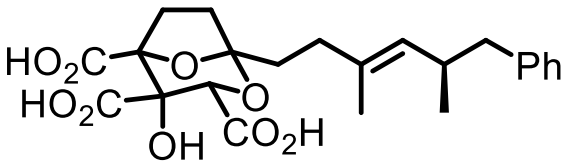
# Studies Towards Squalene Synthase Inhibitors: Total Synthesis of 6,7-Dideoxysqualestatin H5 via an Alkene-Protection Strategy




**Hasanain Ali Abbas Almohseni**

A thesis submitted to the

Board of the Faculty of Physical Sciences

In partial fulfilment of the requirements for the degree of

**DOCTOR OF PHILOSOPHY**

Chemistry Research Laboratory Trinity 2019

Dedicated to ***my parents***

and

***For the Martyrs of Iraqi military who fell in defence the Iraqi lands from ISIS while I was studying in Oxford***

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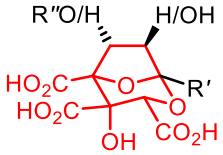
# Abstract


**Studies Towards Squalene Synthase Inhibitors: Total Synthesis of 6,7–Dideoxysqualestatin H5 via an Alkene-Protection Strategy**

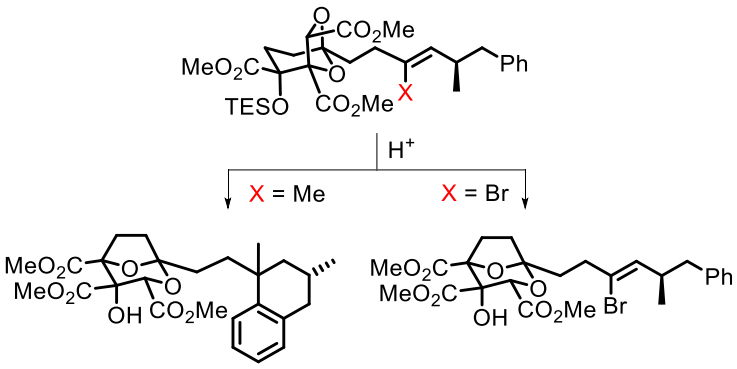
Hasanain A. A. Almohseni

Oriel College, Trinity Term 2019

The zaragozic acids/squalestatins are a family of bicyclic tricarboxylic acids, isolated from a series of different fungi. Members of this class of highly oxygenated natural products show potent inhibitory activity against squalene synthase at the last stage of cholesterol biosynthesis, and so represent attractive candidates for cholesterol-lowering drugs.

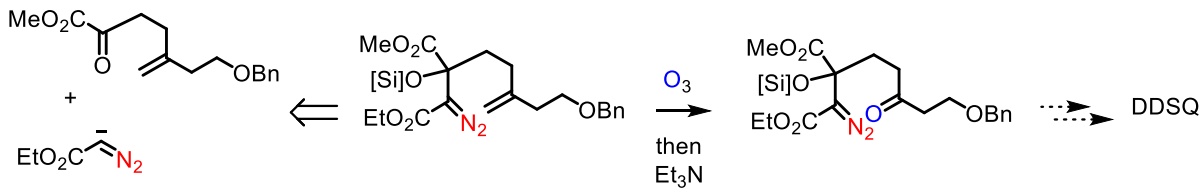



This thesis describes an asymmetric total synthesis of (–)-6,7-dideoxysqualestation H5 (DDSQ), focusing on the use of a bromide substituent to protect the side-chain alkenyl group from electrophilic addition reactions. Specifically, this alkene-protection strategy was used to circumvent an undesired cyclisation reaction during a late-stage acid-catalysed 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement en route to DDSQ.



The synthesis addresses several synthetic challenges, including: efficient construction of the requisite alkenyl bromide functionality in the side-chain; preparation of the crucial β-hydroxy-α-ketoester precursor to the 6,8-cycloadduct; and removal of the bromide substituent through stereoselective methylation cross-coupling in the presence of ester and hydroxyl functionalities.

After the fruitful total synthesis of DDSQ, further work was carried out to extend the scope of Seebach's alkylation of dimethyl tartrate acetonide, enabling access to enantiopure dialkylated products. Also, conditions have been developed for epimerising the monoalkylated tartrate products that may find application in the synthesis of other natural products. Furthermore, to address a key synthetic challenge in a previous synthesis of DDSQ, a concise route to synthesise α-diazo-ε-ketoesters was also developed that demonstrates the utility of chemoselective alkene ozonolysis in the presence of a diazo functionality.



# Acknowledgments

Doing a D Phil, creating this thesis, has been most like a process of learning how to walk for the first time. Without falling and having people surround you to raise you up again, you will not learn easily. To those whom I must acknowledge for helping me to go through this journey.

I would like to express my gratitude to Prof. David Hodgson for his advice, guidance and patience during our many long meetings; and also, his kind support continues with writing this thesis. I much appreciate all his help.

I am grateful to all members (the past and present) in the Hodgson and Smith groups, I was pleased to work with them. Time in the F4 Lab was full of joy, friendship and many laughs, although with some questionable tastes in music!

I thank Younes Fegheh-Hassanpour for providing me a great help in the lab (from day one), for sharing the downside of our chemistry with DDSQ, and also for the unforgettable moment with MoOPH preparation.

I thank also Pascal Delany, my group lab mate, for providing me with so much new (to me) English vocabulary. You still have not taken me to B., but don't worry you are still invited to my 4$^{th}$ w.!

My grateful thanks to Ben Jones, Nick Parker, Owen Smith and Lewis Ibbotson who have read parts of this thesis, corrected errors and challenged some of my interpretations. I thank in particular Zac Lockhart for his reading and useful suggestions to rephrase sentences in several parts of my thesis chapters.

I would like to thank Prof. Tim Claridge for his assistance with NMR analysis; Dr. Niels Munster, Tudor Balan and Francesco Ibba for their assistance in HPLC; Conner Thomson for his generosity with providing me with chiral ligands.

There are so many unforgettable moments in Oxford that have become part of me, like leaving the lab at dawn, walking alone in empty (cold) streets listening to singing birds and to rustling leaves. Many thanks to all those people that I have met in Oxford (throughout my four years) and made my life abroad enjoyable and full of excitement.

I gratefully acknowledge HCED Iraq for financial support.

Last but not least, I express tremendous gratitude towards my parents (Ali and Azhar) and my sisters Dina, Rana, and Nuha, who also own this success, for their love, unwavering support and abundant patience.

# Statement of Authorship

The work described in this thesis is entirely my own, with the exception where reference is cited.

**Signature:**

**Name:** Hasanain A. A. Almohseni **Date:** 09/09/2019

# Abbreviations

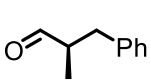
| | |
|---|---|
| Ac | acetyl |
| aq. | aqueous |
| Ar | aromatic |
| Bn | benzoyl |
| Boc | *tert*-butyloxycarbonyl |
| brsm | based on recovered starting material |
| Bu | butyl |
| Bz | benzyl |
| cat | catalytic |
| CoA | co-enzyme A |
| δ | chemical shift |
| DDSQ | 6,7-dideoxysqualestatin H5 |
| DIBAL-H | diisobutylaluminium hydride |
| DTBMS | di-*tert*-butylmethylsilyl |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| $E^+$ | electrophile |
| ee | enantiomeric excess |
| *epi* | epimer |
| equiv | equivalent(s) |
| er | enantiomer ratio |
| Et | ethyl |
| g | gram(s) |
| h | hour(s) |
| HMG | 3-hydroxy-3-methylglutaryl |
| HMPA | hexamethylphosphoramide |
| HPLC | high-performance liquid chromatography |

| | |
|---|---|
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| Im | imidazole |
| $^{i}$Pr | isopropyl |
| IR | infrared |
| lit | literature |
| LDA | lithium diisopropylamide |
| M | molarity |
| Me | methyl |
| mg | milligram(s) |
| min | minute(s) |
| mL | millilitre(s) |
| mmol | millimole(s) |
| MOM | methoxymethyl acetal |
| MoOPH | $MoO_5$.Py.HMPA |
| MS | molecular sieves |
| n | normal– an unbranched chain |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear overhauser effect |
| *p* | para |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| Piv | pivalyl |
| ppm | parts per million |
| Py | pyridine |
| R, $R^1$, $R^2$,.. | generic group |
| $R_f$ | retention factor |
| rt | room temperature |

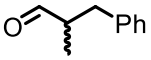
| | |
|---|---|
| SEM | [2-(trimethylsilyl)ethoxy]methyl acetal |
| *t* | *tert* |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TBS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| TES | triethylsilyl |
| TMS | trimethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| Ts | *para*–toluenesulfonyl |
| UV | ultraviolet |
| $\upsilon_{max}$ | infrared absorption maxima |
| ZA | zaragozic acids |

# Nomenclature

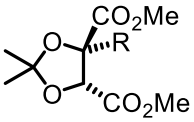
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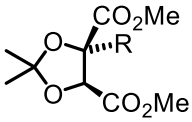

Compounds derived from (*R*)-2-methyl-3-phenylpropanal (*R*-**185**) will be referred to as enantioenriched materials.




Compounds derived from (±)-2-methyl-3-phenylpropanal (**185**) will be referred to as racemic materials.




Will be referred to as an alkylated tartrate (esters are *trans*).




Will be referred to as an epimerised alkylated tartrate (esters are *cis*).

# Chapter 1

# Introduction and Aims

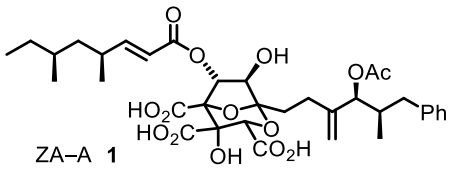
# 1. Introduction

Nature is a rich source of biologically active molecules for drug discovery and pharmaceutical development. A significant number of medicines from natural products have been approved in almost all disease areas.[1] Beside their biological activities, natural products have always fascinated chemists towards their synthesis, not only because they provide exciting synthetic challenges, but also they give us the opportunity to practice the art of constructing a naturally occurring substance.

This thesis describes the work that I have conducted towards the total synthesis of 6,7–dideoxysequalestatin H5, and in this introduction I have briefly reviewed some aspects related to the structure, biological activity, biosynthesis and other synthetic work.

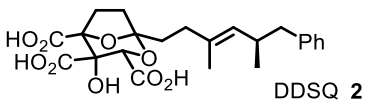
## 1.1 Structural Background of Squalestatins / Zaragozic Acids

The zaragozic acids, also known as squalestatins, constitute a family of bicyclic tricarboxylic acids that display a wide range of biological activities. The first member of this family is triacid **1** (**Figure 1**), which was isolated, characterised and its structure elucidated independently by researchers at Merck[2] and Glaxo[3], named as zaragozic acid A (ZA–A) and squalestatin S1, respectively. A large number of structurally related triacids have since been isolated (**Table 1**), including 6,7–dideoxysqualestatin H5 (DDSQ) (**2**, **Figure 2**), which in the focus of studies described in this thesis.



ZA–A **1**

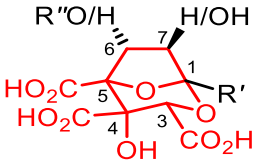
**Figure 1**



DDSQ **2**

**Figure 2**

The various squalestatins / zaragozic acids have the same core and differ only in the nature of the C1 alkyl chain and the C6 acyl chain, with exception that some of them lack oxygenation at C6 and/or C7 (**Table 1**). The key feature of the structure of these molecules is the highly oxygenated 2,8-dioxabicyclo[3.2.1]octane core which contains up to 6 contiguous stereocentres, three of which are quaternary carbons (C1, C4, C5).



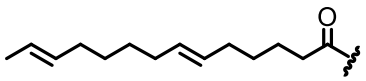
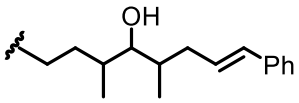
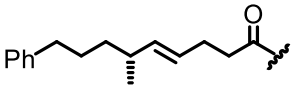
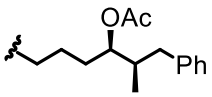
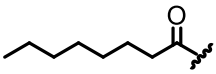
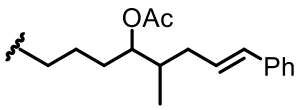
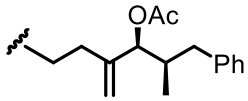
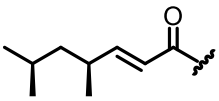
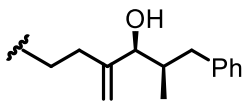
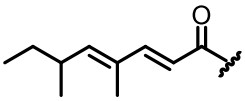
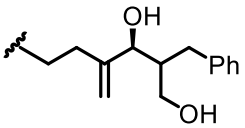
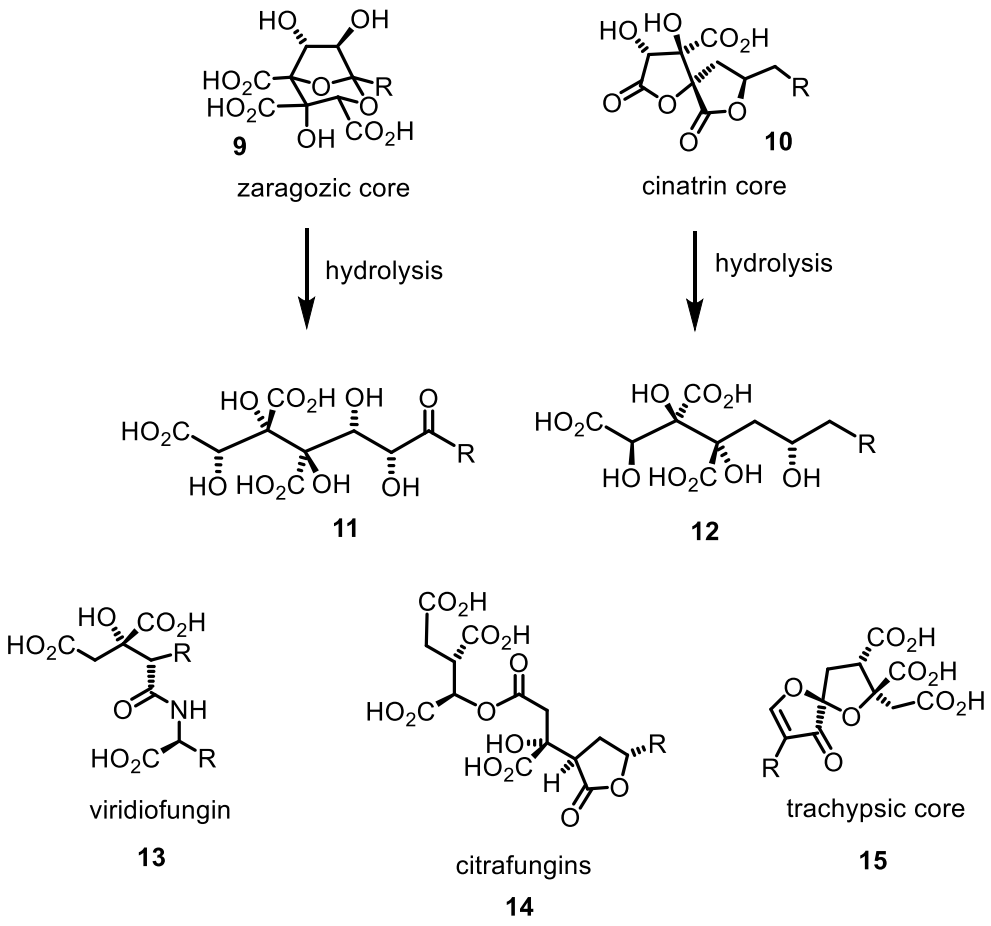

| Compound name | R″ | R′ |
|---|---|---|
| Zaragozic acid B (ZA–B, **3**) |  |  |
| Zaragozic acid C (ZA–C, **4**) |  |  |
| Zaragozic acid D (ZA–D, **5**) |  |  |
| Squalestatin H1 **6** | H |  |
| Squalestatin S2 **7** |  |  |
| Squalestatin T3 **8** |  |  |

**Table 1** Representative squalestatins / zaragozic acids.

Structurally, the tricarboxylic core of this family is closer to those found in cinatrins[4] **10**, trachypsic acid[5] **15** and others (**Scheme 1**). However, the squalestatin/zaragozic acid family was the most widely studied since their isolation.




**Scheme 1** Structural complexity of zaragozic acid core **9** and other similar natural products.

## 1.2 Biological Activity Background of Squalestatins / Zaragozic Acids

Hypercholesterolemia is a significant factor for heart disease, such as atherosclerosis, which is a major cause of mortality.[6] Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are effectively used in reducing cholesterol synthesis and preventing cardiovascular

disease. However, statins also can inhibit the biosynthesis of dolichol, ubiquinone, prenylated proteins and other important biomolecules. Therefore, squalene synthase inhibitors have been a primary focus as an alternative to statins,[7] which theoretically show fewer side effects on other metabolites as they are involved in the advanced stage of the cholesterol biosynthesis pathway (**Figure 3**).

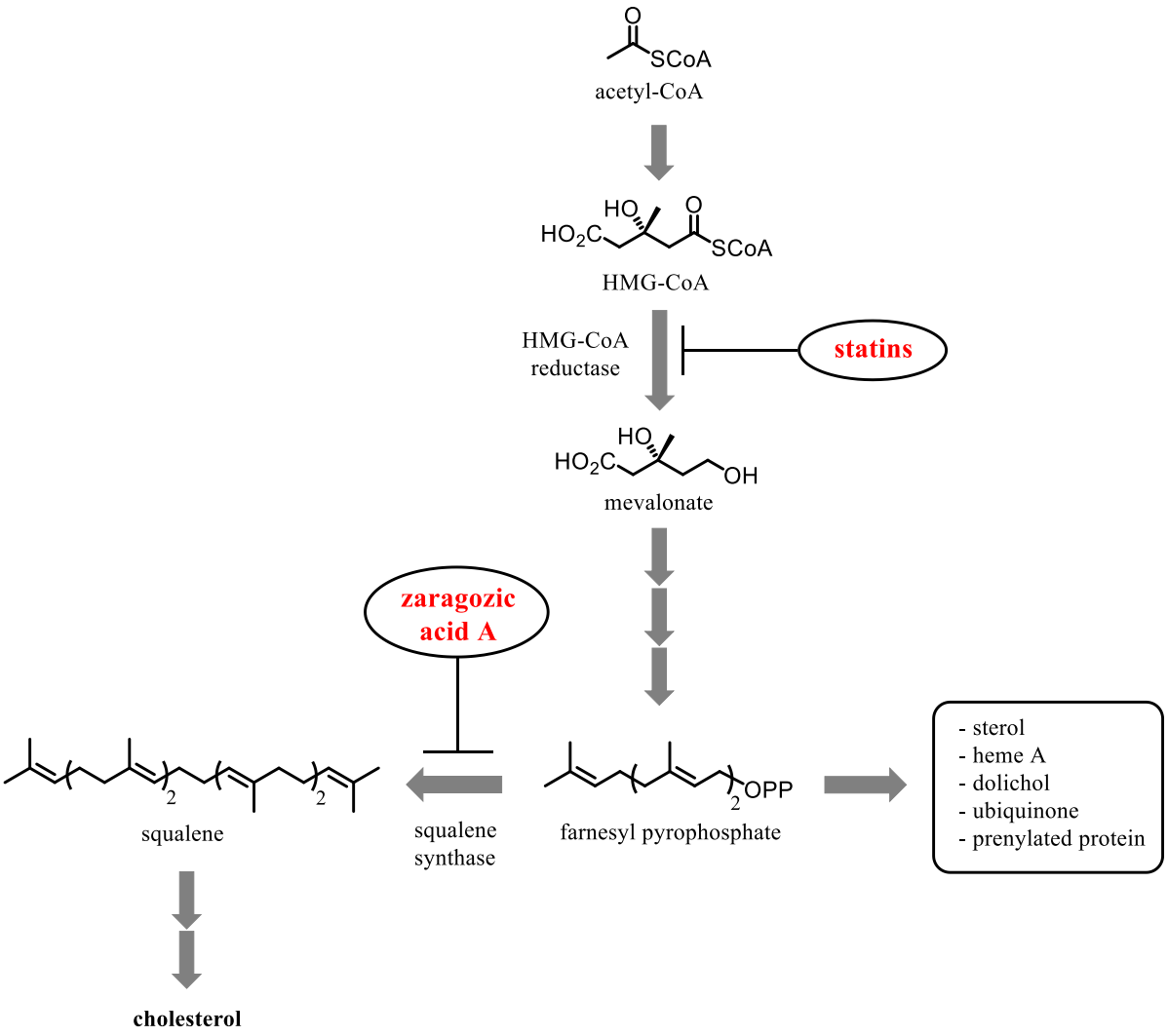



**Figure 3** Biochemical pathways leading to cholesterol synthesis.

Since their isolation, squalestatins / zaragozic acids have attracted significant attention as potent cholesterol–lowering agents, by inhibiting the activity of squalene synthase in human and other species, such as rats, marmosets and mice, at nano to picomolar concentration.[8–10]

The bioreactivity of zaragozic acids could be due to the similarity with a presqualene pyrophosphate intermediate **16** in the reaction catalysed by squalene synthase. While the oxygenated bicyclic core represents the pyrophosphate core, two side-chains are the lipophilic tails (**Figure 4**).[11]

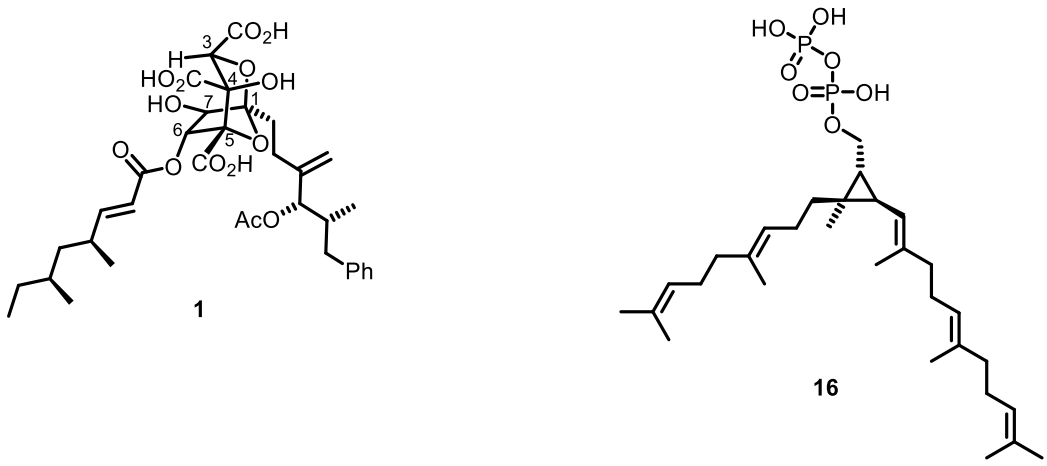



**Figure 4** Structural comparison of ZA–A **1** and presqualene pyrophosphate **16**.

Zaragozic acids have also shown other biological activities, such as antimalarial,[12] antihepatitis C virus,[13] and anticancer.[14] The unusual structure of these natural products, coupled with their promising biological activities, have encouraged synthetic studies by organic chemists.[15–17]

## 1.3 Biosynthesis of Squalestatins / Zaragozic Acids

The biosynthetic origin of ZA–A (**1**) has been investigated by several groups.[18–21] ZA–A is derived from two polyketides: the C1 alkyl side-chain, which forms the bicyclic core; and the C6 acyl side-chain. The skeleton of **1** was suggested to be constructed from benzoic acid, succinic acid, methyl ($CH_2$ or $CH_3$) of methionine and acetate units in combination with $^{18}O_2$ during its biosynthesis by both Rudd and Byrne independently (**Figure 5**).[18,19] Their studies

suggested that the synthesis of C1 alkyl side-chain begins with an aromatic ring (derived from metabolism of phenylalanine *via* benzoic acid) and continues in a polyketide fashion, by addition of five acetate units. While, the acetyl group at C-4′ arises from acetate unit, the methylene at C-3′ and the methyl at C-5′ forms by C-methylation (arise from SAM). Condensation of succinic acid with the C1 polyketide chain forms the C3, C4, C8 and C9 motif. The C6 acyl side-chain is a polyketide formed by linkages of four acetate units and dimethylates at C-4″ and C-6″.

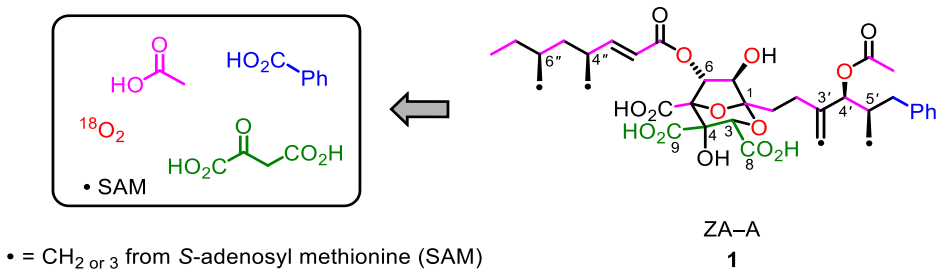
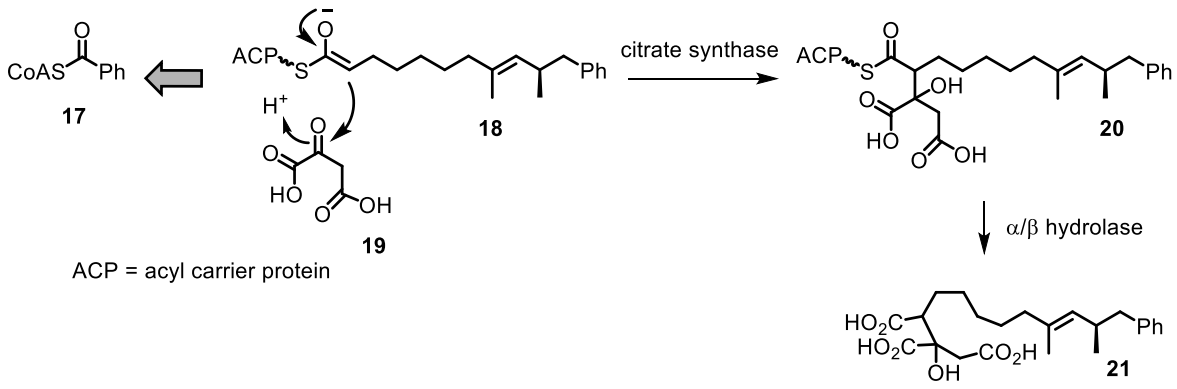


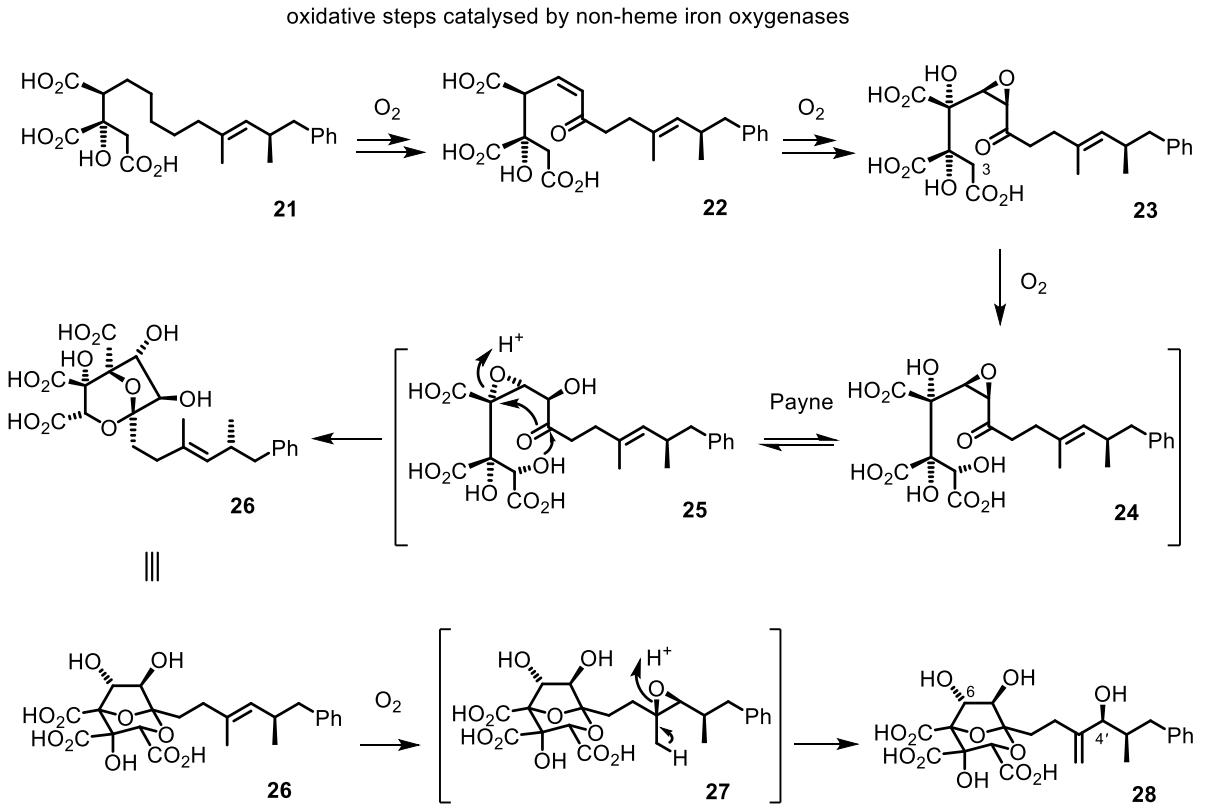

**Figure 5** Biosynthetic origin of ZA–A (**1**).

In 2017, Chooi and co-workers identified and reconstituted the enzymes responsible for the initial biosynthetic steps of ZA–A (**1**) using an engineered fungal heterologous host.[20] The study proposed that the biosynthesis of polyketide citrate intermediate **21** (**Scheme 2**) in *A. nidulans* requires only three enzymes (highly reducing polyketide synthase, citrate synthase and hydrolase) starting from the benzoyl-CoA **17**.




**Scheme 2** Proposed biosynthesis of polyketide citrate **21**.

More recently (2019), Cox and Lebe highlighted seven oxidative steps catalysed by three putative non-heme-iron-dependent enzymes to convert intermediate **21** into the squalestatin precursor **28** (**Scheme 3**).[21] Polyketide citrate **21** oxidises to alcohol, ketone and then to unsaturated ketone **22**. Subsequent epoxidation followed by hydroxylation at C3 would give **24**. Payne rearrangement of **24** followed by acetal formation constructs the desired squalestatin core **26**. Then, epoxidation/rearrangement of **26** would furnish the allylic alcohol **28** (**Scheme 3**).




**Scheme 3** Proposed biosynthesis of the highly functionalised squalestatin precursor **28**.

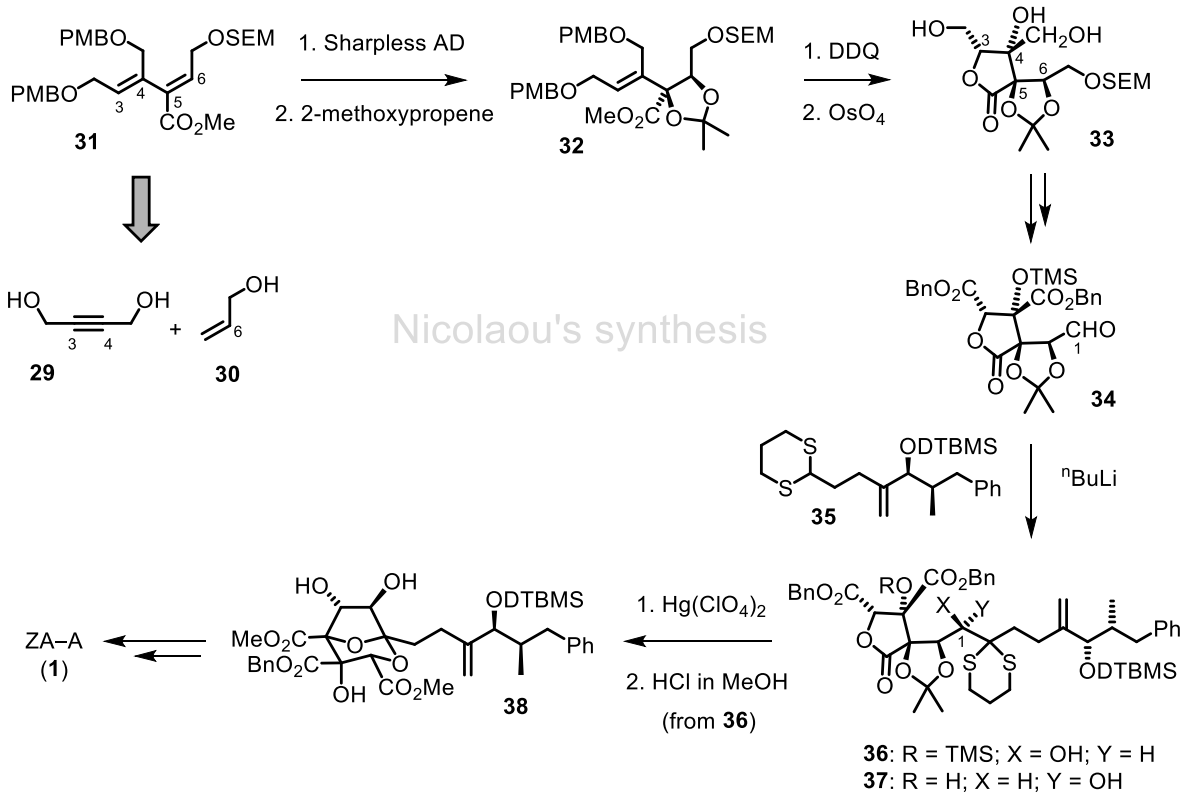
Finally, acylation at C4′ and addition of the C6 acyl side-chain from CoA onto the squalestatin core **28**, catalysed by the acyl transferase, gives ZA–A (**1**).[22]

## 1.4 Total and Formal Syntheses of Squalestatins / Zaragozic Acids

Several research groups have successfully accomplished total and/or formal zaragozic acid syntheses and developed variety of tactics and strategies to construct the 2,8-dioxabicyclo[3.2.1]octane core.[23–25] An aim of this chapter is to outline the main methods used to approach members of this family, to put my studies in context. Previous syntheses of zaragozic acid family–members have been achieved mainly by internal ketalisation as a main theme to construct the acidic core (**Scheme 1**) with a few exceptions. Zaragozic acids A, B, C, D and DDSQ have so far been synthesised.

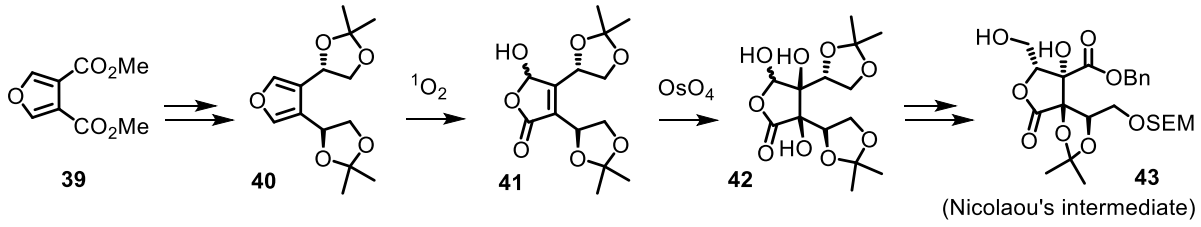
### 1.4.1 Approaches to Zaragozic Acids (A, B, C and D)

The first and asymmetric synthesis (based on a relay approach) of ZA–A (**1**) was reported by Nicolaou's group in 1994.[26,27] The key feature in Nicolaou's synthesis was a double dihydroxylation to introduce absolute stereochemistry at four of the six stereocentres (C3–C6) in the core structure (**Scheme 4**; diene **31** → triol **33**). Then, fourteen steps were required to convert triol **33** to aldehyde **34** and the latter was coupled with the lithiated C1 side-chain **35** to give alcohols **36** and **37** as an approximate 1:1 mixture of diastereoisomers. Removal of the dithiane protecting group of **36** using mercury perchlorate followed by acid-catalysed rearrangement gave the desired dioxabicyclic[3.2.1]octane skeleton **38**. Nine further steps, including introduction of the C6 acyl side-chain, afforded ZA–A (**1**).



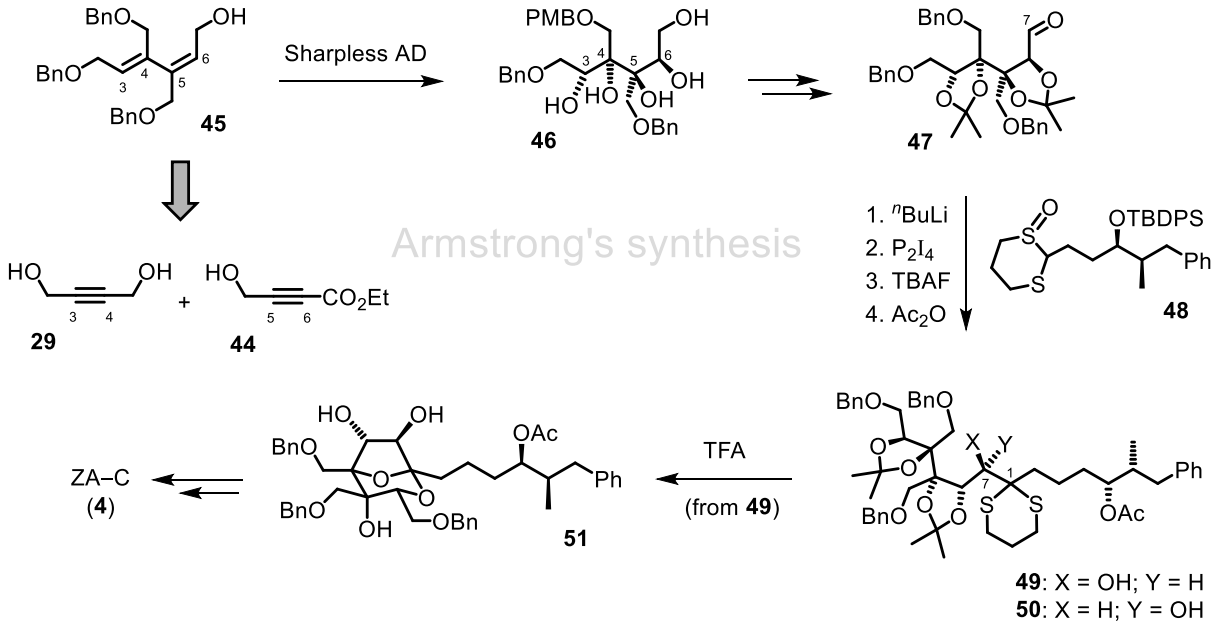

**Scheme 4** The first total synthesis of ZA–A by Nicolaou's group.

Nicolaou's advanced intermediate **43** was also subsequently synthesised by Freeman-Cook and Halcomb, starting from furan diester **39** (**Scheme 5**).[28] Oxidation of the furan ring with singlet oxygen followed by dihydroxylation with $OsO_4$ gave triol **42,** which was further manipulated to provide Nicolaou's intermediate **43**, constituting a symmetry-based formal synthesis of ZA–A (**1**).




**Scheme 5** A symmetry-based formal synthesis of ZA–A (**1**) by Freeman-Cook and Halcomb.

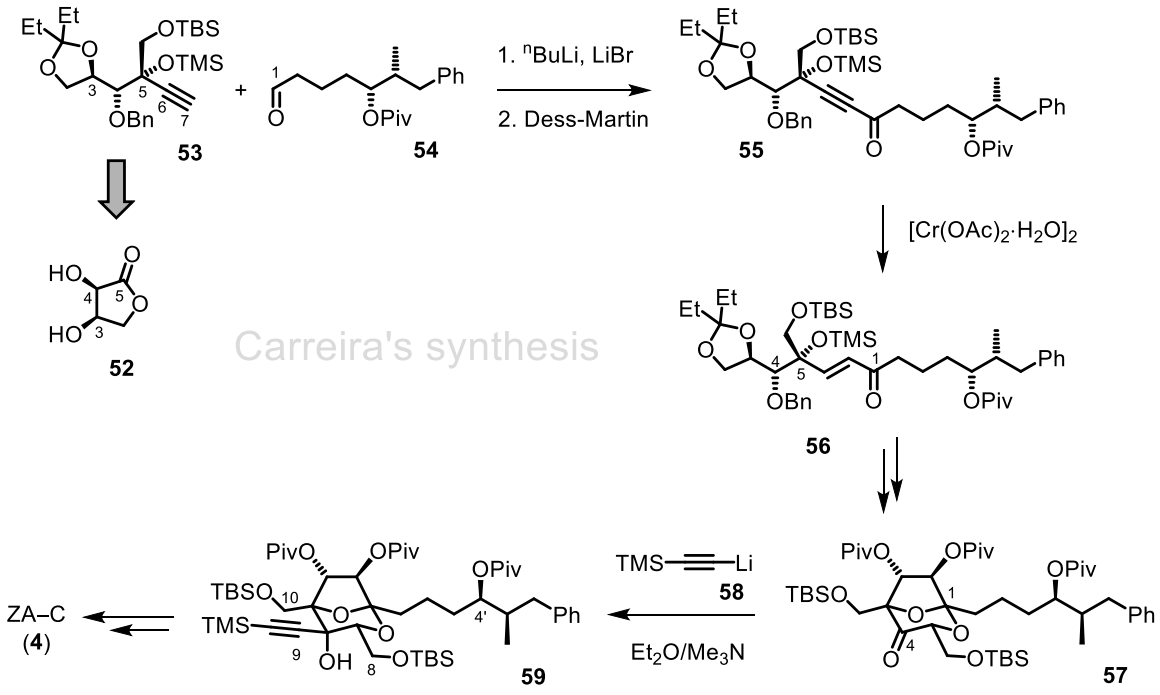
A related strategy to Nicolaou's was used to synthesise ZA–C (**4**) by Armstrong's group,[29,30] however, on a lower oxidation state substrate (**Scheme 6**). A double asymmetric dihydroxylation was employed to control stereochemistry at C3–C6. The C1 side-chain was introduced by coupling the anion of dithiane monosulfoxide **48** with aldehyde **47** to give a mixture of diastereomers at C7. Subsequently, ketalisation of **49** with TFA/$H_2O$ furnished the desired 2,8-dioxabicyclo[3.2.1]octane core **51** with lower oxidation level. Oxidation of the three benzyloxymethyl protected alcohols to acids and acylation at C6 completed the ZA–C (**4**) synthesis.




**Scheme 6** Armstrong's total synthesis of ZA–C (**4**).

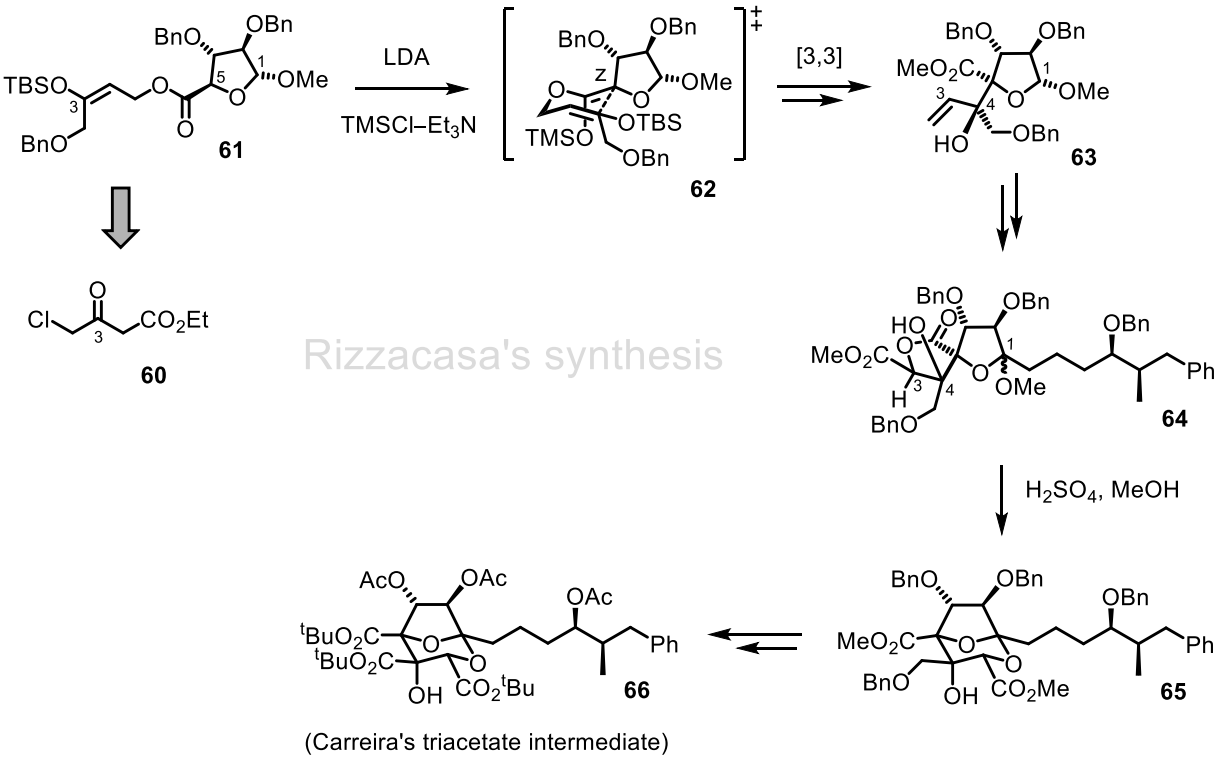
Carreira and Du Bois reported the first synthesis of ZA–C (**4**), in 1994.[31] The synthesis started from D-erythronic-γ-lactone **52**,[32] which already contains two desired stereocentres (C3 and C4), to prepare alkyne **53** (**Scheme 7**). The C1 side-chain was introduced at an early stage by addition of the anion of alkyne **53** to aldehyde **54** followed by Dess-Martin oxidation, to give the desired ynone **55**. Reduction of **55** using chromium(II) acetate, gave the *trans* enone **56**.

Nucleophilic addition of the lithium acetylide **58** in 1:1 $E_2O/Me_3N$ to ketone **57** afforded the desired C4 tertiary alcohol with 6:1 diastereoselectivity. Completion of the synthesis of ZA–C (**4**) was achieved by installation of the C4' acetate, oxidation at C8–C9 and addition of the acyl side-chain at C6.



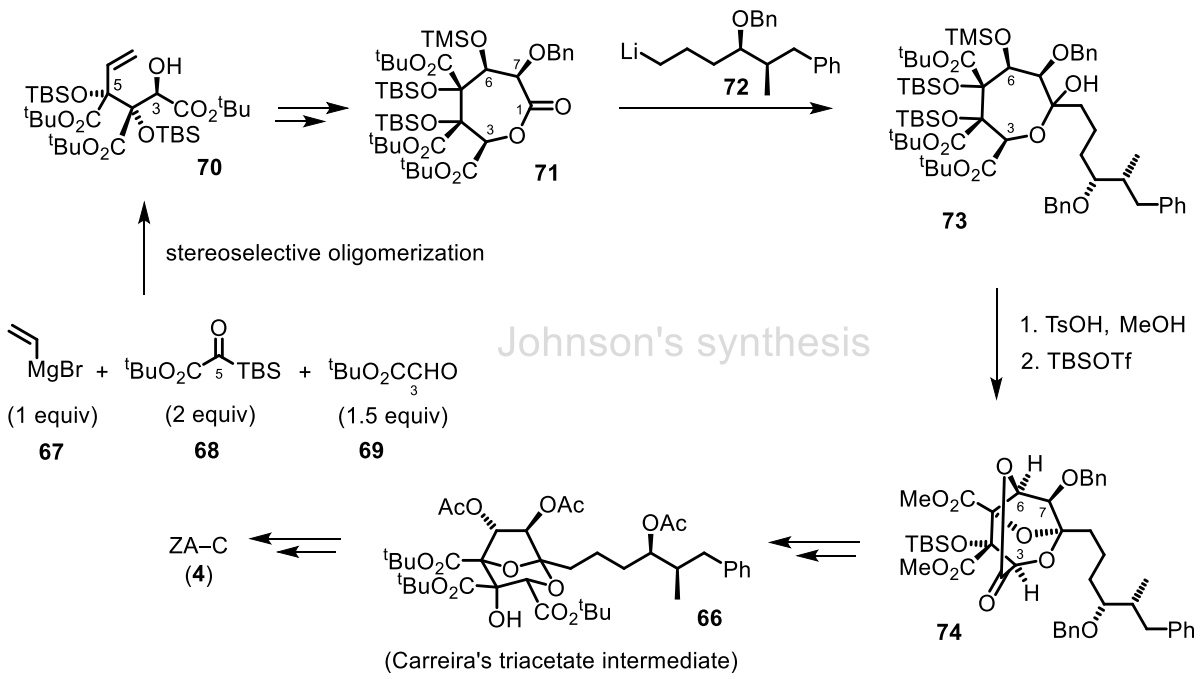

**Scheme 7** Carreira and Du Bois's total synthesis of ZA–C (**4**).

A synthesis of an advanced intermediate in Carreira synthesis of ZA–C (**4**) was subsequently reported by Rizzacasa and co-corkers (**Scheme 8**).[33] The key step was an Ireland-Claisen rearrangement[34] of allylic ester **61**: using LDA in the presence of TMSCl–$Et_3N$ gave mainly *Z*-trimethylsilyl ketene acetal **62**. The acetal intermediate **62** underwent [3,3]-rearrangement and subsequent hydrolysis followed by methylation and TBS-deprotection, to give ester **63** as the major product along with other minor diasteroisomers in 3.6:1 ratio. Ketalisation of ketal **64** using 0.1 M sulfuric acid in MeOH furnished the desired squalestatin core **65** in 44% yield, which was transformed to Carreira's intermediate **66**.



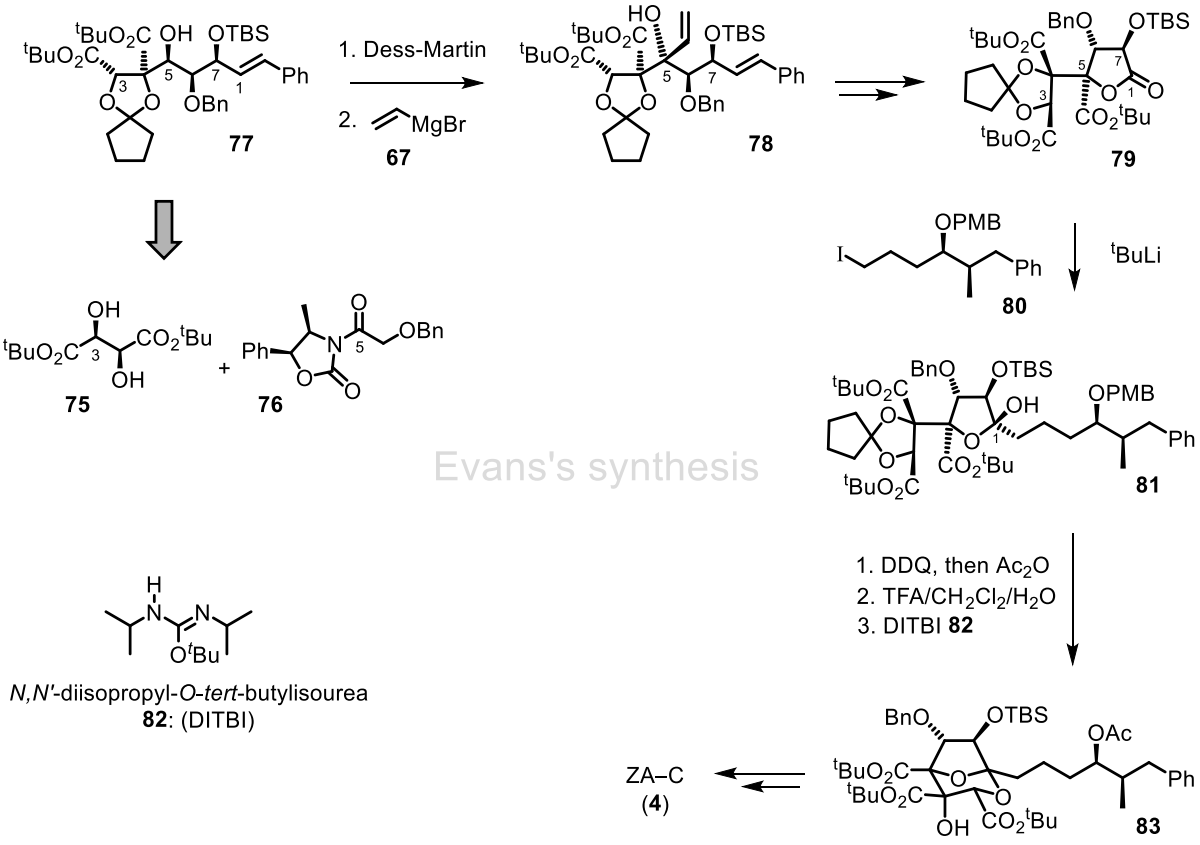

**Scheme 8** Formal synthesis of ZA–C (**4**) through Ireland-Claisen rearrangement.[33]

Another synthesis of ZA–C (**4**) through the advanced Carreira's triacetate intermediate came from the Johnson laboratory (**Scheme 9**).[17] The key feature in Johnson's synthesis was the use of a controlled oligomerization tactic to construct the α-hydroxy ester **70**, which contains two desired stereocentres at C4 and C5; the incorrect configuration at C3 was rectified later in the synthesis. Addition of the lithiated side-chain **72** to the ε-lactone **71** followed by treatment with TsOH/MeOH and TBS–silylation gave the tricyclic ketal **74** with the incorrect configuration at C3 and C6. Further manipulation to correct the stereochemical issues at C3 and C6 led to Carreira's intermediate **66**.



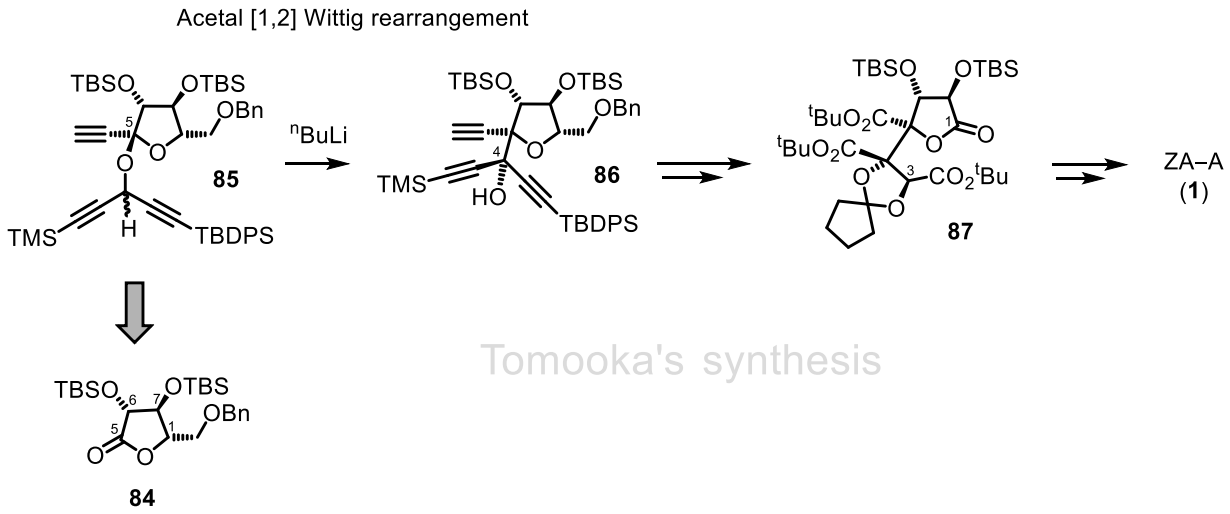

**Scheme 9** Total synthesis of ZA–C (**4**) through stereoselective oligomerization.[17]

In 1994, the Evans group reported an efficient synthesis of ZA–C (**4**) (**Scheme 10**).[35] Starting from di-*tert*-butyl D-tartrate (**75**) and *N*-acyl oxazolidinone **76** to obtain alcohol **77** containing C3–C7 stereogenic centres of the zaragozic acid core, less the C5 carboxyl moiety. Construction of C5 was by Dess-Martin oxidation of **77** followed by addition of vinyl magnesium bromide **67** (a precursor of carboxylic acid moiety in form of the vinyl substituent) to afford the chelate-controlled product **78** with 10:1 selectivity. Addition of the C1 alkyl side-chain **80** to lactone **79**, protecting group manipulations and transketalisation followed by esterification led to the 2,8-dioxabicyclo[3.2.1]octane core **83**. Four further steps provided ZA–C (**4**, **Scheme 10**).



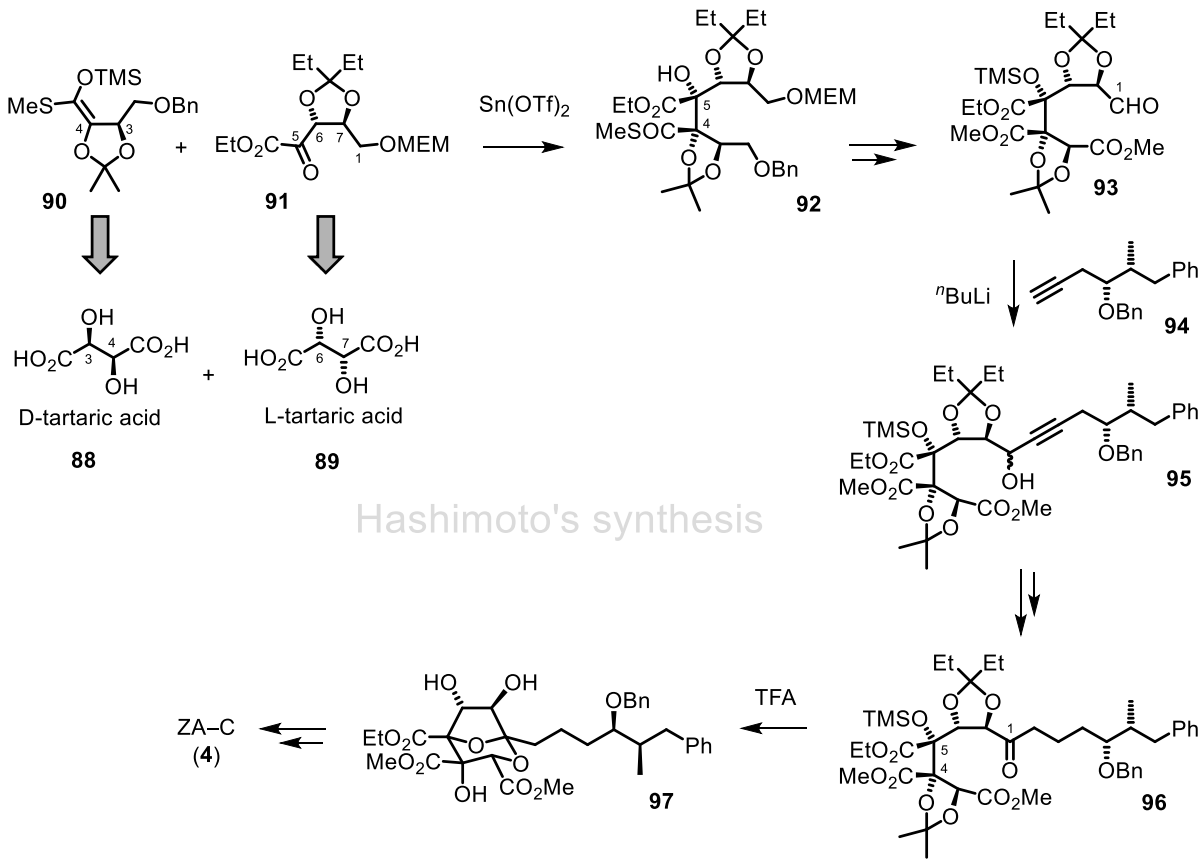

**Scheme 10** Total synthesis of ZA–C (**4**) by Evans.

In a similar approach to Evans, Tomooka and co-workers reported a total synthesis of ZA–A (**1**) based on the [1,2] Wittig rearrangement (**Scheme 11**).[36,37] Treatment of *O*-glycoside **85** with $^{n}$BuLi effected rearrangement to *C*-glycoside **86** with complete retention of configuration at the anomeric centre (C5), along with high diastereoselectivity at C4 (>95% β, 84% dr). Subsequently, *C*-glycoside **86** was converted to lactone **87**, analogous to Evans' lactone (**79**, **Scheme 10**), and then the synthesis of ZA–A (**1**) was completed in another 9 steps (**Scheme 11**).



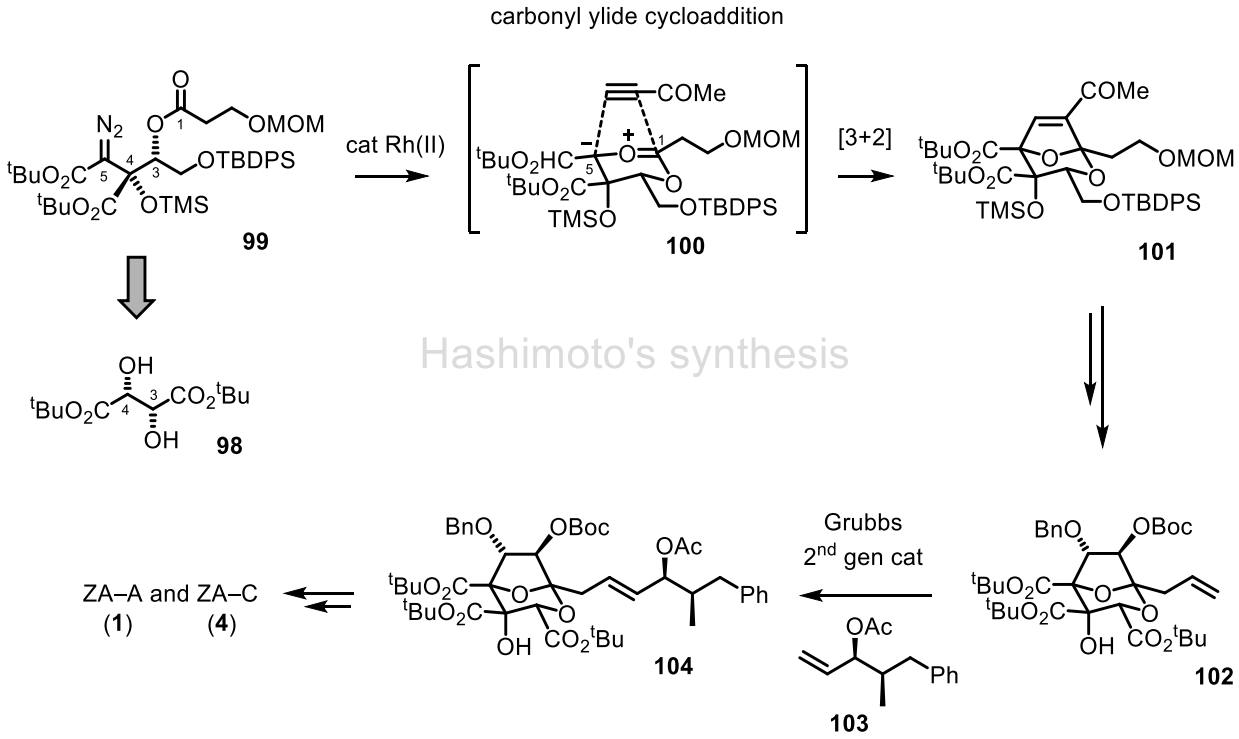

**Scheme 11** Total synthesis of ZA–A (**1**) through [1,2] Wittig rearrangement.

In 2005, Hashimoto and co-workers accomplished a synthesis of ZA–C (**4**) by a $Sn(OTf)_2$-promoted aldol coupling reaction between enolate **90** and α-ketoester **91** to construct the C4 and C5 quaternary stereogenic centres of the squalestatin core (**Scheme 12**).[38] The C1 side-chain was introduced by the addition of acetylide **94** to the aldehyde **93**. Subsequent oxidation and hydrogenation gave ketone **96** which underwent an internal ketalisation to afford the desired bicyclicketal **97** as a single stereoisomer. Then, the latter was transformed to ZA–C (**4**) (**Scheme 12**).




**Scheme 12** Total synthesis of ZA–C (**4**) through an aldol-based strategy.

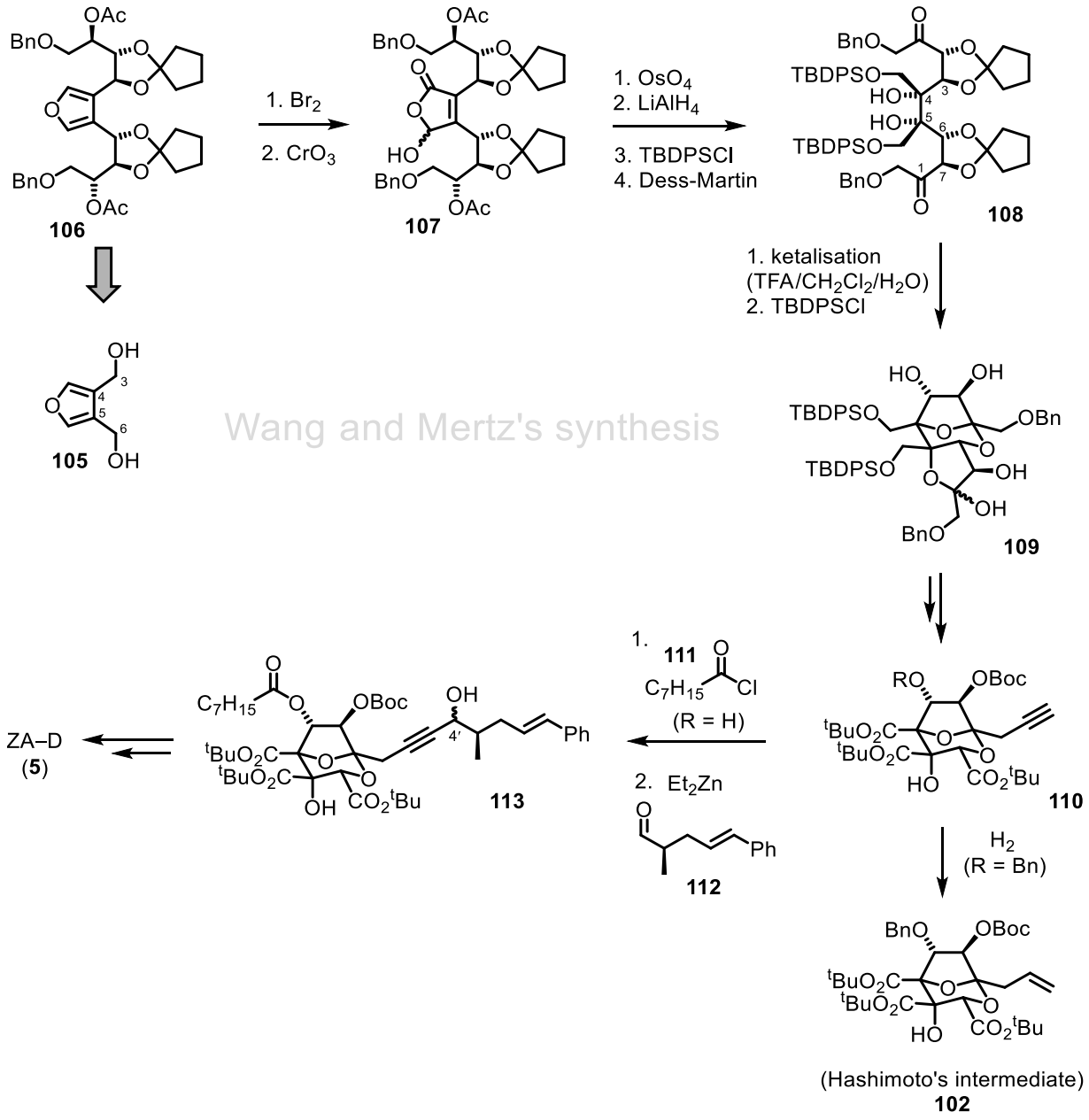
Also, Hashimoto et al. reported a second approach to synthesise ZA–A (**1**) and ZA–C (**4**) *via* a tandem carbonyl ylide formation-cycloadditon (**Scheme 13**).[39] The desired cycloadduct **101** was constructed as a single diastereomer from decomposition of α-diazo ester **99** with a catalytic amount of $Rh_2(OAc)_4$ generating a carbonyl ylide intermediate **100** which underwent 1,3-dipolar cycloaddition with 3-butyn-2-one. The precursor *E*-alkene **104** to ZA–A (**1**) and ZA–C (**4**) was synthesised by olefin cross-metathesis between core **102** and alkene **103** using 5 mol% of 2$^{nd}$-generation Grubbs' catalyst (**Scheme 13**).




**Scheme 13** Total synthesis of ZA–A (**1**) and ZA–C (**4**) through a dipolar cycloaddition stategy.[39]

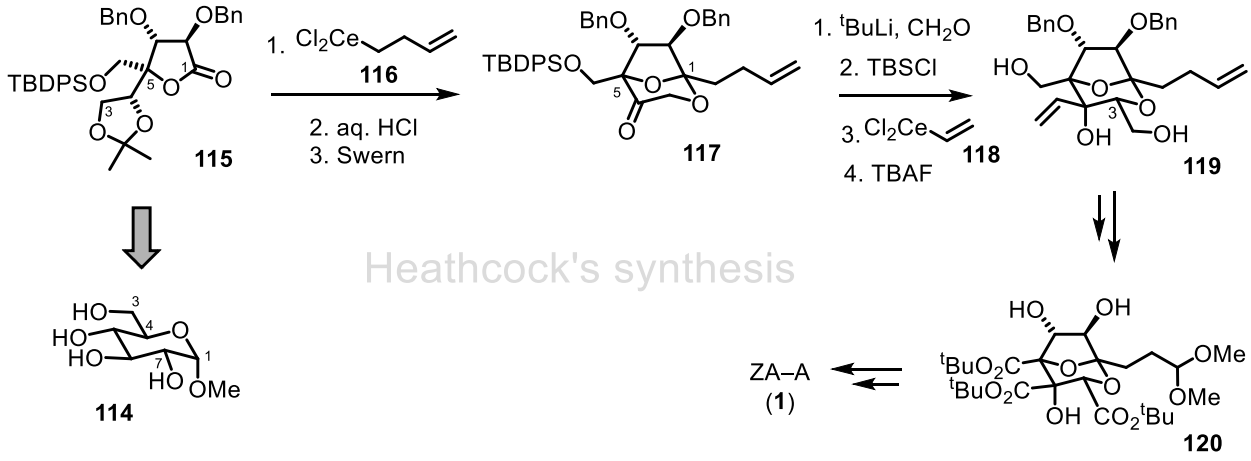
A symmetry-based approach to the first total synthesis of ZA–D (**5**), with additional formal syntheses of ZA–A (**1**) and ZA–C (**4**), was published by Wang and Mertz in 2011.[15,40] Alkyne **110** (**Scheme 14**) represented a general building block for accessing ZA–D (**5**) and Hashimoto's intermediate **102**, for the synthesis of ZA–A (**1**) and ZA–C (**4**) (**Scheme 13**). Diacetate **106**, derived from furan-3,4-dimethanol (**105**), was treated with $Br_2$ and then $CrO_3$ to afford lactone **107** (4:1 epimers). Subsequently, dihydroxylation, global reduction, chemoselective protection and oxidation gave the pseudo $C_2$-symmetrical diketone **108** with the correct stereochemistry at C4 and C5. Ketalisation of **108** using Evans' conditions ($TFA/CH_2Cl_2/H_2O$) followed by silylation gave hemi-acetals **109** (as a 3:1 epimer mixture at 3º OH), which was later manipulated to the desired alkyne core **110**. The formal synthesis of ZA–A (**1**) and ZA–C (**4**) was accomplished through hydrogenation of alkyne **110** giving Hashimoto's intermediate alkene **102**. Esterification of alkyne **110** with octanoyl chloride (**111**)

at C6, followed by $Et_2Zn$-induced alkynylation of aldehyde **112** led to secondary alcohol **113** (1:2 dr at C4′). Alcohol **113** was later unified to the desired configuration of the C4′ stereocentre by Dess-Martin oxidation and an asymmetric Ru catalyst transfer hydrogenation (with dr ≥ 20.1). Finally, the total synthesis of ZA–D (**5**) was completed after chemoselective alkyne reduction, acetylation at C4′ and global deprotection by TFA (**Scheme 14**).




