column chromatography (petrol) to give iodide **297**[164] (3.88 g, 93%) as colourless oil; R_f = 0.61 (petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.87 (1H, m, 1 H of C=CH_2), 4.76 (1H, m, 1 H of C=CH_2), 3.27 (2H, t, *J* 7.0, CH_2I), 2.59 (2H, t, *J* 7.0, C*H*$_2$$CH_2I$), 1.75 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 143.7 (*C*=CH_2), 112.5 (C=*C*H_2), 41.1 (*C*H_2CH_2I), 21.1 (CH_3), 12.2 (CH_2I), 3.3 (CH_2I).

Heptan-2-one (302)[122]

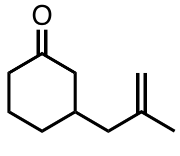


A solution of CuI (118 mg, 0.47 mmol) and Zn (193 mg, 2.96 mmol) in EtOH/H_2O (1.62 mL, 9:1) was sonicated for 10 min before a solution of MVK **294** (0.1 mL, 1.23 mmol) and 1-iodobutane **300** (0.2 mL, 1.85 mmol) in EtOH/H_2O (5.6 mL, 9:1) was added dropwise. Sonication was continued for 30 min before the mixture was poured onto brine (10 mL) and extracted with CH_2Cl_2 (3x10 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give heptan-2-one (**302**) (84.4

mg, 53%) as a colourless oil; R_f = 0.57 (petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.42 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.14 (3H, s, $C{=}OCH_3$), 1.63–1.55 (2H, m, $CH_2CH_2C{=}O$), 1.34–1.26 (4H, m, CH_2CH_2), 0.88 (3H, t, *J* 7.0, CH_3CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 209.6 (C=O), 44.0 ($CH_2C{=}O$), 31.7 (CH_2), 29.0 (CH_3CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.2 (CH_3CH_2).

When CuI (118 mg, 0.47 mmol) and Zn (193 mg, 2.96 mmol) in EtOH/H_2O (1.62 mL, 9:1) was used with MVK **294** (0.1 mL, 1.23 mmol) and iodododecane (0.34 mL, 1.85 mmol) in EtOH/H_2O (5.6 mL, 9:1), tetradecan-2-one (100 mg, 38%) was formed as a colourless oil; R_f = 0.68 (petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.39 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.11 (3H, s, $C{=}OCH_3$), 1.54 (2H, p, *J* 6.0, $CH_2CH_2C{=}O$), 1.32–1.19 (18H, m, CH_2), 0.86 (3H, t, *J* 7.0, CH_3CH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 209.4 (C=O), 43.9 ($CH_2C{=}O$), 32.0 (CH_2), 29.9 (CH_3CH_2), 29.7 (CH_2), 29.64 (CH_2), 29.62 (CH_2), 29.54 (CH_2), 29.51 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 24.0 (CH_2), 22.8 (CH_2), 14.2 (CH_3CH_2).

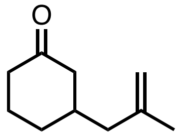
3-(2-Methylallyl)cyclohexan-1-one (304)[131]



Mg turnings (53.0 mg, 2.16 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. THF/Et_2O (2 mL, 1:1) was then added followed by dropwise addition of methallyl bromide **292** (0.22 mL, 2.16 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of CuBr•SMe_2 (488 mg, 2.37 mmol) and LiCl (116 mg, 2.74 mmol) in THF/Et_2O (2 mL, 1:1) at –78 °C. TMSCl (0.35 mL, 2.74 mmol) was then added dropwise before cyclohexenone **299** (0.20 mL, 1.08 mmol) was added to the mixture.

After 2 h, the reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O (3x50 mL), washed with brine (20 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% Et_2O in petrol) to give alkene **304** (21.1 mg, 13%) as colourless oil; $R_f = 0.22$ (20% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 4.78 (1H, s, 1H of CCH_2), 4.67 (1H, s, 1H of CCH_2), 2.41–2.21 (3H, m, $CH_2C{=}O$ and 1H of $CHCH_2C{=}O$), 2.10–1.87 (6H, m, $CH_2CH_2C{=}O$, $CHCH_2$ and 1H of $CHCH_2C{=}O$), 1.74–1.61 (1H, m, 1H of CH_2CH_2CH), 1.68 (3H, s, CH_3), 1.35–1.32 (1H, m, 1H of CH_2CH_2CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 211.7 (C=O), 141.9 ($C{=}CH_2$), 111.9 ($C{=}CH_2$), 47.7 ($CH_2C{=}O$), 45.5 ($CH_2C{=}O$), 41.7 ($CHCH_2C{=}CH_2$), 36.6 (CH), 31.2 (CH_2CH), 25.2 ($CH_2CH_2C{=}O$), 22.0 (CH_3).

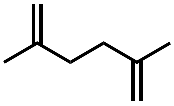
3-(2-Methylallyl)cyclohexan-1-one (304)[131]



To a suspension of $InCl_3$ (45.0 mg, 0.25 mmol) in CH_2Cl_2 (6 mL) were added cyclohexenone **299** (0.2 mL, 2.07 mmol), TMSCl (1.30 mL, 10.3 mmol) and methallylTMS **314** (0.40 mL, 2.3 mmol) at rt. After 30 min, the reaction mixture was quenched with sat. aq $NaHCO_3$, extracted with Et_2O (3x25 mL), the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give 3-(2-Methylallyl)cyclohexan-1-one **(304)** (65.1 mg, 21%) as colourless oil; $R_f = 0.54$ (petrol).

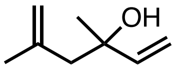
Analytical data identical to previously reported.

2,5-Dimethylhexa-1,5-diene (305)



Mg turnings (89.9 mg, 3.70 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. THF (6 mL) was then added followed by dropwise addition of methallyl bromide **292** (0.37 mL, 3.70 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of MVK **294** (0.10 mL, 1.23 mmol) and CuI (47.0 mg, 0.25 mmol) in THF (6 mL). After 1 h, the reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O (3x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give diene **305**[165] (99.7 mg, 74%) as colourless oil; $R_f = 0.71$ (petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.68 (2H, s, C=CH_2), 4.54 (2H, s, C=CH_2), 2.15 (4H, s, 2xCH_2), 1.73 (6H, s, 2xCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 145.7 (*C*=CH_2), 109.7 (C=*C*H_2), 36.1 (2xCH_2), 22.5 (2xCH_3).

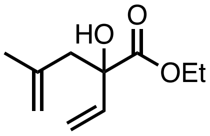
3,5-Dimethylhexa-1,5-dien-3-ol (306)



Mg turnings (89.9 mg, 3.70 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. Et_2O (6 mL) was then added followed by dropwise addition of methallyl bromide **292** (0.37 mL, 3.70 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of MVK **294** (0.10 mL, 1.23 mmol) and CuI (47.0 mg, 0.25 mmol) in THF (6 mL).

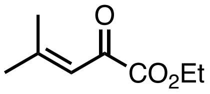
After 1 h, the reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O (3x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% Et_2O in petrol) to give diene **306**[126] (47.0 mg, 30%) as colourless oil; $R_f = 0.29$ (20% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 5.97 (1H, dd, *J* 17.0, *J* 10.0, *H*C=CH_2), 5.24 (1H, dd, *J* 17.0, *J* 1.5, 1H of HC=C*H₂*), 5.04 (1H, dd, *J* 10.0, *J* 1.5, 1H of HC=C*H₂*), 4.93 (1H, m, 1H of C=CH_2), 4.78 (1H, m, 1H of C=CH_2), 2.29 (2H, d, *J* 1.5, CH_2), 1.81 (3H, s, C*H₃*C=CH_2), 1.30 (3H, s, HOCC*H₃*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 145.7 (*C*=CH_2), 143.8 (*C*H=CH_2), 114.0 (CH=*C*H_2), 109.7 (C=*C*H_2), 82.0 (HO*C*CH_3), 45.2 (CH_2), 22.1 (HOC*C*H_3), 21.7 (*C*H_3C=CH_2).

Ethyl 2-hydroxy-4-methyl-2-vinylpent-4-enoate (310)



Mg turnings (94.9 mg, 3.90 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. THF/Et_2O (5 mL, 1:1) was then added followed by dropwise addition of methallyl chloride **308** (0.23 mL, 2.34 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of enone **291** (200 mg, 1.56 mmol) and CuI (59.5 mg, 0.31 mmol) in THF/Et_2O (5 mL, 1:1) at –78 °C. After 2 h, the reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O (3x50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give alcohol **310** (94.8 mg, 33%) as colourless oil; $R_f = 0.29$ (20% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 2940 w, 1726 s, 1448 w, 1254 s, 890 s; ^1H NMR (500 MHz; $CDCl_3$) δ 6.02 (1H, dd, *J* 17.0, *J* 10.0, *H*C=CH$_2$), 5.52 (1H, dd, *J* 17.0, *J* 1.0, 1H of HC=C*H$_2$*), 5.19 (1H, dd, *J* 10.0, *J* 1.0, 1H of HC=C*H$_2$*), 4.88 (1H, dq, *J* 1.5, *J* 1.0, 1H of C=CH$_2$), 4.78 (1H, m, 1H of C=CH$_2$), 4.24 (2H, q, *J* 7.0, C*H$_2$*CH$_3$), 2.64 (1H, dd, *J* 14.0, *J* 1.0, 1H of CH$_2$), 2.40 (1H, dd, *J* 14.0, *J* 1.0, 1H of CH$_2$), 1.78 (3H, s, C*H$_3$*C=CH$_2$), 1.32 (3H, t, *J* 7.0, HOCC*H$_3$*); ^{13}C NMR (125 MHz; CDCl$_3$) δ 174.8 (C=O), 141.2 (*C*=CH$_2$), 139.1 (*C*H=CH$_2$), 115.2 (C=*C*H$_2$), 115.0 (CH=*C*H$_2$), 77.7 (HOC), 62.4 (*C*H$_2$CH$_3$), 46.8 (CH$_2$), 24.1 (*C*H$_3$C=CH$_2$), 14.3 (CH$_2$*C*H$_3$); HRMS *m/z* $(M+H)^+$ found 185.1175, $C_{10}H_{17}O_3$ requires 185.1172.

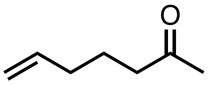
Ethyl 4-methyl-2-oxopent-3-enoate (312)



Mg turnings (893 mg, 36.8 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. THF/Et$_2$O (30 mL, 1:1) was then added followed by dropwise addition of methallyl chloride **308** (2.16 mL, 22.1 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of diethyl oxalate (2.00 mL, 14.7 mmol) in THF/Et$_2$O (30 mL, 1:1) at –85 °C. After 2 h, the reaction was quenched with sat. aq NH$_4$Cl and extracted with Et$_2$O (3x50 mL). The combined organic layers were dried (MgSO$_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% Et$_2$O in petrol) to give enone **312**[130] (1.64 mg, 71%) as colourless oil; $R_f = 0.34$ (10% Et$_2$O in petrol); ^{1}H NMR (400 MHz; CDCl$_3$) δ 6.79 (1H, dt, *J* 4.0, *J* 1.0, CH), 4.32 (2H, q, *J* 7.0, C*H$_2$*CH$_3$), 2.26 (3H, d, *J* 1.0, CH$_3$), 2.04 (3H, d, *J* 1.0, CH$_3$), 1.38 (3H, t, *J* 7.0, CH$_2$C*H$_3$*); ^{13}C NMR (100 MHz; CDCl$_3$) δ 182.1 (C=O), 164.7 (*C*O$_2$Et), 162.6

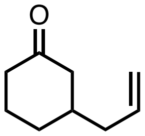
(C=*C*Me$_2$), 119.2 (*C*H=CMe$_2$), 62.3 (*C*H$_2$CH$_3$), 28.6 (C*C*H$_3$), 21.9 (C*C*H$_3$), 14.1 (CH$_2$*C*H$_3$).