**Scheme 14** Total synthesis of ZA–D (**5**) and formal for ZA–A (**1**) and ZA–C (**4**) by Metz and co-workers.[15,40]

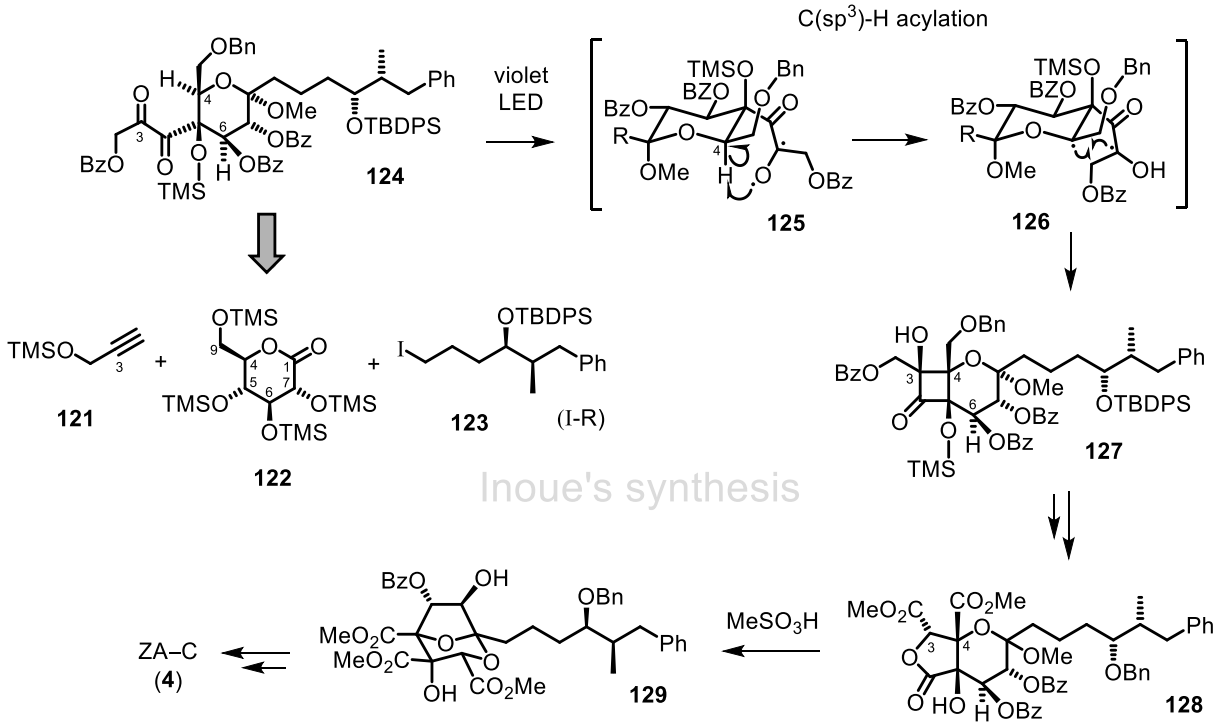
In a relay synthesis, Heathcock and co-workers reported a synthesis of ZA–A (**1**) *via* relay acetal **120** (**Scheme 15**).[41,42] The synthesis commenced with methyl α-D-glucopyranoside **114**, which provided the correct stereochemistry at C6 and C7. Similar to Carreira's synthesis (**Scheme 7**), Heathcock constructed the bicyclic core at a lower (triol) oxidation state. Addition of the C1 side-chain to lactone **115** using the cerium reagent **116**, followed by treatment with aq. HCl and Swern oxidation, furnished ketone **117**. Enolisation of ketone **117** using $^{t}$BuLi and then trapping the anion with formaldehyde followed by silylation introduced the C3 functionality. Highly stereoselective addition of vinylcerium reagent **118** (at C4) followed by treatment with TBAF gave triol **119**. Further functional group transformation, including the oxidation to the three esters, ozonolysis of alkene, debenzylation and formation of the dimethyl acetal, afforded relay acetal intermediate **120** (**Scheme 15**).




**Scheme 15** Total synthesis of ZA–A (**1**) by Heathcock and co-workers.

In 2017, a total synthesis of ZA–C (**4**) was communicated by the Inoue group.[43] The synthesis utilised gluconolactone derivative **122** as a building block that required attachment of the C1 side-chain **123** and C5–alkynyl **121** (**Scheme 16**). The alkynyl moiety would be oxidised to 1,2-diketone **124** after protective groups manipulation. Photoinduced Norrish–Yang

cyclisation[44,45] of 1,2-diketone **124** under violet LED irradiation afforded alcohol **127** with complete regio- and stereoselectivity at C3 and C4, *via* generating 1,2-biradical **125** that abstracted the C4–H selectively resulting 1,4-biradical **126** which underwent C–C formation. Subsequently, cyclobutanone **127** was transformed to alcohol **128**, the precursor of the squalestatin. The ZA core was revealed using methanolic $MeSO_3H$ (**128→129**), which then eight steps further were required to complete the synthesis (**Scheme 16**).

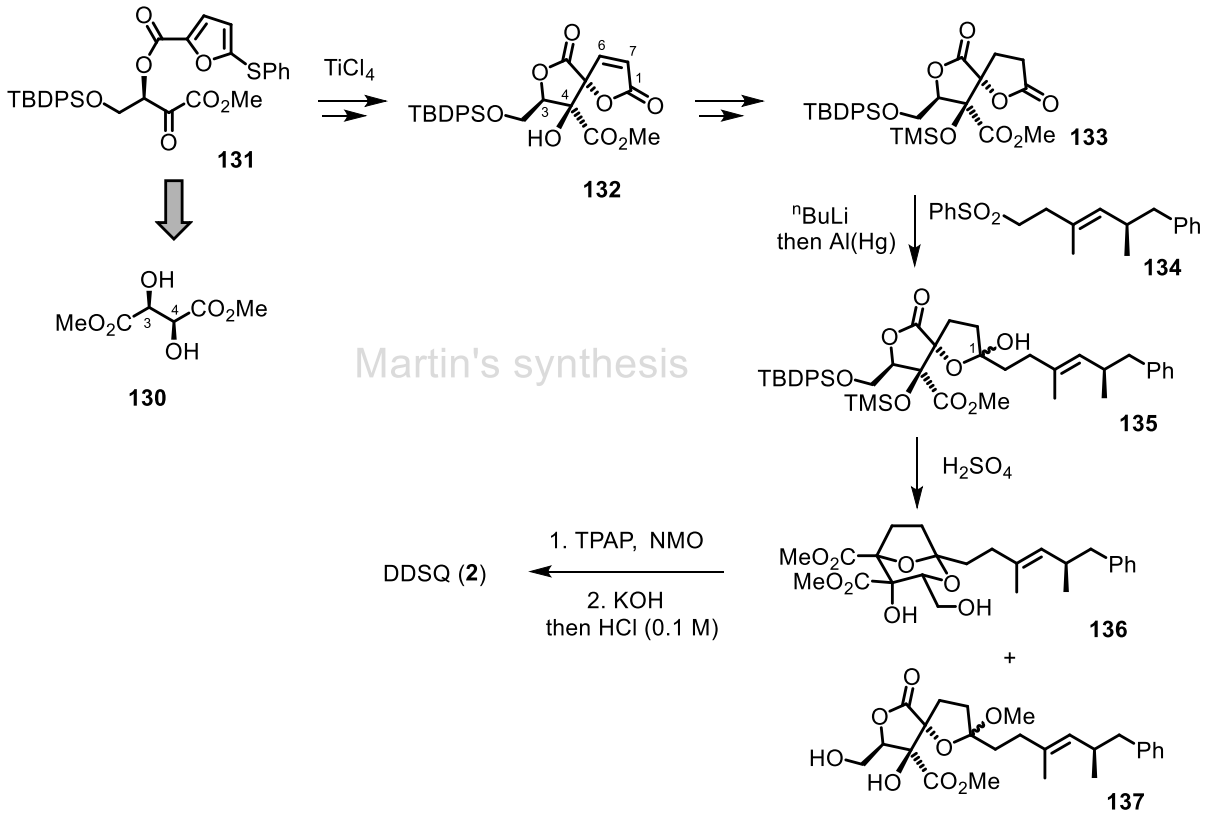



**Scheme 16** Total synthesis of ZA–C (**4**) through regio- and stereoselective C($sp^3$)–H acylation.[43]

## 1.4.2 Synthesis of 6,7–Dideoxysqualestatin H5 (DDSQ)

The first total synthesis of DDSQ (**2**) was reported by Martin's group (**Scheme 17**), and was based on an intramolecular vinylogous aldol reaction of α-ketoester **131** to adduct **132**. This assembles the majority of the framework of the bicyclic core with absolute stereochemistry at

C3–C5.[46] Addition of the dianion of sulfone **134** to lactone **133** followed by reductive desulfonylation gave a 1:1 epimeric mixture of hemiacetals **135**. Ketalisation of the hemiacetals **135** using methanolic $H_2SO_4$ gave a mixture (1:2.5) of the desired 2,8-dioxabicyclo[3.2.1]octane core **136** along with methyl ketals **137** as 1:1 epimeric mixture, which was separable by column chromatography. Oxidation of the primary alcohol in **136** and subsequent saponification of the methyl esters at C4 and C5 gave DDSQ (**2**).

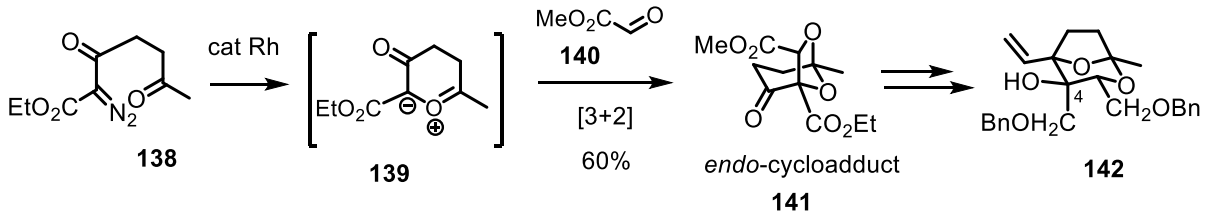



**Scheme 17** Total synthesis of DDSQ (**2**) through intramolecular vinylogous aldol reaction.[46]

## 1.5 Hodgson's Approaches Towards DDSQ

### 1.5.1 Model Studies to the Squalestatins / Zaragozic Acids Core

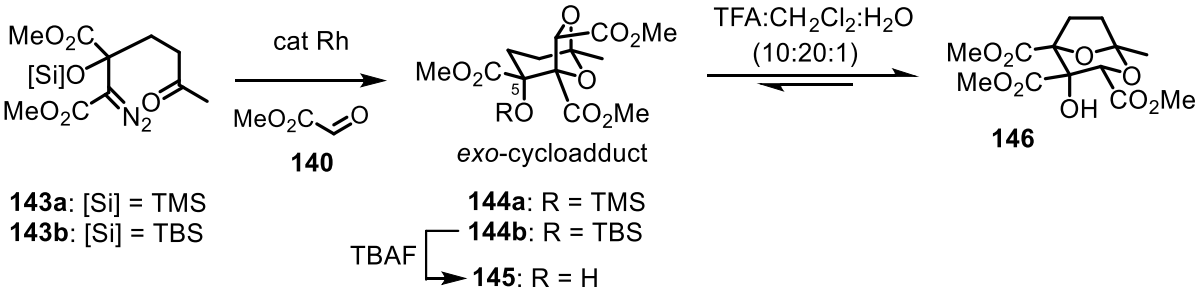
The Hodgson group has been investigating a novel approach towards the synthesis of 6,7-dideoxsqualestatin H5 (DDSQ) **2** over two decades. The key transformation is the use of carbonyl ylide cycloaddition chemistry to construct the 2,8-dioxabicyclo[3.2.1]octane skeleton. A first racemic model study (the C1 alkyl side-chain = Me) was investigated by Bailey (**Scheme 18**).[47] When α-diazoester **138** reacted with methyl glyoxylate **140** in the presence of catalytic $Rh_2(OAc)_4$, *endo*–cycloadduct **141** (with respect to the ylide-containing ring) was formed as a single regio– and stereoisomer (**Scheme 18**). The *endo*- attack was attributed to the influence of a preferred secondary orbital interaction between the ester carbonyl of the methyl glyoxylate (in the *s-trans* conformation) and the carbonyl moiety of the yilde **139**.[48] Consequently, elaboration of **141** into the ZA bicyclic core led to 2,8-dioxabicyclo[3.2.1]octane **142** with the incorrect stereochemistry at C4.




**Scheme 18** First approach to construct the DDSQ (**2**) core by Bailey.[47]

The incorrect C4 epimer for ZA core originated from the *endo*-cycloadduct **141**. Therefore, reversing the selectivity in the cycloaddition to *exo*-cycloadduct product could likely lead to the desired ZA core with the correct stereochemistry at C4.

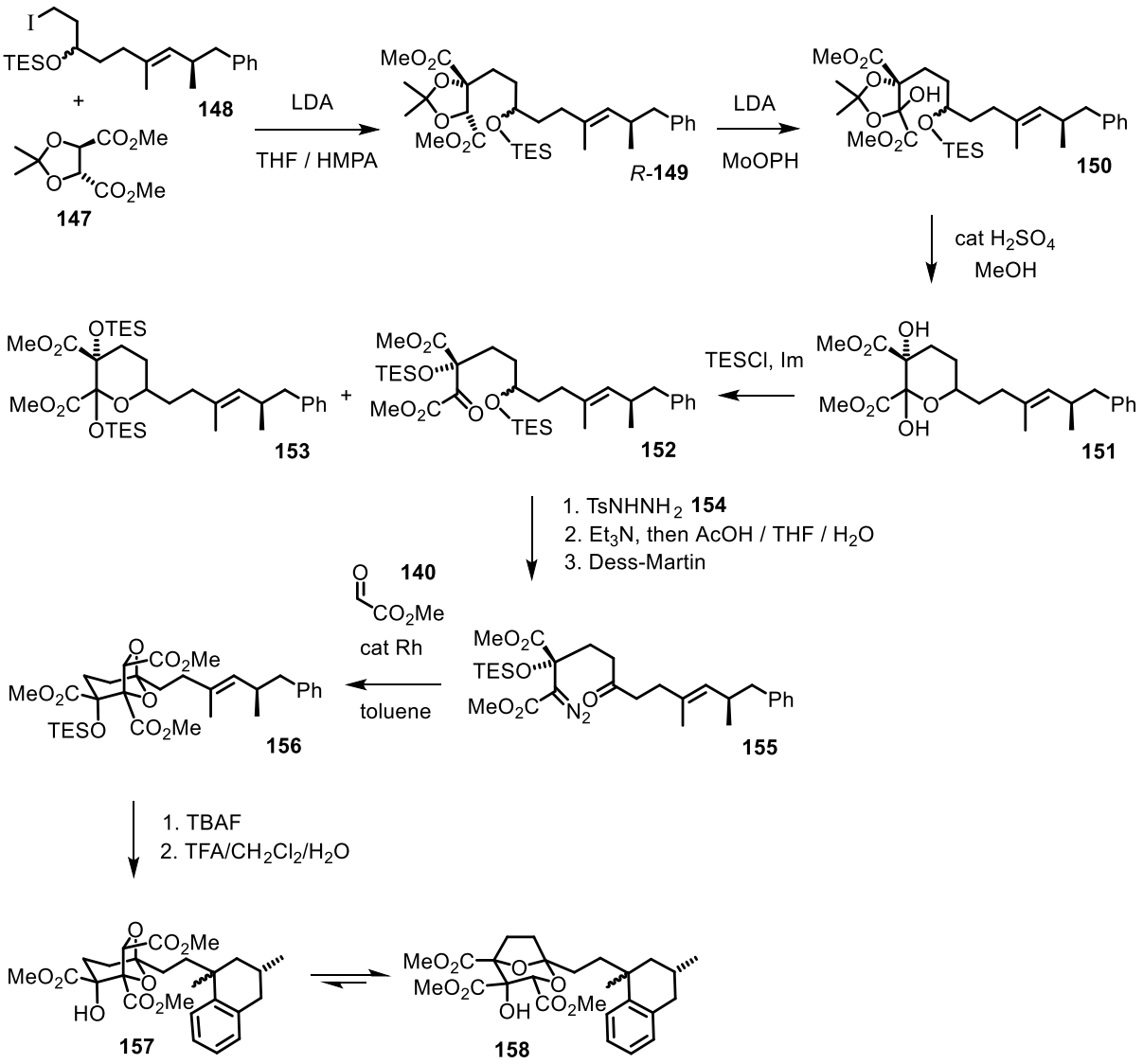
In follow–up studies, Villalonga–Barber further investigated this cycloaddition chemistry. It was hypothesised that modification of the β-keto group of the α-diazoester **138** (**Scheme 18**) to a more sterically demanding β-siloxy functionality would remove the secondary orbital overlap effect and form the desired *exo*–cycloadduct. Indeed, a significant result was obtained when β-silyloxy(ester)-α-diazoester **143a** reacted with glyoxylate **140** in the presence of catalytic $Rh_2(OAc)_4$ to give the required *exo*–cycloadduct **144a** (63%) as the major isomer along with others in a ratio of 7:1:1 (**Scheme 19**). Increasing the bulkiness of the β-siloxy functionality by using TBS led to a higher proportion of the *exo*–cycloadduct **144b** (12:1:1) in 63% yield. The cycloaddition occurs with glyoxylate **140** on the less hindered face (opposite to the siloxy group) avoiding steric interaction between the ester group of methyl glyoxylate and ester functionality at C5. After TBS-deprotection, rearrangement of cycloadduct **145** using Evans conditions ($TFA/CH_2Cl_2/H_2O$) gave the 2,8-dioxabicyclo[3.2.1]octane core **146** of the squalestatins / zaragozic acids at the correct tricarboxylate oxidation level. That acid-catalysed equilibrium had been reached was established by subjecting **146** to Evans conditions, which returned the same 2:1 ratio of **145**:**146** respectively (**Scheme 19**).




**Scheme 19** Construct the tricarboxylate core of DDSQ (**2**) by Villalonga–Barber.[49–51]

### 1.5.2 Sintim's Study Towards DDSQ

With inspiration from the Villalonga–Barber studies, Sintim attempted the first approach towards the total synthesis of DDSQ (**2**) *via* carbonyl ylide cycloaddition as the key step to construct the bicyclic core.[52] Alkylation of lithiated anion of dimethyl L-tartrate acetonide **147** with the C1 alkyl side-chain **148** gave the alkylated tartrate *R*-**149** in 40–70% yield (**Scheme 20**). After extensive investigation, the enolate of alkylated tartrate *R*-**149** was treated with MoOPH, in order to access hydroxylated acetonide **150**. Cleaving the isopropylidene moiety under acidic conditions (0.1 M $H_2SO_4$ in MeOH) gave lactone **151**. Treatment of lactone **151** with TESCl in the presence of imidazole gave ketone **152** along with a trace amount of bis-TES lactone **153**. Hydrazone condensation of ketone **152** with tosylhydrazide **154** gave a hydrazone which on treatment with $Et_3N$ gave a diazo compound. The diazo substrate was selectively desilylated at the secondary ether with a 1:2:1 mixture of AcOH:THF:$H_2O$, followed by Dess–Martin oxidation to give the required cycloaddition precursor, diazoketone **155**. Following the Villalonga–Barber conditions (**Scheme 19**), 1,3-dipolar cycloaddition of diazoketone **155** using cat. $Rh_2(OAc)_4$ and methyl glyoxylate **140** gave the desired *exo*–cycloadduct **156**. Deprotection of TES ether, then acid–catalysed rearrangement was anticipated to give the desired triester DDSQ. However, when cycloadduct **156** was subjected to rearrangement conditions (TFA/$CH_2Cl_2$/$H_2O$) after desilylation, a mixture of two compounds with loss of the unsaturation in the side-chain was obtained. The mixture of compounds was believed to be **157** and **158** based on HRMS, as the presence of TFA likely induced the formation of a tertiary carbocation at the acid-labile trisubstituted alkene, which subsequent cyclised with the aromatic ring (see p. 41). Different conditions (*ie*. temperature, time, acid and ratio of TFA with $CH_2Cl_2$/$H_2O$) all failed to give the desired rearranged compound.



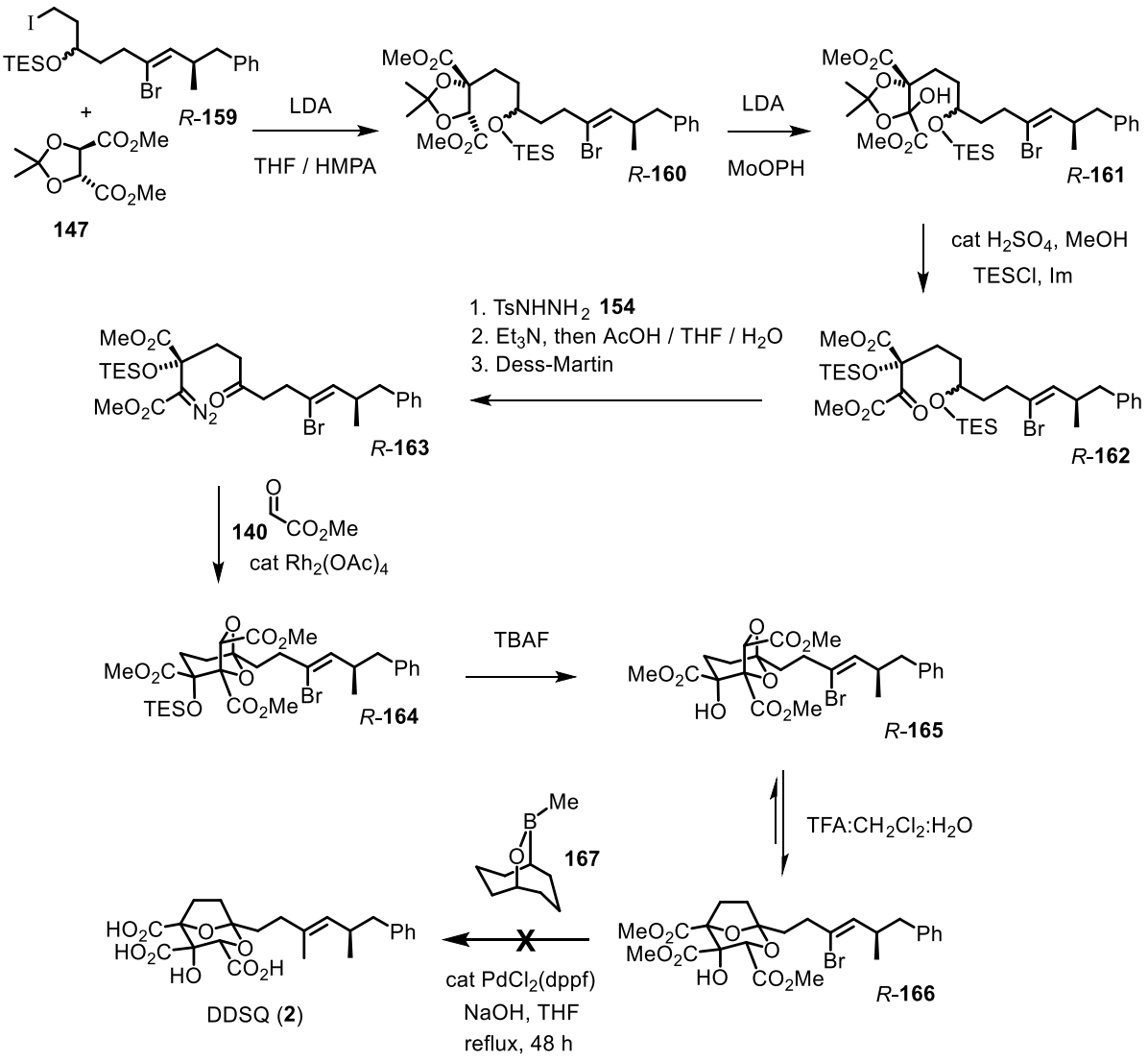

**Scheme 20** Sintim's approach towards DDSQ (**2**).

## 1.5.3. Alkene Protection Against Acid Using a Bromide Substituent Strategy

### 1.5.3.1 Al-Mamari's Study Towards DDSQ

Following Sintim's study, it was considered that masking the alkene (in **156**) could potentially protect this type of electron-rich carbon-carbon double bond from such unwanted cyclisation reactivity. Al-Mamari examined the idea of reducing the propensity of the alkene to protonation

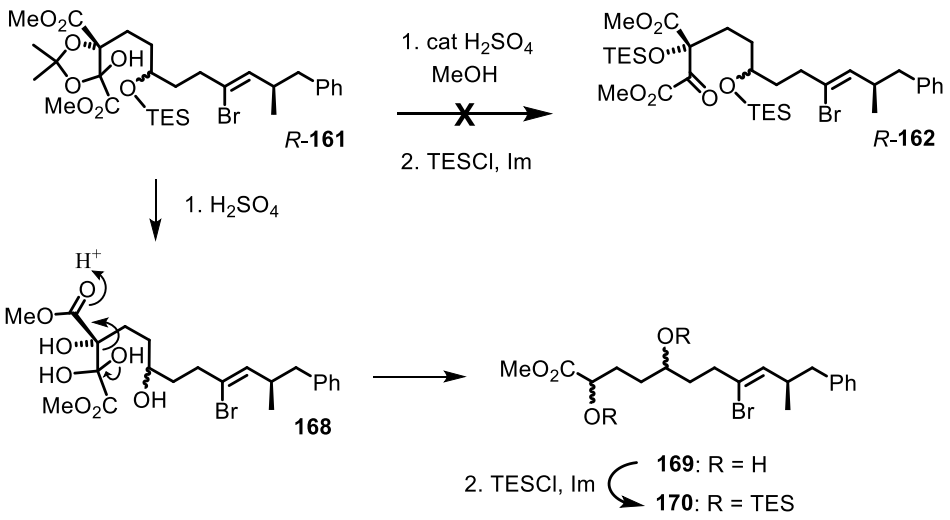
through the presence of a temporary bromide substituent (**Scheme 21**).[53] The stability of a *Z*-alkenyl bromide motif under the TFA rearrangement conditions and the ability to install a methyl group using Suzuki-Miyaura coupling[54] on model studies inspired progression of iodide *R*-**159** towards DDSQ (**2**) (**Scheme 21**). Thus, tartrate alkylation, followed by oxidation of the resulting alkylated tartrate *R*-**160** gave hydroxy acetonide *R*-**161**. The acidic conditions necessary to remove acetone from *R*-**161** resulted in concomitant desilylation, but the silyl group was reinstalled during formation of the bis-TES ether *R*-**162**. This bis-TES ether *R*-**162** underwent condensation with tosylhydrazide **154** followed by $Et_3N$-induced generation of diazo functionality. Under basic reaction conditions, partial desilylation of the secondary TES ether occurred and this was completed by addition of aqueous acetic acid. Dess–Martin oxidation of the resulting secondary alcohol intermediate allowed access to ketone *R*-**163**. This was followed by cycloaddition with methyl glyoxylate **140** to furnish cycloadduct *R*-**164**. After desilylation, the key rearrangement step of the resulting cycloadduct *R*-**165** gave the desired 2,8-dioxabicyclo[3.2.1]octane *R*-**166**, importantly with preservation of the alkenyl bromide. The final steps of the total synthesis were planned to be a one-pot tandem Suzuki–Miyaura methylation and esters hydrolysis. Unfortunately, no evidence of DDSQ (**2**) was observed when the resulting mixture of the rearrangement reaction (*R*-**165** + *R*-**166**) was submitted to the Suzuki-Miyaura conditions. Presumably, the present of unrearranged compound *R*-**165** complicated the reaction mixture. Lack of material as well as time constraints did not allow additional investigation of this reaction by Al-Mamari.




**Scheme 21** Al-Mamari's approach towards DDSQ (**2**).

## 1.5.3.2 Dr. Valade's Study Towards DDSQ

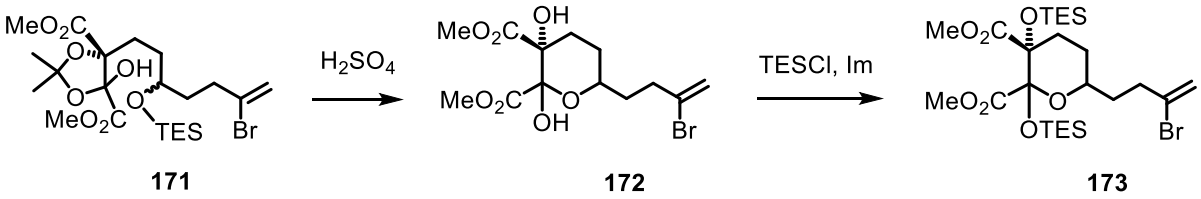
Dr. Valade attempted the route to DDSQ (**2**) based on Al-Mamari's strategy in order to examine the final methylation / esters hydrolysis steps; however, some problems were encountered.[55] Attempted repetition of the hydrolysis / silylation step (*R*-**161**→ *R*-**162**) was unsuccessful and instead of the expected α-keto ester *R*-**162**, protected diol **170** was isolated (**Scheme 22**). Presumably, the diastereomeric mixture of diol **169** was formed as a result of acidic hydrolysis of the hydroxylated acetonide *R*-**161**.




**Scheme 22** Dr. Valade's attempt towards DDSQ (**2**).

### 1.5.3.3 Dr. Humphreys' Model Study

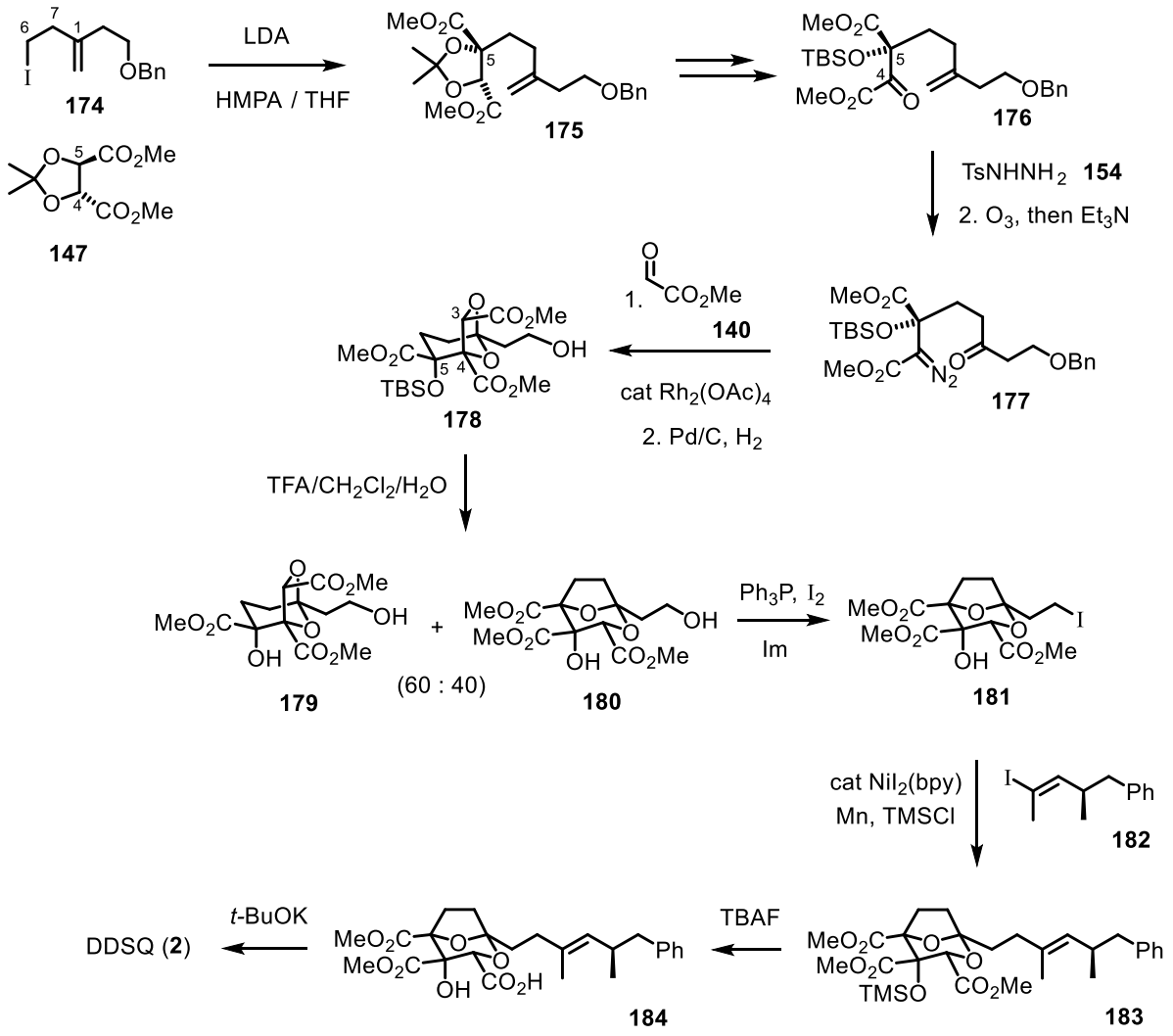
Extensive investigation of this step in a model study with hemiacetal **171**, truncated side-chain, was carried out by Dr. Humphreys (**Scheme 23**).[56] However, following acetonide **171** deprotection, all attempts were unsuccessful in preventing lactol **172** formation, and it was not found possible to access the desired open-chain, *E*-hydroxy, α-ketoester.




**Scheme 23** Dr. Humphreys' attempt for hydrolysis / silylation of **172**.

### 1.5.4 Total Synthesis of DDSQ

Based on an approach initiated by Dr. Arif and finished by Fegheh-Hassanpour at the same time with this study, a total synthesis of DDSQ (**2**) was finally achieved, by a cross–coupling strategy for direct delivery of unsaturated side-chain **182** to the halide core **181** (**Scheme 24**).[57] Alkylation of tartrate acetonide (**147**) with iodide **174**, hydroxylation using MoOPH followed by hydrolysis / silyl protection gave α-ketoester **176**. Hydrazone formation and then a 1–pot ozonolysis / Bamford–Stevens[58] reaction furnished diazoketone **177**. Subsequently, Rh-catalysed cycloaddition of diazoketone **177**, debenzylation and acidic rearrangement gave a 60:40 ratio of the cycloadduct **179** and rearranged core **180**; the rearranged core was unfavoured. Iodination followed by stereoretentive Ni-catalysed $Csp^3$–$Csp^2$ cross–electrophile coupling between iodide core **181** and iodide side-chain **182** gave the TMS triesters DDSQ **183**, a precursor to the natural product. Desilylation of **183** by TBAF was accompanied with hydrolysis of the less hindered C–3 ester to afford diester DDSQ **184**. Subsequent saponification of the more hindered methyl esters at C4 and C5 gave DDSQ (**2**) (**Scheme 24**).

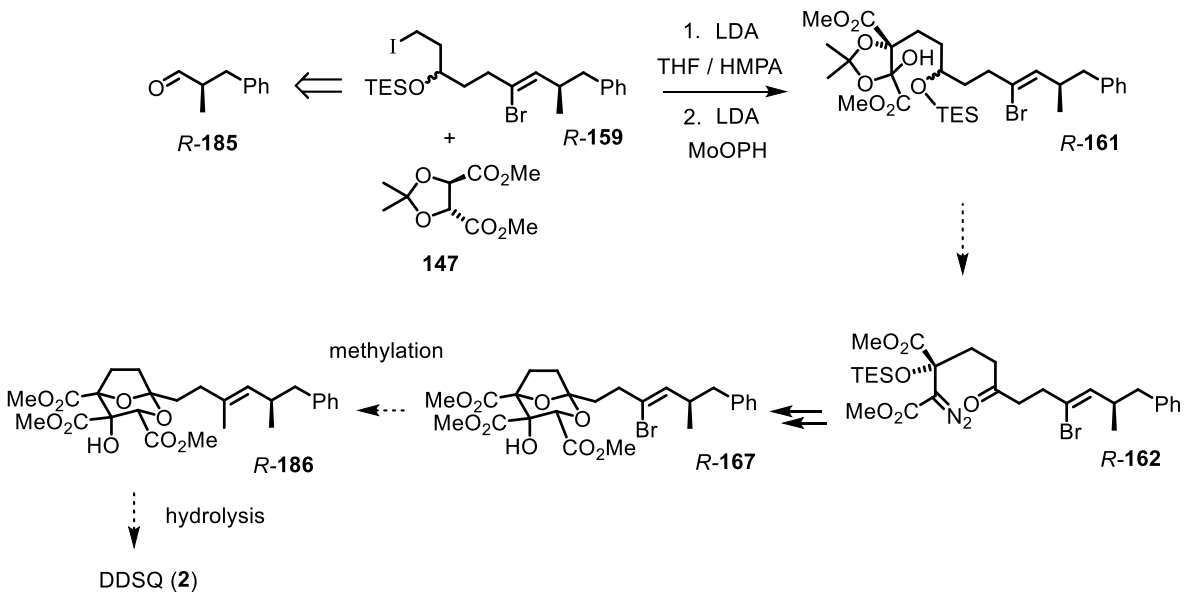



**Scheme 24** Total synthesis of DDSQ (**2**) by Fegheh-Hassanpour.

## 1.6 Project Aims

The main objective of this project was to complete the total synthesis of 6,7-dideoxysqualestatin H5 (DDSQ) **2** *via* the alkene protection strategy which was initiated by Al-Mamari (**Scheme 21**). As discussed earlier, in previous work in the DMH group, acid-catalysed rearrangement of cycloadduct to give the desired bicyclic core was not successful, with concomitant cyclisation of the phenyl group onto the double bond occurring

(**156**→**157**+**158**; **Scheme 20**).[52] The electrophilic attack to the alkene side-chain was prevented by substituting an electron-withdrawing bromine atom.[53] However, the bromide-substituted route suffered from major issues: including low yield of the side-chain *R*-**159** and reproducibility of the crucial hydrolysis/silylation step (*R*-**161**→ *R*-**162**; **Scheme 25**). This study aimed to address these issues, mainly by preparing the side-chain *R*-**159** in useful yields and to investigate the problematic hydrolysis/silylation step. Once achieved, methylation cross-coupling would be sought to access the natural product precursor *R*-**186**, by converting the alkenyl bromide moiety into the corresponding alkenyl methyl group in the presence of esters and alcohol functionalities. Finally, hydrolysis of the ester groups would lead to the target molecule (DDSQ, **2**).




**Scheme 25** A synthetic plan towards DDSQ (**2**).

# Chapter 2

# Results and Discussion, Part I:

## Phenyl Cyclisation

and

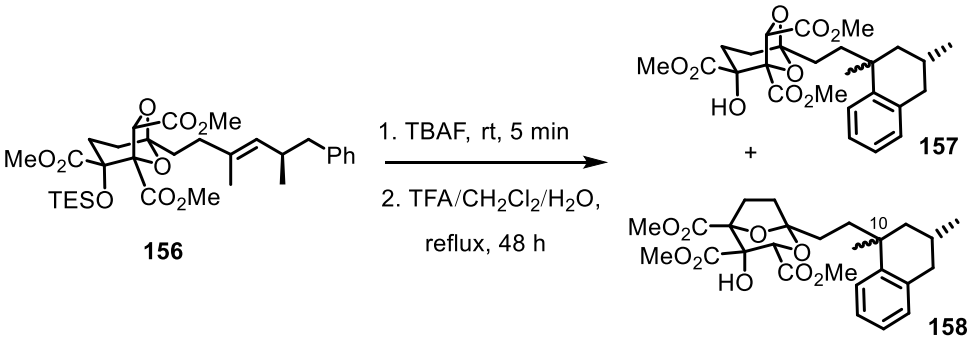
## Synthesis of the Racemic Side-Chain (159)

# 2. Results and Discussion

One of the key aspects of the project was to synthesise the requisite C1 side-chain for the DDSQ (**2**) in a more efficient way and with synthetically useful yields. Initially, several synthetic routes were investigated to prepare the side-chain (*R*-**159**) in a racemic fashion.

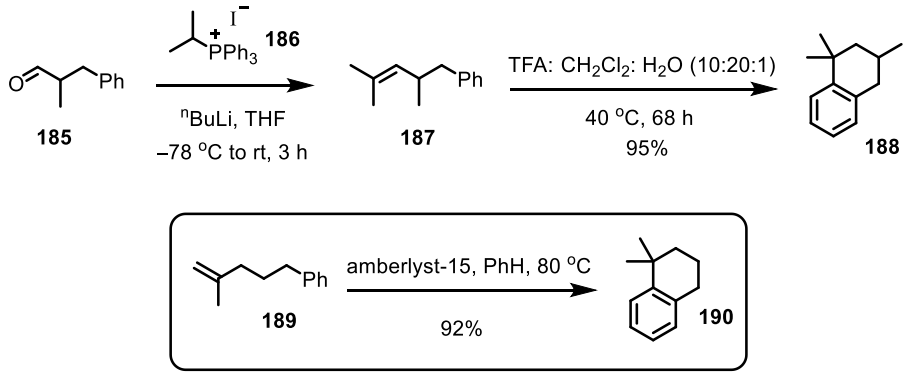
## 2.1 Evidence for the Phenyl Cyclisation

Before embarking on Al-Mamari's route (**Scheme 21**, p. 43), it was considered prudent to first gain more evidence for the cyclised compounds (**157** and **158**, **Scheme 26**). Sintim showed that utilising Evans' conditions [20:10:1 mixture of $CH_2Cl_2$:TFA:$H_2O$] in the key rearrangement step destroyed the double bond (the characteristic doublet at 5.0 ppm in the $^1$H NMR spectrum disappeared). It was believed that Friedel–Crafts cyclisation of the phenyl group with the protonated double bond was occurring, to give tetralins **157** and **158**. Evidence for the cyclised compounds **157** and **158** came from HRMS.[52] In order to have more structural evidence about the cyclised compounds, we ran the rearrangement reaction again (using re-purified 8 mg of **156**, leftover in a mixture of unknown compounds by Sintim in 2002) under the same acidic conditions, without adding the extra step for desilylation. We obtained a complex mixture, that by $^1$H NMR analysis lacked any double bond. If the aromatic ring cyclisation occurred, it made sense that complicated NMR spectra was seen due to likely formation of a mixture of epimers at C10 along with the core only partially rearranging.




**Scheme 26** The proposed products mixture of cycloadduct **156** under TFA conditions.

In support of the above analysis, preparing 2,4-dimethyl-5-phenyl-2-pentene (**187**) as a simpler model system and exposing it to Evans' conditions [TFA:$CH_2Cl_2$:$H_2O$ (10:20:1), 40 °C, 68 h] gave the expected tetralin **188** in 95% yield (**Scheme 27**). Similarly, 2-methyl-5-phenylpentene (**189**) is known to undergo Friedel–Crafts cyclisation with acid to give 1,1-dimethyltetralin (**190**).[59] Presumably, a stabilised tertiary carbocation starts to form from the trisubstituted alkenes, which then undergo cyclisation with the pendant phenyl group.




**Scheme 27** Addition and cyclisation reactions of alkenes with acids.

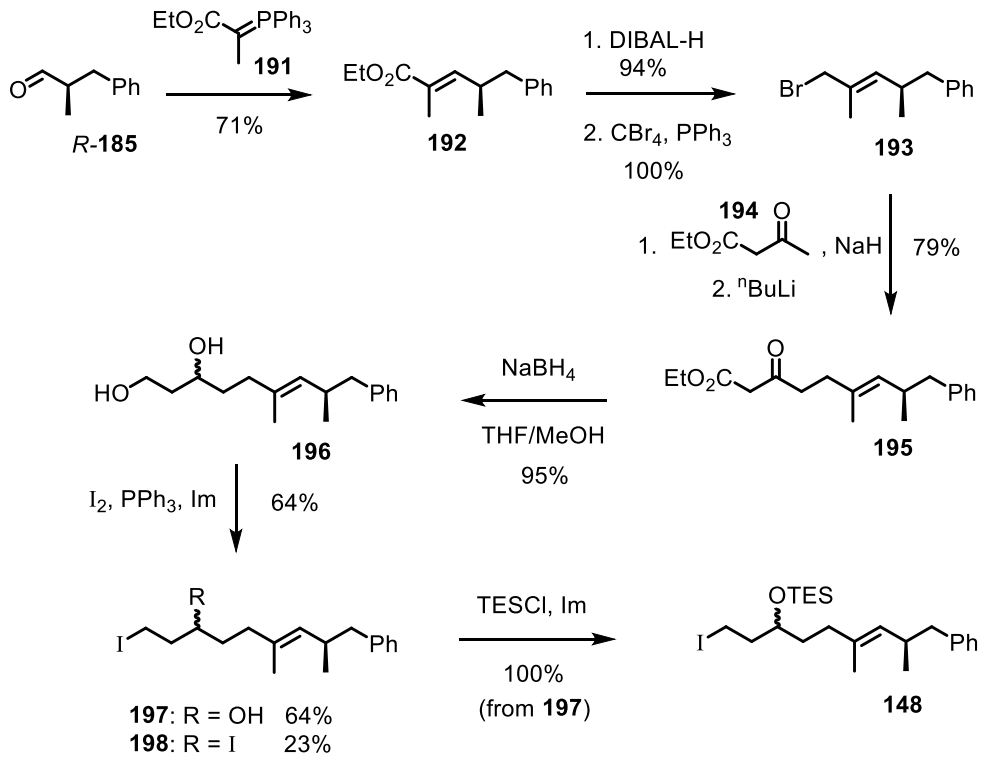
It is clear from Sintim's substrate and the above results with simpler aryl alkenes, that under TFA conditions the alkene moiety is highly reactive to Friedel–Crafts cyclisation with the phenyl group. Therefore, the use of an alkene protecting–group strategy would be mandatory before committing to the key acidic rearrangement step when the alkene group is attached.

Although this problem was addressed at the same time as my study, by Fegheh-Hassanpour *via* introducing the olefin after the rearrangement (**Scheme 24**, p. 46), I focused on the issue of how to directly protect this type of electron-rich C–C double bond from such unwanted reactivity. Therefore, we adopted the challenging Al-Mamari's strategy (discussed on p. 41), aiming first to solve issues with the low yield of the side-chain and the partial epimerisation of the stereogenic centre at the β-carbon to the phenyl during the olefination process (*vide infra*: *R*-**185** → *R*-**200**, **Scheme 29**).

## 2.2 Previous Hodgson's Group Approaches to the Side-Chain

### 2.2.1 Sintim's Approach

Sintim[52] synthesised the side-chain (**148**) starting from (*R*)-2-methyl-3-phenylpropanal (*R*-**185**), which was prepared using Myers chemistry[60,61] (**Scheme 28**). Wittig reaction of aldehyde (*R*-**185**) with ylide **191**, DIBAL-H reduction and then bromination afforded allylic bromide **193**. Bromide **193** was then coupled with the dianion of ethyl acetoacetate **194**, to afford β-ketoester **195** in 79% yield. Following Soai's procedure,[62] β-ketoester **195** was reduced to 1,3-diol **196** and iodination of the latter gave mono iodide **197**, along with substantial amounts of diiodide **198** (~23%). Finally, TES protection of mono iodide **197** afforded the desired side-chain **148** in a quantitative yield (**Scheme 28**).

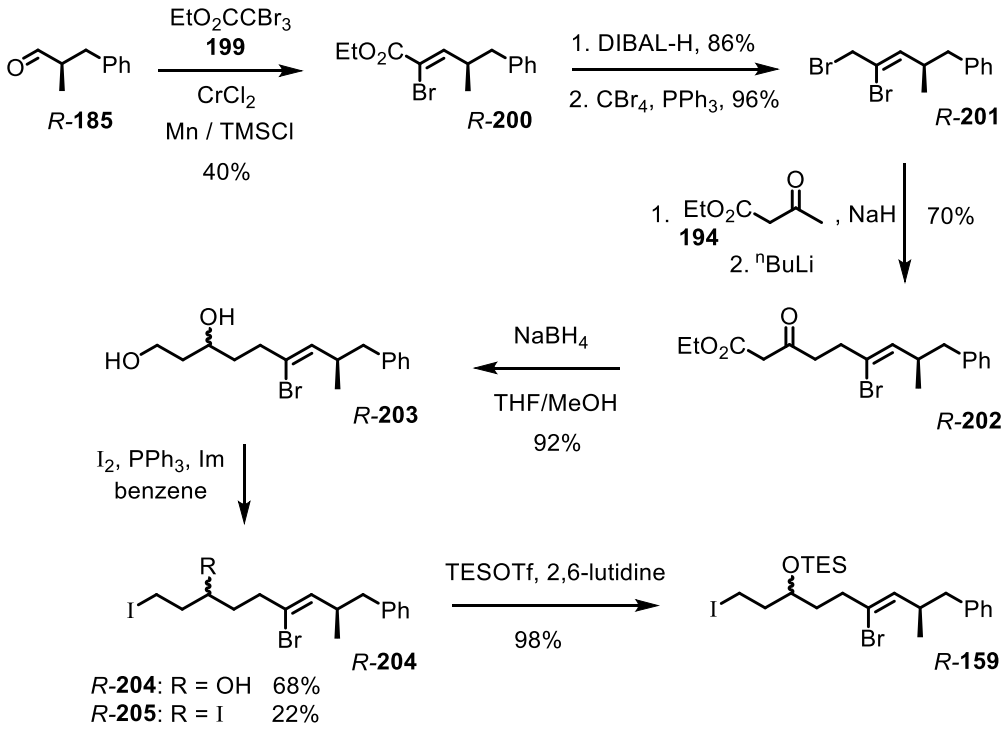



**Scheme 28** Synthesis of the side-chain **148** by Sintim.

## 2.2.2 Al-Mamari's Approach

Al-Mamari[53] replaced the alkenyl methyl group in the side-chain with bromide, to avoid the undesired cyclisation of the phenyl group on the trisubstituted olefin under the acidic conditions of the rearrangement (**Scheme 26**). It was found that the synthesis of the bromine–bearing side-chain was more involved than the Sintim synthesis of the side-chain **148** (**Scheme 28**). Initially, Wittig olefination of aldehyde *R*-**185** with ylide [$BrC(PPh_3)CO_2Et$] was examined first, which gave a separable mixture of *Z*-vinyl bromide *R*-**200** and the *E* isomer (6:1, respectively). During the olefination step, partial epimerisation of the stereogenic centre occurred (86% ee), and therefore this method was not pursued further. In a different strategy, olefination of aldehyde *R*-**185** with ethyl tribromoacetate **199** catalysed by chromium(II) gave *Z*–vinyl bromide *R*-**200**,

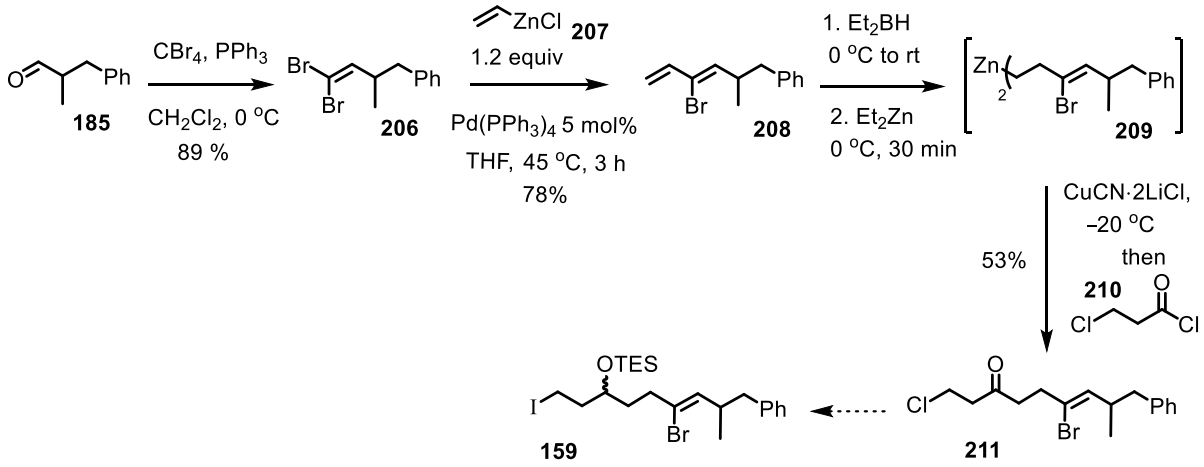
as a single isomer and also without scrambling of the α-stereogenic centre, however, in poor yields between 15–25% and up to 40%. Several attempts to optimise the olefination reaction and many alternative strategies were all unsuccessful to provide *R*-**200** in appreciable quantities. In a similar manner to Sintim's side-chain synthesis, *Z*-vinyl bromide *R*-**200** was transformed to TES iodide *R*-**159** in 6 steps. It was noticeable that the coupling reaction (*R*-**201**→ *R*-**202**) was not reliable with a typical yield between (30–40%) and up to 70%. Overall, the bromine-bearing side-chain was synthesised in ~14% yield over 7 steps starting from aldehyde *R*-**185** (**Scheme 29**).




**Scheme 29** Synthesis of the side-chain *R*-**159** by Al-Mamari.

### 2.2.3 Dr. Arif's Approach

Dr. Arif [63] aimed to prepare the racemic side-chain of DDSQ (**2**) using an organozinc strategy (**Scheme 30**). The sequence began with the Corey-Fuchs olefination of aldehyde (**185**) to give 1,1-dibromoalkene **206**. Dibromalkene **206** was coupled with vinylzinc bromide **207** under Pd-catalysed conditions at 45 °C to afford *Z*-vinyl bromide **208** (78%, *Z*/*E*>99:1). Based on Knochel's work,[64] *Z*-vinyl bromide **208** was treated with $Et_2BH$, $Et_2Zn$ and then CuCN·2LiCl followed by coupling with 3-chloropropionyl chloride **210** to furnish ketone **211** in a moderate yield (**Scheme 30**). The ketone **211** could not be converted to the side chain **159** due to time constraints.

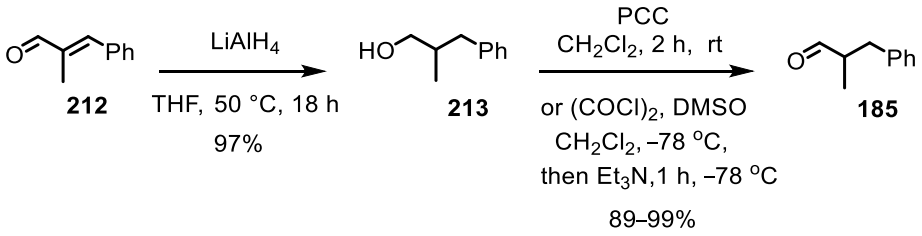



**Scheme 30** Study towards the side-chain **159** by Dr. Arif.

## 2.3 Synthesis of Racemic Side-Chain 159

My first year was chiefly spent on examining different strategies towards the synthesis of racemic side-chain **159** of DDSQ (**2**). For economic and practical reasons, racemic aldehyde **185** was prepared to give sufficient amount to study different strategies before committing to

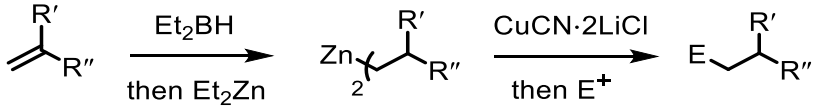
the enantiopure synthesis. The experimental work began with reduction of commercially available α-methyl cinnamaldehyde (**212**) using $LiAlH_4$, to give alcohol **213,** followed by oxidation under Swern conditions,[65] or with PCC, to afford aldehyde **185** (89–99%) (**Scheme 31**).




**Scheme 31** Reduction and oxidation of α-methyl cinnamaldehyde (**212**).

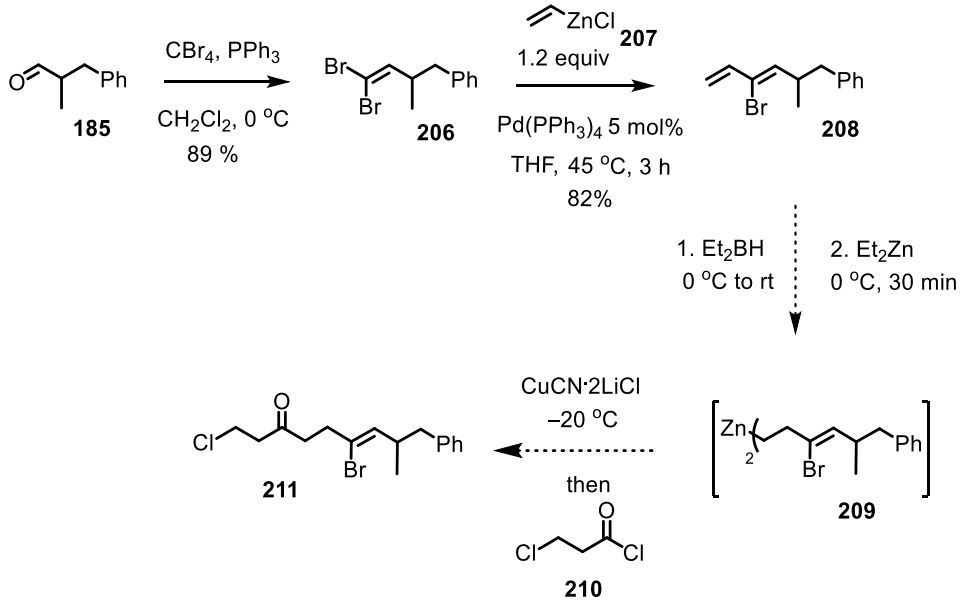
## 2.3.1 Boron-Zinc Strategy

We considered Dr. Arif's strategy to prepare the side-chain **159**, based on the use of boron–zinc exchange chemistry (**Scheme 30**). In 1996, Knochel reported the preparation of dialkylzinc reagent from terminal olefins, involving hydroboration with $Et_2BH$ followed by boron-zinc exchange using neat $Et_2Zn$. The resulting dialkylzincs were reacted with various electrophiles in the presence of a copper salt, CuCN·2LiCl (**Scheme 32**).[64] This method is of great interest since the side-chain **159** of DDSQ (**2**) might be rapidly prepared *via* the addition of homoallylic zinc reagent **208** to 3-chloropropionyl chloride (**210**), as demonstrated by Dr. Arif (**Scheme 30**).




**Scheme 32** Reaction of diorganozincs from alkenes with electrophiles.[64]

Following Dr. Arif's work, dibromide **206** was prepared *via* Corey-Fuchs olefination[66] of aldehyde **185** in 89% yield (**Scheme 33**). Next, a solution of dibromide **206** (1.2 equiv) and 5 mol% $Pd(PPh_3)_4$ was added to a suspension of vinylzinc chloride **207** (prepared from vinylmagnesium bromide and dried $ZnCl_2$) at rt, and then the reaction mixture was stirred at 45 ºC for 5 h. This led to a high yield of *Z*-bromodiene **208** (82%, **Scheme 33**).

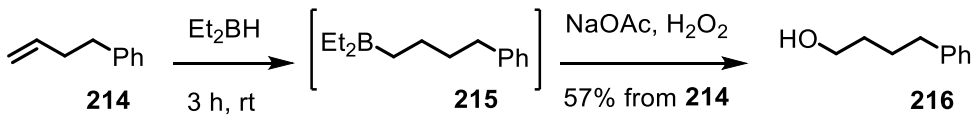



**Scheme 33** Cory-Fuchs olefination, diene formation and boron-zinc exchange strategy.

The next stage was hydroboration of the terminal alkene **208** followed by boron-zinc exchange using $Et_2Zn$. $Et_2BH$ was freshly prepared, by mixing triethylborane and borane-dimethyl sulfide complex at 0 ºC for 5–10 min,[64] before being added to bromodiene **208**. Subsequently, $Et_2Zn$ was added as a solution in hexanes (rather than as a neat liquid as used by Knochel), for safety reasons. To the resulting mixture was added 1 equiv of CuCN·2LiCl (prepared prior to use) and then freshly distilled 3-chloropropionyl chloride **210**. Unfortunately, no reaction was observed, and the starting bromodiene **208** was recovered. Recovery of the starting material suggested that the initial hydroboration step was not successful. To ensure that the

redistribution of $Et_3B$ with the borane-dimethysulfide complex was fully complete, the reaction was repeated under essentially the same conditions, except that when $Et_2BH$ was prepared, the reaction mixture was stirred for longer (~1 h instead of 10 min). Disappointingly, $^1H$ NMR spectra of the resulting mixture was not clean, with recovery of some starting material. Doubling the amount of $Et_2BH$ led to full consumption of the starting material, but with a complex mixture of products being formed during the reaction. The boron-zinc exchange reaction was further tested by altering some of the reaction conditions [including rate of addition, ratio of reagents and temperature (–10 °C or rt)], but without success. Also, toluene was used to dissolve the resulting dialkylzinc, and then evaporated under high vacuum, to ensure the removal of residual $Et_2Zn$;[67] however, no product could be detected. In my hands, the boron-zinc reaction was problematic, and a complex mixture of compounds was always obtained.

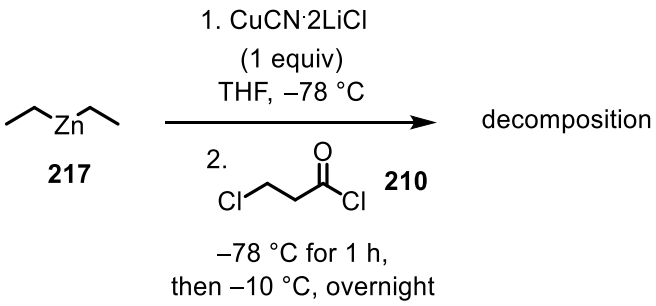
To test the initial hydroboration step in isolation, a simple terminal olefin (**214**) was subjected to Knochel's hydroboration conditions followed by an oxidative work up with hydrogen peroxide.[68] This gave the primary alcohol **216**[69] in 57% yield (**Scheme 34**). Formation of **216** suggested that the hydroboration was not the problematic step.




**Scheme 34** Hydroboration-oxidation of 4-phenyl-1-butene (**214**).

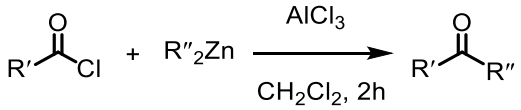
Then, to investigate the zinc–copper transmetallation step in this process, we reacted diethylzinc (**217**) in 1 M in hexanes directly with CuCN·2LiCl, before adding the acyl chloride

(**210**, **Scheme 35**); however, the result was decomposition. This experiment indicated that the ketone formation (from the dialkylzinc) was the problematic step in the boron-zinc strategy.



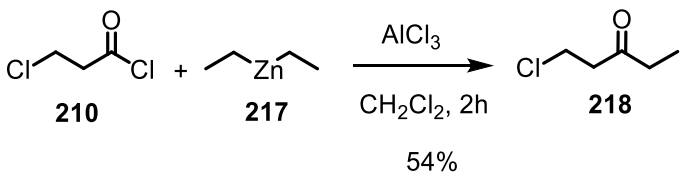

**Scheme 35** Attempted zinc-copper transmetallation followed by acylation.

In considering alternative routes, Nakagawa and co-workers have developed a method to prepare ketones from reactive acid chlorides and simple dialkylzincs in the presence of $AlCl_3$ (**Scheme 36**).[70]




**Scheme 36** Ketones from acid chlorides and dialkylzincs.

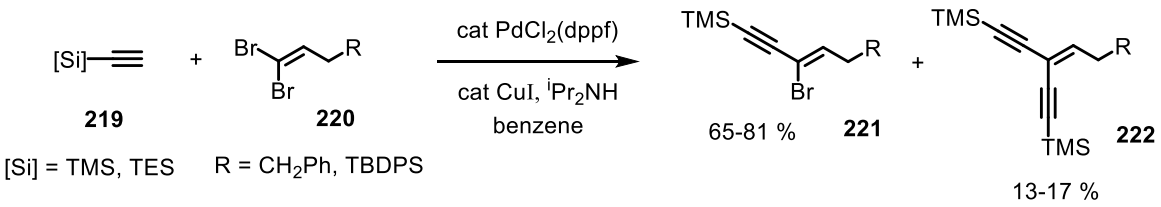
So, the reaction of $Et_2Zn$ (1 equiv) with 3-chloropropanoyl chloride (**210**, 2 equiv) in the presence of $AlCl_3$ was studied as a model system (**Scheme 37**). Ketone **218** was obtained in a low yield (54%; based on $Et_2Zn$), and so, considering the preciousness of the organozinc that we planned to use (**209**, **Scheme 33**, p. 56), this strategy was not investigated further.




**Scheme 37** Reaction of 3-chloropropanoyl chloride (**210**) with diethylzinc (**217**).

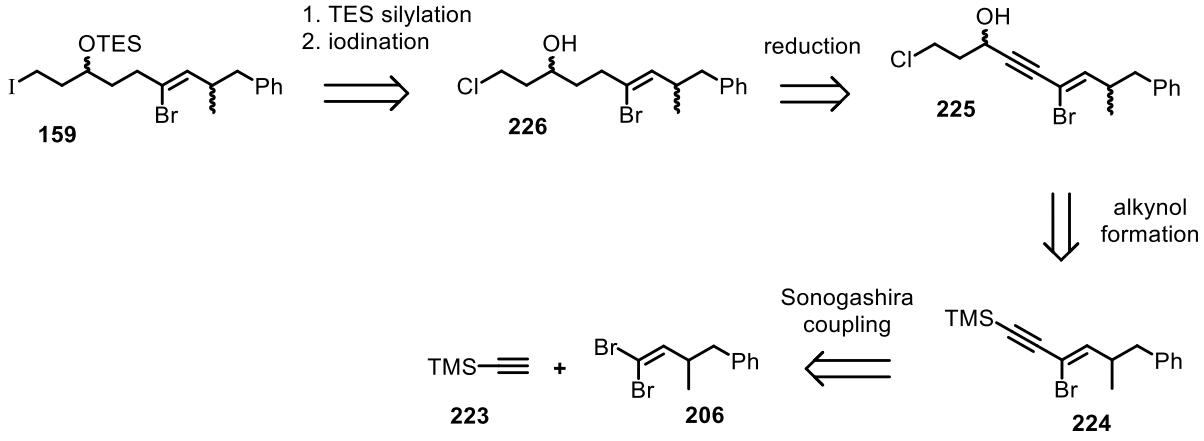
## 2.3.2 Sonogashira Coupling Strategy

The low yield of the above transformations prompted us to design a different strategy. Uenishi and co-workers reported *trans*-selective Sonogashira coupling of 1,1-dibromoalkenes **220** with trialkylsilylacetylenes **219** (**Scheme 38**).[71]




**Scheme 38** Stereoselective Sonogashira coupling of 1,1-dibromoakenes **220** by Uenishi and co-workers.

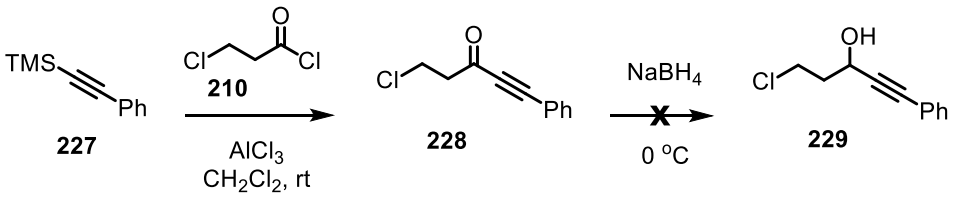
The new route was considered to elaborate dibromide **206** to side-chain **159**, using Uenishi's chemistry to prepare *Z*-bromoenyne **224** as a key step (**Scheme 39**). If we could prepare propargylic alcohol **225** from **224**, then selective reduction of **225** could provide alcohol **226**.[72] Subsequent iodination and silylation could lead to the side-chain **159** (**Scheme 39**).




**Scheme 39** Retrosynthesis of side-chain (**159**).

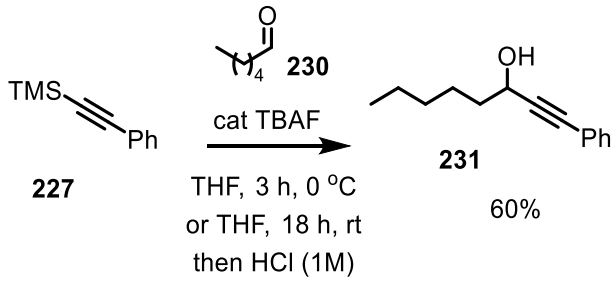
### 2.3.2.1 Alkynylation on a Model Study

Studies to synthesise a propargylic alcohol were carried out first. As a model study, acylation of 1-phenyl-2-(trimethylsilyl)acetylene (**227**) with a β-chloroethyl acyl chloride/$AlCl_3$ complex[73] yielded crude β-chloroketone **228** (~95%, **Scheme 40**). However, column chromatography of the crude **228** led to partial elimination of HCl to give an inseparable mixture consisting of ketone **228** and the undesired unsaturated ketone ($CH_2$=CHCOC≡CPh)[74] in approximately 2:1 ratio, respectively. $NaBH_4$ reduction of the crude β-chloroketone **228** in MeOH or 2-propanol[75] was unsuccessful and a complicated mixture was always obtained.




**Scheme 40** Friedel–Craft acylation of phenyl (trimethylsilyl)acetylene **227**.

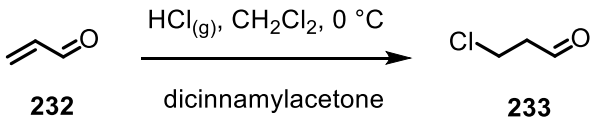
Alternatively, addition of phenyl (trimethylsilyl)acetylene **227** to hexanal (**230**) under TBAF-catalysis[76,77] (10 mol%) gave the propargylic alcohol **231** in a good yield (60%, **Scheme 41**).




**Scheme 41** Alkynylation under TBAF-catalysis.

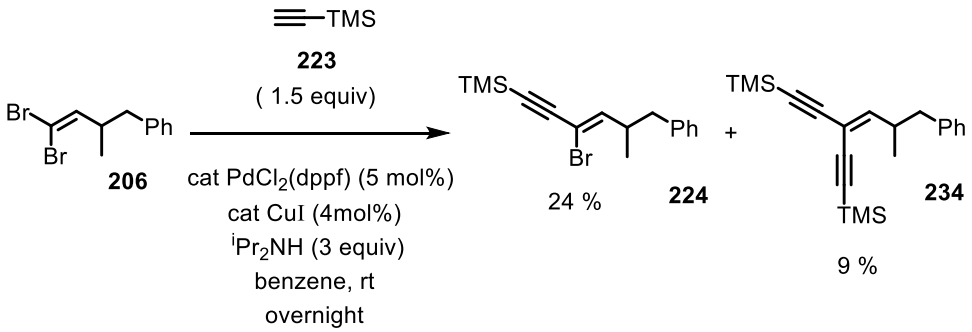
### 2.3.1.2 Synthesis of Aldehyde 233 and *Z*-bromoenyne 224

Prompted by the above result (**Scheme 41**), 3-chloropropanal **233** was synthesised (to be used on the real system with **224**), by bubbling anhydrous HCl gas through a solution of freshly distilled acrolein (**232**) in $CH_2Cl_2$ using dicinnamalacetone as an indicator for the end-point (indicated by changing the colour from yellow to bright red) (**Scheme 42**).




**Scheme 42** Synthesis of 3-chloropropanal **233** from acrolein **232**.

Next, we proceeded with Sonogashira coupling of 1,1-dibromoalkene (**206**) with trimethylsilyl acetylene **223** using $PdCl_2$(dppf) as a catalyst in benzene, which selectively gave 24% of the *Z*-bromoenyne[55] **224** along with 9% of the separable endiyne[55] **234** and traces of starting material (**Scheme 43**).



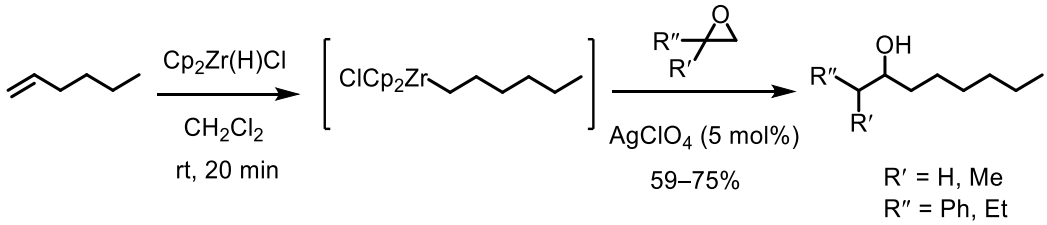

**Scheme 43** Sonogashira coupling of **206**.

The low yield of bromoalkyne **224** (24%) will not allow us to prepare an efficient amount of the side-chain **159** to examine the subsequent chemistry and, therefore, this strategy was not investigated further.