Hept-6-en-2-one (315)[131]



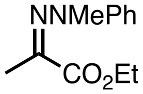
To a suspension of InCl$_3$ (54.0 mg, 0.25 mmol) in CH$_2$Cl$_2$ (8 mL) were added MVK **294** (0.2 mL, 2.47 mmol), TMSCl (1.57 mL, 12.3 mmol) and allylTMS **313** (0.43 mL, 2.7 mmol) at rt. After 30 min, the reaction mixture was quenched with sat. aq NaHCO$_3$, extracted with Et$_2$O (3x25 mL), the combined organic layers were washed with H$_2$O (30 mL) and brine (30 mL), dried (MgSO$_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give hept-6-en-2-one **(315)** (29.4 mg, 11%) as colourless oil; $R_f = 0.54$ (petrol); ^{1}H NMR (400 MHz; CDCl$_3$) δ 5.78 (1H, ddt, *J* 16.0, *J* 10.0, *J* 6.0, *H*C=CH$_2$), 5.01 (2H, m, HC=C*H$_2$*), 2.45 (2H, t, *J* 7.0, CH$_2$C=O), 2.14 (3H, s, CH$_3$), 2.07 (2H, q, *J* 7.0, C*H$_2$*CH), 1.68 (2H, quin, *J* 7.0, C*H$_2$*CH$_2$CH); ^{13}C NMR (100 MHz; CDCl$_3$) δ 209.1 (C=O), 137.9 (*C*HCH$_2$), 115.3 (CH*C*H$_2$), 42.8 (*C*HC=O), 33.2 (*C*H$_2$CH=CH$_2$), 30.9 (CH$_3$), 22.7 (*C*H$_2$CH$_2$CH=CH$_2$).

3-Allylcyclohexan-1-one (316)[131]



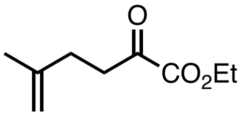
To a suspension of InCl$_3$ (45.0 mg, 0.25 mmol) in CH$_2$Cl$_2$ (6 mL) were added cyclohexenone **299** (0.2 mL, 2.07 mmol), TMSCl (1.30 mL, 10.3 mmol) and allylTMS **313** (0.36 mL, 2.3 mmol) at rt. After 30 min, the reaction mixture was quenched with sat. aq $NaHCO_3$, extracted with Et_2O (3x25 mL), the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (petrol) to give 3-allylcyclohexan-1-one **(316)** (33.1 mg, 12%) as colourless oil; $R_f = 0.56$ (petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 5.93–5.73 (1H, m, C*H*CH_2), 5.17–4.97 (2H, m, CHC*H*$_2$), 2.45–2.23 (3H, m, $CH_2C=O$ and 1H of CHC*H*$_2$C=O), 2.12–1.80 (6H, m, C*H*$_2$$CH_2C=O$, C*H*C*H*$_2$ and 1H of CHC*H*$_2$C=O), 1.41–1.32 (1H, m, 1H of CH_2C*H*$_2$CH), 1.35–1.32 (1H, m, 1H of CH_2C*H*$_2$CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 211.7 (C=O), 136.1 (*C*H=CH_2), 115.9 (CH=*C*H$_2$), 47.7 (*C*H$_2$C=O), 42.1 (*C*H$_2$C=O), 40.7 (CH*C*H$_2$C=CH_2), 38.6 (CH), 31.2 (*C*H$_2$CH), 25.2 (*C*H$_2$$CH_2C=O$).

Ethyl (*E*)-2-(2-methyl-2-phenylhydrazineylidene)propanoate (319)[134]



$PhNMeNH_2$ (2.31 mL, 20.0 mmol) was added dropwise to a solution of ethyl pyruvate (2.22 mL, 20.0 mmol) in Et_2O (50 mL) at rt. After 4 h, the solvent was evaporate under reduced pressure and the residue purified by column chromatography (30% EtOAc in petrol) to give ethyl (*E*)-2-(2-methyl-2-phenylhydrazineylidene)propanoate **(319)** (3.31 g, 75%) as yellow oil; $R_f = 0.28$ (30% EtOAc in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.36–7.29 (2H, m, 2xArCH), 7.16–7.11 (2H, m, 2xArCH), 7.03 (1H, t, *J* 7.0, 2xArCH), 4.36 (2H, t, *J* 7.0, C*H*$_2$$CH_3$), 3.44 (3H, s, NMe), 2.07 (3H, s, $CH_3C=N$), 1.40 (CH_2C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 165.7 (*C*O$_2$Et), 149.9 (C=N), 145.0 (ArC), 129.1 (2xArCH), 122.5 (ArCH), 117.9 (2xArCH), 61.7 (*C*H$_2$$CH_3$), 44.6 (NMe), 17.1 (*C*H$_3$C=N), 14.4 (CH_2*C*H$_3$).

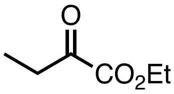
Ethyl 5-methyl-2-oxohex-5-enoate (322)



A solution of hydrazone **319** (200 mg, 0.91 mmol), THF (3 mL) was cooled to –78 °C. To this reaction mixture was added dropwise a pre-cooled (–78 ºC) solution of LDA {freshly prepared by adding dropwise *n*-BuLi (0.40 mL, 2.5 M in hexanes, 1.00 mmol) to a solution of freshly distilled *i*-Pr_2NH (0.13 mL, 1.00 mmol) in THF (5 mL) at 0 °C}. The reaction mixture was further stirred for 2 h at –78 °C, before methallyl bromide (**292**) (0.14 mL, 1.36 mmol) was added dropwise and the mixture was further stirred for 4 h. The reaction mixture was quenched at the same temperature with sat. aq NH_4Cl (10 mL), extracted with EtOAc (3x30 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure. To the residues in THF (5 mL) was added HCl (3 mL, 1 M) and stirred at rt for 2 h. The mixture was extracted with EtOAc (3x30 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (20% EtOAc in petrol) to give ketoester **322** (62.2 mg, 25%, 52% brsm) as colourless oil.

Analytical data identical to previously reported.

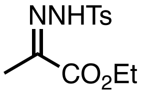
Ethyl 2-oxobutanoate (324)[134]



A solution of hydrazone **319** (200 mg, 0.91 mmol) in THF (3 mL) was cooled to –78 °C. To this reaction mixture was added dropwise a pre-cooled (–78 ºC) solution of

LDA {freshly prepared by adding dropwise *n*-BuLi (0.40 mL, 2.5 M in hexanes, 1.00 mmol) to a solution of freshly distilled *i*-$\mathrm{Pr_2NH}$ (0.13 mL, 1.00 mmol) in THF (5 mL) at 0 °C}. The reaction mixture was further stirred for 2 h at –78 °C, before MeI (0.08 mL, 1.36 mmol) was added dropwise and the mixture was further stirred for 4 h. The reaction mixture was quenched at the same temperature with sat. aq $\mathrm{NH_4Cl}$ (10 mL), extracted with EtOAc (3x30 mL), washed with brine (10 mL), dried ($\mathrm{MgSO_4}$), filtered, evaporated under reduced pressure. To the residues in THF (5 mL) was added HCl (3 mL, 1 M) and stirred at rt for 2 h. The mixture was extracted with EtOAc (3x30 mL), washed with brine (10 mL), dried ($\mathrm{MgSO_4}$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (10% $\mathrm{Et_2O}$ in petrol) to give ethyl 2-oxobutanoate **324** (34.1 mg, 29%) as colourless oil; R_f = 0.50 (10% $\mathrm{Et_2O}$ in petrol); ^{1}H NMR (400 MHz; $\mathrm{CDCl_3}$) δ 4.33 (2H, q, *J* 7.0, $\mathrm{CO_2C}H_2\mathrm{CH_3}$), 2.87 (2H, q *J* 7.0, $\mathrm{CH_3C}H_2\mathrm{C{=}O}$), 1.37 (3H, t, *J* 7.0, $\mathrm{CO_2CH_2C}H_3$), 1.14 (3H, t, *J* 7.0, $\mathrm{C}H_3\mathrm{CH_2C{=}O}$); ^{13}C NMR (100 MHz; $\mathrm{CDCl_3}$) δ 195.1 (C=O), 161.0 ($C\mathrm{O_2Et}$), 62.2 ($\mathrm{CO_2}C\mathrm{H_2CH_3}$), 32.7 ($C\mathrm{H_2C{=}O}$), 14.0 ($\mathrm{CO_2CH_2}C\mathrm{H_3}$), 6.4 ($C\mathrm{H_3CH_2C{=}O}$).

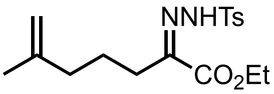
Ethyl (*E*)-2-(2-tosylhydrazineylidene)propanoate (325)



Ethyl pyruvate **318** (2.00 mL, 18.0 mmol) was added to a solution of $\mathrm{TsNHNH_2}$ (4.00 g, 21.6 mmol) in dioxane (30 mL) at rt. The mixture was heated to 70 °C for 2 h before it was cooled to rt, solvent evaporated under reduced pressure and the residue purified by column chromatography (30% EtOAc in petrol) to give a mixture of *E/Z*-hydrazone **325** (4.53 g, 89%, *E/Z* 8:2) as white solids; R_f = 0.31 (30% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3205 w, 2984 w, 1692 s, 1294 s 1166 s, 1082 s, 664 s; ^{1}H

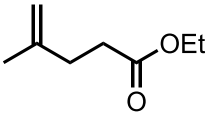
NMR (500 MHz; $CDCl_3$) δ 8.25 (1H, s, NH), 7.81 (2H, m, 2xArH), 7.30 (2H, m, 2xArH), 4.24 (2H, m, C*H₂*CH₃), 2.41 (3H, s, ArCH₃), 2.07 (3H, s, *C*H₃C=N), 1.31 (3H, t, *J* 7.0, CH₂C*H₃*); ^{13}C NMR (125 MHz; $CDCl_3$) δ 163.8 (*C*O₂Et), 144.8 (ArC), 136.2 (C=N), 135.0 (Ar*C*CH₃), 128.2 (2xArCH), 127.9 (2xArCH), 61.9 (*C*H₂CH₃), 21.7 (Ar*C*H₃), 20.1 (*C*H₃C=N), 14.2 (CH₂*C*H₃); HRMS *m/z* (M+Na$^+$) found 307.0721, $C_{12}H_{16}O_4N_2NaS$ requires 307.0723; discernible data for *Z*-isomer: ^{1}H NMR (500 MHz; $CDCl_3$) δ 11.86 (1H, s, NH), 7.87 (2H, m, 2xArH), 4.24 (2H, m, C*H₂*CH₃), 2.41 (3H, s, ArCH₃), 1.97 (3H, s, *C*H₃C=N), 1.31 (3H, t, *J* 7.0, CH₂C*H₃*); ^{13}C NMR (125 MHz; $CDCl_3$) δ 162.4 (*C*O₂Et), 144.3 (ArC), 136.2 (C=N), 135.8 (Ar*C*CH₃), 129.8 (2xArCH), 127.9 (2xArCH), 62.1 (*C*H₂CH₃), 21.7 (Ar*C*H₃), 20.2 (*C*H₃C=N), 14.1 (CH₂*C*H₃).

Ethyl (*Z*)-6-methyl-2-(2-tosylhydrazineylidene)hept-6-enoate (326)



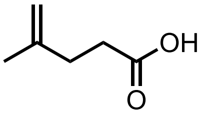
Following the general procedure **A(ii)** using 6-methyl-2-oxohept-6-enoate **(293)** (38.0 mg, 0.206 mmol) and $TsNHNH_2$ (46.0 mg, 0.248 mmol) gave *Z*[166]-hydrazone **326** (37.8 mg, 66%) as colourless oil; $R_f = 0.67$ (20% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 3672 w, 3235 w, 1721 s, 1430 s, 1204 s, 1113 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 11.79 (1H, s, NH), 7.83 (2H, d, *J* 8.0, 2xArCH), 7.30 (2H, d, *J* 8.0, 2xArCH), 4.70 (1H, s, 1H of H₂C=C), 4.61 (1H, s, 1H of H₂C=C), 4.26 (2H, d, *J* 7.0, C*H₂*CH₃), 2.42 (5H, m, ArCH₃ and C*H₂*C=CH₂), 1.92 (2H, t, *J* 7.0, CH₂C*H₂*C=N), 1.66 (3H, s, C*H₃*C=CH₂), 1.61 (2H, t, *J* 7.0, C*H₂*CH₂C=N), 1.32 (3H, t, *J* 7.0, CH₂C*H₃*); ^{13}C NMR (125 MHz; $CDCl_3$) δ 162.3 (CO₂Et), 145.2 (Ar*C*Me), 144.3 (ArC), 139.1 (*C*=CH₂), 135.7 (C=N), 129.7 (ArCH), 128.0 (ArCH), 110.3 (C=*C*H₂), 62.0 (*C*H₂CH₃), 36.9 (*C*H₂C=CH₂), 32.7 (CH_2CH_2C=N), 24.5 (CH_2C=N), 22.4 (CH_3C=CH_2), 21.7 ($ArCH_3$), 14.1 (CH_2CH_3); HRMS *m/z* ($M+Na^+$), found 375.1350, $C_{17}H_{24}N_2NaO_4S$ requires 375.1349.