### 2.3.3 Organozirconium Strategy

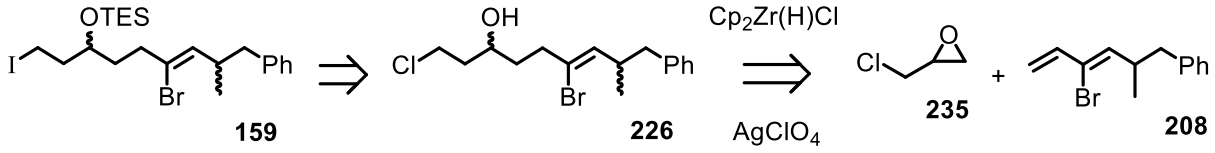
#### 2.3.3.1 Organozirconium Addition to an Epoxide

Wipf and Xu have reported an efficient way to synthesise chain-extended secondary alcohols by adding organozirconocene derivatives to epoxides in the presence of a catalytic amount of $AgClO_4$ (**Scheme 44**).[78]




**Scheme 44** Hydrozirconation of 1-hexene followed by $AgClO_4$-catalysed addition to epoxides.[78]

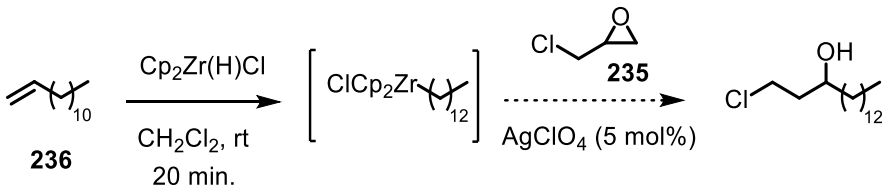
We therefore examined the possibility of synthesising bromoalcohol **226**, a potential precursor of the side-chain **159**, *via* the tandem hydrozirconation-addition reaction of bromodiene **208** with epoxide **235** in the presence of a catalytic $AgClO_4$ (**Scheme 45**).[78]




**Scheme 45** Hydrozirconation strategy.

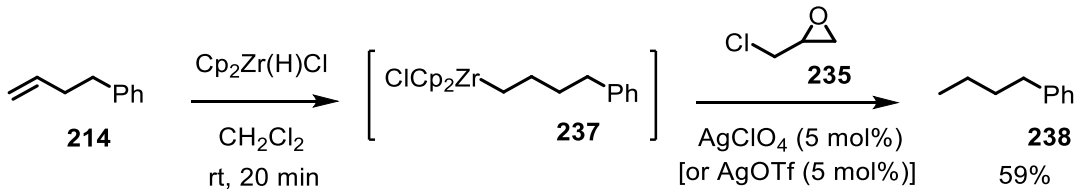
As a model for bromodiene **208**, freshly distilled 1-tridecene (**236**) was treated with *in situ* formed Schwartz reagent [obtained from reduction of $Cp_2ZrCl_2$ with Super Hydride ($LiEt_3BH$) in THF in the dark at 0 ºC] followed by epichlorohydrin **235** and $AgClO_4$ (5 mol%); however,

a complicated mixture was observed (**Scheme 46**). Lack of alkene signals in the $^1$H NMR spectrum indicated that alkene (**236**) underwent hydrozirconation, but not the additional reaction with epoxide **235**.




**Scheme 46** Hydrozirconation of 1-tridecene followed by $AgClO_4$-catalysed addition to epichlorohydrin.

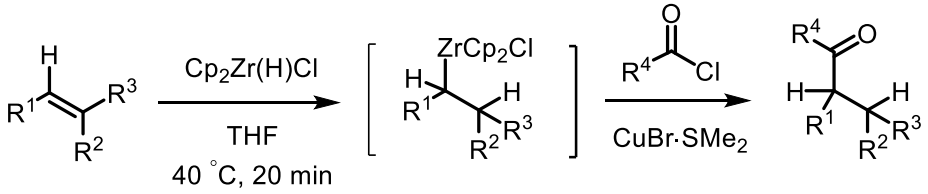
Also, hydrozirconation of 4-phenyl-1-butene (**214**) (as another model for bromodiene **208**) was accomplished with 1.2 equiv of Schwartz reagent (prepared as a white powder from $Cp_2ZrCl_2$ by a standard method[79]); however, no product was formed upon adding epichlorohydrin (**235**) followed by $AgClO_4$; instead, only butylbenzene[80] **238** was obtained. It was thought that the failure of this reaction was due to the quality of $AgClO_4$. The pyrophoric nature of $AgClO_4$, and the difficulty in purifying it,[81] led us to consider using AgOTf[78] instead. However, using the latter with freshly distilled alkene **214**, only gave butylbenzene **238** (**Scheme 47**).




**Scheme 47** Hydrozirconation of **214** followed by attempted $AgClO_4$ (or AgOTf)-catalysed addition of epichlorohydrin.

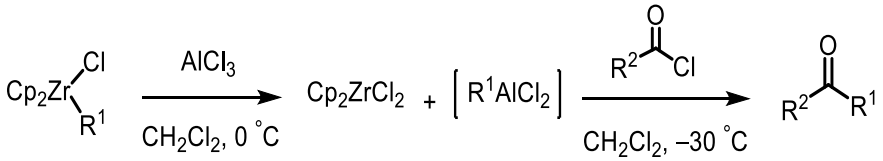
### 2.3.3.2 Organozirconium Addition to an Acid Chloride

A slightly different strategy involving the use of zirconocene derivatives to synthesise ketones from acid chlorides was then examined. Wipf and Xu have also reported transmetalation reactions of organozirconocenes derived from internal and terminal alkenes for the selective synthesis of ketones, using acid chlorides and catalytic amount of copper(I) bromide-dimethyl sulfide complex (**Scheme 48**).[82]



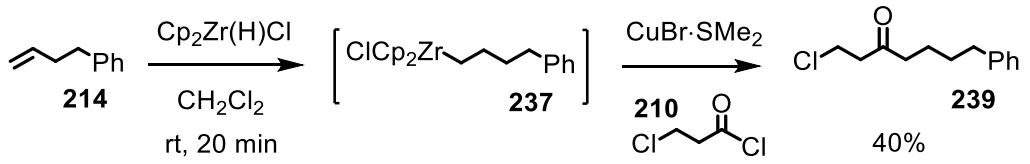

**Scheme 48** Addition of organozirconocene derivatives to acid chlorides in the presence of catalytic copper(I).[82]

Similarly, Carr and Schwartz transmetalated zirconocene derivatives to aluminum using stoichiometric $AlCl_3$, followed by acylation with acid chlorides to generate ketones (**Scheme 49**).[83]



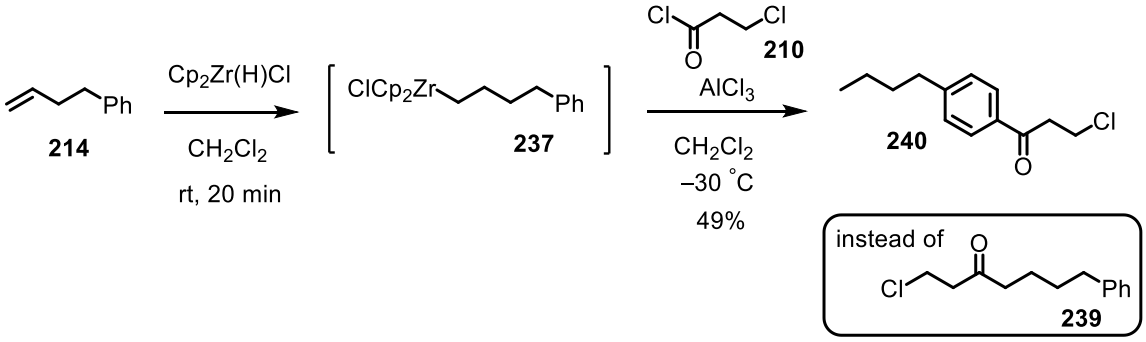

**Scheme 49** Transmetalation from zirconium to aluminum and subsequent addition of acid chlorides.[83]

Hydrozirconation of alkene **214** (as a model) with $Cp_2ZrHCl$ and then transmetalation to the corresponding organocopper species[82] was first tested for the synthesis of ketone **239** using purified $CuBr{\cdot}SMe_2$[84] (**Scheme 50**). In this one–pot reaction, the alkyl cuprate was trapped with **210** to give ketone **239** in 40% yield.



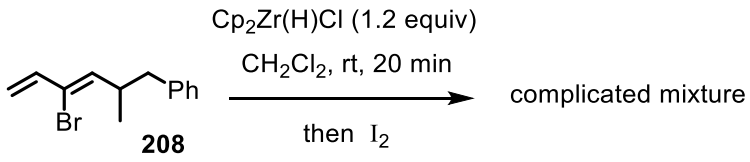

**Scheme 50** Formation of ketone **239** *via* hydrozirconocene chloride.

Also, applying the above method of Carr and Schwartz on alkene **214**, transmetalation of the same zirconocene derivative (**237**) to aluminum using stoichiometric $AlCl_3$ was, however, unsuccessful in promoting the desired acylation reaction.[83] Instead, only Friedel–Crafts acylation occurred, giving acyl chloride **240**[85] in 49% yield (**Scheme 51**).




**Scheme 51** Friedel-Crafts acylation.

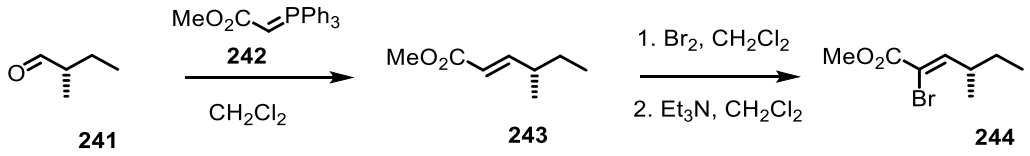
Although ketone **239** was successfully synthesised (**Scheme 50**), applying this chemistry to bromodiene **208** gave only a complex mixture of products. So as to determine the selectivity of Schwartz's reagent between the internal and terminal alkene of bromodiene **208**, the latter was treated with Schwartz reagent followed by iodination. NMR analysis after iodination indicated poor selectivity of Schwartz reagent for the terminal alkene of bromodiene **208**, as judged by the absence of the alkene proton (CBr=CH) at δ 5.85 (**Scheme 52**).




**Scheme 52** Attempted iodination *via* organozirconocene chemistry.

### 2.3.4 *Trans*-Bromination/Dehydrobromination Strategy

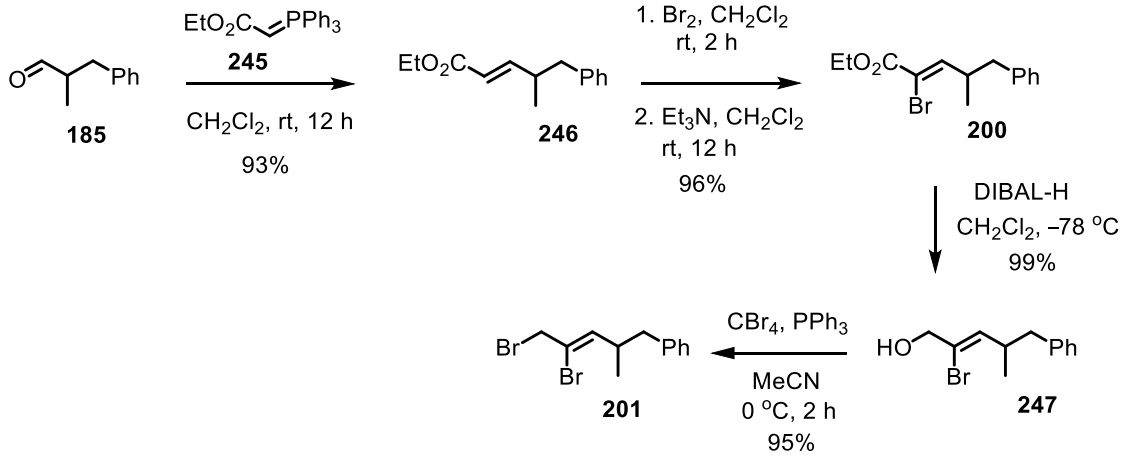
The groups of Trost[86] and Seifert[87] demonstrated that vinyl bromide **244** can be synthesised in a single geometric isomer by bromination and dehydrobromination of alkene **243** in a good yield (~75% from aldehyde **241**); without scrambling of the α-stereogenic centre (**Scheme 53**).




**Scheme 53** Olefination and bromination/dehydrobromination of aldehyde **241**.

It was hoped that using the above chemistry would give the desired *Z*-vinyl bromide *R*-**200** as a single geometric isomer. Thus, solving the problems of the *E/Z* stereoselectivity and also the partial epimerisation of the stereogenic centre at the α-carbon of the aldehyde *R*-**185** that had been observed during previous olefination processes.[53] The final synthetic route to the side-chain **159** started with olefination of aldehyde **185** with ylide **245**, which proceeded smoothly, giving the *E*-unsaturated ester **246** (93%). Pleasingly, subsequent bromination–dehydrobromination gave the desired vinyl bromide **200** as a single geometric isomer [the chemical shift of the vinylic proton (C*H*=CBr) of the desired *Z*-isomer comes at 7.32–7.14 ppm (6H, m, C*H*=CBr and Ar*H*), while in the undesired *E*-isomer (observed by Al-Mamari)[35] it comes at 6.50 ppm (1H, d, $J$ = 10.5), and further NOE studies were performed on **247**

(**Figure 6**)]. After reduction of the vinyl bromide **200** with DIBAL-H, the resulting allylic alcohol **247** was brominated with $CBr_4$ and $PPh_3$ to give dibromide **201** (**Scheme 54**).




**Scheme 54** Successful approach to prepare **201** *via trans*-bromination/dehydrobromination strategy.

NOE studies further confirmed the configuration assignment of vinylic proton of allylic alcohol **247**. Irradiation at 5.89 ppm (C***H***=CBr) saw reciprocal signal enhancement at 4.23 ppm (C***H***$_2$OH). No signal enhancement was observed at 3.01–2.92 ppm (C***H***$CH_3$, **Figure 6**).

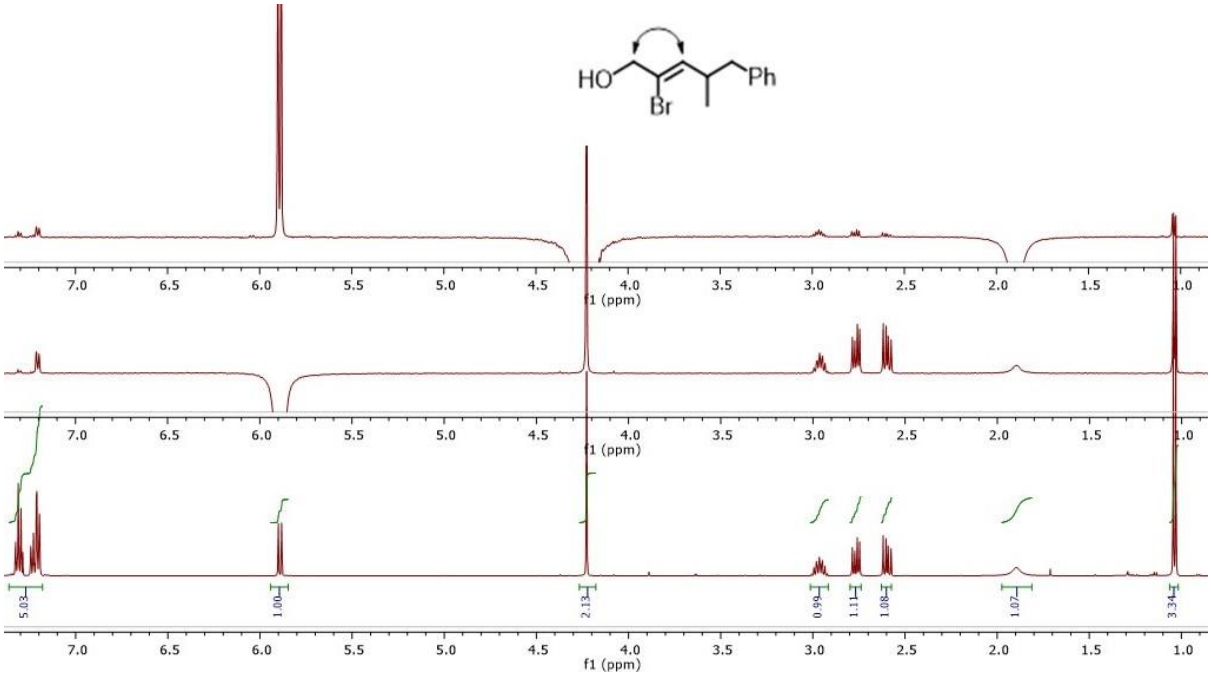
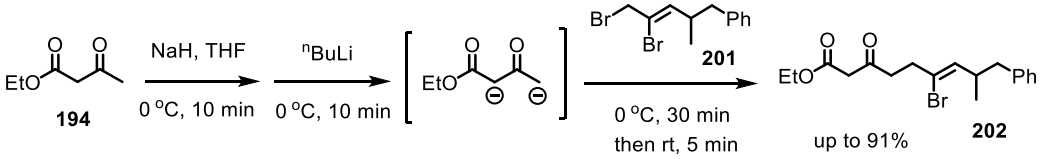


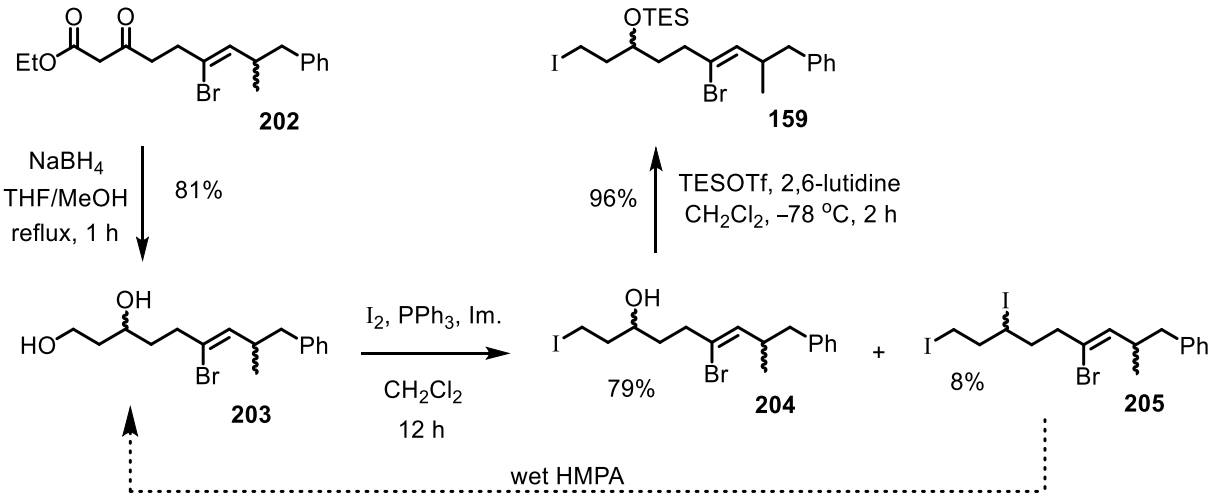

**Figure 6** NOE spectra of *Z*-allylic alcohol **247**.

Coupling dibromide **201** with the double enolate of ethyl acetoacetate **194** (**Scheme 55**) using the methodology of Weiler and co-workers[88,89] was problematic, as observed previously by Al-Mamari and Dr. Valade. Initially, the alkylation of dibromide **201** with the dianion of ethyl acetoacetate (5 equiv) [formed using NaH (5.7 equiv) and $^{n}$BuLi (5.4 equiv) in THF at 0 ºC] led to a mixture of the desired β-ketoester **202** and excess ethyl acetoacetate (**194**), which was difficult to separate. Using 1 equiv of ethyl acetoacetate dianion as coupling agent, the reaction was kept stirring between 0 ºC and room temperature for 1 h, but the dibromide **201** was not fully consumed and the yield of the desired β-ketoester **202** was 30–40%. These issues were overcome by using a slightly modified procedure: using 3 equiv of ethyl acetoacetate dianion and stirring for 30 min at 0 ºC, which gave a high yield of β-ketoester **202** (up to 91%, 23.5 mmol scale) (**Scheme 55**).




**Scheme 55** Coupling dibromide **201** with the double enolate of ethyl acetoacetate **194**.

Reduction of β-ketoester **202** with $NaBH_4$ in THF/MeOH (8:1) gave diol **203** as a mixture of 4 diastereomers (**Scheme 56**). To minimise the diiodination (*cf* **Scheme 29**, p. 53), diol **203** was reacted with 0.6 equiv of $I_2$ in the presence of $PPh_3$ and imidazole, stirring the reaction overnight at room temperature and then adding a further 0.6 equiv of $I_2$ at 0 °C (stirred for 0.5 h) gave the mono iodide (79%) **204** and diiodide **205** (8%) [the latter being (potentially) recyclable using wet HMPA to give diol **203**].[53] Finally, protection of the mono iodide **204** with TESCl afforded TES–iodide **159** in a high yield (47% overall in 8 steps from aldehyde **185**).




**Scheme 56** Synthesis of the side-chain **159**.

In comparison with Al-Mamari's chromium route (**Scheme 29**), the modification on the side-chain synthesis would improve the yield from ~14% to 47%; overall yield from the aldehyde **185**. Having successfully developed an improved more efficient route to the side-chain (**159**), we began studies on the remaining steps to the natural product using the less precious racemic side-chain **159**.

# Chapter 3

# Results and Discussion, Part II:

## Early Studies on the DDSQ Synthesis,

## Synthesis of 2,8-Dioxabicyclic Core 166, the Precursor of the DDSQ H5

and

## Synthesis of Enantioenriched Side-Chain (*R*-159)

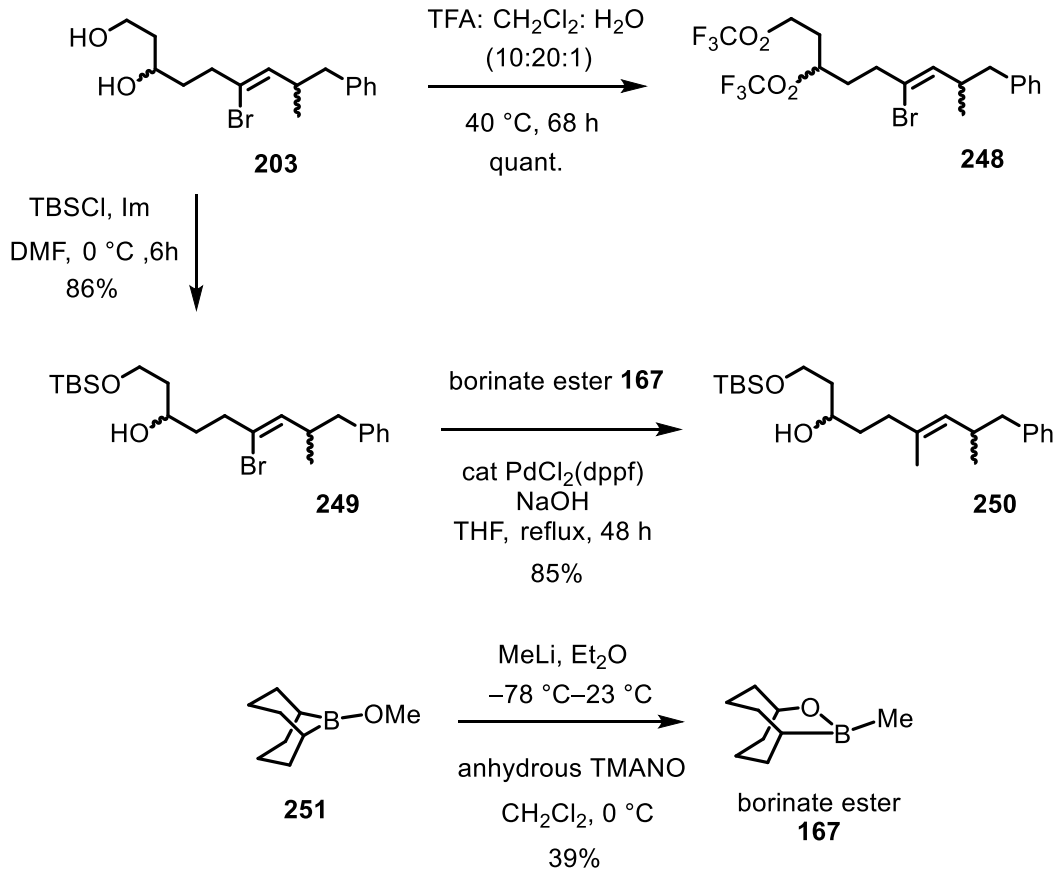
# 3. Results and Discussion

Before progressing further towards the synthesis of DDSQ (**2**), a model study was carried out to examine (in my hands) the viability of alkene protection from an acid (TFA), by the presence of a bromide substituent, and then whether the required methyl group could be installed in a stereoretentive manner. Alkylation of lithiated tartrate with the side-chain **159** and subsequent hydroxylation would lead to hydroxylated tartrate **161** (see the synthetic plan, p. 47). Next, the key problematic hydrolysis/silylation step would be addressed using hydroxylated tartrate **161**, and subsequently the synthesis would be repeated using aldehyde (*R*-**185**) to access the enantioenriched 2,8-dioxabicyclo [3.2.1]octane core *R*-**166**, the precursor to DDSQ.

### 3.1 Early Studies on Alkenyl Bromide Stability and Cross–Coupling Conditions

For our peace of mind, we assessed the stability of the *Z*-alkenyl bromide motif under the TFA rearrangement conditions. Pleasingly, the reaction of 1,3-diol **203** gave the bistrifluoroacetate **248** in quantitative yield (**Scheme 57**), in which the alkenyl bromide was unaffected. Subsequently, we further examined the initial studies by Al-Mamari (*vide infra:* **Scheme 80**) of a stereoretentive Suzuki reaction to install the methyl group.[90] Selective oxidation of *B*-MeO-9-BBN (**251**) with anhydrous trimethylamine *N*-oxide (TMANO, prepared by drying the dihydrate form with DMF)[91] gave borinate ester **167**, which was used as the methylating agent in the Suzuki reaction. After monosilylation of diol **203** with TBSCl, methylation of the resultant alcohol **249** was carried out using borinate ester **167** in the presence of cat $PdCl_2$(dppf), and NaOH as a base, for 48 h (**Scheme 57**). Pleasingly, methylation occurred in a good high yield (85%) and with retention of double bond geometry as determined by $^1$H NMR analysis and by correlation with Martin's side-chain[46] and Sintim's substrates (**Table 2**)

[$\delta_H$ for the olefinic H shifted from 5.5 ppm (1H, d, *J* = 8.5, C*H*=CBr) to 5.0 ppm (1H, d, *J* = 9, C*H*=CCH$_3$)].




**Scheme 57** The stability of the alkenyl bromide group under TFA conditions, and methylation conditions.

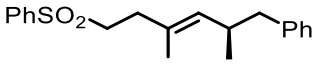
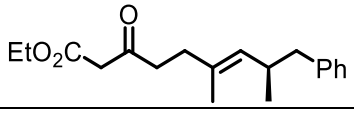
| Compounds | | $^1$H NMR shifts and coupling constants of C*H*=CCH$_3$ |
|---|---|---|
| Martin's side–chain |  | 4.95 ppm (br d, *J* = 8.9) |
| Sintim's substrates | For example:  | 4.99 ppm (d, *J* =9) |

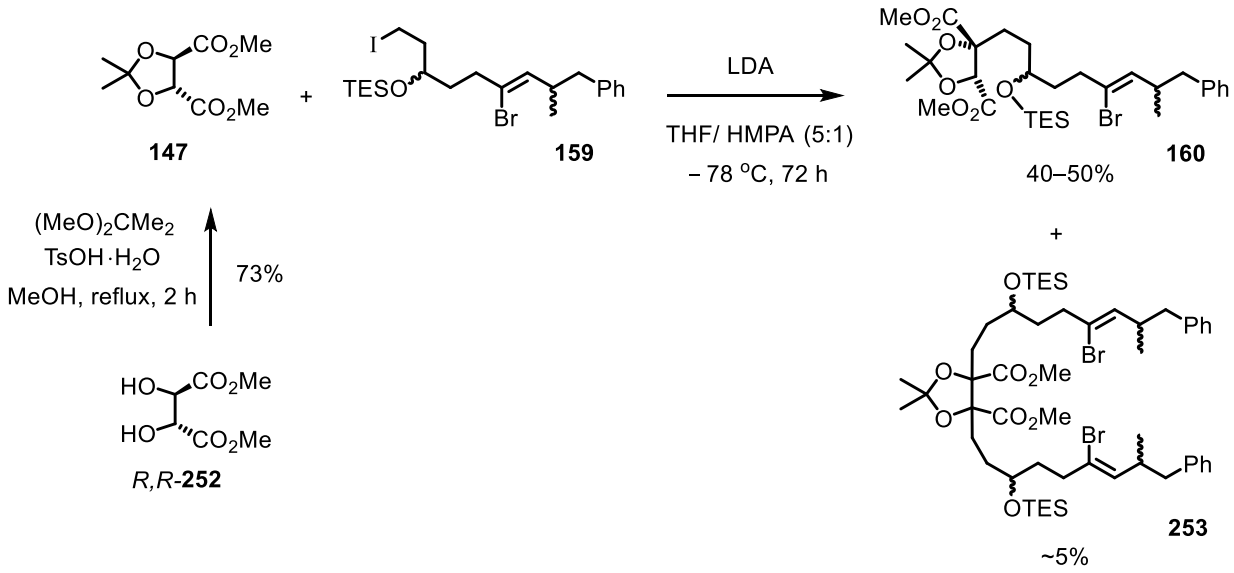


**Table 2** $^1$H NMR shifts and coupling constants of vinylic proton in Martin's and Sintim's compounds.

## 3.2 Synthesis of 2,8-Dioxabicyclic Core 166, the Precursor of the DDSQ H5

### 3.2.1 Alkylation

Alkylation of a slight excess of tartrate acetonide **147** (prepared from dimethyl (*R*,*R*)-tartrate **252** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate)[92] with side-chain **159** gave the desired alkylated tartrate **160** in 40–50% yield (lit[53] 71%) with a small amount of dialkylated tartrate **253** also isolated (**Scheme 58**).

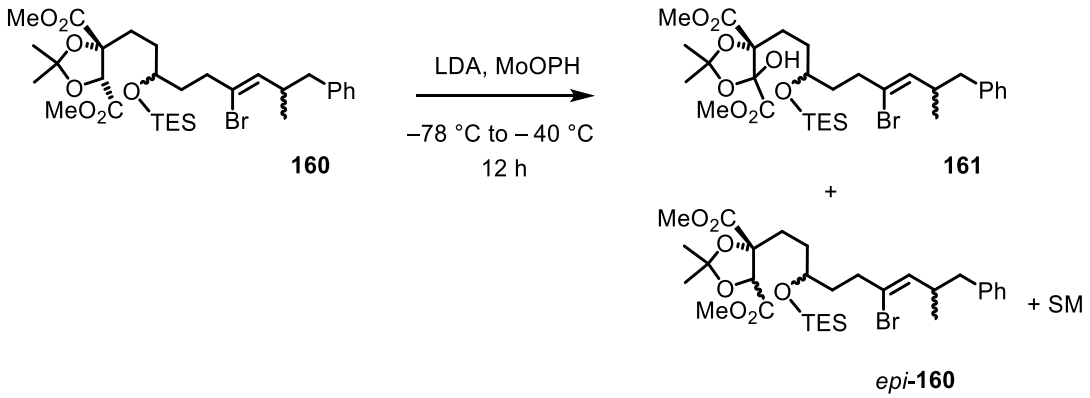



**Scheme 58** Preparation and alkylation of tartrate acetonide **147**.

Further studies on the alkylation chemistry of tartrate acetonide **147** will be discussed in Chapter 5 (p. 105): to understand the origin of the formation of the dialkylation by-product, and also to extend the tartrate alkylation scope by preparing the *R*,*S*-monoalkylated products.

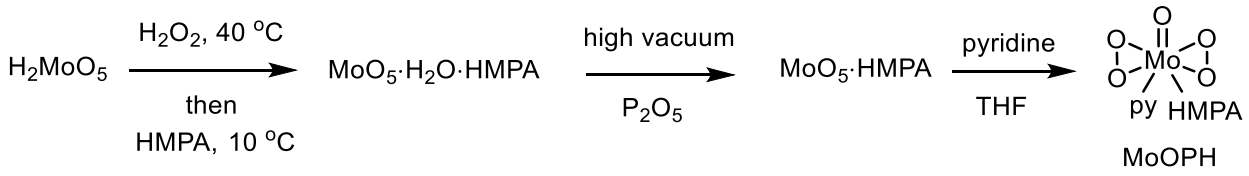
### 3.2.2 Hydroxylation

Next, the enolate of alkylated tartrate **160** was treated with an old batch of MoOPH, in order to access hydroxylated acetonide **161** (**Scheme 59**). The hydroxylated acetonide **161** was obtained in 20–25% yield along with recovered a mixture (~8%) of the starting material and the epimer of the starting material *epi*-**160** (**Scheme 59**).




**Scheme 59** Hydroxylation of alkylated tartrate **160**.

Due to the modest yield, a fresh batch of MoOPH was prepared following a slightly modified procedure using molybdic acid instead of molybdenum(VI) oxide (**Scheme 60**).[93] Treatment of molybdic acid with hydrogen peroxide at 40 ℃ was exothermic, and the reaction mixture was cooled periodically with a water bath to maintain the temperature at 40 ℃, giving a yellow clear solution of $MoO_5$. This was followed by addition of HMPA at 0 ℃, which precipitated the required $MoO_5.H_2O$.HMPA complex as fine yellow crystals, which were then dried over $P_2O_5$ in a vacuum desiccator for 48 h. After removal of the water, pyridine was added according to the original literature,[94] affording MoOPH as a crystalline yellow precipitate.




**Scheme 60** Preparation of MoOPH.

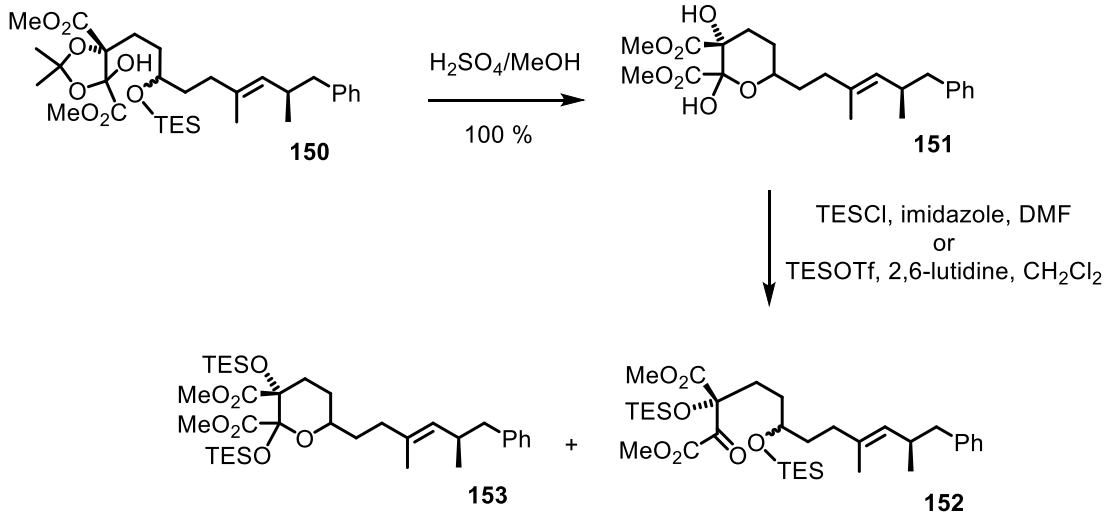
The quality of MoOPH was checked on *dl*-camphor following the general hydroxylation procedure,[95] the hydroxylated product was formed in 74% (lit[95] 77%). Using the new batch of MoOPH, hydroxylated acetonide **161** was obtained in a much improved 59% yield, along with some epimerised starting material *epi*-**161** (~13%). Freshly prepared MoOPH is therefore crucial for obtaining high yields in this transformation. Further optimisation of the reaction conditions by changing the concentration from 0.016 M to 0.21 M, as well as using an addition L-tube to add the freshly prepared (MoOPH), improved the yield of hydroxylated acetonide **161** from 59% to 78% (1.7 mmol scale of the alkylated tartrate **160**, lit[53] 63%).

### 3.2.3 Hydrolysis / Silylation

One of the key steps in our squalestatin synthesis is to cleave the acetonide group of the alkylated and oxidised tartrate, then silylate the resulting tertiary alcohol at C4; this is essential for the construction of the squalestatin core *via* the cycloaddition strategy (see: **Scheme 19**). Initial hydrolysis / silylation studies by previous workers (Sintim and Al-Mamari) on the project successfully converted the hydroxylated acetonides **150** and *R*-**161** to the corresponding α-ketoesters **152** and *R*-**162** (**Scheme 61** and **62**). However, the transformation of *R*-**161** to *R*-**162** in studies by Dr. Valade suffered from issues with reproducibility.

### 3.2.3.1 Background to the Hydrolysis / Silylation

Sintim reported that lactol **151** was formed by hydrolysis of **150** under acidic conditions ($H_2SO_4$ in MeOH) (**Scheme 61**).[52] Subsequent TES protection of lactol **151** using TESCl and imidazole in DMF gave the desired open-chain ketone **152** in 95% yield, with traces of the TES-protected lactol **153**, while the use of TESOTf and 2,6-lutidine in $CH_2Cl_2$ led to an inseparable mixture of **152** and **153** in a ~1:1 ratio (**Scheme 61**).

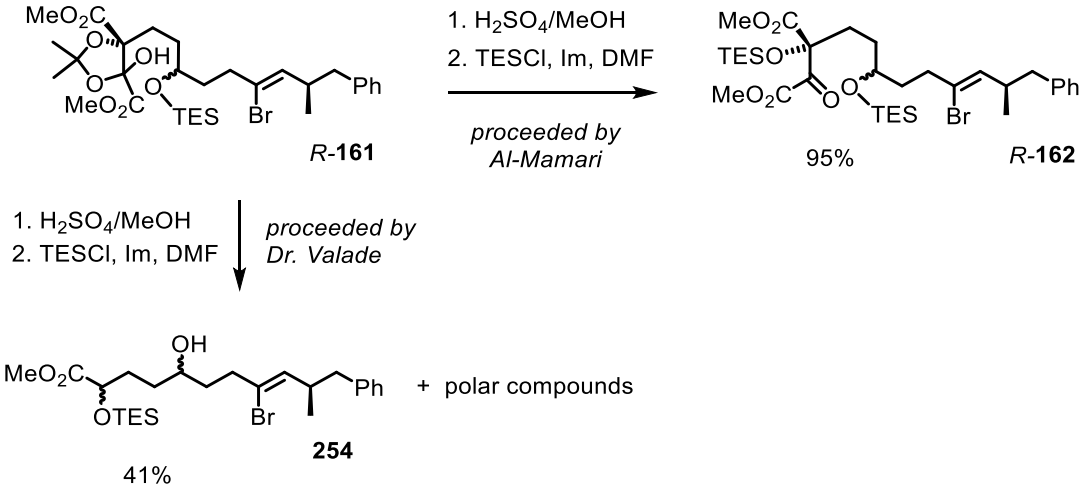



| conditions | 153 | 152 |
|---|---|---|
| TESCl, imidazole | traces | 95% |
| TESOTf, 2,6-lutidine | 50% | 50% |

**Scheme 61** Hydrolysis / silylation studies by Sintim.[52]

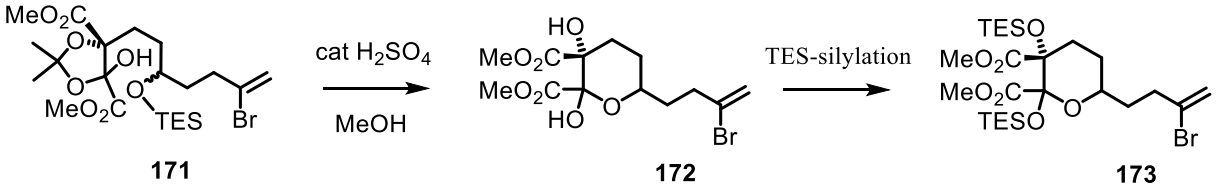
Al-Mamari used these previously developed hydrolysis / silylation conditions (with TESCl) on hydroxylated acetonide *R*-**161** to give the desired ketone *R*-**162** in 95% yield (**Scheme 62**), without any lactol formation. But in other reports in his lab books, the silylation conditions were varied until the last experiment. Whereas, Dr. Valade[55] reported decomposition of the hydroxylated acetonide *R*-**161** to alcohol **254** and other unidentified polar compounds, when

the same conditions were used (**Scheme 62**). Extensive studies to prevent the C–C cleavage (rather than C–O) were all unsuccessful.




**Scheme 62** Hydrolysis / silylation results of **161** by Al-Mamari[53] and Dr. Valade[55].

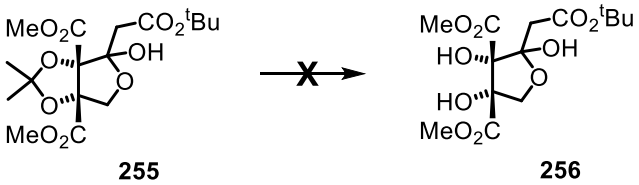
In contrast, Dr. Humphreys[56] attempted the hydrolysis / silylation on simpler model substrate **171** (**Scheme 63**) using the same acidic condition ($H_2SO_4$/MeOH), which led to lactol **172**. Silyation to protect the open-ring tautomer failed and only protected lactol **173** was observed. Using milder acidic conditions to hydrolyse the actetonide group, such as $ZnCl_2$, HCl or thiourea, and also basic conditions, such as KH and 18-crown-6, were all unsuccessful, giving partially deprotected product, decomposed products or recovered starting material. Oxidation (using TPAP / NMO or PCC) and reduction (using $NaBH_4$) of lactol **172** were also considered to convert it into the desired open-chain form; however, all attempts failed.




**Scheme 63** Lactol formation from hydrolysis of **171**.[56]

The above observations indicate that as soon as the secondary hydroxyl is desilylated, it reacts rapidly with the keto group to form a stable lactol, and that silylation of the subsequent lactol in the open-chain form was problematic. A variety of conditions used by both Dr. Valade and Dr. Humphreys to cleave only the acetonide group were unsuccessful with either recovery of starting material or many unidentified products formed. The failure to protect the lactol in the open-ring form meant that progress towards the 2,8-dioxabicyclo [3.2.1]octane core *R*-**166** of DDSQ **2** was not possible.

It is noteworthy that Kelly and co-workers reported on a similar substrate **255** (**Scheme 64**) the inability to cleave the acetonide group despite extensive efforts.[96]

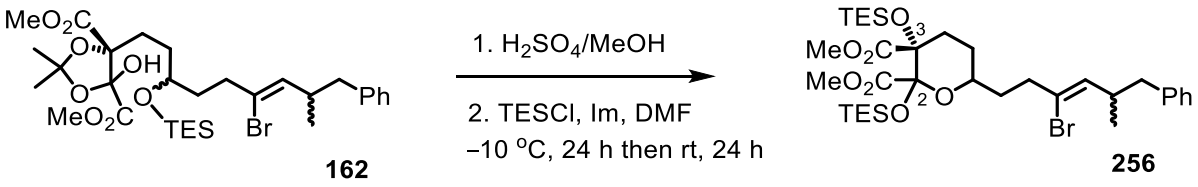



**Scheme 64** Attempts to hydrolyse the acetonide group of **255** by Kelly and co-workers.[96]

### 3.2.3.2 Attempts for Hydrolysis / Silylation

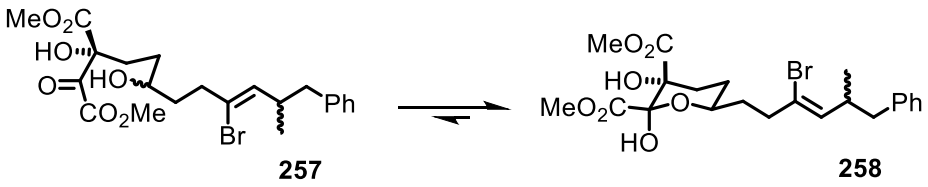
My initial attempts to examine this step were by repeating the original conditions reported by Sintim and Al-Mamari. Hydroxylated acetonide **162** was treated with acidic conditions (0.1 M $H_2SO_4$ in MeOH), in order to cleave the isopropylidene moiety (**Scheme 65**). After 48 h, the reaction mixture was neutralised with pyridine, and the resulted pyridinium sulphate salts were washed with $Et_2O$ followed by standard work-up. $^1$H NMR analysis indicated that the isopropylidene moiety had been removed, along with the TES group. Subsequent bis-silylation was attempted by stirring the crude product with TESCl (6.5 equiv) in the presence of imidazole

in DMF at –10 ºC for 24 h, then at rt for 24 h. This gave a disappointing result, since only the undesired protected lactol **256** was isolated (**Scheme 65**). The $^{13}$C NMR signals for C2 at 125.5 ppm and C3 at 95.8 ppm are characteristic for lactol ester **256**. Unfortunately, there was no diagnostic ketone signal of the α-ketoester form (δ = 190.8, $MeO_2C$–*C*=O)[53] observed in the $^{13}$C NMR spectrum.




**Scheme 65** Hydrolysis / silylation attempted on hydroxylated acetonide **162**.

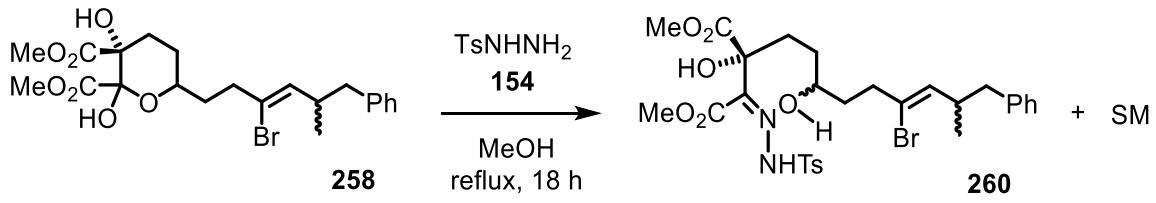
However, at least in my hands the β-elimination products observed by Dr. Valade (**Scheme 62**, p. 77) were not found when using methanolic sulfuric acid for the hydrolysis. To resolve the problematic TES protection step, several conditions were examined. It was considered that dihydroxy α-ketoester **257** would be in tautomeric equilibrium with the lactol ester **258** (**Scheme 66**). With this in mind, the crude mixture obtained from hydrolysis of hydroxylated acetonide **162** was stirred for longer (48 h) with TESCl in the presence of imidazole in DMF at 0 ºC, to hopefully promote selective protection of the less hindered 2º alcohol in the open–chain α-ketoester **257**. However, we could not detect the desired ketone and only lactol **256** was observed. It seems, therefore, that lactol **258** has a strong preference to remain cyclic.




**Scheme 66** Ring–chain tautomerism

Small variation of experimental details in the silylation step could have a significant impact on the equilibrium. It was considered that Al-Mamari might have carried out the TES protection step without removing all of the pyridine during the work-up of the hydrolysis step, which might have helped the opening of the lactol ring. However, deliberately running the protection step of the lactol **258** with a small amount of pyridine present did not succeed, and again the protected lactol **256** was obtained.

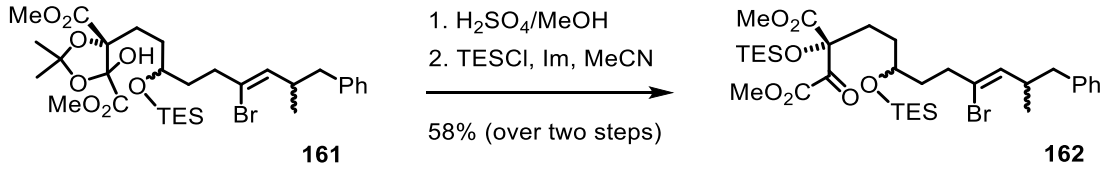
In the open–chain system, the keto functionality α– to the ester group is very electron-deficient; this makes the ketone group potentially more susceptible to nucleophilic attack than normal. Therefore, the crude product from hydrolysis was refluxed with tosyl hydrazide **154** in MeOH in an attempt to induce one–pot lactol ester ring–opening and hydrazone formation (**Scheme 67**).[97,98] After 18 h at reflux, TLC analysis showed less polar compound, which was isolated after column chromatography on silica gel. On the basis of $^{1}$H NMR and mass spectra data, tosyl hydrazone **260** was formed, but in a very low yield (8%) along with recovered starting material. $^{1}$H NMR analysis of **260** indicated that tosyl hydrazone condensation had occurred, as judged by the presence of diagnostic signals at δ = 2.46 (3H, s, $CH_3$Ar), 7.81 (2H, *o*–ArCH) and 7.37 (2H, *m*–ArCH). Also, mass spectral analysis found *m*/*z* 653.1 which is consistent with ($M+H^+$) signal of **260**. Due to the low yield, this reaction was abandoned.




**Scheme 67** Hydrazone formation.

Using different milder acidic conditions, that have been used to cleave acetonide groups, such as $FeCl_3.6H_2O$,[99] $BF_3.Et_2O$,[100] $InCl_3$,[101] $EtAlCl_2$-$Et_3SiH$[102] and tosic acid[103] were all unsuccessful in cleaving the acetonide motif, either returning the starting material or giving many unidentified products.

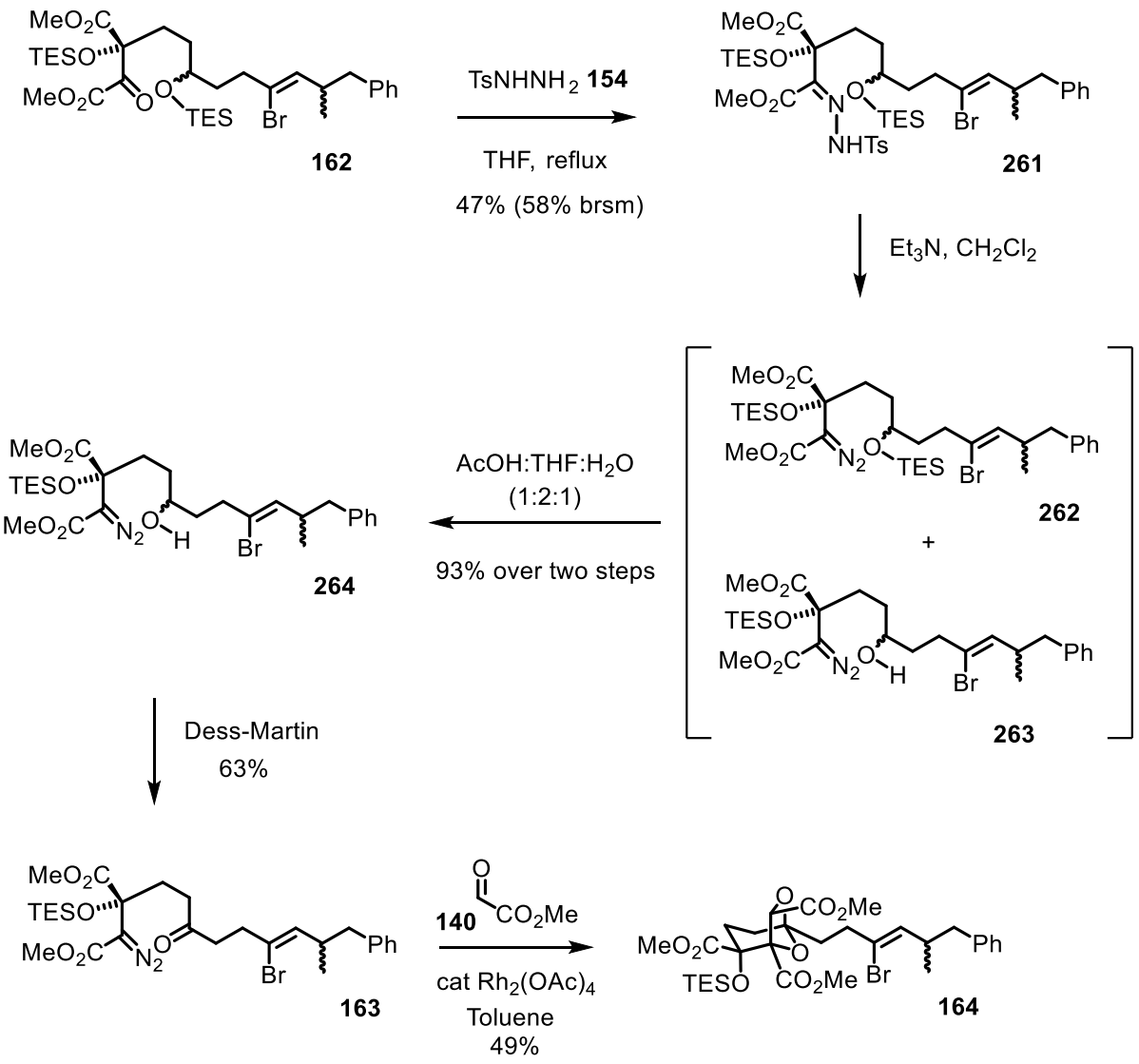
Since none of the above conditions were able to cleave the acetonide moiety successfully, we decided to use the original acidic conditions (0.1 M $H_2SO_4$ in MeOH). We then proceeded to investigate the silylation conditions by varying some parameters such as temperature, silylated reagent and solvent. Performing the silylation reaction of lactol **258** (using TESCl in DMF) at various temperatures (–10 °C to 25 °C) or with TESOTf (in $CH_2Cl_2$), a partially or fully silylated lactol was obtained. Pleasingly, the hydrolysis–silylation of hydroxylated acetonide **161** was finally solved to give the desired α-ketoester **162** (58%, over two steps) using TESCl in the presence of imidazole in MeCN (or $CH_2Cl_2$ with a low yield, 40%) rather than DMF at rt for 48 h (**Scheme 68**). The $^{13}C$ NMR spectrum of ketoester **162** displayed a diagnostic signal of δ = 190.8 ppm, correspondingly to $MeO_2C$–*C*=O. Simply, solvent choice plays a critical role in this transformation, which might be by shifting the equilibrium position towards the open-chain form (**Scheme 66**), enabling the subsequent protection of the latter.




**Scheme 68** A successful attempt to effect hydrolysis / silyation of **161**.

### 3.2.4 Synthesis of the 2,8-Dioxabicyclic Core (166)

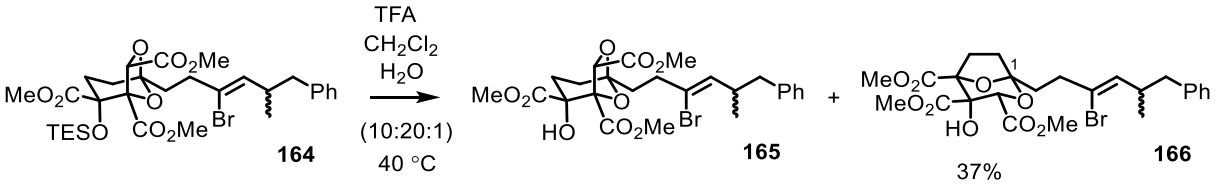
With the racemic α-ketoester **162** now in hand, this provided an opportunity to learn about the subsequent chemistry, before repeating the synthesis from more precious enantioenriched aldehyde *R*-**185**. Hydrazone **261** was formed by condensation of the ketoester **162** with tosylhydrazide **154** in refluxing THF (**Scheme 69**). Purification of hydrazone **261** was very tricky on column chromatography as the compound was not fully stable on silica gel, which was isolated in 47% yield (58% brsm). Elimination of the tosyl group using $Et_3N$ generated the diazo functionality with partial desilylation of the secondary TES ether under the basic reaction conditions (~2:1; respectively). Selective desilylation of this more labile silyl ether group was completed with a 1:2:1 mixture of AcOH:THF:$H_2O$, yielding the diazo alcohol **264** in 93% yield, over two steps. Oxidation of diazo alcohol **264** with Dess–Martin periodinane gave the diazoketone **163** in 63% yield. The 1,3–dipolar cycloaddition of diazoketone **163** with freshly distilled methyl glyoxylate **140** (7 equiv) catalysed by $Rh_2(OAc)_4$, afforded the cycloadduct **164** in 49% yield (**Scheme 69**).




**Scheme 69** Synthesis of cycloadduct **164**.

To our delight, refluxing cycloadduct **164** under Evans' conditions ($CH_2Cl_2$:TFA:$H_2O$) (20:10:1) for 2 days gave a mixture of the desired rearranged 2,8-dioxabicyclic core **166** and unrearranged (desilylated) material **165** in a 60:40 ratio in favour for the rearranged core **166** (**Scheme 70**). Assignments were made on the basis of the signals corresponding to (C*H*–$CO_2$Me) at $\delta_H$ = 4.78 ppm and $\delta_H$ = 5.55 ppm for the rearranged and unrearranged core, respectively. Another characteristic NMR signal is that the $^{13}$C chemical shift for C1 is observed at $\delta_C$ = 108.5 ppm and $\delta_C$ = 111.1 ppm for rearranged and unrearranged material,

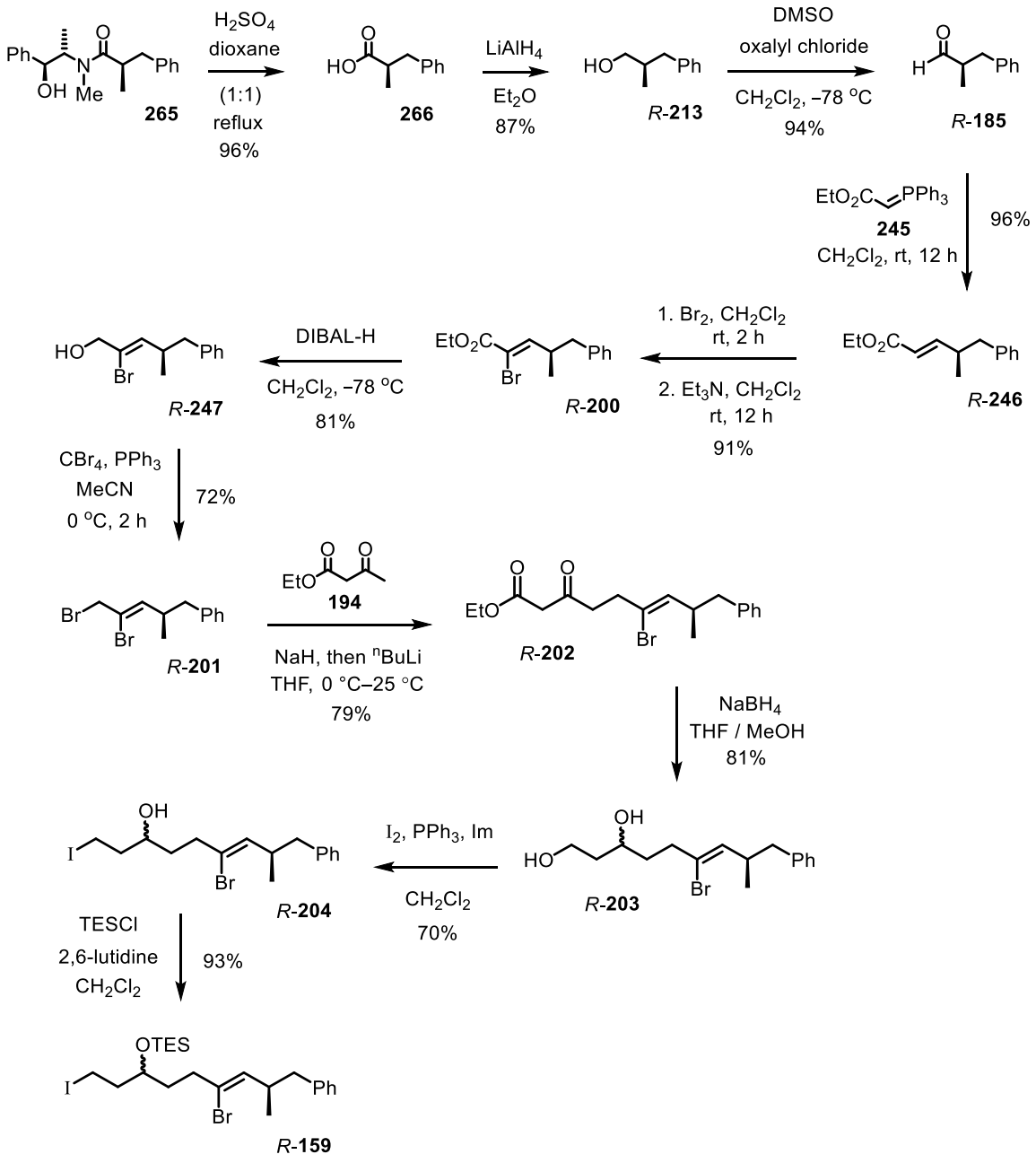
respectively. Pleasingly, the alkenyl bromide was unaffected, in line with the earlier model study (**Scheme 57**, p. 71) and Al-Mamaris' observation. The double bond geometry remained intact as determined by $^{1}$H NMR [the coupling constant of the vinylic proton (C*H*=CBr) of **164** and **166** is 8.5 Hz]. Also, we were able to separate the desired product from the unrearranged material by gradient column chromatography [0–100% $Et_2O$ in petrol, $R_f$ = 0.40 (100% $Et_2O$) for rearrange **166** and $R_f$ = 0.48 (100% $Et_2O$) for unrearranged **165**]. This is significant, as it seems from Al-Mamari's thesis and his related lab book that the rearranged and unrearranged products were not separated, with both being submitted to unsuccessful methylation cross–coupling reaction.




**Scheme 70** Rearrangement to the desired squalestatin core **166**.

### 3.2.5 Synthesis of the Enantioenriched Side-Chain (*R*-159)

The above use of less precious materials bearing a racemic side-chain was important to address issues found in the previous attempted syntheses; although, analysis of compounds was more complicated due to diastereomers. At this stage, with condition for a promising cross–coupling strategy on a model system in hand (p. 71), we proceeded to prepare the enantiopure side-chain *R*-**159** (outlined in **Scheme 71**), starting from Myers' chiral auxiliary chemistry.[61,104,105]




**Scheme 71** Synthesis the enantioenriched side–chain (*R*-**159**).

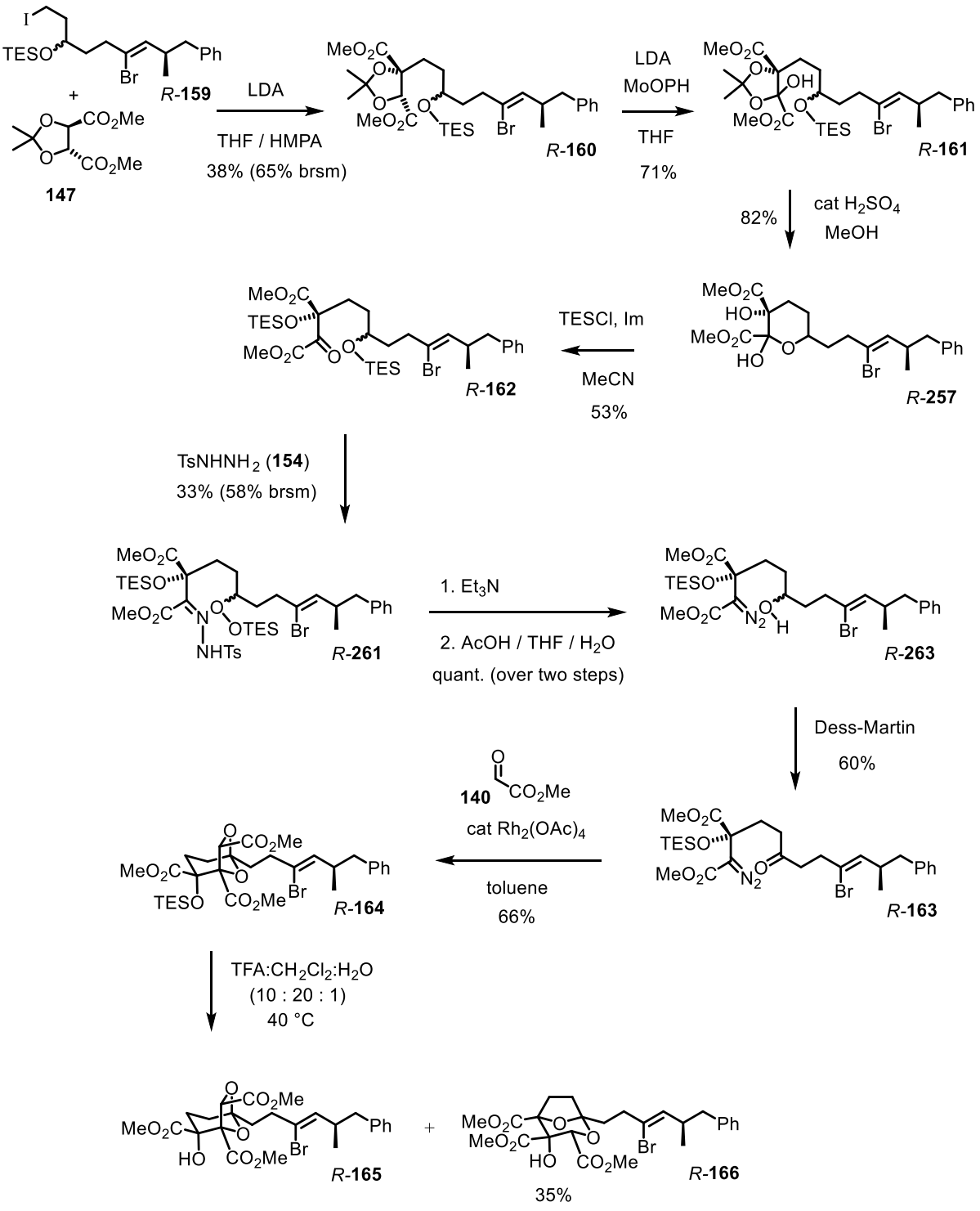
Considering large–scale preparation issues (practicality and efficiency), aldehyde *R*-**185** was prepared from amide **265** in 3 steps. Amide **265** (~8 g, prepared previously in the Hodgson group) was hydrolysed under acidic conditions (9 N $H_2SO_4$ in dioxane) to give carboxylic acid **266**. Reduction of the carboxylic acid **266** using $LiAlH_4$ gave alcohol *R*-**213**, in 87% yield. Oxidation then afforded the required aldehyde *R*-**185**. As in my racemic work, olefination of

aldehyde *R*-**185** with ylide **245** gave the *E*-unsaturated ester *R*-**246** (96%; ≥ 90% ee by HPLC-resolution, but not baseline resolution). Subsequent bromination–dehydrobromination led to the desired vinyl bromide *R*-**200** as a single geometric isomer. After reduction of the vinyl bromide *R*-**200** with DIBAL-H, the resulting allylic alcohol *R*-**247** (81%; 91% ee by full HPLC-resolution) was brominated with $CBr_4$ and $PPh_3$ to give dibromide *R*-**201** in 72% yield. Coupling dibromide *R*-**201** with the double enolate of ethyl acetoacetate (**194**), following my optimised conditions on the racemate (p. 68), gave γ-alkylated β-ketoester *R*-**202** (79%). Reduction of β-ketoester *R*-**202** with $NaBH_4$ in THF/MeOH (8:1) gave diol *R*-**203** as a 1:1 mixture of diastereomers. Iodination of diol *R*-**203** was achieved using 0.6 equiv of $I_2$, stirring the reaction overnight, and then adding a further 0.6 equiv of $I_2$ to give the mono iodide *R*-**204** (70%). The TES–iodide *R*-**159** was prepared by protecting the mono iodide *R*-**204** with TESCl in the presence of imidazole in $CH_2Cl_2$ (93%) (**Scheme 71**).

### 3.2.6 Synthesis of the Enantiopure 2,8-Dioxabicyclic Core (*R*-166)

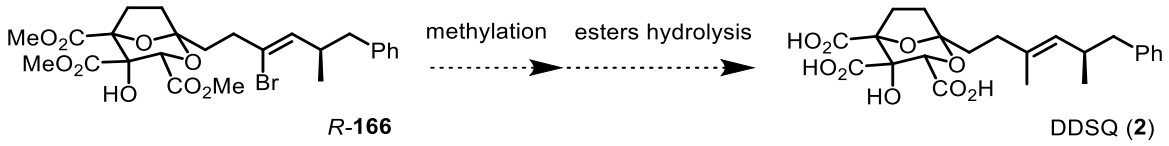
In my hands, alkylation of the TES–iodide *R*-**159** with dimethyl tartrate acetonide **147** in THF/HMPA (4:1) at –78 °C for 3 days gave the alkylated tartrate *R*-**160** in 38% yield (65% brsm) (**Scheme 72**). The enolate of alkylated acetonide *R*-**160** was then formed at –78 °C with LDA, followed by addition of freshly prepared MoOPH to the enolate solution portionwise *via* a solid addition L-tube; the reaction mixture was then allowed to warm to – 40 °C and stirred overnight, to give the hydroxylated tartate *R*-**161** in 71% yield (82% based on recovered epimer of *R*-**160**). As expected from the earlier studies, the acidic conditions necessary to remove acetone from *R*-**161** resulted in concomitant desilylation, but the silyl group was reinstalled during formation of the bis-TES ether *R*-**162** in MeCN from the intermediate lactol. The α-

ketoester *R*-**162** was then converted into the corresponding tosyl hydrazone *R*-**261** by refuxing with tosyl hydrazide **154** in THF. Decomposition of hydrazone *R*-**261** with $Et_3N$, was followed by selective desilylation of the more labile silyl group on the secondary alcohol with AcOH/THF/$H_2O$, which was then oxidised with Dess–Martin periodinane to give the diazoketone *R*-**163**, in 60% yield from *R*-**263**. The 1,3–dipolar cycloaddition of diazoketone *R*-**163** with freshly distilled methyl glyoxylate **140** using a catalytic amount of $Rh_2(OAc)_4$ gave the cycloadduct *R*-**164** in 66% yield. Acid–catalysed rearrangement of cycloadduct *R*-**164** using Evans' conditions ($CH_2Cl_2$: TFA: $H_2O$) (20:10:1) afforded the desired 2,8-dioxabicyclic core *R*-**166** in 35% yield together with cycloadduct *R*-**165** (19%) (**Scheme 72**).




**Scheme 72** Synthesis of the enantiopure 2,8-dioxabicyclic core *R*-**166**.

In summary, the route to 2,8-dioxabicyclic core *R*-**166**, the planned precursor of 6,7−dideoxysqualestatin H5 (DDSQ, **2**), was achieved in 20 steps from α-methylhydrocinnamic acid **265** (25 mmol scale) using the alkenyl bromide approach (**Schemes 71** and **72**). Our strategy of using bromine to mask an electron rich alkene proved to be successful in preventing complications during the late-stage rearrangement of *R*-**164** to the desired 2,8–dioxabicyclic core *R*-**166**, while also being compatible with a variety of other chemistry in the earlier steps of the synthesis. At this stage, it was now necessary to replace Br with Me (using methylation cross–coupling conditions that I examined on a model system, p. 72) and subsequent global ester hydrolysis to finish the challenging synthesis of 6,7–dideoxysqualestatin H5 (**Scheme 73**).




*R*-**166** DDSQ (**2**)

**Scheme 73** Remaining steps in the synthesis of DDSQ (**2**).

# Chapter 4

# Results and Discussion, Part III:

## Model Cross–Couplings

and

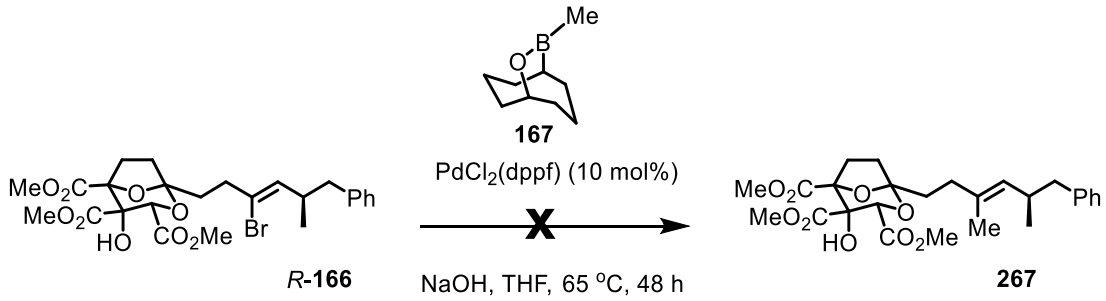
## Methylation and Hydrolysis to DDSQ H5

# 4. Results and Discussion

After successfully using bromide to protect a C–C double bond from acid attack, it was necessary to install the methyl group by converting the alkenyl bromide moiety into the corresponding alkenyl methyl, found in the natural product. Subsequent hydrolysis of the three methyl esters would then provide the long-standing target (DDSQ **2**).

## 4.1 Attempted Methylation Cross-Coupling of Bicyclic Core *R*-166

Having examined the Suzuki methylation cross–coupling in a model study (**Scheme 57**, p. 72), we proceeded with the methylation reaction on the real system. The bicyclic core *R*-**166** was treated with borinate ester **167** (freshly prepared from *B*-OMe-9BBN with MeLi, then oxidised by TMANO)[106] in the presence of cat $PdCl_2$(dppf) and NaOH (3 M) in THF (**Scheme 74**). Unfortunately, after 48 h refluxing, there was no indication of the desired methylated product (**267**). TLC and NMR analysis showed decomposition of the starting material to many unidentified polar fractions.




**Scheme 74** Methylation attempted of bicyclic core *R*-**166**.

So, therefore, the methylation cross–coupling conditions for bicyclic core *R*-**166** required to be re–evaluated and modified accordingly.

## 4.2 Methylation Cross–Coupling Background

Due to lack of success in methylation of the bicyclic core *R*-**166**, it was considered to review the other methods in the literature on methylation cross-coupling with an alkenyl halide.

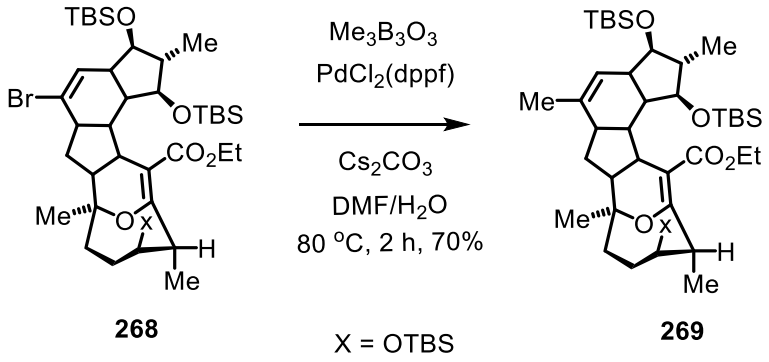
### 4.2.1 Previous Methylation Studies

Cross–coupling reactions of alkenyl halides with methyl organometallic reagents are relatively unexplored. Most of the reactions reported involve using toxic reagents and harsh conditions. For instance: Stille coupling using highly toxic and volatile tetramethyltin,[107] Negishi coupling with pyrophoric dimethylzinc,[108] and methyl Grignard reagents which usually give unreliable and with unsatisfactory yields. Perhaps the most convenient are Suzuki couplings using methyboron reagents, due to the availability of the latter, their non–toxic nature, water tolerance, and mild methods for their preparation. Several methylating reagents are used in Suzuki chemistry to deliver a methyl group to vinyl/aryl halides or triflates, for example: trimethylboroxine,[109] potassium methyl trifluoroborate,[110] methyl borinate ester,[111] methylboronic acid,[112] and using *B*-Me-9BBN.[90,113] Usually, to drive the methylation cross–coupling to complete conversion with acceptable yields, high temperatures (60–150 ºC) are needed with multi-hour reaction times.

Suzuki methylation cross–coupling attracted us partly due to its successful applications with a variety of methods in the literature. Gray *et al*. has used trimethylboroxine with aryl halides in the presence of $Pd(PPh_3)_4$ and $Na_2CO_3$ as a base.[109] Miyaura et al. developed lithium methyltriolborate, $[MeB(OCH_2)_3CCH_3]Li$, as a reagent for methyl transfer to aryl halides in the presence of $Pd(OAc)_2$/RuPhos complex.[114] Molander and co-workers reported that potassium methyltrifluoroborate with various aryl bromides and triflates in the presence of

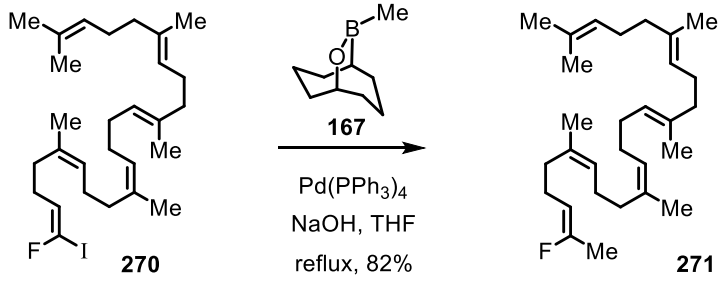
$PdCl_2(dppf)\cdot CH_2Cl_2$ and $Cs_2CO_3$ as a base, afforded the methylated products in moderate to good yields.[110]

Also, there are examples, albeit limited, where methylation cross–couplings have been applied in target synthesis. Evans and Starr, in their last steps of a (–)-FR182877 synthesis, used trimethylboroxine to methylate the cyclic vinyl bromide ester **268** using a large amount of $Cs_2CO_3$ (90 equiv) (**Scheme 75**).[115]



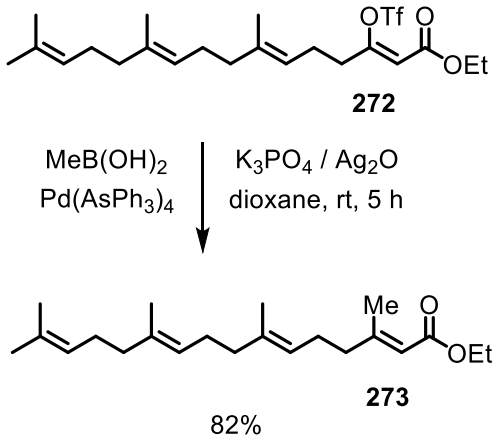

**Scheme 75** Evans' conditions for methylating cyclic vinyl bromide **268**.

Moore and co-workers used Santiago's methylation procedure,[90] with borinate ester **167** (**Scheme 76**), in the last step of the synthesis of squalene epoxidase inhibitors.[111]




**Scheme 76** Methylation of alkenyl dihalide **270**.[111]

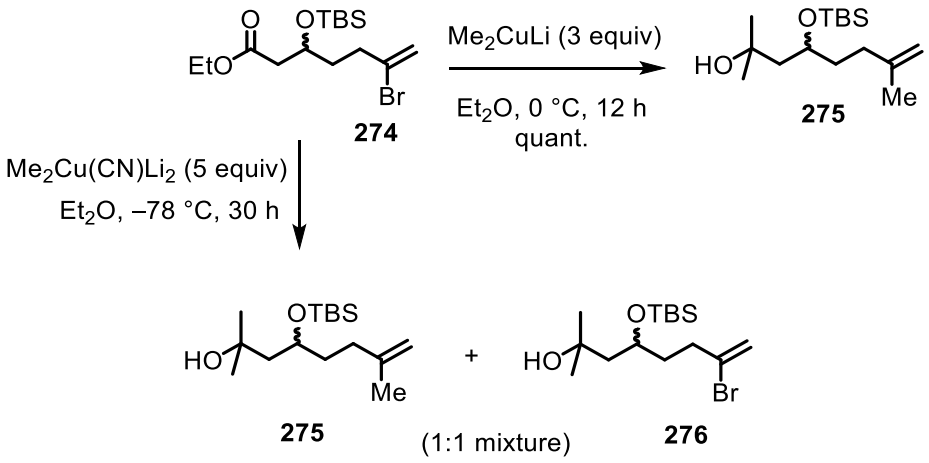
Mu and Gibbs reported the synthesis of *trans*–geranylgeraniol, by coupling of isoprenoid triflate ester **272** with methylboronic acid using $Ag_2O$ and $K_3PO_4$ as bases in dioxane at room temperature (**Scheme 77**).[116]




**Scheme 77** Methylation of alkenyl triflate **272** by Mu and Gibbs.[116]

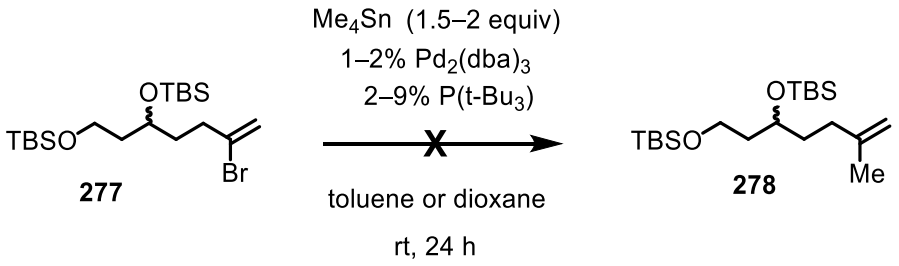
### 4.2.2 Methylation in the Hodgson Group

Methylation of several terminal and internal vinyl bromides were previously studied by Al-Mamari.[53] Starting with cuprate chemistry, using a lower order cuprate $Me_2CuLi$ (3 equiv) and a higher order cyano cuprate $Me_2Cu(CN)Li_2$ (5 equiv) on terminal vinyl bromide **274** as a model, it was found that the methylation took place, but with concomitant attack of the cuprate on the ester group to give tertiary alcohol **275** (**Scheme 78**). Since there are three ester groups in the real system, and without adding extra steps, organocopper chemistry was not the right choice for this transformation.



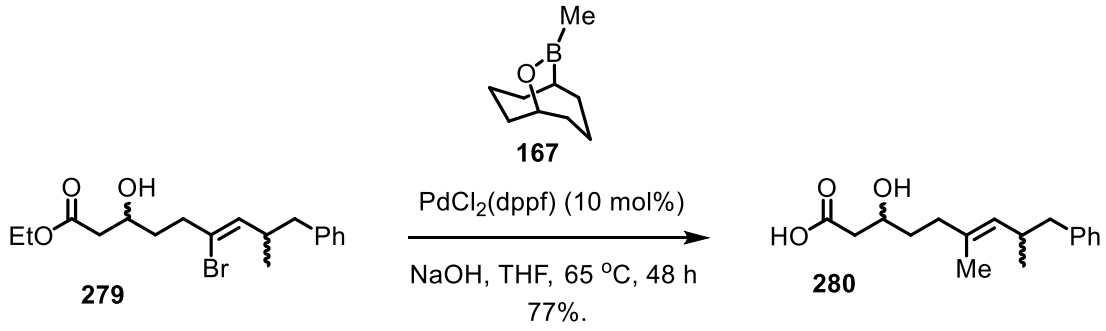

**Scheme 78** Methylation using organocuprate chemistry.[53]

Considering Stille cross–coupling,[117] vinyl bromide **277** was reacted with $Me_4Sn$ in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ in toluene (or dioxane) at rt for 24 h (**Scheme 79**),[53] but unfortunately only unreacted starting material was recovered. Using the air stable phosphonium salt [(*t*-Bu)$_3$PH]$BF_4$ and *i*-$Pr_2NH$ to generate P(*t*-Bu)$_3$ in *situ*,[118] avoiding the direct use of the air–sensitive P(*t*-Bu)$_3$, again gave no coupling with recovery of the starting material.




**Scheme 79** Applying stille chemistry on vinyl bromide **277**.[53]

Finally, methylation utilising Suzuki chemistry[119] on a model system, like vinyl bromide **279** (**Scheme 80**), was carried out using borinate ester **167** in the presence of a catalytic amount of $PdCl_2$(dppf) and aq. NaOH as a base for 48 h.[53] Pleasingly, methylation occurred, along with hydrolysis of the ester group, in a good yield and with retention of C=C double bond geometry (**Scheme 80**).




**Scheme 80** Methylation / hydrolysis of vinyl bromide **279** using organoboron chemistry.[53]

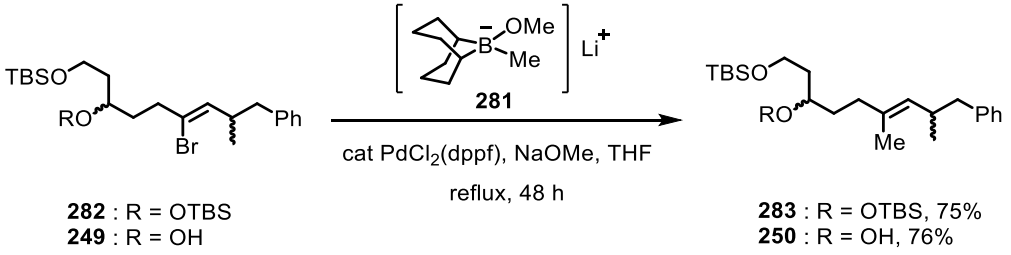
Unfortunately, no evidence of DDSQ (**2**) was observed when a mixture of rearranged *R*-**165** and unrearranged core *R*-**166** (see discussion on p. 43) was submitted to the above conditions by Al-Mamari.

## 4.3 Model studies

My initial exploration of the methylation cross–coupling reaction was performed on vinyl bromide **249** with borinate ester **167** using Al-Mamari's conditions, which proceeded smoothly, to give methylated alcohol **250** (**Scheme 57**, p. 72). However, when these conditions were employed on the bicyclic core (*R*-**166**, **Scheme 74**), no product was detected (similar to Al-Mamari's observations). Probably, the presence of aq. NaOH (3 M) complicated the reaction by hydrolysis of some of the ester groups, especially the least hindered ester at C3.[27] With this in mind, either a softer/weaker base (or re–esterification at the end of the reaction) could be examined. Unfortunately, the methylation of vinyl bromide **249** (as a model) did not proceed to completion using alternative bases, such as powdered $K_2CO_3$ or $K_3PO_4$ suspended in DMF.

With a slight modification, Fürstner and Seidel extended the scope of the Suzuki reaction by using *B*-MeO-9BBN as a vehicle to transfer an alkyl group through formation of a borinate complex with the corresponding organometallic reagent, which then transmetallated to an organopalladium complex in the absence of base.[120] Subsequently, these conditions have been used many times in the preparation of complex natural products.[121]

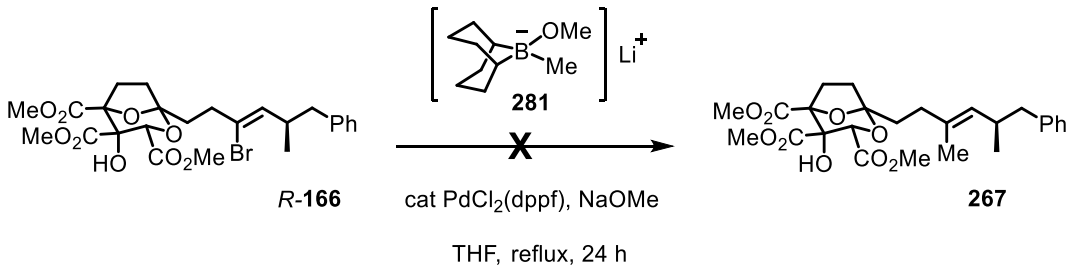
It was of interest to investigate the preparation and reactivity of borinate complex **281** as a methylating agent *in situ*, avoiding the need for base. When the freshly prepared borinate complex **281** (prepared from mixing *B*-MeO-9BBN with MeLi in THF) was refluxed with vinyl bromide **282** [prepared by silylation of alcohol **249** with TBSOTf, 94% yield] in THF in the presence of 10% $PdCl_2$(dppf), only a moderate amount of coupling product *E*-alkene **283** was detected (37%). However, when anhydrous NaOMe (1.5 equiv) was added to accelerate the reaction, the coupling proceeded smoothly, to give alkene **283** in a good yield (75%, **Scheme 81**). These results suggest that the methylation of the potentially sterically congested *Z*-vinylbromide works best when an appropriate base is present. Also, we studied the effect of the presence of a free alcohol group in our model study (**249**) as it is present in the real system (*R*-**166**). Interestingly, there was no effect in terms of the product yield (**Scheme 81**).




**Scheme 81** Methylation of vinyl bromides **282** and **249** using borinate complex **281**.

## 4.4 Second Attempted Methylation Cross–Coupling of Bicyclic Core *R*-166

As model studies indicated that a combination of borinate complex **281** and NaOMe could be more suitable reaction conditions for our substrate *R*-**166**, the methylation cross–coupling was attempted again. Disappointingly, refluxing (~ 60 ºC) bicyclic core *R*-**166** with borinate complex **281** and NaOMe in THF for 24 h (**Scheme 82**) resulted in only decomposition of the starting material by $^{1}$H NMR analysis. The failure of the reaction was attributed to thermal instability of the 2,8-dioxabicyclic core **267**, as it was observed by Fegheh–Hassanpour.[122]

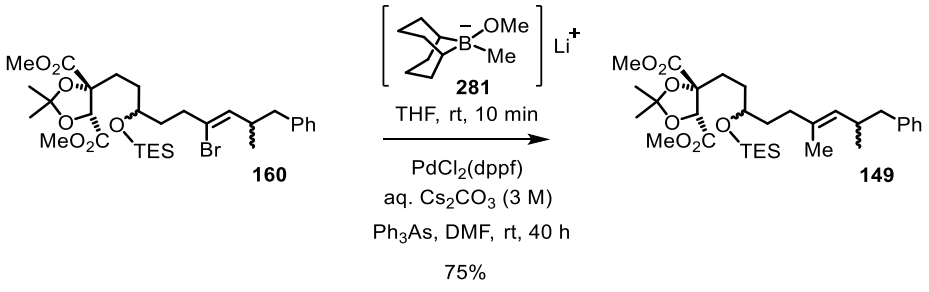



**Scheme 82** Methylation attempted of *R*-**166**.

## 4.5 New model substrate

Methylation cross–coupling conditions on more complex model **160** (**Scheme 83**), which shared more functional groups present in the real substrate *R*-**166**, were investigated; however, this was not found to be straightforward. Although the optimised conditions of the methylation reaction on vinyl bromide **249** (or **282**) afforded the methylated product in a good yield (**Scheme 81**), no reaction was observed when **160** was used under the same conditions. Changing a variety of conditions, for example: concentration, reaction time, temperature (room temperature or reflux) and molar ratios, all were unsuccessful to obtain full conversion (eg: see entries 1–3, **Table 3**) as indicated by $^{1}$H NMR analysis from integrating the proton on the

olefinic bond [chemical shift change from 5.58 ppm (C*H*=CBr) to 4.93 ppm (C*H*=CMe)]. All reactions were monitored by $^1$H NMR due to the similarity between the $R_f$s of starting material and the desired product on silica gel. Also, the effect of the presence of a free hydroxyl group was examined (considering the presence of the unprotected hydroxyl group on the real system) by adding ethyl 2,2-diethylglycolate. When the reaction was quenched at the same time as before (48 h), conversion was actually improved (less than 30% of SM was detected). This suggested that the presence of a proton source helped to accelerate the reaction, therefore the reaction was carried out again under aqueous conditions, which however also led to incomplete conversion. No coupling occurs when only water, rather than aqueous base, is employed. These studies suggest that, for our bromide substrate, using a specific amount of water and a suitable base are necessary for successful methylation cross–coupling. Indeed, changing the base from NaOMe to aq. $Cs_2CO_3$ (3 M) in THF/DMF helped to improve the reaction conversion, with only traces of starting material remaining (entry 5, **Table 3**). Heating the reaction at 50 °C, as expected, led to complete conversion to the desired product **149**, but only in 45% yield (entry 6). The low yield of this reaction could be explained by partial hydrolysis of the ester group with aq. $Cs_2CO_3$.[123] Further investigation were carried out to improve the reaction conditions. We were pleased to find that using co-ligand $Ph_3As$[124–126] (0.3 equiv) led to complete consumption of the starting material with 75% yield of the desired product **149** at rt (**Scheme 83** and entry 7 in **Table 3**).




**Scheme 83** The new model study for methylation.

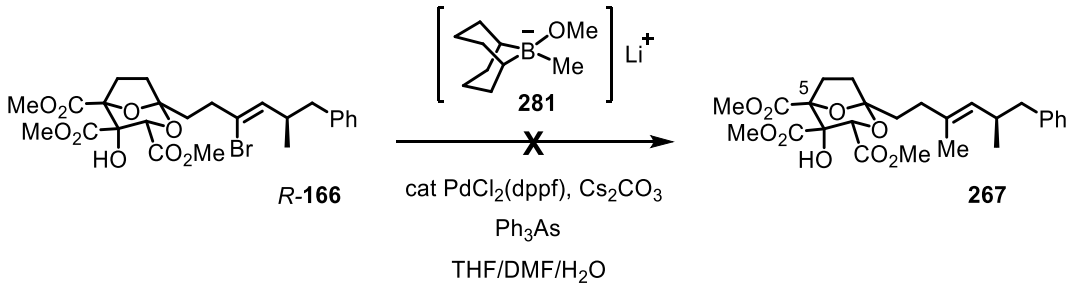
| Entry | Base | Solvent (5:5:1) | Temp. (°C) | **160**:**149**[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | - | THF | 50 | 80:20 | - |
| 2 | NaOMe | THF | rt | 75:25 | - |
| 3 | NaOMe | THF | 50 | 70:30 | - |
| 4 | $Cs_2CO_3$ | THF/DMF | rt | 25:75 | - |
| 5 | $Cs_2CO_3$ | THF/DMF/$H_2O$ | rt | trace **160** | 54 |
| 6 | $Cs_2CO_3$ | THF/DMF/$H_2O$ | 50 | 0 | 45 |
| 7[d] | $Cs_2CO_3$ | THF/DMF/$H_2O$ | rt | 0 | 75 |

[a] Reaction conditions unless otherwise indicated: alkylated tartrate **160** (1 equiv), *B*-MeO-9BBN (2 equiv), MeLi (2 equiv), $PdCl_2$(dppf) (10 mol%), 40 h. [b] Ratio by integration of crude $^1$H NMR spectra. [c] Isolated yield of **149**. [d] $Ph_3AS$ (0.3 equiv) was used.

**Table 3** Optimisation of the conditions for methylation cross–coupling with alkylated tartrate **160**.

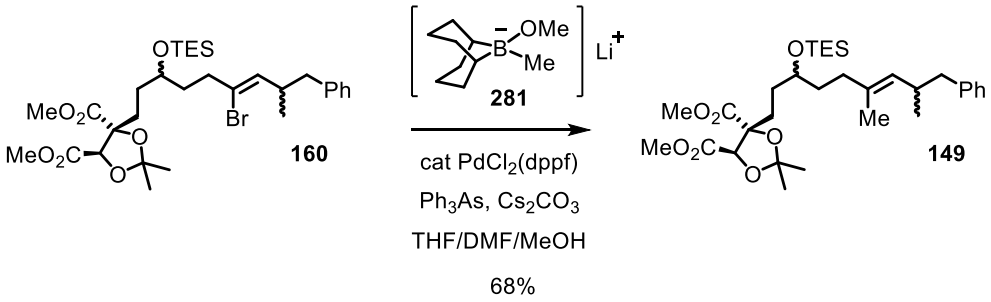
## 4.6 Synthesis of DDSQ Trimethyl Esters 267

Attempted the methylation cross–coupling using the optimised conditions, from substrate **160** (**Table 3**, entry 7), with 2,8-dioxabicyclic core *R*-**166** was unfortunately not successful (**Scheme 84**).




**Scheme 84** Another attempted methylation of bromide *R*-**166**.

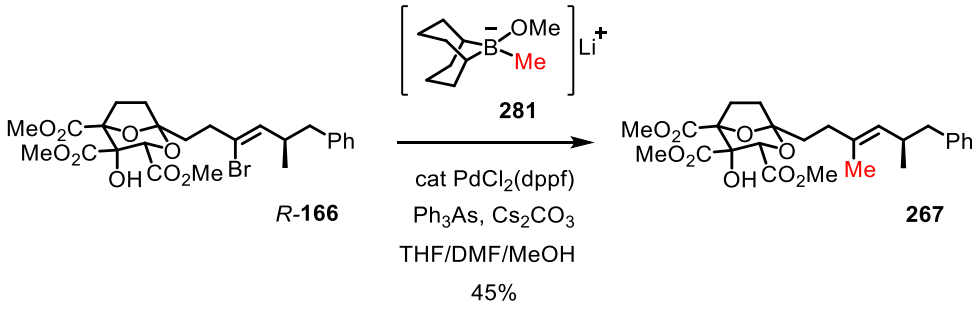
TLC analysis of the crude mixture showed a polar complex mixture had been formed. This mixture was acidified with HCl (1N), extracted with EtOAc (3x) and the combined organic layers evaporated under reduced pressure. $^{1}$H NMR analysis of the obtained mixture indicated the presence of only one ester group (likely at C4, as the ester group at C3 is very susceptible to hydrolysis, followed by the more sterically hindered C5 ester).[2] This result indicated that using a base in the presence of water while stirring for a prolonged period caused complications to the reaction for bromide *R*-**166**. Further investigation showed that switching the solvent mixture to THF/DMF/MeOH at 40 °C for 8 h resulted in full conversion of **160** to the desired product **149** (68%) (**Scheme 85**).




**Scheme 85** Further optimisations of methylation cross–coupling conditions.

With a few milligrams of rearranged core *R*-**166** left in hand, the new modified conditions were carefully applied. Pleasingly, using these conditions on *R*-**166** was finally successful to give 6,7-dideoxysqualestatin H5 trimethyl ester **267**, in 45% yield (~1 mg, **Scheme 86**). Methylation occurred with retention of double bond geometry as determined by $^{1}$H NMR analysis and by correlation with Fegheh–Hassanpour's substrate **184**[57] and the literature.[54,90] The characteristic chemical shift of the vinylic proton of trimethyl ester **267** (at 5.02 ppm, 1H, d, $J$ = 9, C*H*=CCH$_3$) is corresponded with the vinylic proton in Fegheh–Hassanpour's substrate **184** (p. 104) (5.03 ppm, 1H, d, $J$ = 9, C*H*=CCH$_3$). Usefully diagnostic is the fact that the vinylic proton of the undesired *Z*-isomer (observed by Fegheh–Hassanpour)[57] resonates at slightly higher field

(lower ppm) than in the desired *E*-isomer, which is not observed under the methylation conditions.

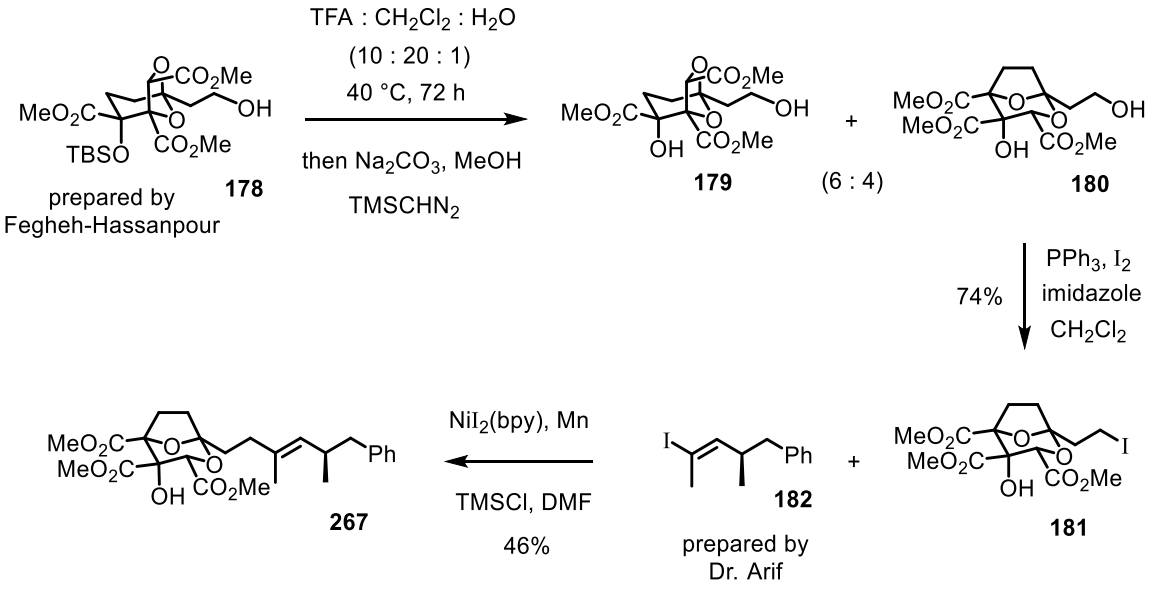



**Scheme 86** Synthesis DDSQ trimethyl ester **267**.

## 4.7 Providing More DDSQ Trimethyl Esters 267

Due to material availability, and considering the time and cost of repeating the synthesis to the natural product from scratch, we decided to make use of substrate (2,8-dioxabicyclic core **178**, **Scheme 87**) that was left over from Fegheh–Hassanpour's studies[57] (*cf* **Scheme 24**, p. 46) (~45 mg). To progress from **178**, acid-catalysed rearrangement of 2,8-dioxabicyclic core **178** using Evans' condition (TFA/$CH_2Cl_2$/$H_2O$) gave unrearranged **179** and rearranged core **180** in a 6:4 ratio, respectively. The rearranged core **180** was not favoured (6:4; **179**:**180**), as also observed previously by Fegheh–Hassanpour.[57] In contrast, in our substrate rearrangement (*R*-**164**→ *R*-**165**+ *R*-**166**, **Scheme 72**, p. 88), the rearranged core *R*-**166** is favoured, which indicates the equilibrium position is sensitive to variation in the C1 side-chain. Nevertheless, the unrearranged diol **179** could be separated and resubmitted to the reaction conditions. In our hands, the yield of the rearrangement step was poor (less than 15%), despite the fact that $TMSCHN_2$ was added at the end of the reaction, in an attempt to re-esterify any carboxylic acids which might have formed.[127] For comparison, in Fegheh-Hassanpour's work, 27% yield was obtained.[57] After several recyclings, the desired rearranged diol **180** was treated with

triphenylphosphine and iodine to give hydroxy iodide **181** in 74% yield (lit[57] 90%). Under Ni-catalysed cross–coupling,[128] a 1:1 mixture of hydroxy iodide **181** and alkenyl iodide **182** (prepared by Dr. Arif)[63] in DMF gave further 6,7-dideoxysqualestatin H5 trimethyl ester **267** in 46% yield (**Scheme 87**). Pleasingly (we initially thought, although see Section 4.8), the tertiary alcohol was not protected with a TMS group as observed in Fegheh–Hassanpour's work, which in that earlier work was probably due to use of a greater excess of TMSCl.

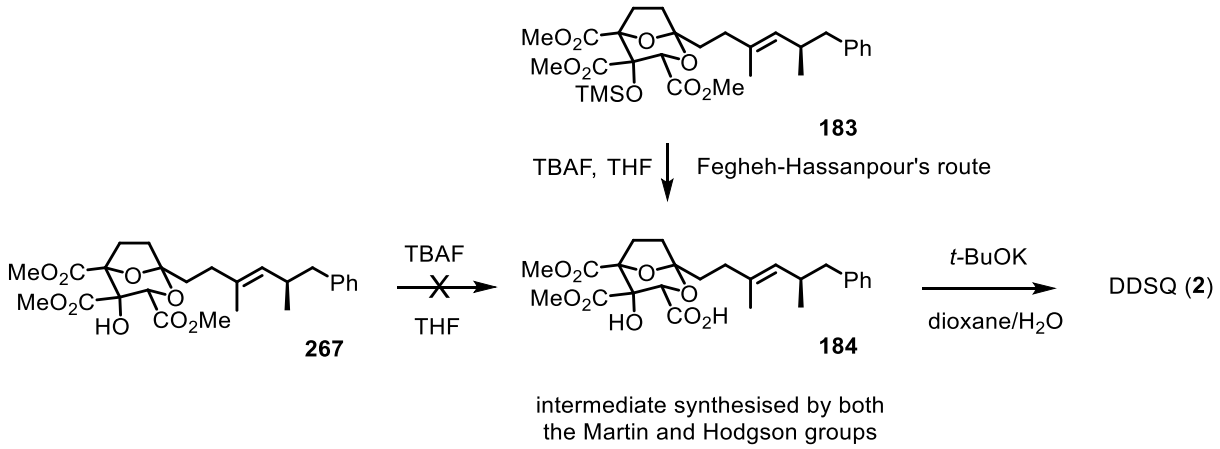



**Scheme 87** Synthesis DDSQ trimethyl ester **267** using Fegheh-Hassanpour and Dr. Arif materials.

## 4.8 Ester Hydrolyses

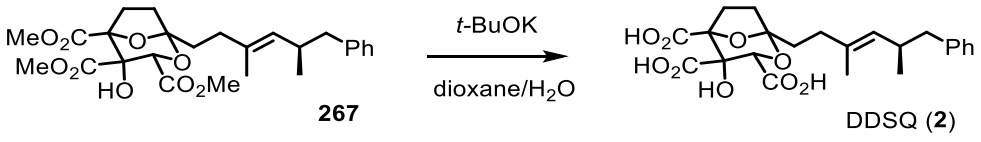
With appreciable amount of DDSQ trimethyl ester **267** in hand, we examined the final step in the DDSQ **2** synthesis. Initially, TBAF was utilised in an attempt to achieve a formal synthesis, by hydrolysing the C3 ester to give the known DDSQ dimethyl esters **184**[57,129] (**Scheme 88**). Unfortunately, under TBAF conditions, **267** decomposed within 30 min at rt. On repeating the reaction at 0 °C for less than 10 min, the $^{1}$H NMR spectrum of the crude mixture showed

epimerisation at C3. In Fegheh–Hassanpour's synthesis, the presence of the silyl group on the alcohol (**183**) appears essential to achieve the deprotection and hydrolysis of the ester group at C3 by TBAF (**Scheme 88**).[57,130]




**Scheme 88** Attempted TBAF-deprotection to achieve a formal synthesis.

Standard basic hydrolysis conditions using NaOH (0.1 M) was also attempted; however, the starting material **267** was recovered after stirring the reaction mixture overnight. With the susceptibility for epimerisation at C3 in mind and encouraged by Nicolaou's chemistry on zaragozic acid A / squalestatin S1, which showed that basic conditions hydrolyse C3 and C5 methyl esters (albeit using LiOH, at rt) without epimerising C3,[27] a global hydrolysis using freshly sublimed *t*-BuOK was attempted. It was thought that low temperature would allow to hydrolyse the C3 ester first, avoiding the possible epimerisation. The reaction mixture was stirred at –10 ºC and then gradually warmed to 50 ºC, to afford (−)-6,7-dideoxysqualestatin H5 (**2**) after acidic wash (0.1 N HCl at 0 ºC) and MeOH/hexane extraction, in 78% yield (**Scheme 89**).[147] Data was in full agreement with the natural isolate (see **Table 4**, p. 171).




**Scheme 89** Hydrolysis to the natural product (DDSQ **2**).

# Chapter 5

# Results and Discussion, Part IV:

## Rationalisation of the Tartrate Dialkylation Observation

and

## Epimerisation of Monoalkylated Tartrates

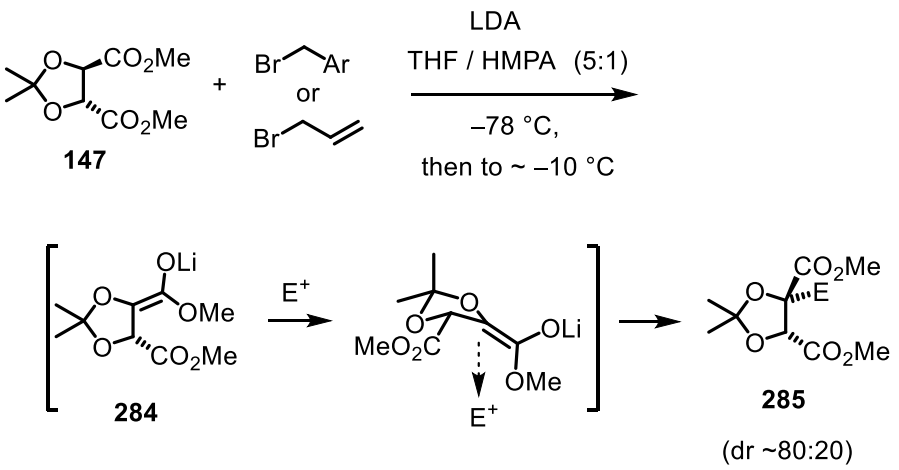
# 5. Results and Discussion

Having finished the total synthesis of DDSQ (**2**), further efforts were carried out to investigate the origin behind the formation of the dialkylation product (see: **Scheme 58**, p. 73); and also to develop epimerisation conditions to access *R*,*S*-monoalkylated products.

## 5.1 Alkylation

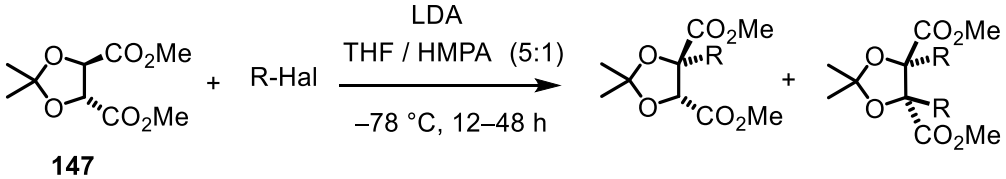
### 5.1.1 Introduction to Alkylation of Tartrate Acetonide 147

In 1981, Seebach and Naef demonstrated that the lithium enolate of (*R*,*R*)-tartrate acetonide **147** could be trapped in a stereoselective manner with reactive alkyl halides, such as allylic halides and benzylic halides, to give the *trans*-ester monoalkylated product as a major diastereomer **285** (**Scheme 90**).[131–133] The *cis* "contrasteric"[134,135] stereoselectivity of the alkylation can be rationalised due to the enolate π-system and beta σ-C–O bond lying mutually orthogonal in an envelope conformation wherein the unenolised ester resides pseudo-equatorial to avoid 1,3-steric interactions with a pseudo-axial methyl of the *gem*-dimethyl group[133–135], and that this axial methyl group then directs electrophile incorporation away from itself (**Scheme 90**).




**Scheme 90** Contrasteric alkylation.

In the Hodgson group, alkylation of dimethyl tartrate acetonide **147** with primary 'non-activated' alkyl iodides were achieved at –78 °C (with work up at the same temperature) in acceptable yields, along with substantial amounts of *trans*-dialkylated products (beside the alkylation of DDSQ side-chain, see **Scheme 91)**. *Trans* stereochemistry assignment for the dialkylated products **287** follow from the observed equivalence of the acetonide methyl groups in all their proton and carbon NMR spectra.




| R | 286a–d | 287a–d |
|---|---|---|
| **a** (Pr) | 66% | 7% |
| **b** (Bu) | 42% | 10% |
| **c** (Hex) | 47% | 9% |
| **d** (prenyl) | 67% | 14% |

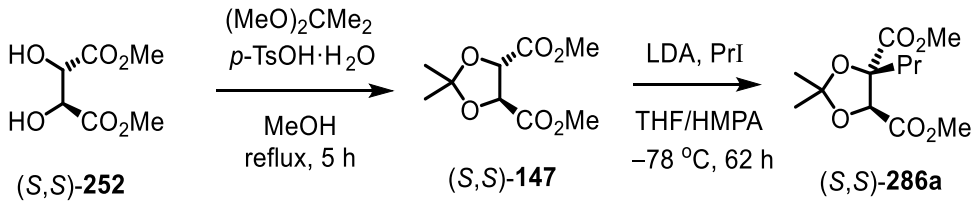
**Scheme 91** Tartrate alkylation with various alkyl halides by Al-Mamari and Dr. Valade.[53,55]

Further efforts were carried out to investigate the reaction pathway to the formation of dialkylated by-products **287** during the alkylation process, and whether the dialkylated by-product was racemic (possibly forming *via* a dienolate) or obtained in high enantioenrichment.

### 5.1.2 Rationalisation of the Dialkylation Observation

In Seebach's original studies in which retention of configuration upon tartrate benzylation was observed for the major diastereomer (formed in 97:3 er), a further intriguing observation was made: that the minor diastereomer was obtained essentially as a racemate (determined by NMR using a chiral shift reagent).[133] It was suggested that the latter principally arose from alkylation of the achiral dienolate (**288**, **Scheme 93**) of **147** followed by protonation by unreacted **147**. In our work, where the major difference in the alkylation conditions is a prolonged reaction time at low temperature and no warming before quenching, the minor diastereomer is not observed – but dialkylated by-product is.

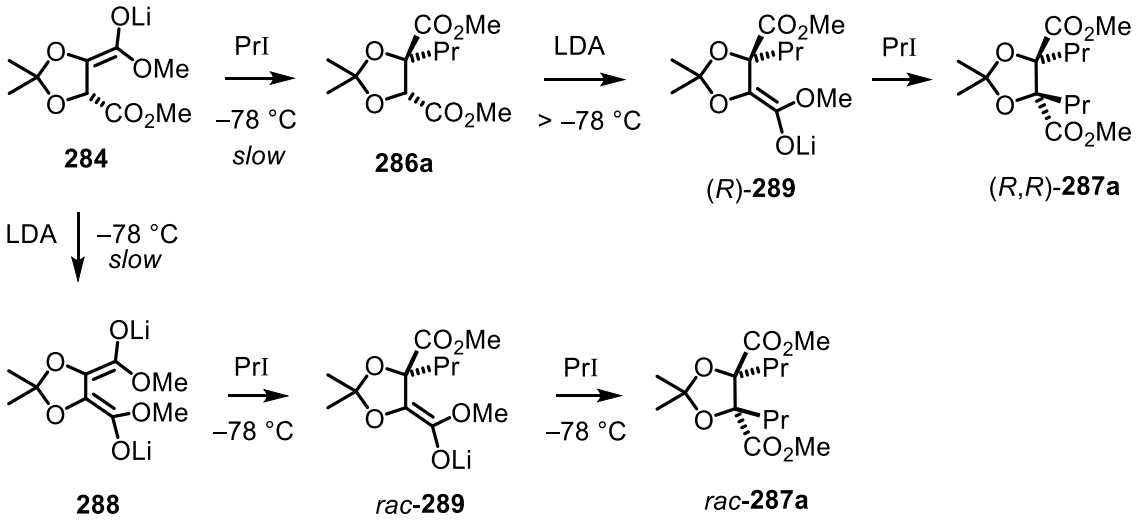
We studied the alkylation reaction in more detail using propyl iodide as a model electrophile for alkylation with tartrate acetonide **147**. Initially, we examined the enantiopurity of (*R*,*R*)-monopropylated tartrate *R*,*R*-**286a** (prepared by Al-Mamari) by chiral HPLC. Since both enantiomer forms of monoalkylated tartrate are required for optimising the HPLC conditions, therefore, we synthesised (*S*,*S*)-monopropylated tartrate (*S*,*S*)-**286a** in a similar manner from (*S*,*S*)-tartrate **252** (**Scheme 92**). Subsequent HPLC studies confirmed the high enantiointegrity of *R*,*R*-monopropylated tartrate **286a** (97:3 er).




**Scheme 92** Preparation of propylated tartrate (*S*,*S*)-**286a**.

An attempt to propylate the monopropylated tartrate *R*,*R*-**286a** under our conditions (–78 °C, 68 h) mainly returned starting material *R*,*R*-**286a** (68%), with only a trace of *trans*-dipropylated product **287a** being isolated (2%). Seebach's observations, together with ours, indicate that the dienolate **288** does form to some extent at –78 °C (**Scheme 93**),[136–138] and both it and the derived alkylated mono-anion *rac*-**289** are quite reactive to alkylation, but protonation of the alkylated mono-anion *rac*-**289** (by unreacted **147**) does not occur at that temperature. Once monoalkylation has occurred from the mono-enolate **284**, then **286a** is not readily deprotonated at –78 °C. Clearly, monoalkylated tartrate can be deprotonated and trapped with electrophiles if the system is warmed above –78 °C: to –30 °C by Molander and Harris,[139] whereas –50 °C was sufficient for oxidation (eg: **Schemes 59**, p. 74). Indeed, it was found that propylation of the monopropylated tartrate *R*,*R*-**286a** can be achieved in 34% yield if the reaction mixture is warmed to –50 °C (**Scheme 93**). Interestingly, the dipropylated material **287a** obtained from propylation of the monopropylated tartrate *R*,*R*-**286a** displayed a low specific rotation value of –1.1 (*c* 1.4, $CHCl_3$). To determine the enantiomeric purity of the dipropylated tartrate, the HPLC conditions were optimised for separating the two enantiomers (*S*,*S* and *R*,*R*-dilkylated tatrate), and the best separation was achieved by using a Chiralpak IC-3 column [99:1 heptane–*i*PrOH, 1.0 ml/min, λ = 230 nm, 10 μL injection]. Chiral HPLC comparison of the *trans*-dipropylated material **287a**, obtained as the by-product from the alkylation of tartrate acetonide **147**, and from propylation of the monopropylated tartrate **286a**, confirmed that the former was essentially racemic (52:48 er), while the latter was highly enantioenriched (98:2 er). Therefore,

to generate (*R*,*R*)- (or (*S*,*S*)-) *C*2-symmetric dialkylated tartrates,[140–142] mono-alkylation should be carried out first, and the isolated monoalkylated material then separately subjected to second alkylation, allowing warming to ~ – 40 °C.




**Scheme 93** Rationalisation of dialkylation observations.

## 5.2 Epimerisation of Monoalkylated Tartrates

To extend the tartrate alkylation scope, we examined the feasibility of preparing the epimers of mono-alkylated tartrate products by epimerisation at the C3 position to lead to the *cis*-ester stereoisomer. Aside from the Hodgson group work with monoalkylated tartrate acetonides towards DDSQ (**2**) described in this thesis, the monoalkylated tartaric acid motif is also directly present in several other natural products, such as hydroxybenzyl-substituted piscidic acid (**290**), congeners (fukiic and cimicifugic acids),[143] Cephalotaxus alkaloids isoharringtonine (**291**) and cephalezomine C (**292**) (**Figure 7**).[144] In these latter natural products, the monoalkylated tartaric acid residues typically possess 2*R*,3*S* stereochemistry; one exception is cephalezomine

D[144], which is the 3*R*-epimer of cephalezomine C (**292**). Since the chiral (*R*,*R*- or *S*,*S*-) tartrate acetonides undergo stereoretentive alkylation, then direct access to the stereochemistry present in the majority of these natural products is not possible. Nevertheless, a couple of isolated examples in the Chinese chemical literature from the late 1980s indicated that subsequent base-induced epimerisation of mono-alkylated (*p*-(benzyloxy)benzylated and prenylated) tartrate acetonides favours *R*,*S* stereochemistry, providing access to piscidic acid (**290**)[145] and the tartrate residue of isoharringtonine (**291**).[146]

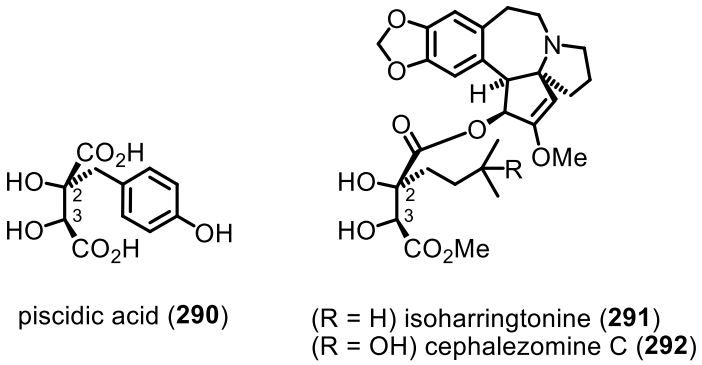
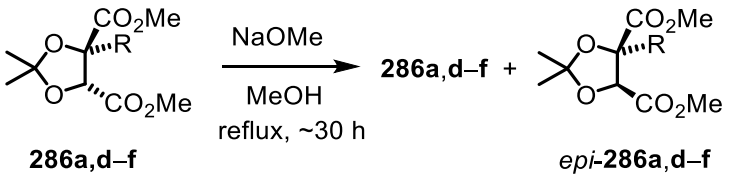



**Figure 7** Natural product examples containing the monoalkylated tartaric acid motif.

We studied the previously reported epimerisation of prenylated tartrate (**286d**)[53] on a 0.5 mmol scale (lit[146] 5 mmol) using NaOMe (1 equiv) in MeOH (0.5 M) at room temperature for 12 h. Under these conditions we observed only partial epimerisation (**286d**:*epi*-**286d** 75:25, [lit[146] 12:88]), but a 25:75 ratio in favour of *epi*-**286d** could be achieved in MeOH (0.06 M) at reflux for 30 h (**Scheme 94**). We established that equilibrium had been reached by subjecting *epi*-**286d** to these latter reaction conditions, which returned the same 25:75 ratio of **286d**:*epi*-**286d**. Other monoalkylated tartrates **286a,e,f** were found to give similar levels of epimerisation (**Scheme 94**), generating the chromatographically separable epimerised tartrates in 54–67% isolated yields.




**286a,d–f** *epi*-**286a**,**d–f**

| R | **286** : *epi*-**286** | yield (*epi*-**286**) |
|---|---|---|
| **286a** (Pr) | 28 : 72 | 54% |
| **286d** (prenyl) | 25 : 75 | 58% |
| **286e** (Bn) | 17 : 83 | 67% |
| **286f** (butenyl) | 25 : 75 | 61% |

NB: **253d–f** were previously prepared in the Hodgson group

**Scheme 94** Epimerisation of monoalkylated tartrates **286a**,**d-f**.

To conclude, the reaction pathways that lead to racemic dialkylated tartrates under our modified alkylation conditions have been rationalised. Base-induced epimerisation of the monoalkylated tartrates favours *cis*-disposition of the ester groups on the five-membered ring, thereby accessing the predominant stereochemistry found in several substituted tartaric acid-containing natural products. These findings on origins of the dialkylated by-products, and on epimerisation conditions of the monoalkylated tartrates, significantly broaden the scope and understanding of Seebach's alkylation chemistry.[199]

# Chapter 6

# Results and Discussion, Part V:

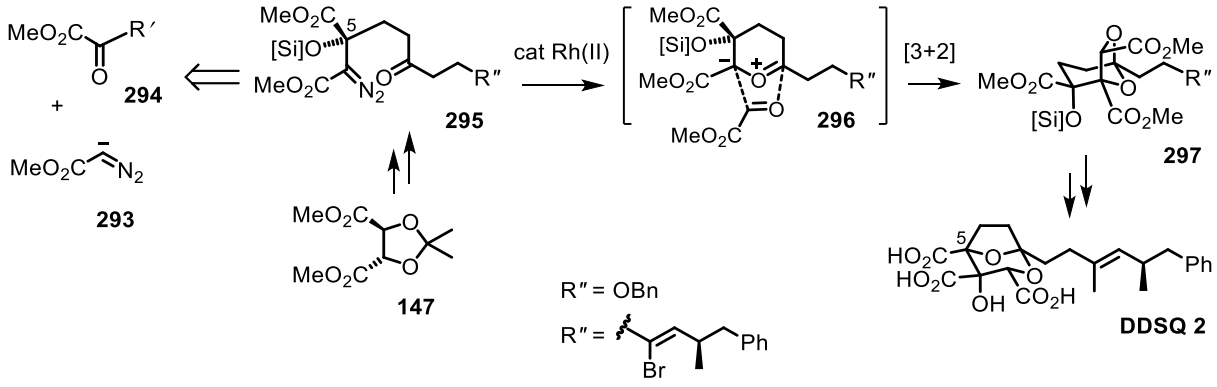
## Synthesis of α-Diazo-ε-Ketoester (334), For Application in DDSQ Synthesis, Based on Aldol-Ozonolysis Strategy

and

## Catalytic Enantioselective Studies Towards β-Silyloxy(ester)-α-Diazoester

# 6. Results and Discussion

As discussed earlier in this thesis, in the Hodgson group, two related strategies were successful to synthesise 6,7-dideoxsqualestatin H5.[57,147] One of the key feature of these syntheses was the stereoselective alkylation of dimethyl tartrate acetonide **147**, used as a chiral building block, to generate the quaternary carbon at C5 of the squalestatin core. Further manipulation of the alkylated product led to diazoketones **295** (**Scheme 95**), which underwent rhodium-catalysed tandem carbonyl ylide formation–intermolecular dipolar cycloadditions (**295**→**297**),[148] followed by acid-catalysed rearrangement to generate the characteristic 2,8-dioxabicyclo [3.2.1]octane core of the squalestatins/zaragozic acids at the correct tricarboxylic acid oxidation level. In principle, a more concise approach to such cycloaddition precursors **295** could proceed by aldol reaction between a diazoacetate anion **293** and a suitable α-ketoester **294** (**Scheme 95**).



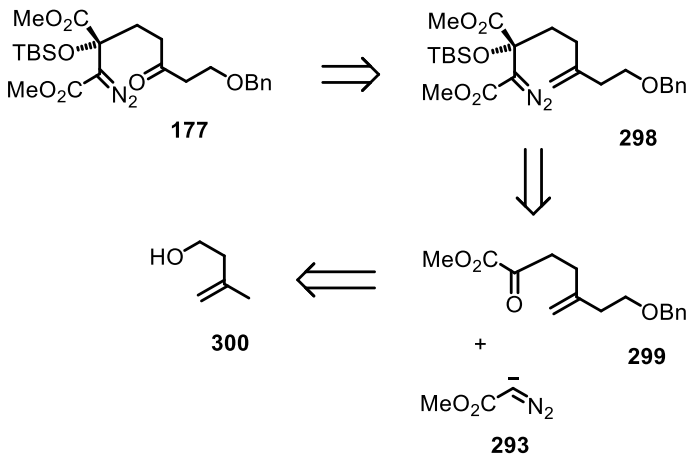

**Scheme 95** Diazoketones **295** leading to synthesise of DDSQ **2**.

After my fruitful total synthesis of DDSQ **2**,[147] preparation of the Fegheh-Hassanpour's intermediate diazoketone **295** (R″ = OBn, see also p. 46), eventually in an asymmetric manner,

became the new target. Potentially, this would allow a significant shortening of the DDSQ synthesis.

## 6.1 New Strategic Route

A new retrosynthesis of β-silyloxy(ester)-α-diazo ester **177** was proposed (**Scheme 96**), using catalytic enantioselective addition of methyl diazoacetate (**293**) to α-ketoester **299** bearing alkene functionality. In a key step, the alkene moiety would be later converted to a ketone by chemoselective ozonolysis, to achieve a formal synthesis of DDSQ **2**.[57]

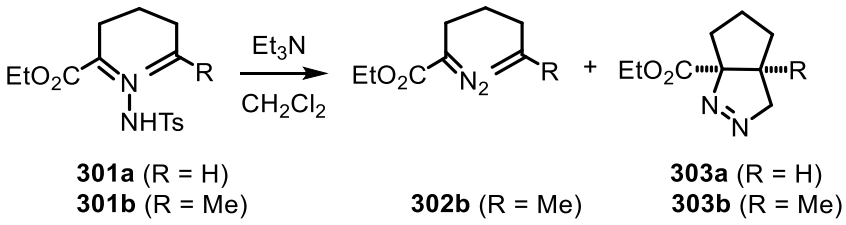



**Scheme 96** proposed route to access diazoketone **177**.

It was considered prudent to test the general racemic validity of this route, before exploring conditions for the enantioselective aldol reaction between diazoacetate **293** and unsaturated α-ketoester **299**.

### 6.1.1 Background to Intramolecular Cycloaddition

One potential problem with the proposal route (**Scheme 96**) is that the α-diazoester functionality could engage in intramolecular cycloaddition with the electron-rich alkene to form a bicyclic pyrazoline.[149–156] In the Hodgson group, Fegheh-Hassanpour observed on simpler substrates that unsaturated hydrazones **301a**,**b**[157] underwent $Et_3N$-induced diazo formation[158,159] in $CH_2Cl_2$ at rt (**Scheme 97**). As anticipated from Dauben's studies,[150] this led hydrazone **301a** to form 1-pyrazoline **303a**, in 92% yield (**Scheme 97**). However, intramolecular cycloaddition was minimised with the 2,2-dialkyl-substituted terminal alkene **301b**, to give a mixture (52%) mainly consisting of unsaturated diazoester **302b** together with only small amounts of bicycle **303b** (**302b**:**303b**, 91:9).

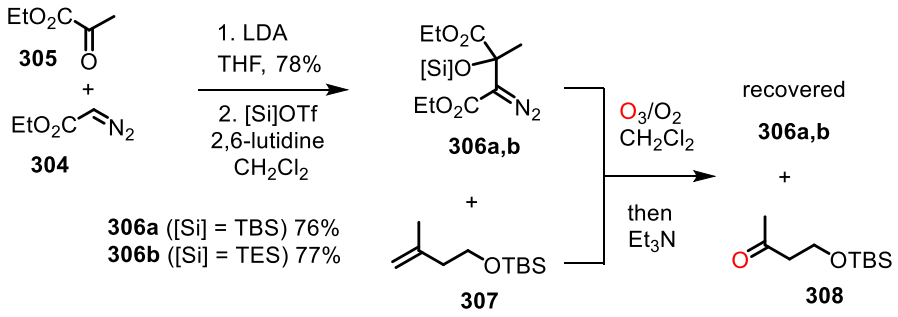



**Scheme 97** Propensity for diazoalkenes to undergo intramolecular cycloaddition.[122]

### 6.1.2 Model Study

Encouraged by the above observation, the stability of the diazo group under ozonolysis conditions was studied in detail. It was considered that electron-rich alkenes should be oxidised faster than diazo functionality α– to an electron-withdrawing group (eg, ester). Therefore, model studies were designed to establish the stability of the α-diazo ester moties towards ozone. Model compounds, **306a,b** (**Scheme 98**) that resemble the diazo pattern in **177** (**Scheme 96**)

were prepared in two steps from commercially available ethyl pyruvate (**305**) and ethyl diazoacetate (**304**) followed by silylation of the hydroxyl group.[160] Then, an equimolar solution of diazo **306a,b** and alkene **307**[122] (which mimics the alkene portion of **177**) was subjected to ozone treatment (–78 °C in $CH_2Cl_2$ in the presence of Sudan red 7B (as an indicator) for ~ 5 min, then $Me_2S$ as a reductant). A mixture of the desired ketone **308** and recovered diazo **306a**(**b**) was obtained, but with extra unidentified peaks in $^1H$ NMR spectra of the crude mixture. However, switching to $Et_3N$[161] from $Me_2S$, and without using the indicator, gave a clean crude mixture of ketone **308** with recovered diazoester **306a** (**Figure 8**), or **306b**.




**Scheme 98** Preparation and stability of α-diazoesters **306a,b** towards ozone.

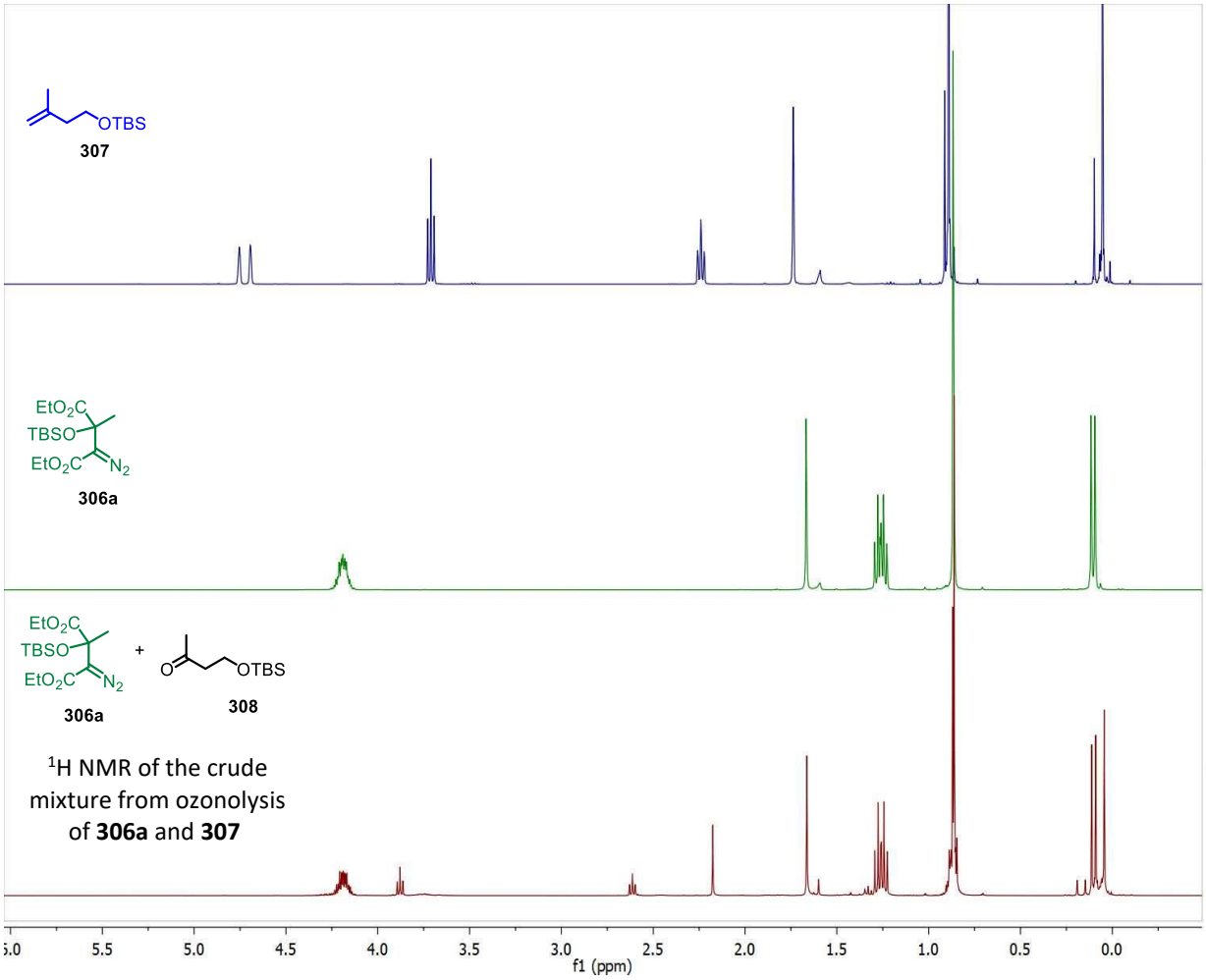
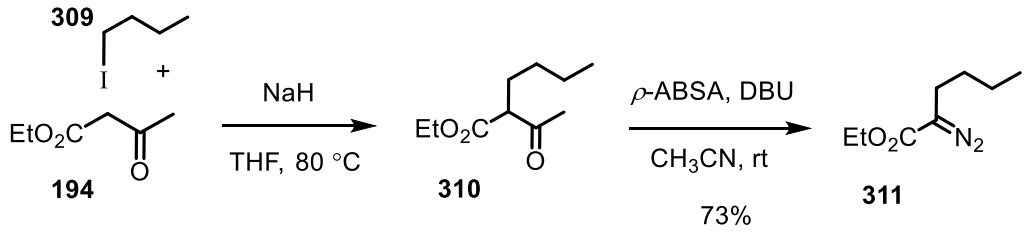



**Figure 8** Comparison of $^{1}$H NMR Spectra of **307** and **306a** with the crude reaction mixture from their ozonolysis.

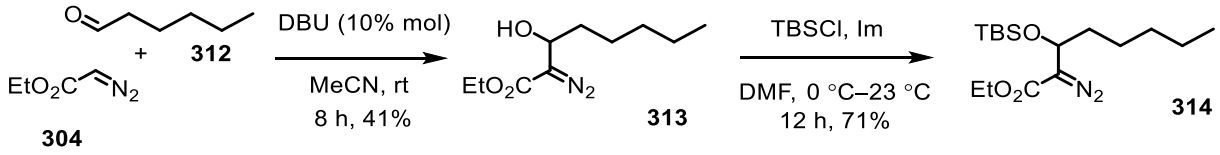
### 6.1.3 Stability of Diazocarbonyl Derivatives Towards Ozone

In order to test the generality of this chemistry, more readily accessible β-substituted α-diazocarbonyl compounds were prepared to determine if steric and/or electronic factors bias the stability of the diazo moiety to ozonolysis. α-Diazoester **311**[162] (**Scheme 99**) was prepared by alkylation of the ethyl acetoacetate **194** with butyl iodide (**309**), followed by diazo transfer using a slight excess (1.2 equiv) of *ρ*-ABSA and DBU.



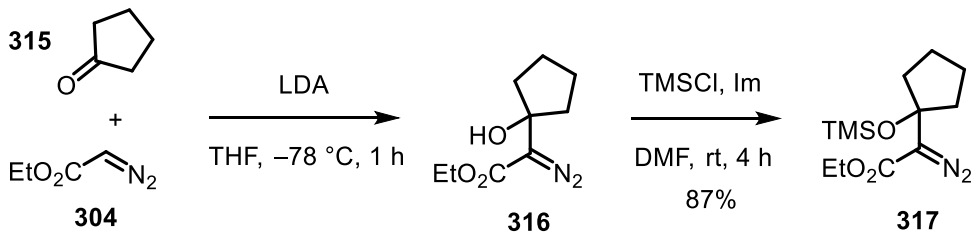

**Scheme 99** Preparation of β-butyl α-diazoester **311**.

Aldol reaction of ethyl diazoacetate **304** with hexanal (**312**) catalysed by DBU gave alcohol **313**[163] (41%) (**Scheme 100**), which was then silylated with TBSCl to afford silyl ether **314** in a good yield (71%).[164]



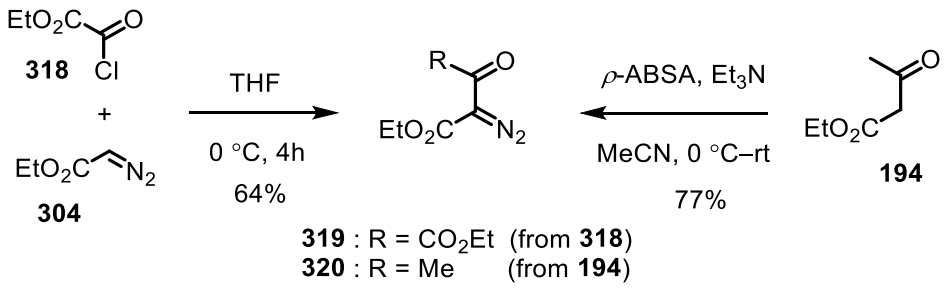

**Scheme 100** Synthesis of silyl ethers **314**.

Also, fully β-substituted α-diazoester **317** was synthesised in two steps (**Scheme 101**). Cyclopentanone (**315**) reacted with lithiated ethyl diazoacetate **304** at –78 °C in THF to afford alcohol **316**[156]. The hydroxy group was silylated with TMSCl in the presence of imidazole to afford TMS ether **317** in 87% yield (**Scheme 101**).



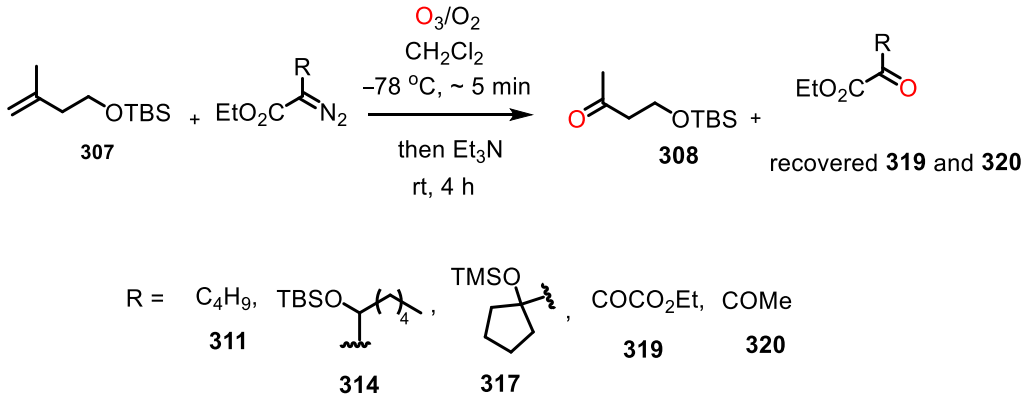

**Scheme 101** Formation of fully β-substituted α-diazoester **317.**

Furthermore, to study the electronic influence on the diazo moiety, β-keto-α-diazoesters **319**[165] and **320**[166] were readily prepared from diazoacetate **304** with acyl chloride **318** and ethyl acetoacetate (**194**), respectively, in good yields (**Scheme 102**).




**Scheme 102** Preparation of β-keto-α-diazoesters.

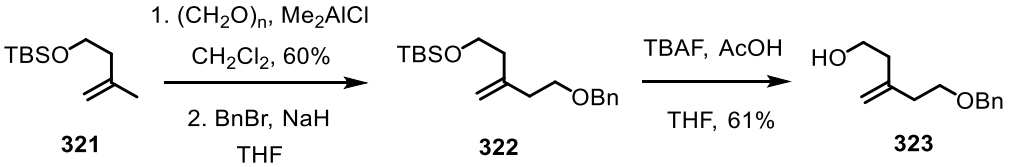
β-Substituted α-diazoesters **311**, **314**, **317** (**Scheme 103**) were then examined, to study the effect of different substitution at β-position on the stability of the α-diazo moiety to ozonolysis; interestingly, they were all reactive at –78 °C, being converted to the corresponding ketones after addition of $Et_3N$. In contrast, β-keto-α-diazoesters **319** and **320** were stable to ozone. The presence of electron–withdrawing functionality at β-position of the α-diazoester clearly further reduces the reactivity of the diazo group towards ozone; β-keto-α-diazoester **319** was stable to ozone even under warming the reaction mixture to –15 °C for 1 h (alkene **307** converts to ketone **308** within 5 min at –78 °C).




**Scheme 103** Examining the tolerance of various β-substituted α-diazoesters towards ozone.

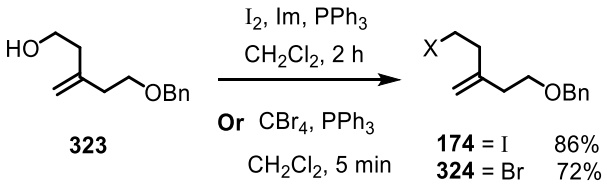
### 6.1.4 Synthesis of Racemic Keto-Diazoesters

Returning to our strategy (**Scheme 96**, p. 115), we focused on a synthesis of the racemic DDSQ intermediate **177**, through diazoacetate anion addition to homoallylic α-ketoester **299**. Homoallylic alcohol **323** was prepared following Fegheh-Hassanpour's route (**Scheme 104**).[57] Refluxing silyl ether **321**[122] with paraformaldehyde and stoichiometric $Me_2AlCl$ in $CH_2Cl_2$ for 2 h afforded the ene derived homoallylic alcohol. Benzylation of the latter with BnBr in the presence of NaH gave alkene **322** in a low yield (~ 30%). Referring to Fegheh-Hassanpour's lab-book, TBAI was used in this reaction. Using a catalytic amount of TBAI doubled the overall reaction yield. Desilylation of the TBS group was also not straightforward, but the problem (low yield) was solved using a catalytic amount of AcOH to give alcohol **323** in 61% yield (**Scheme 104**).[167]



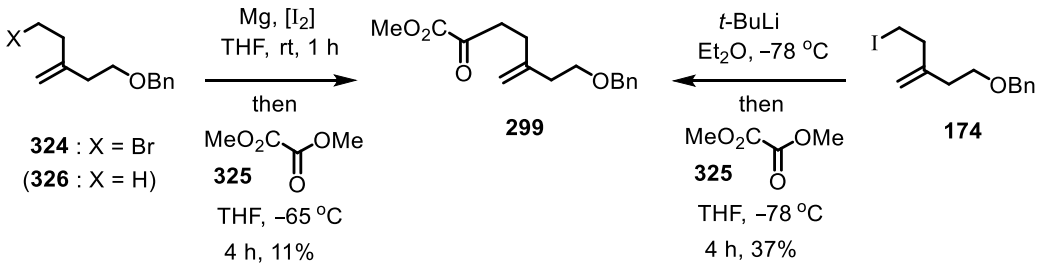

**Scheme 104** Formation of homoallylic alcohol **323** *via* formaldehyde–ene reaction.

Iodination of homoallylic alcohol **323** with $I_2$ in the presence of imidazole and $PPh_3$ in $CH_2Cl_2$ gave iodide **174**[57] in 86% yield. Similarly, **323** was brominated using $CBr_4$ and $PPh_3$ in $CH_2Cl_2$ for a short period (5 min) providing homollylic bromide **324** in 72% yield (**Scheme 105**).