Ethyl 4-methylpent-4-enoate (328)[139]



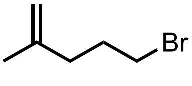
A solution of methallyl alcohol **296** (5.00 mL, 57.8 mmol) and propanoic acid (4.27 mL, 57.3 mmol) in triethyl orthoacetate (125 mL) was heated at reflux for 1 h. Ethanol was removed by fractional distillation through a Vigreux column and heating was continued for a further 1 h. The reaction mixture was cooled to 0 °C, washed with cold H_2O (350 mL) and HCl (100 mL, 1 M) (*caution: exothermic reaction*). The aq layer extracted with Et_2O (3x100 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$ (2x100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow oil. Short-path distillation (50 °C at ~15 mbar) gave ester **328** (4.39 g, 53%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, s, 1H of H_2C=C), 4.69 (1H, s, 1H of H_2C=C), 4.14 (2H, q, *J* 7.0, CH_2CH_3), 2.48–2.32 (4H, m, CH_2C=CH_2 and CH_2C=O), 1.75 (3H, s, CH_3C=CH_2), 1.26 (3H, t, *J* 7.0, CH_2CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (CO_2Et), 144.3 (C=CH_2), 110.4 (C=CH_2), 60.5 (CH_2CH_3), 32.8 (CH_2C=O), 32.8 (CH_2C=CH_2), 22.6 (CH_3C=CH_2), 14.4 (CH_2CH_3).

4-Methylpent-4-enoic acid (329)[140]



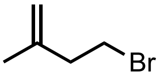
To a solution of ester **328** (4.30 g, 30.2 mmol) in MeOH/H_2O (180 mL, 2:1) at 0 °C was added KOH (6.79 g, 121 mmol). After 10 min, the mixture was heated to reflux. After 4 h, the mixture was cooled to rt and solvent evaporated under reduced pressure. The residue was cooled to 0 °C and acidified with HCl (10 mL, 2 M), extracted with EtOAc (3×50 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue purified by column chromatography (30% EtOAc in petrol) to give acid **329** (2.54 g, 74%) as a colourless oil R_f = 0.22 (30% EtOAc in petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.78 (1H, m, 1H of C=CH_2), 4.72 (1H, m, 1H of C=CH_2), 2.51 (2H, dd, *J* 9.0, *J* 7.0, C*H*$_2$COOH), 2.37 (2H, t, *J* 7.0, C*H*$_2$$CH_2$COOH), 2.11 (3H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 180.0 (COOH), 143.2 (*C*=CH_2), 111.1 (C=*C*H_2), 32.2 (*C*H_2COOH), 32.1 (*C*$H_2$$CH_2$COOH), 22.1 ($CH_3$).

5-Bromo-2-methylpent-1-ene (330)



To a solution of 4-methylpent-4-en-1-ol (1.13 g, 11.3 mmol) in CH_2Cl_2 (5 mL) and Et_3N (4.7 mL, 34.0 mmol) cooled to 0 °C was added dropwise MsCl (1.30 mL, 17.0 mmol) over 15 min. The mixture was stirred at the same temperature for 1 h before it was warmed to rt and stirred for a further 1 h. The mixture was then cooled back to 0 °C and HCl (10 mL, 1 M) was added dropwise, extracted with CH_2Cl_2 (3x30 mL), washed with $NaHCO_3$ (15 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residuals taken to next step without further purification. To a solution of the crude residue in acetone (43 mL) was added LiBr (1.96 g, 22.6 mmol) and the mixture refluxed for 2 h before it was cooled to rt, filtered through a short pad of silica, washed with acetone (2x20 mL) and the residue purified by column chromatography (petrol) to give bromide **330**[167] (0.839 g, 51%) as colourless oil; R_f = 0.48 (petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, s, 1H of $C{=}CH_2$), 4.73 (1H, s, 1H of $C{=}CH_2$), 3.42 (2H, t, *J* 7.0, CH_2Br), 2.17 (2H, t, *J* 7.0, $C\mathit{H}_2CH_2CH_2Br$), 2.00 (2H, quint, *J* 7.0, $C\mathit{H}_2CH_2Br$), 1.73 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 ($\mathit{C}{=}CH_2$), 111.2 ($C{=}\mathit{C}H_2$), 36.2 ($\mathit{C}H_2CH_2CH_2Br$), 33.5 (CH_2Br), 30.7 ($\mathit{C}H_2CH_2Br$), 22.5 ($\mathit{C}H_3$).

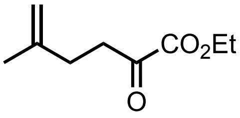
4-Bromo-2-methylbut-1-ene (331)



To a solution of 3-methylbut-3-en-1-ol **142** (5 mL, 49.5 mmol) in CH_2Cl_2 (25 mL) and Et_3N (20.7 mL, 149 mmol) cooled to 0 °C was added dropwise MsCl (5.75 mL, 74.3 mmol) over 15 min. The mixture was stirred at the same temperature for 1 h before it was warmed to rt and stirred for a further 1 h. The mixture was then cooled back to 0 °C and HCl (30 mL, 1 M) was added dropwise, extracted with CH_2Cl_2 (3x30 mL), washed with $NaHCO_3$ (30 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue taken to next step without further purification. To a solution of the crude residue in acetone (200 mL) was added LiBr (9.46 g, 109 mmol) and the mixture refluxed for 2 h before it was cooled to rt, filtered through a short pad of silica, washed with acetone (2x20 mL) and the residuals purified by column chromatography (petrol); to give bromide **142**[168]

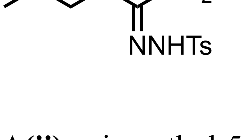
(2.36 g, 32%) as colourless oil; R_f = 0.47 (petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.86 (1H, s, 1H of $C=CH_2$), 4.78 (1H, s 1H of $C=CH_2$), 3.46 (2H, t, *J* 7.0, C*H₂*Br), 2.56 (2H, t, *J* 7.0, CH_2CH_2Br), 1.72 (1H, s, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 142.3 (*C*=CH_2), 112.5 (C=*C*H_2), 40.9 (*C*H_2CH_2Br), 30.5 (*C*H_2Br), 21.9 (CH_3).

Ethyl 5-methyl-2-oxohex-5-enoate (334)



Following the general procedure **A(i)** using Mg turnings (376 mg, 15.48 mmol), 4-bromo-2-methylbut-1-ene **331** (1.00 g, 6.71 mmol) and diethyl oxalate (0.70 mL, 5.16 mmol) to give *α*-ketoester **334**[169] (324 mg, 37%) as colourless oil; R_f = 0.72 (20% Et_2O in petrol); ^{1}H NMR (500 MHz; $CDCl_3$) δ 4.77 (1H, s, 1H of $H_3CC=CH_2$), 4.70 (1H, s, 1H of $H_3CC=CH_2$), 4.33 (2H, q, *J* 7.0, CH_2CH_3), 3.00 (2H, t, *J* 7.0, $CH_2C=O$), 2.35 (2H, t, *J* 7.0, $CH_2CH_2=O$), 1.75 (3H, s, CH_3), 1.38 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.1 (C=O), 161.1 (CO_2Et), 143.6 (*C*=CH_2), 110.8 (C=*C*H_2), 62.5 (*C*H_2CH_3), 37.6 (*C*$H_2C=CH_2$), 30.8 (*C*$H_2C=O$), 22.7 (CH_3), 14.1 (CH_2*C*H_3).

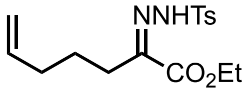
Ethyl (*Z*)-5-methyl-2-(2-tosylhydrazineylidene)hex-5-enoate (337)



Following the general procedure **A(ii)** using ethyl 5-methyl-2-oxohex-5-enoate (**334**) (320 mg, 1.88 mmol) and $TsNHNH_2$ (420 mg, 2.26 mmol) gave *Z*[166]-hydrazone **337**

(537 mg, 84%) as a white solid; R_f = 0.43 (20% EtOAc in petrol); m.p. 42–44 °C; IR (film, υ_{max} cm^{-1}) 3210 w, 2930 w, 1693 m, 1371 s, 1296 s, 1186 s, 1170 s, 1084 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 11.8 (1H, s, NH), 7.83 (2H, d, *J* 8.0, 2xArCH), 7.31 (2H, d, *J* 8.0, 2xArCH), 4.60 (1H, s, 1H of H$_3$CC=C*H$_2$*), 4.54 (1H, s, 1H of H$_3$CC=C*H$_2$*), 4.27 (2H, q, *J* 7.0, C*H$_2$*CH$_3$), 2.58 (2H, t, *J* 7.0, CH$_2$C=N), 2.43 (3H, s, CH$_3$Ar), 2.18 (2H, t, *J* 7.0, C*H$_2$*CH$_2$C=N), 1.65 (3H, s, C*H$_3$*C=CH$_2$), 1.33 (3H, t, *J* 7.0, CH$_2$C*H$_3$*); ^{13}C NMR (125 MHz; CDCl$_3$) δ 162.2 (CO$_2$Et), 144.5 (Ar*C*Me), 144.3 (ArC), 138.7 (*C*=CH$_2$), 135.8 (C=N), 129.7 (ArCH), 128.0 (ArCH), 110.9 (C=*C*H$_2$), 62.0 (*C*H$_2$CH$_3$), 34.8 (*C*H$_2$C=CH$_2$), 31.5 (*C*H$_2$C=N), 22.4 (*C*H$_3$C=CH$_2$), 21.7 (ArCH$_3$), 14.1 (CH$_2$*C*H$_3$); HRMS *m/z* (M+Na$^+$), found 339.1374, $C_{16}H_{23}O_4N_2S$ requires 339.1373.

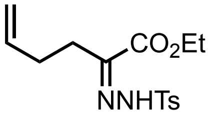
Ethyl (*Z*)-2-(2-tosylhydrazineylidene)hept-6-enoate (338)



Following the general procedure **A** using Mg turnings (1.23 g, 50.6 mmol), 5-bromopent-1-ene **332** (2.0 mL, 16.9 mmol) and diethyl oxalate (1.53 mL, 11.3 mmol). A mixture of crude *α*-ketoester **335** (1.90 g, 11.2 mmol) and TsNHNH$_2$ (2.50 g, 13.4 mmol) gave *Z*[166]–hydrazone **338** (3.04 g, 80% over 2 steps) as a white solid; R_f = 0.44 (20% Et$_2$O in petrol); m.p. 69–71 °C; IR (film, υ_{max} cm^{-1}) 3213 br, 2980 br, 1715 m, 1641 m, 1166 s, 1065 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 11.79 (1H, s, NH), 7.83 (2H, d, *J* 8.0, 2xArCH), 7.31 (2H, d, *J* 8.0, 2xArCH), 5.78–5.68 (1H, m, H$_2$C=C*H*), 4.99–4.92 (2H, m, *H$_2$*C=CH), 4.26 (2H, q, *J* 7.0, C*H$_2$*CH$_3$), 2.48–2.40 (5H, m, C*H$_3$*Ar and C*H$_2$*CH=CH$_2$), 1.96 (2H, q, *J* 7.0, CH$_2$C*H$_2$*C=N), 1.58 (2H, q, *J* 7.5, C*H$_2$*CH$_2$C=N), 1.32 (3H, t, *J* 7.0, CH$_2$C*H$_3$*); ^{13}C NMR (125 MHz; CDCl$_3$) δ 162.2 (*C*O$_2$Et), 144.3

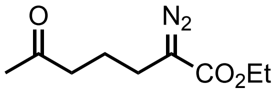
(Ar*C*Me), 139.1 (ArC), 138.2 ($H_2C{=}CH$), 135.8 (C=N), 129.7 (ArCH), 128.0 (ArCH), 115.0 ($H_2C{=}CH$), 62.0 (CH_2CH_3), 32.9 ($CH_2CH{=}CH_2$), 32.5 ($CH_2CH_2C{=}N$), 25.8 ($CH_2CH_2C{=}N$), 21.7 ($ArCH_3$), 14.1 (CH_2CH_3); HRMS *m/z* ($M+Na^+$), found 339.1374, $C_{16}H_{23}N_2O_4S$ requires 339.1373.

Ethyl (*E*)-2-(2-tosylhydrazineylidene)hex-5-enoate (339)



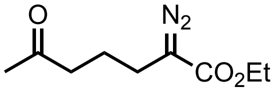
Following the general procedure **A** using Mg turnings (1.23 g, 50.6 mmol), 4-bromobut-1-ene **333** (1.0 mL, 5.88 mmol) and diethyl oxalate (0.53 mL, 3.92 mmol). A mixture of crude *α*-ketoester **336** (612 mg, 3.92 mmol) and $TsNHNH_2$ (876 mg, 4.70 mmol) gave *E*-hydrazone **339** (903 mg, 71%, over 2 steps, containing unknown trace impurity by ^1H NMR) as a white solid; R_f = 0.35 (30% EtOAc in petrol); m.p. 80–82 °C; IR (film, υ_{max} cm^{-1}) 3211 w, 3076 w, 1715 m, 1641 m, 1372 w, 1187 s, 1056 s; ^1H NMR (500 MHz; $CDCl_3$) δ 8.79 (1H, s, NH), 7.86 (2H, d, *J* 8.0, 2xArCH), 7.32 (2H, d, *J* 8.0, 2xArCH), 5.71–5.59 (1H, m, $H_2C{=}CH$), 4.93 (1H, d, *J* 17.0, 1 H of $H_2C{=}CH$), 4.86 (1H, d, *J* 10.0, 1 H of $H_2C{=}CH$), 4.23 (2H, q, *J* 7.0, CH_2CH_3), 2.54 (2H, t, *J* 7.5, $CH_2C{=}N$), 2.43 (3H, s, CH_3Ar), 2.16 (2H, q, *J* 7.5, $CH_2CH_2C{=}N$), 1.31 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 163.7 (CO_2Et), 146.8 (Ar*C*Me), 144.7 (ArC), 136.0 ($H_2C{=}CH$), 134.9 (C=N), 129.7 (ArCH), 128.1 (ArCH), 116.7 ($H_2C{=}CH$), 61.8 (CH_2CH_3), 29.4 ($CH_2CH_2C{=}N$), 25.5 ($CH_2CH_2C{=}N$), 21.7 ($ArCH_3$), 14.2 (CH_2CH_3); HRMS *m/z* ($M+H^+$) found 325.1216, $C_{15}H_{21}N_2O_4S$ requires 325.1217.

Ethyl 2-diazo-6-oxoheptanoate (340)



Following the general procedure **B** using hydrazone **326** (25 mg, 0.071 mmol), CH_2Cl_2 (5 mL) and Et_3N (40 μL, 0.30 mmol) gave diazocarbonyl **340**[146] (8 mg, 57%) as a yellow oil; R_f = 0.43 (30% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 2081 s, 1686 s, 1371 m, 1158 m; ^1H NMR (500 MHz; $CDCl_3$) δ 4.22 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 2.51 (2H, t, *J* 7.0, CH_2C=O), 2.33 (2H, t, *J* 7.5, CH_2CN_2), 2.16 (3H, s, CH_3C=O), 1.80 (2H, quint, *J* 7.0, *J* 7.0, C*H*$_2$CH$_2$CN$_2$), 1.28 (3H, t, *J* 7.0, C*H*$_2$CH$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 208.1 (CH$_3$*C*=O), 167.7 (*C*O$_2$Et), 61.0 (*C*H$_2$CH$_3$), 42.3 (*C*H$_2$C=O), 30.2 (*C*H$_3$C=O), 22.8 (*C*H$_2$CN$_2$), 21.9 (*C*H$_2$CH$_2$CN$_2$), 14.7 (CH$_2$*C*H$_3$) [CN_2 not observed]; HRMS $[M+Na]^+$ found 221.0896, $C_9H_{14}N_2NaO_3$ requires 221.0897.

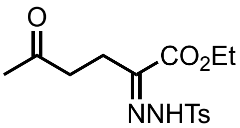
Ethyl 2-diazo-6-oxoheptanoate (340)



Following the general procedure **B** using hydrazone **362** (1.0 g, 3.10 mmol), CH_2Cl_2 (350 mL) and Et_3N (1.73 mL, 12.4 mmol) gave diazoester **340** (348 mg, 57%) as yellow oil; R_f 0.43 (30% Et_2O in petrol).

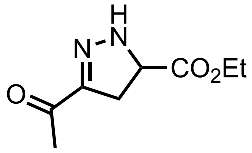
Analytical data identical to that previously reported.

Ethyl (*Z*)-5-oxo-2-(2-tosylhydrazineylidene)hexanoate (341)



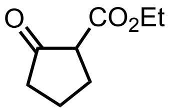
Following the general procedure **B** using hydrazone **337** (180 mg, 0.53 mmol), CH_2Cl_2 (65 mL) and Et_3N (0.30 mL, 2.13 mmol) gave keto hydrazone **341** (36 mg, 20%) as a yellow oil; $R_f = 0.46$ (40% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 2924 w, 1714 s, 1693 m, 1370 s, 1277 s, 1167 s, 1085 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.75 (2H, d, *J* 8.0, 2xArCH), 7.31 (2H, d, *J* 8.0, 2xArCH), 4.25 (2H, q, *J* 7.0, $C\mathit{H_2}CH_3$), 2.72 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.65 (2H, q, *J* 7.5, $C\mathit{H_2}C{=}N$), 2.42 (3H, s, CH_3Ar), 2.14 ($CH_3C{=}O$), 1.31 (3H, t, *J* 7.0, $CH_2C\mathit{H_3}$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.3 (C=O), 162.0 (CO_2Et), 144.4 (Ar*C*Me), 137.1 (ArC), 135.8 (C=N), 129.8 (ArCH), 127.8 (ArCH), 62.2 ($\mathit{C}H_2CH_3$), 38.7 ($\mathit{C}H_2C{=}O$), 30.3 ($\mathit{C}H_3C{=}O$), 26.7 ($\mathit{C}H_2C{=}N$), 21.7 ($ArCH_3$), 14.1 ($CH_2\mathit{C}H_3$); HRMS *m/z* ($M+Na^+$), found 341.1162, $C_{15}H_{21}O_5N_2S$ requires 341.1165.

Ethyl 3-acetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (345)



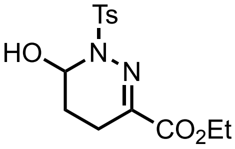
Following the general procedure **B** using hydrazone **337** (100 mg, 0.30 mmol), CH_2Cl_2 (36 mL) and DBU (0.18 mL, 1.18 mmol) gave 2-pyrazoline **345** (22.4 mg, 41%) as a clear oil; $R_f = 0.54$ (40% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3338 br, 2983 w, 1735 s, 1662 s, 1346 m, 1207 s, 1095 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.75 (1H, s, NH), 4.44 (1H, dd, *J* 5.0, *J* 12.5, $C\mathit{H}CO_2Et$), 4.22 (2H, q, *J* 7.0, $C\mathit{H_2}CH_3$), 3.26 (1H, dd, *J* 5.0, *J* 17.5, 1 H of CH_2), 3.10 (1H, dd, *J* 12.5, *J* 17.5, 1 H of CH_2), 2.42 (3H, s, $CH_3C{=}O$), 1.30 (3H, t, *J* 7.0, $CH_2C\mathit{H_3}$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.3 (C=O), 171.9 ($\mathit{C}O_2Et$), 150.7 (C=N), 62.2 ($\mathit{C}H_2CH_3$), 61.7 ($\mathit{C}HCO_2Et$), 33.4 (CH_2), 25.7 ($CH_3C=O$), 14.2 (CH_2CH_3); HRMS *m/z* ($M+H^+$), found 185.0922, $C_8H_{13}O_3N_2$ requires 185.0921.

Ethyl 2-oxocyclopentane-1-carboxylate (353)



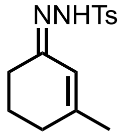
Following the general procedure **B** using hydrazone **338** (500 mg, 1.48 mmol), CH_2Cl_2 (170 mL) and Et_3N (0.82 mL, 5.91 mmol) gave β-ketoester **353**[170] (37 mg, 16%) as a colourless oil; $R_f = 0.54$ (30% EtOAc in petrol); ^1H NMR (500 MHz; $CDCl_3$) δ 4.19 (2H, q, *J* 7.0, CH_2CH_3), 3.14 (1H, t, *J* 9.5, $CHCO_2Et$) 2.33–2.27 (4H, m, $CHCH_2$ and $CHCH_2CH_2$), 2.17–2.10 (1H, m, CH_2CO), 1.89–1.83 (1H, m, CH_2CO), 1.28 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 212.6 (C=O), 169.5 (CO_2Et), 61.5 (CH_2CH_3), 54.9 ($CHCO_2Et$), 38.2 ($CHCH_2$), 27.5 ($CHCH_2CH_2$), 21.1 ($CH_2C=O$), 14.3 (CH_2CH_3).

Ethyl 6-hydroxy-1-tosyl-1,4,5,6-tetrahydropyridazine-3-carboxylate (354)



Following the general procedure **B** using hydrazone **339** (500 mg, 1.54 mmol), CH_2Cl_2 (170 mL) and Et_3N (0.86 mL, 6.17 mmol) gave tetrahydropyridazinol **354** (322 mg, 64%) as a yellow solid; $R_f = 0.58$ (50% EtOAc in petrol); m.p. 122–125 °C; IR (film, υ_{max} cm^{-1}) 3478 br, 2981 w, 1713 w, 1298 w, 1167 s, 1064 s, 726 s, 666 s; ^1H NMR (500 MHz; $CDCl_3$) δ 7.88 (2H, d, *J* 8.0, ArCH), 7.30 (2H, d, *J* 8.0, ArCH), 5.87 (1H, s, C*H*OH), 4.26 (2H, q, *J* 8.0, C*H₂*CH₃), 3.81 (1H, s, OH), 2.68 (1H, dd, *J* 5.0, *J* 18.5, 1H of CH₂C=N), 2.41 (3H, s, ArCH₃), 2.38–2.29 (1H, m, 1H of CH₂C=N), 2.14 (1H, m, 1H of C*H₂*CH₂C=N), 1.57 (1H, m, 1H of C*H₂*CH₂C=N), 1.34 (3H, t, *J* 7.0, CH₂C*H₃*); ^{13}C NMR (125 MHz; CDCl₃) δ 163.4 (*C*O₂Et), 144.6 (Ar*C*Me), 142.7 (ArC), 135.2 (C=N), 129.6 (ArCH), 128.2 (ArCH), 73.4 (CHOH), 61.6 (*C*H₂CH₃), 24.0 (*C*H₂CH₂C=N), 21.7 (ArCH₃), 16.3 (*C*H₂C=N), 14.2 (CH₂*C*H₃); HRMS *m/z* (M+H$^+$), found 327.1009, $C_{14}H_{19}N_2O_5S$ requires 327.1009.

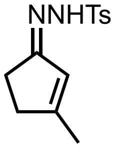
4-Methyl-*N'*-(3-methylcyclohex-2-en-1-ylidene)benzenesulfonohydrazide (357)[171]



Following the general procedure **A(ii)** using 3-methylcyclohex-2-en-1-one (**355**) (2.0 mL, 17.6 mmol) and TsNHNH₂ (4.27 g, 22.9 mmol) in MeOH (15 mL) gave a mixture of *E-/Z-* hydrazone **357** (4.38 g, 89%, 60:40 *E:Z* as determined by ^{1}H NMR NH signals) as a white solid; R_f = 0.35 (30% EtOAc in petrol); ^{1}H NMR (400 MHz; CDCl₃) δ 7.86 (2H, d, *J* 8.0, 2xArCH), 7.73 (1H, s, NH), 7.31 (2H, d, *J* 8.0, 2xArCH), 5.93 (1H, q, *J* 1.5, CH₃C=C*H*), 2.42 (5H, s, ArC*H₃* and C*H₂*C=N), 2.23 (2H, m, CH₂CCH₃), 2.05 (2H, m, C*H₂*CH₂C=N), 1.80 (3H, d, *J* 1.5, CHCC*H₃*); ^{13}C NMR (100 MHz; CDCl₃) δ 169.2 (HC=*C*CH₃), 160.6 (C=N), 144.0 (ArC), 135.7 (ArC), 129.6 (ArCH), 128.0 (ArCH), 126.5 (H*C*=CCH₃), 34.9 (*C*H₂CCH₃), 33.5 (*C*H₂CH₂CCH₃), 26.6 (*C*H₂CN), 21.7 (ArC*C*H₃), 18.1 (HCC*C*H₃). Discernible data for *Z*-isomer: ^{1}H NMR (400 MHz; CDCl₃) δ 6.16 (1H, s, CH₃C=C*H*), 2.30 (2H, m, CH₂C=N), 2.14 (2H, m, C*H₂*CCH₃), 1.85 (3H, s, CHCC*H₃*); ^{13}C NMR (100 MHz; CDCl₃) δ 169.8 (HC=*C*CH₃), 166.7 (C=N), 143.8 (ArC), 129.5 (ArCH), 128.1

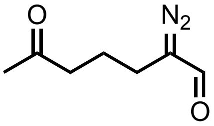
(ArCH), 122.7 (H*C*=CCH$_3$), 34.1 (*C*H$_2$CCH$_3$), 30.1 (*C*H$_2$CN), 21.9 (ArC*C*H$_3$), 18.5 (HCC*C*H$_3$).