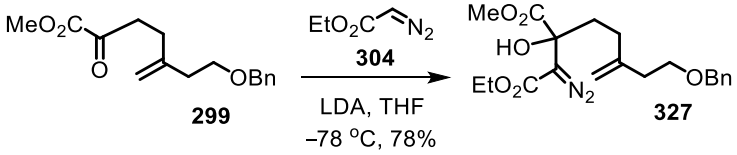

**Scheme 105** Synthesis of halo-alkenes.

Although many methods are known for synthesis of α-ketoesters,[168–170] only a limited number of organometallic additions to oxalates are suitable for the synthesis of homoallylic α-ketoesters (as envisaged in the proposal route, **Scheme 96**, p. 115).[171,172] Grignard chemistry was carried out with homoallylic bromide **324** first. Mg turnings were activated by stirring under $N_2$ at rt for few hours (~3 h),[173] followed by adding an iodine crystal and warmed gently (using a heat gun) until iodine vapour was observed.[174] Subsequently, homoallylic bromide **324** in THF was added. When the freshly prepared Grignard reagent (from bromide **324)** was transferred by a cannula to a solution of freshly distilled dimethyl oxalate (**325**, 5 equiv) in THF at –65 °C, only a low yield of α-ketoester **299** was obtained (11%, **Scheme 106**). Transmetalation of the above Grignard reagent to an organocopper using CuBr,[175] then trapping with oxalate **325** failed to give the desired product; alkene **326** was isolated. In another attempt, halogen–lithium exchange of iodide **174** using *t*-BuLi (2 equiv) at – 78 °C[176] and dropwise addition of the resulting organolithium to a solution of oxalate (**325**, 3 equiv) in $Et_2O$ (at –78 °C) gave a similar yield (~15%). The low yield in this latter reaction could be due to the limited solubility of dimethyl oxalate in $Et_2O$ at –78 °C, as switching from $Et_2O$ to THF led to an improved yield of α-ketoester **299** (37%, **Scheme 106**).



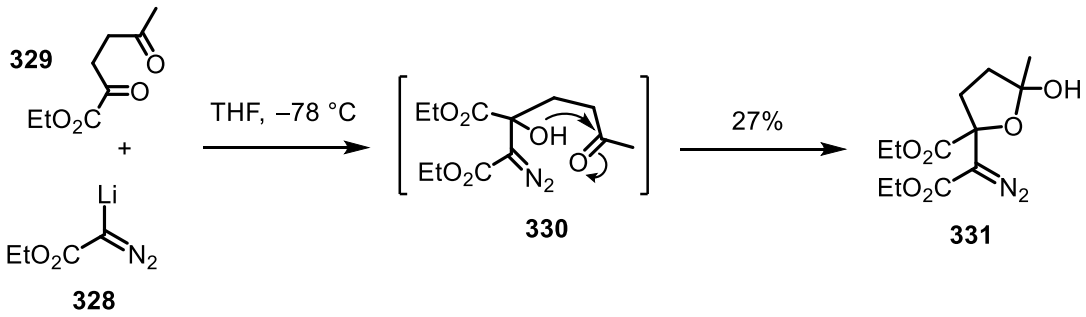

**Scheme 106** Synthesis of unsaturated ketoester **299**.

Next, diazo-alcohol **327** was prepared through the addition of lithiated ethyl diazoacetate **304** (used instead of methyl diazoacetate due to commercially availability) to α-ketoester **299** (78%) (**Scheme 107**). Pleasingly, and following the trend seen with the Fegheh-Hassanpour substrates (**Scheme 97**), no undesired intramolecular cycloaddition was observed for diazo-alcohol **327**.



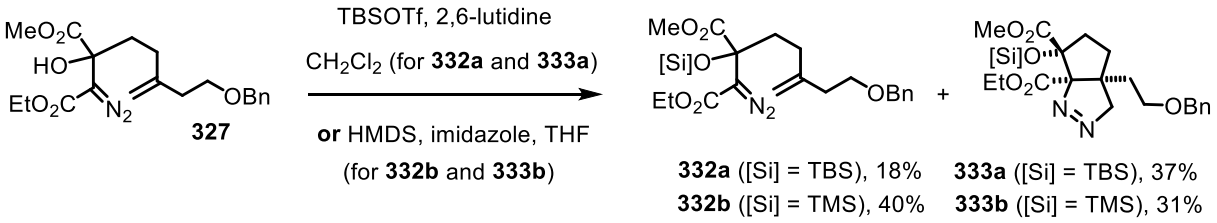

**Scheme 107** Aldol-reaction of **299**.

At this stage, we proceeded to protect the OH group, since otherwise it would likely undergo problematic γ-lactolisation with the ketone subsequently generated on ozonolysis. On a similar motif, γ-lactolisation of α-diazoester **330** was observed by Villalonga-Barber (**Scheme 108**).[177]




**Scheme 108** Addition of α-ketoester **329** to lithiated ethyldiazoacete **327** yielded lactol **331**.

A silyl group was the protecting group that need to be installed to achieve a formal synthesis of DDSQ **2**.[57] Interestingly, when diazo-alcohol **327** was treated with TBSOTf in the presence of 2,6-lutidine ($CH_2Cl_2$, 48 h), a mixture of desired TBS ether **332a** along with cycloadduct **333a** (as a single diastereomer, stereochemistry indicated was supported by NOESY experiments) was obtained (**332a**:**333a**, 1:2; **Scheme 109**). Using DMAP or pyridine as the base was not successful in preventing the 1,3-dipolar cycloaddition, whereas using $Et_3N$ led to retro-aldolisation. The partial formation of cycloadduct **333a** on silylation could be rationalised by a Thorpe–Ingold effect, from the bulky silyl group. With this in mind, it was considered that minimising the steric effect by using a less-hindered silyl group might reduce the bicyclic product formation; indeed on trimethylsilylation, the ratio of silyl-ether **332b** to cycloadduct **333b** was 4:3 in favour of the desired non–cyclic product (**Scheme 109**).




**Scheme 109** Silylation of diazo-alcohol **327**.

The silyl ethers **332a** and **332b** were found to undergo cyclisation when stored as neat samples on the lab-bench, with the rate being slower for **332b** (**Figure 9**). Therefore, they were directly subjected to ozonolysis following their isolation.

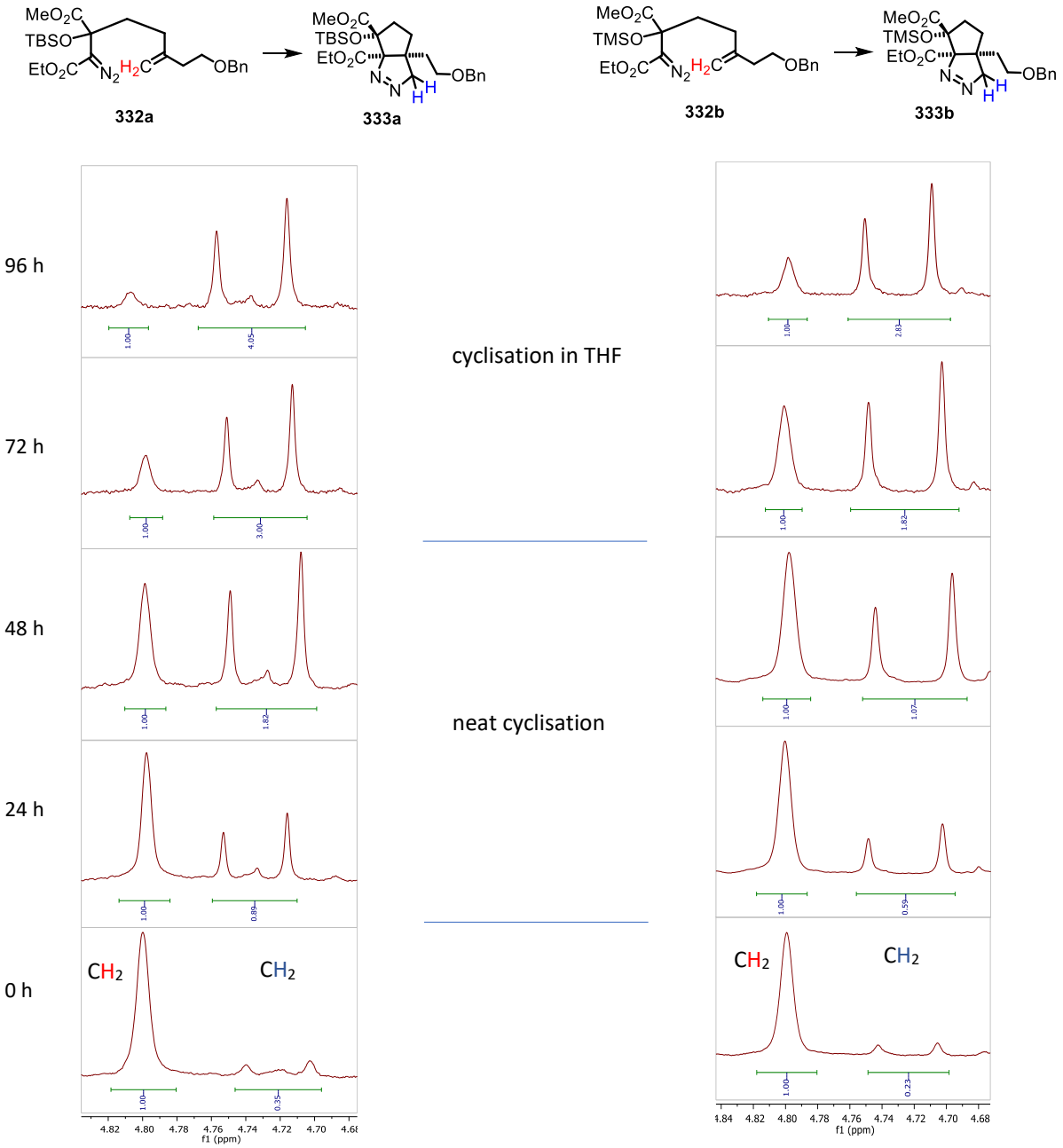
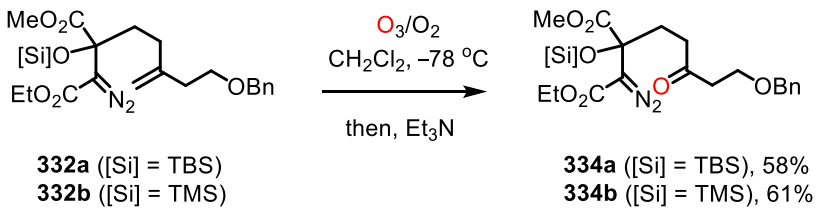



**Figure 9** Comparison of rates of intramolecular cycloaddition of silyl ethers **332a** and **332b**.

Pleasingly, the ozonolysis of silyl-ethers **332a** and **332b** at –78 °C in $CH_2Cl_2$ for ~ 5 min then $Et_3N$ addition led to diazo-ketones **334a** and **334b** (58% and 61%, respectively) (**Scheme 110**).




**332a** ([Si] = TBS)
**332b** ([Si] = TMS)

**334a** ([Si] = TBS), 58%
**334b** ([Si] = TMS), 61%

**Scheme 110** Ozonolysis of silyl-ethers **332a** and **332b**.

The results above demonstrated that the new strategy is successful in the synthesis of α-diazo-ε-ketoesters, based on chemoselective ozonolysis of unsaturated α-diazoesters.

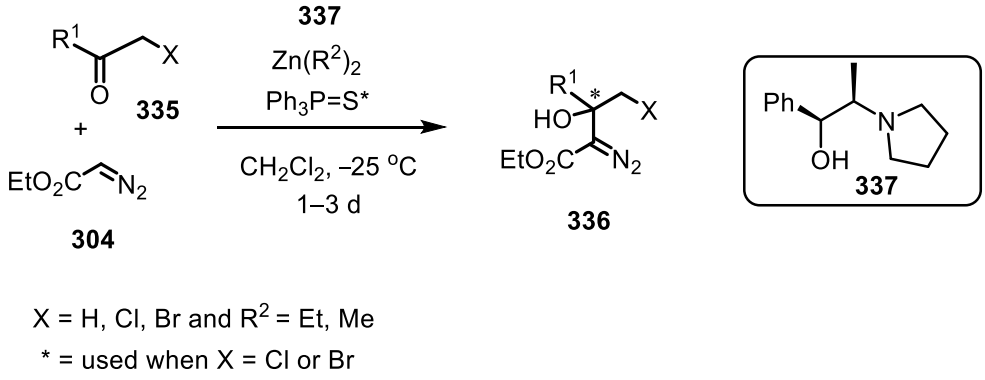
## 6.2 Catalytic Asymmetric Studies Towards the Key Intermediate β-Silyloxy(Ester) α-Diazoester

Having established the validity of the ozonolysis route, we sought to develop conditions for the catalytic enantioselective addition of diazoacetate **293** to ketone **299** (**Scheme 96**, p. 115).

### 6.2.1 Asymmetric Aldol Reactions

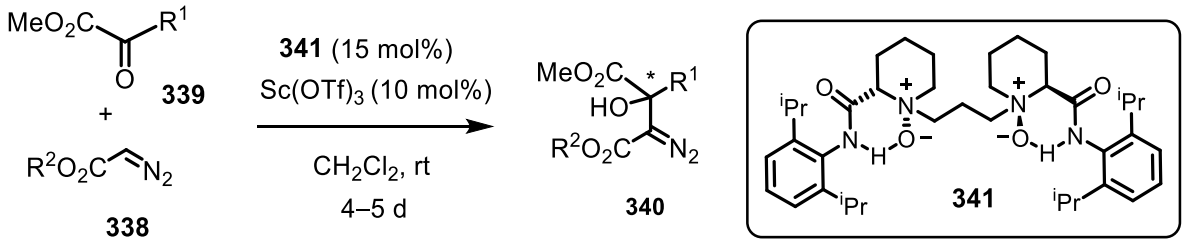
Catalytic asymmetric aldol-type reactions between diazoacetates and ketones or aldehydes remain challenging tasks in organic synthesis. It might be due to the closer p*K*a values of diazoacetates (α-proton to ester) to ketones and aldehydes, which makes them less reactive substrates in asymmetric aldol reactions. In 2009, Cozzi and co-workers reported the enantioselective addition of ethyl diazoacetate **304** to aromatic ketones in the presence of dimethyl or diethyl zinc (to generate a zinc enolate) and amino alcohol ligand **337** (norephedrine–derived) in poor to good yields (20–77%), with ees up to 87% (**Scheme 111**).

Also, when aliphatic ketones ($R^1$ = *i*-Pr or cyclohexyl, X = H) were used, desired products were formed (in 25% and 54% yields, respectively; 74% ee for both substrates).[178]




**Scheme 111** Addition of diazoacetate **304** to ketones by Cozzi and co-workers.[178]

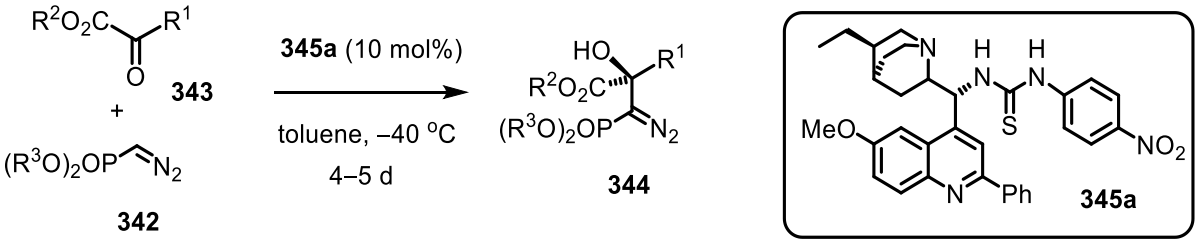
At the same time as Cozzi's report, Feng and co-workers disclosed an asymmetric direct aldol reaction between aromatic and heteroaromatic α-ketoesters and diazoacetate esters ($R^2$ = Me or Et), promoted by an *N*,*N*-dioxide-Sc(III) complex [from $Sc(OTf)_3$ and **341**, (**Scheme 112**)] in good yields and enantioselectivities (52–97%).[179] However, when aliphatic α-ketoesters (such as **339**, $R^1$ = methyl) were used, very poor enantioselectivity (up to 13%) was obtained.




**Scheme 112** Asymmetric aldol-reaction by Feng and co-workers.[179]

Recently, Peng and co-workers have shown that α-diazo-β-hydroxyphosphonate derivatives **344** can be prepared in high yields (41–99%) and enantioselectivities (66–96%) from the

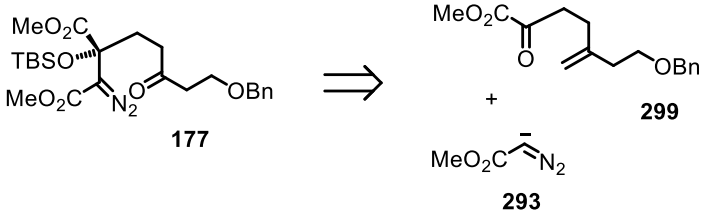
reaction of diazomethylphosphonates **342** with α-ketoesters **343** (with importantly for our studies, aliphatic substrates) in the presence of a hydroquinidine–derived bifunctional thiourea catalyst **345a** (**Scheme 113**).[180] The use of a bulky ester group in α-ketoesters **343** is important; as when $R^2$ replaced from tert-butyl to ethyl group ($R^1$ = Ph and $R^3$ = Me), the enantioselectivity dropped from 94 to 66%.




**Scheme 113** Asymmetric addition of diazomethylphosphonates **342** to α–ketoesters.

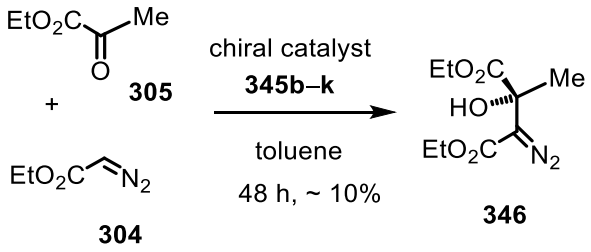
## 6.2.2 Asymmetric Studies on a Model System

Inspired by the above reports, our goal was to obtain enantioenriched diazo compound **177**[57] by enantioselective addition of methyl diazoacetate (**293**) to a challenging enolisable ketoester **299** (**Scheme 114**). Subsequent silylation and alkene-ozonolysis (as studied in the earlier section, p. 124–125) would give a formal synthesis of DDSQ **2**.[57]




**Scheme 114** Proposed route to achieve a formal synthesis of DDSQ **2**.

As a model system, we initially tested the reaction of ethyl diazoacetate (**304**) and ethyl pyruvate (**305**) (both more readily available than the substrates in **Scheme 114**) under Peng's catalytic system using a range of chiral hydrogen-bond donors (**Scheme 115** and **Figure 10**). The catalysts (**345b-j**) were obtained from the Dixon group in Oxford and **345k** was obtained from Sigma-Aldrich.




**Scheme 115** Attempts for enantioselective addition of diazoacetate **304** to pyruvate **305**.

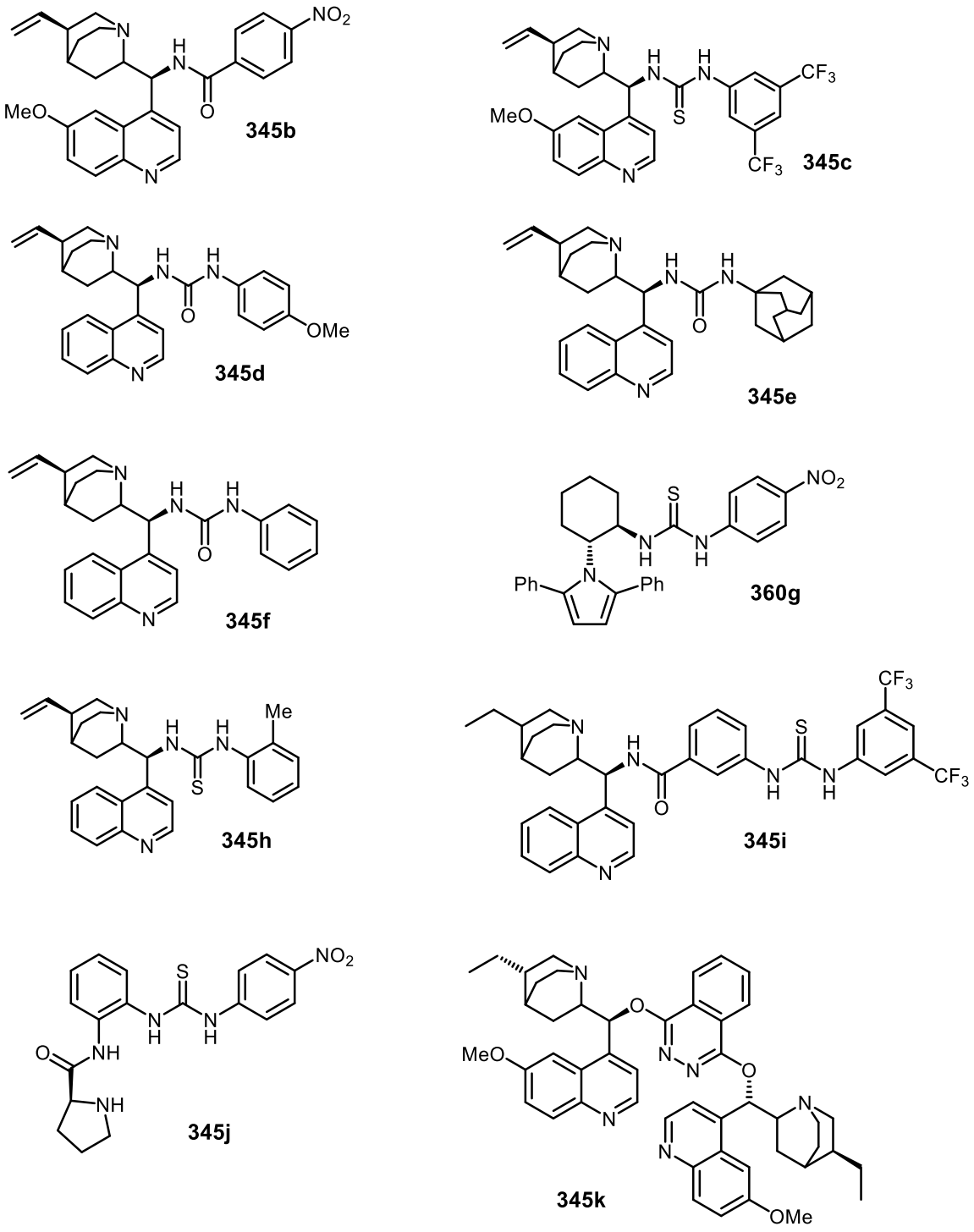


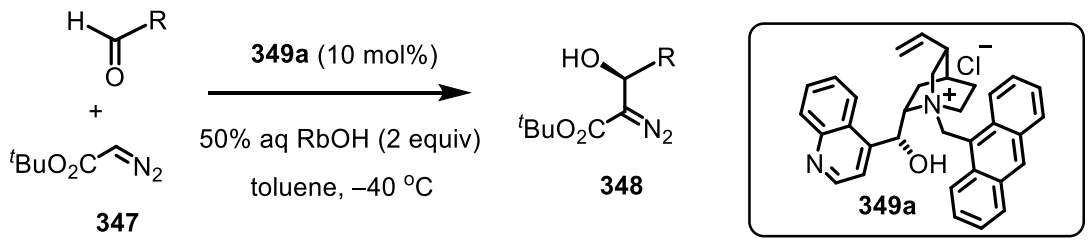

**Figure 10** Chiral catalysts examined.

The use of **345b,d,e,f** and **j** returned starting materials back. **345c,h** and **i** showed traces of product, while **345g** and **k** gave a low yield of the desired β-hydroxy-α-diazoester **346** after flash chromatography (13% and 4%, respectively). Thiourea-derived potential catalysts

(**345c,g,h,i**) were found to be more effective than others in terms of the yield, which could be due to the strong H-bond donor and interaction with the substrate of thioureas.[180] However, HPLC analyses of **346** (**Scheme 115**) using a chiral IC column showed essentially racemic material (with in some cases, ees of ~2–3%).

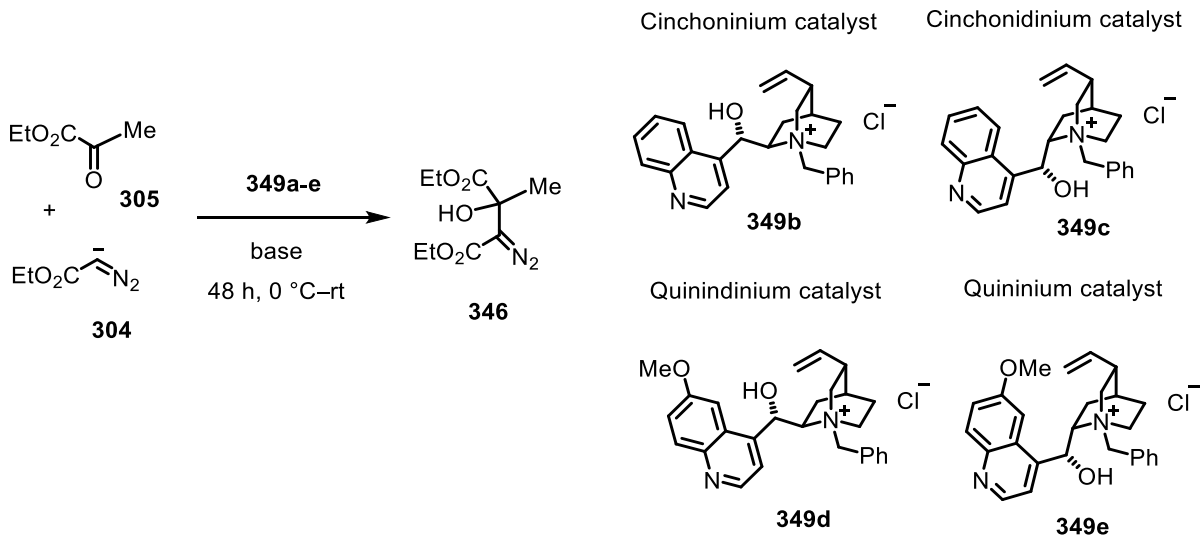
Following the above observations, the reaction was performed at a series of different concentrations (1 M and 1.8 M), temperatures (– 40 °C, –10 °C and rt) and catalyst loadings (10%, 20% and 30%) without success. We noted that a significant racemic background reaction occurred in the absence of catalyst at room temperature (16%) (in toluene for 48 h), hence high temperatures were not screened. In Peng's catalytic system (**Scheme 113**), the phosphonate group in the diazomethylphosphonate species appeared to be important. However, Peng's proposed transition-state model oriented the phosphonate group away from the catalyst. Presumably, the phosphonate group enhances the coordination ability of the substrate. Therefore, Peng's conditions were not investigated any further.

Next, we sought to establish whether we could react ethyl diazoacetate (**304**) with ketoester (**305**) under asymmetric phase–transfer (APT) conditions.[181] Nishida and co-workers have reported condensation of aldehydes with diazoacetate **347** can be carried out under APT conditions using quaternary ammonium salts such as **349a** (**Scheme 116**);[182,183] for aliphatic aldehydes, ees were 22–42%.




**Scheme 116** Condensation of aldehydes with diazoacetate **347** *via* APT.

To test the viability of this methodology in our model system, ethyl diazoacetate **304** was reacted with ethyl pyruvate **305** in the presence of 10% TBAB and aq. KOH (50%) as a base in toluene starting at 0 $^{o}$C before warming to rt. The reaction was monitored by TLC over 48 h, but there were no signs of the desired product **346** (**Scheme 117**); instead, several polar products had formed, and were not separated. These were presumably formed from ester hydrolysis by the aqueous base. Repeating the reaction but with dry KOH, gave 27% yield. Asymmetric phase–transfer catalysts were tested (**Scheme 117**), but these gave trace amounts of the desired alcohol **346**, for which selectivity was not measured. Testing the influence of different parameters, such as solvent ($CH_2Cl_2$, $Et_2O$, and THF), base (NaO*t*-Bu, $Cs_2CO_3$ and $Na_3PO_4$), and stirring speed[184] (900 and 1250 rpm), all failed to improve the low yield. This might be due to the instability of the product under the basic reaction conditions (retro-aldol reaction could occur under basic conditions).[160]



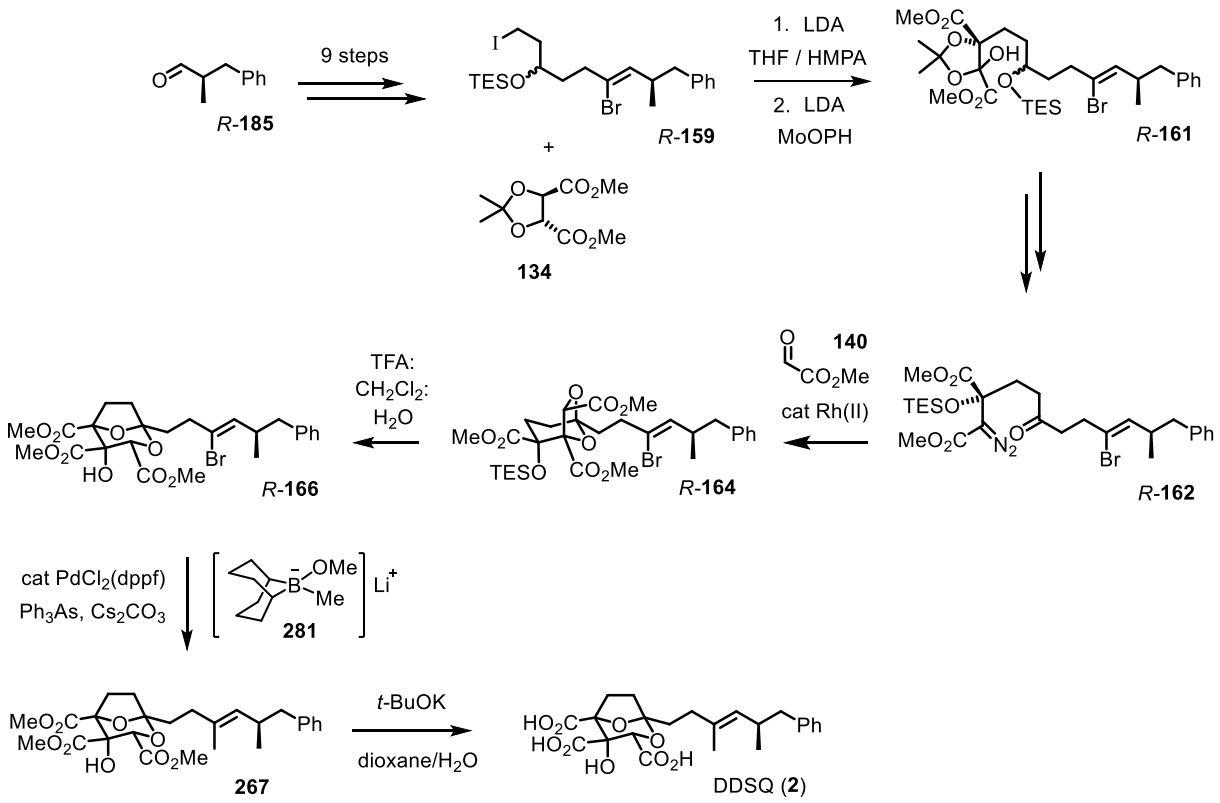

**Scheme 117** Aldol-type reaction between **304** and **305** was examined under APT conditions.

# Chapter 7

# Conclusions

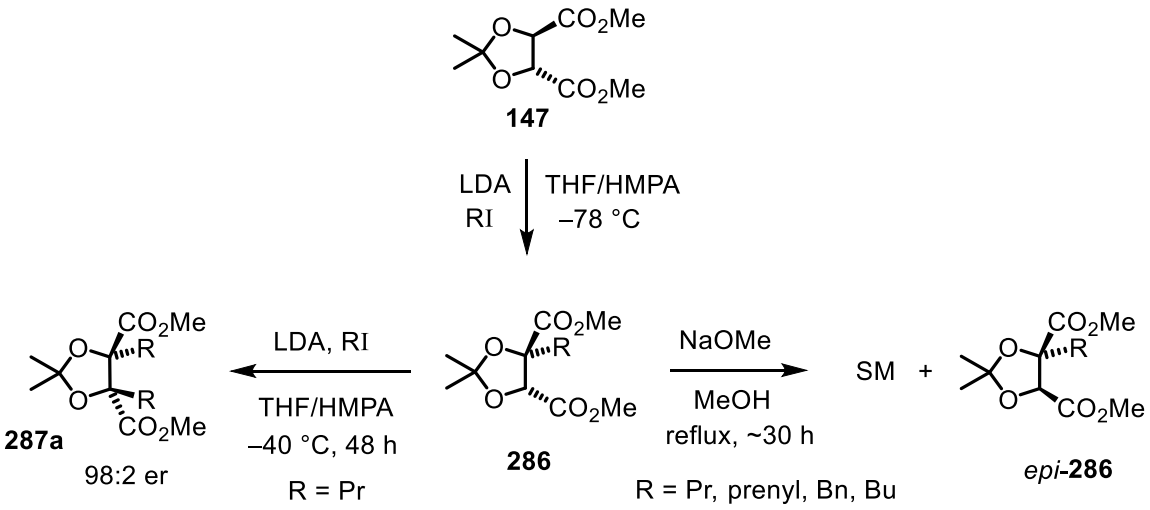
# 7. Conclusions

A total synthesis of DDSQ was achieved *via* an alkene-protection strategy and a well-developed carbonyl ylide [3+2] cycloaddition to construct the cycloadduct (*R*-**162**→*R*-**164**, **Scheme 118)**, the precursor to the squalestatin core. This synthetic strategy shares some of the key transformations from a previous total synthesis reported by Fegheh-Hassanpour; alkylation and rearrangement. However, the alkene-protecting strategy has avoided some issues found in the former synthesis: recovery of unreacted valuable side-chain in the alkylation process; also in our substrate rearrangement (*R*-**164**→*R*-**166**, **Scheme 118**), the rearranged core *R*-**166** is favoured. Pleasingly, and as demonstrated by Al-Mamari, the alkenyl bromide functionality survives several synthetic steps, crucially being presented in the acid-induced rearrangement of cycloadduct *R*-**164** to the desired 2,8–dioxabicyclic core *R*-**166**. Finally, the natural product DDSQ was obtained by removing the bromide substituent through stereoselective methylation of alkenyl bromide *R*-**166** with methyl borinate ester **281**, which occurs in the presence of esters and hydroxyl functionalities, followed by global ester hydrolysis. The bromide-protecting strategy for an alkene should find application in other synthetic endeavours.



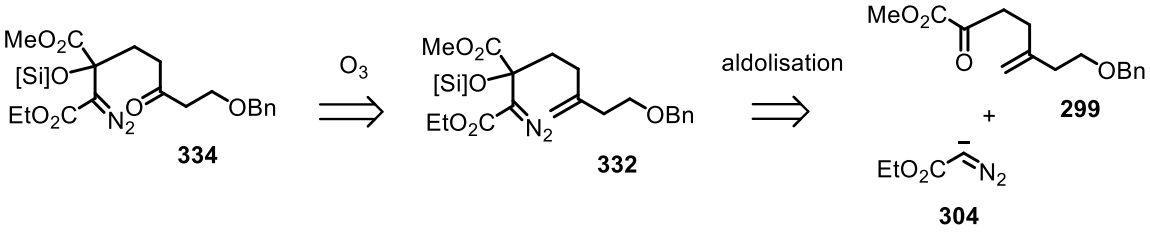

**Scheme 118** Overview of the total synthesis of DDSQ.[147]

Further studies on Seebach's alkylation of dimethyl tartrate **147** were carried out to investigate the origin behind the formation of dialkylated by-products during the alkylation process. These studies identified conditions to obtain enantioenriched dialkylated products. Epimerisation conditions were also established, to access *R,S*-monoalkylated products in 54–67% isolated yields (**Scheme 119**).




**Scheme 119** Dialkylation and epimerisation of mono alkylated dimethyl tartrate **286**.[199]

Additionally, a more concise approach to Fegheh-Hassanpour's cycloaddition precursor (**177**; **Scheme 24,** p. 46) was accomplished, using a close ($CO_2Et$ instead of $CO_2Me$) and racemic model system. The chemistry involved aldol reaction between a diazoacetate anion **304** and an unsaturated α-ketoester **299**, followed by chemoselective alkene ozonolysis of the resulting unsaturated diazoester **332** as a key step (**Scheme 120**). This route investigated the impact of a disubstituted alkene on intramolecular diazo-alkene cycloaddition; and the β-steric effect on the reactivity of an α-diazoester moiety towards ozone.




**Scheme 120** A new approach to DDSQ **2**.[200]

Efforts to develop conditions for the catalytic enantioselective addition of diazoacetate **304** to ketone **299** have, so far, been unsuccessful.

# Chapter 8

# Experimental

## 8.1 General Techniques

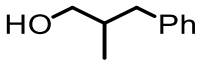
All reactions requiring anhydrous conditions were carried out in flame–dried glassware under an atmosphere of nitrogen (or argon), the later having been passed through a column of calcium chloride and silica gel. THF, $CH_2Cl_2$, toluene and DMF were obtained from Grubbs' drying stills.[185] Methanol was dried over activated 4 Å MS under argon. Diisopropylamine, triethylamine and 2,6-lutidine were distilled under nitrogen from $CaH_2$. *n*-BuLi in hexanes was titrated by adding a solution of 2-propanol (1.0 M in toluene with 0.2% of 1,10–phenanthroline) slowly to a solution of *n*-BuLi in toluene until the end-point: a change of colour from clear to red then yellow. MeLi in ether was titrated by adding slowly MeLi to a solution of *N*-benzylbenzamide (100 mg in 5 mL THF) at –20 °C; the end-point was marked by a colour change from clear to blue. LiCl was dried in a vacuum oven (~110 °C) for 24 h prior to use. Commercial starting materials were used without further purification, unless otherwise stated. Petrol (petroleum ether) 40–60 °C was used in flash column chromatography, which was carried out using silica gel (VWR chemicals, BDH), and monitored by TLC (Merck 60 F254) plates. TLC plates were viewed using ultraviolet light (λmax = 254/365 nm) and by immersion in $KMnO_4$ or anisaldehyde stains, followed by heating. HPLC was performed on a Dionex UltiMate 3000 (for **286**) and Shimadzu Prominence-i LC-2030 (for **287**). Infrared spectra were obtained using a PerkinElmer FT–IR spectrometer (Universal ATR Sampling Accessory) with absorption maxima quoted in wavenumbers ($cm^{-1}$). Peaks are described as broad (br), weak (w), medium (m) and strong (s). Nuclear magnetic resonance ($^1H$ NMR, $^{13}C$ NMR and $^{19}F$ NMR) spectra were recorded on Bruker Avance UltraShield AVC 500, AVX 500 and AVF 400, in $CDCl_3$ and $CD_3OD$, referenced to solvent peaks. Chemical shifts are quoted in parts per million (ppm). The splittings are quoted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), triplet of triplets (tt), doublet of doublet of doublets (ddd), doublet of quartets (dq), multiplet (m) and pseudo (p). Proton coupling constants (*J*) are

reported to the nearest 0.5 Hz. $[\alpha]_D^{25}$ = values are given in $10^{-1}$ deg $cm^2$ $g^{-1}$. Concentrations (c) are given in $g/cm^3$. The $^{13}C$ signal of $CN_2$ was often not observed due to quadrupolar relaxation. Low resolution mass spectra were obtained using electrospray ionisation (ESI). High-resolution mass spectra were obtained by electrospray ionisation, using a Thermo Fisher Orbitrap Exactive mass spectrometer. IR, optical rotation, and HRMS data for the previously prepared DDSQ compounds were taken by Al-Mamari.[53]

## 8.2 Experimental Procedures

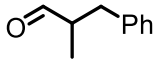
### 8.2.1 Early Model Studies Towards the Side-Chain

**2-Methyl-3-phenylpropan-1-ol (213)**




To a suspension of $LiAlH_4$ (4.0 g, 107 mmol) in THF (150 mL) at 0 °C was added dropwise α-methyl cinnamaldehyde **212** (10 mL, 71.6 mmol). After 30 min, the reaction mixture was warmed to rt and then allowed to stir at 50 °C for 12 h. The reaction mixture was then quenched with sat. aq. $NH_4Cl$ (150 mL), filtered, extracted with EtOAc (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (30% EtOAc in petrol) to give alcohol **213**[60] (10.4 g, 97%), as a colourless oil; $R_f$ = 0.51 (5% EtOAc in petrol); $^1H$ NMR (200 MHz; $CDCl_3$) δ 7.40–7.14 (5H, m, ArH), 3.62–3.42 (2H, m, C*H*$_2$OH), 2.77 (1H, dd, *J* = 13 and 6, CH*H*Ph), 2.43 (1H, dd, *J* = 13 and 8, C*H*HPh), 1.91–2.01 (1H, m, C*H*$CH_3$), 0.93 (3H, d, *J* = 7, $CH_3$); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 140.7 (Ar*C*), 129.6 (Ar*C*H) 128.7 (Ar*C*H), 126.3 (Ar*C*H), 68.1 ($CH_2OH$), 40.2 (*C*$H_2$Ph), 38.3 (*C*H$CH_3$), 16.9 ($CH_3$).

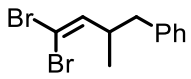
**2-Methyl-3-phenylpropanal (185)**




**Method A**, DMSO (12 ml, 173 mmol) was added dropwise to oxalyl chloride (7.6 ml, 87 mmol) in $CH_2Cl_2$ (90 mL) at –78 °C and the resulting mixture was stirred for 5 min. Alcohol **213** (10.3 g, 69.0 mmol) was then added to the reaction mixture at –78 °C. After 2 h, $Et_3N$ (50 mL, 359 mmol) was added and the mixture was stirred for an additional 1 h. The reaction mixture was warmed to rt, then water (100 mL) was added, extracted with $CH_2Cl_2$ (3 × 150 mL). The combined organic layers were washed with 1% HCl (2 × 150 mL), then with $H_2O$ (2 × 200 mL) and dried ($MgSO_4$). Evaporation under reduced pressure gave aldehyde **185**[60] (9.6 g, 94%), as a yellow liquid; $R_f$ = 0.51 (5% EtOAc in petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 9.74 (1H, s, C*H*O), 7.37–7.14 (5H, m, ArH), 3.17–3.02 (1H, m, C*H*$CH_3$), 2.85–2.60 (2H, m, C*H*$_2$Ph), 1.10 (3H, d, *J* = 7.0, $CH_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 204.3 (CHO), 138.8 (Ar*C*), 129.6 (Ar*C*H), 128.8 (Ar*C*H), 126.4 (Ar*C*H), 48.0 ($CH_2$), 36.6 (*C*H$CH_3$), 13.2 ($CH_3$).

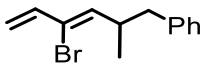
**Method B**, to a suspension of PCC (21.5 g, 99.8 mmol) in $CH_2Cl_2$ (150 mL) with 3 Å MS (40 g) was added alcohol **213** (10.0 g, 66.5 mmol) in $CH_2Cl_2$ (150 mL). The reaction mixture was stirred for 2 h, then $Et_2O$ (300 mL) was added and supernatant was decanted from the black slurry. The insoluble residue was washed with $Et_2O$ (3 × 40 mL). The combined organic layers were passed through a short pad of Florisil® and evaporated under reduced pressure. Purification of the residue by column chromatography (5% EtOAc in petrol) gave aldehyde **185** (8.8 g, 90%), as a colourless oil. Data as above.

**(4,4-Dibromo-2-methylbut-3-en-1-yl)benzene (206)**




To a solution of $CBr_4$ (37 g, 331 mmol) in $CH_2Cl_2$ (90 mL) at 0 °C was added a solution of $PPh_3$ (58.7 g, 262 mmol) in $CH_2Cl_2$ (90 mL) dropwise over 30 min. The mixture was stirred at 0 °C for 10 min, before a solution of aldehyde **185** (8.3 g, 148 mmol) in $CH_2Cl_2$ (112 mL) was added over 10 min. After 1 h at 0 °C, water (150 mL) was added and the aq. layer extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. To the residue was added $CH_2Cl_2$ (20 mL) and silica gel (50 g) and the resulting suspension was filtered (to remove triphenylphosphine oxide). The combined filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (petrol) gave dibromoalkene **206**[186] (14.7 g, 86%), as a colourless oil; $R_f$ = 0.51 (Petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.40–7.10 (5H, m, ArH), 6.26 (1H, d, *J* = 9, C*H*$CBr_2$), 2.85–2.67 (2H, m, C$H_2$Ph), 2.64–2.48 (1H, m, C*H*$CH_3$), 1.02 (3H, d, *J* = 6.5, $CH_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 143.4 (*C*H=C), 139.2 (Ar*C*), 129.3 (Ar*C*H) 128.4 (Ar*C*H), 126.4 (Ar*C*H), 88.2 (*C*$Br_2$), 42.0 (*C*$H_2$Ph), 40.1 (*C*H$CH_3$), 18.6 ($CH_3$).

**(*Z*)-(4-Bromo-2-methylhexa-3,5-dien-1-yl)benzene (208)**




To a suspension of vinylzinc chloride [prepared freshly by adding vinylmagnesium bromide (2 ml, 1.0 M in THF, 1.97 mmol) to a solution of dry $ZnCl_2$ (1.6 ml, 1.0 M in $Et_2O$, 1.64 mmol) dropwise at 0 °C, then allowing the resulting suspension to warm to rt over 25 min] was added dropwise (*via* cannula) a solution of dibromoalkene **206** (500 mg, 1.64 mmol) and $Pd(PPh_3)_4$

(90 mg, 0.08 mmol) in THF (3 mL) at rt. After 3 h at 45 °C, the reaction mixture was quenched with sat. aq. $NH_4Cl$ (5 ml), filtered and extracted with $Et_2O$ (15 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (petrol) to give bromodiene **208**[186] (340 mg, 82%); as a colourless oil, $R_f$ = 0.46 (petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.33–7.17 (5H, m, ArH), 6.29 (1H, ddd, *J* = 16, 10.5 and 1, C*H*=$CH_2$), 5.85 (1H, d, *J* = 9, C*H*=CBr), 5.54 (1H, d, *J* = 16, CH=CH*H*), 5.18 (1H, d, *J* = 10, CH=C*H*H), 3.15–3.03 (1H, m, C*H*$CH_3$), 2.79 (1H, dd, *J* = 13.5 and 6, C*H*HPh), 2.58 (1H, dd, *J* = 13.5 and 8, CH*H*Ph), 1.03 (3H, d, *J* = 7, $CH_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 139.9 (*C*H=CBr), 139.8 (Ar*C*), 135.9 (*C*H=$CH_2$), 129.4 (Ar*C*H), 128.3 (Ar*C*H), 126.2 (Ar*C*H), 124.9 (CH=*C*Br), 117.7 (CH=*C*$H_2$), 42.4 (*C*$H_2$Ph), 38.0 (*C*H$CH_3$), 19.0 ($CH_3$).

**General Boron-Zinc exchange procedure**

Preparation of $Et_2BH$: $Et_2BH$ was prepared by mixing $Et_3B$ (1.4 ml, 1.0 M in THF, 1.4 mmol) and $BH_3.Me_2S$ complex (0.33 ml, 2.0 M in ether, 0.66 mmol) at 0 °C. The reaction mixture was used after 10–30 min of stirring.

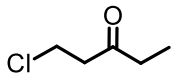
Hydroboration: A 25 ml Schlenk-flask was charged with bromodiene **208** (0.5 g, 2 mmol) and cooled to 0 °C, then $Et_2BH$ was added over 15 min. The reaction mixture was allowed to warm to rt. After 3 h at rt, the solvents were removed under vacuum (0.9 mbar, 0 °C, 0.5 h).

Boron-Zinc Transmetalation: The organoborane was diluted with THF (1 ml) and $Et_2Zn$ (4 ml, 1.0 M in hexanes, 4 mmol) was then added at 0 °C. After 0.5 h at 0 °C, excess $Et_2Zn$ and formed $Et_3B$ were removed under reduced pressure (0.9 mbar, 0 °C, 3 h).

Addition of Electrophile: The organozinc was diluted with THF (2 ml) and cooled to –78 °C. CuCN·2LiCl [prepared from CuCN (161 mg, 1.8 mmol) and dry LiCl (178 mg, 4.2 mmol)] was added and the reaction mixture stirred for 15 min, then warmed to rt for ~5 min and cooled back to –78 °C. 3-Chloropropionyl chloride (**210**) (254 mg, 2 mmol) was added dropwise, and

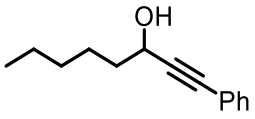
the reaction mixture stirred for 30 min at –78 °C. After 18 h at –10 °C, sat. aq. $NH_4Cl$ (10 ml) was added, diluted with $Et_2O$ (15 ml) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and evaporated under reduce pressure.

**1-Chloropentan-3-one (218)**



To a suspension of $AlCl_3$ (0.5 g, 4 mmol) in $CH_2Cl_2$ (3 mL) at –50 °C was added a solution of 3-chloropropionyl chloride **210** (0.4 mL, 4 mmol) in $CH_2Cl_2$ (1 mL) over 15 min. After 1 h, the mixture was warmed to –30 °C. Then, a solution of $Et_2Zn$ (2 ml, 1.0 M in THF, 2 mmol) in $CH_2Cl_2$ (2 mL) was added over 30–60 min. After 2h, water (3 mL) was added at 0 °C. The aq. layer was extracted with $Et_2O$ (3 x 5 mL). The combined organic layers were washed with 5% aq. $NaHCO_3$ (5 mL), water (5 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (10% EtOAc in petrol) gave ketone **218**[187] (131 mg, 54%), as a brown liquid; $R_f$ = 0.5 (10% EtOAc in petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 3.71 (2H, t, *J* = 6.5, $ClCH_2CH_2$), 2.86 (2H, t, *J* = 6.5, $ClCH_2CH_2$), 2.45 (2H, q, *J* = 7, $OCH_2CH_3$), 1.36 (3H, t, *J* = 7, $CH_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 208.1 (C=O), 44.6 ($ClCH_2CH_2$), 38.5 ($ClCH_2CH_2$), 36.6 ($COCH_2CH_3$), 7.6 ($CH_3$).

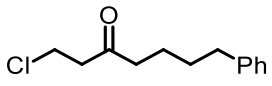
**1-Phenyloct-1-yn-3-ol (231)**



To a solution of 1-phenyl-2-trimethylsilyl acetylene **227** (300 µL, 1.51 mmol) and hexanal (0.16 mL, 1.32 mmol) in THF (2 mL) at 0 °C was added TBAF (100 µL, 1 M in THF, 0.1 mmol). After 3 h, aq. HCl (1.0 mL, 1 M) was added, with further stirring for 15 min at rt. The

reaction mixture was neutralised with aq. $NaHCO_3$ (~ 2 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (10% EtOAc in petrol) to give propargylic alcohol **231**[188] (100 mg, 60%), as a pale yellow liquid; $R_f$ = 0.32 (10% EtOAc in petrol); $^1$H NMR (200 MHz) δ 7.49–7.21 (5H, m, ArH), 4.61 (1H, q, *J* = 6, C*H*OH), 1.90–1.74 (3H, m, CH*H*C*H*$_2$CHOH), 1.55–1.47 (1H, m, C*H*H), 1.42–1.28 (4H, m, $CH_2CH_2$), 0.92 (3H, t, *J* = 7, $CH_3$); $^{13}$C(100 MHz) δ 131.8 (ArC), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 122.8 (Ar*C*H), 90.4 (C(OH)*C*≡C), 84.8 (C(OH)C≡*C*), 63.0 (CHOH), 37.9 ($CH_2$), 31.6 ($CH_2$), 25.0 ($CH_2$), 22.7 ($CH_2$), 14.1 ($CH_3$).

**1-Chloro-7-phenylheptan-3-one (239)**

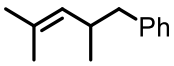



A solution of 4-phenyl-1-butene **214 (**113 μL, 0.75 mmol) in THF (3 mL) was reacted with $Cp_2Zr(H)Cl$ **(**232 mg, 0.9 mmol) at rt and then heated at 35 ℃ for 30 min. The reaction mixture was then cooled to rt, followed by adding 3–chloropropionyl chloride (**210**) (86 μL, 0.9 mmol) and copper(I) bromide dimethylsulfide complex (13 mg, 0.08 mmol). After 1.5 h, $Et_2O$ (10 mL) was added and extracted with sat. aq. $NaHCO_3$ (10 mL). The aq. layer was extracted with $Et_2O$ (2 × 10 mL), dried ($Na_2SO_4$), filtered through short pad of silica gel and concentrated under reduced pressure. Purification of the residue by column chromatography afforded ketone **239** (68 mg, 40%), as a colourless oil; $R_f$ = 0.4 (5% EtOAc in petrol); $\nu_{max}$/cm$^{-1}$ (film) 3084 w, 3026 w, 2934 s, 2858 s, 1714 s, 1603 m, 1495 m, 1453 s, 1406 m, 1371 s, 1296 m, 1176 m, 1097 s, 1078 s, 1030s , 746 s, 699 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.32–7.26 (2H, m, ArH), 7.21–7.16 (3H, m, ArH), 3.73 (2H, t, *J* = 6.5, $CH_2Cl$), 2.86 (2H, t, *J* = 6.5, C*H*$_2$$CH_2Cl$), 2.63 (2H, t, *J* = 7, C*H*$_2$Ph), 2.46 (2H, t, *J* = 6.5, C*H*$_2$$COCH_2CH_2Cl$), 1.68–1.63 (4H, m,

$CH_2CH_2CH_2CH_2$); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 207.5 (CO), 142.2 (Ar*C*), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 125.9 (Ar*C*H), 45.0 ($COCH_2CH_2Cl$), 43.3 ($CH_2COCH_2CH_2Cl$), 38.5 ($CH_2Cl$), 35.8 ($CH_2Ph$), 31.0 ($CH_2$), 23.2 ($CH_2$); HRMS *m/z* ($M^+$): found 225.1043, $C_{13}H_{18}OCl$ requires 225.1040.

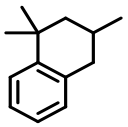
## 8.2.2 Model Studies and Methylation Cross–Coupling Optimisation

### 2,4-Dimethyl-5-phenyl-2-pentene (187)



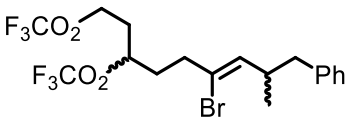

*n*-BuLi (1.3 mL, 2.5 M in hexanes, 3.3 mmol) was added dropwise to a solution of isopropyltriphenylphosphonium iodide **186** (1.6 g, 3.7 mmol) in THF (8 mL) at –78 °C. The mixture was warmed to rt, stirred for 30 min, then the dark red solution was re-cooled to –78 °C and a solution of aldehyde **185** (0.25 g, 1.69 mmol) in THF (4 mL) was added dropwise. After stirring at rt for 4 h, the mixture was quenched with water (30 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (20% $Et_2O$ in petrol) gave alkene **187**[189] (175 mg, 60%), as a colourless liquid; $R_f$ = 0.71 (20% $Et_2O$ in petrol). $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.30–7.13 (5H, m, ArH), 4.99 (1H, dquint, *J* = 9, 1.5, C*H*=$C(CH_3)_2$), 2.69–2.48 (3H, m, $CHCH_2Ph$), 1.67 (3H, d, *J* = 1.5, one $CH_3$ of =$C(CH_3)_2$), 1.46 (3H, d, *J* = 1.5, second $CH_3$ of =$C(CH_3)_2$), 0.95 (3H, d, *J* = 6.5, $CHCH_3$); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 141.4 (Ar*C*), 130.6 (C=*C*H), 130.5 (*C*=CH), 129.4 (Ar*C*H) 128.1 (Ar*C*H), 125.7 (Ar*C*H), 44.2 ($CH_2Ph$), 34.8 ($CHCH_3$), 25.9 ($CH_3$), 20.9 ($CHCH_3$), 17.9 ($CH_3$).

**1,1,3-Trimethyl-1,2,3,4-tetrahydronaphthalene (188)**



To a solution of alkene **187** (100 mg, 0.57 mmol) in $CH_2Cl_2$ (4.2 mL) was added TFA (2.1 mL) and $H_2O$ (210 μL). The reaction mixture was heated at 40 °C for 48 h, then cooled to rt, sat. aq. $NaHCO_3$ (5 mL) added and extracted with $Et_2O$ (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($K_2CO_3$) and evaporated under reduced pressure to give tetralin **188**[190,191] (94 mg, 95%) as a colourless liquid; $R_f$ = 0.71 (0.5% $Et_2O$ in petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 7.33 (1H, d, *J* = 7.5, ArH), 7.19–7.02 (3H, m, ArH), 2.84–2.74 (1H, m, CH*H*Ar), 2.44–2.34 (1H, m, C*H*HAr), 2.04–1.91 (1H, m, C*H*$CH_3$), 1.67–1.59 (1H, m, $C(CH_3)_2CH$*H*), 1.42–1.32 (4H, m, $C(CH_3)_2CH$*H* and $CH_3$), 1.25 (3H, s, $CH_3$), 1.05 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 145.6 (Ar*C*), 136.3 (Ar*C*), 129.0 (Ar*C*H) 126.7 (Ar*C*H), 126.0 (Ar*C*H), 125.4 (Ar*C*H), 48.5 ($C(CH_3)_2CH_2$), 39.9 (*C*$H_2$Ar), 35.1 (*C*$(CH_3)_2$), 32.9 ($CH_3$), 31.9 ($CH_3$), 25.9 (*C*H$CH_3$), 22.6 (CH*C*$H_3$).

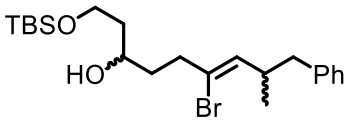
**(*Z*)-6-Bromo-8-methyl-9-phenylnon-6-ene-1,3-diyl bis(2,2,2-trifluoroacetate) (248)**




To a solution of 1,3-diol **203** (100 mg, 0.30 mmol) in $CH_2Cl_2$ (2.20 mL) were added TFA (1.10 mL) and $H_2O$ (110 μL). The reaction mixture was heated at 40 °C for 48 h. The mixture was then concentrated under reduced pressure to give bistrifluoroacetate **248** (156 mg, quant), as a yellow oil, a 1:1 diastereomeric mixture; $R_f$ = 0.35 (4% EtOAc in petrol); $\nu_{max}$/cm$^{-1}$(film) 3027

w, 1784 s, 1454 w, 1220 s, 1148 s, 775 m, 731 m, 700 m; $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.30–7.14 (5H, m, ArH), 5.54–5.49 (1H, m, CH=CBr), 5.15–5.04 (1H, m, $CHOCOCF_3$), 4.41–4.33 (2H, m, $CH_2OCOCF_3$), 2.94–2.83 (1H, m, C*H*$CH_3$), 2.71–2.64 (1H, m, CH*H*Ph), 2.59–2.51 (1H, m, C*H*HPh), 2.50–2.40 (2H, m, $CH_2CBr$), 2.12 (2H, q, *J* = 6, $OCH_2CH_2CHO$), 2.01–1.89 (2H, m, C$H_2CH_2CBr$), 0.97 (3H, d, *J* = 6.5, CHC$H_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 157.3 (2 x q, $J_{C\text{-}F}$ = 42, C=O), 140.0 (Ar*C*), 136.2, 136.1 (*C*=CBr), 129.4, 129.3 (Ar*C*H) 128.3, 128.3 (Ar*C*H), 126.2, 126.1 (Ar*C*H), 124.5, 124.4 (C=*C*Br), 114.7 (2 x Q, $J_{C\text{-}F}$ = 286, $CF_3$), 74.9, 74.7 (*C*H$OCOCF_3$), 61.6 (*C*$H_2OCOCF_3$), 42.5 (*C*$H_2$Ph), 38.1, 38.0 (*C*H$CH_3$), 37.0, 36.9 (*C*$H_2CH_2CBr$), 32.5, 32.3, 32.2 ($CH_2CH_2CBr$ and $OCH_2CH_2CHO$), 19.1 ($CHCH_3$); $^{19}$F NMR (377 MHz) δ –75.1; HRMS *m*/*z* ($M+Na^+$) found: 541.0421. $C_{20}H_{21}O_4{}^{79}BrF_6{}^{23}Na$ requires 541.0419.

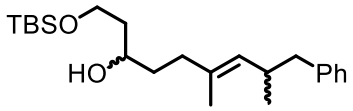
**(*Z*)-6-Bromo-1-((*tert*-butyldimethylsilyl)oxy)-8-methyl-9-phenylnon-6-en-3-ol (249)**




To a solution of 1,3-diol **203** (0.97 mg, 3.05 mmol) and imidazole (477 mg, 7.01 mmol) in DMF (8 mL) at 0 °C was added a solution of TBSCl (480 mg, 3.2 mmol) in DMF (8 mL). The mixture was stirred for 6 h at 0 °C, then water (5 mL) was added, extracted with $Et_2O$ (2 × 10 mL), washed with brine (5 mL), and dried ($Na_2SO_4$). Evaporation under reduced pressure followed by column chromatography (20% $Et_2O$ in petrol) gave TBS ether **249** (1.15 g, 86%), as a colourless oil, a 1:1 diastereomeric mixture; $R_f$ = 0.34 (20% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 3448 br, 2967 m, 2928 m, 2856 m, 1466 m, 1079 s, 885 m, 625 s; $^{1}$H NMR (400 MHz; $CDCl_3$) δ 7.29–7.13 (5H, m, ArH), 5.53 (1H, d, *J* = 8.5, CH=CBr), 3.92–3.85 (1H, m, C*H*OH), 3.83–3.66 (2H, m, $CH_2$OTBS), 3.47 and 3.42 (1H, 2 x s, CHO*H*), 2.95–2.82 (1H, m, C*H*$CH_3$), 2.73–

2.64 (1H, m, CH*H*Ph), 2.61–2.42 (3H, m, C$H_2$ and CH*H*Ph), 1.71–1.56 (4H, m, 2 x $CH_2$), 0.96 (3H, pdd, *J* = 6.5, 4, CHC$H_3$), 0.89 (9H, s, OSiC$Me_3$), 0.08 (6H, s, OSi($CH_3$)$_2$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 140.3, 140.2 (Ar*C*), 134.2, 134.1 (*C*=CBr), 129.4, 129.3 (Ar*C*H) 128.2 (Ar*C*H), 127.2 (C=*C*Br), 126.0 (Ar*C*H) 71.1, 70.9 (*C*HOH), 63.0 (*C*$H_2$OTBS), 42.7, 42.6 (*C*$H_2$Ph), 38.4, 38.3, 38.0, 37.9, 37.8, 37.7, (all $CH_2$), 36.1, 35.9 (*C*HC$H_3$), 26.0 (SiC*Me*$_3$) 19.3, 19.2 (CH*C*$H_3$), 18.2 (Si*C*$Me_3$), -5.4 (OSi($CH_3$)$_2$), -5.4 (OSi($CH_3$)$_2$); HRMS *m*/*z* (M+H$^+$) found: 441.1822. $C_{22}H_{38}O_2{}^{79}Br^{28}Si$ requires 441.1819.

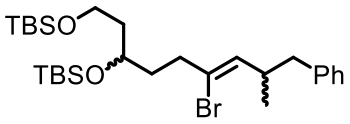
**(*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-6,8-dimethyl-9-phenylnon-6-en-3-ol (250)**




MeLi (112 μL, 1.6 M in $Et_2O$, 0.18 mmol) was added to a solution of *B*-OMe-9BBN (180 μL, 1 M in hexanes, 0.18 mmol) in THF (1 mL). After 10 min, $PdCl_2$(dppf) (11 mg, 10 mol%) and NaOMe (12 mg, 0.22 mmol) were added, followed by a solution of TBS ether **249** (66 mg, 0.15 mmol) in THF (0.5 mL) dropwise. After refluxing for 48 h, the mixture was cooled to rt, added water (1 mL), extracted with $Et_2O$ (2 × 5 mL), washed with brine (2 mL) and dried ($MgSO_4$). Evaporation under reduced pressure followed by column chromatography (5% EtOAc in petrol) gave *E*-alkene **250** (42 mg, 75%), as a colourless oil, a 1:1 diastereomeric mixture; $R_f$ = 0.33 (5% EtOAc in petrol); $\nu_{max}$/cm$^{-1}$(film) 3386 br, 2955 m, 2925 m, 2856 s, 1495 m, 1254 m, 1083 s, 834 s, 776 s, 698 m, 663 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.28–7.10 (5H, m, ArH), 5.00 (1H, d, *J* = 9, C*H*=C$CH_3$), 3.92–3.85 (1H, m, C*H*OH), 3.83–3.69 (2H, m, $CH_2$OTBS), 3.37 and 3.35 (1H, 2 x d, *J* = 2.5, CHO*H*), 2.67–2.56 (1H, m, C*H*C$H_3$), 2.55–2.49 (2H, m, $CH_2$Ph), 2.13–1.91 (2H, m, $CH_2$), 1.67–1.44 (4H, m, 2 x $CH_2$), 1.42 (3H, s, =C$CH_3$), 0.94 (3H, 2 x d, *J* = 6.5, CHC$H_3$), 0.90 (9H, s, OSiC$Me_3$), 0.08 (6H, s, OSi($CH_3$)$_2$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 141.3, 141.3 (Ar*C*), 134.1 (*C*=C$CH_3$), 130.5, 130.5 (C=*C*C$H_3$), 129.4

(Ar*C*H) 128.1, 128.1 (Ar*C*H), 125.7 (Ar*C*H) 72.0, 71.9 (*C*HOH), 63.0 (*C*$H_2$OTBS), 42.1 (*C*$H_2$Ph), 38.4, 38.3, 35.9, 35.8, 35.6, (all $CH_2$), 34.7 (*C*HCH$_3$), 26.0 (SiC*Me*$_3$), 21.0, 20.9 (CH*C*H$_3$), 18.2 (Si*C*Me$_3$), 16.2, 16.2 (=C*C*H$_3$), –5.4 (one $CH_3$ of OSi(CH$_3$)$_2$), –5.4 (another $CH_3$ of OSi(CH$_3$)$_2$). HRMS *m*/*z* (M+H$^+$) found: 377.2876. $C_{23}H_{41}O_2Si$ requires 377.2873.

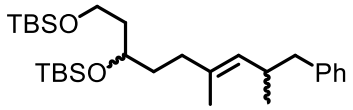
**(*Z*)-5-(3-Bromo-5-methyl-6-phenylhex-3-en-1-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (282)**




To a solution of TBS ether **249** (50.0 mg, 0.11 mmol) in $CH_2Cl_2$ (1.5 mL) at 0 °C was added 2,6-lutidine (40 μL, 0.3 mmol) followed by TBSOTf (47 μL, 0.20 mmol). The mixture was stirred for 2 h at 0 °C, then sat. aq. $NaHCO_3$ (2 mL) added, extracted with EtOAc (2 × 5 mL) and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure. Purification the residue by column chromatography (5% $Et_2O$ in petrol) gave bis-TBS ether **282** (59 mg, 94%) as a colourless oil, a 1:1 diastereomeric mixture; $R_f$ = 0.65 (5% $Et_2O$ in petrol); $\nu_{max}$/cm$^{-1}$(film) 3064 w, 2955 s, 2359 w, 1658 w, 1603 w, 1496 m, 1472 m, 1361 m, 1256 s, 1036 m, 1006 m, 836 s, 775 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.31–7.16 (5H, m, ArH), 5.49 (1H, d, *J* = 8.5, CH=CBr), 3.87–3.79 (1H, m, CHOTBS), 3.71–3.64 (2H, m, $CH_2$OTBS), 2.95–2.84 (1H, m, C*H*CH$_3$), 2.72 (1H, dd, *J* = 13.5 and 6 ,CH*H*Ph), 2.25 (1H, dd, *J* = 13.5 and 8 ,CH*H*Ph), 2.48–1.41 (2H, m, $CH_2$CBr), 1.76–1.59 (4H, m, C*H*$_2$CH(OTBS)C*H*$_2$), 0.97 (3H, d, *J* = 6.5, CHC*H*$_3$), 0.91 (18H, s, 2 x OSiCMe$_3$), 0.06 (12H, s, 2 x OSi(CH$_3$)$_2$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 140.2 (Ar*C*), 133.7, (*C*=CBr), 129.4 (Ar*C*H) 128.3 (Ar*C*H), 127.7, 127.6 (C=*C*Br), 126.1 (Ar*C*H) 68.5 (*C*HOTBS), 60.0 (*C*$H_2$OTBS), 42.7 (*C*$H_2$Ph), 40.1, 38.0 (2 x $CH_2$), 37.5, 37.5 (*C*HCH$_3$), 26.3, 36.2 ($CH_2$), 26.1, 26.1 (SiC*Me*$_3$), 19.2 (CHCH$_3$), 18.4, 18.3

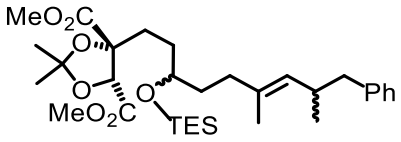
(Si*C*Me$_3$), –4.3, –4.4 (one CH$_3$ of OSi(CH$_3$)$_2$), –5.1, –4.4 (another CH$_3$ of OSi(CH$_3$)$_2$); HRMS *m*/*z* (M+H$^+$) found: 555.2672. $C_{28}H_{52}{}^{79}BrO_2{}^{28}Si_2$ requires 555.2684.

**(*E*)-5-(3,5-Dimethyl-6-phenylhex-3-en-1-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (283)**




Following the procedure to **250** above, but using bis-TBS ether **282** (55 mg, 0.1 mmol), gave after column chromatography (petrol) bis-TBS *E*-alkene **283** (37 mg, 76%), as a colourless oil, a 1:1 diastereomeric mixture; $R_f$ = 0.63 (0.5% Et$_2$O in petrol); $\nu_{max}$/cm$^{-1}$(film) 2977s, 2931s, 2861s, 1644 m, 1444 s, 1382s , 1350 s, 1298 m, 1257 m, 1125 br, 1043 m, 837 s, 775 m; $^1$H NMR (400 MHz; CDCl$_3$) δ 7.28–7.11 (5H, m, ArH), 4.98 (1H, d, *J* = 9, C*H*=CCH$_3$), 3.82–3.74 (1H, m, CHOTBS), 3.72–3.63 (2H, m, CH$_2$OTBS), 2.67–2.56 (1H, m, C*H*CH$_3$), 2.55–2.48 (2H, m, CH$_2$Ph), 2.04–1.87 (2H, m, C*H*$_2$CCH$_3$), 1.66 (2H, q, *J* = 6.5, C*H*$_2$CH$_2$OTBS), 1.55–1.46 (2H, m, C*H*$_2$CH$_2$CCH$_3$), 1.42 (3H, d, *J* = 1, =CCH$_3$), 0.95 (3H, d, *J* = 6.5, CHC*H*$_3$), 0.91 (18H, s, 2 x OSiCMe$_3$), 0.06 (12H, s, 2 x OSi(CH$_3$)$_2$); $^{13}$C NMR (100 MHz; CDCl$_3$) δ 141.3 (Ar*C*), 134.4, 134.4 (*C*=CCH$_3$), 130.2, 130.2 (C=*C*CH$_3$), 129.4, 129.4 (Ar*C*H) 128.1 (Ar*C*H), 125.7 (Ar*C*H) 69.4 (*C*HOTBS), 60.2, 60.2 (*C*H$_2$OTBS), 44.2, 44.2 (*C*H$_2$Ph), 40.2, 40.2, 36.2, 36.1, 35.4, 35.4 (all CH$_2$), 34.7 (*C*HCH$_3$), 26.1, 26.1 (SiC*Me*$_3$), 20.9, 20.9 (CH*C*H$_3$), 18.5, 18.3 (Si*C*Me$_3$), 16.3 (=CCH$_3$), –4.2, –4.4 (one CH$_3$ of OSi(CH$_3$)$_2$), –5.1 (another CH$_3$ of OSi(CH$_3$)$_2$); HRMS *m*/*z* (M+H$^+$) found: 491.3734. $C_{29}H_{55}O_2{}^{28}Si_2$ requires 491.3735.