4-Methyl-*N'*-(3-methylcyclopent-2-en-1-ylidene)benzenesulfonohydrazide (358)



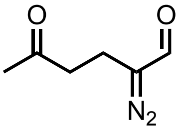
Following the general procedure **A(ii)** using 3-methylcyclopent-2-en-1-one (**356**) (2.0 mL, 20.4 mmol) and TsNHNH$_2$ (4.94 g, 26.5 mmol) gave an *E-/Z-* mixture of hydrazone **358** (4.20 g, 78%, 14:86 *E:Z* as determined by ^{1}H NMR NH signals) as a white solid; R_f = 0.51 (30% EtOAc in petrol); m.p. 149–151 °C; IR (film, υ_{max} cm^{-1}) 3212 w, 2914 w, 1625 w, 1330 s, 1163 s, 1092 s; ^{1}H NMR (500 MHz; CDCl$_3$) δ 7.86 (2H, d, *J* 8.0, 2xArCH), 7.53 (1H, s, NH), 7.30 (2H, d, *J* 8.0, 2xArCH), 5.91 (1H, s, CH$_3$C=C*H*), 2.43 (7H, d, *J* 16.0, ArC*H$_3$* and C*H$_2$*C*H$_2$*C=N), 1.91 (3H, s, CHCC*H$_3$*); ^{13}C NMR (125 MHz; CDCl$_3$) δ 169.0 (HC=*C*CH$_3$), 160.8 (C=N), 144.0 (ArC), 135.7 (ArC), 129.7 (ArCH), 128.1 (ArCH), 126.7 (H*C*=CCH$_3$), 34.9 (*C*H$_2$CCH$_3$), 26.6 (*C*H$_2$CN), 21.7 (ArC*C*H$_3$), 18.1 (HCC*C*H$_3$); HRMS *m/z* (M+H$^+$) found 265.1004, $C_{13}H_{17}N_2O_2S$ requires 265.1005; discernible data for *E*-isomer: ^{1}H NMR (500 MHz; CDCl$_3$) δ 6.22 (1H, s, CH$_3$C=C*H*), 2.59 (2H, m, CH$_2$C=N), 1.96 (3H, s, CHCC*H$_3$*); ^{13}C NMR (125 MHz; CDCl$_3$) δ 169.8 (HC=*C*CH$_3$), 166.5 (C=N), 143.9 (ArC), 129.6 (ArCH), 128.1 (ArCH), 119.7 (H*C*=CCH$_3$), 34.1 (*C*H$_2$CCH$_3$), 30.3 (*C*H$_2$CN), 21.8 (ArC*C*H$_3$), 18.8 (HCC*C*H$_3$).

2-Diazo-6-oxoheptanal (359)



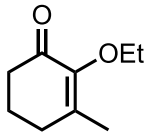
Following the general procedure **B** using hydrazone **357** (500 mg, 1.80 mmol) in CH_2Cl_2 (200 mL) and Et_3N (1.00 mL, 7.2 mmol) to give *s-E*/*s-Z*-diazoaldehyde **359** (172 mg, 63%, 84:16 *s-E*:*s-Z*, as determined by ^1H NMR CHO signal and NOE studies) as a yellow oil; $R_f = 0.39$ (50% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 2936 w, 2084 s, 1712 s, 1629 s, 1167 s; ^1H NMR (500 MHz; $CDCl_3$) δ 9.56 (1H, s, CHO), 2.50 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.35 (2H, t, *J* 7.5, CH_2CN_2), 2.14 (3H, s, CH_3), 1.79 (2H, p, *J* 7.0, *J* 7.0, $CH_2CH_2CN_2$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.9 ($C{=}OCH_3$), 182.8 (CHO), 70.7 (CN_2), 42.2 ($CH_2C{=}O$), 30.2 (CH_3), 21.3 ($CH_2CH_2CN_2$), 20.6 (CH_2CN_2); HRMS *m/z* ($M+H^+$), found 155.0814, $C_7H_{11}N_2O_2$ requires 155.0815; discernible data for *Z*-diazoaldehyde: ^1H NMR (500 MHz; $CDCl_3$) δ 9.19 (1H, s, CHO), 2.54 (2H, t, *J* 7.0, $CH_2C{=}O$), 2.46 (2H, t, *J* 7.5, CH_2CHN_2), 2.17 (3H, s, CH_3), 1.84 (2H, t, *J* 7.0, $CH_2CH_2CHN_2$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.4 ($C{=}OCH_3$), 185.4 (CHO), 41.7 ($CH_2C{=}O$), 30.2 (CH_3), 22.8 ($CH_2CH_2CHN_2$), 22.3 (CH_2CHN_2).

2-Diazo-5-oxohexanal (360)



Following the general procedure **B** using hydrazone **358** (1.00 g, 3.78 mmol) in CH_2Cl_2 (420 mL) and Et_3N (2.1 mL, 15.2 mmol) to give *s-E*/*s-Z*-diazoaldehyde **360** (338 mg, 64%, 86:14 *E:Z,* as determined by ^1H NMR CHO signal and NOE studies) as a yellow oil; R_f = 0.38 (50% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 2927 w, 2087 s, 1712 s, 1615 s, 1280 w, 1146 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.47 (1H, s, CHO), 2.75 (2H, t, *J* 6.0, $CH_2C=O$), 2.54 (2H, t, *J* 6.0, CH_2CN_2), 2.16 (3H, s, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.7 (*C*=OCH_3), 182.9 (CHO), 71.2 (CN_2), 41.0 (*C*$H_2C=O$), 29.9 (CH_3), 16.4 (*C*H_2CN_2); HRMS *m/z* (M–H$^+$), found 139.0510, $C_6H_7N_2O_2$ requires 139.0513; discernible data for *Z*-diazoaldehyde: ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.23 (1H, s, CHO), 2.67 (2H, t, *J* 6.0, $CH_2C=O$), 2.19 (3H, s, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 206.6 (*C*=OCH_3), 185.5 (CHO), 42.9 (*C*$H_2C=O$), 30.1 (CH_3), 17.2 (*C*H_2CHN_2).

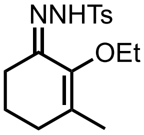
2-Ethoxy-3-methylcyclohex-2-en-1-one (361)



To a solution of H_2O_2 (9.86 mL, 116 mmol, 30%) in MeOH (35 mL) at 0 °C was added 3-methylcyclohex-2-en-1-one (**355**) (4.0 mL, 35.3 mmol) followed by dropwise aq NaOH (2.9 mL, 17.6 mmol, 6 M) maintaining the temperature below 5 °C. After 45 min, the mixture was poured onto ice (5 g) and extracted with CH_2Cl_2 (3x15 mL), dried ($MgSO_4$), concentrated under reduced pressure to give the corresponding epoxide[172] (5.80 g) which was used directly in the next step. The crude epoxide (5.80 g, 46.0 mmol) in EtOH (5 mL) was added to a refluxing solution of Na (1.50 g, 69.0 mmol) in EtOH (20 mL). After 5 min, the mixture was cooled to 0 °C and poured onto ice (5 g), extracted with CH_2Cl_2 (3x15 mL), washed with brine (15 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% EtOAc in petrol) to give *α*-ethoxyenone **361** (1.38 g, 25% over

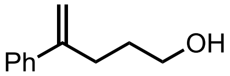
2 steps) as colourless oil; R_f = 0.4 (20% EtOAc in petrol); IR (film, υ_{max} cm^{-1}) 3441 br, 2930 m, 1673 s, 1432 w, 1196 w, 730 w; ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.78 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 2.38 (2H, t, *J* 7.0, CH$_2$C=O), 2.33 (2H, t, *J* 7.0, C*H*$_2$CCH$_3$), 1.87 (5H, m, C*H*$_2$CH$_2$CCH$_3$ and CCH$_3$), 1.22 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 194.9 (C=O), 148.1 (*C*=CCH$_3$), 146.1 (C=*C*CH$_3$), 67.6 (*C*H$_2$CH$_3$), 38.7 (*C*H$_2$C=O), 31.4 (*C*H$_2$CCH$_3$), 22.2 (*C*H$_2$CH$_2$CCH$_3$), 17.8 (C*C*H$_3$), 15.5 (CH$_2$*C*H$_3$); HRMS *m/z* (M$^+$) found 155.10667, $C_9H_{14}O_2$ requires 155.10666.

(*E*)-*N'*-(2-Ethoxy-3-methylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (362)



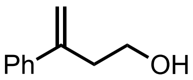
Following the general procedure **A(ii)** using 2-ethoxy-3-methylcyclohex-2-en-1-one (**361**) (1.32 g, 8.51 mmol) and $TsNHNH_2$ (1.90 g, 10.2 mmol) gave *E*–hydrazone **362** (2.57 g, 94%) as a white solid; R_f = 0.48 (40% EtOAc in petrol); m.p. 115–117 °C IR (film, υ_{max} cm^{-1}) 3211 w, 2929 w, 1639 w, 1402 m, 1162 s; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.95 (1H, s, NH), 7.87 (2H, d, *J* 8.0, 2xArCH), 7.28 (2H, d, *J* 8.0, 2xArCH), 3.68 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 2.39 (3H, s, C=CCH$_3$), 2.33 (2H, t, *J* 7.5, CH$_2$CN), 2.11 (2H, t, *J* 7.0, C*H*$_2$CCH$_3$), 1.77 (3H, s, ArCH$_3$), 1.68 (2H, pent. *J* 7.0, *J* 7.0, C*H*$_2$CH$_2$CN), 1.23 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 150.7 (C=N), 145.1 (C=*C*OEt) 143.9 (ArC), 135.6 (ArC), 133.4 (C=*C*CH$_3$), 129.5 (ArCH), 128.3 (ArCH), 67.4 (*C*H$_2$CH$_3$), 30.1 (*C*H$_2$CCH$_3$), 25.1 (*C*H$_2$CN), 21.7 (ArC*C*H$_3$), 20.8 (*C*H$_2$CH$_2$CN), 17.5 (C=C*C*H$_3$), 15.6 (CH$_2$*C*H$_3$); HRMS *m/z* (M+H$^+$) found 323.14236, $C_{16}H_{23}N_2O_3S$ requires 323.14239.

4-Phenylpent-4-en-1-ol (376)[153]



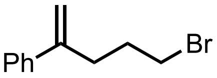
A degassed solution of pent-4-yn-1-ol (**375**) (2.00 mL, 21.5 mmol), $PhB(OH)_2$ (3.93 g, 32.2 mmol) and $Pd(PPh_3)_4$ (1.24 g, 1.07 mmol) in dioxane (54 mL) was stirred at rt for 10 min before AcOH (0.25 mL, 4.30 mmol) was added and the mixture was heated at 80 °C over night. The mixture was then cooled to rt and diluted with MeOH (40 mL), solvent evaporated under reduced pressure, filtered through a short pad of silica and the residue purified by column chromatography (10% EtOAc in petrol) to give alcohol **376** (1.57 g, 45%) as colourless oil; $R_f = 0.26$ (10% EtOAc in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.46–7.28 (5H, m, ArCH), 5.31 (1H, d, *J* 1.0, 1H of $C{=}CH_2$), 5.11 (1H, q, *J* 1.0, 1H of $C{=}CH_2$), 3.69 (2H, t, *J* 7.0, CH_2OH), 2.63 (2H, ddd, *J* 7.0, *J* 1.0, CCH_2), 1.74 (2H, m, CH_2CH_2OH), 1.48 (1H, s, OH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 148.1 ($C{=}CH_2$), 141.4 (ArC), 128.2 (2xArCH), 127.6 (ArCH), 126.1 (2xArCH), 112.2 ($C{=}CH_2$), 61.9 (CH_2OH), 31.7 (CCH_2), 31.2 (CH_2CH_2OH).

3-Phenylbut-3-en-1-ol (377)[153]



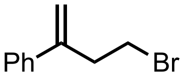
A degassed solution of but-3-yn-1-ol (**199**) (2.00 mL, 26.4 mmol), $PhB(OH)_2$ (4.83 g, 39.6 mmol) and $Pd(PPh_3)_4$ (1.53 g, 1.32 mmol) in dioxane (66 mL) was stirred at rt for 10 min before AcOH (0.30 mL, 5.28 mmol) was added and the mixture was heated at 80 °C over night. The mixture was then cooled to rt and diluted with MeOH (50 mL), solvent evaporated under reduced pressure, filtered through a short pad of silica and the residue purified by column chromatography (10% EtOAc in petrol) to give alcohol **377** (637 mg, 16%) as colourless oil; R_f = 0.29 (10% EtOAc in petrol); ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.45–7.28 (5H, m, ArCH), 5.43 (1H, d, *J* 1.0, 1H of C=CH$_2$), 5.18 (1H, q, *J* 1.0, 1H of C=CH$_2$), 3.74 (2H, t, *J* 7.0, C*H*$_2$OH), 2.81 (2H, td, *J* 7.0, *J* 1.0, C*H*$_2$CH$_2$OH), 1.52 (1H, s, OH); ^{13}C NMR (100 MHz; CDCl$_3$) δ 144.9 (*C*=CH$_2$), 140.4 (ArC), 128.1 (2xArCH), 127.6 (ArCH), 126.1 (2xArCH), 114.5 (C=*C*H$_2$), 60.9 (CH$_2$OH), 38.5 (*C*H$_2$CH$_2$OH).

(5-Bromopent-1-en-2-yl)benzene (378)



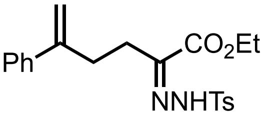
To a solution of 4-phenylpent-4-en-1-ol (**376**) (1.56 g, 9.62 mmol) in CH$_2$Cl$_2$ (50 mL) and Et$_3$N (4.02 mL, 58.5 mmol) cooled to 0 °C was added dropwise MsCl (1.12 mL, 14.4 mmol) over 15 min. The mixture was stirred at the same temperature for 1 h before it was warmed to rt and stirred for a further 1 h. The mixture was then cooled back to 0 °C and HCl (10 mL, 1 M) was added dropwise, extracted with CH$_2$Cl$_2$ (3x20 mL), washed with NaHCO$_3$ (15 mL), the combined organic layers were dried (MgSO$_4$), filtered, evaporated under reduced pressure and the residue taken to next step without further purification. To a solution of the crude residue in acetone (85 mL) was added LiBr (1.84 g, 21.2 mmol) and the mixture refluxed for 2 h before it was cooled to rt, filtered through a short pad of silica, washed with acetone (2x40 mL) and the residue purified by column chromatography (5% Et$_2$O in petrol) to give bromide **378**[173] (1.90 g, 88%) as colourless oil; R_f = 0.52 (5% Et$_2$O in petrol); ^{1}H NMR (400 MHz; CDCl$_3$) δ 7.45–7.26 (5H, m, ArCH), 5.34 (1H, d, *J* 1.0, 1H of C=CH$_2$), 5.13 (1H, q, *J* 1.0, 1H of C=CH$_2$), 3.42 (2H, t, *J* 7.0, C*H*$_2$Br), 2.70 (2H, m, CCH$_2$), 2.02 (2H, m, C*H*$_2$CH$_2$Br); ^{13}C NMR (100 MHz; CDCl$_3$) δ 146.6 (*C*=CH$_2$), 140.2 (ArC), 128.5 (2xArCH), 127.8 (ArCH), 126.2 (2xArCH), 113.2 (C=*C*H_2), 35.9 (CH_2Br), 31.6 (C*C*H_2), 29.9 (*C*H_2CH_2Br).

(4-Bromobut-1-en-2-yl)benzene (379)



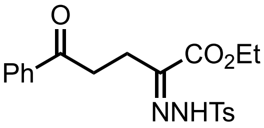
To a solution of 3-phenylbut-3-en-1-ol (**377**) (2.89 g, 19.5 mmol) in CH_2Cl_2 (10 mL) and Et_3N (8.15 mL, 58.5 mmol) cooled to 0 °C was added dropwise MsCl (2.26 mL, 29.3 mmol) over 15 min. The mixture was stirred at the same temperature for 1 h before it was warmed to rt and stirred for a further 1 h. The mixture was then cooled back to 0 °C and HCl (20 mL, 1 M) was added dropwise, extracted with CH_2Cl_2 (3x30 mL), washed with $NaHCO_3$ (15 mL), the combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the residue taken to next step without further purification. To a solution of the crude residue in acetone (85 mL) was added LiBr (3.73 g, 42.9 mmol) and the mixture refluxed for 2 h before it was cooled to rt, filtered through a short pad of silica, washed with acetone (2x40 mL) and the residue purified by column chromatography (5% Et_2O in petrol) to give bromide **379**[173] (2.95 g, 72%) as colourless oil; R_f = 0.55 (5% Et_2O in petrol); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.20 (5H, m, ArCH), 5.40 (1H, d, *J* 1.0, 1H of C=CH_2), 5.17 (1H, q, *J* 1.0, 1H of C=CH_2), 3.45 (2H, t, *J* 7.0, CH_2Br), 3.08 (2H, t, *J* 7.0, C*H₂*CH_2Br); ^{13}C NMR (100 MHz; $CDCl_3$) δ 145.5 (*C*=CH_2), 139.9 (ArC), 128.6 (2xArCH), 127.9 (ArCH), 126.2 (2xArCH), 115.0 (C=*C*H_2), 39.0 (CH_2Br), 31.2 (*C*H_2CH_2Br).

Ethyl (*Z*)-5-phenyl-2-(2-tosylhydrazineylidene)hex-5-enoate (383)



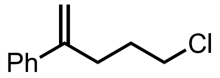
Mg turnings (276 mg, 11.4 mmol) were carefully flame dried under high vacuum (~1 mbar) for 15 min and then allowed to cool to rt under argon. THF/Et_2O (4 mL, 1:1) was then added followed by dropwise addition of (4-Bromobut-1-en-2-yl)benzene **379** (1.00 g, 4.74 mmol). The mixture was stirred for 15 min and then transferred dropwise to a solution of diethyl oxalate (0.52 mL, 3.79 mmol) in THF/Et_2O (4 mL, 1:1) at –78 °C. After 1 h, the reaction was quenched with sat. aq NH_4Cl and extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure to give α-ketoester **381** (902 mg) as colourless oil, which was used in the next step without further purification. A mixture of α-ketoester and $TsNHNH_2$ (1.06 g, 5.68 mmol) in MeOH (6 mL) was heated to 45 °C overnight. The mixture was then cooled to rt, solvent evaporated under reduced pressure and the residue purified by column chromatography (20% Et_2O in petrol) to give hydrazone **383** (548 mg, 36%) as a white solid; R_f = 0.44 (20% Et_2O in petrol); m.p. 68–70 °C; IR (film, υ_{max} cm^{-1}) 3205 w, 2934 w, 1692 s, 1370 s, 1169 s, 1084 s; ^1H NMR (500 MHz; $CDCl_3$) δ 11.82 (1H, s, NH), 7.85 (2H, d, *J* 8.0, 2xArCH), 7.35–7.29 (7H, m, 2xArCH and 5xArCH), 5.24 (1H, s, 1H of C=CH_2), 4.98 (1H, s, 1H of C=CH_2), 4.22 (2H, q, *J* 7.0, C*H*$_2$$CH_3$), 2.69 (2H, m, C$CH_2$), 2.61 (2H, m, CH_2C*H*$_2$CN), 2.44 (3H, s, ArCH_3), 1.29 (3H, t, *J* 7.0, CH_2C*H*$_3$); ^{13}C NMR (125 MHz; $CDCl_3$) δ 162.1 (*C*O_2Et), 147.0 (*C*=CH_2), 144.3 (C=N), 140.7 (ArC), 138.4 (ArC), 135.7 (Ar*C*CH_3), 129.7 (2xArCH), 128.4 (2xArCH), 128.0 (2xArCH), 127.6 (ArCH), 126.1 (2xArCH), 113.2 (C=*C*H_2), 62.0 (*C*$H_2$$CH_3$), 32.6 (C*C*$H_2$), 32.2 ($CH_2$*C*$H_2$C=N), 21.7 (Ar$CH_3$), 14.0 ($CH_2$*C*$H_3$); HRMS *m/z* (M+$H^+$) found 401.1528, $C_{21}H_{25}O_4N_2S$ requires 401.1529.

Ethyl (*Z*)-5-oxo-5-phenyl-2-(2-tosylhydrazineylidene)pentanoate (385)



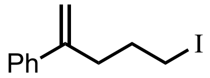
A solution of hydrazone **383** (250 mg, 0.62 mmol) in CH_2Cl_2 (75 mL) was cooled to –78 °C. A stream of O_3 in oxygen was bubbled through the solution. Ozone treatment was terminated when the colour of the reaction mixture changed from colourless to light blue. The excess O_3 was removed by bubbling N_2 through the reaction mixture. After 10 min, Et_3N (0.35 mL, 2.50 mmol) was added and the reaction mixture was warmed to rt. After stirring for 3 h, the reaction mixture was passed through a pad of silica, evaporated under reduced pressure and purified by column chromatography (20% Et_2O in petrol); to give ketohydrazone **385** (71.0 mg, 28%) as colourless oil; R_f = 0.38 (20% Et_2O in petrol); IR (film, υ_{max} cm^{-1}) 3207 w, 2983 w, 1687 s, 1209 s, 1167 s, 1085 s; ^1H NMR (500 MHz; $CDCl_3$) δ 11.82 (1H, s, NH), 7.96–7.94 (2H, m, 2xArCH), 7.64–7.50 (5H, m, 5xArCH), 7.05 (2H, d, *J* 8.0, 2xArCH), 4.29 (2H, q, *J* 7.0, CH_2CH_3), 3.24 (2H, t, *J* 7.0, O=CCH_2), 2.91 (2H, t, *J* 7.0, CH_2CH_2CN), 2.32 (3H, s, $ArCH_3$), 1.34 (3H, t, *J* 7.0, CH_2CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 198.2 (C=O), 162.0 (CO_2Et), 144.9 (C=N), 137.2 (ArC), 136.8 (ArC), 135.4 ($ArCCH_3$), 133.2 (ArCH), 129.5 (2xArCH), 128.6 (2xArCH), 128.1 (2xArCH), 127.6 (2xArCH), 62.1 (CH_2CH_3), 34.1 (CCH_2), 26.5 (CH_2CH_2C=N), 21.6 ($ArCH_3$), 14.0 (CH_2CH_3); HRMS *m/z* ($M+H^+$) found 403.1319, $C_{20}H_{23}O_5N_2S$ requires 403.1322.

(5-Chloropent-1-en-2-yl)benzene (387)[154]



A degassed solution of 5-chloropent-1-yne (**386**) (2.00 mL, 18.9 mmol), $PhB(OH)_2$ (2.76 g, 22.7 mmol) and $Pd(PPh_3)_4$ (0.655 g, 0.57 mmol) in dioxane (38 mL) was stirred at rt for 10 min before AcOH (0.11 mL, 1.89 mmol) was added and the mixture was heated at 80 °C over night. The mixture was then cooled to rt and diluted with MeOH (40 mL), solvent evaporated under reduced pressure, filtered through a short pad of silica and the residue purified by column chromatography (5% Et_2O in petrol) to give (5-chloropent-1-en-2-yl)benzene (**387**) (0.515 g, 15%) as colourless oil; R_f = 0.51 (5% Et_2O in petrol); ^1H NMR (400 MHz; $CDCl_3$) δ 7.46–7.27 (5H, m, ArCH), 5.34 (1H, d, *J* 1.0, 1H of $C{=}CH_2$), 5.13 (1H, q, *J* 1.0, 1H of $C{=}CH_2$), 3.56 (2H, t, *J* 7.0, CH_2Cl), 2.70 (2H, ddd, *J* 7.0, *J* 1.0, CCH_2), 1.93 (2H, m, CH_2CH_2Cl); ^{13}C NMR (100 MHz; $CDCl_3$) δ 146.7 ($C{=}CH_2$), 140.4 (ArC), 128.2 (2xArCH), 127.6 (ArCH), 126.1 (2xArCH), 113.2 ($C{=}CH_2$), 44.8 (CH_2Cl), 32.3 (CCH_2), 30.8 (CH_2CH_2Cl).