**Dimethyl (4*R*,5*R*)-4-((*E*)-6,8-dimethyl-9-phenyl-3-((triethylsilyl)oxy)non-6-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (149)**

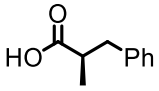



To a solution of *B*-OMe-9BBN (93 μL, 1 M in hexane, 0.093 mmol) in THF (400 μL) was added MeLi (78 μL, 1.2 M in $Et_2O$, 0.093 mmol). Meanwhile, a mixture of $PdCl_2$(dppf) (3 mg, 10 mol%), aq. $Cs_2CO_3$ (45 mg, 3 M, 0.138 mmol), $AsPh_3$ (4 mg, 30 mol%) and alkylated tartrate **160** (30 mg, 0.046 mmol) was prepared in DMF (400 μL) at rt. To the mixture containing **160** and the catalyst system, the borinate complex solution was added dropwise and then the mixture stirred at rt for 40 h. The reaction mixture was then quenched with water (1 mL), extracted with $Et_2O$ (3 × 2 mL), washed with brine (2 mL) and dried ($MgSO_4$). Evaporation under reduced pressure followed by column chromatography (10−30% EtOAc in petrol) gave *E*-alkene tartrate **149** (20 mg, 75%), as a colourless oil, a mixture of 4 diastereoisomers. $R_f$ = 0.53 (20% EtOAc in petrol); $\nu_{max}/cm^{-1}$(film) 3019 s, 2956 s, 2876 m, 1750 m, 1453 m, 1384 m; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.27–7.10 (5H, m, ArH), 4.93 (2H, d, *J* = 8, C*H*=CCH$_3$ and C*H*CO$_2$Me), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.62–3.53 (1H, m, C*H*OTES), 2.63–2.54 (1H, m, C*H*CH$_3$), 2.51 (1H, pd, *J* = 7, CH$_2$Ph), 2.00–1.74 (4H, m, 2 x CH$_2$), 1.68–1.59 (5H, m, CH$_2$ and one Me of CMe$_2$), 1.47–1.41 (5H, m, CH$_2$ and second Me of CMe$_2$), 1.38 (3H, s, =CCH$_3$), 0.94 (12H, pq, *J* = 7.5, OSi(CH$_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.57 (6H, q, *J* = 7.5, OSi(C*H*$_2$CH$_3$)$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 172.6, 172.5 (*C*O$_2$Me), 169.0, 168.8 (*C*O$_2$Me), 141.3 (Ar*C*), 134.0, 134.0 (*C*=CCH$_3$), 130.4, 130.4 (C=*C*CH$_3$), 129.4 (Ar*C*H) 128.1, 128.1 (Ar*C*H), 125.7 (Ar*C*H), 112.8, 112.7 (*C*Me$_2$), 86.1, 85.8 (*quat.* C), 80.3, 80.2 (*C*HCO$_2$Me), 71.9, 71.9 (*C*HOTES), 53.0 (OMe), 52.5, 52.4 (OMe), 44.2, 42.1 (*C*H$_2$Ph), 36.0, 35.9, 35.5, 35.4 (all CH$_2$), 34.7, 34.7 (*C*HCH$_3$), 31.4, 31.1, 30.7, 30.2 (all CH$_2$), 27.9, 27.8,

26.2, 26.1 (C(*C*H$_3$)$_2$), 20.9, 20.9 (CH*C*H$_3$), 16.2, 16.2 (=C*C*H$_3$), 7.1 (OSi(CH$_2$*C*H$_3$)$_3$), 5.2, 5.2 (OSi(*C*H$_2$CH$_3$)$_3$); HRMS *m*/*z* (M+Na$^+$) found: 599.3371. $C_{32}H_{52}O_7{}^{28}Si$ requires 599.3374.

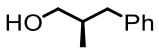
### 8.2.3 Total Synthesis of (–)-6,7-Dideoxysqualestatin H5

**(*R*)-2-Methyl-3-phenylpropanoic acid (266)**



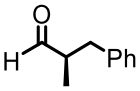

Amide **265**[55] (6.4 g, 20 mmol) in dioxane (32 mL) was treated with aq. $H_2SO_4$ (32 mL, 4.5 M) at rt. The mixture was refluxed for 6 h and then cooled to 0 °C. The pH of the mixture was adjusted to pH ~10 by the slow addition of 50% (w/w) aq. NaOH, and the resulting mixture was partitioned between water (120 mL) and $CH_2Cl_2$ (240 mL). The aq. layer was separated and extracted with $CH_2Cl_2$ (200 mL). The aq. layer was acidified to pH ~ 2 by the slow addition of aq. $H_2SO_4$ (2 M) and then extracted with $CH_2Cl_2$ (2 × 200 mL). The organic layers were combined and concentrated to a volume of ~30 mL, and the concentrate was then washed with HCl (10 mL, 1 M) to remove residual dioxane. The resulting organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure to afford acid **266**[60], as a pale yellow liquid (3.2 g, 96%); $R_f$ = 0.51 (5% EtOAc in petrol); $^1$H NMR (400 MHz; $CDCl_3$) δ 10.02 (1H, br, $CO_2H$), 7.43–7.22 (5H, m, ArH), 3.15 (1H, dd, *J* = 13.5 and 6, CH*H*Ph), 2.90–2.78 (1H, m, C*H*CH$_3$), 2.74 (1H, dd, *J* = 13.5 and 8, C*H*HPh), 1.24 (3H, d, *J* = 7.0, CH$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 182.6 ($CO_2H$), 139.2 (Ar*C*), 129.1 (Ar*C*H) 128.6 (Ar*C*H), 126.6 (Ar*C*H), 41.4 ($CH_2$), 39.4 (*C*HCH$_3$), 16.6 ($CH_3$).

**(*R*)-2-Methyl-3-phenylpropan-1-ol (*R*-213)**



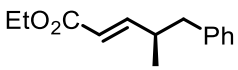

To a suspension of $LiAlH_4$ (4.3 g, 59 mmol) in $Et_2O$ (40 mL) was slowly added a solution of acid **266** (10 mL, 71.6 mmol) in $Et_2O$ (40 mL) and heated to reflux. After 3 h, the mixture was cooled to 0 °C, and Fieser work-up[192] was performed. The solvent was concentrated under reduced pressure and the residues were purified by column chromatography (30% EtOAc in petrol) to give alcohol *R*-**213**[60] (2.5 g, 86%); as a colourless oil; $R_f$ = 0.37 (30% EtOAc in petrol); Data as above (p. 138).

**(*R*)-2-Methyl-3-phenylpropanal (*R*-185)**




Following the procedure above A to **185**, using alcohol *R*-**213** (160 mg, 1.0 mmol), gave after column chromatography (10% $Et_2O$ in petrol) aldehyde *R*-**185**[60] (148 mg, 94%), as a colourless oil. Data as above (p. 139).

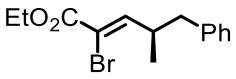
**(−)-(*R*,*E*)-Ethyl 4-methyl-5-phenylpent-2-enoate (*R*-246)**




A mixture of ethyl (triphenylphosphoranylidene)acetate (9.5 g, 27 mmol) and (*R*)-2-methyl-3-phenylpropanal **245**[105] (3.7 g, 25 mmol) in $CH_2Cl_2$ (23 mL) was stirred for 48 h at rt. The solution was then diluted with hexane (15 mL), filtered through Celite® and evaporated under reduced pressure. The residue was purified by column chromatography (10% EtOAc in petrol)

to give *E*-enoate *R*-**246**[193,194] (5.23 g, 96%) as a colourless oil; $R_f$ = 0.78 (10% EtOAc in petrol); $[\alpha]_D^{25}$ = −52 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3027 w, 2976 s, 2928 m, 1715 s, 1650 m, 1454 m, 1367 w, 1267 m, 1204 w, 1174 s, 1040 m, 745 m, 699 m; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.25–7.03 (5H, m, ArH), 6.88 (1H, dd, *J* = 15.5, 6.5, C*H*=CHCO$_2$), 5.68 (1H, d, *J* = 15.5, CH=C*H*CO$_2$), 4.10 (2H, q, *J* = 7, OC*H*$_2$CH$_3$), 2.69 (1H, dd, *J* = 12, 5, C*H*HPh), 2.60–2.46 (2H, m, CH*H*Ph and C*H*CH$_3$), 1.20 (3H, t, *J* = 7, OCH$_2$C*H*$_3$), 0.97 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 166.9 (*C*O$_2$Et), 153.6 (*C*H=CHCO$_2$), 139.7 (Ar*C*), 129.2 (Ar*C*H), 128.4 (Ar*C*H), 126.3 (Ar*C*H), 120.0 (=*C*HCO$_2$), 60.3 (CO$_2$*C*H$_2$CH$_3$), 42.5 (*C*H$_2$Ph), 38.3 (*C*HCH$_3$), 18.8 (CH*C*H$_3$), 14.4 (CO$_2$CH$_2$*C*H$_3$); HRMS *m*/*z* (M+H$^+$) found: 219.1380. $C_{14}H_{19}O_2$ requires 219.1379.

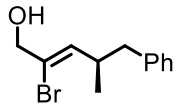
**(−)-(*R*,*Z*)-Ethyl 2-bromo-4-methyl-5-phenylpent-2-enoate (*R*-200)**




Bromine (1.65 mL, 32.2 mmol) was added dropwise to a stirred solution of *E*-enoate *R*-**246** (5.20 g, 23.8 mmol) in $CH_2Cl_2$ (46 mL) at 0 °C. After 2 h, the solution was diluted with sat. aq. $Na_2S_2O_3$ (20 mL), extracted with $Et_2O$ (2×30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. $Et_3N$ (16.5 mL, 119 mmol) was added to a stirred solution of the residue in $CH_2Cl_2$ (46 mL) at rt. After 12 h, the heterogeneous mixture was concentrated under reduced pressure followed by column chromatography (5% EtOAc in petrol) to give *Z*-α-bromoenoate *R*-**200** (6.43 g, 91%) as a pale yellow oil; $R_f$ = 0.48 (5% EtOAc in petrol); $[\alpha]_D^{25}$ = −7.6 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3028 w, 2961 s, 2872 m, 2360 w, 1731 s, 1625 m, 1454 m, 1367 w, 1249 s, 1094 w, 1035 m, 749 m, 700 m; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.32–7.14 (6H, m, ArH and CH=CBr), 4.27 (2H, q, *J* = 7, OC*H*$_2$CH$_3$), 3.11–3.00 (1H, m, C*H*CH$_3$), 2.81 (1H, dd, *J* =

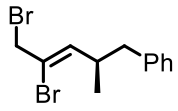
13.5, 6.5, CH*H*Ph), 2.62 (1H, dd, *J* = 13.5, 8, C*H*HPh), 1.33 (3H, t, *J* = 7, $OCH_2CH_3$), 1.06 (3H, d, *J* = 6.5, $CHCH_3$), $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 162.6 (*C*$O_2$Et), 150.4 (*C*H=CBr), 139.1 (Ar*C*), 129.2 (Ar*C*H), 128.5 (Ar*C*H), 126.4 (Ar*C*H), 115.5 (CH=*C*Br), 62.6 ($OCH_2CH_3$), 41.7 ($CH_2Ph$), 38.7 (*C*$HCH_3$), 18.3 ($CHCH_3$), 14.3 ($OCH_2CH_3$); HRMS *m*/*z* ($M+NH_4^+$) found: 314.0752. $C_{14}H_{21}{}^{79}BrNO_2$ requires 314.0750.

**(−)-(*R*,*Z*)-2-Bromo-4-methyl-5-phenylpent-2-en-1-ol (*R*-247)**



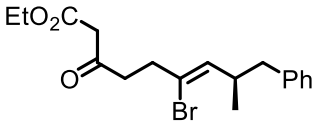

DIBAL–H (60 mL, 1.0 M in hexanes, 62.2 mmol) was added dropwise to a solution of *Z*-α-bromoenoate *R*-**200** (6.16 g, 20.7 mmol) in $CH_2Cl_2$ (180 mL) at –78 °C. After stirring at –78 °C for 2 h, the mixture was diluted with ether and warmed to 0 °C. Water (2.4 mL) was added dropwise, followed by 15% aq. NaOH (2.4 mL), and then further of water (6 mL). The mixture was stirred for 15 min, dried ($MgSO_4$), and filtered. Evaporation under reduced pressure followed by column chromatography (10% EtOAc in petrol) gave allylic alcohol *R*-**247** (4.29 g, 81%), as a yellow oil; $R_f$ = 0.16 (10% EtOAc in petrol); $[\alpha]_D^{23} = -8.0$ (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3605 s, 3480 br, 3028 s, 2927 s, 2253 s, 1494 m, 1453 s, 1378 s, 1262 m, 1100 m, 907 s; $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.30–7.20 (5H, m, ArH), 5.86 (1H, d, *J* = 9, CH=CBr), 4.13 (2H, s, C*H*$_2$OH), 2.92–2.80 (1H, m, C*H*$CH_3$), 2.66 (1H, dd, *J* = 13.5, 6.5, CH*H*Ph), 2.49 (1H, dd, *J* = 13.5, 8, C*H*HPh), 1.79 (1H, br, OH), 0.93 (3H, d, *J* = 6.5, $CHCH_3$); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 139.8 (Ar*C*), 135.3 (*C*=CBr), 129.3 (Ar*C*H) 128.3 (Ar*C*H), 126.2 (Ar*C*H), 125.8 (C=*C*Br), 68.5 ($CH_2OH$), 42.4 ($CH_2Ph$), 37.5 (*C*$HCH_3$), 19.0 ($CH_3$); HRMS *m*/*z* ($M+NH_4^+$) found: 272.0642. $C_{12}H_{18}{}^{79}BrNO$ requires 272.0645.

**(−)-(*R,Z)*-(4,5-Dibromo-2-methylpent-3-enyl)benzene (*R*-201)**




To a stirred solution of allylic alcohol *R*-**201** (900 mg, 3.52 mmol) and $Ph_3P$ (2.77 g, 10.5 mmol) in MeCN (22 mL) was added $CBr_4$ (3.50 g, 10.5 mmol) at 0 °C. After 1 h at 0 °C, the reaction mixture was allowed to warm to rt, and then passed through a short silica gel column using 20% ether in petrol. Evaporation under reduced pressure followed by column chromatography (petrol) gave allylic bromide *R*-**201** (1.06 g, 95%), as a yellow oil; $R_f$ = 0.31 (petrol); $[\alpha]_D^{23}$ = −3.8 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 3028 m, 2964 m, 2252 s, 1495 m, 1453 s, 1214 s, 908 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.31–7.15 (5H, m, ArH), 5.96 (1H, d, *J* = 9, CH=CBr), 4.21 (2H, s, $CH_2Br$), 2.95–2.83 (1H, m, C*H*$CH_3$), 2.73 (1H, dd, *J* = 13.5, 6.5, CH*H*Ph), 2.57 (1H, dd, *J* = 13.5, 7.5, C*H*HPh), 1.00 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 139.6 (Ar*C*), 139.4 (*C*=CBr), 129.4 (Ar*C*H) 128.4 (Ar*C*H), 126.3 (Ar*C*H), 121.6 (C=*C*Br), 41.1 ($CH_2Ph$), 39.0 ($CH_2Br$), 38.2 (*C*HCH$_3$), 18.7 ($CH_3$); HRMS *m*/*z* ($M^+$) found: 315.9465. $C_{12}H_{14}{}^{79}Br_2$ requires 315.9457.

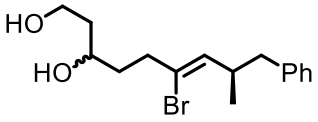
**(−)-(*R,Z*)-Ethyl 6-bromo-8-methyl-3-oxo-9-phenylnon-6-enoate (*R*-202)**




The procedure of Huckin and Weiler[88] was followed with slight modifications. Ethyl acetoacetate (4.20 mL, 33.4 mmol) was added dropwise to a suspension of NaH (1.48 g, 60% in mineral oil, 37.0 mmol) in THF (250 mL) at 0 °C. The resulting mixture was stirred for 10 min until the solution became clear. *n*-BuLi (13.8 mL, 2.5 M in hexanes, 34.6 mmol) was added

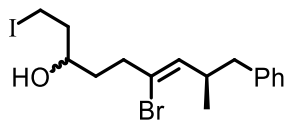
dropwise over 30 min and the reaction mixture was stirred at 0 °C for 10 min. A solution of allylic bromide *R*-**201** (3.8 g, 11.9 mmol) in THF (20 mL) at 0 °C was then added *via* cannula over 5 min. The reaction mixture was then stirred at 0 °C for 30 min, then at rt for 10 min and quenched with HCl (20 mL, 2M). The mixture was extracted with $Et_2O$ (2 x 100 mL). The combined organic layers were washed with water until pH was neutralised (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (0–20% $Et_2O$ in petrol) gave β-ketoester *R*-**202** (3.44 g, 79%), as a pale yellow oil; $R_f$ = 0.2 (10% $Et_2O$ in petrol); $[\alpha]_D^{23} = -11.4$ (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 2962 m, 2927 m, 1746 s, 1716 s, 1651 m, 1495 m, 1454 m, 1368 m, 1317 s, 1033 s, 746 s, 700 s; $^1$H NMR (400 MHz; $CDCl_3$) δ (discernable) of major **keto–tautomer**: 7.22–7.06 (5H, m, ArH), 5.49 (1H, d, *J* = 8.5, CH=CBr), 4.13 (2H, q, *J* = 7, OC*H*$_2$CH$_3$), 3.34 (2H, s, $CH_2(CO)_2$), 2.83–2.72 (1H, m, *CH*CH$_3$), 2.71–2.56 (5H, m, C*H*$_2$C*H*$_2$CO and CH*H*Ph), 2.46 (1H, dd, *J* = 13.5, 7.5, C*H*HPh), 1.29 (3H, t, *J* = 7, OCH$_2$C*H*$_3$), 0.89 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ (discernable) of major **keto–tautomer**: 201.3 (CH$_2$*C*OCH$_2$), 167.1 (*C*O$_2$Et), 140.0 (Ar*C*), 135.4 (*C*=CBr), 129.4 (Ar*C*H) 128.2 (Ar*C*H), 126.1 (Ar*C*H), 125.0 (C=*C*Br), 61.6 (O*C*H$_2$CH$_3$), 49.6 (CO*C*H$_2$CO), 42.5 (*C*H$_2$Ph), 41.8 and 38.0 (*C*H$_2$*C*H$_2$CO), 35.5 (*C*HCH$_3$), 19.2 (CH*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$); $^1$H NMR (400 MHz; $CDCl_3$) δ (discernable) of minor **enol–tautomer**: 12.00 (0.1 H, s, CH=CO*H*), 4.91 (0.1 H, s, C*H*=COH); $^{13}$C NMR (100 MHz; $CDCl_3$) δ (discernable) of minor **enol–tautomer**: 135.45 (*C*=CBr), 129.3 (Ar*C*H), 90.2 (*C*H=COH), 60.2 (O*C*H$_2$CH$_3$), 42.5 (*C*H$_2$Ph), 39.0 and 38.3 (*C*H$_2$*C*H$_2$CO), 34.1 (*C*HCH$_3$), 19.1 (CH*C*H$_3$), 14.4 (OCH$_2$*C*H$_3$); HRMS *m*/*z* (M+NH$_4^+$) found: 384.1168. $C_{18}H_{27}{}^{79}BrNO_3$ requires 384.1169.

**(−)-(8*R*,*Z*)-6-Bromo-8-methyl-9-phenylnon-6-ene-1,3-diol (*R*-203)**




A solution of β-ketoester *R*-**202** (1.6 g, 4.5 mmol) in THF (80 mL) was added to a suspension of $NaBH_4$ (1.0 g, 27 mmol) in THF (80 mL). The reaction mixture was heated to reflux. MeOH (18 mL) was added dropwise to the refluxing mixture over 10 min and then reflux continued for 1 h. The mixture was then allowed to cool to rt and water (50 mL) was added. The mixture was extracted with $Et_2O$ (3 x 100 mL) and the combined organic layers dried ($MgSO_4$). Evaporation under reduced pressure followed by column chromatography (20% petrol in $Et_2O$) gave 1,3-diol *R*-**203** (1.2 g, 81%), as a yellow oil, a 1:1 epimeric mixture at C–3; $R_f$ = 0.19 (20% petrol in $Et_2O$); $[\alpha]_D^{23}$ = −8.1 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3351 br, 3027 m, 2925 s, 1654 w, 1602 w, 1495 m, 1453 s, 1059 s, 744 s, 700 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.30–7.15 (5H, m, ArH), 5.53 (1H, d, *J* = 8.5, CH=CBr), 3.89–3.60 (3H, m, C*H*$_2$OH and C*H*OH), 3.01–2.84 (3H, m, C*H*$CH_3$ and 2 x OH), 2.72–2.41 (4H, m, $CH_2$C*H*$_2$CBr and $CH_2$Ph), 1.73–1.58 (4H, m, C*H*$_2$CH(OH)C*H*$_2$), 0.98 (3H, pt, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 140.3, 140.1 (Ar*C*), 134.4, 134.3 (*C*=CBr), 129.3, 129.2 (Ar*C*H) 128.2 (Ar*C*H), 126.8 (C=*C*Br), 126.1, 126.0 (Ar*C*H) 70.9, 70.5 (*C*HOH), 61.6 (*C*$H_2$OH), 42.6, 42.5 (*C*$H_2$Ph), 38.4, 38.3, 37.9, 37.8, 37.6 (*C*$H_2$*C*$H_2$CH(OH)*C*$H_2$), 36.2, 35.8 (*C*H$CH_3$), 19.4, 19.2 ($CH_3$); HRMS *m*/*z* (M+$NH_4^+$) found: 344.1222. $C_{16}H_{27}{}^{79}BrNO_2$ requires 344.1220.

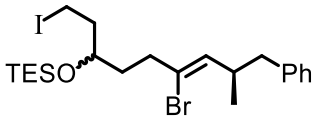
**(−)-(8*R*,*Z*)-6-Bromo-1-iodo-8-methyl-9-phenylnon-6-en-3-ol (*R*-204)**




A solution of $Ph_3P$ (2.0 g, 7.6 mmol), imidazole (0.9 g, 13 mmol) and $I_2$ (1.0 g, 3.9 mmol) in $CH_2Cl_2$ (75 mL) was added dropwise *via* cannula over 30 min to a stirred solution of 1,3-diol

*R*-**203** (2.2 g, 6.7 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. After a further 1 h at 0 °C, the solution was warmed to rt and stirred overnight. The solution was then re–cooled to 0 °C, and $I_2$ (1.0 g, 3.9 mmol) was added portionwise over 5 min. The suspension was then stirred for 30 min at 0 °C, then filtered through Celite®, washed through with $CH_2Cl_2$ (30 mL) and concentrated under reduced pressure. Purification of the residue by column chromatography (3% acetone in petrol) gave iodo alcohol *R*-**204** (2.04 g, 70%), as a yellow oil, a 1:1 epimeric mixture at C–3; $R_f$ = 0.24 (3% acetone in petrol); $[\alpha]_D^{23}$ = −32.2 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 3424 br, 2925 w, 1651 m, 1494 w, 1453 w; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.31–7.15 (5H, m, ArH), 5.56–5.50 (1H, m, CH=CBr), 3.71–3.63 (0.5H, m, C*H*OH), 3.47–3.39 (0.5H, m, C*H*OH), 3.33–3.16 (2H, m, $CH_2$I), 2.99–2.85 (1H, m, C*H*$CH_3$), 2.72–2.47 (4H, m, $CH_2$ and $CH_2$Ph), 1.99–1.82 (2H, m, $CH_2$), 1.75–1.59 (2H, m, $CH_2$), 1.41 (0.5H, d, *J* = 5.5, CHO*H*), 1.28 (0.5H, d, *J* = 5.5, CHO*H*), 1.03–0.97 (3H, m, CHC*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 140.4, 140.1 (Ar*C*), 134.8, 134.6 (*C*=CBr), 129.3, 129.3 (Ar*C*H) 128.3, 128.3 (Ar*C*H), 126.6, 126.6 (C=*C*Br), 126.1, 126.1 (Ar*C*H), 70.6, 70.2 (*C*HOH), 42.7, 42.6 (*C*$H_2$Ph), 41.2, 40.7, 38.0, 37.9, 37.9, 37.5 (all $CH_2$), 35.6, 34.9 (*C*HCH$_3$), 19.6, 19.3 ($CH_3$), 2.6, 3.0 ($CH_2$I); HRMS *m*/*z* (M+$NH_4^+$) found: 454.0240. $C_{16}H_{26}{}^{79}$BrINO requires 454.0237.

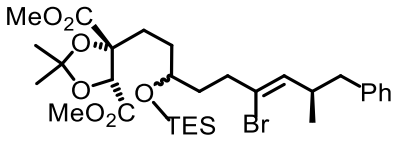
**(−)-(((8*R*,*Z*)-6-Bromo-1-iodo-8-methyl-9-phenylnon-6-en-3-yl)oxy)triethylsilane (*R*-159)**




2,6-Lutidine (1.8 mL, 16 mmol) and TESOTf (1.8 mL, 8.2 mmol) were added to a stirred solution of iodo alcohol *R*-**204** (2.0 g, 4.5 mmol) in $CH_2Cl_2$ (140 mL) at −78 °C. After 2 h, the mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic layers were washed with HCl (50 mL, 0.1 M), water (2 × 50 mL), brine

(2 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (10% $Et_2O$ in petrol) gave iodide ***R*-159** (2.3 g, 93%), as a colourless oil, a 1:1 epimeric mixture at C–3; $R_f$ = 0.69 (10% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −26.1 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 2952 w, 2866 w, 1495 w, 1451 w; $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.30–7.15 (5H, m, ArH), 5.50 (1H, d, *J* = 8.5, CH=CBr), 3.78–3.69 (1H, m, C*H*OTES), 3.24–3.14 (2H, m, $CH_2I$), 2.93–2.83 (1H, m, C*H*$CH_3$), 2.71 (1H, dd, *J* = 13.5, 6.5, CH*H*Ph), 2.53 (1H, dd, *J* = 13.5, 8, C*H*HPh), 2.41 (2H, t, *J* = 7.5, $CH_2CBr$), 1.98–1.91 (2H, m, $CH_2$), 1.76–1.59 (2H, m, $CH_2$), 1.01−0.94 (12H, m, $OSi(CH_2CH_3)_3$ and $CHCH_3$), 0.63 (6H, q, *J* = 7.5, $OSi(CH_2CH_3)_3$); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 140.1 (Ar*C*), 134.2 (*C*=CBr), 129.4 (Ar*C*H) 128.3, 128.3 (Ar*C*H), 126.9 (C=*C*Br), 126.0 (Ar*C*H), 71.2, 71.2 (*C*HOTES), 42.6, 42.6 ($CH_2Ph$), 40.9, 40.8 ($CH_2$), 38.0 ($CHCH_3$), 37.3, 35.6, 35.5 (all $CH_2$), 19.2, 19.2 ($CHCH_3$), 7.1 ($OSi(CH_2CH_3)_3$), 5.3 ($OSi(CH_2CH_3)_3$), 3.0, 2.9 ($CH_2I$); HRMS *m*/*z* ($M+NH_4^+$) found: 568.1097. $C_{22}H_{40}{}^{79}BrINOSi$ requires 568.1102.

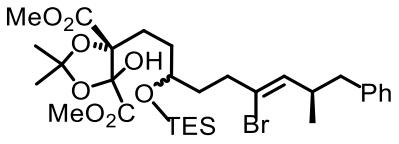
**(−)-Dimethyl (4*R*,5*R*)-4-((8*R*,*Z*)-6-bromo-8-methyl-9-phenyl-3-((triethylsilyl)oxy)non-6-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (*R*-160)**




A solution of LDA [prepared from *i*-$Pr_2NH$ (760 μL, 5.4 mmol) and *n*-BuLi (2.16 mL, 2.5 M in hexanes, 1.76 mmol)] in THF (26 mL) at −78 ºC, was added dropwise over 1 h to a mixture of dimethyl-2,3-*O*-isopropylidine-*L*-tartrate (**147**) (1.0 mL, 5.4 mmol) and iodide ***R*-159** (2.3 g, 4.17 mmol) in THF (66 mL) and HMPA (16 mL) at −78 ºC. After 72 h at −78 ºC, the mixture was quenched with sat. aq. $NH_4Cl$ (25 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of

the residue by column chromatography (10% $Et_2O$ in petrol) gave alkylated tartrate *R*-**160** (1 g, 38%; (65% brsm)), as a yellow oil, an ~1:1 epimeric mixture at C–3'; $R_f$ = 0.18 (5% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −42.1 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3059 s, 2956 s, 1756 s, 1655 m, 1495 m, 1455 m, 1375 m, 1265 s, 1104 m, 807 s, 743 s, 739 s; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.29–7.14 (5H, m, ArH), 5.47 (1H, d, *J* = 8.5, CH=CBr), 4.94 and 4.92 (1H, 2 x s, C*H*($CO_2Me$)), 3.82 (3H, s, OMe), 3.80 (3H, s, OMe), 3.65–3.57 (1H, m, C*H*OTES), 2.91–2.82 (1H, m, C*H*$CH_3$), 2.72–2.67 (1H, m, C*H*HPh), 2.54–2.48 (1H, m, CH*H*Ph), 2.42–2.34 (2H, m, $CH_2CBr$), 1.97–1.89 (1H, m, C($CO_2Me$)C*H*H$CH_2$CHOTES), 1.81–1.70 (1H, m, C($CO_2Me$)CH*H*$CH_2$CHOTES), 1.64–1.58 (7H, m, C($CO_2Me$)$CH_2$C*H*$_2$CHOTES, C*H*$_2CH_2CBr$ and one Me of $CMe_2$), 1.44 (3H, s, one Me of $CMe_2$), 0.97–0.92 (12H, m, OSi($CH_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.60–0.54 (6H, m, OSi(C*H*$_2CH_3$)$_3$); $^{13}C$ NMR (125 MHz; $CDCl_3$) δ 172.6, 172.4 (*C*$O_2$Me), 169.0, 168.7 (*C*$O_2$Me), 140.2, 140.2 (Ar*C*), 134.0, 133.9 (*C*=CBr), 129.4 (Ar*C*H) 128.3, 128.3 (Ar*C*H), 127.2 (C=*C*Br), 126.1 (Ar*C*H), 112.9, 112.7 (*C*$Me_2$), 86.1, 85.7 (*quat.* C), 80.3, 80.3 (*C*H$CO_2$Me), 71.0, 70.9 (*C*HOTES), 53.0 (OMe), 52.47, 52.45 (OMe), 42.6, 42.6 (*C*$H_2$Ph), 38.0, 37.5 (*C*H$CH_3$), 36.1, 36.0, 31.2, 30.9, 30.5, 30.2, 27.9, 27.8 (all $CH_2$), 26.2, 26.1 (C(*C*$H_3$)$_2$), 19.2 (CH*C*$H_3$), 7.1 (OSi($CH_2$*C*$H_3$)$_3$), 5.2 (OSi(*C*$H_2CH_3$)$_3$); HRMS *m*/*z* ($M+NH_4^+$) found: 658.2766, $C_{31}H_{53}{}^{79}BrNO_7Si$ requires 658.2769.

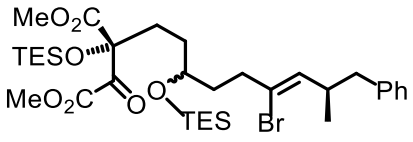
**(−)-Dimethyl (4*R*)-4-((8*R*,*Z*)-6-bromo-8-methyl-9-phenyl-3-((triethylsilyl)oxy)non-6-en-1-yl)-5-hydroxy-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (*R*-161)**




Alkylated tartrate *R*-**160** (1.0 g, 1.55 mmol) in THF (8 mL) at −78 ºC was added over 30 min to a stirred solution of LDA [prepared from *i*-$Pr_2NH$ (0.3 mL, 2.0 mmol) and *n*-BuLi (0.8 mL,

2.5 M in hexanes, 2.0 mmol)] in THF (6 mL) at –78 ºC. After 15 min, MoOPH[93,94] (1.6 g, 3.8 mmol) was added *via* a solid addition tube over 5 min at –78 ºC. The reaction mixture was stirred for additional 30 min, then warmed to −40 ºC. The mixture was stirred at −40 ºC overnight, then warmed to −20 ºC for 1 h before sat. aq. $Na_2SO_3$ (10 mL) was added. The mixture was then allowed to warm to rt over 1 h, extracted with $Et_2O$ (3 × 20 mL), and the combined organic layers washed with sat. aq. $CuSO_4$ (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (0–50% $Et_2O$ in petrol) gave hydroxy acetonide *R*-**161** (726 mg, 71%), as a yellow oil, a mixture of 4 diastereomers; $R_f$ = 0.13 (40% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −20.1 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 3426 br, 2963 s, 2086 w, 1752 s, 1644 m, 1421 m, 1264 s, 806 s, 738 s; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.29–7.14 (5H, m, ArH), 5.48–5.43 (1H, m, CH=CBr), 4.06, 4.58, 4.51 and 4.50 (1H, 4 x s, OH), 3.89, 3.80, 3.78 and 3.70 (6H, 4 x s, 2 x OMe), 3.69–3.58 (1H, m, C*H*OTES), 2.90–2.81 (1H, m, C*H*$CH_3$), 2.72–2.66 (1H, m, C*H*HPh), 2.54–2.47 (1H, m, CH*H*Ph), 2.43–2.35 (2H, m, $CH_2$CBr), 2.15–1.81 (2H, m, C($CO_2$Me)C*H*$_2CH_2$), 1.78–1.53 (10H, m, C*H*$_2CH_2$CBr, C($CO_2$Me)$CH_2$C*H*$_2$ and $CMe_2$), 0.98–0.92 (12H, m, OSi($CH_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.61–0.53 (6H, m, OSi(C*H*$_2CH_3$)$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 171.7, 170.3, 170.2, 170.1, 169.3, 169.2 (*C*$O_2$Me), 140.1, 140.1 (Ar*C*), 134.0, 133.9, 133.8, 133.7 (*C*=CBr), 129.3, 129.3 (Ar*C*H) 128.2, 128.2 (Ar*C*H), 127.3, 127.2, 127.2, 127.1 (C=*C*Br), 126.0, 126.0, 126.0 (Ar*C*H), 114.3, 114.3, 113.6, 113.5 (*C*$Me_2$), 102.2, 102.0, 101.9, 101.8 (*C*OH), 92.9, 92.7, 91.7, 91.1 (*quat.* C), 70.9, 70.8, 70.7, 70.6 (*C*HOTES), 54.1, 54.1, 54.0, 52.7, 52.5 (OMe), 42.6, 42.6, 42.6, 42.6 (*C*$H_2$Ph), 38.0, 38.0, 37.9, 37.9 , 37.9, 37.7, 37.5, 37.4, 37.2, 36.0, 35.9, 35.7, 31.9, 31.9, 31.4, 31.3, 31.3, 31.2, 31.2, 30.9 29.3, 29.2, 28.7, 28.6, 28.4, 28.3, 27.5, 27.5, then 19.1, 19.1 (CH*C*$H_3$), 7.1 (OSi($CH_2$*C*$H_3$)$_3$), 5.2, 5.2, 5.2, 5.1 (OSi(*C*$H_2CH_3$)$_3$); HRMS *m*/*z* (M+H$^+$) found: 657.2454. $C_{31}H_{50}{}^{79}BrO_8Si$ requires 657.2453.

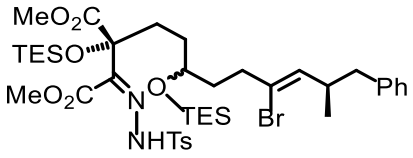
**(−)-Dimethyl (2*R*)-2-((8*R*,*Z*)-6-bromo-8-methyl-9-phenyl-3-((triethylsilyl)oxy)non-6-en-1-yl)-3-oxo-2-((triethylsilyl)oxy)succinate (*R*-162)**




A mixture of hydroxy acetonide *R*-**161** (122 mg, 0.185 mmol) and $H_2SO_4$ (17 mL, 0.1 M in MeOH) was stirred at rt. After 24 h, pyridine (0.4 mL, 5.0 mmol) was added, the mixture was concentrated under reduced pressure and the residue was diluted with $Et_2O$ (30 mL) and filtered. The filtrate was concentrated under reduced pressure to give the lactol (73 mg, 82%), which was not required to further purification. To the lactol (73 mg) in MeCN (3 mL) at −10 °C was added freshly distilled TESCl (0.2 mL, 1.2 mmol) and imidazole (204 mg, 3.0 mmol). The reaction mixture was stirred at −10 °C for 24 h, and then at rt for 24 h. The mixture was then concentrated under reduced pressured and purified by chromatography (florisil®, 0−20% $Et_2O$ in petrol) to give bis-TES ether *R*-**162** (57 mg, 53%), as a colourless oil, an ~1:1 epimeric mixture at C–3'; $R_f$ = 0.7 (60% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −18.6 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 3055 m, 2957 s, 2877 m, 1741 s, 1455 m, 1266 s, 1092 m, 1015 m, 739 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.29−7.15 (5H, m, ArH), 5.49 (1H, d, *J* = 8.5, CH=CBr), 3.84 (3H, s, OMe), 3.77 (3H, s, OMe), 3.70−3.63 (1H, m, C*H*OTES), 2.94−2.83 (1H, m, C*H*$CH_3$), 2.75−2.66 (1H, m, C*H*HPh), 2.57–2.49 (1H, m, CH*H*Ph), 2.41 (2H, t, *J* = 7.5, $CH_2$CBr), 2.24−1.92 (2H, m, C($CO_2$Me)C*H*$_2$$CH_2$), 1.72−1.45 (4H, m, C*H*$_2$$CH_2$CBr and C($CO_2$Me)$CH_2$C*H*$_2$), 1.00−0.91 (21H, m, 2 × OSi($CH_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.73−0.56 (12H, m, 2 × OSi(C*H*$_2$$CH_3$)$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 190.9 (C=O), 170.2 (*C*$O_2$Me), 163.1 (*C*$O_2$Me), 140.2 (ArC), 134.0 (*C*=CBr), 129.4 (ArCH), 128.1 (ArCH), 127.1 (C=*C*Br), 125.9 (ArCH), 84.2 (*quat* C), 72.2, 71.0 (*C*HOTES), 52.8, 52.6, 52.6 (2 x OMe), 42.5, 42.5 (*C*$H_2$Ph), 37.9, 37.8 (*C*H$CH_3$), 37.4, 37.2, 35.5, 35.3, 32.5, 32.2, 30.1, 29.7 (all $CH_2$), 19.2 (CH*C*$H_3$), 6.9, 6.8, 6.7, 6.6

(OSi($CH_2CH_3$)$_3$), 5.8, 5.7, 5.1, 5.0 (OSi($CH_2CH_3$)$_3$); HRMS *m*/*z* ($M+NH_4^+$) found: 730.3168. $C_{34}H_{61}{}^{79}BrNO_7Si_2$ requires 730.3164.

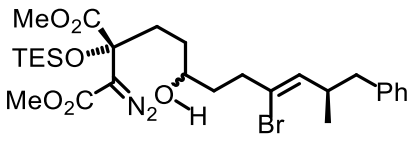
**(−)-Dimethyl (*Z*)-2-((8*R*,*Z*)-6-bromo-8-methyl-9-phenyl-3-((triethylsilyl)oxy)non-6-en-1-yl)-3-(2-(*p*-tolyl)hydrazineylidene)-2-((triethylsilyl)oxy)succinate (*R*-261)**




A mixture of bis-TES ether *R*-**162** (90 mg, 0.126 mmol) and $TsNHNH_2$ (35 mg, 0.19 mmol) in THF (1.5 mL) was refluxed for 20 h. The mixture was concentrated under reduced pressure and purified by column chromatography (0−60% $Et_2O$ in petrol) to give *Z*[195]-hydrazone *R*-**261** (52 mg, 47% (58% brsm)), as a pale yellow oil, an ~1:1 epimeric mixture at C–3'; $R_f$ = 0.61 (60% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −21.5 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 3180 br, 2956 m, 2932 m, 1752 s, 1704 s, 1496 m, 1053 m; $^1$H NMR (400 MHz; $CDCl_3$) δ 11.72 , 11.69 (1H, 2 x s, NH), 7.84 (2H, d, *J* = 8.5, 2 x ArCH), 7.32−7.23 (4H, m, 4 x ArCH), 7.30−7.14 (3H, m, 3 x ArCH), 5.52 (1H, d, *J* = 8.5, CH=CBr), 3.75 (3H, s, OMe), 3.67 (3H, s, OMe), 3.65−3.59 (1H, m, C*H*OTES), 2.94−2.83 (1H, m, C*H*$CH_3$), 2.72 (1H, dd, *J* = 13.5, 6, CH*H*Ph), 2.54−2.47 (1H, m, CH*H*Ph), 2.45−2.36 (3H, s, Ar–*Me* and 2H, m, $CH_2$CBr), 2.08−1.82 (2H, m, C($CO_2$Me) C*H*$_2$$CH_2$CHOTES), 1.71−1.59 (2H, m, $CH_2$), 1.50−1.37 (1H, m, CH*H*), 1.35−1.24 (1H, m, C*H*H), 1.00−0.93 (12H, m, OSi($CH_2CH_3$)$_3$ and CH$CH_3$), 0.80−0.74 (9H, m, OSi($CH_2CH_3$)$_3$), 0.64−0.56 (6H, m, OSi(C*H*$_2$$CH_3$)$_3$), 0.42−0.33 (6H, m, OSi(C*H*$_2$$CH_3$)$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 172.4, 172.4 (*C*$O_2$Me), 162.0 (NC*C*$O_2$Me), 144.6, 140.1 (Ar*C*), 137.1, 137.0 (*C*=CBr), 135.6 (Ar*C*Me), 133.9, 133.9 (N*C*$CO_2$Me), 129.8, 129.3, 128.2, 128.2 , 128.1 128.1(Ar*C*H), 127.5, 127.4 (C=*C*Br), 126.0 (Ar*C*H), 80.9, 80.7 (*quat. C*), 71.3, 71.1 (*C*HOTES), 52.4, 52.3 (OMe), 42.6, 42.6 (*C*$H_2$Ph), 38.0, 38.0, 37.6, 37.3, 36.2, 35.9, 33.7,

33.1, 31.1, 31.0, then 21.7 (Ar–*Me*), 19.1, 19.1 (CH*C*$H_3$), 7.1, 7.1, (OSi($CH_2$*C*$H_3$)$_3$), 7.0 (OSi($CH_2$*C*$H_3$)$_3$), 6.3 (OSi(*C*$H_2$CH$_3$)$_3$), 5.3, 5.2 (OSi(*C*$H_2$CH$_3$)$_3$); HRMS *m/z* (M+$NH_4^+$) found: 898.3526. $C_{41}H_{69}{}^{79}BrN_3O_8SSi_2$ requires 898.3522.

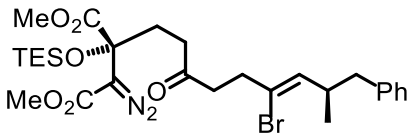
**(−)-Dimethyl 2-((8*R*,*Z*)-6-bromo-3-hydroxy-8-methyl-9-phenylnon-6-en-1-yl)-3-diazo-2-((triethylsilyl)oxy)succinate (*R*-263)**




To the *Z*-hydrazone *R*-**261** (66 mg, 0.075 mmol) in $CH_2Cl_2$ (200 μL) was added $Et_3N$ (50 μL, 0.36 mmol) dropwise at rt. After 2 h, the mixture was concentrated to give a (6:4) mixture of diazo bis−TES ether and diazo alcohol; to this mixture in THF (300 μL) was added AcOH (150 μL) and water (150 μL). After 5 h stirring at rt, the mixture was quenched with aq. sat. $NaHCO_3$ (2 mL), extracted with EtOAc (2 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (10−30% $Et_2O$ in petrol) gave diazo alcohol *R*-**263** (42 mg, 92%, from *R*-**261**), as a yellow oil, an ~1:1 epimeric mixture at C–3'; $R_f$ = 0.34 (30% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −23.4 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$ (film) 3518 m, 3027 w, 2955 s, 2877 s, 2098 s, 1747 s, 1707 s, 1495 m, 1437 s, 1315 s, 1141 m, 742 s; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.29−7.14 (5H, m, ArH), 5.53−5.45 (1H, m, CH=CBr), 3.77−3.71 (6H, m, 2 x OMe), 3.70−3.61 and 3.57−3.49 (1H, m, C*H*OH), 2.98−2.82 (1H, m, C*H*$CH_3$), 2.73−2.34 (4H, m, $CH_2$Ph, and $CH_2$CBr), 2.18−1.84 (2H, m, C($CO_2$Me)C*H*$_2$$CH_2$), 1.73−1.34 (4H, m, C*H*$_2$CH(OH)C*H*$_2$), 1.02−0.91 (12 H, m, OSi($CH_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.66−0.55 (6H, m, OSi(C*H*$_2$CH$_3$)$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 171.9, 171.8 (*C*$O_2$Me), 165.3 (NC*C*$O_2$Me), 140.4, 140.1 (Ar*C*), 134.5, 134.3 (*C*=CBr), 129.3, 129.3 (Ar*C*H) 128.3, 128.2 (Ar*C*H), 126.9, 126.8 (C=*C*Br), 126.2, 126.0 (Ar*C*H), 76.2, 176.0 (*quat. C*), 70.4, 69.6 (*C*HOH), 64.9 (C=$N_2$),

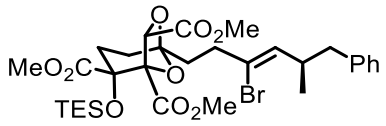
52.9, 52.8 (OMe), 52.0, 51.9 (OMe), 42.8, 42.6 (*C*$H_2$Ph), 37.9, 37.6 (*C*HCH$_3$), 63.1, 35.3, 34.6, 31.5, 29.8 (all $CH_2$), then 19.5, 19.3 (CH*C*H$_3$), 7.0, 6.7 (OSi(CH$_2$*C*H$_3$)$_3$), 5.9, 5.2 (OSi(*C*H$_2$CH$_3$)$_3$); HRMS *m*/*z* (M+$NH_4^+$) found: 628.2414. $C_{28}H_{47}{}^{79}BrN_3O_6Si$ requires 628.2412.

**(−)-Dimethyl 2-((*R*,*Z*)-6-bromo-8-methyl-3-oxo-9-phenylnon-6-en-1-yl)-3-diazo-2-((triethylsilyl)oxy)succinate (*R*-163)**



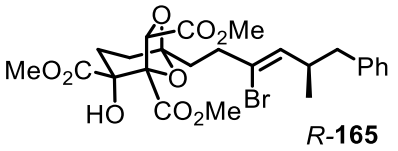

To diazo alcohol *R*-**263** (20 mg, 0.032 mmol) in $CH_2Cl_2$ (1 mL) at rt was added Dess−Martin periodinane (35 mg, 0.083 mmol). After 3 h, the mixture was filtered through Celite® and then purified by column chromatography (10−40% $Et_2O$ in petrol) to give ketone *R*-**163** (12 mg, 60%), as a yellow oil; $R_f$ = 0.57 (60% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −24.9 (*c*=1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(film) 2956 s, 2877 s, 2098 s, 1711 s, 1437 s, 1260 s, 1138 m, 738 s; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.28−7.12 (5H, m, ArH), 5.53 (1H, d, *J* = 8.5, CH=CBr), 3.75 (3H, s, OMe), 3.73 (3H, s, OMe), 2.89−2.79 (1H, m, C*H*CH$_3$), 2.70−2.49 (7H, m, $CH_2$Ph, CH*H* and 2 x $CH_2$), 2.44−2.37 (1H, m, CH*H*) 2.29−2.18 (2H, m, $CH_2$), 0.97−0.90 (12H, m, OSi(CH$_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.65−0.55 (6H, m, OSi(C*H*$_2$CH$_3$)$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 207.7 (C=O), 171.5 (*C*O$_2$Me), 165.2 (NC*C*O$_2$Me), 140.0 (Ar*C*), 135.1 (*C*=CBr), 129.4 (Ar*C*H) 128.2 (ArCH), 126.1 (Ar*C*H), 125.5 (C=*C*Br), 75.5 (*quat. C*), 64.8 (C=$N_2$), 53.0 (OMe), 52.1 (OMe), 42.5 (*C*$H_2$Ph), 41.7 ($CH_2$), 38.0 (*C*HCH$_3$), 37.4 ($CH_2$), 35.7 ($CH_2$), 32.3 ($CH_2$), 19.1 (CH*C*H$_3$), 7.0 (OSi(CH$_2$*C*H$_3$)$_3$), 5.8 (OSi(*C*H$_2$CH$_3$)$_3$); HRMS *m*/*z* (M+$NH_4^+$) found: 626.2246. $C_{28}H_{45}{}^{79}BrN_3O_6Si$ requires 626.2256.

**(−)-Trimethyl (1*S*,2*R*,5*R*,7*S*)-5-((*R*,*Z*)-3-bromo-5-methyl-6-phenylhex-3-en-1-yl)-2-((triethylsilyl)oxy)-6,8-dioxabicyclo[3.2.1]octane-1,2,7-tricarboxylate (*R*-164)**

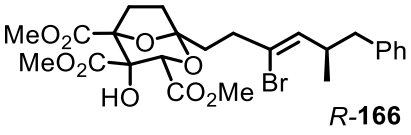



A mixture of ketone *R*-**163** (26 mg, 0.043 mmol), freshly distilled methyl glyoxylate[196] (25 mg, 0.28 mmol) and $Rh_2(OAc)_4$ (~1 mg, cat) in toluene (1.5 mL) was refluxed at 110 °C for 2 h. The mixture was then concentrated under reduced pressure and purified by column chromatography (0−20% EtOAc in petrol) to give cycloadduct *R*-**164** (19 mg, 66%), as a colourless oil; $R_f$ = 0.39 (60% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −13.7 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 2955 s, 2876 s, 1840 s, 1755 s, 1495 s, 1438 s, 1375 m, 1264 s, 1197 m, 1013 s, 738 s; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.26−7.15 (5H, m, ArH), 5.59 (1H, d, *J* = 8.5, CH=CBr), 5.55 (1H, s, C*H*$CO_2$Me), 3.81 (3H, s, OMe), 3.70 (3H, s, OMe), 3.69 (3H, s, OMe), 2.92−2.83 (1H, m, C*H*$CH_3$), 2.75−2.65 (3H, m, C*H*$_2$$CH_2$CBr and CH*H*Ph), 2.5 (1H, ddd, *J* = 13.5, 8, C*H*HPh), 2.40 (1H, ddd, *J* = 14, 12.5, 6, 1H*$_{endo}$* of TESOC($CO_2$Me)CH*H*$CH_2$), 2.17−2.06 (2H, m, $CH_2$CBr), 1.87 (1H, td, *J* = 13, 5.5, 1H*$_{endo}$* of TESOC($CO_2$Me)$CH_2$CH*H*), 1.76 (1H, pdd, *J* = 14, 5, TESOC($CO_2$Me)CH*H*$CH_2$), 1.66 (1H, pdd, *J* = 13, 5.5, TESOC($CO_2$Me)$CH_2$CH*H*), 0.97−0.91 (12H, m, OSi($CH_2$C*H*$_3$)$_3$ and CHC*H*$_3$), 0.69−0.59 (6H, m, OSi(C*H*$_2$$CH_3$)$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 173.4 (*C*$O_2$Me), 169.4 (*C*$O_2$Me), 166.8 (*C*$O_2$Me), 140.2 (Ar*C*), 134.1 (*C*=CBr), 129.4 (Ar*C*H) 128.2 (Ar*C*H), 126.7 (C=*C*Br), 126.0 (Ar*C*H), 111.1 (O−C−O), 90.3 (TESOC*C*$CO_2$Me), 77.5 (*C*H$CO_2$Me), 77.3 (TESO*C*$CO_2$Me), 52.7 (OMe), 52.6 (OMe), 52.5 (OMe), 42.6 (*C*$H_2$Ph), 38.0 (*C*H$CH_3$), 35.9, 35.1, 29.9, 29.8 (4 x $CH_2$), 19.1 (CH*C*$H_3$), 7.2 (OSi($CH_2$*C*$H_3$)$_3$), 6.7 (OSi(*C*$H_2$$CH_3$)$_3$); HRMS *m*/*z* ($M+NH_4^+$) found: 686.2351. $C_{31}H_{49}{}^{79}BrNO_9Si$ requires 686.2354.

**(−)-Trimethyl (1*S*,2*R*,5*R*,7*S*)-5-((*R*,*Z*)-3-bromo-5-methyl-6-phenylhex-3-en-1-yl)-2-hydroxy-6,8-dioxabicyclo[3.2.1] octane-1,2,7-tricarboxylate (*R*-165) and (−)-Trimethyl (1*R*,3*S*,4*S*,5*R*)-1-((*R*,*Z*)-3-bromo-5-methyl-6-phenylhex-3-en-1-yl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (*R*-166)**



*R*-**165**

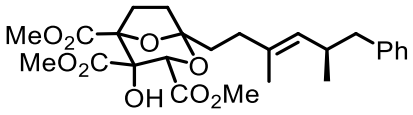


*R*-**166**

To a solution of cycloadduct *R*-**164** (19 mg, 0.028 mmol) in $CH_2Cl_2$ (210 μL) were added TFA (105 μL) and $H_2O$ (10.5 μL). The reaction mixture was heated at 40 °C for 48 h. The mixture was then concentrated under reduced pressure and purified by column chromatography (5−30% EtOAc in petrol). First eluted, cycloadduct alcohol *R*-**165** (3 mg, 19%), as a colourless oil; $R_f$ = 0.48 (100% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −8.2 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 3462 br, 2925 s, 1736 s, 1456 s, 1260 s, 1092 m, 796 s, 737 s; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.26−7.14 (5H, m, ArH), 5.58 (1H, d, *J* = 8.5, CH=CBr), 5.47 (1H, s, C*H*$CO_2$Me), 3.92 (3H, s, OMe), 3.75 (3H, s, OMe), 3.71 (3H, s, OMe), 2.94−2.83 (1H, m, C*H*$CH_3$), 2.82−2.55 (3H, m, C*H*$_2$$CH_2$CBr and CH*H*Ph), 2.51 (1H, dd, *J* = 13.5, 8, C*H*HPh), 2.36−2.27 (1H, m, HOC($CO_2$Me)CH*H*$CH_2$), 2.25−1.92 (4H, m, $CH_2$CBr, HOC($CO_2$Me)CH*H*$CH_2$ and HOC($CO_2$Me)$CH_2$CH*H*), 1.81−1.73 (1H, m, HOC($CO_2$Me)$CH_2$CH*H*), 0.95 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 173.8 (*C*$CO_2$Me), 169.1 (*C*$CO_2$Me), 166.9 (*C*$CO_2$Me), 140.2 (Ar*C*), 134.3 (*C*=CBr), 129.4 (Ar*C*H) 128.3 (Ar*C*H), 126.7 (C=*C*Br), 126.0 (Ar*C*H), 111.8 (O−C−O), 89.4 (HOC*C*$CO_2$Me), 77.7 (*C*H$CO_2$Me), 74.1 (HO*C*$CO_2$Me), 52.9 (OMe), 53.2 (OMe), 52.7 (OMe), 42.6 (*C*$H_2$Ph), 38.0 (*C*H$CH_3$), 35.8, 34.9, 29.9, 29.5 (4 x $CH_2$), 19.1 (CH*C*H$_3$); HRMS *m*/*z* (M+$NH_4^+$) found: 572.1491. $C_{25}H_{35}{}^{79}BrNO_9$ requires 572.1490.

Second eluted, alkenyl bromide *R*-**166** (5.5 mg, 35%) as a colourless oil; $R_f$ = 0.40 (100% $Et_2O$ in petrol); $[\alpha]_D^{23}$ = −7.3 (*c*=1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 3452 br, 2923 s, 1731 s, 1456 s, 1261 s, 1093 m, 795 s, 731 s; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.29−7.14 (5H, m, ArH), 5.58 (1H, d, *J* = 8.5, CH=CBr), 4.79 (1H, s, C*H*$CO_2$Me), 3.89 (3H, s, OMe), 3.77 (6H, s, 2 x OMe), 3.65 (1H, s, OH), 3.06−2.98 (1H, m, $H_{endo}$ of C($CO_2$Me)CH*H*$CH_2$), 2.95−2.85 (1H, m, C*H*$CH_3$), 2.71−2.55 (4H, m, $CH_2$Ph and $CH_2$), 2.26−2.14 (2H, m, $CH_2$), 2.05−1.93 (2H, m, $CH_2$), 1.90−1.82 (1H, m, $H_{exo}$ of C($CO_2$Me)CH*H*$CH_2$), 0.98 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 170.0 (*C*$O_2$Me), 168.8 (*C*$O_2$Me), 167.5 (*C*$O_2$Me), 140.3 (Ar*C*), 134.8 (*C*=CBr), 129.3 (Ar*C*H) 128.3 (Ar*C*H), 126.4 (C=*C*Br), 126.2 (Ar*C*H), 108.5 (O−*C*−O), 88.0 (*C*$CO_2$Me), 75.2 (*C*OH), 74.9 (*C*H$CO_2$Me), 53.5 (OMe), 53.0 (OMe), 52.8 (OMe), 42.7 (*C*$H_2$Ph), 38.0 (*C*H$CH_3$), 36.0, 35.4, 31.4, 29.3 (4 x $CH_2$), 19.5 (CH*C*$H_3$); HRMS *m*/*z* (M + $NH_4^+$) found: 572.1490. $C_{25}H_{35}{}^{79}BrNO_9$ requires 572.1490.

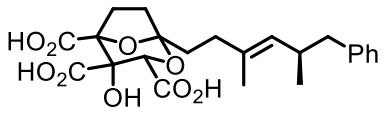
**(−)-Trimethyl (1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-2,8-Dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (267)**




To a solution of *B*-MeO-9-BBN (7 μL, 1.0 M in hexane, 0.007 mmol) in THF (30 μL) was added MeLi (6 μL, 1.2 M in $Et_2O$, 0.007 mmol) and stirred for 5 min at rt. Meanwhile, a mixture of $PdCl_2$(dppf) (0.4 mg, 15 mol%), $Cs_2CO_3$ (3.5 μL, 3 M in MeOH), $Ph_3As$ (0.4 mg, 40 mol%) and alkenyl bromide *R*-**166** (3 mg, 0.0036 mmol) in DMF (30 μL) was prepared at rt. To the mixture containing *R*-**166** and the catalyst system, the borinate complex solution was added dropwise and then the reaction mixture was stirred at 40 ºC for 6 h. The reaction mixture was then quenched with water (1 mL), extracted with EtOAc (3 × 4 mL), and the combined organic

layers washed with brine (2 mL) and dried ($MgSO_4$). Evaporation under reduced pressured followed by column chromatography (0−40% EtOAc in petrol) gave 6,7-dideoxysqualestatin H5 trimethyl ester **267** (0.8 mg, 45%) as a colourless oil, $R_f$ = 0.15 (40% EtOAc in petrol); $[\alpha]_D^{25}$ = –37.9 (*c*= 0.53, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 3078 br, 2956 s, 2925 s, 2854 s, 1768 s, 1739 s, 1439 s, 1266 s; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.24–7.11 (5H, m, ArCH), 5.02 (1H, d, *J* = 9, C*H*=$CCH_3$), 4.86 (1H, s, C*H*$CO_2Me$), 3.89 (3H, s, OMe), 3.77 (3H, s, OMe), 3.76 (3H, s, OMe), 3.16–3.05 (1H, m, $H_{endo}$ of C($CO_2Me$)CH*H*$CH_2$), 2.67–2.58 (1H, m, C*H*$CH_3$), 2.54–2.48 (2H, m, $CH_2Ph$), 2.21–1.95 (8H, m, $H_{exo}$ of C($CO_2Me$)CH*H*$CH_2$, C($CO_2Me$)$CH_2$C*H*$_2$, C*H*$_2$C*H*$_2$CMe and OH), 1.46 (3H, d, *J* = 1, =$CCH_3$), 0.93 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}C$ NMR (125 MHz; $CDCl_3$) δ 170.1 (*C*$O_2$Me), 168.9 (*C*$O_2$Me), 167.7 (*C*$O_2$Me), 141.3 (*C*=CH), 133.2 (Ar*C*), 130.8 (C=*C*H), 129.4 (Ar*C*H), 128.2 (Ar*C*H), 125.8 (ArCH), 109.3 (O−*C*−O), 88.2 (*C*$CO_2$Me), 75.3 (*C*OH), 75.0 (*C*H$CO_2$Me), 53.5 (OMe), 53.0 (OMe), 52.8 (OMe), 44.1 (*C*$H_2$Ph), 35.2 (*C*H$CH_3$), 34.7, 33.5, 31.3, 29.3 (4 x $CH_2$), 21.0 (CH*C*$H_3$), 16.3 (=C*C*$H_3$); HRMS *m/z* ($M+Na^+$) found 513.2094, $C_{26}H_{34}O_9Na$ requires 513.2095.

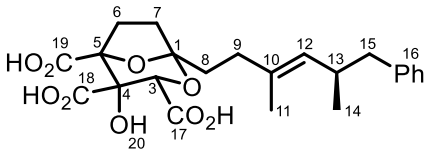
**(−)-(1*S*,3*S*,4*S*,5*R*)-1-((*R*,*E*)-3,5-Dimethyl-6-phenylhex-3-en-1-yl)-4-hydroxy-2,8-dioxabicyclo [3.2.1]octane-3,4,5-tricarboxylic acid (6,7-dideoxysqualestatin H5**, **2)**




To a mixture of 6,7–dideoxysqualestatin H5 trimethyl ester **267** (2.0 mg, 0.0041 mmol) and KO*t*-Bu (5.0 mg, 0.045 mmol) was added 1,4-dioxane (0.25 mL) and $H_2O$ (0.36 mL) at 0 °C, and then slowly warmed to rt over 1 h and left to stir for 2 h. The reaction mixture was then refluxed at 110 °C overnight. The solvent was evaporated, and $H_2O$ (2.5 mL) added. The mixture was washed with $Et_2O$ (2 x 2.5 mL), acidified with HCl (1 mL, 0.1 M), extracted with

EtOAc (3 x 5 mL) and the combined organic layers washed with brine (2.5 mL). The combined organic layers were evaporated under reduced pressure to give 1.6 mg of material that was re–dissolved in MeOH (0.5 mL). The solution was extracted with *n*-hexane (2 x 0.5 mL), and the methanolic layer was concentrated under reduced pressure to give 6,7-dideoxysqualestatin H5 (**2**) (1.4 mg 78%); $[\alpha]_D^{25}$ = –12.9 (*c*= 0.09, MeOH); $\nu_{max}/cm^{-1}$(film) 3437 br, 2956 w, 2530 br, 1730 s, 1452 w, 1050 s, 880 s; $^1$H NMR (500 MHz; $CD_3OD$) δ 7.23 (2H, t, *J* = 7.5, ArCH), 7.16–7.11 (3H, m, ArCH), 5.04 (1H, d, *J* = 9, C*H*=$CCH_3$), 4.84 (1H, s, C*H*$CO_2$Me), 3.79 (1H, s, OH), 3.23–3.15 (1H, m, $H_{endo}$ of C($CO_2$Me)CH*H*$CH_2$), 2.70–2.62 (1H, m, C*H*$CH_3$), 2.59 (1H, dd, *J* = 13, 6, C*H*HPh), 2.48 (1H, dd, *J* = 13, 8, CH*H*Ph), 2.22–2.10 (2H, m, C($CO_2$Me)$CH_2$C*H*$_2$), 2.08–1.94 (4H, m, C*H*$_2$C*H*$_2$$CCH_3$), 1.90–1.84 (1H, m, 1H*exo* of C($CO_2$Me)C*H*H$CH_2$), 1.43 (3H, d, *J* = 1, CC*H*$_3$), 0.96 (3H, d, *J* = 6.5, CHC*H*$_3$); $^{13}$C NMR (125 MHz; $CD_3OD$) δ 173.5 ($CO_2$H), 172.5 ($CO_2$H), 171.2 ($CO_2$H), 142.4 (ArC), 135.0 (*C*=CH), 131.7 (C=*C*H), 130.3 (ArCH), 129.0 (ArCH), 126.7 (ArCH), 109.8 (O–C–O), 89.5 (*C*$CO_2$Me), 76.2 (*C*OH), 75.9 (*C*H$CO_2$Me), 45.1 (*C*$H_2$Ph), 36.5 (*C*H$CH_3$), 35.9 (C($CO_2$Me)*C*$H_2$$CH_2$), 34.7 (C($CO_2$Me)$CH_2$*C*H$_2$), 32.2 ($CH_2$*C*$H_2$$CCH_3$), 30.3 (*C*$H_2$$CH_2$$CCH_3$), 21.4 (CH*C*$H_3$), 16.1 (C*C*$H_3$); HRMS *m/z* ($M+Na^+$) found: 471.1625, $C_{23}H_{28}O_9Na$ requires 471.1626.

**Table 4: NMR data comparison of synthetic 6,7-dideoxysqualestatin H5 (2) with natural isolate**[197]

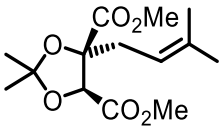



| Position* | Natural Isolate[197] | | Synthetic | |
|---|---|---|---|---|
| | *$^{1}$H NMR* | *$^{13}$C NMR* | *$^{1}$H NMR* | *$^{13}$C NMR* |
| 1 | | 109.8 | | 109.8 |
| 3 | | 75.7 | 4.84 (1H, s, C*H*$CO_2$Me) | 75.9 |
| 4 | | 76.0 | | 76.2 |
| 4-OH | | | 3.79 (1H, s, OH) | |
| 5 | | 89.3 | | 89.5 |
| 6 | 3.18 (1H, m)<br>1.87 (1H, m) | 35.8 | 3.22–3.15 (1H, m)<br>1.90–1.84 (1H, m) | 35.9 |
| 7 | 2.23–2.09 (2H, m) | 34.6 | 2.22–2.10 (2H, m) | 34.7 |
| 8 | 2.0–1.90 (4H, m) | 30.3 | 2.08–1.94 (4H, m) | 30.3 |
| 9 | | 32.0 | | 32.2 |
| 10 | | 142.3 | | 142.4 |
| 11 | 1.44 (3H, d, *J* 1) | 21.3 | 1.43 (3H, d, *J* 1) | 21.4 |
| 12 | 5.04 (1H, m) | 131.7 | 5.04 (1H, d, *J* 9) | 131.7 |
| 13 | 2.66 (1H, m) | 36.3 | 2.70–2.62 (1H, m) | 36.5 |
| 14 | 0.96 (3H, d, *J* 7) | 16.0 | 0.96 (3H, d, *J* 6.5) | 16.1 |
| 15 | 2.59 (1H, dd, *J* 13, 6)<br>2.47 (1H, dd, *J* 13, 8) | 45.0 | 2.59 (1H, dd, *J* 13, 6)<br>2.48 (1H, dd, *J* 13, 8) | 45.1 |
| 16<br>Aromatic ring | 7.23 (2H, t, *J* 7)<br>7.17–7.10 (3H, m) | 134.9<br>130.2<br>128.9<br>126.6 | 7.24–7.20 (2H, m)<br>7.15–7.12 (3H, m) | 135.0<br>130.3<br>129.0<br>126.7 |
| 17−19<br>*C*OOH | | 173.1<br>172.1<br>170.8 | | 173.5<br>172.5<br>171.2 |

*NMR spectra of the natural isolate were recorded on a Bruker AM500, while the synthetic spectra were recorded on a Bruker AVC500 ($^{1}$H NMR–500 MHz and $^{13}$C NMR–125 MHz, $CD_3OD$).

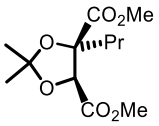
## 8.2.4 Epimerisation of Monoalkylated Tartrates

**Dimethyl (4*R*,5*S*)-2,2-dimethyl-4-(3-methylbut-2-enyl)-1,3-dioxolane-4,5-dicarboxylate (*epi*-286d).**



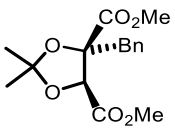

Prenylated tartrate **286d** (25 mg, 0.08 mmol) and NaOMe (5.5 mg, 0.1 mmol) in MeOH (1.3 mL) was heated at reflux for 30 h. $H_2O$ (0.5 mL) was then added and the reaction mixture extracted with $Et_2O$ (2×5 mL). The combined organic layers were washed with brine (2 mL), dried ($Na_2SO_4$) and evaporated under reduced pressured. $^1$H NMR analysis of the residue indicated 75:25 *epi*-**286d**:**286d**. Purification of the residue by gradient column chromatography (0–10% $Et_2O$ in petrol) gave the epimeric prenylated tartrate *epi*-**286d**[146] (14.5 mg, 58%) as a colourless liquid. $R_f$ = 0.21 (20% $Et_2O$ in petrol); $[\alpha]_D^{25}$ = −12.8 (*c* 0.6, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(neat) 2989 m, 2954 m, 2917 m, 1850 w, 11764 s, 1738 s, 1437 m, 1381 m, 1220 s, 1107 s, 867 w; $\delta_H$(400 MHz, $CDCl_3$) 5.22 (1H, t, *J* = 7.5, $CH_2CH$=$C(CH_3)_2$), 4.50 (1H, s, C*H*$CO_2$Me), 3.80 (3H, s, $CO_2$Me), 3.71 (3H, s, $CO_2$Me), 2.75 (1H, dd, *J* = 15 and 7, CH*H*CH=$C(CH_3)_2$), 2.63 (1H, dd, *J* = 15 and 8, C*H*HCH=$C(CH_3)_2$), 1.74 (3H, s, one $CH_3$ of $C(CH_3)_2$), 1.66 (3H, s, one $CH_3$ of $C(CH_3)_2$), 1.60 (3H, s, one $CH_3$ of CH=$C(CH_3)_2$), 1.40 (3H, s, one $CH_3$ of CH=$C(CH_3)_2$); $\delta_C$(100 MHz, $CDCl_3$) 171.8 ($CO_2$Me), 168.2 ($CO_2$Me), 137.3 (CH=$C(CH_3)_2$), 116.8 (CH=$C(CH_3)_2$), 111.8 ($C(CH_3)_2$), 86.8 ($CCH_2CH$=$C(CH_3)_2$), 79.5 ($CHCO_2$Me), 52.7 ($CO_2Me$), 52.6 ($CO_2Me$), 33.6 ($CH_2CH$=$(CH_3)_2$), 26.9 (CH=$C(CH_3)_2$), 26.6 (CH=$C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 18.2($C(CH_3)_2$); HRMS *m*/*z* ($M+H^+$) found: 287.1489, $C_{14}H_{23}O_6$ requires 287.1489.

**Dimethyl (4*R*,5*S*)-2,2-dimethyl-4-propyl-1,3-dioxolane-4,5-dicarboxylate (*epi*-286a).**




Following the procedure for *epi*-**286d** above, but using propylated tartrate **286a** (56 mg, 0.21 mmol), gave a residue (72:28, *epi*-**286a**:**286a**) which was purified by gradient column chromatography (0–10% $Et_2O$ in petrol), to give *epi*-**286a** (30 mg, 54%) as a colourless liquid. $R_f$ = 0.13 (20% $Et_2O$ in petrol); $[\alpha]_D^{25}$ = −38.5 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(neat) 2959 m, 2876 w, 1764 s, 1737 s, 1438 m, 1381 m, 1218 s, 1136 s, 1102 s, 1023 m, 959 w; $\delta_H$(400 MHz, $CDCl_3$) δ 4.45 (1H, s, C*H*$CO_2$Me), 3.79 (3H, s, $CO_2$Me), 3.70 (3H, s, $CO_2$Me), 2.10 (1H, ddd, *J* = 14, 12 and 4.5, CH*H*$CH_2CH_3$), 1.76 (1H, ddd, *J* = 14, 12 and 5, CH*H*$CH_2CH_3$), 1.60 (3H, s, one $CH_3$ of $C(CH_3)_2$), 1.56–1.45 (1H, m, $CH_2CH$*H*$CH_3$), 1.41 (3H, s, one $CH_3$ of $C(CH_3)_2$), 1.38–1.28 (1H, m, $CH_2CH$*H*$CH_3$), 0.94 (3H, t, *J* = 7.5, $CH_2C$*H*$_3$); $\delta_c$(100 MHz, $CDCl_3$) 171.9 (*C*$O_2$Me), 168.1 (*C*$O_2$Me), 111.8 (*C*$(CH_3)_2$), 86.9 (*C*$CH_2CH_2CH_3$), 80.9 (*C*H$CO_2$Me), 52.6 ($CO_2$*Me*), 52.6 ($CO_2$*Me*), 38.4 (*C*$H_2CH_2CH_3$), 26.9 (2 x C(*C*$H_3)_2$), 17.5 ($CH_2$*C*$H_2CH_3$), 14.3 ($CH_2CH_2$*C*$H_3$); HRMS *m/z* ($M+H^+$) found 261.1332, $C_{12}H_{21}O_6$ requires 261.1332.

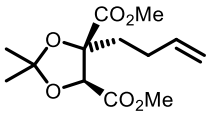
**Dimethyl (4*R*,5*S*)-4-benzyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (*epi*-286e)**




Following the procedure for *epi*-**286d** above, but using benzylated tartrate **286e** (49 mg, 0.16 mmol), gave a residue (83:17, *epi*-**286e**:**286e**) which was purified by gradient column chromatography (0–10% $Et_2O$ in petrol), to give *epi*-**286e** (33 mg, 67%) as a colourless liquid. $R_f$ = 0.22 (20% $Et_2O$ in petrol); $[\alpha]_D^{25}$ = −4.1 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$(film) 2988 w, 2953 w,

1765 s, 1735 s, 1437 m, 1382 m, 1209 s, 1140 s, 1139 w, 774 w, 701 m; $\delta_H$(400 MHz, $CDCl_3$) 7.37−7.23 (5H, m, ArH), 4.39 (1H, s, C*H*$CO_2$Me), 3.87 (3H, s, $CO_2$Me), 3.76 (3H, s, $CO_2$Me), 3.36 (1H, d, *J* = 14, CH*H*Ph), 3.22 (1H, d, *J* = 14, C*H*HPh), 1.56 (3H, s, one $CH_3$ of C(C*H*$_3$)$_2$), 1.00 (3H, s, one $CH_3$ of C(C*H*$_3$)$_2$); $\delta_C$(100 MHz, $CDCl_3$) 171.8 (*C*$O_2$Me), 168.0 (*C*$O_2$Me), 134.5 (quat. ArC), 131.4 (ArC), 128.4 (ArC), 127.4 (ArC), 111.7 (*C*(CH$_3$)$_2$), 86.2 (*C*$CH_2$Ph), 78.4 (*C*HCO$_2$Me), 52.8 (CO$_2$*Me*), 52.7 (CO$_2$*Me*), 39.9 (*C*$H_2$Ph), 26.9 (C(*C*H$_3$)$_2$), 26.3 (C(*C*H$_3$)$_2$); HRMS *m*/*z* [M+H$^+$] found: 309.1333, $C_{16}H_{21}O_6$ requires 309.1332.

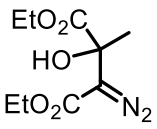
**Dimethyl (4*R*,5*S*)-2,2-dimethyl-4-(but-3-enyl)-1,3-dioxolane-4,5-dicarboxylate (*epi*-286f).**




Following the procedure for *epi*-**286d** above, but using butenylated tartrate **286f** (49 mg, 0.18 mmol), gave a residue (75:25, *epi*-**286f**:**286f**) which was purified by gradient column chromatography (0–10% $Et_2O$ in petrol), to give *epi*-**286f** (30 mg, 61%) as a colourless liquid. $R_f$ = 0.21 (20% $Et_2O$ in petrol); $[\alpha]_D^{25}$ = −24.6 (*c* 1.0, $CHCl_3$); $\nu_{max}$/cm$^{-1}$(neat) 2985 m, 2954 m, 1767 s, 1736 s, 1438 m, 1382 m, 1247 m, 1210 s, 1107 s, 668 m; $\delta_H$(400 MHz, $CDCl_3$) 5.86–5.74 (1H, m, $CH_2$C*H*=$CH_2$), 5.08–4.95 (2H, m, $CH_2$CH=C*H*$_2$), 4.48 (1H, s, C*H*$CO_2$Me), 3.79 (3H, s, $CO_2$Me), 3.71 (3H, s, $CO_2$Me), 2.31–2.20 (2H, m, C*H*H$CH_2$CH=$CH_2$ and $CH_2$CH*H*CH=$CH_2$), 2.13–2.03 (1H, m, $CH_2$C*H*HCH=$CH_2$), 1.94–1.84 (1H, m, CH*H*$CH_2$CH=$CH_2$), 1.61 (3H, s, one $CH_3$ of C(C*H*$_3$)$_2$), 1.42 (3H, s, one $CH_3$ of C(C*H*$_3$)$_2$); $\delta_C$(100 MHz, $CDCl_3$) 171.6 (*C*$O_2$Me), 168.0 (*C*$O_2$Me), 137.3 (*C*H=$CH_2$), 115.4 (CH=*C*$H_2$), 112.0 (*C*(CH$_3$)$_2$), 86.4 (*C*$CH_2CH_2$CH=$CH_2$), 80.9 (*C*HCO$_2$Me), 52.7 (CO$_2$*Me*), 52.6 (CO$_2$*Me*), 35.5 (*C*$H_2CH_2$CH=$CH_2$), 28.3 ($CH_2$*C*$H_2$CH=$CH_2$), 26.9 (C(*C*H$_3$)$_2$), 26.9 (C(*C*H$_3$)$_2$); HRMS *m*/*z* (M+H$^+$) found: 273.1332, $C_{13}H_{21}O_6$ requires 273.1332.

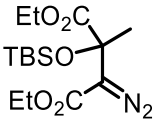
## 8.2.5 Preparation and Stability of β-Substituted α-Diazoesters Towards Ozone

### Diethyl 3-diazo-2-hydroxy-2-methylsuccinate (346)



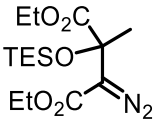

The procedure of Padaw and co-workers[156] was followed with slight modifications. A solution of LDA [prepared from *n*-BuLi (3.1 mL, 1,4 M in hexanes, 4.6 mmol) and *i*-$Pr_2NH$ (600 μL, 4.6 mmol) in THF (5 mL) at –78 °C] was added dropwise to a stirred solution of ethyl diazoacetate (**304**) (525 mg, 4.60 mmol) and ethyl pyruvate (**305**) (534 mg, 4.60 mmol) in THF (20 mL) at –78 °C. The solution was warmed to rt and stirred for 3 h, and then AcOH (0.26 mL, 4.6 mmol) added dropwise. The mixture was extracted with $Et_2O$ (2 x 15 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (10% $Et_2O$ in petrol) to give diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**346**) (825 mg, 78%), as a yellow liquid; $R_f$ = 0.27 (30% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 3380 br, 2956 m, 2096 s, 1745 s and 1698 s; $^1H$ NMR (400 MHz; $CDCl_3$) δ 4.29–4.16 (4H, m, 2 x OC*H*$_2$Me), 4.13 (1H, s, OH), 1.56 (3H, s, Me), 1.30–1.22 (6H, m, 2 x $OCH_2$*Me*); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 173.8 (*C*$O_2$Et), 165.7 (*C*$O_2$Et), 71.6 (quat. C), 62.9 ($OCH_2$), 61.3 ($OCH_2$), 23.8 (Me), 14.5 ($OCH_2CH_3$), 14.2 ($OCH_2CH_3$); HRMS *m/z* ($M+Na^+$) found: 253.0795, $C_9H_{14}O_5N_2{}^{23}Na$ requires 253.0794.

**Diethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-diazo-2-methylsuccinate (306a)**




TBSOTf (0.4 mL, 1.7 mmol) was added to 2,6-lutidine (0.3 mL, 2.6 mmol) in $CH_2Cl_2$ (1 mL) and stirred for 10 min at 0 °C. A solution of diethyl 3-diazo-2-hydroxy-2-methylsuccinate **350** (200 mg, 0.87 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was then added. The mixture was warmed to rt and stirred for 48 h. The mixture was quenched with water (4 mL), extracted with $CH_2Cl_2$ (3 x 10 mL), washed with brine (10 mL) and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by column chromatography (10% $Et_2O$ in petrol) to give TBS ether **306a** (227 mg 76%); $R_f$ = 0.3 (20% $Et_2O$ in petrol); $\nu_{max}$/cm$^{-1}$(film) 2956 m, 2931 m, 2858 m, 2096 s, 1745 s, 1698 s, 1464 m, 1309 s, 1255 s, 1144 s, 1069 s, 839 w; $^1$H NMR (400 MHz; $CDCl_3$) δ 4.25–4.14 (4H, m, 2 x OC*H*$_2$CH$_3$), 1.66 (3H, s, Me), 1.30–1.22 (6H, m, 2 x OCH$_2$C*H*$_3$), 0.86 (9H, s, OSiC(CH$_3$)$_3$), 0.11 and 0.08 (6H, 2 x s, OSi(CH$_3$)$_2$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 172.0 (*C*O$_2$Et), 165.0 (*C*O$_2$Et), 73.7 (quat. C), 62.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 25.7 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$) –3.0 (OSi(CH$_3$)$_2$), –3.5 (OSi(CH$_3$)$_2$); HRMS [M+Na$^+$] found: 367.1656. $C_{15}H_{28}O_5N_2{}^{28}Si^{23}Na$ requires 367.1659.

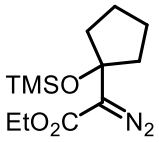
**Diethyl 3-diazo-2-methyl-2-((triethylsilyl)oxy)succinate (306b)**




Following the procedure for silyl ether **306a** above, but using TESOTf, diethyl 3-diazo-2-hydroxy-2-methylsuccinate **350** (200 mg, 0.87 mmol) gave after column chromatography (10% $Et_2O$ petrol) TES ether **306b** (230 mg, 77%), as a yellow oil; $R_f$ = 0.3 (20% $Et_2O$ in petrol).

$\nu_{max}$/cm$^{-1}$(film) 2956 m, 2931 m, 2858 m, 2096 s, 1745 s, 1698 s, 1464 m, 1309 s, 1255 s, 1144 s, 1069 s, 839 w; $^{1}$H NMR (400 MHz; $CDCl_3$) δ 4.25–4.13 (4H, m, 2 x OC*H*$_2$CH$_3$), 1.67 (3H, s, Me), 1.27 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 1.24 (3H, t, *J* 7, OCH$_2$C*H*$_3$), 0.93 (9H, t, *J* 8, OSi(CH$_2$C*H*$_3$)$_3$), 0.62 (6H, q, *J* = 8, OSi(C*H*$_2$CH$_3$)$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 172.0 (*C*O$_2$Et), 165.1 (*C*O$_2$Et), 73.6 (quat. C), 61.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$) 6.9 (OSi(CH$_2$*C*H$_3$)$_3$), 6.1 (OSi(*C*H$_2$CH$_3$)$_3$); HRMS [M+Na$^+$] found: 367.1656. $C_{15}H_{28}O_5N_2{}^{23}Na^{28}Si$ requires 367.1659.

**Ethyl 2-diazo-2-(1-((trimethylsilyl)oxy)cyclopentyl)acetate (317)**

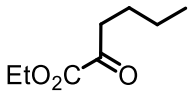



TMSCl (127 µL, 1.0 mmol) was added slowly to a solution of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate[156] **316** (100 mg, 0.50 mmol) and imidazole (170 mg, 2.50 mmol) in DMF (1.4 mL) at 0 °C. After 4 h at rt, $Et_2O$ (5 mL) was added, the organic layer was washed with water (2 x 2 mL), brine (2 mL) and dried ($Na_2SO_4$). After evaporation under reduced pressure, the residue was purified by column chromatography (0–10% $Et_2O$ in petrol) to give silyl ether **317** (118 mg, 87%), as a yellow liquid; $R_f$ = 0.59 (10% $Et_2O$ in petrol); $\nu_{max}$/cm$^{-1}$(film) 2960 m, 1714 s, 1370 w, 1204 m, 1040 m; $^{1}$H NMR (400 MHz; $CDCl_3$) δ 4.22 (2H, q, *J* = 7, OC*H*$_2$CH$_3$), 2.05–1.99 (2H, m, CH$_2$), 1.94–1.86 (2H, m, CH$_2$), 1.84–1.78 (2H, m, CH$_2$), 1.70–1.63 (2H, m, CH$_2$), 1.28 (3H, t, *J* = 7.0, OCH$_2$C*H*$_3$), 1.10 (OTMS); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 165.7 (*C*O$_2$Et), 81.0 (*C*OTMS), 61.6 (O*C*H$_2$CH$_3$), 40.1 (2 x CH$_2$), 22.8 (2 x CH$_2$), 14.7 (OCH$_2$*C*H$_3$), 1.5 (OSi(CH$_3$)$_3$); HRMS *m*/*z* (M+Na$^+$) found: 293.1292. $C_{12}H_{22}O_3N_2{}^{23}Na^{28}Si$ requires 293.1291.

### 8.2.5.1 General Procedure for Ozonolysis

A stream of $O_3/O_2$ was bubbled through a mixture of α-diazoester (1 mmol) and alkene **307**[198] (1 mmol) in $CH_2Cl_2$ at −78 °C until the colour of the reaction mixture changed from yellow to blue (~5 min). Then the excess of $O_3$ was removed by bubbling $N_2$ through the reaction mixture, following by addition of $Et_3N$ (3 mmol). After 4 h, the reaction mixture was evaporated under reduced pressure and the residue analysed by $^1$H NMR.

**Ethyl 2-oxohexanoate (350)**

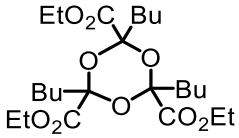



Following the general ozonolysis procedure above, α-diazoester **311** (100 mg, 0.58 mmol) was oxidised to give after column chromatography (5% EtOAc in petrol) an inseparable mixture of α-ketoester **350** and the corresponding trimer **351** (66 mg, 73%, ~60:40 respectively, by integration at **350** [δ $CH_2CH_2CO$] and **351** [δ $CH_2CH_2CO$] peaks), as a colourless liquid; $R_f$ = 0.56 (5% EtOAc in petrol); $\nu_{max}$/cm$^{-1}$(film) 2961 m, 2935 m, 1750 s, 1727 s, 1466 s, 1275 m, 1246 m, 1142 m, 1120 m, 1048 s, 856 m.

Data for α-ketoester **350**:

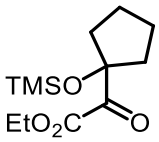
$^1$H NMR (400 MHz; $CDCl_3$) δ 4.30 (2H, q, $J$ = 7, $OCH_2CH_3$), 2.81 (2H, t, $J$ = 7, $CH_2CH_2CO$), 1.68–1.55 (2H, m, $CH_2CH_2CO$), 1.42–1.27 (5H, m, $CH_2$ and $CO_2CH_2CH_3$), 0.91 (3H, t, $J$ = 7, $OCH_2CH_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 194.9 (C=O), 161.5 ($CO_2$Et), 62.5 ($CO_2CH_2CH_3$), 39.1 ($CH_2CO$), 25.2 ($CH_2CH_2CO$), 22.2 ($CH_3CH_2CH_2$), 14.1 ($OCH_2CH_3$), 13.9 ($CH_2CH_3$); HRMS $m/z$ ($M+Na^+$) found: 181.0836. $C_8H_{14}O_3{}^{23}Na$ requires 181.0835.

Data for **triethyl 2,4,6-tributyl-1,3,5-trioxane-2,4,6-tricarboxylate 351**:



$^{1}$H NMR (400 MHz; $CDCl_3$) δ 4.27–4.21 (1H, m, OC*H*$_2$CH$_3$), 2.10–1.91 (1H, m, CH$_2$C*H*$_2$CO), 1.42–1.27 (5H, m, 2 x CH$_2$ and CO$_2$CH$_2$C*H*$_3$), 0.88 (2H, t, OCH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 168.2 (*C*O$_2$Et), 107.6 (quat. C), 62.1 (CO$_2$*C*H$_2$CH$_3$), 31.6 (*C*H$_2$CO), 25.0 (*C*H$_2$CH$_2$CO), 22.6 (CH$_3$*C*H$_2$CH$_2$), 14.2 (OCH$_2$*C*H$_3$), 13.8 (CH$_2$*C*H$_3$).

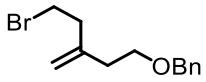
**Ethyl 2-oxo-2-(1-((trimethylsilyl)oxy)cyclopentyl)acetate (352)**



Following the general ozonolysis procedure above, TMS ether **317** (47 mg, 0.17 mmol) was oxidised to give after column chromatography (10% Et$_2$O in petrol) α-ketoester **352** (17 mg, 39%), as a colourless liquid; $R_f$ = 0.5 (10% Et$_2$O in petrol); $\nu_{max}$/cm$^{-1}$(film) 2958 m, 1727 s, 1251 s, 1216 m, 1066 s, 1028 m, 917 m, 839 s; $^{1}$H NMR (400 MHz; $CDCl_3$) δ 4.31 (2H, q, *J* = 7, OC*H*$_2$CH$_3$), 2.26–2.15 (2H, m, CH$_2$), 1.93–1.87 (2H, m, CH$_2$), 1.85–1.78 (2H, m, CH$_2$), 1.77–1.69 (2H, m, CH$_2$), 1.36 (3H, t, *J* = 7, OCH$_2$C*H*$_3$), 0.13 (3H, s, OTMS); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 200.0 (C=O), 165.2 (*C*O$_2$Et), 88.8 (*C*OTMS), 61.9 (O*C*H$_2$CH$_3$), 39.0 (2 x CH$_2$), 24.7 (2 x CH$_2$), 14.2 (OCH$_2$*C*H$_3$), 1.8 (OSi(CH$_3$)$_3$); HRMS *m*/*z* (M+Na$^+$) found: 281.1180. C$_{12}$H$_{22}$O$_4$$^{23}$Na$^{28}$Si requires 281.1179.

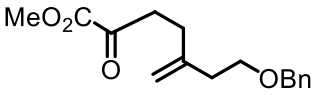
## 8.2.6 Synthesis of α-Diazo-ε-Ketoesters (334).

### (((5-Bromo-3-methylenepentyl)oxy)methyl)benzene (324)




$Ph_3P$ (365 mg, 1.39 mmol) and $CBr_4$ (577 mg, 1.74 mmol) was added to a solution of 5-(benzyloxy)-3-methylenepentan-1-ol[57] **323** (240 mg, 1.16 mmol) in $CH_2Cl_2$ (8 mL) at rt. After 10 min, the reaction mixture was poured into sat. aq. $NaHCO_3$ (5 mL) and the aq. layer was extracted with $CH_2Cl_2$ (2 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (5% $Et_2O$ in petrol) to give bromide **324** (225 mg, 72%), as a colourless oil; $R_f$ = 0.41 (5% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2858 w, 1646 m, 1453 m, 1208 m, 1098 s, 901 s, 736 s, 697 s; $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.40–7.25 (5H, m, Ar*H*), 4.94 (1H, s, C=CH*H*), 4.89 (1H, s, C=C*H*H), 4.53 (2H, s, C$H_2$Ph), 3.59 (2H, t, *J* = 7, C$H_2$OBn), 3.47 (2H, t, *J* = 7, $CH_2Br$), 2.62 (2H, t, *J* = 7, C$H_2CH_2Br$), 2.36 (2H, t, *J* = 7.0, C$H_2CH_2$OBn; $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 143.7 (*C*=$CH_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 113.4 (C=*C*$H_2$), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 39.7 (*C*$H_2CH_2Br$), 35.9 (*C*$H_2CH_2$OBn), 31.0 ($CH_2Br$); HRMS *m*/*z* ($M+Na^+$) found: 291.0354. $C_{13}H_{17}O^{79}Br^{23}Na$ requires 291.0355.

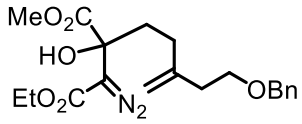
### Methyl 7-(benzyloxy)-5-methylene-2-oxoheptanoate (299)




To a solution of (((5-iodo-3-methylenepentyl)oxy)methyl)benzene (**174**)[57] (100 mg, 0.31 mmol) in $Et_2O$ (3 mL) at –78 °C was added *t*-BuLi (0.44 mL, 1.7 M in pentane, 0.75 mmol) dropwise. After 1 h, the reaction mixture was transferred slowly by cannula to a solution of

dimethyl oxalate (**325**) (186 mg, 1.58 mmol) in THF (0.5 mL) at –78 °C and stirred for 4 h. Then, sat. aq. $NH_4Cl$ (2 mL) was added and the mixture allowed to warm to rt. The aq. layer was extracted with $Et_2O$ (2 x 5 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (20% $Et_2O$ in petrol) gave α-ketoester **299** (32 mg, 37%), as a colourless liquid; $R_f$ = 0.15 (20% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2931 m, 1743 s, 1452 w, 1276 m, 1099 m, 716 w; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.40–7.26 (5H, m, Ar*H*), 4.84 (1H, s, C=CH*H*), 4.80 (1H, s, C=C*H*H), 4.51 (2H, s, C$H_2$Ph), 3.86 (3H, s, $CO_2Me$), 3.58 (2H, t, *J* = 7, C$H_2$OBn), 3.00 (2H, t, *J* = 7, $CH_2C$=O), 2.42–2.33 (4H, m, C$H_2$C(=$CH_2$)C$H_2$); $^{13}C$ NMR (125 MHz; $CDCl_3$) δ 193.6 (C=O), 161.5 (*C*$O_2$Me), 144.7 (*C*=$CH_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=*C*$H_2$), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 53.1 ($CO_2$*Me*), 37.7 (*C*$H_2CH_2$OBn), 36.5 (*C*$H_2CH_2$C=O), 29.3 ($CH_2$*C*$H_2$C=O); HRMS *m*/*z* ($M+Na^+$) found: 299.1254. $C_{16}H_{20}O_4{}^{23}Na$ requires 299.1264.

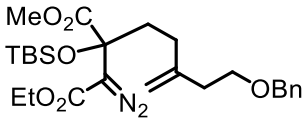
**4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-3-diazo-2-hydroxysuccinate (327)**



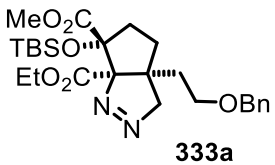

A solution of LDA [prepared from *n*-BuLi (90 µL, 2.5 M in hexanes, 0.22 mmol) and *i*-$Pr_2NH$ (30 µL, 0.22 mmol) in THF (1 mL) at −78 °C] was added dropwise to a solution of ethyl diazoacetate (**304**) (23 µL, 0.22 mmol) and α-ketoester **299** (36 mg, 0.13 mmol) in THF (350 µL) at – 78 °C. After 2 h, the reaction mixture was quenched with $NH_4Cl$ (2 mL), extracted with $Et_2O$ (2 x 5 mL), and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by short column chromatography (10% EtOAc in petrol) to give diazo-alcohol **327** (40 mg, 78%), as a yellow oil; $R_f$ = 0.25 (50% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 3390

br, 3027 w, 2920 m, 1732 s, 1453 m, 1261 s, 1097 s, 739 m, 699 m; $^{1}$H NMR (500 MHz; $CDCl_3$) δ 7.39–7.26 (5H, m, Ar*H*), 4.82 (1H, s, C=C*H*H), 4.80 (1H, s, C=CH*H*), 4.50 (2H, s, C$H_2$Ph), 4.28–416 (2H, m, $CO_2CH_2CH_3$), 3.78 (3H, s, $CO_2Me$), 3.56 (2H, t, *J* = 7, C$H_2$OBn), 2.34 (2H, t, *J* = 7, C$H_2CH_2$OBn), 2.32–2.26 (1H, m, CH*H*C(OH)), 2.02–1.97 (1H, m, C*H*HC(OH)), 1.96–1.90 (2H, m, C$H_2CH_2$C(OH)), 1.27 (3H, t, *J* = 7, $CO_2CH_2CH_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 173.6 (*C*$O_2$Me), 165.9 (*C*$O_2$Et), 145.2 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=*C*$H_2$), 73.8 (quat. *C*(OH)$CO_2$Me), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.4 ($CO_2CH_2CH_3$), 53.6 ($CO_2Me$), 36.4 and 34.6 ($CH_2C(=CH_2)CH_2$), 29.7 ($CH_2C(OH)$), 14.5 ($CO_2CH_2CH_3$); HRMS *m*/*z* ($M+H^+$) found: 391.1882. $C_{20}H_{27}O_6N_2$ requires 391.1863.

**4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-2-((*tert*-butyldimethylsilyl)oxy)-3-diazosuccinate (332a)** and **6a-Ethyl 6-methyl (3a*R*, 6*S*, 6a*R*)-3a-(2-(benzyloxy)ethyl)-6-((*tert*-butyl dimethylsilyl)oxy)-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a (3*H*)-dicarboxylate (333a)**




**332a**



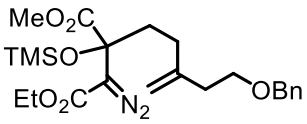

**333a**

TBSOTf (35 µL, 0.15 mmol) was added to a solution of 2,6-lutidine (26 µL, 0.22 mmol) in $CH_2Cl_2$ (200 µL) at 0 °C and stirred for 15 min. A solution of diazo-alcohol **327** (30 mg, 0.076 mmol) in $CH_2Cl_2$ (200 µL) was added. The reaction mixture was stirred for 48 h at rt, then water was added, extracted with $CH_2Cl_2$ (2 × 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude mixture was purified by column chromatography (0–20% $Et_2O$ in petrol).

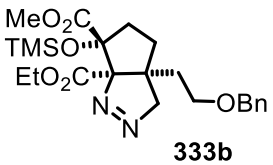
First eluted TBS ether **332a** (7 mg, 18%), as a yellow oil; $R_f$ = 0.23 (20% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2953 m, 2857 m, 2096 s, 1745 s, 1701 s, 1454 w, 1369 m, 1304 s, 1254 m, 1135 s, 838 s, 780 m; $^1$H NMR (400 MHz; $CDCl_3$) δ 7.37–7.26 (5H, m, Ar*H*), 4.80 (2H, s, C=C$H_2$), 4.50 (2H, s, C$H_2$Ph), 4.26–4.11 (2H, m, $CO_2CH_2CH_3$), 3.72 (3H, s, $CO_2Me$), 3.55 (2H, t, *J* = 7, C$H_2$OBn), 2.33 (2H, t, *J* = 7, C$H_2CH_2$OBn), 2.24–1.94 (4H, m, C$H_2CH_2$C(OTBS)), 1.24 (3H, t, *J* = 7, $CO_2CH_2CH_3$), 0.88 (9H, s, $OSiCMe_3$), 0.11 and 0.05 (6H, 2 x s, $OSi(CH_3)_2$); $^{13}$C NMR (100 MHz; $CDCl_3$) δ 173.6 (*C*$O_2$Me), 145.6 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.2 (C=*C*$H_2$), 76.0 (quat. *C*(OTBS)$CO_2$Me), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.1 ($CO_2CH_2CH_3$), 52.8 ($CO_2Me$), 36.9 and 36.4 (*C*$H_2$C(=$CH_2$)*C*$H_2$), 30.2 (*C*$H_2$C(OH)), 25.9 (SiC(*C*$H_3$)$_3$), 18.6 (Si*C*$(CH_3)_3$), 14.6 ($CO_2CH_2CH_3$), –3.4 and –3.08 (2 x $SiCH_3$); HRMS *m*/*z* ($M+H^+$) found: 505.2729. $C_{26}H_{41}O_6N_2{}^{28}Si$ requires 505.2728.

Second eluted cycloadduct **333a** (14 mg, 37%), as a pale yellow oil; $R_f$ = 0.34 (20 % $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2928 m, 2855 m, 1741 s, 1454 m, 1365 w, 1313 m, 1253 s, 1100 m, 1056 m, 838 s, 779 m; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.38–7.27 (5H, m, Ar*H*), 4.73 (1H, d, *J* = 18.5, CH*H*N=N), 4.52–4.43 (3H, m, C$H_2$Ph and CH*H*N=N), 4.21–4.14 (2H, m, $CO_2CH_2CH_3$), 3.79 (3H, s, $CO_2Me$), 3.57–3.48 (2H, m, C$H_2$OBn), 2.41–2.32 (1H, m, CH*H*C(OTBS)), 2.09–2.02 (1H, m, CH*H*$CH_2$C(OTBS)), 1.88–1.78 (2H, m, C*H*HC(OTBS) and CH*H*$CH_2$OBn), 1.65–1.60 (1H, m, C*H*H$CH_2$OBn), 1.57–1.50 (1H, m, C*H*H$CH_2$C(OTBS)), 1.25 (3H, t, *J* = 7, $CO_2CH_2CH_3$), 0.82 (9H, s, $OSiCMe_3$), 0.05 (6H, 2 x s, $OSi(CH_3)_2$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 172.0 (*C*$O_2$Me), 168.2 (*C*$O_2$Et), 138.1 (Ar*C*), 128.6 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (Ar*C*H), 110.5 (quat. *C*$CO_2$Et), 90.9 ($CH_2$N=N), 87.1 (quat. *C*(OTBS)$CO_2$Me), 73.4 (*C*$H_2$Ph), 67.8 (*C*$H_2$OBn), 61.9 ($CO_2CH_2CH_3$), 52.3 ($CO_2Me$), 49.6 (quat. *C*$CH_2$N=N), 37.4 (*C*$H_2$C(OTBS)), 35.3 (*C*$H_2CH_2$OBn), 34.5 (*C*$H_2CH_2$C(OTBS)), 25.7 (SiC(*C*$H_3$)$_3$), 18.5 (Si*C*$(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$), –3.1 and –4.0 (2 x $SiCH_3$); HRMS *m*/*z* ($M+H^+$) found: 505.2732. $C_{26}H_{41}O_6N_2{}^{28}Si$ requires 505.2728.

**4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-methylenepentyl)-3-diazo-2-((trimethylsilyl)oxy) succinate (332b)** and **6a-Ethyl 6-methyl (3a*R*, 6*S*, 6a*R*)-3a-(2-(benzyloxy)ethyl)-6-((trimethylsilyl)oxy)-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a(3*H*)-dicarboxylate (333b)**




**332b**




**333b**

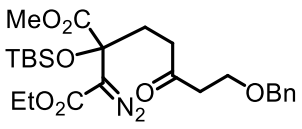
Hexamethyldisilazane (66 µL, 0.32 mmol) was added to a solution of diazo-alcohol **327** (30 mg, 0.076 mmol) and imidazole (11 mg, 0.16 mmol) in THF (0.8 mL) at rt. After 48 h, the reaction mixture was concentrated by blowing nitrogen, followed by purification of the residue by column chromatography (0–10% $Et_2O$ in petrol).

First eluted TMS ether **332b** (14 mg, 40%), as a yelow oil; $R_f$ = 0.26 (20% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2954 m, 2096 s, 1744 s, 1701 s, 1454 m, 1369 m, 1304 s, 1251 s, 1135 m, 844 s; $^1H$ NMR (400 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.80 (2H, s, C=C$H_2$), 4.51 (2H, s, C$H_2$Ph), 4.26–4.11 (2H, m, $CO_2CH_2CH_3$), 3.73 (3H, s, $CO_2Me$), 3.56 (2H, t, *J* = 7, C$H_2$OBn), 2.34 (2H, t, *J* = 7, C$H_2CH_2$OBn), 2.22–1.92 (4H, m, C$H_2CH_2$C(OTBS)), 1.25 (3H, t, *J* = 7, $CO_2CH_2CH_3$), 0.13 (9H, s, OTMS); $^{13}C$ NMR (100 MHz; $CDCl_3$) δ 171.8 (*C*$O_2$Me), 164.9 (*C*$O_2$Et), 145.6 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.1 (C=*C*$H_2$), 76.2 (quat. *C*(OTMS)$CO_2$Me), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.0 ($CO_2CH_2CH_3$), 52.8 ($CO_2Me$), 36.7 and 36.5 (*C*$H_2$C(=$CH_2$)*C*$H_2$), 30.2 (*C*$H_2$C(OTMS)), 14.6 ($CO_2CH_2CH_3$), 1.4 (OTMS); HRMS *m*/*z* ($M+H^+$) found: 463.2258. $C_{23}H_{35}O_6N_2{}^{28}Si$ requires 463.2258.

Second eluted cycloadduct **333b** (11 mg, 31%), as a pale yellow oil; $R_f$ = 0.34 (20% $Et_2O$ in petrol); $\nu_{max}/cm^{-1}$(film) 2951 m, 2928 m, 1741 s, 1455 m, 1254 s, 1101 m, 1056 m, 839 s, 779 m; $^1H$ NMR (500 MHz; $CDCl_3$) δ 7.38–7.27 (5H, m, Ar*H*), 4.72 (1H, d, *J* = 18.5, CH*H*N=N),

4.53–4.42 (3H, m, C*H*$_2$Ph and CH*H*N=N), 4.21–4.14 (2H, m, $CO_2CH_2CH_3$), 3.80 (3H, s, $CO_2Me$), 3.56–3.47 (2H, m, C*H*$_2$OBn), 2.33 (1H, dt, *J* = 13.5 and 7.5, CH*H*C(OTBS)), 2.12–2.04 (1H, m, CH*H*CH$_2$C(OTBS)), 1.85 (1H, dt, *J* = 13.5 and 5.5, CH*H*CH$_2$OBn), 1.75 (1H, ddd, *J* = 13.5, 7.5 and 6.5, C*H*HC(OTBS)), 1.64–1.52 (1H, m, C*H*HCH$_2$OBn and C*H*HCH$_2$C(OTBS)), 1.24 (3H, t, *J* = 7, $CO_2CH_2CH_3$), 0.10 (9H, s, $OSi(CH_3)_3$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 172.4 (*C*$O_2$Me), 167.8 (*C*$O_2$Et), 138.2 (Ar*C*), 128.6 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 110.1 (quat. *C*$CO_2$Et), 91.9 ($CH_2N$=N), 87.0 (quat. *C*(OTBS)$CO_2$Me), 73.4 (*C*$H_2$Ph), 67.7 (*C*$H_2$OBn), 61.8 ($CO_2CH_2CH_3$), 52.3 ($CO_2Me$), 49.6 (quat. *C*$CH_2$N=N), 37.5 (*C*$H_2$C(OTBS)), 35.5 (*C*$H_2CH_2$OBn), 34.8 (*C*$H_2CH_2$C(OTBS)), 14.2 ($CO_2CH_2CH_3$), 1.6 ($Si(CH_3)_3$); HRMS *m*/*z* ($M+H^+$) found: 463.2251. $C_{23}H_{35}O_6N_2{}^{28}Si$ requires 463.2258.

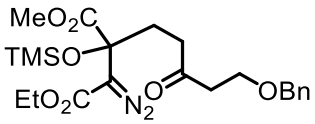
**4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-oxopentyl)-2-((tert-butyl dimethylsilyl)oxy)-3-diazosuccinate (334a)**




Following the general procedure for ozonolysis above, using TBS ether **332a** (4 mg, 0.008 mmol), gave after column chromatography (0–40% $Et_2O$ in petrol) diazo-ketone **334a** (2.3 mg, 58%), as a yellow oil; $R_f$ = 0.53 (50% $Et_2O$ in petrol); $\nu_{max}$/cm$^{-1}$(film) 2931 m, 2856 m, 2095 s, 1747 s, 1700 s, 1456 w, 1305 m, 1256 m, 1132 m, 838 m; $^1$H NMR (500 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.50 (2H, s, C*H*$_2$Ph), 4.24–4.12 (2H, m, $CO_2CH_2CH_3$), 3.75–3.68 (5H, m, $CO_2$Me and C*H*$_2$OBn), 2.69 (2H, t, *J* = 6, C*H*$_2CH_2$OBn), 2.67–2.61 (1H, m, CH*H*C(OTBS)), 2.51–2.44 (1H, m, C*H*HC(OTBS)), 2.27–2.21 (2H, m, C*H*$_2CH_2$C(OTBS)), 1.24 (3H, t, *J* = 7, $OCH_2CH_3$), 0.86 (9H, s, $OSiCMe_3$), 0.09 and 0.04 (6H, 2 x s, $OSi(CH_3)_2$); $^{13}$C NMR (125 MHz; $CDCl_3$) δ 207.7 (C=O), 171.4 (*C*$O_2$Me), 164.8 (*C*$O_2$Et), 138.2 (ArC), 128.5 (ArCH), 127.8

(ArCH), 127.8 (ArCH), 75.6 (quat. *C*(OTBS)$CO_2$Me), 73.4 (*C*$H_2$Ph), 65.4 (*C*$H_2$OBn), 61.2 ($CO_2$*C*$H_2CH_3$), 52.9 ($CO_2$*Me*), 43.2 (O=C–*C*$H_2$), 37.8 (O=C–*C*$H_2$), 32.2 (*C*$H_2$C(OTBS)), 25.9 (SiC(*C*$H_3$)$_3$), 18.6 (Si*C*($CH_3$)$_3$), 14.6 ($CO_2CH_2$*C*$H_3$), –3.5 and –3.9 (2 x Si$CH_3$); HRMS *m*/*z* (M+$Na^+$) found: 529.2341. $C_{25}H_{38}O_7N_2{}^{23}Na^{28}Si$ requires 529.2340.

**4-Ethyl 1-methyl 2-(5-(benzyloxy)-3-oxopentyl)-3-diazo-2-((tri methylsilyl)oxy)succinate (334b)**




Following the procedure for ozonolysis above, using TMS ether **3336** (6 mg, 0.013 mmol), gave after column chromatography (0–40% $Et_2O$ in petrol) diazo-ketone **334b** (3.7 mg, 61%), as a yellow oil; $R_f$ = 0.51 (50% $Et_2O$ in petrol); $\nu_{max}$/$cm^{-1}$(film) 2953 w, 2871 w, 2096 s, 1747 s, 1702 s, 1455 w, 1369 m, 1305 s, 1251 s, 1135 m, 845 s. $^1$H NMR (500 MHz; $CDCl_3$) δ 7.37–7.27 (5H, m, Ar*H*), 4.50 (2H, s, C*H*$_2$Ph), 4.27–4.11 (2H, m, $CO_2$C*H*$_2CH_3$), 3.75–3.71 (5H, m, $CO_2$Me and C*H*$_2$OBn), 2.70 (2H, t, *J* = 6.5, C*H*$_2CH_2$OBn), 2.66–2.58 (1H, m, CH*H*C(OTMS)), 2.48–2.41 (1H, m, C*H*HC(OTMS)), 2.26–2.20 (2H, m, C*H*$_2CH_2$C(OTMS)), 1.25 (3H, t, *J* = 7, $OCH_2$C*H*$_3$), 0.11 (3H, s, OTMS). $^{13}$C NMR (125 MHz; $CDCl_3$) δ 207.8 (C=O), 171.5 (*C*$O_2$Me), 164.8 (*C*$O_2$Et), 138.2 (ArC), 128.6 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 75.8 (quat. *C*(OTMS)$CO_2$Me), 73.4 (*C*$H_2$Ph), 65.4 (*C*$H_2$OBn), 61.2 ($CO_2$*C*$H_2CH_3$), 53.0 ($CO_2$*Me*), 43.2 (O=C–*C*$H_2$), 37.7 (O=C–*C*$H_2$), 32.2 (*C*$H_2$C(OTMS)), 14.6 ($CO_2CH_2$*C*$H_3$), 1.3 (OTMS). RMS *m*/*z* (M+$Na^+$) found: 487.1867. $C_{22}H_{32}O_7N_2{}^{23}Na^{28}Si$ requires 487.1871.

# Chapter 9

# References

## 9. References


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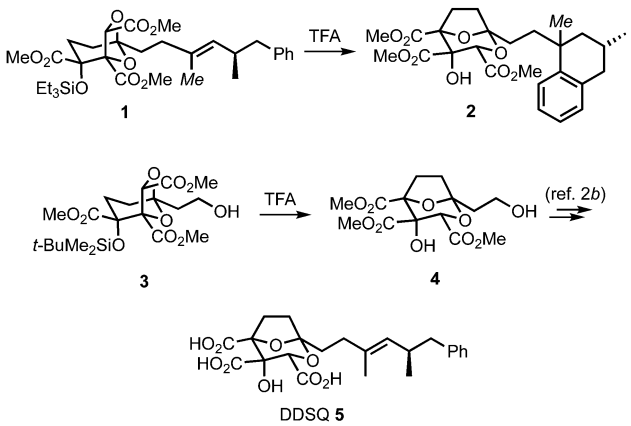
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# Alkene protection against acid using a bromide substituent: application in a total synthesis of (−)-6,7-dideoxysqualestatin H5†

Hasanain A. A. Almohseni,‡ Hamad H. Al Mamari,§ Anne Valade,¶ Herman O. Sintim ‖ and David M. Hodgson *

**The presence of a bromide substituent, instead of a hydrogen or methyl group, on a carbon–carbon double bond, protects the alkene from addition reactions when exposed to trifluoroacetic acid. This concept is used to circumvent concomitant loss of unsaturation in a late-stage acid-catalysed 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement towards (−)-6,7-dideoxysqualestatin H5. The inertness of the alkenyl bromide functionality is demonstrated through several synthetic transformations in the assembly of the rearrangement substrate. Completion of the natural product synthesis is facilitated by post-rearrangement removal of the bromide substituent through stereoselective C–C cross-coupling in the presence of ester and hydroxyl functionalities.**

(−)-6,7-Dideoxysqualestatin H5 (DDSQ) **5** (Scheme 1) is a member of the zaragozic acid/squalestatin family of natural products which display a variety of interesting bioactivities.[1,2] Structurally, DDSQ possesses a synthetically challenging 2,8-dioxabicyclo[3.2.1]octane core bearing a hydroxyl and three carboxylic acid groups and an unsaturated hydrocarbon side-chain at C-1. In an earlier study, we attempted to access DDSQ through acid-catalysed transketalisation of the advanced intermediate **1**.[3] Rearrangement to the desired core could be induced, however concomitant loss of the unsaturation in the side-chain by protonation/Friedel–Crafts cyclisation to give tetralin **2** could not be avoided. Although this problem could be solved by introducing the olefin after the rearrangement (**3** → **4** → **5**),[2b] we became intrigued by the issue of how to directly protect this type of electron-rich carbon–carbon double bond from such unwanted reactivity. While masking the alkene could potentially be achieved in numerous ways,[4] we were attracted to the idea of reducing its propensity to protonation through the presence of a temporary halide substituent. Here, we communicate the realisation of this concept, and its application in a synthesis of DDSQ **5** by halide replacement of the alkenyl methyl group in rearrangement substrate **1** (italicised Me).




Scheme 1 Transketalisation approaches to (−)-6,7-dideoxysqualestatin H5 **5**.

The *Z*-alkenyl halide functionality envisaged in the rearrangement substrate for DDSQ synthesis discussed above would not only have to remain inert during transketalisation. It would also be required to pass unscathed through several synthetic steps in the construction of the substrate (*vide infra*), and yet would need enough reactivity to undergo stereoretentive (and chemoselective – in the presence of ester functionality) cross-coupling with a methyl donor;[5] we therefore focused on bromide (rather than iodide or chloride) as the halide substituent. Before embarking on the target synthesis with this modification in place, the following observations provided initial support for the idea of alkene protection from an acid such as TFA, by a bromide substituent. 2-Methyl-1-octene (**6a**, Scheme 2) is known to be entirely converted to the corresponding tertiary

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† Electronic supplementary information (ESI) available: Experimental procedures, model studies and copies of $^{1}$H NMR and $^{13}$C NMR spectra of all new compounds. See DOI: 10.1039/c8cc02690d

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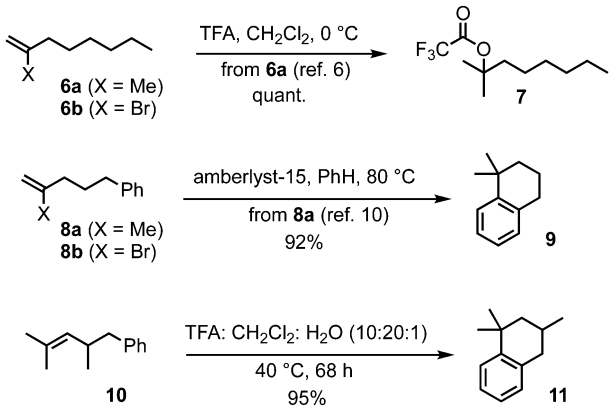
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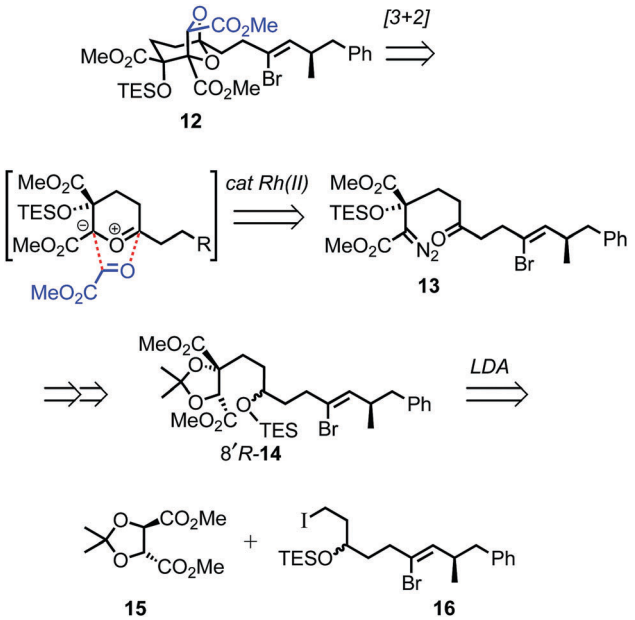
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Scheme 2 Addition and cyclisation reactions of alkenes with acids.

trifluoroacetate **7** within 20 min using TFA (5 equiv.) in $CH_2Cl_2$ at 0 °C,[6,7] whereas 2-bromo-1-octene (**6b**)[8] was recovered unchanged from exposure to the acidic conditions typically necessary to induce the acid-catalysed 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement [TFA/$CH_2Cl_2$/$H_2O$ (10 : 20 : 1), 40 °C, 48–68 h].[2b,9] Also, 2-methyl-5-phenylpentene (**8a**) is known to undergo Friedel–Crafts cyclisation to 1,1-dimethyltetralin (**9**) with acid,[10] and, similarly, we found 2,4-dimethyl-5-phenyl-2-pentene (**10**) with TFA gave the corresponding tetralin **11** in 95% yield (Scheme 2); in contrast, 2-bromo-5-phenylpentene (**8b**)[11] was recovered quantitatively from exposure to the standard TFA rearrangement conditions.

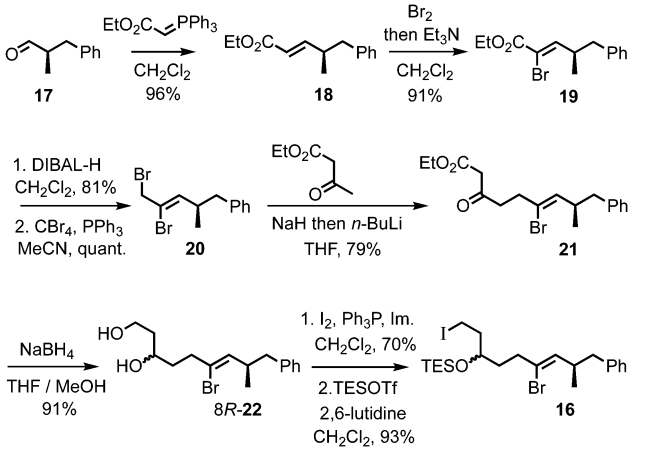
For the prospective synthesis of (−)-DDSQ **5**, the *Z*-alkenyl bromide-bearing rearrangement substrate **12** was anticipated to be available through a Rh(II)-catalysed tandem carbonyl ylide formation and cycloaddition of a diazoketone **13** with methyl glyoxylate (Scheme 3).[12] In turn, diazoketone **13** was considered as being accessible from substituted tartrate **14**, with the latter




Scheme 3 Outline of projected route to *Z*-alkenyl bromide-bearing rearrangement substrate **12**.

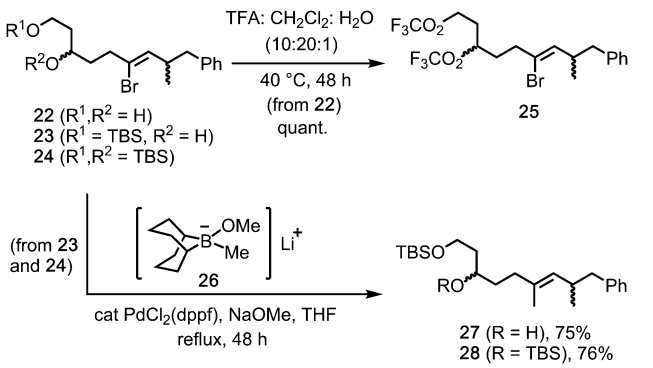
expected to arise through application of Seebach's tartrate alkylation methodology[2b,13] using the enolate of tartrate **15** and iodide **16**.

Access to the *Z*-alkenyl bromide-containing iodide **16** for tartrate alkylation was achieved from *R*-aldehyde **17**[14] (Scheme 4). Wittig olefination (known to proceed without erosion of enantiointegrity with such an ester-stabilised ylide on a related α-methyl aldehyde[15]) to give *E*-enoate **18**, was followed by bromination–dehydrobromination[15] to give the *Z*-α-bromoenoate **19**. The dianion of ethyl acetoacetate[16] was efficiently alkylated with the derived allylic bromide **20**, and the resulting β-ketoester **21** was reduced to the 1,3-diol **22** using $NaBH_4$ in MeOH/THF.[17] Iodination of the primary alcohol and TES protection of the secondary alcohol gave the iodide **16**.




Scheme 4 Synthesis of iodide **16**.

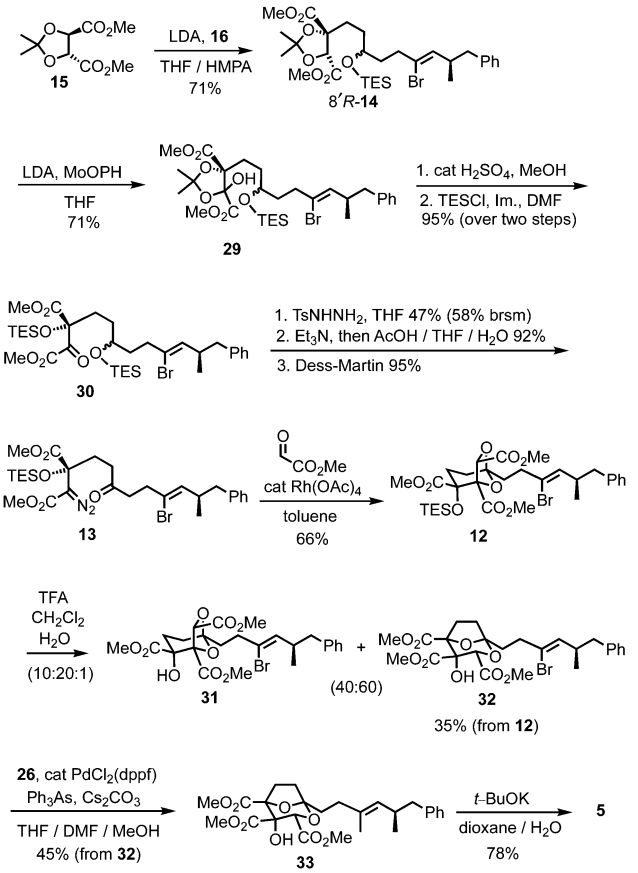
Initial availability of the 1,3-diol **22** (from *rac*-**17**) provided an early opportunity to test the stability of the *Z*-alkenyl bromide motif under the TFA rearrangement conditions. Pleasingly, reaction of 1,3-diol **22** gave the bistrifluoroacetate **25** (quant., Scheme 5), in which the alkenyl bromide was unaffected. Moreover, stereoretentive Suzuki reactions between the 1,3-diol-derived mono- and bis-TBS ethers **23** and **24** and the borinate complex **26** (from MeLi and 9-MeO-9-BBN)[5] gave *E*-alkenes **27** and **28** in 75% and 76% yields, respectively.[18]




Scheme 5 Stability of alkenyl bromide functionality to TFA, and stereoretentive methylation.

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The chemistry in Scheme 5 encouraged progression of iodide **16** towards (−)-DDSQ **5**. Thus, tartrate alkylation,[2b,13] followed by oxidation[19] of the resulting alkylated tartrate **14** gave hydroxy acetonide **29** (Scheme 6). The acidic conditions necessary to remove acetone from **29** resulted in concomitant desilylation, but the silyl group was reinstalled during formation of the bis-TES ether **30** from the intermediate lactol. This bis-TES ether **30** underwent condensation with tosylhydrazide, followed by $Et_3N$-induced generation of diazo functionality;[20] under the basic reaction conditions partial desilylation of the secondary TES ether occurred and this was completed by addition of aqueous acetic acid. The lability of the secondary TES ether under mild conditions was crucial, as it, along with mild Dess–Martin oxidation of the resulting intermediate secondary alcohol, allowed access to ketone **13** in which both the tertiary TES ether and the diazo functionality were retained.[9]




Scheme 6 Completion of the synthesis of (−)-6,7-dideoxysqualestatin H5 **5**.

Following cycloaddition of diazoketone **13** with methyl glyoxylate, we were pleased to observe that, in line with the model study (Scheme 5), rearrangement of the resulting cycloadduct **12** could be induced with preservation of the alkenyl bromide, to give the 2,8-dioxabicyclo[3.2.1]octane **32**.[21] Further Suzui methylation studies with alkylated tartrate **14** (from *rac*-**17**) as a closer (ester-containing) model system to **32**, led to the identification of $Cs_2CO_3$ (in MeOH) as the preferred base and $Ph_3As$ as additive in DMF.†[22] Application of these conditions to alkenyl bromide **32** gave the squalestatin trimethyl ester **33**, which underwent global saponification using anhydrous KOH[23] to give **5**.[2]

The present work exemplifies prevention of electrophilic attack (protonation/Friedel–Crafts cyclisation) of an alkene by using a vinylic bromine substituent. Conceptually, this differs from earlier approaches, that mask a C=C bond by transient addition of elements across it, which are then subsequently eliminated.[4] During the sequence to prepare **5**, the alkenyl bromide functionality is also robust enough to survive a variety of other chemistry (Schemes 4 and 6), before being selectively replaced in a C–C bond-forming event at the penultimate step. The strategy should find application in other synthetic endeavours.

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## Conflicts of interest

There are no conflicts to declare.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# Alkylation of lithiated dimethyl tartrate acetonide with unactivated alkyl halides and application to an asymmetric synthesis of the 2,8-dioxabicyclo[3.2.1]octane core of squalestatins/zaragozic acids

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## Abstract

(*R,R*)-Dimethyl tartrate acetonide **7** in THF/HMPA undergoes deprotonation with LDA and reaction at −78 °C during 12–72 h with a range of alkyl halides, including non-activated substrates, to give single diastereomers (at the acetonide) of monoalkylated tartrates **17**, **24**, **33a–f**, **38a,b**, **41** of *R,R*-configuration, i.e., a stereoretentive process (13–78% yields). Separable *trans*-dialkylated tartrates **34a–f** can be co-produced in small amounts (9–14%) under these conditions, and likely arise from the achiral dienolate **36** of tartrate **7**. Enolate oxidation and acetonide removal from γ-silyloxyalkyl iodide-derived alkylated tartrates **17** and **24** give ketones **21** and **26** and then Bamford–Stevens-derived diazoesters **23** and **27**, respectively. Only triethylsilyl-protected diazoester **27** proved viable to deliver a diazoketone **28**. The latter underwent stereoselective carbonyl ylide formation–cycloaddition with methyl glyoxylate and acid-catalysed rearrangement of the resulting cycloadduct **29**, to give the 3,4,5-tricarboxylate-2,8-dioxabicyclo[3.2.1]octane core **31** of squalestatins/zaragozic acids. Furthermore, monoalkylated tartrates **33a**,**d**,**f**, and **38a** on reaction with NaOMe in MeOH at reflux favour (≈75:25) the *cis*-diester epimers *epi*-**33a**,**d**,**f** and *epi*-**38a** (54–67% isolated yields), possessing the *R,S*-configuration found in several monoalkylated tartaric acid motif-containing natural products.

## Introduction

Since their isolation was reported in the early 1990s [1,2], the squalestatins/zaragozic acids (e.g., squalestatin S1/zaragozic acid A (**1**), Figure 1) have been of enduring interest to synthetic chemists, due to a combination of a synthetically challenging densely functionalised 2,8-dioxabicyclo[3.2.1]octane core [3-6], combined with an increasing range of intriguing biological ac-

tivities [7-11]. Here, we report in detail the evolution of chemistry that provides an asymmetric entry to the tricarboxylate core of these natural products, with particular focus on tartrate alkylation methodology to establish the fully-substituted C-5 stereocentre (squalestatin numbering).

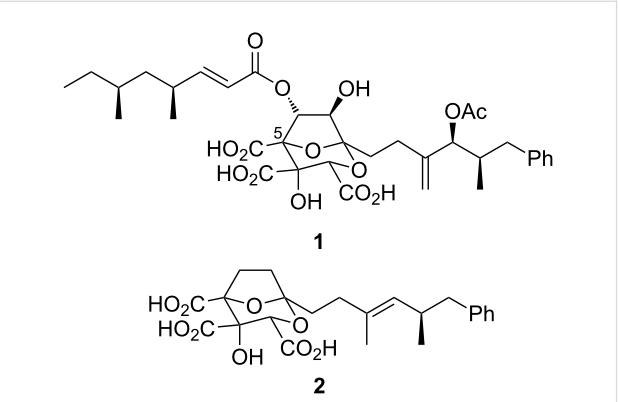
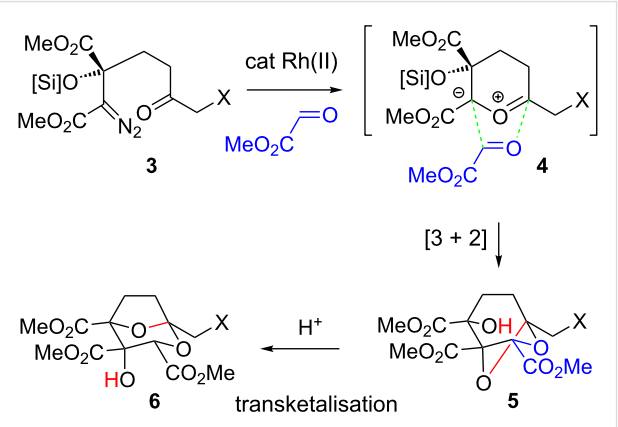


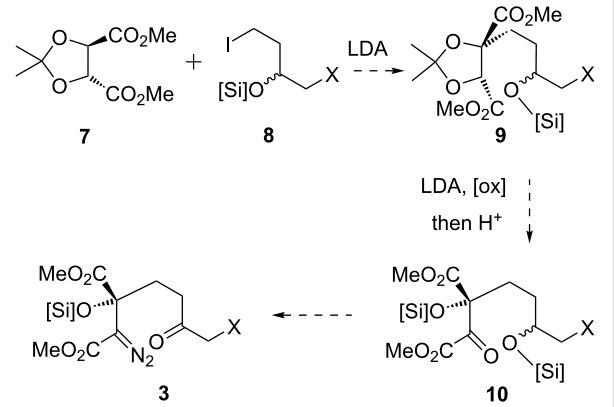

**Figure 1:** Squalestatin S1/zaragozic acid A (**1**) and DDSQ (**2**).

Our studies in this area have recently culminated in two communicated syntheses of 6,7-dideoxysqualestatin H5 (DDSQ (**2**), Figure 1) [12,13]. The centrepiece of both of these strategies is a rhodium(II)-catalysed tandem carbon ylide formation from a diazoketone **3** (Scheme 1) and stereoselective [3 + 2] cycloaddition with a glyoxylate (**3** → **4** → **5**) [14,15], followed by an acid-catalysed rearrangement to generate the desired dideoxysqualestatin core **6** with the requisite tricarboxylate functionality installed. While we had earlier established the viability of this approach in a racemic model study (X = H) [14], extension to an asymmetric variant of our aldol route (α-diazoacetate ester anion addition to an α-ketoester) to the cycloaddition substrate **3** (X = H) did not appear promising [16].




**Scheme 1:** Carbonyl ylide cycloaddition–rearrangement to the squalestatin core [12,13].

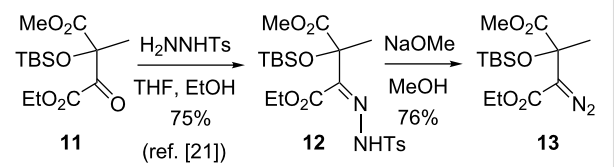
An alternative and asymmetric route to such substrates, ultimately successful, built on stereoselective alkylation of enolates of tartrates (e.g., **7**, Scheme 2) was originally reported by Seebach and co-workers for 'activated' (allylic, benzylic) alkyl halides [17-19]. If an alkylated tartrate **9** could be accessed from a silyloxy-substituted alkyl iodide **8** and subsequently oxidised (for example via a second tartrate enolate) with acetonide removal, this would give an α-ketoester **10**. The latter should in principle be a progenitor to the desired α-diazo ester **3**, following condensation with tosylhydrazide, then Bamford–Stevens-type base-induced sulfinate elimination [20] and oxidation of the secondary silyl ether.




**Scheme 2:** Tartrate alkylation strategy to cycloaddition substrate.

## Results and Discussion

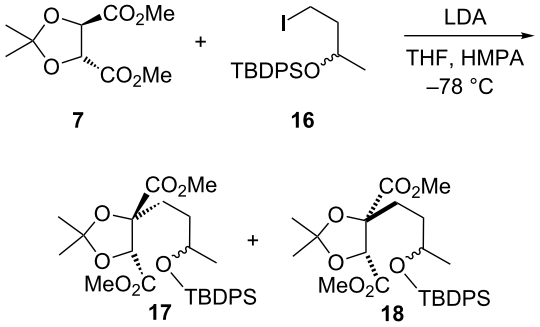
The general viability of the α-ketoester to α-diazoester functional group interconversion envisaged in Scheme 2 (**10** → **3**) was readily established on a simpler but closely structurally-related system (Scheme 3). Thus, the known *Z*-hydrazone **12**, previously prepared by us from α-ketoester **11** in 75% yield [21], gave α-diazo ester **13** in 76% yield following reaction with NaOMe. Furthermore, our earlier racemic model study had established that deprotection and oxidation of a secondary silyl ether in the presence of α-diazo ester functionality was feasible, which constitutes precedent for the generation of the ketone functionality in **3** [14]. These observations led us to examine the possibility of substrate assembly through Seebach's tartrate alkylation methodology.



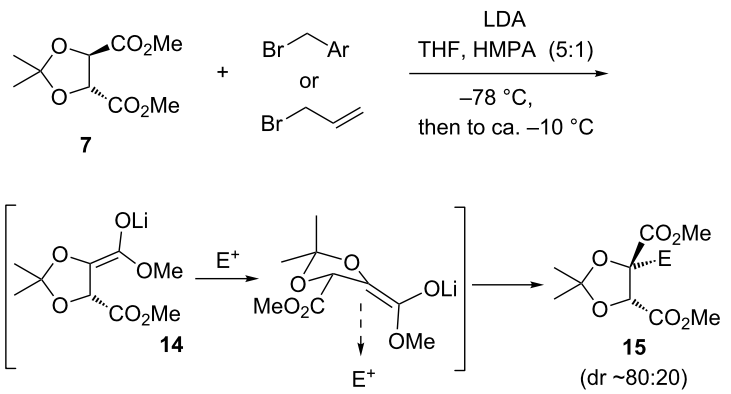

**Scheme 3:** Conversion of α-ketoester to α-diazoester.

In 1981, Seebach and Naef communicated that (*R*,*R*)-tartrate acetonide **7** could be deprotonated and undergo stereoselective alkylation (≈80:20 dr) with reactive organohalides (Scheme 4) [17]. The process was valuable, because it allowed direct elaboration of a chiral pool building block that was readily available as either antipode [22,23], with the major alkylated diastereomer **15** being generated in 97:3 er [18]. The study was also notable in showing that the intermediate ester enolate **14** possessed sufficient stability not to undergo significant β-elimination under conditions of its generation and its alkylation: slow addition of pre-cooled LDA (−70 °C) to a mixture of the acetonide and electrophile in THF/HMPA at −78 °C, followed by slow warming to ≈−10 °C before work-up. Finally, the reaction displayed remarkable stereoselectivity, in that the electrophile was introduced on ostensibly the more hindered face of the enolate (that is, *cis* ("contrasteric") [24] to the unenolised ester group). The former observation was rationalised due to the enolate π-system and potentially cleavable beta σ-C–O bond lying mutually orthogonal, while the latter was subsequently ascribed to alkylation occurring from an envelope conformation wherein the unenolised ester resided pseudoequatorial to avoid 1,3-steric interactions with a pseudoaxial methyl of the *gem*-dimethyl group [18,24]; it was proposed that the axial methyl group directed electrophile incorporation away from itself (Scheme 4).

The fragile nature of the lithium ester enolate of dimethyl tartrate acetonide (to β-elimination with loss of acetone) was evident from Seebach's work, which concluded that only especially reactive halides (methyl, benzylic, allylic) were feasible electrophiles; with iodoethane, 1-iodo-2-methylpropane and chloromethoxymethane no alkylation products were formed [17-19]. Given these rather discouraging observations in the context of our proposed chemistry (Scheme 2), we were pleased to find that initial studies with (*R*,*R*)-tartrate **7** and a 3-silyloxy-1-iodobutane **16** did generate alkylated tartrates (Scheme 5). Following Seebach's protocol, with warming overnight to room temperature, gave a 50% yield (90% based on recovered iodide **16**) of a separable 76:24 mixture of alkylated tartrates **17** and **18**, respectively. The relative stereochemistry was assigned by analogy with Seebach's findings for substituted tartrates: that the diastereomer with the ring methine *cis* to the ester group (i.e., **17**) always displays the higher chemical shift (≈5 ppm vs ≈4.5 ppm in $CDCl_3$) [18], and was further supported by 1D NOESY experiments on both alkylated tartrates **17** and **18**. The use of DMPU as co-solvent [18,25] reversed the ratio, with the currently undesired diastereomer **18** becoming favoured (37:63, **17**:**18**). However, with HMPA the proportion of **17** improved significantly (>90:10, **17**:**18**) if the reaction was maintained at −78 °C for several hours before quenching at that temperature, giving isolated yields of 30–50% for **17**. The absolute configuration of **17** was based on the chemical correlation studies of Seebach [17-19] and of Pan [26] for benzylations, and subsequently those of Nagano [27] and of Li [28] for allylations, i.e., stereoretentive (contrasteric) alkylation. As noted above, Seebach recorded 97:3 er (by NMR using a chiral shift reagent)




**Scheme 5:** Tartrate alkylation with a non-activated alkyl iodide.



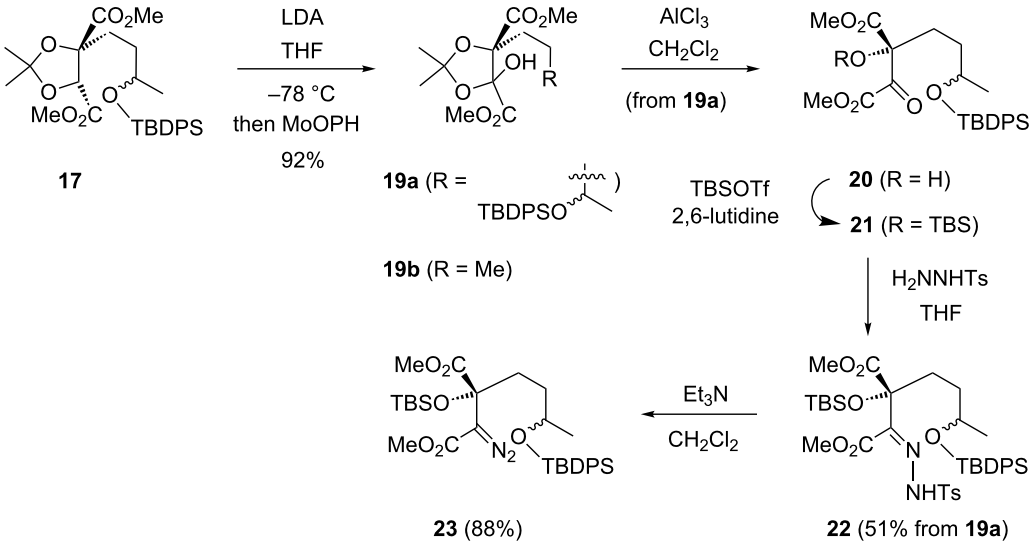

**Scheme 4:** Seebach's tartrate alkylation and rationalisation of stereoselectivity [17-19].

for a benzylated tartrate [18]; in the present case, chiral HPLC comparison of **17** with the corresponding adduct from *S*,*S*-tartrate (*ent*)-**7** indicated they were both of >98:2 enantiopurity in the tartrate portion.

Before exploring the scope of the alkylation chemistry further, it was considered prudent for the proposed asymmetric approach to the dideoxysqualestatin core **6** (Scheme 1 and Scheme 2) to establish the viability of the rest of sequence outlined in Scheme 2 from an alkylated tartrate. While further C–C bond formation by enolate formation at the remaining methine on a monoalkylated tartrate acetonide had been reported by Molander and Harris [29], and by Kelly and co-workers [30]; the question whether such an enolate could be oxidised required investigation. Although the reaction of alkylated tartrate **17** with NaHMDS/2-(phenylsulfonyl)-3-phenyloxaziridine [31] gave an unidentifiable mixture, the use of LDA and MoOPH [32,33] at −78 °C followed by warming to −50 °C for 3 h gave the hydroxy acetonide **19a** (Scheme 6) in 92% yield as a mixture of 4 diastereomers. Similarly, the enolate of the simpler propylated tartrate **33a** [12] reacted with MoOPH to give the analogous hydroxy acetonide **19b** in 96% yield (3:1 dr); if the MoOPH was added to the enolate which had been warmed to −40 °C, a more typical hydroxylation temperature, then a reduced yield of **19b** was observed (53%). Indirect hydroxylation of the propylated tartrate enolate was also attempted using $CBr_4$ (at −78 °C) as a more readily available/convenient electrophile, which also gave the hydroxy acetonide **19b** presumably by way of hydrolysis on work-up of an intermediate bromo acetonide, albeit in significantly reduced yield (33%).

In contrast to a simple hydroxy acetonide (formally derived from an α-hydroxy aldehyde and acetone) [34], hydroxy acetonide **19a** was found stable to mild bases such as $Et_3N$ and $iPr_2NH$, whereas the use of NaH or NaHMDS in THF both decomposed **19a** into unidentifiable polar products. Attempted acid-induced loss of acetone with PTSA in MeOH, PPTS in refluxing MeOH, or 80% AcOH at reflux [27] all led to quantitative recovery of hydroxy acetonide **19a**, whereas 5% aq HCl resulted in acetonide removal and concomitant desilylation. Initial Lewis acids screened either failed to react ($PdCl_2(MeCN)_2$), or led to complex mixtures ($BF_3$, YbOTf, TBSOTf). More encouragingly, both $AlCl_3$ and $FeCl_3$ were found to cleave the acetonide **19a** at rt, with the TBDPS group only being partially lost (≈15%) in both cases. $AlCl_3$ was observed to deprotect the TBDPS ether more slowly than $FeCl_3$, and adjustment of the reaction conditions with $AlCl_3$ (to 2 equiv in $CH_2Cl_2$, −78 °C, followed by slow warming to −50 °C) cleanly provided α-ketoester **20** (Scheme 6). α-Ketoesters can be prone to hydrate easily (2D TLC analysis of **20** indicated decomposition); therefore, **20** and the derived tertiary TBS ether **21** were carried on directly to form hydrazone **22** (51% yield over 3 steps from hydroxy acetonide **19a**). Unlike with hydrazone **12** (Scheme 3), application of NaOMe was not conducive to effective diazo formation from hydrazone **22**, giving a mixture of unidentified products; however, hydrazone **22** was cleanly converted into α-diazo ester **23** (88%) using $Et_3N$ [35,36].