(5-Iodopent-1-en-2-yl)benzene (388)



To a solution of (5-chloropent-1-en-2-yl)benzene (**387**) (500 mg, 2.78 mmol) in butanone (20 mL) was added NaI (832 mg, 5.55 mmol) and the mixture refluxed for 2 h before it was cooled to rt, filtered through a short pad of silica, washed with acetone (2x30 mL) and the residue purified by column chromatography (petrol) to give alkyl iodide **388** (739 mg, 98%) as colourless oil; R_f = 0.87 (petrol); IR (film, υ_{max} cm^{-1}) 3081 w, 3055 w, 2935 w, 1626 w, 1262 s, 898 s, 777 s, 703 s; ^1H NMR (400 MHz;

$CDCl_3$) δ 7.46–7.28 (5H, m, ArCH), 5.34 (1H, d, *J* 1.0, 1H of C=CH_2), 5.14 (1H, q, *J* 1.0, 1H of C=CH_2), 3.19 (2H, t, *J* 7.0, C*H*₂I), 2.65 (2H, ddd, *J* 7.0, *J* 1.0, CCH_2), 1.95 (2H, p, *J* 7.0, C*H*₂CH_2I); ^{13}C NMR (100 MHz; $CDCl_3$) δ 146.6 (*C*=CH_2), 140.6 (ArC), 128.5 (2xArCH), 127.7 (ArCH), 126.2 (2xArCH), 113.6 (C=*C*H₂), 35.9 (C*C*H₂), 31.7 (CH_2*C*H₂CH_2I), 6.76 (*C*H₂I); HRMS *m/z* (M+H$^+$) found 273.0134, $C_{11}H_{14}I$ requires 723.0135.

Chapter 8

Appendix

8. Appendix

8.1 Single Crystal X–ray Diffraction Determination

Low temperature[174] single crystal X-ray diffraction studies were carried out at 150 K using CuK_α radiation on an Oxford Diffraction SuperNova diffractometer equipped with an area detector and graphite monochromator, within the University of Oxford Chemistry Department. Raw frame data were reduced using CrysAlisPro(Agilent) and the structures were solved using superflip.[175] Full-matrix least-squares refinements of the structures were carried out using CRYSTALS.[176] The Flack x parameter[177] refined to -0.01(2) and Bayesian analysis of the Bijvoet pairs[175c] gave the Hooft y parameter as 0.01(1) and the probability that the structure was the correct hand of >99.99% given that the crystal was enantiopure, thus determining the absolute configuration. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and copies of these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

8.1.1 X-ray Crystallography, 1

Compound **152** was crystallised *via* vapour diffusion by dissolving 5 mg of **152** in ethyl acetate (*c.a.* 5 mL) and using pentane as the volatile component. Further details about the refinement are documented in the CIF. The crystallographic data have been deposited with the CCDC as entry 1544840.

Compound Number	**152**
CCDC	1544840
Identification code	056JDJ17

Empirical formula	$C_{20}H_{34}O_{10}Si$	
Formula weight	462.57	
Temperature	150 K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	$P\ 2_1$	
Unit cell dimensions	a = 9.57910 Å	α = 90°
	b = 8.51190 Å	β = 100.9121°
	c = 15.0831Å	γ = 90 °
Volume	1207.58 $Å^3$	
Z,Z'	Z: 2 Z': 0	
Density (calculated)	1.27 Mg m^{-3}	
Absorption coefficient	1.297 mm^{-1}	
F(000)	496.0	
Crystal size	0.24 x 0.32 x 0.50 mm^3	
Theta range for data collection	4.701° to 76.226°	
Reflections collected	24093	
Independent reflections	4839	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2σ(I)]	$R^1 = 0.0248$, $wR^2 = 0.0660$	
R indices (all data)	$R^1 = 0.0249$, $wR^2 = 0.0661$	

Table 4: X-ray crystallographic data and structure refinement for **152**, 056JDJ17.

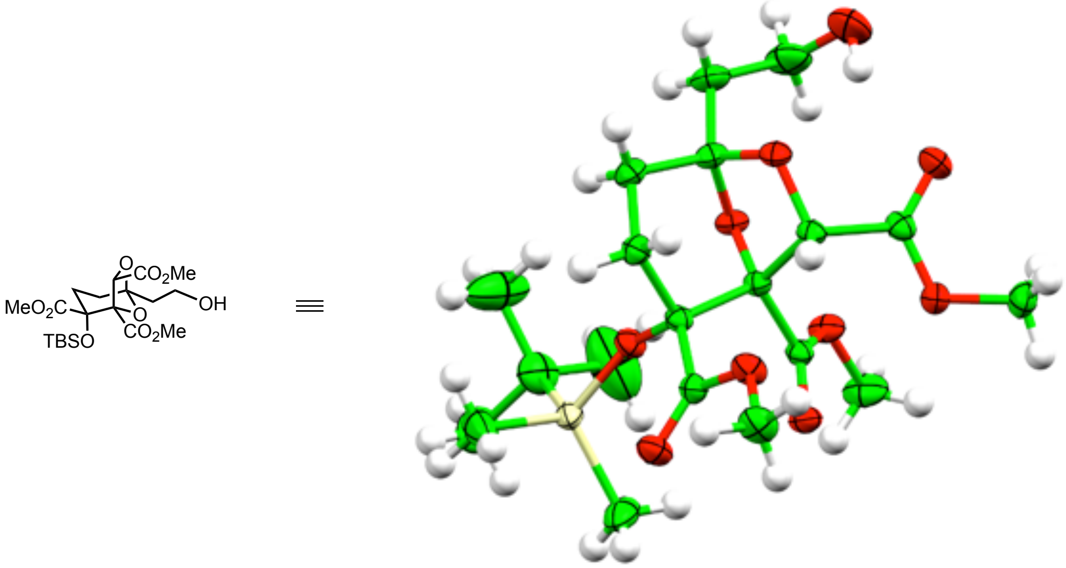


Figure 15: Solid-state structure of **152**. Displacement ellipsoid plots are drawn at 50% probability.

8.1.2 X-ray Crystallography, 2

Compound **256** was crystallised *via* vapour diffusion by dissolving 5 mg of **256** in ethyl acetate (*c.a.* 5 mL) and using pentane as the volatile component. Further details about the refinement are documented in the CIF.

Compound Number	**256**	
Identification code	055JDJ17	
Empirical formula	$C_{17}H_{27}IO_9Si$	
Formula weight	530.39	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	$P\ 2_1\ 2_1\ 2_1$	
Unit cell dimensions	a = 8.4335 Å	α = 90°

	b = 13.7796 Å	β = 90°
	c = 19.4856 Å	γ = 90°
Volume	2264.43 Å^3	
Z,Z’	Z: 4 Z': 0	
Density (calculated)	1.56 Mg m^{-3}	
Absorption coefficient	12.003 mm^{-1}	
F(000)	1072.0	
Crystal size	0.18 x 0.33 x 0.45 mm ^{3}	
Theta range for data collection	3.929° to 76.408°	
Reflections collected	50207	
Independent reflections	4743	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.016	
Final R indices [$I>2\sigma(I)$]	R^1 = 0.0385, wR^2 = 0.1138	
R indices (all data)	R^1 = 0.0387, wR^2 = 0.1140	

Table 5: X-ray crystallographic data and structure refinement for **256**, 055JDJ17.

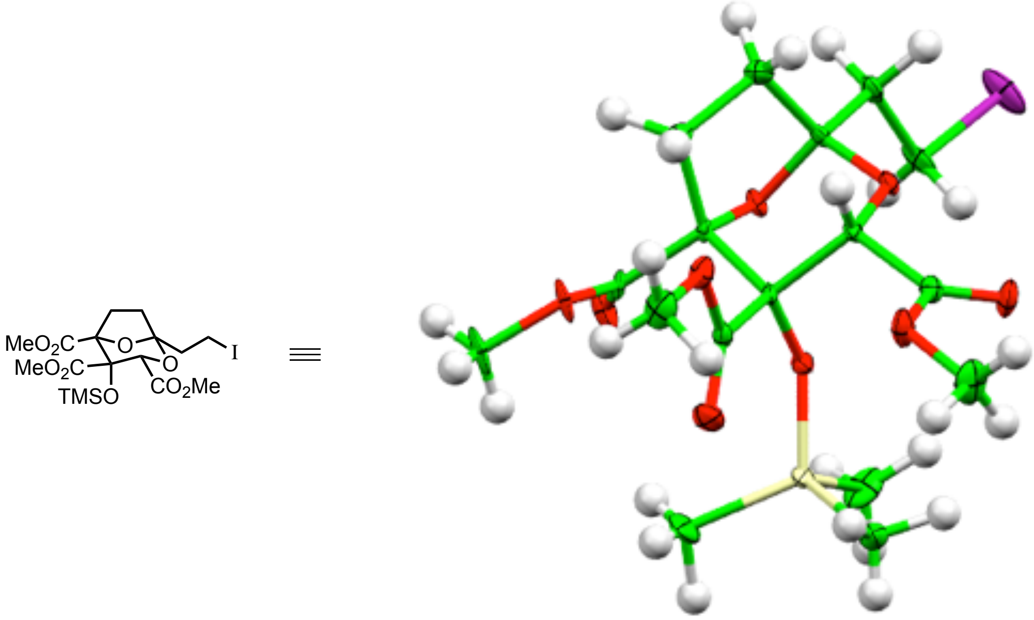


Figure 16: Solid-state structure of **256**. Displacement ellipsoid plots are drawn at 50% probability.

8.1.3 X-ray Crystallography, 3

Compound **354** was crystallised *via* vapour diffusion by dissolving 5 mg of **354** in benzene (*c.a.* 5 mL) and using pentane as the volatile component. Further details about the refinement are documented in the CIF. The crystallographic data have been deposited with the CCDC as entry 1815202.

Compound Number	**354**
Moiety Formula	$C_{14}H_{18}N_2O_5S$
CCDC	1815202
Space Group	P 2_1/c
a [Å]	10.0967(3)
b [Å]	11.1751(3)
c [Å]	13.8100(4)
α [°]	90
β [°]	104.850(3)

γ [°]	90
V [Å^3]	1506.16(8)
Z	4
T [K]	150
Total Reflections	14431
R_{int}	0.0218
Reflections, Restraints, Parameters (I>-3.0/ σ (I))	3124, 0, 199
Min. and Max. Residual Density, [eÅ^{-3}]	-0.40, 0.28
R_1 (I>2σ(I)) **wR_2**	0.0299 0.0781

Table 6: X-ray crystallographic data and structure refinement for **354**.

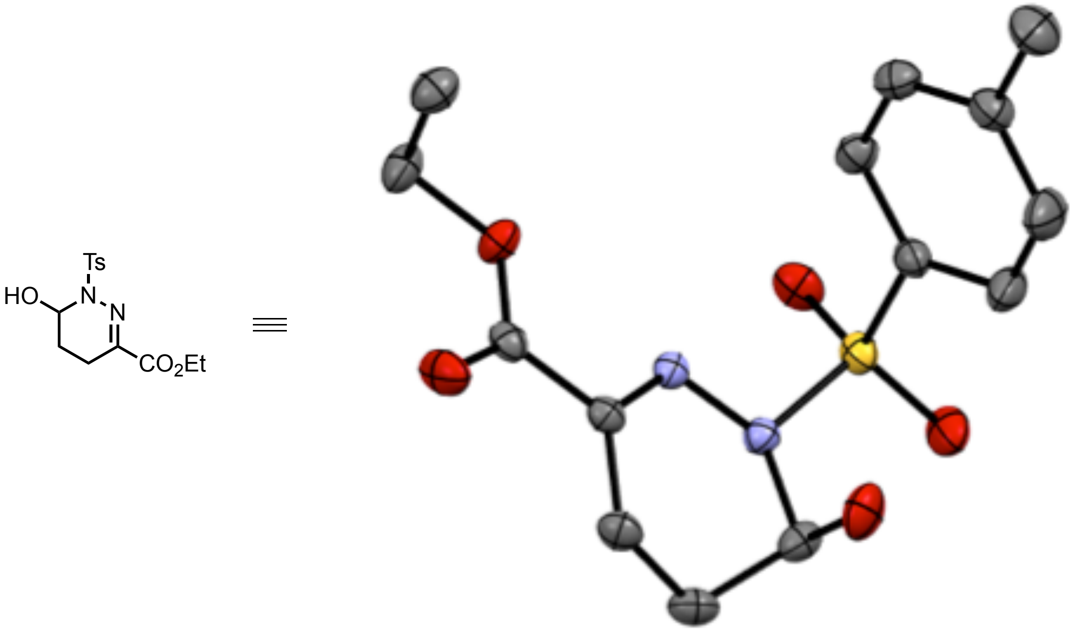
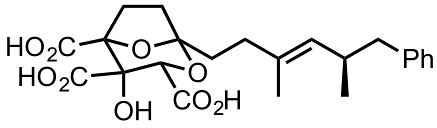


Figure 17: Solid-state structure of **354**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