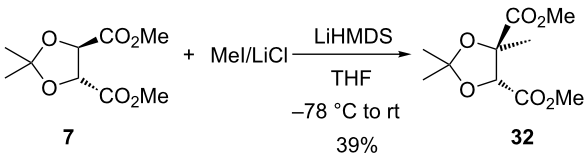
TBDPS protection for the secondary alcohol had originally been selected principally for its likely tolerance to potential (hydroxy) acetonide removal conditions, and with the possibili-



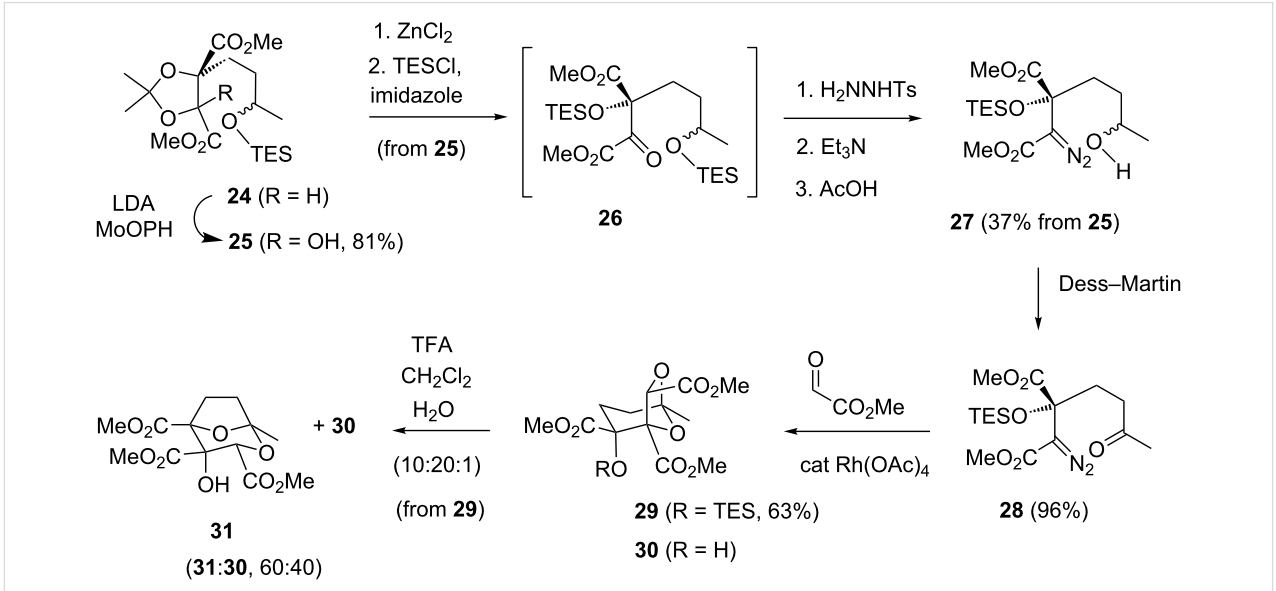

**Scheme 6:** Alkylated tartrate to diazoester sequence.

ty [37,38] of its selective deprotection in α-diazo ester **23** in the presence of the tertiary TBS ether. It was considered important that the tertiary alcohol remain masked during projected oxidation of the released secondary alcohol to give the ketone functionality in the cycloaddition substrate, as otherwise essentially irretrievable five-membered lactol formation would be expected [39]. Unfortunately, various reagents (TBAF/AcOH [40], NaH/HMPA [41], $Bu_4OH$/DMF [40], NaOMe/MeOH) failed to selectively deprotect the secondary TBDPS ether in α-diazo ester **23** in the presence of the tertiary TBS ether. Reassessment of the protecting group strategy led us to TES protection at both alcohols, on the basis that this group should be robust enough to withstand the enolate manipulation chemistry, that desilylation of the secondary TES ether during acetonide removal could be restored in the subsequent tertiary alcohol silylation step, that selective 2° over 3° TES ether desilylation should be readily achievable using AcOH [14], and that the remaining tertiary TES ether should be potentially labile enough to be removed under typical transketalisation conditions (TFA/$CH_2Cl_2$/$H_2O$ (10:20:1), 40 °C, 48–68 h [14], cf, Scheme 1), thereby circumventing the separate prior desilylation step in our earlier racemic model study [14]. In the event, application of this TES protection approach did provide access to diazo alcohol **27** (Scheme 7). As anticipated from the above deprotection studies with TBDPS ether **23**, 1% aq HCl removed both the acetonide and TES groups in hydroxy acetonide **25**. Subsequent silylation using TESOTf gave the bis-TES ketone **26**, which was not purified but taken on through diazo formation and desilylation to give diazo alcohol **27** (17% from **25**). The efficiency of the sequence from hydroxy acetonide **25** to diazo alcohol **27** could be improved (to 37%) using $ZnCl_2$ for the initial deprotection and TESCl in the silylation; the latter minimises formation of the undesired silylated six-membered lactol form of **26**. The remaining steps to the model core **31** (Scheme 7) closely mirrored our previous racemic synthesis of **31** (from the corresponding 3° TBS ether) [14], and this strategy was subsequently also successfully applied in our most recent total synthesis of DDSQ (**2**) [13].

We now returned to study the Seebach alkylation chemistry in more detail. In 2008, Lipton and co-workers had observed that the cyclopentylidene derivative of diethyl tartrate reacted with LiHMDS in the presence of LiCl and MeI, to give exclusively the corresponding *trans*-monomethylated tartrate in 72% yield [42]; this compares with methylation of acetonide tartrate **7** by Seebach, which was reported to give an inseparable mixture of monomethylated product (86:14 dr), dimethylated, and recovered **7** (50%, 79:15:6, respectively) [17-19]. Application of Lipton's conditions to tartrate **7**, cleanly gave the *trans*-monomethylated product **32**, albeit in moderate yield (39%, Scheme 8); however, extension to a higher alkylating agent (PrI) was unsuccessful, returning only ≈25% of tartrate **7** in an impure state.

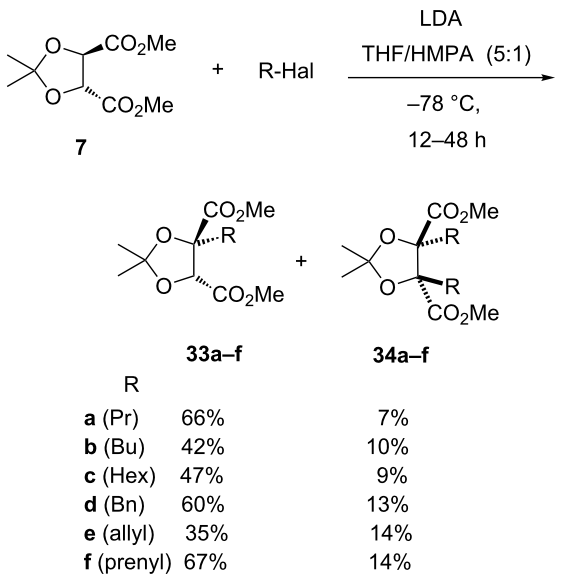



**Scheme 8:** Tartrate acetonide methylation.




**Scheme 7:** TES protection approach to the squalestatin core.

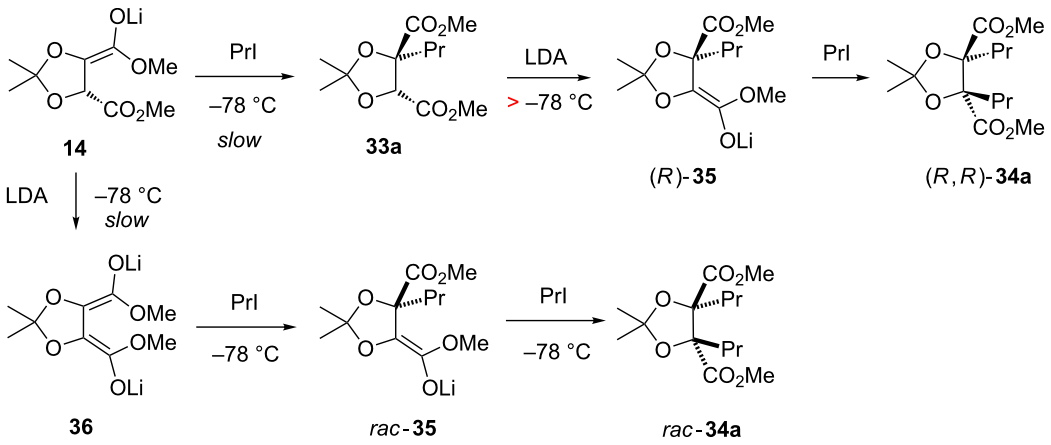
In contrast to the unsuccessful propylation with LiHMDS/LiCl mentioned above, following our modified Seebach's protocol, propylation could be achieved to give propylated tartrate **33a** [12] (Scheme 9), in 66% yield and 97:3 er by chiral HPLC, with the *trans*-dipropylated product **34a** also being separately isolated, in 7% yield. Other primary 'non-activated' alkyl iodides also led to alkylated tartrates **33b**,**c** and the corresponding dialkylated side-products **34b**,**c** (Scheme 9). Under our modified alkylation conditions, 'activated' bromides (benzyl, allyl and prenyl), previously examined by Seebach [17-19], all gave the corresponding monoalkylated tartrates **33d–f** also as single diastereomers (along with separable *trans*-dialkylated material **34d–f**, Scheme 9). These latter results indicate that it is the modified reaction conditions, rather than the nature of the alkylating agent, which leads to the improved diastereoselectivity [43]. The *trans* stereochemistry assignment for the dialkylated products **34** follow from the observed equivalence of the acetonide methyl groups in all their proton and carbon NMR spectra.




| R | 33a–f | 34a–f |
|---|---|---|
| **a** (Pr) | 66% | 7% |
| **b** (Bu) | 42% | 10% |
| **c** (Hex) | 47% | 9% |
| **d** (Bn) | 60% | 13% |
| **e** (allyl) | 35% | 14% |
| **f** (prenyl) | 67% | 14% |

**Scheme 9:** Tartrate alkylation with various alkyl halides.

In Seebach's original studies, which established retention on tartrate alkylation for the major diastereomer (formed, as noted above, in 97:3 er), a further intriguing observation was made: that the minor diastereomer was obtained in virtually racemic form (determined by NMR using a chiral shift reagent) [18,19]. It was suggested that the latter principally arose from alkylation (then protonation, by unreacted **7**) [19] of the (achiral) dienolate **36** (Scheme 10) of **7**. In the current work, where the major difference is prolonged reaction time at low temperature and no warming before quenching, the minor diastereomer is not observed – but dialkylated byproduct **34** is. An attempt to propylate the monopropylated tartrate **33a** under our conditions mainly returned starting **33a** (68%), with only a trace of *trans*-dipropylated product **34a** being isolated (2%). Seebach's observations, together with ours, indicate that the dienolate **36** does form to some extent at −78 °C (Scheme 10) [44-46], and both it and the derived alkylated mono-anion *rac*-**35** are quite reactive to alkylation, but protonation of the alkylated mono-anion *rac*-**35** (by unreacted **7**) does not occur at that temperature; also, once monoalkylation has occurred from the mono-enolate **14**, then **33a** is not readily deprotonated at −78 °C. Clearly, monoalkylated tartrate can be deprotonated and trapped with electrophiles if the system is warmed above −78 °C: to −30 °C by Molander and Harris [29], whereas −50 °C was sufficient for the enolate oxidation steps in Scheme 6 and Scheme 7. Indeed, propylation of the monopropylated tartrate **33a** can be achieved in 34% yield, if the reaction mixture is warmed to −50 °C




**Scheme 10:** Rationalisation of dialkylation observations.

(Scheme 10). Chiral HPLC comparison of the *trans*-dipropylated material **34a** obtained as the byproduct from the alkylation of tartrate acetonide **7**, and from propylation of the monopropylated tartrate **33a**, confirmed that the former was essentially racemic (52:48 er), while the latter was 98:2 er. Therefore, if one wishes to generate (*R*,*R*)- (or (*S*,*S*)-) *C*2-symmetric dialkylated tartrates [47-49], an important conclusion from the above observations and analysis is that monoalkylation should be carried out first, and the isolated monoalkylated material then separately subjected to a second alkylation, allowing warming to ≈−40 °C.

Our first synthesis of 6,7-dideoxysqualestatin H5 (DDSQ (**2**), Figure 1), required extension of the above tartrate alkylation chemistry to a homoallylic halide as the electrophile (Scheme 11) [12]. An initial experiment with 4-bromobut-1-ene (**37a**) was not encouraging, delivering the homo-allylated product **38a** in only 13% yield. It was suspected that competing elimination (to give butadiene) contributed to the low yield. Support for this was found with the real system, where the corresponding diene **39** was isolated in up to 36% yield. In our earlier studies, typically approximately equimolar quantities of tartrate and alkylating agent were used, but with the halide now being synthetically more valuable, efforts focused on conditions which gave the best yields using it as the limiting agent. A slight excess of tartrate relative to iodide produce the homoallylated tartrate **38b** in 34% yield, but this could be improved to 60–78% by using 100% excess of tartrate [12]. It was also noted that minimal contact time between the sensitive iodide **37b** and HMPA at low temperature before slow addition of the pre-cooled LDA minimised diene formation, with the excess residual unreacted tartrate being most conveniently removed by distillation on large-scale. Our second synthesis of DDSQ (**2**) introduced the full side-chain through alkylation with iodide **40** to give the alkylated tartrate **41** in 71% yield, and used only a slight excess of tartrate **7** and LDA (1.2 and 1.5 equiv, respectively) for 72 h at −78 °C [13]. These examples demonstrate the viability of the tartrate alkylation chemistry with more complex and valuable electrophiles.

While monoalkylated tartrate acetonides were applied in squalestatin syntheses as highlighted above, the monoalkylated tartaric acid motif is also directly present in several natural products, such as hydroxybenzyl-substituted piscidic acid (**42**) and congeners (fukiic and cimicifugic acids) [50], and the Cephalotaxus alkaloids isoharringtonine (**43**) and cephalezomine C (**44**) [51]. In these latter natural products, the monoalkylated tartaric acid residues typically possess 2*R*,3*S* stereochemistry (Figure 2); one exception is cephalezomine D [51], which is the 3*R*-epimer of cephalezomine C (**44**). Since the chiral (*R*,*R*- *S*,*S*-) tartrate acetonides undergo stereoretentive alkylation, then direct access to the stereochemistry present in the majority of these natural products is not possible. Nevertheless, a couple of isolated examples in the Chinese chemical literature from the late 1980s indicated that subsequent base-induced epimerisation of monoalkylated (*p*-(benzyloxy)benzyl-

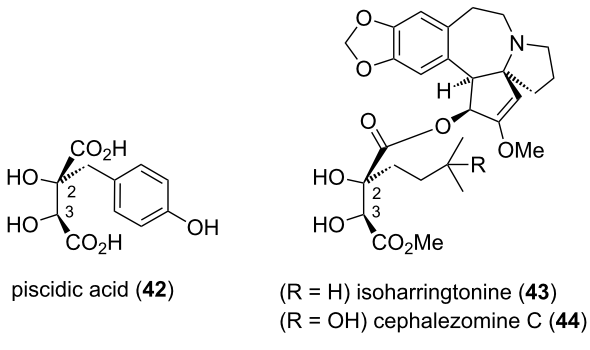
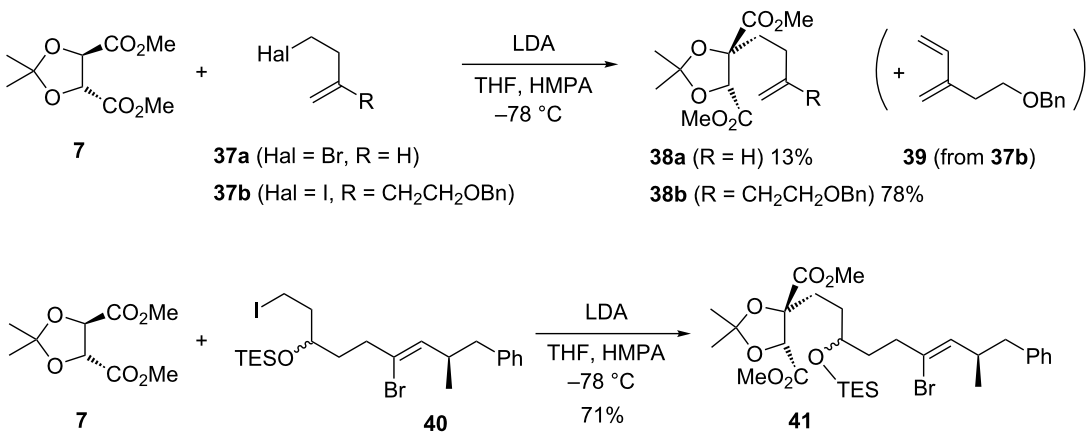


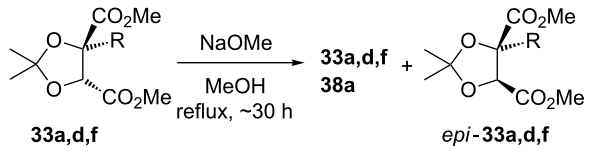

**Figure 2:** Natural product examples containing the monoalkylated tartaric acid motif.




**Scheme 11:** Tartrate alkylation chemistry with more complex alkyl iodides [12,13].

ated and prenylated) tartrate acetonides favours *R*,*S* stereochemistry, providing access to piscidic acid (**42**) [26] and the tartrate residue of isoharringtonine (**43**) [28].

We studied the previously reported epimerisation of prenylated tartrate **33f**, on 0.5 mmol scale ([28] 5 mmol), using NaOMe (1 equiv) in MeOH (0.5 M) at room temperature for 12 h. Under these conditions we observed only partial epimerisation (**33f**/*epi*-**33f** 75:25, [[28] 12:88]), but a 25:75 ratio in favour of *epi*-**33f** could be achieved in MeOH (0.06 M) at reflux for 30 h (Scheme 12). That equilibrium had been reached was established by subjecting *epi*-**33f** to these latter reaction conditions, which returned the same 25:75 ratio of **33f**/*epi*-**33f**. Other monoalkylated tartrates were found to give similar levels of epimerisation (Scheme 12), generating the chromatographically separable epimerised tartrates in 54–67% isolated yields.




| R | **33**/**38a**:*epi*-**33**/**38a** | yield (*epi*-**33**/**38a**) |
|---|---|---|
| **33f** (prenyl) | 25:75 | 58% |
| **33a** (Pr) | 28:72 | 54% |
| **33d** (Bn) | 17:83 | 67% |
| **38a** (butenyl) | 25:75 | 61% |

**Scheme 12:** Epimerisation of monoalkylated tartrates.

## Conclusion

Contrary to the seminal observations of Seebach and Naef, we have demonstrated that lithiated dimethyl tartrate acetonide can undergo stereoretentive alkylation even with "non-activated" alkyl halides, in synthetically useful yields and high er. Optimal reaction conditions are prolonged reaction time at −78 °C, followed by quenching at that temperature; these conditions also avoid cogeneration of the (racemic) diastereomer side-product originally observed on warming. Essentially racemic dialkylated tartrate is observed as a minor side-product under our modified conditions. The reaction pathways that lead to these racemic products under the different reaction conditions have been rationalised. Application of this methodology to generate the 6,8-dioxabicyclo[3.2.1]octane core of the squalestatins/zaragozic acids in an asymmetric fashion, is shown to evolve from a carefully orchestrated sequence of oxidation and judicious protecting group manipulation. Base-induced epimerisation of the monoalkylated tartrates favours *cis*-disposition of the ester groups on the five-membered ring, thereby accessing the predominant stereochemistry found in several substituted tartaric acid-containing natural products. Our findings on tartrate alkylation with non-activated alkyl halides, on origins of side-products, and on conditions for epimerisation of the monoalkylated tartrates, significantly broaden the scope and understanding of Seebach's alkylation chemistry.

## Supporting Information

### Supporting Information File 1

Experimental procedures, characterisation data and $^{1}H$ and $^{13}C$ NMR spectra for all new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-116-S1.pdf]

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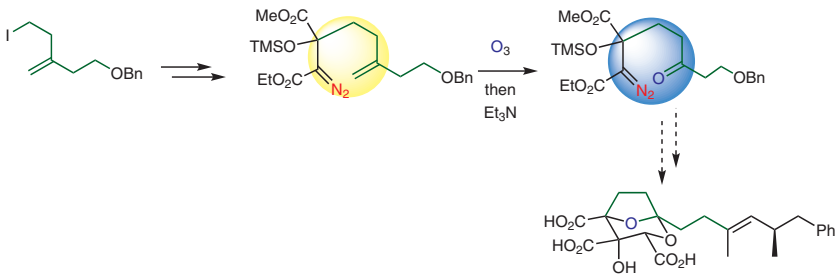
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Synthesis H. A. A. Almohseni et al. Paper

# Alkene Ozonolysis in the Presence of Diazo Functionality: Accessing an Intermediate for Squalestatin Synthesis

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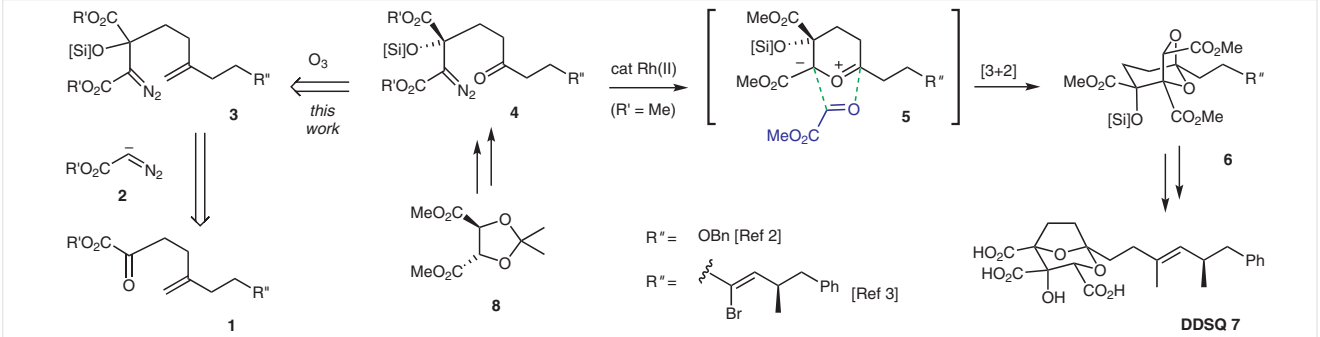
**Abstract** Studies on both the propensity for intramolecular cycloaddition between diazo and alkene functionality, and the tolerance of α-substituted α-diazoesters towards ozone in the presence of an alkene, led to chemoselective alkene ozonolysis of an ε-unsaturated-α-diazoester to give a key racemic diazoketone for the synthesis of 6,7-dideoxysqualestatin H5.

**Key words** 6,7-dideoxysqualestatin H5, squalestatin synthesis, alkene ozonolysis, intramolecular cycloaddition, diazo stability, pyrazoline

We recently reported two syntheses of 6,7-dideoxysqualestatin H5 (DDSQ) **7** (Scheme 1).[2,3] Both syntheses proceeded through diazoketones **4**, which underwent rhodium(II)-catalysed tandem carbonyl ylide formation–intermolecular dipolar cycloadditions (**4**→**5**→**6**),[4] followed by acid-catalysed rearrangement to generate the characteristic 2,8-dioxabicyclo[3.2.1]octane core of the squalestatins / zaragozic acids at the correct tricarboxylic acid oxidation level. Also, in both cases, the silyloxyester stereocentre was created by stereoselective alkylation of dimethyl tartrate acetonide (**8**), with five to six steps being subsequently required to produce the diazoketones **4**. In principle, a more concise approach to such cycloaddition precursors **4** could proceed by aldol reaction between a diazoacetate anion **2** and an unsaturated α-ketoester **1**, followed by chemoselective alkene ozonolysis of the resulting unsaturated diazodiester **3** (Scheme 1). Here, we report the realisation of this latter strategy, despite concerns over both intrinsic instability of the aldol product to spontaneous intramolecular cycloaddition between the diazo and alkene functionality, and of undesired conversion of diazo into keto functionality by ozone.

Before embarking on the above route (**1**→**3**→**4**), it was considered prudent to first establish on simpler substrates the proclivity of α-diazoester functionality to engage in intramolecular cycloaddition with an electron-rich alkene to form bicyclic pyrazolines.[5]

Unsaturated hydrazones **9a**,**b**[6] underwent $Et_3N$-induced diazo formation[7] in $CH_2Cl_2$ at room temperature (Scheme 2). As anticipated from Dauben's studies,[5b] this led hydrazone **9a** to form 1-pyrazoline **11a**, in 92% yield (Scheme 2).

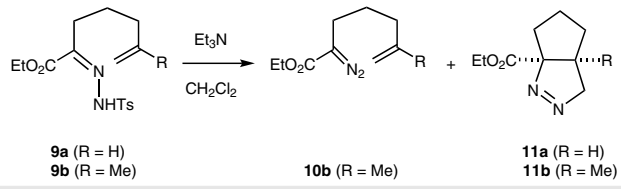



**Scheme 1** Approaches to 6,7-dideoxysqualestatin H5 (**7**)

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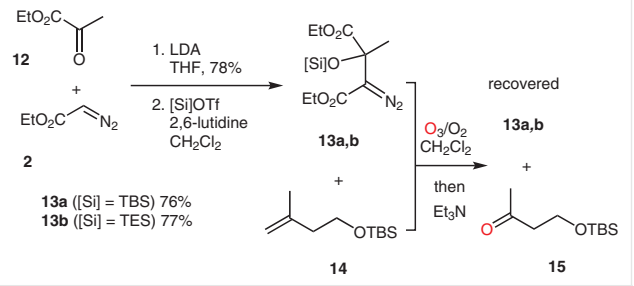
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However, intramolecular cycloaddition was minimised with the 2,2-dialkyl-substituted terminal alkene **9b**, to give a mixture (52%), mainly consisting of unsaturated diazoester **10b** together with only small amounts of bicycle **11b** (**10b**/**11b**, 91:9).



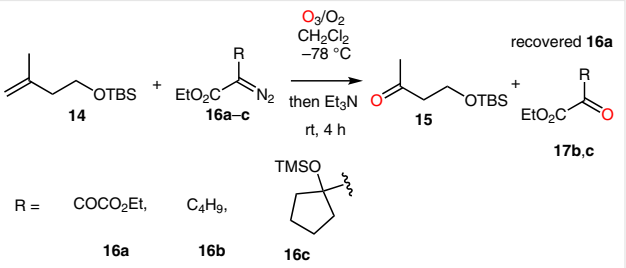

**Scheme 2** Propensity for diazoalkenes to undergo intramolecular cycloaddition

The stability of the α-diazoester motif towards ozone was next examined. The diazo moiety could be oxidised to a carbonyl group by ozone.[6,8] Model compounds **13a**,**b** (Scheme 3), which contain the diazo moiety in a similar environment to diazodiester **3** (Scheme 1), were prepared by aldol reaction between ethyl pyruvate (**12**) and the anion of ethyl diazoacetate (**2**),[9] followed by silylation. Equimolar solutions of α-diazoesters **13a**,**b** and alkene **14**, the latter mimicking the alkene portion of **3**, were exposed to ozone at –78 °C in $CH_2Cl_2$, followed by addition of $Et_3N$.[10] Pleasingly, these conditions gave ketone **15**, with diazoesters **13a**,**b** being recovered intact (Scheme 3, see also the Supporting Information, Figure S1).




**Scheme 3** Preparation and stability of α-diazoesters **13a**,**b** towards ozone

The presence of further electron-withdrawing functionality on the diazocarbonyl likely reduces the reactivity of the diazo group towards ozone.[11] For example, α-diazo-β-ketoester **16a**[12] (Scheme 4) was stable to ozone even at –15 °C for 1 h (alkene **14** converted into ketone **15** within 5 min at –78 °C), whereas, the diazo moiety in **13a** (Scheme 3, $CO_2Me$ instead of $CO_2Et$) is converted into the corresponding ketone on ozonolysis at –15 °C.[6] α-Substituted α-diazoesters **16b**,**c** (Scheme 4) were also examined to study the effect of different substitution on the stability of the diazo moiety to ozonolysis; however, they were both reactive to ozonolysis at –78 °C, being converted into the corresponding ketones **17b**,**c** after addition of $Et_3N$.

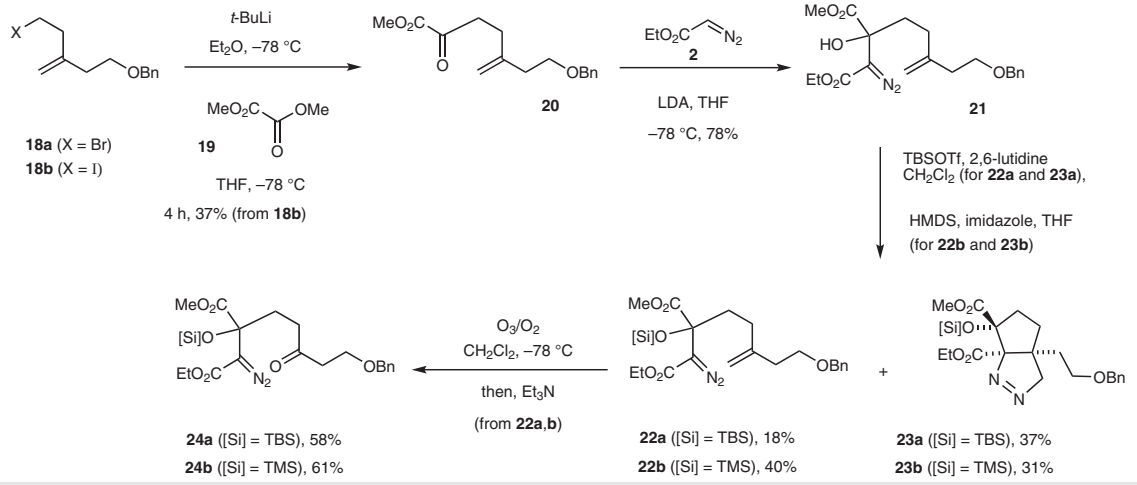



**Scheme 4** Examining the tolerance of α-substituted α-diazoesters **16** towards ozone

Following the above observations, we focused on a synthesis of the racemic DDSQ intermediate **4** (Scheme 1, R″ = OBn), through diazoacetate anion addition to homoallylic α-ketoester **20** (Scheme 5). Although many methods are known for the synthesis of α-ketoesters,[13] only a limited number of organometallic additions to oxalates are suitable for the synthesis of homoallylic α-ketoesters.[14] When the freshly prepared Grignard reagent from bromide **18a** (available from the corresponding alcohol,[2] see experimental) was added to a solution of dimethyl oxalate (**19**) in THF at –65 °C, only a low yield of α-ketoester **20** was obtained (11%). Halogen–lithium exchange of iodide **18b**[2] using *t*-BuLi (2 equiv) at –78 °C[15] and dropwise addition of the resulting organolithium to a solution of oxalate **19** in $Et_2O$ (at –78 °C) gave a similar yield (ca. 15%). The low yield could be due to the limited solubility of dimethyl oxalate in $Et_2O$ at –78 °C, because switching from $Et_2O$ to THF led to an improved yield of α-ketoester **20** (37%). Next, diazo-alcohol **21** was prepared through the addition of lithiated ethyl diazoacetate **2** to α-ketoester **20** (78%).

Pleasingly, and following the trend seen with the model studies (Scheme 2), no undesired intramolecular cycloaddition was observed for diazo-alcohol **21**. At this stage, we proceeded to protect the OH group, since otherwise it would be highly likely to undergo problematic γ-lactolisation with the ketone subsequently generated on ozonolysis.[16] A silyl group was the protecting group of choice for this purpose. Interestingly, when diazo-alcohol **21** was treated with TBSOTf in the presence of 2,6-lutidine ($CH_2Cl_2$, 48 h), a mixture of desired TBS ether **22a** along with cycloadduct **23a** (as a single diastereomer)[17] was obtained (**22a**/**23a**, 1:2). Using DMAP or pyridine as the base was not successful in preventing the 1,3-dipolar cycloaddition, whereas using $Et_3N$ led to retro-aldolisation. The partial formation of cycloadduct **23a** on silylation could be rationalised by a Thorpe–Ingold effect, from the bulky silyl group. With this in mind, it was considered that minimising the steric effect by using a less-hindered silyl group might reduce the bicyclic product formation; indeed, on trimethylsilylation, the ratio of silyl ether **22b** to cycloadduct **23b** was 4:3 in favour of the desired non-cyclic product. Finally, ozonolysis of silyl ethers **22a** and **22b** led to diazoketones **24a** and **24b** (58% and 61%, respectively). The silyl ethers

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**Scheme 5** Synthesis of α-diazo-ε-ketoesters **24a**,**b**

**22a**,**b** should be directly subjected to ozonolysis following their isolation because they undergo intramolecular cyclisation to cycloadducts **23a**,**b** with the rate being slower for **22b** (see the Supporting Information, Figure S2).

In summary, we have developed a strategy for the synthesis of α-diazo-ε-ketoesters, for application in squalestatin synthesis, based on chemoselective ozonolysis of unsaturated α-diazoesters. To survive ozonolysis, α-diazoester functionality requires to be either further substituted with a β-carbonyl group or be sterically shielded by substituents at the β-position. Further studies will focus on construction of the enantiomerically enriched intermediate for the natural product (DDSQ).

All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen in flame-dried glassware. Tetrahydrofuran (THF), dichloromethane and dimethylformamide (DMF) were obtained from Grubbs' drying stills.[18] Flash column chromatography was carried out using silica gel (VWR chemicals, BDH), monitored by thin-layer chromatography (TLC) (Merck 60 $F_{254}$) plates. TLC plates were viewed using ultraviolet light ($\lambda_{max}$ = 254/365 nm) and immersion in $KMnO_4$, followed by heating. Except where stated otherwise, commercially available reagents were used as received. Infrared spectra were obtained with a PerkinElmer FTIR 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). Nuclear magnetic resonance ($^1H$ NMR and $^{13}C$ NMR) spectra were recorded with Bruker Avance AVIIIHD 400, NEO 400, and AVIIIHD 500 spectrometers in $CDCl_3$ (referenced to residual $CHCl_3$ singlet at δ = 7.27 ppm for $^1H$ NMR spectra, and to the central line of $CDCl_3$ triplet at δ = 77.16 ppm for $^{13}C$ NMR spectra). Chemical shifts are quoted in parts per million (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), doublet of doublets (dd), triplet of triplets (tt), doublet of doublet of doublets (ddd), doublet of quartets (dq), or multiplet (m). The $^{13}C$ signal of $CN_2$ was often not observed due to quadrupolar relaxation. High-resolution mass spectra were obtained by electrospray ionization, with a Thermo Fisher Orbitrap Exactive mass spectrometer.

## Procedures

### (a) Propensity of Diazoalkenes to Undergo Intramolecular Cycloaddition

#### Ethyl 3a,4,5,6-Tetrahydrocyclopenta[*c*]pyrazole-6a(3*H*)-carboxylate (11a)

To a solution of hydrazone **9a**[6] (500 mg, 1.42 mmol) in $CH_2Cl_2$ (2 mL) was added $Et_3N$ (0.62 mL, 4.4 mmol) and stirred at r.t. After 3 h, the mixture was passed through a short pad of silica (ca. 2 cm), and washed through with $CH_2Cl_2$ (20 mL). The eluent was evaporated under reduced pressure and the mixture was purified by column chromatography (30% $Et_2O$ in petrol) to give 1-pyrazoline **11a**.

Yield: 240 mg (92%); yellow oil; $R_f$ = 0.52 (30% EtOAc in petrol).

IR (film): 296 (w), 2871 (w), 1730 (s), 1556 (w), 1267 (s), 1222 (s), 1094 (s) $cm^{-1}$.

$^1H$ NMR (500 MHz; $CDCl_3$): δ = 4.67 (dd, *J* = 18.5, 9 Hz, 1 H, CH-CH*H*N=N), 4.40 (dd, *J* = 18.5, 3 Hz, 1 H, CHC*H*HN=N), 4.23–4.15 (m, 2 H, C$H_2$CH$_3$), 2.64 (tt, *J* = 9, 3 Hz, 1 H, C*H*CH$_2$N=N), 2.40–2.34 (m, 1 H, CH*H*CCO$_2$Et), 2.32–2.24 (m, 1 H, C*H*HCCO$_2$Et), 1.85–1.76 (m, 1 H, CH-CH*H*CH$_2$), 1.69–1.61 (m, 1 H, CHCH$_2$CH*H*), 1.40–1.34 (m, 1 H, CHC*H*-HCH$_2$), 1.25 (t, *J* = 8 Hz, 3 H, COCH$_2$C*H*$_3$), 1.12–1.02 (m, 1 H, CHCH$_2$C*H*H).

$^{13}C$ NMR (125 MHz; $CDCl_3$): δ = 170.5 (*C*O$_2$Et), 106.8 (quat. *C*CO$_2$Et), 86.1 (CH$_2$N=N), 61.8 (COCH$_2$CH$_3$), 39.3 (CHCH$_2$N=N), 34.3 (*C*H$_2$CCO$_2$Et), 34.2 (CH*C*H$_2$CH$_2$), 24.0 (CHCH$_2$*C*H$_2$), 14.2 (COCH$_2$*C*H$_3$).

HRMS *m*/*z* [M + Na]$^+$ calcd for $C_9H_{14}N_2{}^{23}NaO_2$: 205.0948; found: 205.0949.

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**Ethyl 2-Diazo-6-methylhept-6-enoate (10b) and Ethyl 3a-Methyl-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6a(3*H*)-carboxylate (11b)**

To a solution of hydrazone **9b**[6] (45 mg, 0.13 mmol) in $CH_2Cl_2$ (3 mL) was added $Et_3N$ (53.0 µL, 0.38 mmol) and the solution was stirred at r.t. After 3 h, the mixture was passed through a short pad of silica (ca. 2 cm), and washed through with $CH_2Cl_2$ (20 mL). The eluent was evaporated under reduced pressure and the mixture was purified by column chromatography (30% $Et_2O$ in petrol) to give an inseparable mixture of diazoalkene **10b** and cycloadduct **11b** (13 mg, 52%, 91:9 respectively, by integration at **10b** [δ C=$CH_2$] and **11b** [δ $CH_2$N=N] peaks), as a yellow oil; $R_f$ = 0.54 (30% $Et_2O$ in petrol).

IR (film): 2934 (w), 2361 (w), 2078 (s), 1688 (s), 1447 (m), 1371 (m), 1304 (m), 1157 (s), 1110 (s) $cm^{-1}$.

HRMS [M + Na]$^+$ calcd for $C_{10}H_{16}N_2{}^{23}NaO_2$: 219.1109; found: 219.1106.

Data for diazoalkene **10b**

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.73 (s, 1 H, C=C*H*H), 4.68 (s, 1 H, C=CH*H*), 4.22 (q, *J* = 7 Hz, 2 H, COC$H_2$CH$_3$), 2.30 (t, *J* = 7.5 Hz, 2 H, C$H_2$C=CH$_2$), 2.07 (t, *J* = 7.5 Hz, 2 H, CH$_2$CN=N), 1.71 (s, 3 H, C$H_3$C=CH$_2$), 1.66 (m, 2 H, C$H_2$CH$_2$CN=N), 1.27 (t, *J* = 7 Hz, 3 H, COCH$_2$C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$): δ = 169.7 (*C*O$_2$Et), 144.9 (*C*=CH$_2$), 110.7 (C=*C*H$_2$), 60.9 (CO*C*H$_2$CH$_3$), 36.9 (*C*H$_2$CN=N), 25.7 (*C*H$_2$CH$_2$CN=N), 22.9 (*C*H$_2$C=CH$_2$), 22.4 (*C*H$_3$C=CH$_2$), 14.7 (COCH$_2$*C*H$_3$).

Data for cycloadduct **11b**

$^1$H NMR (500 MHz; $CDCl_3$): δ = 4.53 (d, *J* = 18 Hz, 0.1 H, CH*H*N=N), 4.34 (d, *J* = 18 Hz, 0.1 H, C*H*HN=N), 2.52–2.41 (C*H*H), 1.11 (s, 0.3 H, quat. CCH$_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$): δ = 167.8 (*C*O$_2$Et), 105.7 (quat. *C*CO$_2$Et), 91.7 (CH$_2$N=N), 61.7 (COCH$_2$CH$_3$), 47.2 (quat. *C*CH$_3$), 42.5 (CH$_2$*C*CO$_2$Et), 34.0 (CH$_2$CH$_2$*C*CO$_2$Et), 23.3 (*C*H$_2$CCH$_3$), 22.2 (quat. C*C*H$_3$).

**(b) Preparation and Stability of α-Substituted α-Diazoesters towards Ozone**

α-Diazo-β-ketoester **16a** was prepared according to a reported procedure[12] and α-diazoester **16b** was prepared by following a procedure reported by Wang and co-workers.[19]

**Diethyl 3-Diazo-2-hydroxy-2-methylsuccinate (25)**

The procedure of Padwa and co-workers[5h] was followed with slight modifications. A solution of LDA [prepared from *n*-BuLi (3.1 mL, 1.4 M in hexanes, 4.6 mmol) and *i*-Pr$_2$NH (600 µL, 4.6 mmol) in THF (5 mL) at –78 °C] was added dropwise to a stirred solution of ethyl diazoacetate (**2**) (525 mg, 4.60 mmol) and ethyl pyruvate (**12**) (534 mg, 4.60 mmol) in THF (20 mL) at –78 °C. The solution was warmed to r.t. and stirred for 3 h, and then AcOH (0.26 mL, 4.6 mmol) was added dropwise. The mixture was extracted with $Et_2O$ (2 × 15 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography (10% $Et_2O$ in petrol) to give diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (825 mg, 78%), as a yellow liquid; $R_f$ = 0.27 (30% $Et_2O$ in petrol).

IR (film): 3380 (br), 2956 (m), 2096 (s), 1745 (s), 1698 (s) $cm^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.29–4.16 (m, 4 H, 2 × OC$H_2$Me), 4.13 (s, 1 H, OH), 1.56 (s, 3 H, Me), 1.30–1.22 (m, 6 H, 2 × OCH$_2$C$H_3$).

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 173.8 (*C*O$_2$Et), 165.7 (*C*O$_2$Et), 71.6 (quat. C), 62.9 (OCH$_2$), 61.3 (OCH$_2$), 23.8 (Me), 14.5 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$C$H_3$).

HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_9H_{14}O_5N_2{}^{23}Na$: 253.0794; found: 253.0795.

**Diethyl 2-[(*tert*-Butyldimethylsilyl)oxy]-3-diazo-2-methylsuccinate (13a)**

TBSOTf (0.4 mL, 1.7 mmol) was added to 2,6-lutidine (0.3 mL, 2.6 mmol) in $CH_2Cl_2$ (1 mL) and the solution was stirred for 10 min at 0 °C. A solution of diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (200 mg, 0.87 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was then added. The mixture was warmed to r.t. and stirred for 48 h. The reaction was quenched with water (4 mL), and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), washed with brine (10 mL) and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by column chromatography (10% $Et_2O$ in petrol) to give TBS ether **13a**.

Yield: 227 mg (76%); $R_f$ = 0.3 (20% $Et_2O$ in petrol).

IR (film): 2956 (m), 2931 (m), 2858 (m), 2096 (s), 1745 (s), 1698 (s), 1464 (m), 1309 (s), 1255 (s), 1144 (s), 1069 (s), 839 (w) $cm^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.25–4.14 (m, 4 H, 2 × OC$H_2$CH$_3$), 1.66 (s, 3 H, Me), 1.30–1.22 (m, 6 H, 2 × OCH$_2$C$H_3$), 0.86 [s, 9 H, OSiC(CH$_3$)$_3$], 0.11 and 0.08 [2 × s, 6 H, OSi(CH$_3$)$_2$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 172.0 (*C*O$_2$Et), 165.0 (*C*O$_2$Et), 73.7 (quat. C), 61.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 25.7 [SiC(*C*H$_3$)$_3$], 18.4 [Si*C*(CH$_3$)$_3$], 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$), –3.0 (OSi*C*H$_3$), –3.5 (OSi*C*H$_3$).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_5N_2{}^{28}Si^{23}Na$: 367.1659; found: 367.1656.

**Diethyl 3-Diazo-2-methyl-2-[(triethylsilyl)oxy]succinate (13b)**

By following the procedure for silyl ether **13a** above, but using TESOTf, diethyl 3-diazo-2-hydroxy-2-methylsuccinate (**25**) (200 mg, 0.87 mmol) gave, after column chromatography (10% $Et_2O$ in petrol), TES ether **13b**.

Yield: 230 mg (77%); yellow oil; $R_f$ = 0.3 (20% $Et_2O$ in petrol).

IR (film): 2956 (m), 2931 (m), 2858 (m), 2096 (s), 1745 (s), 1698 (s), 1464 (m), 1309 (s), 1255 (s), 1144 (s), 1069 (s), 839 (w) $cm^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.25–4.13 (m, 4 H, 2 × OC$H_2$CH$_3$), 1.67 (s, 3 H, Me), 1.27 (t, *J* = 7 Hz, 3 H, OCH$_2$C$H_3$), 1.24 (t, *J* = 7 Hz, 3 H, OCH$_2$C$H_3$), 0.93 [t, *J* = 8 Hz, 9 H, OSi(CH$_2$C$H_3$)$_3$], 0.62 [q, *J* = 8 Hz, 6 H, OSi(C$H_2$CH$_3$)$_3$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 172.0 (*C*O$_2$Et), 165.1 (*C*O$_2$Et), 73.6 (quat. C), 61.9 (OCH$_2$), 60.9 (OCH$_2$), 25.9 (Me), 14.6 (OCH$_2$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$), 6.9 [OSi(CH$_2$*C*H$_3$)$_3$], 6.1 [OSi(*C*H$_2$CH$_3$)$_3$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_5N_2{}^{23}Na^{28}Si$: 367.1659; found: 367.1656.

**Ethyl 2-Diazo-2-{1-[(trimethylsilyl)oxy]cyclopentyl}acetate (16c)**

TMSCl (127 µL, 1.0 mmol) was added slowly to a solution of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate[5h] (100 mg, 0.50 mmol) and imidazole (170 mg, 2.50 mmol) in DMF (1.4 mL) at 0 °C. After 4 h at r.t., $Et_2O$ (5 mL) was added, the organic layer was washed with water (2 × 2 mL), brine (2 mL) and dried ($Na_2SO_4$). After evaporation under reduced pressure, the residue was purified by column chromatography (0–10% $Et_2O$ in petrol) to give silyl ether **16c**.

Yield: 118 mg (87%); yellow liquid; $R_f$ = 0.59 (10% $Et_2O$ in petrol).

IR (film): 2960 (m), 1714 (s), 1370 (w), 1204 (m), 1040 (m) $cm^{-1}$.

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$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.22 (q, *J* = 7 Hz, 2 H, $OCH_2CH_3$), 2.05–1.99 (m, 2 H, $CH_2$), 1.94–1.86 (m, 2 H, $CH_2$), 1.84–1.78 (m, 2 H, $CH_2$), 1.70–1.63 (m, 2 H, $CH_2$), 1.28 (t, *J* = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.10 [s, 9 H, $OSi(CH_3)_3$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 165.7 ($CO_2Et$), 81.0 (*C*OTMS), 60.6 ($OCH_2CH_3$), 40.1 (2 × $CH_2$), 22.8 (2 × $CH_2$), 14.7 ($OCH_2CH_3$), 1.5 [$OSi(CH_3)_3$].

HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_{12}H_{22}O_3N_2{}^{23}Na^{28}Si$: 293.1291; found: 293.1292.

### General Procedure for Ozonolysis

A stream of $O_3/O_2$ was bubbled through a mixture of α-diazoester (1 mmol) and alkene **14**[20] (1 mmol) in $CH_2Cl_2$ at –78 °C until the colour of the reaction mixture changed from yellow to blue (ca. 5 min). Then the excess of $O_3$ was removed by bubbling $N_2$ through the reaction mixture, followed by addition of $Et_3N$ (3 mmol). After 4 h at r.t., the reaction mixture was evaporated under reduced pressure and the residue was analysed by $^1$H NMR (see the Supporting Information, Figure S1).

### Ethyl 2-Oxohexanoate (17b)

By following the general ozonolysis procedure above, α-diazoester **16b** (100 mg, 0.58 mmol) was oxidised to give after column chromatography (5% EtOAc in petrol) an inseparable mixture of α-ketoester **17b** and the corresponding trioxane trimer **26** (66 mg, 73%, ca. 60:40, respectively, by integration at **17b** [δ $CH_2CH_2CO$] and **26** [δ $CH_2CH_2CO$] peaks), as a colourless liquid; $R_f$ = 0.56 (5% EtOAc in petrol).

IR (film): 2961 (m), 2935 (m), 1750 (s), 1727 (s), 1466 (s), 1275 (m), 1246 (m), 1142 (m), 1120 (m), 1048 (s), 856 (m) cm$^{-1}$.

### Data for α-Ketoester 17b

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.30 (q, *J* = 7 Hz, 2 H, $OCH_2CH_3$), 2.81 (t, *J* = 7 Hz, 2 H, $CH_2CH_2CO$), 1.68–1.55 (m, 2 H, $CH_2CH_2CO$), 1.42–1.27 (m, 5 H, $CH_2$ and $CO_2CH_2CH_3$), 0.91 (t, *J* = 7 Hz, 3 H, $CH_2CH_3$).

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 194.9 (C=O), 161.5 ($CO_2Et$), 62.5 ($CO_2CH_2CH_3$), 39.1 ($CH_2CO$), 25.2 ($CH_2CH_2CO$), 22.2 ($CH_3CH_2CH_2$), 14.1 ($OCH_2CH_3$), 13.9 ($CH_2CH_3$).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_8H_{14}O_3{}^{23}Na$: 181.0835; found: 181.0836.

### Data for Triethyl 2,4,6-Tributyl-1,3,5-trioxane-2,4,6-tricarboxylate (26)

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.27–4.21 (m, 2 H, $OCH_2CH_3$), 2.10–1.91 (m, 2 H, $CH_2CH_2CO$), 1.42–1.27 (m, 5 H, 2 × $CH_2$ and $CO_2CH_2CH_3$), 0.88 (t, 3 H, *J* = 7 Hz, 2 H, $OCH_2CH_3$).

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 168.2 ($CO_2Et$), 107.6 (quat. C), 62.1 ($CO_2CH_2CH_3$), 31.6 ($CH_2CO$), 25.0 ($CH_2CH_2CO$), 22.6 ($CH_3CH_2CH_2$), 14.2 ($OCH_2CH_3$), 13.8 ($CH_2CH_3$).

### Ethyl 2-Oxo-2-{1-[(trimethylsilyl)oxy]cyclopentyl}acetate (17c)

By following the general ozonolysis procedure above, TMS ether **16c** (47 mg, 0.17 mmol) was oxidised to give, after column chromatography (10% $Et_2O$ in petrol), α-ketoester **17c**.

Yield: 17 mg (39%); colourless liquid; $R_f$ = 0.5 (10% $Et_2O$ in petrol).

IR (film): 2958 (m), 1727 (s), 1251 (s), 1216 (m), 1066 (s), 1028 (m), 917 (m), 839 (s) cm$^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 4.31 (q, *J* = 7 Hz, 2 H, $OCH_2CH_3$), 2.26–2.15 (m, 2 H, 2 × H of $CH_2$), 1.93–1.87 (m, 2 H, 2 × H of $CH_2$), 1.85–1.78 (m, 2 H, 2 × H of $CH_2$), 1.77–1.69 (m, 2 H, 2 × H of $CH_2$), 1.36 (t, *J* = 7 Hz, 3 H, $OCH_2CH_3$), 0.13 [s, 9 H, $OSi(CH_3)_3$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 200.0 (C=O), 165.2 ($CO_2Et$), 88.8 (*C*OTMS), 61.9 ($OCH_2CH_3$), 39.0 (2 × $CH_2$), 24.7 (2 × $CH_2$), 14.2 ($OCH_2CH_3$), 1.8 [$OSi(CH_3)_3$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{22}O_4{}^{23}Na^{28}Si$: 281.1179; found: 281.1180.

### (c) Synthesis of α-Diazo-ε-ketoesters 24a,b

### {[(5-Bromo-3-methylenepentyl)oxy]methyl}benzene (18a)

$Ph_3P$ (365 mg, 1.39 mmol) and $CBr_4$ (577 mg, 1.74 mmol) were added to a solution of 5-(benzyloxy)-3-methylenepentan-1-ol[2] (240 mg, 1.16 mmol) in $CH_2Cl_2$ (8 mL) at r.t. After 10 min, the reaction mixture was poured into sat. aq. $NaHCO_3$ (5 mL) and the aq. layer was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (5% $Et_2O$ in petrol) to give bromide **19a**.

Yield: 225 mg (72%); colourless oil; $R_f$ = 0.41 (5% $Et_2O$ in petrol).

IR (film): 2858 (w), 1646 (m), 1453 (m), 1208 (m), 1098 (s), 901 (s), 736 (s), 697 (s) cm$^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 7.40–7.25 (m, 5 H, Ar*H*), 4.94 (s, 1 H, C=CH*H*), 4.89 (s, 1 H, C=*CH*H), 4.53 (s, 2 H, $CH_2Ph$), 3.59 (t, *J* = 7 Hz, 2 H, $CH_2OBn$), 3.47 (t, *J* = 7 Hz, 2 H, $CH_2Br$), 2.62 (t, *J* = 7 Hz, 2 H, $CH_2CH_2Br$), 2.36 (t, *J* = 7.0 Hz, 2 H, $CH_2CH_2OBn$).

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 143.7 (*C*=$CH_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 113.4 (C=$CH_2$), 73.1 ($CH_2Ph$), 68.9 ($CH_2OBn$), 39.7 ($CH_2CH_2Br$), 35.9 ($CH_2CH_2OBn$), 31.0 ($CH_2Br$).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}O^{79}Br^{23}Na$: 291.0355; found: 291.0354.

### Methyl 7-(Benzyloxy)-5-methylene-2-oxoheptanoate (20)

To a solution of {[(5-iodo-3-methylenepentyl)oxy]methyl}benzene (**18b**)[2] (100 mg, 0.31 mmol) in $Et_2O$ (3 mL) at –78 °C was added *t*-BuLi (0.44 mL, 1.7 M in pentane, 0.75 mmol) dropwise. After 1 h, the reaction mixture was transferred slowly by cannula to a solution of dimethyl oxalate (**19**) (186 mg, 1.58 mmol) in THF (0.5 mL) at –78 °C and stirred for 4 h. Then, sat. aq. $NH_4Cl$ (2 mL) was added and the mixture was allowed to warm to r.t. The aq. layer was extracted with $Et_2O$ (2 × 5 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (20% $Et_2O$ in petrol) gave α-ketoester **20**.

Yield: 32 mg (37%); colourless liquid; $R_f$ = 0.15 (20% $Et_2O$ in petrol).

IR (film): 2931 (m), 1743 (s), 1452 (w), 1276 (m), 1099 (m), 716 (w) cm$^{-1}$.

$^1$H NMR (500 MHz; $CDCl_3$): δ = 7.40–7.26 (m, 5 H, Ar*H*), 4.84 (s, 1 H, C=CH*H*), 4.80 (s, 1 H, C=*CH*H), 4.51 (s, 2 H, $CH_2Ph$), 3.86 (s, 3 H, $CO_2Me$), 3.58 (t, 2 H, *J* = 7 Hz, $CH_2OBn$), 3.00 (t, *J* = 7 Hz, 2 H, $CH_2C$=O), 2.42–2.33 (m, 4 H, $CH_2C(=CH_2)CH_2$).

$^{13}$C NMR (125 MHz; $CDCl_3$): δ = 193.6 (C=O), 161.5 ($CO_2Me$), 144.7 (*C*=$CH_2$), 138.4 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=$CH_2$), 73.1 ($CH_2Ph$), 68.9 ($CH_2OBn$), 53.1 ($CO_2CH_3$), 37.7 ($CH_2CH_2OBn$), 36.5 ($CH_2CH_2C$=O), 29.3 ($CH_2CH_2C$=O).

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HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}O_4{}^{23}Na$: 299.1264; found: 299.1254.

### 4-Ethyl 1-Methyl 2-[5-(Benzyloxy)-3-methylenepentyl]-3-diazo-2-hydroxysuccinate (21)

A solution of LDA [prepared from *n*-BuLi (90 μL, 2.5 M in hexanes, 0.22 mmol) and *i*-$Pr_2NH$ (30 μL, 0.22 mmol) in THF (1 mL) at −78 °C] was added dropwise to a solution of ethyl diazoacetate (**2**) (23 μL, 0.22 mmol) and α-ketoester **20** (36 mg, 0.13 mmol) in THF (350 μL) at −78 °C. After 2 h, the reaction was quenched with $NH_4Cl$ (2 mL), and the mixture was extracted with $Et_2O$ (2 × 5 mL), and dried ($MgSO_4$). After evaporation under reduced pressure, the residue was purified by a short column chromatography (10% EtOAc in petrol) to give diazo-alcohol **21**.

Yield: 40 mg (78%); yellow oil; $R_f$ = 0.25 (50% $Et_2O$ in petrol).

IR (film): 3390 (br), 3027 (w), 2920 (m), 1732 (s), 1453 (m), 1261 (s), 1097 (s), 739 (m), 699 (m) cm$^{-1}$.

$^1$H NMR (500 MHz; $CDCl_3$): δ = 7.39–7.26 (m, 5 H, Ar*H*), 4.82 (s, 1 H, C=CH*H*), 4.80 (s, 1 M, C=C*H*H), 4.50 (s, 2 H, C$H_2$Ph), 4.28–4.16 (m, 2 H, $CO_2CH_2CH_3$), 3.78 (s, 3 H, $CO_2$Me), 3.56 (t, *J* = 7 Hz, 2 H, C$H_2$OBn), 2.34 (t, *J* = 7 Hz, 2 H, C$H_2CH_2$OBn), 2.32–2.26 [m, 1 H, CH*H*C(OH)], 2.02–1.97 [m, 1 H, C*H*HC(OH)], 1.96–1.90 [m, 2 H, $CH_2CH_2$C(OH)], 1.27 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$): δ = 173.6 (*C*$O_2$Me), 165.9 (*C*$O_2$Et), 145.2 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.5 (C=*C*$H_2$), 73.8 (quat. *C*(OH)$CO_2$Me), 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.4 ($CO_2CH_2CH_3$), 53.6 ($CO_2CH_3$), 36.4 and 34.6 ($CH_2C$(=$CH_2$)$CH_2$), 29.7 ($CH_2$C(OH)), 14.5 ($CO_2CH_2CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}O_6N_2$: 391.1863; found: 391.1882.

### 4-Ethyl 1-Methyl 2-[5-(Benzyloxy)-3-methylenepentyl]-2-[(*tert*-butyldimethylsilyl)oxy]-3-diazosuccinate (22a) and 6a-Ethyl 6-Methyl (3a*R*,6*S*,6a*R*)-3a-[2-(Benzyloxy)ethyl]-6-[(*tert*-butyldimethylsilyl)oxy]-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a(3*H*)-dicarboxylate (23a)

TBSOTf (35 μL, 0.15 mmol) was added to a solution of 2,6-lutidine (26 μL, 0.22 mmol) in $CH_2Cl_2$ (200 μL) at 0 °C and stirred for 15 min. A solution of diazo-alcohol **21** (30 mg, 0.076 mmol) in $CH_2Cl_2$ (200 μL) was added and the reaction mixture was stirred for 48 h at r.t., then water (1 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (2 × 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude mixture was purified by column chromatography (0–20% $Et_2O$ in petrol).

First eluted TBS ether **22a** (7 mg, 18%), as a yellow oil; $R_f$ = 0.23 (20% $Et_2O$ in petrol).

IR (film): 2953 (m), 2857 (m), 2096 (s), 1745 (s), 1701 (s), 1454 (w), 1369 (m), 1304 (s), 1254 (m), 1135 (s), 838 (s), 780 (m) cm$^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Ar*H*), 4.80 (s, 2 H, C=$CH_2$), 4.50 (s, 2 H, C$H_2$Ph), 4.26–4.11 (m, 2 H, $CO_2CH_2CH_3$), 3.72 (s, 3 H, $CO_2$Me), 3.55 (t, *J* = 7 Hz, 2 H, C$H_2$OBn), 2.33 (t, *J* = 7 Hz, 2 H, C$H_2CH_2$OBn), 2.24–1.94 [m, 4 H, $CH_2CH_2$C(OTBS)], 1.24 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 0.88 (s, 9 H, OSiC$Me_3$), 0.11 and 0.05 [2 × s, 6 H, OSi$(CH_3)_2$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 173.6 (*C*$O_2$Me), 145.6 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.2 (C=*C*$H_2$), 76.0 [quat. *C*(OTBS)$CO_2$Me], 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.1 ($CO_2CH_2CH_3$), 52.8 ($CO_2CH_3$), 36.9 and 36.4 [$CH_2C$(=$CH_2$)$CH_2$], 30.2 [$CH_2$C(OH)], 25.9 [SiC$(CH_3)_3$], 18.6 [Si*C*$(CH_3)_3$], 14.6 ($CO_2CH_2CH_3$), −3.4 and −3.08 (2 × Si$CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}O_6N_2{}^{28}Si$: 505.2728; found: 505.2729.

Second eluted cycloadduct **23a** (14 mg, 37%), as a pale-yellow oil; $R_f$ = 0.34 (20% $Et_2O$ in petrol).

IR (film): 2928 (m), 2855 (m), 1741 (s), 1454 (m), 1365 (w), 1313 (m), 1253 (s), 1100 (m), 1056 (m), 838 (s), 779 (m) cm$^{-1}$.

$^1$H NMR (500 MHz; $CDCl_3$): δ = 7.38–7.27 (m, 5 H, Ar*H*), 4.73 (d, *J* = 18.5 Hz, 1 H, CH*H*N=N), 4.52–4.43 (m, 3 H, C$H_2$Ph and CH*H*N=N), 4.21–4.14 (m, 2 H, $CO_2CH_2CH_3$), 3.79 (s, 3 H, $CO_2$Me), 3.57–3.48 (m, 2 H, C$H_2$OBn), 2.41–2.32 [m, 1 H, CH*H*C(OTBS)], 2.09–2.02 [m, 1 H, CH*H*$CH_2$C(OTBS)], 1.88–1.78 [m, 2 H, C*H*HC(OTBS) and CH*H*$CH_2$OBn], 1.65–1.60 (m, 1 H, C*H*H$CH_2$OBn), 1.57–1.50 [m, 1 H, C*H*H$CH_2$C(OTBS)], 1.25 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 0.82 (s, 9 H, OSiC$Me_3$), 0.05 [2 × s, 6 H, OSi$(CH_3)_2$].

$^{13}$C NMR (125 MHz; $CDCl_3$): δ = 172.0 (*C*$O_2$Me), 168.2 (*C*$O_2$Et), 138.1 (Ar*C*), 128.6 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (Ar*C*H), 110.5 (quat. *C*$CO_2$Et), 90.9 ($CH_2$N=N), 87.1 [quat. *C*(OTBS)$CO_2$Me], 73.4 (*C*$H_2$Ph), 67.8 (*C*$H_2$OBn), 61.9 ($CO_2CH_2CH_3$), 52.3 ($CO_2CH_3$), 49.6 (quat. *C*$CH_2$N=N), 37.4 [$CH_2$C(OTBS)], 35.3 ($CH_2CH_2$OBn), 34.5 [$CH_2CH_2$C(OTBS)], 25.7 [SiC$(CH_3)_3$], 18.5 [Si*C*$(CH_3)_3$], 14.2 ($CO_2CH_2CH_3$), −3.1 and −4.0 (2 × Si$CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}O_6N_2{}^{28}Si$: 505.2728; found: 505.2732.

### 4-Ethyl 1-Methyl 2-[5-(Benzyloxy)-3-methylenepentyl]-3-diazo-2-[(trimethylsilyl)oxy] Succinate (22b) and 6a-Ethyl 6-Methyl (3a*R*,6*S*,6a*R*)-3a-[2-(Benzyloxy)ethyl]-6-[(trimethylsilyl)oxy]-3a,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-6,6a(3*H*)-dicarboxylate (23b)

Hexamethyldisilazane (66 μL, 0.32 mmol) was added to a solution of diazo alcohol **21** (30 mg, 0.076 mmol) and imidazole (11 mg, 0.16 mmol) in THF (0.8 mL) at r.t. After 48 h, the reaction mixture was concentrated by blowing nitrogen, followed by purification of the residue by column chromatography (0–10% $Et_2O$ in petrol).

First eluted TMS ether **22b** (14 mg, 40%), as a yellow oil; $R_f$ = 0.26 (20% $Et_2O$ in petrol).

IR (film): 2954 (m), 2096 (s), 1744 (s), 1701 (s), 1454 (m), 1369 (m), 1304 (s), 1251 (s), 1135 (m), 844 (s) cm$^{-1}$.

$^1$H NMR (400 MHz; $CDCl_3$): δ = 7.37–7.27 (m, 5 H, Ar*H*), 4.80 (s, 2 H, C=$CH_2$), 4.51 (s, 2 H, C$H_2$Ph), 4.26–4.11 (m, 2 H, $CO_2CH_2CH_3$), 3.73 (s, 3 H, $CO_2$Me), 3.56 (t, *J* = 7 Hz, 2 H, C$H_2$OBn), 2.34 (t, *J* = 7 Hz, 2 H, C$H_2CH_2$OBn), 2.22–1.92 [m, 4 H, $CH_2CH_2$C(OTBS)], 1.25 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 0.13 [s, 9 H, OSi$(CH_3)_3$].

$^{13}$C NMR (100 MHz; $CDCl_3$): δ = 171.8 (*C*$O_2$Me), 164.9 (*C*$O_2$Et), 145.6 (*C*=$CH_2$), 138.5 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.1 (C=*C*$H_2$), 76.2 [quat. *C*(OTMS)$CO_2$Me], 73.1 (*C*$H_2$Ph), 68.9 (*C*$H_2$OBn), 61.0 ($CO_2CH_2CH_3$), 52.8 ($CO_2CH_3$), 36.7 and 36.5 [$CH_2C$(=$CH_2$)$CH_2$], 30.2 [$CH_2$C(OTMS)], 14.6 ($CO_2CH_2CH_3$), 1.4 [OSi$(CH_3)_3$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{35}O_6N_2{}^{28}Si$: 463.2258; found: 463.2258.

Second eluted cycloadduct **23b** (11 mg, 31%), as a pale-yellow oil; $R_f$ = 0.34 (20% $Et_2O$ in petrol).

IR (film): 2951 (m), 2928 (m), 1741 (s), 1455 (m), 1254 (s), 1101 (m), 1056 (m), 839 (s), 779 (m) cm$^{-1}$.

$^1$H NMR (500 MHz; $CDCl_3$): δ = 7.38–7.27 (m, 5 H, Ar*H*), 4.72 (d, *J* = 18.5 Hz, 1 H, CH*H*N=N), 4.53–4.42 (m, 3 H, C$H_2$Ph and CH*H*N=N), 4.21–4.14 (m, 2 H, $CO_2CH_2CH_3$), 3.80 (s, 3 H, $CO_2CH_3$), 3.56–3.47 (m, 2 H, C$H_2$OBn), 2.33 [dt, *J* = 13.5, 7.5 Hz, 1 H, CH*H*C(OTBS)], 2.12–2.04

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[m, 1 H, CH*H*CH$_2$C(OTBS)], 1.85 (dt, *J* = 13.5, 5.5 Hz, 1 H, CH*H*CH$_2$OBn), 1.75 [ddd, *J* = 13.5, 7.5, 6.5, 1 H, C*H*HC(OTBS)], 1.64–1.52 [m, 1 H, C*H*-HCH$_2$OBn and C*H*HCH$_2$C(OTBS)], 1.24 (t, *J* = 7 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 0.10 [s, 9 H, OSi(CH$_3$)$_3$].

$^{13}$C NMR (125 MHz; CDCl$_3$): δ = 172.4 (*C*O$_2$Me), 167.8 (*C*O$_2$Et), 138.2 (Ar*C*), 128.6 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 110.1 (quat. *C*CO$_2$Et), 91.9 (CH$_2$N=N), 87.0 (quat. *C*(OTBS)CO$_2$Me), 73.4 (*C*H$_2$Ph), 67.7 (*C*H$_2$OBn), 61.8 (CO$_2$*C*H$_2$CH$_3$), 52.3 (CO$_2$CH$_3$), 49.6 (quat. *C*CH$_2$N=N), 37.5 [*C*H$_2$C(OTBS)], 35.5 (*C*H$_2$CH$_2$OBn), 34.8 [*C*H$_2$CH$_2$C(OTBS)], 14.2 (CO$_2$CH$_2$*C*H$_3$), 1.6 [Si(*C*H$_3$)$_3$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{35}O_6N_2{}^{28}Si$: 463.2258; found: 463.2251.

### 4-Ethyl 1-Methyl 2-[5-(Benzyloxy)-3-oxopentyl]-2-[(*tert*-butyldimethylsilyl)oxy]-3-diazosuccinate (24a)

By following the general procedure for ozonolysis above, TBS ether **22a** (4 mg, 0.008 mmol) gave, after column chromatography (0–40% Et$_2$O in petrol), diazoketone **24a**.

Yield: 2.3 mg (58%); yellow oil; $R_f$ = 0.53 (50% Et$_2$O in petrol).

IR (film): 2931 (m), 2856 (m), 2095 (s), 1747 (s), 1700 (s), 1456 (w), 1305 (m), 1256 (m), 1132 (m), 838 (m) cm$^{-1}$.

$^1$H NMR (500 MHz; CDCl$_3$): δ = 7.37–7.27 (m, 5 H, Ar*H*), 4.50 (s, 2 H, C*H*$_2$Ph), 4.24–4.12 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 3.75–3.68 (m, 5 H, CO$_2$CH$_3$ and C*H*$_2$OBn), 2.69 (t, *J* = 6 Hz, 2 H, C*H*$_2$CH$_2$OBn), 2.67–2.61 [m, 1 H, CH*H*C(OTBS)], 2.51–2.44 [m, 1 H, C*H*HC(OTBS)], 2.27–2.21 [m, 2 H, C*H*$_2$CH$_2$C(OTBS)], 1.24 (t, *J* = 7 Hz, 3 H, OCH$_2$C*H*$_3$), 0.86 [s, 9 H, OSiC(C*H*$_3$)$_3$], 0.09 and 0.04 [2 × s, 6 H, OSi(C*H*$_3$)$_2$].

$^{13}$C NMR (125 MHz; CDCl$_3$): δ = 207.7 (C=O), 171.4 (*C*O$_2$Me), 164.8 (*C*O$_2$Et), 138.2 (ArC), 128.5 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 75.6 [quat. *C*(OTBS)CO$_2$Me], 73.4 (*C*H$_2$Ph), 65.4 (*C*H$_2$OBn), 61.2 (CO$_2$*C*H$_2$CH$_3$), 52.9 (CO$_2$CH$_3$), 43.2 (O=C*C*H$_2$), 37.8 (O=C*C*H$_2$), 32.2 [*C*H$_2$C(OTBS)], 25.9 [SiC(*C*H$_3$)$_3$], 18.6 [Si*C*(CH$_3$)$_3$], 14.6 (CO$_2$CH$_2$*C*H$_3$), –3.5 and –3.9 (2 × SiCH$_3$).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{38}O_7N_2{}^{23}Na^{28}Si$: 529.2340; found: 529.2341.

### 4-Ethyl 1-Methyl 2-[5-(Benzyloxy)-3-oxopentyl]-3-diazo-2-[(trimethylsilyl)oxy]succinate (24b)

By following the procedure for ozonolysis above, TMS ether **22b** (6 mg, 0.013 mmol) gave, after column chromatography (0–40% Et$_2$O in petrol), diazoketone **24b**.

Yield: 3.7 mg (61%); yellow oil; $R_f$ = 0.51 (50% Et$_2$O in petrol).

IR (film): 2953 (w), 2871 (w), 2096 (s), 1747 (s), 1702 (s), 1455 (w), 1369 (m), 1305 (s), 1251 (s), 1135 (m), 845 (s) cm$^{-1}$.

$^1$H NMR (500 MHz; CDCl$_3$): δ = 7.37–7.27 (m, 5 H, Ar*H*), 4.50 (s, 2 H, C*H*$_2$Ph), 4.27–4.11 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 3.75–3.71 (m, 5 H, CO$_2$C*H*$_3$ and C*H*$_2$OBn), 2.70 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$CH$_2$OBn), 2.66–2.58 [m, 1 H, CH*H*C(OTMS)], 2.48–2.41 [m, 1 H, C*H*HC(OTMS)], 2.26–2.20 [m, 2 H, C*H*$_2$CH$_2$C(OTMS)], 1.25 (t, *J* = 7 Hz, 3 H, OCH$_2$C*H*$_3$), 0.11 (s, 3 H, OTMS).

$^{13}$C NMR (125 MHz; CDCl$_3$): δ = 207.8 (C=O), 171.5 (*C*O$_2$Me), 164.8 (*C*O$_2$Et), 138.2 (ArC), 128.6 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 75.8 [quat. *C*(OTMS)CO$_2$Me], 73.4 (*C*H$_2$Ph), 65.4 (*C*H$_2$OBn), 61.2 (CO$_2$*C*H$_2$CH$_3$), 53.0 (CO$_2$CH$_3$), 43.2 (O=C*C*H$_2$), 37.7 (O=C*C*H$_2$), 32.2 [*C*H$_2$C(OTMS)], 14.6 (CO$_2$CH$_2$*C*H$_3$), 1.3 (OTMS).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}O_7N_2{}^{23}Na^{28}Si$: 487.1871; found: 487.1867.

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## Supporting Information

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