8.2 Tabular Comparison of NMR Data between Natural and Synthetic (–)-6,7-dideoxysqualestatin H5



^{1}**H NMR** – (500 MHz, CD_3OD)	
Natural Isolate[178]	**Synthetic**
7.23 (2H, t, *J* 7)	7.24–7.20 (2H, m)
7.17–7.10 (3H, m)	7.15–7.12 (3H, m)
5.04 (1H, m)	5.04 (1H, d, *J* 9)
3.18 (1H, m)	3.22–3.15 (1H, m, H_{endo} of C^6H_2)
2.66 (1H, m)	2.68–2.62 (1H, m)
2.59 (1H, dd, *J* 13, 6)	2.59 (1H, dd, *J* 13, 6)
2.47 (1H, dd, *J* 13, 8)	2.48 (1H, d, *J* 13, 8)
2.23–2.09 (2H, m)	2.23–2.11 (2H, m)
2.0–1.90 (4H, m)	2.09–1.93 (4H, m)
1.87 (1H, m)	1.90–1.83 (1H, m, 1H_{exo} of C^6H_2)
1.44 (3H, d, *J* 1)	1.43 (3H, d, *J* 1)
0.96 (3H, d, *J* 7)	0.96 (3H, d, *J* 6)

^{13}**C NMR** – (100 MHz, CD_3OD)	
Natural Isolate[178]	**Synthetic**
173.1	173.5
172.1	172.4
170.8	171.1
142.3	142.4
134.9	135.0
131.7	131.7
130.2	130.3
128.9	129.0
126.6	126.7
109.8	109.8
89.3	89.5
76.0	76.2
75.7	75.9
45.0	45.1
36.3	36.5
35.8	35.9
34.6	34.7
32.0	32.2
30.3	30.3
21.3	21.4
16.0	16.1

8.3 Diazoaldehyde Rotamers

NMR investigations of *s-cis*/*trans* isomerism in α-diazoaldehyde **359,** arising from partial double bond character in the N_2C-CHO bond, were undertaken on a sample in $CDCl_3$ at temperatures from 298 to 233 K. At 298 K there was clear evidence of isomer exchange between *s-cis* and *s-trans* forms in 1D NOESY spectra. At 233 K this process was slowed sufficiently such that no exchange between isomers could be detected. Under these conditions, NOEs between the aldehydic protons and neighbouring CH_2 protons indicated the major isomer (~ 82%) to adopt the *s-trans* conformation (**Figure 18**).

To investigate the barrier to rotation between isomers, as series of 1D magnetisation transfer experiments were undertaken over a range of temperatures from 263 to 298 K. Probe temperatures were pre-calibrated using a methanol standard. 1D EXSY experiments were recorded using the Bruker selective 1D NOESY sequence *selnogp* with selection of the major rotamer –CHO proton using a 80 ms Gaussian 180^o pulse. Chemical exchange to the minor rotamer was monitored by increasing the exchange mixing times from 20 to 500 ms. Plots of the normalised exchange peak intensity (I_{minor}/I_{major}) *versus* mixing time were used to derive exchange rate constants from the initial, linear regions of build-up profiles (**Figure 19**). These data (**Table 7**) were used to derive thermodynamic parameters from the respective Eyring plot (**Figure 20**) and Arrhenius plot (**Figure 21**): $\Delta H^{\ddagger}$ =72.8 ± 0.4 kJ mol^{-1}; $\Delta S^{\ddagger}$ =-3.5 ± 1.3 J K^{-1} mol^{-1}; $\Delta G^{\ddagger}$ (298 K) =73.8 ± 0.1 kJ mol^{-1}; Ea = 75.1 ± 0.4 kJ mol^{-1}.

	Normalised Exchange peak intensity							
Mixing time /s		**263 K**	**273 K**	**278 K**	**283 K**	**288 K**	**293 K**	**298 K**
0.02		-	0.0009	0.0023	0.0038	0.0057	0.0099	0.0177
0.05		0.0002	0.0026	0.0037	0.0078	0.0137	0.0237	0.0397
0.1		0.0014	0.0044	0.0089	0.0159	0.0278	0.0466	0.0740
0.15		0.0020	0.0071	0.0118	0.0241	0.0406	0.0661	0.1015
0.2		0.0030	0.0095	0.0167	0.0306	0.0526	0.0829	0.1254
0.25		0.0034	0.0114	0.0192	0.0386	0.0631	0.0997	0.1445
0.3		0.0038	0.0135	0.0242	0.0452	0.0738	0.1134	0.1593
0.5		0.0063	0.0222	0.0392	0.0686	0.1092	0.1546	0.1952
Rate constant (s^{-1})		0.013	0.044	0.078	0.152	0.262	0.434	0.702
Standard error		0.0007	0.0006	0.0015	0.0036	0.0047	0.0123	0.0125

Table 7: 1D EXSY normalised exchange peak intensities as a function of mixing times for *α*-diazoaldehyde **359**, recorded for temperatures from 263 to 298 K. Exchange rate constants were derived from linear regions of these build-up profiles. Standard errors were dervied using the LINEST function of Excel and were used to estimate upper and lower limits of thermodynamic parameters.

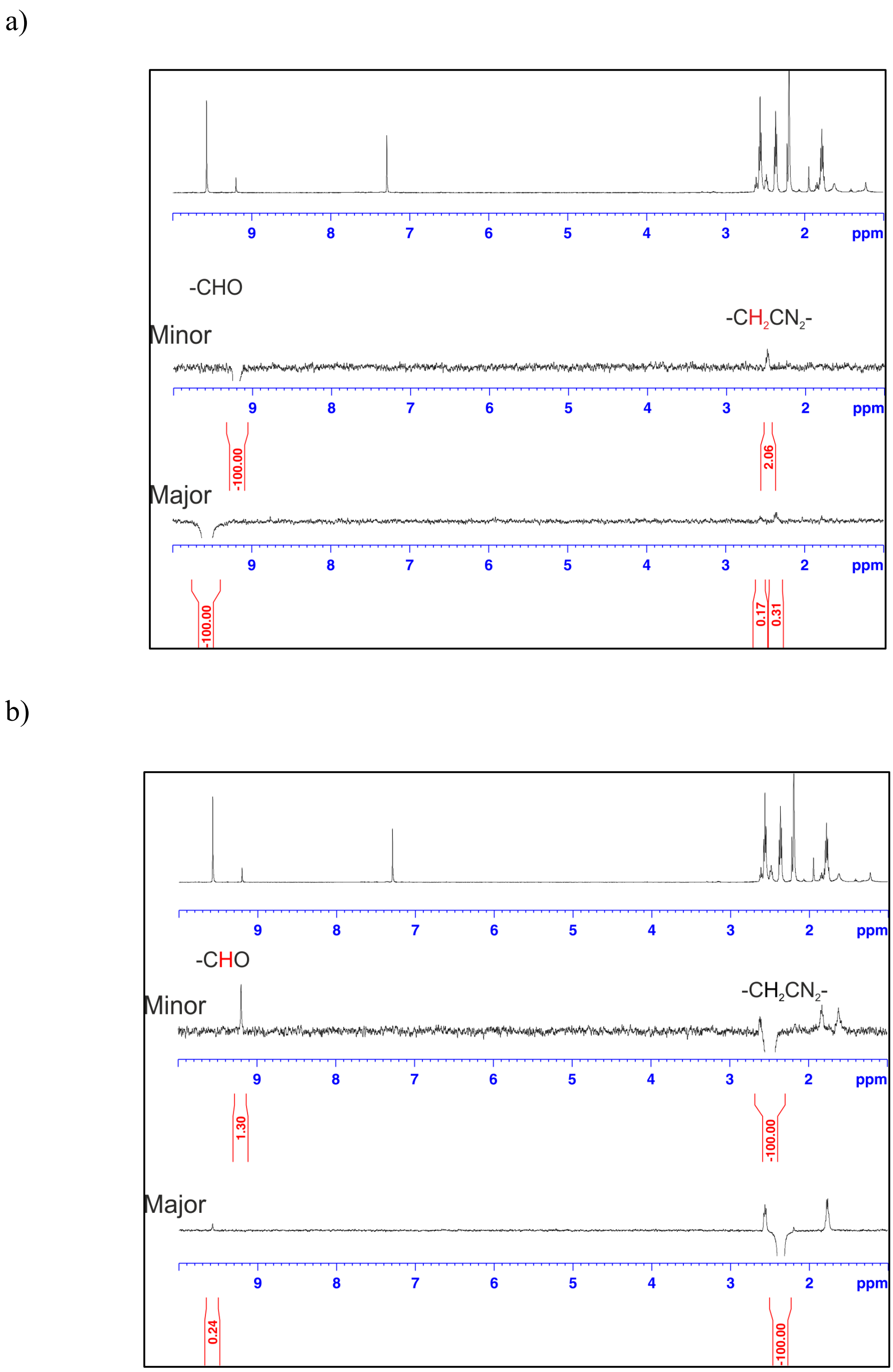


Figure 18: 1D NOESY spectra (800 ms mixing) at 233 K with reference 1D ^{1}H spectrum shown above. a) Irradiation of aldehyde protons; b) irradiation of -CH_2CN_2- protons. Integrals in NOESY spectra are intended to illustrate relative intensity differences only.

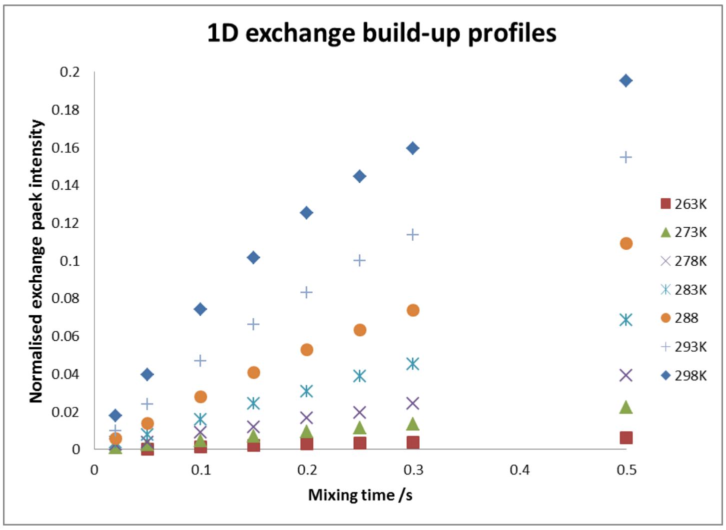


Figure 19: Temperature dependent 1D EXSY build-up profiles for α-diazoaldehyde **359**.

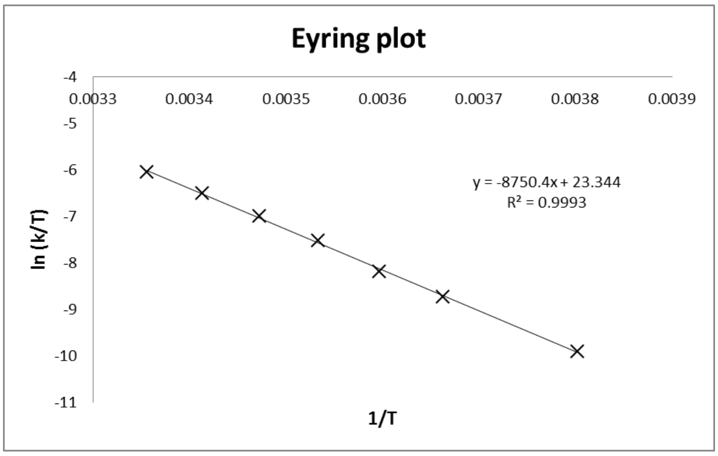


Figure 20: Eyring plot for α-diazoaldehyde **359.**

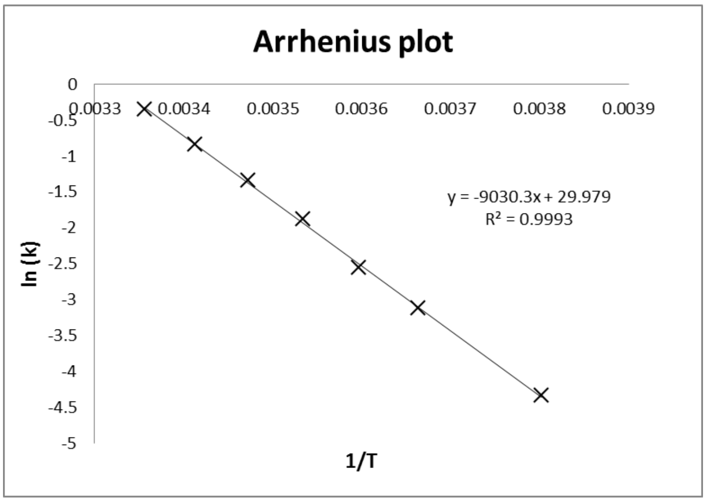


Figure 21: Arrhenius plot for α-diazoaldehyde **359.**

Chapter 9

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9. References

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